

# BMJ Open Comparison of a single high-sensitivity cardiac troponin T measurement with the HEART score for rapid rule-out of acute myocardial infarction in a primary care emergency setting: a cohort study

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## ABSTRACT

**Objective** This study aims to compare the rule-out safety of a single high-sensitivity cardiac troponin T (hs-cTnT) with the History, ECG, Age, Risk factors and Troponin (HEART) score in a low-prevalence primary care setting of acute myocardial infarction (AMI).

**Participants** Patients with non-specific symptoms suggestive of AMI were consecutively enrolled at a primary care emergency clinic in Oslo, Norway from November 2016 to October 2018.

**Methods** After initial assessment by a general practitioner, hs-cTnT samples were drawn. AMI was ruled-out by a single hs-cTnT <5 ng/L measured ≥3 hours after symptom onset. The HEART score was calculated retrospectively; a score ≤3 of 10 points was considered low risk. We also calculated a modified HEART score using more sensitive hs-cTnT thresholds. The primary outcome was the diagnostic performance for the rule-out of AMI at the index event; the secondary the composite of AMI or all-cause death at 90 days.

**Results** Among 1711 patients, 61 (3.6%) were diagnosed with AMI, and 569 (33.3%) patients were assigned to single rule-out (<5 ng/L). With no AMIs in this group, the negative predictive value (NPV) and sensitivity were both 100.0% (95% CI 99.4% to 100.0% and 94.1% to 100.0%, respectively), and the specificity 34.5% (32.2% to 36.8%). The original HEART score triaged more patients as low risk (n=871), but missed five AMIs (NPV 99.4% (98.7% to 99.8%); sensitivity 91.8% (81.9% to 97.3%) and specificity 52.5% (50.0% to 54.9%). The modified HEART score increased the low-risk sensitivity to 98.4% (91.2% to 100.0%), with specificity 38.7% (36.3% to 41.1%). The 90-day incidence of AMI or death in the single rule-out and the original and modified low-risk HEART groups were 0.0%, 0.7%, and 0.2%, respectively.

**Conclusion** In a primary care emergency setting, a single hs-cTnT strategy was superior to the HEART score in ruling out AMI. This rapid and safe approach may enhance the assessment of patients with chest pain outside of hospitals.

**Trial registration number** NCT02983123.

## Strengths and limitations of this study

- The diagnostic ability to rule-out acute myocardial infarction by a single high-sensitivity cardiac troponin T was investigated and compared with the History, ECG, Age, Risk factors and Troponin (HEART) score in a primary care population.
- The observational cohort comprised a low-risk population enrolled in a primary care emergency setting with few missing data.
- The study was embedded in the daily routine at the clinic, reducing bias and increasing the internal validity of the results.
- The study may not be adequately powered, as the total number of events was low.
- The HEART score was calculated retrospectively.

## INTRODUCTION

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is an important differential diagnosis in patients presenting with acute chest pain in primary care.<sup>1 2</sup> Patients with chest pain or other symptoms suggestive of NSTE-ACS are often admitted to hospitals for further examination due to limited reliable diagnostic decision tools.<sup>3–5</sup>

The last decade has seen an increased focus on the diagnostic assessment with troponins outside of hospitals. Point-of-care (POC) troponin assays, used in general practice<sup>6 7</sup> or by emergency medical services (EMS),<sup>8 9</sup> are useful in identifying high-risk patients. Still, they may not be sufficiently safe to rule-out acute myocardial infarction (AMI).<sup>9 10</sup> The History, ECG, Age, Risk factors and Troponin (HEART) score,<sup>11 12</sup> initially developed for the emergency departments (EDs), has proven to be a valuable decision aid for the EMS, identifying low-risk and high-risk patients in the prehospital setting.<sup>13 14</sup> The diagnostic



parameters of the HEART score were improved when the conventional troponin assay was replaced with a high-sensitivity cardiac troponin (hs-cTn) assay.<sup>15 16</sup> In addition, high diagnostic performance has recently been demonstrated for novel hs-cTn POC assays in hospital cohorts, but these are not yet validated for primary care.<sup>17 18</sup> Therefore, a strategy that safely excludes AMI outside the hospital ED is still needed.<sup>10 14</sup>

We recently found a high rule-out safety for AMI in a primary care emergency setting using the European Society of Cardiology's (ESC) 0/1 hour algorithm for hs-cTnT.<sup>19</sup> As serial hs-cTnT measurements represent a logistic challenge in many primary care settings,<sup>20</sup> it was of interest to investigate the diagnostic and prognostic performance of a single hs-cTnT measurement. For the hospital setting, high rule-out safety has been demonstrated for an undetectable (<5 ng/L) hs-cTn measurement in patients presenting to the ED more than 3 hours after symptom onset.<sup>21 22</sup> However, evidence of the safety of a single hs-cTnT rule-out approach remains sparse for the primary care setting. Further, to the best of our knowledge, the single hs-cTnT rule-out approach has not yet been validated and compared with the HEART score in a primary care emergency setting, where patients have a low pretest probability for acute coronary syndrome (ACS).

The aim of this study was, therefore, to investigate whether the single hs-cTnT strategy was safe to rule-out AMI in patients presenting with non-specific symptoms in a primary care emergency setting, and compare it with the HEART score.

## METHODS

### Study design and population

This study was a planned secondary analysis of the prospective, observational One hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome (OUT-ACS) study,<sup>19</sup> conducted from November 2016 to October 2018 at the Oslo Accident and Emergency Outpatient Clinic (OAEOC); the main primary care emergency clinic in Oslo, Norway.

The OAEOC is staffed by general practitioners (GPs) and nurses and offers serial hs-cTnT sampling to rule-out AMI at the OAEOC observation unit 24 hours a day, all year. Patients (18 years and older) with acute non-traumatic chest pain or other non-specific symptoms admitted at the clinic for hs-cTnT, were consecutively enrolled. Patients with potential atypical AMI presentation, for example, acute dyspnoea, acute fatigue or diaphoresis, were also eligible. In cases of a highly suspected ACS, including ST-segment elevation myocardial infarction, patients were directly hospitalised and not available for study enrolment. Patients with chronic kidney disease (estimated glomerular filtration rate of <30 mL/min/1.73 m<sup>2</sup>) were excluded (figure 1). Further details regarding the study setting and participants have been described previously.<sup>19</sup>

### Clinical assessment and measurement of hs-cTnT

Medical history, physical examination, pulse oximetry and a 12-lead ECG were obtained by the GP for all patients presenting to the OAEOC with symptoms suggestive of ACS. If indicated, chest X-ray and capillary blood measurements (C-reactive protein, haemoglobin and blood glucose) could be performed. The standard clinical approach at the OAEOC offers hs-cTnT measurements to patients considered in need of further tests to rule-out AMI, but without the need of immediate hospitalisation (online supplemental table 1). The decision is left to the discretion of the treating GP.

