Prediction of Major Adverse Cardiac Events in Patients with suspected Acute Myocardial Infarction

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ABSTRACT

Background: Early and accurate detection of short-term major adverse cardiac events (MACE) in patients with suspected acute myocardial infarction (AMI) is an unmet clinical need.

Objectives: We aimed to test the hypothesis that adding clinical judgment and ECG findings to the ESC high-sensitivity cardiac troponin(hs-cTn) 0/1h-algorithm would further improve its performance to predict MACE.

Methods: Patients presenting with suspected AMI to an emergency department have been enrolled in a prospective multicenter diagnostic study. The primary endpoint was MACE including all-cause death, cardiac arrest, AMI, cardiogenic shock, sustained ventricular arrhythmia, and high-grade atrioventricular block within 30 days including index events. Secondary endpoint was MACE+unstable angina (UA) receiving early(≤24h) revascularization.

Results: Among 3123 patients, the ESC hs-cTnT 0/1h-algorithm triaged significantly more patients towards rule-out as compared to the extended algorithm (60% (95%CI, 59-62%) vs. 45% (95%CI, 43-46%); p<0.001), while maintaining similar 30-day MACE rates (0.6% (95%CI, 0.3-1.1%) vs. 0.4% (95%CI, 0.1-0.9%); p=0.429) resulting in similar negative predictive value (NPV 99.4% (95%CI, 98.9-99.6%) vs. 99.6% (95%CI, 99.2-99.8%); p=0.097). The ESC hs-cTnT 0/1h-algorithm ruled-in fewer patients (16% (95%CI, 14.9-17.5%) vs. 26% (95%CI, 24.2-27.2%); p<0.001) as compared to the extended algorithm, albeit with a higher positive predictive value (PPV 76.6% (95%CI, 72.8-80.1%) vs. 59% (95%CI, 55.5-62.3%); p<0.001). For 30-day MACE+UA, the ESC hs-cTnT 0/1h-algorithm had higher PPV for rule-in, while the extended algorithm had higher NPV for the rule-out. Similar findings emerged when using hs-cTnI.

Conclusion: The ESC hs-cTn 0/1h-algorithm better balanced efficacy and safety in the prediction of MACE, the extended algorithm for MACE+UA.

Condensed Abstract

Among 3123 patients, the high-sensitivity cardiac troponin T (hs-cTnT) 0/1h-algorithm triaged significantly more patients towards rule-out as compared to the extended algorithm (60% vs. 45%; p<0.001), while maintaining similar 30-day rates of all-cause death, cardiac arrest, acute myocardial infarction, cardiogenic shock, sustained ventricular arrhythmia, and high-grade atrioventricular block including index events (0.6% (95%CI, 0.3-1.1%) vs. 0.4% (95%CI, 0.1-0.9%); p=0.429). The ESC hs-cTnT-0/1h-algorithm ruled-in fewer patients (16% (95%CI, 14.9-17.5%) vs. 26% (95%CI, 24.2-27.2%); p<0.001) as compared to the extended algorithm, albeit with a higher positive predictive value (PPV 76.6% (95%CI, 72.8-80.1%) vs. 59% (95%CI, 55.5-62.3%); p<0.001). Similar findings emerged when using hs-cTnI.

Key Words: Acute myocardial infarction, high-sensitivity cardiac troponin, electrocardiography, clinical assessment, major adverse cardiac events

Clinical Trial Registration: ClinicalTrials.gov number, NCT00470587,

https://clinicaltrials.gov/ct2/show/NCT00470587

Abbreviations

126 ACS - Acute coronary syndrome

127 AMI - Acute myocardial infarction

128 CAD – Coronary artery disease

129 ED – Emergency department

130 ECG – Electrocardiography

131 hs-cTn – High-sensitivity cardiac troponin

132 MACE - Major adverse cardiac events

133 NPV – Negative predictive value

134 PPV – Positive predictive value

135 UA - Unstable angina

136 VAS - Visual analoge scale

137

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INTRODUCTION

Acute chest discomfort accounts for about 10% of all presentations to the emergency department (ED).(1)(2)(3)(4) Among patients with acute chest discomfort, the early detection of acute myocardial infarction (AMI) has high priority, since AMI is common, associated with high mortality within the first hours, and amendable with effective treatment.(1)(2)(3) Efficient risk stratification is mainly based on three diagnostic columns: detailed clinical assessment including chest pain characteristics, the 12-lead electrocardiogram (ECG) and cardiac troponin (cTn) as a blood biomarker of cardiomyocyte injury.(2)(3)(4)

The clinical introduction of cardiac troponin (cTn) assays with higher analytical sensitivity (hs-cTn) has allowed to largely overcome the sensitivity deficit for AMI at emergency department (ED) presentation associated conventional cTn assays and, thereby, substantially increased the early diagnostic accuracy for AMI.(3)(5)(6)(7) Very high diagnostic accuracy for AMI within the first hours after ED presentation has allowed the shortening of the time-interval to the second hs-cTn measurement and reduced the time to rule-out and/or rule-in. (3)(5)(6)(7)

Among the rapid hs-cTn-based strategies, the European Society of Cardiology (ESC) hs-cTnT/I 0/1h-algorithms are particularly appealing, as they seem to combine very high safety with high efficacy in the early rule-out or rule-in of AMI.(8)(9)(10)

While it is mandatory to use the ESC hs-cTnT/I 0/1h-algorithms, like all other hs-cTn-based strategies, in conjunction with full clinical assessment and the 12-lead ECG,(3) it is unknown how to best combine these diagnostic variables and how possible combinations would affect its performance characteristics. As the ESC hs-cTnT/I 0/1h-algorithms have been optimized for the rule-out and rule-in of AMI, the incremental value of the additional diagnostic variables seems to be small for AMI.(8)(9)(10) However, it might be substantial for the accurate prediction of major adverse cardiac events (MACE) within 30 days, the second key task for

164 physicians in the ED necessary for the decision whether early discharge and outpatient
165 management or in-hospital diagnostic and therapeutic assessment is indicated. A recent pilot
166 study provided a pragmatic suggestion on how to combine the hs-cTnT 0/1h-algorithm with
167 clinical assessment and the ECG: “the extended algorithm”.(11)

168 We aimed to externally validate in a large prospective multicenter study the
169 performance characteristics of “the extended algorithm” in the prediction of short-term MACE
170 and compare it to that of the ESC hs-cTnT/I 0/1h-algorithms.

