Rapid Rule-out of Acute Myocardial Infarction With a Single High-Sensitivity Cardiac Troponin T Measurement Below the Limit of Detection

A Collaborative Meta-analysis

John W. Pickering, PhD*; Martin P. Than, MBBS*; Louise Cullen, MBBS, PhD; Sally Aldous, MBChB, PhD; Ewoud ter Avest, MD, PhD; Richard Body, MBChB, PhD; Edward W. Carlton, MBChB; Paul Collinson, MBChir, MD; Anne Marie Dupuy, MD, PhD; Ulf Ekelund, MD, PhD; Kai M. Eggers, MD, PhD; Christopher M. Florkowski, MBBS, MD; Yonathan Freund, MD, PhD; Peter George, MBBS; Steve Goodacre, MB, ChB, MSc, PhD; Jaimi H. Greenslade, PhD; Kai M. Eggers, MD, PhD; Allan S. Jaffe, MD; Sarah J. Lord, MBBS, MSc; Arash Mokhtari, MD; Christian Mueller, MD; Andrew Munro, MBChB; Sebbane Mustapha, MD, PhD; William Parsonage, MBBS, DM; W. Frank Peacock, MD; Christopher Pemberton, PhD; A. Mark Richards, MD, PhD; Juan Sanchis, MD, PhD; Lukas P. Staub, MD, PhD; Richard Troughton, MBChB, PhD; Raphael Twerebold, MD; Karin Wildi, MD; and Joanna Young, PhD

Background: High-sensitivity assays for cardiac troponin T (hs-cTnT) are sometimes used to rapidly rule out acute myocardial infarction (AMI).

Purpose: To estimate the ability of a single hs-cTnT concentration below the limit of detection (<0.005 μg/L) and a nonischemic electrocardiogram (ECG) to rule out AMI in adults presenting to the emergency department (ED) with chest pain.

Data Sources: EMBASE and MEDLINE without language restrictions (1 January 2008 to 14 December 2016).

Study Selection: Cohort studies involving adults presenting to the ED with possible acute coronary syndrome in whom an ECG and hs-cTnT measurements were obtained and AMI outcomes adjudicated during initial hospitalization.

Data Extraction: Investigators of studies provided data on the number of low-risk patients (no new ischemia on ECG and hs-cTnT measurements <0.005 μg/L) and the number who had AMI during hospitalization (primary outcome) or a major adverse cardiac event (MACE) or death within 30 days (secondary outcomes), by risk classification (low or not low risk). Two independent epidemiologists rated risk of bias of studies.

Data Synthesis: Of 9241 patients in 11 cohort studies, 2825 (30.6%) were classified as low risk. Fourteen (0.5%) low-risk patients had AMI. Sensitivity of the risk classification for AMI ranged from 87.5% to 100% in individual studies. Pooled estimated sensitivity was 98.7% (95% CI, 96.6% to 99.5%). Sensitivity for 30-day MACEs ranged from 87.9% to 100%; pooled sensitivity was 98.0% (CI, 94.7% to 99.3%). No low-risk patients died.


Conclusion: A single hs-cTnT concentration below the limit of detection in combination with a nonischemic ECG may successfully rule out AMI in patients presenting to EDs with possible emergency acute coronary syndrome.

Primary Funding Source: Emergency Care Foundation.

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REVIEW

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Rapid Rule-out of AMI With Cardiac Troponin T Measurement

Our objective was to test the utility of a single hs-cTnT measurement below the LoD combined with an ECG without evidence of acute ischemia to safely identify patients at low risk for AMI on presentation to the ED. The index test was ECG and hs-cTnT measurement at ED presentation. Patients with a negative test result, defined as no new ischemic changes on the ECG (ST-segment changes or T-wave inversion indicative of cardiac ischemia) and hs-cTnT concentrations below the LoD (<0.005 μg/L) of the Roche Diagnostics hs-cTnT assay (sometimes called the fifth-generation troponin T assay [Table 2 of Supplement 2]) were classified as having low risk for AMI and subsequent adverse events. The secondary index test used the LoB (0.003 μg/L) instead of the LoD.

We calculated the proportion of patients in each study classified as being at low risk for AMI using the index test. We validated the clinical performance of the index test by calculating the sensitivity (1 — false-negative rate) of non-low-risk classification for AMI during the initial hospitalization. The chi-square test for equality of sensitivities (null hypothesis) was applied. We also report the negative predictive value (NPV) because this has been used to assess performance in many troponin biomarker studies, but because this is prevalence-dependent, we chose to use sensitivity for the primary analysis. For completeness, we also report test specificity and the positive predictive value (PPV), although we note that it is not currently intended that patients should be stratified as high-risk (ruled in) using the proposed strategy.

