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ORIGINAL INVESTIGATIONS

Outcome of Applying the ESC 0/1-hour Algorithm in Patients With Suspected Myocardial Infarction

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ABSTRACT

BACKGROUND The European Society of Cardiology (ESC) recommends the 0/1-h algorithm for rapid triage of patients with suspected non–ST-segment elevation myocardial infarction (MI). However, its impact on patient management and safety when routinely applied is unknown.

OBJECTIVES This study sought to determine these important real-world outcome data.

METHODS In a prospective international study enrolling patients presenting with acute chest discomfort to the emergency department (ED), the authors assessed the real-world performance of the ESC 0/1-h algorithm using high-sensitivity cardiac troponin T embedded in routine clinical care and its associated 30-day rates of major adverse cardiac events (MACE) (the composite of cardiovascular death and MI).

RESULTS Among 2,296 patients, non–ST-segment elevation MI prevalence was 9.8%. In median, 1-h blood samples were collected 65 min after the 0-h blood draw. Overall, 94% of patients were managed without protocol violations, and 98% of patients triaged toward rule-out did not require additional cardiac investigations including high-sensitivity cardiac troponin T measurements at later time points or coronary computed tomography angiography in the ED. Median ED stay was 2 h and 30 min. The ESC 0/1-h algorithm triaged 62% of patients toward rule-out, and 71% of all patients underwent outpatient management. Proportion of patients with 30-day MACE were 0.2% (95% confidence interval: 03% to 0.5%) in the rule-out group and 0.1% (95% confidence interval: 0% to 0.2%) in outpatients. Very low MACE rates were confirmed in multiple subgroups, including early presenters.

CONCLUSIONS These real-world data document the excellent applicability, short time to ED discharge, and low rate of 30-day MACE associated with the routine clinical use of the ESC 0/1-h algorithm for the management of patients presenting with acute chest discomfort to the ED. (J Am Coll Cardiol 2019;74:483–94)

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CT = computed tomography

ECG = electrocardiography

ED = emergency department

ESC = European Society of Cardiology

hs-cTn = high-sensitivity cardiac troponin

hs-cTnT = high-sensitivity cardiac troponin T

MACE = major adverse cardiac event

MI = myocardial infarction

NSTEMI = non-ST-segment-elevation myocardial infarction

Patients with symptoms suggestive of acute 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). In addition, rapid and safe rule-out of MI is of major medical and economic importance because it allows the timely detection and treatment of alternative causes of acute chest pain (2). Many of the alternative causes of acute chest pain are benign, so that rule-out of MI allows patient reassurance and often consideration of discharge from the ED and outpatient management (2,3).

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Electrocardiography (ECG) and serial sampling of cardiac troponin (cTn) complement clinical assessment and form the diagnostic cornerstones for MI in the ED (2,3). Supported by evidence from large diagnostic studies, the latest guidelines of the European Society of Cardiology (ESC) for the first time recommended the use of a 0/1-h algorithm to rapidly rule out or rule in non-ST-segment elevation myocardial infarction (NSTEMI) based on high-sensitivity cardiac troponin (hs-cTn) concentrations at presentation and their absolute 1-h changes (2,4–6). In these observational studies, study measurements were performed blinded to the treating physician. Accordingly, patients were not actually managed according to the triage recommendation of the ESC 0/1-h algorithm. Therefore, several important questions related to the use of the ESC 0/1-h algorithm in routine clinical practice remain unknown (7). These include the feasibility, for example, the exact time interval passed between the 0-h and 1-h blood draw, the adherence, for example, the percentage of patients managed without protocol violations, the triage-performance, quantified as the proportion of patients triaged toward rule-out or rule-in, as well as the proportion of patients undergoing outpatient management, the impact on patient flow in the ED as quantified by the time to ED discharge, and ultimately, the associated 30-day rates of major adverse cardiac events (MACE) in the rule-out group as well as in outpatients when embedding the ESC 0/1-h algorithm in clinical routine in a busy ED (3–6).

The aim of this prospective multicenter study was to document this important information.

METHODS

STUDY DESIGN AND POPULATION. Adult patients presenting to the ED with symptoms suggestive of MI such as acute chest discomfort and/or angina pectoris were prospectively recruited at 2 large university

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hospitals—the University Hospital Basel, Switzerland and the Cardiovascular Institute of Buenos Aires, Argentina—between October 2015 and June 2017 after written informed consent was obtained. Patients presenting with ST-segment elevation MI were excluded. This study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the local ethics committees. The authors designed the studies, and gathered and analyzed the data according to the STARD guidelines for studies of diagnostic accuracy (8) (Online Table 1), vouched for the data and analysis, wrote the paper, and decided to submit it for publication.

ROUTINE CLINICAL ASSESSMENT AND MANAGEMENT. Patients underwent clinical assessment that included medical history, physical examination, standard blood test including serial measurements of high-sensitivity cardiac troponin T (hs-cTnT), 12-lead ECG, continuous ECG rhythm monitoring, and pulse oximetry. In both institutions, the ESC 0/1-h algorithm was an integral part of the local standard operating procedures for the management of patients with suspected NSTEMI (2). The patients' management was left to the discretion of the attending physicians, who were unaware of the documentation of the outcome measures of this study. Treating physicians were free to overrule the triage recommendation of the ESC 0/1-h algorithm whenever deemed necessary. In fact, when introduced for routine clinical care (October 1, 2015, in Basel and January 1, 2016, in Buenos Aires) and during continuing medical education ever since, ED physicians were advised to always put the triage recommendation provided by the ESC 0/1-h algorithm into perspective with full clinical assessment and the detailed analysis of the ECG (2,3).

hS-cTnT MEASUREMENTS. As required by the ESC 0/1-h algorithm, hs-cTnT was routinely determined at presentation to the ED and after 1 h. Serial sampling on the ED was discontinued already after the first measurement if a patient qualified for direct rule-out (0-h hs-cTnT <5 ng/l and chest pain onset >3 h before ED presentation) or direct rule-in of NSTEMI (0-h hs-cTnT ≥52 ng/l) according to the ESC 0/1-h algorithm. Average turnaround time from blood sampling until availability of the hs-cTnT concentration in the electronic health record of the patient was approximately 1 h.