Blood samples for the analyses of hs-cTnT were drawn from all included patients at 0, 1 and 4 hours. Only the first hs-cTnT was considered in this subanalysis. Presenting symptoms, risk factors and time variables were registered at a predefined study form (online supplemental table 2). The upper reference limit (URL) for hs-cTnT (Elecys Troponin T hs STAT assay, Roche Diagnostics, Switzerland) was 14 ng/L with a coefficient of variation of <10%, limit of detection (LoD) of 5 ng/L and limit of blank of 3 ng/L (additional details in the online supplemental appendix).<sup>23</sup>

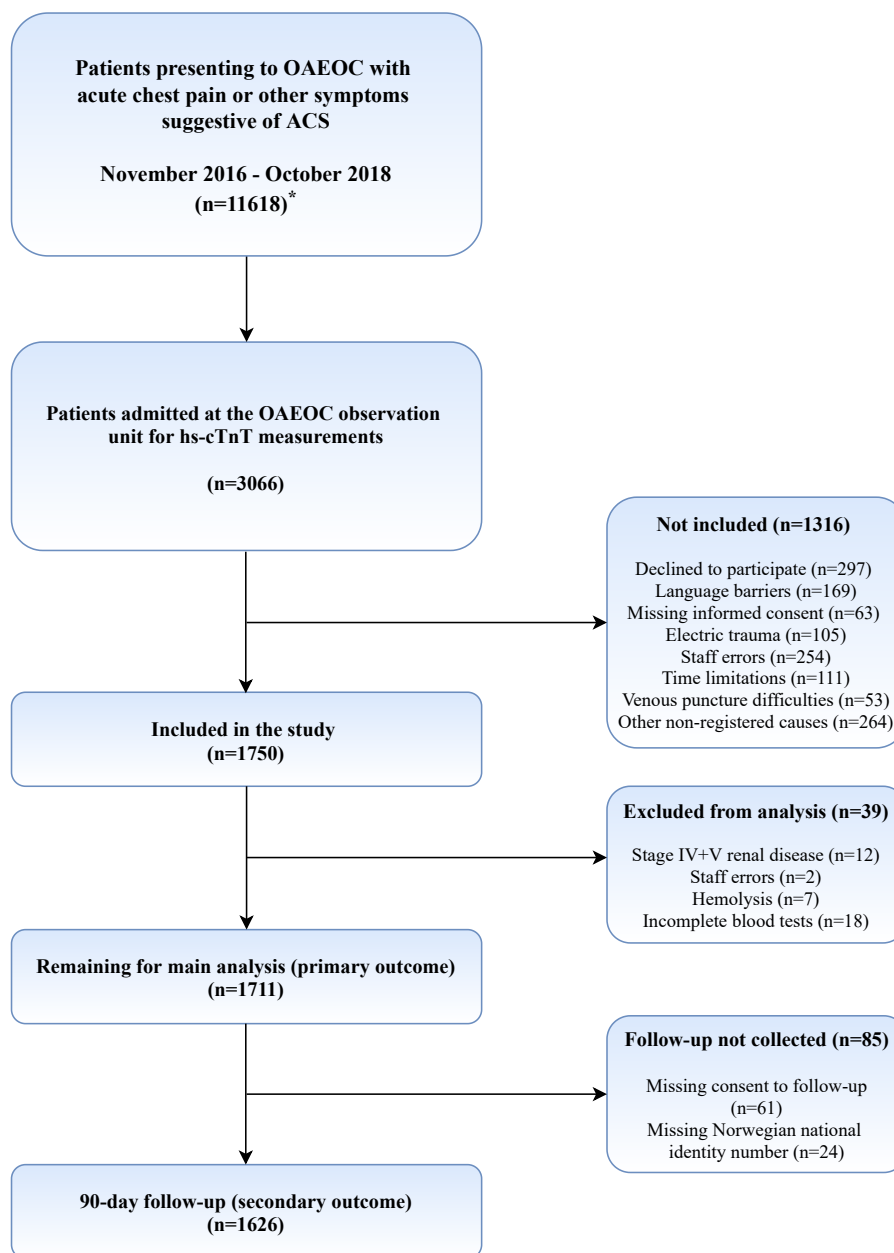
### Single hs-cTnT strategy

According to the ESC 0/1 hour algorithm for hs-cTnT,<sup>2</sup> the single hs-cTnT rule-out strategy applies for patients where the first hs-cTnT is <5 ng/L, sampled 3 hours or more after symptom onset. A patient is triaged towards direct rule-in if the initial hs-cTnT is ≥52 ng/L. Patients with values between these thresholds remain in the observation group in need of repeated hs-cTnT measurements. Following the guidelines, the troponin result should always be interpreted in conjunction with the clinical assessment and the ECG.<sup>2</sup>

### HEART score

The original HEART score stratifies the risk for a major adverse cardiac event (MACE) during the first 6 weeks following presentation to an ED with symptoms suggestive of ACS.<sup>11 12</sup> Each of the five components (History, ECG, Age, Risk factors and Troponin) provide a score of 0–2 points (table 1). Patients with a HEART score of 0–3 points (low risk) are considered suitable for rapid discharge, a score of 4–6 points (intermediate risk) signifies the need of further observation and patients with 7–10 points (high risk) are recommended early invasive strategies.<sup>11 12</sup>

In this study, the subjective History component was based on the presenting composition of non-typical and typical symptoms of ACS,<sup>11</sup> as defined by the study investigators (online supplemental table 3). Only typical elements scored 2 points, a combination of typical and non-typical scored 1 point and only non-typical scored 0 points. The ECG component was calculated using the ECG obtained and interpreted by the GP at presentation. ECG with ischaemic ST-segment depression scored 2 points, non-specific changes in either the ST-segment,



**Figure 1** Patient flow chart. Study enrolment at the primary care emergency clinic during the OUT-ACS study. \*Critically ill patients are brought directly to hospital by the ambulance services. ACS, acute coronary syndrome; hs-cTnT, high-sensitivity cardiac troponin T; OAEOC, Oslo Accident and Emergency Outpatient Clinic; OUT-ACS, One hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome.

T-inversions, Q-waves or left/right bundle branch block of unknown clinical significance scored 1 point and an ECG interpreted as normal scored 0 points. Among the Risk factors, obesity (BMI >30) was not systematically recorded. For the Troponin component, the first hs-cTnT sampled at the clinic was used, regardless of the time interval from symptom onset to blood draw. Hs-cTnT  $\leq 14$  ng/L scored 0 points, hs-cTnT 15–41 ng/L 1 point and hs-cTnT  $\geq 42$  ng/L 2 points.

### Modified HEART score

Since the single hs-cTnT rule-out strategy is based on hs-cTnT  $< 5$  ng/L and the original HEART score operates with hs-cTnT  $\leq 14$  ng/L as the lowest cut-off value, we modified the HEART score by altering the Troponin component to more sensitive hs-cTnT thresholds. Inspired by a recent published study using a modified HEART score,<sup>24</sup> a hs-cTnT  $< 5$  ng/L resulted in 0 points, 1 point for hs-cTnT between LoD and URL (5–14 ng/L), and 2 points for hs-cTnT  $> URL$  ( $> 14$  ng/L). The four first components (History, ECG, Age and Risk factors) remained unchanged.

