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ARTICLE

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Jasper Boeddinghaus, MD,[1,2*] Dimitrios Doudesis, PhD,[2,3*] Pedro Lopez-Ayala, MD,[1*] Kuan Ken Lee, MD PhD,[2,3] Luca Koechlin, MD,[1,4] Karin Wildi, MD,[1,5] Thomas Nestelberger, MD,[1] Raphael Borer, MSc,[1] Òscar Miró, MD,[6] F. Javier Martin-Sanchez, MD,[7] Ivo Strebel, PhD,[1] Maria Rubini Giménez, MD,[1] Dagmar I. Keller, MD,[8] Michael Christ, MD,[9] Anda Bularga, MD,[2] Ziwen Li, PhD,[2] Amy V Ferry, PhD,[2] Chris Tuck, BSc,[2] Atul Anand, MD,[2] Alasdair Gray, MD,[3,10] Nicholas L Mills, MD PhD,[2,3#] and Christian Mueller, MD[1#] for the CoDE-ACS and APACE Investigators[†]

[1] Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel, Switzerland
[2] BHF/University Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK
[3] Usher Institute, University of Edinburgh, Edinburgh, UK
[4] Department of Cardiac Surgery, University Hospital Basel, University of Basel, Switzerland
[5] Department of Intensive Care, University Hospital Basel, University of Basel, Switzerland
[6] Emergency Department, Hospital Clinic, Barcelona, Catalonia, Spain
[7] Servicio de Urgencias, Hospital Clínico San Carlos, Madrid, Spain
[8] Emergency Department, University Hospital Zurich, Zurich, Switzerland
[9] Emergency Department, Kantonsspital Luzern, Switzerland
[10] Emergency Medicine Research Group Edinburgh, Royal Infirmary of Edinburgh, United Kingdom

[*]Contributed equally
[#]Contributed equally
[†]Investigators listed at the end of the article

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Twitter: @CRIBasel, @HighSTEACS, @J_Boeddinghaus, @DDoudesis, @LopezAyalaP

Corresponding author:
Professor Nicholas L Mills
BHF/University Centre for Cardiovascular Science
The University of Edinburgh
Royal Infirmary of Edinburgh
Edinburgh EH16 4SA
United Kingdom

Telephone: 0044 131 242 6515
E-mail: nick.mills@ed.ac.uk

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Abstract

Background: CoDE-ACS is a validated clinical decision-support tool that uses machine learning with or without serial cardiac troponin measurements at a flexible timepoint to calculate the probability of myocardial infarction (MI). How CoDE-ACS performs at different timepoints for serial measurement and compares with guideline recommended diagnostic pathways that rely on fixed thresholds and timepoints is uncertain.

Methods: Patients with possible MI without ST-segment elevation were enrolled at 12 sites in five countries and underwent serial high-sensitivity cardiac troponin I concentration measurement at 0, 1 and 2 hours. Diagnostic performance of the CoDE-ACS model at each timepoint was determined for index type 1 MI and the effectiveness of previously validated low- and high-probability scores compared with guideline recommended ESC 0/1h, ESC 0/2h and High-STEACS pathways.

Results: In total 4,105 patients (age 61 [50-74] years, 32% women) were included where 575 (14%) had type 1 MI. At presentation, CoDE-ACS identified 56% of patients as low-probability, with a negative predictive value and sensitivity of 99.7% (95% confidence interval [CI] 99.5-99.9%) and 99.0% (98.6-99.2%), ruling out more patients than the ESC 0h and High-STEACS (25% and 35%) pathways. CoDE-ACS incorporating a second cTn measurement identified 65% or 68% of patients as low probability at 1 or 2 hours, for an identical negative predictive value of 99.7% (99.5-99.9%), 19% or 18% as high-probability with a positive predictive value of 64.9% (63.5-66.4%) and 68.8% (67.3-70.1%), and 16% or 14% as intermediate probability. In comparison, the ESC 0/1h, ESC 0/2h and High-STEACS pathways after serial measurements identified 49%, 53% and 71% of patients as low-risk with a negative predictive value of 100% (99.9-100%), 100% (99.9-100%) and 99.7% (99.5-

99.8%), and 20%, 19% or 29% as high-risk with a positive predictive value of 61.5% (60.0-63.0%), 65.8% (64.3-67.2%), and 48.3% (46.8-49.8%) resulting in 31%, 28% or 0% who require further observation in the Emergency Department, respectively.

Conclusions: CoDE-ACS performs consistently irrespective of the timing of serial cardiac troponin measurement identifying more patients as low-probability with comparable performance to guideline recommended pathways for MI. Whether care guided by probabilities can improve the early diagnosis of MI requires prospective evaluation.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT00470587

Clinical Perspective

What is new?

- CoDE-ACS is a clinical decision-support tool that uses machine learning to calculate the probability of myocardial infarction. This was the first evaluation of performance across different timepoints for serial cardiac troponin measurement and first systematic comparison with guideline recommended diagnostic pathways.
- CoDE-ACS combines cardiac troponin as a continuous measure with age, sex, comorbidities, and the time between measurements. Here it was compared with diagnostic pathways that rely on fixed thresholds and timepoints for measurement.
- CoDE-ACS can be applied flexibly enabling healthcare providers to perform serial troponin measurements if and when needed, and to define low- and high-probability scores according to local preferences.

