Influence of age on the diagnosis of myocardial infarction

ORIGINAL ARTICLE

Influence of age on the diagnosis of myocardial infarction

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Short Title: Age and cardiac troponin

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Abstract:	306
Text:	4,674
References:	41
Figure legends:	234

Abstract

Background: The 99th centile of cardiac troponin, derived from a healthy reference population, is recommended as the diagnostic threshold for myocardial infarction, but troponin concentrations are strongly influenced by age. Our aim was to assess the diagnostic performance of cardiac troponin in older patients presenting with suspected myocardial infarction.

Methods and results: In a secondary analysis of a multicentre trial of consecutive patients with suspected myocardial infarction, we assessed the diagnostic accuracy of high-sensitivity cardiac troponin I at presentation for the diagnosis of type 1, type 2 or type 4b myocardial infarction across three age groups (<50, 50-74 and ≥75 years) using guideline recommended sex-specific and age-adjusted 99th centile thresholds.

In 46,435 consecutive patients aged 18-108 years (mean 61±17 years), 5,216 (11%) had a diagnosis of myocardial infarction. In patients <50 (n=12,379), 50-74 (n=22,380) and ≥75 (n=11,676) years, the sensitivity of the guideline recommended threshold was similar at 79.2% (95% confidence interval [CI] 75.5-82.9), 80.6% (95% CI 79.2-82.1) and 81.6% (95% CI 79.8-83.2), respectively. The specificity decreased with advancing age from 98.3% (95% CI 98.1-98.5) to 95.5% (95% CI 95.2-95.8) and 82.6% (95% CI 81.9-83.4). The use of age-adjusted 99th centile thresholds improved the specificity (91.3% [90.8-91.9%] *versus* 82.6% [95% CI 81.9-83.4]) and positive predictive value (59.3% [57.0-61.5%] *versus* 51.5% [49.9-53.3%]) for myocardial infarction in patients ≥75 years but failed to prevent the decrease in either parameter with increasing age and resulted in a marked reduction in sensitivity compared to use of the guideline recommended threshold (55.9% [53.6-57.9%] *versus* 81.6% [79.8-83.3%].

Conclusion: Age alters the diagnostic performance of cardiac troponin, with reduced specificity and positive predictive value in older patients when applying the guideline

recommended or age-adjusted 99th centiles. Individualised diagnostic approaches rather than the adjustment of binary thresholds are needed in an aging population.

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Keywords: acute coronary syndrome, myocardial infarction, troponin, elderly, aging

Non-standard Abbreviations and Acronyms

APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation

BACC = Biomarkers in Acute Cardiac Care

ECG = Electrocardiogram

High-STEACS = High-Sensitivity Troponin in the Evaluation of Patients with Suspected Acute Coronary Syndrome

hs-cTnI = High-sensitivity cardiac troponin I

IL = Illinois state

NPV = Negative predictive value

PPV = Positive predictive value

TRAPID-MI = High Sensitivity Cardiac Troponin T assay for rapid Rule-out of Acute Myocardial Infarction

UDMI = Universal definition of myocardial infarction

URL = Upper reference limit

Clinical Perspective:

What is new?

- In older patients presenting with suspected myocardial infarction, the majority of cardiac troponin elevations are explained by acute or chronic myocardial injury or type 2 myocardial infarction.
- The specificity and positive predictive value of high-sensitivity cardiac troponin to identify myocardial infarction decreases with age and is observed whether applying sex-specific or age-adjusted 99th centile diagnostic thresholds or a "rule-in" threshold for the triage of patients at high probability of myocardial infarction.
- Serial troponin testing incorporating an absolute change in troponin concentration increased discrimination for myocardial infarction in older patients.

What are the clinical implications?

- In older patients presenting with suspected myocardial infarction, clinicians should be cautious when interpreting a single troponin measurement.
- Clinicians should routinely perform serial cardiac troponin measurements and consider absolute changes in concentration to identify those older patients with elevated troponin concentrations more likely to have myocardial infarction.

Introduction

The 99th centile upper reference limit (URL) of cardiac troponin, derived from a cohort of healthy individuals, is used as the threshold to indicate myocardial injury and potential infarction.[1] This value is influenced by the characteristics of the reference population used for derivation.[2-5] Elevated concentrations of cardiac troponin above the 99th centile are frequently observed in older adults[3, 4, 6-8], including amongst those presenting to the Emergency Department without myocardial infarction[9-11] and in the general hospitalised older population.[12] The application of diagnostic thresholds derived from younger reference populations may incorrectly suggest myocardial infarction in older patients, resulting in inappropriate treatment and potential harm.

The relationship between age and cardiac troponin has been noted for both troponin I and T assays, with the observed 99th centile URL for older adults in the general population double the reference value for cardiac troponin I, and three-fold the value for troponin T.[3] Cardiovascular comorbidities including hypertension, diabetes mellitus, left ventricular dysfunction and existing ischemic heart disease are independently associated with chronic elevations in cardiac troponin.[3, 4, 6, 7, 9] The higher prevalence of these conditions amongst older patients further complicates the interpretation of cardiac troponin in an aging and increasingly multimorbid society.

Age-adjusted thresholds that use the observed 99th centile within different age groups to guide the diagnosis have been proposed as a means of increasing the specificity of cardiac troponin for myocardial infarction in older patients.[13-15] An alternative strategy to increase the specificity is the use of a threshold above the 99th centile. Introduced in recent practice guidelines, direct rule-in approaches using the presentation troponin concentration and a

threshold approximately 3-times the 99th centile value to identify patients at high probability of myocardial infarction are reported to have greater specificity and a positive predictive value (PPV) of up to 75%.[14]

Previous evaluations on the impact of age when applying either strategy have focused on the identification of any form of myocardial infarction.[8, 11, 16, 17] While both type 1 and type 2 myocardial infarction represent important clinical entities, they have divergent treatment strategies and an understanding of how age impacts diagnostic performance specifically for type 1 myocardial infarction would help guide treatment decisions in older patients.

In this pre-specified secondary analysis of a multicentre trial of consecutive patients with suspected acute coronary syndrome, we evaluate the impact of age and cardiovascular co-morbidities on the performance of high-sensitivity cardiac troponin I for the diagnosis of myocardial infarction using the guideline recommended sex-specific 99th centile, age-adjusted sex-specific 99th centiles derived in a general population and a universal "rule-in" threshold above the 99th centile. In addition, we assess the performance of each threshold in combination with absolute and relative change in troponin concentration for the diagnosis of myocardial infarction.

Methods

Study population

The High-Sensitivity Troponin in the Evaluation of Patients with Suspected Acute Coronary Syndrome (High-STEACS) a stepped-wedge cluster randomized controlled trial that evaluated the implementation of a high-sensitivity cardiac troponin I assay in consecutive patients presenting with suspected acute coronary syndrome across 10 secondary and tertiary hospitals in Scotland (https://www.clinicaltrials.gov. Unique identifier: NCT01852123). A detailed description of this trial has been reported previously.[18] In summary, all patients attending the Emergency Department between June 2013 and March 2016 in whom the attending clinician suspected acute coronary syndrome and underwent cardiac troponin sampling were considered eligible for inclusion. Patients were excluded if they had been admitted previously during the trial period or were not resident in Scotland. Patients were enrolled using an electronic form integrated into the clinical care pathway completed at the time of cardiac troponin sampling.

For this secondary analysis, patients with ST-segment elevation myocardial infarction, those in whom the presentation high-sensitivity cardiac troponin sample was unavailable, those with an adjudicated diagnosis of type 4a myocardial infarction, or where a final diagnosis could not be adjudicated, were excluded.

Cardiac troponin testing

Cardiac troponin testing was performed at presentation and repeated 6 or 12 hours after the onset of symptoms at the discretion of the attending clinician in accordance with international guidelines in use during enrolment.[19] Cardiac troponin was measured using the ARCHITECT$_{STAT}$ high-sensitive troponin I assay (Abbott Laboratories, Abbott Park, IL).

This assay has a limit of detection of between 1.2 ng/L and 1.9 ng/L, an inter-assay coefficient of variation of less than 10% at 4.7 ng/L, and a 99th centile URL of 34 ng/L in men and 16 ng/L in women. Sex-specific URL was determined by the manufacturer based on 4590 samples from healthy men and women aged 21 to 75 years.[20]

Diagnostic adjudication

All patients with a high-sensitivity cardiac troponin I concentration above the 99th centile were adjudicated and classified according to the Fourth Universal Definition of Myocardial Infarction.[1, 18, 21] Two physicians independently reviewed all clinical information, with discordant diagnoses resolved by an independent third physician. Type 1 myocardial infarction was defined as myocardial necrosis (any high-sensitivity cardiac troponin I concentration above the sex-specific 99th percentile with a rise or fall in troponin where serial testing was performed) in the context of a presentation with suspected acute coronary syndrome and symptoms or signs of myocardial ischemia. Patients with myocardial necrosis, symptoms or signs of myocardial ischaemia, and evidence of increased myocardial oxygen demand or decreased supply secondary to an alternative condition without evidence of acute atherothrombosis were defined as type 2 myocardial infarction. Type 4a myocardial infarction was defined in patients with symptoms or signs of myocardial ischemia following percutaneous coronary intervention where hs-cTnI concentrations were 5-fold greater than the 99th centile, or increased further if elevated prior to the procedure. Type 4b myocardial infarction was defined where myocardial ischemia and myocardial necrosis were associated with stent thrombosis documented at angiography. Patients with high sensitivity cardiac troponin I concentrations above the 99th centile without symptoms or signs of myocardial ischaemia were classified as having myocardial injury. All non-ischaemic myocardial injury was classified as acute, unless a change of ≤20% was observed on serial testing,[1] or the final

adjudicated diagnosis was chronic heart failure or chronic renal failure, where the classification was chronic myocardial injury. The term myocardial infarction is used to denote patients with an adjudicated diagnosis of type 1, type 2 or type 4b myocardial infarction. A detailed summary of the adjudication process is provided in the **Supplementary online material**.

Statistical analysis

Baseline characteristics are summarised as number (%) for categorical variables, and continuous variables are summarised as mean (standard deviation) or median (25^{th} to 75^{th} percentile) when not normally distributed. The study population was divided into three clinically relevant age groups: young (<50 years), middle-aged (50-74 years) and older adults (≥75 years). For additional analyses, the population was divided by 5-year intervals between the ages of 40 and 90 years to create 12 groups. Patients aged below 40 and greater than or equal to 90 years were pooled into groups of <40 and ≥90 years respectively. Group wise comparisons were performed using χ^2, Kruskal–Wallis or one-way analysis of variance (ANOVA) tests as appropriate.

We evaluated the proportion of patients with at least one troponin concentration above the sex-specific 99^{th} centile URL for each age category. Diagnostic performance was assessed using sensitivity, specificity, negative predictive value (NPV) and PPV and calculated using a 2x2 confusion matrix. Corresponding 95% confidence intervals (CI) were calculated using bootstrapping with replacement and a sample of 1,000. We calculated diagnostic performance for a high-sensitivity cardiac troponin I concentration at presentation above the guideline recommended sex-specific 99^{th} centile (16 ng/L women, 34 ng/L men)[1], age-adjusted 99^{th} centile thresholds in patients >60 years (age <60 years = 34 ng/L men, 16 ng/L women; age

60-69 years = 42 ng/L men, 17 ng/L women; age ≥70 years = 86 ng/L men, 39 ng/L women) and a universal rule-in threshold (64 ng/L) recommended by the European Society of Cardiology.[14] Age-adjusted thresholds were previously derived in 19,501 individuals in the Generation Scotland Scottish Family Health Study.[3] Overall performance was assessed using area under the curve (AUC) and compared between thresholds and age groups using a DeLong's test.

A sensitivity analysis was undertaken using the 99th centile as the diagnostic threshold restricted to patients presenting with chest pain. Additional analysis restricted to patients with serial samples taken within 24 hrs of admission was performed to assess the impact of the change in cardiac troponin concentration from serial samples on diagnostic performance. We evaluated models that incorporated absolute or relative change in troponin concentration of 15 ng/L or 20% as recommended in international guidelines in combination with the presentation troponin concentration stratified by age group and threshold. [14, 15, 22] The impact of change in cardiac troponin concentration on discrimination was assessed using using the AUC and compared between thresholds and age groups using a DeLong's test.[1]

Logistic regression was used to explore the influence of cardiovascular comorbidities on the probability of myocardial infarction given a cardiac troponin value greater than the sex-specific 99th centile. A history of ischemic heart disease, myocardial infarction, heart failure, cerebrovascular disease (defined as previous ischemic or haemorrhagic stroke), chronic renal impairment (defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 determined by Modified Diet in Renal Disease equation) and diabetes mellitus were added individually (Model 1) and collectively (Model 2) to a baseline model including a binary explanatory variable of presentation troponin above the sex-specific 99th centile. Collinearity

was assessed visually and by calculation of the generalised variance inflation factor. All analyses were performed in R Version 3.5.1.

Ethical approval

The study was approved by the Scotland Research Ethics Committee, the Public Benefit and Privacy Panel for Health and Social Care, and by each National Health Service Health Board. Individual patient consent was not required and data from consecutive patients was collected prospectively from the electronic record, deidentified and linked within secure National Health Service Safe Havens.

Patient and public involvement

Patients and lay representatives were members of the steering committee for the trial and all related studies and were involved in the design, conduct and approval of this study.

Results

A total of 46,435 of the 48,282 patients enrolled in the trial were included in the analysis population. Patients with ST-elevation myocardial infarction (n=925), those in whom the final diagnosis could not be adjudicated according to the Fourth Universal Definition of Myocardial Infarction (n=890), those with an adjudicated diagnosis of type 4a myocardial infarction (n=9), and those without a presentation high-sensitivity cardiac troponin result (n=23) were excluded.

Baseline characteristics

Participants were aged between 18-108 years (mean 61±17 years). Baseline characteristics for the population are shown in **Table 1** (***Table S1***). Compared to younger patients, those ≥75 years were more often female and less likely to present with chest pain or ischemia on 12-lead electrocardiogram ($p<0.001$ for all). There was a higher prevalence of cardiovascular co-morbidity in patients ≥75 years including ischemic heart disease, heart failure, diabetes mellitus and chronic kidney disease ($p<0.001$ for all). Over half of patients ≥75 years had two or more chronic cardiovascular health conditions compared to a third between 50-74 years old (56% *versus* 32% respectively, $p<0.001$).

