BACKGROUND: Guidelines acknowledge the emerging role of high-sensitivity cardiac troponin (hs-cTnI) for risk stratification and the early rule-out of myocardial infarction, but multiple thresholds have been described. We evaluate the safety and effectiveness of risk stratification thresholds in patients with suspected acute coronary syndrome.

METHODS: Consecutive patients with suspected acute coronary syndrome (n=48,282) were enrolled in a multicenter trial across 10 hospitals in Scotland. In a prespecified secondary and observational analysis, we compared the performance of the limit of detection (<2 ng/L) and an optimized risk stratification threshold (<5 ng/L) using the Abbott high-sensitivity troponin I assay. Patients with myocardial injury at presentation, with ≤2 hours of symptoms or with ST-segment elevation myocardial infarction were excluded. The negative predictive value was determined in all patients and in subgroups for a primary outcome of myocardial infarction or cardiac death within 30 days. The secondary outcome was myocardial infarction or cardiac death at 12 months, with risk modeled using logistic regression adjusted for age and sex.

RESULTS: In total, 32,837 consecutive patients (61±17 years, 47% female) were included, of whom 23,260 (71%) and 12,716 (39%) had hs-cTnI concentrations of <5 ng/L and <2 ng/L at presentation. The negative predictive value for the primary outcome was 99.8% (95% CI, 99.7%–99.8%) and 99.9% (95% CI, 99.8%–99.9%) in those with hs-cTnI concentrations of <5 ng/L and <2 ng/L, respectively. At both thresholds, the negative predictive value was consistent in men and women and across all age groups, although the proportion of patients identified as low risk fell with increasing age. Compared with patients with hs-cTnI concentrations of ≥5 ng/L but <99th centile, the risk of myocardial infarction or cardiac death at 12 months was 77% lower in those <5 ng/L (5.3% vs 0.7%; adjusted odds ratio, 0.23 [95% CI, 0.19–0.28]) and 80% lower in those <2 ng/L (5.3% vs 0.3%; adjusted odds ratio, 0.20 [95% CI, 0.14–0.29]).

CONCLUSIONS: Use of risk stratification thresholds for hs-cTnI identify patients with suspected acute coronary syndrome and at least 2 hours of symptoms as low risk at presentation irrespective of age and sex.


© 2019 The Authors. Circulation is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited.

Hana Bularga, MD
Kuan Ken Lee, MD
Stacey Stewart, MSc
Amy V. Ferry, MSc
Andrew R. Chapman, MD, PhD
Lucy Marshall, MSc
Fiona E. Strachan, PhD
Anne Cruickshank, MD
Donagh Maguire, MD, PhD
Colin Berry, MD, PhD
Iain Findlay, MD
Aanoo S.V. Shah, MD, PhD
David E. Newby, MD, PhD
Nicholas L. Mills, MD, PhD*
Atul Anand, MD, PhD*
On behalf of the High-STEACS Investigators†
Clinical Perspective
What Is New?
• In 32,837 consecutive patients with suspected acute coronary syndrome and at least 2 hours of symptoms, we evaluated the performance of 2 risk stratification thresholds for a high-sensitivity cardiac troponin I assay.
• An optimized risk stratification threshold of <5 ng/L identified twice as many patients at presentation as low risk compared with the limit of detection (<2 ng/L), with an equivalent negative predictive value for myocardial infarction or cardiac death at 30 days.
• Compared with the diagnostic threshold, patients with cardiac troponin I concentrations <2 ng/L or <5 ng/L were 80% and 77% lower risk of subsequent cardiac events at 12 months, respectively.

What Are the Clinical Implications?
• The use of separate risk stratification and diagnostic thresholds for high-sensitivity cardiac troponin will improve the safety of our assessment of cardiovascular risk in patients with suspected acute coronary syndrome.
• Incorporating a risk stratification threshold into the early evaluation of these patients will enable the majority of patients to avoid unnecessary hospital admission with major benefits for patients and healthcare providers.

The way in which cardiac troponin testing is used in clinical practice is evolving rapidly in parallel with major improvements in assay precision and sensitivity.1,2 High-sensitivity cardiac troponin assays are essential for the diagnosis of acute myocardial infarction but are increasingly also used in the assessment of cardiovascular risk to identify patients in the emergency department who are low risk and could be directly discharged.3,9 Given that fewer than 10% of patients with suspected acute coronary syndrome have myocardial infarction,10 this application of high-sensitivity cardiac troponin testing has major potential to reduce unnecessary hospital admissions with benefits for patients and healthcare providers.