METHODS

Study design and patient population

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is a prospective international multicenter diagnostic study with twelve centers in five European countries aiming to advance the early diagnosis of AMI (ClinicalTrials.gov registry, number NCT00470587).(12)(13)(14) Adult patients presenting to the emergency department (ED) with symptoms suggestive of AMI (such as acute chest discomfort and angina pectoris) with an onset or peak within the last 12 hours were recruited. Enrolment was independent of renal function, while patients with terminal kidney failure on chronic dialysis were excluded. For this analysis, patients with ST-segment elevation MI, patients in whom the final diagnosis remained unclear even after central adjudication and at least one elevated hs-cTnT concentration possibly indicating AMI, as well as patients with no available hs-cTnT/I concentrations determined upon presentation to the ED and after 1 hour were also not eligible and therefore excluded. The most common reasons for missing samples after 1 hour were early transfer to the catheter laboratory or coronary care unit and diagnostic procedures around the 1-hour window that precluded blood draw at 1 hour.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients. The authors designed the study, gathered and analysed the data, vouched for the data and analysis, wrote the paper, and decided to submit for possible publication. The STARD Checklist can be found in the online-only supplement (**supplemental Table 1**).(15)

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, continuous ECG rhythm monitoring and pulse oximetry. Management of patients was independent of this diagnostic study and left to the discretion of the attending physician.

Reference Standard: Adjudicated 30-Day MACE

Two independent cardiologists adjudicated the presence (or absence) of 30-day MACE including all-cause death, cardiac arrest, AMI, cardiogenic shock, sustained ventricular arrhythmia, and high-grade atrioventricular block (the primary endpoint), including the index event. The secondary endpoint was 30-day MACE plus unstable angina (UA) receiving early (≤24h) revascularization. Any early (≤24h) revascularization was considered including revascularization performed for mainly medical reasons such as recurrent episodes of UA as well as revascularizations performed mainly for convenience reasons such as an available catheter laboratory slot. As UA has a much better prognosis as AMI, it was not included in the primary endpoint.(3)

The adjudicators reviewed all available medical records - patient history, physical examination, results of laboratory testing, radiologic testing, ECG, echocardiography, cardiac exercise stress test, lesion severity and morphology in coronary angiography - pertaining to the patient from the time of ED presentation to 90-days follow up. Follow-up information was obtained directly from patients by telephone calls or in a written form, as well as from the patient's hospital notes, the family physician's or involved cardiologists' records, and the national registry on mortality. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist. Adjudication was performed centrally in a core lab. For the diagnosis of AMI it included two sets of serial cTn measurements: serial cTn measurements obtained as part of routine clinical care locally (several cTn assays), and serial measurements of hs-cTnT from study blood draws performed centrally in a core laboratory in order to take

advantage of the higher sensitivity and higher overall diagnostic accuracy offered by the hs-cTnT assays.(16) AMI was defined and hs-cTn levels interpreted as recommended in current guidelines.(4) 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 value above the 99th percentile together with a significant rise and/or fall. Absolute changes in hs-cTnT were used to determine significant changes based on the diagnostic superiority of absolute over relative changes.(17)(18) Based on studies of the biological variation of cTnT (19)(20), as well as on data from previous chest pain cohort studies, (21)(22)(23) a significant absolute change was defined as a rise or fall of at least 10 ng/l within six hours, or 6 ng/l within three hours. Unstable angina was diagnosed in patients with ischemic symptoms at rest or minor exercise with normal (hs)-cTn levels or mild elevations without dynamic changes (criteria for AMI not met) but requiring urgent (≤24h) revascularization. The following criteria were interpreted as increasing the likelihood for unstable angina versus non-cardiac chest pain: typical angina pectoris at rest; worsening/deterioration of a previously stable angina; cardiac stress test showing myocardial ischaemia; coronary angiography revealing a diameter stenosis of at least 70%, fractional flow reserve documenting functional significance of a coronary lesion, and sudden cardiac death or AMI occurred during 60-days follow-up.

Blood sampling, laboratory methods, and the ESC hs-cTnT/I-0/1h-algorithms, which were optimized for the early rule-out and rule-in of AMI and incorporate assay-specific hs-cTnT/I concentrations at ED presentation and their absolute changes within 1h,(3) are described in the online supplement.

Extended Algorithm

The extended algorithm classified patients as rule-out, if in addition to the hs-cTnT/I 0/1h-algorithm triage recommendation also clinical assessment revealed only a low or moderate likelihood for ACS (<70%) and the ECG did not show possible ischemic changes including ST-

segment depression (≥1mV in at least two contiguous leads), pathological Q-waves or T-inversion. Patients with at least one of these criteria were reclassified towards observe or rule-in. To qualify for rule-in, patients had to fulfill the criteria of the ESC hs-cTnT/I 0/1h-algorithm triage recommendation for rule-in or a hs-cTnT/I concentration above the 99th percentile combined with either a high likelihood for ACS (≥70%) and/or an ischemic ECG. The rationale for modifying the rule-in criteria was that in these patients with a high pre-test probability, an hs-cTnT level >14ng/l (hs-cTnI >26ng/L) should have a positive predictive value (PPV) sufficient for rule-in. The remaining patients were classified to the observe zone (**Supplemental Figure 2A and 2B**).

Pre-test probability for an ACS as the cause of the presenting symptoms was quantified 90 minutes after presentation by the treating ED physician using a visual analogue scale (VAS). At this time point, the ED physician had completed his/her clinical assessment including patient history, chest pain characteristics, detailed physical examination including vital signs and reviewed the ECG and the first local cTn measurement. A low or moderate likelihood for ACS was defined as <70%, while a high likelihood was defined as ≥70%.