**Table 1** The original HEART score for patients with chest pain

History	Highly suspicious for ACS	2 points
	Moderately suspicious	1 point
	Slightly or not suspicious	0 points
ECG	Significant ST-depression	2 points
	Non-specific changes*	1 point
	Normal	0 points
Age	≥65 years	2 points
	46–64 years	1 point
	≤45 years	0 points
Risk factors†	≥3 risk factors or previous CAD	2 points
	One or two risk factors	1 point
	No risk factors	0 points
Troponin	≥3 × URL	2 points
	>1 to <3 × URL	1 point
	≤URL	0 points
Total	Low risk	0–3 points
	Intermediate risk	4–6 points
	High risk	7–10 points

Reproduced after the original HEART score<sup>12</sup> with permission from the authors.

\*Left bundle branch block, left ventricular hypertrophy, repolarisation changes, pacemaker.

† Risk factors: hypertension, diabetes mellitus, current or history of smoking, hypercholesterolaemia, obesity (BMI >30 kg/m<sup>2</sup>) and family history of coronary artery disease.

ACS, acute coronary syndrome; BMI, body mass index; ECG, electrocardiogram; HEART, History, ECG, Age, Risk factors and Troponin; hs-cTnT, high-sensitivity cardiac troponin T; URL, upper reference limit.

The HEART scores were applied and calculated retrospectively. During the HEART score assessments, the study investigators were blinded to patient identity, final diagnosis and other information not part of the HEART calculations.

### Outcome measures

The primary outcome was the diagnostic performance for the rule-out of AMI at the index event for the three different strategies (single hs-cTnT, original and the modified HEART score).

The composite of AMI or all-cause death at 90 days was the secondary outcome, as a measure of the prognostic performance of the three different rule-out strategies. The 90-day follow-up data were collected through linkage with the Norwegian Cardiovascular Disease Registry<sup>25</sup> as previously described.<sup>19</sup>

### Final adjudication of AMI

For patients discharged home from the OAEOC, the final diagnosis was made by the treating GP based on all available information, including clinical assessment, repeated ECGs, 0, 1 and 4 hours hs-cTnT and additional lab analyses. The absence of a 0–4 hour hs-cTnT delta in accordance with the *Third Universal Definition of Myocardial*

*Infarction*(1) served as a reference standard for ruling out AMI, as previously specified.<sup>19</sup> For the hospitalised patients, the final diagnosis was also based on the *Third Universal Definition of Myocardial Infarction*(1) and adjudicated by two independent cardiologists with access to all collected data from the index episode, including data from the OAEOC and hospital discharge documents. In 19/227 of the cases, a third cardiologist was involved in solving disagreements.

### Statistical analysis

Numbers were presented as frequencies and percentages, means and standard deviations (SDs), or medians and IQRs, as appropriate. Comparisons of baseline characteristics between the single rule-out approach and the two low-risk HEART groups were made using the Pearson  $\chi^2$  test or the Fisher exact test for categorical variables, whereas the Kruskal-Wallis test was used when comparing continuous variables. We used two-sided hypothesis testing with a significance level set at  $\alpha=0.05$ . The sample size calculation for the main study has been described previously.<sup>19</sup>

The rule-out performance of the three strategies were assessed by calculating sensitivity and the negative predictive values (NPVs), with corresponding 95% CIs (online supplemental table 4). In addition, the specificity and positive predictive values (PPVs) were estimated to assess the accuracy of the rule-in and the high-risk HEART groups, and likelihood ratios were estimated for all categories. The overall diagnostic performance of the three strategies was illustrated by the area under the ROC (receiver operating characteristics) curve (AUC). To visualise the large intermediate groups in need of further testing, we used the predefined cut-off values for each group. The AUCs were compared using the 95% CIs and the McNemar's test with the single hs-cTnT strategy as the referent.

IBM SPSS V.26.0 (SPSS, IBM, Armonk, New York, USA), and Stata V.16.0 (Stata Corp, College Station, Texas, USA.) were used in the calculations.

### Ethics

The study was approved by the Regional Committee North for Medical and Health Research Ethics (no. 2016/1241) and the Oslo University Hospital Information Security and Privacy Office (no. 2016/13308). Participation was based on written, informed consent. The OUT-ACS study is registered at ClinicalTrials.gov (NCT02983123) and was conducted in accordance with the STARD (Standards for Reporting Diagnostic Accuracy Studies) guidelines.<sup>26</sup>

### Patient and public involvement

The patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research. However, we have involved users from our formalised 'patient-contributors-to-research' group established by the Medical Department of Oslo University Hospital. We received clear indications that a fast and reliable rule-out of AMI in patients with chest pain has a high

priority among users (patients). These inputs helped in the design and interpretation of the study.

## RESULTS

### Study participants

During the OUT-ACS study enrolment period (November 2016–October 2018), 3066 patients were transferred to the OAEOC observation unit for hs-cTnT measurements, with 1750 patients included in the study (figure 1). Thirty-nine patients were excluded from the primary analysis (figure 1), yielding 1711 participants.<sup>19</sup> For 1529 (89.4%) of the patients, the first hs-cTnT was measured 3 hours or more after symptom onset (table 2). The median time from OAEOC presentation to first blood sample was 136 min (IQR 100–194).

### Triage and baseline characteristics

After a single hs-cTnT measurement, 569 (33.3%) patients were assigned towards rule-out, 1098 (64.2%) to the observation group in need of further hs-cTnT measurements, while 44 (2.6%) patients were assigned towards rule-in. The original HEART score categorised 871 (50.9%) of 1711 patients as low risk, 760 (44.4%) as intermediate risk and 80 (4.7%) as high risk. By applying the modified HEART score with more sensitive troponin thresholds, 639 (37.3%) patients were triaged towards low risk, 876 (51.2%) as intermediate risk and 196 (11.5%) towards the high-risk group. Baseline characteristics of the single hs-cTnT rule-out and the low-risk HEART groups are shown in table 2.

### Diagnostic and prognostic performance

AMI was diagnosed in 61 (3.6%) of 1711 patients at the index observation. Among the 569 patients directly ruled-out by the single hs-cTnT strategy, there were no incidents of AMI during the index episode. Hence, this approach had a rule-out sensitivity and NPV of 100.0% (figure 2 and table 3). Thirty-two (5.6%) of the direct rule-out patients were hospitalised for other non-cardiac causes, whereas the remaining patients were discharged home (online supplemental table 5).

The HEART score risk-stratified more patients towards low risk (n=871) but missed five AMIs (0.6%) during the index episode (details in online supplemental table 6). This gives a sensitivity of 91.8% (95% CI 81.9% to 97.3%) and NPV 99.4% (95% CI 98.7% to 99.8%, figure 2 and table 3). By applying the modified HEART score, only one patient with AMI (0.2%) was misclassified as low risk (n=639), improving sensitivity to 98.4% (95% CI 91.2% to 100.0%) and NPV to 99.8% (95% CI 98.9% to 100.0%). The number of low-risk patients in need of hospitalisation was 66 (7.6%) and 40 (6.3%) in the original and modified HEART groups (online supplemental table 5).

