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A 1-h Combination Algorithm Allows Fast Rule-Out and Rule-In of Major Adverse Cardiac Events

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ABSTRACT

BACKGROUND A 1-h algorithm based on high-sensitivity cardiac troponin T (hs-cTnT) testing at presentation and again 1 h thereafter has been shown to accurately rule out acute myocardial infarction.

OBJECTIVES The goal of the study was to evaluate the diagnostic accuracy of the 1-h algorithm when supplemented with patient history and an electrocardiogram (ECG) (the extended algorithm) for predicting 30-day major adverse cardiac events (MACE) and to compare it with the algorithm using hs-cTnT alone (the troponin algorithm).

METHODS This prospective observational study enrolled consecutive patients presenting to the emergency department (ED) with chest pain, for whom hs-cTnT testing was ordered at presentation. Hs-cTnT results at 1 h and the ED physician's assessments of patient history and ECG were collected. The primary outcome was an adjudicated diagnosis of 30-day MACE defined as acute myocardial infarction, unstable angina, cardiogenic shock, ventricular arrhythmia, atrioventricular block, cardiac arrest, or death of a cardiac or unknown cause.

RESULTS In the final analysis, 1,038 patients were included. The extended algorithm identified 60% of all patients for rule-out and had a higher sensitivity than the troponin algorithm (97.5% vs. 87.6%; $p < 0.001$). The negative predictive value was 99.5% and the likelihood ratio was 0.04 with the extended algorithm versus 97.8% and 0.17, respectively, with the troponin algorithm. The extended algorithm ruled-in 14% of patients with a higher sensitivity (75.2% vs. 56.2%; $p < 0.001$) but a slightly lower specificity (94.0% vs. 96.4%; $p < 0.001$) than the troponin algorithm. The rule-in arms of both algorithms had a likelihood ratio >10.

CONCLUSIONS A 1-h combination algorithm allowed fast rule-out and rule-in of 30-day MACE in a majority of ED patients with chest pain and performed better than the troponin-alone algorithm. (J Am Coll Cardiol 2016;67:1531-40)

Chest pain is a common presenting complaint among patients in the emergency department (ED) (1). Whether the chest pain is caused by an acute coronary syndrome (ACS) (i.e., acute myocardial infarction [AMI] or unstable angina [UA]) is of prime diagnostic concern. A large portion of patients with chest pain undergo lengthy assessment in the ED or are admitted to rule out ACS, often with stress testing, creating a substantial health care burden (2,3). However, few of these patients prove

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AMI = acute myocardial infarction

ECG = electrocardiogram

ED = emergency department

ESC = European Society of Cardiology

hs-cTnT = high-sensitivity cardiac troponin T

MACE = major adverse cardiac events

NPV = negative predictive value

PPV = positive predictive value

STEMI = ST-segment elevation myocardial infarction

UA = unstable angina

to have ACS, leaving room to significantly improve our assessment of patients with chest pain.

The main methods used to determine the likelihood of ACS in the ED are patient history, electrocardiogram (ECG), and cardiac troponins. The new high-sensitivity cardiac troponin assays allow use of shorter time intervals for repeated blood samples (4). Results by Reichlin et al. (4,5) indicate that a diagnostic algorithm with high-sensitivity cardiac troponin T (hs-cTnT) sampling at ED presentation and 1 h thereafter safely rules-out and rules-in AMI during the index visit. This algorithm has received a Class I recommendation in the latest European Society of Cardiology (ESC) guidelines for non-ST-segment elevation ACS (6).

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However, in clinical practice, it is the likelihood of ACS and short-term adverse cardiac events (rather than only index visit AMI) that is decisive for further management. The algorithm also has not been evaluated by external groups or in EDs with an ACS prevalence <25% to 30% (4,5). Furthermore, the algorithm uses hs-cTnT alone to decide patient disposition; in routine care, management decisions in patients with chest pain are based on the entire clinical picture, including troponin results, patient history, and ECGs (7). Accordingly, the ESC guidelines and Reichlin et al. state that the algorithm should always be used together with an assessment of patient history and ECG (5,6). The diagnostic performance of this combination, however, has not been studied thus far.

The goal of the present study was to evaluate the diagnostic accuracy of the 1-h algorithm supplemented with patient history and ECG for predicting a major adverse cardiac event (MACE) within 30 days and to compare it with the algorithm based on hs-cTnT testing alone.

METHODS

This study was conducted at Skåne University Hospital (Lund, Sweden), a tertiary care teaching hospital. The ED has an annual census of approximately 65,000 and is staffed mainly by emergency physicians.

