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Comparison of fourteen rule-out strategies for acute myocardial infarction☆

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ABSTRACT

Background: The clinical availability of high-sensitivity cardiac troponin (hs-cTn) has enabled the development of several innovative strategies for the rapid rule-out of acute myocardial infarction (AMI). Due to the lack of direct comparisons, selection of the best strategy for clinical practice is challenging.
Methods: In a prospective international multicenter diagnostic study enrolling 3696 patients presenting with suspected AMI to the emergency department, we compared the safety and efficacy of 14 different hs-cTn-

Abbreviations: AMI, Acute myocardial infarction; ED, Emergency department; cTn, Cardiac troponin; hs-cTn, High-sensitivity cardiac troponin; STARD, Standards for Reporting of Diagnostic Accuracy Studies (STARD); ECG, Electrocardiogram; NPV, Negative predictive value; MACE, Major adverse cardiovascular event; CV, Coefficient of variation; LoD, Limit of detection; LoB, Limit of blank; ESC, European Society of Cardiology; ADP, Advanced diagnostic protocol; NICE, National Institute for Health and Care Excellence; IQR, Interquartile range.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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based strategies: hs-cTn concentrations below the limit of detection (LoD), dual-marker combining hs-cTn with copeptin, ESC 0 h/1 h-algorithm, 0 h/2 h-algorithm, 2 h-ADP-algorithm, NICE-algorithm, and ESC 0 h/3 h-algorithm, each using either hs-cTnT or hs-cTnI. The final diagnosis of AMI was adjudicated by two independent cardiologists using all available clinical information including cardiac imaging and serial hs-cTn concentrations.
Results: AMI was the final diagnosis in 16% of patients. Using hs-cTnT, safety quantified by the negative predictive value (NPV) and sensitivity was very high (99.8–100% and 99.5–100%) and comparable for all strategies, except the dual-marker approach (NPV 98.7%, sensitivity 96.7%). Similarly, using hs-cTnI, safety quantified by the NPV and sensitivity was very high (99.7–100% and 98.9–100%) and comparable for all strategies, except the dual-marker approach (NPV 96.9%, sensitivity 90.4%) and the NICE-algorithm (NPV 99.1%, sensitivity 94.7%). Efficacy, quantified by the percentage of patients eligible for rule-out, differed markedly, and was lowest for LoD-algorithm (15.7–26.8%).
Conclusion: All rapid rule-out algorithms, except the dual-marker strategy and the NICE-algorithm using hs-cTnI, favorably combine safety and efficacy, and can be considered for routine clinical practice.
Clinical trial registration: NCT00470587, http://clinicaltrials.gov/show/NCT00470587.

1. Introduction

Acute myocardial infarction (AMI) is a major cause of death and disability worldwide [1]. Patients with symptoms suggestive of AMI account for 10% of all emergency department (ED) consultations, and ultimately only 10–20% of these patients are diagnosed with AMI. Fast identification of AMI for early treatment is of paramount clinical importance, but since the majority of patients will not have an AMI, the rapid rule-out is of major medical and economic importance [1–4]. A delay in ruling-out AMI defers the diagnosis of the actual underlying disease and is associated with increased resource use, cost and overcrowding in the ED [4].

Progress in laboratory technology has led to the development of cardiac troponin (cTn) assays with higher analytical sensitivity (hs-cTn) in an effort to contribute to overcoming the sensitivity deficit for AMI at ED presentation when using conventional cTn assays [4,5]. Hs-cTn assays provide high diagnostic accuracy for AMI at ED presentation and thereby allow a shortening of the time-interval to the second hs-cTn measurement [4,6–16]. Based on this concept, several rapid rule-out strategies for AMI using hs-cTn concentrations have recently been developed [4,6–16]. Most of these rapid rule-out strategies require two serial hs-cTn measurements. In contrast, the dual-marker strategy combining two different pathophysiological signals with reciprocal release kinetics, namely cTn and copeptin, was developed to allow safe rule-out of AMI with a single blood draw [10,11,17]. Copeptin, the c-terminal part of the vasopressin prohormone, is currently seen as a non-specific and quantitative marker for endogenous stress that seems to peak at the very onset of AMI [18,19].

Due to limited data regarding direct comparisons among the different hs-cTn-based strategies, and particularly the lack of data directly comparing the dual-marker strategy with other rapid rule-out strategies, selection of the best approach for clinical practice is challenging [10,11,17,18].

Therefore, the aim of this multicenter study was to directly compare the safety and efficacy of different rapid hs-cTn-based rule-out strategies for AMI in one large patient cohort.

