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High-Sensitivity Cardiac Troponin I Assay for Early Diagnosis of Acute Myocardial Infarction

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BACKGROUND: The aim of this study was to validate the clinical performance of the Beckman Access high-sensitivity cardiac troponin I (hs-cTnI) assay.

METHODS: We enrolled patients presenting to the emergency department with symptoms suggestive of acute myocardial infarction (AMI). Final diagnoses were centrally adjudicated by 2 independent cardiologists with all clinical information including cardiac imaging twice: first, using serial hs-cTnT (Elecsys, primary analysis), and second, using hs-cTnI (Architect, secondary analysis) measurements in addition to the clinically used hs-cTn. hs-cTnI Access was measured at presentation and at 1 h. The primary objective was a direct comparison of diagnostic accuracy as quantified by the area under the ROC curve (AUC) of hs-cTnI Access vs the hs-cTnT Elecsys and hs-cTnI Architect assays. Secondary objectives included the derivation and validation of an hs-cTnI Access-specific 0/1-h algorithm.

RESULTS: AMI was the adjudicated final diagnosis in 243 of 1579 (15.4%) patients. The AUC at presentation for hs-cTnI Access was 0.95 (95% CI, 0.94–0.96), higher than hs-cTnI Architect [0.92 (95% CI, 0.91–0.94; $P < 0.001$)] and comparable to hs-cTnT Elecsys [0.94 (95% CI, 0.93–0.95; $P = 0.12$)]. Applying the derived hs-cTnI Access 0/1-h algorithm (derivation cohort n = 686) to the validation cohort (n = 680), 60% of patients were ruled out [sensitivity, 98.9% (95% CI, 94.3–99.8)], and 15% of patients were ruled in [specificity, 95.9% (95% CI, 94.0–97.2)]. Patients ruled out by the 0/1-h algorithm had a survival rate of 100% at 30 days. Findings were confirmed in the secondary analyses by the adjudication including serial measurements of Architect hs-cTnI.

CONCLUSIONS: Diagnostic accuracy and clinical utility of the Beckman hs-cTnI Access assay are very high and at least comparable to Roche hs-cTnT and Abbott hs-cTnI assays.

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Patients with symptoms suggestive of an acute myocardial infarction (AMI)[10] such as chest discomfort or angina pectoris account for about 10% of all emergency department (ED) consultations worldwide *(1)*. Early diagnosis of AMI as a life-threatening disorder is important for immediate initiation of appropriate, evidence-based therapy. For early rule out and rule in of AMI, electrocardiography (ECG) and cardiac troponin (cTn) form the diagnostic cornerstones and complement clinical assessment *(2–4)*.

Since high-sensitivity cTn (hs-cTn) assays were introduced, reliable measurement of cTn concentrations around the 99th percentile and within the reference interval became possible *(2)*, which increased diagnostic accuracy for AMI at presentation *(3–5)*. During the past decade, 2 hs-cTn assays have been extensively investigated in large diagnostic studies, including the success-

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[10] Nonstandard abbreviations: AMI, acute myocardial infarction; ED, emergency department; ECG, electrocardiography; cTn, cardiac troponin; hs-cTn, high-sensitivity cardiac troponin; ESC, European Society of Cardiology; APACHE, advantageous predictors of acute coronary syndrome evaluation; UA, unstable angina; AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; IQR, interquartile range; MACE, major adverse cardiovascular event.

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ful derivation and validation of rapid 0/1-h algorithms *(6–20)*. These rapid-triage algorithms are recommended by the European Society of Cardiology (ESC) in clinical practice guidelines as a class I recommendation *(6, 10, 19, 21)*.

Recently, the Beckman hs-cTnI Access assay was developed *(22–24)*. Here, we aimed to directly compare in a large multicenter diagnostic study the diagnostic accuracy of the hs-cTnI Access assay with the 2 established hs-cTn assays: Roche hs-cTnT Elecsys and Abbott hs-cTnI Architect. In addition, we sought to follow the ESC recommendations and to derive and validate an assay-specific 0/1-h algorithm by using hs-cTnI Access concentrations at ED presentation and absolute 1-h changes for the very early triage of patients toward rule out or rule in of AMI.

Materials and Methods

STUDY DESIGN AND POPULATION

Advantageous predictors of acute coronary syndrome evaluation (APACE) is an ongoing prospective international multicenter study with 12 centers in 5 countries aiming to advance the early diagnosis of AMI (ClinicalTrials.gov registry, number NCT00470587) *(3, 6, 8, 11, 12, 14, 15, 25–28)*. To best reflect the clinical application of hs-cTn, patients with ST-elevation myocardial infarction were excluded (see the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol65/issue7).

ADJUDICATED FINAL DIAGNOSIS

Adjudication of the final diagnosis was performed by 2 independent cardiologists at the core laboratory (University Hospital Basel) by applying the Fourth Universal Definition of AMI with 2 sets of data: first, all available medical records obtained during clinical care pertaining to the patient from the time of ED presentation to 90-day follow-up, including history, physical examination, and results of laboratory testing including serial clinical hs-cTn concentrations, radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity and morphology in coronary angiography, and cardiac MRI; second, study-specific assessments including detailed chest pain characteristics with 34 predefined criteria, serial hs-cTnT blood concentrations (primary analysis) obtained from study samples, and clinical follow-up by telephone and/or mail. In situations of disagreement about the diagnosis, all cases were reviewed and adjudicated in conjunction with a third cardiologist.

To address the uncommon but previously described phenomenon of discrepant results for hs-cTnT and hs-cTnI and the corresponding underestimation of the true performance of hs-cTnI-based early algorithms using an adjudication founded at least in part on serial hs-cTnT measurements *(26, 29)*, we performed a second adjudication using serial hs-cTnI (rather than hs-cTnT) blood concentrations from study samples for internal validation as a secondary analysis.

AMI was defined and hs-cTn interpreted as recommended in the current Fourth Universal Definition guidelines *(30)*. In brief, MI (including type 1 and type 2) 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 1 cTn value above the 99th percentile together with a significant rising and/or falling. The criteria used to define a rise and/or fall in contemporary cTn and hs-cTnT/hs-cTnI are described in detail in the method section in the online Data Supplement. All other patients were classified in the categories of unstable angina (UA), noncardiac chest pain, cardiac but noncoronary disease (e.g., tachyarrhythmia, perimyocarditis), and symptoms of unknown origin with normal concentrations of hs-cTn.

INVESTIGATIONAL hs-cTn MEASUREMENTS

Blood samples for determination of hs-cTnI Access, hs-cTnI Architect, and hs-cTnT Elecsys were collected into tubes containing lithium heparin plasma or serum. Additional samples were collected at 1, 2, 3, and 6 h (±20 min for each timepoint) after presentation. Serial sampling was discontinued when a patient was released or transferred to the catheter laboratory for acute treatment. After centrifugation, samples were frozen at −80 °C until assayed in a blinded fashion in a dedicated core laboratory.

