

## Misdiagnosis of Myocardial Infarction Related to Limitations of the Current Regulatory Approach to Define Clinical Decision Values for Cardiac Troponin

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**Background**—Misdiagnosis of acute myocardial infarction (AMI) may significantly harm patients and may result from inappropriate clinical decision values (CDVs) for cardiac troponin (cTn) owing to limitations in the current regulatory process.

**Methods and Results**—In an international, prospective, multicenter study, we quantified the incidence of inconsistencies in the diagnosis of AMI using fully characterized and clinically available high-sensitivity (hs) cTn assays (hs-cTnI, Abbott; hs-cTnT, Roche) among 2300 consecutive patients with suspected AMI. We hypothesized that the approved CDVs for the 2 assays are not biologically equivalent and might therefore contribute to inconsistencies in the diagnosis of AMI. Findings were validated by use of sex-specific CDVs and parallel measurements of other hs-cTnI assays. AMI was the adjudicated diagnosis in 473 patients (21%). Among these, 86 patients (18.2%) had inconsistent diagnoses when the approved uniform CDV was used. When sex-specific CDVs were used, 14.1% of female and 22.7% of male AMI patients had inconsistent diagnoses. Using biologically equivalent CDV reduced inconsistencies to 10% ( $P<0.001$ ). These findings were confirmed with parallel measurements of other hs-cTn assays. The incidence of inconsistencies was only 7.0% for assays with CDVs that were nearly biologically equivalent. Patients with inconsistent AMI had long-term mortality comparable to that of patients with consistent diagnoses ( $P=NS$ ) and a trend toward higher long-term mortality than patients diagnosed with unstable angina ( $P=0.05$ ).

**Conclusions**—Currently approved CDVs are not biologically equivalent and contribute to major inconsistencies in the diagnosis of AMI. One of 5 AMI patients will receive a diagnosis other than AMI if managed with the alternative hs-cTn assay.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00470587.

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**Key Words:** acute cardiac care ■ biological markers ■ myocardial infarction ■ troponin

Acute myocardial infarction (AMI) is a major cause of death and disability worldwide. Patients with symptoms suggestive of AMI account for  $\approx 10\%$  of all emergency department (ED) consultations, even though only 10% to 20% of them are diagnosed as experiencing an AMI. Rapid identification of AMI is of paramount clinical importance for early treatment and management.<sup>1-3</sup>

### Editorial see p 2029 Clinical Perspective on p 2040

Misdiagnosis of AMI and inconsistencies in the diagnosis of AMI may significantly harm patients. First and most important, withholding evidence-based therapies such rhythm monitoring for 24 to 48 hours, antiplatelet therapy, high-dose statins, intense

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lifestyle modifications, and early revascularization may increase morbidity and mortality in patients with AMI.<sup>2-5</sup> Second, therapies approved for AMI may even be harmful for patients with other diagnoses such as peptic ulcer.<sup>2-5</sup> Accordingly, misdiagnosis of AMI is a common cause for malpractice claims.<sup>4</sup> The clinical introduction of the universal definition of AMI has led to a harmonization worldwide in the diagnosis of AMI and thereby contributed to a reduction in diagnostic inconsistencies.<sup>2,3,5,6</sup> Cardiac troponin (cTn) I and T are 2 proteins unique to the heart that are specific and sensitive biomarkers of cardiomyocyte damage.<sup>2,3,6</sup> According to the universal definition of AMI, a cTnI or cTnT level above the 99th percentile of a healthy reference population is a condition *sine qua non* for the diagnosis of AMI.<sup>6</sup> There are limitations to the current regulatory approach to define clinical decision values (CDVs) for cTn. Manufacturers are asked to establish the 99th percentile in a healthy reference population. Because there is a lack of consensus on how to define healthy and because possible effects of age and sex on levels of cTnI and cTnT have recently been identified, the current regulatory process has come under scrutiny.<sup>7-11</sup> Apparently, differences in these cohorts of healthy individuals are substantial and may lead to major differences in the resulting 99th percentiles and therefore the biologically nonequivalent CDV. The younger the reference population is and the more stringent the criteria to define cardiac health are, the lower the resulting 99th percentile is.<sup>7,12-14</sup> The clinical availability of fully developed high-sensitivity assays for both cTnI and cTnT in Europe and other countries now provides for the first time the methodological requirement to quantify the clinical consequences of the limitations of the current regulatory approach to define the CDVs. The aim of this large multicenter study was to explore remaining sources for misdiagnosis of AMI after the introduction of the universal definition of AMI<sup>6</sup> and to quantify inconsistencies in the diagnosis of AMI related to the limitations of the current regulatory process on how to define CDVs for cTn.<sup>7-9,13</sup>

## Methods

### Study Design and Population

The Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective, international, multicenter study designed to advance the early diagnosis of AMI.<sup>15-19</sup> From April 2006 to September 2012, consecutive adult patients presenting to the ED with symptoms suggestive of AMI with an onset or peak within the last 12 hours were recruited after providing written informed consent.

Patients were enrolled regardless of their renal function. Only patients with terminal kidney failure requiring regular dialysis were excluded. For this analysis, patients were also excluded if high-sensitivity (hs) cTnI (Abbott) or hs-cTnT (Roche) levels were not available or if the final diagnosis remained unclear after adjudication and at least 1 cTn level was elevated (possibly indicating the presence of AMI; Figure 1 in the online-only Data Supplement). The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees.

