Normal presenting levels of high-sensitivity troponin and myocardial infarction

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ABSTRACT
Objective To analyse whether levels of high-sensitivity cardiac troponin (hs-cTn) below their respective 99th percentile can be used as a single parameter to rule out acute myocardial infarction (AMI) at presentation.

Design Prospective, multicentre study.

Main outcome measures We measured hs-cTn using four different methods (hs-cTnT Roche, hs-cTnI Siemens, hs-cTnI Beckman Coulter and hs-cTnI Abbott) in consecutive patients presenting to the emergency department with acute chest pain. Two independent cardiologists adjudicated the final diagnosis. Patients were followed for death or AMI during a mean period of 24 months.

Results Among 2072 consecutive patients with hs-cTnT measurements available, 21.4% had an adjudicated diagnosis of AMI (sensitivity 89.6%, 95% CI 86.4% to 92.3%, negative predictive value (NPV) 96.5%, 95% CI 95.4% to 97.4%). Among 1180 consecutive patients with hs-cTnI Siemens measurements available, 20.0% had AMI (sensitivity 94.1%, 95% CI 90.3% to 96.7%, NPV 98.0%, 95% CI 96.6% to 98.9%). Among 1151 consecutive patients with hs-cTnI Beckman Coulter measurements available, 19.7% had AMI (sensitivity 92.1%, 95% CI 87.8% to 95.2%, NPV 97.5%, 95% CI 96.0% to 98.5%). Among 1567 consecutive patients with hs-cTnI Abbott measurements available, 20.0% had AMI (sensitivity 77.2%, 95% CI 72.1% to 81.7%, NPV 94.3%, 95% CI 92.8% to 95.5%).

Conclusions Normal hs-cTn levels at presentation should not be used as a single parameter to rule out AMI as 6–23% of adjudicated AMI cases had normal levels of hs-cTn levels at presentation. Our data highlight the lack of standardisation among hs-cTn assays resulting in substantial differences in sensitivity and NPV at the 99th percentile.

INTRODUCTION
Coronary artery disease (CAD) is the most common manifestation of cardiovascular disease and it is associated with high morbidity and mortality.1 There are different clinical manifestations of CAD including silent ischemia, stable angina pectoris, unstable angina pectoris, acute myocardial infarction (AMI), sudden death and heart failure.1

In Europe and in the USA, almost 15 million patients per year present to the emergency department (ED) with chest pain or other symptoms suggestive of AMI.2 As in most patients acute chest pain is caused by benign disorders and not by AMI, rapid rule out of AMI is fundamental.3 Delayed rule out of AMI increases resource use and time spent in the ED, patient anxiety and the problem of overcrowding in the ED, which itself is associated with increased mortality and morbidity.3

Since the late 1980s, when cardiac troponins (cTns) were first described as biochemical markers for cardiomyocyte damage, there have been important advances in cTn assay technology, which have led to an improvement in the clinical ability to detect and quantify cardiomyocyte damage.4 According to current guidelines, a test with a high ability to diagnose and rule out AMI has to meet two basic criteria: First, it has to detect increased cTn levels in blood that surpass the 99th percentile of cTn levels in a normal reference population, with an imprecision corresponding to ≤10% coefficient of variation (CV) at the upper reference limit.5–7 Second, a high-sensitivity assay should be able to measure in at least 50% of healthy individuals concentration levels over the assay’s limit of detection (LOD) but below the 99th percentile.6 None of the earlier generation cTn assays, still in clinical use in many institutions, does fulfil these requirements.6 High-sensitivity cardiac troponin (hs-cTn) assays have a 10-fold to 100-fold lower LOD and meet the demand of analytical precision.6 This enables physicians to detect AMI earlier and more frequently in patients presenting with chest pain.2 7 The aim of our study was to determine whether hs-cTn values below the 99th percentile can be used as a single parameter to rule out the diagnosis of AMI at presentation.

