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Prospective Validation of the 0/1-h Algorithm for Early Diagnosis of Myocardial Infarction

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ABSTRACT

BACKGROUND The safety of the European Society of Cardiology (ESC) 0/1-h algorithm for rapid rule-out and rule-in of non–ST-segment elevation myocardial infarction (NSTEMI) using high-sensitivity cardiac troponin (hs-cTn) has been questioned.

OBJECTIVES This study aimed to validate the diagnostic performance of the 0/1-h algorithm in a large multicenter study.

METHODS The authors prospectively enrolled unselected patients in 6 countries presenting to the emergency department with symptoms suggestive of NSTEMI. Final diagnosis was centrally adjudicated by 2 independent cardiologists. Hs-cTnT and hs-cTnI blood concentrations were measured at presentation and after 1 h. Safety of rule-out was quantified by the negative predictive value (NPV) for NSTEMI, accuracy of rule-in by the positive predictive value (PPV), and overall efficacy by the proportion of patients triaged towards rule-out or rule-in within 1 h.

RESULTS Prevalence of NSTEMI was 17%. Among 4,368 patients with serial hs-cTnT measurements available, safety of rule-out (NPV 99.8%, 2,488 of 2,493), accuracy of rule-in (PPV 74.5%, 572 of 768), and overall efficacy were high by assigning three-fourths of patients either to rule-out (57%, 2,493 to 4,368) or rule-in (18%, 768 to 4,368). Similarly, among 3,500 patients with serial hs-cTnI measurements, safety of rule-out (NPV 99.7%, 1,528 of 1,533), accuracy of rule-in (PPV 62.3%, 498 of 800), and overall efficacy were high by assigning more than two-thirds of patients either to rule-out (44%, 1,533 of 3,500) or rule-in (23%, 800 of 3,500). Excellent safety was confirmed in multiple subgroup analyses including patients presenting early (≤3 h) after chest pain onset.

CONCLUSIONS The ESC 0/1-h algorithm using hs-cTnT and hs-cTnI is very safe and effective in triaging patients with suspected NSTEMI. (Advantageous Predictors of Acute Coronary Syndromes Evaluation [APACE]; NCT00470587; and Biomarkers in Acute Cardiac Care [BACC]; NCT02355457) (J Am Coll Cardiol 2018;72:620–32)

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Patients with symptoms suggestive of myocardial infarction (MI) account for about 10% of all emergency department (ED) consultations (1). Rapid identification of MI as a life-threatening disorder is important for the early initiation of appropriate, evidence-based, and effective therapy (2,3). Rapid and safe rule-out of MI is also of major medical and economic importance because it allows the timely detection and treatment of alternative causes of acute chest pain and possible early discharge for outpatient management (2,3).

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Electrocardiography (ECG) and cardiac troponin (cTn) form the diagnostic cornerstones for MI and complement clinical assessment (2–4). The clinical introduction of high-sensitivity cardiac troponin (hs-cTn) assays has allowed the development of more rapid triage algorithms, including the European Society of Cardiology (ESC) 0/1-h algorithm (2–15). The ESC hs-cTn 0/1-h algorithm, which should always be used in conjunction with all other clinical information including clinical assessment and the ECG, uses assay-specific cutoff levels for hs-cTnT and hs-cTnI derived from dedicated diagnostic studies to triage patients very early to either rule-out or rule-in of MI (2–15).

Recently, concern has been articulated that this algorithm has not been prospectively validated in a large study, that previous studies had not included a sufficient number of early presenters (≤3 h after chest pain onset) to ensure safety particularly in this vulnerable subgroup and that the performance characteristics of the ESC 0/1-h algorithm may not be sufficient for routine clinical application (12,16). We therefore aimed to validate the ESC 0/1-h algorithm in a large multicenter diagnostic study with a high number of early presenters.

METHODS

STUDY DESIGN AND POPULATION. This analysis combined pooled patient-level data from 2 large diagnostic studies with no study-specific interventions to maximize generalizability and particularly the number of early presenters: first, the APACE (Advantageous Predictors of Acute Coronary Syndrome Evaluation; NCT00470587) study, which is an ongoing prospective international multicenter study with 12 centers in 5 European countries (Switzerland, Italy, Spain, Poland, and Czech Republic) designed to contribute to advancing the early diagnosis of MI (5–7,13,17–21); and second, the BACC (Biomarkers in Acute Cardiac Care; NCT02355457) study, which is an ongoing prospective single-center study performed by the University Heart Center Hamburg, Germany (5–8,13,14). Adult patients presenting to the ED with symptoms suggestive of MI such as acute chest discomfort and/or angina pectoris were recruited after written informed consent was obtained. In both

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
cTn = cardiac troponin
ECG = electrocardiography
ED = emergency department
ESC = European Society of Cardiology
hs-cTn = high-sensitivity cardiac troponin
LR = likelihood ratio
MACE = major adverse cardiac event
MI = myocardial infarction
NPV = negative predictive value
NRI = net reclassification improvement
NSTEMI = non-ST-segment elevation myocardial infarction
PPV = positive predictive value
UA = unstable angina

Research and an unrestricted grant from Abbott Diagnostics. The investigated high-sensitivity cardiac troponin T and I assays were partly donated by Roche and Abbott, who had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication. Dr. Twerenbold has received research support from the Swiss National Science Foundation (P300PB_167803), the Swiss Heart Foundation, the University Hospital of Basel, the University of Basel, and the Cardiovascular Research Foundation Basel; and speaker honoraria/consulting honoraria from Roche Diagnostics, Abbott Diagnostics, Siemens, Singulex, Thermo Scientific, and Brahms. Dr. Neumann was supported by a grant from the German Heart Foundation/German Foundation of Heart Research and the Else Kröner Fresenius Stiftung; and has received consulting honoraria from Acarix. Dr. Rubini Giménez has received speaker honoraria from Abbott. Dr. Boeddinghaus has received speaker honoraria/consulting honoraria from Siemens. Dr. Wildi has received research funding from FAG Basel and the Gottfried and Julia Bangerter-Rhyner Foundation. Dr. Reichlin has received research grants from the Goldschmidt-Jacobson-Foundation, the Swiss National Science Foundation (PASMP3-136995), the Swiss Heart Foundation, the Professor Max Cloëtta Foundation, the Uniscientia Foundation Vaduz, the University of Basel, and the Department of Internal Medicine, University Hospital Basel; and has received speaker honoraria from Brahms and Roche. Dr. Blankenberg has received research funding from Abbott Diagnostics, Bayer, Boehringer Ingelheim, Siemens, Singulex, and Thermo Fisher; has received consulting honoraria from Bayer, Thermo Fisher, Roche Diagnostics, and Novartis; has received speaker honoraria from Abbott Diagnostics, Bayer, Boehringer Ingelheim, Siemens, Thermo Fisher, AstraZeneca, Medtronic, Pfizer, and Roche Diagnostics; and has served on advisory boards for Bayer, Boehringer Ingelheim, Thermo Fisher, Roche Diagnostics, and Novartis. Dr. Mueller has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the KTI, the European Union, the Stiftung für Kardiovaskuläre Forschung Basel, Abbott, Alere, AstraZeneca, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, Singulex, Sphingotec, and the Department of Internal Medicine, University Hospital Basel; and has received speakers/consulting honoraria from Abbott, Alere, AstraZeneca, Biomerieux, Boehringer Ingelheim, BMS, Brahms, Cardiorentis, Novartis, Roche, Siemens, and Singulex. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The hs-cTnI and hs-cTnT assays were donated by Roche and Abbott, who had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