The hs-cTnI Access assay (ACCESS hsTnI, Beckman Coulter) has an overall 99th percentile concentration of 18 ng/L (women, 12 ng/L; men, 20 ng/L) with a corresponding CV of <5%. Limit of blank and limit of detection have been determined to be 1.7 ng/L and 2.3 ng/L, respectively. The hs-cTnT Elecsys assay (Elecsys 2010 high-sensitivity troponin T, Roche Diagnostics) has a 99th percentile upper reference limit of 14 ng/L (women, 9 ng/L; men, 16 ng/L) with a corresponding CV of 10% at 13 ng/L *(2)*. Limit of blank and limit of detection have been determined to be 3 ng/L and 5 ng/L, respectively *(2)*. The hs-cTnI Architect assay (ARCHITECT STAT hs-cTnI, Abbott Laboratories) has a 99th percentile upper reference limit of 26 ng/L (women, 16 ng/L; men, 34 ng/L) with a corresponding CV of <5% and a limit of detection of 1.9 ng/L *(31–33)*. Estimated glomerular filtration rate was calculated according to the abbreviated Modification of Diet in Renal Disease formula *(34)*.

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DERIVATION AND VALIDATION OF THE hs-cTnI ACCESS 0/1-h ALGORITHM

We used the concept of the current hs-cTn 0/1-h algorithms suggested by the ESC *(15)* (see Fig. 1 in the online Data Supplement). The hs-cTnI Access 0/1-h algorithm was developed in a derivation sample of randomly (1:1 fashion) selected patients with available hs-cTnI Access measurements at ED presentation and after 1 h and directly compared with the established ESC 0/1-h algorithms. The optimal decision values derived in the derivation sample were rounded to give whole values in ng/L (see online Data Supplement).

STATISTICAL ANALYSIS

For the primary analysis, serial hs-cTnT (Elecsys 2010) concentrations were used as part of the study-specific data set in the final adjudication. For the secondary analysis, serial hs-cTnI (Architect) concentrations were used as part of the study-specific data set in the final adjudication. ROC curves were constructed to assess the sensitivity and specificity throughout the concentrations of hs-cTnI Access, hs-cTnT Elecsys, and hs-cTnI Architect. Correlations between hs-cTnI Access and hs-cTnT Elecsys or hs-cTnI Architect concentrations at presentation were determined with use of Pearson correlation coefficients. Subgroup analyses were performed in patients presenting to the ED soon (≤3 h) and late (>3 h) after chest pain onset/maximum in women and men. We further included analyses using sex-specific cutoffs and investigated the performance of the ESC 0/3-h algorithm by using hs-cTnI Access. The areas under the ROC curves (AUCs) were compared as recommended by DeLong et al. *(35)* or by *z* statistic, as appropriate (see online Data Supplement).

Safety was assessed with use of the negative predictive value (NPV) and the sensitivity for AMI in the rule-out group, accuracy of the rule-in strategy as the positive predictive value (PPV), and specificity for AMI in the rule-in group, whereas efficacy was quantified as the percentage of patients triaged toward rule out or rule in for AMI within 1 h.

Results

CHARACTERISTICS OF PATIENTS

From June 2010 to October 2014, 1579 patients eligible for this analysis were enrolled (see Fig. 2 in the online Data Supplement). Thirty-seven percent of patients (n = 580) presented to the ED within the first 3 h after chest pain onset. Baseline characteristics of all patients are shown in Table 1 and of patients in the derivation and validation cohorts in Table 2 in the online Data Supplement.

ADJUDICATED FINAL DIAGNOSIS

The adjudicated final diagnosis was AMI in 243 of 1579 patients [15%; 218/1579 type 1 (13.8%), 25/1579 type 2 MI (1.6%)], UA in 131/1579 (8%), cardiac symptoms of origin other than coronary artery disease such as tachyarrhythmia, Takotsubo cardiomyopathy, heart failure, or myocarditis in 248 of 1579 (16%), noncardiac symptoms in 903 of 1579 (57%), and unknown in 54 of 1579 (3%). Final diagnoses according to the second final adjudication including hs-cTnI (Architect) were similar (see online Data Supplement).

CONCENTRATIONS OF hs-cTnI ACCESS AT PRESENTATION ACCORDING TO FINAL DIAGNOSES AND CORRELATION WITH HS-CTNT ELECSYS AND hs-cTnI ARCHITECT

Concentrations of hs-cTnI Access at ED presentation were significantly higher in patients with AMI than in patients with other final diagnoses ($P < 0.001$). Median concentrations of hs-cTnI Access in patients with AMI were 108 ng/L (interquartile range [IQR], 27–492), with UA 6.5 ng/L (IQR, 3.6–12.5), with cardiac but not coronary disease 6.6 ng/L (IQR, 3.2–17.1), with noncardiac disease 2.5 ng/L (IQR, 1.5–4.6), and with unknown diagnosis 3.2 ng/L (IQR, 2.2–5.1; Fig. 1). Similar findings emerged according to the second final adjudicated diagnosis including hs-cTnI (Architect; see Fig. 3 in the online Data Supplement). Concentrations of hs-cTnI Access and hs-cTnT Elecsys or hs-cTnI Architect at presentation showed a high correlation ($r = 0.86$ and $r = 0.96$, both $P < 0.001$; see Fig. 4 in the online Data Supplement).

DIAGNOSTIC ACCURACY FOR AMI

The diagnostic accuracy of measurements obtained at presentation, as quantified by AUCs, for the hs-cTnI Access assay was 0.95 (95% CI, 0.94–0.96) and comparable to hs-cTnT Elecsys 0.94 (95% CI, 0.93–0.95; $P = 0.12$), but higher than hs-cTnI Architect 0.92 (95% CI, 0.91–0.94; $P < 0.001$; Fig. 2A). For hs-cTnI Access, the AUCs for concentrations at 1 h, 2 h, and 3 h were 0.97 (95% CI, 0.96–0.99), 0.98 (95% CI, 0.97–0.99), and 0.98 (95% CI, 0.97–0.99), respectively (Table 2A). Similar findings emerged according to the second final adjudicated diagnosis including hs-cTnI (Architect; see Fig. 5A in the online Data Supplement). Using sex-specific cutoff concentrations increased sensitivity and NPV in women at the cost of specificity and PPV. For men, specificity and PPV increased at the cost of sensitivity and NPV (Table 3).