2. Methods

2.1. Study design and population

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective diagnostic multicenter study enrolling adult patients presenting to the ED with symptoms suggestive for AMI at 12 centers in 5 European countries (Switzerland, Spain, Italy, Czech Republic, Poland) [18,20–22]. We enrolled unselected consecutive patients presenting with any kind of acute chest discomfort with onset and/or peak within the last 12 h, who were providing written informed consent. Only patients with terminal kidney failure on chronic hemodialysis were excluded. Accordingly, patients were enrolled irrespective of their pre-test probability for AMI as long as acute chest discomfort was their key presenting symptom. For this analysis patients were also excluded if A) baseline hs-cTnI (Architect) or hs-cTnT (Elecsys) concentrations were not available or B) the final diagnosis remained unclear after adjudication and at least one hs-cTn concentration was elevated (possibly indicating presence of AMI) or C) patients had ST-elevation myocardial infarction (Online Suppl., eFigure 1).

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The authors designed the study, gathered, and analyzed the data according to the STARD guidelines for studies of diagnostic accuracy (Supplemental), vouched for the data and analysis, wrote the paper, and decided to publish.

2.2. Routine clinical assessment

All patients underwent a clinical assessment that included medical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood test, and chest radiography. Concentrations of (hs-)cTn were measured at presentation and serially thereafter as long as clinically indicated using different local (hs)-cTn assays in clinical use at the participating institutions. Treatment of patients was left to discretion of the attending physician.

2.3. Adjudicated final diagnosis and clinical endpoints

Adjudication of the final diagnosis was performed centrally in a core lab (University Hospital Basel) for all patients. Two independent cardiologists reviewed all available medical records – patient history, physical examination, results of laboratory testing, radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity and morphology in coronary angiography – pertaining to the patient from the time of ED presentation to 90-day follow up. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated with a third cardiologist (Online Supplement). In order to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by hs-cTn [23–28], the adjudicating cardiologists had access to serial concentrations of cTn/hs-cTn measured locally as part of routine clinical care as well as serial hs-cTnT concentrations measured in a central laboratory from the serial study blood samples for all rule-out algorithms including hs-cTnT. With the intention to address the phenomenon of discrepancies between hs-cTnT and hs-cTnI [29] and the resulting underestimation of the performance of hs-cTnI-based algorithms using an adjudication based at least in part on serial hs-cTnT measurements, we performed a second adjudication using serial hs-cTnI blood concentrations, measured in the central laboratory from study samples. This methodology provides the highest possible accuracy and allows overcoming diagnostic challenges related to this rare, but existing finding.

AMI was defined and cTn levels interpreted as recommended in current guidelines [1,3,4,23]. In brief, AMI 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 one hs-cTnT/I value above the 99th percentile together with a significant rise and/or fall. All other patients were classified as "no AMI" for this analysis.

After hospital discharge, patients were contacted 3, 12 and 24 months after discharge by telephone or in written form performed by trained researchers. Information regarding death during follow-up was furthermore obtained from the hospital or general practitioners records and the national registry.

As all strategies aim to triage patients towards rule-out of AMI, the sensitivity and negative predictive value (NPV) for AMI of each strategy was the primary safety endpoint. The percentage of patients triaged towards rule-out of AMI was the primary efficacy endpoint. The secondary safety endpoint was the sensitivity and NPV for major cardiac adverse events (MACE) in the rule-out group of each strategy within 30 days, defined as death (unless clearly non-cardiac), cardiac arrest, AMI (with index event), urgent coronary revascularization (<24 h), cardiogenic shock, and ventricular arrhythmia or high-degree atrioventricular block needing intervention, in the rule-out group of each strategy. This additional endpoint was chosen to investigate to what extent the patients triaged towards rule-out of AMI would be also appropriate candidates for rapid discharge from the ED and outpatient management.

2.4. Measurement of Hs-cTnI and Hs-cTnT concentrations

Blood samples for determination of hs-cTnI (Architect) and hs-cTnT (Elecsys) were collected at presentation to the ED, as well as serially at 1, 2, 3 and 6 h. When treatment required transferring the patient to the catheter laboratory or coronary care unit, serial sampling was discontinued. After centrifugation, samples were either measured directly from fresh samples in sites that had the laboratory infrastructure at the time of patient enrollment or frozen at −80 °C until assayed in a blinded fashion in a dedicated core laboratory. The hs-cTnI assay has a 99th percentile concentration of 26.2 ng/L with a corresponding co-efficient of variation (CV) of <5% and a limit of detection (LoD) of 1.9 ng/L [30]. The limit of blank (LoB) and LoD of the hs-cTnT assay were determined to be 3 ng/L and 5 ng/L, respectively. The 99th percentile of a healthy reference population was reported at 14 ng/L with an imprecision corresponding to 10% coefficient of variation (CV) at 13 ng/L [31]. Calculation of the glomerular filtration rate was performed using the abbreviated Modification of Diet in Renal disease formula [32].

