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

Raphael Twerenbold, MD[a,b*]; Johannes Tobias Neumann, MD[b,c*]; Nils Arne Sörensen[b,c], MD; Francisco Ojeda, PhD[b]; Mahir Karakas, MD[b,c]; Jasper Boeddinghaus, MD[a]; Thomas Nestelberger, MD[a]; Patrick Badertscher, MD[a]; Maria Rubini Giménez, MD[a]; Christian Puelacher, MD[a]; Karin Wildi, MD[a]; Nikola Kozhuharov, MD[a]; Dominik Breitenbuecher, MD[a]; Ewelina Biskup, MD[a]; Jeanne du Fay de Lavallaz, MD[a]; Dayana Flores, MD[a]; Desiree Wussler, MD[a]; Òscar Miró, MD[d]; F. Javier Martín Sánchez, MD[e]; Beata Morawiec, MD[f]; Jiri Parenica, MD[g]; Nicolas Geigy, MD[h]; Dagmar I. Keller, MD[i]; Tanja Zeller, PhD[b,c]; Tobias Reichlin, MD[a]; Stefan Blankenberg, MD[b,c]; Dirk, MD[b,c#]; Christian Mueller, MD[a#].
*Both authors have contributed equally and should be considered first author.
[#] Both authors have contributed equally and should be considered last author.

[a] Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland; [b] Department of General and Interventional Cardiology, University Heart Center Hamburg, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [c] German Centre for Cardiovascular Research (DZHK), Partner Site Hamburg/Luebeck/Kiel, Hamburg, Germany; [d] Emergency Department, Hospital Clinic, Barcelona, Catalonia, Spain; [e] Servicio de Urgencias, Hospital Clínico San Carlos, Madrid, Spain; [f] 2nd Department of Cardiology, Medical University of Silesia, Zabrze, Poland; [g] Department of Cardiology, University Hospital Brno, Brno, Czech Republic and Medical Faculty, Masaryk University, Brno, Czech Republic; [h] Emergency Department, Kantonsspital Baselland, Liestal, Switzerland; [i] Emergency Department, University Hospital Zurich, Zurich, Switzerland.

Short Title: Validation of the ESC 0/1h-Algorithm

Funding: The APACE study was supported by research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the KTI, the European Union, the Stiftung für kardiovaskuläre Forschung Basel; Abbott, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, and Singulex. The BACC study was supported by the German Center of Cardiovascular Research and an unrestricted grant from Abbott Diagnostics. The investigated high-sensitivity cardiac troponin T and I 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.

Disclosures: Dr. Twerenbold reports receiving 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 as well as speaker honoraria/consulting honoraria from Roche Diagnostics, Abbott Diagnostics, Siemens, Singulex and Brahms. Dr. Neumann reports consulting honoraria from Acarix. Dr. Rubini reports receiving speaker honoraria from Abbott. Dr. Boeddinghaus reports receiving speaker honoraria/consulting honoraria from Siemens. Dr. Reichlin reports receiving 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 as well as speaker honoraria from Brahms and Roche. Dr Blankenberg reports receiving honoraria from Abbott Diagnostics, Siemens, Thermo Fisher and Roche Diagnostics and serving as a consultant for Thermo Fisher. Dr. Mueller reports receiving 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, Astra Zeneca, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, Singulex, Sphingotec, and the Department of Internal Medicine, University Hospital Basel, as well as speaker honoraria/consulting honoraria from Abbott, Alere, Astra Zeneca, Biomerieux, Boehringer Ingelheim, BMS, Brahms, Cardiorentis, Novartis, Roche, Siemens, and Singulex. All other authors declare that they have no conflict of interest with this study. 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.

Address for correspondence:
Mr. Dirk Westermann, MD
Department of General and Interventional Cardiology
University Heart Center Hamburg, University Hospital Hamburg Eppendorf
Martinistr 52, 20246 Hamburg, Germany
Telephone: +49 407 410 568 00
Fax: +49 407 410 536 22
E-Mail: d.westermann@uke.de
Twitter Handle: @CRIBasel, @RTwerenbold, @baccstudy

ABSTRACT

Background: The safety of the European Society of Cardiology (ESC) 0/1h-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: We aimed to validate the diagnostic performance of the 0/1h-algorithm in a large multicentre study.

Methods: We prospectively enrolled unselected patients presenting to the emergency department with symptoms suggestive of NSTEMI in six countries. Final diagnosis was centrally adjudicated by two independent cardiologists. Hs-cTnT and hs-cTnI blood concentrations were measured at presentation and after one hour. 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 1h.

