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Early diagnosis of myocardial infarction with point-of-care high-sensitivity cardiac troponin I.

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Abstract: BACKGROUND: Until now, high-sensitivity cardiac troponin (hs-cTn) assays were mainly developed for large central laboratory platforms. OBJECTIVES: This study aimed to assess the clinical performance of a point-of-care (POC)-hs-cTnI assay in patients with suspected myocardial infarction (MI). METHODS: This study enrolled patients presenting to the emergency department with symptoms suggestive of MI. Two cardiologists centrally adjudicated the final diagnosis using all clinical data including cardiac imaging. The primary objective was to directly compare diagnostic accuracy of POC-hs-cTnI-TriageTrue versus best-validated central laboratory assays. Secondary objectives included the derivation and validation of a POC-hs-cTnI-TriageTrue-specific 0/1-h algorithm. RESULTS: MI was the adjudicated final diagnosis in 178 of 1,261 patients (14%). The area under the curve (AUC) for POC-hs-cTnI-TriageTrue at presentation was 0.95 (95% confidence interval [CI]: 0.93 to 0.96) and was at least comparable to hs-cTnT-Elecsys (AUC: 0.94; 95% CI: 0.93 to 0.96; p = 0.213) and hs-cTnI-Architect (AUC: 0.92; 95% CI: 0.90 to 0.93; p < 0.001). A single cutoff concentration <3 ng/l at presentation identified 45% of patients at low risk with a negative predictive value (NPV) of 100% (95% CI: 99.4% to 100%). A single cutoff concentration >60 ng/l identified patients at high risk with a positive predictive value (PPV) of 76.8% (95% CI: 68.9% to 83.6%). The 0/1-h algorithm ruled out 55% of patients (NPV: 100%; 95% CI: 98.8% to 100%), and ruled in 18% of patients (PPV: 76.8%; 95% CI: 67.2% to 84.7%). Ruled-out patients had cumulative event rates of 0% at 30 days and 1.6% at 2 years. This study confirmed these findings in a secondary analysis including hs-cTnI-Architect for central adjudication. CONCLUSIONS: The POC-hs-cTnI-TriageTrue assay provides high diagnostic accuracy in patients with suspected MI with a clinical performance that is at least comparable to that of best-validated central laboratory assays. (Advantageous Predictors of Acute Coronary Syndromes Evaluation Study [APACE]; NCT00470587).

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Early Diagnosis of Myocardial Infarction With Point-of-Care High-Sensitivity Cardiac Troponin I

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ABSTRACT

BACKGROUND Until now, high-sensitivity cardiac troponin (hs-cTn) assays were mainly developed for large central laboratory platforms.

OBJECTIVES This study aimed to assess the clinical performance of a point-of-care (POC)-hs-cTnI assay in patients with suspected myocardial infarction (MI).

METHODS This study enrolled patients presenting to the emergency department with symptoms suggestive of MI. Two cardiologists centrally adjudicated the final diagnosis using all clinical data including cardiac imaging. The primary objective was to directly compare diagnostic accuracy of POC-hs-cTnI-TriageTrue versus best-validated central laboratory assays. Secondary objectives included the derivation and validation of a POC-hs-cTnI-TriageTrue–specific 0/1-h algorithm.

RESULTS MI was the adjudicated final diagnosis in 178 of 1,261 patients (14%). The area under the curve (AUC) for POC-hs-cTnI-TriageTrue at presentation was 0.95 (95% confidence interval [CI]: 0.93 to 0.96) and was at least comparable to hs-cTnT-Elecsys (AUC: 0.94; 95% CI: 0.93 to 0.96; $p = 0.213$) and hs-cTnI-Architect (AUC: 0.92; 95% CI: 0.90 to 0.93; $p < 0.001$). A single cutoff concentration <3 ng/l at presentation identified 45% of patients at low risk with a negative predictive value (NPV) of 100% (95% CI: 99.4% to 100%). A single cutoff concentration >60 ng/l identified patients at high risk with a positive predictive value (PPV) of 76.8% (95% CI: 68.9% to 83.6%). The 0/1-h algorithm ruled out 55% of patients (NPV: 100%; 95% CI: 98.8% to 100%), and ruled in 18% of patients (PPV: 76.8%; 95% CI: 67.2% to 84.7%). Ruled-out patients had cumulative event rates of 0% at 30 days and 1.6% at 2 years. This study confirmed these findings in a secondary analysis including hs-cTnI-Architect for central adjudication.

CONCLUSIONS The POC-hs-cTnI-TriageTrue assay provides high diagnostic accuracy in patients with suspected MI with a clinical performance that is at least comparable to that of best-validated central laboratory assays. (Advantageous Predictors of Acute Coronary Syndromes Evaluation Study [APACE]; NCT00470587) (J Am Coll Cardiol 2020;75:1111–24)

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ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

CI = confidence interval

cTn = cardiac troponin

cTnT/I = cardiac troponin T and/or I

CV = coefficient of variation

ED = emergency department

ESC = European Society of Cardiology

hs-cTn = high-sensitivity cardiac troponin

IQR = interquartile range

MI = myocardial infarction

NPV = negative predictive value

POC = point-of-care

PPV = positive predictive value

More than 10 million patients worldwide present to emergency departments (ED) each year with symptoms suggestive of myocardial infarction (MI) such as chest discomfort or angina pectoris (1). For the diagnosis of MI, electrocardiography and cardiac troponin (cTn) make up the diagnostic cornerstones and complement clinical assessment (2,3).

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The introduction of high-sensitivity cardiac troponin (hs-cTn) assays made it possible to reliably measure cTn concentrations around the 99th percentile and in the normal range (2), thereby increasing the diagnostic accuracy and reducing the time to diagnosis with the use of rapid hs-cTnT/I-based triage algorithms (3,4). Among the hs-cTnT/I-based rapid triage algorithms, the hs-cTnT/I 0/1-h algorithms have been extensively validated and seem to provide the best balance of safety and efficacy (5,6). Accordingly, they are recommended with a Class I recommendation in current clinical practice guidelines (6).

However, until now, successful clinical implementation of these rapid algorithms was restricted to hospitals working with large central laboratory platforms, as current hs-cTnT/I assays require measurement in a large central laboratory platform (7). Whereas point-of-care (POC) testing for cTnT/I has also been available for several years and can reduce the turnaround time as compared to the central laboratory by 30 to 60 min depending on the efficacy of the local laboratory work flow, previous POC-cTnT/I assays had poor analytical and clinical sensitivity (6). The clinical availability of a POC-hs-cTnT/I assay would allow combining the medical and economic advantages of POC testing with those of the hs-cTnT/I 0/1-h algorithms (4,6).

Several modifications of the original cartridge, which included control of sample flow and the introduction of internal controls in each cartridge, improved the analytical sensitivity and precision and led to the development of the POC-hs-cTnI-TriageTrue assay (TriageTrue High Sensitivity Troponin I Test, Quidel Corporation, San Diego, California) (8). We aimed to assess the clinical performance of the POC-hs-cTnI-TriageTrue assay in patients with suspected MI. In addition, we sought to define optimal cutoff concentrations at presentation to identify patients at low or high risk and to derive and validate an assay-specific 0/1-h algorithm for ruling out and ruling in MI.

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METHODS

STUDY DESIGN AND POPULATION. The APACE (Advantageous Predictors of Acute Coronary Syndromes Evaluation) study is an ongoing prospective international multicenter study that includes 12 centers in 5 countries and is aimed at advancing the early diagnosis of MI (NCT00470587) (3).

Adult patients presenting to the ED with symptoms suggestive of MI with an onset or peak within the last 12 h were recruited. Although enrollment was independent of renal function, we excluded patients with terminal kidney failure on chronic dialysis. The study was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committees. Written informed consent was obtained from all patients.