STUDY DESIGN AND DATA COLLECTION. This prospective observational study included patients presenting during weekdays between 9:00 AM and 9:00 PM from February 2013 to April 2014. Consecutive patients ≥18 years of age who presented with non-traumatic chest pain/discomfort to the ED and for whom hs-cTnT testing was ordered at presentation (0 h) were eligible for enrollment after providing written informed consent. We did not enroll patients assessed in the ED as having ST-segment elevation myocardial infarction (STEMI) because this diagnosis is not based on biomarkers. We also did not enroll patients with severe communication barriers, such as patients who did not speak Swedish/English or who had dementia. Enrolled patients had a second blood sample for hs-cTnT analyzed 1 h after the first sample. Patients who were enrolled but had an adjudicated final diagnosis of STEMI were excluded. Patients were also excluded if there was hemolysis with a hemoglobin concentration >0.1 g/dl, H-index ≥100 (the manufacturer-recommended level) in either the 0- or 1-h sample because this can cause falsely low results. Those with a missing 1-h hs-cTnT sample or missing physician assessments of the history or ECG were excluded as well. This study was approved by the regional ethics committee in Lund and is reported in accordance with Standards for the Reporting of Diagnostic Accuracy Studies (8).

Clinical data and 1-h troponin samples were collected by research assistants, blinded to the study hypothesis; these assistants received training on how to collect data in a standardized fashion by using a custom-made study questionnaire.

The ED physicians were approached shortly after seeing the patient to obtain their assessment of the likelihood of ACS based on the patient history ("gestalt") before hs-cTnT results were available. The patient history could be assessed as high, intermediate, low, or very low risk of ACS. To obtain an unbiased assessment from the physician, the questionnaire provided no guidance on how to differentiate the different risk levels.

The physicians then assessed whether the ECG showed signs of acute ischemia. We similarly did not provide a definition of signs of acute ischemia, but the questionnaire included the definitions of significant ST-segment elevation, ST-segment depression, T-wave inversion, and Q waves as provided by the universal AMI guidelines (9).

Samples for hs-cTnT were collected in lithium heparin tubes and analyzed with the Cobas e602 (Roche Diagnostics, Basel, Switzerland). This assay has a limit of blank of 3 ng/l, a limit of detection of 5 ng/l, and the coefficient of variation is <10% at the 99th percentile cutoff point of 14 ng/l (10).

Further diagnostic testing and treatment were performed, as in routine care, at the discretion of the responsible physician. Testing included serial troponin measurements, radiography, stress testing, and coronary angiography as deemed appropriate.

The ED physicians were not blinded to the 1-h hs-cTnT result but were unaware of the study protocol.

OUTCOMES AND ADJUDICATION PROCESS. The primary outcome was a MACE within 30 days, including the index visit. MACE was defined as an adjudicated diagnosis of AMI, UA, cardiac arrest, cardiogenic shock, ventricular arrhythmia requiring intervention, atrioventricular block requiring intervention, or death of a cardiac or unknown cause. The secondary outcome was MACE without UA within 30 days.

A detailed account of the adjudication process is provided in Online Appendix 1. In short, the final diagnosis of 30-day MACE used in the analyses was decided by independent reviews of 2 cardiologists and, in case of disagreement, by a third cardiologist. All cardiologists were blinded to the data form, the algorithm incorporating patient history and ECG, and the 1-h hs-cTnT test result. The adjudicated diagnoses were based on all available clinical information from all hospitals in Sweden (as discussed later) within 60 days from the index visit, such as patient history and results of blood samples, ECG, echocardiography, stress test, and coronary angiography.

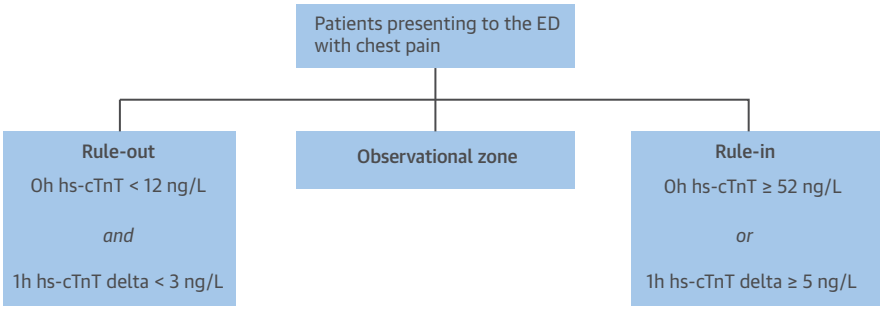
AMI was defined according to the universal definition requiring a significant rise or fall in hs-cTnT level with at least 1 value above the 99th percentile, combined with symptoms or signs of cardiac ischemia (9). The definitions of significant rise or fall used in this study are detailed in Online Appendix 2. In order to not misclassify late presenters in the troponin plateau phase, an AMI diagnosis could still be adjudicated in patients with elevated hs-cTnT levels in the absence of a significant rise or fall, if it was deemed to be the most likely diagnosis based on all available data.

