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Machine learning for myocardial infarction compared to guideline recommended diagnostic pathways

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50 **Abstract**

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

56

57 **Methods:** Patients with possible MI without ST-segment elevation were enrolled at 12 sites
58 in five countries and underwent serial high-sensitivity cardiac troponin I concentration
59 measurement at 0, 1 and 2 hours. Diagnostic performance of the CoDE-ACS model at each
60 timepoint was determined for index type 1 MI and the effectiveness of previously validated
61 low- and high-probability scores compared with guideline recommended ESC 0/1h, ESC
62 0/2h and High-STEACS pathways.

63

64 **Results:** In total 4,105 patients (age 61 [50-74] years, 32% women) were included where 575
65 (14%) had type 1 MI. At presentation, CoDE-ACS identified 56% of patients as low-
66 probability, with a negative predictive value and sensitivity of 99.7% (95% confidence
67 interval [CI] 99.5-99.9%) and 99.0% (98.6-99.2%), ruling out more patients than the ESC 0h
68 and High-STEACS (25% and 35%) pathways. CoDE-ACS incorporating a second cTn
69 measurement identified 65% or 68% of patients as low probability at 1 or 2 hours, for an
70 identical negative predictive value of 99.7% (99.5-99.9%), 19% or 18% as high-probability
71 with a positive predictive value of 64.9% (63.5-66.4%) and 68.8% (67.3-70.1%), and 16% or
72 14% as intermediate probability. In comparison, the ESC 0/1h, ESC 0/2h and High-STEACS
73 pathways after serial measurements identified 49%, 53% and 71% of patients as low-risk
74 with a negative predictive value of 100% (99.9-100%), 100% (99.9-100%) and 99.7% (99.5-

75 99.8%), and 20%, 19% or 29% as high-risk with a positive predictive value of 61.5% (60.0-
76 63.0%), 65.8% (64.3-67.2%), and 48.3% (46.8-49.8%) resulting in 31%, 28% or 0% who
77 require further observation in the Emergency Department, respectively.

78

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

83

84 **Clinical Trial Registration:** <https://clinicaltrials.gov/ct2/show/NCT00470587>

85

86 **Clinical Perspective**

87 **What is new?**

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

98

99 **What are the clinical implications?**

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

107 **Introduction**

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

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

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

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

136

137 **Methods**

138 **Study design and population**

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

155 STROBE guidelines²⁴ (**Supplemental Table 1**), vouched for the data and analysis, wrote the
156 paper, and decided to submit it for publication.

157

158 **The CoDE-ACS score and pathway**

159 The methodology for the derivation and validation of the CoDE-ACS score was described in
160 detail previously.¹⁵ In brief, given the features that inform the diagnosis differ for ruling in
161 and ruling out myocardial infarction, separate XGBoost models to estimate the probability of
162 myocardial infarction were trained in consecutive patients with and without myocardial
163 injury at presentation, defined as a high-sensitivity cardiac troponin I concentration above or
164 below the sex-specific 99th percentile upper reference limit on the first measurement.

165 XGBoost models using a second serial measurement at a flexible timepoint were then trained,
166 resulting in four separate models. Each model combines cardiac troponin as a continuous
167 measure with age, sex, time from symptom onset, the presence of chest pain, known ischemic
168 heart disease, hyperlipidemia, heart rate, systolic blood pressure, Killip class, myocardial
169 ischemia on the electrocardiogram, renal function and hemoglobin. These models were
170 combined within a single clinical decision support system called CoDE-ACS, which
171 computes a score (0–100) corresponding to an individual patient’s probability of myocardial
172 infarction (<https://decision-support.shinyapps.io/code-acs>). We previously derived and
173 validated CoDE-ACS scores of less than 3 and more than 60 to classify the greatest
174 proportion of patients as low or high probability that achieved prespecified performance
175 criteria.^{23,25,26} Whilst CoDE-ACS is designed to be used flexibly by clinicians and healthcare
176 providers with decisions guided by individual probabilities, we applied these scores in a
177 pathway that recommended serial measurement in those with scores of 3 to 60 indicating
178 intermediate probability to facilitate comparison with current guideline recommended
179 accelerated diagnostic pathways.