### 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. Levels of cTn were measured at presentation and serially thereafter as long as clinically indicated. Treatment of patients was left to the discretion of the attending physician.

### Measurement of Sensitive and hs-cTn

Blood samples for the determination of hs-cTnI (Abbott) and hs-cTnT (Roche) were collected at presentation to the ED and serially at 1, 2, 3, and 6 hours. When treatment required transferring the patient to the catheter laboratory or coronary care unit, serial sampling was interrupted. After centrifugation, samples were frozen at  $-80^{\circ}\text{C}$  until assayed in a blinded fashion in a dedicated core laboratory. The Abbott hs-cTnI assay used was the final precommercial release version of the ARCHITECT High Sensitive STAT Troponin I assay (Abbott Laboratories). Samples were thawed, mixed, and centrifuged before analysis according to the manufacturer's instructions. The hs-cTnI assay has a 99th percentile concentration of 26.2 ng/L with a corresponding coefficient of variation (CV) of  $<5\%$  and a limit of detection (LoD) of 1.9 ng/L.<sup>12</sup> The sex-specific 99th percentile has been defined as 15.6 ng/L in women and 34.2 ng/L in men. Long-term stability of TnI and a very high correlation between plasma and serum have been demonstrated.<sup>12,20</sup> The limit of blank and LoD of the Roche hs-cTnT assay were determined to be 3 and 5 ng/L, respectively. The 99th percentile of a healthy reference population was reported to be 14 ng/L with an imprecision corresponding to 10% CV at 13 ng/L.<sup>21</sup> The sex-specific 99th percentile has been defined as 8.9 ng/L in women and 15.5 ng/L in men.<sup>22</sup>

The Siemens sensitive Ultra cTnI assay was performed with the use of the ADVIA Centaur immunoassay system (Siemens), with an LoD of 6 ng/L, a 99th percentile cutoff point of 40 ng/L, and a CV of  $<10\%$  at 30 ng/L.<sup>23</sup> The Siemens hs-cTnI assay, an experimental prototype assay, was performed with the use of the Dimension Vista 1500 immunoassay system (Siemens), with an LoD of 0.5 ng/L, a 99th percentile cutoff point of 9 ng/L, and a CV of  $<10\%$  at 3 ng/L.<sup>24</sup> The Beckman-Coulter hs-cTnI assay was measured on the Access 2 analyzer with the use of an investigational prototype assay. According to the manufacturer, the LoD is 2 ng/L and the 99th percentile of a healthy reference population is 9 ng/L with a 10% CV lower than the 99th percentile.<sup>20</sup>

Calculation of the glomerular filtration rate was performed by the abbreviated Modification of Diet in Renal Disease formula.<sup>25</sup>

### Adjudicated Final Diagnosis

Two independent cardiologists reviewed all available medical records—patient history, physical examination, results of laboratory testing, radiological testing, ECG, echocardiography, cardiac exercise test, and lesion severity and morphology in coronary angiography—pertaining to the patient from the time of ED presentation to the 90-day follow-up. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated with a third cardiologist. For all patients recruited from all sites, the adjudication of the final diagnosis was performed centrally in the core laboratory (University Hospital Basel) using hs-cTnT Roche levels with CDV as recommended by the manufacturer and as described in detail in the Methods section in the online-only Data Supplement.

AMI was defined and cTn levels were interpreted as recommended in current guidelines.<sup>2,6,9</sup> 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 1 hs-cTnT value above the 99th percentile, together with a significant rise or fall.<sup>9</sup> For hs-cTnT, the 99th percentile (14 ng/L) was used as the cutoff for myocardial necrosis.<sup>26,27</sup> Absolute changes in hs-cTnT were used to determine significant changes on the basis of the diagnostic superiority of absolute over relative changes.<sup>17,28</sup> On the basis of studies of the biological variation of cTn<sup>29,30</sup> and data from previous chest pain cohort studies,<sup>23,31</sup> a significant absolute change was defined as a rise or fall of at least 10 ng/L within 6 hours. In patients, in whom a 6-hour hs-cTnT level was not available, changes were assessed at earlier time points. In an assumption of linearity, an absolute change of 6 ng/L within 3 hours was considered. All other patients were classified as not having AMI for this analysis.

### Follow-Up

After hospital discharge, patients were followed up by trained researchers at 3, 12, and 24 months by telephone or in written form.