2.5. Fourteen rapid rule-out strategies

Seven rapid hs-cTn-based strategies were analyzed, each using either hs-cTnT or hs-cTnI. In the ***dual-marker strategy***, combining copeptin and hs-cTn [10,11,18], patients were ruled out if both biomarkers at baseline were below the defined cut-off concentration (9 pmol/L for copeptin, 99th percentile for hs-cTn). While also higher copeptin cut-off concentrations had been suggested in some studies, we chose the lowest cut-off suggested in order to maximize NPV and sensitivity [10,11,17,18]. In the algorithm using ***undetectable levels (<LoD)*** *of hs-cTn* [12,13], the rule-out criterion was fulfilled if hs-cTn at ED presentation was below the LoD (5 ng/L for hs-cTnT and 2 ng/L for hs-cTnI). The ***ESC 0 h/1 h-algorithm*** is based on hs-cTn concentrations at presentation and after 1 h, respective the absolute unsigned change (Δ) at 1 h. A patient was ruled-out if the initial concentration was <5 ng/L (LoD) in patients presenting >3 h after chest pain onset or if <12 ng/L and Δ0–1 h was <3 ng/L irrespective of chest pain onset with hs-cTnT [14], and <2 ng/L (LoD) in patients presenting >3 h after chest pain onset or if <5 ng/L and Δ0–1 h <2 ng/L with hs-cTnI [15,33]. The ***0 h/2 h-algorithm*** for hs-cTnT rules-out if 0 h and 2 h concentrations are <14 ng/L and Δ0–2 h <4 ng/L [16], while when using hs-cTnI, 0 h and 2 h concentrations had to be <6 ng/L and Δ0–2 h <2 ng/L [7]. ***2 h-ADP-algorithm*** combines a TIMI-score of ≤1 with a non-ischemic ECG and normal hs-cTn levels at presentation and 2 h for ruling-out [9,34]. ***The United Kingdom National Institute for Health and Care Excellence (NICE)*** has recently published diagnostic guidance on the use of hs-cTn assays *(NICE DG15)* based on a systematic review of clinical and cost- effectiveness [35]. For hs-cTnT, rule-out of AMI is assumed safe if the 0 h concentration is below the LoB or the 0 h and 2 h concentrations below 99th percentile and the relative change 0 h–2 h <20%. For hs-cTnI, either the 0 h concentration should be below the LoD or 0 h and 3 h concentrations below 99th percentile. Rule-out criterion according to the ***ESC 0/3 h-algorithm*** in early presenting patients (<6 h since chest pain onset) is fulfilled if 0 h and 3 h hs-cTn are below the 99th percentile, patients are pain free and if GRACE-score is <140 [36]. In patients with chest pain onset ≥6 h, a single hs-cTn concentration below the 99th percentile is combined with the need to be pain free and a GRACE-score <140 (Online Suppl., eFigures 2, 3 and 4).

The 14 strategies were applied in all eligible patients in this dataset. Due to different requirements for the 14 strategies (e.g. copeptin measurements for the dual-marker strategy, a 1 h sample for the ESC 0 h/1 h-algorithm, a 2 h sample for the 0 h/2 h-algorithm, a 3 h sample for the ESC 0 h/3 h-algorithm), the final number of patients eligible for respective analyses varied from strategy to strategy. For demonstration of comparability of these subgroups, baseline demographic and clinical findings were compared (eTables 1 and 2) among the patients stratified to the respective strategy.

2.6. Statistical analysis

The baseline data are expressed as medians ± interquartile range (IQR) for continuous variables, and for categorical variables as numbers and percentages. Continuous variables were compared with the Mann-Whitney-*U* test, and categorical variables using the Pearson chi-square test. Baseline characteristics were reported twice to give consideration to the adjudication of final diagnosis using hs-cTnT as well as hs-cTnI. Safety was quantified as the NPV and sensitivity for AMI and MACE at 30 days in the rule-out zone of each rule-out strategy, exact binomial 95% confidence intervals (95% CI) are reported. Efficacy was quantified as the percentage of the overall cohort assigned to the rule-out zone by the respective strategy. Cumulative incidence of MACE at 30 days were assessed by Kaplan-Meier curves and compared with log rank test.