Although the universal definition of myocardial infarction recommends the use of sex-specific 99th centile or upper reference limits from a normal reference population as the diagnostic threshold for myocardial infarction,3 there is less consensus on the optimal troponin threshold for the evaluation of cardiovascular risk.4,5 The ideal risk stratification threshold would permit the greatest number of patients without myocardial infarction to be classified as low risk without compromising safety. The limit of detection has been proposed,11–13 but assay performance at this level is variable, potentially reducing the consistency and effectiveness of this approach.14–17 We previously defined the optimal risk stratification threshold as the highest troponin concentration that gave a negative predictive value for myocardial infarction or cardiac death at 30 days of at least 99.5%6 to maximize the number of patients identified as low risk while maintaining safety. This was achieved using a high-sensitivity cardiac troponin I assay at a concentration <5 ng/L, which identified two-thirds of patients as low risk at presentation and misclassified fewer than 1 in 200 patients. The only subgroup that did not meet this target for safety were those who presented within 2 hours of symptoms onset, and guidelines now clearly state that serial testing is required in these early presenters.3,7

The use of risk stratification thresholds in diagnostic pathways has been evaluated in retrospective analyses of cohort studies8,9 but have not been prospectively validated.4,18 Many approaches have been proposed, often in small cohorts of selected patients attending a single center, with a limited number of patients in high-risk subgroups. As such, there remains uncertainty as to the performance of these thresholds in practice, where patients are often older and more likely to have comorbidities. Our aim was to compare the diagnostic performance of an optimized risk stratification threshold with the limit of detection, in the patient population in whom risk stratification thresholds have been advocated by international guidelines.3 In a prespecified secondary and observational analysis of a multicenter trial of consecutive patients with suspected acute coronary syndrome, we evaluate diagnostic performance in patients presenting with at least 2 hours of symptoms by age and in subgroups to provide reliable estimates for clinical practice. In a substudy of the trial population, we explore the generalizability of this approach by evaluating performance of these risk stratification thresholds across different high-sensitivity assays.

METHODS

Transparency and Openness Promotion
The 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.

Study Population
High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome) was 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
the ARCHITECT ng/L. For the purpose of this analysis, all patients with an
with prior studies we defined this as any concentration <2
ng/L at presentation were measured to evaluate effectiveness
of these risk stratification thresholds. Secondary outcomes of
cardiac catheterization, coronary intervention and new medi-
tical therapy were collected from local and national databases
as previously described.19

Adjudication of the Diagnosis of
Myocardial Infarction
Clinical information was collected from a standardized elec-
tronic patient record (TrakCare; InterSystems Corporation,
Cambridge, MA) linked to local and national datasets. Electrocardiographic data including algorithmic interpretation
was available by electronic capture in a subgroup of patients
(MUSE, GE Healthcare). All unique interpretation codes gen-
erated by this system (n=4291) were reviewed by a consensus
panel who selected codes consistent with possible ischemia
(n=180). Example electrocardiograms featuring these codes
were then reviewed independently by at least 2 physicians
to determine reliability for clinically significant myocardial
ischemia. The final list of 119 codes (see Appendix in the
online-only Data Supplement) were then applied to the study
population with electronic electrocardiograms to determine
whether myocardial ischemia was present for each patient.
Two physicians from our adjudication panel indepen-
dently reviewed all clinical information to classify patients
with any high-sensitivity cardiac troponin measurement
>99th centile on serial testing during the index presenta-
tion in accordance with the third Universal Definition of
Myocardial Infarction.28 Myocardial infarction following
discharge and all death outcomes were also independently
adjudicated by 2 physicians blinded to study phase and any
disagreements were resolved by a third physician.

Study Outcomes
The primary safety outcome was type 1 or 4b myocardial
infarction during the index presentation, or subsequent type
1 or 4b myocardial infarction or cardiac death within 30
days of the index presentation. The secondary safety out-
come was subsequent type 1 or 4b myocardial infarction
or cardiac death at 12 months. Type 2 myocardial infarction
was not included in the composite outcome, as by defini-
tion these patients present with alternative, often noncar-
diac conditions that determine whether they require hospital
admission or discharge.

The number and proportion of patients with high-sensi-
tivity cardiac troponin concentrations less than 2 ng/L or 5
ng/L at presentation were measured to evaluate effectiveness
of the risk stratification threshold of 5 ng/L, the lower thresh-
old of <2 ng/L for cardiac troponin I, and <3 ng/L for cardiac
troponin T, as these thresholds are equivalent to the limit of
detection and limit of blank, respectively.

Statistical Analysis
Baseline characteristics are summarized as percentages for
categorical variables, mean (standard deviation) or median
(interquartile range) as appropriate. The negative predictive
value was determined using 2×2 tables to calculate the true
and false negative rates for the primary outcome, comparing
patients with cardiac troponin concentrations at presentation
less than 2 ng/L and less than the risk stratification threshold

Cardiac Troponin Testing
As previously described, cardiac troponin testing was per-
formed at presentation and repeated 6 or 12 hours after the
onset of symptoms at the discretion of the attending clinici-
an in accordance with national and international guidelines
in use during enrollment.19,23,24 In all patients during both
phases of the trial, cardiac troponin was measured using the
ARCHITECT ng/L, high-sensitive troponin I assay (Abbott
Laboratories, Abbott Park, IL). This assay has a limit of detec-
tion of between 1.2 ng/L and 1.9 ng/L,25 and for consistency
with prior studies we defined this as any concentration <2
ng/L.26 For the purpose of this analysis, all patients with an
undetectable troponin concentration were assigned a value
of 1.0 ng/L. The inter-assay coefficient of variation is less
than 10% at 4.7 ng/L and the sex-specific 99th centile diagnostic
thresholds are 16 ng/L for women and 34 ng/L for men.27
High-sensitivity cardiac troponin I concentrations were only
disclosed to clinicians during the implementation phase of the
trial, but given risk stratification thresholds were not used to
guide clinical decisions we pooled data from both phases of
the trial for the purpose of this analysis.