The PPV in the single rule-in and the original and modified high-risk HEART scores were 77.3% (95% CI 63.8% to 86.8%), 22.5% (95% CI 15.5% to 31.5%) and

10.7% (95% CI 7.6% to 14.9%), respectively (table 3). In the single hs-cTnT rule-out group, one patient was considered high risk by both HEART scores (online supplemental table 7). The original and modified HEART score means were 3.6 (SD 1.6) and 4.2 (SD 1.8) points, respectively (online supplemental table 8).

The corresponding overall diagnostic performance, illustrated by the AUC for the three different strategies, was 0.85 (95% CI 0.81 to 0.89), 0.77 (95% CI 0.73 to 0.82), and 0.74 (95% CI 0.70 to 0.78) (figure 3). Using McNemar's two-sided test, the results demonstrated that the single hs-cTnT strategy performed better than the original and modified HEART scores ( $p < 0.01$ ).

The prognostic performance of the three rule-out approaches, as demonstrated by the composite of AMI or all-cause death at 90 days, was 0.0% for the single rule-out strategy and 0.7% and 0.2% for the original and modified low-risk HEART groups (figure 2 and table 3).

## DISCUSSION

In the current secondary analysis of the OUT-ACS study, the single rule-out approach (hs-cTnT  $< 5$  ng/L in patients presenting with symptom onset  $\geq 3$  hours), had an excellent diagnostic and prognostic safety in a primary care emergency setting, with one-third of the participants triaged towards direct rule-out. Both the sensitivity and the NPV were 100.0%, with no incidents of AMI or death for the following 90 days.

The original low-risk HEART score was less safe than the single rule-out strategy. Even though more patients were triaged towards low risk and early discharge, this entailed missing five AMIs, which we consider unacceptable. The sensitivity and the NPV in the low-risk HEART group improved with the modified HEART score, with only one missing AMI. On the other hand, the modified high-risk group had more false positives than the single rule-in group, which would have contributed to more hospitalisations. Similar data were found in an ED cohort, where patients with a modified HEART score  $> 3$  points had a lower risk for MACE than the original HEART score using a conventional troponin assay.<sup>27</sup> All aspects considered, in our study, the simple single troponin approach was superior to both HEART scores when applied in a primary care emergency setting. In a recent hospital cohort, similar rule-out sensitivity was found after 6 weeks for the low-risk HEART group and the hs-cTnT  $< \text{LoD}$  strategy.<sup>28</sup> Although 6-week MACE was not reported in our study, several studies from the ED setting are in line with our results. One study demonstrated higher rule-out sensitivity for the hs-cTnT-only ( $< 3$  ng/L) strategy when compared with the modified low-risk HEART group.<sup>24</sup> In a 1 year low-risk cohort, the safety of the hs-cTnT  $< \text{LoD}$  strategy was not improved by the HEART score in late presenters (chest pain onset  $\geq 3$  hours).<sup>29</sup> And even though a direct comparison is not possible, our findings are somewhat consistent with a

**Table 2** Baseline characteristics

	OUT-ACS study, total <sup>19</sup> n=1711 (100.0%)	Single hs-cTnT, rule-out group n=569 (33.3%)	Original HEART, low-risk group n=871 (50.9%)	Modified HEART, low-risk group n=639 (37.3%)	P value
Female sex, n (%)	816 (47.7)	340 (59.8)	384 (44.1)	306 (47.9)	<0.001
Age, median (IQR)	56 (45–68)	47 (38–56)	46 (38–55)	43 (35–51)	<0.001
<b>Risk factors for CVD, n (%)</b>					
Current/history of smoking	449 (26.2)	156 (27.4)	214 (24.6)	141 (22.1)	0.098
Previous coronary artery disease	317 (18.5)	40 (7.0)	9 (1.0)	5 (0.8)	<0.001
Hypertension	448 (26.2)	83 (14.6)	92 (10.6)	48 (7.5)	<0.001
Dyslipidaemia	422 (24.7)	94 (16.5)	78 (9.0)	50 (7.8)	<0.001
Other CVD*	288 (16.8)	51 (9.0)	71 (8.2)	47 (7.4)	0.59
Diabetes mellitus	171 (10.0)	44 (7.7)	42 (4.8)	21 (3.3)	0.002
COPD	80 (4.7)	7 (1.2)	10 (1.1)	5 (0.8)	0.71
Family history of CVD	691 (40.4)	253 (44.5)	333 (38.2)	245 (38.3)	0.037
<b>Presenting acute symptoms, n (%)</b>					
Chest pain	1486 (86.8)	525 (92.3)	791 (90.8)	588 (92.0)	0.56
<i>Constricting</i>	1239 (72.4)	439 (77.2)	637 (73.1)	475 (74.3)	0.23
<i>Sharp</i>	404 (23.6)	168 (29.5)	263 (30.2)	201 (31.5)	0.76
<i>Tearing</i>	64 (3.7)	19 (3.3)	39 (4.5)	30 (4.7)	0.45
<i>Burning</i>	208 (12.2)	81 (14.2)	127 (14.6)	99 (15.5)	0.81
<i>Respiratory dependent</i>	302 (17.7)	126 (22.1)	215 (24.7)	164 (25.7)	0.34
<i>Chest wall tenderness</i>	205 (12.0)	80 (14.1)	135 (15.5)	104 (16.3)	0.56
<i>Movement dependent</i>	219 (12.8)	93 (16.3)	146 (16.8)	115 (18.0)	0.72
Other pain (abdomen, back or neck)	48 (2.8)	15 (2.6)	15 (1.7)	10 (1.6)	0.34
No pain	177 (10.3)	29 (5.1)	65 (7.5)	41 (6.4)	0.20
Pain radiation	972 (56.8)	369 (64.9)	534 (61.3)	401 (62.8)	0.40
Dyspnoea	901 (52.7)	327 (57.5)	489 (56.1)	369 (57.7)	0.80
Palpitations	637 (37.2)	232 (40.8)	367 (42.1)	278 (43.5)	0.63
Syncope/presyncope	460 (26.9)	155 (27.2)	259 (29.7)	189 (29.6)	0.55
Acute fatigue	571 (33.4)	188 (33.0)	295 (33.9)	223 (34.9)	0.79
Nausea/vomiting	732 (42.8)	251 (44.1)	377 (43.3)	285 (44.6)	0.87
Diaphoresis	561 (32.8)	184 (32.3)	310 (35.6)	221 (34.6)	0.44
<b>Symptom onset to first hs-cTnT, n (%)</b>					
<3 hours	182 (10.6)	0 (0.0)	114 (13.1)	80 (12.5)	<0.001
3 to <6 hours	609 (35.6)	225 (39.5)	316 (36.3)	231 (36.2)	0.38
6 to <12 hours	409 (23.9)	148 (26.0)	186 (21.4)	137 (21.4)	0.081
12 to <24 hours	224 (13.1)	82 (14.4)	104 (11.9)	76 (11.9)	0.31
≥24 hours	287 (16.8)	114 (20.0)	151 (17.3)	115 (18.0)	0.42