All hypothesis testing was two-tailed and a *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows 23.0 (SPSS Inc., Chicago, USA) and MedCalc 9.6.4.0 (MedCalc software, Mariakerke, Belgium).

3. Results

3.1. Patient characteristics

Between April 2006 and August 2015, 3696 patients eligible for this analysis were enrolled (Online Suppl., Fig. 1S). Baseline characteristics are shown in Tables 1 and 2 for strategies using hs-cTnT and hs-cTnI,

Table 1
Baseline characteristics of patients for strategies using hs-cTnT, final diagnosis adjudicated with hs-cTnT.

Characteristic	all (n = 3696)	AMI (n = 602)	no AMI (n = 3094)	*p*-Value
Age, in years	61 (49–74)	72 (60–80)	59 (47–73)	<0.001
Male gender, n (%)	2508 (67.9)	442 (73.4)	2066 (66.8)	0.001
Risk factors, n (%)				
Hypertension	2272 (61.5)	473 (78.6)	1799 (58.1)	<0.001
Hypercholesterolemia	1799 (48.7)	402 (66.8)	1397 (45.2)	<0.001
Diabetes	631 (17.1)	165 (27.4)	466 (15.1)	<0.001
Current or previous smoking	2310 (62.5)	403 (66.9)	1907 (61.6)	0.02
Family history	1072 (29.0)	186 (30.9)	886 (28.6)	0.3
History, n (%)				
Coronary artery disease	1239 (33.5)	296 (49.2)	943 (30.5)	<0.001
Previous AMI	869 (23.5)	223 (37.0)	646 (20.9)	<0.001
Previous revascularization	1017 (27.5)	233 (38.7)	748 (25.3)	<0.001
Peripheral artery disease	270 (5.6)	77 (12.8)	130 (4.2)	<0.001
Previous stroke	202 (5.5)	55 (9.1)	147 (4.8)	<0.001
ECG findings, n (%)				
Left bundle branch block	71 (1.9)	23 (3.8)	48 (1.6)	<0.001
ST-segment depression	309 (8.4)	159 (26.4)	150 (4.8)	<0.001
T-wave inversion	437 (11.8)	149 (24.8)	288 (9.3)	<0.001
Body-mass index (kg/m^2)	26 (24–30)	26 (24–29)	26 (24–30)	0.8
eGFR	85 (69–101)	74 (56–94)	86 (71–103)	<0.001
Medication at presentation, n (%)				
ASA	1338 (36.2)	303 (50.3)	1035 (33.5)	<0.001
Vitamin-K antagonists	372 (10.1)	67 (11.1)	305 (9.9)	0.3
B-blockers	1265 (34.2)	255 (42.4)	1010 (32.6)	<0.001
Statins	1278 (33.6)	269 (44.7)	1009 (32.6)	<0.001
ACEIs/ARBs	1428 (38.6)	312 (51.8)	1116 (36.1)	<0.001
Calcium antagonists	631 (17.1)	125 (20.8)	506 (16.4)	0.01

Hs-cTnT = high-sensitivity cardiac troponin T; AMI = acute myocardial infarction; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ASA = acetylsalicylic acid; ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Table 2
Baseline characteristics of patients for strategies using hs-cTnI, final diagnosis adjudicated with hs-cTnI.