SUBGROUP ANALYSES ACCORDING TO SEX AND TIME SINCE CHEST PAIN ONSET

Diagnostic accuracy at presentation was also very high in the predefined subgroups (see Table 3 in the online Data

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Table 1. Baseline characteristics of the patients.[a]

	All patients (*n* = 1579)	AMI (*n* = 243)	No AMI (*n* = 1336)	*P* value
Age, year	60 (48–74)	73 (59–80)	58 (46–71)	<0.001
Female sex, no. (%)	512 (32)	63 (26)	449 (34)	0.02
Time since CPO, h[b]	5 (2–12)	5 (2–12)	5 (2–12)	0.90
Early presenters (within 3 h after CPO)	580 (37%)	95 (39%)	485 (37%)	0.44
Risk factors, no. (%)				
Hypertension	927 (59)	176 (72)	751 (56)	<0.001
Hypercholesterolemia	753 (48)	166 (68)	587 (44)	<0.001
Diabetes	261 (17)	61 (26)	200 (15)	<0.001
Current smoking	404 (26)	53 (22)	351 (26)	0.14
History of smoking	583 (37)	113 (47)	470 (57)	0.001
History, no. (%)				
Coronary artery disease	505 (32)	110 (45)	395 (30)	<0.001
Previous MI	364 (23)	90 (37)	274 (21)	<0.001
Previous revascularization	433 (27)	98 (40)	335 (25)	<0.001
Peripheral artery disease	80 (5)	33 (14)	47 (4)	<0.001
Previous stroke	99 (3)	20 (8)	79 (6)	0.17
ECG findings, no. (%)				
Left bundle branch block	49 (3)	11 (5)	38 (3)	0.16
ST-segment depression	119 (8)	55 (23)	64 (5)	<0.001
T-wave inversion	109 (7)	28 (12)	81 (6)	0.002
No significant ECG abnormalities	1268 (80)	139 (57)	1129 (84)	<0.001
Body mass index, kg/m^2				
Laboratory findings	26 (24–30)	26 (24–29)	26 (24–30)	0.94
Creatinine clearance, mL/min/m^2	85 (70–101)	75 (59–94)	86 (72–102)	<0.001
Chronic medication, no. (%)				
Aspirin	537 (34)	122 (50)	415 (31)	<0.001
Vitamin K antagonists	175 (11)	32 (13)	143 (11)	0.26
β blockers	510 (32)	92 (38)	418 (31)	0.04
Statins	550 (35)	111 (46)	439 (33)	<0.001
ACEIs/ARBs	600 (38)	124 (51)	476 (36)	<0.001
Calcium antagonists	225 (14)	51 (21)	174 (13)	0.001
Nitrates	160 (10)	46 (19)	114 (9)	<0.001

[a] Numbers are presented as median (IQR) or numbers (%).
[b] CPO, chest pain onset; ECG denotes electrocardiogram; ACEIs, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin receptor blockers.

Supplement). For example, among patients who presented within 3 h after chest pain onset (580/1579, 37%), the AUC for hs-cTnI Access was 0.94 (95% CI, 0.92–0.97); hs-cTnT Elecsys, 0.93 (95% CI, 0.90–0.95); and hs-cTnI Architect, 0.91 (95% CI, 0.88–0.94) ($P = 0.12$ and $P = 0.001$ for respective direct comparisons; Fig. 2B). Again, similar findings emerged according to the second final adjudicated diagnosis including hs-cTnI (Architect; see Fig. 5B in the online Data Supplement).

DERIVATION OF THE hs-cTnI ACCESS 0/1-h ALGORITHM

Optimal thresholds for rule out of AMI were defined in the derivation cohort (n = 686) as either an hs-cTnI Access concentration at presentation <4 ng/L in patients with an onset of chest pain >3 h (direct rule out) or as an hs-cTnI Access concentration at presentation <5 ng/L and an absolute change within 1 h of <4 ng/L for all patients (irrespective of time since chest pain onset). Optimal thresholds for rule in of AMI were defined as either an hs-cTnI Access concentration at presentation ≥50

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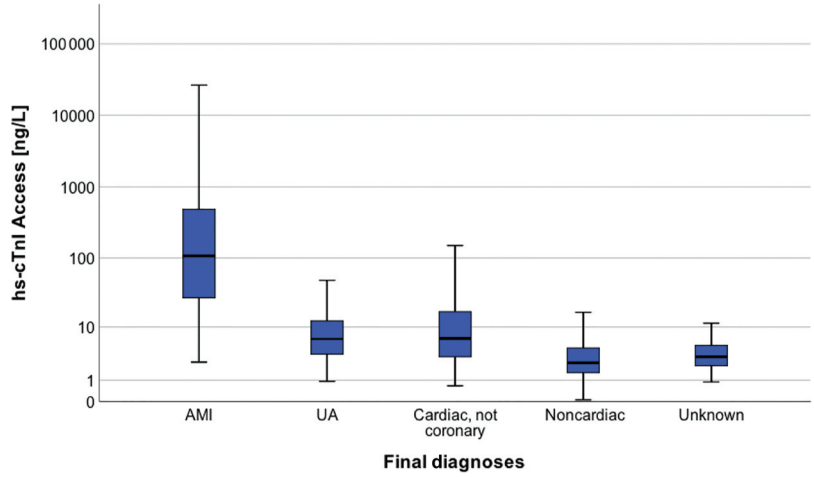

Fig. 1. Boxplots showing concentrations of hs-cTnI Access at presentation according to the final diagnoses.
Boxes represent medians and IQRs, and whiskers display the smallest and the largest nonoutliers.

ng/L (direct rule in) or an absolute change within 1 h of ≥15 ng/L. Patients fulfilling neither of the above criteria for rule out or for rule in were classified as observe. The diagnostic performance of the hs-cTnI Access 0/1-h algorithm in the derivation cohort is shown in Fig. 3A, and see Fig. 6A in the online Data Supplement. Direct rule out based on a single hs-cTnI Access concentration at presentation was feasible in 206 of 686 patients (30%). Overall, the hs-cTnI Access 0/1-h algorithm allowed a definite triage after 1 h in 483 of 686 patients (70%; either rule out or rule in).