For the secondary analysis, we assessed the clinical performance of the index test for prediction of MACEs within 30 days of presentation by calculating the test sensitivity, NPV, specificity, and PPV. Additional analyses were conducted using the LoB as the diagnostic threshold for hs-cTnT. We used a random-effects bivariate model (15) to obtain the summary estimates of sensitivity (principal summary measure), specificity, NPV, and PPV and their 95% CIs, which reflect the degree of heterogeneity among studies. A summary receiver-operating characteristic curve was used to show the discriminative ability of the index test. We quantified heterogeneity with the $I^2$ statistic, which reflects the proportion of variation in point estimates among studies beyond that expected by chance. $I^2$ values less than 25%, 25% to less than 75%, and 75% or greater were considered to represent low, moderate, and high heterogeneity, respectively (16).

We conducted all analyses using R, version 3.2.2 (17), specifically the “mada” package for meta-analysis of diagnostic accuracy.

METHODS

We developed and followed a protocol (Supplement 1, available at Annals.org) and report findings according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines (12). We searched MEDLINE and EMBASE without language restrictions from 1 January 2008 (when the hs-cTnT assay was released) to 14 December 2016 using the terms chest pain, chest discomfort, acute coronary syndrome, acute myocardial infarction, troponin, high sensitive/sensitivity, and emergency room/department (Table 1 of Supplement 2, available at Annals.org).

Study Selection

Two reviewers (J.W.P. and J.Y.) independently screened titles and abstracts, including conference abstracts, and identified potential cohorts from the full-text articles. When only conference abstracts were available, a further manual search was conducted based on author names for full-text articles. A third reviewer (M.P.T.) confirmed exclusion or inclusion of cohorts. Principal investigators and lead authors for each eligible cohort were contacted. We excluded cohorts if the investigators were unable to provide data.

Eligible studies were prospective studies that were published in peer-reviewed journals, recruited patients evaluated in the ED for possible acute coronary syndrome with an ECG and hs-cTnT measurement, and reported on our primary end point. We excluded studies that did not prospectively collect data; adjudicate for AMI using the universal definition (Supplement 1); or address the calibration error of hs-cTnT assay batch numbers 157120, 160197, and 163704 (produced between October 2009 and April 2012, with the latest expiration date of October 2012) by confirming that no samples from affected batches were included in the original study, excluding samples from affected batches, or assigning new values of the calibrator set applied to the original analyzer results (thereby providing exact and correct results).

Data Synthesis and Analysis

The primary end point was index admission AMI according to the Global Task Force definition, which requires biochemical evidence of myocardial necrosis and clinical evidence of myocardial ischemia (ischemic symptoms, ECG changes, or imaging evidence) (13). Patients with ST-segment elevation MI on the initial ECG were excluded from our analysis. There was no restriction on the troponin assay used for adjudication of AMI. We evaluated 2 secondary end points: death or occurrence of a major adverse cardiac event (MACE), both within 30 days after first presentation (including during the initial hospitalization). Major adverse cardiac events included death, cardiac arrest, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia or high-degree atrioventricular block requiring intervention, and AMI (14).

Prepublication
Data Extraction and Quality Assessment
Study investigators supplied summary 2 × 2 tables for each test with AMI, MACE, and mortality outcomes along with a summary of cohort demographic characteristics.

Two independent epidemiologists (S.J.L. and L.K.S.) who had not participated in any of the included studies adjudicated study risk of bias and applicability for AMI. Assessments were made independently, followed by a meeting in which discrepancies were identified and resolved by discussion. When required, questions were posed to study authors for further clarification before the final assessment. The evaluation was done using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies, version 2) tool (18). When available, information about characteristics and AMI prevalence for excluded patients was also assessed to inform judgment of risk of bias.

Role of the Funding Source
The Emergency Care Foundation administers a fellowship grant enabling Dr. Pickering to undertake this and other work. The Emergency Care Foundation had no role in the design, conduct, or publication of this research. No specific grants or commercial funding were obtained for this study.

RESULTS
The systematic search identified 596 citations, from which 27 potentially eligible cohorts were identified (Figure 1). Lead authors and primary investigators were contacted. An additional 16 cohorts were excluded (Table 3 of Supplement 2).

