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Early diagnosis of acute myocardial infarction in patients with pre-existing coronary artery disease using more sensitive cardiac troponin assays

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Aims We sought to examine the diagnostic and prognostic utility of sensitive cardiac troponin (cTn) assays in patients with pre-existing coronary artery disease (CAD).

Methods and results We conducted a multicentre study to examine the diagnostic accuracy of one high-sensitive and two sensitive cTn assays in 1098 consecutive patients presenting with symptoms suggestive of acute myocardial infarction (AMI), of whom 401 (37%) had pre-existing CAD. Measurements of Roche high-sensitive cTnT (hs-cTnT), Siemens cTnI-Ultra, Abbott-Architect cTnI and the standard assay (Roche cTnT) were performed in a blinded fashion. The final diagnosis was adjudicated by two independent cardiologists. Acute myocardial infarction was the final diagnosis in 19% of CAD patients. Among patients with diagnoses other than AMI, baseline cTn levels were elevated above the 99th percentile with Roche hs-cTnT in 40%, with Siemens TnI-Ultra in 15%, and Abbott-Architect cTnI in 13% of them. In patients with pre-existing CAD, the diagnostic accuracy at presentation, quantified by the area under the receiver operator characteristic curve (AUC), was significantly greater for the sensitive cTn assays compared with the standard assay (AUC for Roche hs-cTnT, 0.92; Siemens cTnI-Ultra, 0.94; and Abbott-Architect cTnI, 0.93 vs. AUC for the standard assay, 0.87; $P < 0.01$ for all comparisons). Elevated levels of cTn measured with the sensitive assays predicted mortality irrespective of pre-existing CAD, age, sex, and cardiovascular risk factors.

Conclusion Sensitive cTn assays have high-diagnostic accuracy also in CAD patients. Mild elevations are common in non-AMI patients and test-specific optimal cut-off levels tend to be higher in CAD patients than in patients without history of CAD. Sensitive cTn assays also retain prognostic value. (ClinicalTrials.gov number, NCT00470587).

Keywords Acute myocardial infarction • Coronary artery disease • Troponin • Diagnosis • Prognosis

Introduction

Acute myocardial infarction (AMI) is a major cause of death and disability. Its rapid and accurate diagnosis is critical for effective evidence-based medical management and treatment,[1,2] but still an unmet clinical need. Delayed 'rule-in' increases morbidity and mortality, particularly in patients with pre-existing coronary artery disease (CAD).[3,4] Delayed 'rule-out' prolongs the time spent in the emergency department (ED), increasing patients' anxiety, and causes enormous costs for the health-care system.[5]

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More sensitive cardiac troponin (cTn) assays with a limit of detection (LoD) below the 99th percentile of a reference population and improved precision have recently become available in clinical practice.[6–8] These assays improved the early diagnosis of AMI in unselected patients with acute chest pain.[9,10] However, their diagnostic accuracy in patients with pre-existing CAD is uncertain, as recently elevated cTn levels were found in >10% of patients with stable CAD.[11,12]

Also for several other reasons, patients with pre-existing CAD merit particular attention. First, they are at increased risk for both AMI as well as anxiety related to non-cardiac causes of chest pain. Secondly, interpretation of a 12-lead electrocardiography (ECG) is challenging in these patients: pre-existing ST-segment and T-wave alterations are frequent, and new ST-segment elevation is less common in patients with pre-existing CAD.[13] Thirdly, the utility of CT angiography is considerably reduced in such patients.[14,15] Fourthly, the impact of myocardial loss is particularly devastating when the ventricles have already suffered previous assaults, and delayed diagnosis of AMI yields especially severe consequences.[3,4] We therefore examined the diagnostic performance of more sensitive cTn assays for the early diagnosis of AMI in patients with pre-existing CAD, presenting with acute chest pain to the ED.

Methods

Study design and population

The Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) Study is an ongoing prospective multicentre study designed, coordinated by the University Hospital Basel. From April 2006 to June 2009, a total of 1247 consecutive patients presenting to the ED with chest pain suggestive of AMI with onset or peak within the last 12 h were recruited. Patients with end-stage renal failure requiring dialysis were excluded. Pre-existing CAD was defined as history of previous AMI, previous coronary revascularization for obstructive CAD, or known coronary artery stenosis exceeding 50%. For analysis, patients were included if baseline values of all four cTn assays were available.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients. The authors designed the study, gathered and analysed the data, vouch for the data and analysis, wrote the paper, and made the decision to submit it for publication. The assays were donated by the manufacturers, who had no role in the design of the study, data analysis, manuscript, or decision to submit for publication.