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TABLE 1 Baseline Characteristics of the Patients in the Diagnostic Dataset A

	All Patients (N = 4,368)	NSTEMI (n = 735)	No NSTEMI (n = 3,633)	p Value
Age, yrs	62 (50–74)	71 (60–79)	60 (48–73)	<0.001
Male	2,921 (67)	528 (72)	2,393 (66)	0.002
Risk factors				
Hypertension	2,739 (63)	572 (78)	2,167 (60)	<0.001
Hypercholesterolemia	1,988 (46)	438 (60)	1,550 (43)	<0.001
Current smoking	1,069 (24)	181 (25)	888 (24)	0.916
History of smoking	1,541 (35)	289 (39)	1,252 (34)	0.012
History				
Coronary artery disease	1,459 (33)	340 (46)	1,119 (31)	<0.001
Previous MI	919 (21)	237 (32)	682 (19)	<0.001
Peripheral artery disease	236 (5)	81 (11)	155 (4)	<0.001
Previous stroke	258 (6)	50 (7)	208 (6)	0.259
ECG findings				
ST-segment depression	339 (8)	167 (23)	172 (5)	<0.001
T-wave inversion	373 (9)	100 (14)	273 (8)	<0.001
No significant ECG changes	3,539 (81)	438 (60)	3,101 (85)	<0.001
Chest pain characteristics				
Early presenters (≤3 h after CPO)	1,322 (30)	223 (30)	1,099 (30)	0.962
Hours since chest pain onset*	5.0 (2.0–14.0)	5.5 (2.0–13.0)	5.0 (2.0–14.0)	0.741
Hours since chest pain peak*	3.0 (1.5–6.5)	3.0 (2.0–8.0)	3.0 (1.5–6.0)	0.025
Pressure-like chest pain*	1,924 (67)	338 (76)	1,586 (66)	<0.001
Radiating chest pain*	1,694 (59)	289 (65)	1,405 (58)	0.009
Duration >30 min*	1,782 (62)	273 (61)	1,509 (63)	0.596
Vital signs				
Heart frequency, beats/min	77 (66–89)	80 (68–92)	76 (66–88)	<0.001
Systolic blood pressure, mm Hg	143 (128–159)	145 (128–161)	142 (128–158)	0.055
Diastolic blood pressure, mm Hg	81 (72–91)	81 (71–92)	82 (73–91)	0.595
Body mass index, kg/m^2	26 (23–29)	27 (24–29)	26 (23–29)	0.017
Creatinine clearance, ml/min/1.73 m^2	85 (66–99)	72 (53–89)	87 (70–101)	<0.001
Long-term medication				
ASA	1,561 (36)	360 (49)	1,201 (33)	<0.001
Anticoagulant agents	526 (12)	94 (13)	432 (12)	0.495
B-blockers	1,577 (36)	322 (44)	1,255 (35)	<0.001
Statins	1,498 (34)	321 (44)	1,177 (32)	<0.001
ACE inhibitors/ARBs	1,789 (41)	392 (53)	1,397 (38)	<0.001
Calcium antagonists	660 (15)	145 (10)	515 (14)	<0.001
Nitrates	390 (9)	101 (14)	289 (8)	<0.001

Values are median (interquartile range) or n (%). Creatinine clearance was calculated using CKD-EPI (chronic kidney disease epidemiology collaboration) formula. *Detailed chest pain characteristics only available in the APACE study.

ASA = acetylsalicylic acid; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CPO = chest pain onset; ECG = electrocardiogram; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction.

studies, enrollment was independent of renal function, whereas patients with terminal kidney failure on chronic dialysis were excluded in the APACE study. Each study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees.

Patients presenting with ST-segment elevation myocardial infarction were excluded. The assay-specific hs-cTnT and hs-cTnI cutoff criteria of the investigated ESC 0/1-h algorithm were originally derived in 2 small subsets of the contributing APACE study. The present analyses include all patients enrolled in the APACE study, with the exception of those patients that contributed to the derivation of the ESC 0/1-h hs-cTnT or ESC 0/1-h hs-cTnI algorithm, and all patients enrolled in the BACC study.

From all the prospectively recruited patients, 2 diagnostic datasets were constructed: diagnostic dataset A with complete serial hs-cTnT measurements (0-h and 1-h samples) and diagnostic dataset B with complete serial hs-cTnI measurements. The most common reasons for missing samples after 1 h were early transfer to the catheter laboratory or coronary care unit and diagnostic procedures around the 1-h window that precluded blood draw at 1 h (Online Figure 1).

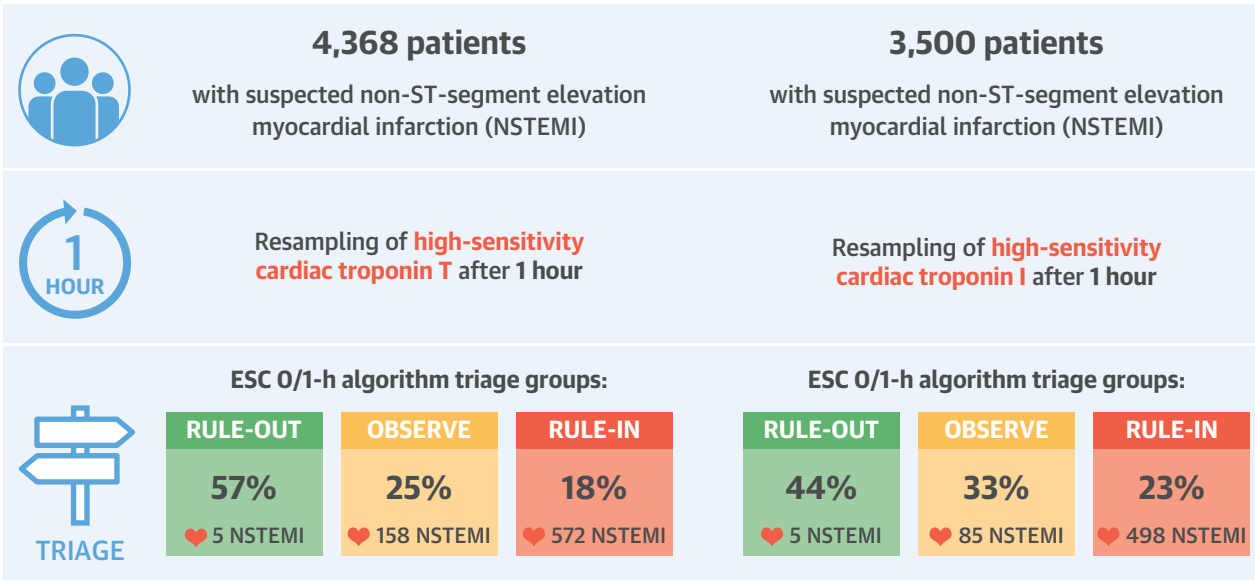
For the prognostic analyses, a common prognostic dataset was constructed with complete serial measurements of hs-cTnT and hs-cTnI. The authors designed the studies, gathered, and analyzed the data according to the STARD guidelines for studies of diagnostic accuracy (22) (Online Table 1), vouched for the data and analysis, wrote the paper, and decided to publish.

