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# Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin ☆

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ABSTRACT

*Background:* We examined whether undetectable levels of high-sensitivity cardiac Troponin (hs-cTn) can be used to rule out acute myocardial infarction (AMI) with a single blood draw at presentation to the emergency department (ED).

*Methods and results:* In a prospective multicenter study we used 4 different hs-cTn assays (hs-cTnT Roche, and hs-cTnI Siemens, hs-cTnI Beckman Coulter and hs-cTnI Abbott) in consecutive patients presenting with acute chest pain. The final diagnosis of AMI was adjudicated by two independent cardiologists using all available data including serial hs-cTnT levels. Mean follow up was 24 months. Among 2072 consecutive patients with available hs-cTnT levels, 21% had an adjudicated diagnosis of AMI. Among AMI patients, 98.2% had initially detectable levels of hs-cTnT (sensitivity 98.2%, 95%CI 96.3%–99.2%, negative predictive value (NPV) 98.6%, 95%CI 97.0%–99.3%). Undetectable levels of hs-cTnT ruled out AMI in 26.5% of patients at presentation. The NPV was similar with the three hs-cTnI assays: among 1180 consecutive patients with available hs-cTnI (Siemens), the NPV was 98.8%; among 1151 consecutive patients with available hs-cTnI (Beckman Coulter), the NPV was 99.2%; among 1567 consecutive patients with available hs-cTnI (Abbott), the NPV was 100.0%. The percentage of patients with undetectable levels of hs-cTnI was similar among the three hs-cTnI assays and ranged from 11.4% to 13.9%.

*Conclusions:* Undetectable levels of hs-cTn at presentation have a very high NPV and seem to allow the simple and rapid rule out of AMI. This criteria applies to much more patients with hs-TnT as compared to the investigated hs-cTnI assays.



## 1. Introduction

Acute myocardial infarction (AMI) is a major cause of death and disability worldwide. Patients with symptoms suggestive of AMI account for about 10% of all emergency department (ED) consultations, even so only 10–20% of them eventually suffer from AMI. Rapid identification of this diagnosis is critical for early treatment and management of these patients [1].

In the early 90s several studies showed that cardiac troponins (cTn) were proteins unique to heart and specific and sensitive biomarkers of myocardial damage [2–4]. Currently cTn and 12-lead electrocardiogram (ECG) form the diagnostic cornerstones of clinical assessment in the evaluation of chest pain patients [5,6]. A limitation of conventional cTn assays is their low sensitivity at the time of a patient's presentation, owing to a delayed increase of circulating

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levels for 3 to 4 h and requiring serial sampling for 6 to 9 h in a significant number of patients [2].

Delays in confirming the diagnosis of AMI (rule in) may increase the risk of complications [7] but also delays in excluding the diagnosis (rule out) interfere with the evaluation of alternative diagnoses and contribute to overcrowding in the ED and increasing the cost to the health care system.

Recent studies reported that using more sensitive cTn assays can improve the accuracy of the diagnosis of AMI at the time of presentation to the ED. However using the conventional cut-off (99th percentile) the sensitivities (often < 90%) are not high enough to allow immediately clinical decision making [8–13]. In contrast, using undetectable levels of hs-cTnT as the criteria for rule out of AMI at presentation seemed to provide very high sensitivity and NPV in initial pilot studies [8,10]. Our aim was to evaluate undetectable levels of four hs-cTn assays (hs-cTnT Roche, hs-cTnI Siemens, hs-cTnI Beckman Coulter & hs-cTnI Abbott) for the rapid rule out of AMI.

## 2. Methods

### 2.1. Study design and population

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international multicenter study designed and coordinated by the University Hospital Basel Switzerland [10,14,15]. From April 2006 to November 2011, consecutive patients older than 18 years presenting to the ED with symptoms suggestive of AMI with an onset or peak within the last 12 h were recruited, after informed consent was obtained.

Patients with terminal kidney failure requiring regular dialysis were excluded. For this analysis patients were also excluded if A) hs-cTnT (Roche), hs-cTnI (Siemens), hs-cTnI (Beckman Coulter) or hs-cTnI (Abbott), levels at presentation were not available for their respective analysis, B) the final diagnosis remained unclear after adjudication.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The authors designed the study, gathered and analysed the data, vouch for the data and analysis, wrote the paper, and decided to publish.

### 2.2. Routine clinical assessment

All patients underwent a clinical assessment that included medical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood test, and chest radiography [10]. Levels of cTn were measured at presentation and after 6–9 h, as long as clinically indicated. Timing and treatment of patients were left to discretion of the attending physician.