For this analysis, we excluded patients with ST-segment elevation MI, patients in whom the diagnosis remained unknown even after final adjudication and had at least 1 elevated hs-cTn concentration, thereby possibly indicating MI, as well as patients with missing measurements of the POC-hs-cTnI-TriageTrue, hs-cTnT-Elecsys (Elecsys 2010 High-Sensitivity Troponin T, Roche Diagnostics, Rotkreuz, Switzerland) or hs-cTnI-Architect (ARCHITECT STAT High-Sensitivity Troponin I, Abbott Laboratories, Abbott Park, Illinois) assays. For the derivation and validation of the 0/1-h algorithm, patients with missing 1-h concentrations of POC-hs-cTnI-TriageTrue were also excluded.

This study was designed and data were gathered and analyzed according to the STARD (Standards for Reporting of Diagnostic Accuracy Studies) guidelines (9) (Online Table 1). Details on the clinical assessment and the central adjudication of the final diagnosis of patients is given in the Online Appendix. In brief, 2 independent cardiologists performed the central adjudication of the final diagnosis at the core laboratory (University Hospital Basel) applying the universal definition of MI (10).

INVESTIGATIONAL hs-cTn MEASUREMENTS. Blood samples for determination of POC-hs-cTnI-TriageTrue were collected in tubes containing ethylenediaminetetraacetic acid plasma. Tubes containing lithium heparin plasma or serum were used for the hs-cTnI-Architect and hs-cTnT-Elecsys assays. Additional samples were collected at 1, 2, 3, and 6 h after presentation. Serial sampling was discontinued when a patient was discharged or transferred to the catheter laboratory for treatment. After centrifugation, samples were frozen at −80°C until assayed in a blinded fashion in a dedicated core laboratory.

According to the manufacturer, the POC-hs-cTnI-TriageTrue assay on the Triage MeterPro System has an overall 99th percentile concentration of 20.5 ng/l (females 14.4 ng/l, males 25.7 ng/l) with a corresponding coefficient of variation (CV) of 5.6% overall, 5.9% for females, and 5.4% for males (Online Figure 1). Limits of blank, detection, and quantification were determined to be 0.6 ng/l, 1.5 ng/l, and 2.1 ng/l for plasma, and 0.6 ng/l, 1.7 ng/l, and 2.8 ng/l for whole blood, respectively. Seventy-two percent of male and female normal patients in a healthy reference population had POC-hs-cTnI-TriageTrue concentrations above the limit of detection (Online Figure 2, Online Table 2). The hs-cTnT-Elecsys assay has a 99th percentile concentration of 14 ng/l with an

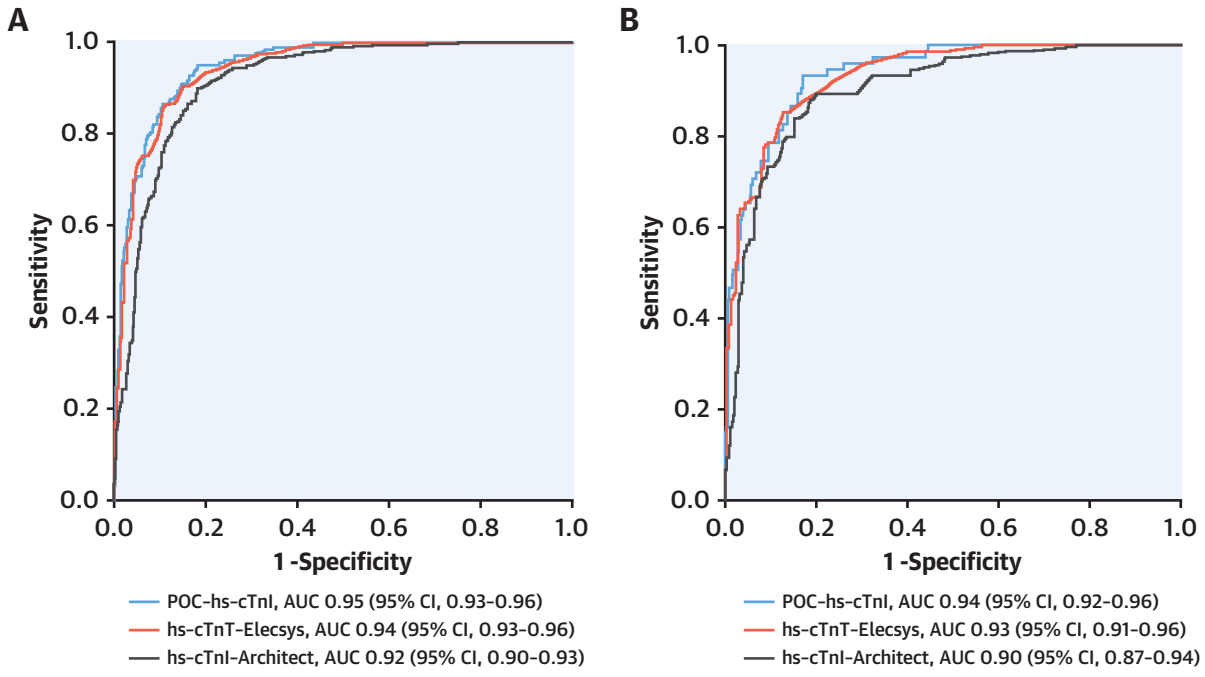
TABLE 1 Baseline Characteristics of the Patients

	All Patients (N = 1,261)	MI (n = 178, 14%)	No MI (n = 1,083, 86%)	p Value
Age, yrs	60 (47–73)	74 (61–81)	58 (46–70)	<0.001
Female	409 (32)	47 (26)	362 (33)	0.064
Time since CPO, h	5 (2–12)	5 (2–12)	5 (2–12)	0.768
Early presenters, within 3 h after CPO	487 (39)	75 (42)	412 (38)	0.299
Risk factors				
Hypertension	737 (58)	130 (73)	607 (56)	<0.001
Hypercholesterolemia	665 (53)	129 (73)	467 (43)	<0.001
Diabetes	214 (17)	45 (26)	169 (16)	0.001
Current smoking	314 (25)	38 (21)	276 (26)	0.232
History of smoking	477 (38)	87 (49)	390 (36)	0.001
History				
Coronary artery disease	387 (31)	82 (46)	305 (28)	<0.001
Previous MI	280 (22)	71 (40)	209 (19)	<0.001
Previous revascularization	338 (27)	76 (43)	261 (24)	<0.001
Peripheral artery disease	59 (5)	25 (14)	34 (3)	<0.001
Previous stroke	81 (6)	19 (11)	62 (6)	0.020
ECG findings				
Left bundle branch block	44 (4)	10 (6)	34 (3)	0.119
ST-segment depression	90 (7)	40 (23)	50 (5)	<0.001
T-wave inversion	86 (7)	18 (10)	68 (6)	0.076
No significant ECG abnormalities	1,008 (80)	104 (58)	904 (84)	<0.001
Body mass index, kg/m^2	26 (24–29)	26 (24–29)	26 (24–30)	0.532
Laboratory findings				
eGFR, ml/min/1.73 m^2	85 (70–100)	75 (60–92)	86 (71–102)	<0.001
Chronic medication				
Aspirin	428 (34)	93 (52)	335 (31)	<0.001
Vitamin K antagonists	146 (12)	27 (15)	119 (11)	0.106
Beta-blockers	405 (32)	72 (40)	333 (31)	0.010
Statins	436 (35)	87 (49)	349 (32)	<0.001
ACE inhibitors/ARB	491 (39)	97 (55)	394 (36)	<0.001
Calcium antagonists	197 (16)	42 (24)	155 (14)	0.002
Nitrates	114 (9)	31 (17)	83 (8)	<0.001

Values are median (interquartile range) or n (%).