The hs-cTnT assay (Elecsys 2010 high-sensitivity troponin T; Roche Diagnostics, Rotkreuz, Switzerland) has a 99th percentile concentration of 14 ng/l with a corresponding CV of 10% at 13 ng/l (9). Limit of blank and limit of detection have been determined to be 3 ng/l and 5 ng/l, respectively. None of the hs-cTnT measurements in this analysis were affected by the 2010 to 2012 calibration shift (10).

ESC hs-cTnT 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, triages patients presenting with acute chest discomfort and/or angina pectoris toward rule-out, observe, and rule-in on the basis of assay-specific hs-cTnT cutoff concentrations obtained at presentation and after 1 h (Online Figure 1A) (2). The assay-specific cutoff concentration of hs-cTnT were derived and validated in diagnostic multicenter studies, in which study measurements were performed blinded to the treating physician and an adjudicated final diagnosis, done by 2 independent cardiologists on the basis of serial hs-cTn sampling, cardiac imaging, and clinical follow-up, served as the reference standard against which the triage recommendation of the 0/1-h algorithm was compared (Online Figure 1B) (4,5). According to these simulations of the exclusive use of the ESC 0/1-h algorithm, patients triaged toward rule-out indicate a very low likelihood of NSTEMI (<0.5%), whereas patients triaged toward rule-in have a likelihood of NSTEMI of about 70% to 85% and therefore, in general, are appropriate candidates for admission to a monitored unit and early coronary angiography (3–5). Many, but not all patients, in whom NSTEMI is ruled out are candidates for early discharge from the ED. Alternative causes of chest pain with a life-threatening potential (e.g., aortic dissection, pulmonary embolism, pneumothorax) or a need for in-hospital management (e.g., severe pneumonia) need to be considered (2,3).

FOLLOW-UP. One month after discharge, patients were contacted by telephone calls or in written form to evaluate the possible recurrence of chest pain and the occurrence of MACE including cardiovascular death and MI. Follow-up information was furthermore obtained from the patient's electronic health care records, the family physician's records, and the national registry on mortality.

MAIN OUTCOME MEASURES. Feasibility was assessed by the observed time interval between the 0-h and 1-h blood draws, targeting 60 min. Adherence was assessed as the percentage of patients managed without protocol violations (e.g., rule-out of NSTEMI with a single measurement [rather than 2] in early presenters, defined as patients presenting within the first 3 h after chest pain onset). In addition, we assessed the use of ED resources, quantified as the percentage of patients triaged toward rule-out by the ESC 0/1-h algorithm who needed additional cardiac investigations in the ED including hs-cTnT

TABLE 1 Baseline Characteristics According to ESC 0/1-h Algorithm Triage Groups and Management Decision

		ESC 0/1-h Algorithm Triage				Management Decision		
	Overall (N = 2,296)	Rule-Out (n = 1,420)	Observe (n = 581)	Rule-In (n = 295)	p Value	Outpatient (n = 1,619)	Inpatient (n = 677)	p Value
Age, yrs	60 (49–71)	55 (44–65)	71 (60–78)	68 (59–80)	<0.001	57 (46–68)	68 (57–77)	<0.001
Female	819 (36)	587 (41)	153 (26)	79 (27)	<0.001	616 (38)	203 (30)	<0.001
Time since CPO, h	6 (2–15)	5 (2–13)	6 (3–23)	5 (2–12)	<0.001	5 (2–12)	6 (3–24)	<0.001
Early presenters, ≤3 h after CPO	819 (36)	546 (38)	162 (28)	111 (38)	<0.001	613 (38)	206 (30)	0.001
Cardiovascular risk factors								
Hypertension	1161 (51)	555 (39)	415 (71)	191 (65)	<0.001	710 (44)	451 (67)	<0.001
Hypercholesterolemia	947 (41)	483 (34)	316 (54)	148 (50)	<0.001	578 (36)	369 (55)	<0.001
Diabetes mellitus	289 (13)	98 (7)	127 (22)	64 (22)	<0.001	147 (9)	142 (21)	<0.001
Current smoking	444 (19)	286 (20)	96 (17)	62 (21)	0.131	309 (19)	135 (20)	0.636
Family history of premature CAD	361 (16)	230 (16)	82 (14)	49 (17)	0.460	239 (15)	122 (18)	0.050
History								
Known CAD	656 (29)	290 (20)	244 (42)	122 (41)	<0.001	375 (23)	281 (42)	<0.001
Previous myocardial infarction	382 (17)	160 (11)	147 (25)	75 (25)	<0.001	206 (13)	176 (26)	<0.001
Previous PCI	519 (23)	240 (17)	190 (33)	89 (30)	<0.001	302 (19)	217 (32)	<0.001
Previous CABG	157 (7)	47 (3)	71 (12)	39 (13)	<0.001	85 (5)	72 (11)	<0.001
Peripheral artery disease	74 (3)	20 (1)	34 (6)	20 (7)	<0.001	31 (2)	43 (6)	<0.001
Previous stroke	52 (2)	16 (1)	19 (3)	17 (6)	<0.001	24 (1)	28 (4)	<0.001
Chronic kidney disease	129 (6)	17 (1)	68 (12)	44 (15)	<0.001	39 (2)	90 (13)	<0.001
hs-cTnT								
hs-cTnT at presentation, ng/l	8 (4–15)	5 (3–7)	16 (12–23)	73 (27–205)	–	6 (3–10)	20 (9–57)	–
hs-cTnT after 1 h, ng/l	9 (5–19)	6 (4–8)	17 (13–24)	79 (37–218)	–	7 (5–11)	22 (10–63)	–
1-h change, ng/l	1 (0–2)	1 (0–1)	1 (1–2)	11 (6–41)	–	1 (0–1)	2 (1–9)	–