METHODS
Study design and population
Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective, international, multicentre study coordinated and designed by the University Hospital Basel (ClinicalTrials.gov number, NCT00470587).2 Consecutive adult patients were enrolled from
April 2006 to August 2011 if presenting to the ED with symptoms suggestive of AMI such as acute chest pain, angina pectoris at rest or other thoracic sensations presumably caused by myocardial ischemia with an onset or peak within the last 12 h. Patients were excluded if presenting with terminal kidney failure requiring dialysis. Patients were excluded if presenting with terminal kidney failure requiring dialysis. Patients were excluded if presenting with terminal kidney failure requiring dialysis. Patients were excluded if presenting with terminal kidney failure requiring dialysis. Patients were excluded if presenting with terminal kidney failure requiring dialysis. Patients were excluded if presenting with terminal kidney failure requiring dialysis. Patients were excluded if presenting with terminal kidney failure requiring dialysis. Patients were excluded if presenting with terminal kidney failure requiring dialysis. 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Follow-up
The primary endpoint was all-cause-mortality and AMI rate during follow-up. Further information is described in the online supplementary material.

Statistical analysis
Categorical variables are presented as percentages and continuous variables are presented as median and interquartile range (IQR). Continuous, skewed distributed variables were compared using the Mann–Whitney U test and categorical variables were compared using the Pearson \( \chi^2 \)–square test. Kaplan–Meier analysis was performed for the endpoint of death during follow-up and for the AMI rate during follow-up. Statistical significance was determined with the log-rank test. All hypothesis testing was two-tailed and \( p \) value < 0.05 was described as statistically significant. All statistical tests were performed using SPSS for Windows 21.0 (SPSS Inc., Chicago, Illinois) and MedCalc 11.2.1.0 (MedCalc Software).

RESULTS

Patient characteristics
Figure 1 displays the detailed flow of patients. A total of 2245 patients consented to inclusion in this multicentre study, of whom 2072 were available for inclusion in the analysis of hs-cTnT levels, 1180 were included for analysis of hs-cTnI (Siemens), 1151 for analysis of hs-cTn (Beckman Coulter) and 1567 for the analysis of hs-cTn (Abbott). Table 1 provides baseline characteristics of all included patients with hs-cTnT measurements. Baseline characteristics of the patients with hs-cTnI measurements were similar to the ones with hs-cTnT (data not shown).

The diagnosis of AMI was adjudicated in 444 (21.4%) patients with hs-cTnT measurements, in 236 (20.0%) with hs-cTnI (Siemens), in 227 (19.7%) with hs-cTnI (Beckman Coulter) and in 311 (19.8%) with hs-cTnI measurements (Abbott).

At presentation, all four hs-cTn assays showed significantly higher levels in patients with AMI compared with patients without AMI. These results, the results of the second adjudication of the final diagnosis based on hs-cTnT values and the results of the subgroup analysis of patients with non-ST-elevation myocardial infarction (NSTEMI) are shown in the online supplementary material.

Normal levels of hs-cTnT at presentation were measured in 222 (94.1%) patients with hs-cTnT measurements, in 209 (92.1%) with hs-cTnT (Beckman Coulter) at presentation and diagnosed AMI, 222 (94.1%) had initially elevated hs-cTnI levels (Siemens), 61.8% presented with normal levels of hs-cTnI (Abbott) and in 78.7% presented with normal levels of hs-cTnI (Beckman Coulter).

Normal levels of hs-cTnT at presentation were measured in 63.3% of patients, 58.3% of patients presented with normal levels of hs-cTnT (Siemens), in 61.8% presented with normal levels of hs-cTnI (Beckman Coulter) and 78.7% presented with normal levels of hs-cTnI (Abbott).