### 2.3. Adjudicated final diagnosis

Adjudication of final diagnoses was performed centrally in the core lab (University Hospital Basel) for all patients twice: Once according to conventional cTn levels used onsite (this method was used in the initial analyses to examine the performance of hs-cTn assays [10,14,16–18] and once including levels of Roche hs-cTnT in order to also take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by hs-cTn assays [19,20] this allows the additional detection of small AMIs that were missed by the adjudication based on conventional cTn assays). Two independent cardiologists reviewed all available medical records – patient history, physical examination, results of laboratory testing (including hs-cTnT levels), radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity and morphology in coronary angiography – pertaining to the patient from the time of ED presentation to 90-day follow up. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

AMI was defined and cTn levels interpreted as recommended in current guidelines [5,21]. In brief, AMI was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least one cTn value above the 99th percentile (or for the conventional cTn assays above the 10% imprecision value if not fulfilled at the 99th percentile) together with a significant rising and/or falling [17,21,22]. The criteria used to define rise and/or fall in conventional cTn and hs-cTnT and the assumption of linearity are described in detail in the Methods section in the online-only Data Supplement.

All other patients were classified as "No AMI" for this analysis, including in this group the categories of unstable angina (UA), Non Cardiac Chest Pain (NCCP), cardiac but non coronary disease (e.g. tachyarrhythmias, perimyocarditis), and symptoms of unknown origin with normal levels of hs-cTnT.

### 2.4. Measurement of hs-cTn

Blood samples for determination of hs-cTnT (Roche), hs-cTnI (Siemens), hs-cTnI (Beckman Coulter) and hs-cTnI (Abbott), were collected at presentation to the ED, in serum tubes for hs-cTnT and in heparin plasma tubes for the three assays of hs-cTnI.

Additional samples were collected at 1, 2, 3 and 6 h. When treatment required transferring the patient to the catheter laboratory or coronary care unit, because the diagnosis of AMI was certain, serial sampling was disrupted. After centrifugation, samples were frozen at −80 °C until assayed in a blinded fashion in a dedicated core laboratory.

The Roche hs-cTnT assay was measured on the Elecsys 2010 (Roche Diagnostics). The limit of blank (LoB) and limit of detection (LoD) were determined to be 3 ng/l and 5 ng/l respectively. The 99th-percentile of a healthy reference population was reported at 14 ng/l with an imprecision corresponding to 10% coefficient of variation (CV) at 13 ng/l. Levels below 5 ng/l were considered undetectable. In the last 876 recruited patients (Patients 1196–2072) measurements were performed with lots that required the revision of the calibration curve and accordingly corrected using non-linear regression correction. The Siemens hs-cTnI assay was performed with the use of the Dimension Vista® 1500 immunoassay system (Siemens), with a LoD of 0.5 ng/l, the imprecision level CV of less than 10% at 3 ng/l, and a 99th percentile cut-off point of 9 ng/l (all data according to the manufacturer). Levels below 0.5 ng/l were considered undetectable. Beckman Coulter hs-cTnI was measured on the Access 2 analyzer using an investigational prototype assay. According to the manufacturer, LoD is 2 ng/l and the 99$^{th}$percentile of a healthy reference population is 9 ng/l with a 10% CV lower than the 99th percentile. Levels below 2 ng/l were considered undetectable. The Abbott hs-cTnI assay used was the final pre-commercial release version of the ARCHITECT High Sensitive *STAT* Troponin I (hsTnI) assay (Abbott Laboratories, Abbott Park, IL) blinded by laboratory technicians to patient data. Samples were thawed, mixed, and centrifuged (for 30 min at 3000 RCF and 4 °C for serum samples or for 10 min, twice, at 3000 RCF for plasma samples) prior to analysis and according to manufacturer's instructions. The hsTnI assay has a 99th percentile concentration of 26.2 ng/l with a corresponding co-efficient of variation (CV) of <5% and a limit of detection of 1.9 ng/l [23]. Long-term stability of TnI has been demonstrated previously [24]. Calculation of the glomerular filtration rate was performed using the abbreviated Modification of Diet in Renal disease formula [25].

### 2.5. Follow up and prognostic endpoint

After hospital discharge, patients were contacted by telephone interview or written form after 3, 12 and 24 months of follow up. In case of reported clinical event – in particular cardiovascular events – since presentation to the ED were reviewed by asking the patients and traced by establishing contact with the respective family physician or treatment institution. The primary endpoints were all-cause mortality and AMI rate during 30-days follow up, information regarding death was obtained from the national registry on mortality, the hospital's diagnosis registry or family physician's records. Patients were followed for a mean time of 24 months.

## 3. Statistical methods

The data are expressed as medians ± interquartile range (IQR) for continuous variables, and for categorical variables as numbers and percentages. Continuous variables were compared with the Mann-Whitney–*U* test, and categorical variables using the Pearson chi-square test. Kaplan–Meier analysis was performed for the endpoint of death and AMI, and log-rank testing was used to assess statistical significance.

All hypothesis testing was two-tailed and p-value of less than 0.05 was considered statistically significant. All statistical analysis were performed using SPSS for Windows 21.0 (SPSS Inc, Chicago, IL) and MedCalc 9.6.4.0 (MedCalc software).

## 4. Results

### 4.1. Characteristics of patients

The detailed flow of patients in this observational study is shown in Fig. 1. A total of 2072 consecutive patients had levels of hs-cTnT available, the first 1180 consecutive patients had levels of hs-cTnI (Siemens) available, the first 1151 consecutive patients had levels of hs-cTnI (Beckman Coulter) available and the first 1567 consecutive patients had levels of hs-cTnI (Abbott) available.