180 **Guideline recommended accelerated diagnostic pathways**

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

186

187 **Adjudication of the diagnosis of myocardial infarction**

188 Two independent cardiologists performed adjudication of the final diagnosis according to the
189 Fourth Universal Definition of Myocardial Infarction³ using two sets of data. First, all
190 available medical records were reviewed including the history, physical examination,
191 laboratory testing, serial cardiac troponin concentrations from the local assay, radiological
192 testing, electrocardiography, echocardiography, exercise testing, and coronary angiography
193 from the time of presentation to 90-days; and second, study-specific assessments were
194 reviewed including chest pain characteristics, serial high-sensitivity cardiac troponin I
195 concentrations (Abbott Laboratories, Abbott Park, IL) using study samples, and follow-up by
196 telephone or mail. Where there was disagreement over the diagnosis, cases were reviewed
197 and adjudicated in conjunction with a third cardiologist. Myocardial infarction was diagnosed
198 when there was myocardial injury identified using sex-specific 99th percentile upper
199 reference limits (>16 ng/L in women and >34 ng/L in men) in a clinical setting consistent
200 with myocardial ischemia with a significant rise and/or fall on serial testing. Patients with
201 myocardial infarction were further classified into type 1 and type 2 myocardial infarction.^{2,3}
202 Further details are provided in the **Online Supplement**.

203

204 **Study endpoints and follow up**

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

212

213 **Statistical analysis**

214 Baseline characteristics are summarized in those with and without myocardial infarction as
215 percentages for categorical variables, and mean (standard deviation [SD]) or median
216 (interquartile range [IQR]) for continuous variables, as appropriate. The proportion of
217 patients classified as low-, intermediate and high-probability or stratified to rule out, observe
218 and rule in groups was calculated at presentation and following serial troponin measurements
219 for the CoDE-ACS and guideline recommended diagnostic pathways. Sensitivity, specificity,
220 negative predictive value, positive predictive value and effectiveness were determined using
221 2×2 tables to calculate the true and false negative rates for the primary and secondary
222 diagnostic outcome for each pathway. The Wilson score method without continuity
223 correction was used to calculate 95% confidence intervals (CI). Model discrimination and
224 calibration were assessed by calculating the area under the receiver-operating-characteristic
225 curve (AUROC), by visual inspection of the calibration and calculation of the Brier score.
226 The Brier score is a measure of both discrimination and calibration and is calculated by
227 taking the mean squared difference between predicted probabilities and the observed
228 outcome.²⁹ Cumulative incidence curves were plotted to illustrate cardiac and all-cause death
229 in patients stratified by the CoDE-ACS score and guideline recommended diagnostic

230 pathways with differences assessed using the Gray's test.³⁰ All hypothesis testing was two-

231 tailed, and P values of less than 0.05 were considered to indicate statistical significance.

232 Statistical analyses were performed using R version 4.2.0 (Vienna, Austria).

233

234 **Results**

235 **Study cohort and index diagnosis**

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

245

246 **Performance of CoDE-ACS and diagnostic pathways at presentation**

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

257

258 At presentation the ESC 0/1h- and ESC 0/2h-algorithms ruled out myocardial infarction in
259 25% (1,039/4,105) of patients with a negative predictive value and sensitivity of 100% (99.9-
260 100%) and 100% (99.9-100%), respectively, and ruled in myocardial infarction in 13%
261 (524/4,105) of patients with a positive predictive value and specificity of 67.7% (66.3-69.2%)
262 and 95.2% (94.5-95.8%), respectively. The remaining 2,542 (62%) patients were neither
263 ruled out or ruled in at presentation and serial cardiac troponin testing is recommended.

264

265 At presentation the High-STEACS pathway identified 35% (1,419/4,105) patients as low risk
266 of myocardial infarction with a negative predictive value and sensitivity of 100% (95%CI,
267 99.9-100%) and 100% (95%CI, 99.9-100%), respectively, and 18% (746/4,105) of patients as
268 high risk with a positive predictive value and specificity of 60.6% (59.1-62.1%) and 91.7%
269 (90.8-92.5%), respectively. The remaining 1,940 (47%) had intermediate cardiac troponin
270 concentrations at presentation or presented within 3 hours of symptom onset and serial testing
271 is recommended (**Table 2**).