A total of 8,179 (18%) patients had at least one cardiac troponin measurement above the sex-specific 99th centile. For those aged <50, 50-74 and ≥75 years, the proportion of patients with at least one measure above the sex-specific 99th centile was 5%, 16% and 34% respectively ($p<0.001$ for difference between groups). In patients aged ≥90 years, 49% had one cardiac troponin above the sex-specific 99th centile (***Figure S1***). Myocardial infarction was the final adjudicated diagnosis in 5,216 (11%) of patients with the prevalence highest in those aged ≥75 years (18%). In patients with at least one troponin measurement greater than the sex-

specific 99th centile, the proportion of those with type 1 myocardial infarction decreased with advancing age as type 2 myocardial infarction, acute myocardial injury and chronic myocardial injury increased (**Figure 1**).

Diagnostic performance of the 99th centile at presentation

In patients aged <50, 50-74 and ≥75 years, the sensitivity of the guideline recommended sex-specific 99th centile at presentation for a diagnosis of myocardial infarction was similar at 79.2% (95% confidence interval [CI] 75.5-82.9), 80.6% (95% CI 79.2-82.1) and 81.6% (95% CI 79.8-83.2), respectively. The specificity fell with advancing age from 98.3% (95% CI 98.1-98.5) to 95.5% (95% CI 95.2-95.8) and 82.6% (95% CI 81.9-83.4) for those aged <50, 50-74 and ≥75 years respectively. The PPV for those aged <50, 50-74 and ≥75 years was 63.0% (95% CI 59.1-67.1), 70.1% (95% CI 68.5-71.8) and 51.6% (95% CI 49.8-53.2) respectively (**Table 2**, **Figure 2,** ***Table*** **S2**).

In a sensitivity analysis restricted to those with chest pain at presentation (n=33,446), the sensitivity for myocardial infarction was similar compared to patients presenting with any symptom, while specificity and PPV were markedly increased across all age groups. In patients ≥75 years, the specificity and PPV were 89.8% (95% CI 89.0-90.6) and 70.4% (95% CI 68.5-72.4), respectively (***Figure S2, Table S3***).

Diagnostic performance of age-adjusted 99th centile thresholds

Applying age-adjusted thresholds resulted in higher specificity and PPV for myocardial infarction in patients ≥75 years at the expense of a marked reduction in sensitivity (**Table 2, Figure 2,** ***Table S2***). In patients ≥75 years, sensitivity, specificity and PPV were 55.9% (95% CI 53.5-57.9), 91.3% (95 % CI 90.8-91.9) and 59.3% (95% CI 57.1-61.4), respectively.

Despite the use of age-adjusted thresholds the specificity and PPV remained lower in patients ≥75 years compared with patients <50 or 50-74 years old. Compared to the guideline recommended sex-specific 99th centile, discrimination was reduced (AUC 0.81 [95% CI 0.80-0.82] versus 0.87 [95% CI 0.87-0.88], p<0.001).

Diagnostic performance of a universal rule-in threshold above the 99th centile

Applying a universal rule-in threshold of 64 ng/L resulted in increased specificity and PPV for myocardial infarction, with reduced sensitivity across all age groups, compared with sex-specific or age-adjusted 99th centile thresholds (**Table 2, Figure 2,** ***Table S2***). In patients ≥75 years, sensitivity, specificity and PPV were 50.1% (95% CI 48.0-52.2), 92.7% (95 % CI 92.2-93.2) and 60.9% (95% CI 58.7-63.1), respectively. Specificity and PPV remained lower in patients ≥75 years compared with those <50 or 50-74 years. Compared to the guideline recommended sex-specific 99th centile, discrimination was reduced (AUC 0.75 [95% CI 0.75-0.76] *versus* 0.87 [95% CI 0.87-0.88], p<0.001).

Diagnostic performance of serial measurements

In a sensitivity analysis restricted to those with serial samples taken within 24 hrs of admission (n=20,881 [age <50 3,962 (19%); age 50-74 10,826 (52%); age ≥ 75 6,093 (29%)]) both a relative change of 20% and absolute change of 15 ng/L significantly improved discrimination across all groups compared to a presentation sample alone (p<0.001 for all) (**Table 3**). In patients aged ≥75 years, an age-adjusted threshold in combination with an absolute delta of 15 ng/L achieved the greatest discrimination (AUC 0.94 [95% CI 0.93-0.95) compared with the sex-specific 99th centile or universal rule-in threshold (0.88 [95% CI 0.87-0.89] and 0.82 [95% CI 0.81-0.83], respectively). Overall discrimination was greatest when applying the sex-specific 99th centile with an absolute change of 15 ng/L compared to the

application of this delta criterion in combination with either an age-adjusted or universal rule-in threshold ($p<0.001$ for both).

Impact of cardiovascular comorbidity on diagnostic performance

An elevated troponin above the 99th centile was associated with myocardial infarction across all age groups, but this relationship was weakest in patients ≥75 years old (**Table 4**). Several cardiovascular comorbidities were strongly associated with myocardial infarction and altered the PPV of a presentation troponin above the sex-specific 99th centile for myocardial infarction **(*Figure S4*)**. Adjusting for cardiovascular comorbidities did not alter the association between a high-sensitivity cardiac troponin above the 99th centile and a diagnosis of myocardial infarction, but did improve overall discrimination across all age groups (age <50 years [$p=0.003$]; age 50-74 years [$p<0.001$]; age ≥75 years [$p<0.001$]).

Sensitivity analysis of diagnostic performance for type 1 myocardial infarction

Compared with a diagnosis of any type of myocardial infarction, assessing the diagnostic performance of each threshold specifically for type 1 myocardial infarction resulted in similar sensitivity across all age groups with reduced specificity and PPV, particularly in older patients. Using the guideline recommended sex-specific 99th centile, specificity and PPV in patients ≥75 years was 78.8% [95% CI 78.0-79.6] and 36.8% [95% CI 35.0-38.3], respectively **(Figure 3, *Table S4*).**

Discussion

We report the effect of our aging population on the diagnostic challenge facing clinicians evaluating patients with suspected acute coronary syndrome. Our analysis is informed by 46,435 consecutive patients, aged 18-108, and we report several important findings. First, cardiac troponin concentrations above the recommended sex-specific 99th centile are common in older patients, affecting almost half of those over 90 years old. In older age groups, the majority of cardiac troponin elevations are explained by acute or chronic myocardial injury or type 2 myocardial infarction. Second, the specificity and PPV of the guideline recommended 99th centile for diagnosing myocardial infarction decreases with advancing age. The decrease in these parameters is more pronounced when restricting the diagnosis to type 1 myocardial infarction. Third, the use of an age-adjusted 99th centile or a universal rule-in threshold of 64 ng/L resulted in superior specificity and PPV for myocardial infarction compared to the sex-specific 99th centile, with a threshold of 64 ng/L achieving the greatest improvement in these parameters. However, no approach achieved parity in diagnosis between older and younger patients with specificity and PPV reducing with advancing age regardless of threshold adopted and alternatives to the guideline recommended approach resulted in a marked reduction in sensitivity in older persons. Fourth, while cardiovascular co-morbidities are common in older patients and related to a diagnosis of myocardial infarction, they did not alter the strength of association between an elevated cardiac troponin and the diagnosis. Fifth, serial troponin testing incorporating an absolute change in troponin concentration increased discrimination for myocardial infarction in older patients and was superior to any single test strategy. Our findings highlight the challenge of interpreting elevated cardiac troponin concentrations in older adults and the limitations of single test strategies to rule-in myocardial infarction in this population.

The majority of patients diagnosed with myocardial infarction are over 70 years of age.[23] With an aging population, these numbers will continue to rise. Our observation of complexity among older patients, notably the higher frequency of atypical symptoms and non-diagnostic electrocardiogram findings, may result in clinicians placing greater reliance on the potential objectivity of blood biomarkers of myocardial necrosis. We observed a decrease in chest pain as a presenting symptom in older patients and have previously reported that many older patients with myocardial infarction do not present with chest pain.[18] Importantly, we included all patients in whom a clinician suspected acute coronary syndrome, including 6,995 (17%) patients in whom the primary presenting symptom was not chest pain. For meaningful interpretation of the diagnostic performance of cardiac troponin, it is important that assessments are carried out in study populations representative of those seen in clinical practice. Selective inclusion criteria which result in the exclusion of older patients reduces generalisability and risks mirroring previous biases that resulted in the systematic under diagnosis of myocardial infarction in women.[20]

Our finding of reduced specificity of the sex-specific 99th centile in older patients is consistent with previous literature assessing both sensitive and high sensitivity assays for the diagnosis of myocardial infarction.[8, 11, 24] Reiter et al compared the performance of sensitive troponin assays between patients above and below 70 years using in cohort of 1,098 patients from the APACE study.[11] Boeddinghaus *et al* assessed the impact of age on the performance a 0/1-hour chest pain pathway using the 99th centile diagnostic threshold for both high sensitivity cardiac troponin I and T assays in a cohort of 3,123 patients from APACE, BACC and TRAPID-MI with chest pain.[16] Both studies reported that specificity for myocardial infarction decreased with advancing age.

We found the use of age-adjusted thresholds improved specificity and PPV in older patients compared to the 99th centile, a finding mirrored in several observational studies.[8, 11, 16] Reclassification of patients using an age-adjusted diagnostic threshold has also been shown to improve the identification of patients at increased short term mortality.[17] Parallels could be drawn with the use of sex-specific thresholds which are recommended in the Fourth UDMI.[1, 20] Is it therefore time to consider adopting age-adjusted thresholds? There are several factors to consider. First, age is not a dichotomous variable. Deriving the 99th centile in a population by age still confers the same issues inherent with a universal 99th centile: defining normality in a heterogenous group. Second, higher cardiac troponin thresholds may disadvantage older patients with fewer comorbidities. Third, elevated cardiac troponin levels above the 99th centile are associated with adverse outcomes in both young and old patients and implementing higher thresholds may normalise values that still confer risk, limiting opportunity for intervention.[25] Fourth, age-adjusted 99th centiles did not prevent a decline in diagnostic performance of troponin testing in older patients. Finally, overall discrimination was greatest when using an absolute change in cardiac troponin in combination with the 99th centile as the diagnostic threshold. For these reasons, we do not support the adoption of age-adjusted thresholds for the diagnosis of myocardial infarction.

The latest European Society of Cardiology guidelines have included new rule-in thresholds above the 99th centile to identify those with a high probability of myocardial infarction using a single presentation cardiac troponin test.[14] This extends the concept of safety from a single low cardiac troponin concentration to an idea that high presentation concentrations are very likely to correlate with the severity of coronary artery disease.[25, 26] Rule-in thresholds were designed to maximise the specificity and PPV of testing with their recommendation based on observational data from cohorts of consented patients with chest pain as the primary

presenting symptom.[16, 24, 28] We found application of a rule-in threshold of 64 ng/L achieved the greatest specificity and PPV for both myocardial infarction and type 1 myocardial infarction across all ages when compared to both sex-specific 99th centiles and age-adjusted thresholds. This approach is analogous to the use of optimized rule out or risk stratification thresholds which prioritize high sensitivity and NPV to identify patients at presentation who are unlikely to have myocardial infarction on serial testing. However, unlike these thresholds, we observed that a rule-in threshold did not have consistent or adequate performance across age groups or key cardiovascular comorbidities. Despite higher specificity and PPV, 2 in every 5 patients 75 years old or over with a presentation cardiac troponin above 64 ng/L did not have myocardial infarction, and 1 in every 2 patients 75 years old did not have a final diagnosis of type 1 myocardial infarction. In addition, sensitivity was decreased across all age groups. This may miss diagnoses of myocardial infarction and other forms of myocardial injury which confer clinically relevant and prognostic information.[29] Ultimately, any increase in a binary threshold comes at the cost of decreased sensitivity, regardless of age. While defining optimal thresholds for a series of age groups and comorbidities to achieve a predefined specificity or PPV may be possible, these would be impractical to apply in clinical practice.

Regardless of threshold, diagnostic performance was reduced in older patients. We observed an increase in type 2 myocardial infarction and myocardial injury with age. Cardiac troponin is not specific for myocardial infarction and there is little evidence that the magnitude of cardiac troponin can distinguish the mechanism of release and the differentiation of acute from chronic causes of injury requires serial testing.[1, 30-34] Given the ease of access to early re-testing within 1 hour, and the improvements in diagnostic performance when incorporating an absolute change in troponin concentration, clinicians should consider whether the rule-in

of myocardial infarction on the basis of a single presentation cardiac troponin sample should be applied to older or more complex patients. Patients requiring immediate or expedited revascularisation are often identifiable by clinical features and decisions based on presentation troponin concentrations should firstly focus on safe rule-out and minimizing the risk of missed myocardial infarction.

We observed a lower specificity and PPV when using high-sensitivity cardiac troponin to diagnose type 1 myocardial infarction compared with a diagnosis of type 1, type 2 or type 4b infarction. While chest pain diagnostic pathways predominately assist with patient triage, they are also used to guide the early administration of antiplatelet therapy and anticoagulation which are not indicated in patients with type 2 myocardial infarction and conversely may cause harm. Clinicians should be aware of these changes when considering the risks and benefits of early management strategies in older patients.

Few studies have assessed the impact of comorbidities on diagnostic performance of troponin testing. We found that although several cardiovascular comorbidities were associated with the diagnosis of myocardial infarction, their presence did not alter the odds of myocardial infarction in those with an elevated cardiac troponin above the 99th centile. This suggests the cardiovascular comorbidities we assessed do not directly influence the diagnostic performance of a binary rule-in strategy using cardiac troponin at the sex-specific 99th centile. There are several potential explanations for these findings. Firstly, older patients free from cardiovascular disease may still exhibit higher baseline cardiac troponin concentrations than younger reference populations used to derive 99th centile thresholds.[5, 6] Age may therefore have a stronger association with cardiac troponin concentrations than individual comorbidities. Second, non-cardiovascular comorbidities were not collected as part of the

High-STEACS trial. Conditions such as chronic obstructive pulmonary disease and other inflammatory conditions are associated with elevations in cardiac troponin.[9, 35-37] Third, we cannot exclude the impact of unmeasured subclinical cardiovascular disease in our cohort. Objective measures of disease severity such as natriuretic peptide concentrations or echocardiography could add to the granularity of a binary comorbidity status. Approaches to sequentially exclude patients from reference populations used to derive the 99th centile using such testing has been shown to impact the threshold level, particularly in older patients.[8, 38, 39]

Of note, the addition of comorbidities to our baseline model resulted in an improvement in model discrimination suggesting approaches which consider multiple individual patient factors could offer an alternative to threshold-based diagnosis.[40] One such example is the MI^3 model, which utilizes machine learning to provide individual probability estimates and has been shown to perform favorably in an observational study with superior specificity and PPV compared with universal thresholds.[41, 42] Further research is required to explore the efficacy of such approaches and understand the effectiveness of integration into clinical practice.