Results: Prevalence of NSTEMI was 17%. Among 4368 patients with serial hs-cTnT measurements available, safety of rule-out (NPV 99.8%, 2488/2493), accuracy of rule-in (PPV 74.5%, 572/768) and overall efficacy was high by assigning three fourths of patients either to rule-out (57%, 2493/4368) or rule-in (18%, 768/4368). Similarly, among 3500 patients with serial hs-cTnI measurements, safety of rule-out (NPV 99.7%, 1528/1533), accuracy of rule-in (PPV 62.3%, 498/800) and overall efficacy was high by assigning more than two thirds of patients either to rule-out (44%, 1533/3500) or rule-in (23%, 800/3500). Excellent safety was confirmed in multiple subgroup analyses including patients presenting early (≤3 hours) after chest pain onset.

Conclusions: The ESC 0/1h-algorithm using hs-cTnT and hs-cTnI is very safe and effective in triaging patients with suspected NSTEMI.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00470587 (APACE) and NCT02355457 (BACC).

Condensed Abstract: The European Society of Cardiology (ESC) recommends the 0/1h-algorithm using high-sensitivity cardiac troponin (hs-cTn) T or I for rapid rule-out and rule-in of Non-ST-Segment-Elevation Myocardial Infarction. However, its safety has been questioned. We aimed to validate the diagnostic performance in a large multicentre study. Among 4368 patients with available hs-cTnT and 3500 patients with available hs-cTnI measurements, safety of rule-out (negative predictive value 99.8% and 99.7%, respectively), accuracy of rule-in (positive predictive value 74.5% and 62.3%, respectively) and overall efficacy was very high by assigning more than two thirds of patients either to rule-out or rule-in within one hour.

Key Words: myocardial infarction, diagnostic algorithms, rule-in, rule-out, diagnosis of myocardial infarction, troponin

Abbreviations

ECG = electrocardiography
ED = emergency department
ESC = European Society of Cardiology
Hs-cTn = high-sensitivity cardiac troponin
MI = myocardial infarction
MACE = major adverse cardiac event

LR = likelihood ratio
NPV = negative predictive value
NSTEMI = Non-ST-Segment-Elevation Myocardial Infarction
PPV = positive predictive value

Introduction

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 as it allows the timely detection and treatment of alternative causes of acute chest pain and possible early discharge for outpatient management (2,3).

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) 0/1h-algorithm (2-15). The ESC hs-cTn 0/1h-algorithm, which should always be used in conjunction with all other clinical information including clinical assessment and the ECG, uses assay-specific cut-off 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 (≤3h after chest pain onset) to ensure safety particularly in this vulnerable subgroup and that the performance characteristics of the ESC 0/1h-algorithm may not be sufficient for routine clinical application.(12,16) We therefore aimed to validate the ESC 0/1h-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 two large diagnostic studies with no study-specific interventions to maximize generalizability and particularly the number of early presenters: **first**, the Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE, NCT00470587) study, which is an ongoing prospective international multicentre study with twelve centers in five European countries (Switzerland, Italy, Spain, Poland, Czech Republic) designed to contribute to advancing the early diagnosis of MI;(5-7,13,17-21) **second**, the Biomarkers in Acute Cardiac Care (BACC, 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 was obtained. In both studies enrolment was independent of renal function, while patients with terminal kidney failure on chronic dialysis were excluded in APACE. 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 cut-off criteria of the investigated ESC 0/1h-algorithm were originally derived in two 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 0/1h-hs-cTnT or ESC 0/1h-hs-cTnI-algorithm, as well as all patients enrolled in the BACC-study.

From all the prospectively recruited patients, two diagnostic datasets were constructed: Diagnostic dataset A with complete serial hs-cTnT measurements (0h and 1h samples) and diagnostic dataset B with complete serial hs-cTnI measurements. The most common reasons for

missing samples after one hour were early transfer to the catheter laboratory or coronary care unit and diagnostic procedures around the 1h-window that precluded blood draw at one hour. (**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 analysed 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 discretion of the attending physician.

Adjudicated final diagnosis

Adjudication of the final diagnosis was performed centrally in each study by two 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 BACC and 90-day follow up for patients in APACE. 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 setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least one 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 method section in the online-only supplement. All other patients were classified in the categories of unstable angina (UA), stable angina (in BACC only; in APACE the chest pain episode leading to ED presentation was adjudicated to either UA, if ischemic and not fulfilling criteria for MI, or non-cardiac, if non-ischemic), non-cardiac chest pain (NCCP), cardiac but non-coronary 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 one hour. 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, IL, USA) analyser (Online Appendix).