Table 1 shows baseline characteristics of all patients in the analysis of hs-cTnT. Baseline characteristics of patients in the analysis of hs-cTnI (Siemens), hs-cTnI (Beckman Coulter) and hs-cTnI (Abbott) were similar.

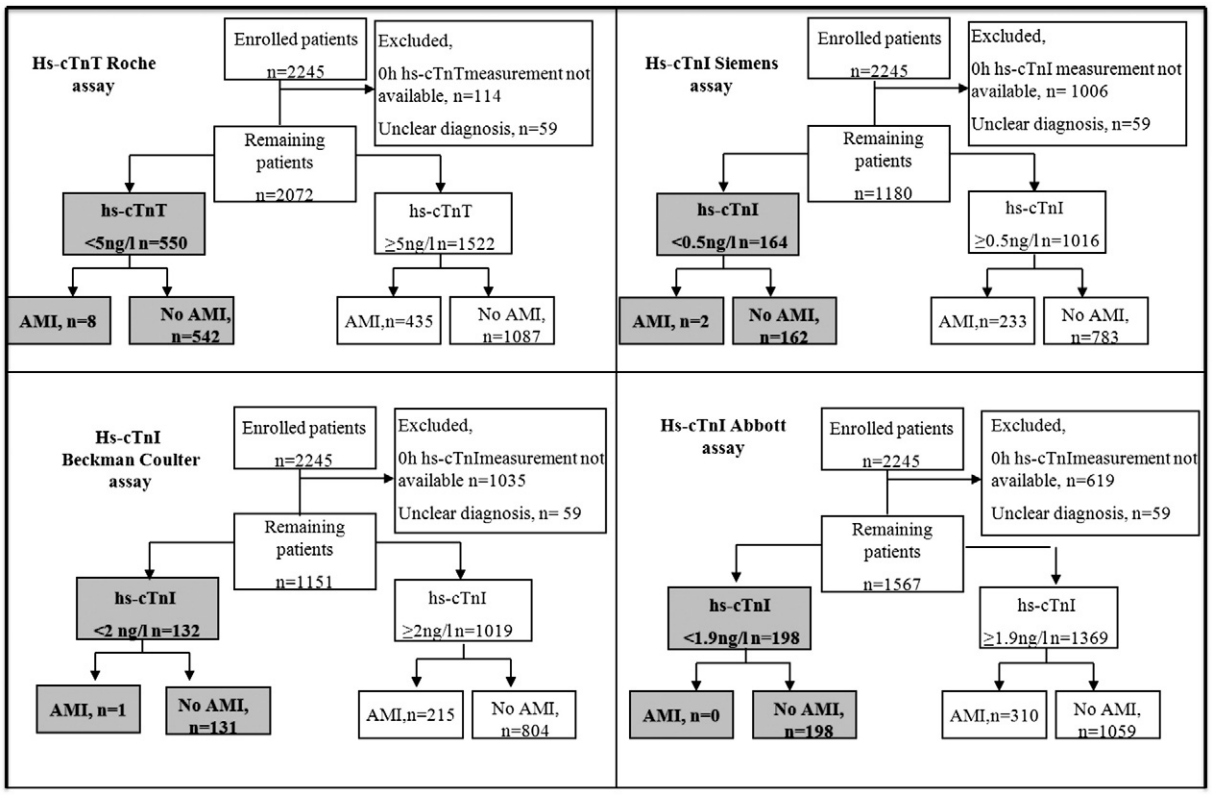


**Fig. 1.** Study flow diagram.

The adjudicated final diagnosis was AMI in 443 patients (21%) in the analysis of hs-cTnT, in 20% in the analysis of hs-cTnI (Siemens), in 19% in the analysis of hs-cTnI (Beckman Coulter) and in 20% in the analysis of hs-cTnI (Abbott).

**Table 1**
Baseline characteristics of included patients.

| Characteristics | All patients (n = 2072) | AMI (n = 443) | No AMI (n = 1629) | p-value |
|---|---|---|---|---|
| Age, yrs | 62 (50–75) | 71 (59–79) | 60 (48–73) | <0.001 |
| Male gender | 68.8 | 72.7 | 67.7 | 0.045 |
| Previous CHD | 34.3 | 44.0 | 31.7 | <0.001 |
| Previous AMI | 23.7 | 30.0 | 22.0 | 0.001 |
| Hypercholesterolemia | 45.0 | 57.6 | 41.6 | <0.001 |
| Hypertension | 63.6 | 77.9 | 59.7 | <0.001 |
| Body mass index kg/m$^2$ | 27 (24–30) | 26 (24–29) | 27 (24–30) | 0.456 |
| Diabetes mellitus [Δ] | 17.6 | 26.0 | 15.3 | <0.001 |
| Smoking [†] | 61.3 | 63.0 | 60.8 | 0.387 |
| Family history of ischemic heart diseasec [‡] | 42.9 | 48.0 | 41.2 | 0.033 |
| Previous coronary intervention | 23.5 | 25.3 | 23.0 | 0.306 |
| Peripheral vascular disease | 6.4 | 11.5 | 5.0 | <0.001 |
| Previous apoplexy | 5.2 | 8.6 | 4.2 | <0.001 |
| ASA at presentation | 37.0 | 45.8 | 34.6 | <0.001 |
| Statin at presentation | 35.0 | 39.5 | 33.8 | 0.025 |
| ACE inhibitor at presentation | 21.9 | 28.9 | 20.0 | <0.001 |
| Beta-blocker at presentation | 35.3 | 39.5 | 34.1 | 0.036 |
| eGFR | 75 (60–90) | 66 (51–83) | 77 (62–91) | <0.001 |
| Time since chest pain onset, h ok | | | | |
| <3 | 24.4 | 24.2 | 24.4 | |
| ≥3[*] | 75.6 | 75.8 | 75.6 | |