ACE = angiotensin-converting-enzyme; ARB = angiotensin receptor blockers; CPO = chest pain onset; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; MI = myocardial infarction.

FIGURE 1 Diagnostic Accuracy of hs-cTn Assays at Presentation for the Diagnosis of MI



Receiver-operating characteristic curves describing the diagnostic performance of the 3 high-sensitivity cardiac troponin (hs-cTn) assays at presentation for the diagnosis of myocardial infarction (MI) in **(A)** all patients and **(B)** patients presenting early with chest pain onset within the last 3 h. AUC = area under the curve; CI = confidence interval; cTnI (T) = cardiac troponin I (T); POC = point of care.

imprecision corresponding to a CV of 10% at 13 ng/l. Above 30 ng/l, the cTnT interassay CV were between 1% and 5% (2). The limits of blank and detection were determined to be 3 ng/l and 5 ng/l, respectively (2). The hs-cTnI-Architect assay has a 99th percentile concentration of 26 ng/l with a corresponding CV of 10% at 5.6 ng/l (11). The limits of blank and detection ranged from 0.7 to 1.3 ng/l and 1.1 to 1.9 ng/l, respectively (11). The estimated glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula (12).

SINGLE CUTOFF CONCENTRATIONS AT PRESENTATION FOR RISK STRATIFICATION. We established the safety of single cutoff concentrations at presentation, quantified by the negative predictive value (NPV) and sensitivity, to identify patients at low risk for MI. We also established the accuracy, quantified by the positive predictive value (PPV) and specificity, to identify patients at high risk for MI. Optimal cutoff concentrations for rule-out were pre-defined to achieve an NPV and a sensitivity of ≥99.5% and ≥99%, respectively. For the rule-in of MI, we pre-defined a PPV and a specificity of ≥75% and ≥95%, respectively (Online Figure 3A).

DERIVATION AND VALIDATION OF THE POC-hs-cTnI-TriageTrue 0/1-H ALGORITHM. Using the concept of the current European Society of Cardiology (ESC) hs-cTnT/I 0/1-h algorithms (6) (Online Figure 3B), the POC-hs-cTnI-TriageTrue 0/1-h algorithm was developed in a derivation sample of randomly (1:1 fashion) selected patients with available POC-hs-cTnI-TriageTrue measurements at ED presentation and after 1 h. It was then directly compared with the established ESC hs-cTnT/I 0/1-h algorithms (Online Appendix).

FOLLOW-UP AND CLINICAL ENDPOINTS. Patients were contacted at 3, 12, and 24 months after discharge by telephone calls or in written form. We obtained information regarding death during follow-up from the patient's hospital records, the family physician's records, and the national death registry. The co-primary prognostic endpoints were cumulative event rates at 30 days and at 2 years. The secondary prognostic endpoint was major adverse cardiac events defined as the composite of all-cause mortality, MI including index events, cardiogenic shock, ventricular tachyarrhythmias, or higher-degree atrioventricular block at 30 days.

STATISTICAL ANALYSIS. For the primary analysis, we used serial hs-cTnT-Elecsys concentrations as part of the study-specific dataset in the final adjudication. For the secondary sensitivity analysis, we used serial hs-cTnI-Architect concentrations as part of the study-specific dataset in the final adjudication. Receiver-operating characteristic curves were constructed to assess the sensitivity and specificity of the concentrations of the POC-hs-cTnI-TriageTrue, hs-cTnT-Elecsys, and hs-cTnI-Architect assays and to compare the ability of the respective hs-cTn concentrations at ED presentation to diagnose MI. In addition, we used binary logistic regression to combine POC-hs-cTnI-TriageTrue concentrations at ED presentation with early absolute POC-hs-cTnI-TriageTrue changes. Accordingly, we compared the ability of POC-hs-cTnI-TriageTrue concentrations at 1, 2, and 3 h as well as absolute 1-, 2-, and 3-h changes and their combinations with POC-hs-cTnI-TriageTrue concentrations at ED presentation to diagnose MI. We performed subgroup analyses for patients presenting early (≤3 h) and late (>3 h) to the ED after chest pain onset or maximum as well as for differences in sex. Spearman correlations among POC-hs-cTnI-TriageTrue, hs-cTnT-Elecsys, and hs-cTnI-Architect were performed, and Bland-Altman plots were constructed. Furthermore, we directly compared the performance of the novel POC-hs-cTnI-TriageTrue 0/1-h algorithm with the current ESC hs-cTnT/I 0/1-h algorithms. The areas under the curves (AUC), specifically receiver-operating characteristic curves, were compared as recommended by DeLong et al. (13).

To assess the diagnostic performance of the assay's 99th percentile, single POC-hs-cTnI-TriageTrue cutoff concentrations, and the POC-hs-cTnI-TriageTrue 0/1-h algorithm, safety was assessed as the NPV and the sensitivity for MI in the rule-out group. Accuracy was assessed as the PPV and specificity for MI in the rule-in group, and efficacy was quantified by the percentage of patients triaged toward ruling out or ruling in MI either at presentation or within 1 h. We calculated 95% confidence intervals (CIs) for proportions by bootstrapping with 1,000 resamples. Further details are given in the Online Appendix.

All hypothesis testing was 2-tailed and p values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, New York) and MedCalc version 17.6 (MedCalc Software, Ostend, Belgium).

TABLE 2 Diagnostic Accuracy of POC-hs-cTnI-TriageTrue for Single Concentrations, Absolute Changes, and Their Combination During Serial Sampling

Time Point of Hs-cTnI	ROC AUC (95% CI)
Presentation	0.95 (0.93–0.96)
After 1 h	0.97 (0.95–0.98)
After 2 h	0.97 (0.96–0.99)
After 3 h	0.98 (0.97–0.99)
Delta 1 h	0.81 (0.75–0.87)
Delta 2 h	0.82 (0.76–0.88)
Delta 3 h	0.92 (0.84–0.99)
Presentation and delta 1 h	0.97 (0.96–0.98)
Presentation and delta 2 h	0.97 (0.96–0.99)
Presentation and delta 3 h	0.99 (0.98–0.99)

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

AUC = area under the curve; hs-cTnI = high-sensitivity cardiac troponin I; POC = point-of-care; ROC = receiver-operating characteristic curve.

RESULTS

PATIENT CHARACTERISTICS. From February 2011 to September 2014, 1,261 patients eligible for this analysis were enrolled (Online Figure 4). Thirty-nine percent of patients presented to the ED within the first 3 h after the onset of chest pain. The median age was 60 years (interquartile range [IQR]: 47 to 73 years), and 32% were female (**Table 1**, Online Table 3).

ADJUDICATED FINAL DIAGNOSIS. The adjudicated final diagnosis was MI in 178 of 1,261 patients (14%); unstable angina in 113 of 1,261 (9%); cardiac symptoms of origin other than coronary artery disease such as tachyarrhythmia, Takotsubo syndrome, heart failure, or myocarditis in 208 of 1,261 (17%); noncardiac symptoms in 714 of 1,261 (57%); and unknown in 48 of 1,261 (4%).