Study Populations
Eleven cohorts with a total of 9241 participants (range, 166 to 2831 participants) were included (Table 4). Overall, 63.9% of participants were male (range, 54.6% to 70.6%), with a mean age of 61.1 years (range, 54.5 to 70.6 years). Prevalence of AMI ranged from 7.0% to 23.3%, with an overall prevalence for the pooled populations of 15.4%. Study inclusion criteria were reasonably consistent, but there were differences in exclusion: Renal failure requiring dialysis was specified in 3 studies (4, 19, 25), and 1 study excluded patients with atypical presentations, such as fatigue or dizziness (26) (Table 4 of Supplement 2).

Study Methods and Risk of Bias
All studies prospectively recruited patients presenting to EDs with symptoms suggestive of acute coronary syndrome. Three studies enrolled a consecutive sample of patients, with all eligible patients included in the present analysis and appropriate exclusions (Table 5 of Supplement 2) (23–25). Four other cohorts enrolled consecutive patients during set times of the day (19, 20, 27). Two studies did not perform a second troponin measurement on some low-risk patients (25, 26). Overall, 9 cohorts were classified as having high or unclear risk of bias for patient selection, study flow, or both (4, 20–23, 25–27). Of these, 3 studies reported additional information on patient characteristics and outcomes in eligible patients who were not enrolled or not included in the analysis, with each study reporting similar or lower rates of AMI or acute coronary syndrome in excluded patients (21, 26–28). One study reported on the proportion of index troponin tests that were indeterminate due to hemolyzed samples (11 of 1167 [0.9%]) (27). All studies performed the index test (hs-cTnT and ECG) and the reference standard according to a prespecified protocol for data collection and reported data to allow classification at the prespecified LoD and LoB cut points.

All studies followed Global Task Force recommendations to define AMI, and 10 studies used independent adjudication to verify end points. Second blood samples for clinical care purposes and later outcome adjudication were drawn at least 6 hours after symptom onset, except in the 2 studies where no second blood draw was done for some low-risk patients (25, 26) and in 1 study where some low-risk patients were discharged after a second blood sample 2 hours after the first (22). Six cohorts used hs-cTnT clinically and therefore also for adjudication purposes (19, 22–24, 26, 27), one of which had undergone readjudication after the initial study (19, 29).

Figure 1. Flow diagram describing the process of identifying cohorts.
### Table. Cohort Characteristics

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Sweden</td>
<td>United Kingdom</td>
<td>Australia</td>
<td>New Zealand</td>
<td>France</td>
</tr>
<tr>
<td>Participants, n</td>
<td>1138</td>
<td>833</td>
<td>832</td>
<td>452</td>
<td>304</td>
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<tr>
<td>Mean age (SD), y</td>
<td>60.6 (17.5)</td>
<td>54.8 (13.8)</td>
<td>54.5 (45–65)*</td>
<td>63 (14.5)</td>
<td>57 (17)</td>
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<tr>
<td>Male, %</td>
<td>54.6</td>
<td>59.8</td>
<td>61.2</td>
<td>60</td>
<td>64.1</td>
</tr>
<tr>
<td>Mean eGFR (SD), ml/min/1.73 m²</td>
<td>84 (26)</td>
<td>NA</td>
<td>85 (70–90)*</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mean creatinine level (SD)</td>
<td>85 (48)</td>
<td>82.4 (24)</td>
<td>84.0 (44.1)</td>
<td>NA</td>
<td>89 (44)</td>
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<td>Diabetes, %</td>
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<td>8.2</td>
<td>13</td>
<td>NA</td>
<td>13.5</td>
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<tr>
<td>Hypertension, %</td>
<td>43.5</td>
<td>35.2</td>
<td>43.5</td>
<td>NA</td>
<td>36.8</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
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<td>23.6</td>
<td>42.7</td>
<td>NA</td>
<td>36.5</td>
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<tr>
<td>Family history of IHD, %</td>
<td>22.6</td>
<td>31.8</td>
<td>46.2</td>
<td>NA</td>
<td>31.9</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>13.0</td>
<td>28.6</td>
<td>27.8</td>
<td>NA</td>
<td>40.1</td>
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<tr>
<td>Prior MI, %</td>
<td>19.9</td>
<td>5.8</td>
<td>17.1</td>
<td>NA</td>
<td>26.0</td>
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<tr>
<td>Prior stroke, %</td>
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<td>NA</td>
<td>9.3</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Prior hospitalization for CHF, %</td>
<td>NA</td>
<td>NA</td>
<td>4.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Aspirin use, %</td>
<td>28.6</td>
<td>18.7</td>
<td>26.1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>COPD, %</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>β-Blocker use, %</td>
<td>30.4</td>
<td>NA</td>
<td>19.6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ACEI/ARB use, %</td>
<td>30.8</td>
<td>NA</td>
<td>18.3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Statin use, %</td>
<td>29.8</td>
<td>NA</td>
<td>27.3</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Median length of stay (IQR), d</td>
<td>NA</td>
<td>NA</td>
<td>1.1 (0.4–3.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

