

## Original Investigation

# Diagnosis of Myocardial Infarction Using a High-Sensitivity Troponin I 1-Hour Algorithm

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**IMPORTANCE** Rapid and accurate diagnosis of acute myocardial infarction (AMI) currently constitutes an unmet need.

**OBJECTIVE** To test a 1-hour diagnostic algorithm to diagnose AMI using a high-sensitivity troponin I assay with a new cutoff level of 6 ng/L.

**DESIGN, SETTING, AND PARTICIPANTS** The Biomarkers in Acute Cardiac Care study is a prospective study that investigated the application of the troponin I assay for the diagnosis of AMI in 1040 patients presenting to the emergency department with acute chest pain from July 19, 2013, to December 31, 2014. Results were validated in 2 independent cohorts of 4009 patients. Final follow-up was completed on July 1, 2015, and data were assessed from July 2 to December 15, 2015.

**EXPOSURE** Acute chest pain suggestive of AMI.

**MAIN OUTCOMES AND MEASURES** Accurate diagnosis or exclusion of AMI and 12-month mortality in patients with acute chest pain.

**RESULTS** Of the 1040 patients included from the study cohort, 673 (64.7%) were male and had a median age of 65 (interquartile range, 52-75) years. With application of a low troponin I cutoff value of 6 ng/L, the rule-out algorithm showed a high negative predictive value of 99.8% (95% CI, 98.6%-100.0%) after 1 hour for non-ST-segment elevation MI type 1. The 1-hour approach was comparable to a 3-hour approach. Similarly, a rule-in algorithm based on troponin I levels provided a high positive predictive value with 82.8% (95% CI, 73.2%-90.0%). Moreover, application of the cutoff of 6 ng/L resulted in lower follow-up mortality (1.0%) compared with the routinely used 99th percentile (3.7%) for this assay. Two independent cohorts further validated the performance of this algorithm with high negative and positive predictive values.

**CONCLUSIONS AND RELEVANCE** Patients with possible AMI can be triaged within 1 hour after admission with no loss of safety compared with a 3-hour approach, when a low and sensitive cutoff is applied. This concept enables safe discharge or rapid treatment initiation after 1 hour.

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**E**arly diagnosis of acute myocardial infarction (AMI) in patients presenting with acute chest pain improves clinical outcome. Moreover, rapid exclusion of AMI is important to triage patients in view of limited resources in the emergency department. Measurement of cardiac troponin levels, as a marker of myocyte necrosis, is essential for diagnosing AMI.<sup>1</sup> Compared with sensitive troponin assays, high-sensitivity troponin assays enhance the accuracy and speed of the diagnosis,<sup>1-4</sup> improve outcome, and are cost-effective.<sup>5</sup>

Therefore, current European Society of Cardiology guidelines recommend the use of high-sensitivity troponin assays on admission and after 3 hours. A value above the 99th percentile of the specific assay and a relative rise or fall is the recommended cutoff for a diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI).<sup>6,7</sup> Recent studies suggest that AMI can be diagnosed earlier than 3 hours, when values below the 99th percentile are used as cutoff values. This concept was incorporated into the 2015 European Society of Cardiology guidelines for NSTEMI as an alternative to the standard approach.<sup>8</sup> We aimed to develop an algorithm for accurate and rapid exclusion and diagnosis of AMI after 1 hour using a cutoff below the 99th percentile and compare it with the recommended 3-hour approach.

## Methods

### Study Overview

The present study investigates the application of a high-sensitivity troponin I assay in 3 cohorts of patients with acute chest pain. We aimed to identify an optimal cutoff using troponin I levels for diagnosing NSTEMI in a cohort of 1040 patients with acute chest pain suggestive of AMI (the Biomarkers in Acute Cardiac Care [BACC] cohort).<sup>9</sup> With this cutoff, we identified or excluded AMI in patients with acute chest pain. We tested a 1-hour vs a 3-hour algorithm and compared the diagnostic accuracy of the calculated lower cutoff vs the 99th percentile and evaluated follow-up mortality. We then validated this lower troponin cutoff level in 2 independent cohorts, including the 2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker trial (ADAPT)<sup>10</sup> and Advantageous Predictors of Acute Coronary Syndrome Evaluation Study (APACE)<sup>11</sup> with 1748 and 2261 patients, respectively. The current analysis was prespecified in the BACC study protocol. The study complied with the Declaration of Helsinki,<sup>12</sup> and the ethics committee of the University Medical Center Hamburg-Eppendorf approved the study protocol. All patients provided written informed consent.