ESC 0/1h-algorithm

The ESC 0/1h-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 towards rule-out, observe and rule-in based on assay-specific levels of hs-cTn obtained at presentation and

after one hour **(Online Figure 2)** (2). The specific cut-off 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 while type 1 NSTEMI was the secondary diagnostic endpoint. The primary prognostic endpoint was overall mortality at 30 days and one year while the secondary prognostic endpoint was major adverse cardiac event (MACE), defined as the composite of overall mortality and MI (including the index event), at 30 days and one year. Rule-out safety of the ESC 0/1h-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 0/1h-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 ($\leq$3h) after chest pain onset,(21,25) subgroup analysis in this vulnerable group of early presenters was predefined. Additional predefined subgroup analyses were performed according to sex, age older than 65 years, pre-existing coronary artery disease, renal dysfunction [defined as glomerular filtration rate < 60ml/min/1.73m^2], and contributing study cohort.

Statistical analysis

As the ESC 0/1h-Algorithm contains three triage categories (rule-out/observe/rule-in), 2x3s tables were constructed to assess its diagnostic performance. All diagnostic performance measures (proportions, predictive values and LR for NSTEMI in the three triage categories) were derived from these 2x3 tables as described in detail in **Online Figure 3.** Mortality and MACE during follow-up was analyzed using Kaplan-Meier survival curves. Net reclassification improvement analysis was used to compare the ability of the ESC hs-cTnT and the hs-cTnI 0/1h-algorithms to correctly classify patients according to risk of one-year mortality and incidence of MACE. Further details on the statistical analysis can be found in the method section of the Online Appendix.

Results

Characteristics of patients

From May 2006 to April 2016, 5856 patients with suspected MI were recruited in six 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 0/1h-algorithms, 4368 patients with serial samples of hs-cTnT (diagnostic dataset A) and 3500 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 3468 patients with both hs-cTnT and hs-cTnI 0/1h-samples available used for comparison of prognostic performance of hs-Tn (common prognostic dataset).

Thirty percent of patients were early presenters (≤3h after chest pain onset) and thirty percent were admitted to the ED by ambulance. Baseline characteristics of the two 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 735/4368 patients (17%), UA in 462/4368 (11%), stable angina in 16/4368 (0.4%), cardiac symptoms of origin other than CAD, such as tachyarrhythmia, takotsubo cardiomyopathy, heart failure or myocarditis, in 814/4368 (19%), non-cardiac symptoms in 2226/4368 (51%) and unknown in 115/4368 patients (3%). Among the 735 patients presenting with NSTEMI, 572 (78%) were diagnosed as type 1 NSTEMI.

Discrepancies between the discharge diagnosis by the treating physician and the adjudicated final diagnosis of NSTEMI were present in 5.7% (250/4368) of patients.

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 55ng/L and 93.6ng/L, respectively) as compared to patients with other final diagnoses (median 7ng/L and 4.0ng/L, respectively, $p<0.001$ for comparisons). Similarly, absolute 1h-changes were higher in patients with NSTEMI as compared to patients with other final diagnoses for both hs-cTn assays (median absolute 1h-change: 10ng/L and 35.2ng/L versus 1ng/L and 0.7ng/L, respectively, $p<0.001$ comparisons). Median time between the first and second blood draw for serial hs-cTn measurement was 60 [59, 68] minutes with 90% of all samples collected within 46-84 minutes after the first blood draw.

Diagnostic performance of the ESC 0/1h-algorithm using hs-cTnT

The concept and condensed diagnostic performance of the ESC 0/1h-algorithm using hs-cTnT and hs-cTnI is visualized in the **Central Illustration**.

Using hs-cTnT, the ESC 0/1h-algorithm triaged 57% (2493/4368) of patients towards rule-out **(Figure 1)**. Direct rule-out based on 0h-hs-cTnT-concentrations <5ng/L was feasible in 16% (706/4368) of patients, missing no NSTEMI (NPV 100.0% [706/706]). Overall, safety of rule-out was very high (NPV 99.8% [2488/2493]; LR 0.01 [(5/735):(2488/3633)]).