Values are presented as median ± IQR or %. CHD = coronary heart disease; AMI = acute myocardial infarction; ASA = acetylsalicylic acid; ACE = angiotensin converting enzyme; eGFR = estimated Glomerular Filtration Rate.

[Δ] n = 2051.

[†] n = 2065.

[‡] n = 1550.

[*] Overall in 46 patients the onset of symptoms within the 12 h period preceding presentation could not be precisely defined. In this table were added to the group with chest-pain onset.

Levels of all four hs-cTn at presentation were significantly higher in the group of patients who had AMI compared to the no AMI group (hs-cTnT median 65.6 ng/l (IQR 28.0–173.0) versus (vs.) 7.4 ng/l (IQR 3.1–13.1) $p < 0.001$; hs-cTnI Siemens median 268.2 ng/l (IQR 42.0–1587.7) vs. 3.8 ng/l (IQR 1.1–10.9) $p < 0.001$; hs-cTnI Beckman Coulter median 167.4 ng/l (IQR 28.1–955.7) vs. 4.6 ng/l (IQR 2.8–9.0) $p < 0.001$); hs-cTnI Abbott median 176.6 ng/l (IQR 27.9–948.1) vs. 3.6 ng/l (IQR 2.2–7.6) $p < 0.001$).

The criteria of undetectable levels of hs-cTnT (<5 ng/l) was present in 26.5%, 13.9% with hs-cTnI Siemens (<0.5 ng/l), in 11.4% with hs-cTnI Beckman Coulter (<2 ng/l) and in 12.6% with hs-cTnI Abbott (<1.9 ng/l).

### 4.2. Undetectable levels of hs-cTn for rapid rule out of AMI

Among the 443 patients who had AMI in the analysis of hs-cTnT, 435 patients (98.2%) had detectable hs-cTnT levels (≥5 ng/l) at presentation and 8 patients (2.0%) had undetectable levels (<5 ng/l) (sensitivity: 98.2%, 95% CI: 96.3%–99.2%, NPV: 98.6%, 95% CI: 97.0%–99.3%).

In the analysis of hs-cTnI (Siemens), among the 235 patients who had AMI, 233 patients (99.1%) had detectable hs-cTnI levels (≥0.5 ng/l) and 2 patients (0.9%) had undetectable levels (<0.5 ng/l) (sensitivity: 99.2%, 95% CI: 96.6%–99.9%, NPV: 98.8%, 95% CI: 95.2%–99.8%).

In the analysis of hs-cTnI (Beckman Coulter), among the 216 patients who had AMI, 215 patients (99.5%) had initially detectable hs-cTnI levels (≥2 ng/l) and 1 patient (0.5%) had undetectable levels (<2 ng/l) (sensitivity: 99.5%, 95% CI: 97.1%–100%, NPV: 99.2%, 95% CI: 95.2%–100%).

In the analysis of hs-cTnI (Abbott), among the 310 patients who had AMI, all the patients (100%) had initially detectable hs-cTnI levels (≥1.9 ng/l) and none had undetectable levels (<1.9 ng/l) (sensitivity: 100.0%, 95% CI: 98.8%–100%, NPV: 100.0%, 95% CI: 98.15%–100.0%).

### 4.3. Time since chest pain onset

In the analysis of hs-cTnT, among the 8 patients with AMI and undetectable hs-cTnT levels, 7 were early presenters (<3 h). As shown

in the Table 2, early presenters (<3 h) tended to have lower sensitivity and NPV (sensitivity 94.4%, 95% CI (87.7%–97.7%), NPV 96.4%, 95% CI (92.0%–98.5%) than late presenters (≥3 h); (sensitivity 99.4%, 95% CI (97.6%–99.9%), NPV 99.5%, 95% CI (97.9%–99.9%)) but still very high levels. Results in the analysis using hs-cTnI (Beckman Coulter), hs-cTnI (Siemens) and hs-cTnI (Abbott) were similar, as is shown in the Table 2.