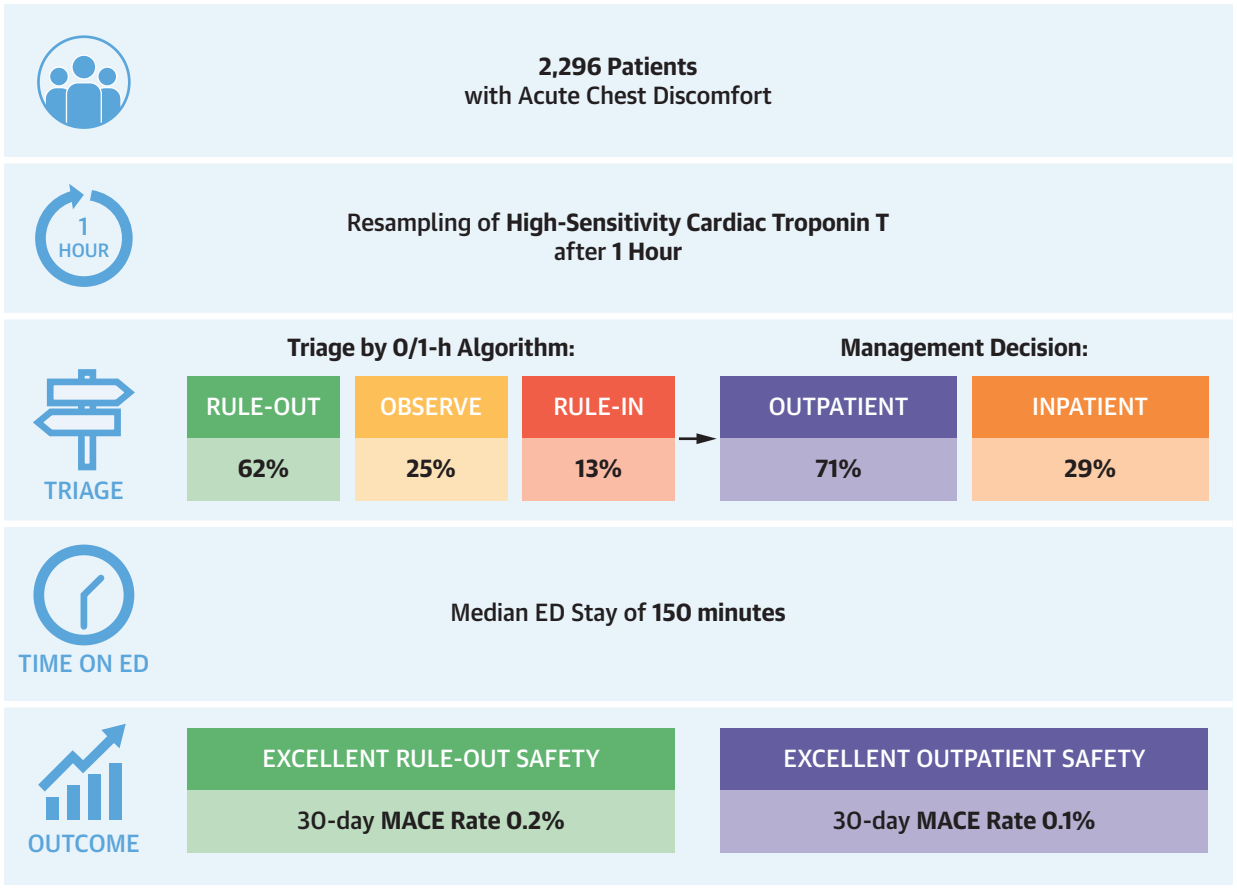
Values are median (interquartile range) or n (%). Continuous variables were compared with the Mann-Whitney *U* test, and categorical variables using the Pearson chi-square test or Fisher exact test, as appropriate.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CPO = chest pain onset; ESC = European Society of Cardiology; PCI = percutaneous coronary intervention; hs-cTnT = high-sensitivity cardiac troponin T.

measurements at later time points (e.g., 3 to 12 h) or coronary computed tomography (CT) angiography, and the percentage of patients ruled-in and hospitalized in a monitored unit and/or undergoing early coronary angiography (i.e., within 24 h). The impact on patient flow in the ED was quantified by the time to ED discharge/transfer and the percentage of ruled-out patients managed as outpatients.

The coprimary outcome measures were triage-performance and associated 30-day MACE rates of the ESC 0/1-h algorithm and subsequent outpatient management. Patients were classified as outpatients if they were directly discharged from the ED within the first 24 h without prior transfer to a cardiac catheterization laboratory, intensive care unit, observation unit, or regular ward. Triage-performance was quantified by the proportion of patients triaged toward rule-out or rule-in of NSTEMI by the ESC 0/1-h algorithm as well as by the proportion of outpatient management. MACE rates in the rule-out group and in outpatients were quantified by the proportion of patients with MACE within the first 30 days, defined as the composite of cardiovascular death and MI including the index event. Diagnosis of MI was adjudicated by an independent cardiologist not involved in the actual treatment of the respective patients within each participating institution including hs-cTnT according to the universal definition of MI (2,11,12). In brief, MI was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least 1 hs-cTnT value above the 99th percentile together with a significant rise or fall. To help put the findings of this post-implementation study into the appropriate clinical context, we added a direct comparison with a pre-implantation cohort enrolled in 7 hospitals (University Hospital Basel, University Hospital Zürich, Kantonsspital Bruderholz, and Kantonsspital Liestal, all in Switzerland; Zabrze University Hospital, Poland; Brno University Hospital, Czech Republic; and Hospital del Mar, Barcelona, Spain), using identical inclusion and exclusion criteria as well as identical criteria to quantify and

CENTRAL ILLUSTRATION **European Society of Cardiology 0/1-h Algorithm: Real-World Performance Summary**



Twerenbold, R. et al. J Am Coll Cardiol. 2019;74(4):483–94.

The ESC 0/1-h algorithm allows a very rapid, efficient, and safe triage of patients with acute chest discomfort. ED = emergency department; MACE = major adverse cardiac events.

compare time to ED discharge, proportion of outpatient management, and 30-day MACE rates including adjudication of MI (13).