Routine clinical assessment

All patients underwent an initial clinical assessment that included history-taking, a physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood tests, and chest radiography. Cardiac troponin I or cTnT, CK-MB, and myoglobin were measured at presentation and 6–9 h after, or as long as clinically indicated. The precise timing of clinical post-baseline measurements and the treatment of patients were left to the discretion of the attending physician.

Adjudicated final diagnosis

To determine the final diagnosis for each patient, two independent cardiologists reviewed all available medical records from the time of the patient's arrival in the ED to the end of the 90-day follow-up period. When there was disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

An AMI, ST-elevation or Non-ST-elevation myocardial infarction, was defined in accordance with current guidelines.[16] In brief, an AMI was diagnosed when there was evidence of myocardial necrosis in association with clinical signs of myocardial ischaemia and/or ECG findings suggestive of myocardial ischaemia. Necrosis was diagnosed by a 30% rising and/or falling pattern of the local cTn level, with at least one value above the 99th percentile, at a level of imprecision of <10% (for detailed information see Supplementary material online, Appendix).[6,17] The following cTn assays were used for the adjudication of the final diagnosis at participating hospitals: Abbott-Axsym cTnI ADV, Beckmann Coulter Accu cTnI, and Roche cTnT. All three are well-validated current cTn assays with comparable performance in the diagnosis of AMI.[6,17] Unstable angina (UA) was diagnosed when a patient had normal cTn levels and typical angina at rest, a deterioration of a previously stable angina, in cases of positive cardiac exercise testing or cardiac catheterization showing coronary arteries with stenosis of 70% or more of the vessel diameter, or when the diagnosis was uncertain but follow-up information showed that the patient had an AMI or a sudden cardiac death within 60 days after presentation. Further predefined diagnostic categories included cardiac but not coronary symptoms (e.g. tachyarrhythmias), non-cardiac causes, and symptoms of unknown origin. If AMI was ruled out in the ED but no sufficient diagnostic procedures were performed to establish a conclusive diagnosis, symptoms were classified as being of unknown origin.

Cardiac troponin analysis

Blood samples for determination of cTn levels with four cTn assays one high-sensitive cTnT (hs-cTnT) assay: Roche high-sensitive-cTnT;[18] two sensitive cTnI assays: Siemens cTnI-Ultra,[7,8] Abbott-Architect cTnI;[18] and one standard cTnT assay: Roche cTnT,[18,19] were collected into tubes containing potassium EDTA or serum within the first hour of the patient's presentation to the ED. Additional samples were collected at 1, 2, 3, and 6 h. Serial sampling was discontinued when the diagnosis of AMI was certain and treatment required transferring the patient to the catheter laboratory or coronary care unit. After centrifugation, samples were frozen at −80°C until they were assayed in a blinded fashion in two batches in a dedicated core laboratory. In contrast to the standard assay, the more sensitive cTn assays have a LoD below the 99th percentile of a normal reference population.[7,8,18]

All Roche assays were performed with the use of the Elecsys 2010 system (Roche Diagnostics): cTnT (fourth generation) with a LoD of 0.01 ng/mL, a 99th percentile cut-off point of <0.01 ng/mL, and a coefficient of variation of <10% at 0.035 ng/mL; and high-sensitive-cTnT with a LoD of 0.003 ng/mL (3 ng/L), a 99th percentile cut-off point of 0.014 ng/mL (14 ng/L), and a coefficient of variation of <10% at 0.013 ng/mL (13 ng/L).[20] The Siemens cTnI-Ultra assay was performed with the use of the ADVIA Centaur immunoassay system (Siemens), with a LoD of 0.006 ng/mL (6 ng/L), a 99th percentile cut-off point of 0.04 ng/mL (40 ng/L), and a coefficient of variation of <10% at 0.03 ng/mL (30 ng/L), as specified by the manufacturer.[7–9] The Abbott-Architect cTnI assay was performed with the use of the Architect system (Abbott Diagnostics), with a LoD of 0.01 ng/mL (10 ng/L), a 99th percentile cut-off point of 0.028 ng/mL (28 ng/L), and a coefficient of variation of <10% at 0.032 ng/mL (32 ng/L), as specified by the manufacturer.