### BACC Cohort

#### Study Population and Design

This study prospectively recruited 1040 patients presenting with acute chest pain in the emergency department of the University Medical Center Hamburg-Eppendorf from July 19, 2013, to December 31, 2014. Patients were included if they presented with acute chest pain and/or other symptoms suggestive of AMI, were older than 18 years, were willing to partici-

### Key Points

**Question** Is it possible to rule out myocardial infarction (MI) after 1 hour using a high-sensitivity troponin I assay with a low cutoff concentration?

**Findings** In this diagnostic-test study, a low troponin I cutoff level of 6 ng/L showed a high negative predictive value of 99.8% after 1 hour for non-ST-segment elevation MI type 1, which was comparable to a 3-hour approach. Two independent cohorts further validated the performance of this algorithm.

**Meaning** Patients with suspected acute MI can be triaged within 1 hour after admission and with no loss of safety compared with a 3-hour approach, when a low and sensitive cutoff was applied.

pate in the study, and were able to give written informed consent. All patients underwent a routine clinical assessment as described in the current European Society of Cardiology guidelines.<sup>6</sup> Blood was drawn directly at admission, after 1 hour, and after 3 hours. A primary diagnosis of AMI was adjudicated according to current guidelines<sup>6</sup> based on a high-sensitivity troponin T assay (Elecsys; Roche Diagnostics). The final discharge diagnosis used for the index event was additionally based on all available clinical, laboratory, and imaging findings in the course of the hospital stay. Two cardiologists (J.T.N. and N.A.S.) who were unaware of the study troponin I data adjudicated the diagnosis independently. If the adjudicators disagreed about the diagnosis, a third cardiologist (D.W.) refereed. Moreover, NSTEMI type 1 or 2 was diagnosed based on the third universal definition of myocardial infarction.<sup>7</sup> More detailed study-specific assessment is available in eMethods in the Supplement.

### Definition of the Best-Performing Troponin I Cutoff

The troponin I level was determined using a high-sensitivity troponin I immunoassay (ARCHITECT i2000SR; Abbott Diagnostics). The limit of detection for the assay was 1.9 (range, 0-50 000) ng/L. The assay had a 10% coefficient of variation at a concentration of 5.2 ng/L. Intra-assay and interassay coefficients of variation of this assay were 4.26% and 6.29%.<sup>13</sup> The 99th percentile was 27 ng/L in the general population.<sup>14</sup> This assay was used in all 3 studies (BACC, ADAPT,<sup>10</sup> and APACE<sup>11</sup>).

We defined the optimal troponin I cutoff level to exclude NSTEMI using values of 2, 3, 4, 5, 5.2 (for the 10% coefficient of variation), 6, 7, 8, 9, 10, 15, 20, and 27 (as the 99th percentile of this assay) ng/L. The cutoff level with the combination of the highest negative predictive value (NPV), maximum number of individuals with AMI excluded, exceeding the 10% coefficient of variation of 5.2 ng/L, and being an integral number was considered optimal.

### Troponin I Algorithm

Exclusion of NSTEMI was defined by a troponin I level less than 6 ng/L (defined as the optimal cutoff in the BACC study) at admission and after 1 hour or at admission and after 3 hours. For comparison, we calculated exclusion of NSTEMI using only the admission value.