STATISTICAL ANALYSIS. All continuous variables are expressed as median (interquartile range) and all categorical variables as numbers and percentages. Details on the statistical analysis can be found in the Methods section of the Online Appendix.

RESULTS

PATIENT CHARACTERISTICS. Overall, 2,296 patients presenting with symptoms suggestive of MI were eligible for this analysis (Online Figure 2). Median age was 60 years, 36% were women, 29% had known coronary artery disease, and 36% were early presenters that presented to the ED within the first 3 h after chest pain onset (**Table 1**, Online Table 2). Prevalence of NSTEMI at the time of index admission was 9.8% (224 of 2,296).

FEASIBILITY. Median time between the 0-h and 1-h-blood draw was 65 min (61 to 72 min), as compared with the targeted 60 min (Online Figure 3).

ADHERENCE AND RESOURCE USE. Overall, 94% (95% confidence interval [CI]: 93% to 95%) of patients were managed without protocol violations. The most frequent protocol violation was ED discharge without collection of a second (1-h) hs-cTnT measurement in 123 patients presenting within the first 3 h after chest pain onset (5%). In 4 patients (0.2%) presenting within the first 3 h after chest pain onset treated as inpatients, no serial hs-cTnT testing was performed after the initial measurement. Two patients

TABLE 2 Patient Management and Outcomes According to the ESC 0/1-h Algorithm Triage Recommendation and Clinical Management Decision

		ESC 0/1-h Algorithm Triage			Management Decision	
	Overall (N = 2,296)	Rule-Out (n = 1,420)	Observe (n = 581)	Rule-In (n = 295)	Outpatient (n = 1,619)	Inpatient (n = 677)
In-hospital management						
Time spent on the ED, min	150 (134–235)	150 (130–215)	156 (143–273)	150 (140–265)	150 (130–205)	180 (140–318)
Overnight stays, nights	0 (0–2)	0 (0–0)	1 (0–5)	5 (3–9)	0 (0–0)	5 (2–8)
Outpatient management	1,619 (70.5)	1,243 (87.5)	352 (60.6)	24 (8.1)	1,619 (100.0)	0 (0.0)
Procedures during 30-day follow-up						
Cardiac stress testing	196 (8.5)	125 (8.8)	58 (10.0)	13 (4.4)	104 (6.4)	92 (13.6)
Functional imaging	144 (6.3)	86 (6.1)	46 (7.9)	12 (4.1)	68 (4.2)	76 (11.2)
Ergometry	131 (5.7)	81 (5.7)	39 (6.7)	11 (3.7)	61 (3.8)	70 (10.3)
Coronary angiography	402 (17.5)	82 (5.8)	109 (18.8)	211 (71.5)	14 (0.9)	388 (57.3)
Revascularization	269 (11.7)	62 (4.4)	69 (11.9)	151 (51.2)	10 (0.6)	272 (40.2)
PCI	218 (9.5)	49 (3.5)	53 (9.1)	116 (39.3)	1 (0.1)	217 (32.1)
CABG	54 (2.4)	1 (0.1)	17 (2.9)	36 (12.2)	0 (0.0)	54 (8.0)
No CAD testing	1,730 (75.3)	1,226 (86.3)	426 (73.3)	78 (26.4)	1,503 (92.8)	227 (33.5)
Outcomes during 30-day follow-up						
MACE	231 (10.1)	3 (0.2)	31 (5.3)	197 (66.8)	1 (0.1)	230 (34.0)
Myocardial infarction	227 (9.9)	2 (0.1)	30 (5.2)	195 (66.1)	0 (0.0)	227 (33.5)
At index admission	224 (9.8)	0 (0.0)	29 (5.0)	195 (66.1)	0 (0.0)	224 (33.1)
Death	8 (0.3)	2 (0.1)	1 (0.2)	5 (1.7)	1 (0.1)	7 (1.0)
Cardiovascular death	5 (0.2)	1 (0.1)	1 (0.2)	3 (1.0)	1 (0.1)	4 (0.6)

Values are median (interquartile range) or n (%). Continuous variables were compared with the Kruskal-Wallis or Mann-Whitney *U* test, and categorical variables using the Pearson chi-square test or Fisher exact test, as appropriate. MACE was defined as the composite of myocardial infarction (including index event) and cardiovascular death within 30 days after index presentation to the emergency department. Functional imaging was defined as stress echocardiography or myocardial perfusion scintigraphy.

ED = emergency department; MACE = major adverse cardiac event; other abbreviations as in Table 1.

(0.1%: 1 patient with NSTEMI in the rule-in group, 1 patient with unstable angina in the rule-out group) were admitted to the hospital, but left the hospital against medical advice on the day of admission. In 3 patients (0.1%), first hs-cTnT retesting was performed after 3 h instead of 1.

Among all patients triaged toward rule-out by the ESC 0/1-h algorithm, 2% (95% CI: 2% to 3%) required additional cardiac investigations on the ED including hs-cTnT measurements at later time points (e.g., 3 to 12 h) or coronary CT angiography. Subsequent cardiac stress testing within 30 days was performed in 9% of patients in the rule-out group and in 6% of outpatients, which was not performed during ED stay. Among patients triaged toward rule-in, 46% (95% CI: 41% to 52%) were hospitalized in a monitored unit and 67% (95% CI: 61% to 72%) underwent early coronary angiography.