ROUTINE CLINICAL ASSESSMENT. Patients underwent clinical assessment that included medical history, physical examination, standard blood test including serial measurements of local (hs)-cTn, 12-lead ECG, chest radiography (if requested), continuous ECG rhythm monitoring, and pulse oximetry. Management of patients was left to the discretion of the attending physician.

ADJUDICATED FINAL DIAGNOSIS. Adjudication of the final diagnosis was performed centrally in each study by 2 independent cardiologists in a dedicated core laboratory applying the universal definition of MI (23) using all available medical records obtained during clinical care including history, physical examination, results of laboratory testing including serial levels of hs-cTnT, 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 30-day follow-up for patients in the BACC study and 90-day follow-up for patients in the APACE study. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

MI was defined and cTn interpreted as recommended in the current guidelines (1–3,24). In brief, MI was diagnosed when there was evidence of myocardial necrosis in association with a clinical

CENTRAL ILLUSTRATION **Performance of the European Society of Cardiology (ESC) 0/1-h Algorithm**



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Diagnostic performance of the ESC 0/1-h algorithm using high-sensitivity cardiac troponin T **(left)** and I **(right)** based on serial blood sampling after 1 h.

setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least 1 cTn value above the 99th percentile together with a significant rising and/or falling. The criteria used to define a rise and/or fall in cTn and the cTn assays available for the adjudication are described in detail in the Methods section in the Online Appendix. All other patients were classified in the categories of unstable angina (UA), stable angina (in the BACC study only; in the APACE study, the chest pain episode leading to ED presentation was adjudicated to either UA, if ischemic and not fulfilling criteria for MI, or noncardiac, if nonischemic), noncardiac chest pain, cardiac but noncoronary disease (e.g., tachyarrhythmias, perimyocarditis, Takotsubo cardiomyopathy, heart failure), and symptoms of unknown origin with normal levels of cTn.

MEASUREMENTS OF HS-cTnT AND HS-cTnI. Blood samples (plasma and serum) were collected at the time of the patient's presentation to the ED and after 1 h. Levels of hs-cTnT were determined on the Elecsys (Roche Diagnostics, Rotkreuz, Switzerland) and levels of hs-cTnI on the Architect (STAT hs-cTnI, Abbott Laboratories, Lake Bluff, Illinois) analyzers (Online Appendix).

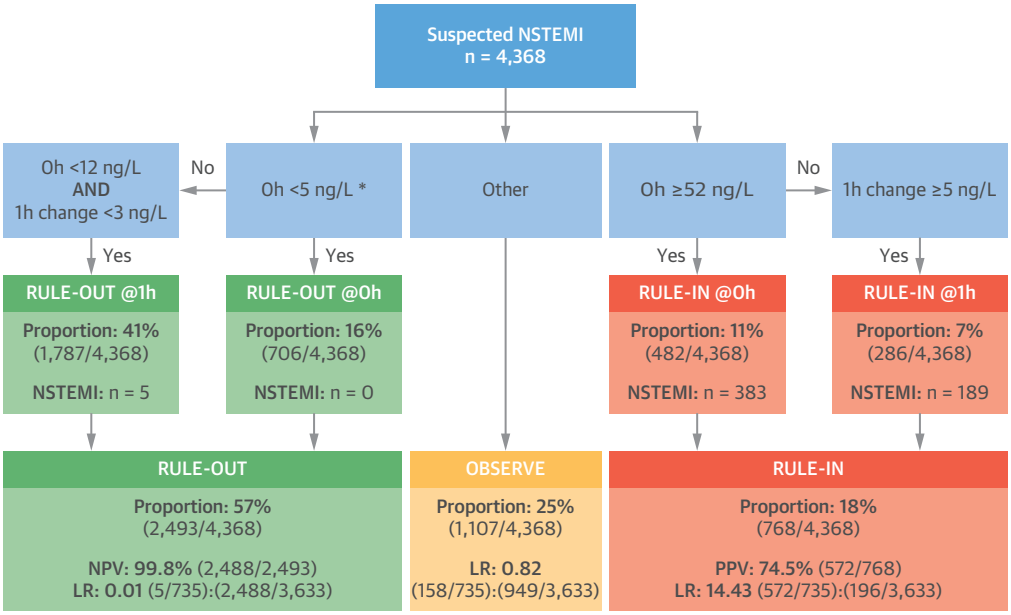
ESC 0/1-H ALGORITHM. The ESC 0/1-h algorithm, which should always be used in conjunction with all clinical information available including the ECG and clinical assessment, triages patients presenting with suspected non-ST-segment elevation myocardial infarction (NSTEMI) very early toward rule-out, observe and rule-in based on assay-specific levels of hs-cTn obtained at presentation and after 1 h (Online Figure 2) (2). The specific cutoff levels of hs-cTnT and hs-cTnI had been derived in previous diagnostic studies (2,3,5–15).

FOLLOW-UP. Patients were contacted 1, 3, and 12 months after discharge by telephone calls or in written form. Additionally, information regarding death during follow-up was obtained from the patient's hospital notes, the family physician's records, and the national registry on mortality.

OUTCOME MEASURES. The primary diagnostic endpoint was NSTEMI (type 1 and 2) at presentation to the ED, whereas type 1 NSTEMI was the secondary diagnostic endpoint. The primary prognostic endpoint was overall mortality at 30 days and 1 year, whereas the secondary prognostic endpoint was a major adverse cardiac event (MACE), defined as the composite of overall mortality and MI (including the

FIGURE 1 Diagnostic Performance of the ESC 0/1-h Algorithm Using hs-cTnT

Disease \ Triage	RULE-OUT All (@0h)	OBSERVE All	RULE-IN All (@0h)	Total
no NSTEMI	2,488 (706)	949	196 (99)	3,633
NSTEMI	5 (0)	158	572 (383)	735
Total	2,493 (706)	1,107	768 (482)	4,368