ACEI = angiotensin-converting enzyme inhibitor; ADAPT = 2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker; APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation; ARB = angiotensin II–receptor blocker; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; IHD = ischemic heart disease; IQR = interquartile range; MI = myocardial infarction; NA = not available; RATPAC = Randomised Assessment of Treatment Using Panel Assay of Cardiac Markers.

* Median (IQR).

Other cohorts used various clinical troponin concentrations, and persons adjudicating outcomes were blinded to hs-cTnT concentrations (Table 4 of Supplement 2). If the troponin concentration was elevated but an increase or decrease was not recorded, other causes of the elevated concentration were considered by the adjudicators. If no clear alternative cause was evident and the clinical presentation was suggestive of an acute coronary syndrome, an adjudicated diagnosis of AMI was made. In all studies except the Nelson cohort (22), experienced clinical researchers who were blinded to the study protocol adjudicated the outcomes. In the Nelson cohort, adjudicators were not blinded to the study protocol, but 1 of 2 cardiologists assessed the outcome and, when necessary, an independent cardiologist reviewed unclear assessments (Table 4 of Supplement 2). Six studies received supporting grants or reagents from Roche (4, 19, 20, 23, 25).

### Primary Outcome

The index test classified 30.6% (range, 3.8% to 73.5%) of patients as being at low risk for AMI (Table 6 of Supplement 2). Overall, 14 patients with a negative test result had AMI (false-negative cases). In 7 of these cases, the time between symptom onset and blood sampling was less than 3 hours (<2 hours in 4 cases). The pooled estimate of sensitivity of this test was 98.7% (95% CI, 96.6% to 99.5%), with sensitivities of individual cohorts between 87.5% and 100% (P < 0.001 for test for equality of sensitivities) (Figure 2). Heterogeneity was high (I² = 90.3%). The pooled NPV was 99.3% (CI, 97.3% to 99.8%), and NPVs varied from 96.5% to 100% (Figure 3). The pooled negative likelihood ratio was 0.04 (CI, 0.02 to 0.08). The RATPAC (Randomised Assessment of Treatment Using Panel Assay of Cardiac Markers) cohort had the greatest proportion of patients classified as low risk (73.5%) but also had low sensitivity (89.6%) (Table 6 of Supplement 2). The range of specificities was broad (Figures 1 and 2 of Supplement 2).

### Secondary Outcomes

Eight cohorts (n = 8059) provided data on MACEs within 30 days. There were 21 MACEs (including index admission AMI) after a negative index test result. The pooled estimate of sensitivity for MACEs was 98.0% (CI, 94.7% to 99.3%), with sensitivities in individual cohorts ranging from 87.9% to 100% (Figure 4 of Supplement 2).

A total of 126 (1.3%) patients died within the 30-day follow-up, none of whom had been classified as low risk by the primary index test (Table 6 of Supplement 2).

### Sensitivity Analysis

Nine cohorts provided data on index admission AMI outcomes with the LoB as the threshold for hs-cTnT. A total of 19.6% of patients were classified as low risk (hs-cTnT below the LoB and no ischemic changes on ECG), with a pooled sensitivity of 99.1% (CI, 97.4% to 99.7%) and NPV of 99.0% (CI, 93.7% to 99.8%) for index admission AMI (Figure 5 and Table 7 of Supplement 2).

The pooled sensitivity for AMI for the index test among the cohorts that used hs-cTnT for adjudication of AMI (19, 22–24) was marginally greater (99.0% [CI, 95.5% to 99.8%]) than that for the cohorts that used other troponin assays (98.4% [CI, 94.7% to 99.5%]).
DISCUSSION

In this collaborative meta-analysis, a nonischemic ECG plus an hs-cTnT concentration less than 0.005 μg/L classified a substantial proportion of patients presenting to EDs with chest pain as being at low risk for AMI in a diverse sample of international locations. Integrating such an early screening approach into existing investigative strategies may enable patients to be safely discharged to outpatient follow-up earlier than in current practice.