What are the clinical implications?

- CoDE-ACS performed consistently whether testing was performed at 0, 1 or 2 hours, identifying more patients as low-probability of myocardial infarction and fewer that require further observation with comparable diagnostic performance than guideline recommended pathways.
- CoDE-ACS could reduce unnecessary testing and hospital admission for observation, but prospective studies are needed to determine whether care guided by probabilities improves the diagnosis of myocardial infarction.

Introduction

Myocardial infarction remains one of the leading causes of death worldwide.[1] Each year, more than 15 million patients present with possible myocardial infarction to the Emergency Department in Europe and North America, resulting in substantial use of resources and crowding.[2,3] Early recognition of those patients with and without myocardial infarction is important to guide treatment and to prevent unnecessary investigation or hospital admission. As a consequence, international guidelines recommend the use of high-sensitivity cardiac troponin assays and ESC 0/1h- and ESC 0/2h serial testing algorithms to rule out or rule in myocardial infarction or pathways that are optimised for a single troponin measurement to rule out myocardial infarction, such as the High-STEACS pathway.[2,4–7] These accelerated diagnostic pathways use fixed cardiac troponin thresholds for all patients, which do not account for age or comorbidities known to influence troponin and do not consistently apply sex-specific thresholds.[8–12] Furthermore, the ESC 0/1h- and ESC 0/2h-algorithms require serial measurements at precise time-points with limited flexibility, which can be challenging to deliver and has limited adoption in clinical practice.[13,14]

To overcome these challenges and encourage adoption of accelerated diagnostic pathways, the Collaboration for the Diagnosis and Evaluation of Acute Coronary Syndrome (CoDE-ACS) investigators developed a decision support tool that uses machine learning to combine cardiac troponin as a continuous measure with features known to influence cardiac troponin concentrations that calculates the probability of myocardial infarction for an individual patient.[15] CoDE-ACS provided excellent diagnostic performance and could in theory be applied flexibly with serial testing if needed at a timepoint that is convenient for the patient and clinician.[15] However, whether CoDE-ACS performs consistently at different timepoints for serial cardiac troponin testing is not known, and the performance compared to guideline

recommended accelerated diagnostic pathways that use fixed thresholds and timepoints has not been systematically studied.

Our aim was to compare the performance of CoDE-ACS at presentation with performance using serial cardiac troponin measurements at 1 or 2 hours, and to compare this to guideline recommended diagnostic pathways that use fixed timepoints.

Methods

Study design and population

A secondary analysis was performed in the prospective, international, multicenter APACE (Advantageous Predictors of Acute Coronary Syndromes Evaluation) cohort study (www.clinicaltrials.gov NCT00470587).[16–20] Patients were enrolled at twelve centres in five countries. The study was carried out according to the principles of the Declaration of Helsinki and approved by local ethics committees in each country. All patients provided written informed consent. Adult patients ≥18 years old presenting to an Emergency Department with symptoms suggestive of myocardial infarction were enrolled. For this analysis patients with ST-segment elevation myocardial infarction, an unknown final diagnosis after adjudication, and those where cardiac troponin values were missing at 0, 1, or 2 hours were excluded. The most common reasons for missing samples were early transfer to the catheter laboratory or coronary care unit and diagnostic procedures that precluded blood draws at these timepoints. Cardiac troponin I concentrations were measured in stored samples using the Abbott Architect *STAT* high-sensitive troponin I assay (Abbott Laboratories, Abbott Park, IL). This assay has an inter-assay coefficient of variation of <10% at 4.7 ng/L[21,22], a uniform 99th percentile of 26.2ng/L and a sex-specific 99th percentile of 16 ng/L in females and 34 ng/L in males.[23] The authors designed the study, gathered, and analyzed the data according to the

STROBE guidelines[24] (**Supplemental Table 1**), vouched for the data and analysis, wrote the paper, and decided to submit it for publication.

The CoDE-ACS score and pathway

The methodology for the derivation and validation of the CoDE-ACS score was described in detail previously.[15] In brief, given the features that inform the diagnosis differ for ruling in and ruling out myocardial infarction, separate XGBoost models to estimate the probability of myocardial infarction were trained in consecutive patients with and without myocardial injury at presentation, defined as a high-sensitivity cardiac troponin I concentration above or below the sex-specific 99th percentile upper reference limit on the first measurement. XGBoost models using a second serial measurement at a flexible timepoint were then trained, resulting in four separate models. Each model combines cardiac troponin as a continuous measure with age, sex, time from symptom onset, the presence of chest pain, known ischemic heart disease, hyperlipidemia, heart rate, systolic blood pressure, Killip class, myocardial ischemia on the electrocardiogram, renal function and hemoglobin. These models were combined within a single clinical decision support system called CoDE-ACS, which computes a score (0–100) corresponding to an individual patient's probability of myocardial infarction (https://decision-support.shinyapps.io/code-acs). We previously derived and validated CoDE-ACS scores of less than 3 and more than 60 to classify the greatest proportion of patients as low or high probability that achieved prespecified performance criteria.[23,25,26] Whilst CoDE-ACS is designed to be used flexibly by clinicians and healthcare providers with decisions guided by individual probabilities, we applied these scores in a pathway that recommended serial measurement in those with scores of 3 to 60 indicating intermediate probability to facilitate comparison with current guideline recommended accelerated diagnostic pathways.