### 4.4. Mortality and AMI Rate in patients with undetectable hs-cTn levels

Patients were followed during a mean period of time of 24 months. As shown in Fig. 2, no patient with undetectable levels of hs-cTnT at presentation died during the first 30 days. In contrast, 1.8% of patients with detectable levels (n = 28, 24 with AMI, 4 with other diagnosis, $p < 0.001$) died. In the analysis of hs-cTnI (Siemens) 0.6% of all patients with undetectable levels at presentation (n = 1, with AMI) died. In contrast, 2.0% of patients with detectable levels (n = 20, 17 with AMI, 3 with other diagnosis, $p = 0.01$) died. In the analysis of hs-cTnI (Beckman Coulter) none of all patients with undetectable levels at presentation died, whereas 1.9% of patients with detectable levels at presentation died (n = 19, 15 with AMI, 4 with other diagnosis, $p = 0.007$). In the analysis of hs-cTnI (Abbott) none of all patients with undetectable levels at presentation died, whereas 1.9% of patients with detectable levels at presentation died (n = 26, 22 with AMI, 4 with other diagnosis, $p = 0.05$).

As shown in Fig. 3, during the 30 first days, 1.6% of patients with undetectable levels of hs-cTnT at presentation had an AMI (including the index event diagnosed in the ED). In contrast, 28.5% of patients with detectable levels had an AMI ($p < 0.001$). In the analysis of hs-cTnI (Siemens) 1.8% of all patients with undetectable levels at presentation had an AMI during follow up. In contrast, 23.2% of patients with detectable levels had an AMI ($p < 0.001$). In the analysis of hs-cTnI (Beckman Coulter) 0.8% of all patients with undetectable levels at presentation had an AMI during 30-day follow up, whereas 22.5% of patients with detectable levels at presentation had an AMI ($p < 0.001$). In the analysis of hs-cTnI (Abbott) none of the patients with undetectable levels at presentation had an AMI during 30-day follow up, whereas 22.9% of patients with detectable levels at presentation had an AMI ($p < 0.001$).

Results referring to the 24 months follow up are described in detail in the Results section in the online-only Data Supplement.

## 5. Discussion

This analysis derived from a prospective multicenter study evaluated the criteria of undetectable levels using four different hs-cTn assays as a single variable to rule out the diagnosis of AMI in patients with acute chest pain at the time of presentation to the ED.

We report three major findings that extend and corroborate previous experience with hs-cTn assays [8–13]. First, the percentage of patients having undetectable levels of hs-cTn at presentation varied substantially among the four different hs-cTn assays used and was much higher for hs-cTnT (26.5%) as compared to the hs-cTnI assays (11.4–13.9%). These differences among hs-cTn assays may be related to analytical differences of the specific assays, as well as potential differences between hs-cTnT and hs-cTnI. The incidence of undetectable hs-cTnT levels in this cohort was similar as the incidence reported in the recent pilot study using the same assay [8]. Second, undetectable levels of hs-cTn at presentation have a very high NPV (around 99%) that seems to allow the rapid and safe rule out of AMI, particularly in patients presenting 3 h or more since the onset of chest pain. The NPV found in this study was similar to the value reported in previous pilot studies (99.8–100%), in which the final diagnosis was adjudicated based on conventional and less sensitive cTn assays [8,10,11]. One of the strengths of our study was the adjudication using values of hs-cTnT in conjunction with all available data. This is critical to reliably diagnose also patients with small AMIs, which may have been misclassified with the use of conventional cTn. Thereby, our data clearly extend previous works and help to reassure physicians that even small AMIs can be reliably ruled-out using the criteria of undetectable levels of hs-cTn at presentation. Third, mortality and AMI rate during 30-days follow up were very low in patients with undetectable hs-cTn levels, compared to patients whose levels were detectable at presentation. Our data confirm multiple previous reports regarding the low mortality in patients with acute chest pain and normal or even undetectable hs-cTn concentrations [8,26]. And highlight that hs-cTn levels, as quantitative, markers of cardiomyocyte damage, provide prognostic information even within the normal range.

These findings indicate the clinical utility of novel hs-cTn assays in patients with acute chest pain at presentation to the ED, reducing the need of serial blood testing, shortening the time to clinical decision making and hospital discharge, and decreasing the number of unnecessary hospitalizations with associated costs. Our observations

**Table 2**
Sensitivity and specificity of different hs-cTn assays for AMI at respective upper limit stratified by time from symptom onset.