Table 1. Baseline Characteristics

Characteristic	No. (%) of Patients			P Value <sup>a</sup>
	All (N = 1040)	NSTEMI (n = 184)	Non-AMI (n = 799)	
Age, median (25th-75th percentile), y	65.0 (52.0-75.0)	70.0 (60.4-77.0)	64.0 (51.0-74.0)	<.001
Male sex	673 (64.7)	124 (67.4)	506 (63.3)	.31
BMI, median (25th-75th percentile)	26.0 (23.5-29.4)	26.2 (23.7-29.7)	26.0 (23.4-29.4)	.67
Hypertension	719 (69.1)	146 (79.3)	539 (67.4)	.002
Hyperlipoproteinemia	456 (43.8)	103 (56.0)	333 (41.7)	<.001
Diabetes	150 (14.4)	39 (21.2)	102 (12.8)	.005
Former smoker	332 (31.9)	59 (32.1)	263 (32.9)	.86
Current smoker	241 (23.2)	41 (22.3)	172 (21.5)	.84
History of CAD, bypass, or PCI	349 (33.6)	80 (43.5)	260 (32.5)	.006
History of AMI	162 (15.6)	41 (22.3)	115 (14.4)	.01
Atrial fibrillation	222 (21.3)	42 (22.8)	177 (22.2)	.84
Congestive heart failure	150 (14.4)	40 (21.7)	104 (13.0)	.004
CRP level, median (25th-75th percentile), mg/L	4.9 (4.9-7.1)	4.9 (4.9-9.3)	4.9 (4.9-7.0)	.14
Creatinine level, median (25th-75th percentile), mg/dL	1.0 (0.8-1.2)	1.1 (0.8-1.3)	1.0 (0.8-1.1)	<.001
eGFR, median (25th-75th percentile), mL/min/1.73m <sup>2</sup>	77.0 (58.5-93.2)	66.9 (51.0-83.3)	79.9 (60.0-94.2)	<.001
Time to admission troponin assay, median (25th-75th percentile), min	22.0 (14.0-37.0)	20.0 (13.0-33.0)	23.0 (15.0-38.0)	.01
Time to 1-h troponin assay, median (25th-75th percentile), min	84.0 (75.4-101.0)	81.0 (73.0-96.1)	85.0 (76.0-102.1)	.01

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; CRP to nanomoles per liter, multiply by 9.524.

<sup>a</sup> For categorical variables, Fisher exact test was performed; for continuous variables, the Mann-Whitney test. All comparisons were between the NSTEMI and non-AMI groups.

To identify NSTEMI, the following algorithms based on troponin I levels were considered: 1 hour after admission a value higher than 6 ng/L combined with an increase or decrease of at least 12 ng/L from the admission value was defined to identify NSTEMI; and 3 hours after admission a value higher than 6 ng/L combined with an increase or decrease of at least 12 ng/L from the admission value was defined as NSTEMI. This increase was used to increase the positive predictive value (PPV) of a true identification to minimize false-positive inclusion and therefore prevent unnecessary invasive procedures. The rule-in algorithm was compared with different absolute changes (6 and 18 ng/L) and a relative change of 20%, as recommended by the current guidelines.<sup>15</sup> Patients in whom NSTEMI could not be identified or excluded were termed a *gray-zone* group with elevated but nondynamic troponin I values.

#### Follow-up

Follow-up mortality is reported 12 months after admission. The median follow-up time for mortality was 313 days. Final follow-up was completed on July 1, 2015.

#### Independent Validation Cohorts for the Algorithm

The BACC study derived the 1-hour algorithm to exclude and/or identify AMI, which was validated in 2 independent cohorts. The first cohort is from the ADAPT study<sup>10</sup> and consists of 1748 patients with suspected AMI who presented at the emergency department. Troponin I levels were measured on admission and after 2 hours, which was not the same time point as in our study. Moreover, we used a second validation cohort

of 2261 patients with suspected AMI. This cohort (APACE)<sup>11</sup> was described recently, and troponin I levels were measured at admission and 1 hour.