VALIDATION OF THE hs-cTnI ACCESS 0/1-h ALGORITHM

Applying the derived optimal cutoff criteria to the internal validation cohort, 409 of 680 patients (60%) could be classified as rule out with a corresponding NPV of 99.8%

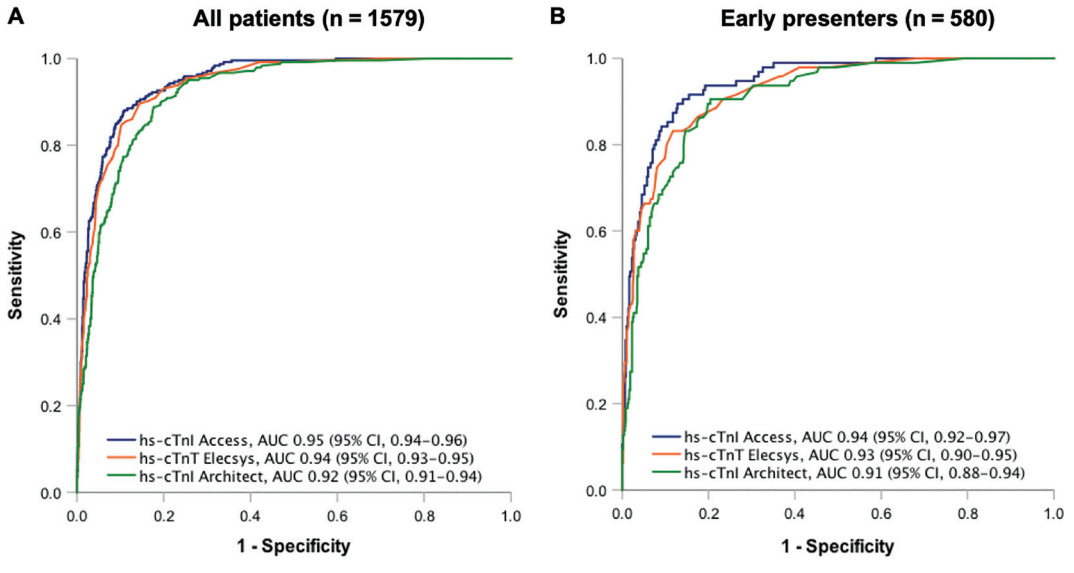

Fig. 2. Diagnostic accuracy of hs-cTn assays at presentation for the diagnosis of AMI.
ROC curves describing the diagnostic performance of the 3 hs-cTn assays at presentation for the diagnosis of AMI in all patients (A) and patients (B) presenting early with chest pain onset within the last 3 h.

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Table 2. A diagnostic accuracy expressed as ROC AUC (95% CI) for single concentrations, absolute changes, and their combination during serial sampling.

	hs-cTnI Access ROC AUC (95% CI)	hs-cTnT Elecsys	hs-cTnI Architect	Combination of hs-cTnI Access and hs-cTnT Elecsys
hs-cTn at presentation	0.95 (0.94–0.96)	0.94 (0.93–0.95)	0.92 (0.91–0.94)	0.94 (0.92–0.95)
hs-cTn after 1 h	0.97 (0.96–0.99)	0.96 (0.95–0.97)	0.95 (0.93–0.96)	0.95 (0.94–0.97)
hs-cTn after 2 h	0.98 (0.97–0.99)	0.96 (0.95–0.97)	0.95 (0.94–0.96)	0.96 (0.95–0.97)
hs-cTn after 3 h	0.98 (0.97–0.99)	0.96 (0.94–0.98)	0.96 (0.95–0.98)	0.97 (0.95–0.99)
hs-cTn 1-h delta[a]	0.96 (0.93–0.99)	0.91 (0.88–0.93)	0.92 (0.90–0.94)	0.93 (0.91–0.95)
hs-cTn 2-h delta	0.96 (0.93–0.99)	0.94 (0.92–0.96)	0.91 (0.89–0.93)	0.95 (0.93–0.97)
hs-cTn 3-h delta	0.97 (0.95–0.99)	0.95 (0.92–0.98)	0.95 (0.91–0.98)	0.94 (0.89–0.99)
hs-cTn at presentation and 1-h delta	0.96 (0.95–0.97)	0.96 (0.95–0.97)	0.94 (0.93–0.96)	0.96 (0.95–0.97)
hs-cTn at presentation and 2-h delta	0.96 (0.95–0.97)	0.97 (0.96–0.98)	0.93 (0.92–0.95)	0.97 (0.96–0.98)
hs-cTn at presentation and 3-h delta	0.98 (0.96–0.99)	0.97 (0.95–0.99)	0.96 (0.94–0.98)	0.97 (0.95–0.99)

[a] Delta values refer to the absolute (unsigned) change between the concentration of hs-cTnI at baseline and after 1 h, 2 h, or 3 h.

(95% CI, 98.6–100) and a sensitivity of 98.9% (95% CI, 94.3–99.8; see Fig. 3B and see Fig. 6B in the online Data Supplement). Direct rule out based on a single hs-cTnI Access concentration at presentation was feasible in 219 of 680 patients (32%). One patient with AMI was missed out of 680 patients with suspected AMI in the validation sample (see Table 4 in the online Data Supplement for detailed patient characteristics). The 0/1-h algorithm classified 92 of 680 patients (14%) as rule in with a corresponding PPV of 73.9% (95% CI, 64.1–81.8) and a specificity of 95.9% (95% CI, 94.0–97.2). Direct rule in based on a single hs-cTnI Access concentration at presentation was feasible in 74 of 680 patients (11%). Overall, the hs-cTnI Access 0/1-h algorithm allowed a definite diagnosis after 1 h in 501 of 680 patients (74%; either rule out or rule in). The remaining 179 of 626 patients (26%) were classified to observe, with an AMI prevalence of 15%. Similar findings emerged when assessing the diagnostic performance of the hs-cTnI Access 0/1-h algorithm in the validation cohort with the second final adjudication including hs-cTnI (Architect; see Fig. 7 in the online Data Supplement).

DIRECT COMPARISON OF THE hs-cTnI ACCESS 0/1-h ALGORITHM WITH THE ESC 0/1-h ALGORITHMS BY USE OF THE hs-cTnI (ELECSYS), hs-cTnI (ARCHITECT), AND THE hs-cTnI ACCESS ESC 0/3-h ALGORITHM

Overall, the diagnostic performance of the hs-cTnI Access 0/1-h algorithm was similar to that of the hs-cTnT Elecsys 0/1-h algorithm and the hs-cTnI Architect 0/1-h algorithm (see Figs. 8 and 9 in the online Data Supplement) and superior to the ESC 0/3-h algorithm using hs-cTnI Access because it provided similar safety but higher efficacy (see online Data Supplement).

PROGNOSTIC PERFORMANCE OF THE hs-cTnI ACCESS 0/1-h ALGORITHM

Median follow-up time was 735 days (IQR, 410–772) with 9 deaths occurring within 30 days and 60 deaths within 2 years. Cumulative 30-day survival rates were 100% (0 events), 98.7% (5 events), and 98.0% (4 events; log-rank, $P = 0.001$) in the rule out, observe, and rule-in groups, respectively. At 2 years, cumulative survival rates were 98.4% (10 events), 90.1% (31 events), and 89.2% (19 events), respectively (log-rank, $P < 0.001$; Fig. 4).