| Time from symptom onset (h) | Assay and cutoff | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|---|---|---|---|---|---|
| All patients | hs-cTnT (Roche)5 ng/l | 98.0 (96.1–99.0) | 33.3 (31.0–35.6) | 28.7 (26.4–31.0) | 98.4 (96.8–99.2) |
| | hs-cTnI (Siemens)0.5 ng/l (S) | 99.2 (96.6–99.9) | 17.1 (14.8–19.7) | 22.9 (20.4–25.7) | 98.8 (95.2–99.8) |
| | hs-cTnI (Beckman)2 ng/l | 99.5 (97.1–100) | 14.0 (11.9–16.4) | 21.1 (18.7–23.8) | 99.2 (95.2–100) |
| | hs-cTnI (Abbott)1.9 ng/l | 100.0 (98.8–100) | 15.8 (13.4–17.9) | 22.6 (20.5–25.0) | 100.0 (98.2–100) |
| <3 h | hs-cTnT (Roche)5 ng/l | 94.4 (87.8–97.7) | 40.7 (35.9–45.7) | 30.2 (25.4–35.4) | 96.4 (92.0–98.5) |
| | hs-cTnI (Siemens)0.5 ng/l | 100.0 (90.1–99.8) | 19.3 (14.6–25.1) | 20.3 (15.5–26.2) | 100.0 (90.2–99.8) |
| | hs-cTnI (Beckman)2 ng/l | 97.7 (86.2–99.9) | 17.2 (12.6–22.9) | 18.3 (13.6–24.0) | 97.5 (85.3–99.9) |
| | hs-cTnI (Abbott)1.9 ng/l | 100.0 (94.6–100) | 19.0 (14.6–24.0) | 22.2 (17.6–27.3) | 100.0 (93.5–100) |
| ≥3h* | hs-cTnT (Roche)5 ng/l | 99.1 (97.2–99.8) | 30.9 (28.3–33.6) | 28.3(25.7–30.9) | 99.2 (97.5–99.8) |
| | hs-cTnI (Siemens)0.5 ng/l | 98.9 (95.8–99.8) | 16.4 (13.8–19.4) | 23.7 (20.8–26.9) | 98.3 (93.5–99.7) |
| | hs-cTnI (Beckman)2 ng/l | 100.0 (97.3–100) | 13.0 (10.7–15.8) | 21.9 (19.1–25.0) | 100.0 (95.0–99.9) |
| | hs-cTnI (Abbott)1.9 ng/l | 100.0 (98.5–100) | 14.8 (12.6–17.2) | 22.8 (20.4–25.5) | 100.0 (97.5–100) |
| <6h | hs-cTnT (Roche)5 ng/l | 96.9 (93.4–98.6) | 37.0 (33.8–40.3) | 29.0 (25.8–32.4) | 97.8 (95.4–99.0) |
| <6 | hs-cTnI (Siemens)0.5 ng/l | 100.0 (95.9–99.9) | 17.1 (14.0–20.8) | 21.4 (18.0–25.2) | 100.0 (94.6–99.9) |
| | hs-cTnI (Beckman)2 ng/l | 99.0 (93.8–100) | 15.3 (12.3–1.9) | 19.5(16.2–23.2)) | 98.7 (91.9–99.9) |
| | hs-cTnI (Abbott)1.9 ng/l | 100.0 (98.5–100) | 14.8 (12.6–17.2) | 22.9 (20.4–25.5) | 100.0 (97.5–100) |
| ≥6h* | hs-cTnT (Roche)5 ng/l | 99.1 (96.4–99.8) | 29.2 (26.1–32.6) | 28.4 (25.3–31.8) | 99.1 (96.6–99.9) |
| | hs-cTnI (Siemens)0.5 ng/l | 98.4 (93.7–99.7) | 17.2 (13.8–21.0) | 24.5 (20.9–28.6) | 97.5 (90.3–99.6) |
| | hs-cTnI (Beckman)2 ng/l | 100.0 (96.0–99.9) | 12.6 (9.7–16.1) | 22.8 (19.2–26.7) | 100.0 (92.0–99.8) |
| | hs-cTnI (Abbott)1.9 ng/l | 100.0 (97.8–100) | 14.0 (11.3–17.0) | 24.2 (21.1–27.6) | 100.0 (83.4–99.6) |

Cut off set at the lower limit of detection. CI = Confidence interval; PPV = positive predictive value; NPV = negative predictive value; hscTnT = high-sensitivity cardiac troponin.
* Overall, in 46 patients the onset of symptoms within the 12 h period preceding presentation could not be precisely defined. In this table these patients were added to the group with chest-pain ≥3 h and ≥6 h.