The diagnosis of UA required normal or slightly elevated hs-cTnT levels without a significant rise or fall and a history consistent with UA (defined as rest angina, new-onset angina of Canadian Cardiovascular Society grade III or higher, or increasing angina) and at least 1 of the following: stenosis ≥70% in a vessel according to coronary angiography; positive stress test result if no angiography was performed; or new ischemic ECG changes in patients managed without stress testing or angiography. A diagnosis of UA could also be adjudicated in patients who were discharged after AMI was ruled out and were subsequently diagnosed with AMI or died of cardiac or unknown cause within 30 days from the index visit.

The other components of the 30-day MACE outcome were defined according to published standardized data definitions (11).

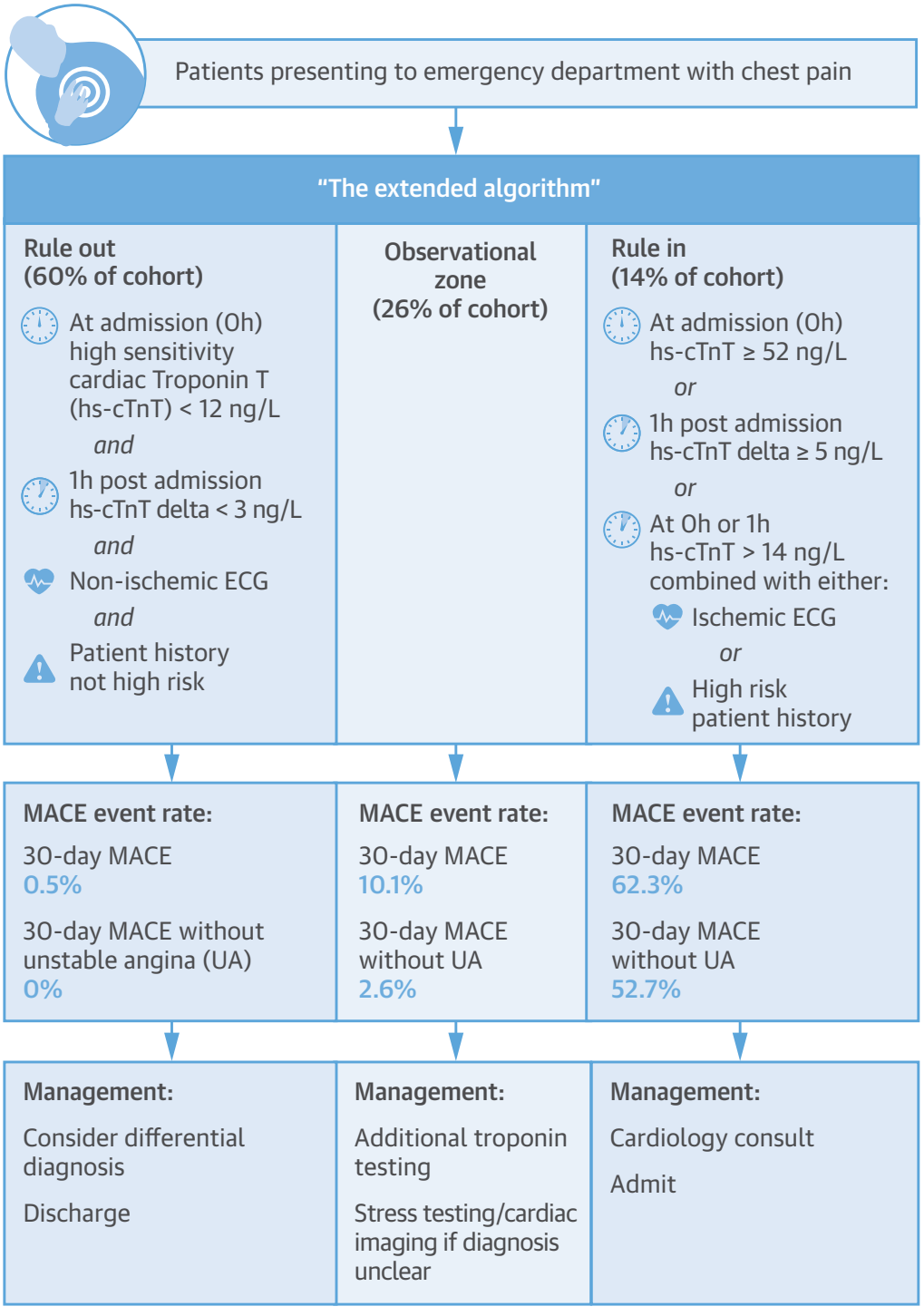
FOLLOW-UP. Because all hospitals in Region Skåne use the same computerized patient record system, we had access to charts from all hospitals in the region and to all diagnostic examinations, including those ordered by primary care physicians. This form of extensive electronic medical record follow-up has been shown to be as accurate as telephone follow-up (12). All admissions to in-hospital care in Sweden are registered in the National Patient Register; we obtained data from this register to ensure that hospital visits outside our region were not missed. Charts were ordered for patients who sought care at hospitals outside of our region. Deaths and causes of death were obtained from patient charts, the

FIGURE 1 Troponin Algorithm



This algorithm used only high-sensitivity cardiac troponin T (hs-cTnT) testing at presentation (0 h) and 1 h for rule-out and rule-in of emergency department (ED) patients presenting with chest pain.