Statistical analysis

Safety for rule-out of MACE or MACE+UA was quantified by the resulting negative predictive value (NPV) and likelihood ratio, accuracy for rule-in of MACE or MACE+UA was quantified by the resulting PPV and likelihood ratio, and efficacy was defined as the percentage of patients triaged to either rule-out or rule-in of MACE or MACE+UA. We used the cross tables derived by the application of assay and algorithm specific cut-off criteria for rule-out or rule-in to calculate diagnostic performance parameters and its 95% confidence interval (95%CI). Likelihood ratios (LRs) with 95% CIs were calculated to assess the specific value of each specific rule-out or rule-in algorithm. We used McNemar's statistics or Generalized score statistics as appropriate to compare sensitivity, specificity, NPV and PPV, between both

algorithms and predefined subgroups. Subgroups analyses have been performed in patients presenting within 2h from chest pain onset, gender, age, known CAD and estimated glomerular filtration rate.

All hypothesis testing was two-tailed, and P values of less than 0.05 were considered to indicate statistical significance. No adjustments for multiple comparisons were made. All statistical analyses were performed with the use of IBM SPSS Statistics for Windows and MAC, version 25.0 (SPSS Inc Chicago, IL) and R 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

From April 2006 to August 2015, 3123 patients eligible for this analysis were enrolled (**supplemental Figure 1A**). Patients triaged towards rule-out by the ESC hs-cTnT 0/1h-algorithm and the extended algorithm were younger, and less often had cardiovascular risk factors, pre-existing coronary artery disease (CAD), ECG abnormalities, and cardiovascular medication as compared with patients triaged towards observe and rule-in (**supplemental Tables 2 and 3**).

Reclassifications

The ESC hs-cTnT-0/1h-algorithm triaged 1880 patients (60% (95%CI, 58.5-61.9%) towards rule-out. Among these, in 209 (11%) patients integrated clinical judgment for ACS was 70% or higher, 72 (4%) patients had ST-segment depression, 131 (7%) patients had significant Q-waves and 103 (6%) patients had T-wave inversion. At least one of these criteria was present in 487 (26%) patients in the rule-out group. The extended algorithm reclassified these patients to observe (relative increase of 66%) and additionally, 297 previously classified observe patients have been reclassified to rule-in (relative increase of 61%; **Central Illustration, Figure 1)**.

Prognostic performance for MACE

Within 30 days MACE occurred in 524 (17%) patients **(Table 1 and 2).** The ESC hs-cTnT 0/1h-algorithm triaged significantly more patients towards rule-out as compared to the extended algorithm (60% (95%CI, 58.5-61.9%) vs. 45% (95%CI, 42.9-46.4%); p<0.001), while maintaining similar 30-day MACE rates (0.6% (95%CI, 0.3-1.1%) vs. 0.4% (95%CI, 0.1-0.9%); p=0.429) resulting in similar negative predictive value (NPV 99.4% (95%CI, 98.9-

99.6%) vs. 99.6% (95%CI, 99.2-99.8%); p=0.097 and likelihood ratio (0.03 (95%CI, 0.02-0.06) vs. 0.02 (95%CI, 0.01-0.04), **Figure 2A, 2B, 2C**).

Among the 487 patients reclassified towards observe by the extended algorithm, 30-day MACE rate was 1.1% (6 patients, 2 patients with type 1 MI (T1MI)) and 16% (86 patients, 55 patients with T1MI, 15 with T2MI) among patients reclassified towards rule-in (**Central Illustration**). These 30-day MACE rates were significantly lower as compared to the other observe and rule-in patients triaged by the hs-cTnT component (both p<0.001). Detailed information on patients triaged towards rule-out of AMI with MACE are given in **supplemental Table 4.**

The ESC hs-cTnT 0/1h-algorithm ruled-in fewer patients (16% (95%CI, 14.9-17.5%) vs. 26% (95%CI, 24.2-27.2%); p<0.001 as compared to the extended algorithm, albeit with a higher positive predictive value (76.6% (95%CI, 72.8-80.1%) vs. 59% (95%CI, 55.5-62.3%); p<0.001), and a higher likelihood ratio for 30-day MACE (16.3 (95%CI, 13.5-19.5) vs. 7.1 (95%CI, 6.4-7.9)). With the ESC hs-cTnT 0/1h-algorithm fewer patients remained in the observe zone as compared to the extended algorithm (24% (95%CI 22.2-25.2%) vs. 30% (95%CI 28.1-31.3%; p<0.001).

After excluding T2MI from MACE a similar negative predictive value for rule-out (NPV 99.4% (95%CI, 98.9-99.6%) vs. 99.4% (95%CI, 98.6-99.9%), p=0.997 but a lower positive predictive value for rule-in (76.6% (95%CI, 72.8-80.1%) vs. 69.5% (95%CI, 65.4-73.4%), p<0.001 for MACE and MACE without T2MI, respectively. Similar findings are reported when the we used the extended algorithm (NPV 99.6% (95%CI, 99.2-99.8%) vs. 99.6% (95%CI, 99.2-99.8%), p=0.989 and PPV 68.5% (95%CI, 65.2-71.6%) vs. 53.2% (95%CI, 49.8-56.7%), p<0.001, for MACE and MACE without T2MI, respectively (**Supplemental Table 10**).