Our study has several strengths. The enrollment of consecutive patients using clinician suspicion of acute coronary syndrome eliminates selection bias. This ensured our analysis included a wide range of patients, representative of the changing demographics observed in clinical practice, including more than a thousand patients aged over 90 years, a group largely excluded from cardiovascular studies. A further strength is the adjudication of myocardial infarction according to the Fourth UDMI, particularly given the increase in type 2 myocardial infarction and myocardial injury in older patients.

There are limitations which should be considered. Although our study reflected aging demographics, our local population is predominantly Caucasian, and findings may differ in a more ethnically diverse population. Our analysis was also based on cardiac troponin I measured using the Abbott ARCHITECT$_{STAT}$ high-sensitivity assay. The 99th centile is assay dependent. Cardiac troponin I and T are not biologically equivalent nor is their relationship to age or cardiovascular risk.[3] Our findings must therefore be interpreted with caution when considering other cardiac troponin assays. However, reduced performance with advancing age has now been observed in both high-sensitivity cardiac troponin I and T assays.[16] We also recognise the challenge of diagnostic adjudication using routine healthcare data, particularly in the older population where diagnostic procedures such as coronary angiography are performed less frequently.

In conclusion, age has a significant impact on the diagnostic performance of cardiac troponin at the guideline recommended 99th centile for myocardial infarction, with reduced performance in older patients. The use of age-adjusted 99th centile thresholds or a higher universal rule-in threshold did not achieve parity between middle-aged and older patients. Individualised diagnostic approaches and serial testing to determine absolute change in troponin concentration rather than adjustment of binary thresholds are needed to avoid disadvantaging older patients.

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Supplementary materials list

a) Appendix A

- Table S1-6
- Figure S1-3

b) Appendix B

- Expanded methodology

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Figure legends

Figure 1: Cardiac troponin testing and adjudicated diagnosis by age.

Panel A: Histogram showing the number of patients with one cardiac troponin concentration >sex-specific 99th centile by age in all study patients. The number of patients with a cardiac troponin >sex-specific 99th centile increases with age (n=46,435).

Panel B: Bar chart showing adjudicated diagnoses in patients with one cardiac troponin value >99th centile as a proportion of each age group. With advancing age, the proportion with type 1 myocardial infarction decreases as non-type 1 infarction and myocardial injury increase (n=8,179).

Figure 2: Diagnostic performance of the sex-specific 99th centile and alternative thresholds

The sensitivity (A), specificity (B) and positive predictive value (PPV) (C) of the recommended sex-specific 99th centile, age-adjusted thresholds and a universal rule-in threshold above the 99th centile across age groups plotted with a line of best fit.

Figure 3: Diagnostic performance of the sex-specific 99th centile for the diagnosis of type 1 myocardial infarction

The sensitivity (A), specificity (B) and positive predictive value (PPV) (C) of the recommended sex-specific 99th centile for the diagnosis of type 1 myocardial infarction (red) compared with any myocardial infarction (black) plotted with a line of best fit.

Appendices

Data availability statement

The High-STEACS trial makes use of several routine electronic health care data sources that are linked, de-identified, and held in our national safe haven, which is accessible by approved individuals who have undertaken the necessary governance training. Summary data can be made available upon request to the corresponding author.

Table 1: Baseline characteristics stratified by age group

	Overall (N = 46,435)	<50 (N = 12,379)	50-75 (N = 22,380)	>75 (N = 11,676)	p-value
Patient demographics					
Age (years)	61 (±17)	39 (±9)	61 (±7)	82 (±5)	<0.001
Sex (Male)	24,726 (53%)	7,203 (58%)	12,412 (55%)	5,111 (44%)	<0.001
Chest pain as presenting symptom*	33,480 (83%)	9,989 (92%)	16,524 (84%)	6,967 (70%)	<0.001
Time from chest pain onset to presentation					
≤2hrs (Early)	7,767 (17%)	1,847 (15%)	3,900 (17%)	2,020 (17%)	<0.001
≥12hrs (Late)	14,406 (31%)	4,397 (36%)	6,980 (31%)	3,029 (26%)	<0.001
Past medical history					
Myocardial infarction	4,059 (9%)	424 (3%)	2,252 (10%)	1,383 (12%)	<0.001
Ischemic heart disease	11,472 (25%)	740 (6%)	5,899 (26%)	4,833 (41%)	<0.001
Hypercholesterolemia	18,603 (40%)	1,213 (10%)	10,376 (46%)	7,014 (60%)	<0.001
Cerebrovascular disease	2,767 (6%)	109 (1%)	1,161 (5%)	1,497 (13%)	<0.001
Chronic kidney disease	9,828 (21%)	943 (8%)	4,042 (18%)	4,843 (41%)	<0.001
Diabetes mellitus	3,315 (7%)	161 (1%)	1,776 (8%)	1,378 (12%)	<0.001
Heart failure	3,990 (9%)	196 (2%)	1,555 (7%)	2,239 (19%)	<0.001
Presence of multimorbidity	14,590 (31%)	806 (7%)	7,189 (32%)	6,595 (56%)	<0.001
Previous Revascularisation					
Percutaneous coronary intervention	3,574 (8%)	389 (3%)	2,251 (10%)	934 (8%)	<0.001
Coronary artery bypass grafting	756 (2%)	36 (<1%)	429 (2%)	291 (2%)	<0.001
Medications at presentation					
Aspirin	12,650 (27%)	859 (7%)	6,735 (30%)	5,056 (43%)	<0.001
P2Y12 inhibitor	4,397 (9%)	281 (2%)	2,179 (10%)	1,937 (17%)	<0.001
Dual antiplatelet therapy†	1,559 (3%)	185 (1%)	893 (4%)	481 (4%)	<0.001
ACE inhibitor or ARB	14,981 (32%)	1,353 (11%)	8,284 (37%)	5,344 (46%)	<0.001
Beta-blocker	12,670 (27%)	1,411 (11%)	6,650 (30%)	4,609 (39%)	<0.001
Lipid lowering therapy	18,603 (40%)	1,213 (10%)	10,376 (46%)	7,014 (60%)	<0.001
Oral anticoagulation‡	3,088 (7%)	169 (1%)	1,246 (6%)	1,673 (14%)	<0.001
Physiological Parameters§					
Heart rate, beats per minute	86 (±26)	84 (±24)	86 (±27)	87 (±26)	0.010
Systolic blood pressure, mmHg	139 (±29)	137 (±26)	140 (±29)	140 (±30)	0.26

GRACE score	142 (±37)	88 (±24)	128 (±30)	164 (±28)	<0.001
Electrocardiogram§					
Normal	2,516 (37%)	295 (52%)	1,266 (42%)	955 (30%)	<0.001
Myocardial ischemia	1,739 (26%)	132 (23%)	872 (29%)	735 (23%)	<0.001
ST-segment elevation	243 (4%)	43 (8%)	112 (4%)	88 (3%)	<0.001
ST-segment depression	1,185 (18%)	71 (12%)	587 (20%)	527 (17%)	<0.001
T-wave inversion	1,188 (18%)	105 (18%)	579 (19%)	504 (16%)	0.001
Haematology and clinical chemistry					
Haemoglobin, g/L	136 (±21)	143 (±20)	138 (±20)	126 (±22)	<0.001
Estimated glomerular filtration rate, mL/min	88 (±24)	109 (±16)	88 (±19)	67 (±20)	<0.001
Presentation high sensitivity troponin I, ng/mL	3 [1-11]	1 [1-2]	3 [2-9]	10 [5-29]	<0.001
Peak high sensitivity troponin I, ng/mL	4 [1-13]	1 [1-3]	3 [2-11]	12 [5-41]	<0.001
Serial troponin measurement¶	22,162 (48%)	4,364 (35%)	11,379 (51%)	6,419 (55%)	<0.001
Adjudicated Diagnosis					
Myocardial Infarction	5,216 (11%)	442 (4%)	2,614 (12%)	2,160(18%)	<0.001
Type 1 myocardial infarction	4,064 (9%)	378 (3%)	2,162 (10%)	1,524 (13%)	<0.001
Type 2 myocardial infarction	1,116 (2%)	59 (0%)	427 (2%)	630 (5%)	<0.001
Type 4b myocardial infarction	36 (<1%)	5 (<1%)	25 (<1%)	6 (<1%)	0.037
Acute myocardial injury	1,676 (4%)	111 (1%)	544 (2%)	1,021 (9%)	<0.001
Chronic myocardial injury	1,287 (3%)	102 (1%)	427 (2%)	758 (6%)	<0.001
No myocardial injury	38,256 (82%)	11,724 (95%)	18,795 (84%)	7,737 (66%)	<0.001

Presented as number (%), mean (±SD) or median [25th percentile, 75th percentile]

Abbreviations: ACE = Angiotensin-converting enzyme; ARB = Angiotensin receptor blocker; GRACE = Global Registry of Acute Cardiac Events

*Chest pain as presenting symptom is reported for the 87% (40,475/46,435) of patients where primary symptom data was available

† Two medications from aspirin, clopidogrel, prasugrel and ticagrelor

‡ Includes warfarin or novel anticoagulants

§Electrocardiographic and physiological data reported for the 83% (6,762/8,179) patients with myocardial infarction or myocardial injury who had electrocardiographic data available.

¶Serial testing defined as two or more tests within 24 hours of presentation.

Table 2: Diagnostic performance of presentation high sensitivity cardiac troponin I for myocardial infarction by age group and threshold

Age group (years)	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Rule-in (%)	AUC (95% CI)
Sex-specific 99th centile*										
<50	346	203	11739	91	79.2 (75.5-82.9)	98.3 (98.1-98.5)	63.0 (59.1-67.1)	99.2 (99.1-99.4)	4.4	0.89 (0.87-0.91)
50-74	2088	889	18902	501	80.6 (79.2-82.1)	95.5 (95.2-95.8)	70.1 (68.5-71.8)	97.4 (97.2-97.6)	13.3	0.88 (0.87-0.89)
≥75	1758	1653	7869	396	81.6 (79.9-83.2)	82.6 (81.9-83.4)	51.6 (49.8-53.2)	95.2 (94.7-95.7)	29.2	0.82 (0.79-0.81)
Overall	4192	2745	38510	988	80.9 (79.8-82.0)	93.3 (93.1-93.6)	60.4 (59.3-61.6)	97.5 (97.3-97.6)	14.9	0.87 (0.87-0.88)
Age-adjusted 99th centile thresholds†										
<50	346	203	11739	91	79.2 (75.5-82.9)	98.3 (98.1-98.5)	63.0 (59.1-67.1)	99.2 (99.1-99.4)	4.4	0.89 (0.87-0.91)
50-74	1878	719	19072	711	72.5 (70.8-74.2)	96.4 (96.1-96.6)	72.3 (70.6-74.0)	96.4 (96.1-96.7)	11.6	0.84 (0.84-0.86)
≥75	1203	827	8695	951	55.9 (53.5-57.9)	91.3 (90.8-91.9)	59.3 (57.1-61.4)	90.1 (89.5-90.7)	17.4	0.74 (0.73-0.75)
Overall	3427	1749	39506	1753	66.2 (64.9-67.4)	95.8 (95.6-95.9)	66.2 (64.9-67.5)	95.8 (95.6-95.9)	11.1	0.81 (0.80-0.82)
Universal rule-in threshold (>64 ng/L)										
<50	258	125	11817	179	59.0 (54.2-63.4)	99.0 (98.8-99.1)	67.4 (62.6-71.8)	98.5 (98.3-98.7)	3.1	0.79 (0.77-0.81)
50-74	1435	445	19346	1154	55.4 (53.5-57.2)	97.7 (97.5-98.0)	76.3 (74.4-78.2)	94.4 (94.1-94.7)	8.4	0.77 (0.76-0.78)
≥75	1079	693	8829	1075	50.1 (48.0-52.2)	92.7 (92.2-93.2)	60.9 (58.7-63.1)	89.1 (88.5-89.7)	15.2	0.71 (0.70-0.73)
Overall	2772	1263	39992	2408	53.5 (52.2-54.9)	96.9 (96.8-97.1)	68.7 (67.3-70.2)	94.3 (94.1-94.5)	8.7	0.75 (0.75-0.76)

Presented as number or % (95% confidence intervals) as appropriate.
*Sex-specific 99th centile = 34 ng/L men, 16 ng/L women.
†Age-adjusted thresholds = age <60: >32 ng/L men, >16 ng/L women; age 60-69: > 42 ng/L men, >17 ng/L women; age ≥70: 86 ng/L men, 39 ng/L women

Abbreviations: AUC = Area under the curve, FN=false negatives, FP=false positives, NPV = negative predictive value, PPV = positive predictive value, TN=true negatives, TP=true positives

1

Table 3: Discrimination of high-sensitivity cardiac troponin I at presentation in combination with an absolute or relative change in cardiac troponin concentration

Age (years)	**<50**			**50-75**			**≥75**			**Overall**		
Criteria	**hs-cTnI**	**hs-cTnI + 20%Δ**	**hs-cTnI +15ng/LΔ**	**hs-cTnI**	**hs-cTnI + 20%Δ**	**hs-cTnI +15ng/LΔ**	**hs-cTnI**	**hs-cTnI + 20%Δ**	**hs-cTnI +15ng/LΔ**	**hs-cTnI**	**hs-cTnI + 20%Δ**	**hs-cTnI + 15ng/LΔ**
Threshold	*AUC (95% confidence interval)*											
Sex-specific 99th centile	0.85 (0.83-0.88)	0.94 (0.93-0.95)	0.97 (0.96-0.98)	0.85 (0.84-0.86)	0.93 (0.93-0.96)	0.96 (0.95-0.96)	0.78 (0.77-0.79)	0.86 (0.85-87)	0.88 (0.87-0.89)	0.83 (0.83-0.84)	0.91 (0.91-0.92)	0.94 (0.93-0.94)
Age-adjusted 99th centile	0.85 (0.83-0.88)	0.94 (0.93-0.95)	0.97 (0.96-0.98)	0.81 (0.80-0.82)	0.91 (0.90-0.91)	0.94 (0.93-0.95)	0.69 (0.58-0.71)	0.80 (0.79-0.81)	0.94 (0.93-0.95)	0.77 (0.76-0.78)	0.87 (0.86-0.87)	0.91 (0.90-0.91)
64ng/L	0.76 (0.73-0.78)	0.78 (0.77-0.86)	0.82 (0.81-0.83)	0.73 (0.72-0.74)	0.85 (0.84-0.86)	0.90 (0.90-0.91)	0.67 (0.66-0.69)	0.78 (0.77-0.80)	0.82 (0.81-0.83)	0.71 (0.71-0.72)	0.88 (0.87-0.89)	0.88 (0.87-0.89)

Abbreviations: AUC = area under the curve, hs-cTnI = high sensitivity cardiac troponin I, Δ = delta

Table 4: Logistic regression models for determinants of myocardial infarction.