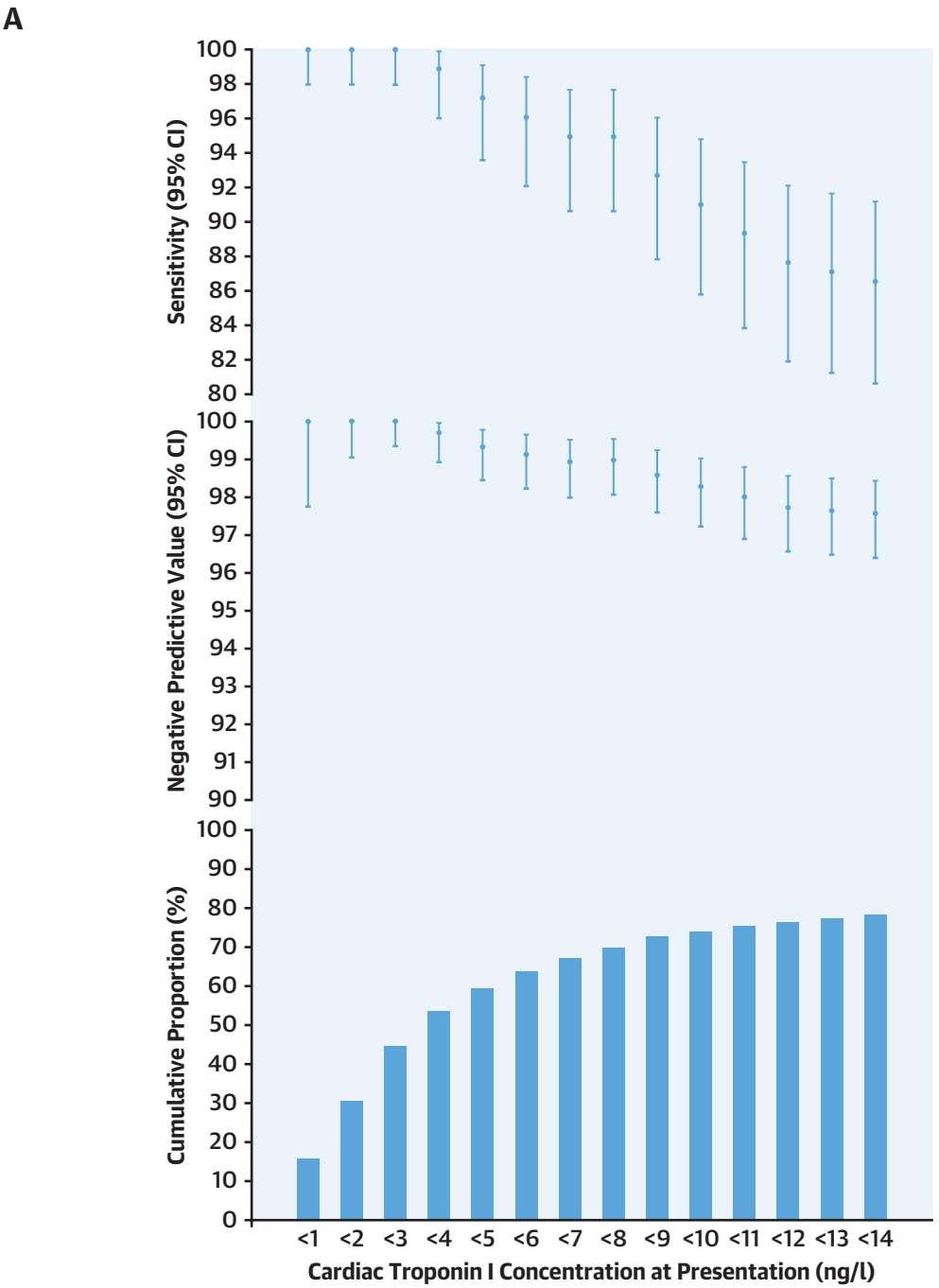
CONCENTRATIONS AT PRESENTATION ACCORDING TO FINAL DIAGNOSES. POC-hs-cTnI-TriageTrue concentrations were higher in patients with MI than in patients with other final diagnoses ($p < 0.001$). The median POC-hs-cTnI-TriageTrue concentrations were

TABLE 3 Diagnostic Performance of the 99th Percentile (20.5 ng/l) at Different Time Points

Time Point of Blood Draw	Sensitivity % (95% CI)	NPV % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)
0 h	79.8 (73.1–85.4)	96.5 (95.2–97.6)	92.3 (90.6–93.9)	63.1 (56.4–69.4)
1 h	86.4 (79.8–91.5)	97.7 (96.5–98.6)	91.3 (89.3–93.0)	60.8 (53.8–67.4)
2 h	91.6 (85.1–95.9)	98.6 (97.5–99.3)	90.6 (88.4–92.6)	59.6 (52.1–66.7)
3 h	93.0 (80.9–98.5)	98.9 (96.7–99.8)	88.7 (84.5–92.1)	54.8 (42.7–66.5)

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

FIGURE 2 Single Cutoff Concentrations of POC-hs-cTnI at Presentation and Risk of MI



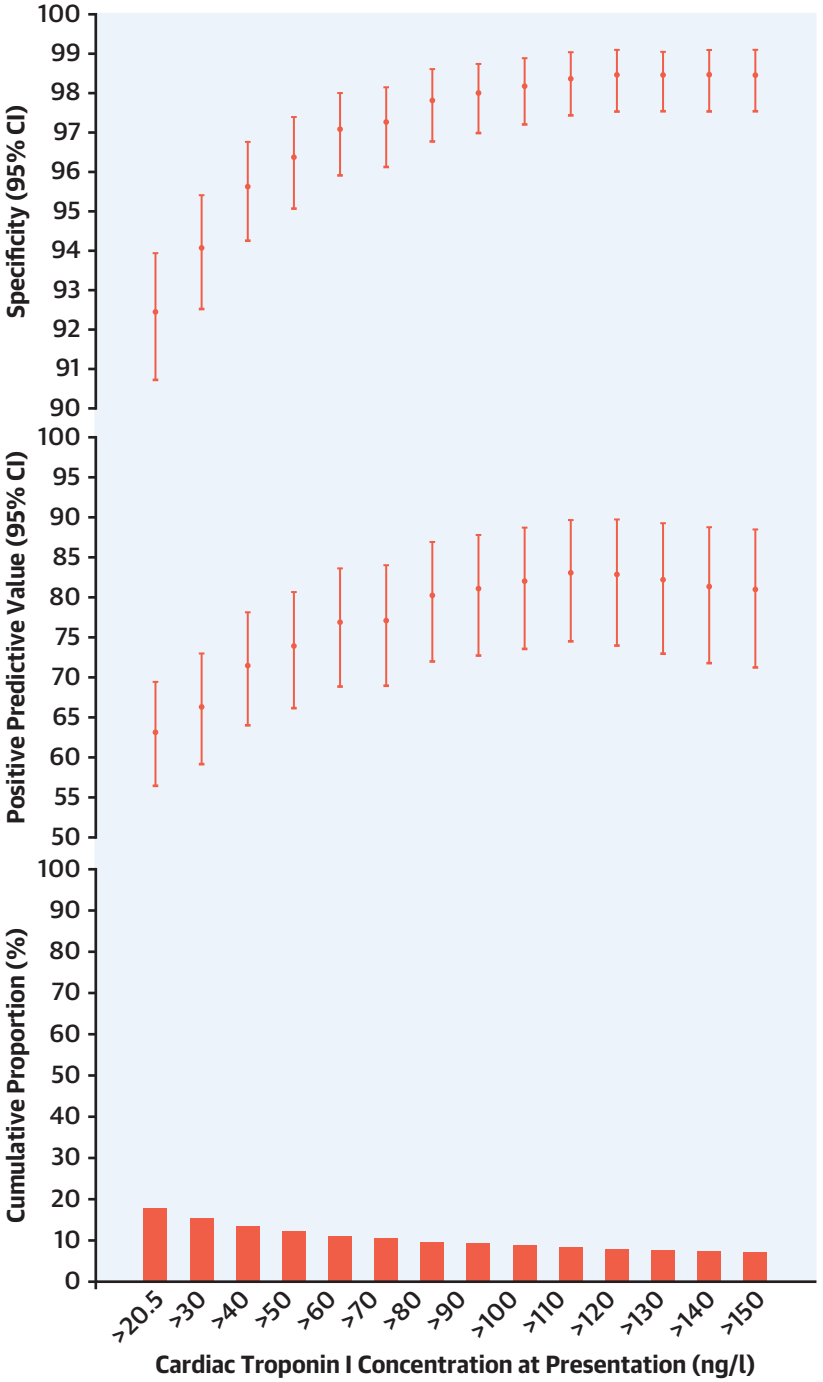
Troponin I Concentration (ng/l)	<1	<2	<3	<4	<5	<6	<7	<8	<9	<10	<11	<12	<13	<14
Cumulative Events (n)	0	0	0	2	5	7	9	9	13	16	19	22	23	24
Cumulative Events (%)	0	0	0	0.3	0.7	0.9	1.1	1.0	1.4	1.7	2.0	2.3	2.4	2.4
Cumulative Number (n)	200	386	562	675	749	805	845	880	917	932	949	963	975	986
Cumulative Number (%)	16	31	45	54	59	64	67	70	73	74	75	76	77	78

(A) Performance of single cutoff concentrations at presentation of POC-hs-cTnI-TriageTrue to identify patients at low risk for MI. **(B)** Performance of single cutoff concentrations at presentation of POC-hs-cTnI-TriageTrue to identify patients at high risk for MI. Abbreviations as in Figure 1.