In the substudy, samples were also analyzed using the
Siemens Atellica high-sensitivity cardiac troponin I assay and
Roche Elecsys high-sensitivity cardiac troponin T assays.5,22
For these assays the limit of detection is 1.6 ng/L and 5 ng/L
respectively, and the limit of blank for the cardiac troponin T
assay is 3 ng/L. For all 3 assays, we evaluated performance of
his work at St George’s University Hospitals NHS Foundation
Trust in London. He was the principal investigator in a num-
ber of randomized controlled trials and was involved in
design and conduct of these trials in accordance with the
Declaration of Helsinki. Individual patient consent was not
sought. This approach ensured that consecutive patients presen-
ting with suspected acute coronary syndrome were included
without selection bias. All patients presenting to emergency
departments between June 10, 2013, and March 3, 2016, were
screened by the attending clinician and prospectively included in the trial if cardiac troponin was
requested for suspected acute coronary syndrome.

For this prespecified secondary and observational analysis,
we evaluate the performance of high-sensitivity cardiac tro-
ponin I in patients without evidence of myocardial injury at
presentation (cardiac troponin concentrations below the sex-
specific 99th centile), excluding those patients who presented
early (<2 hours from symptom onset to the initial blood draw),
or those with a ST-segment elevation myocardial infarction.

Substudy Population
To evaluate the generalizability of risk stratification thresh-
olds we used stored samples from a substudy of the trial to
cmpare the performance of different high-sensitivity cardiac
troponin I assays (Abbott ARCHITECT ng/L, and Siemens Atellica,
Siemens Healthineers) and high-sensitivity cardiac troponin
T (Roche Elecsys, Roche Diagnostics). Participants provided
informed consent for additional blood sampling and storage,
as described previously.20–22 The analysis population was
defined in the substudy using the same inclusion and exclu-
sion criteria as for the trial population.

Circulation. 2019;140:1557–1568. DOI: 10.1161/CIRCULATIONAHA.119.042866
November 5, 2019 1559

hospitals in Scotland (URL: https://www.clinicaltrials.gov.
Unique identifier: NCT01852123). The study design has been
described in detail previously19 and was conducted with the
approval of the Scotland Research Ethics Committee in accor-
dance with the Declaration of Helsinki. Individual patient
consent was not sought. This approach ensured that consecutive patients presenting with suspected acute coronary syndrome were included without selection bias. All patients presenting to emergency departments between June 10, 2013, and March 3, 2016, were screened by the attending clinician and prospectively included in the trial if cardiac troponin was requested for suspected acute coronary syndrome.

For this prespecified secondary and observational analysis,
we evaluate the performance of high-sensitivity cardiac tro-
ponin I in patients without evidence of myocardial injury at
presentation (cardiac troponin concentrations below the sex-
specific 99th centile), excluding those patients who presented
early (<2 hours from symptom onset to the initial blood draw),
or those with a ST-segment elevation myocardial infarction.

Substudy Population
To evaluate the generalizability of risk stratification thresh-
olds we used stored samples from a substudy of the trial to
cmpare the performance of different high-sensitivity cardiac
troponin I assays (Abbott ARCHITECT ng/L, and Siemens Atellica,
Siemens Healthineers) and high-sensitivity cardiac troponin
T (Roche Elecsys, Roche Diagnostics). Participants provided
informed consent for additional blood sampling and storage,
as described previously.20–22 The analysis population was
defined in the substudy using the same inclusion and exclu-
sion criteria as for the trial population.

Cardiac Troponin Testing
As previously described, cardiac troponin testing was per-
formed at presentation and repeated 6 or 12 hours after the
onset of symptoms at the discretion of the attending clinici-
an in accordance with national and international guidelines
in use during enrollment.19,23,24 In all patients during both
phases of the trial, cardiac troponin was measured using the
ARCHITECT ng/L, high-sensitive troponin I assay (Abbott
Laboratories, Abbott Park, IL). This assay has a limit of detec-
tion of between 1.2 ng/L and 1.9 ng/L,25 and for consistency
with prior studies we defined this as any concentration <2
ng/L.26 For the purpose of this analysis, all patients with an
undetectable troponin concentration were assigned a value
of 1.0 ng/L. The inter-assay coefficient of variation is less than
10% at 4.7 ng/L and the sex-specific 99th centile diagnostic
thresholds are 16 ng/L for women and 34 ng/L for men.27
High-sensitivity cardiac troponin I concentrations were only
disclosed to clinicians during the implementation phase of the
trial, but given risk stratification thresholds were not used to
guide clinical decisions we pooled data from both phases of
the trial for the purpose of this analysis.