	Age <50 years			Age 50-74 years			Age ≥75		
Explanatory variable	**Baseline OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Baseline OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Baseline OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**
Troponin >sex-specific 99th centile	1.86* (1.84-1.88)	-	1.86* (1.83-1.87)	1.96* (1.95 - 1.98)	-	1.96* (1.94-1.98)	1.60* (1.56-1.62)	-	1.60* (1.56-1.6)
Comorbidity									
Ischemic heart disease	-	1.02* (1.01-1.03)	1.00 (0.98-.01)	-	1.00 (1.00-1.01)	0.99 (0.98-1.00)	-	1.04* (1.03-1.06)	1.03* (1.02-1.05)
Previous myocardial infarction	-	1.02* (1.01-1.04)	1.01 (0.99-1.03)	-	1.02* (1.01-1.03	1.03* (1.02-1.04)	-	1.06 * (1.04-1.08)	1.04* (1.02-1.06)
Cerebrovascular disease	-	1.01 (0.98-1.03)	0.99 (0.97-1.01)	-	0.98† (0.97-0.99)	0.98† (0.97-1.00)	-	1.00 (0.98-1.02)	0.98 (0.98-1.01)
Chronic kidney disease	-	0.99 (0.99-1.00)	0.99 (0.98-1.00)	-	0.98* (0.97-0.98)	0.98* (0.96-0.99)	-	0.97* (0.96-0.98)	0.97* (0.96-0.98)
Diabetes mellitus	-	1.10* (1.09-1.13)	1.10* (1.08-1.12)	-	1.06* (1.04-1.07)	1.07* (1.06-1.09)	-	1.05* (1.03-1.07)	1.04* (1.02-1.06)
Heart failure	-	0.98† (0.97-1.00)	0.97† (0.95-0.99)	-	0.98† (0.97-1.00)	0.97† (0.97-0.98)	-	1.01 (1.00-1.03)	0.99 (0.97-1.01)
AUC	0.89	-	0.90†	0.88		0.90*	0.81		0.83*

	(0.87-0.91)		(0.88-0.92)	(0.87-0.89)		(0.89-0.91)	(0.79-0.82)		(0.82-0.84)

Abbreviations: AUC = area under the curve; OR = odds ratio

†p-value <0.05

*p-value < 0.001

Comparison of Baseline vs Model 2 using De Long's test: Age <50, p= 0.003; Age 50-74, p=<0.001 ; Age ≥75, p=<0.001

1

Figure 1

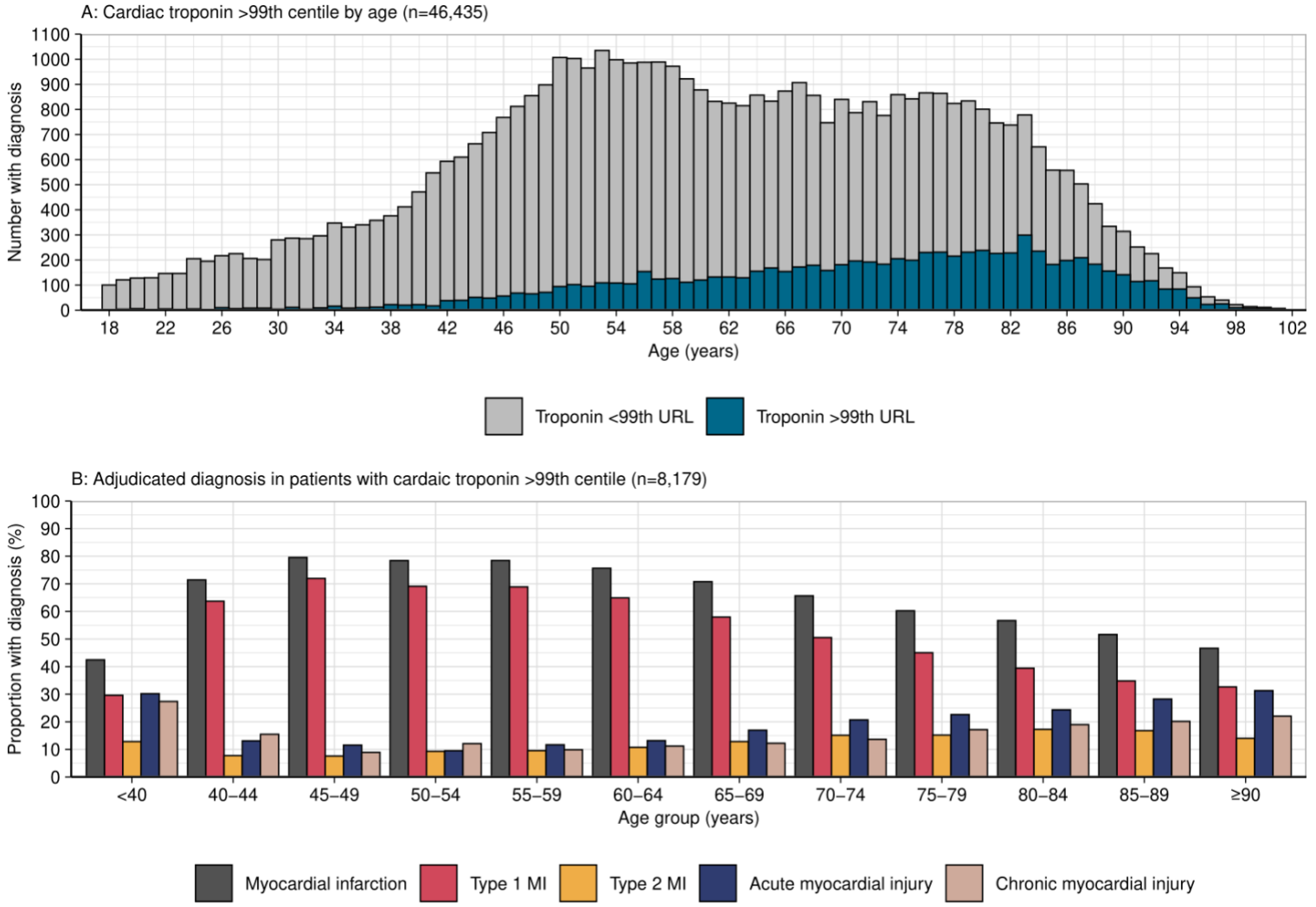

A: Cardiac troponin >99th centile by age (n=46,435)
Number with diagnosis
Age (years)
Troponin <99th URL
Troponin >99th URL
B: Adjudicated diagnosis in patients with cardaic troponin >99th centile (n=8,179)
Proportion with diagnosis (%)
<40
40–44
45–49
50–54
55–59
60–64
65–69
70–74
75–79
80–84
85–89
≥90
Age group (years)
Myocardial infarction
Type 1 MI
Type 2 MI
Acute myocardial injury
Chronic myocardial injury

Figure 2

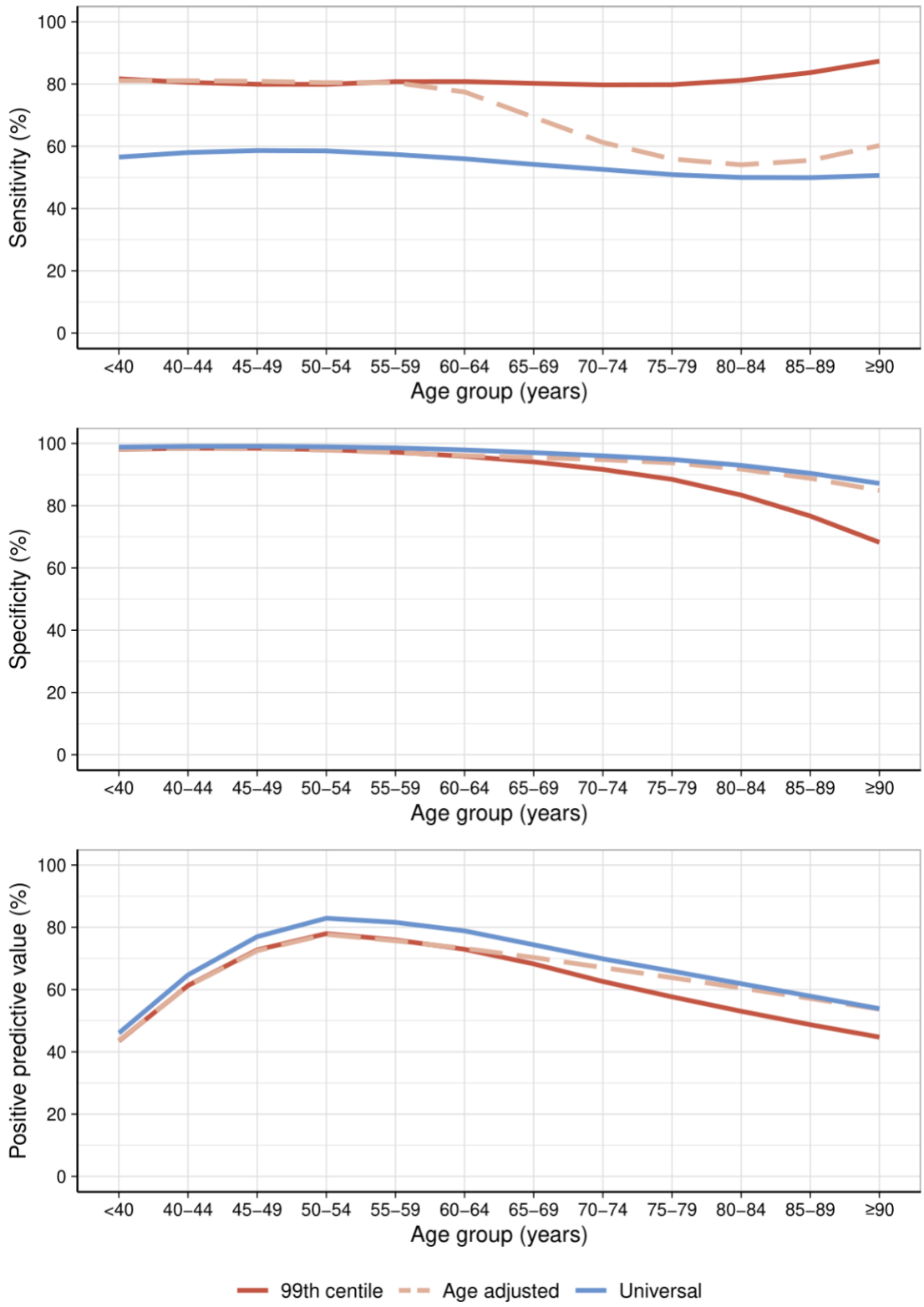
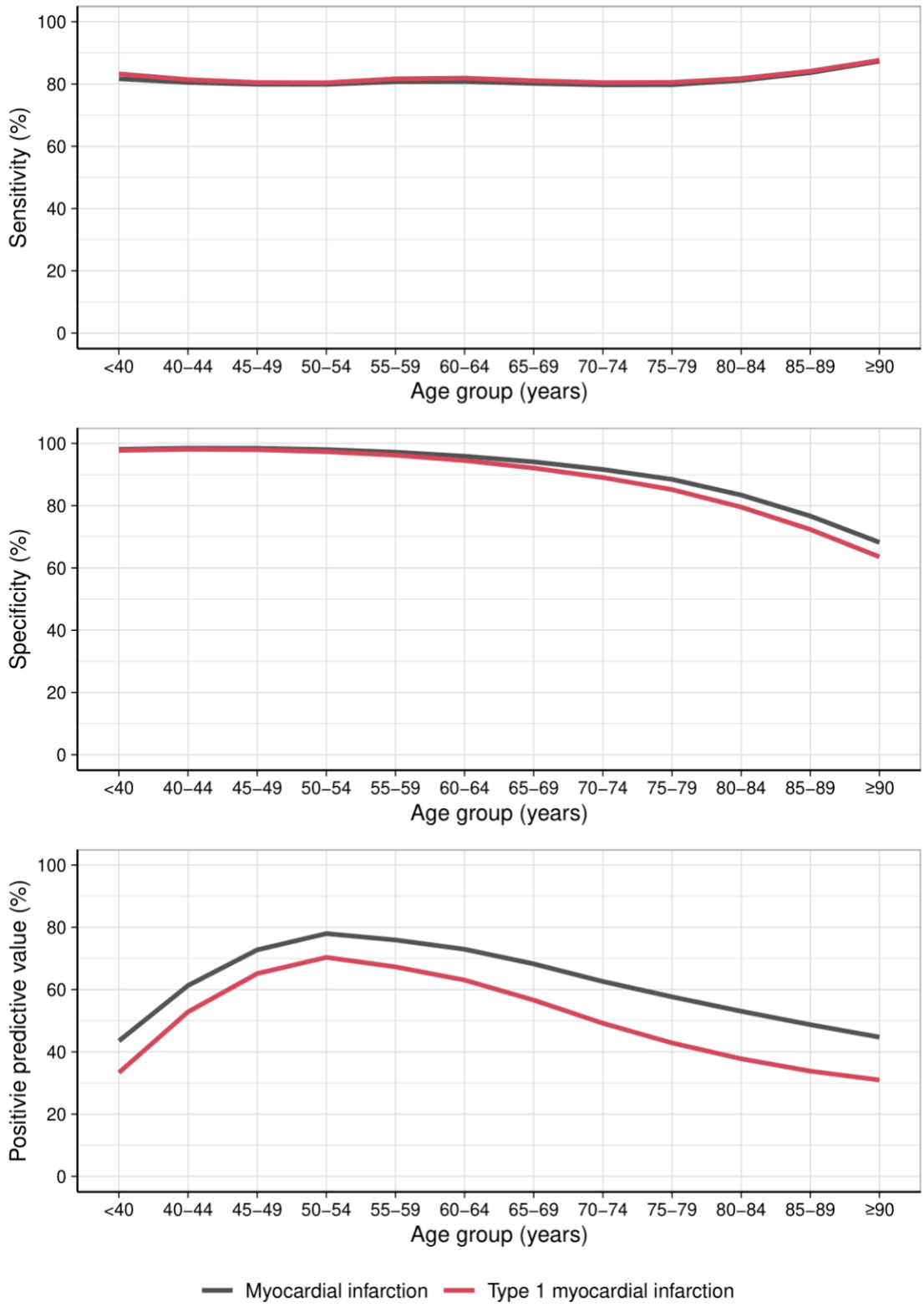

Sensitivity (%)
Specificity (%)
Positive predictive value (%)
100
80
60
40
20
0
<40
40–44
45–49
50–54
55–59
60–64
65–69
70–74
75–79
80–84
85–89
≥90
Age group (years)
99th centile
Age adjusted
Universal

Figure 3


Sensitivity (%)
Specificity (%)
Positivie predictive value (%)
0
20
40
60
80
100
<40
40–44
45–49
50–54
55–59
60–64
65–69
70–74
75–79
80–84
85–89
≥90
Age group (years)
Myocardial infarction
Type 1 myocardial infarction

SUPPLEMENTAL MATERIAL

Influence of age on the diagnosis of myocardial infarction

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Short Title: Age and cardiac troponin

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SUPPLEMENTARY APPENDIX A

Figures and Tables

Supplementary Tables

Online Table 1: Baseline characteristics stratified by age.