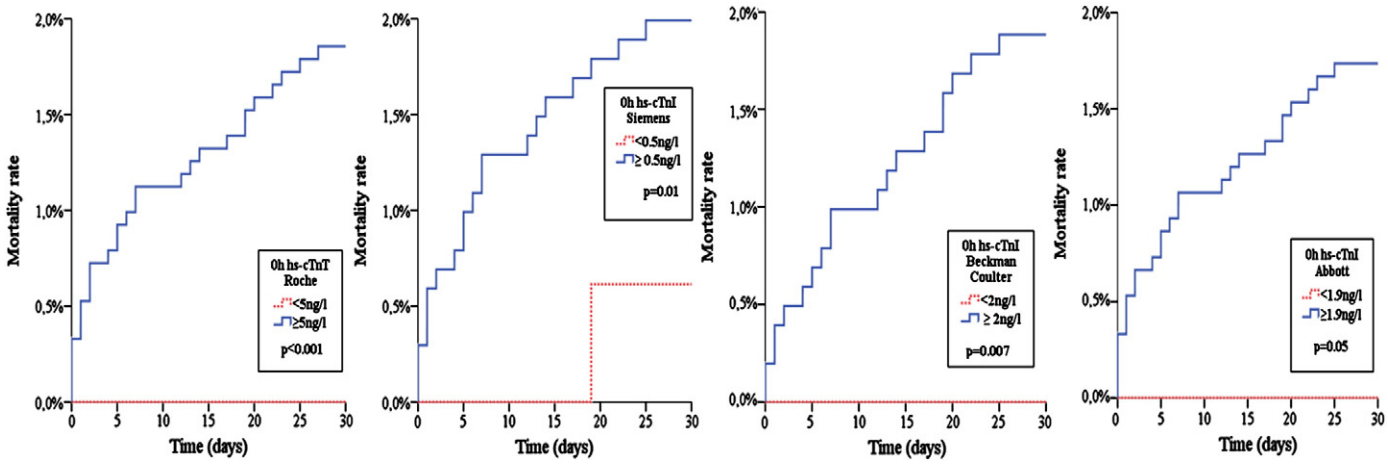


**Fig. 2.** Cumulative mortality rate within 30 days according to the hs-cTn for selected cut-offs.

also help clinicians understand that the LoD is not a biological, but an assay-specific criteria. Due to the lower sensitivity of the hs-cTnT as compared to the hs-cTnI assays, twice as many patients met the criteria of undetectable levels with hs-cTnT as compared to hs-cTnI. Once better characterization of these novel hs-cTn assays clearly defines biological criteria such as e.g. the 20th percentile or the 30th percentile of healthy individuals, these warrant to be evaluated as decision limits for the early rule out of AMI. One critical und until now largely unmet need for this standardization is the use of one specific reference populations for all hs-cTn assays to determine theier 20th or 30th percentile [27].

It is important to highlight that hs-cTn values should only be used in conjunction with the 12-lead ECG and full clinical assessment. The additional information provided by the other immediately available clinical tools should allow the physician to even reach NPV exceeding those reported for the exclusive use of hs-cTn values in this analysis. For those patients with undetectable levels of hs-cTn at presentation who continue to be perceived at risk of AMI after initial evaluation, an early second measurement of hs-cTn will often provide added diagnostic value and help clinical decision making [10].

## 6. Study limitations

Several limitations of our study merit consideration. First, we analysed the performance of undetectable levels using four different novel hs-cTn assays (hs-cTnT Roche; hs-cTnI Siemens; hs-cTnI Beckman Coulter; hs-cTnI Abbott). As our findings regarding NPV were consistent among the four different assays, we assume that it can be generalized to all hs-cTn assays. Of course, this assumption needs to be confirmed in additional studies. Second, the analysis of the three hs-cTnI assays was based on only the first ~1100 consecutive patients enrolled. Therefore the 95% CI for the NPVs with these assays are wider compared to hs-cTnT. Third, even though this algorithm may be excellent for the exclusion of AMI, other less dangerous ischemic pathologies as unstable angina may not be diagnosed, therefore further studies will be necessary to evaluate approaches to rule out the diagnosis of unstable angina. Fourth, since our study was prospective and observational, we cannot determine with precision the clinical benefit associated. Fifth, our analysis showed a high NPV also in patients with impaired renal function, however we cannot generalize this findings to patients with terminal kidney failure requiring dialysis, since they were excluded from our study. Sixth, although one of the strengths of our study was the adjudication of diagnosis using the values of hs-cTnT, this could theoretically bias a direct comparision of the diagnostic accuracy of hs-cTnI versus hs-cTnI, however should not affect the key message of this paper. Seventh, not prespecified post-hoc analysis revealed that the NPV for undetectable levels of hs-cTnT in the last 876 patients, in whom hs-cTnT levels had to be recalculated, was slightly lower than in the first 1195 patients. Therefore, our overall result for hs-cTnT (NPV 98.0%) may slightly underestimate the "true" NPV for hs-cTnT.