Nine included studies were classified as having high risk of bias due to reported nonconsecutive, non-

**Table**—Continued

<table>
<thead>
<tr>
<th>Cohort, Year (Reference)</th>
<th>Prevalence, %</th>
<th>TP/(TP+FN)</th>
<th>Sensitivity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lund, 2016 (26)</td>
<td>7</td>
<td>79/80</td>
<td>0.988 (0.932–1.000)</td>
</tr>
<tr>
<td>RATPAC, 2011 (21)</td>
<td>8</td>
<td>60/67</td>
<td>0.896 (0.797–0.957)</td>
</tr>
<tr>
<td>ADAPT–Brisbane, 2012 (20)</td>
<td>8.1</td>
<td>66/67</td>
<td>0.985 (0.920–1.000)</td>
</tr>
<tr>
<td>Nelson, 2015 (22)</td>
<td>9.7</td>
<td>44/44</td>
<td>1.000 (0.920–1.000)</td>
</tr>
<tr>
<td>Paris, 2011 (25)</td>
<td>10.5</td>
<td>32/32</td>
<td>1.000 (0.891–1.000)</td>
</tr>
<tr>
<td>Manchester, 2011 (4)</td>
<td>12.7</td>
<td>83/83</td>
<td>1.000 (0.957–1.000)</td>
</tr>
<tr>
<td>Leeuwarden, 2016 (27)</td>
<td>13</td>
<td>34/34</td>
<td>1.000 (0.897–1.000)</td>
</tr>
<tr>
<td>Montpellier, 2015 (23)</td>
<td>14.5</td>
<td>21/24</td>
<td>0.875 (0.676–0.973)</td>
</tr>
<tr>
<td>APACE, 2009 (19)</td>
<td>20.8</td>
<td>587/588</td>
<td>0.998 (0.991–1.000)</td>
</tr>
<tr>
<td>Heidelberg, 2015 (24)</td>
<td>22</td>
<td>145/145</td>
<td>1.000 (0.975–1.000)</td>
</tr>
<tr>
<td>ADAPT–Christchurch, 2012 (20)</td>
<td>23.3</td>
<td>258/259</td>
<td>0.996 (0.979–1.000)</td>
</tr>
</tbody>
</table>

Summary estimates

0.987 (0.966–0.995)
random patient selection or exclusions due to missing data. Recruiting patients 24 hours a day, 7 days a week, is challenging in the ED setting, and it is almost inevitable that some patients will be excluded, if only because of lack of available staff. In such situations, characterization of excluded populations would be valuable.

The prevalence of AMI and the proportion of patients identified as low risk varied among studies, allowing us to explore the clinical performance of this strategy in populations with different baseline risks. This is important because, given that this strategy does not include a formal assessment of risk factors or types of symptoms, decisions to override or not override the strategy may vary considerably across sites and among attending physicians. In this study, the pooled sensitivity and NPV of this strategy were high; nevertheless, 2 sites had much lower sensitivities (<90%), statistical heterogeneity was high, and the lower 95% confidence bound of the point estimate for sensitivity (96.6%) was less than the consensus goal of 99% (30), all of which could indicate that the strategy is not universally safe. Therefore, although the pooled estimates of sensitivity and NPV were favorable, we could not make an unequivocal recommendation.

The RATPAC cohort, with a sensitivity of 89.6%, had a notably high proportion of low-risk patients, was younger and had fewer comorbidities than other cohorts, and had low prevalence of AMI (8.0%). The Montpellier cohort was the smallest of the studies (n = 166), and the low sensitivity (87.5%) was due to just 3 false-negative results. Although these 2 cohorts may be considered statistical outliers and differences between these and other studies may be possible to identify, we do not believe that ignoring them is justifiable. Other settings are also likely to have differences that result in low sensitivity. We recommend that implementation be audited to ensure adequate safety.

Because troponin may not be detectable in the circulation immediately after myocardial injury, some patients with AMI who present very early after onset of pain may not have detectable troponin. For this reason, guidelines recommend a second sample approximately 3 hours after symptom onset in these patients (6). We observed that 50% of patients with false-negative results had blood sampling within 3 hours of symptom onset and therefore recommend a cautious approach to implementation to exclude patients presenting soon after symptom onset. Data are currently insufficient to establish a minimum safe duration below 3 hours.