272

273 **Performance of CoDE-ACS and diagnostic pathways at 1 hour**

274 At one hour, the CoDE-ACS score had good discrimination and calibration for the index
275 diagnosis of type 1 myocardial infarction using serial cardiac troponin measurements (area
276 under the receiver operating curve = 0.959, 95% CI 0.953-0.966, Brier score = 0.065; **Figure**
277 **1**). A score of less than 3 at one hour identified 65% (2,671/4,105) of patients as low
278 probability of myocardial infarction with a negative predictive value and sensitivity of 99.7%
279 (99.5-99.8%) and 98.6% (98.2-98.9%), respectively. A score of greater than 60 at one hour
280 identified 19% (770/4,105) of patients as high probability with a positive predictive value and
281 specificity of 64.9% (63.5-66.4%) and 92.4% (91.5-93.1%), respectively. The remaining 664
282 (16%) were of intermediate probability (**Supplemental Figure 2A**).

283 At one hour, the ESC 0/1h-algorithm ruled out myocardial infarction in 49% (2,014/4,105) of
284 patients with a negative predictive value and sensitivity of 100% (95%CI, 99.9-100%) and
285 100% (95%CI, 99.9-100%), respectively, and ruled in myocardial infarction in 20%
286 (829/4,105) with a positive predictive value and specificity of 61.5% (60.0-63.0%) and
287 91.0% (90.0-91.8%), respectively. The remaining 1,262 (31%) were neither ruled out or ruled
288 in at one hour and further observation is recommended (**Table 2**).

289

290 **Performance of CoDE-ACS and diagnostic pathways at 2 hours**

291 At two hours, the CoDE-ACS score had good discrimination and calibration for the index
292 diagnosis of type 1 myocardial infarction using serial cardiac troponin measurements (area
293 under the receiver operating curve = 0.967, 95% CI 0.961-0.973, Brier score = 0.057; **Figure**
294 **1**). A score of less than 3 identified 68% (2,785/4,105) of patients as low probability of
295 myocardial infarction with a negative predictive value and sensitivity of 99.7% (99.5-99.9%)
296 and 98.8% (98.4-99.1%), respectively. A score of greater than 60 identified 18% (736/4,105)
297 of patients as high probability with a positive predictive value and specificity of 68.8% (67.3-
298 70.1%) and 93.5% (92.7-94.2%), respectively. The remaining 584 (14%) patients were of
299 intermediate probability (**Supplemental Figure 2B**).

300

301 At two hours, the ESC 0/2h-algorithm ruled out myocardial infarction in 53% (2,156/4,105)
302 of patients with a negative predictive value and sensitivity of 100% (99.9-100%) and 100%
303 (99.9-100%), respectively, and ruled in myocardial infarction in 19% (768/4,105) of patients
304 with a positive predictive value and specificity of 65.8% (64.3-67.2%) and 95.2% (91.7-
305 93.3%), respectively. The remaining 1,181 (28%) were neither ruled out or ruled in at two
306 hours and further observation is recommended.

307

308 At two hours, the High-STEACS pathway identified 71% (2,923/4,105) patients as low risk
309 of myocardial infarction with a negative predictive value and sensitivity of 99.7% (99.5-
310 99.8%) and 98.6% (98.2-98.9%), respectively, and 29% (1,182/4,105) of patients as high risk
311 of myocardial infarction with a positive predictive value and specificity of 48.3% (46.8-
312 49.8%) and 82.8% (81.6-83.9%), respectively (**Table 2**).

313

314 **Performance of CoDE-ACS and diagnostic pathways for any myocardial infarction and** 315 **by sex**

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

320

321 **Using individual probabilities with CoDE-ACS to guide patient care**

322 As CoDE-ACS can be applied flexibly according to local preferences and individual
323 probabilities can be used to guide care, we validated performance of the models across a
324 range of probabilities (**Table 3**). For example, a more conservative institution may use a
325 score of less than 2, which would identify 44% (1806/4,105) of patients as low probability at
326 presentation with a higher negative predictive value and sensitivity of 99.9% (95%CI, 99.8-
327 100%) and 99.8% (95%CI, 99.6-99.9%), respectively. Similarly a less conservative
328 institution may use a lower score of more than 50 to identify 15% (603/4,105) of patients as
329 high probability at presentation with a lower positive predictive value and specificity of
330 68.2% (95%CI, 66.7-69.6%) and 94.6% (95%CI, 93.8-95.2%), respectively.