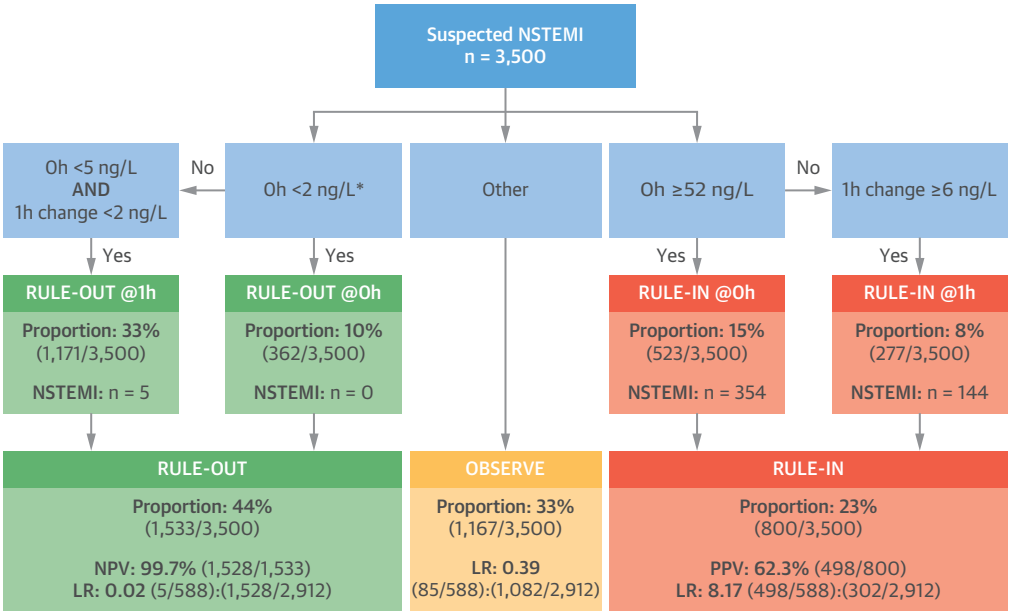
A 2 × 3 table and flow chart depicting the diagnostic performance of the European Society of Cardiology (ESC) 0/1-h algorithm for rapid rule-out and rule-in of myocardial infarction among patients presenting with suspected non-ST-segment elevation myocardial infarction (NSTEMI) using high-sensitivity cardiac troponin T (hs-cTnT) (Elecsys) in diagnostic dataset A. **Counts in parentheses** in the 2 × 3 table indicate the number of patients directly triaged based on the 0-h blood sample (@0h), only. *If chest pain onset >3 h before ED presentation. 1h change = absolute (unsigned) change of high-sensitivity cardiac troponin within the first hour; ED = emergency department; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

index event), at 30 days and 1 year. Rule-out safety of the ESC 0/1-h algorithm was quantified by the negative predictive value (NPV) and likelihood ratio (LR) for NSTEMI in the rule-out group. Accuracy of rule-in, which aims to identify patients eligible for early coronary angiography, was quantified by the positive predictive value (PPV) and LR for NSTEMI in the rule-in group. Efficacy of the ESC 0/1-h algorithm was quantified by the proportion of patients triaged to either rule-out or rule-in. Given previous evidence suggesting suboptimal performance of other rapid rule-out approaches in patients presenting to the ED early (≤3 h) after chest pain onset (21,25), subgroup analysis in this vulnerable group of early presenters was pre-defined. Additional pre-defined subgroup analyses were performed according to sex, age older than 65 years, pre-existing coronary artery disease (CAD), renal dysfunction (defined as glomerular filtration rate <60 ml/min/1.73m^2), and contributing study cohort.

STATISTICAL ANALYSIS. Because the ESC 0/1-h algorithm contains 3 triage categories (rule-out/observe/rule-in), 2 × 3 tables were constructed to assess its diagnostic performance. All diagnostic performance measures (proportions, predictive values, and LR for NSTEMI in the 3 triage categories) were derived from these 2 × 3 tables as described in detail in Online Figure 3. Mortality and MACE during follow-up were analyzed using Kaplan-Meier survival curves. Net reclassification improvement (NRI) analysis was used to compare the ability of the ESC hs-cTnT and the hs-cTnI 0/1-h algorithms to correctly

FIGURE 2 **Diagnostic Performance of the ESC 0/1-h Algorithm Using hs-cTnI**

Disease \ Triage	RULE-OUT All	RULE-OUT (@0h)	OBSERVE All	RULE-IN All	RULE-IN (@0h)	Total
no NSTEMI	1,528	(362)	1,082	302	(169)	2,912
NSTEMI	5	(0)	85	498	(354)	588
Total	1,533	(362)	1,167	800	(523)	3,500



A 2 × 3 table and flow chart depicting the diagnostic performance of the ESC 0/1-h algorithm for rapid rule-out and rule-in of myocardial infarction among patients presenting with suspected NSTEMI using high-sensitivity cardiac troponin I (hs-cTnI) (Architect) in diagnostic dataset B. **Counts in parentheses** in the 2 × 3 table indicate number of patients directly triaged based on the 0-h blood-sample (@0h), only. *If chest pain onset >3 h before ED presentation. Abbreviations as in Figure 1.

classify patients according to risk of 1-year mortality and incidence of MACE. Further details on the statistical analysis can be found in the Methods section of the Online Appendix.

RESULTS

CHARACTERISTICS OF PATIENTS. From May 2006 to April 2016, 5,856 patients with suspected MI were recruited in 6 European countries. After exclusion of 234 patients presenting with ST-segment elevation myocardial infarction and patients that were part of the original hs-cTnT or hs-cTnI cutoff derivation of the ESC 0/1-h algorithms, 4,368 patients with serial samples of hs-cTnT (diagnostic dataset A) and 3,500 patients with serial samples of hs-cTnI (diagnostic dataset B) were eligible for this analysis (Online Figure 1, **Table 1**). There was an overlap of 3,468 patients with both hs-cTnT and hs-cTnI 0/1-h samples available used for comparison of prognostic performance of hs-cTn (common prognostic dataset).

Thirty percent of patients were early presenters (≤3 h after chest pain onset), and 30% were admitted to the ED by ambulance. Baseline characteristics of the 2 contributing studies were clinically comparable, but differed statistically in various baseline characteristics, representing an international real-world clinical scenario (Online Table 2). Clinical assessment included a conventional, less sensitive cTn assay in 25%, a sensitive cTn assay in 2%, and a hs-cTn assay in 73%.