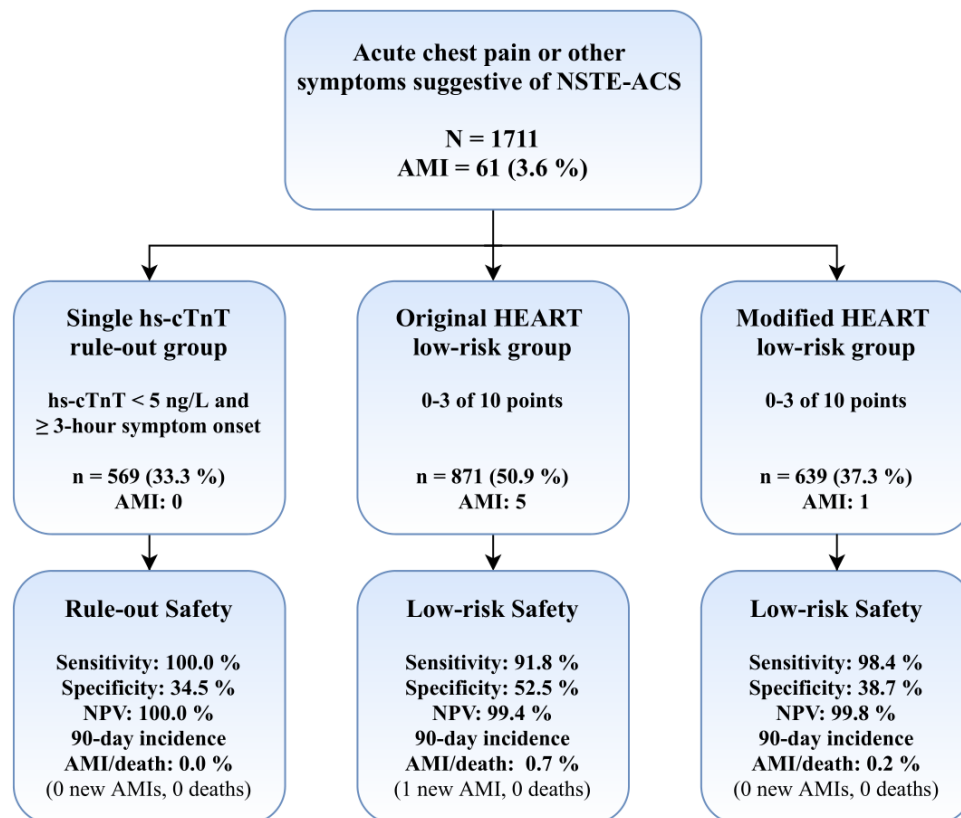
All values are presented as n (%) and median (IQR). P values are calculated for comparisons across all three groups (single rule-out and the two low-risk HEART groups). The Pearson  $\chi^2$  test or the Fisher exact test were used for the categorical variables and the Kruskal-Wallis test for the continuous variables.

\*Includes atrial fibrillation, other arrhythmias, cardiomyopathies, cerebral stroke, heart failure or valvular disease.

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HEART, History, ECG, Age, Risk factors and Troponin; hs-cTnT, high-sensitivity cardiac troponin T; OAECC, Oslo Accident and Emergency Outpatient Clinic.

previous study from the High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome) investigators, where clinical risk scores

did not enhance the diagnostic rule-out performance when lower cut-off values for high-sensitivity cardiac troponin I (hs-cTnI) were applied.<sup>30</sup>



**Figure 2** The diagnostic and prognostic safety of the three rule-out strategies at the primary care emergency clinic. AMI, acute myocardial infarction; HEART, History, ECG, Age, Risk factors and Troponin; hs-cTnT, high-sensitivity cardiac troponin T; NPV, negative predictive value; NSTE-ACS, non-ST-segment elevation acute coronary syndrome.

Our evaluation of the HEART score outside of hospitals differs from the previous EMS studies<sup>13 14</sup> by not including patients with a highly suspected ACS. This is reflected by the low mean of both the original and the modified HEART scores (online supplemental table 8). Our study population comprised patients with low-to-intermediate risk in need of additional tests for a safe AMI rule-out, but not considered in urgent need of hospitalisation. This is also apparent from the delay in time to first hs-cTnT measurement, as the low-risk patients were rarely prioritised for rapid initial assessment. Our study also included patients with atypical symptoms such as acute fatigue, diaphoresis and acute dyspnoea without chest pain. The study was embedded in the regular clinical practice at the primary care clinic, which might increase both the external and internal validity of the results.

A recent cost–benefit analysis from the Netherlands demonstrated that patients categorised as low-risk HEART incurred high hospital expenses with limited benefits for each patient.<sup>31</sup> Performing the initial hs-cTn workup of low-risk patients outside of hospitals might reduce unnecessary hospital admissions, health-care utilisation and costs. Further implementation and cost–benefit studies in primary care are warranted.

Prehospital studies among paramedics have demonstrated that POC troponin assays should not be used to rule-out AMI due to low sensitivity.<sup>9 10</sup> However, the

newer POC devices might perform better if tested at primary care emergency clinics, where they would be less subject to movement and temperature alterations. The novel hs-cTnI POC assays with diagnostic performance comparable to central lab assays may also show themselves valuable decision aids in primary care in the future.<sup>17 18</sup>

Some limitations need to be addressed: first, only 61 (3.6%) of 1711 patients in the OUT-ACS study were diagnosed with an AMI. Hence, the calculations on the diagnostic performance are based on few events and should be interpreted with care.

Second, the AMI diagnoses might be subject to verification bias, as the adjudication committee only evaluated hospitalised patients. For all patients discharged home, the final diagnosis was made by the discharging GP at the OAEOC. It would not have been ethical or feasible to admit all 1711 patients to the hospital for a similar diagnostic workup.

Third, there is no current consensus on how the subjective History component in the HEART score should be assessed.<sup>32</sup> We based this component on the presenting symptoms registered at index and retrospectively categorised them as typical or non-typical for NSTE-ACS, as defined in online supplemental table 3.

Fourth, by assessing the HEART score retrospectively, the Risk factor ‘obesity’ was missing for all participants, as body mass index (BMI) was not systematically reported.