Using our search strategies, we identified additional studies that reported use of “undetectable” hs-cTnT to rule out AMI in patients presenting with chest pain but were otherwise ineligible for inclusion in this meta-analysis. The largest was the registry study by Bandstein and colleagues, which reported that among 8907 patients with initial hs-cTnT concentrations less than 0.005 μg/L (61% of the cohort), only 15 (0.17%) had AMI within 30 days where no ischemic changes had been noted on initial presentation (8). Other studies defined hs-cTnT detectability thresholds using either the LoB (<0.003 μg/L) or the LoD (<0.005 μg/L). The studies by Aldous and associates reported a sensitivity of 96% for hs-cTnT below the LoB, which is inadequate for clinical use (31, 32). Other studies report sensitivities of 98.2% to 100% for hs-cTnT below the LoD (4, 5, 8, 33–37).

Recent guidelines from the National Institute for Health and Care Excellence (7) and the European Soci-

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**Table 3. Forest plots for acute myocardial infarction and summary estimates for NPV.**

<table>
<thead>
<tr>
<th>Cohort, Year (Reference)</th>
<th>Prevalence, %</th>
<th>TN/(TN+FN)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lund, 2016 (26)</td>
<td>7</td>
<td>339/340</td>
<td>0.997 (0.983–1.000)</td>
</tr>
<tr>
<td>RATPAC, 2011 (21)</td>
<td>8</td>
<td>605/612</td>
<td>0.989 (0.977–0.995)</td>
</tr>
<tr>
<td>ADAPT–Brisbane, 2012 (20)</td>
<td>8.1</td>
<td>269/270</td>
<td>0.996 (0.978–1.000)</td>
</tr>
<tr>
<td>Nelson, 2015 (22)</td>
<td>9.7</td>
<td>80/80</td>
<td>1.000 (0.948–1.000)</td>
</tr>
<tr>
<td>Paris, 2011 (25)</td>
<td>10.5</td>
<td>156/156</td>
<td>1.000 (0.976–1.000)</td>
</tr>
<tr>
<td>Manchester, 2011 (4)</td>
<td>12.7</td>
<td>232/232</td>
<td>1.000 (0.983–1.000)</td>
</tr>
<tr>
<td>Leeuwarden, 2016 (27)</td>
<td>13</td>
<td>56/56</td>
<td>1.000 (0.926–1.000)</td>
</tr>
<tr>
<td>Montpellier, 2013 (23)</td>
<td>14.5</td>
<td>83/86</td>
<td>0.965 (0.901–0.993)</td>
</tr>
<tr>
<td>APACE, 2009 (19)</td>
<td>20.8</td>
<td>627/628</td>
<td>0.998 (0.991–1.000)</td>
</tr>
<tr>
<td>Heidelberg, 2015 (24)</td>
<td>22</td>
<td>25/25</td>
<td>1.000 (0.817–1.000)</td>
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<tr>
<td>ADAPT–Christchurch, 2012 (20)</td>
<td>23.3</td>
<td>339/340</td>
<td>0.997 (0.983–1.000)</td>
</tr>
</tbody>
</table>

**Notes:**
- ADAPT = 2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker; APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation; FN = false-negative; NPV = negative predictive value; RATPAC = Randomised Assessment of Treatment Using Panel Assay of Cardiac Markers; TN = true-negative.
ety of Cardiology (6) have included diagnostic pathways where the first step is to rule out patients if the first hs-cTnT measurement is less than the LoD (7) or the LoB (6). A multicenter analysis of the European Society of Cardiology pathway noted that an hs-cTnT measurement below the LoD was not responsible for any of the false-negative results recorded (38). In the systematic review that informed the National Institute for Health and Care Excellence guidelines (7), 5 studies used LoB or LoD diagnostic thresholds. These studies were published near the time of the release of a technical bulletin (no. 12-023) by Roche Diagnostics, which recommended recalibration of the hs-cTnT assay results from production batches 157120, 160197, and 163704 from 2009 to 2012 (39). Consequently, some hs-cTnT results from the affected batches were incorrectly reported as lower than the true values (in the absence of recalibration). Wildi and colleagues compared results from the faulty assays against remeasured samples with an unaffected batch in 867 patients and showed that the incorrect results negatively affected rule-out strategies using low concentrations of hs-cTnT (40). Only 1 of these studies (41) addressed this issue directly, and 1 other study (4) reported to us that the batches were not affected.