## Statistical Analysis

The primary outcome measure was the percentage of patients with an adjudicated diagnosis of AMI inconsistently assigned a diagnosis of AMI or non-AMI at presentation using the approved CDVs of the hs-cTnI and hs-cTnT assays. The selection of these assays for the primary analysis is further supported by their overall comparable diagnostic accuracy for the early diagnosis of AMI.<sup>32</sup> Therefore, inconsistencies in the diagnosis of AMI cannot be attributed to different diagnostic performance of the assays. Among several criteria,<sup>2,3,6,33</sup> the diagnosis of AMI invariably requires a cTn level above the CDV. Therefore, we quantified inconsistencies about the diagnosis of AMI by the position of level pairs (troponin values of different assays at the same time point taken) according to quadrants defined by the CDV for each assay. This analysis was done twice: once using a uniform CDV for both sexes and once using the sex-specific CDV for each assay. Because hs-cTnT was used for the adjudication, the CDV of the hs-cTnT assay (14 ng/L) was used as the reference to determine the biologically equivalent CDV for the other assays by linear regression analysis. Subgroup analysis was predefined to explore potential contributing causes for inconsistencies. To explore whether and to what extent preanalytical aspects (eg, small differences from the time the sample was frozen at  $-80^{\circ}\text{C}$  until measurements were performed) could have played a role, we selected the subgroup of patients in whom the measurements of hs-cTnT and cTnI-ultra (Siemens) were performed from the same tube and on the same day. Patients with AMI were further classified as either MI type I or MI type II.<sup>6</sup> MI type 4B (related to stent thrombosis) is rare in patients presenting to the ED and has a lot in common with other type 1 MIs. Therefore MI type 4B events were classified with MI type 1 for this analysis.

Data are expressed as median $\pm$ interquartile range for continuous variables and as numbers and percentages for categorical variables. Continuous variables were compared with the Mann-Whitney *U* test, and categorical variables were compared by use of the Pearson  $\chi^2$  test. All hypothesis testing was 2 tailed, and values of  $P<0.05$  were considered statistically significant. All statistical analyses were performed with SPSS for Windows 22.0 (SPSS Inc) and MedCalc 9.6.4.0 (MedCalc software).

## Results

### Patient Characteristics

The baseline characteristics of 2300 patients with suspected AMI are shown in the Table. The adjudicated final diagnosis was AMI in 21% of patients, unstable angina in 9%, cardiac but noncoronary artery symptoms in 13%, noncardiac cause in 52%, and symptoms of unknown origin in 5%. Among the 473 AMI patients, 74 (16%) had ST-segment-elevation MI, and 399 (84%) had non-ST-segment-elevation MI. In the group of patients with non-ST-segment-elevation MI, 85% were classified as type 1 and 15% as type 2 AMI. Baseline levels of hs-cTnT Roche and hs-cTnI Abbott according to final diagnosis are shown in Figure II in the online-only Data Supplement.

### Correlation Between hs-cTnI and hs-cTnT

For hs-cTn levels measured at presentation (2300 pairs) and for all time points (6559 pairs), hs-cTnI and hs-cTnT levels correlated closely ( $r=0.813$  and  $r=0.790$ , both  $P<0.001$ ; Figure 1A). The correlation was comparable in patients with an adjudicated diagnosis of AMI ( $r=0.797$  and  $r=0.770$ , both  $P<0.001$ ; Figure 1B and 1C) and in patients with other diagnoses ( $r=0.799$  and  $r=0.808$ , both  $P<0.001$ ). Distribution of hs-cTnI and hs-cTnT values in quadrants according to the approved uniform CDVs in patients with an adjudicated diagnosis of AMI was comparable to that in the overall cohort regardless of the adjudicated diagnosis. Detectable levels

**Table. Baseline Characteristics**

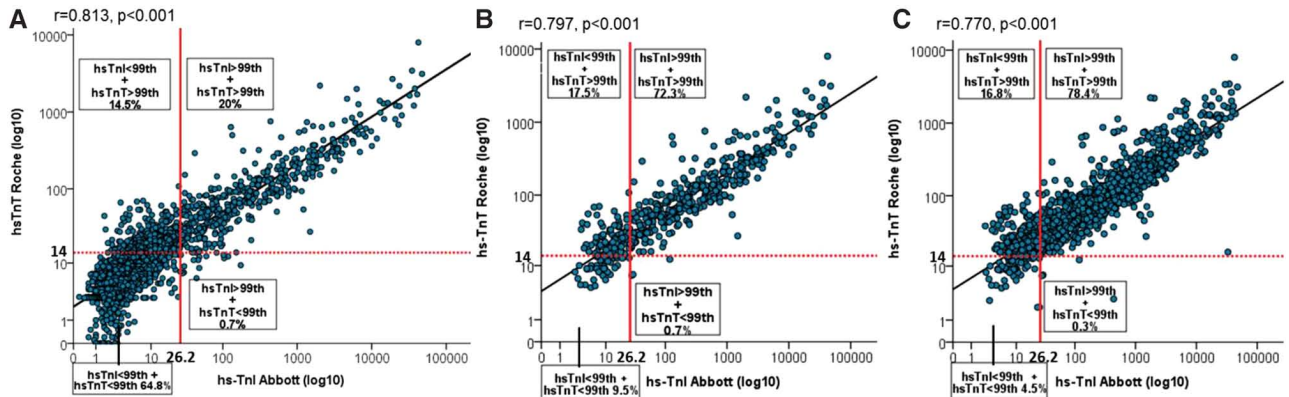
Characteristic	All (n=2300)	AMI (n=473)	No AMI (n=1827)	P-Value
Age, y	62 (49–75)	72 (59–80)	60 (47–73)	<0.001
Risk factors, n (%)				
Hypertension	1432 (62)	368 (78)	1064 (58)	<0.001
Hypercholesterolemia	1147 (50)	309 (65)	838 (46)	<0.001
Diabetes mellitus	401 (18)	125 (27)	276 (15)	<0.001
Current or previous smoking	1415 (62)	302 (64)	1113 (61)	0.2
Family history	569 (27)	137 (32)	432 (26)	0.01
History, n (%)				
Coronary artery disease	794 (35)	220 (47)	574 (31)	<0.001
Previous AMI	525 (23)	148 (31)	377 (21)	<0.001
Previous revascularization	621 (27)	156 (33)	465 (26)	0.001
Peripheral artery disease	145 (6)	60 (13)	85 (5)	<0.001
Previous stroke	126 (6)	43 (9)	83 (5)	<0.001
ECG findings, n (%)				
Left bundle-branch block	69 (3)	25 (5)	44 (2)	0.001
ST-segment elevation	102 (5)	70 (15)	32 (2)	<0.001
ST-segment depression	266 (12)	155 (34)	111 (6)	<0.001
T-wave inversion	317 (14)	121 (26)	196 (11)	<0.001
Body-mass index, kg/m <sup>2</sup>	26 (24–30)	26 (24–29)	26 (24–30)	0.3
eGFR, mL·min <sup>-1</sup> ·1.73 m <sup>-2</sup>	85 (69–101)	74 (57–94)	87 (71–103)	<0.001
Medication at presentation, n (%)				
ASA	828 (36.0)	219 (46)	609 (33)	<0.001
Vitamin K antagonists	194 (8)	44 (9)	150 (8)	0.4
$\beta$ -Blockers	790 (34)	194 (41)	596 (33)	0.001
Statins	798 (35)	199 (42)	599 (33)	<0.001
ACEIs/ARBs	867 (38)	231 (50)	636 (35)	<0.001
Calcium antagonists	326 (14)	87 (18)	239 (13)	0.003
Nitrates	259 (11)	87 (18)	172 (9)	<0.001