Rule-in was feasible in 18% (768/4368) of patients with appropriate accuracy (PPV 74.5%, [572/768], LR 14.43 [(572/735):(196/3633)]). Takotsubo cardiomyopathy, myocarditis, heart failure, and unstable angina 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 0h- and 1h-hs-cTnT-samples in 75% (3261/4368) of patients. Baseline characteristics 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 to the rule-out group Details on the five NSTEMI-patients (0.1%) incorrectly ruled-out by the ESC 0/1h-algorithm are listed in **Online Table 5**.

Diagnostic performance of the ESC 0/1h-algorithm using hs-cTnI

Using hs-cTnI, the ESC 0/1h-algorithm triaged 44% (1533/3500) of patients towards rule-out **(Figure 2)**. Direct rule-out based on 0h-hs-cTnT-concentrations <2ng/L was feasible in 10% (362/3500) of patients, missing no NSTEMI (NPV 100.0% [362/362]). Overall, safety of rule-out was very high (NPV 99.7% [1528/1533]; LR 0.02 [(5/588):(1528/2912)]).

Rule-in was feasible in 23% (800/3500) of patients with appropriate accuracy (PPV 62.3%, [498/800]; LR 8.17 [(498/588):(302/2912)]). Takotsubo cardiomyopathy, myocarditis, heart failure, and unstable angina 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 0h- and 1h-hs-cTnI-samples in 67% (2333/3500) of patients. 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 five NSTEMI-patients (0.1%) incorrectly ruled-out by the ESC 0/1h-algorithm are listed in **Online Table 8**.

Subgroup analysis:

A) Early presenters

In patients presenting to the ED early after chest pain onset, e.g. within 3 hours (=early presenters; 1322/4368 in diagnostic dataset A, 1064/3500 in diagnostic dataset B), rule-out safety and rule-in accuracy of the ESC 0/1h-algorithm were similar to those observed in late presenters for both hs-cTnT and hs-cTnI **(Table 2, Figure 3)**.

B) Other subgroups

Additional subgroup analyses according to sex, age, presence of coronary artery disease and renal dysfunction confirmed very high and comparable rule-out safety and rule-in accuracy while differences in overall efficacy could be observed. High performance of the ESC 0/1h-alghorithm 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 0/1h-algorithm, as quantified by the NPV and LR, was very high and tended to be even higher as compared to the safety for the diagnosis of both type 1 and 2 NSTEMI. In contrast, the PPV and LR of the triage towards rule-in decreased and was lower as compared to the main analysis (**Online Figure 4)**.

Prognostic performance to predict death and MACE during follow-up

Among the 3468 patients in the common prognostic dataset with both serial hs-cTnT and hs-cTnI measurements available (overlap of diagnostic dataset A and B), median follow-up time was 390 days [IQR 365-772] and 82% (2854/3468) of patients had completed one-year follow-

up. Only 0.06% (2/3468) of patients were lost to follow-up within one year. The ESC 0/1h-algorithm allowed a powerful discrimination between low-risk of all-cause mortality at 30 days and one year in the rule-out group (for hs-cTnT 0.1% and 0.8%, respectively; for hs-cTnI 0.1% and 1.0%, respectively), intermediate risk in the observational group (for hs-cTnT 0.7% and 7.2%, respectively; for hs-cTnI 0.4% and 5.7%, respectively), and high-risk in the rule-in group (for hs-cTnT 2.8% and 10.4%, respectively; for hs-cTnI 2.5% and 8.0%, respectively; log-rank $p<0.001$ for comparisons between triage strata of each algorithm, **Figure 4)**. Similarly, the ESC 0/1h-algorithm using both hs-cTnT and hs-cTnI strongly discriminated the risk of MACE (including index events) at 30 days and one year in the three strata (**Online Figure 5).** According to net reclassification improvement analysis, the ESC hs-cTnT 0/1h-algorithm was superior to the ESC hs-cTnI 0/1h-algorithm to assign risk of one-year mortality (NRI 16.1, $p<0.001$) and one-year MACE (NRI 12.3, $p<0.001$) within the respective rule-out, observe and rule-in groups. Triage by the ESC 0/1h-algorithm using hs-cTnT and hs-cTnI both provided incremental prognostic information regarding mortality and incidence of MACE at one year independent of NSTEMI diagnosis **(Online Table 10)**. Prognostic findings were confirmed when assessed in the diagnostic dataset A and B individually (**Online Figures 6 and 7)**.