In the substudy, samples were also analyzed using the
Siemens Atellica high-sensitivity cardiac troponin I assay and
Roche Elecsys high-sensitivity cardiac troponin T assays.5,22
For these assays the limit of detection is 1.6 ng/L and 5 ng/L
respectively, and the limit of blank for the cardiac troponin T
assay is 3 ng/L. For all 3 assays, we evaluated performance of
of 5 ng/L. As we expected the negative predictive value to approach 100%, we estimated the proportion by sampling from a binomial likelihood distribution with a Jeffreys prior, as such approaches have good coverage for proportions that approach 0 or 1 (B distribution shape parameters both 0.5). 23 Analysis by stratification was used to compare performance in different subgroups. For age, the negative predictive value was calculated for each integer age value between 20 and 90 years, and plotted with a line of best fit and 95% CI. The negative predictive value was also determined separately in those with and without prior history of ischemic heart disease, diabetes mellitus, stroke, heart failure and renal impairment (estimated glomerular filtration rate <60 mL/min/1.73 m² determined by Modified Diet in Renal Disease equation) or myocardial ischemia on the electrocardiogram at presentation.

For the secondary outcome, the rates of myocardial infarction or cardiac death were compared in patients with cardiac troponin concentration at presentation less than 2 ng/L, less than 5 ng/L, and 5 ng/L to the sex-specific 99th centile. In a post-hoc analysis, we also compared the rates of myocardial infarction or cardiac death in patients with cardiac troponin concentrations below these risk stratification thresholds. Logistic regression modelling for the primary and secondary outcomes was performed using patients with cardiac troponin concentrations between 5 ng/L and the sex-specific 99th centile as a reference group. Odds ratios were adjusted for differences in age and sex. All analyses were performed using R (version 3.5.1).

RESULTS

The trial enrolled 48,282 consecutive patients (61±17 years, 47% women) across 10 hospitals in Scotland. A total of 32,837 patients (68%) remained in the analysis population (58±1 years, 47% women) after excluding those with cardiac troponin concentrations >99th centile at presentation (n=7795), and those presenting ≤2 hours of symptom onset (n=6469) or with ST-segment elevation myocardial infarction (n=925), and where the event or cardiac death within 30 days of presentation. This composite measure included 475 patients with an index myocardial infarction, and 78 and 49 patients with a subsequent myocardial infarction or cardiac death within 30 days, respectively. The majority of composite events occurred in those with cardiac troponin concentrations between 5 ng/L and the 99th centile where the event rate was 4.8% (462 of 9577) at 30 days. There were 55 events in 23,260 patients (0.2%) with cardiac troponin concentrations less than 5 ng/L, and 15 events in the subgroup of 12,716 patients (0.1%) less than 2 ng/L. Of these composite events, cardiac death within 30 days occurred in 45 of 9577 patients with troponin concentrations between 5 ng/L and the 99th centile (0.5%), 4 of 23,260 patients less than 5 ng/L (0.02%) and 1 patient from 12,716 below 2 ng/L (0.01%, Table 2).

The negative predictive value for the primary outcome at 30 days in patients with cardiac troponin concentrations less than the risk stratification threshold of 5 ng/L at presentation was 99.8% (95% CI, 99.7%–99.8%). The negative predictive value in the subgroup of patients with cardiac troponin concentrations <2 ng/L was 99.9% (95% CI, 99.8%–99.9%). Although the prevalence of the primary outcome varied between sites (range, 0.8%–2.1%), the negative predictive value remained consistent across all sites (Table II in the online-only Data Supplement). In patients presenting within 2 hours of symptom onset (n=6469), the negative predictive value was lower at both thresholds (99.0% [95% CI, 98.7%–99.3%] for those <5 ng/L and 99.6% [95% CI, 99.3%–99.8%] for patients <2 ng/L, Table III in the online-only Data Supplement). Confusion matrices and other diagnostic metrics for the trial and analysis populations are shown in Tables IV and V in the online-only Data Supplement.

Diagnosis Performance of Risk Stratification Thresholds

In the analysis population, 1.6% (517 of 32,837) of patients experienced a primary outcome event of index myocardial infarction, or subsequent myocardial infarction or cardiac death within 30 days of presentation. This composite measure included 475 patients with an index myocardial infarction, and 78 and 49 patients with a subsequent myocardial infarction or cardiac death within 30 days, respectively. The majority of composite events occurred in those with cardiac troponin concentrations between 5 ng/L and the 99th centile where the event rate was 4.8% (462 of 9577) at 30 days. There were 55 events in 23,260 patients (0.2%) with cardiac troponin concentrations less than 5 ng/L, and 15 events in the subgroup of 12,716 patients (0.1%) less than 2 ng/L. Of these composite events, cardiac death within 30 days occurred in 45 of 9577 patients with troponin concentrations between 5 ng/L and the 99th centile (0.5%), 4 of 23,260 patients less than 5 ng/L (0.02%) and 1 patient from 12,716 below 2 ng/L (0.01%, Table 2).

The negative predictive value for the primary outcome at 30 days in patients with cardiac troponin concentrations less than the risk stratification threshold of 5 ng/L at presentation was 99.8% (95% CI, 99.7%–99.8%). The negative predictive value in the subgroup of patients with cardiac troponin concentrations <2 ng/L was 99.9% (95% CI, 99.8%–99.9%). Although the prevalence of the primary outcome varied between sites (range, 0.8%–2.1%), the negative predictive value remained consistent across all sites (Table II in the online-only Data Supplement). In patients presenting within 2 hours of symptom onset (n=6469), the negative predictive value was lower at both thresholds (99.0% [95% CI, 98.7%–99.3%] for those <5 ng/L and 99.6% [95% CI, 99.3%–99.8%] for patients <2 ng/L, Table III in the online-only Data Supplement). Confusion matrices and other diagnostic metrics for the trial and analysis populations are shown in Tables IV and V in the online-only Data Supplement.