#### Statistical Analysis

Data were analyzed from July 2 to December 16, 2015. Continuous variables are described by quartiles; categorical variables, as absolute numbers and percentages. Different binary diagnostic tests for the diagnosis of NSTEMI or NSTEMI type 1 were considered as described above. Fifty-seven patients with STEMI were excluded, because biomarker measurements are not relevant for this diagnosis. The diagnoses compared were NSTEMI (or NSTEMI type 1) vs non-AMI, the latter consisting of cardiac noncoronary chest pain, noncardiac chest pain, unstable angina pectoris, and stable angina. For the binary tests, sensitivity, specificity, NPV, and PPV were computed, together with exact binomial 95% CIs. The analyses were additionally performed for different subgroups. We separated patients by age (<75 or ≥75 years), hypertension (yes or no), heart failure (yes or no), atrial fibrillation (yes or no), sex (male or female), history of coronary artery disease (yes or no), history of AMI (yes or no), and renal function (estimated glomerular filtration rate <45 or ≥45 mL/min/1.73m<sup>2</sup>). To test for equality of predictive values, we used the methods of Kosinski.<sup>16</sup> Receiver operating characteristic curves were produced for troponin I levels measured on admission and 1 and 3 hours after admission from BACC study data. The area under the receiver operating characteristic curve was also computed for each troponin I measurement. Survival curves for the rule-out, gray-zone, and rule-in groups for the different algorithms were

Table 2. Rule-Out Results Using Troponin I Assay

Troponin I Cutoff Level by Time After Admission	NSTEMI			NSTEMI Type 1		
	NPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	NPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
≤6 ng/L						
Admission only	97.1 (95.2-98.4)	92.2 (87.2-95.7)	61.0 (57.4-64.4)	98.5 (97.0-99.4)	93.8 (87.5-97.5)	61.0 (57.4-64.4)
Admission and 1 h	99.0 (97.5-99.7) <sup>a,b</sup>	97.6 (94.1-99.4)	53.3 (49.7-56.9)	99.8 (98.6-100.0) <sup>d,e</sup>	99.1 (94.9-100.0)	53.3 (49.7-56.9)
Admission and 3 h	99.5 (98.1-99.9) <sup>c</sup>	98.8 (95.8-99.9)	49.7 (46.1-53.4)	100.0 (98.5-100.0) <sup>f</sup>	100.0 (94.9-100.0)	49.7 (46.1-53.4)
≤27 ng/L (99th Percentile)						
Admission and 1 h	94.8 (93.0-96.3)	77.5 (70.5-83.6)	92.6 (90.5-94.3)	98.4 (97.2-99.2)	89.6 (82.2-94.7)	92.6 (90.5-94.3)
Admission and 3 h	97.0 (95.5-98.1)	87.6 (81.7-92.2)	90.7 (88.4-92.7)	99.1 (98.1-99.7)	94.3 (88.1-97.9)	90.7 (88.4-92.7)

Abbreviations: NPV, negative predictive value; NSTEMI, non-ST-segment elevation myocardial infarction.

<sup>d</sup>P = .04 vs admission.

<sup>e</sup>P = .33 vs 3 hours.

<sup>a</sup>P = .01 vs admission.

<sup>f</sup>P = .03 vs admission.

<sup>b</sup>P = .21 vs 3 hours.

<sup>c</sup>P = .004 vs admission.

Table 3. Rule-In Results Using Troponin I Assay

Criteria to Diagnose NSTEMI	NSTEMI (95% CI)			NSTEMI Type 1 (95% CI)		
	PPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Troponin I level >6 ng/L at admission	35.2 (30.9-39.7)	92.2 (87.2-95.7)	61.0 (57.4-64.4)	25.7 (21.5-30.2)	93.8 (87.5-97.5)	61.0 (57.4-64.4)
Troponin I level >6 ng/L at 1 h and absolute delta from admission to 1 h ≥12 ng/L	87.1 (79.6-92.6)	59.8 (52.0-67.2)	98.0 (96.7-98.9)	82.8 (73.2-90.0)	67.9 (58.2-76.7)	98.0 (96.7-98.9)
Troponin I level >6 ng/L at 3 h and absolute delta from admission to 3 h ≥12 ng/L	84.6 (78.0-89.9)	77.6 (70.6-83.7)	96.8 (95.3-98.0)	78.6 (69.8-85.8)	83.0 (74.5-89.6)	96.8 (95.3-98.0)

Abbreviations: NSTEMI, non-ST-elevation myocardial infarction; PPV, positive predictive value.

produced using the Kaplan-Meier method. Survival curve differences were tested with the log-rank test if the curves compared contained no common individuals or otherwise by fitting a Cox proportional hazards regression model with a group variable indicator as the only predictor and using a corrected variance estimate to account for the correlated observations.<sup>17</sup> All analyses were performed using R software (version 3.2.2; R Foundation for Statistical Computing).