Discussion

This large multicentre study, including a large subgroup of early presenters (n=1322), was performed to address recent concerns regarding the suitability for routine clinical care of the new ESC hs-cTn 0/1h-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) We report **six major findings**:

First, the safety of the triage towards rule-out of NSTEMI, as quantified by NPV (99.7-99.8%) and LR (0.01-0.02), 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 0/1h-algorithm.(2,3,5-15) **Second,** PPV (62-74%) and LR (8-14) of the triage towards 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 towards rule-in with diagnoses other than MI including Takotsubo cardiomyopathy, myocarditis, heart failure and unstable angina. This clinical perspective is critically important when discussing what constitutes an appropriate PPV for the rule-in zone.[12] **Third**, the ESC 0/1h-algorithm was highly effective allowing triage of more than two thirds of patients towards 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 0/1h-algorithm overall had similar performance characteristics in the vulnerable subgroup of early presenters (<3h) as compared to the overall cohort. While the point estimates for NPV, PPV and LR were slightly lower in early presenters as compared to 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 towards rule-out or rule-in was slightly higher in early presenters as compared to late presenters, further documenting the suitability for routine clinical care of the ESC 0/1h-algorithm in early presenters. Of note, this is the largest cohort of early presenters ever tested for the performance of the ESC 0/1h-algorithm. Robust findings were obtained from multiple subgroup analyses including sex, age, presence of coronary artery disease and renal

dysfunction, confirming excellent safety of rule-out and reasonable accuracy of rule-in. **Fifth**, the ESC 0/1h-algorithm allowed powerful and reliable risk-stratification of short-term and long-term risk of mortality and MACE. E.g. 30-day mortality was 29-times and 24-times higher in patients triaged towards rule-in as compared to patients triaged towards rule-out with hs-cTnT and hs-cTnI, respectively. **Sixth**, while this study did not aim to directly compare hs-cTnT and hs-cTnI, we observed differences in three performance measures between the ESC hs-cTnT 0/1h-algorithm and the ESC hs-cTnI 0/1h-algorithm in favour of the former. The ESC hs-cTnT 0/1h-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 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 most accurate and valid estimates for the ESC hs-cTnT 0/1h-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 0/1h-algorithm (17). Similarly, two recent studies using adjudication mainly based on cTnI invariably underestimated the true performance of early algorithms using hs-cTnT.(9,12) In 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 cut-off levels currently suggested by the ESC balance safety and efficacy well (5-11,20,26,27). The ESC 0/1h-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 three times larger than the previous study, assesses both hs-cTnT and hs-cTnI, uses a hs-cTn-assay for adjudication of goldstandard 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 algorithm, 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 pre-analytical 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 0/1h-algorithm with quantified clinical judgment seems particular valuable, as it has been shown to help identify patients with unstable angina, the more benign ACS phenotype.(2,10) Moreover, it is important to mention that beyond the ESC 0/1h-algorithm, also other early biomarker-based strategies have been developed and seem to justify clinical use.(2,4,8,17,20,26-29).

Study limitations

Some **limitations** merit consideration when interpreting these findings. **First,** our study was conducted in ED patients with symptoms suggestive of NSTEMI. Further studies are required to quantify the utility of the ESC 0/1h-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 1h-sample and therefore were excluded from this analysis. It is very unlikely that the performance of the ESC hs-cTn 0/1h-algorithm would be

worse in these, particularly as a common reason for a missing blood samples at one hour were logistic issues related to e.g. 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 0/1h-algorithm using hs-cTnT and hs-cTnI. **Fifth**, we cannot generalize our findings to patients with terminal kidney failure on chronic dialysis since they were excluded from one of the two contributing studies and therefore underrepresented.

Conclusions

In conclusion, this large multicentre 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 0/1h-algorithm using hs-cTnT and hs-cTnI and documented that it is safe and effective in triaging patients with suspected NSTEMI**.**

Clinical Perspectives

Competency in Medical Knowledge: The European Society of Cardiology 0/1h-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 very safe and effective in triaging patients with suspected NSTEMI.

Translational Outlook: Further studies are needed to precisely quantify the clinical impact of the 0/1h-algorithm on patients' management and outcomes observed in the real-life setting.

References

1. Amsterdam EA, Wenger NK, Brindis RG et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:2354-94.
2. Roffi M, Patrono C, Collet JP et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315.
3. Thygesen K, Mair J, Giannitsis E et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 2012;33:2252-7.
4. Twerenbold R, Boeddinghaus J, Nestelberger T et al. Clinical Use of High-Sensitivity Cardiac Troponin in Patients With Suspected Myocardial Infarction. J Am Coll Cardiol 2017;70:996-1012.
5. Reichlin T, Twerenbold R, Wildi K et al. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2015;187:E243-52.
6. Reichlin T, Schindler C, Drexler B et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arch Intern Med 2012;172:1211-8.