Normal levels of hs-cTnT at presentation for rule out of AMI
In patients with hs-cTnT measurements and diagnosed AMI, 398 (89.6%) presented with elevated levels of hs-cTnT and 46 (10.4%) had normal levels at presentation. As shown in table 2, the sensitivity of hs-cTnT at the time of presentation using the conventional 99th percentile at 14 ng/l was 89.6% (95% CI 86.4% to 92.3%) and the negative predictive value (NPV) was 96.5% (95% CI 95.4% to 97.4%). In patients with hs-cTnI (Siemens) measurements at presentation and the diagnosis of AMI, 222 (94.1%) had initially elevated hs-cTnI levels (≥9 ng/l) and 14 (5.9%) showed normal levels, resulting in a sensitivity of 94.1% (95% CI 90.3% to 96.7%) and a NPV of 98.0% (95% CI 96.6% to 98.9%). In patients with hs-cTnI measurements (Beckman Coulter) at presentation and diagnosed AMI, 209 (92.1%) showed initially elevated hs-cTnI levels (≥9 ng/l) and 18 patients (7.9%) had normal levels. Thus, the sensitivity for AMI with this assay was 92.1% (95% CI 87.8% to 95.2%) and the NPV was 97.5% (95% CI 96.0% to 98.5%). In patients with hs-cTnI (Abbott) measurements at presentation and the diagnosis of AMI, 240 (77.2%) had initially elevated hs-cTnI levels (≥26.2 ng/l) and 71 (22.8%) showed normal levels, resulting in a sensitivity of 77.2% (95% CI 72.1% to 81.7%) and a NPV of 94.3% (95% CI 92.8% to 95.5%).

All four hs-cTnT assays showed their highest sensitivity and their highest NPV in patients presenting after 6 h from symptom onset (Roche, n=999; Siemens, n=572; Beckman Coulter, n=561; Abbott, n=775). Further details of patients presenting after 6 h and the results of subgroup analysis of patients with measurements available for all four hs-cTnT assays are described in the online supplementary material.

Table 1 Baseline characteristics of included patients
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=2072)</th>
<th>AMI (n=443)</th>
<th>No AMI (n=1629)</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62 (50–75)</td>
<td>71 (59–79)</td>
<td>60 (48–73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>68.8</td>
<td>72.5</td>
<td>67.8</td>
<td>0.055</td>
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<tr>
<td>Previous CHD</td>
<td>34.3</td>
<td>44.1</td>
<td>31.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>23.7</td>
<td>30.2</td>
<td>21.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>45.0</td>
<td>57.4</td>
<td>41.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63.6</td>
<td>77.7</td>
<td>59.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index kg/m²</td>
<td>23 (24–30)</td>
<td>26 (24–29)</td>
<td>27 (24–30)</td>
<td>0.438</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>17.6</td>
<td>25.9</td>
<td>15.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking†</td>
<td>61.3</td>
<td>62.9</td>
<td>60.8</td>
<td>0.426</td>
</tr>
<tr>
<td>Family history of ischemic heart disease‡</td>
<td>42.9</td>
<td>48.1</td>
<td>41.4</td>
<td>0.027</td>
</tr>
<tr>
<td>Previous coronary intervention</td>
<td>23.5</td>
<td>25.5</td>
<td>22.9</td>
<td>0.263</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>6.4</td>
<td>11.5</td>
<td>5.0</td>
<td>&lt;0.001</td>
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<tr>
<td>Previous apoplexy</td>
<td>5.2</td>
<td>8.6</td>
<td>4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASA at presentation</td>
<td>37.0</td>
<td>45.9</td>
<td>34.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin at presentation</td>
<td>35.0</td>
<td>39.6</td>
<td>33.7</td>
<td>0.020</td>
</tr>
<tr>
<td>ACE inhibitor at presentation</td>
<td>21.9</td>
<td>28.8</td>
<td>20.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( β )-blocker at presentation</td>
<td>35.3</td>
<td>39.4</td>
<td>34.2</td>
<td>0.040</td>
</tr>
<tr>
<td>GFR (MDRD)</td>
<td>85 (68–102)</td>
<td>75 (58–94)</td>
<td>87 (71–103)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time since chest pain onset, h</td>
<td>(&lt;3)</td>
<td>24.4</td>
<td>24.1</td>
<td>24.4</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>75.6</td>
<td>75.9</td>
<td>75.6</td>
<td>( ≥3)</td>
</tr>
<tr>
<td>ST-segment elevation</td>
<td>3.0</td>
<td>5.8</td>
<td>2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>5.1</td>
<td>16.9</td>
<td>2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>12.0</td>
<td>34.0</td>
<td>6.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| Values are presented as medians (IQR) or %.
* n=2051.
† n=2005.
‡ n=1550.
§ Overall, in 41 patients the onset of symptoms within the 12 h period preceding presentation could not be precisely defined. In this table they were added to the group with chest-pain onset over 3 h.
AMI, acute myocardial infarction; ASA, acetylsalicylic acid; ACE, angiotensin converting enzyme; CHD, coronary heart disease; GFR (MDRD), glomerular filtration rate (modification of diet in renal disease).