MACE-FREE SURVIVAL WITHIN 30 DAYS

Major adverse cardiovascular event (MACE)-free survival (including the index event) was 98.6% within 30 days in patients triaged toward rule out, 79.8% in patients triaged toward observe, and 26.6% in patients triaged toward rule in by the hs-cTnI Access 0/1-h algorithm (log-rank, $P < 0.001$).

Discussion

This large multicenter study was performed to validate the diagnostic performance and clinical utility of the Beckman hs-cTnI Access assay for the early diagnosis of AMI. We report 7 findings.

First, the diagnostic accuracy of hs-cTnI Access was excellent for concentrations obtained at ED presentation and absolute 1-h, 2-h, and 3-h changes and their combinations, with an AUC ranging from 0.95 to 0.98. Second, the diagnostic accuracy of hs-cTnI Access was comparable to hs-cTnT Elecsys and higher than hs-cTnI Architect. This finding was consistent in the overall population and in early presenters. Assay characteristics that may have contributed to the observed small difference in diagnostic accuracy as quantified by the AUC include

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Table 3. Diagnostic performance of uniform and sex-specific cutoffs.

	Final adjudication including hs-cTnT Elecsys[a]				Final adjudication including hs-cTnI Architect[a]			
hs-cTnI Access	Sensitivity	NPV	Specificity	PPV	Sensitivity	NPV	Specificity	PPV
Uniform 99th percentile 18 ng/L	84.0 (78.8–88.0)	96.9 (95.8–97.7)	91.2 (89.6–92.6)	63.6 (58.2–68.6)	88.3 (83.5–91.8)	97.9 (96.9–98.5)	91.3 (89.6–92.6)	63.2 (57.8–68.3)
Men 99th percentile 20 ng/L	80.2 (74.8–84.8)	96.3 (95.1–97.2)	92.4 (90.8–93.7)	65.7 (60.1–70.8)	84.8 (79.6–88.9)	97.3 (96.2–98.0)	92.4 (90.9–93.7)	65.7 (60.1–70.8)
Women 99th percentile 12 ng/L	89.3 (84.8–92.6)	97.8 (96.8–98.5)	86.3 (84.4–88.0)	54.3 (49.4–59.1)	93.9 (90.0–96.3)	98.8 (98.0–99.3)	86.4 (84.4–88.1)	54.0 (49.1–58.8)
Men Youden[b] 15.2 ng/L	87.2 (81.6–91.3)	97.2 (95.8–98.1)	88.5 (86.2–90.4)	60.6 (54.6–66.4)	91.7 (86.6–95)	98.3 (97.1–99)	88.4 (86.2–90.3)	59.8 (53.8–65.6)
Women Youden 10.9 ng/L	85.7 (75–92.3)	97.9 (96–98.9)	92 (89.1–94.2)	60 (49.7–69.5)	90.2 (80.2–95.4)	98.6 (96.9–99.3)	92.2 (89.4–94.4)	61.1 (50.8–70.5)
hs-cTnI Architect								
Uniform 99th percentile 26 ng/L	74.1 (68.2–79.2)	95.0 (93.7–96.1)	90.3 (88.6–91.8)	58.3 (52.7–63.6)	80.0 (74.4–84.7)	96.4 (95.2–97.3)	90.7 (89.1–92.2)	59.5 (54.0–64.9)
Men 99th percentile 34 ng/L	67.5 (61.4–73.1)	94.0 (92.5–95.1)	91.9 (90.3–93.3)	60.3 (54.4–65.9)	72.6 (66.5–78.0)	95.2 (93.9–96.2)	92.2 (90.7–93.5)	61.4 (55.5–67.0)
Women 99th percentile 16 ng/L	82.7 (77.5–87.0)	96.5 (95.3–97.4)	85.9 (83.9–87.6)	51.5 (46.6–56.5)	87.4 (82.5–91.1)	97.6 (96.5–98.3)	86.0 (84.0–87.7)	51.5 (46.6–56.5)
Men Youden 11.8 ng/L	88.9 (83.5–92.7)	97.3 (95.9–98.2)	81.1 (78.3–83.5)	48.8 (43.4–54.2)	91.1 (85.9–94.5)	98 (96.7–98.8)	80.6 (77.9–83.1)	47 (41.6–52.4)
Women Youden 10.3 ng/L	90.5 (80.7–95.6)	98.4 (96.6–99.3)	83.3 (79.6–86.5)	43.2 (35–51.7)	95.1 (86.5–98.3)	99.2 (97.7–99.7)	83.6 (79.9–86.7)	43.9 (35.8–52.5)
hs-cTnT-Elecsys								
Uniform 99th percentile 14 ng/L	93.0 (89.1–95.6)	98.4 (97.5–99.0)	80.2 (77.9–82.2)	46.0 (41.7–50.5)	92.6 (88.5–95.3)	98.4 (97.5–99.0)	79.4 (77.2–81.5)	43.4 (39.1–47.8)
Men 99th percentile 16 ng/L	90.1 (85.7–93.3)	97.9 (96.9–98.6)	83.8 (81.7–85.6)	50.2 (45.6–54.9)	89.1 (84.4–92.5)	97.8 (96.8–98.5)	82.9	47.0 (42.4–51.7)
Women 99th percentile 9 ng/L	97.5 (94.7–98.9)	99.3 (98.5–99.7)	63.3 (60.7–65.9)	32.6 (29.3–36.1)	97.0 (93.9–98.5)	99.2 (98.3–99.6)	62.6 (60.0–65.2)	30.7 (27.4–34.1)
Men Youden 16.6 ng/L	90 (84.7–93.6)	97.6 (96.3–98.5)	83.5 (81–85.8)	52.6 (47–58.1)	89.9 (84.5–93.6)	97.8 (96.4–98.6)	82.6 (80–85)	49.4 (43.8–54.9)
Women Youden 14.5 ng/L	88.9 (78.8–94.5)	98.2 (96.4–99.1)	85.5 (82–88.5)	46.3 (37.6–55.1)	85.2 (74.3–92)	97.7 (95.7–98.8)	84.7 (81.1–87.7)	43 (34.5–51.9)

[a] Sex-specific 99th percentiles were used according to the manufacturer.
[b] Youden denotes Youden's index (sensitivity + specificity − 1).