CENTRAL ILLUSTRATION **A 1-h Algorithm for Chest Pain Evaluation: Patient Presenting to the ED**



Mokhtari, A. et al. J Am Coll Cardiol. 2016;67(13):1531–40.

For patients presenting to the emergency department (ED) with chest pain, the extended algorithm combines high-sensitivity cardiac troponin T (hs-cTnT) testing at 0 h and 1 h with the patient history and electrocardiogram (ECG) to predict the risk of a 30-day major adverse cardiac event (MACE) with and without unstable angina (UA). Rule-out, rule-in, and observational zone arms are shown, together with suggested courses of action.

Swedish population registry, and the national death registry. No patient was lost to follow-up.

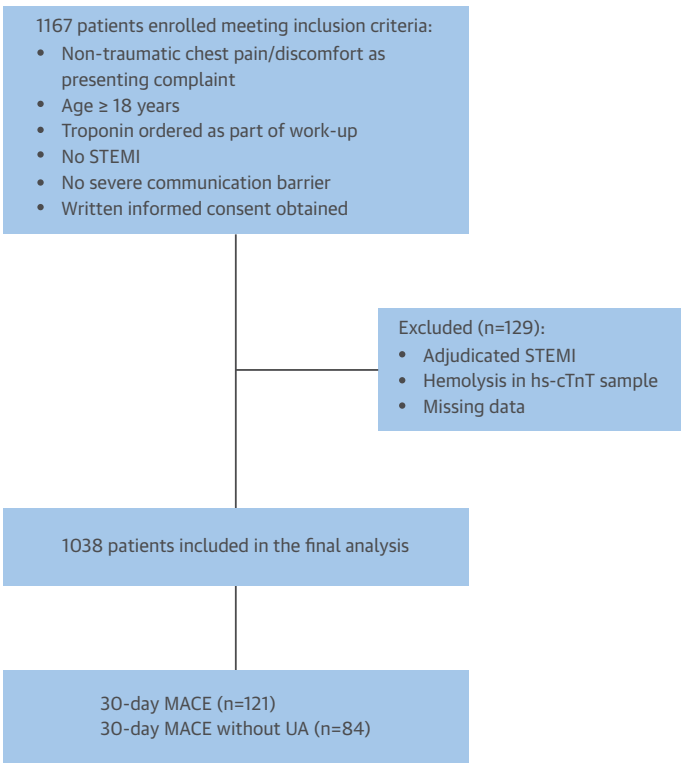
ALGORITHMS. The algorithm proposed by Reichlin et al. (4) (**Figure 1**) is based on hs-cTnT results alone and rules out patients with a presentation hs-cTnT level <12 ng/l and an hs-cTnT change <3 ng/l from 0 to 1 h (1-h delta). Patients are ruled in when the 0-h hs-cTnT level is ≥52 ng/l or the 1-h delta is ≥5 ng/l. The remaining patients are placed in an "observational zone." We refer to this algorithm as the "troponin algorithm."

We also evaluated a prespecified algorithm that included the troponin algorithm supplemented with the ED physician's assessment of patient history and ECG (**Central Illustration**), both of which have good interobserver reliability with kappa values of 0.75 and 0.85, respectively (13), as well as being predictive of adverse cardiac events independently of troponin levels (13,14). In this "extended algorithm," rule-out also required a history assessed as non-high risk (intermediate, low, or very low risk) and the absence of acute ischemia on ECG. We further added a variable to the rule-in arm, allowing rule-in of patients with a 0-h or 1-h hs-cTnT level >14 ng/l if combined with either a high-risk history and/or an ischemic ECG. The rationale was that in these patients with a high pretest probability, an hs-cTnT level >14 ng/l should have a positive predictive value sufficient for rule-in. This approach is in accordance with the American College of Cardiology Foundation expert consensus document (7).

STATISTICAL ANALYSES. For descriptive data, mean ± SD was used because all continuous variables were found to have roughly symmetrical distributions. Categorical variables are described with proportions. Comparisons between groups were performed by using Pearson's chi-square and Fisher exact tests for categorical variables, and independent Student *t* test and 1-way analysis of variance for continuous variables, as appropriate based on test assumptions.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios (LRs) were calculated for the algorithms. Comparisons of sensitivity and specificity were performed by using McNemar's test. Tests were 2-tailed, and a p value <0.05 was considered significant. When calculating the 1-h delta, hs-cTnT results <5 ng/l were assigned a value of 2.5 ng/l. Sample size calculations are provided (Online Appendix 3). SPSS version 21 (IBM SPSS Statistics, IBM Corp., Armonk, New York) and MedCalc version 14.8.1 (MedCalc Software bvba, Ostend, Belgium) were used for all statistical analyses.