7. Rubini Gimenez M, Twerenbold R, Jaeger C et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. Am J Med 2015;128:861-870 e4.
8. Neumann JT, Sorensen NA, Schwemer T et al. Diagnosis of Myocardial Infarction Using a High-Sensitivity Troponin I 1-Hour Algorithm. JAMA cardiology 2016;1:397-404.
9. Mueller C, Giannitsis E, Christ M et al. Multicenter Evaluation of a 0-Hour/1-Hour Algorithm in the Diagnosis of Myocardial Infarction With High-Sensitivity Cardiac Troponin T. Ann Emerg Med 2016;68:76-87 e4.
10. Mokhtari A, Borna C, Gilje P et al. A 1-h Combination Algorithm Allows Fast Rule-Out and Rule-In of Major Adverse Cardiac Events. J Am Coll Cardiol 2016;67:1531-40.
11. Jaeger C, Wildi K, Twerenbold R et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. Am Heart J 2016;171:92-102 e1-5.
12. Pickering JW, Greenslade JH, Cullen L et al. Assessment of the European Society of Cardiology 0-Hour/1-Hour Algorithm to Rule-Out and Rule-In Acute Myocardial Infarction. Circulation 2016;134:1532-1541.
13. Reichlin T, Hochholzer W, Bassetti S et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858-67.
14. Haaf P, Drexler B, Reichlin T et al. High-sensitivity cardiac troponin in the distinction of acute myocardial infarction from acute cardiac noncoronary artery disease. Circulation 2012;126:31-40.
15. Hollander JE, Than M, Mueller C. State-of-the-Art Evaluation of Emergency Department Patients Presenting With Potential Acute Coronary Syndromes. Circulation 2016;134:547-64.

16. Crea F, Jaffe AS, Collinson PO et al. Should the 1h algorithm for rule in and rule out of acute myocardial infarction be used universally? Eur Heart J 2016;37:3316-3323.

17. Boeddinghaus J, Reichlin T, Cullen L et al. Two-Hour Algorithm for Triage toward Rule-Out and Rule-In of Acute Myocardial Infarction by Use of High-Sensitivity Cardiac Troponin I. Clin Chem 2016;62:494-504.

18. Rubini Gimenez M, Twerenbold R, Reichlin T et al. Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction. Eur Heart J 2014;35:2303-11.

19. Rubini Gimenez M, Reiter M, Twerenbold R et al. Sex-specific chest pain characteristics in the early diagnosis of acute myocardial infarction. JAMA internal medicine 2014;174:241-9.

20. Reichlin T, Cullen L, Parsonage WA et al. Two-hour algorithm for triage toward rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Am J Med 2015;128:369-79 e4.

21. Rubini Gimenez M, Hoeller R, Reichlin T et al. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. Int J Cardiol 2013;168:3896-901.

22. Bossuyt PM, Reitsma JB, Bruns DE et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015;351:h5527.

23. Thygesen K, Alpert JS, White HD et al. Universal definition of myocardial infarction. Circulation 2007;116:2634-53.

24. Thygesen K, Alpert JS, White HD et al. Universal definition of myocardial infarction. Circulation 2007;116:2634-53.

25. Shah AS, Anand A, Sandoval Y et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015;386:2481-8.

26. Than M, Cullen L, Reid CM et al. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. Lancet 2011;377:1077-84.

27. Than M, Cullen L, Aldous S et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. J Am Coll Cardiol 2012;59:2091-8.

28. Mueller C, Giannitsis E, Mockel M et al. Rapid rule out of acute myocardial infarction: novel biomarker-based strategies. European heart journal Acute cardiovascular care 2017;6:218-222.

29. Mockel M, Searle J, Hamm C et al. Early discharge using single cardiac troponin and copeptin testing in patients with suspected acute coronary syndrome (ACS): a randomized, controlled clinical process study. Eur Heart J 2015;36:369-76.

Figure Legends

Central Illustration: Summarized Performance of the ESC 0/1h-Algorithm. Diagnostic performance of the European Society of Cardiology (ESC) 0/1h-algorithm using high-sensitivity cardiac troponin T (left column) and I (right column) based on serial blood sampling after one hour.