Continued on the next page

FIGURE 2 Continued

B



Troponin I Concentration (ng/l)	>20.5	>30	>40	>50	>60	>70	>80	>90	>100	>110	>120	>130	>140	>150
Cumulative Events (n)	142	128	120	113	106	101	97	94	91	88	82	78	74	72
Cumulative Events (%)	63	66	71	74	77	77	80	81	82	83	83	82	81	81
Cumulative Number (n)	225	193	168	153	138	131	121	116	111	106	99	95	91	89
Cumulative Number (%)	18	15	13	12	11	10	10	9	9	8	8	8	7	7

109 ng/l (IQR: 25 to 425 ng/l) in patients with MI, 6.2 ng/l (IQR: 3.8 to 14.3 ng/l) in those with unstable angina, 5.9 ng/l (IQR: 2.7 to 17.8 ng/l) in cardiac noncoronary artery disease, 2.1 ng/l (IQR: 1.2 to 4.0 ng/l) in noncardiac disease, and 3.3 ng/l (IQR: 2.1 to 5.2 ng/l) in patients with an unknown diagnosis (Online Figure 5A).

DIAGNOSTIC ACCURACY FOR MI AND DIAGNOSTIC PERFORMANCE OF THE 99TH PERCENTILE AT DIFFERENT TIME POINTS. The diagnostic accuracy of measurements obtained at presentation, quantified by AUC, of the POC-hs-cTnI-TriageTrue assay was 0.95 (95% CI: 0.93 to 0.96), 0.94 (95% CI: 0.93 to 0.96; $p = 0.213$) for hs-cTnT-Elecsys, and 0.92 (95% CI: 0.90 to 0.93; $p < 0.001$) for hs-cTnI-Architect (**Figure 1A**). The AUC for POC-hs-cTnI-TriageTrue concentrations at 1, 2, and 3 h were 0.97 (95% CI: 0.95 to 0.98), 0.97 (95% CI: 0.96 to 0.99), and 0.98 (95% CI: 0.97 to 0.99), respectively (**Table 2**). The diagnostic performance of the 99th percentile at the available time points is shown in **Table 3**.

SUBGROUP ANALYSES ACCORDING TO TIME SINCE CHEST PAIN ONSET AND SEX. Diagnostic accuracy at presentation was high in all the pre-defined subgroups (Online Table 4). In early presenters (with onset of chest pain within 3 h, 487 of 1,261, 39%), the AUC for POC-hs-cTnI-TriageTrue was 0.94 (95% CI: 0.92 to 0.96), 0.93 (95% CI: 0.91 to 0.96; $p = 0.490$) for hs-cTnT-Elecsys, and 0.90 (95% CI: 0.87 to 0.94; $p = 0.001$) for hs-cTnI-Architect (**Figure 1B**).

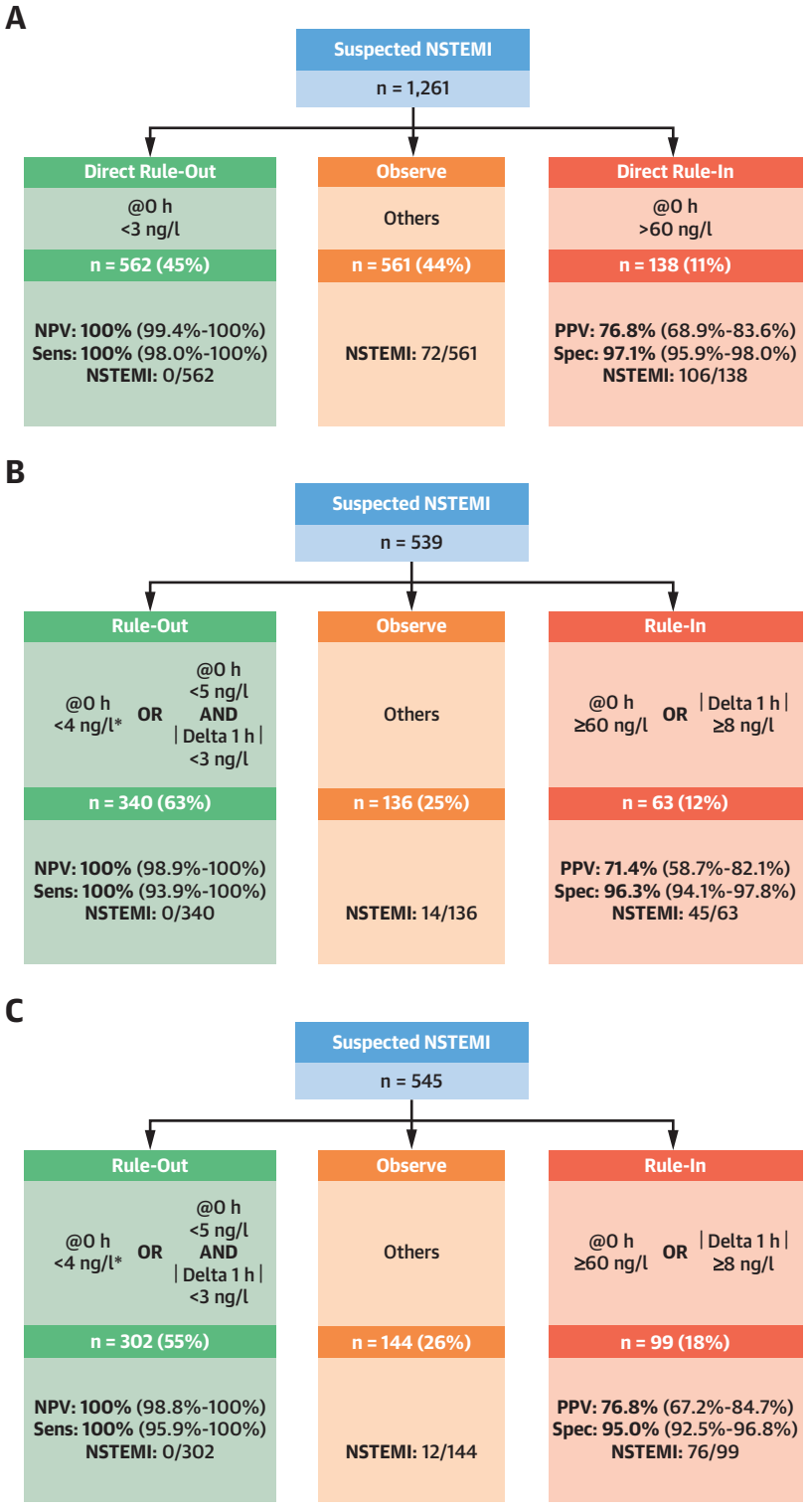
OPTIMAL CUTOFF CONCENTRATIONS AT PRESENTATION FOR RISK STRATIFICATION. A single cutoff concentration of <3 ng/l met the pre-defined NPV and sensitivity of ≥99.5% and ≥99% for rule-out. Among 1,261 patients, 562 (45%) were classified as low risk with a cumulative event rate of 0%. The NPV was 100% (95% CI: 99.4% to 100%), and the sensitivity was 100% (95% CI: 98.0% to 100%) (**Figure 2A**). When incorporating a safety criterion of chest pain onset >3 h, the optimal single cutoff concentration was <4 ng/l. Thirty-three percent of patients were classified as low risk with a cumulative event rate of 0%. The NPV was 100% (95% CI: 99.1% to 100%), and the sensitivity was 100% (95% CI: 98.0% to 100%) (Online Figure 6). A single cutoff concentration of >60 ng/l met the pre-defined PPV of 75% for rule-in. Among 1,261 patients, 138 (11%) were classified as high risk with a cumulative event rate of 77% (106 of 138 patients with non-ST-segment elevation MI). The PPV was 76.8% (95% CI: 68.9% to 83.6%), and the specificity was 97.1% (95% CI: 95.9% to −98.0%) (**Figure 2B**). The performance of a single cutoff strategy to identify low- and high-risk patients is shown in **Figure 3A**.