Guideline recommended accelerated diagnostic pathways

The ESC 0/1h and ESC 0/2 h serial testing algorithms to rule out or rule in myocardial infarction and the High-STEACS pathway optimised for single sample rule out of myocardial infarction were applied as previously described[8,27,28] and recommended by current guidelines.[2,5] Further details of these clinical pathways are provided in the **Online Supplement**.

Adjudication of the diagnosis of myocardial infarction

Two independent cardiologists performed adjudication of the final diagnosis according to the Fourth Universal Definition of Myocardial Infarction[3] using two sets of data. First, all available medical records were reviewed including the history, physical examination, laboratory testing, serial cardiac troponin concentrations from the local assay, radiological testing, electrocardiography, echocardiography, exercise testing, and coronary angiography from the time of presentation to 90-days; and second, study-specific assessments were reviewed including chest pain characteristics, serial high-sensitivity cardiac troponin I concentrations (Abbott Laboratories, Abbott Park, IL) using study samples, and follow-up by telephone or mail. Where there was disagreement over the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist. Myocardial infarction was diagnosed when there was myocardial injury identified using sex-specific 99th percentile upper reference limits (>16 ng/L in women and >34 ng/L in men) in a clinical setting consistent with myocardial ischemia with a significant rise and/or fall on serial testing. Patients with myocardial infarction were further classified into type 1 and type 2 myocardial infarction.[2,3] Further details are provided in the **Online Supplement**.

Study endpoints and follow up

Effectiveness was defined as the proportion of patients classified as low-probability or ruled out at presentation and on serial cardiac troponin measurements. The primary diagnostic endpoint was index diagnosis of type 1 myocardial infarction. The secondary diagnostic endpoint was index myocardial infarction including type 1 or type 2 myocardial infarction. Follow-up for cardiac death or all-cause death was performed at 3, 12 and 24 months. Information regarding the cause of death was obtained from the patient's hospital records, the family physician's records and the national death registry.

Statistical analysis

Baseline characteristics are summarized in those with and without myocardial infarction as percentages for categorical variables, and mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables, as appropriate. The proportion of patients classified as low-, intermediate and high-probability or stratified to rule out, observe and rule in groups was calculated at presentation and following serial troponin measurements for the CoDE-ACS and guideline recommended diagnostic pathways. Sensitivity, specificity, negative predictive value, positive predictive value and effectiveness were determined using 2×2 tables to calculate the true and false negative rates for the primary and secondary diagnostic outcome for each pathway. The Wilson score method without continuity correction was used to calculate 95% confidence intervals (CI). Model discrimination and calibration were assessed by calculating the area under the receiver-operating-characteristic curve (AUROC), by visual inspection of the calibration and calculation of the Brier score. The Brier score is a measure of both discrimination and calibration and is calculated by taking the mean squared difference between predicted probabilities and the observed outcome.[29] Cumulative incidence curves were plotted to illustrate cardiac and all-cause death in patients stratified by the CoDE-ACS score and guideline recommended diagnostic

pathways with differences assessed using the Gray's test.[30] All hypothesis testing was two-tailed, and P values of less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed using R version 4.2.0 (Vienna, Austria).

Results

Study cohort and index diagnosis

The cohort comprised of 4,105 patients (median age 61 [IQR 50-74], 32% women) with possible myocardial infarction enrolled between April 2006 and February 2019 (**Supplemental Figure 1**). In total 575 (14%) patients were adjudicated to have an index diagnosis of type 1 myocardial infarction. Patients with type 1 myocardial infarction were older and more likely to be male with known cardiovascular risk factors and coronary artery disease than those without myocardial infarction (**Table 1**). Type 2 myocardial infarction was adjudicated in a further 145 (4%) patients. Baseline characteristics of patients that were excluded due to missing serial cardiac troponin measurements were comparable (**Supplemental Table 2**).

Performance of CoDE-ACS and diagnostic pathways at presentation

At presentation the CoDE-ACS score had good discrimination and calibration for the index diagnosis of type 1 myocardial infarction using a single cardiac troponin measurement (area under the receiver operating curve = 0.950, 95% confidence interval [CI] 0.943-0.958, Brier score = 0.061; **Figure 1**). A score of less than 3 at presentation identified 56% (2,280/4,105) of patients as low probability of myocardial infarction with a negative predictive value and sensitivity of 99.7% (99.5-99.9%) and 99.0% (98.6-99.2%), respectively. A score of greater than 60 at presentation identified 13% (516/4,105) of patients as high probability with a positive predictive value and specificity of 72.9% (71.5-74.2%) and 96.0% (95.4-96.6%), respectively. The remaining 1,309 (32%) were of intermediate probability at presentation and serial cardiac troponin testing is recommended.