## Results

### Baseline Demographics

We included 1040 patients with a median age of 65 (interquartile range, 52-75) years; 673 patients (64.7%) were male and 367 (35.3%) were female (Table 1). Of all patients, 184 were classified as having NSTEMI, 57 as having STEMI, and 799 as having non-AMI. Patients with STEMI were excluded from the cutoff definition. The median time from admission to the first troponin I assay was 22 minutes; to the 1-hour measurement, 84 minutes.

### Cutoff Definition

The best performing cutoff value was calculated to be 6 ng/L. The NPV was 99.8% (95% CI, 98.6%-100.0%) with only 1 false-negative finding for NSTEMI type 1; the NPV was 99.0% (95%

CI, 97.5%-99.7%) with 4 false-negative findings for all patients with NSTEMI. This cutoff value exceeds the level for the 10% coefficient of variation of 5.2 ng/L, which is an important measure of assay precision (eTable 1 in the Supplement).

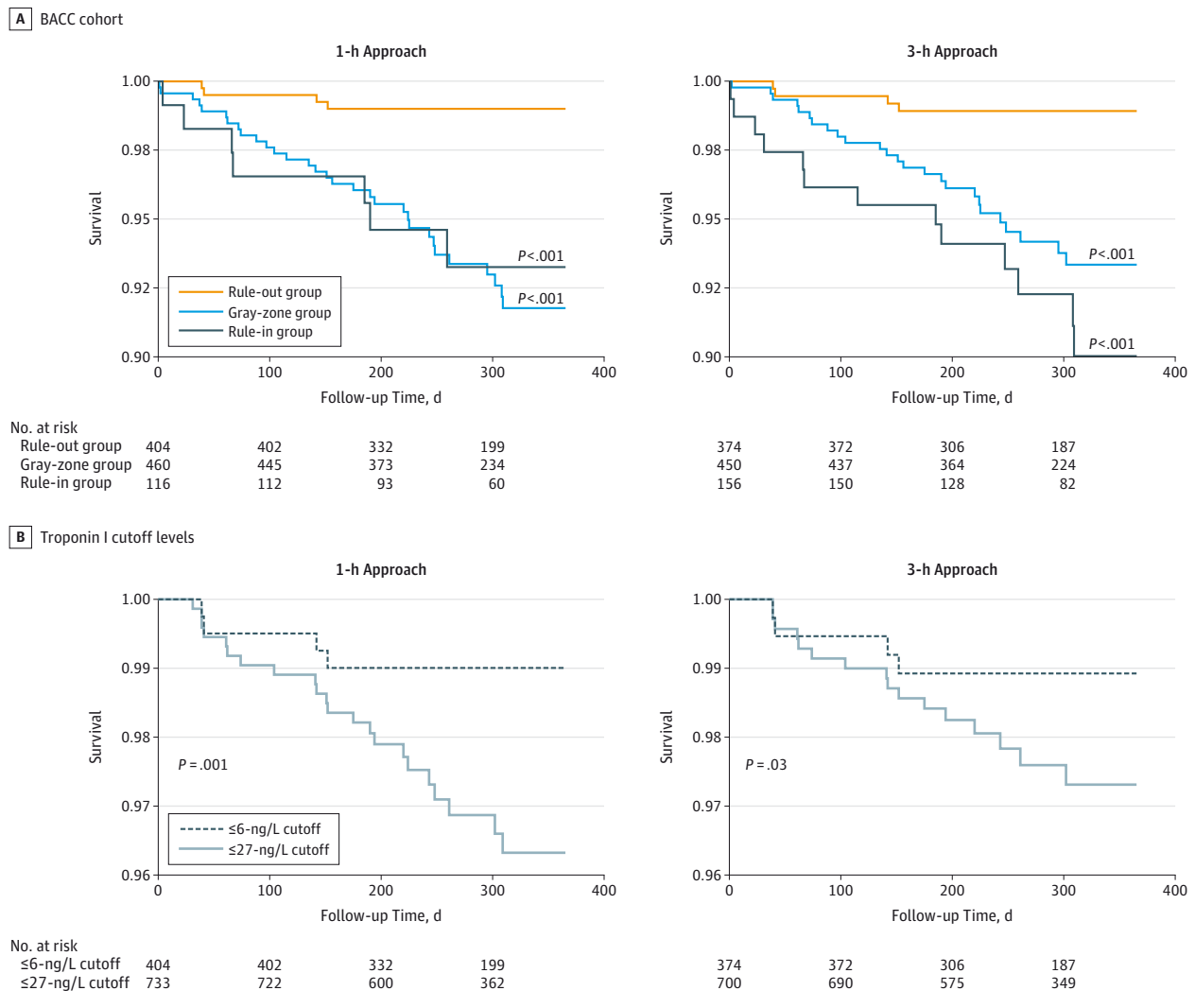
### Using the Troponin I Cutoff Level to Exclude AMI