Characteristic	all (n = 3696)	AMI (n = 582)	no AMI (n = 3114)	*p*-Value
Age, in years	61 (49–74)	72 (59–80)	59 (47–73)	<0.001
Male gender, n (%)	2508 (67.9)	424 (72.9)	2084 (66.9)	0.005
Risk factors, n (%)				
Hypertension	2272 (61.5)	455 (78.2)	1817 (58.3)	<0.001
Hypercholesterolemia	1799 (48.7)	380 (65.3)	1419 (45.6)	<0.001
Diabetes	631 (17.1)	156 (26.8)	475 (15.3)	<0.001
Current or previous smoking	2310 (62.5)	393 (67.5)	1917 (61.6)	0.007
Family history	1072 (29.0)	181 (31.1)	891 (28.6)	0.2
History, n (%)				
Coronary artery disease	1239 (33.5)	285 (49.0)	954 (30.6)	<0.001
Previous AMI	869 (23.5)	217 (37.3)	652 (20.9)	<0.001
Previous revascularization	1017 (27.5)	224 (38.5)	793 (25.5)	<0.001
Peripheral artery disease	270 (5.6)	72 (12.4)	135 (4.3)	<0.001
Previous stroke	202 (5.5)	50 (8.6)	152 (4.9)	0.001
ECG findings, n (%)				
Left bundle branch block	71 (1.9)	22 (3.8)	49 (1.6)	<0.001
ST-segment depression	309 (8.4)	155 (26.6)	154 (4.9)	<0.001
T-wave inversion	437 (11.8)	148 (25.4)	289 (9.3)	<0.001
Body-mass index (kg/m^2)	26 (24–30)	26 (24–29)	26 (24–30)	0.9
eGFR	85 (69–101)	75 (57–94)	86 (71–102)	<0.001
Medication at presentation, n (%)				
ASA	1338 (36.2)	283 (48.6)	1055 (33.9)	<0.001
Vitamin-K antagonists	372 (10.1)	65 (11.2)	307 (9.9)	0.3
b-blockers	1265 (34.2)	246 (42.3)	1019 (32.7)	<0.001
Statins	1278 (33.6)	251 (43.1)	1027 (33.0)	<0.001
ACEIs/ARBs	1428 (38.6)	294 (50.5)	1134 (36.4)	<0.001
Calcium antagonists	631 (17.1)	120 (20.6)	511 (16.4)	0.02

Hs-cTnI = high-sensitivity cardiac troponin I; AMI = acute myocardial infarction; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ASA = acetylsalicylic acid; ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

respectively. AMI was the final diagnosis in 16.3% and 15.7% of patients as adjudicated using hs-cTnT and hs-cTnI respectively. Overall, baseline characteristics were similar among selected patient groups for the respective strategies (Online Suppl., eTables 1 and 2).

3.2. Performance of the seven rule-out strategies using hs-cTnT

The dual-marker strategy with copeptin triaged 48.3% (945/1957) of patients towards rule-out, thereby providing a NPV of 98.7% and a sensitivity of 96.7%, 12 AMI patients being incorrectly ruled-out. The LoD-strategy triaged 26.8% (989/3696) of patients towards rule-out, this resulted in a NPV 99.8% and a sensitivity of 99.7% with two patients with missed AMI. The ESC 0/1 h-algorithm triaged 60.4% (1824/3020) of patients towards rule-out with a NPV of 99.8% and a sensitivity of 99.2%, four patients with AMI were incorrectly assigned to rule-out. Using the 0 h/2 h-algorithm, 64.8% (1603/2473) of patients were triaged towards rule-out with a NPV of 99.9% and a sensitivity of 99.5%, two patients with AMI were missed. Applying the 2 h-ADP-algorithm (efficacy 36.7%, (908/2473)), no patient with AMI was missed, resulting in a NPV and sensitivity of 100%. The NICE-approach triaged towards rule-out 51.6% of patients (1276/2473) with a NPV of 99.8% and a sensitivity of 99.5%, two patients with AMI were missed. The ESC 0/3 h-algorithm triaged towards rule-out 44.6% of patients (851/1908) with a NPV of 99.8% and a sensitivity of 99.4%. Two patients with AMI were incorrectly ruled-out by this strategy. Performance characteristics of the applied strategies are shown in Table 3 and Fig. 1, details of missed patients with the respective strategy are shown in the Online Suppl. eTable 4.

3.3. Performance of the seven rule-out strategies using hs-cTnI

The dual-marker strategy with copeptin triaged 54% of patients (1057/1957) towards rule-out with a NPV of 96.9% and a sensitivity of 90.4%. Thirty-three patients with AMI were incorrectly ruled-out. The LoD-strategy triaged 15.7% of patients (582/3696) towards rule-out with a NPV and sensitivity of 100% with no missed AMI. The ESC 0/1 h-algorithm triaged 51.7% of patients (1522/2945) towards rule-out with a NPV of 99.9% and a sensitivity of 99.8%, one patient with AMI was incorrectly ruled-out. Applying the 0 h/2 h-algorithm and the 2 h-ADP-strategy, 53.2% (1254/2357) and 36.6% (863/2357) of patients were triaged towards rule-out with a NPV and sensitivity of 100% since no patient with AMI was missed by these two strategies. The NICE-algorithm triaged towards rule-out 80% of patients (965/1209) with a NPV of 99.1% and a sensitivity of 94.7%, nine patients with AMI were missed. The ESC 0/3 h-algorithm triaged towards rule-out 54.9% of patients (956/1742) with a NPV of 99.7% and a sensitivity of 98.9%, three patients with AMI were incorrectly ruled-out by this strategy. Performance characteristics of all strategies are shown in Table 3 and Fig. 1, details of missed patients with the respective strategy are shown in the Online Suppl. (eTable 5).