At presentation the ESC 0/1h- and ESC 0/2h-algorithms ruled out myocardial infarction in 25% (1,039/4,105) of patients with a negative predictive value and sensitivity of 100% (99.9-100%) and 100% (99.9-100%), respectively, and ruled in myocardial infarction in 13% (524/4,105) of patients with a positive predictive value and specificity of 67.7% (66.3-69.2%) and 95.2% (94.5-95.8%), respectively. The remaining 2,542 (62%) patients were neither ruled out or ruled in at presentation and serial cardiac troponin testing is recommended.

At presentation the High-STEACS pathway identified 35% (1,419/4,105) patients as low risk of myocardial infarction with a negative predictive value and sensitivity of 100% (95%CI, 99.9-100%) and 100% (95%CI, 99.9-100%), respectively, and 18% (746/4,105) of patients as high risk with a positive predictive value and specificity of 60.6% (59.1-62.1%) and 91.7% (90.8-92.5%), respectively. The remaining 1,940 (47%) had intermediate cardiac troponin concentrations at presentation or presented within 3 hours of symptom onset and serial testing is recommended (**Table 2**).

Performance of CoDE-ACS and diagnostic pathways at 1 hour

At one hour, the CoDE-ACS score had good discrimination and calibration for the index diagnosis of type 1 myocardial infarction using serial cardiac troponin measurements (area under the receiver operating curve = 0.959, 95% CI 0.953-0.966, Brier score = 0.065; **Figure 1**). A score of less than 3 at one hour identified 65% (2,671/4,105) of patients as low probability of myocardial infarction with a negative predictive value and sensitivity of 99.7% (99.5-99.8%) and 98.6% (98.2-98.9%), respectively. A score of greater than 60 at one hour identified 19% (770/4,105) of patients as high probability with a positive predictive value and specificity of 64.9% (63.5-66.4%) and 92.4% (91.5-93.1%), respectively. The remaining 664 (16%) were of intermediate probability (**Supplemental Figure 2A**).

At one hour, the ESC 0/1h-algorithm ruled out myocardial infarction in 49% (2,014/4,105) of patients with a negative predictive value and sensitivity of 100% (95%CI, 99.9-100%) and 100% (95%CI, 99.9-100%), respectively, and ruled in myocardial infarction in 20% (829/4,105) with a positive predictive value and specificity of 61.5% (60.0-63.0%) and 91.0% (90.0-91.8%), respectively. The remaining 1,262 (31%) were neither ruled out or ruled in at one hour and further observation is recommended (**Table 2**).

Performance of CoDE-ACS and diagnostic pathways at 2 hours

At two hours, the CoDE-ACS score had good discrimination and calibration for the index diagnosis of type 1 myocardial infarction using serial cardiac troponin measurements (area under the receiver operating curve = 0.967, 95% CI 0.961-0.973, Brier score = 0.057; **Figure 1**). A score of less than 3 identified 68% (2,785/4,105) of patients as low probability of myocardial infarction with a negative predictive value and sensitivity of 99.7% (99.5-99.9%) and 98.8% (98.4-99.1%), respectively. A score of greater than 60 identified 18% (736/4,105) of patients as high probability with a positive predictive value and specificity of 68.8% (67.3-70.1%) and 93.5% (92.7-94.2%), respectively. The remaining 584 (14%) patients were of intermediate probability (**Supplemental Figure 2B**).

At two hours, the ESC 0/2h-algorithm ruled out myocardial infarction in 53% (2,156/4,105) of patients with a negative predictive value and sensitivity of 100% (99.9-100%) and 100% (99.9-100%), respectively, and ruled in myocardial infarction in 19% (768/4,105) of patients with a positive predictive value and specificity of 65.8% (64.3-67.2%) and 95.2% (91.7-93.3%), respectively. The remaining 1,181 (28%) were neither ruled out or ruled in at two hours and further observation is recommended.

At two hours, the High-STEACS pathway identified 71% (2,923/4,105) patients as low risk of myocardial infarction with a negative predictive value and sensitivity of 99.7% (99.5-99.8%) and 98.6% (98.2-98.9%), respectively, and 29% (1,182/4,105) of patients as high risk of myocardial infarction with a positive predictive value and specificity of 48.3% (46.8-49.8%) and 82.8% (81.6-83.9%), respectively (**Table 2**).

Performance of CoDE-ACS and diagnostic pathways for any myocardial infarction and by sex

The effectiveness and diagnostic performance of CoDE-ACS and all diagnostic pathways for the secondary endpoint of any myocardial infarction and in females and males are shown in **Supplemental Table 3 and 4**. The findings were consistent with the analysis of the primary diagnostic outcome.