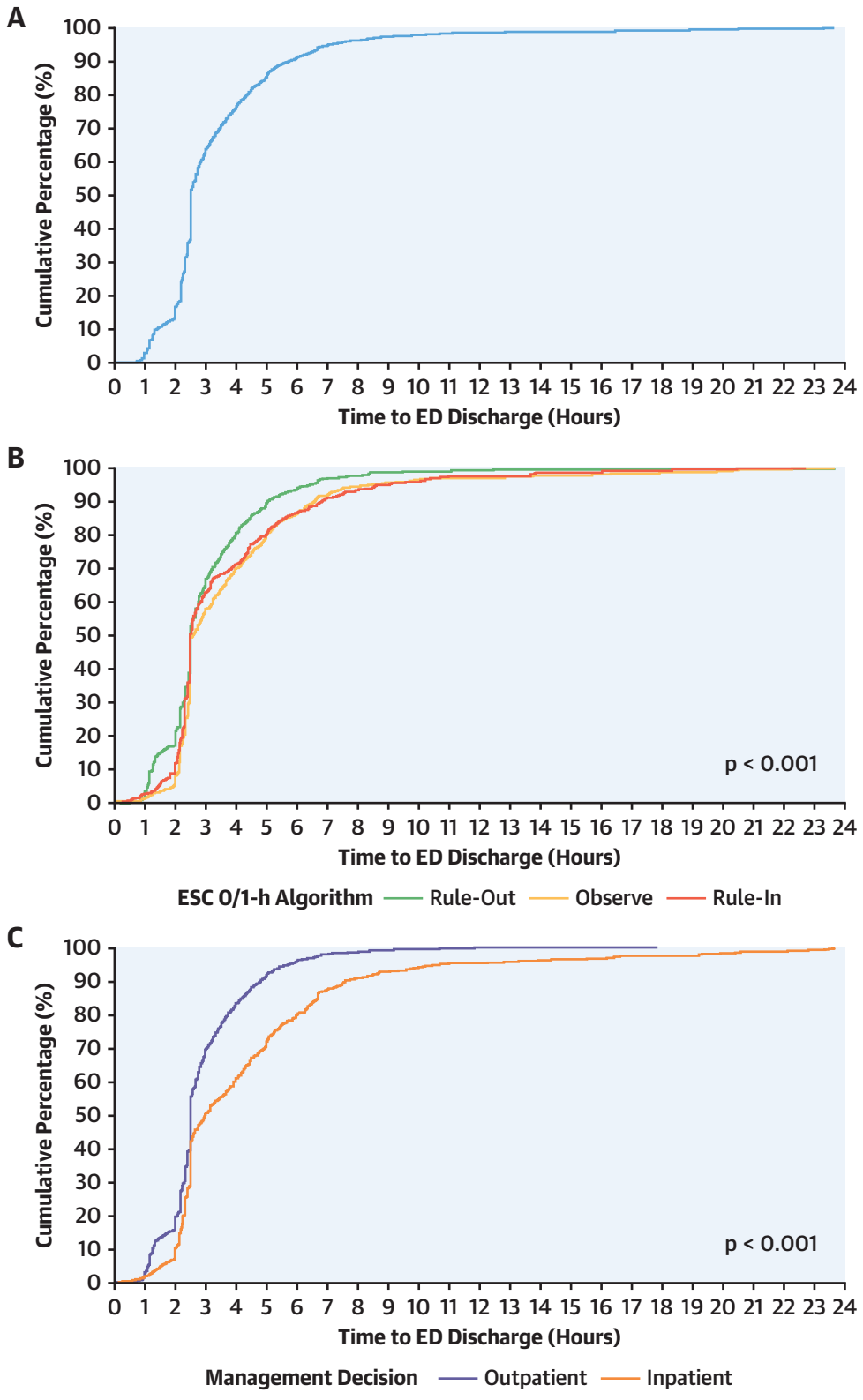
IMPACT ON PATIENT FLOW IN THE ED AND TRIAGE-PERFORMANCE. Main findings are summarized in the **Central Illustration**. Median time to discharge or transfer from the ED was 2 h 30 min (2 h 14 min to 3 h 55 min) in the overall population (**Table 2, Figure 1**).

The ESC 0/1-h algorithm triaged 62% (95% CI: 60% to 64%) of patients toward rule-out and 13% (95% CI: 12% to 14%) toward rule-in, leaving only 25% (95% CI: 23% to 27%) in the observe zone (**Figure 2**). Twenty-two percent (95% CI: 21% to 24%) of patients were eligible for direct rule-out and 8% (95% CI: 7% to 9%) for direct rule-in of NSTEMI on the basis of the 0-h hs-cTnT concentration only without the need for serial hs-cTnT testing at 1 h.

Ultimately, 71% (95% CI: 69% to 72%) of patients were managed as outpatients. Among patients triaged toward rule-out of NSTEMI, 88% (95% CI: 86% to 89%) were discharged directly from the ED for outpatient management. In those, 92% (95% CI: 91% to 94%) did not undergo any further outpatient testing for coronary artery disease. Baseline characteristics and patient management according to disposition in each triage group are fully listed in Online Tables 3 and 4.