Values are expressed as median $\pm$ interquartile range when appropriate. ACEI indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; and eGFR, estimated glomerular filtration rate.

(higher than or equal to the LoD) of hs-cTnI and hs-cTnT were observed in 87.7% and 75.5% of all samples ( $P<0.001$ ;  $n=6559$ ). The scatter between hs-cTnI and hs-cTnT seemed rather uniform throughout the entire range of hs-cTn values.

### Diagnostic Inconsistencies for AMI

AMI was the adjudicated diagnosis in 473 patients (21%). Among these, 86 patients (18.2%) had inconsistent diagnoses using the uniform CDV at presentation. The incidence was 17.1% for the analysis of all level pairs obtained during serial sampling. These inconsistencies seemed to be due at least in part to the fact that the approved CDV for hs-cTnI is not biologically equivalent to the approved CDV for hs-cTnT (Figure 2).



**Figure 1.** Distribution of high-sensitivity cardiac troponin I (hs-TnI) and high-sensitivity cardiac troponin T (hs-TnT) values in quadrants according to the approved uniform clinical decision values (A) at any time during serial sampling in the overall cohort regardless of the adjudicated diagnosis, (B) in patients with an adjudicated diagnosis of acute myocardial infarction for levels at presentation, and (C) at any time during serial sampling.

The biologically equivalent hs-cTnI value corresponding to the CDV for hs-cTnT was less than half the approved CDV for hs-cTnI. Therefore, nearly all of these inconsistencies were related to the underdiagnosis of AMI with hs-cTnI. The diagnostic accuracy for AMI of the different assays is shown in Table I in the online-only Data Supplement. At the approved CDV, hs-cTnT had higher sensitivity, whereas hs-cTnI had higher specificity and PPV.

With the hs-cTnI sex-specific CDV, 14.1% of women and 22.7% of men with AMI had inconsistent diagnoses at presentation, again nearly all of them related to underdiagnosis of AMI with hs-cTnI (Figure 3A and 3B). Median cTn values in patients with inconsistent diagnoses of AMI were lower than in patients with consistent diagnoses, indicating smaller infarct size (Table I in the online-only Data Supplement).

These findings were confirmed with parallel measurements using other sensitive cTn and hs-cTn assays, showing that most did not have biologically equivalent CDV (Figure 4A–4F). The incidence of inconsistencies for level pairs obtained at presentation in patients with AMI was as low as 7.0% for assays with CDVs that were nearly biologically equivalent.

### Diagnostic Inconsistency With Biologically Equivalent CDVs

Using the hs-cTnI (Abbott) biologically equivalent CDV for hs-cTnT (8.7 instead of 26.2 ng/L) reduced inconsistencies in the diagnosis of AMI to 86 of 473 AMIs (18.2%; 83 underdiagnoses with hs-cTnI, 3 underdiagnoses with hs-cTnT) to 47 of 473 (22 underdiagnoses with Abbott, 25 underdiagnoses with Roche; 9.9%;  $P<0.001$ ).

These findings were replicated with the use of other hs-cTn assays; for example, using the sensitive Ultra cTnI (Siemens) biologically equivalent CDV for hs-cTnT (9.4 instead of 40 ng/L) reduced inconsistencies from 17% to 10.3% ( $P<0.001$ ).