ADJUDICATED FINAL DIAGNOSIS. The adjudicated final diagnosis was NSTEMI in 735 of 4,368 patients (17%), UA in 462 of 4,368 (11%), stable angina in 16 of 4,368 (0.4%), cardiac symptoms of origin other than

TABLE 2 Diagnostic Performance of the ESC 0/1-h Algorithm According to Time Between CPO and First Blood Draw

	Time Since CPO	N		Triage Group: Rule-Out All (Direct)	Triage Group: Observe All	Triage Group: Rule-In All (Direct)	Proportion Rule-Out
Hs-cTnT							
All patients	Any	4,368	No NSTEMI	2,488 (706)	949	196 (99)	57 (2,493/4,368)
			NSTEMI	5 (0)	158	572 (383)	
Late presenters	>3 h	3,046	No NSTEMI	1,712 (706)	693	129 (75)	56 (1,713/3,046)
			NSTEMI	1 (0)	133	398 (310)	
Early presenters	≤3 h	1,322	No NSTEMI	776 (n.a.)	256	67 (24)	59 (780/1,322)
			NSTEMI	4 (n.a.)	45	174 (73)	
Very early presenters	<2 h	564	No NSTEMI	360 (n.a.)	87	26 (8)	64 (362/564)
			NSTEMI	2 (n.a.)	21	68 (23)	
Extremely early presenters	<1 h	193	No NSTEMI	125 (n.a.)	29	8 (3)	65 (125/193)
			NSTEMI	0 (n.a.)	3	28 (7)	
Hs-cTnI							
All patients	Any	3,500	No NSTEMI	1,528 (362)	1,082	302 (169)	44 (1,533/3,500)
			NSTEMI	5 (0)	85	498 (354)	
Late presenters	>3 h	2,436	No NSTEMI	1,043 (363)	764	225 (132)	43 (1,045/2,436)
			NSTEMI	2 (0)	56	346 (289)	
Early presenters	≤3 h	1,064	No NSTEMI	485 (n.a.)	318	77 (37)	46 (488/1,064)
			NSTEMI	3 (n.a.)	29	152 (65)	
Very early presenters	<2 h	443	No NSTEMI	223 (n.a.)	117	33 (15)	50 (223/443)
			NSTEMI	0 (n.a.)	11	59 (23)	
Extremely early presenters	<1 h	171	No NSTEMI	78 (n.a.)	58	9 (1)	46 (78/171)
			NSTEMI	0 (n.a.)	3	23 (5)	

Values are % (n/N) except as noted otherwise.

Direct = counts of patients applicable for direct triage toward rule-out or rule-in based on the 0-h blood sample only; LR = likelihood ratio; n.a. = not applicable; NPV = negative predictive value; PPV = positive predictive value; All = counts of patients triaged based on the 0-h AND 1-h blood samples; other abbreviations as in Table 1.

Continued on the next page

CAD, such as tachyarrhythmia, Takotsubo cardiomyopathy, heart failure, or myocarditis, in 814 of 4,368 (19%), noncardiac symptoms in 2,226 of 4,368 (51%), and unknown in 115 of 4,368 patients (3%). Among the 735 patients presenting with NSTEMI, 572 (78%) were diagnosed as having type 1 NSTEMI.

Discrepancies between the discharge diagnosis by the treating physician and the adjudicated final diagnosis of NSTEMI were present in 5.7% of patients (250 of 4,368).

BLOOD CONCENTRATIONS OF HS-cTnT AND HS-cTnI. At ED presentation, concentrations of hs-cTnT and hs-cTnI were significantly higher in patients with NSTEMI (median 55.0 ng/l and 93.6 ng/l, respectively) as compared with patients with other final diagnoses (median 7.0 ng/l and 4.0 ng/l, respectively; $p < 0.001$ for comparisons). Similarly, absolute 1-h changes were higher in patients with NSTEMI as compared to patients with other final diagnoses for both hs-cTn assays (median absolute 1-h change: 10.0 ng/l and 35.2 ng/l versus 1.0 ng/l and 0.7 ng/l, respectively; $p < 0.001$ comparisons). Median time between the first and second blood draw for serial hs-cTn measurement was 60 min (interquartile range: 59 to 68 min) with 90% of all samples collected within 46 to 84 min after the first blood draw.

DIAGNOSTIC PERFORMANCE OF THE ESC 0/1-H ALGORITHM USING HS-cTnT. The concept and condensed diagnostic performance of the ESC 0/1-h algorithm using hs-cTnT and hs-cTnI are visualized in the Central Illustration.

Using hs-cTnT, the ESC 0/1-h algorithm triaged 57% of patients (2,493 of 4,368) toward rule-out (Figure 1). Direct rule-out based on 0-h hs-cTnT-concentrations <5 ng/l was feasible in 16% of patients (706 of 4,368), missing no NSTEMI (NPV 100.0% [706 of 706]). Overall, safety of rule-out was very high (NPV 99.8% [2,488 of 2,493]; LR 0.01 [(5 of 735):(2,488 of 3,633)]).

Rule-in was feasible in 18% of patients (768 of 4,368) with appropriate accuracy (PPV 74.5%, [572 of 768], LR 14.43 [(572 of 735):(196 of 3,633)]). Takotsubo cardiomyopathy, myocarditis, heart failure, and UA accounted for 36% of non-MI diagnosis in the rule-in group.

Overall efficacy was high allowing rule-out or rule-in based on the 0-h and 1-h hs-cTnT samples in 75% of patients (3,261 of 4,368). Baseline characteristics

TABLE 2 Continued

Proportion Direct Rule-Out	NPV Rule-Out	LR Rule-Out	Proportion Rule-In	Proportion Direct Rule-In	PPV Rule-In	LR Rule-In	Proportion Rule-Out or Rule-In
16 (706/4,368)	99.8 (2,488/2,493)	0.010 (5/735):(2,488/3,633)	18 (768/4,368)	11 (482/4,368)	74.5 (572/768)	14.43 (572/735):(196/3,633)	75 (3,261/4,368)
23 (706/3,046)	99.9 (1,712/1,713)	0.003 (1/512):(1,712/2,534)	17 (527/3,046)	13 (385/3,046)	75.5 (398/527)	15.27 (398/512):(129/2,534)	74 (2,240/3,046)
n.a.	99.5 (776/780)	0.025 (4/223):(776/1,099)	18 (241/1,322)	7 (97/1,322)	72.2 (174/241)	12.80 (174/223):(67/1,099)	77 (1,021/1,322)
n.a.	99.4 (360/362)	0.029 (2/91):(360/473)	17 (94/564)	5 (31/564)	72.3 (94/564)	13.59 (68/91):(26/473)	81 (456/564)
n.a.	100.0 (125/125)	0.000 (0/31):(125/165)	19 (36/193)	5 (10/193)	77.8 (28/36)	18.29 (28/31):(8/162)	83 (161/193)
10 (362/3,500)	99.7 (1,528/1,533)	0.016 (5/588):(1,528/2,912)	23 (800/3,500)	15 (523/3,500)	62.3 (498/800)	8.17 (498/588):(302/2,912)	67 (2,333/3,500)
15 (363/2,436)	99.8 (1,043/1,045)	0.010 (2/404): (1,043/2,032)	23 (571/2,436)	17 (421/2,436)	60.6 (346/571)	7.73 (346/404):(225/2,032)	66 (1,616/2,436)
n.a.	99.4 (485/488)	0.030 (3/184):(485/880)	22 (229/1064)	10 (102/1,064)	66.4 (152/229)	9.44 (152/184):(77/880)	67 (717/1,064)
n.a.	100.0 (223/223)	0.000 (0/70): (223/373)	21 (92/443)	9 (38/443)	64.1 (59/92)	9.53 (59/70):(33/373)	71 (315/443)
n.a.	100.0 (78/78)	0.000 (0/26):(78/145)	19 (32/171)	4 (6/171)	71.9 (23/32)	14.25 (23/26):(9/145)	64 (110/171)

and treatment characteristics of patients assigned to rule-out, observe, and rule-in are listed in Online Tables 3 and 4. Invasive management and administration of cardiovascular medication was substantially more frequent in the rule-in group as compared with the rule-out group. Details on the 5 NSTEMI patients (0.1%) incorrectly ruled out by the ESC 0/1-h algorithm are listed in Online Table 5.