Statistical analysis

Continuous variables are presented as means (±SD) or medians (with the inter-quartile range), and categorical variables as numbers and percentages. Continuous variables were compared with the use of the Mann–Whitney test and categorical variables with the use of the Pearson-χ^2-square test. Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity of cTn measurements obtained at specific times with the four assays and to compare their ability to diagnose AMI. Logistic regression was used to combine cTn levels at presentation with early changes in cTn levels. The comparison of areas under the ROC curves (AUC) was performed as recommended by DeLong *et al.*[21] The optimal cut-off values were determined by the minimal distance of the ROC-curve to the point (0;1) of the graph. We used the relevant cross table at this cut-off point to calculate sensitivity and its 95% confidence interval (95% CI), and determined the troponin values around this cut-off, that corresponded to the 95% CI.[22] Sensitivities and specificities were compared with a Mc Nemar χ^2 test in the case of paired binary outcomes.[23] In the case of independent binary outcomes, we used the χ^2 test to compare sensitivity, specificity, and positive, and negative predictive values. For the analysis of the prognostic value of the sensitive cTn assays, we did Kaplan–Meier analysis and presented cumulative survival rates at 1 year, subgrouping for pre-existing CAD, diagnosed AMI and elevated sensitive cTn levels above the 99th percentile. We estimated 95% CIs estimated by the standard error. Furthermore, we performed a separate Cox regression analysis for each assay including the cTn elevation above the 99th percentile, pre-existing CAD, age, sex, and cardiovascular risk factors that represented independent predictors for death (arterial hypertension and diabetes) and for AMI during follow-up (arterial hypertension and hypercholesterolaemia) in univariate regression models. All hypothesis testing was two-tailed, and *P*-values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with the use of SPSS for Windows, version 15.0 (SPSS), MedCalc software, version 10.3.0 (MedCalc), and the R statistical package (online at http://www.R-project.org).

Results

Characteristics of the patients

Of the 1247 consecutively enrolled patients, measurement of all four cTn assays was obtained at presentation from 1098 patients, of whom 401 (37%) had pre-existing CAD. Patients with pre-existing CAD differed in several baseline characteristics from those without pre-existing CAD (*Table 1*).

Acute myocardial infarction was the adjudicated final diagnosis in 19% of patients with pre-existing CAD when compared with 14% in patients without pre-existing CAD ($P < 0.01$). In patients with pre-existing CAD, other adjudicated diagnoses included UA in 27%, cardiac symptoms from causes other than CAD in 10%, non-cardiac causes in 34%, and symptoms of unknown origin in 10% (*Table 2*).

Cardiac troponin levels at presentation

Among the patients, whose final diagnosis was not an AMI, patients with pre-existing CAD had significantly higher baseline levels of all three more sensitive cTn compared with patients without a history of CAD: median levels in CAD patients were 0.014 mg/dL (IQR: 0.009–0.024), with hs-cTnT; 0.01 mg/dL (IQR: 0.004–0.025), with cTnI-Ultra; and 0.003 mg/dL (IQR: 0–0.011), with Abbott-Architect cTnI; compared with 0.005 mg/dL (IQR: 0.003–0.009), with hs-cTnT; 0.004 mg/dL (IQR: 0.001–0.011), with cTnI-Ultra; and 0.000 mg/dL (IQR: 0.000–0.002), with Abbott-Architect cTnI in patients without a history of CAD ($P < 0.001$ for all comparisons).

Forty per cent of the CAD patients, with a final diagnosis other than AMI, had elevated baseline levels above the 99th percentile with the hs-cTnT, 15% had elevated baseline levels above the 99th percentile with the Siemens cTnI-Ultra, and 13% had elevated baseline levels above the 99th percentile with the Abbott-Architect cTnI assay. Among patients without a history of CAD the percentages were significantly smaller (18%, 9 and 7%; $P < 0.001$, $P = 0.002$, and $P = 0.004$, respectively; see *Figure 1*). Among all patients with elevated cTn levels above the 99th percentile measured with the hs-cTnT, the Siemens cTnI-Ultra, and the Abbott-Architect cTnI assay 24%, 10 and 9%, had UA while 34%, 9 and 7% had non-cardiac chest pain, respectively (see *Table 3*).