Figure 1: Diagnostic Performance of the ESC 0/1h- Algorithm using High-Sensitivity Cardiac Troponin T. 2x3 table and flow-chart depicting the diagnostic performance of the European Society of Cardiology (ESC) 0/1h-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. 1h change = absolute (unsigned) change of high-sensitivity cardiac troponin within the first hour; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value. Counts in parentheses in the 2x3 table indicate number of patients directly triaged based on the 0h-blood-sample (@0h), only. *if chest pain onset >3 hours before ED presentation.

Figure 2: Diagnostic Performance of the ESC 0/1h-Algorithm using High-Sensitivity Cardiac Troponin I. 2x3 table and flow-chart depicting the diagnostic performance of the European Society of Cardiology (ESC) 0/1h-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 I (hs-cTnI, Architect®) in diagnostic dataset B. 1h change = absolute (unsigned) change of high-sensitivity cardiac troponin within the first hour; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value. Counts in parentheses in the 2x3 table indicate number of patients

directly triaged based on the 0h-blood-sample (@0h), only. *if chest pain onset >3 hours before ED presentation.

Figure 3: Subgroup Analyses on the ESC 0/1h-Algorithm's Performance. Forest plots indicating safety of rule-out, quantified by the negative predictive value (NPV) for Non-ST-segment-elevation myocardial infarction (left column), accuracy of rule-in, quantified by the positive predictive value (PPV, middle column), and overall efficacy, quantified by the proportion of patients triaged to rule-out or rule-in (right column) among different predefined patients' subgroups including 95% confidence intervals and interaction p-vales based on the ESC 0/1h-algorithm **(A)** using high-sensitivity cardiac troponin T (Elecsys®) and **(B)** using high-sensitivity cardiac troponin I (Architect®). CAD = coronary artery disease; CPO = chest pain onset; Obs = Observe group; RD = renal dysfunction, defined as estimated glomerular filtration rate < 60ml/min/1.73m^2; RI = rule-in group; RO = rule-out group. Data on renal function was not available in all patients.

Figure 4: Overall Mortality According to Triage Group by the ESC 0/1h-Algorithm. Kaplan-Meier curves depicting overall mortality within one year for patients triaged to the rule-out (green lines), observe (orange lines) und rule-in (red lines) group by the European Society of Cardiology (ESC) 0/1-algorithm using **(A)** high-sensitivity cardiac troponin T (hs-cTnT, Elecsys®) and **(B)** high-sensitivity cardiac troponin I (hs-cTnI, Architect®).

Table 1: Baseline Characteristics of the Patients in the Diagnostic Dataset A

	All patients (n=4368)	**NSTEMI (n=735)**	**No NSTEMI (n=3633)**	**p-value**
Age – years	62 [50,74]	71 [60,79]	60 [48,73]	<0.001
Male gender	2921 (67)	528 (72)	2393 (66)	0.002
Risk factors				
Hypertension	2739 (63)	572 (78)	2167 (60)	<0.001
Hypercholesterolemia	1988 (46)	438 (60)	1550 (43)	<0.001
Current smoking	1069 (24)	181 (25)	888 (24)	0.916
History of smoking	1541 (35)	289 (39)	1252 (34)	0.012
History				
Coronary artery disease	1459 (33)	340 (46)	1119 (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	3539 (81)	438 (60)	3101 (85)	<0.001
Chest pain characteristics				
Early presenters (≤3h after CPO)	1322 (30)	223 (30)	1099 (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*	1924 (67)	338 (76)	1586 (66)	<0.001
Radiating chest pain*	1694 (59)	289 (65)	1405 (58)	0.009
Duration >30 minutes*	1782 (62)	273 (61)	1509 (63)	0.596
Vital signs				
Heart frequency – bpm	77 [66,89]	80 [68,92]	76 [66,88]	<0.001
Systolic blood pressure – mmHg	143 [128,159]	145 [128,161]	142 [128,158]	0.055
Diastolic blood pressure - mmHg	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 – $ml/min/1.73m^2$	85 [66,99]	72 [53,89]	87 [70,101]	<0.001
Chronic medication				
ASA	1561 (36)	360 (49)	1201 (33)	<0.001
Anticoagulants	526 (12)	94 (13)	432 (12)	0.495
B-blockers	1577 (36)	322 (44)	1255 (35)	<0.001

Statins	1498 (34)	321 (44)	1177 (32)	<0.001
ACEIs/ARBs	1789 (41)	392 (53)	1397 (38)	<0.001
Calcium antagonists	660 (15)	145 (10)	515 (14)	<0.001
Nitrates	390 (9)	101 (14)	289 (8)	<0.001

Numbers are presented as median [q1, q3] or numbers (%). *detailed chest pain characteristics only available in the APACE study. ASA = acetylsalicylic acid; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CPO = chest pain onset; ECG = electrocardiogram; NSTEMI = Non-ST-Segment-Elevation Myocardial Infarction; Creatinine clearance was calculated using CKD-EPI (chronic kidney disease epidemiology collaboration) formula.