Diagnosis Performance of Risk Stratification Thresholds in Subgroups

The proportion of patients with cardiac troponin concentration below 5 ng/L and 2 ng/L thresholds varied markedly by age, but the negative predictive value of these approaches to risk stratification were
identical across all age groups (Figure 1). The lower bounds of the 95% CI was >99.5% for both thresholds even in the oldest patients. In patients >65 years old (n=11,837), the proportion identified as low risk with a high-sensitivity troponin concentration below the 2 ng/L risk stratification threshold was diminished at only 11% (1303 of 11,837), compared with 46% (5463 of 11,837) with cardiac troponin concentrations <5 ng/L.

Central estimates of negative predictive value were below 99.5% for both risk stratification thresholds in patients with a prior history of ischemic heart disease, diabetes mellitus, stroke, heart failure and renal impairment, although the upper bound of the 95% CIs crossed the prespecified safety margin of 99.5% (Figure 2). In those with available electronic electrocardiograms and evidence of myocardial ischemia, the negative predictive value was 99.6% (95% CI, 99.3%–99.9%) in those with cardiac troponin concentrations less than 5 ng/L and 99.7% (95% CI, 99.2%–100.0%) in those below 2 ng/L.

The proportion of patients with cardiac troponin concentrations below both thresholds differed widely

---

| Table 1. Baseline Characteristics of Participants, by Presentation hs-cTnI |
|---------------------------------|------------------|------------------|------------------|------------------|------------------|
| Characteristics                | All              | <2 ng/L           | 2 ng/L – 99th centile | <5 ng/L           | 5 ng/L – 99th centile |
| Demographics                   |                  |                  |                  |                  |                  |
| No. of patients                | 32,837           | 12,716           | 20,121           | 23,260           | 9,577            |
| Age, y                         | 58.4 (17.1)      | 47.8 (13.9)      | 65.1 (15.4)      | 53.6 (15.7)      | 70.1 (14.5)      |
| Male sex                       | 17,478 (53)      | 5,620 (44)       | 11,858 (59)      | 11,519 (50)      | 5,959 (62)       |
| Presenting complaint           |                  |                  |                  |                  |                  |
| Chest pain                     | 24,085 (73)      | 9,793 (77)       | 14,292 (71)      | 17,830 (77)      | 6,255 (65)       |
| Dyspnea                        | 1001 (3)         | 169 (1)          | 832 (4)          | 398 (2)          | 603 (6)          |
| Palpitation                    | 825 (3)          | 269 (2)          | 556 (3)          | 540 (2)          | 285 (3)          |
| Syncope                        | 1,162 (4)        | 216 (2)          | 946 (5)          | 574 (3)          | 588 (6)          |
| Other                          | 1,197 (4)        | 306 (2)          | 891 (4)          | 722 (3)          | 475 (5)          |
| Past medical history           |                  |                  |                  |                  |                  |
| Ischemic heart disease         | 7,467 (23)       | 1,309 (10)       | 6,158 (31)       | 3,863 (17)       | 3,604 (38)       |
| Myocardial infarction          | 2,537 (8)        | 432 (3)          | 2,105 (11)       | 1,287 (6)        | 1,250 (13)       |
| Stroke or transient ischemic attack | 1,700 (5)       | 231 (2)          | 1,469 (7)        | 735 (3)          | 965 (10)         |
| Percutaneous coronary intervention | 2,416 (7)       | 461 (4)          | 1,955 (10)       | 1,351 (6)        | 1,065 (11)       |
| Coronary artery bypass grafting | 477 (2)          | 58 (1)           | 419 (2)          | 207 (1)          | 270 (3)          |
| Diabetes mellitus              | 1,867 (6)        | 253 (2)          | 1,614 (8)        | 782 (3)          | 1,085 (11)       |
| Heart failure                  | 1,956 (6)        | 130 (1)          | 1,826 (9)        | 535 (2)          | 1,421 (15)       |
| Medications                    |                  |                  |                  |                  |                  |
| Aspirin                        | 8,277 (25)       | 1,654 (13)       | 6,623 (33)       | 4,619 (20)       | 3,658 (38)       |
| Clopidogrel                    | 2,555 (8)        | 437 (3)          | 2,118 (11)       | 1,307 (6)        | 1,248 (13)       |
| Ticagrelor                     | 225 (1)          | 43 (0.3)         | 182 (1)          | 129 (1)          | 96 (1)           |
| Oral anticoagulant             | 1,951 (6)        | 219 (2)          | 1,732 (9)        | 753 (3)          | 1,198 (13)       |
| ACE inhibitor or ARB           | 9,799 (30)       | 1,969 (16)       | 7,830 (39)       | 5,470 (24)       | 4,329 (45)       |
| ß-blocker                      | 8,398 (26)       | 1,943 (15)       | 6,455 (32)       | 4,863 (21)       | 3,535 (37)       |
| Statin                         | 12,264 (37)      | 2,594 (20)       | 9,670 (48)       | 7,002 (30)       | 5,262 (55)       |
| Loop diuretics                 | 3,420 (10)       | 356 (3)          | 3,064 (15)       | 1,176 (5)        | 2,244 (23)       |
| Laboratory results             |                  |                  |                  |                  |                  |
| Presentation hs-cTnI           | 2.4 [1.0, 5.7]   | 1.0 [1.0, 1.1]   | 4.5 [2.9, 8.7]   | 1.6 [1.0, 2.8]   | 9.0 [6.3, 14.0]  |
| Peak hs-cTnI                   | 2.7 [1.0, 6.0]   | 1.0 [1.0, 1.3]   | 5.0 [3.0, 9.7]   | 1.8 [1.0, 3.0]   | 10.0 [7.0, 15.5] |
| Serial hs-cTnI test            | 13,554 (41)      | 4,552 (36)       | 9,002 (45)       | 8,954 (39)       | 4,600 (48)       |
| GFR, mL/min/1.73 m²            | 88 (24)          | 96 (19)          | 82 (25)          | 92 (21)          | 76 (27)          |