Diagnostic accuracy of cardiac troponin in the early diagnosis of acute myocardial infarction

In patients with pre-existing CAD, the diagnostic accuracy for AMI, quantified by the AUC, was significantly higher with the sensitive cTn assays than that with the standard assay (AUC for Roche hs-cTnT, 0.92; 95% CI: 0.89–0.95; for Siemens cTnI-Ultra, 0.94; 95% CI: 0.91–0.96; and for Abbott-Architect cTnI, 0.93; 95% CI: 0.90–0.95; vs. AUC for the standard assay, 0.87; 95% CI: 0.83–0.90; $P = 0.01$, $P = 0.003$, $P = 0.007$, respectively, for comparisons; *Table 4*, Supplementary material online, *Table S4B* and *Figure 2A*). Overall, the diagnostic accuracy was similar among the three sensitive assays ($P > 0.05$).

Optimal cut-off for cardiac troponin in the early diagnosis of acute myocardial infarction determined by receiver operating characteristic curve

The optimal cut-off value to separate AMI from non-AMI determined by ROC analysis in CAD patients was more than twice the 99th percentile for hs-cTnT [0.030 ng/mL (30 ng/L)], and close to the 99th percentile for both sensitive cTnI assays [0.034 ng/mL (34 ng/L) for Abbott-Architect cTnI and 0.046 ng/mL (46 ng/L) for Siemens cTnI-Ultra; see *Table 5* and *Figure 2A*]. The optimal cut-off value to separate AMI from non-AMI in patients without a history of CAD was close to the 99th percentile for hs-cTnT [0.020 ng/mL (20 ng/L)] and half the 99th percentile for Abbott-Architect cTnI [0.015 ng/mL (15 ng/L); see *Table 5* and *Figure 2C*].

Diagnostic performance in the early diagnosis of acute myocardial infarction at the 99th percentile

Overall, at the 99th percentile, all cTn assays showed lower specificity in patients with pre-existing CAD when compared with

Table 1 Baseline characteristics of the patients

	All patients (n = 1098)	Patients with a history of CAD[a] (n = 401)	Patients without a history of CAD (n = 697)	P-value*	Patients with a history of CAD		
					Acute myocardial infarction		P-value
					Yes (n = 77)	No (n = 324)	
Male gender, no (%)	756 (67)	307 (77)	424 (61)	<0.001	58 (75)	249 (77)	0.78
Age, year							
Median	64	72	59	<0.001	75	70	<0.001
Inter-quartile range	51–75	59–79	47–72		68–84	57–78	
Risk factors, no (%)							
Hypertension	693 (63)	320 (82)	361 (53)	<0.001	63 (82)	267 (82)	0.90
Hypercholesterolaemia	492 (45)	282 (71)	210 (30)	<0.001	49 (64)	233 (72)	0.15
Diabetes	217 (20)	126 (31)	91 (13)	<0.001	26 (34)	100 (31)	0.59
Current smoking	265 (24)	74 (19)	191 (27)	0.001	18 (23)	56 (17)	0.21
History of smoking	391 (36)	194 (48)	197 (28)	<0.001	31 (40)	163 (50)	0.11
History, no (%)							
Previous myocardial infarction	271 (25)	271 (68)	0	<0.001	54 (70)	217 (67)	0.60
Previous revascularization	296 (27)	295 (74)	1 (0)[b]	<0.001	49 (64)	245 (76)	0.03
Previous PCI	254 (23)	253 (63)	1 (0)[b]	<0.001	37 (48)	216 (67)	0.002
Previous CABG	111 (10)	111 (28)	0	<0.001	24 (31)	87 (27)	0.45
Peripheral artery disease	76 (7)	57 (14)	19 (3)	<0.001	15 (20)	42 (13)	0.14
Impaired kidney function	115 (11)	88 (22)	27 (4)	<0.001	23 (30)	65 (20)	0.06
Previous stroke	64 (6)	32 (8)	32 (5)	0.02	11 (14)	21 (7)	0.02
Vital Status, median (IQR)							
Heart rate, b.p.m.	75 (66–89)	71 (62–82)	78 (68–92)	<0.001	80 (65–97)	69 (61–79)	<0.001
Systolic blood pressure, mmHg	142 (127–160)	138 (124–157)	144 (129–161)	<0.001	140 (118–162)	138 (124–155)	0.87
Diastolic blood pressure, mmHg	84 (74–93)	80 (70–89)	86 (77–95)	<0.001	78 (67–88)	80 (71–89)	0.28
Body mass index	26 (24–30)	27 (24–30)	26 (24–29)	0.062	26 (24–29)	27 (24–30)	0.05
Medication							
ACE inhibitors/AT-II blockers	536 (49)	270 (67)	266 (38)	<0.001	53 (69)	203 (63)	0.33
ASA	420 (38)	297 (74)	123 (18)	<0.001	56 (73)	241 (75)	0.77
Beta-blockers	411 (37)	288 (72)	123 (18)	<0.001	47 (61)	241 (74)	0.02
Calcium antagonists	184 (17)	120 (30)	64 (9)	<0.001	21 (5)	99 (30)	0.57
Diuretics	299 (27)	170 (42)	129 (19)	<0.001	45 (58)	125 (38)	0.002
Lipid-lowering drugs	393 (36)	293 (73)	100 (14)	<0.001	48 (62)	245 (76)	0.02
Nitrates/molsidomin	132 (12)	109 (27)	23 (3)	<0.001	29 (38)	80 (25)	0.02
ECG							
Potential ischaemic ECG changes	247 (23)	109 (27)	138 (20)	0.004	41 (53)	68 (21)	<0.001
ST-segment elevation	58 (5)	19 (5)	39 (6)	0.556	12 (16)	7 (2)	<0.001
ST-segment depression	131 (12)	57 (14)	74 (11)	0.071	29 (38)	28 (8)	<0.001
Abnormal Q-wave	112 (10)	75 (19)	37 (5)	<0.001	14 (18)	61 (19)	0.90
Left bundle branch block	42 (4)	25 (6)	17 (2)	0.001	13 (17)	12 (4)	<0.001
T-wave inversion	147 (13)	71 (18)	76 (11)	0.001	24 (31)	47 (14)	0.001