Prognostic performance for MACE+UA

Within 30 days, MACE+UA occurred in 806 (26%) patients. Among patients triaged towards rule-out, the ESC hs-cTnT 0/1h-algorithm had lower NPV, and higher negative LR as compared to the extended algorithm: 91.7% (95%CI 90.4-92.9) versus 95.3% (95%CI 94-96.3), and 0.26 (95%CI 0.23-0.3) versus 0.14 (95%CI 0.11-0.18; all p<0.001). Among patients triaged towards rule-in, the ESC hs-cTnT 0/1h-algorithm had higher PPV, and positive LR as compared to the extended algorithm: 77% (95%CI 73.2-80.5) versus 68.5% (95%CI 65.2-71.6) and positive LR 9.5 (95%CI 8.0-11.7) vs. 6.2 (95%CI 5.5-7.1; all p<0.001; **Figure 2A, 2B, 3A and 3B).**

Subgroups analysis

A total of 830 patients (27%) presented within 2h from chest pain onset. In these patients the ESC hs-cTnT 0/1h-algorithm classified 532 patients (77%) as rule-out. For MACE, NPV was 99.3% (95%CI 98.1-99.7). Using the extended algorithm, 263 patients (38%) were classified as ruled-out. For MACE, NPV was 100% (95%CI 98.6-100); (p=0.955 for comparison, respectively, **Supplemental Figure 4 and Supplemental Table 11**). Both algorithms showed consistent and overall favorable performance characteristics in additional subgroup analyses according to sex, age, known CAD and estimated glomerular filtration rate (**Supplemental Figure 4 and Supplemental Table 11**).

Overall, the results for the ESC hs-cTnI 0/1h-algorithm and it's extended algorithm were comparable and are shown in the online supplemental.

DISCUSSION

This prospective, multicenter diagnostic study enrolling unselected patients presenting with acute chest discomfort to the ED used central adjudication to externally validate the performance of an extended algorithm, a pragmatic approach combining the ESC hs-cTnT/I 0/1h-algorithm with quantified clinical assessment and the ECG for the prediction of 30-day MACE. We report five major findings:

First, adding the two additional criteria (VAS for ACS <70% and ischaemic ECG findings) as a requirement for triage towards rule-out, significantly reduced the percentage of patients triaged towards rule-out as compared to the ESC hs-cTnT-0/1h-algorithm only (45% versus 60%). Among all reclassified patients, non-cardiac causes of chest pain were the most common final adjudicated diagnoses and 30-day MACE occurred in only 1.1%. These estimates will help clinicians to appropriately manage patients triaged towards rule-out by the ESC hs-cTnT-0/1h-algorithm, in whom either the VAS for ACS or the ECG still suggests the presence of an ACS. As an alternative to subjective clinical judgement by the treating physician, a formal score could be used to help in the prediction of 30-day MACE. This strategy of using well-validated scores such as the HEART score of the TIMI-risk score in addition to early hs-cTnT/I based algorithms has been evaluated in two recent studies and found not to provide an incremental value, but substantially reduced rule-out efficacy.(24)(25) Current guidelines recommend a conservative approach and advocate prolonged monitoring including an additional measurement of hs-cTnT/I 3-6h after presentation in these patients.(3)

Second, among patients triaged towards rule-out, the extended algorithm achieved similar NPV for 30-day MACE (both >99%) as compared to the ESC hs-cTnT-0/1h-algorithm alone, while sensitivity was higher using the extended algorithm (99.0% versus 97.7%; p=0.014). Therefore, overall the ESC hs-cTnT-0/1h-algorithm seemed to better balance safety and efficacy. It is important to highlight that the MACE rate including all-cause death, cardiac

arrest, AMI, cardiogenic shock, sustained ventricular arrhythmia, and high-grade atrioventricular block in the rule-out group of the ESC hs-cTnT-0/1h-algorithm only was 0.6%, and thereby within the range requested by ED physicians in a recent survey for patients considered for discharge from the ED.(26)

Third, the extended algorithm had a higher rule-in rate, albeit a lower PPV as compared to the ESC hs-cTnT-0/1h-algorithm (59% versus 77%). As AMI at presentation was the dominant event contributing to 30-day MACE, it is a matter of debate, which PPV is sufficient to justify a homogenous management in the rule-in group including early coronary angiography.

Fourth, including patients with UA receiving early revascularization to MACE, led to an increase in MACE from 524 to 804 patients (relative increase of 53%) and a MACE event rate of 26% in the overall cohort. This reflects the enrolment of unselected – both high-risk and low-risk- patients with suspected AMI and the adjudication of AMI including type 1 and type 2. Furthermore, excluding T2MI from MACE resulted in a similar NPV for rule-out but a lower PPV for rule-in. For 30-day MACE plus UA, the extended algorithm significantly increased NPV as compared to the ESC hs-cTnT-0/1h-algorithm, while the later again achieved higher PPV for rule-in.

Fifth, using hs-cTnI, the performance of the extended algorithm relative to the ESC hs-cTnI 0h/1h-algorithm overall were similar to that observed for hs-cTnT. Similar findings have been found in several predefined subgroups especially in early presenters within 2h after chest pain onset (NPV 99.3% and 100%), for the ESC hs-cTnT-0/1h-algorithm and the extended algorithm, respectively.

These findings extend and corroborate insights gained in the single-centre pilot study of the extended-algorithm.(11) There, in patients triaged towards rule-out for 30-day MACE, the NPV

was 99.9% (95%CI, 99.2-100%) for the ESC 0/1h-hs-cTnT-algorithm and 100% (95%CI, 99.4-100%) for the extended algorithm. In patients triaged towards rule-in, the PPV was 65.4% (95%CI, 55.2–74.5) and 52.7% (95%CI, 44.3–61.1), respectively.(11) Again, for 30-day MACE+UA, the extended algorithm had higher NPV, but lower PPV as compared to the ESC 0/1h hs-cTnT-algorithm.

The management of patients, in whom the three diagnostic pillars for suspected AMI including the ESC 0/1h-algorithm, the ECG, and clinical assessment summarized in the integrated clinical judgment, consistently suggest rule-out of AMI, is usually straight forward and consists of rapid discharge from the ED followed by appropriate outpatient management,(3) In contrast, the subgroup of patients, in whom the ESC hs-cTnT-0/1h-algorithm suggests rule-out of AMI, but in whom either the VAS for ACS or the ECG still suggests the presence of an ACS, remains controversial. While prolonged initial monitoring and additional hs-cTnT/I measurements at about 3h for sure are reasonable next steps for the vast majority of these patients, the most critical decision is whether to admit or to prefer an outpatient management in case the 3h-messurements still does not provide evidence of AMI. The low, but not very low risk of MACE observed in these patients in this large study, should provide for joined informed decision making by the physician and the patient. Patient preferences, availability of same day or next day non-invasive imaging and/or coronary angiography, and absence or presence of comorbidities possibly decreasing the benefit/risk ratio of an early invasive approach including dementia, very high age, severe renal dysfunction, and known atherosclerosis in the aortic arch will have to be considered. These arguments are similar to those guiding the management regarding possible ACS in patients triaged towards the observe zone.(12)