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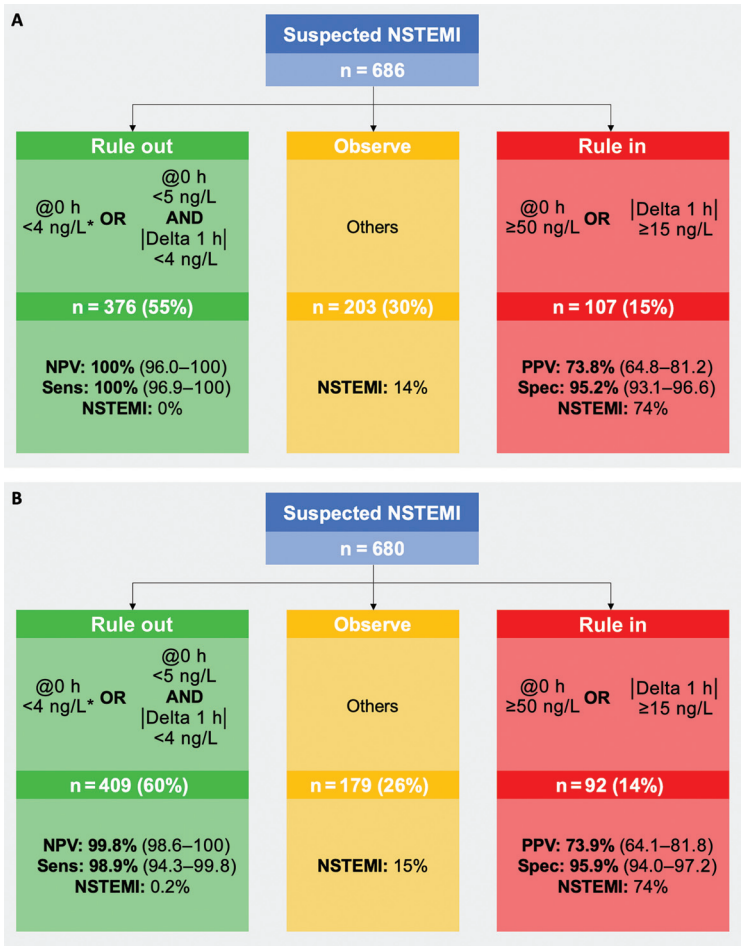

Fig. 3. Performance of the high-sensitivity cardiac troponin I Access 0/1-h algorithm in the derivation and validation cohort.

Performance of the hs-cTnI Access 0/1-h algorithm in the derivation cohort (A) and validation cohort (B). |Delta 1 h| denotes absolute (unsigned) change of hs-cTnI within 1 h. * Chest pain onset >3 h before presentation to the emergency department. NSTEMI, non-ST-elevation myocardial infarction; sens., sensitivity; spec., specificity.

different epitopes of the cTnI molecule captured by the antibodies selected for the 2 assays, resulting in different detection of cTnI split products and complexes and differences in the vulnerability to preanalytical and analytical confounders. Using sex-specific cutoff concentrations increased sensitivity and NPV in women at the cost of specificity and PPV. For men, specificity and PPV increased at the cost of sensitivity and NPV. As manufacturer-derived 99th-percentile cutoffs often are not biological equivalent *(27)*, they did not provide identical sensitivity and specificity. Those cutoffs for hs-cTnT Elecsys provide higher sensitivity, and those for hs-cTnI Access and hs-cTnI Architect higher specificity. Third, application of the derived 0/1-h algorithm for hs-cTnI Access in the independent validation cohort resulted in a very high safety in the rule-out zone with an NPV of 99.8% and a high PPV of 73.9% in the rule-in zone for AMI. Fourth, the overall performance of the 0/1-h algorithm for hs-cTnI Access was comparable to that of the established 0/1-h algorithms for hs-cTnT Elecsys and hs-cTnI Architect and also similar to their performance in previous studies *(6, 10, 15, 21)*. Furthermore, the ESC 0/3-h algorithm using hs-cTnI Access showed high safety and accuracy, but overall efficacy was lower than for the 0/1-h algorithm. Fifth, overall efficacy of the novel hs-cTnI Access 0/1-h algorithm was high, with about 75% of patients assigned to either rule out or rule in within 1 h, and only about 25% of patients remaining in the observe zone. Of note, 43% of all patients were either directly ruled out or ruled in for AMI at presentation according to a single hs-cTnI Access concentration without the need for serial hs-cTnI sampling. Sixth, these

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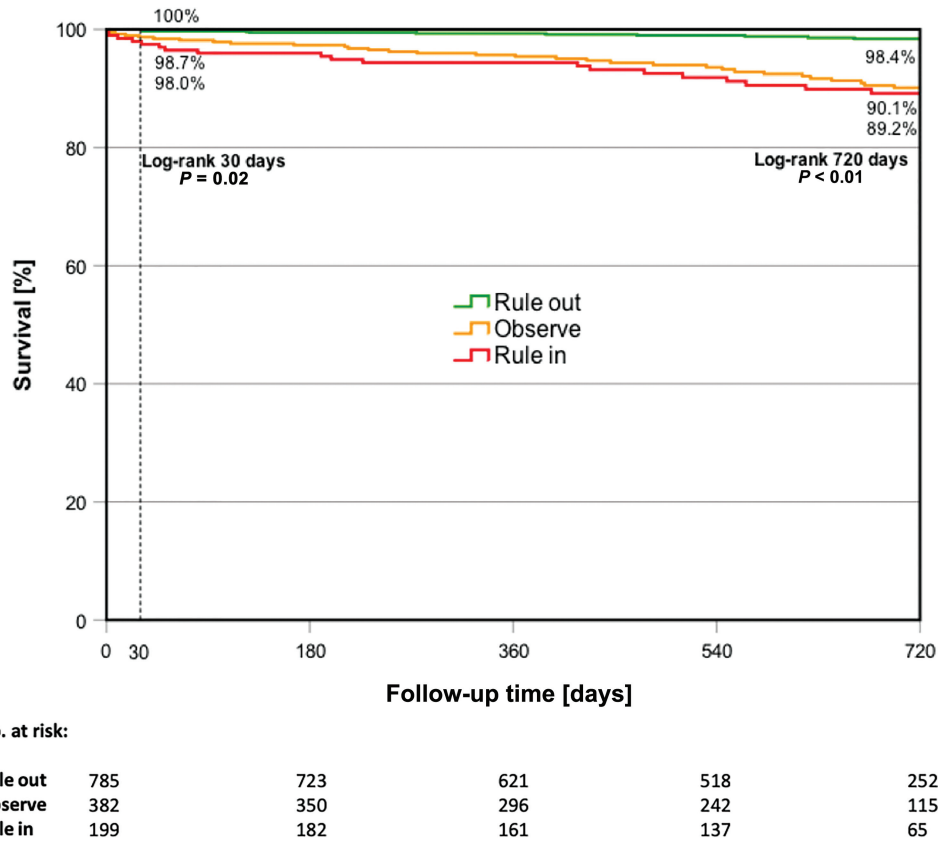

Fig. 4. Short- and long-term survival of patients classified according to the hs-cTnI Access 0/1-h algorithm.
Kaplan–Meier curves depicting overall survival within 30 days and 720 days according to classification of the hs-cTnI Access 0/1-h algorithm. No., number.

findings were internally validated with a second adjudication including serial hs-cTnI Architect concentrations. Thereby, the reference standard applied in this large diagnostic study of patients presenting with suspected AMI seems to be very stringent and robust *(36)*. By adding a secondary analysis that included hs-cTnI (rather than hs-cTnT as in the primary analysis) in addition to the clinical and imaging information available for the adjudication of the final diagnosis, the generalizability of our findings was further increased. Seventh, survival in patients assigned to the rule-out zone by the 0/1-h algorithm was 100% after 30 days and 98.4% after 2 years, underscoring the safety of early discharge from the ED for most patients classified as rule out, with further outpatient management as clinically appropriate. Similarly, MACE-free survival within 30 days in patients triaged toward rule out was very high at 98.6%. Of note, the rather high rate of all-cause mortality during follow-up and MACE within 30 days in observe patients can be at least in part explained by the high incidence of chronic cardiac diseases such as chronic heart failure that are directly associated with high rates of both overall mortality and MACE.