DIAGNOSTIC PERFORMANCE OF THE ESC 0/1-H ALGORITHM USING HS-cTnI. Using hs-cTnI, the ESC 0/1-h algorithm triaged 44% of patients (1,533 of 3,500) toward rule-out (**Figure 2**). Direct rule-out based on 0-h hs-cTnI concentrations <2 ng/l was feasible in 10% of patients (362 of 3,500), missing no NSTEMI (NPV 100.0% [362 of 362]). Overall, safety of rule-out was very high (NPV 99.7% [1,528 of 1,533]; LR 0.02 [(5 of 588):(1,528 of 2,912)]).

Rule-in was feasible in 23% of patients (800 of 3,500) with appropriate accuracy (PPV 62.3%, [498 of 800]; LR 8.17 [(498 of 588):(302 of 2,912)]). Takotsubo cardiomyopathy, myocarditis, heart failure, and UA accounted for 34% of non-MI diagnosis in the rule-in group.

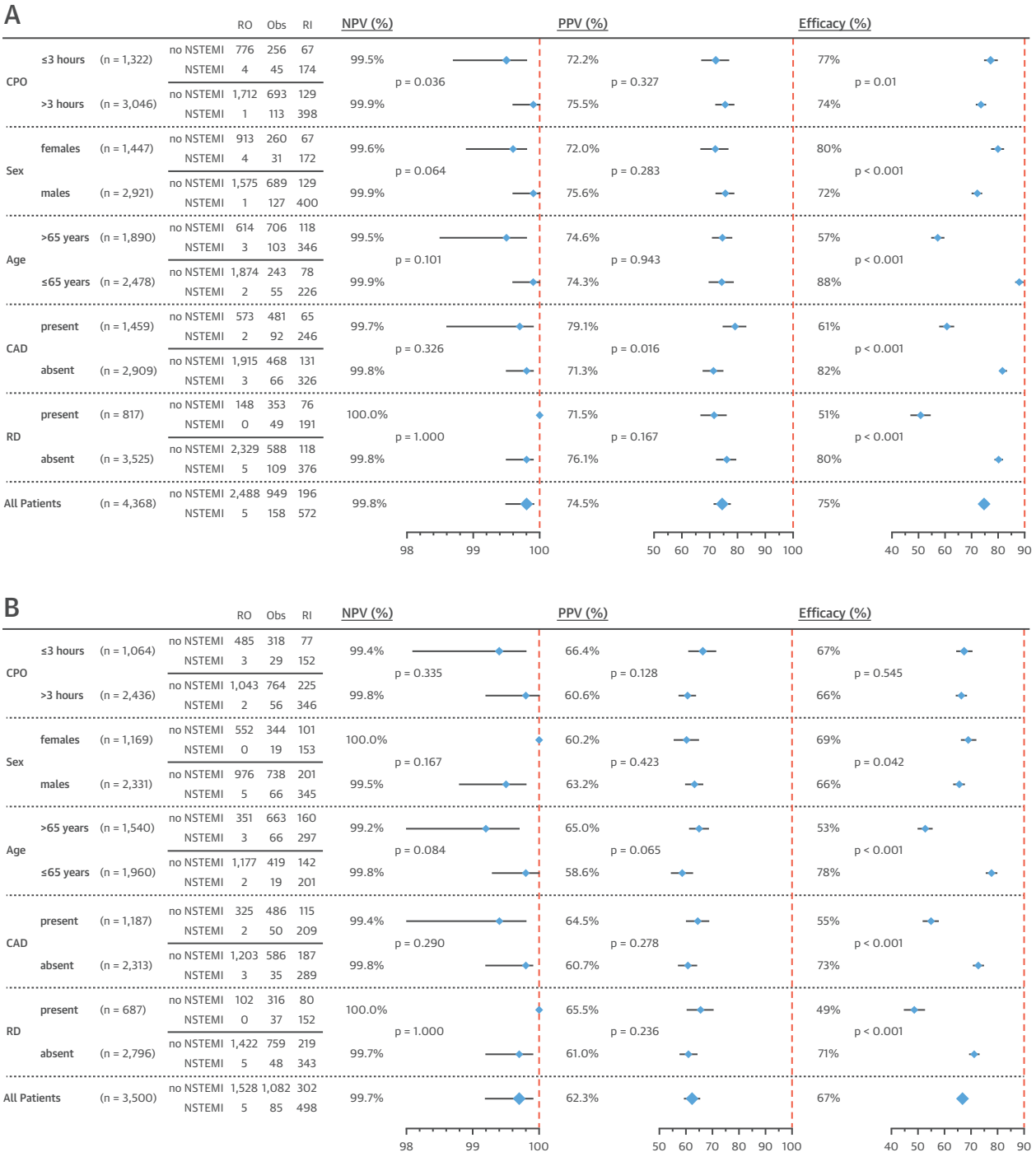
Overall efficacy was high, allowing rule-out or rule-in based on the 0-h and 1-h hs-cTnI samples in 67% of patients (2,333 of 3,500). Baseline characteristics and treatment characteristics of patients assigned to rule-out, observe, and rule-in are listed in Online Tables 6 and 7. Details on the 5 NSTEMI patients (0.1%) incorrectly ruled out by the ESC 0/1-h algorithm are listed in Online Table 8.

SUBGROUP ANALYSIS. Early presenters. In patients presenting to the ED early after chest pain onset, for example, within 3 h (i.e., early presenters; 1,322 of 4,368 in diagnostic dataset A, 1,064 of 3,500 in diagnostic dataset B), rule-out safety and rule-in accuracy of the ESC 0/1-h algorithm were similar to those observed in late presenters for both hs-cTnT and hs-cTnI (**Table 2, Figure 3**).

Other subgroups. Additional subgroup analyses according to sex, age, presence of CAD, and renal dysfunction confirmed very high and comparable rule-out safety and rule-in accuracy, whereas differences in overall efficacy could be observed. High performance of the ESC 0/1-h algorithm was confirmed in both contributing study cohorts (Online Table 9).