### Subgroup Analysis Concerning Potential Preanalytical Contributors

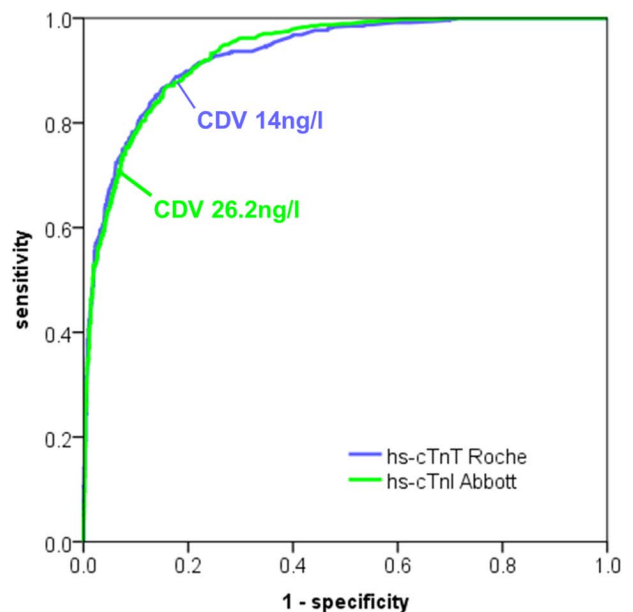
Preanalytical aspects did not seem to be relevant contributors to the observed inconsistencies because findings in the subgroup with identical preanalytical conditions and in fresh samples were similar to those in the overall cohort (Figure III and Methods section in the online-only Data Supplement).

### Long-Term Mortality in Patients With Inconsistent AMI Diagnoses

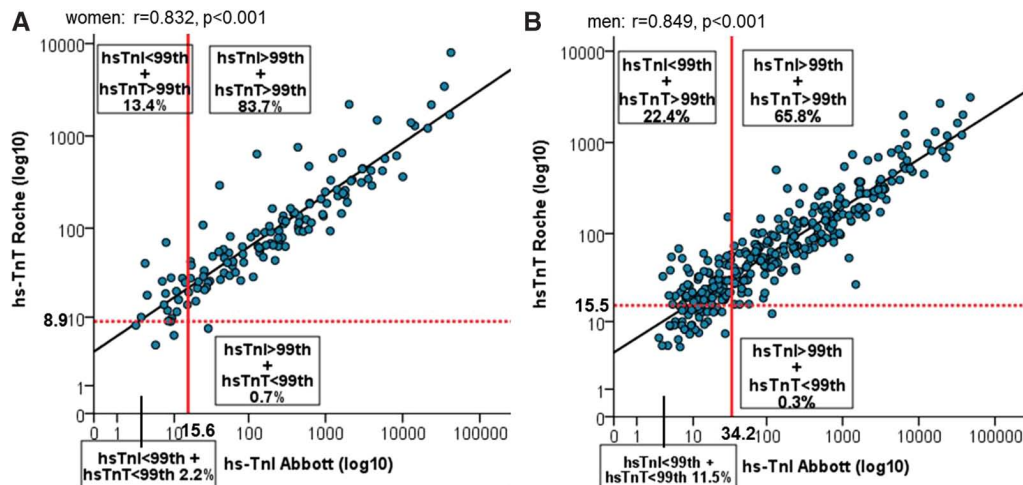
Patients with inconsistent AMI diagnoses (eg, Roche<sup>+</sup>/Abbott<sup>-</sup> or Roche<sup>-</sup>/Abbott<sup>+</sup>) resulting from biologically nonequivalent CDVs for different pairs of cTn assays had long-term mortality (12 deaths among 86 patients) comparable to that of patients with consistent AMI diagnoses (Roche<sup>+</sup>/Abbott<sup>+</sup>; 66 deaths among 387 patients;  $P=NS$  for all comparisons; Figure 5A and 5B). Patients with inconsistent AMI diagnoses for Roche/Abbott had higher mortality than patients consistently diagnosed as unstable angina (15 deaths in 216 patients;  $P=0.05$ ).

### Discussion

Misdiagnosis of AMI may occur in patients with or without ST-segment elevation and may significantly harm patients.<sup>5</sup>