FIGURE 2 Patient Flow



The flow diagram depicts the number of patients included and excluded and subsequent adjudicated diagnoses. hs-cTnT = high-sensitivity cardiac troponin T; MACE = major adverse cardiac events; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

RESULTS

We enrolled 1,167 patients in the study, with 129 excluded due to STEMI, hemolysis, or missing data, leaving 1,038 patients in the final analyses (**Figure 2**). To assess for possible selection bias, data on 485 consecutive patients with chest pain presenting outside of inclusion hours, as well as the 129 excluded patients and those with missing data, were compared with the included patients regarding age, sex, and AMI prevalence. There were generally no important differences, but the AMI prevalence was somewhat lower among excluded patients (Online Appendix 4). One reason for missing data: occasionally, several patients presented simultaneously, and a 1-h hs-cTnT test could not be obtained on time in all patients.

Characteristics of the included patients are provided in **Table 1**. A 30-day MACE was adjudicated in 121 patients (11.7%) and 30-day MACE without UA in 84 (8.1%) (**Table 2**). Of the remaining 917 patients, 120

TABLE 1 Baseline Patient Characteristics

	All Patients (N = 1,038)	Extended Algorithm		
		Rule-Out (n = 625)	Observational Zone (n = 267)	Rule-In (n = 146)
Demographics				
Age, yrs	60.7 ± 17.5	53.6 ± 16.5	71.4 ± 12.6	71.6 ± 12.9
Male	562 (54.1)	294 (47)	166 (62.2)	102 (69.9)
Arrival by ambulance	432 (41.6)	187 (29.9)	154 (57.7)	91 (62.3)
Medical history				
Diabetes	144 (13.9)	46 (7.4)	55 (20.6)	43 (29.5)
Hypertension	460 (44.3)	184 (29.4)	175 (65.5)	101 (69.2)
Hypercholesterolemia	240 (23.1)	106 (17.0)	80 (30.0)	54 (37.0)
Previous AMI	205 (19.7)	57 (9.1)	90 (33.7)	58 (39.7)
Previous revascularization	213 (20.5)	61 (9.8)	99 (37.1)	53 (36.3)
Stable angina	217 (20.9)	54 (8.6)	107 (40.1)	56 (38.4)
Previous stroke/TIA	97 (9.3)	32 (5.1)	42 (15.7)	23 (15.8)
Other risk factors				
Family history of CAD*	243 (23.4)	155 (24.8)	55 (20.6)	33 (22.6)
Current or past smoker	586 (56.5)	326 (52.2)	162 (60.7)	98 (67.1)
Prior medication				
Aspirin/$P2Y_{12}$ inhibitor	306 (29.5)	118 (18.9)	118 (44.2)	70 (47.9)
Nitrates	241 (23.2)	74 (11.8)	104 (39.0)	63 (43.2)
Statin	306 (29.5)	117 (18.7)	121 (45.3)	68 (46.6)
Clinical findings				
Systolic BP, mm Hg	145 ± 24	143 ± 22	148 ± 27	147 ± 27
Diastolic BP, mm Hg	84 ± 14	85 ± 14	83 ± 15	84 ± 15
Symptom onset to 0-h hs-cTnT test†				
≤3 h	324 (31.2)	186 (29.8)	76 (28.5)	62 (42.5)
>3 h	698 (67.2)	429 (68.6)	186 (69.7)	83 (56.8)
Physician assessments				
Acute ischemia on ECG	66 (6.4)	0	25 (9.4)	41 (28.1)
High-risk history	141 (13.6)	0	50 (18.7)	91 (62.3)
Physician level of experience‡				
Intern	374 (36.0)	248 (39.7)	82 (30.7)	44 (30.1)
Resident	442 (42.6)	246 (39.4)	118 (44.2)	78 (53.4)
Specialist	222 (21.4)	131 (21.0)	67 (25.1)	24 (16.4)

Values are mean ± SD or n (%). *Defined as close relative with acute myocardial infarction (AMI), angina, or cardiac death before 55 years of age. †n = 1,022. ‡Generally, interns were post-graduate year 0 to 2; residents, post-graduate year 2 to 7; and specialists, post-graduate year ≥7.

BP = blood pressure; CAD = coronary artery disease; ECG = electrocardiogram; hs-cTnT = high-sensitivity cardiac troponin T; TIA = transient ischemic attack.

had a cardiovascular but non-ACS cause of chest pain (e.g., myocarditis, stable angina, arrhythmia), and the rest had a noncardiac cause (e.g., pulmonary, chest wall disease, nonspecified chest pain). Details on diagnostic investigations performed are presented in Online Appendix 5.