When we used the 1-hour algorithm with 2 consecutive measurements of troponin I levels, the NPV for NSTEMI type 1 after 1 hour was 99.8% (95% CI, 98.6%-100.0%); after 3 hours, 100.0% (95% CI, 98.5%-100.0%) (Table 2). When all patients with NSTEMI underwent analysis (not stratified according to type 1 or 2), 406 patients (39.0%) could be discharged; of these, 4 (1.0%) had false-negative findings, resulting in an NPV of 99.0% (95% CI, 97.5%-99.7%). For comparison, when only the first measurement of troponin I levels directly after admission was used to rule out AMI, the NPV was 97.1% (95% CI, 95.2%-98.4%). However, 14 of 489 patients (2.9%) had false-negative findings. The application of the 99th percentile as a cutoff (27 ng/L) for exclusion resulted in substantially lower NPVs after 1 hour (94.8%; 95% CI, 93.0%-96.3%) and after 3 hours (97.0%; 95% CI, 95.5%-98.1%) compared with 6 ng/L.

### Confounding Factors to Exclude AMI

Different subgroups underwent analysis to assess the effect of sex (eTables 2 and 3 in the Supplement), age, kidney func-

Figure 1. Survival Curves According to the Diagnostic Algorithm



A, Patients in the Biomarkers in Acute Cardiac Care (BACC) cohort are stratified as having acute myocardial infarction (AMI) (rule-in group), exclusion of AMI (rule-out group), and elevated but nondynamic troponin I levels (gray-zone group). P values are calculated as comparisons with the rule-out group. B, Patients are stratified by the cutoff value of the high-sensitivity troponin I assay ( $\leq 6$  vs  $\leq 27$  ng/L).

tion, the presence of atrial fibrillation, history of heart failure, known coronary artery disease, history of AMI, and hypertension on the outcome (eFigure 1 in the Supplement). We found no significant differences between most subgroups when comparing the NPV and PPV. Only the presence of atrial fibrillation resulted in a significantly reduced PPV after 1 and 3 hours. Nevertheless, the NPV was still relatively high, at 96.1% and 97.8%, respectively. The presence of reduced kidney function, history of coronary artery disease, AMI, heart failure, and hypertension and being older had no significant effect on the NPV or the PPV.

#### Using the Troponin I Cutoff Level to Diagnose AMI

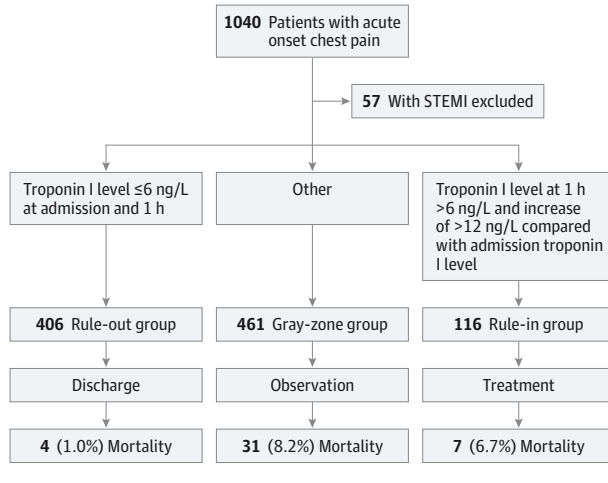
The PPV was 82.8% (95% CI, 73.2%-90.0%) using the 1-hour algorithm and 78.6% (95% CI, 69.8%-85.8%) after 3 hours for patients with NSTEMI type 1 (Table 3). For all patients with NSTEMI, application of this algorithm achieved a PPV