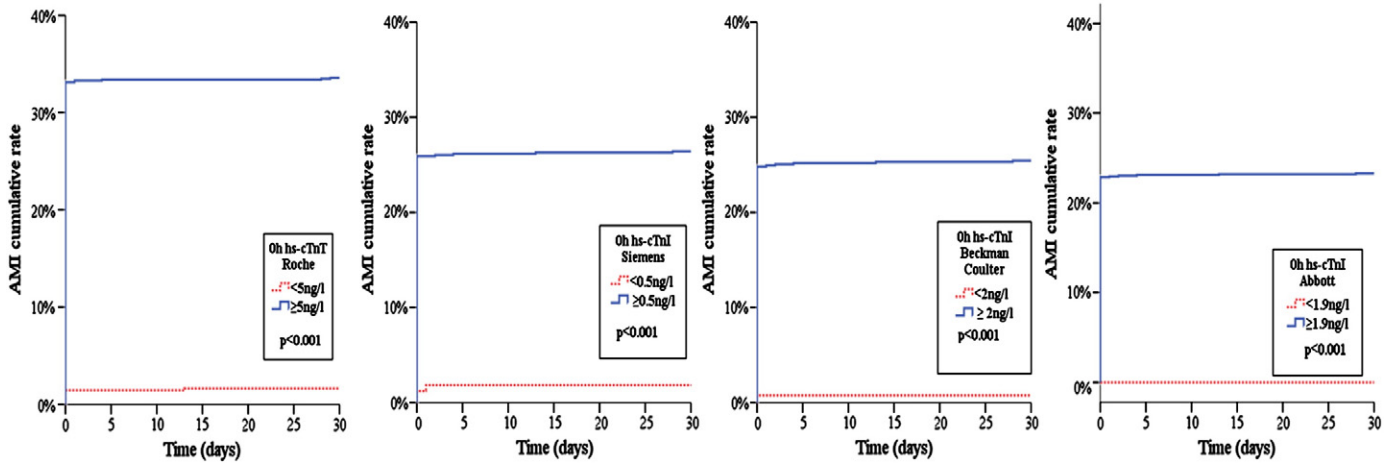


**Fig. 3.** Cumulative rate of AMI within 30 days according to the hs-cTn for selected cut-offs.

## 7. Conclusions

In conclusion, undetectable levels of hs-cTnT and hs-cTnI at presentation to the ED of patients with acute chest pain have a very high NPV for AMI, particularly in patients presenting 3 h or more since chest pain onset. Therefore using them as a suitable variable in conjunction with other clinical information including the 12-lead ECG, undetectable levels seem a very safe and effective tool to rule out AMI. This criteria applies to much more patients with hs-cTnT as compared to the investigated hs-cTnI assays. Our findings support the hypothesis that hs-cTn measurements may reduce the need for serial blood testing, shortening the time at the ED, decreasing overcrowding and the number of unnecessary hospital admissions as well as associated costs.

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## Conflict of interest

Prof. Mueller has received research grants from the Swiss National Science Foundation (PP00B-102853) and the Swiss Heart Foundation, the StiftungfürkardiovaskuläreForschung Basel, 8sense, Abbott, ALERE, Brahms, Critical Diagnostics, Nanosphere, Roche, Siemens, and the Department of Internal Medicine, of the University Hospital Basel, as well as speaker honoraria from Abbott, ALERE, Brahms, Novartis, Roche, and Siemens. We disclose that Dr. Reichlin has received research grants from the Swiss National Science Foundation (PASMP3-136995), the Swiss Heart Foundation, the University of Basel, the Professor Max Cloetta Foundation and the Department of Internal Medicine, University Hospital Basel as well as speakers honoraria from Brahms and Roche. All other authors declare that they have no conflict of interest with this study. The hs-cTn assays were donated by their respective manufacturers, who had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2013.06.049.

## References

[1] Nawar EW, Niska RW, Xu J. National Hospital Ambulatory Medical Care Survey: 2005 emergency department summary. Adv Data 2005;2007:1–32.
[2] Hamm CW, Goldmann BU, Heeschen C, Kreymann G, Berger J, Meinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. N Engl J Med 1997;337:1648–53.
[3] Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335:1342–9.
[4] Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. N Engl J Med 1996;335:1333–41.
[5] Thygesen K, Alpert JS, White HD. Joint ESCAAHAWHFTFftRoMI. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173–95.
[6] Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 2010;31:2197–204.
[7] Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000;342:1163–70.
[8] Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. J Am Coll Cardiol 2011;58:1332–9.
[9] Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56:254–61.
[10] Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858–67.
[11] Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA 2011;306:2684–93.
[12] Venge P, Johnston N, Lindahl B, James S. Normal plasma levels of cardiac troponin I measured by the high-sensitivity cardiac troponin I access prototype assay and the impact on the diagnosis of myocardial ischemia. J Am Coll Cardiol 2009;54:1165–72.
[13] Twerenbold R, Jaffe A, Reichlin T, Reiter M, Mueller C. High-sensitive troponin T measurements: what do we gain and what are the challenges? Eur Heart J 2012;33:579–86.
[14] Reichlin T, Hochholzer W, Stelzig C, et al. Incremental value of copeptin for rapid rule out of acute myocardial infarction. J Am Coll Cardiol 2009;54:60–8.
[15] Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124:136–45.
[16] Apple FS, Jesse RL, Newby LK, et al. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biochemical markers of acute coronary syndromes. Clin Chem 2007;53:547–51.
[17] Apple FS, Wu AH, Jaffe AS. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: how to use existing assays clinically and for clinical trials. Am Heart J 2002;144:981–6.
[18] Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 2012;33:2252–7.
[19] Reichlin T, Schindler C, Drexler B, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arch Intern Med 2012;172:1211–8.
[20] Haaf P, Drexler B, Reichlin T, et al. High-sensitivity cardiac troponin in the distinction of acute myocardial infarction from acute cardiac noncoronary artery disease. Circulation 2012;126:31–40.
[21] Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 2012;33:2252–7.
[22] Apple FS, Jesse RL, Newby LK, et al. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biochemical markers of acute coronary syndromes. Circulation 2007;115:e352–5.
[23] Kavsak PA, Hill SA, McQueen MJ, Devereaux PJ. In process citation Clin Chem 2013;59:574–6.
[24] Koerbin G, Tate J, Potter JM, Cavanaugh J, Glasgow N, Hickman PE. Characterisation of a highly sensitive troponin I assay and its application to a cardio-healthy population. Clin Chem Lab Med 2012;50:871–8.
[25] Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–54.
[26] Hochholzer W, Reichlin T, Twerenbold R, et al. Incremental value of high-sensitivity cardiac troponin T for risk prediction in patients with suspected acute myocardial infarction. Clin Chem 2011;57:1318–26.
[27] Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem 2012;58:1574–81.