Online Table 2: Diagnostic performance of presentation high sensitivity cardiac troponin I in patients with suspected acute coronary syndrome by age and threshold.

Online Table 3: Diagnostic performance of presentation high-sensitivity cardiac troponin at the sex-specific 99th centile in patients with suspected acute coronary syndrome and chest pain as the presenting symptom.

Online Table 4: Diagnostic performance of presentation high-sensitivity cardiac troponin at the sex-specific 99th centile for the diagnosis of type 1 myocardial infarction.

Online Table 5: Timing of serial samples by age group

Online Table 6: Diagnosis between discordant threshold groups by age

Supplementary Figures

Online Figure 1: Cardiac troponin >99th centile upper reference limit by age group in whole population

Online Figure 2: Diagnostic accuracy of the sex-specific 99th centile at presentation in patients with chest pain

Online Figure 3: Three panel forest plot displaying positive predictive value of presentation high-sensitivity cardiac troponin I with a sex-specific 99th centile diagnostic threshold stratified by age groups

Online Table 1: Baseline characteristics stratified by age

Age (years)	All (N = 46,435)	<40 (N = 5,454)	40-44 (N = 2,884)	45-49 (N = 4,041)	50-54 (N = 5,008)	55-59 (N = 4,856)	60-64 (N = 4,207)	65-69 (N = 4,216)	70-74 (N = 4,093)	75-79 (N = 4,230)	80-84 (N = 3,714)	85-89 (N = 2,376)	≥90 (N = 1,356)
Patient demographics													
Age	61 (±17)	31 (±6)	42 (±1)	47 (±1)	52 (±1)	57 (1±)	62 (±1)	67 (±1)	72 (±1)	77 (±1)	82 (±1)	87 (±1)	93 (±3)
Male	24,726 (53%)	3,323 (61%)	1,673 (58%)	2,207 (55%)	2,802 (56%)	2,690 (55%)	2,430 (58%)	2,311 (55%)	2,179 (53%)	2,045 (48%)	1,658 (45%)	946 (40%)	462 (34%)
Presenting symptom chest pain*	33,480 (83%)	4,357 (93%)	2,361 (92%)	3,271 (91%)	4,019 (90%)	3,767 (88%)	3,076 (83%)	2,926 (80%)	2,736 (77%)	2,733 (74%)	2,205 (70%)	1,335 (66%)	694 (60%)
Time from chest pain onset to presentation													
≤2hrs (Early)	7,767 (17%)	734 (13%)	447 (15%)	666 (16%)	862 (17%)	824 (17%)	770 (18%)	728 (17%)	716 (17%)	735 (17%)	656 (18%)	398 (17%)	231 (17%)
≥12hrs (Late)	14,406 (31%)	2,020 (37%)	1,031 (36%)	1,346 (33%)	1,689 (34%)	1,487 (31%)	1,320 (31%)	1,315 (31%)	1,169 (29%)	1,169 (28%)	952 (26%)	593 (25%)	315 (23%)
Past medical history													
Myocardial infarction	4,059 (9%)	61 (1%)	124 (4%)	239 (6%)	410 (8%)	458 (9%)	477 (11%)	429 (10%)	478 (12%)	530 (13%)	423 (11%)	277 (12%)	153 (11%)
Ischaemic heart disease	11,472 (25%)	92 (2%)	199 (7%)	449 (11%)	825 (16%)	1,092 (22%)	1,153 (27%)	1,306 (31%)	1,523 (37%)	1,753 (41%)	1,576 (42%)	977 (41%)	527 (39%)
Hypercholesterolaemia	18,603 (40%)	139 (3%)	335 (12%)	739 (18%)	1,393 (28%)	1,904 (39%)	2,034 (48%)	2,402 (57%)	2,643 (65%)	2,780 (66%)	2,305 (62%)	1,342 (56%)	587 (43%)
Cerebrovascular disease	2,767 (6%)	24 (<1%)	27 (1%)	58 (1%)	137 (3%)	180 (4%)	208 (5%)	293 (7%)	343 (8%)	470 (11%)	462 (12%)	353 (15%)	212 (16%)
Chronic kidney disease	9,828 (21%)	423 (8%)	205 (7%)	315 (8%)	511 (10%)	694 (14%)	740 (18%)	904 (21%)	1,193 (29%)	1,520 (36%)	1,547 (42%)	1,079 (45%)	697 (51%)

Diabetes mellitus	3,315 (7%)	19 (<1%)	50 (2%)	92 (2%)	203 (4%)	295 (6%)	368 (9%)	412 (10%)	498 (12%)	578 (14%)	456 (12%)	240 (10%)	104 (8%)
Heart failure	3,990 (9%)	42 (1%)	49 (2%)	105 (3%)	162 (3%)	225 (5%)	264 (6%)	373 (9%)	531 (13%)	690 (16%)	684 (18%)	506 (21%)	359 (26%)
Multimorbidity	14,590 (31%)	97 (2%)	214 (7%)	495 (12%)	903 (18%)	1,269 (26%)	1,374 (33%)	1,638 (39%)	2,005 (49%)	2,326 (55%)	2,136 (58%)	1,377 (58%)	756 (56%)
Previous Revascularisation													
Percutaneous coronary intervention	3,574 (8%)	44 (1%)	114 (4%)	231 (6%)	386 (8%)	467 (10%)	466 (11%)	462 (11%)	470 (11%)	430 (10%)	318 (9%)	143 (6%)	43 (3%)
Coronary artery bypass grafting	756 (2%)	<5 (<1%)	8 (<1%)	27 (1%)	31 (1%)	74 (2%)	83 (2%)	112 (3%)	129 (3%)	139 (3%)	107 (3%)	35 (1%)	10 (1%)
Medications at presentation													
Aspirin	12,650 (27%)	136 (2%)	232 (8%)	491 (12%)	894 (18%)	1,220 (25%)	1,336 (32%)	1,547 (37%)	1,738 (42%)	1,845 (44%)	1,652 (44%)	977 (41%)	582 (43%)
P2Y12 inhibitor	4,397 (9%)	45 (1%)	72 (2%)	164 (4%)	305 (6%)	390 (8%)	439 (10%)	492 (12%)	553 (14%)	649 (15%)	626 (17%)	434 (18%)	228 (17%)
Dual antiplatelet therapy†	1,559 (3%)	38 (1%)	47 (2%)	100 (2%)	158 (3%)	177 (4%)	201 (5%)	181 (4%)	176 (4%)	183 (4%)	155 (4%)	94 (4%)	49 (4%)
ACEi or ARB	14,981 (32%)	216 (4%)	394 (14%)	743 (18%)	1,254 (25%)	1,586 (33%)	1,643 (39%)	1,826 (43%)	1,975 (48%)	2,137 (51%)	1,762 (47%)	996 (42%)	449 (33%)
Beta-blocker	12,670 (27%)	411 (8%)	364 (13%)	636 (16%)	969 (19%)	1,236 (25%)	1,294 (31%)	1,505 (36%)	1,646 (40%)	1,762 (42%)	1,493 (40%)	887 (37%)	467 (34%)
Lipid lowering therapy	18,603 (40%)	139 (3%)	335 (12%)	739 (18%)	1,393 (28%)	1,904 (39%)	2,034 (48%)	2,402 (57%)	2,643 (65%)	2,780 (66%)	2,305 (62%)	1,342 (56%)	587 (43%)
Oral anticoagulation‡	3,088 (7%)	56 (1%)	41 (1%)	72 (2%)	103 (2%)	140 (3%)	205 (5%)	336 (8%)	462 (11%)	595 (14%)	575 (15%)	341 (14%)	162 (12%)
Physiological parameters§													
Heart rate, beats per minute	86 (±26)	85 (±26)	83 (±25)	84 (±23)	83 (±24)	84 (±26)	85 (±26)	88 (±31)	87 (±27)	86 (±26)	87 (±26)	86 (±26)	88 (±26)
Systolic blood pressure, mmHg	139 (±29)	134 (±22)	138 (±27)	139 (±28)	139 (±28)	142 (±28)	142 (±27)	140 (±28)	137 (±30)	138 (±29)	139 (±30)	141 (±29)	142 (±31)

GRACE score	142 (±37)	76 (±23)	85 (±19)	97 (±24)	104 (±22)	113 (±24)	124 (±25)	134 (±25)	147 (±30)	153 (±26)	163 (±29)	169 (±27)	175 (±27)
Electrocardiogram§													
Normal ECG	2,516 (37%)	84 (53%)	88 (60%)	123 (46%)	208 (47%)	247 (47%)	255 (46%)	280 (40%)	276 (35%)	286 (32%)	311 (31%)	204 (27%)	154 (29%)
Ischaemia on ECG	1,739 (26%)	22 (14%)	27 (18%)	83 (31%)	126 (29%)	144 (28%)	181 (32%)	195 (28%)	226 (29%)	204 (23%)	253 (25%)	161 (21%)	117 (22%)
ST-segment elevation	243 (4%)	19 (12%)	8 (5%)	16 (6%)	28 (6%)	21 (4%)	20 (4%)	17 (2%)	26 (3%)	26 (3%)	28 (3%)	20 (3%)	14 (3%)
ST-segment depression	1,185 (18%)	10 (6%)	11 (8%)	50 (19%)	74 (17%)	96 (18%)	116 (21%)	134 (19%)	167 (21%)	141 (16%)	188 (19%)	115 (15%)	83 (15%)
T-wave inversion	1,188 (18%)	25 (16%)	26 (18%)	54 (20%)	90 (21%)	112 (21%)	116 (21%)	130 (19%)	131 (17%)	157 (17%)	152 (15%)	120 (16%)	75 (14%)
Haematology and clinical chemistry													
Haemoglobin, g/L	136 (±21)	144 (±20)	142 (±20)	142 (±19)	141 (±19)	140 (±19)	138 (±20)	136 (±20)	133 (±22)	129 (±22)	126 (±21)	123 (±22)	120 (±22)
Estimated glomerular filtration rate, mL/min	88 (±24)	116 (±15)	106 (±15)	102 (±15)	98 (±15)	93 (±17)	88 (±18)	82 (±19)	76 (±20)	72 (±20)	67 (±20)	63 (±19)	58 (±19)
Presentation high sensitivity troponin I, ng/mL	3 [1-11]	1 [1-2]	1 [1-3]	1 [1-3]	2 [1-4]	2 [1-6]	3 [2-9]	4 [2-13]	6 [3-17]	7 [4-20]	10 [5-29]	13 [6-35]	17 [8-54]
Peak high sensitivity troponin I, ng/mL	4 [1-13]	1 [1-2]	1 [1-3]	2 [1-3]	2 [1-5]	3 [1-7]	4 [2-11]	5 [2-16]	7 [3-22]	8 [4-26]	11 [5-41]	15 [7-49]	20 [9-79]
Serial troponin measurement¶	22,162 (48%)	1,433 (26%)	1,168 (40%)	1,763 (44%)	2,409 (48%)	2,456 (51%)	2,151 (51%)	2,176 (52%)	2,187 (53%)	2,296 (54%)	2,101 (57%)	1,328 (56%)	694 (51%)
Adjudicated Diagnosis													
Myocardial Infarction	5,279 (11%)	76 (1%)	120 (4%)	246 (6%)	393 (8%)	483 (10%)	507 (12%)	589 (14%)	632 (15%)	670 (16%)	696 (19%)	481 (20%)	313 (23%)
Type 1 myocardial infarction	4,064 (9%)	53 (1%)	107 (4%)	218 (5%)	349 (7%)	425 (9%)	429 (10%)	478 (11%)	481 (12%)	498 (12%)	484 (13%)	323 (14%)	219 (16%)
Type 2 myocardial infarction	1,116 (2%)	23 (<1%)	13 (<1%)	23 (1%)	47 (1%)	59 (1%)	71 (2%)	106 (3%)	144 (4%)	168 (4%)	212 (6%)	156 (7%)	94 (7%)

Type 4b myocardial infarction	36 (<1%)	0 (0%)	0 (0%)	5 (<1%)	<5 (<1%)	<5 (<1%)	7 (<1%)	5 (<1%)	7 (<1%)	<5 (<1%)	0 (0%)	<5 (<1%)	0 (0%)
Acute myocardial injury	1,676 (4%)	54 (1%)	22 (1%)	35 (1%)	48 (1%)	72 (1%)	87 (2%)	140 (3%)	197 (5%)	250 (6%)	299 (8%)	262 (11%)	210 (15%)
Chronic myocardial injury	1,287 (3%)	49 (1%)	26 (1%)	27 (1%)	61 (1%)	61 (1%)	74 (2%)	101 (2%)	130 (3%)	190 (4%)	233 (6%)	187 (8%)	148 (11%)
No myocardial injury	38,256 (82%)	5,275 (97%)	2,716 (94%)	3,733 (92%)	4,500 (90%)	4,236 (87%)	3,539 (84%)	3,386 (80%)	3,134 (77%)	3,120 (74%)	2,486 (67%)	1,446 (61%)	685 (51%)

Presented as number (%), mean (±SD) or median [inter-quartile range]

Abbreviations: ACE = Angiotensin-converting enzyme; ARB = Angiotensin receptor blocker; GRACE = Global Registry of Acute Cardiac Events

*Chest pain as presenting symptom is reported for the 87% (40,475/46,435) of patients where primary symptom data was available

† Two medications from aspirin, clopidogrel, prasugrel and ticagrelor

‡ Includes warfarin or novel anticoagulants

§Electrocardiographic and physiological data reported for the 83% (6,762/8,179) patients with myocardial infarction or myocardial injury who had electrocardiographic data available.