The absence of recalibration information in the cohort described by Bandstein and colleagues (8) may explain the large number of patients categorized as having low risk for AMI in that cohort and the much smaller proportion of low-risk patients in our analysis—samples with reported concentrations in the range of 0.003 to 0.008 μg/L may be as much as 0.007 μg/L higher when correctly calibrated (39, 42). Of note, the reported hs-cTnT result can easily change from below to above the LoD after correction or remeasurement; a previous study found that the number of values below the LoD decreased from 71.0% to 33.8% after correction (42). In our meta-analysis, we carefully accounted for recalibration requirements before performing any data analysis. No data from miscalibrated batches were included in our meta-analysis.

The specificity of detectable hs-cTnT was, not surprisingly, poor, given that the proposed threshold should not be used to rule in AMI, nor should it be used to identify patients at high risk for AMI. Several hs-cTnT algorithms have been proposed and evaluated that include a separate rule-in threshold for hs-cTnT (38, 43, 44).

Because the LoD and LoB are assay specific and future troponin T assays may have different values, it is important to recognize that this analysis applies to a specific assay and not to the use of the LoD or LoB for all assays. Also, the analytic reliability of the LoD as a cutoff is vulnerable to variation in manufacturer batches. Furthermore, variation in setup, calibration, and operation of analyzers in laboratories at individual sites means that, in practice, expecting these assays to universally perform well and consistently at such low values is optimistic.

Limitations of this study include intercohort variation in troponin assays used to adjudicate outcomes. There were also methodological differences in outcome adjudication among the studies, including variation in the timing of late (second) reference troponin samples (Table 4 of Supplement 2). There was considerable heterogeneity, which we were unable to assess by patient-level metaregression because patient-specific data could not be shared. Seven studies identified as possibly meeting inclusion criteria declined to participate or did not respond to our invitation. On the basis of the apparent timing of hs-cTnT measurement, 4 of those studies may have used assay batches affected by the calibration error.

Future research should include an assessment of the current strategy in combination with a validated diagnostic strategy that accounts for risk factors and symptoms on presentation, such as those found in the HEART (History, ECG, Age, Risk factors, and initial Troponin) (45), ADAPT (2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker) (46), and EDACS (Emergency Department Assessment of Chest pain Score) (47) pathways. The National Institute for Health and Care Excellence has recently recommended this approach in conjunction with an LoD strategy (48). The incorporation of risk and symptoms may reassure physicians of the safety of the early rule-out strategy, although possibly at the risk of lower efficacy. In addition, further research on hs-cTnT kinetics is needed to establish the minimum safe duration after symptom onset for the first blood sample. Finally, a pragmatic implementation trial to assess the performance of the strategy in a real-life ED setting is required. This may include assessments of the cost-efficacy and the costs and benefits of the strategy.

In conclusion, this meta-analysis of 11 clinically and geographically diverse cohorts using hs-cTnT results assessed the safety of an early rule-out strategy for AMI. In most but not all settings, patients investigated for acute coronary syndrome with hs-cTnT below the LoD and a nonspecific ECG had very low risk for AMI or for MACEs within 30 days. The point estimate for sensitivity was 98.7% (CI, 96.6% to 99.5%). Acute myocardial infarction may be ruled out in a substantial proportion of patients after only 1 blood draw. At this time, we do not recommend a single-blood draw strategy in patients presenting within 3 hours of symptom onset. Moreover, because the strategy had considerable heterogeneity of sensitivity among sites, it should not be used without careful additional clinical assessment to identify patients with a high likelihood of underlying critical coronary stenosis. Local audits of implementation should take place to ensure safety and efficacy.
Rapid Rule-out of AMI With Cardiac Troponin T Measurement

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Requests for Single Reprints: Martin Than, MBBS, Emergency
Department, Christchurch Hospital, Private Bag 4710,
Christchurch 8140, New Zealand; e-mail, martinthan@xtra.co
.nz.