Using individual probabilities with CoDE-ACS to guide patient care

As CoDE-ACS can be applied flexibly according to local preferences and individual probabilities can be used to guide care, we validated performance of the models across a range of probabilities (**Table 3**). For example, a more conservative institution may use a score of less than 2, which would identify 44% (1806/4,105) of patients as low probability at presentation with a higher negative predictive value and sensitivity of 99.9% (95%CI, 99.8-100%) and 99.8% (95%CI, 99.6-99.9%), respectively. Similarly a less conservative institution may use a lower score of more than 50 to identify 15% (603/4,105) of patients as high probability at presentation with a lower positive predictive value and specificity of 68.2% (95%CI, 66.7-69.6%) and 94.6% (95%CI, 93.8-95.2%), respectively.

Outcomes at 30-days and one year stratified by CoDE-ACS and diagnostic pathways

At 30-days and one year, there were 20 (0.5%) and 68 (1.7%) deaths from a cardiac cause and 30 (0.7%) and 146 (3.6%) deaths from any cause, respectively. Overall, patients identified by CoDE-ACS as low risk had a lower rate of cardiac death and all-cause mortality at 30-days and one year when compared to patients identified as intermediate or high risk (e.g., at one year, cardiac death 0.6% *versus* 4.1% and 3.2%; all-cause death 1.6% *versus* 9.2% and 5.6%, Gray`s test *P<0.001*; **Figure 2**). Patients identified as intermediate-probability were older, presented earlier to hospital, more often had known coronary artery disease and previous myocardial infarction with revascularization, and more frequently had impaired kidney function. **(Supplemental Table 5).** Outcomes across a range of CoDE-ACS probabilities are reported in **Supplemental Table 6**. Similarly cardiac death and all-cause death at 30-days and one year were lower in those ruled out, compared to those triaged for further observation or ruled in by the guideline recommended diagnostic pathways (Gray`s test *P<0.001* for all pathways; **Supplement Figures 3-5**).

Discussion

In this international multicenter study enrolling patients with symptoms suggestive of myocardial infarction, we compared the performance of the CoDE-ACS decision support tool using machine learning for the diagnosis of myocardial infarction across different timepoints for serial cardiac troponin measurement and with guideline recommended diagnostic pathways that rely on fixed timepoints for testing.

We report several findings that are relevant to the application of clinical decision-support tools in practice. First, discrimination of CoDE-ACS for myocardial infarction was similar at presentation and with serial cardiac troponin measurements at one or two hours enabling subsequent measurements to be taken at a flexible and convenient timepoint. Second, compared to guideline recommended pathways, CoDE-ACS identified more patients as low-probability of myocardial infarction with an overall comparable negative predictive value, and fewer patients as high-probability with an improved positive predictive value. In particular, the CoDE-ACS score to identify patients as high-probability of myocardial infarction was superior to the 99th percentile threshold used to identify high-risk patients in the High-STEACS pathway. Third, CoDE-ACS identified fewer patients as intermediate-probability than were triaged for further observation by the ESC 0/1h- and ESC 0/2h-algorithms. Finally, we validated low- and high-probability scores that are more or less conservative, so CoDE-ACS could be applied flexibly by healthcare providers in diagnostic pathways that optimise patient flow according to local pressures.

Whilst CoDE-ACS offers increased flexibility and a more personalised approach to the assessment of patients with possible myocardial infarction, it is important to acknowledge that existing guideline recommended pathways perform well. Our study confirms the

372 excellent performance of existing guideline recommended pathways using fixed thresholds
373 and timepoints for the early diagnosis of myocardial infarction.[8,31–36] All clinical pathways
374 irrespective of timepoints of serial testing identified low-risk patients with negative predictive
375 values greater than 99.7% and the overall performance was consistent in patients with type 1
376 and type 2 myocardial infarction. Our findings therefore corroborate evidence and support
377 current international guideline recommendations.[2,7]
378
379 In the initial derivation of the CoDE-ACS decision support tool probability thresholds were
380 defined to achieve a predefined negative predictive value of at least 99.5% for low-
381 probability and a positive predictive value of at least 80% for high-probability of myocardial
382 infarction. In this external validation, CoDE-ACS incorporating cardiac troponin
383 concentrations at presentation or at one or two hours met this predefined negative predictive
384 value. In contrast, the diagnostic performance of CoDE-ACS to identify patients as high-
385 probability of myocardial infarction was lower than in the original study with a positive
386 predictive value of 72.9% at presentation. This may be due to differences in the prevalence of
387 myocardial infarction between the training dataset of unselected consecutive patients with
388 possible myocardial infarction and the validation dataset here where informed consent was
389 required for enrolment. Despite this the positive predictive value of the previously defined
390 CoDE-ACS score was higher than the 99th percentile and the ESC 0/1h- or ESC 0/2-hour
391 direct rule-in thresholds. Furthermore, compared to guideline recommended pathways using
392 fixed cardiac troponin thresholds at precise timepoints, CoDE-ACS identified more patients
393 as low-probability suggesting that the use of individual probabilities may increase efficiency
394 in the Emergency Department by improving the early identification of those with and without
395 myocardial infarction.