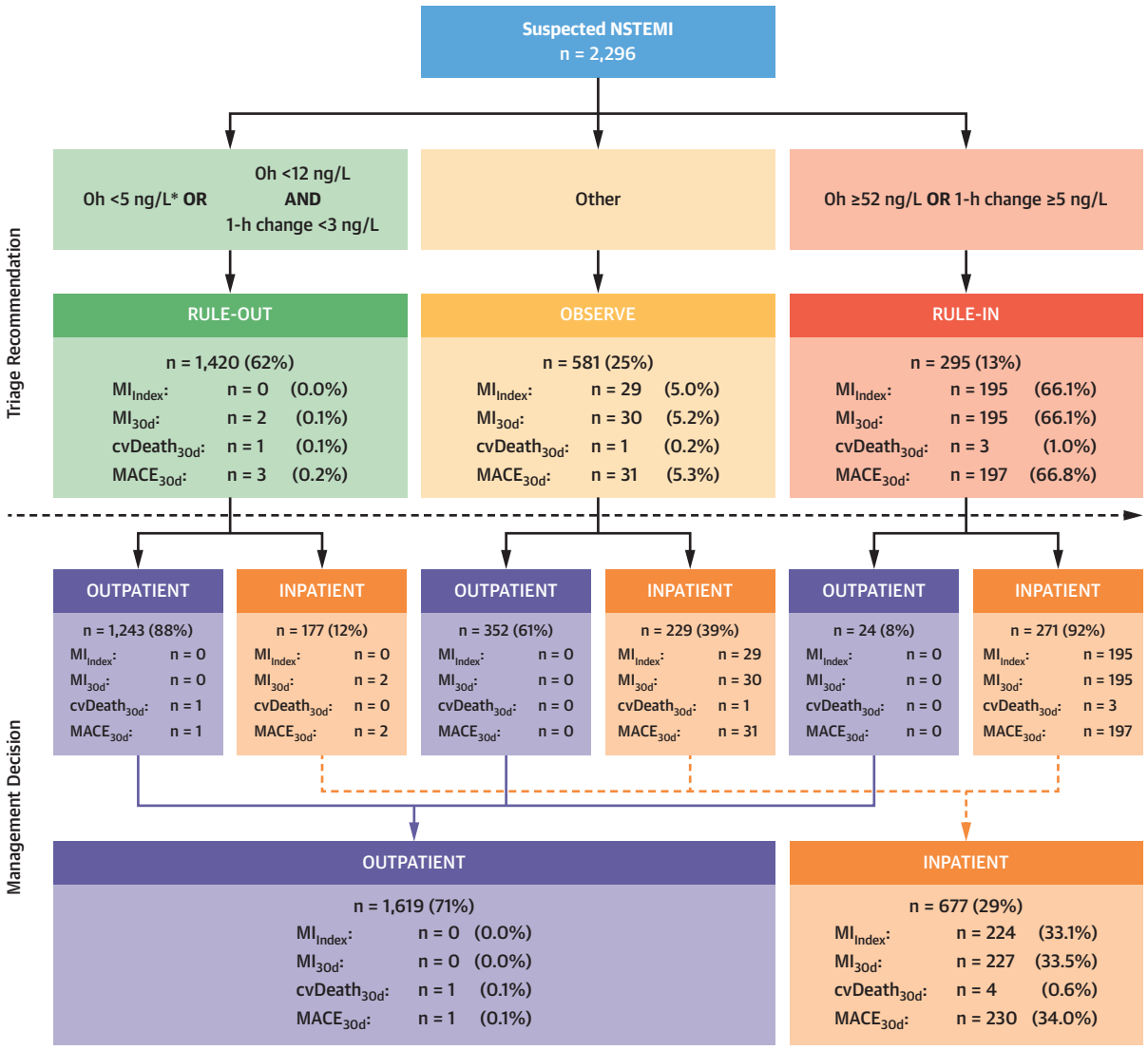
ASSOCIATED 30-DAY MACE RATES. Data on 30-day follow-up were available in all patients (100%). Within 30 days, MACE rate was 0.2% (95% CI: 0.0% to 0.5%) in the rule-out group and 0.1% (95% CI: 0.0% to 0.2%) in outpatients. No patient with MI at index admission was incorrectly triaged toward rule-out for NSTEMI (missed MI rate 0%) or treated as outpatient (inappropriate discharge rate 0%). Subsequent MI within 30 days occurred in 2 patients (0.1%; 95% CI:

FIGURE 1 Cumulative Distribution of Time to Discharge From the ED



(A) Time to discharge in the overall population; **(B)** according to the triage by the ESC 0/1-h algorithm; **(C)** according to the management decision. ED = emergency department; ESC = European Society of Cardiology.

FIGURE 2 Real-World Performance of the ESC 0/1-h Algorithm Using hs-cTnT

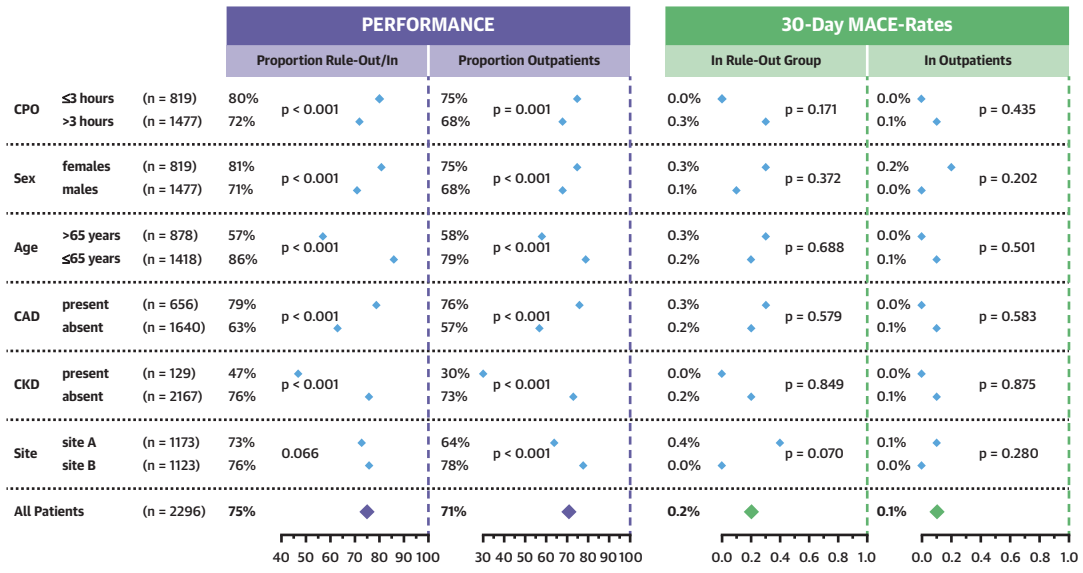


Flow-chart depicting the real-world performance of the ESC 0/1-h algorithm for rapid triage of suspected myocardial infarction (MI). Triage recommendations (rule-out vs. observe vs. rule-in of MI) are depicted in the **upper panel**, whereas final management decisions (outpatient vs. inpatient) are depicted in the **lower panel**. *If chest pain onset >3 h before presentation to the emergency department. 1-h change = absolute (unsigned) change of high-sensitivity cardiac troponin T (hs-cTnT) within 1 h; $cvDeath_{30d}$ = cardiovascular death at 30 days; ESC = European Society of Cardiology; $MACE_{30d}$ = major adverse cardiac events at 30 days; MI_{30d} = myocardial infarction at 30 days including the index event; MI_{Index} = myocardial infarction at index presentation; NSTEMI = non-ST-segment elevation myocardial infarction.