Our findings corroborate and extend previous work on the development and validation of algorithms for the safe and effective rule-out and rule-in of MACE in patients with symptoms suggestive of AMI.(11)(24)(25) Pioneering work by research groups in Asia-Pacific 15 years

ago, at a time when only cTn assays with poor sensitivity were available, resulted in the first accelerated diagnostic protocols (ADP).(11)(27)(28) These required the use of a formal risk score in addition to the ECG and cTn to achieve a very high NPV for MACE, and allowed the rapid rule-out in 9% of patients. The development of hs-cTn assays then enabled two advances of major clinical relevance. The first advance was to obviate the need of formal risk stratification for safe rule-out, while maintaining high NPV for MACE, which increased the likelihood for adaptation and adherence, and also substantially increased the percentage of patients eligible for early rule-out.(11)(24)(25) E.g. the ESC 0/1h hs-cTnT/I, the ESC 0/2h hs-cTnT/I, and the High-STEACS-algorithm triage more than 50% of patients towards rule-out and provide comparable and very high safety. (3)(11)(29) The second major advance was the addition of a rule-in component that also provides well-structured guidance to physicians for the early identification of those acute chest discomfort patients requiring immediate hospitalisation in a monitored unit, early coronary revascularization, early initiation of high-intensity statin and potent dual antiplatelet therapy.(11) Thereby, from being only helpful for the early identification of a small group of low-risk patients, these algorithms have matured towards highly effective clinical decision support tools that provide detailed guidance for patient management in about 75% of unselected patients presenting with acute chest discomfort to the ED.

When diagnosed with hs-cTnT/I assays, UA seems to more closely reflect the pathophysiology and outcomes of stable CAD than AMI.(3)(30) UA patients have substantially lower 30-day mortality including fatal MI as compared to patients with NSTEMI.(31) Likely due to these differences, early invasive strategies and potent dual antiplatelet therapy seem to provide less incremental benefit as compared to patients with NSTEMI.(3)(32)(33) Still, the appropriate detection of UA is of considerable importance and the extended algorithm seems to be a valuable tool in this regard. As the ESC 0/1h hs-cTnT/I-algorithms were designed to detect AMI, and as UA, by definition, is not associated with acute cardiomyocyte injury, the ESC

0/1h-hs cTnT/I-algorithms cannot detect UA. As an alternative to formal quantification of integrated clinical judgment, as done as part of the extended algorithm, UA can of course also be assessed and diagnosed using individualized clinical judgment based on history, chest pain characteristics, physical examination, and the ECG by the treating physician. It is worth mentioning that in our cohort patients with unstable angina underwent early PCI, which was likely combined with dual antiplatelet therapy and sometimes together with anticoagulation if indicated and this probably contributed to their clinical stabilization and to their low risk of suffering other MACE at 30 days. This finding should not misinterpret that unstable angina patients can be safely discharged from the ED without further evaluation. Further clinical trials are necessary to compare different management strategies based on these algorithms to clarify the best treatment in these patients.

Limitations

Some limitations merit consideration when interpreting these findings. **First,** our study was conducted in ED patients with symptoms suggestive of AMI. Further studies are required to quantify the utility of both algorithms 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 AMI. **Second,** some patients did not have a 1h sample and therefore were excluded from this analysis. It is very unlikely that the performance of both algorithms would be worse in these, particularly as a common reason for a missing blood samples at 1 hour were logistic issues related to e.g. early transfer to the catheter laboratory. **Third**, although we used a very stringent methodology to adjudicate the presence or absence of AMI including central adjudication by experienced cardiologists, imaging and serial measurements of hs-cTn, we still may have misclassified a small number of patients.(4) However, it is unlikely that these rare misclassifications did affect the relative performance of the extended algorithm versus the ESC 0/1h hs-cTnT/I-algorithm. **Fourth,** in this prospective study, no specific sample size calculation was performed. Although

this secondary analysis from a multicenter study is one of the largest ever performed, it still may have been underpowered for some subgroup analyses. **Fifth,** we cannot generalize our findings to patients with terminal kidney failure on chronic dialysis since they were excluded from this study. **Sixth,** these algorithms were derived and validated in patients capable of providing informed consent. Their use is discouraged in extreme conditions such as e.g. patients after cardiopulmonary resuscitation, in shock or respiratory failure, as they have not been tested in these.

In conclusion, the ESC hs-cTn 0/1h-algorithm better balanced efficacy and safety in the prediction, both rule-out and rule-in, of 30-day MACE, while the extended algorithm is the preferred option for the rule-out of 30-day MACE+UA.

Clinical Perspectives

- **Competency in Medical Knowledge:** It has been hypothesized that adding clinical judgment and ECG findings to the European Society of Cardiology (ESC) high-sensitivity cardiac troponin (hs-cTn) 0/1h-algorithm would further improve its performance to predict short-term major adverse cardiac events (MACE).
- **Competency in Patient Care:** The ESC hs-cTn 0/1h-algorithm better balanced efficacy and safety in the prediction of MACE, while an extended algorithm combining hs-cTn with the clinical judgment and the ECG performed better for rule-out if unstable angina is included to short-term MACE.
- **Translational Outlook:** The findings of the present study help guide the management of patients in whom hs-cTn, the ECG, and clinical judgment provide discordant results.