Data are number of patients (%), mean (SD), or median [IQR]. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; and hs-cTnI, high-sensitivity cardiac troponin I.
in these subgroups, but in every subgroup with prior cardiovascular disease, at least twice as many patients were identified as low risk using a risk stratification threshold of 5 ng/L compared with 2 ng/L (Figure 3). Invasive cardiac procedures and changes to preventative cardiac medications were rarely undertaken or initiated following emergency department assessment (Table VI in the online-only Data Supplement). Cardiac catheterization occurred in fewer than 1 in 100 patients below either threshold and new antiplatelet therapy was commenced in fewer than 1 in 25.

### Secondary Safety Outcomes at 12 months

Subsequent myocardial infarction or cardiac death following discharge from hospital occurred in 2.0% (667 of 32 837) of patients at 12 months. Event rates were similar between patients with cardiac troponin concentrations at presentation below 2 ng/L and 5 ng/L (35 of 12 716 [0.3%] vs 161 of 23 260 [0.7%], respectively), and were lower than those with cardiac troponin concentrations of 5 ng/L to the 99th centile at presentation (506 of 9577 [5.3%]; Table 2 and Figure 4). Lower cardiac troponin concentrations were associated with fewer subsequent events at 12 months; patients with concentrations <2 ng/L had a lower event rate than those with concentrations between these thresholds (126 of 10 544 [1.2%], Figure II in the online-only Data Supplement). When accounting for substantial differences in age and sex between these groups, the risk of subsequent myocardial infarction or cardiac death at 12 months was 80% lower in those below 2 ng/L (adjusted odds ratio, 0.20 [95% CI, 0.14–0.29]), and 77% lower in those less than 5 ng/L (adjusted odds ratio, 0.23 [95% CI, 0.19–0.28]), compared with patients with troponin concentrations between 5 ng/L and the 99th centile. At both 30 days and 1 year, adjusted risk estimates of myocardial infarction and cardiac death were similar for those with cardiac troponin concentrations <2 ng/L and <5 ng/L, and for those patients with concentrations between these thresholds (adjusted odds ratio, 0.30 [95% CI, 0.24–0.36], Table VII in the online-only Data Supplement).

### Diagnostic Performance of Risk Stratification Thresholds for Different High-Sensitivity Assays

In our substudy, 1185 patients presenting more than 2 hours from symptom onset were evaluated using the Siemens Atellica cardiac troponin I assay, and 1042 patients evaluated using the Roche Elecsys troponin T assay (Table VIII in the online-only Data Supplement). Using the Siemens assay, 55% and 15% of patients had a cardiac troponin I concentration <5 ng/L and <2 ng/L at presentation with a negative predictive value of 99.3% (95% CI, 98.5%–99.8%) and 99.2% (97.4%–99.9%), respectively. For the cardiac troponin T assay, 46% and 24% of patients were <5 ng/L and <3 ng/L at presentation, with a negative predictive value of 99.1% (95% CI, 98.0%–99.7%) and 99.4% (95% CI, 98.2%–99.9%) respectively (Table IX in the online-only Data Supplement).

### DISCUSSION

In this prespecified secondary analysis from the HighSTEACS trial, we have evaluated the use of risk stratification thresholds for high-sensitivity cardiac troponin I in 32 837 consecutive patients with suspected acute coronary syndrome. We report several important findings for clinicians managing patients with this common presentation. First, in patients with at least 2 hours of symptoms prior to testing, a cardiac troponin concent-
tration below 5 ng/L identifies a group at very low risk of immediate or future cardiac events, with a negative predictive value greater than 99.5%. Second, this performance is maintained regardless of age, sex, and the presence of myocardial ischemia on the electrocardiogram. Third, using a risk stratification threshold of 5 ng/L identifies twice as many patients at low risk at presentation when compared with the limit of detection. Fourth, the negative predictive value of applying a risk stratification threshold of 5 ng/L is consistent across high-sensitivity cardiac troponin I and T assays. Fifth, patients with cardiac troponin concentrations above the risk stratification threshold of 5 ng/L are consistent across high-sensitivity cardiac troponin I and T assays. Fifth, patients with cardiac troponin concentrations above the risk stratification threshold of 5 ng/L, but below the diagnostic threshold, represent a high-risk group with a 7-fold greater risk of subsequent myocardial infarction or cardiac death over 12 months compared with those below either risk stratification threshold. Taken together, we suggest the use of separate risk stratification and diagnostic thresholds for cardiac troponin, will substantially improve our ability to identify patients at risk compared with the binary approach used in practice today.