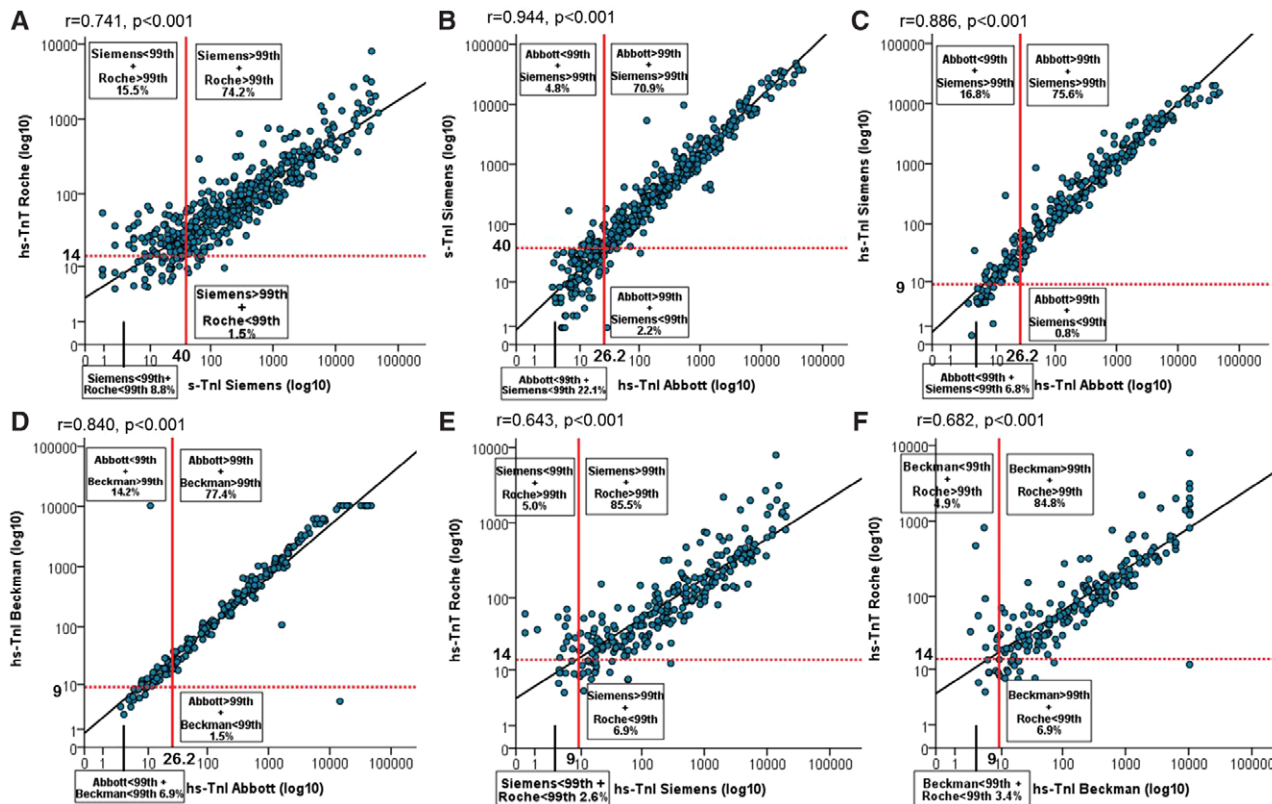
**Figure 2.** Receiver-operating characteristics curve for acute myocardial infarction (AMI). The approved clinical decision values (CDVs) for high-sensitivity cardiac troponin I (hs-TnI) and high-sensitivity cardiac troponin T (hs-TnT) are not biologically equivalent and therefore differ in their sensitivity and specificity for AMI.



**Figure 3.** Distribution of high-sensitivity cardiac troponin I (hs-TnI) and high-sensitivity cardiac troponin T (hs-TnT) values at presentation in quadrants according to the sex-specific clinical decision values in patients with an adjudicated diagnosis of acute myocardial infarction: (A) in women; and (B) in men.

This large, multicenter study reports 8 major findings about the misdiagnosis of AMI related to the limitations of the current regulatory process on how to define CDVs for cTn. First, among level pairs of hs-cTnI and hs-cTnT, the correlation was high and similar for levels obtained at presentation and during serial sampling, as well as in the overall diagnostic cohort and in patients adjudicated to have AMI. Second

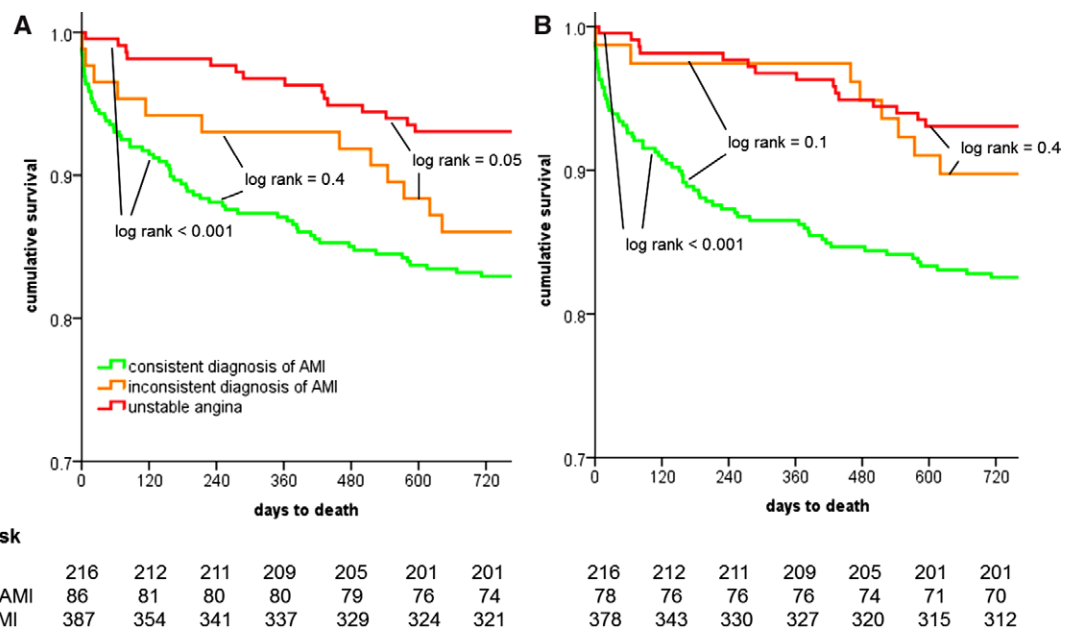
and most important, with the use of the approved uniform CDV, the 99th percentile of healthy individuals, almost 1 of 5 AMI patients had inconsistent diagnoses using hs-cTnI versus hs-cTnT. This means that of 100 patients diagnosed as having AMI in institution A with hs-cTnT, 20 patients would receive a diagnosis other than AMI if treated in institution B using hs-cTnI. It is important to highlight that these assays