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Table 1 MACE rate ESC hs-cTnT 0/1h-algorithm

	all patients (n = 3123)		Rule Out (n = 1880; 60%)		Observe Zone (n = 738; 24%)		Rule In (n = 505; 16%)	
MACE	524	17%	11	0.6%	126	17%	387	77%
MACE+UA	806	26%	155	8.2%	262	36%	389	77%
T1MI during index visit	424	14%	3	0.2%	78	11%	343	70%
T2MI during index visit	68	2.2%	0	0.0%	25	3.4%	43	8.5%
T1MI during follow up	34	1.1%	3	0.2%	19	2.6%	12	2.4%
UA	300	9.6%	146	7.8%	151	21%	3	0.6%
Cardiogenic shock	10	0.3%	0	0.0%	3	0.4%	7	1.4%
Ventricular arrhythmia	6	0.2%	0	0.0%	2	0.3%	4	0.8%
High-grade AV Block	10	0.3%	3	0.2%	3	0.4%	4	0.8%
Cardiac death	16	0.5%	1	0.1%	3	0.4%	12	2.4%
Non cardiac death	10	0.3%	1	0.1%	6	0.8%	3	0.6%

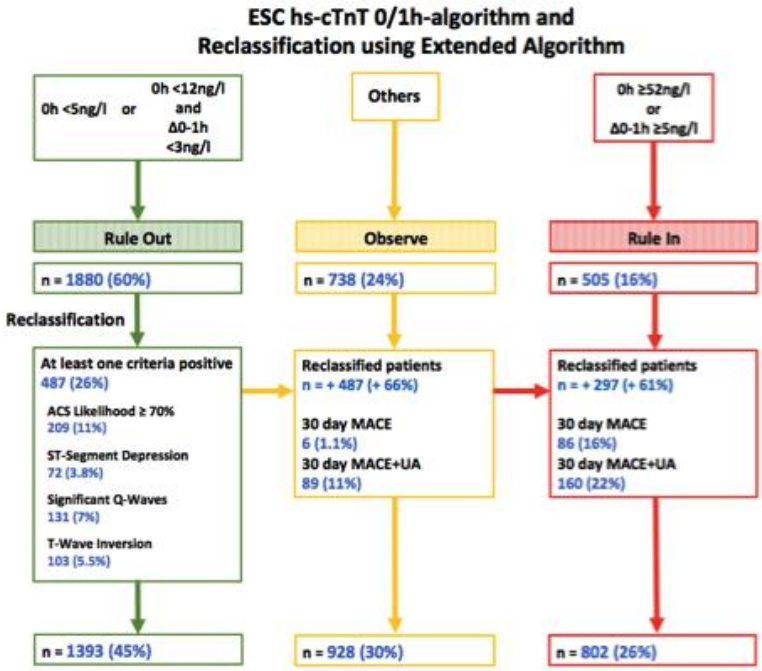
Table Legend: MACE: major adverse cardiac event, MACE-UA: major adverse cardiac event with unstable angina
T1MI: Type 1 myocardial infarction; T2MI: Type 2 myocardial infarction UA: unstable angina; values are presented in n and %

Table 2 MACE Rate Extended Algorithm

	all patients (n = 3123)		Rule Out (n = 1393; 45%)		Observe Zone (n = 928; 30%)		Rule In (n = 802; 26%)	
MACE	524	17%	5	0.4%	46	5.0%	473	59%
MACE+UA	806	26%	66	4.7%	191	21%	549	69%
T1MI during index visit	424	14%	1	0.1%	25	2.7%	398	50%
T2MI during index visit	68	2.2%	0	0.0%	10	1.1%	58	7.2%
T1MI during follow up	34	1.1%	0	0.0%	8	0.9%	26	3.2%
UA	300	9.6%	61	4.4%	151	16%	88	11%
Cardiogenic shock	10	0.3%	0	0.0%	0	0.0%	10	1.2%
Ventricular arrhythmia	6	0.2%	0	0.0%	2	0.2%	4	0.5%
High-grade AV Block	10	0.3%	2	0.1%	3	0.3%	5	0.6%
Cardiac death	16	0.5%	1	0.1%	0	0%	15	1.9%
Non cardiac death	10	0.3%	1	0.1%	1	0.1%	8	1.0%

Table Legend: MACE: major adverse cardiac event, MACE-UA: major adverse cardiac event with unstable angina
T1MI: Type 1 myocardial infarction; T2MI: Type 2 myocardial infarction UA: unstable angina; values are presented in n and %

Figure Legends



Central Illustration **Reclassified patients using the extended algorithm**

Hs-cTnT concentrations are presented in ng/L. 0h/1h = hs-cTnT at presentation and after 1 hour. Δ0h-1h = absolute change of hs-cTnT within the first hour. ESC: European Society of Cardiology; Hs-cTnT: High-sensitivity cardiac troponin T; MACE: major adverse cardiac event; MACE+UA: major adverse cardiac event with unstable angina; NPV: negative predictive value; PPV: positive predictive value; Pos.LR: positive likelihood ratio; Neg.LR: negative likelihood ratio; * if chest pain onset >3h

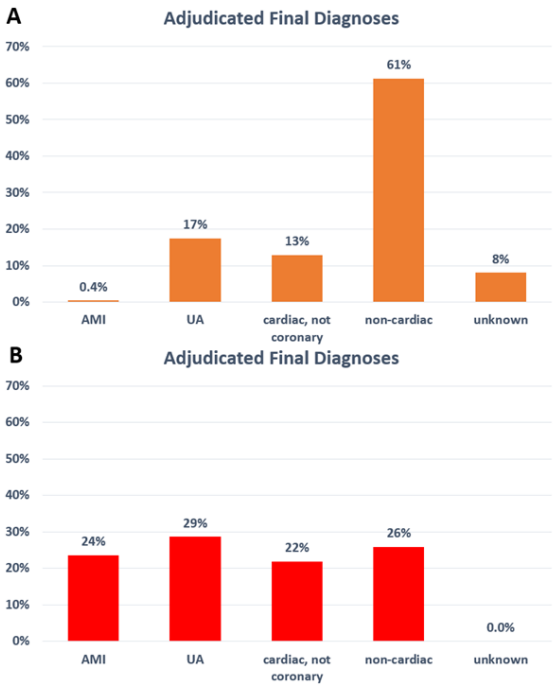


Figure 1 **Adjudicated Final Diagnoses**

Adjudicated final diagnoses among reclassified patients to the observe zone (A) and to rule-in (B). AMI: acute myocardial infarction; UA: unstable angina