331

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

333 At 30-days and one year, there were 20 (0.5%) and 68 (1.7%) deaths from a cardiac cause
334 and 30 (0.7%) and 146 (3.6%) deaths from any cause, respectively. Overall, patients
335 identified by CoDE-ACS as low risk had a lower rate of cardiac death and all-cause mortality
336 at 30-days and one year when compared to patients identified as intermediate or high risk
337 (e.g., at one year, cardiac death 0.6% *versus* 4.1% and 3.2%; all-cause death 1.6% *versus*
338 9.2% and 5.6%, Gray's test $P < 0.001$; **Figure 2**). Patients identified as intermediate-
339 probability were older, presented earlier to hospital, more often had known coronary artery
340 disease and previous myocardial infarction with revascularization, and more frequently had
341 impaired kidney function. (**Supplemental Table 5**). Outcomes across a range of CoDE-ACS
342 probabilities are reported in **Supplemental Table 6**. Similarly cardiac death and all-cause
343 death at 30-days and one year were lower in those ruled out, compared to those triaged for
344 further observation or ruled in by the guideline recommended diagnostic pathways (Gray's
345 test $P < 0.001$ for all pathways; **Supplement Figures 3-5**).

346

347 **Discussion**

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

353

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

368

369 Whilst CoDE-ACS offers increased flexibility and a more personalised approach to the
370 assessment of patients with possible myocardial infarction, it is important to acknowledge
371 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.

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

408

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

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

427

428 Some limitations merit consideration when interpreting our findings. First, CoDE-ACS was
429 derived and validated using one specific high-sensitivity cardiac troponin I assay and it needs
430 to be trained and validated for other high-sensitivity cardiac troponin assays. Second, the ESC
431 0/1h and ESC 0/2h pathways were trained for an endpoint of all non-ST segment elevation
432 myocardial infarction using a uniform diagnostic threshold for males and females, whereas the
433 CoDE-ACS models were trained for a diagnosis of type 1, 4b and 4c myocardial infarction in
434 a population where sex-specific thresholds were used to guide care. The reference standard in
435 this study was based on sex-specific upper reference limits and comprised of type 1, 4b and 4c
436 myocardial infarction, thereby creating a potential disadvantage for the ESC 0/1h and ESC
437 0/2h pathways. Despite these differences, CoDE-ACS and the clinical pathways performed
438 consistently in men and women and for a diagnosis of all myocardial infarction. Furthermore,
439 this potential source of bias is balanced by performing our comparison in the same dataset that
440 was used to define the thresholds for the ESC 0/1h and ESC 0/2h pathways. Third, although
441 using a rigorous method to adjudicate the final diagnosis, a small number of patients may have
442 been misclassified. Fourth, we were not able to determine the performance of CoDE-ACS and
443 guideline recommended pathways stratified by race and ethnicity, as patients in the APACE
444 trial were enrolled across Europe where the majority of patients are white Caucasian and this
445 information was not collected. Finally, the performance of CoDE-ACS and the clinical

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

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

456

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535 **Author contributions**

536 JB, DD, NLM and CM conceived the study and its design. APACE Investigators were
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538 KKL, NLM and CM interpreted the data. JB, DD, NLM and CM drafted the manuscript. JB,
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543

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820 **Figure Legends**

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

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

825 B) Calibration plot of the CoDE-ACS score with the observed proportion of patients with
826 myocardial infarction. The dashed line represents perfect calibration. Each point represents
827 100 patients.

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

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835 **Tables**836 **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)

837 Values are median [interquartile range]; n (%). †Two medications from aspirin, clopidogrel, prasugrel, or
838 ticagrelor. ‡Includes warfarin or novel oral anticoagulants. Abbreviations: PCI=percutaneous coronary
839 intervention; CABG=coronary artery bypass grafting; ACE=angiotensin converting enzyme; ARB=angiotensin
840 receptor blockers; eGFR=estimated glomerular filtration rate.
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843 **Table 2. Diagnostic performance for type 1 myocardial infarction.**

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845 **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%

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847 **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%

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

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	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%

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	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%

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