In comparison to guideline recommended pathways, CoDE-ACS only classified one out of seven patients as intermediate-probability of myocardial infarction, while the ESC 0/1h- and ESC 0/2h-algorithms triaged one out of three patients towards the observe zone. This group is known to be heterogeneous, and includes some patients with chronic myocardial injury for whom dedicated treatment options are currently not clearly defined by international guidelines.[2,7,37] Patients identified as intermediate-probability were older, presented earlier to hospital, more often had known coronary artery disease and previous myocardial infarction with revascularization, and more frequently had impaired kidney function. This may explain why they had higher rates of cardiac and all-cause death than patients identified as at high-probability of myocardial infarction. By providing clinicians with individual probabilities the CoDE-ACS clinical decision-support tool could help clinicians to identify patients in whom further investigation and treatment maybe warranted.

All guideline recommended clinical diagnostic pathways use criteria based on consensus and data from cohort studies and randomized trials.[31,33,38] They all use fixed thresholds and require blood sampling at defined timepoints. The latter can be challenging to deliver in busy Emergency Departments and limits the adoption of these pathways into clinical practice.[13] Implementing CoDE-ACS into routine clinical care could overcome this challenge by enabling healthcare providers to perform serial troponin measurements if and when needed, and to define low- and high-probability scores according to local preferences. For example, in a more conservative healthcare system, lower CoDE-ACS scores might be preferred to identify patients at very low-probability of myocardial infarction. We have evaluated alternative probability scores and found that a score of less than two at presentation still identifies 44% of patients at low-probability with a negative predictive value of 99.9% and sensitivity of 99.7%. Alternatively, in healthcare systems with limited capacity in the

Emergency Department, less conservative CoDE-ACS scores to identify those as high-probability could be applied. This would further reduce the proportion of patients at intermediate-probability who require observation and further work-up in the Emergency Department. We previously demonstrated that CoDE-ACS performs consistently across subgroups such as women and the elderly. Future studies have to determine if care guided by probabilities rather than binary thresholds could reduce inequalities.

Some limitations merit consideration when interpreting our findings. First, CoDE-ACS was derived and validated using one specific high-sensitivity cardiac troponin I assay and it needs to be trained and validated for other high-sensitivity cardiac troponin assays. Second, the ESC 0/1h and ESC 0/2h pathways were trained for an endpoint of all non-ST segment elevation myocardial infarction using a uniform diagnostic threshold for males and females, whereas the CoDE-ACS models were trained for a diagnosis of type 1, 4b and 4c myocardial infarction in a population where sex-specific thresholds were used to guide care. The reference standard in this study was based on sex-specific upper reference limits and comprised of type 1, 4b and 4c myocardial infarction, thereby creating a potential disadvantage for the ESC 0/1h and ESC 0/2h pathways. Despite these differences, CoDE-ACS and the clinical pathways performed consistently in men and women and for a diagnosis of all myocardial infarction. Furthermore, this potential source of bias is balanced by performing our comparison in the same dataset that was used to define the thresholds for the ESC 0/1h and ESC 0/2h pathways. Third, although using a rigorous method to adjudicate the final diagnosis, a small number of patients may have been misclassified. Fourth, we were not able to determine the performance of CoDE-ACS and guideline recommended pathways stratified by race and ethnicity, as patients in the APACE trial were enrolled across Europe where the majority of patients are white Caucasian and this information was not collected. Finally, the performance of CoDE-ACS and the clinical

diagnostic pathways was assessed in a cohort that had completed enrolment and care was not guided by CoDE-ACS. Prospective implementation studies are needed to evaluate the impact of providing diagnostic probabilities instead of triage decisions based on fixed cardiac troponin thresholds following implementation of CoDE-ACS into clinical practice.

In conclusion, CoDE-ACS performs consistently irrespective of the timing of serial cardiac troponin measurement identifying more patients as low-probability with comparable performance to guideline recommended pathways for myocardial infarction. CoDE-ACS could reduce unnecessary testing and hospital admission for observation, but prospective studies are needed to determine whether care guided by probabilities improves the diagnosis of myocardial infarction.

CoDE-ACS (Collaboration for the Diagnosis and Evaluation of Acute Coronary Syndrome) Investigators to be listed as contributors

A Mark Richards (Christchurch Heart Institute, Department of Medicine, University of Otago, Christchurch, New Zealand; Cardiovascular Research Institute, National University of Singapore); Chris Pemberton, Richard W Troughton (Christchurch Heart Institute, Department of Medicine, University of Otago Christchurch, New Zealand); Sally J Aldous (Cardiology, Christchurch Hospital, New Zealand); Anthony FT Brown, Emily Dalton, Chris Hammett, Tracey Hawkins, Shanen O'Kane, Kate Parke, Kimberley Ryan, Jessica Schluter, (Royal Brisbane and Women's Hospital, Brisbane, Australia; Stephanie Barker, Jennifer Blades, Andrew R Chapman, Takeshi Fujisawa, Dorien M Kimenai, Michael McDermott, David E Newby, Stacey D Schulberg, Anoop SV Shah, Andrew Sorbie, Grace Soutar, Fiona E Strachan, Caelan Taggart, Daniel Perez Vicencio, Yiqing Wang, Ryan Wereski, Kelly