¶Serial testing defined as two or more tests within 24 hours of presentation.

Online Table 2: Diagnostic performance of presentation high sensitivity cardiac troponin I in patients with suspected acute coronary syndrome by age and threshold (n=46,435).

Age group (years)	True positives	False positives	True negatives	False negatives	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Rule-in (%)
Sex-specific 99th centile									
<40	63	101	5277	13	83.0 (74.3-90.7)	98.1 (97.8-98.5)	38.4 (31.3-46.1)	99.8 (99.6-99.9)	3.0
40-44	95	43	2721	25	79.1 (71.3-85.9)	98.4 (98.0-98.9)	68.8 (61.0-76.6)	99.1 (98.7-99.4)	4.8
45-49	188	59	3741	53	78.0 (72.2-82.9)	98.5 (98.0-98.8)	76.1 (70.4-81.1)	98.6 (98.2-98.9)	6.1
50-54	320	102	4510	76	80.8 (76.7-84.6)	97.8 (97.3-98.2)	75.8 (71.3-79.7)	98.3 (98.0-98.7)	8.4
55-59	398	122	4250	86	82.2 (78.9-85.7)	97.2 (96.7-97.7)	76.5 (72.9-80.0)	98.0 (97.6-98.4)	10.7
60-64	394	148	3559	106	78.9 (75.0-82.5)	96.0 (95.4-96.6)	72.7 (69.1-76.4)	97.1 (96.6-97.6)	12.9
65-69	473	218	3414	111	81.0 (77.8-84.2)	94.0 (93.2-94.7)	68.4 (64.9-72.0)	96.9 (96.3-97.4)	16.4
70-74	503	299	3169	122	80.5 (77.4-83.5)	91.4 (90.4-92.3)	62.8 (59.4-65.9)	96.3 (95.6-96.9)	19.6
75-79	525	406	3158	141	78.8 (75.6-81.9)	88.6 (87.6-89.7)	56.5 (53.1-59.7)	95.7 (95.1-96.4)	22.0
80-84	558	489	2529	138	80.2 (77.5-83.1)	83.8 (82.5-85.1)	53.3 (50.3-56.3)	94.8 (94.0-95.6)	28.2
85-89	401	417	1480	78	83.8 (80.5-86.9)	78.1 (76.1-79.9)	49.1 (45.8-52.5)	95.0 (93.9-96.1)	34.4
≥90	274	341	702	39	87.6 (84.0-91.2)	67.3 (64.5-70.1)	44.5 (40.6-48.5)	94.8 (93.2-96.3)	45.4
Age-adjusted thresholds									

<40	63	101	5277	13	83.0 (74.3-90.7)	98.1 (97.8-98.5)	38.4 (31.3-46.1)	99.8 (99.6-99.9)	3.0
40-44	95	43	2721	25	79.1 (71.3-85.9)	98.4 (98.0-98.9)	68.8 (61.0-76.6)	99.1 (98.7-99.4)	4.8
45-49	188	59	3741	53	78.0 (72.2-82.9)	98.5 (98.0-98.8)	76.1 (70.4-81.1)	98.6 (98.2-98.9)	6.1
50-54	320	102	4510	76	80.8 (76.7-84.6)	97.8 (97.3-98.2)	75.8 (71.3-79.7)	98.3 (98.0-98.7)	8.4
55-59	398	122	4250	86	82.2 (78.9-85.7)	97.2 (96.7-97.7)	76.5 (72.9-80.0)	98.0 (97.6-98.4)	10.7
60-64	367	138	3569	133	73.5 (69.6-77.4)	96.3 (95.7-96.9)	72.7 (69.0-76.5)	96.4 (95.8-97.0)	12.0
65-69	451	197	3435	133	77.2 (73.8-80.6)	94.6 (93.8-95.3)	69.6 (65.7-73.3)	96.3 (95.6-96.9)	15.4
70-74	342	160	3308	283	54.7 (51.1-58.7)	95.4 (94.7-96.1)	68.1 (64.3-71.9)	92.1 (91.2-93.1)	12.3
75-79	367	215	3349	299	55.1 (51.3-59.0)	94.0 (93.2-94.8)	63.2 (59.2-67.2)	91.8 (91.0-92.7)	13.8
80-84	388	252	2766	308	55.8 (52.0-59.5)	91.7 (90.6-92.6)	60.6 (57.1-64.3)	90.0 (88.9-91.0)	17.2
85-89	257	197	1700	222	53.7 (49.2-58.2)	89.7 (88.3-91.0)	56.7 (52.5-61.6)	88.5 (87.1-89.9)	19.1
≥90	191	163	880	122	61.0 (55.8-66.1)	84.4 (82.1-86.6)	53.9 (48.5-59.2)	87.8 (85.8-89.8)	26.1
Universal threshold >99th centile									
<40	43	62	5316	33	56.4 (45.6-68.1)	98.8 (98.6-99.1)	40.9 (31.6-50.6)	99.4 (99.2-99.6)	1.9
40-44	69	26	2738	51	57.5 (49.1-66.7)	99.1 (98.7-99.4)	72.7 (63.5-81.3)	98.2 (97.7-98.7)	3.3
45-49	146	37	3763	95	60.4 (54.1-66.4)	99.0 (98.7-99.3)	79.7 (73.8-85.1)	97.5 (97.0-98.0)	4.5

50-54	225	56	4556	171	56.8 (51.9-61.7)	98.8 (98.5-99.1)	80.0 (75.1-84.8)	96.4 (95.8-96.9)	5.6
55-59	285	56	4316	199	58.8 (54.3-63.1)	98.7 (98.4-99.0)	83.5 (79.5-87.4)	95.6 (95.0-96.2)	7.0
60-64	277	77	3630	223	55.5 (51.3-59.8)	97.9 (97.5-98.4)	78.3 (74.1-82.6)	94.2 (93.5-94.9)	8.4
65-69	314	110	3522	270	53.8 (49.8-58.0)	97.0 (96.4-97.5)	74.1 (69.9-78.3)	92.9 (92.1-93.7)	10.1
70-74	334	146	3322	291	53.4 (49.6-57.5)	95.8 (95.1-96.4)	69.6 (65.5-73.4)	91.9 (91.0-92.8)	11.7
75-79	332	172	3392	334	49.9 (46.1-53.7)	95.2 (94.5-95.9)	66.0 (61.6-70.4)	91.0 (90.2-91.9)	11.9
80-84	361	215	2803	335	51.9 (48.1-55.6)	92.9 (92.0-93.8)	62.7 (59.0-66.5)	89.3 (88.2-90.4)	15.5
85-89	222	167	1730	257	46.4 (41.9-51.0)	91.2 (90.1-92.5)	57.2 (52.5-62.0)	87.1 (85.6-88.6)	16.4
≥90	164	139	904	149	52.3 (46.9-57.5)	86.7 (84.5-88.8)	54.0 (48.4-59.8)	85.8 (83.8-87.9)	22.3

Presented as number or % (95% confidence intervals) as appropriate.
Sex-specific 99th centile = 34 ng/L men, 16 ng/L women.
Age-adjusted thresholds = age <60: >32ng/L men, >16ng/L women; age 60-69: > 42ng/L men, >17ng/L women; age ≥70: 86ng/L men, 39g/L women)
Uniform rule-in threshold >99th centile = >64 ng/L
Abbreviations: NPV = negative predictive value, PPV = positive predictive value, URL = upper reference limit

Online Table 3: Diagnostic performance of presentation high-sensitivity cardiac troponin at the recommended sex-specific 99th centile in patients with suspected acute coronary syndrome and chest pain as the presenting symptom (n=33,480).

Age group (years)	True positives	False positives	True negatives	False negatives	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Rule-in (%)
<40	52	64	4229	12	81.3 (71.7-90.1)	98.5 (98.1-98.9)	44.6 (35.7-54.6)	99.7 (99.6-99.9)	2.7
40-44	74	25	2239	23	76.4 (67.8-84.0)	98.9 (98.4-99.3)	74.7 (66.0-83.3)	99.0 (98.5-99.4)	4.2
45-49	151	25	3047	48	75.9 (69.9-81.6)	99.2 (98.9-99.5)	85.7 (80.0-90.6)	98.4 (98.0-98.9)	5.4
50-54	277	64	3618	60	82.2 (77.9-86.2)	98.3 (97.8-98.7)	81.3 (77.3-85.5)	98.4 (97.9-98.7)	8.5
55-59	325	62	3303	77	80.8 (77.3-84.6)	98.2 (97.7-98.6)	84.1 (80.3-87.4)	97.7 (97.2-98.2)	10.3
60-64	314	63	2610	89	77.8 (74.0-81.7)	97.6 (97.1-98.2)	83.3 (79.1-87.0)	96.7 (96.0-97.3)	12.3
65-69	361	82	2396	87	80.5 (76.7-84.1)	96.7 (96.0-97.4)	81.5 (77.8-84.9)	96.5 (95.7-97.1)	15.1
70-74	392	116	2138	90	81.3 (77.6-84.6)	94.9 (94.0-95.8)	77.2 (73.5-80.9)	95.9 (95.2-96.8)	18.6
75-79	395	139	2078	121	76.5 (72.8-80.1)	93.7 (92.7-94.7)	74.0 (70.3-77.8)	94.5 (93.6-95.4)	19.5
80-84	413	159	1525	108	79.3 (76.0-82.8)	90.5 (89.2-91.9)	72.2 (68.4-75.7)	93.4 (92.2-94.6)	25.9
85-89	292	146	831	66	81.5 (77.7-85.5)	85.1 (82.9-87.3)	66.7 (62.3-71.3)	92.6 (91.1-94.4)	32.8

≥90	199	99	363	33	85.7 (81.0-90.1)	78.6 (75.1-82.1)	66.7 (61.7-72.3)	91.6 (89.0-94.1)	42.9
Overall	3245	1044	28377	814	79.9 (78.6-81.1)	96.5 (96.2-96.7)	75.6 (74.4-77.0)	97.2 (97.0-97.4)	12.8

Presented as number or % (95% confidence intervals) as appropriate.
Abbreviations: PPV = positive predictive value, URL = upper reference limit

1

Online Table 4: Diagnostic performance of presentation high-sensitivity cardiac troponin at the recommended sex-specific 99th centile for the diagnosis of type 1 myocardial infarction

Age group (years)	True positives	False positives	True negatives	False negatives	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Rule-in (%)
Sex-specific 99th centile									
<40	45	119	5282	8	85.0 (74.5-94.0)	97.8 (97.4-98.1)	27.4 (20.8-34.1)	99.8 (99.8-99.9)	3.0
40-44	85	53	2724	22	79.3 (71.1-86.3)	98.1 (97.6-98.6)	61.6 (53.1-70.2)	99.2 (98.8-99.5)	4.8
45-49	171	76	3747	47	78.4 (72.5-83.7)	98.0 (97.6-98.4)	69.2 (63.2-74.8)	98.8 (98.4-99.1)	6.1
50-54	284	138	4521	65	81.4 (77.2-85.2)	97.0 (96.5-97.5)	67.3 (62.7-71.8)	98.6 (98.2-98.9)	8.4
55-59	351	169	4262	74	82.6 (78.9-86.1)	96.2 (95.6-96.7)	67.5 (63.6-71.5)	98.3 (97.9-98.7)	10.7
60-64	346	196	3582	83	80.7 (76.7-84.1)	94.8 (94.1-95.5)	63.9 (60.2-67.8)	97.7 (97.2-98.2)	12.9
65-69	391	300	3438	87	81.8 (78.3-85.1)	92.0 (91.1-92.8)	56.6 (52.9-60.3)	97.5 (97.0-98.0)	16.4
70-74	389	413	3199	92	80.9 (77.3-84.2)	88.6 (87.5-89.6)	48.5 (44.9-51.9)	97.2 (96.6-97.8)	19.6
75-79	394	537	3195	104	79.1 (75.3-82.8)	85.6 (84.5-86.7)	42.3 (39.2-45.7)	96.8 (96.2-97.4)	22.0
80-84	399	648	2582	85	82.5 (79.2-85.7)	80.0 (78.5-81.3)	38.2 (35.3-41.1)	96.8 (96.1-97.5)	28.2
85-89	268	550	1503	55	83.0 (78.7-86.9)	73.3 (71.2-75.1)	32.9 (29.6-35.9)	96.5 (95.5-97.3)	34.4