[a]CAD, coronary artery disease.
[b]Patient with aortal dissection and consecutive coronary dissection but without relevant coronary artery disease.
*χ^2 test for comparison of proportions of patients with a history of coronary artery disease and patients without coronary artery disease.

Table 2 Final diagnoses of the patients

	All patients ($n = 1098$)	History of CAD[a] ($n = 401$)	No history of CAD ($n = 697$)	*P*-value*
Acute myocardial infarction	173 (16)	77 (19)	96 (14)	0.02
ST-segment elevation	41 (4)	15 (4)	26 (4)	0.99
Non-ST-segment elevation	132 (12)	62 (16)	70 (10)	0.01
UA	152 (14)	108 (27)	44 (6)	<0.001
Cardiac cause, but not CAD	147 (13)	39 (10)	108 (16)	0.01
Non-cardiac cause	528 (48)	136 (34)	392 (56)	<0.001
Unknown	98 (9)	41 (10)	57 (8)	0.25

[a]CAD, coronary artery disease.
*χ^2 test for comparison of proportions of patients with a history of coronary artery disease and patients without coronary artery disease.

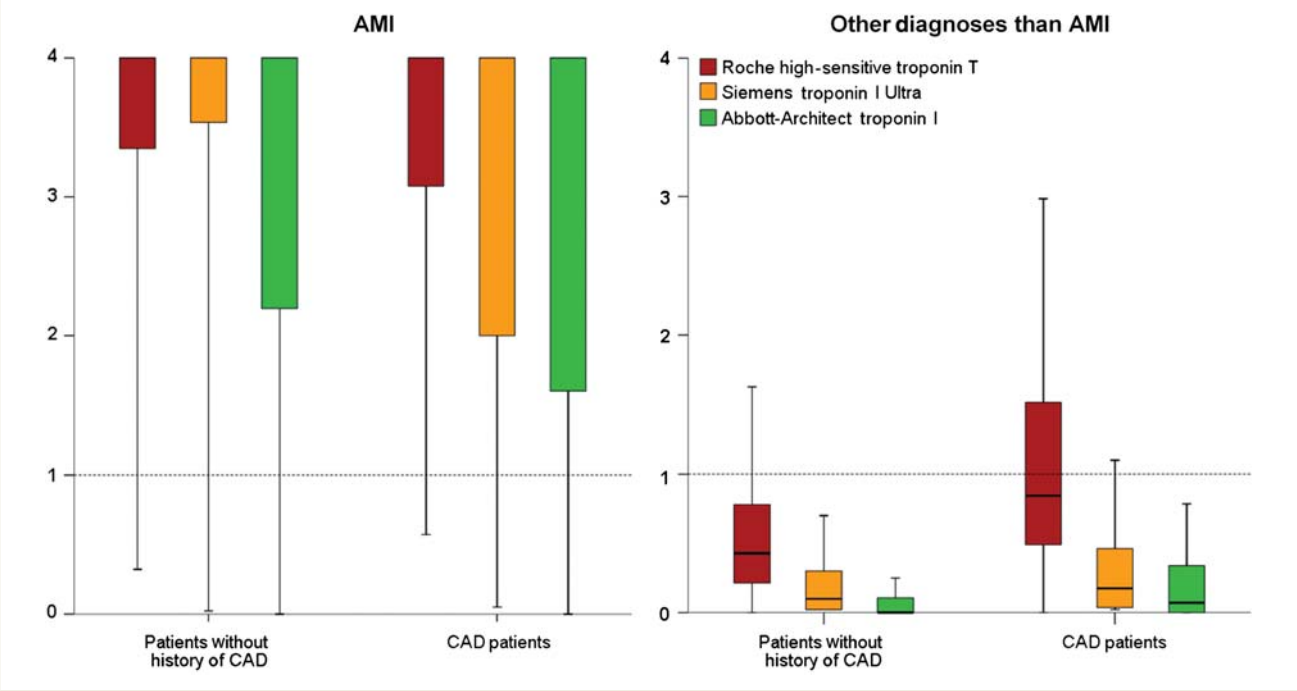

Figure 1 Baseline levels of sensitive troponin assays at presentation. Cardiac troponin levels at presentation displayed as multiples of the 99th percentile. Boxes represent inter-quartile ranges, while whiskers display ranges (without outliers further than 1.5 inter-quartile ranges). CAD denotes coronary artery disease. Left side: in patients with final diagnosis of acute myocardial infarction, troponin levels compared within assays were similar in patients with pre-existing coronary artery disease compared with patients without a history of coronary artery disease (all $P > 0.05$). Right side: in patients with final diagnosis other than acute myocardial infarction, troponin levels compared within assays were significantly higher in patients with pre-existing coronary artery disease (all $P < 0.001$).