These findings corroborate and extend previous pilot studies with hs-cTnI Access *(22–24)* and may have important clinical implications for clinical laboratories that choose to use the Beckman hs-cTnI assay in practice, providing the benefits of the 0/1-h algorithm to their patients presenting with suspected AMI. Adoption of current clinical practice guideline recommendations without the logistical challenges and costs of introducing an additional analyzer exclusively for the measurement of hs-cTn also will be of economic value to those institutions *(9, 10, 37)*.

Previous work with hs-cTnI Access has focused on its analytical characterization *(22, 24)* and its use within a single-measurement rule-out strategy *(23)*. In a secondary analysis of 1871 patients presenting to a tertiary ED with symptoms of AMI, type 1 myocardial infarction was present in 5.2% of patients. About one-third of patients

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had an hs-cTnI Access <2 ng/L, which provided a sensitivity of 99.0% (95% CI, 94.4%–100%) and NPV of 99.8% (95% CI, 99.1%–100%) for the early rule out of type 1 MI. Using slightly higher rule-out cutoffs (e.g., <3 ng/L, <4 ng/L, or <5 ng/L) still provided very high sensitivity (98%–99%) and NPV (99.5%) and further improved rule-out efficacy. In full agreement with these observations, our study revealed optimal thresholds for rule out of AMI (type 1 and type 2 AMI) as either an hs-cTnI Access concentration at presentation <4 ng/L in patients with an onset of chest pain >3 h (direct rule out) or as an hs-cTnI Access concentration at presentation <5 ng/L and an absolute change within 1 h of <4 ng/L for all patients (irrespective of time since chest pain onset).

These findings highlight the critical balance between rule-out safety as quantified by sensitivity and NPV and rule-out efficacy as quantified by the percentage of patients eligible for rapid rule out. They also highlight the fact that when a single-measurement rule-out strategy is used, time from chest pain onset needs to be carefully assessed. Single-measurement rule-out strategies should not be used in patients presenting very early (<3h) after chest pain onset but provide a very attractive and simple option for patients presenting later than 3 h after chest pain onset *(7, 10, 13, 38)*. These findings also extend and corroborate previous work with other hs-cTnT/I assays *(6, 10, 19, 21, 36)*. Accordingly, the same concept and caveats apply to the most appropriate clinical use of any of the 3 hs-cTn assays and their respective 0/1-h algorithms in the early diagnosis of AMI *(6, 10, 11, 15, 19, 21)*.

First, these algorithms should only be applied after ST-elevation myocardial infarction has been ruled out by the ECG performed at presentation. Second, although the hs-cTnI Access 0/1-h algorithm had a very high NPV and sensitivity for AMI, the algorithm should always be used in conjunction with all other clinical information including a detailed assessment of chest pain characteristics, physical examination, and the ECG. Additional measurements of hs-cTnI at, for example, 3 h are advised whenever the patient remains symptomatic or clinical judgment still argues in favor of AMI. These additional measurements will help to detect the rare but existing phenomenon of delayed release of hs-cTn into the circulation, particularly in early presenters *(10)*. It will also help to detect rare but possible errors in the handling of the clinical blood samples. Third, not all patients triaged toward rule out of AMI are appropriate candidates for early discharge from the ED. Fourth, patients triaged toward rule in in general are candidates for early coronary angiography. About 75% of patients triaged toward rule in will be found to have AMI. Most of the remaining patients in the rule-in zone will still benefit from coronary angiography for diagnostic and possible therapeutic purposes because they will be found to have Takotsubo cardiomyopathy, myocarditis, and UA *(10)*. Fifth, just as with other immunoassays, rare cases with "false-negative" or "false-positive" results due to heterophilic antibodies *(5, 39)* have been described for previous-generation hs-cTnI assays and should be considered whenever hs-cTn results seem to make no sense.

Some limitations merit consideration when interpreting these findings. First, this study was conducted in ED patients with symptoms suggestive of AMI. Further studies are required to quantify the utility of rule-out and rule-in strategies in patients with either a higher pretest probability (e.g., in a coronary care unit setting) or in patients with a lower pretest probability (e.g., in a general practitioner setting) for AMI and in the inherently challenging group of critically ill patients *(30)*. Second, the data presented were obtained from a prospective diagnostic study. Studies applying the diagnostic algorithms prospectively for clinical decision-making are warranted *(40, 41)*. Third, not all patients with acute chest pain had a second set of laboratory measurements at 1 h and later. The most common reasons for missing blood samples were logistical issues in the ED that precluded blood draw around the 1-h window. This limitation is inherent to studies enrolling consecutive patients and is very unlikely to have affected the main findings of the present study. Fourth, although we used a very stringent methodology to adjudicate the presence or absence of AMI including central adjudication by experienced cardiologists, we still may have misclassified a small number of patients *(37)*. Fifth, our findings are specific to the hs-cTnI Access assay. The derived 0/1-h algorithm cannot be generalized to other hs-cTnI assays. Furthermore, percentiles used for each assay presented were not determined in the same reference population, which is a possible reason why assay-specific findings may vary. Sixth, we cannot generalize our findings to patients with terminal kidney failure requiring dialysis because they were excluded from this study.

In conclusion, the diagnostic accuracy of hs-cTnI Access for AMI is very high and at least comparable to both well-established hs-cTn assays. The novel 0/1-h algorithm allows triage toward safe rule out and accurate rule in of AMI within 1 h in the majority of patients presenting with chest pain to the ED.

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The authors designed the study, gathered and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish. J. Boeddinghaus, T. Nestelberger, R. Twerenbold, L. Koechlin, P. Badertscher, M. Rubini Gimenez, K. Wildi, C. Puelacher, T. Reichlin, and C. Mueller had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the manuscript.