3.4. Prognostic performance of rule-out strategies by 30-day MACE

The incidence of 30-day MACE was low for the patients triaged towards rule-out based on any of the investigated strategies, with an incidence of 30-day MACE ranging from 0.1 to 1.8% using hs-cTnT and from 0% to 3.7% using hs-cTnI (eFigure 5).

Similarly, the incidence of 90-, 360- and 720-day MACE was low for the patients triaged towards rule-out with any of the investigated strategies (eTable 6).

3.5. Subgroup analysis in early presenting patients

A total of 1907 patients (51.6%) presented within 3 h of chest pain onset. Overall, sensitivity and NPV were comparable in early presenters for all 14 strategies as compared to that found in the overall patient populations (eTable 3).

4. Discussion

This large multicenter study directly compared the safety and efficacy of 14 different rapid hs-cTn-based rule-out strategies for AMI to help physicians and institutions in their selection of their preferred option. We report five major findings.

First, all examined hs-cTn-based rapid rule-out strategies, except for the dual-marker strategy using copeptin and the NICE-algorithm using hs-cTnI, provide very high and comparable sensitivity and NPV for AMI, documenting high safety. **Second**, the efficacy of the different hs-cTn-based rapid rule-out strategies as quantified by the percentage of patients triaged towards rule-out varied substantially among the different strategies. It was lowest for the LoD-strategy, and highest for the ESC 0 h/1 h-algorithm, the 0/2 h-algorithm and the NICE-algorithm. **Third**, the incidence of 30-day MACE among patients triaged towards rule-out was very low and comparable among the different strategies. Similarly, the incidence of 90-day and 360-day MACE among patients triaged towards rule-out was low and comparable among the different strategies. **Fourth**, findings in the vulnerable subgroup of early presenters overall were similar to those obtained for the whole cohort for

Table 3
Performance of the 14 different rule-out strategies regarding rule-out of AMI.

	n	AMI, n (%)	Missed AMI, n (%)	Sensitivity (95% CI)	NPV (95% CI)	Efficacy, n (%)
Hs-cTnT						
Copeptin and hs-cTnT	1957	358 (18.3%)	12 (3.4%)	96.7% (94.2–98.1%)	98.7% (97.8–99.3%)	945 (48.3%)
LoD hs-cTnT	3696	602 (16.3%)	2 (0.3%)	99.7% (98.8–100%)	99.8% (99.3–100%)	989 (26.8%)
ESC 0 h/1 h-algorithm	3020	484 (16.0%)	4 (0.8%)	99.2% (97.9–99.8%)	99.8% (99.4–99.9%)	1824 (60.4%)
0 h/2 h-algorithm	2473	364 (14.7%)	2 (0.5%)	99.5% (98.0–99.9%)	99.9% (99.6–100%)	1603 (64.8%)
2 h-ADP-algorithm	2473	358 (14.6%)	0 (0%)	100% (99.0–100%)	100% (99.6–100%)	908 (36.7%)
NICE-algorithm	2473	364 (14.7%)	2 (0.1%)	99.5% (98.0–99.9%)	99.8% (99.4–100%)	1276 (51.6%)
ESC 0 h/3 h-algorithm	1908	313 (16.4%)	2 (0.6%)	99.4% (97.7–99.9%)	99.8% (99.2–100%)	851 (44.6%)
Hs-cTnI						
Copeptin and hs-cTnI	1957	345 (17.6%)	33 (9.6%)	90.4% (86.8–93.3%)	96.9% (95.6–97.8%)	1057 (54.0%)
LoD hs-cTnI	3696	582 (15.7%)	0 (0%)	100% (99.4–100%)	100% (99.4–100%)	582 (15.7%)
ESC 0 h/1 h-algorithm	2945	457 (15.5%)	1 (0.2%)	99.8% (98.8–100%)	99.9% (99.6–100%)	1522 (51.7%)
0 h/2 h-algorithm	2357	337 (14.3%)	0 (0%)	100% (98.9–100%)	100% (99.7–100%)	1254 (53.2%)
2 h-ADP-algorithm	2357	337 (14.3%)	0 (0%)	100% (98.9–100%)	100% (99.6–100%)	863 (36.6%)
NICE-algorithm	1209	169 (14.0%)	9 (0.7%)	94.7% (90.1–97.5%)	99.1% (98.2–99.6%)	965 (80.0%)
ESC 0 h/3 h-algorithm	1742	270 (15.5%)	3 (1.1%)	98.9% (96.8–99.8%)	99.7% (99.0–99.9%)	956 (54.9%)

Hs-cTnT = high-sensitivity cardiac troponin T; Hs-cTnI = high-sensitivity cardiac troponin I; AMI = acute myocardial infarction; LoD = limit of detection; ADP = accelerated diagnostic protocol; NICE = The United Kingdom National Institute for Health and Care Excellence; ESC = European Society of Cardiology; NPV = negative predictive value.