EXTENDED VERSUS TROPONIN ALGORITHM. Both the extended algorithm and the troponin algorithm categorized a clear majority of patients for rule-out or rule-in (74% and 75%, respectively) (**Table 3**). The extended algorithm identified somewhat fewer patients for rule-out than the troponin algorithm (60.2% vs. 65.7%; 95% confidence interval [CI]: 4.0 to 7.0; $p < 0.001$).

The rule-out arm of the extended algorithm had a markedly higher sensitivity than the troponin algorithm for 30-day MACE (97.5% vs. 87.6%; 95% CI: 4.0 to 15.8; $p < 0.001$), missing only 3 patients with UA (Online Appendix 6) compared with 1 AMI and 14 UA patients missed by using the troponin algorithm. The NPV was 99.5% (producing a post-test probability of 0.5%) and the LR was 0.04 with the extended algorithm versus an NPV of 97.8% (post-test probability: 2.2%) and an LR of 0.17 with the troponin algorithm. The rule-in arm of the extended algorithm was also more sensitive than that of the troponin algorithm (75.2% vs. 56.2%; 95% CI: 10.5 to 27.5; $p < 0.001$) but had a slightly lower specificity (94.0% vs. 96.4%; 95% CI: 1.4% to 3.4; $p < 0.001$). The proportion of patients in the observational zone was not significantly different between the 2 algorithms (25.7% vs. 24.6%; 95% CI: -0.8 to 3.1; $p = 0.28$).

For the outcome of 30-day MACE without UA (**Table 4**), there were no significant differences in sensitivity in the rule-out arms between the extended algorithm and the troponin algorithm (100% vs. 98.8%; 95% CI: -1.2 to 3.5; $p = 1.00$). For both the extended and the troponin algorithm, NPV (100% vs. 99.9%) and LR (0 vs. 0.02) were excellent.

EXTENDED ALGORITHM: DIAGNOSES AND SUBGROUP ANALYSES. A final adjudicated diagnosis of a noncardiac cause of chest pain was significantly more common, and cardiovascular causes less common, in the rule-out patients compared with the observational and rule-in patients (Online Appendix 7). No patient in the rule-out arm had an aortic dissection and only 5 (0.8%) had a pulmonary embolism. In the observational zone, the majority of patients had a noncardiac cause of pain. No patient had an aortic dissection and only 2 (0.7%) had a pulmonary embolism. Among the rule-in patients, 80% had a cardiovascular cause of their pain, primarily AMI.

In the subgroup analyses, there were no significant differences in NPV for rule-out with regard to physician experience, patient sex or age, chest pain duration, or ongoing versus abated chest pain (Online Appendix 8).

DISCUSSION

In this study of ED patients with chest pain, we evaluated the ability of a 1-h algorithm combining hs-cTnT, patient history, and ECG to predict 30-day MACE with and without UA, and compared the results with a previously published algorithm based on hs-cTnT level alone.

To be clinically acceptable, a diagnostic algorithm for ED patients with chest pain should identify

those patients whose risk of AMI and UA is below the test threshold at which patients are more likely to derive harm than benefit from further testing (15). This threshold for ACS has been calculated to be approximately 2% (16). Furthermore, studies suggest that many ED physicians will only accept a <1% risk of 30-day MACE without UA in discharged patients (17). We therefore found it reasonable that for a diagnostic algorithm to be clinically useful, ruled-out patients should have a <2% risk of MACE within 30 days and a <1% risk of MACE without UA.

The present results showed that the extended algorithm met these criteria. Ruled-out patients had a 0.5% risk of MACE within 30 days, and almost no risk of MACE without UA, with the algorithm only missing 3 patients with UA. The 95% CIs were narrow and made it almost certain that the true event rates were below the mentioned thresholds. With very low LRs, a low event rate will also be achieved in settings with a higher overall prevalence.

In comparison, patients ruled out by using the troponin algorithm had a 2.2% risk of MACE within 30 days, with the lower bound of the CI showing a true risk possibly as high as 3.6%. Missed cases were almost exclusively patients with UA. This finding was not surprising because troponins have a poor sensitivity for ruling out UA (18), a diagnosis of which relies on assessments of ECG and history (19). Furthermore, because the LR was a moderate 0.17, the event rate will be higher in settings with a higher overall prevalence than ours. The troponin algorithm, however, performed well for the outcome of 30-day MACE without UA, with ruled-out patients having a risk of 0.1%, supporting previous findings by Reichlin et al. (4,5).

TABLE 2 30-Day MACE

	All Patients (N = 1,038)	Extended Algorithm		
		Rule-Out (n = 625)	Observational Zone (n = 267)	Rule-In (n = 146)
30-day MACE*	121 (11.7)	3 (0.5)	27 (10.1)	91 (62.3)
AMI during index visit	78 (7.5)	0	5 (1.9)	73 (50.0)
AMI during follow-up†	3 (0.3)	0	1 (0.4)	2 (1.4)
UA	39 (3.8)	3 (0.5)	21 (7.9)	15 (10.3)
Cardiogenic shock	0	0	0	0
Cardiac arrest	1 (0.1)	0	0	1 (0.7)
Ventricular arrhythmia‡	0	0	0	0
High-grade AV block‡	1 (0.1)	0	1 (0.4)	0
Cardiac death	4 (0.4)	0	1 (0.4)	3 (2.1)
Death of unknown cause	0	0	0	0
30-day MACE without UA	84 (8.1)	0	7 (2.6)	77 (52.7)

Values are n (%). *Patients could experience >1 event but were only counted once. †No AMI during index visit. ‡Requiring intervention.