DIAGNOSTIC PERFORMANCE FOR THE DIAGNOSIS OF TYPE 1 NSTEMI ONLY. For the diagnosis of type 1 NSTEMI only, rule-out safety of the ESC 0/1-h algorithm, as quantified by the NPV and LR, was very high and tended to be even higher as compared with the

FIGURE 3 Subgroup Analyses on the ESC 0/1-h Algorithm's Performance



Forest plots indicating safety of rule-out, quantified by the NPV for NSTEMI, accuracy of rule-in, quantified by the PPV, and overall efficacy, quantified by the proportion of patients triaged to rule-out or rule-in among different pre-defined patients' subgroups including 95% confidence intervals and interaction p values based on the ESC 0/1-h algorithm **(A)** using hs-cTnT (Elecsys) and **(B)** using hs-cTnI (Architect). Data on renal function were not available in all patients. CAD = coronary artery disease; CPO = chest pain onset; Obs = Observe group; RD = renal dysfunction, defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2; RI = rule-in group; RO = rule-out group; other abbreviations as in Figures 1 and 2.

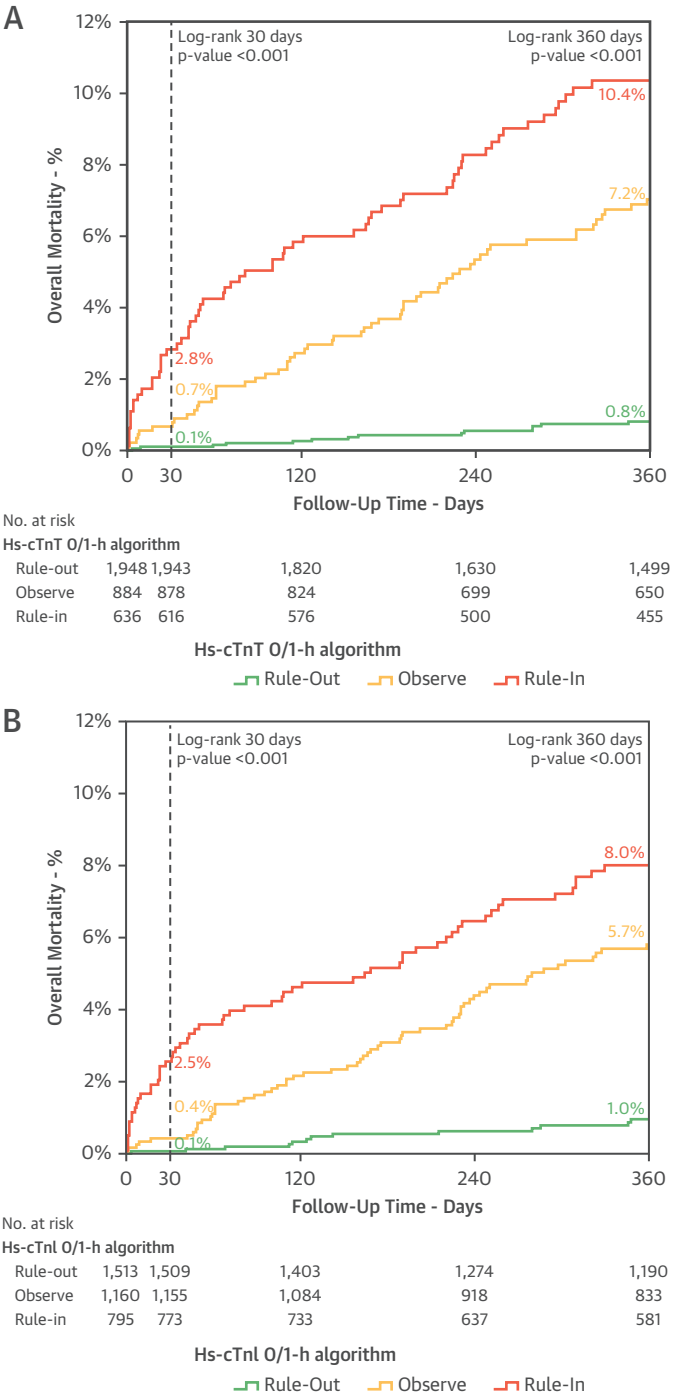
safety for the diagnosis of both type 1 and 2 NSTEMI. By contrast, the PPV and LR of the triage toward rule-in decreased and was lower as compared with the main analysis (Online Figure 4).

PROGNOSTIC PERFORMANCE TO PREDICT DEATH AND MACE DURING FOLLOW-UP. Among the 3,468 patients in the common prognostic dataset with both serial hs-cTnT and hs-cTnI measurements available (overlap of diagnostic datasets A and B), median follow-up time was 390 days (interquartile range: 365 to 772 days), and 82% of patients (2,854 of 3,468) had completed 1-year follow-up. Only 0.06% of patients (2 of 3,468) were lost to follow-up within 1 year. The ESC 0/1-h algorithm allowed a powerful discrimination between low risk of all-cause mortality at 30 days and 1 year in the rule-out group (0.1% and 0.8% for hs-cTnT, respectively; 0.1% and 1.0% for hs-cTnI, respectively), intermediate risk in the observational group (0.7% and 7.2% for hs-cTnT, respectively; 0.4% and 5.7% for hs-cTnI, respectively), and high-risk in the rule-in group (2.8% and 10.4% for hs-cTnT, respectively; 2.5% and 8.0% for hs-cTnI, respectively; log-rank $p < 0.001$ for comparisons between triage strata of each algorithm) (**Figure 4**). Similarly, the ESC 0/1-h algorithm using both hs-cTnT and hs-cTnI strongly discriminated the risk of MACE (including index events) at 30 days and 1 year in the 3 strata (Online Figure 5). According to NRI analysis, the ESC hs-cTnT 0/1-h algorithm was superior to the ESC hs-cTnI 0/1-h algorithm in assigning risk of 1-year mortality (NRI 16.1; $p < 0.001$) and 1-year MACE (NRI 12.3; $p < 0.001$) within the respective rule-out, observe, and rule-in groups. Triage by the ESC 0/1-h algorithm using hs-cTnT and hs-cTnI both provided incremental prognostic information regarding mortality and incidence of MACE at 1 year independent of NSTEMI diagnosis (Online Table 10). Prognostic findings were confirmed when assessed in the diagnostic datasets A and B individually (Online Figures 6 and 7).

DISCUSSION

This large multicenter study, including a large subgroup of early presenters (n = 1,322), was performed to address recent concerns regarding the suitability for routine clinical care of the new ESC hs-cTn 0/1-h algorithm (12,16). This algorithm is recommended for use in conjunction with all other clinical information including chest pain characteristics (19) and the ECG for the early triage of patients presenting with suspected NSTEMI to the ED (2).

FIGURE 4 Overall Mortality According to Triage Group by the ESC 0/1-h Algorithm



Kaplan-Meier curves depicting overall mortality within 1 year for patients triaged to the rule-out **(green lines)**, observe **(yellow lines)**, und rule-in **(orange lines)** groups by the ESC 0/1-h algorithm using **(A)** hs-cTnT (Elecsys) and **(B)** hs-cTnI (Architect). Abbreviations as in **Figures 1 and 2**.