0% to 0.4%) triaged to the rule-out group (days 5 and 8), that were both treated as inpatients. No MI within 30 days occurred in outpatients. One female patient triaged to the rule-out group and treated as outpatient was found dead on day 29 without any evidence supporting a specific noncardiovascular cause of death and therefore accounted for the 1 adjudicated cardiovascular death observed in the rule-out and outpatient group. Details of the 3 patients with a 30-day MACE that were missed by the ESC 0/1-h algorithm are listed in Online Table 5.

COMPARISON WITH PRE-IMPLEMENTATION COHORT. Baseline characteristics of patients with suspected NSTEMI enrolled in the pre-implementation cohort (Online Table 6) were comparable to that in the post-implementation cohort, for example, median age 59 years versus 60 years. Median time to ED discharge was 4 h 45 min (3 h 19 min to 6 h 30 min), which was

FIGURE 3 Forest Plots Indicating Efficacy and Safety of the ESC 0/1-h Algorithm in Pre-Defined Subgroups



The **first column** indicates triage-performance of the ESC 0/1-h algorithm, quantified by the proportion of patients either ruled-out or ruled-in for non–ST-segment elevation myocardial infarction. The **second column** indicates proportion of outpatient management. The **third and fourth columns** indicate 30-day MACE rates in patients assigned to rule-out and rule-in outpatients, respectively. CAD = coronary artery disease; CKD = chronic kidney disease; CPO = chest pain onset; ESC = European Society of Cardiology; MACE = major adverse cardiac events; site A = University Hospital of Basel, Switzerland; site B = Instituto Cardiovascular de Buenos Aires, Argentina.

significantly longer as compared with that in the post-implementation cohort ($p < 0.001$) (Online Table 7). Overall, 61% of patients in the pre-implementation cohort were managed as outpatients, which was a significantly lower proportion than in the post-implementation cohort ($p < 0.001$). Within 30 days, MACE rate was 1.7% (95% CI: 1.0% to 2.4%) in outpatients in the pre-implementation cohort, which was significantly higher as compared with the rate in the post-implementation cohort ($p < 0.001$).

PERFORMANCE OF THE ESC 0/1-H ALGORITHM IN PRE-DEFINED SUBGROUPS. Pre-defined subgroup analyses of the ESC 0/1-h algorithm's performance according to time since chest pain onset, sex, age, presence of known coronary artery disease or chronic kidney disease, as well as recruitment site, revealed highly robust findings documenting very low 30-day MACE rates in the rule-out group and in outpatients in all subgroups (no significant interaction p values) (**Figure 3**). By contrast, triage-performance differed between most of the observed subgroups. For example, in the vulnerable subgroup of early presenters, presenting to the ED within the first 3 h after chest pain onset, 30-day MACE rate in the rule-out group and in outpatients were 0.0% (0 of 546 and 0 of 613, respectively), as compared with 0.3% (3 of 874) and 0.1% (1 of 1,006) in late presenters ($p = 0.171$ and 0.435, respectively). In early presenters, 80% (95% CI: 78% to 83%) of patients were either triaged toward rule-out or rule-in and 75% (95% CI: 72% to 78%) underwent outpatient management as compared with 72% (95% CI: 69% to 74%) and 68% (95% CI: 66% to 71%) in late presenters, respectively ($p < 0.001$ and 0.001).

Data on predictors for hospital admission, cardiac stress testing and revascularization among patients ruled out for NSTEMI, as well as on predictors of outpatient management in patients triaged toward the observe or rule-in group by the ESC 0/1-h algorithm can be found in the result section of the Online Appendix, Online Tables 8 to 12.

DISCUSSION

To the best of our knowledge, this is the first international multicenter study that investigates in detail the real-world performance of the ESC 0/1-h algorithm using hs-cTnT applied in routine clinical care in unselected patients presenting with acute chest discomfort suggestive of NSTEMI to the ED. We report 7 major novel findings:

First, the routine application of the ESC 0/1-h algorithm seems to be highly feasible also in busy EDs, as the median time to the 1-h blood sample was 65 min. Second, adherence to the ESC 0/1-h algorithm was high with 94% of all patients assessed without protocol violations. The most frequent protocol violation was ED discharge without collection of a 1-h hs-cTnT measurement in patients presenting within the first 3 h after chest pain onset. It is important to highlight that direct rule-out by the ESC 0/1-h algorithm is not permitted in such early presenters, because very low but still rising hs-cTnT concentrations could be potentially missed. Use of the ESC 0/1-h algorithm within a clinical decision support system embedded in the electronic patient document has the potential to further reduce the likelihood of protocol violations. Third, only 2% of all patients in the rule-out group did require additional cardiac investigations including hs-cTnT measurements at later time points or CT angiography in the ED. Fourth, median ED length of stay was 2.5 h, which is substantially shorter as in the pre-implementation cohort and reported when using alternative ED protocols for patients with suspected NSTEMI both in the United States (14,15) or Europe (13,16). A recent European multicenter study assessed the real-world impact of the introduction of hs-cTnT within the ESC 0/3-h algorithm on clinical management and reported a median ED stay duration of about 6.5 h when using a conventional, nonsensitive cTnT assay and 5 h after the introduction of hs-cTnT, applied according to the ESC 0/3-h algorithm (13). Similarly, median ED stay duration was 6.3 h in low-risk patients in a recent Dutch study (16), 8.6 h in a U.S. study routinely using coronary CT angiography, and even >24 h in their control group (14). Therefore, the use of the ESC 0/1-h algorithm seems to further accelerate the clinical management of patients with suspected NSTEMI and thereby may help reducing ED crowding, which is known to be associated with adverse outcomes (17). The reduction in treatment costs associated with the profound reduction in length of stay in the ED is likely also substantial, particularly as the need for additional cardiac investigations in patients triaged toward rule-out was very low. Fifth, triage-performance of the ESC 0/1-h algorithm was high and allowed rapid rule-out or rule-in of NSTEMI in 3 patients of 4 within 1 h of resampling. Ultimately, 71% of patients were managed as outpatients, which is a higher proportion as in the pre-implementation cohort and reported when using alternative ED protocols for patients with suspected NSTEMI both in the United States (14,15) or Europe (13,16). These real-world findings are highly comparable to data from previous diagnostic studies that estimated the efficacy of the 0/1-h algorithm using hs-cTnT (4,5). Sixth, and likely of utmost importance, the observed 30-day MACE rates were very low in the rule-out group and in outpatients, and lower as compared with that observed in the pre-implementation cohort and reported when using alternative ED protocols for patients with suspected NSTEMI both in the United States (14,15) or Europe (13,16). Seventh, subgroup analyses according to time since chest pain onset, sex, age, known coronary artery disease, presence of chronic kidney disease as well as recruitment site confirmed very low MACE rates and high triage-performance of the ESC 0/1-h algorithm in all predefined subgroups.