Williams (BHF Centre for Cardiovascular Science, University of Edinurgh, Edinburgh, United Kingdom); Christopher J Weir (Usher Institute, University of Edinburgh, Edinburgh, United Kingdom); Colin Berry (Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom); Alan Reid (Department of Biochemistry, Queen Elizabeth University Hospital, Glasgow, United Kingdom); Donogh Maguire (Emergency Medicine Department, Glasgow Royal Infirmary, Glasgow, United Kingdom); Paul O Collinson (Departments of Clinical Blood Sciences and Cardiology, St. George's, University Hospitals National Health Service Trust and St. George's University of London, London, United Kingdom); Yader Sandoval (Minneapolis Heart Institute, Minneapolis Heart Institute Foundation, Minneapolis, USA); Stephen W Smith (Department of Emergency Medicine, Hennepin County Medical Center and University of Minnesota, Minneapolis).

APACE (Advantageous Predictors of Acute Coronary Syndromes Evaluation) Investigators to be listed as contributors

Desiree Wussler, Tamar Muench-Gerber, Jonas Glaeser, Carlos Spagnuolo, Gabrielle Huré, Juliane Gehrke, Christian Puelacher, Danielle M. Gualandro, Samyut Shrestha (Cardiovascular Research Institute Basel and Department of Cardiology, University Hospital Basel, University of Basel, Switzerland); Damian Kawecki, Beata Morawiec, Piotr Muzyk (2nd Department of Cardiology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Poland); Franz Buergler (Emergency Department, Kantonsspital Liestal, Switzerland); Andreas Buser (Department of Hematology and Regional Blood Transfusion Service, Swiss Red Cross, University Hospital Basel, Basel, Switzerland); Katharina Rentsch (Department of Laboratory Medicine, University Hospital Basel, University of Basel, Basel, Switzerland); Raphael Twerenbold (University Center of Cardiovascular Science & Department of Cardiology, University Heart and Vascular Center

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Author contributions

JB, DD, NLM and CM conceived the study and its design. APACE Investigators were responsible for the acquisition of data. JB and DD performed the analysis. JB, DD, PLA, KKL, NLM and CM interpreted the data. JB, DD, NLM and CM drafted the manuscript. JB, DD, PLA, KKL, LK, KW, TN, RB, OM, JMS, IS, MRG, DIK, MC, AB, CL, AVF, CT, AA, AG, NLM and CM revised the manuscript critically for important intellectual content. All authors provided their final approval of the version to be published. All authors are accountable for the work.

Conflicts of interest

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Figure Legends

Figure 1. Diagnostic performance of the CoDE-ACS score using presentation, 1h and 2h cardiac troponin measurements.

A) Receiver-operating-characteristic (ROC) curve illustrating discrimination of CoDE-ACS for type 1 myocardial infarction.

B) Calibration plot of the CoDE-ACS score with the observed proportion of patients with myocardial infarction. The dashed line represents perfect calibration. Each point represents 100 patients.

Figure 2. Cumulative incidence of cardiac death as stratified by the CoDE-ACS incorporating 1h measurements and 2h measurements.

Tables

Table 1. Baseline characteristics.

	All patients	No type 1 myocardial infarction	Type 1 myocardial infarction
Number of patients	4,105	3,530	575
Age, years	61 (50, 74)	60 (48, 73)	69 (59, 79)
Sex			
Female	1,321 (32%)	1,165 (33%)	156 (27%)
Male	2,784 (68%)	2,365 (67%)	419 (73%)
Early presenter (≤3 hours from symptom onset)	2,077 (51%)	1,812 (52%)	265 (46%)
Previous medical conditions			
Myocardial infarction	970 (24%)	786 (22%)	184 (32%)
Ischemic heart disease	1,375 (33%)	1,132 (32%)	242 (42%)
Cerebrovascular disease	224 (5%)	179 (5%)	45 (8%)
Diabetes mellitus	746 (18%)	581 (16%)	165 (29%)
Previous revascularisation			
PCI	1,037 (25%)	858 (24%)	179 (31%)
CABG	333 (8%)	253 (7%)	80 (14%)
Medications at presentation			
Aspirin	1,526 (37%)	1,236 (35%)	290 (50%)
Dual anti-platelet therapy†	1,628 (40%)	1,322 (37%)	306 (53%)
ACE or ARB	1,681 (41%)	1,374 (39%)	307 (53%)
Beta-blocker	1,429 (35%)	1,179 (33%)	250 (43%)
Electrocardiogram result§			
Abnormal	1,644 (40%)	1,276 (36%)	368 (64%)
Myocardial ischaemia	739 (18%)	503 (14%)	236 (42%)
ST segment elevation	70 (2%)	67 (2%)	3 (1%)
Physiological parameters			
Heart rate, beats per minute	76 (66, 88)	76 (66, 89)	76 (67, 87)
Systolic blood pressure, mmHg	140 (126, 156)	140 (125, 155)	144 (130, 160)
Haematology and clinical chemistry measurements			