AV = atrioventricular; MACE = major adverse cardiac event; UA = unstable angina; other abbreviation as in Table 1.

The troponin algorithm received a Class I recommendation in the 2015 ESC guidelines for non-ST-segment elevation ACS (6). Our study was the first to evaluate its performance for an outcome of 30-day MACE instead of only the index visit AMI and in a setting with a lower prevalence of ACS. The present results indicate that the troponin algorithm can safely rule out AMI and adverse cardiac events within 30 days but not UA. Hence, rule-out patients may still need further testing. The ESC guidelines also recommend that the troponin algorithm be used in conjunction with patient history and ECG, a combination not previously studied. Our study indicates that adding patient history and ECG as in the extended algorithm allows a safe rule-out of UA also, thereby identifying a large number of patients who need no further cardiac testing.

It might be argued that it is not useful to identify patients with UA, and some even suggest that UA should be excluded from the ACS spectrum in the era of high-sensitivity troponin assays (20). If UA is deemed unimportant, our results suggest that the troponin algorithm is an accurate and sufficient tool to predict the risk of cardiac events in ED patients with chest pain. However, in this observational study, patients with suspected UA were admitted and treated as in routine care. Had they been discharged and treatment withheld, their 30-day event rate would likely have been somewhat higher. Even in the era of high-sensitivity cardiac troponin assays, patients with UA have a significant 30-day risk of AMI or death (21). To our knowledge, no study has shown

TABLE 3 Algorithmic Diagnostic Accuracy for 30-Day MACE

	Troponin Algorithm % (95% CI)	Extended Algorithm % (95% CI)	p Value
Rule-out	n = 682	n = 625	
Sensitivity	87.6 (80.4–92.9)	97.5 (92.9–99.5)	<0.001
Specificity	72.7 (69.7–75.6)	67.8 (64.7–70.9)	<0.001
NPV	97.8 (96.4–98.8)	99.5 (98.6–99.9)	
LR	0.17 (0.11–0.27)	0.04 (0.01–0.11)	
Rule-in	n = 101	n = 146	
Sensitivity	56.2 (46.9–65.2)	75.2 (66.5–82.6)	<0.001
Specificity	96.4 (95.0–97.5)	94.0 (92.3–95.5)	<0.001
PPV	67.3 (57.3–76.3)	62.3 (53.9–70.2)	
LR	15.6 (10.8–22.6)	12.5 (9.5–16.5)	
Observational zone	n = 255	n = 267	
PPV	14.9 (10.8–19.9)	10.1 (6.8–14.4)	
LR	1.3 (1.0–1.8)	0.9 (0.6–1.2)	

CI = confidence interval; LR = likelihood ratio; MACE = major adverse cardiac event; NPV = negative predictive value; PPV = positive predictive value.

TABLE 4 Algorithmic Diagnostic Accuracy for 30-Day MACE Without UA

	Troponin Algorithm % (95% CI)	Extended Algorithm % (95% CI)	p Value
Rule-out	n = 682	n = 625	
Sensitivity	98.8 (93.5–100.0)	100.0 (95.7–100.0)	1.00
Specificity	71.4 (68.4–74.2)	65.5 (62.4–68.5)	<0.001
NPV	99.9 (99.2–100.0)	100.0 (99.4–100.0)	
LR	0.02 (0.00–0.12)	0.00 (0.00–0.07)	
Rule-in	n = 101	n = 146	
Sensitivity	78.6 (68.3–86.8)	91.7 (83.6–96.6)	0.001
Specificity	96.3 (94.9–97.4)	92.8 (90.9–94.3)	<0.001
PPV	65.4 (55.2–74.5)	52.7 (44.3–61.1)	
LR	21.4 (15.2–30.2)	12.7 (10.0–16.1)	
Observational zone	n = 255	n = 267	
PPV	6.7 (3.9–10.5)	2.6 (1.1–5.3)	
LR	0.8 (0.5–1.3)	0.3 (0.2–0.6)	

Abbreviations as in Tables 2 and 3.

that patients with UA can safely be discharged from the ED and left untreated. We believe it is important to identify patients with UA because this condition changes management.