**Figure 4.** Distribution of sensitive cardiac troponin (s-Tn) and high-sensitivity cardiac troponin (hs-Tn) I and T values at presentation in quadrants according to the approved uniform clinical decision values in patients with an adjudicated diagnosis of acute myocardial infarction. (A) Pairs of hs-TnT and s-TnI Ultra (Siemens); (B) pairs of hs-TnI (Abbott) and s-TnI Ultra (Siemens); (C) pairs of hs-TnI (Abbott) and hs-TnI (Siemens); (D) pairs of hs-TnI (Abbott) and hs-TnI (Beckman Coulter); (E) pairs of hs-TnT and hs-TnI (Siemens); and (F) pairs of hs-TnT and hs-TnI (Beckman Coulter).

overall have comparable diagnostic accuracy for the early diagnosis of AMI.<sup>32</sup> Therefore, the observed inconsistencies cannot be attributed to differences in diagnostic accuracy. Inconsistencies seemed to be attributable to a large extent to the fact that the approved CDV for hs-cTnI is not biologically equivalent to the approved CDV for hs-cTnT. In fact, the biologically equivalent hs-cTnI value corresponding to the CDV for hs-cTnT was less than half the approved CDV for hs-cTnI. This finding is supported by a recent observation that the 99th percentile of hs-cTnI in an Australian cohort of healthy individuals was also less than half the approved CDV for this assay.<sup>12</sup> The observation that most of the inconsistencies were related to underdiagnosis of AMI with hs-cTnI does not indicate that the hs-cTnI assay would have lower sensitivity. In fact, our data confirmed previous investigations documenting even higher analytical sensitivity for hs-cTnI versus hs-cTnT with a substantially higher percentage of patients with detectable hs-cTnI versus hs-cTnT levels.<sup>13</sup> Therefore, among 2 excellent hs-cTn assays that overall have very high and comparable diagnostic accuracy in the early diagnosis of AMI,<sup>32</sup> the test with even higher analytical sensitivity applied clinically as approved in many countries worldwide results in a substantial underdiagnosis of AMI because the approved CDV is much higher than the biologically equivalent CDV of hs-cTnT. It is important to highlight that the use of hs-cTnT as reference and for adjudication does not affect the main findings of the study. If we would have used hs-cTnI as the reference, the percentage of inconsistencies would have been identical, merely with the majority of inconsistencies resulting from overdiagnosis of AMI with hs-cTnT. In addition, it is important to emphasize that our findings do not and should not be used to criticize manufacturers or regulators but rather to quantify the limitations of the current process and to encourage them to pursue new roads for the definition

of CDV. To put the implications of these inconsistencies into perspective, it might help to highlight that the change in AMI incidence resulting from these inconsistencies is of a magnitude similar to that of the change in AMI incidence occurring when switching clinically from a conventional cTn assay to an hs-cTn assay.<sup>34</sup> Third, the discrepancies resulting from biologically nonequivalent CDVs affected all patients regardless of their final diagnosis and therefore are also independent of the details of the adjudication. For example, they result in discrepancies of similar magnitude between the diagnoses of pericarditis and perimyocarditis, with the respective differences in patient management. Fourth, the incidence of inconsistencies could not be significantly reduced with the use of sex-specific CDVs because the sex-specific CDV for hs-cTnI is not biologically equivalent to the sex-specific CDV for hs-cTnT in both women and men. Fifth, these findings were confirmed in parallel measurements with several other hs-cTnI assays. Sixth, the incidence of inconsistencies was as low as 7.0% for level pairs of hs-cTnI assays with CDVs that were nearly biologically equivalent, further supporting the hypothesis that more than half of the observed inconsistencies in the diagnosis of AMI could be avoided by a new regulatory process that ensures that CDVs for cTn are biologically equivalent. Seventh, preanalytical issues did not seem to be relevant contributors to our findings. Among 1355 patients with parallel measurements of hs-cTnT and sensitive Ultra cTnI performed from the same tube and on the same day, as well as hs-cTnI and hs-cTnT in fresh samples, findings were similar to those of the overall cohort. Eighth, patients with inconsistent AMI diagnoses had long-term mortality comparable to that of patients with consistent AMI diagnosis. This observation supports the conclusion that these events are clinically meaningful and require detection and appropriate treatment.



**Figure 5.** Kaplan–Meier survival curves in patients with consistent diagnoses of acute myocardial infarction (AMI), patients with inconsistent diagnoses resulting from biologically nonequivalent clinical decision values for the different pairs of cardiac troponin assays, and patients with diagnoses of unstable angina. **A**, Pairs of high-sensitivity cardiac troponin (hs-cTn) T and hs-cTnI (Abbott); and **B**) pairs of hs-cTnT and sensitive cTnI Ultra (Siemens).