of 87.1% (95% CI, 79.6%-92.6%) after 1 hour and 84.6% (95% CI, 78.0%-89.9%) after 3 hours. When a relative delta of 20% was used, the PPV for patients with NSTEMI was 39.9% (95% CI, 33.4%-46.7%) after 1 hour and 40.1% (95% CI, 34.4%-46.0%) after 3 hours (eTable 4 in the Supplement). With a higher absolute delta of 18 ng/L, the PPV was 88.2% (95% CI, 80.4%-93.8%) after 1 hour and 88.7% (95% CI, 82.2%-93.4%) after 3 hours. The area under the receiver operating characteristic curve is shown in eFigure 2 in the Supplement.

#### Validation of the Algorithm in 2 Independent Cohorts

In the first validation cohort (ADAPT<sup>10</sup>), which included a 2-hour diagnostic algorithm for 1748 individuals, 249 NSTEMIs were observed (eTables 5 and 6 in the Supplement). The NPV directly after admission was 99.6% (95% CI, 99.1%-99.9%) and improved to 99.7% (95% CI, 99.2%-99.4%) after

**Figure 2. Diagnostic Algorithm for Rule-Out and Rule-In Groups Among Patients Presenting With Acute-Onset Chest Pain**



STEMI indicates ST-segment elevation myocardial infarction.

2 hours. Using the rule-in algorithm, we observed a PPV of 81.5% (95% CI, 75.3%-86.3%).

The second validation cohort (APACE<sup>11</sup>) included 2261 patients with 429 NSTEMIs and used a comparable 1- and 3-hour algorithm. The NPV at baseline was 98.6% (95% CI, 98.6%-99.2%) and improved to 99.2% (95% CI, 98.4%-99.2%) and 99.1% (95% CI, 97.1%-99.8%) after 1 and 3 hours, respectively. The PPV after 1 hour was 80.4% (95% CI, 75.1%-84.9%); after 3 hours, 68.8% (95% CI, 59.2%-77.3%). Both cohorts analyzed NSTEMI as the final diagnosis and did not differentiate between NSTEMI types 1 and 2.

### Secondary Events During Follow up

Patients in the BACC cohort were followed up for 12 months (Figure 1A). During the follow-up period, 4.2% of the overall population died. The 12-month mortality rate among the rule-out population was 1.0% (4 patients). The mortality rate was significantly higher in patients with NSTEMI (7 patients [6.7%]) and in the gray-zone group (31 [8.2%]; each  $P < .001$ ) (Figure 2). The difference between rule-in and gray-zone groups did not reach statistical significance. We found no change in mortality when exclusion of AMI was calculated by a 1- compared with a 3-hour approach. When we used the 99th percentile cutoff, mortality in the rule-out group was significantly higher, at 22 patients (3.7%) compared with the suggested troponin I level cutoff of 6 ng/L after 1 hour ( $P = .001$ ) (Figure 1B).

## Discussion

The primary finding of this study is that a rapid 1-hour algorithm with a troponin I level cutoff lower than the routinely used 99th percentile enables safe diagnosis of AMI. This cutoff enables a rapid triage that excludes AMI and a faster initiation of evidence-based treatment for patients diagnosed as having AMI. Results using the 1-hour algorithm were compa-

table (ie, not inferior) to those of the 3-hour algorithm. The troponin I cutoff level of 6 ng/L performed significantly better compared with the 99th percentile in view of increased accuracy and a lower rate of mortality during follow-up.