≥90	193	422	715	26	88.2 (83.8-92.3)	62.9 (60.3-65.7)	31.5 (27.8-35.3)	96.5 (95.1-97.8)	45.4
Overall	3316	3621	38750	748	81.6 (80.3-82.8)	91.5 (91.2-91.7)	47.8 (46.6-49.0)	98.1 (98.0-98.2)	14.9
Age-adjusted thresholds									
<40	45	119	5282	8	85.0 (74.5-94.0)	97.8 (97.4-98.1)	27.4 (20.8-34.1)	99.8 (99.8-99.9)	3.0
40-44	85	53	2724	22	79.3 (71.1-86.3)	98.1 (97.6-98.6)	61.6 (53.1-70.2)	99.2 (98.8-99.5)	4.8
45-49	171	76	3747	47	78.4 (72.5-83.7)	98.0 (97.6-98.4)	69.2 (63.2-74.8)	98.8 (98.4-99.1)	6.1
50-54	284	138	4521	65	81.4 (77.2-85.2)	97.0 (96.5-97.5)	67.3 (62.7-71.8)	98.6 (98.2-98.9)	8.4
55-59	351	169	4262	74	82.6 (78.9-86.1)	96.2 (95.6-96.7)	67.5 (63.6-71.5)	98.3 (97.9-98.7)	10.7
60-64	321	184	3594	108	74.9 (70.7-79.0)	95.1 (94.4-95.8)	63.6 (59.7-67.7)	97.1 (96.5-97.6)	12.0
65-69	373	275	3463	105	78.0 (74.2-81.6)	92.6 (91.8-93.4)	57.5 (53.9-61.5)	97.1 (96.5-97.6)	15.4
70-74	275	227	3385	206	57.2 (52.6-61.7)	93.7 (92.9-94.5)	54.8 (50.6-58.9)	94.3 (93.5-95.1)	12.3
75-79	284	298	3434	214	57.0 (52.4-61.4)	92.0 (91.1-92.9)	48.8 (44.8-52.8)	94.1 (93.4-94.9)	13.8
80-84	286	354	2876	198	59.1 (54.9-63.4)	89.0 (87.9-90.1)	44.7 (40.6-48.6)	93.6 (92.7-94.4)	17.2
85-89	181	273	1780	142	56.1 (50.8-61.4)	86.8 (85.3-88.2)	40.0 (35.7-44.8)	92.6 (91.4-93.7)	19.1

≥90	137	217	920	82	62.5 (56.4-68.5)	81.0 (78.7-83.2)	38.8 (33.8-43.8)	91.8 (90.1-93.4)	26.1
Overall	2793	2383	39988	1271	68.7 (67.3-70.1)	94.4 (94.2-94.6)	53.9 (52.6-55.4)	96.9 (96.8-97.1)	11.1
Universal threshold >99th centile									
<40	34	71	5330	19	64.1 (51.2-76.7)	98.7 (98.4-99.0)	32.4 (23.3-41.5)	99.6 (99.5-99.8)	1.9
40-44	62	33	2744	45	57.9 (48.5-66.7)	98.8 (98.4-99.2)	65.3 (55.6-75.0)	98.4 (97.9-98.9)	3.3
45-49	137	46	3777	81	62.8 (56.6-68.7)	98.8 (98.5-99.1)	74.8 (68.4-80.8)	97.9 (97.5-98.3)	4.5
50-54	211	70	4589	138	60.4 (55.0-65.7)	98.5 (98.1-98.8)	75.0 (69.9-79.9)	97.1 (96.6-97.5)	5.6
55-59	264	77	4354	161	62.0 (57.4-66.8)	98.3 (97.9-98.6)	77.4 (73.0-81.6)	96.4 (95.9-97.0)	7.0
60-64	248	106	3672	181	57.8 (53.3-62.6)	97.2 (96.6-97.7)	70.1 (65.4-74.7)	95.3 (94.6-95.9)	8.4
65-69	265	159	3579	213	55.4 (51.1-60.0)	95.7 (95.1-96.4)	62.5 (57.8-67.0)	94.4 (93.6-95.1)	10.1
70-74	270	210	3402	211	56.1 (51.7-60.8)	94.2 (93.4-94.9)	56.2 (51.7-60.4)	94.2 (93.4-94.9)	11.7
75-79	262	242	3490	236	52.6 (48.2-57.1)	93.5 (92.7-94.3)	52.1 (47.6-56.6)	93.7 (92.9-94.4)	11.9
80-84	275	301	2929	209	56.8 (52.4-61.1)	90.7 (89.7-91.7)	47.8 (43.8-51.7)	93.3 (92.4-94.2)	15.5
85-89	159	230	1823	164	49.2 (43.9-54.6)	88.8 (87.6-90.2)	41.0 (36.2-45.9)	91.7 (90.5-92.9)	16.4

≥90	121	182	955	98	55.2 (48.6-61.4)	84.0 (81.8-86.2)	40.0 (34.6-45.3)	90.7 (88.8-92.4)	22.3
Overall	2308	1727	40644	1756	56.8 (55.2-58.4)	95.9 (95.7-96.1)	57.2 (55.7-58.8)	95.9 (95.7-96.0)	8.7

Presented as number or % (95% confidence intervals) as appropriate.
Sex-specific 99th centile = 34 ng/L men, 16 ng/L women.
Age-adjusted thresholds = age <60: >32ng/L men, >16ng/L women; age 60-69: > 42ng/L men, >17ng/L women; age ≥70: 86ng/L men, 39g/L women)
Uniform rule-in threshold >99th centile = >64 ng/L
Abbreviations: NPV = negative predictive value, PPV = positive predictive value, URL = upper reference limit

Online Table 5: Timing of serial samples by age group (n=20,881)

Age (years)	**<50 N=3,962**	**50-75 N=10,826**	**≥ 75 N=6,093**	**Overall N=20,881**
Time from presentation troponin to repeat sample (hrs)				
<3 hrs	778 (20%)	1,511 (14%)	554 (8.9)	2,833 (14%)
3-6 hrs	1,037 (26%)	2,208 (20%)	863 (14%)	4,108 (20%)
6-9 hrs	816 (21%)	2,585 (24%)	1,664 (27%)	5,065 (24%)
9-12 hrs	778 (20%)	2,674 (25%)	1,665 (27%)	5,117 (25%)
>12 hrs	553 (15%)	1,848 (17%)	1,357 (22%)	3,758 (18%)
Presented as number (%)				

Online Table 6: Diagnosis between discordant threshold groups. a) sex-specific 99th centile and age-adjusted; b)age-adjusted threshold and 64ng/L ; c) sex-specific 99th centile and 64ng/L

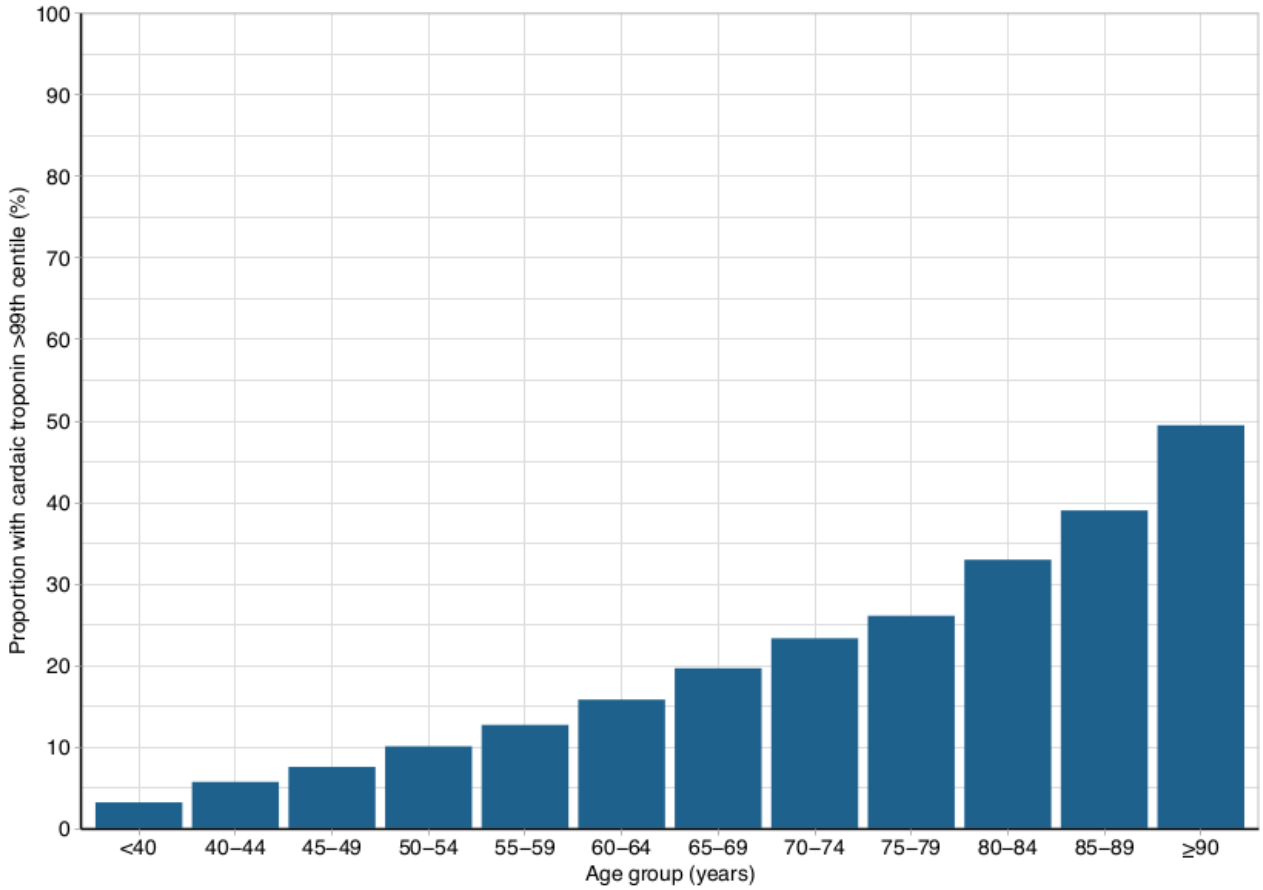
a) Patients with presentation troponin samples between the sex-specific 99th centile and age-adjusted threshold			
Age group	**<50 (n=0)**	**50-75 (n=380)**	**>75 (n=1,381)**
Myocardial Infarction	n/a	210 (55%)	555 (40%)
Type 1	n/a	157 (41%)	366 (27%)
Type 2	n/a	53 (14%)	189 (14%)
Type 4 b/c	n/a	1 (0.3%)	3 (0.2%)
Acute myocardial injury	n/a	88 (23%)	454 (33%)
Chronic myocardial Injury	n/a	81 (21%)	369 (27%)

b) Patients with presentation troponin samples between the age-adjusted threshold and 64ng/L			
Age group	**<50 (n=166)**	**50-75 (n=756)**	**>75 (n=387)**
Myocardial Infarction	88 (53%)	469 (62%)	167 (43%)
Type 1	68 (41%)	364 (48%)	100 (26%)
Type 2	20 (12%)	105 (14%)	67 (17%)
Type 4 b/c	0 (0%)	5 (0.7%)	1 (0.3%)
Acute myocardial injury	30 (18%)	139 (18%)	116 (30%)
Chronic myocardial Injury	48 (29%)	143 (19%)	103 (27%)

c) Patients with presentation troponin samples between the sex-specific 99th centile and 64ng/L			
Age group	**<50 (n=166)**	**50-75 (n=1,097**	**>75 (n=1,639)**
Myocardial Infarction	88 (53%)	653 (60%)	679 (41%)
Type 1	68 (41%)	503 (46%)	437 (27%)
Type 2	20 (12%)	150 (14%)	242 (15%)
Type 4 b/c	0 (0%)	5 (0.5%)	4 (0.2%)
Acute myocardial injury	30 (18%)	221 (20%)	522 (32%)
Chronic myocardial Injury	48 (29%)	218 (20%)	434 (26%)

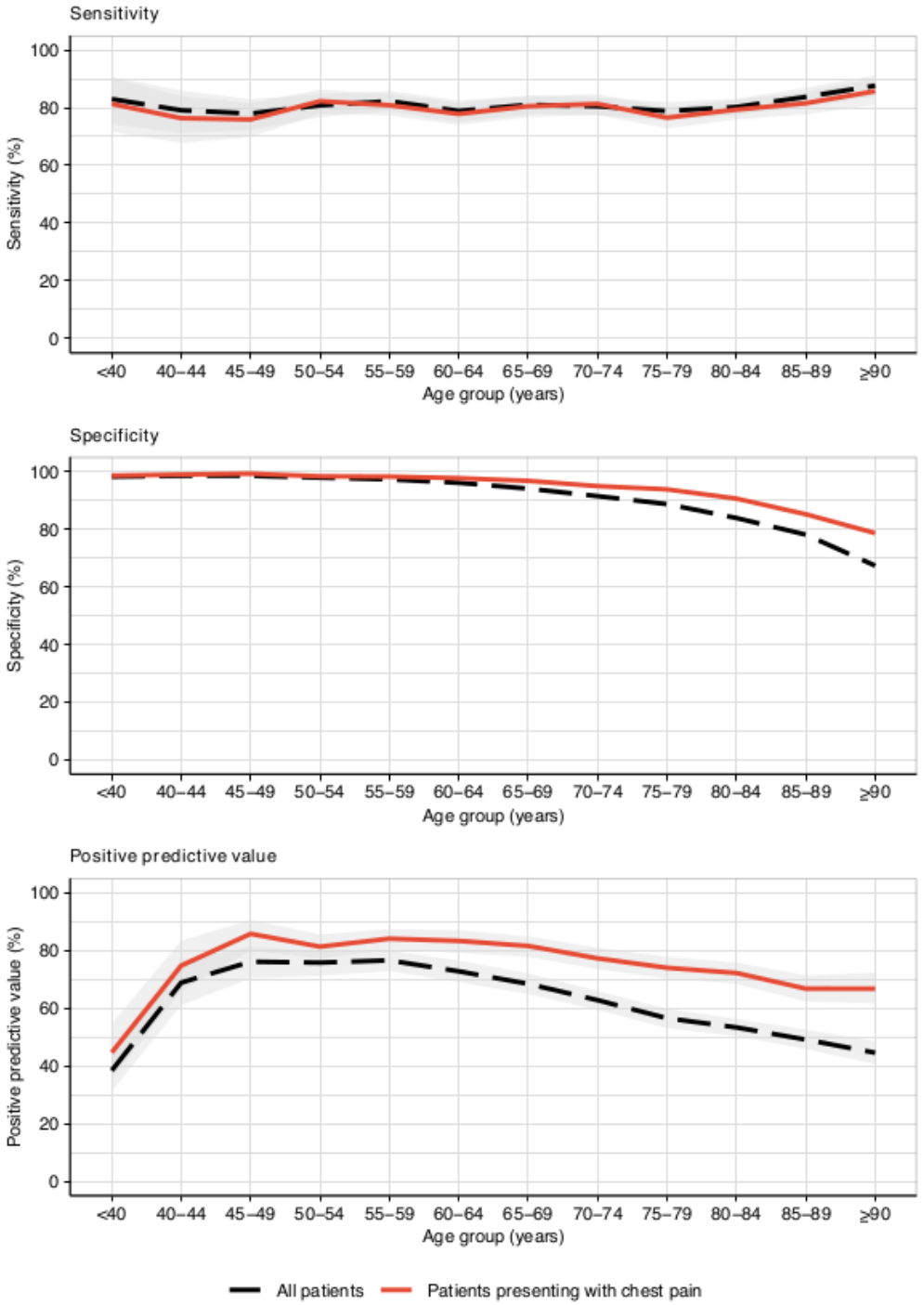
Online Figure 1: Cardiac troponin >99th centile upper reference limit by age group in whole population

Bar plot showing the proportion of patients with at least one cardiac troponin >99th centile upper reference limit by age group for the whole study population.