High-STEACS is the largest clinical trial to evaluate consecutive patients with suspected acute coronary syndrome reported to date.19 This analysis of 32,837 patients is larger than the combined number of patients from 30 observational cohort studies, who were included in 2 recent major retrospective meta-analyses of risk stratification using high-sensitivity cardiac troponin I and T.8,9 The negative predictive value of the risk stratification threshold of 5 ng/L for myocardial infarction or cardiac death at 30 days was found to be 99.5% (95% CI, 99.3%–99.6%) across 19 of these cohorts using cardiac troponin I,8 which is similar to the 99.8% (95% CI, 99.7%–99.8%) observed here, and was 99.3% (95% CI, 97.3%–99.8%) in 11 cohorts using cardiac troponin T.9 Taken together these findings suggest that a single risk stratification threshold could be safely applied for both high-sensitivity cardiac troponin I and T assays.

The American Heart Association/American College of Cardiology and European Society of Cardiology guidelines for the management of acute coronary syndromes recommend the diagnostic threshold for myocardial infarction at the 99th centile as an appropriate limit for exclusion in patients except in early presenters.3,30 Alternative approaches have been suggested, such as those described in the recent COMPASS-MI study, which uses a range of thresholds in combination with serial testing and change between two cardiac troponin measures to estimate the negative and positive predictive value for...
individual patients. As demonstrated in our prior work, the gain in effectiveness from increasing the threshold above 5 ng/L is small, and the negative predictive value for our safety outcome is lower than 99.5% at higher concentrations. Similarly, the 0/1 hour pathway recommended by the European Society of Cardiology uses multiple thresholds, but not the 99th centile to rule in and rule out myocardial infarction, at presentation or at 1 hour.

These varied approaches acknowledge that patients without myocardial injury at presentation are at risk of cardiovascular events; in the present study more than 1 in 20 patients with cardiac troponin measures between the risk stratification and diagnostic thresholds experienced a subsequent myocardial infarction or cardiac death within 12 months of presentation. Troponin is a continuous marker of cardiovascular risk and low concentrations can be used to estimate long-term cardiovascular risk. This can be informative for clinical decision making, but results need to be interpreted in the context of the individual patient, and these thresholds have not been optimized for this purpose. However, what is clear is that those with intermediate troponin concentrations are at higher risk of future events, and the use of the 99th centile alone does not appear to be an appropriate threshold to risk stratify patients with suspected acute coronary syndrome.

Figure 2. Safety of cardiac troponin I risk stratification thresholds by subgroups. Forest plot showing the number of patients in each subgroup, true negatives (TN) and false negatives (FN) with the negative predictive value (NPV) for the primary outcome, stratified by patients with cardiac troponin concentrations below 2 ng/L (black) and below 5 ng/L (red). *ECG ischemia data available in 7167/32837 (22%) of patients.

There are a number of strengths to our study. The trial design avoided selection bias through the inclusion of consecutive patients ensuring our analysis population included both low- and high-risk individuals, an equal proportion of men and women, patients who presented outside routine hours, and those who were unlikely to survive. Enrollment was across 10 hospitals in Scotland including both secondary and tertiary care centers. Despite differences in the prevalence of the primary outcome between sites, the proportion of patients identified as low risk and the safety of risk stratification with cardiac troponin was consistent across sites. Within our substudy, we have further explored the generalizability of our findings, demonstrating equivalent diagnostic performance of the same risk stratification threshold for other high-sensitivity cardiac troponin I and T assays. By using robust and established regional and national registries we ensured follow-up was complete in all patients who remained resident in Scotland through linkage of electronic health-care records.
adjudicated in accordance with the Universal Definition of Myocardial Infarction.

There are approximately 20 million presentations with suspected acute coronary syndrome to the emergency departments in the United States and Europe every year. The adoption of a safe and effective approach to rule out of myocardial infarction would have a considerable impact on healthcare provision. Using an optimized risk stratification threshold of 5 ng/L compared with the limit of detection (<2 ng/L) identifies twice as many low-risk patients. This is particularly relevant in older patients with established cardiovascular disease, where the clinical assessment of pretest probability is more challenging. The optimized risk stratifi-

---

Figure 3. Proportion of patients identified as low risk at the <2 ng/L and <5 ng/L risk stratification thresholds by subgroups. Proportion of patients in each subgroup with cardiac troponin concentrations below 2 ng/L (gray) or 5 ng/L (red) at presentation.