Current author addresses and author contributions are avail-
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Current Author Addresses: Dr. Pickering: Department of Medicine, University of Otago Christchurch, PO Box 4345, Christchurch 8140, New Zealand.
Dr. Than: Emergency Consultant, Emergency Department, Christchurch Hospital, Private Bag 4710, Christchurch 8140, New Zealand.
Dr. Cullen and Greenslade: Department of Emergency Medicine, Royal Brisbane and Women’s Hospital, Butterfield Street, Herston, Queensland 4029, Australia.
Dr. Aldous: Cardiologist, Cardiology Department, Christchurch Hospital, Private Bag 4710, Christchurch 8140, New Zealand.
Dr. ter Avest: Emergency Consultant, Department of Emergency Medicine, Medical Centre Leeuwarden, Postbus 888, 8901 BR Leeuwarden, the Netherlands.
Dr. Body: Emergency Consultant, Central Manchester University Hospitals NHS Foundation Trust, Oxford Road, Manchester M13 9PL, United Kingdom.
Dr. Carlton: Emergency Consultant, Emergency Department, Southmead Hospital, North Bristol NHS Trust, Southmead Road, Bristol BS10 5NB, United Kingdom.
Dr. Collinson: Consultant Chemical Pathologist and Professor of Cardiovascular Biomarkers, Departments of Clinical Blood Sciences and Cardiology, St. George’s University Hospitals NHS Foundation Trust, Blackshaw Road, Tooting, London SW17 0QT, United Kingdom.
Dr. Dupuy: Physician and Biologist, Hôpital Lapeyronie, Laboratoire de Biochimie et d’Hormonologie, 371 Avenue du Doyen Gaston Giraud, 34295 Montpellier, cédex 5, France.
Dr. Ekelund: Emergency Consultant, Department of Emergency and Internal Medicine, Skåne University Hospital, Klinikgatan 15, 221 85 Lund, Sweden.
Dr. Eggers: Cardiologist, Department of Medical Sciences, Uppsala University, Box 256, 751 05 Uppsala, Sweden.
Dr. Florkowski: Clinical Biochemist and Associate Professor, Department of Pathology, University of Otago Christchurch, PO Box 4345, Christchurch 8140, New Zealand.
Dr. Freund: Emergency Department, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, 75013 Paris, France.
Dr. George: Clinical Biochemist and Professor Department of Pathology, University of Otago Christchurch, PO Box 4345, Christchurch 8140, New Zealand.
Dr. Goodacre: Professor of Emergency Medicine, School of Health and Related Research, University of Sheffield, England Regent Court, Regent Street, Sheffield S1 4DA, United Kingdom.
Dr. Jaffe: Professor of Cardiology and Professor of Laboratory Medicine and Pathology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.
Dr. Lord: Epidemiologist, Head of Epidemiology and Medical Statistics, School of Medicine, The University of Notre Dame Australia, 160 Oxford Street, Darlinghurst, New South Wales 2010, Australia.
Dr. Mohktari: Physician, Department of Emergency and Internal Medicine, Skåne University Hospital, Klinikgatan 15, 221 85 Lund, Sweden.
Dr. Mueller: Cardiologist and Professor, Universitätsspital Basel, Kardiologie, Petersgraben 4, 4031 Basel, Switzerland.
Dr. Munro: Emergency Physician, Emergency Department, Private Bag 18, Nelson Hospital, Nelson 7042, New Zealand.
Dr. Mustapha: Emergency Consultant, Emergency Department, Hôpital Lapeyronie, Laboratoire de Biochimie et d’Hormonologie, 371 Avenue du Doyen Gaston Giraud, 34295 Montpellier, cédex 5, France.
Dr. Parsonage: Cardiologist, Cardiology Department, Royal Brisbane and Women’s Hospital, Butterfield Street, Herston, Queensland 4029, Australia.
Dr. Peacock: Emergency Physician and Professor, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.
Dr. Pemberton: Biochemist and Associate Professor, Christchurch Heart Institute, Department of Medicine, University of Otago Christchurch, PO Box 4345, Christchurch 8140, New Zealand.
Dr. Richards and Troughton: Cardiologist and Professor, Christchurch Heart Institute, Department of Medicine, University of Otago Christchurch, PO Box 4345, Christchurch 8140, New Zealand.
Dr. Sanchis: Cardiologist and Professor of Cardiology, Catedrático de Medicina (Cardiología), CIBERCV, Universidad de Valencia, Jefe de la Unidad de Hemodinámica y Cardiología intervencionista, Hospital Clínico Universitario, 46010 Valencia, Spain.
Dr. Staub: Epidemiologist, NHMRC Clinical Trials Centre, University of Sydney, Locked Bag 77, Camperdown, New South Wales 1450, Australia.
Dr. Twerenbold: Cardiologist, Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), Universitätsspital Basel, Kardiologie, Petersgraben 4, 4031 Basel, Switzerland.
Dr. Wildi: Senior Physician, Anaesthesiology and Surgical Intensive Care Unit, Universitätsspital Basel, Kardiologie, Petersgraben 4, 4031 Basel, Switzerland.
Dr. Young: Research Scientist, Emergency Department, Christchurch Hospital, Private Bag 4710, Christchurch 8140, New Zealand.

Drafting of the article: J.W. Pickering, L. Cullen, E.W. Carlson, A.S. Jaffe, A. Munro, W. Parsonage, L.P. Staub.