DERIVATION OF THE POC-HS-cTnI-TriageTrue 0/1-H ALGORITHM. Optimal thresholds for the rule-out of MI were defined in the derivation cohort ($n = 539$) as either a POC-hs-cTnI-TriageTrue concentration <4 ng/l at presentation in patients with an onset of chest pain >3 h (direct rule-out) or as a POC-hs-cTnI-TriageTrue concentration <5 ng/l at presentation and an absolute change <3 ng/l within 1 h for all patients (irrespective of time since chest pain onset). Optimal cutoff criteria for the rule-in of MI were defined as either a POC-hs-cTnI-TriageTrue concentration ≥60 ng/l at presentation (direct rule-in) or an absolute change ≥8 ng/l within 1 h. Patients fulfilling neither of the above-mentioned criteria for rule-out or for rule-in were classified as observe. The diagnostic performance of the POC-hs-cTnI-TriageTrue 0/1-h algorithm in the derivation cohort is shown in **Figure 3B** and Online Figure 7A.

VALIDATION OF THE POC-HS-cTnI-TriageTrue 0/1-H ALGORITHM. By applying the derived cutoff criteria to the internal validation cohort, 302 of 545 patients (55%) could be classified as rule-out with a corresponding NPV of 100% (95% CI: 98.8% to 100%) and a sensitivity of 100% (95% CI: 95.9% to 100%) (**Figure 3C**, Online Figure 7B). Direct rule-out based on a single POC-hs-cTnI-TriageTrue concentration at presentation was feasible in 164 of 545 patients (30%). The POC-hs-cTnI-TriageTrue 0/1-h algorithm classified 99 of 545 patients (18%) as rule-in with a corresponding PPV of 76.8% (95% CI: 67.2% to 84.7%) and a specificity of 95.0% (95% CI: 92.5% to 96.8%). Direct rule-in based on a single POC-hs-cTnI-TriageTrue concentration at presentation was feasible in 66 of 545 patients (12%). Overall, the POC-hs-cTnI-TriageTrue 0/1-h algorithm allowed a definite triage decision after 1 h in 401 of 545 patients (73%; either rule-out or rule-in). The remaining 144 of 545 patients (26%) were classified as observe with a prevalence of MI of 8%.

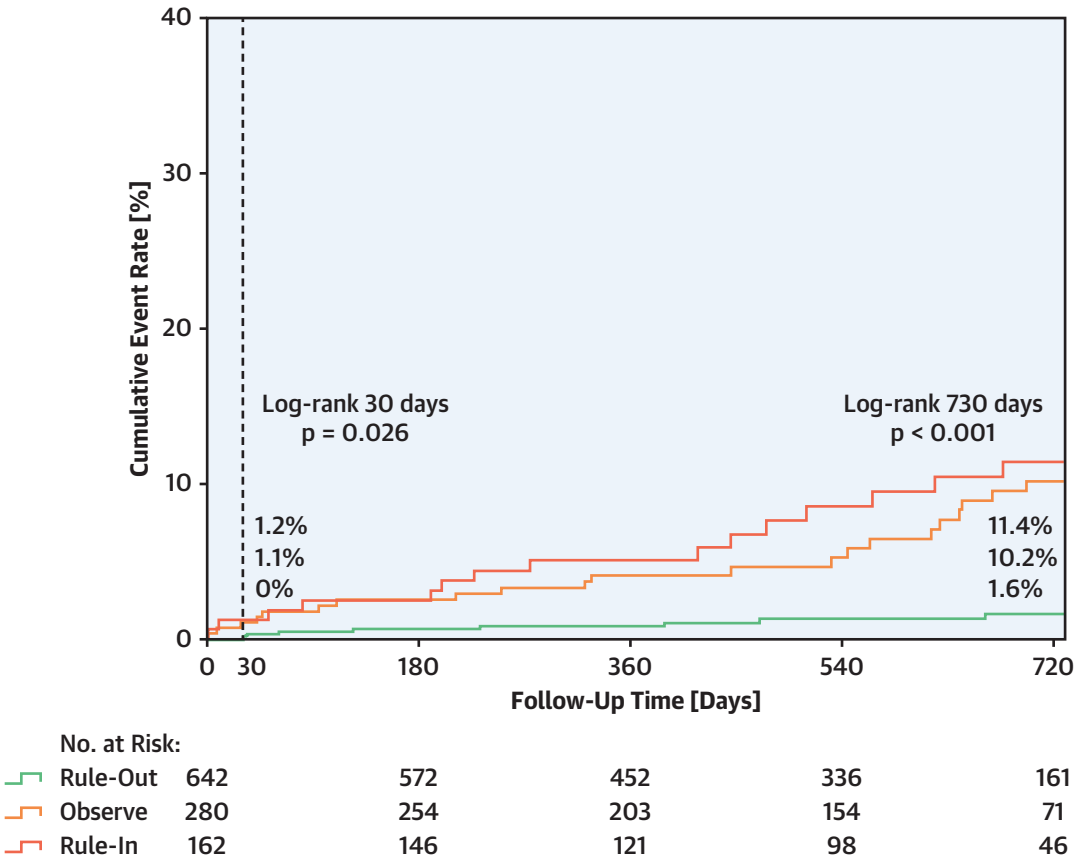
DIRECT COMPARISON OF THE POC-hs-cTnI-TriageTrue 0/1-H ALGORITHM WITH THE ESC 0/1-H ALGORITHMS USING hs-cTnT-ELECSYS AND hs-cTnI-ARCHITECT. The diagnostic performance of the POC-hs-cTnI-TriageTrue 0/1-h algorithm was similar to that of the hs-cTnT-Elecsys and the hs-cTnI-Architect 0/1-h algorithms (Online Appendix, Online Figures 8 and 9). The efficacy for direct rule-out or rule-in based on the 0-h sample alone was 43% (95% CI: 40% to 46%) for the POC-hs-cTnI-TriageTrue

FIGURE 3 Performance of POC-hs-cTnI for Triage of Patients With Suspected MI



(A) Performance of POC-hs-cTnI-TriageTrue single cutoff concentrations at presentation in the overall population to identify patients at low or high risk. Performance of the POC-hs-cTnI-TriageTrue 0/1-h algorithm in the **(B)** derivation cohort and **(C)** validation cohort. Delta 1 h denotes absolute (unsigned) change of hs-cTnI within 1 h. *If chest pain onset >3 h before presentation to the emergency department. NPV = negative predictive value; NSTEMI = non-ST-segment elevation myocardial infarction; PPV = positive predictive value; Sens = sensitivity; Spec = specificity; other abbreviations as in Figure 1.