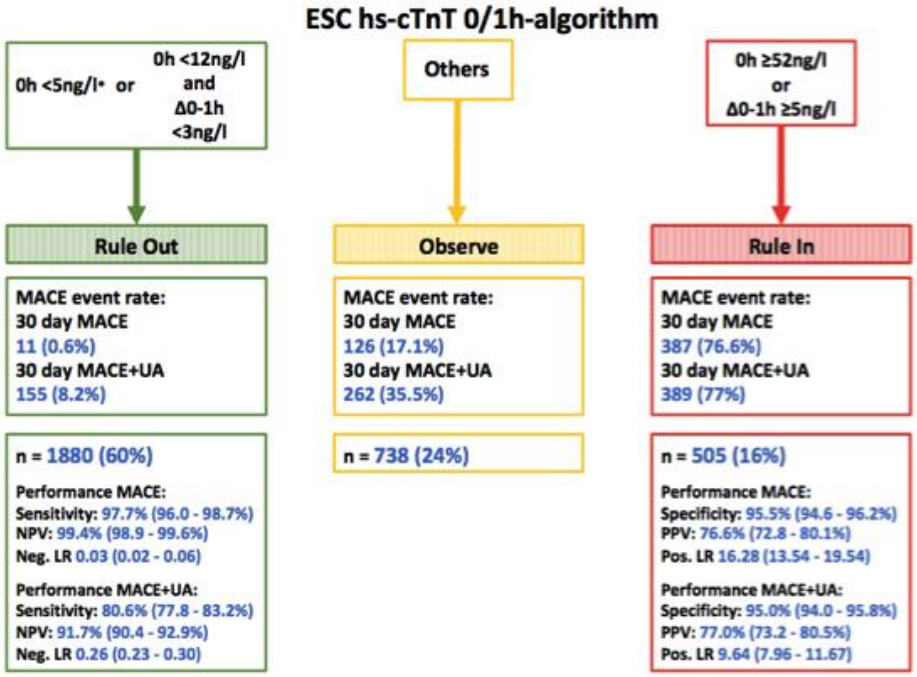


Figure 2A **ESC Hs-cTnT 0/1h-algorithm: criteria and performance**

Hs-cTnT concentrations are presented in ng/L. 0h/1h = hs-cTnT at presentation and after 1 hour. Δ0h-1h = absolute change of hs-cTnT within the first hour. ESC: European Society of Cardiology; Hs-cTnT: High-sensitivity cardiac troponin T; MACE: major adverse cardiac event; MACE+UA: major adverse cardiac event with unstable angina; NPV: negative predictive value; PPV: positive predictive value; Pos.LR: positive likelihood ratio; Neg.LR: negative likelihood ratio; * if chest pain onset >3h

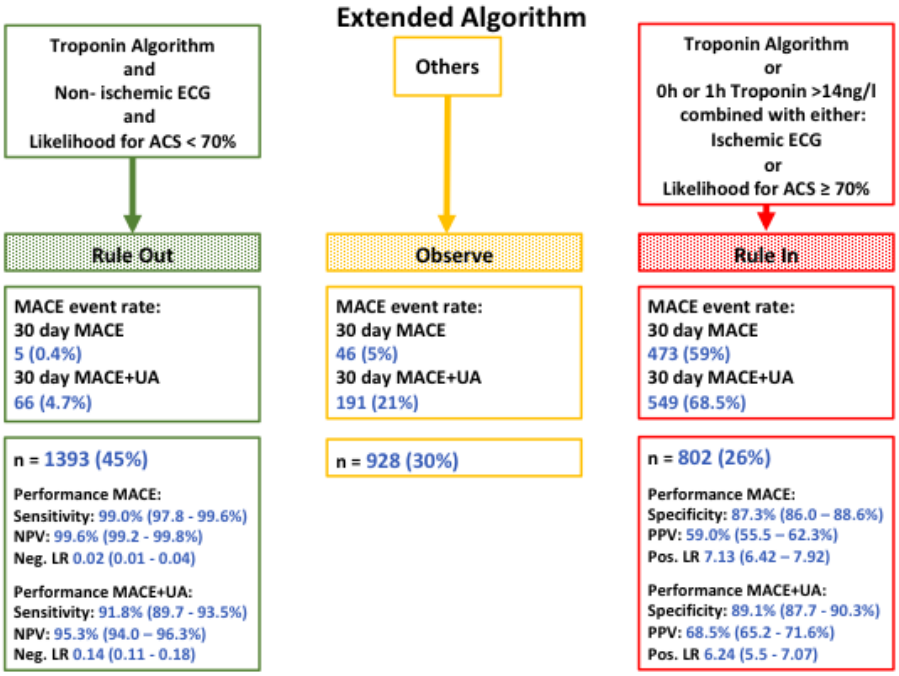


Figure 2B **Extended algorithm: criteria and performance**

Hs-cTnT concentrations are presented in ng/L. 0h/1h = hs-cTnT at presentation and after 1 hour. Δ0h-1h = absolute change of hs-cTnT within the first hour. ESC: European Society of Cardiology; Hs-cTnT: High-sensitivity cardiac troponin T; MACE: major adverse cardiac event; MACE+UA: major adverse cardiac event with unstable angina; NPV: negative predictive value; PPV: positive predictive value; Pos.LR: positive likelihood ratio; Neg.LR: negative likelihood

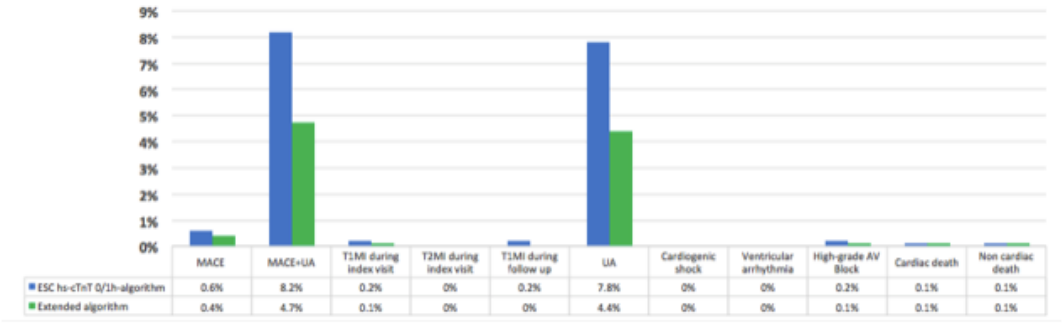


Figure 2C **MACE Rate in both Rule-out groups**

ESC: European Society of Cardiology; Hs-cTnT: High-sensitivity cardiac troponin T; MACE: major adverse cardiac event; MACE+UA: major adverse cardiac event with unstable angina; UA: unstable angina; T1MI: Type 1 myocardial infarction; T2MI: Type myocardial infarction.