Haemoglobin, g/L	143 (132, 153)	143 (133, 153)	143 (131, 154)
eGFR, ml/min	88 (70, 101)	89 (72, 102)	80 (62, 93)
Presentation high-sensitivity cardiac troponin I, ng/l	4 (2, 14)	3 (2, 8)	123 (34, 621)
Second high-sensitivity cardiac troponin I, ng/L	4 (2, 16)	4 (2, 8)	197 (55, 858)
Third high-sensitivity cardiac troponin I, ng/L	5 (2, 18)	4 (2, 9)	265 (78, 1,249)
Peak high-sensitivity cardiac troponin I, ng/L	5 (3, 21)	4 (2, 9)	310 (94, 1,390)

Values are median [interquartile range]; n (%). †Two medications from aspirin, clopidogrel, prasugrel, or ticagrelor. ‡Includes warfarin or novel oral anticoagulants. Abbreviations: PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; ACE=angiotensin converting enzyme; ARB=angiotensin receptor blockers; eGFR=estimated glomerular filtration rate.

Table 2. Diagnostic performance for type 1 myocardial infarction.

A. Rule out

	True negative	False negative	True positive	False positive	NPV (95% CI)	Sensitivity (95% CI)	Proportion ruled out
Using presentation troponin							
CoDE-ACS algorithm	2274	6	569	1256	99.7 (99.5-99.9)	99.0 (98.6-99.2)	56%
ESC 0h-algorithm	1039	0	575	2491	100 (99.9-100)	100 (99.9-100)	25%
High-STEACS pathway	1419	0	575	2111	100 (99.9-100)	100 (99.9-100)	35%
Using serial troponin at 1 h							
CoDE-ACS algorithm	2663	8	567	867	99.7 (99.5-99.8)	98.6 (98.2-98.9)	65%
ESC 0/1h-algorithm	2014	0	575	1516	100 (99.9-100)	100 (99.9-100)	49%
Using serial troponin at 2 h							
CoDE-ACS algorithm	2778	7	568	752	99.7 (99.5-99.9)	98.8 (98.4-99.1)	68%
ESC 0/2h-algorithm	2156	0	575	1374	100 (99.9-100)	100 (99.9-100)	53%
High-STEACS pathway	2915	8	567	607	99.7 (99.5-99.8)	98.6 (98.2-98.9)	71%

B. Rule in

	True negative	False negative	True positive	False positive	PPV (95% CI)	Specificity (95% CI)	Proportion ruled in
Using presentation troponin							
CoDE-ACS algorithm	3390	199	376	140	72.9 (71.5-74.2)	96.0 (95.4-96.6)	13%
ESC 0h-algorithm	3361	220	355	169	67.7 (66.3-69.2)	95.2 (94.5-95.8)	13%
High-STEACS pathway	3236	123	452	294	60.6 (59.1-62.1)	91.7 (90.8-92.5)	18%
Using serial troponin at 1 h							
CoDE-ACS algorithm	3260	75	500	270	64.9 (63.5-66.4)	92.4 (91.5-93.1)	19%
ESC 0/1h-algorithm	3211	65	510	319	61.5 (60.0-63.0)	91.0 (90.0-91.8)	20%
Using serial troponin at 2 h							
CoDE-ACS algorithm	3300	69	506	230	68.8 (67.3-70.1)	93.5 (92.7-94.2)	18%
ESC 0/2h-algorithm	3267	70	505	263	65.8 (64.3-67.2)	95.2 (91.7-93.3)	19%
High-STEACS pathway	2915	8	567	607	48.3 (46.8-49.8)	82.8 (81.6-83.9)	29%

Table 3. Diagnostic performance of different CoDE-ACS scores at presentation.

	Threshold	True negative	False negative	True positive	False positive	NPV (95% CI)	Sensitivity (95% CI)	Proportion ruled out
Low probability CoDE-ACS scores								
More conservative	1	809	0	575	2721	100 (99.9-100.0)	100 (99.9-100)	20%
More conservative	2	1805	1	574	1725	99.9 (99.8-100)	99.8 (99.6-99.9)	44%
Selected	**3**	**2274**	**6**	**569**	**1256**	**99.7 (99.5-99.9)**	**99.0 (98.6-99.2)**	**56%**
Less conservative	4	2457	10	565	1073	99.6 (99.3-99.7)	98.3 (97.8-98.6)	60%
Less conservative	5	2585	13	562	945	99.5 (99.2-99.7)	97.7 (97.2-98.2)	63%

	Threshold	True negative	False negative	True positive	False positive	PPV (95% CI)	Specificity (95% CI)	Proportion ruled in
High probability CoDE-ACS scores								
Less conservative	50	3338	164	411	192	68.2 (66.7-69.6)	94.6 (93.8-95.2)	15%
Less conservative	55	3360	179	396	170	70.0 (68.5-71.3)	95.2 (94.5-95.8)	14%
Selected	**61**	**3390**	**199**	**376**	**140**	**72.9 (71.5-74.2)**	**96.0 (95.4-96.6)**	**13%**
More conservative	65	3402	220	355	128	73.5 (72.1-74.8)	96.4 (95.8-96.9)	12%
More conservative	70	3427	249	326	103	76.0 (74.7-77.3)	97.1 (96.5-97.6)	10%