**Table 3** Diagnostic and prognostic performance of the single hs-cTnT strategy and the two HEART scores

N (%)	Classification	Index episode				Diagnostic performance				Prognostic performance n=1626 90-day AMI or death
		Total n=1711	AMI n=61	Sensitivity (95% CI)	Specificity (95% CI)	NPV or PPV (95% CI)	LR (95% CI)			
Single hs-cTnT*	<b>Rule-out</b> ( <i>&lt;</i> LoD)	569 (33.3%)	0	100.0% (94.1% to 100.0%)	34.5% (32.2% to 36.8%)	NPV: 100% (99.4% to 100.0%)	LR-: 0.0	0/541 (0.0%)		
	<b>Observation</b>	1098 (64.2%)	27	-	-	-	LR: 0.7 (0.5 to 0.9)	36/1042 (3.5%)		
	<b>Rule-in</b>	44 (2.6%)	34	55.7% (42.5% to 68.5%)	99.4% (98.9% to 99.7%)	PPV: 77.3% (63.8% to 86.8%)	LR+: 92.0 (47.7 to 177.4)	34/43 (79.1%)		
The original HEART score †	<b>Low risk</b> (0–3 points)	871 (50.9%)	5	91.8% (81.9% to 97.3%)	52.5% (50.0% to 54.9%)	NPV: 99.4% (98.7% to 99.8%)	LR-: 0.2 (0.1 to 0.4)	6/829 (0.7%)		
	<b>Intermediate risk</b> (4–6 points)	760 (44.4%)	38	-	-	-	LR: 1.4 (1.2 to 1.7)	43/722 (6.0%)		
	<b>High risk</b> (7–10 points)	80 (4.7%)	18	29.5% (18.5% to 42.6%)	96.2% (95.2% to 97.1%)	PPV: 22.5% (15.5% to 31.5%)	LR+: 7.9 (5.0 to 12.4)	21/75 (28.0%)		
The modified HEART score ‡	<b>Low risk</b> (0–3 points)	639 (37.3%)	1	98.4% (91.2% to 100.0%)	38.7% (36.3% to 41.1%)	NPV: 99.8% (98.9% to 100.0%)	LR-: 0.04 (0.0 to 0.3)	1/611 (0.2%)		
	<b>Intermediate risk</b> (4–6 points)	876 (51.2%)	39	-	-	-	LR: 1.3 (1.0 to 1.5)	42/827 (5.1%)		
	<b>High risk</b> (7–10 points)	196 (11.5%)	21	34.4% (22.7% to 47.7%)	89.4% (87.8% to 90.8%)	PPV: 10.7% (7.6% to 14.9%)	LR+: 3.3 (2.2 to 4.7)	27/188 (14.4%)		

The three different diagnostic strategies applied in the study population (n=1711). The 2x2 tables used in the calculations of the diagnostic performance are listed in online supplemental table 4.

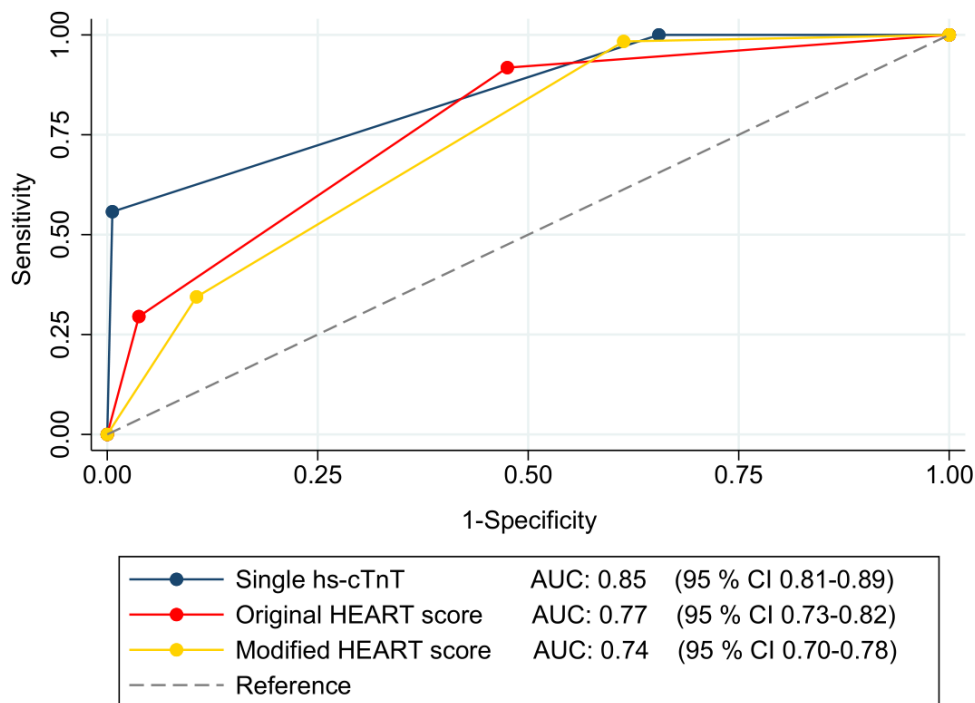
\*Single hs-cTnT strategy with hs-cTnT criteria—*<*LoD rule-out: hs-cTnT *<*5 ng/L and  $\geq$ 3 hours symptom onset; single rule-in: hs-cTnT  $\geq$ 52 ng/L.<sup>2</sup>

†The original HEART score with hs-cTnT criteria—0 point:  $\leq$ 14 ng/L, 1 point: 15–41 ng/L and 2 points:  $\geq$ 42 ng/L.<sup>11 12</sup>

‡The modified HEART score with hs-cTnT criteria—0 point: *<*5 ng/L, 1 point: 5–14 ng/L and 2 points: *>*14 ng/L.

AMI, acute myocardial infarction; HEART, History, ECG, Age, Risk factors and Troponin score; hs-cTnT, high-sensitivity cardiac troponin T; LoD, limit of detection; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.





**Figure 3** The overall diagnostic performance of the single hs-cTnT strategy, the original HEART score and the modified HEART score were illustrated by the AUC, which was achieved using the predefined cut-off values for the three different strategies. The single hs-cTnT rule-in and high-risk HEART groups are shown in the lower-left corner, the single hs-cTnT rule-out and low-risk HEART groups in the upper right. The large intermediate groups represent the patients in need of further tests. AUC, area under the curve; HEART, History, ECG, Age, Risk factors and Troponin; hs-cTnT, high-sensitivity cardiac troponin T.

Finally, the T component was based on the first hs-cTnT sample collected, regardless of symptom onset. Two of the five missed AMIs in the original low-risk HEART group had a symptom onset less than 3 hours before blood draw (online supplemental table 6). By using 3 hour onset as a prerequisite before rapid discharge, the diagnostic performance would have been improved. The onset of symptoms should, therefore, be taken into consideration if implemented in clinical practice.

In conclusion, when applying a hs-cTnT assay, the single hs-cTnT strategy (<5 ng/L with symptom onset  $\geq 3$  hours) was superior to the original HEART score in ruling out AMI in a primary care emergency setting. The rule-out safety of the HEART score was improved when lower troponin thresholds were used but at the cost of a low PPV. The single hs-cTnT strategy might have a great potential for simplifying and accelerating the triage of patients presenting with acute non-specific AMI symptoms in primary care, hence reducing unnecessary advanced testing, crowding in the EDs, and overall expenses.