These findings extend and corroborate previous work related to the clinical evaluation of hs-cTn assays in the early diagnosis of MI that allowed the development of several novel hs-cTn-based strategies accelerating the triage of patients with suspected NSTEMI (4–6,18–25). In 2011, the ESC introduced a 0/3-h algorithm for accelerated patients' triage, which is still the standard of care in many institutions worldwide and allows the rule-out of NSTEMI in about 40% to 45% of patients with appropriate safety (2,26). Besides, a 0/2-h algorithm combining serial hs-cTnI testing with a clinical risk score, the Thrombolysis In Myocardial Infarction (TIMI) score, has been developed, allowing rule-out of NSTEMI in 42% of patients with a 30-day MACE rate of 0.8% (19). Alternatively, a recent large meta-analysis comprising 22,457 patients investigated a single hs-cTnI cutoff approach and reported high efficacy (49% of patients ruled out) and high safety with a 30-day MACE rate of 0.5% among ruled-out patients (25). In addition, a recent U.S. study investigated the efficacy and safety of the routine application of the HEART (history, electrocardiogram, age, risk factors and troponin) score and serial cTnI testing at 0 h and 3 h (27). This approach allowed rule-out in 31% of patients with a 30-day MACE rate of 0.4%. Compared with all the aforementioned strategies, the investigated ESC 0/1-h algorithm, as currently suggested by the ESC with a Class I recommendation, tended to result in a higher rule-out proportion (62%) and lower 30-day MACE rate (0.2%). However, patients' population differ between studies and a direct comparison is still missing. Additionally, and in contrast to most other algorithms, the ESC 0/1-h algorithm also offers a clearly defined rule-in pathway.

The acceptable miss rate for MACE is still a matter of debate and differs between health care systems. However, on the basis of clinical surveys, harm/benefit analyses, and most expert opinions,

acceptable miss rates at 30 days should be <1% to 2% in industrial countries (28,29), which is 5 to 10 times higher than observed in this study.

The findings of the present study have enormous clinical implications. Many hospitals worldwide are currently switching from a conventional to a hs-cTn assay, particularly after clearance of the first hs-cTnT in the United States in Spring 2017. Besides, many institutions that already use hs-cTn in clinical routine still interpret it in the context of the ESC 0/3-h algorithm despite the promising results of the ESC 0/1-h algorithm, as they first await confirmation by real-world data.

As for any diagnostic algorithm, the following concepts and caveats apply to the most appropriate clinical use of the ESC 0/1-h algorithm: First, the ESC 0/1-h algorithm should only be applied in the appropriate clinical setting: hemodynamically stable patients presenting with symptoms suggestive of MI to the ED after ST-segment elevation MI has been ruled out by the ECG performed at presentation. As written informed consent was required for this and nearly all other previous studies on early triage algorithms, very few patients in shock and/or respiratory failure were enrolled. Second, although 30-day MACE rates in the rule-out group of the ESC 0/1-h algorithm were very low, and no NSTEMI was missed at index presentation, it should always be used in conjunction with all other clinical information including detailed assessment of chest pain characteristics, physical examination, and the ECG. Additional measurements of hs-cTnT at, for example, 3 h are advised whenever the patient remains symptomatic or clinical judgment still argues in favor of NSTEMI. These will help to detect the rare, but existing phenomenon of delayed release of hs-cTnT into the circulation, particularly in early presenters (2). It will also help to detect rare, but possible, errors in the handling of the clinical blood samples. Third, not all patients triaged toward rule-out of NSTEMI are appropriate candidates for early discharge from the ED.

STUDY LIMITATIONS. First, we can only comment on the performance of the ESC 0/1-h algorithm using hs-cTnT. It is likely that also the real-world performance of the ESC 0/1-h algorithm using hs-cTnI is similar to that estimated in the large diagnostic studies. However, this hypothesis should be verified appropriately for each hs-cTnI assay in future studies. Second, this study was conducted in ED patients with symptoms suggestive of NSTEMI such as acute chest discomfort and/or angina pectoris. 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. Third, we cannot comment on the utility of the ESC 0/1-h algorithm in patients with terminal kidney failure on chronic dialysis, because these patients were excluded from the initial studies deriving and validating this algorithm (4,5).

CONCLUSIONS

The routine use of the ESC 0/1-h algorithm using hs-cTnT in patients with acute chest discomfort is clinically highly applicable and associated with very low 30-day MACE rates in the rule-out group and in outpatients. The observed short ED stay length of only 2.5 h may be an important contribution to further accelerate and improve patient management in the often overcrowded EDs.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: Routine application of the ESC 0/1-h hs-cTnT algorithm facilitates rapid triage of patients with acute chest discomfort and is associated with low 30-day rates of major adverse cardiovascular events.

TRANSLATIONAL OUTLOOK: Additional clinical studies are needed to compare the performance of the 0/1-h algorithm with other rapid triage strategies for patients presenting with possible acute myocardial infarction.

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KEY WORDS 0/1-h algorithm, acute myocardial infarction, high-sensitivity cardiac troponin, outcome, rule-out, safety

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