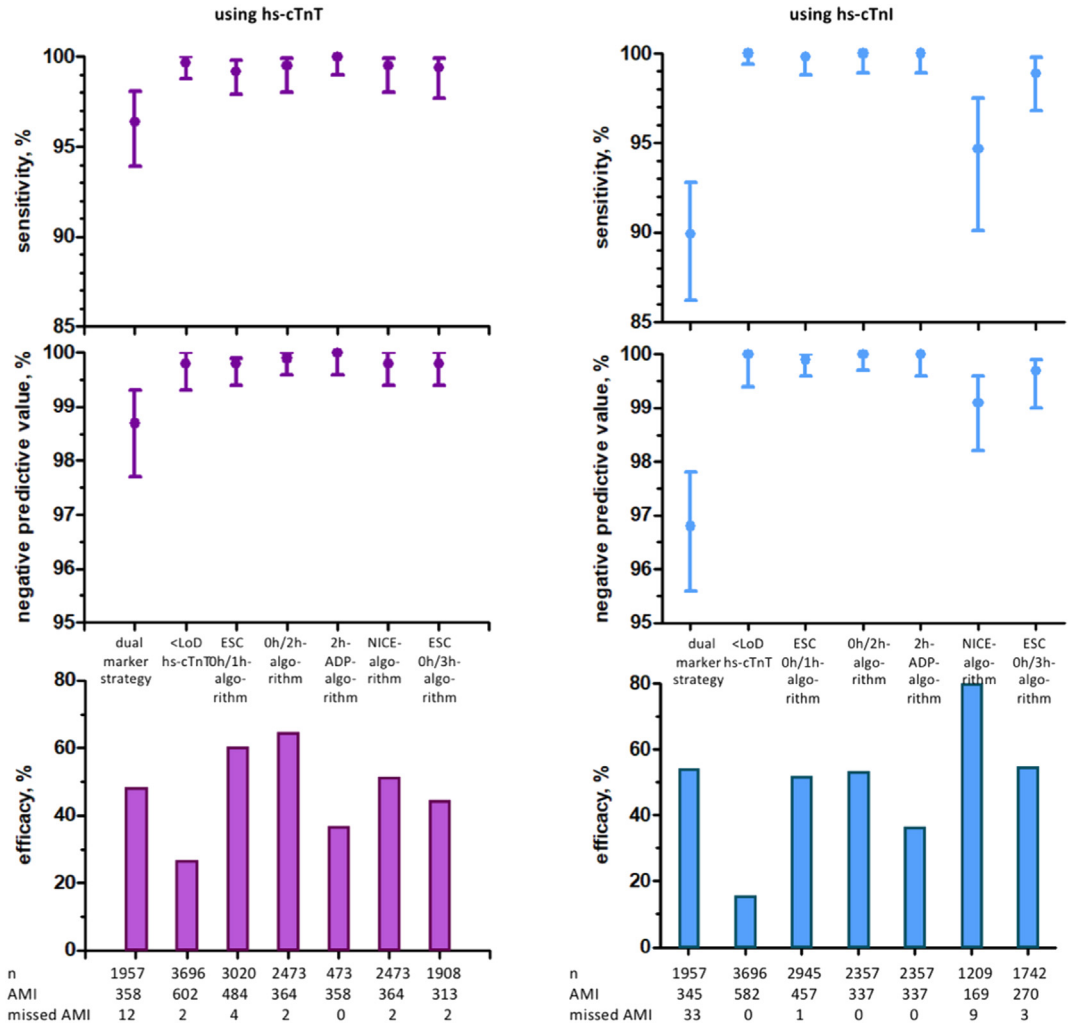

Fig. 1. Sensitivities, negative predictive values and efficacies with the corresponding 95% confidence intervals of the different rule-out strategies using hs-cTnT (left) and hs-cTnI (right).

the different strategies. **Fifth**, no systematic difference was shown between the rule-out strategies according to the applied hs-cTn assay, except for the NICE algorithm, where hs-cTnT performed significantly better than hs-cTnI: 9/169 patients with AMI were missed by using hs-cTnI compared to 2/364 patients by applying hs-cTnT. This difference in performance might be due to a different time definition for the two assays (repeated measurement after 2 h in hs-cTnT and after 3 h in hs-cTnI), the additional relative change criterion recommended in the hs-cTnT strategy, and the biological not equivalence of the cutoffs for hs-cTnT and hs-cTnI [29].