### Diagnosing AMI

Patients presenting with acute chest pain at the emergency department make heavy use of limited medical resources. Therefore, the need for fast but safe decision making is urgent. A rapid discharge might result from a single high-sensitivity troponin I assay finding.<sup>18-20</sup> As recently shown by Shah et al,<sup>19</sup> this single-measurement approach enables a safe exclusion of AMI with only 0.4% false-negative findings. In that study, however, the median time from admission until blood sampling was 54 minutes, which might explain why patients with a very early presentation were still detected. To prevent a premature discharge of patients at high risk for future ischemic episodes, especially when patients with recent onset of chest pain (within 2 hours) are taken into account, consecutive measurements might be crucial.<sup>21</sup> An approach using 2 consecutive measurements increases sensitivity and specificity, although prolonging the time until the final diagnosis can be made. Herein we show that the accuracy of the 1-hour approach was comparable to the 3-hour approach. Both approaches were superior to a single on-admission determination. The 1-hour approach does not yet integrate any clinical measurement such as electrocardiography, which will further increase the safety of this rule-out strategy.

The rule-in algorithm identified patients with a high accuracy after 1 hour, comparable to a 3-hour approach with preserved specificity. This approach prevents inappropriate cost-intensive management, which includes possibly harmful coronary angiographies. The algorithm performed evenly well in clinically important subgroups, whereas only atrial fibrillation had an effect on the PPV.

The validation of our algorithm in other cohorts (ADAPT and APACE) demonstrated similar high performance by integrating all available cohorts with shorter than the guideline-recommended rule-out window with this specific troponin I assay. Results of this validation testing strengthen the concept of a rapid rule out after 1 hour only, which is now recommended by the NSTEMI European Society of Cardiology guidelines as an alternative to the standard 3-hour approach.<sup>8</sup>

### Cutoff Definition

Guideline-based cutoff values to rule out AMI were derived from the 99th percentile of a specific troponin assay measured in the healthy population. These assays were characterized as sensitive assays, defined by a coefficient of variation near the 99th percentile. Imprecision was relatively high with values below the coefficient of variation. The current high-sensitivity assays, in which precision is high at low cutoff values, are different.

To determine a valid algorithm, we calculated different cutoff values to identify the best-performing one. These calculations resulted in a troponin I cutoff level of 6 ng/L. This cutoff value was higher than that for the 10% coefficient of variation as a marker of imprecision of this specific troponin assay.

For comparison we used a cutoff based on the 99th percentile of the troponin I assay. Many patients with the final diagnosis of AMI were not identified by the 99th percentile cutoff and would have been discharged without the correct diagnosis in our study.

### Secondary Events During Follow-up

The 1- and 3-hour algorithms using a cutoff value of 6 ng/L resulted in lower mortality than the 99th percentile cutoff, and mortality using the 1-hour algorithm was identical to that of the 3-hour algorithm. Patients diagnosed as having NSTEMI by our algorithm had a significantly higher mortality. Highest mortality was observed in the gray-zone group. This group of patients with continuously elevated but stable troponin levels, which are not necessarily related to coronary disease, requires thorough monitoring and reevaluation.

### Strengths and Limitations

An important strength of this study is the application of 2 contemporary high-sensitivity troponin assays. The troponin T assay was used for the final diagnosis with other available

and recommended tools, such as electrocardiography, cardiac imaging, and coronary angiography, as well as clinical judgement. In contrast, only the troponin I assay was used for the rule-out and rule-in algorithms. Furthermore, the algorithm was extensively validated using 4009 patients from different geographical regions in other diseases cohorts. Nevertheless, the values presented herein are assay specific and cannot be applied to other assays without additional studies.

## Conclusions

The application of a 1-hour algorithm with a troponin I cutoff level of 6 ng/L in patients with suspected AMI allows for accurate and rapid exclusion and identification of AMI. The 1- and 3-hour approaches yielded results that were not statistically different, whereas the 1-hour approach would allow faster diagnosis or discharge. A low cutoff performed significantly better than the 99th percentile as cutoff in view of follow-up mortality.

### ARTICLE INFORMATION

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**Study concept and design:** Neumann, Sørensen, Schwemer, Renné, Schnabel, Mueller, Cullen, Blankenberg, Karakas, Westermann.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Neumann, Sørensen, Makarova, Karakas, Westermann.

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**Study supervision:** Schwemer, Parsonage, Schnabel, Landmesser, Mueller, Cullen, Blankenberg, Karakas, Westermann.

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