Assay, normal hs-cTnI levels were defined as below 26.2 ng/l and elevated levels as \( ≥26.2 \) ng/l. Long-term stability of TnI has been demonstrated previously. Good correlation between plasma and serum has been demonstrated. Further information to the adjudication of the final diagnosis and to measurements of hs-cTn are described in the online supplementary material.

Early presenters
The majority (60.9%, 28 of 46) of patients with AMI who had normal levels of hs-cTnT at presentation were early presenters (<3 h from symptom onset). As shown in table 2, early presenters showed lower values in sensitivity for the cut-off value 14 ng/l (73.8%, 95% CI 64.5% to 81.9%) and in NPV (92.3%, 95% CI 89.0% to 94.8%) compared to late presenters (≥3 h). There specificity is 94.7% (95% CI 91.7% to 96.8%) and NPV is 98.1% (95% CI 97.0% to 98.9%).

Death and AMI rate during the follow-up period
As outlined in figure 2 and figure 3, during the first 30 days of follow-up, mortality rate and AMI rate were significantly higher in patients with elevated hs-cTn at presentation than in patients with normal hs-cTn at presentation. Further details are described in the online supplementary material.

DISCUSSION
We performed a prospective, international, multicentre study enrolling unselected patients presenting to the ED with acute chest pain. The aim of this analysis was to evaluate four different hs-cTn assays and to assess whether hs-cTn values below their respective 99th percentile can be used as a single parameter to rule out the diagnosis of AMI at presentation. We report five major findings:

First, the percentage of AMI patients having normal levels of hs-cTn at presentation varied substantially among the four different hs-cTn assays used and ranged from 6% to 23%. These differences among hs-cTn assays may be related to analytical details of