Figure 4. Cumulative incidence of myocardial infarction or cardiac death at 12 months. Plots stratified by cardiac troponin concentration at presentation: (A) below 2 ng/L (gray) and between 2 ng/L and 99th centile (blue); (B) below 5 ng/L (red) and between 5 ng/L and 99th centile (blue).
cation threshold maintains an excellent safety profile across all age groups and identifies 4 times as many patients >65 years old as low risk. It is well recognized that cardiac troponin concentrations increase with age where they reflect the presence and control of traditional cardiovascular risk factors, such as hypertension and hypercholesterolemia, the burden of coronary artery disease, vulnerable plaque, and left ventricular hypertrophy or myocardial fibrosis. This property of cardiac troponin as a dynamic barometer of heart health provides the pathophysiological basis to explain its powerful role in the risk stratification of patients with suspected acute coronary syndrome.

Although the safety profile of both the 5 ng/L and 2 ng/L thresholds appear excellent, prospective trials in which patients are assessed and clinical decisions are guided using this approach are needed to ensure that the very low event rates observed here are not a consequence of hospital admission for further investigation and treatment. In our present analysis, we confirm our previous findings in patients who present within 2 hours of symptoms onset, and suggest that serial testing is required in early presenters to maintain the very high negative predictive value of this approach in all patient groups (Table III in the online-only Data Supplement). In those presenting more than 2 hours from symptom onset, we further explored the performance of risk stratification thresholds across subgroups. Despite our large sample size, it is possible we were underpowered to evaluate safety in smaller subgroups, such as those with a prior history of ischemic heart disease, diabetes mellitus, stroke, heart failure and renal impairment. In these subgroups, the central estimate, but not the upper bound of the CI for the negative predictive value, was below 99.5% for both risk stratification thresholds. There was evidence of heterogeneity between those with and without prior ischemic heart disease. However, even in those with established risk factors or cardiovascular conditions, all estimates of negative predictive value encompassed our prespecified safety margin of 99.5%. The safety and effectiveness of introducing risk-stratification thresholds into clinical practice is currently being addressed in the HISTORIC trial (High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction; https://www.clinicaltrials.gov. Unique identifier: NCT03005158), and in the LoDED study (Limit of Detection of Troponin and ECG Discharge; ISRCTN 86184521).

There are some study limitations relevant to this analysis. We were unable to report use of noninvasive diagnostic testing in our study population, and electrocardiograms were only available for a proportion of patients. However, our analysis shows that the negative predictive value of the optimized risk stratification threshold and 2 ng/L was similar in the presence or absence of myocardial ischemia. In the absence of ST-segment elevation, other abnormalities on the electrocardiogram appear to be less important in patients who have very low cardiac troponin concentrations. This analysis evaluates the risk stratification threshold of a single troponin assay, but we have provided evidence in our substudy of the consistency of this approach for other high-sensitivity cardiac troponin I and T assays. Recent reports also support the validity of this approach across differing high-sensitivity cardiac troponin I and T assays. The assay’s precision and analytical variation at the risk stratification threshold is likely to influence the clinical utility of using very low cardiac troponin concentrations, and we have not evaluated assay performance or the implications of misclassification here. Although the trial was conducted across 10 different hospitals in Scotland, all are part of a single healthcare system, and additional studies would be helpful in countries where less selective cardiovascular testing is performed. However, we have previously observed similar safety and effectiveness in a meta-analysis of 19 cohorts across 9 countries.

In conclusion, the use of a risk stratification threshold for high-sensitivity cardiac troponin I in the evaluation of patients with suspected acute coronary syndrome presenting at least 2 hours from symptom onset identifies the majority of patients at low risk of immediate and future cardiovascular events. The use of an optimized risk stratification threshold of 5 ng/L compared with 2 ng/L, classifies twice as many patients as low risk. Although the proportion identified as low risk is reduced in older patients, the safety of this approach is maintained across patients irrespective of age or sex. The adoption of risk stratification thresholds in clinical practice has potential to improve both the effectiveness and safety of the evaluation of patients with suspected acute coronary syndrome with major benefits for patients and healthcare providers.
Acknowledgments

The authors thank researchers from the Emergency Medicine Research Group of Edinburgh and Edinburgh Clinical Trials Unit for support during the conduct of this trial.

Sources of Funding

This trial was funded by the British Heart Foundation (SP/12/10/29922) with support from a Research Excellence Award (RE/18/5/34216). CWN was supported by NHS Lothian through the Edinburgh Clinical Trials Unit. Abbott Laboratories provided cardiac troponin assay reagents, calibrators, and controls without charge. AA is supported by a Clinical Lectureship from the Chief Scientist Office (PCL/18/05). AB, ASVs, DEN, and NLM are supported by the British Heart Foundation through the award of a Scholarship (SS/C/09/002/26360), an Intermediate Clinical Research Fellowship (FS/19/17/34172), Chair (CH/09/002) and the Butler Senior Clinical Research Fellowship (FS/16/14/32023), respectively. DEN is the recipient of a Wellcome Trust Senior Investigator Award (WT103782AIA).

Disclosures

NLM has acted as a consultant for Abbott Diagnostics, Siemens Healthineers, and LumiraDx, and the University of Edinburgh has received research grants from Abbott Diagnostics and Siemens Healthineers. The other authors report no conflicts.

REFERENCES


Original Research Article

High-Sensitivity Troponin for Risk Stratification

Bularga et al. Circulation. 2019;140:1557–1568. DOI: 10.1161/CIRCULATIONAHA.119.042866

Downloaded from http://ahajournals.org by on December 13, 2019

November 5, 2019

1567