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## ONLINE SUPPLEMENTARY APPENDIX

*To the manuscript*

**Comparison of a single high-sensitivity cardiac Troponin T measurement with the HEART score for rapid rule-out of acute myocardial infarction in a primary care emergency setting: a cohort study**

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Oslo, Norway, 2021

**ONLINE TABLE 1 Selection of patients with chest pain or other symptoms suggestive of NSTEMI-ACS at the OAEOC**

<b>GP triage</b>	<b>NSTEMI-ACS not suspected</b>  = Other causes/disorders more likely	<b>NSTEMI-ACS mild to moderately suspected</b>  = In need of further tests to rule-out AMI without urgent need of hospitalisation	<b>NSTEMI-ACS or STEMI highly suspected</b>  = In need of urgent hospitalisation for more advanced testing/care
<b>Examples</b>	<ul style="list-style-type: none"> <li>• Myalgia</li> <li>• Costochondritis</li> <li>• Tietze's syndrome</li> <li>• Stress</li> <li>• Anxiety</li> <li>• Panic disorder</li> <li>• Pulmonary infection</li> <li>• COPD</li> <li>• Pulmonary embolism</li> <li>• Gastric reflux</li> <li>• Gastritis</li> <li>• Gastric ulcer</li> <li>• Cholelithiasis</li> <li>• Acute pancreatitis</li> </ul>	<ul style="list-style-type: none"> <li>• Pain-free but mild to moderately suspected history/clinical presentation</li> <li>• Patients without classic cardiac chest pain, but concomitant symptoms of unknown origin consistent with possible CAD (e.g. single syncope, acute dyspnoea or acute fatigue)</li> <li>• Including the elderly, diabetics, and patients with several comorbidities</li> </ul>	<ul style="list-style-type: none"> <li>• History/clinical presentation highly suspicious</li> </ul> <i>And/or</i> <ul style="list-style-type: none"> <li>• Ongoing or recurrent cardiac-suspected chest pain</li> </ul> <i>And/or</i> <ul style="list-style-type: none"> <li>• Ischaemic suspected ECG (including significant ST-segment elevation/depression or new LBBB)</li> </ul> <i>And/or</i> <ul style="list-style-type: none"> <li>• Haemodynamic instability</li> </ul> <i>And/or</i> <ul style="list-style-type: none"> <li>• Respiratory distress</li> </ul>
<b>Further management</b>	Home with/without treatment <b>OR</b> hospitalised due to other conditions	Admission at the OAEOCs observation unit for serial hs-cTnT measurements in order to rule-out AMI	Direct transfer to hospital by ambulance (usually within 20-60 minutes after OAEOC arrival)

AMI: acute myocardial infarction; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; GP: general practitioner; hs-cTnT: high-sensitivity cardiac troponin T; NSTEMI-ACS: non-ST-segment elevation acute coronary syndrome; OAEOC: Oslo Accident and Emergency Outpatient Clinic; STEMI: ST-segment elevation myocardial infarction

**ONLINE TABLE 2 Details in the predefined study form**

<b>Basics</b>	<ul style="list-style-type: none"> <li>• Norwegian personal identity number (later replaced by a study ID)</li> <li>• Sex and Age</li> </ul>
<b>Time variables (time/date)</b>	<ul style="list-style-type: none"> <li>• Onset of symptoms</li> <li>• Arrival at the OAEOC</li> <li>• Admission at the OAEOC observation unit</li> <li>• Hs-cTnT measurements</li> <li>• OAEOC discharge</li> </ul>
<b>Risk factors for cardiovascular disease</b>	<ul style="list-style-type: none"> <li>• Current or history of smoking last ten years</li> <li>• Diabetes mellitus</li> <li>• Chronic obstructive pulmonary disease</li> <li>• Previous history of CAD</li> <li>• Hypertension</li> <li>• Hypercholesterolemia</li> <li>• Other CVD (valvular disease, previous cerebral stroke, cardiomyopathies, atrial fibrillation other arrhythmias),</li> <li>• History of CAD in first-degree sibling &lt;60 years of age</li> </ul>
<b>Presenting acute symptoms</b>	<ul style="list-style-type: none"> <li>• Chest pain <ul style="list-style-type: none"> <li>○ Constricting</li> <li>○ Tearing</li> <li>○ Burning</li> <li>○ Sharp</li> <li>○ Respiratory-dependent</li> <li>○ Position-dependent</li> <li>○ Palpation-dependent</li> </ul> </li> <li>• Pain radiation (arms, neck, jaws, upper abdomen, scapulae)</li> <li>• Acute dyspnoea</li> <li>• Acute fatigue</li> <li>• Syncope, pre-syncope</li> <li>• Observed or reported diaphoresis</li> <li>• Nausea or vomiting</li> <li>• Palpitations</li> <li>• Other pain: upper abdomen or upper back/scapulae only</li> <li>• No pain</li> </ul>
<b>ICD-10 discharge codes</b>	<ul style="list-style-type: none"> <li>• Given by GP responsible for OAEOC discharge</li> </ul>
<b>Further disposition after OAEOC discharge</b>	<ul style="list-style-type: none"> <li>• Home/no follow-up</li> <li>• Advised to contact regular GP</li> <li>• Referral to hospital outpatient clinic</li> <li>• Admitted at a municipality (primary care) short term facility</li> <li>• Left during observation</li> <li>• Admitted hospital</li> <li>• Direct transfer to the cath lab</li> </ul>

CAD: coronary artery disease; CVD: cardiovascular disease; GP: general practitioner; hs-cTnT: high-sensitivity cardiac troponin T; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision; OAEOC: Oslo Accident and Emergency Outpatient Clinic

### Laboratory analysis

Venous blood samples were collected in serum tubes and stored locally at room temperature (approximately 20 °C) for a maximum of 30 minutes before centrifugation, then stored in a refrigerator before being sent to the laboratory every four hours, as per standard procedure at the primary care emergency clinic. Hs-cTnT was analysed at the Department of Medical Biochemistry at Oslo University Hospital Ullevaal on the Cobas 8000 e602 and later the Cobas 8000 e801 Module Analyzer using the Elecsys Troponin T hs STAT assay (Roche Diagnostics, Switzerland). The cTnT has a stability of 24 hours with storage at 2-8 °C,<sup>[1,2]</sup> and similar stability has previously been demonstrated for hs-cTnT samples stored under the conditions in our study.<sup>[3]</sup> EQA (external quality assessment) material from Noklus (Bergen, Norway) and Equalis (Equalis AB, Uppsala, Sweden) was regularly analysed at the central lab with good performance during the inclusion period. The coefficient of variation (CV) was 6 % at concentrations  $\geq 20$  ng/L and 10 % at concentrations  $< 20$  ng/L.

**ONLINE TABLE 3 The History component of the HEART score used in the OUT-ACS study**

Non-typical elements for ACS	Typical elements for ACS
<ul style="list-style-type: none"> <li>• Sharp or burning chest pain</li> <li>• Pain in the upper abdomen or upper back/scapulae only</li> <li>• Palpation, position or respiratory-dependent pain</li> <li>• Acute fatigue</li> <li>• Syncope/pre-syncope</li> <li>• Palpitations</li> </ul>	<ul style="list-style-type: none"> <li>• Constricting or tearing retrosternal chest pain</li> <li>• Radiation of pain to arms, neck or jaws</li> <li>• Diaphoresis (observed or reported)</li> <li>• Vomiting, nausea</li> <li>• Acute dyspnoea</li> </ul>

Following the original HEART score,<sup>[4]</sup> the History is considered highly suspicious and given 2 points if only typical elements are reported, 1 point if the medical history contains a combination of both non-typical and typical elements, and 0 points if all elements in are considered non-typical.