<table>
<thead>
<tr>
<th>Time from symptom onset (h)</th>
<th>Assay and cut-off</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>hs-cTnT, 14 ng/l</td>
<td>89.6 (86.4 to 92.3)</td>
<td>77.7 (75.6 to 79.7)</td>
<td>52.3 (48.7 to 55.9)</td>
<td>96.5 (95.4 to 97.4)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 9 ng/l (S)</td>
<td>94.1 (90.3 to 96.7)</td>
<td>71.4 (68.4 to 74.3)</td>
<td>45.1 (40.7 to 49.6)</td>
<td>98.0 (96.6 to 98.9)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 9 ng/l (B)</td>
<td>92.1 (87.8 to 95.2)</td>
<td>75.0 (72.1 to 77.8)</td>
<td>47.5 (42.8 to 52.3)</td>
<td>97.5 (96.1 to 98.5)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 26.2 ng/l (A)</td>
<td>77.2 (72.1 to 81.7)</td>
<td>92.6 (91.0 to 94.0)</td>
<td>72.1 (66.9 to 76.8)</td>
<td>94.3 (92.8 to 95.5)</td>
</tr>
<tr>
<td>&lt;3</td>
<td>hs-cTnT, 14 ng/l</td>
<td>73.8 (64.5 to 81.9)</td>
<td>84.2 (80.2 to 87.6)</td>
<td>55.6 (47.1 to 64.0)</td>
<td>92.3 (89.0 to 94.8)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 9 ng/l (S)</td>
<td>93.8 (82.8 to 98.7)</td>
<td>79.8 (74.1 to 84.8)</td>
<td>48.9 (38.3 to 59.6)</td>
<td>98.4 (95.4 to 99.7)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 9 ng/l (B)</td>
<td>88.6 (75.4 to 96.2)</td>
<td>85.0 (79.6 to 89.4)</td>
<td>53.4 (41.4 to 65.2)</td>
<td>97.5 (94.2 to 99.2)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 26.2 ng/l (A)</td>
<td>50.8 (38.2 to 63.2)</td>
<td>97.9 (95.6 to 99.2)</td>
<td>85.0 (70.2 to 94.3)</td>
<td>89.6 (85.7 to 92.7)</td>
</tr>
<tr>
<td>≥3</td>
<td>hs-cTnT, 14 ng/l</td>
<td>94.7 (91.7 to 96.8)</td>
<td>75.6 (73.1 to 78.0)</td>
<td>51.5 (47.5 to 55.5)</td>
<td>98.1 (97.0 to 98.9)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 9 ng/l (S)</td>
<td>94.2 (89.8 to 97.0)</td>
<td>68.6 (65.1 to 72.0)</td>
<td>44.3 (39.3 to 49.3)</td>
<td>98.0 (96.1 to 99.0)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 9 ng/l (B)</td>
<td>92.9 (88.2 to 96.2)</td>
<td>71.8 (68.3 to 75.1)</td>
<td>46.3 (41.1 to 51.6)</td>
<td>97.5 (95.7 to 98.7)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 26.2 ng/l (A)</td>
<td>84.4 (79.3 to 88.7)</td>
<td>91.0 (89.0 to 92.7)</td>
<td>70.3 (64.7 to 75.5)</td>
<td>95.9 (94.4 to 97.1)</td>
</tr>
<tr>
<td>&lt;6</td>
<td>hs-cTnT, 14 ng/l</td>
<td>83.9 (78.5 to 88.5)</td>
<td>79.6 (76.8 to 82.3)</td>
<td>52.1 (46.8 to 57.3)</td>
<td>94.9 (93.1 to 96.4)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 9 ng/l (S)</td>
<td>92.0 (85.3 to 96.3)</td>
<td>73.6 (69.5 to 77.4)</td>
<td>44.0 (37.6 to 50.6)</td>
<td>97.6 (95.5 to 98.9)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 9 ng/l (B)</td>
<td>88.9 (81.4 to 94.1)</td>
<td>77.2 (73.2 to 80.9)</td>
<td>46.6 (39.6 to 53.7)</td>
<td>96.9 (94.6 to 98.4)</td>
</tr>
<tr>
<td>≥ 6</td>
<td>hs-cTnT, 14 ng/l</td>
<td>65.3 (56.9 to 73.0)</td>
<td>94.8 (92.7 to 96.3)</td>
<td>73.4 (64.9 to 80.9)</td>
<td>92.5 (90.2 to 94.4)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 9 ng/l (S)</td>
<td>95.5 (91.8 to 97.8)</td>
<td>75.6 (72.4 to 78.6)</td>
<td>52.5 (47.5 to 57.5)</td>
<td>98.3 (97.0 to 99.2)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 9 ng/l (B)</td>
<td>96.0 (90.8 to 98.7)</td>
<td>69.0 (64.5 to 73.2)</td>
<td>46.1 (39.9 to 52.4)</td>
<td>98.4 (96.3 to 99.5)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 26.2 ng/l (A)</td>
<td>95.0 (89.4 to 98.1)</td>
<td>72.6 (68.2 to 76.7)</td>
<td>48.3 (41.7 to 54.9)</td>
<td>98.2 (96.1 to 99.3)</td>
</tr>
<tr>
<td></td>
<td>hs-cTnI, 26.2 ng/l (A)</td>
<td>87.4 (81.4 to 92.0)</td>
<td>90.3 (87.7 to 92.5)</td>
<td>71.2 (64.5 to 77.3)</td>
<td>96.3 (94.4 to 97.7)</td>
</tr>
</tbody>
</table>

Cut-off set at the 99th percentile of a healthy reference population. (A), Abbott; (B), Beckman Coulter; CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; hs-cTnI, high-sensitivity cardiac troponin I; NPV, negative predictive value; PPV, positive predictive value; (S), Siemens.