FIGURE 4 Cumulative Event Rates at 30 Days and 2 Years in Patients Classified According to the POC-hs-cTnI-TriageTrue 0/1-h Algorithm



Kaplan-Meier curves depicting cumulative event rates within 30 days and at 2 years according to the triage decision provided by the POC-hs-cTnI 0/1-h algorithm. No. = number; other abbreviations as in Figure 1.

0/1-h algorithm and was, therefore, even higher than the 25% (95% CI: 22% to 27%) of hs-cTnT-Elecsys and the 22% (95% CI: 20% to 25%) of hs-cTnI-Architect.

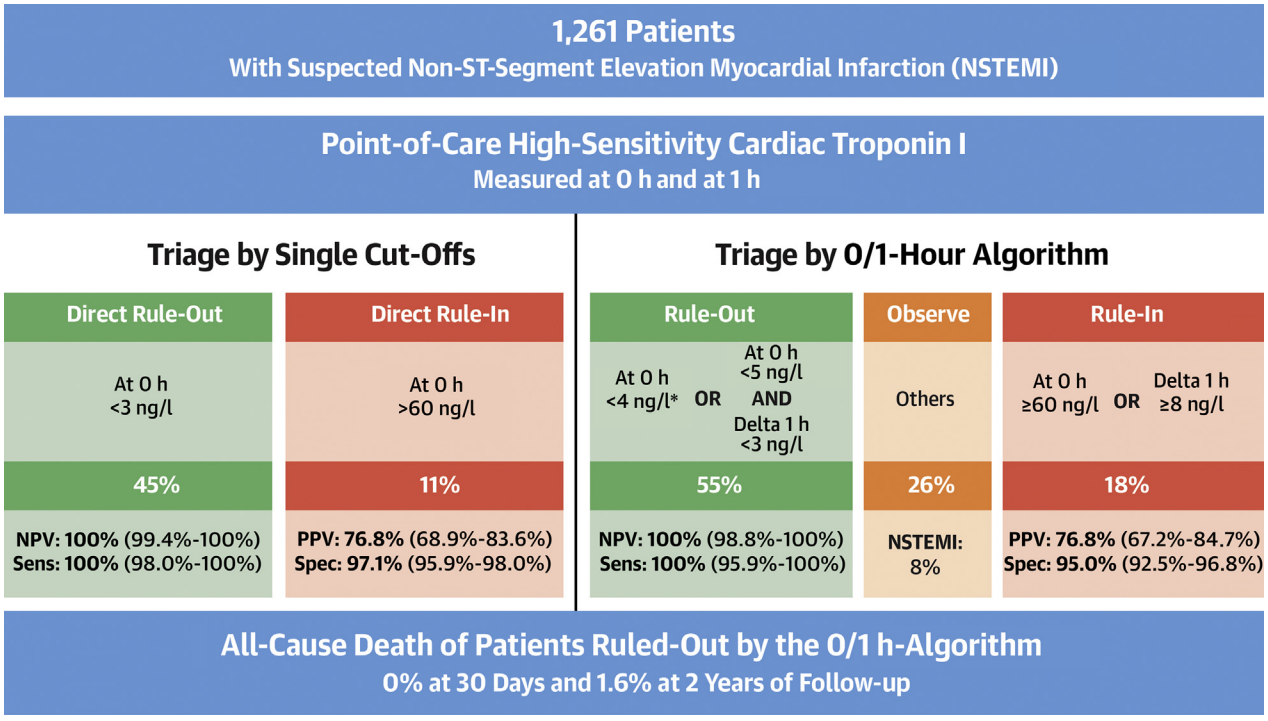
PROGNOSTIC PERFORMANCE OF THE POC-hs-cTnI-TriageTrue 0/1-h ALGORITHM. The median follow-up was 727 days (IQR: 376 to 756 days) with 5 deaths (3 cardiovascular) occurring within 30 days and 44 deaths (21 cardiovascular) within 2 years. The cumulative 30-day event rates were 0% (0 events), 1.1% (3 events), and 1.2% (2 events; log rank, $p = 0.026$) in the rule-out, observe, and rule-in groups, respectively. At 2 years, the cumulative event rates were 1.6% (8 events), 10.2% (21 events), and 11.4% (15 events), respectively (log rank, $p < 0.001$) (Figure 4).

CUMULATIVE MAJOR ADVERSE CARDIAC EVENTS AT 30 DAYS. The cumulative major adverse cardiac events rate (including the index event) was 0.2% (1 event) at 30 days in patients triaged to rule-out, 12.5% (35 events) in patients triaged to observe, and 75.3% (122 events) in patients triaged to rule-in by the POC-hs-cTnI-TriageTrue 0/1-h algorithm (log rank, $p < 0.001$).

SENSITIVITY ANALYSIS. Overall, the sensitivity analysis with final diagnoses according to the final adjudication including hs-cTnI-Architect concentrations revealed similar findings and thereby confirmed the findings from the primary analysis (Online Appendix, Online Figures 5B and 9 to 11).

CORRELATION OF POC-hs-cTnI-TriageTrue WITH LABORATORY-BASED hs-cTn ASSAYS. POC-hs-cTnI-TriageTrue concentrations at ED presentation showed high correlation with hs-cTnT-Elecsys ($\rho = 0.829$; $p < 0.001$) and hs-cTnI-Architect ($\rho = 0.844$; $p < 0.001$) (Online Figure 12).

CENTRAL ILLUSTRATION **Performance of the Point-of-Care High-Sensitivity Cardiac Troponin I TriageTrue Assay in Patients With Suspected Myocardial Infarction**



Boeddinghaus, J. et al. J Am Coll Cardiol. 2020;75(10):1111–24.

Diagnostic performance of the point-of-care (POC)-high-sensitivity cardiac troponin I (hs-cTnI)-TriageTrue assay in patients with suspected myocardial infarction (MI). Using POC-hs-cTnI-TriageTrue single cutoff concentrations at presentation allow to identify patients at low or high risk of MI. An assay-specific 0/1-h algorithm can promptly and safely rule out and accurately rule in MI in almost three-fourths of patients. Delta 1 h denotes absolute (unsigned) change of hs-cTnI within 1 h. *If chest pain onset >3 h before presentation to the emergency department. NPV = negative predictive value; NSTEMI = non-ST-segment elevation myocardial infarction; PPV = positive predictive value; Sens = sensitivity; Spec = specificity.

DISCUSSION

We performed a large prospective multicenter study using central adjudication by 2 independent cardiologists to assess the clinical performance of POC-hs-cTnI-TriageTrue in the early diagnosis of MI (Central Illustration). We report 7 major findings:

First, the diagnostic accuracy of the POC-hs-cTnI-TriageTrue assay was very high and at least comparable to that provided by the best validated central laboratory-based hs-cTnT-Elecsys and hs-cTnI-Architect assays. This finding was consistent in the overall population, as well as in early presenters. Although the sample size was high enough to demonstrate a statistically significant difference in the AUC in favor of POC-hs-cTnI-TriageTrue, the difference observed was numerically small. It therefore remains unclear whether this difference also is of clinical significance. Second, a low single cutoff concentration of <3 ng/l at presentation identified nearly one-half of patients as low risk with an NPV of 100% (95% CI: 99.4% to 100%). No patient with an index non-ST-segment elevation MI was missed. About 1 out of 10 patients was identified to be at high risk for MI by a single cut off concentration above 60 ng/l at presentation with a PPV of 76.8% (95% CI: 68.9% to 83.6%). Third, the use of POC-hs-cTnI-TriageTrue allowed us to successfully derive a POC-hs-cTnI-TriageTrue 0/1-h algorithm in the derivation cohort, defined by either a POC-hs-cTnI-TriageTrue concentration <4 ng/l at presentation in patients with an onset of chest pain >3 h (direct rule-out) or a POC-hs-cTnI-TriageTrue concentration <5 ng/l at presentation and an absolute change <3 ng/l within