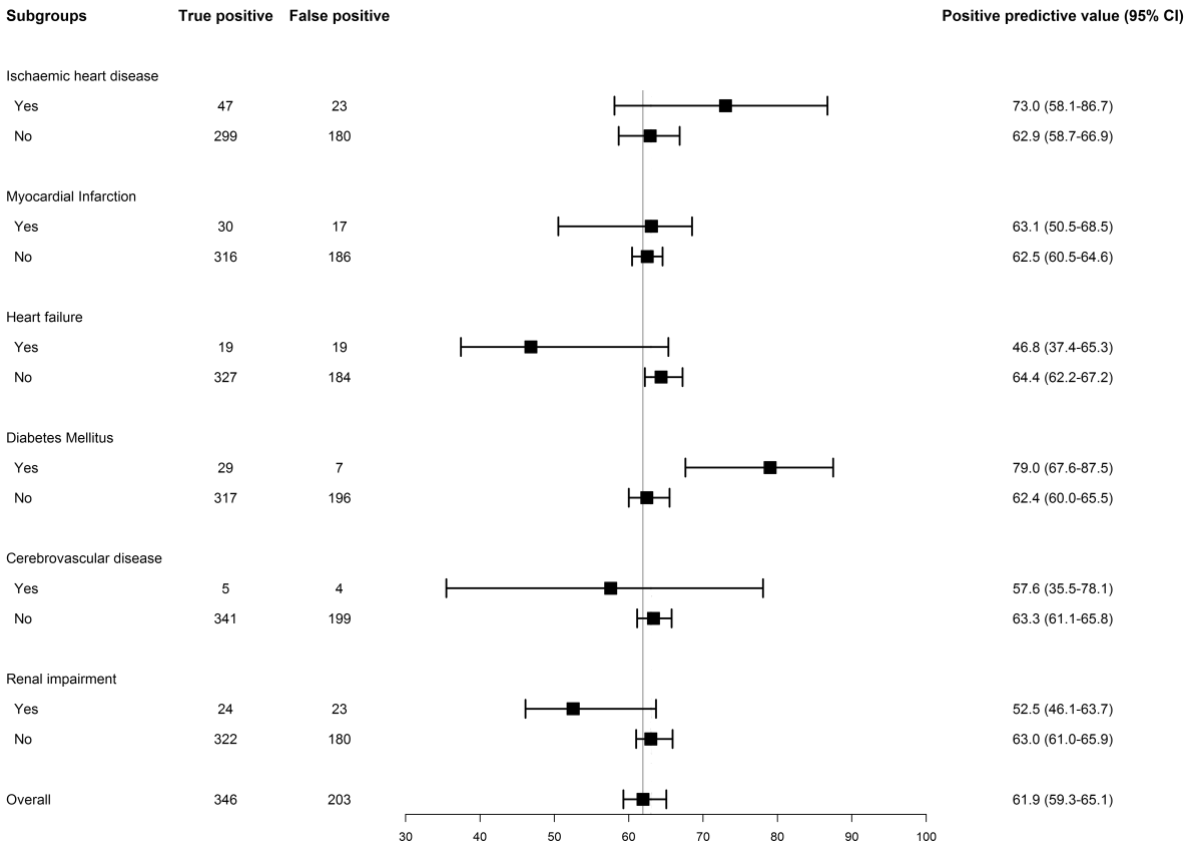
Online Figure 2: Diagnostic accuracy of the 99th centile at presentation in patients with chest pain

Line plot with error bars representing 95% confidence interval. The sensitivity, specificity and positive predictive value (PPV) of the 99th centile across age groups restricted to patients presenting with chest pain. (Online Table 3).



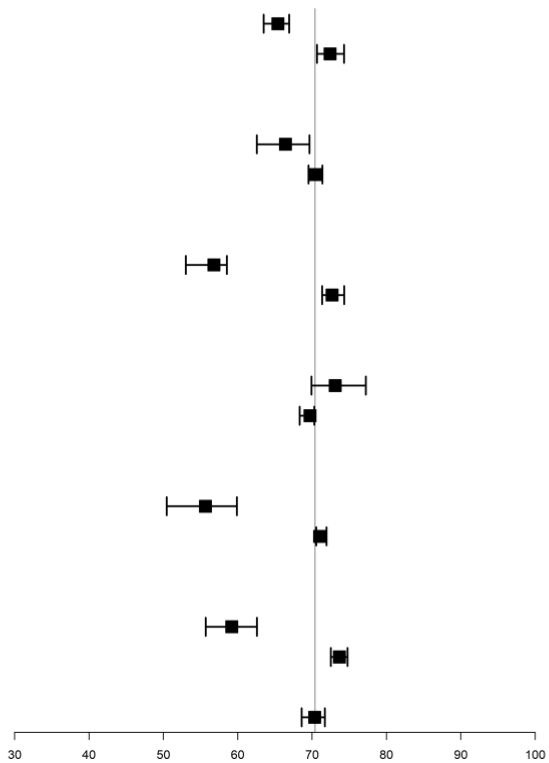
Online Figure 3: Three panel forest plot displaying positive predictive value of presentation high-sensitivity cardiac troponin I with a sex-specific 99th centile diagnostic threshold stratified by age groups

a) Age <50 years

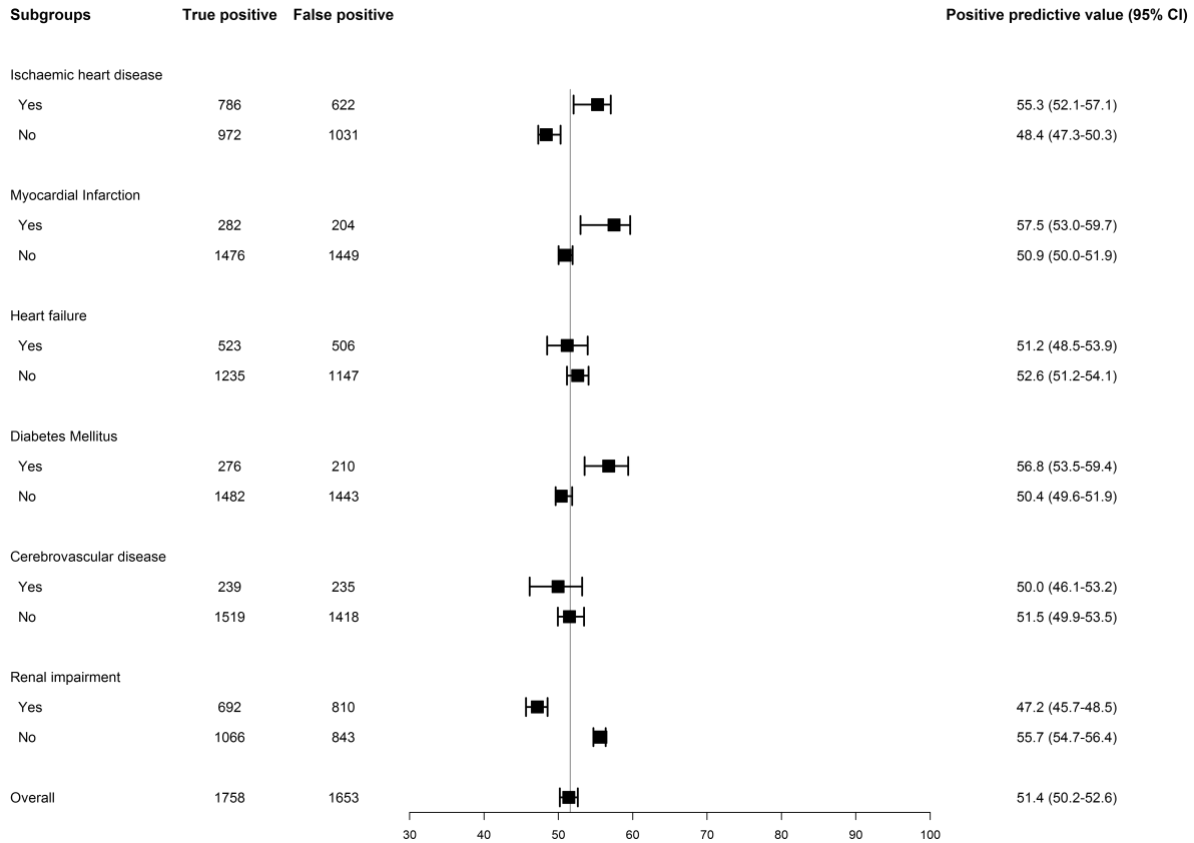


b) Age 50-74 years

Subgroups	True positive	False positive	Positive predictive value (95% CI)
Ischaemic heart disease			
Yes	577	310	65.4 (63.5-66.9)
No	1511	579	72.4 (70.7-74.3)
Myocardial Infarction			
Yes	265	137	66.4 (62.6-69.7)
No	1823	752	70.5 (69.5-71.4)
Heart failure			
Yes	281	204	56.8 (53.0-58.5)
No	1807	685	72.7 (71.4-74.3)
Diabetes Mellitus			
Yes	358	129	73.1 (69.9-77.2)
No	1730	760	69.7 (68.3-70.3)
Cerebrovascular disease			
Yes	124	94	55.7 (50.5-59.9)
No	1964	795	71.0 (70.6-71.9)
Renal impairment			
Yes	448	310	59.2 (55.7-62.6)
No	1640	579	73.7 (72.5-74.8)
Overall	2088	889	70.4 (68.6-71.7)



c) Age ≥75 years



SUPPLEMENTARY APPENDIX B

Methodology

Adjudication according to the Fourth Universal Definition of Myocardial Infarction

All patients with high-sensitivity cardiac troponin I (hs-cTnI) concentrations above the sex-specific 99th centile were classified according to the Third Universal Definition of Myocardial Infarction in use at the time of the trial. In this pre-specified secondary analysis, we updated this classification in accordance with the Fourth Universal Definition of Myocardial Infarction. The final diagnosis was adjudicated according to a pre-specified list (cardiac diagnoses: acute aortic dissection, acute heart failure, cardiomyopathy, chronic heart failure, hypertensive heart disease, myopericarditis, non-ST segment elevation myocardial infarction, ST-segment elevation myocardial infarction, recent myocardial infarction, tachyarrhythmia, Takotsubo cardiomyopathy or valvular heart disease; non-cardiac diagnoses: acute kidney injury, chronic kidney disease, chronic obstructive pulmonary disease, gastrointestinal bleed, pulmonary embolism, sepsis, or other). Two physicians independently reviewed all clinical information, blinded to study phase, with discordant diagnoses resolved by a third reviewer. Clinical information included the dates and times of presentation and final discharge, the initial emergency department assessment and final discharge letter as documented in the electronic care record, with summaries of all investigations undertaken during the index presentation including the electrocardiogram. The adjudication panel had access to raw clinical information including haemoglobin, creatinine and high-sensitivity cardiac troponin I concentrations, and the reports from invasive coronary angiography. Type 1 myocardial infarction was defined as myocardial necrosis (any hs-cTnI concentration above the 99th centile with a rise and/or fall in hs-cTnI concentration where serial testing was performed) in the context of a presentation with suspected acute coronary syndrome with symptoms or signs of myocardial ischemia on

the electrocardiogram. Patients with symptoms or signs of myocardial ischemia and evidence of increased oxygen demand or decreased supply (for example, tachyarrhythmia, hypotension, or anaemia) secondary to an alternative pathology and myocardial necrosis were defined as type 2 myocardial infarction. The classification of type 2 myocardial infarction also includes patients with coronary vasospasm, embolism or spontaneous dissection without evidence of atherothrombosis related to coronary artery disease. Type 4a myocardial infarction was defined in patients with symptoms or signs of myocardial ischemia following percutaneous coronary intervention where hs-cTnI concentrations were 5-fold greater than the 99th centile, or increased further if elevated prior to the procedure. Type 4b myocardial infarction was defined where myocardial ischemia and myocardial necrosis were associated with stent thrombosis documented at angiography. Myocardial injury was defined if hs-cTnI concentrations were above the 99th centile in the absence of any clinical features of myocardial ischemia. Myocardial ischaemia was defined as All non-ischemic myocardial injury was classified as acute, unless a change of <20% was observed on serial testing or the final adjudicated diagnosis was chronic heart failure or chronic renal failure, where the classification was chronic myocardial injury.

Transparency and openness

The High-Sensitivity Troponin in the Evaluation of Patients with Suspected Acute Coronary Syndrome (High-STEACS) trial makes use of multiple routine electronic health care data sources that are linked, deidentified, and held in our national safe haven, which is accessible by approved individuals who have undertaken the necessary governance training. Summary data and the analysis code can be made available upon request from the corresponding author.

High-STEACS Trial Investigators

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Trial managers: Dr Fiona E Strachan and Mr Christopher Tuck.

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Trial steering committee: Prof Ian Ford (chair, independent), Prof Nicholas L Mills, Prof David E Newby, Prof Alasdair Gray, Prof Keith AA Fox, Prof Colin Berry, Dr Simon Walker, Prof Paul O Collinson, Prof Fred S Apple, Mr Alan Reid, Dr Anne Cruikshank, Dr Iain Findlay, Dr Shannon Amoils (independent), Dr David A McAllister, Dr Donogh Maguire, Ms Jennifer Stevens (independent), Prof John Norrie (independent), and Prof Christopher Weir.

Adjudication panel: Dr Anoop SV Shah, Dr Atul Anand, Dr Andrew R Chapman, Dr Kuan Ken Lee, Dr Jack PM Andrews, Dr Philip D Adamson, Dr Alastair Moss, Dr Mohamed S Anwar, Dr John Hung, Prof Nicholas L Mills.

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