Figure 2  Cumulative mortality rate within 30 days according to the respective 99th percentile of hs-cTn. Access the article online to view this figure in colour.

One of the basic criteria that must be met to diagnose AMI is the detection of a rise and/or fall of cTn that surpass the 99th percentile of cTn levels in a normal reference population. As with the specific assays, differences among the reference population chosen to define the respective 99th percentiles of each assay as well as potential pathophysiological differences including release kinetics between cTnI and cTnT. The incidence of normal hs-cTn levels in this cohort of unselected acute chest pain patients was similar to the incidence reported in the previous studies recruiting unselected patients. Second, the vast majority of patients with acute chest pain and normal levels of hs-cTn did not have an AMI. The NPV of the hs-cTn assays examined for normal levels of hs-cTnI ranged from 94% to 98%. Third, for all four assays, sensitivity and NPV were higher in patients presenting after 6 h from symptom onset. These results indicate that the rule out of AMI could possibly be performed with a single hs-cTn measurement in conjunction with the 12-lead ECG and a full clinical assessment in patients presenting within 6 h from symptom onset. However, all four assays showed a lower sensitivity in patients presenting within 3 h from symptom onset. This observation confirmed the time-dependent release of cTn from the injured myocardium. It also highlights the need for particular caution regarding the rule out of AMI with hs-cTn in early presenters, especially regarding the high difference in sensitivity of hs-cTnI assays in early presenters. Fourth, differences in NPV and PPV at the 99th percentile among the different hs-cTnI assays were substantial and did not seem to be adequately explained by differences in assay sensitivities. We consider the lack of standardisation, including the use of different reference populations to define the respective 99th percentiles, the most likely explanation for these substantial differences among hs-cTnI assays. For example, more than three times as many patients with AMI had hs-cTnI levels in the normal range with the Abbott assay as compared with the Siemens or Beckman Coulter assay.

Acute coronary syndromes

Figure 3  Cumulative rate of AMI within 30 days according to the respective 99th percentile of hs-cTn. Access the article online to view this figure in colour.

hs-cTnT= high-sensitivity cardiac troponin T; hs-cTnI= high-sensitivity cardiac troponin I; AMI= acute myocardial infarction
Acute coronary syndromes

LIMITATIONS
Several potential limitations of this study should be mentioned. First, we assessed the performance of normal levels of four different hs-cTn assays. Although we obtained consistent results in all four assays and consequently suppose that it can be generalised to all hs-cTn assays, further studies need to confirm this assumption. Second, we cannot comment on patients with terminal kidney failure requiring dialysis as these patients were excluded from analysis. Third, as it is a prospective, observational study, we cannot determine the exact clinical benefit associated with risk stratification and improved diagnosis. Fourth, we underlined that one of the strengths of our study was the adjudication of diagnosis using the values of hs-cTnT. Although it could theoretically bias a direct comparison of the diagnostic accuracy of hs-cTnT versus hs-cTnI, we do not expect an alteration of the key message of our study.

CONCLUSIONS
Among consecutive patients with acute chest pain, depending on the hs-cTn assay used, 6% to 23% of adjudicated AMI cases had normal levels of hs-cTnT levels at presentation. Therefore, although the majority of acute chest pain patients with normal levels of hs-cTnT will be found to have causes other than AMI, normal hs-cTnT levels at presentation should not be used as a single parameter to rule out AMI. This caveat applies particularly to early presenters. In addition, our data highlight the lack of standardisation among hs-cTn assays resulting in substantial differences in NPV and PPV at the 99th percentile.

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Contributors Guarantors: RH, CM. Study concept, design and supervision: CM. Conduct of the study: all authors. Analysis and interpretation of data: RH, MR, CM. Drafting of the manuscript: RH, MR, CM. Critical revision of the manuscript for important intellectual content and approval of the final version of the manuscript: all authors.

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