We report 6 major findings:

First, the safety of the triage toward rule-out of NSTEMI, as quantified by NPV (99.7% to 99.8%) and LR (0.01 to 0.02), was very high for hs-cTnT and hs-cTnI, and similar to the estimates observed in previous studies, which had derived the different components of the ESC hs-cTn 0/1-h algorithm (2,3,5–15). Second, PPV (62% to 74%) and LR (8 to 14) of the triage toward rule-in seemed appropriate for the selection of patients eligible for early coronary angiography, which may allow the detection and rapid revascularization of the culprit lesion in a large portion of NSTEMI patients. In addition, coronary angiography is also required for accurate diagnosis in a substantial percentage of patients assigned toward rule-in with diagnoses other than MI including Takotsubo cardiomyopathy, myocarditis, heart failure, and UA. This clinical perspective is critically important when discussing what constitutes an appropriate PPV for the rule-in zone (12). Third, the ESC 0/1-h algorithm was highly effective, allowing triage of more than two-thirds of patients toward rule-out or rule-in of MI. Of note, direct rule-out of NSTEMI based on a single hs-cTnT/I-concentration was feasible in 16% and 10%, and provided excellent safety, as no NSTEMI was missed. Fourth, the ESC 0/1-h algorithm overall had similar performance characteristics in the vulnerable subgroup of early presenters (≤3 h) as compared with the overall cohort. Although the point estimates for NPV, PPV, and LR were slightly lower in early presenters as compared with late presenters, their 95% confidence intervals widely overlapped and clearly reject the hypothesis of a substantially lower performance in early presenters. Also, the percentage of patients triaged toward rule-out or rule-in was slightly higher in early presenters as compared with late presenters, further documenting the suitability for routine clinical care of the ESC 0/1-h algorithm in early presenters. Of note, this is the largest cohort of early presenters ever tested for the performance of the ESC 0/1-h algorithm. Robust findings were obtained from multiple subgroup analyses including sex, age, presence of CAD, and renal dysfunction, confirming excellent safety of rule-out and reasonable accuracy of rule-in. Fifth, the ESC 0/1-h algorithm allowed powerful and reliable risk stratification of short-term and long-term risk of mortality and MACE. That is, 30-day mortality was 29 times and 24 times higher in patients triaged toward rule-in as compared with patients triaged toward rule-out with hs-cTnT and hs-cTnI, respectively. Sixth, although this study did not aim to directly compare hs-cTnT and hs-cTnI, we observed differences in 3 performance measures between the ESC hs-cTnT 0/1-h algorithm and the ESC hs-cTnI 0/1-h algorithm in favor of the former. The ESC hs-cTnT 0/1-h algorithm had higher PPV for NSTEMI, higher efficacy, and also seemed to better risk-stratify patients regarding long-term mortality. The differences in PPV and efficacy are caused, at least to a large extent, by the fact that serial measurements of hs-cTnT, but not hs-cTnI, were part of the extensive clinical information available for the adjudication of the final diagnosis in all patients. Accordingly, our methodology provided the most accurate and valid estimates for the ESC hs-cTnT 0/1-h algorithm, but due to some differences in the hs-cTnT and hs-cTnI signal, may have slightly underestimated the true performance of the ESC hs-cTnI 0/1-h algorithm (17). Similarly, 2 recent studies using adjudication mainly based on cTnI invariably underestimated the true performance of early algorithms using hs-cTnT (9,12). By contrast, the differences in risk-prediction are supported by previous studies and likely reflect true pathophysiological differences between cTnT and cTnI (18).

Our findings corroborate and extend previous work on the development and validation of safe and effective rule-out and rule-in strategies for NSTEMI and highlight that the hs-cTnT and hs-cTnI cutoff levels currently suggested by the ESC balance safety and efficacy well (5–11,20,26,27). The ESC 0/1-h algorithm using hs-cTnT has been externally validated before in a smaller patient cohort, confirming high safety of rule-out (9). However, in contrast to this previous study, the present validation study is more than 3 times larger than the previous study, assesses both hs-cTnT and hs-cTnI, uses a hs-cTn assay for adjudication of gold standard diagnosis, and comprises a subset of the vulnerable subgroup of early presenters that is more than twice as large, and thereby substantially increases the generalizability of our findings. The findings of this study, including the fact that no patient with NSTEMI was missed by both the hs-cTnT and the hs-cTnI algorithms, further corroborate recent observations made in other diagnostic studies indicating a small number of patients with discordant hs-cTnT and hs-cTnI signals (9,12). The exact pathophysiological reasons for this phenomenon are unknown, but may include patient- and event-related factors, as well as preanalytical and analytical factors.

It is important to highlight that all hs-cTn-based diagnostic algorithms should always be used in conjunction with all other information available to the clinicians, including vital signs, the 12-lead ECG, and chest pain characteristics (2,4,19). The combination of the ESC 0/1-h algorithm with quantified clinical judgment seems particular valuable, as it has

been shown to help identify patients with UA, the more benign acute coronary syndrome phenotype (2,10). Moreover, it is important to mention that beyond the ESC 0/1-h algorithm, other early biomarker-based strategies also have been developed and seem to justify clinical use (2,4,8,17,20,26–29).

STUDY LIMITATIONS. First, our study was conducted in ED patients with symptoms suggestive of NSTEMI. Further studies are required to quantify the utility of the ESC 0/1-h algorithm in patients with either higher (e.g., in a coronary care unit setting) or lower pre-test probability (e.g., in a general practitioner setting) for NSTEMI. Second, some patients did not have a 1-h sample and therefore were excluded from this analysis. It is very unlikely that the performance of the ESC hs-cTn 0/1-h algorithm would be worse in these patients, particularly as a common reason for a missing blood samples at 1 h were logistic issues related to, for example, early transfer to the catheter laboratory. Third, although we used the most stringent methodology to adjudicate the presence or absence of NSTEMI including central adjudication by experienced cardiologists and serial measurements of hs-cTn, we still may have misclassified a small number of patients (3,23). Fourth, the fact that serial measurements of hs-cTnT, but not hs-cTnI, were part of the extensive clinical information available for the adjudication of the final diagnosis in all patients created an important bias for the direct comparison of the diagnostic performance of the ESC 0/1-h algorithm using hs-cTnT and hs-cTnI. Fifth, we cannot generalize our findings to patients with terminal kidney failure on chronic dialysis because they were excluded from 1 of the 2 contributing studies and therefore are underrepresented.

CONCLUSIONS

This large multicenter study using central adjudication and integrating a large population of early presenters was able to address recent concerns regarding the suitability for routine clinical care of the new ESC 0/1-h algorithm using hs-cTnT and hs-cTnI, and documented that it is safe and effective in triaging patients with suspected NSTEMI.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: The European Society of Cardiology 0/1-h algorithm based on high-sensitivity cardiac troponin T or I, used in conjunction with all other clinical information including chest pain characteristics and the ECG, is safe and effective in triaging patients with suspected NSTEMI.

TRANSLATIONAL OUTLOOK: Further studies are needed to precisely quantify the clinical impact of the 0/1-h algorithm on patient management and outcomes in clinical practice.

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KEY WORDS diagnosis of myocardial infarction, diagnostic algorithms, myocardial infarction, rule-in, rule-out, troponin

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.