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References

1. Twerenbold R, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Badertscher P, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. J Am Coll Cardiol 2017;70:996–1012.
2. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56:254–61.
3. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858–67.
4. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med 2009;361:868–77.
5. Mair J, Lindahl B, Hammarsten O, Müller C, Giannitsis E, Huber K, et al. How is cardiac troponin released from injured myocardium? Eur Heart J Acute Cardiovasc Care 2018;7:553–60.
6. Rubini Gimenez M, Twerenbold R, Jaeger C, Schindler C, Puelacher C, Wildi K, et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. Am J Med 2015;128:861–70.e4.
7. Shah AS V, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015;6736:1–8.
8. Rubini Giménez M, Hoeller R, Reichlin T, Zellweger C, Twerenbold R, Reiter M, et al. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. Int J Cardiol 2013;168:3896–901.
9. Mueller C, Giannitsis E, Möckel M, Huber K, Mair J, Plebani M, et al. Rapid rule out of acute myocardial infarction: novel biomarker-based strategies. Eur Heart J Acute Cardiovasc Care 2017;6:218–22.
10. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2016;37:267–315.
11. Boeddinghaus J, Reichlin T, Cullen L, Greenslade JH,

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Parsonage WA, Hammett C, et al. Two-hour algorithm for triage toward rule-out and rule-in of acute myocardial infarction by use of high-sensitivity cardiac troponin I. Clin Chem 2016;62:494–504.
12. Nestelberger T, Wildi K, Boeddinghaus J, Twerenbold R, Reichlin T, Giménez MR, et al. Characterization of the observe zone of the ESC 2015 high-sensitivity cardiac troponin 0h/1h-algorithm for the early diagnosis of acute myocardial infarction. Int J Cardiol 2016;207:238–45.
13. Boeddinghaus J, Twerenbold R, Nestelberger T, Wildi K, Mueller C. Measurement of cardiac troponin for exclusion of myocardial infarction. Lancet 2016;387:2288.
14. Jaeger C, Wildi K, Twerenbold R, Reichlin T, Rubini Gimenez M, Neuhaus J-D, et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. Am Heart J 2016;171:92–102.e5.
15. Reichlin T, Cullen L, Parsonage WA, Greenslade J, Twerenbold R, Moehring B, et al. Two-hour algorithm for triage toward rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Am J Med 2015;128:369–79.e4.
16. Than M, Cullen L, Aldous S, Parsonage WA, Reid CM, Greenslade J, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. J Am Coll Cardiol 2012;59:2091–8.
17. Meller B, Cullen L, Parsonage WA, Greenslade JH, Aldous S, Reichlin T, et al. Accelerated diagnostic protocol using high-sensitivity cardiac troponin T in acute chest pain patients. Int J Cardiol 2015;184:208–15.
18. Than M, Aldous S, Lord SJ, Goodacre S, Frampton CM, Troughton R, et al. A 2-hour diagnostic protocol for possible cardiac chest pain in the emergency department: a randomized clinical trial. JAMA Intern Med 2014;174:51–8.
19. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arch Intern Med 2012;172:1211–8.
20. Neumann JT, Sörensen NA, Schwemer T, Ojeda F, Bourry R, Sciacca V, et al. Diagnosis of myocardial infarction using a high-sensitivity troponin I 1-hour algorithm. JAMA Cardiol 2016;1:397.
21. Reichlin T, Twerenbold R, Wildi K, Gimenez MR, Bergsma N, Haaf P, et al. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. CMAJ 2015;187:E243–52.
22. Pretorius CJ, Tate JR, Wilgen U, Cullen L, Ungerer JPJ. A critical evaluation of the Beckman Coulter Access hsTnI: analytical performance, reference interval and concordance. Clin Biochem 2018;55:49–55.
23. Greenslade J, Cho E, Van Hise C, Hawkins T, Parsonage W, Ungerer J, et al. Evaluating rapid rule-out of acute myocardial infarction using a high-sensitivity cardiac troponin I assay at presentation. Clin Chem 2018;64:820–9.
24. Kavsak PA, Malinowski P, Roy C, Clark L, Lamers S. Assessing matrix, interferences and comparability between the Abbott Diagnostics and the Beckman Coulter high-sensitivity cardiac troponin I assays. Clin Chem Lab Med 2018;56:1176–81.
25. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124:136–45.
26. Wildi K, Gimenez MR, Twerenbold R, Reichlin T, Jaeger C, Heinzelmann A, et al. Misdiagnosis of myocardial infarction related to limitations of the current regulatory approach to define clinical decision values for cardiac troponin. Circulation 2015;131:2032–40.
27. Boeddinghaus J, Reichlin T, Nestelberger T, Twerenbold R, Meili Y, Wildi K, et al. Early diagnosis of acute myocardial infarction in patients with mild elevations of cardiac troponin. Clin Res Cardiol 2017;106:457–67.
28. Boeddinghaus J, Nestelberger T, Twerenbold R, Neumann JT, Lindahl B, Giannitsis E, et al. Impact of age on the performance of the ESC 0/1h-algorithms for early diagnosis of myocardial infarction. Eur Heart J 2018;39:3780–94.
29. Mueller C, Giannitsis E, Christ M, Ordóñez-Llanos J, deFilippi C, McCord J, et al. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. Ann Emerg Med 2016;68:76–87.e4.
30. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237–69.
31. Koerbin G, Tate J, Potter JM, Cavanaugh J, Glasgow N, Hickman PE. Characterisation of a highly sensitive troponin I assay and its application to a cardio-healthy population. Clin Chem Lab Med 2012;50:871–8.
32. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem 2012;58:1574–81.
33. Krintus M, Kozinski M, Boudry P, Capell NE, Köller U, Lackner K, et al. European multicenter analytical evaluation of the Abbott ARCHITECT STAT high sensitive troponin I immunoassay. Clin Chem Lab Med 2014;52:1657–65.
34. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–54.
35. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.
36. Boeddinghaus J, Twerenbold R, Nestelberger T, Badertscher P, Wildi K, Puelacher C, et al. Clinical validation of a novel high-sensitivity cardiac troponin I assay for early diagnosis of acute myocardial infarction. Clin Chem 2018;64:1347–60.
37. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 2012;33:2252–7.
38. Boeddinghaus J, Nestelberger T, Twerenbold R, Wildi K, Badertscher P, Cupa J, et al. Direct comparison of 4 very early rule-out strategies for acute myocardial infarction using high-sensitivity cardiac troponin I. Circulation 2017;135:1597–611.
39. Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, et al. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem 2018;64:645–55.
40. Twerenbold R, Jaeger C, Gimenez MR, Wildi K, Reichlin T, Nestelberger T, et al. Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction. Eur Heart J 2016;37:3324–32a.
41. Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Chapman AR, et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. Lancet 2018;392:919–28.

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