The following classification of which elements are considered non-suspicious or suspicious are defined by the OUT-ACS study investigators in this table, based on symptoms reported at the initial examination.

ACS: acute coronary syndrome; HEART: History, ECG, Age, Risk factors and Troponin; OAEOC: Oslo Accident and Emergency Outpatient Clinic

**ONLINE TABLE 4 Separate 2x2-tables used in the calculation of the diagnostic performance for the three different strategies**

	Single hs-cTnT		Original HEART score		Modified HEART score	
	Rule-out group	Rule-in group	Low-risk group	High-risk group	Low-risk group	High-risk group
<b>True positive</b>	61	34	56	18	60	21
<b>False positive</b>	1081	10	784	62	1012	175
<b>False negative</b>	0	27	5	43	1	40
<b>True negative</b>	569	1640	866	1588	638	1475
<b>Total</b>	<b>1711</b>	<b>1711</b>	<b>1711</b>	<b>1711</b>	<b>1711</b>	<b>1711</b>

The diagnostic performance for each rule-out, rule-in, low-risk, and high-risk groups were calculated separately.

HEART: History, ECG, Age, Risk factors and Troponin; hs-cTnT: high-sensitivity cardiac troponin T

**ONLINE TABLE 5 Disposition after ended observation at the OAEOC**

n (%)	Single hs-cTnT			Original HEART score			Modified HEART score		
	Rule out	Observation	Rule in	Low risk	Inter-mediate	High risk	Low risk	Inter-mediate	High risk
No follow-up	163 (28.6)	230 (20.9)	1 (2.3)	247 (28.4)	141 (18.6)	6 (7.5)	190 (29.7)	180 (20.5)	24 (12.2)
Contact regular GP	344 (60.5)	631 (57.5)	1 (2.3)	513 (58.9)	431 (56.7)	32 (40.0)	374 (58.5)	512 (58.4)	90 (45.9)
Admitted municipal short term facility	0 (0.0)	21 (1.9)	2 (4.5)	2 (0.2)	17 (2.2)	4 (5.0)	2 (0.3)	16 (1.8)	5 (2.6)
Referral to hospital outpatient clinic	20 (3.5)	47 (4.3)	0 (0.0)	27 (3.1)	35 (4.6)	5 (6.3)	20 (3.1)	31 (3.5)	16 (8.2)
Left during observation	10 (1.8)	15 (1.4)	0 (0.0)	16 (1.8)	9 (1.2)	0 (0.0)	13 (2.0)	12 (1.4)	0 (0.0)
Admitted hospital	32 (5.6)	153 (13.9)	37 (84.1)	66 (7.6)	124 (16.3)	32 (40.0)	40 (6.3)	122 (13.9)	60 (30.6)
Direct coronary angiography	0 (0.0)	1 (0.1)	3 (6.8)	0 (0.0)	3 (0.4)	1 (1.3)	0 (0.0)	3 (0.3)	1 (0.5)
<b>Total N = 1711</b>	<b>569 (33.3)</b>	<b>1098 (64.2)</b>	<b>44 (2.6)</b>	<b>871 (50.9)</b>	<b>760 (44.4)</b>	<b>80 (4.7)</b>	<b>639 (37.3)</b>	<b>125 (51.2)</b>	<b>196 (11.5)</b>

GP: general practitioner; HEART: History, ECG, Age, Risk factors, Troponin; hs-cTnT: high-sensitivity cardiac troponin T; OAEOC: Oslo Accident and Emergency Outpatient Clinic



**ONLINE TABLE 6 Misclassification in the original low-risk HEART score group**

Sex	Age	HEART score	Symptom onset to first hs-cTnT, hours	hs-cTnT at the OAEOC			Disposition after OAEOC	Adjudicated final diagnosis
				0-hour	1-hour	4-hour		
Female	40	3	1.8	30	69	X	Hospital	AMI
Male	59	3	2.3	9	12	37	Hospital	AMI
Female	57	3	5.7	13	X	X	Hospital	AMI
Male*	32	3	9.5	378	481	X	Hospital	AMI
Female	70	3	18.1	5	6	13	Home	AMI

\*Also misclassified by the modified low-risk HEART score.

AMI: acute myocardial infarction; HEART: History, ECG, Age, Risk factors and Troponin; hs-cTnT: high-sensitivity cardiac troponin T; OAEOC: Oslo Accident and Emergency Outpatient Clinic; X: not measured due to hospitalisation

**ONLINE TABLE 7 Classification of the HEART scores compared to single hs-cTnT approach and the 0/1-hour algorithm for hs-cTnT**

			Original HEART score		Modified HEART score	
			n	%	n	%
<b>Single hs-cTnT (n=1711)</b>	<b>Rule-out (n=569)</b>	Low risk	430	75.6	430	75.6
		Intermediate	138	24.3	138	24.3
		High risk	1	0.2	1	0.2
	<b>Observation (n=1098)</b>	Low risk	440	40.1	208	18.9
		Intermediate	595	54.2	711	64.8
		High risk	63	5.7	179	16.3
	<b>Rule-in (n=44)</b>	Low risk	1	2.3	1	2.3
		Intermediate	27	61.4	27	61.4
		High risk	16	36.4	16	36.4
<b>0/1-hour algorithm (n=1711)<sup>[5]</sup></b>	<b>Rule-out (n=1311)</b>	Low risk	815	62.2	617	47.1
		Intermediate	490	37.4	658	50.2
		High risk	6	0.5	36	2.7
	<b>Observation (n=334)</b>	Low risk	50	15.0	19	5.7
		Intermediate	231	69.2	178	53.3
		High risk	53	15.9	137	41.0
	<b>Rule-in (n=66)</b>	Low risk	6	9.1	3	4.5
		Intermediate	39	59.1	40	60.6
		High risk	21	31.8	23	34.8

The total HEART scores were stratified into three risk groups; low-risk (0-3 points), intermediate-risk (4-6 points), and high-risk (7-10 points), and further classified according to the single hs-cTnT strategy and the ESC 0/1-hour algorithm.

ESC: European Society of Cardiology; HEART: History, ECG, Age, Risk factors and Troponin; hs-cTnT: high-sensitivity cardiac troponin T

**ONLINE TABLE 8 Distribution of the calculated HEART scores**

Classification	Points	Original HEART score		Modified HEART score	
		n	%	n	%
Low risk	0	4	0.2	3	0.2
	1	110	6.4	74	4.3
	2	305	17.8	239	14.0
	3	452	26.4	323	18.9
Intermediate risk	4	377	22.0	350	20.5
	5	242	14.1	302	17.7
	6	141	8.2	224	13.1
High risk	7	60	3.5	130	7.6
	8	16	0.9	53	3.1
	9	4	0.2	13	0.8
	10	0	0.0	0	0.0
<b>Total</b>		<b>1711</b>	<b>100.0</b>	<b>1711</b>	<b>100.0</b>
<b>Mean (SD)</b>		3.64 (1.568)		4.22 (1.785)	

SD: standard deviation; HEART: History, ECG; Age; Risk factors; Troponin

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