1 h for all patients (irrespective of time since chest pain onset) for triage to rule-out. Applying this POC-hs-cTnI-TriageTrue 0/1-h algorithm in the internal validation cohort demonstrated very high safety in the rule-out zone with an NPV of 100% (95% CI: 98.8% to 100%) and a sensitivity of 100% (95% CI: 95.9% to 100%). In addition, the accuracy for rule-in of MI was high with a PPV of 76.8% (95% CI: 67.2% to 84.7%). The high safety of this approach is further highlighted by the fact that both type 1 and type 2 MI were included in this analysis. Fourth, the performance of the POC-hs-cTnI-TriageTrue 0/1-h algorithm was comparable to that of the established guideline-recommended 0/1-h algorithms and was also similar to their performance in previous studies (6,14). However, the higher efficacy of the POC-hs-cTnI-TriageTrue 0/1-h algorithm for direct triage toward rule-out or rule-in is an advantage over the 0/1-h algorithms using the hs-cTnT-Elecsys and hs-cTnI-Architect assays. Based on a single POC-hs-cTnI-TriageTrue concentration at presentation, 43% (95% CI: 40% to 46%) of patients were either directly ruled out or in for MI without the need for serial hs-cTnI sampling. This proportion was higher than the 25% (95% CI: 22% to 27%) for hs-cTnT-Elecsys and 22% (95% CI: 20% to 25%) for hs-cTnI-Architect. Fifth, the overall efficacy of the novel POC-hs-cTnI-TriageTrue 0/1-h algorithm was high in that it assigned almost three-fourths of patients to either rule-out or rule-in zones within 1 h, and only one-fourth of patients to the observe zone. Sixth, these findings were confirmed in a sensitivity analysis using a secondary adjudication including serial hs-cTnI-Architect concentrations. Therefore, the reference standard applied in this large diagnostic study of patients presenting with suspected MI seems to be very stringent and robust (15). By adding a secondary analysis that included hs-cTnI-Architect (rather than hs-cTnT-Elecsys as in the primary analysis) in addition to the clinical and imaging data available for the adjudication of the final diagnosis, the generalizability of our findings was further increased. Seventh, the cumulative event rates in patients assigned to the rule-out zone by the 0/1-h algorithm were 0% at 30 days and 1.6% at 2 years, further underscoring the safety of early discharge from the ED for most patients classified as rule-out, with further outpatient management as clinically appropriate.

These findings extend and corroborate previous work on POC-cTn testing and may have substantial medical and economic implications (16–19). With the clinical availability of a POC-hs-cTnI-TriageTrue assay with an at least comparable diagnostic accuracy to the best-validated central laboratory hs-cTnT/I assays and a very safe and highly efficacious POC-hs-cTnI-TriageTrue 0/1-h algorithm, the time to diagnosis and to discharge from the ED can be expected to reduce even further than currently achieved with central laboratory–based hs-cTnT/I 0/1-h algorithms (5,6,14,20,21). Moreover, it would allow extending the use of the hs-cTnI 0/1-h algorithm to settings without a central laboratory including smaller hospitals, ambulances, and general practices.

To date, the major disadvantage in POC-cTn assays has been the lack of high-sensitivity assays, matching the analytical and clinical performance of central laboratory testing (22,23). For example, a prospective comparison in 261 chest pain patients of the AQT90-flex POCT-cTnT assay reported an insufficient sensitivity (68%) and also a higher number of analytically false-positive results as compared to hs-cTnT-Elecsys (23). To overcome the lack of sensitivity, 1 strategy was to use POC-cTn in combination with a formal clinical risk score (24). A recent prospective diagnostic study of the POC-cTnI (i-Stat, Abbott Laboratories) in combination with the T-MACS (Troponin-only Manchester Acute Coronary Syndromes) decision aid in 716 patients reported a very high sensitivity (99%), but also required a 3-h sample and had lower efficacy (31%) compared with the POC-hs-cTnI-TriageTrue 0/1-h algorithm derived in this study (24). However, with the introduction of POC tests that have a similar sensitivity to that of central laboratory hs-cTn assays, formal risk scores, and the use of a 3-h sample in all patients might become unnecessary (25).

Our findings are supported by encouraging data from a recent pilot study of the new POC-I-Stat TnI-Nx assay (Abbott Diagnostics), showing comparable AUC versus hs-cTnI-Architect (26). Similarly, the PATHFAST cTnI-II assay (LSI Medience Corporation; Mitsubishi Chemical Europe, Dusseldorf, Germany), which runs on a table device (weight 62 pounds, width 13.5 inches, depth 22.4 inches, height 18.7 inches) demonstrated high sensitivity (27) as well as diagnostic performance comparable to that of hs-cTnI-Architect (28). In contrast to the PATHFAST analyzer, the POC Triage system (Quidel) is much smaller (weight 1.5 pounds, width 6.25 inches, depth 8.5 inches, height 2.75 inches), facilitating a broader use such as in the ambulance or private practice (29). Due to U.S. Food and Drug Administration regulations, the clinical introduction of hs-cTnT/I assays as well as the clinical implementation of rapid hs-cTnT/I-based triage algorithms has been delayed in the United States compared with in, for example, Europe.

However, to date several hs-cTnT/I assays have received U.S. Food and Drug Administration clearance and multiple U.S. institutions have implemented hs-cTnT/I-based rapid diagnostic algorithms using U.S. Food and Drug Administration-approved assays (J. Januzzi, December 2019).

STUDY LIMITATIONS. First, this study was conducted in ED patients with symptoms suggestive of MI. Further studies are required to quantify the utility of rule-out and rule-in strategies in patients with either a higher pre-test probability (e.g., in a coronary care unit setting) or in patients with a lower pre-test probability (e.g., in a general practitioner setting) for MI. Second, the data presented were obtained from a prospective diagnostic study. Studies applying the diagnostic algorithms prospectively for clinical decision making are warranted. 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 logistic 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 MI, including central adjudication by experienced cardiologists, we still may have misclassified a small number of patients. This would invariably have led to an underestimation of the true diagnostic accuracy of the novel 0/1-h algorithm. Fifth, although all laboratory procedures were performed according to stringent standardized operating procedures, human error in the handling of the study-specific blood samples may have occurred in a small number of samples leading to incorrect results pertaining to an individual patient. This again would invariably have led to an underestimation of the true diagnostic accuracy of the novel POC-hs-cTnI-TriageTrue 0/1-h algorithm. Sixth, we cannot generalize our findings to patients with terminal kidney failure requiring dialysis, because they were excluded from this study.

CONCLUSIONS

POC-hs-cTnI-TriageTrue provides very high diagnostic accuracy in patients with suspected MI. Its clinical performance is at least comparable to that of the 2 best-validated central laboratory assays. The availability of POC-hs-cTnI-TriageTrue will further facilitate the implementation of early triage algorithms and thereby provide major benefits for patients and health care systems.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: A POC hs-cTnI assay has diagnostic accuracy comparable to that of laboratory-based hs-cTn assays and can be used to rapidly identify patients at low or high risk of MI.

TRANSLATIONAL OUTLOOK: Prospective trials are needed to compare the value of implementing POC-hs-cTnI assays to that of conventional strategies in the assessment of patients with suspected acute coronary syndromes.

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KEY WORDS 0/1-h algorithm, diagnosis of myocardial infarction, guidelines, high-sensitivity cardiac troponin I, point of care, rule in, rule out

APPENDIX For supplemental methods, results, figures, tables, and the rest of the APACE investigators, please see the online version of this paper.