Compared with the troponin algorithm, the extended algorithm also allowed rule-in of patients with an hs-cTnT level >14 ng/l combined with either a high-risk history and/or ischemic ECG. The extended algorithm thereby ruled-in a markedly larger proportion of patients with 30-day MACE, with only a small decrease in specificity. Both algorithms had a PPV lower than the 80% previously reported for the troponin algorithm (4,5), but this finding was expected based on the lower AMI prevalence in our study compared to previous studies (4,5). In routine care, patients with an elevated hs-cTnT level are often admitted. However, in a setting with a 9% AMI prevalence, an hs-cTnT level >14 ng/l has a PPV of only 30% (22). Not surprisingly, at many hospitals, only 1 in 4 admitted patients with chest pain are proven to have ACS (23–25). With a PPV for 30-day MACE of 62%, the extended algorithm should significantly improve on current clinical practice.

The extended algorithm thus provides a disposition strategy in approximately 75% of patients at the return of the 1-h hs-cTnT test, and 60% of all patients may potentially be discharged without further cardiac assessment, potentially reducing ED crowding, admissions, use of stress testing, and costs. Future studies should evaluate the performance and effects of the algorithm when implemented in routine care.

Previous studies indicated that physician assessment of patient history and ECG can predict 30-day MACE risk but cannot alone identify patients for safe rule-out (14,26). In the present study, we achieved this goal by combining assessments of the history and ECG with the troponin algorithm (4). Some studies have used an approach of combining scores, such as the Thrombolysis In Myocardial Infarction score, with negative serial troponin findings for rule-out (27). In comparison, the extended algorithm identified a larger proportion of patients for safe rule-out and stratified the remaining patients according to risk. Because history, ECG, and troponins are the cornerstones of ACS diagnosis, we believe that including all 3 factors in an algorithm is clinically sensible and will probably appeal to physicians. In this context, the HEART (History, ECG, Age, Risk factors, Troponin) score also includes all 3 variables (28). Compared with the extended algorithm, however, studies thus far suggest that the HEART score identifies fewer patients for rule-out (28).

In our study, to reflect real-life practice, the assessment of the ECG and history were made by physicians with different levels of experience. The performance of the extended algorithm did not change with physician experience, indicating that the algorithm can safely be used by junior physicians.

The extended algorithm is primarily intended to help with early patient disposition. If the algorithm can be validated in other populations, we suggest discharging rule-out patients from the ED after assessment for important differential diagnoses and consider outpatient follow-up. Such low-risk patients do not benefit from hospital admission (29) and often prefer outpatient follow-up when informed of their risk (30). With a probability of ACS below the test threshold, stress testing most likely would be more harmful than beneficial (16). For rule-in patients, we recommend cardiology consultation and hospital admission because the 30-day risk of MACE is >60%. After admission, additional hs-cTnT testing would be warranted in some cases (e.g., to identify AMI patients with a later troponin rise) and echocardiography and/or coronary angiography in most cases.

Patients in the observational zone had a risk of ACS clearly above the test threshold. We would therefore recommend further evaluation and additional troponin testing and, in the absence of a clear-cut alternative diagnosis, stress testing and/or cardiac imaging.

STUDY LIMITATIONS. This study was performed at a single university hospital, and the results are not necessarily generalizable to other centers, even though the AMI prevalence was similar to that in other studies (3,13,22,23). Patients were not included at all hours of the day or during weekends. The patients, however, were consecutively enrolled and, when compared with patients seeking care outside of

inclusion hours, there were no significant differences with regard to age, sex, or prevalence of AMI. Our prevalence of AMI and UA was similar to that in previous studies with 24-h patient inclusion at our ED (24,25), indicating that the present sample was representative of our entire ED population with chest pain.

At the time of the study, patients at our hospital were sometimes discharged based on a single hs-cTnT measurement <15 ng/l >6 h after symptom onset. Because this approach has not been conclusively shown to safely rule out AMI (18), the ED physicians were not blinded to the 1-h hs-cTnT level to prevent inadvertent discharge of patients with ACS. The physicians, however, were unaware of the study protocol and were informed at daily meetings that patients should not be managed based on the 1-h hs-cTnT level other than to prevent erroneous discharge. The adjudicating cardiologists were blinded to the 1-h hs-cTnT, and the final diagnosis of AMI was, therefore, independent of these samples, minimizing risk of incorporation bias.

As in routine care, not all patients underwent stress testing/cardiac imaging and, despite careful adjudication, a few cases of UA might have been missed. If so, however, these cases had an uneventful 60-day follow-up.

CONCLUSIONS

A 1-h combination algorithm allowed fast rule-out and rule-in of 30-day MACE in a majority of ED patients with chest pain and performed better than the 1-h algorithm based on hs-cTnT level alone.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with chest pain presenting to the ED, combining hs-cTnT levels on arrival and 1 h later with the patient history and ECG more effectively identified MACE within 30 days than screening based on hs-cTnT alone.

TRANSLATIONAL OUTLOOK: Future studies should evaluate the performance of this algorithm in a wide variety of care settings.

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APPENDIX For supplemental materials, please see the online version of this article.