Table 2: Diagnostic Performance of the ESC 0/1h-Algorithm According to Time Between Chest Pain Onset and First Blood Draw

	Time since CPO	N		Triage Group: Rule-out All (direct)	Observe All	Rule-in All (direct)	Proportion Rule-out	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
Hs-cTnT															
All Patients	any	4368	no NSTEMI	2488 (706)	949	196 (99)	57% (2493/4368)	16% (706/4368)	99.8% (2488/2493)	0.010 (5/735):(2488/3633)	18% (768/4368)	11% (482/4368)	74.5% (572/768)	14.43 (572/735):(196/3633)	75% (3261/4368)
			NSTEMI	5 (0)	158	572 (383)									
Late Presenters	>3h	3046	no NSTEMI	1712 (706)	693	129 (75)	56% (1713/3046)	23% (706/3046)	99.9% (1712/1713)	0.003 (1/512):(1712/2534)	17% (527/3046)	13% (385/3046)	75.5% (398/527)	15.27 (398/512):(129/2534)	74% (2240/3046)
			NSTEMI	1 (0)	133	398 (310)									
Early Presenters	≤3h	1322	no NSTEMI	776 (n.a.)	256	67 (24)	59% (780/1322)	n.a.	99.5% (776/780)	0.025 (4/223):(776/1099)	18% (241/1322)	7% (97/1322)	72.2% (174/241)	12.80 (174/223):(67/1099)	77% (1021/1322)
			NSTEMI	4 (n.a.)	45	174 (73)									
Very Early Presenters	<2h	564	no NSTEMI	360 (n.a.)	87	26 (8)	64% (362/564)	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)
			NSTEMI	2 (n.a.)	21	68 (23)									
Extremely Early Presenters	<1h	193	no NSTEMI	125 (n.a.)	29	8 (3)	65% (125/193)	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)
			NSTEMI	0 (n.a.)	3	28 (7)									
Hs-cTnI															
All Patients	any	3500	no NSTEMI	1528 (362)	1082	302 (169)	44% (1533/3500)	10% (362/3500)	99.7% (1528/1533)	0.016 (5/588):(1528/2912)	23% (800/3500)	15% (523/3500)	62.3% (498/800)	8.17 (498/588):(302/2912)	67% (2333/3500)
			NSTEMI	5 (0)	85	498 (354)									
Late Presenters	>3h	2436	no NSTEMI	1043 (363)	764	225 (132)	43% (1045/2436)	15% (363/2436)	99.8% (1043/1045)	0.010 (2/404): (1043/2032)	23% (571/2436)	17% (421/2436)	60.6% (346/571)	7.73 (346/404):(225/2032)	66% (1616/2436)
			NSTEMI	2 (0)	56	346 (289)									
Early Presenters	≤3h	1064	no NSTEMI	485 (n.a.)	318	77 (37)	46% (488/1064)	n.a.	99.4% (485/488)	0.030 (3/184):(485/880)	22% (229/1064)	10% (102/1064)	66.4% (152/229)	9.44 (152/184):(77/880)	67% (717/1064)
			NSTEMI	3 (n.a.)	29	152 (65)									
Very Early Presenters	<2h	443	no NSTEMI	223 (n.a.)	117	33 (15)	50% (223/443)	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)
			NSTEMI	0 (n.a.)	11	59 (23)									
Extremely Early Presenters	<1h	171	no NSTEMI	78 (n.a.)	58	9 (1)	46% (78/171)	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)
			NSTEMI	0 (n.a.)	3	23 (5)									

CPO = chest pain onset; LR = Likelihood ratio; n.a. = not applicable; NPV = negative predictive value; PPV = positive predictive value; Total = counts of patients triaged based on 0h- AND 1h-blood-sample; (direct) = counts of patients applicable for direct triage towards rule-out or rule-in based on the 0h-blood-sample only.