These findings corroborate and extend previous work on the derivation and validation of safe and effective AMI rule-out strategies for patients presenting with symptoms suggestive of AMI to the ED. While the dual-marker strategy and the NICE-algorithm using hs-cTnI were found to have clearly lower safety, and therefore do not seem to be appropriate for routine clinical care, all other hs-cTn-based strategies generally fulfilled the high safety requirements for this important clinical task. Beyond lower safety, the dual-marker strategy has the significant logistic disadvantage of requiring the installation and 24/7-implementation of an additional analyzer in the clinical laboratory, and the need to educate physicians in the clinical use of a relatively incomplete understood biomarker [17].

The availability of multiple different options for both hs-cTnT and hs-cTnI should ensure that interdisciplinary teams from most institutions should be able to agree on the use of one of them. Local preferences may differ in multiple aspects including economic pressure and affinity for risk scores [37]. The higher the economic pressure in an ED, the more likely that even small differences among the examined rapid strategies in the time until availability of the hs-cTn information for clinical decision-making may be of importance. Strategies that mandate the use of specific risk scores (TIMI in the 2 h-ADP and GRACE in the ESC 0 h/3 h-algorithm) may be less attractive in settings, in which the use of these scores is not standard of care in all chest pain patients. Overall, given their very high efficacy and their high feasibility, the ESC 0 h/1 h-algorithm, the 0 h/2 h-algorithm, and the NICE-strategy using hs-cTnT appear as the most attractive options. An additional advantage of the ESC 0 h/1 h-algorithm and the 0/2 h-algorithm is that they also have a rule-in arm that facilitates the early triage towards rule-in and therefore the rapid selection of patients for admission to a monitored unit and early coronary angiography [37].

It is important to highlight that all rule-out algorithms should always be used in conjunction with all available clinical information, including chest pain characteristics, the 12-(or 16-) lead ECG, as well as the physician's expertise and common sense. Including such information may reduce the proportion of patients actually ruled-out. This might affect the hs-cTn-only-based algorithms to a larger extent than the algorithms that already includes some clinical information (e.g. 2 h ADP or ESC 0 h/3 h algorithm). As also clearly stated in current guidelines [4], prolonged monitoring and additional measurements of hs-cTn after 3–6 h is indicated if the first two hs-cTn measurements are not conclusive and the clinical condition is still suggestive of an acute coronary syndrome. If there is clinical suspicion of myocardial ischemia despite

negative initial cardiac biomarkers, serial sampling should be continued since late-risers in hs-cTn have been described in about 1% of patients [38].

Some limitations of this study should be considered when interpreting these findings. **First**, this was a secondary analysis from a large diagnostic multicenter study designed to improve the early diagnosis of AMI. As such, no specific power analysis was performed to justify the current sample size. **Second**, we cannot comment on the performance of rule-out strategies in patients with terminal renal failure [39] since they were excluded. **Third**, as in all real-life studies enrolling consecutive patients, not all data were available in all patients, e.g. for logistic reasons copeptin concentrations had been measured only in the first half of the cohort and not all patients had a study blood draw at 2 h or 3 h. As baseline characteristics were highly comparable among the 14 subgroups, no relevant selection bias was apparent. **Fourth**, we explored the safety and efficacy of rule-out protocols using the two most widely used hs-cTn assays. We assume that similar findings can be expected with other hs-cTn assays, which will become clinically available in the near future. Of course, this assumption has to be tested in future studies. **Fifth**, for all of the analyzed algorithms, a small proportion of the overall cohort (the initially enrolled patients) was used for derivation. As the proportion was low and as all algorithms were affected, the findings related to the direct comparison still remain valid. In addition, this methodological approach was the only one allowing a comparison with the dual-marker strategy, as copeptin concentrations are only available in the first 1957 patients.

In conclusion, all examined rapid rule-out algorithms, except for the dual-marker algorithm and the NICE-algorithm using hs-cTnI, favorably combine safety and efficacy, and can be considered for routine clinical practice.

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Appendix A. Supplementary data

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