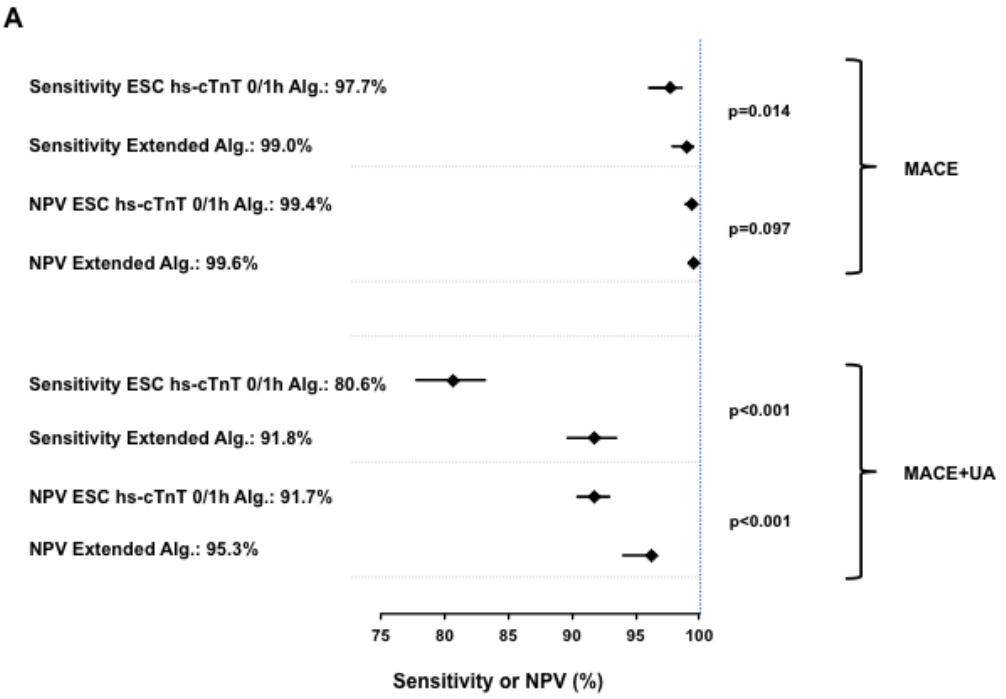


Figure 3A	**Forest plots for sensitivity and negative predictive value including interaction p-value in both algorithms**

Forest plots indicating sensitivity and negative predictive values (NPV) for the troponin and the extended algorithm and interaction p-values

Alg.: algorithm; MACE: major adverse cardiac event; MACE+UA: major adverse cardiac event with unstable angina

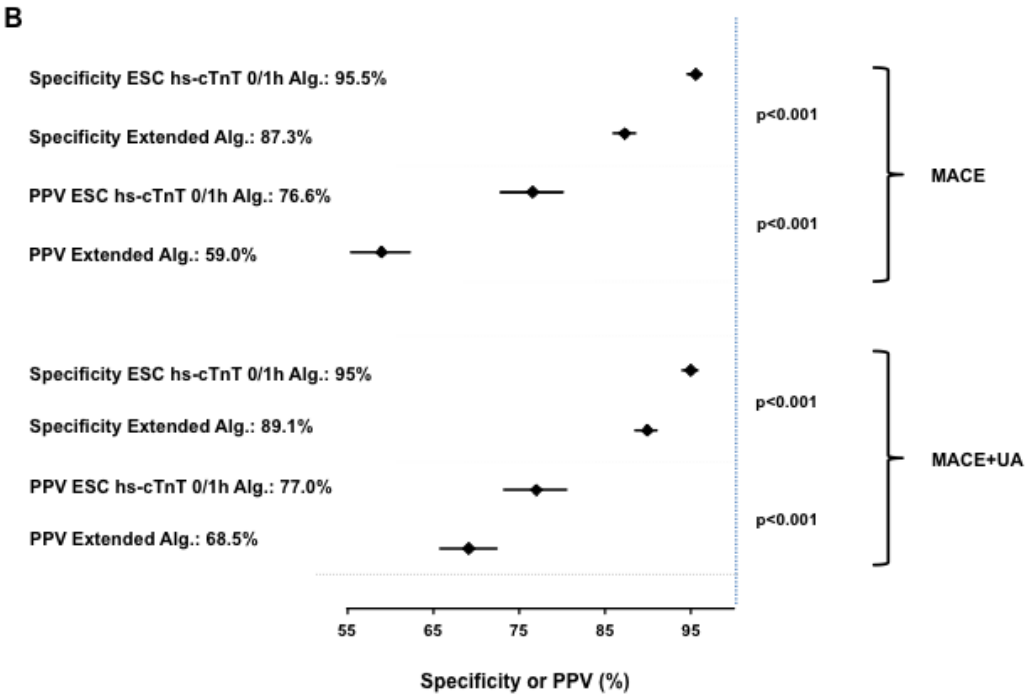


Figure 3B	**Forest plots for specificity and positive predictive value including interaction p-value in both algorithms**

Forest plots indicating specificity and positive predictive values (PPV) for the troponin and the extended algorithm and interaction p-values

Alg.: algorithm; MACE: major adverse cardiac events; MACE+UA: major adverse cardiac event with unstable angina