The findings of this large multicenter study corroborate and extend other recent observations that had begun to challenge the current regulatory process to define CDVs for cTn, the 99th percentile of healthy individuals, by documenting the effect of population selection.<sup>7,9,12,13,35</sup> In the current regulatory process, each manufacturer defines the 99th percentile in a separate cohort of healthy individuals. Apparently, differences in these cohorts of healthy individuals are substantial and lead to major differences in the resulting 99th percentiles (the CDV). The younger the reference population is and the more stringent the criteria to define cardiac health are, the lower the resulting 99th percentile is.<sup>7,12–14</sup>

Our findings also have an impact on clinical trials that use AMI as the primary end point and highlight the potential underreporting or overreporting of AMI events, depending on the assay used. That could substantially affect the reporting of AMI rates that test the efficacy or safety of drug compounds being considered for approval in case of imbalance in the assay type. In some trials, the ratio of the peak cTn to the 99th percentile is expressed as a multiple to provide a gross estimate of AMI size. This measure is based on the assumption that the 99th percentiles of different cTn assays are biologically identical. The findings of this study clearly highlight that this assumption seems to be incorrect and accordingly raise serious concerns about the use of this measure in clinical trials.

How could a new regulatory process be designed to provide biologically equivalent CDVs for cTn? It is necessary to examine the problem from several perspectives to find a cut point or cut points that have high sensitivity and specificity in all circumstances. One might consider 2 novel approaches. First, all manufacturers could use the same cohort of healthy individuals for the derivation of the respective 99th percentile of all clinical assays. Although this solution seems rather obvious and has been discussed by laboratory experts, regulators, and diagnostic companies for many years, the lack of data quantifying the limitations of the current regulatory process might well have delayed implementation. Second, if this collaborative effort among different manufacturers fails, an alternative would be to appropriately define the CDV (99th percentile) of 1 hs-cTn assay in a very large, well-characterized cohort of healthy individuals and to perform parallel measurements with all other clinical hs-cTn assays in a disease cohort such as APACE to establish biologically equivalent CDVs, for example, via linear regression or receiver-operating characteristics curve analysis. Our findings are supported by inconsistencies about AMI diagnosis observed with the use of 2 conventional cTn assays applying the 10% CV level as CDVs, which resulted in 11.1% inconsistencies.<sup>36</sup>

One cannot reiterate often enough the clinical rule that levels of cTn must always be used and interpreted in conjunction with all other clinical information.<sup>9</sup> On the other hand, regardless of the clinical presentation, regardless of the ECG findings, and regardless of the findings during coronary angiography, unless there is a rise in cTn above the 99th percentile indicating relevant cardiomyocyte damage, a nonfatal clinical event cannot be classified as AMI. Therefore, despite the clinical rule mentioned above, cTn has become such a crucial diagnostic tool that its regulatory aspects should fulfill the highest standards. Unfortunately, our data clearly show that currently this does not seem to be the case.

Several limitations of this study should be considered in the interpretation of our findings. First, we quantified inconsistencies exclusively in the diagnosis of AMI. It is important to highlight that patients with other diagnoses possibly underlying acute chest pain (eg, pericarditis versus perimyocarditis) also will receive inconsistent diagnoses as a result of the biologically nonequivalent CDVs. However, we are unable to quantify their incidence with sufficient precision. Therefore, this analysis tends to underestimate the clinical implications of biologically nonequivalent CDVs of cTn. Second, our main findings were obtained by measuring in parallel the 2 hs-cTn assays that have been approved for clinical use in Europe and many other countries. Accordingly, the CDVs of these assays are well established. The CDVs of some of the precommercial hs-cTnI assays used for the validation of our findings may be considered less well established. Third, although this study included patients with various types of chronic kidney disease and various degrees of renal dysfunction, patients with terminal kidney disease on chronic hemodialysis were excluded. Therefore, we cannot comment on CDVs of cTnI or cTnT in those patients. Fourth, this study cannot quantify the increase in morbidity or mortality possibly associated with missing these 18% of AMI patients with discordant CDVs, who usually have small AMIs. Given the substantial reduction in morbidity and mortality shown by currently available treatments for AMI, including rhythm monitoring, antiplatelet therapy, high-dose statins, intense lifestyle modifications, and early revascularization,<sup>2,23</sup> we assume that overall the harm could be substantial.

## Conclusions

Currently approved CDVs for cTn are not biologically equivalent and therefore contribute to major inconsistencies in the diagnosis of AMI. One of 5 AMI patients will receive a diagnosis other than AMI if managed with the alternative hs-cTn assay.

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### CLINICAL PERSPECTIVE

In an international, prospective, multicenter study, we quantified the incidence of inconsistencies in the diagnosis of acute myocardial infarction (AMI) using fully characterized and clinically available high-sensitivity cardiac troponin (hs-cTn) assays (hs-cTnI, Abbott; hs-cTnT, Roche) among 2300 consecutive patients with suspected AMI. Currently approved clinical decision values are not biologically equivalent and contribute to major inconsistencies in the diagnosis of AMI: Almost 1 of 5 AMI patients had inconsistent diagnoses with the use of hs-cTnI versus hs-cTnT. The incidence of inconsistencies was significantly reduced with clinical decision values that were nearly biologically equivalent, supporting the assumption that half of the observed inconsistencies in the diagnosis of AMI could be avoided by a new regulatory process that ensures that clinical decision values for cTn are biologically equivalent. Patients with inconsistent AMI diagnoses had long-term mortality comparable to that of patients with consistent diagnoses of AMI. This finding suggests that these events require detection and appropriate treatment.

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