patients without a history of CAD (*Table 4*). The decrease in specificity was particularly pronounced with hs-cTnT (59% in CAD patients vs. 81% in patients without a history of CAD, $P < 0.001$).

Diagnostic accuracy of cardiac troponin in the diagnosis of ACS (acute myocardial infarction or unstable angina)

The diagnostic accuracy for acute coronary syndroms (ACS), quantified by the AUC, was similarly low with the three sensitive cTn assays in patients with pre-existing CAD, (AUC for Roche hs-cTnT, 0.66; 95% CI: 0.61–0.70; for Siemens cTnI-Ultra, 0.67; 95% CI: 0.62–0.72; and for Abbott-Architect cTnI, 0.67; 95% CI: 0.63–0.72), but moderate to high in patients without a history of CAD (AUC for Roche hs-cTnT 0.89; 95% CI: 0.86–0.91; AUC for Siemens cTnI-Ultra,0.86, 95% CI: 0.83–0.89; AUC for Abbott-Architect cTnI, 0.86, 95% CI: 0.83–0.88; $P < 0.001$ for all comparisons of AUC in patients with vs. without a history of CAD). For the diagnosis of acute coronary syndromes (AMI or UA), the negative predictive value of a measured cTn-value

Table 3 Final diagnoses of patients with cardiac troponin levels above the 99th percentile

	High-sensitive troponin T ($n = 402$)	Siemens troponin I ultra ($n = 257$)	Abbott-Architect troponin I ($n = 229$)
Acute myocardial infarction	162 (40)	155 (60)	146 (64)
ST-segment elevation	125 (31)	119 (46)	114 (50)
Non-ST-segment elevation	37 (9)	36 (14)	32 (14)
UA	58 (14)	26 (10)	21 (9)
Cardiac cause, but not CAD	71 (18)	44 (17)	39 (17)
Non-cardiac cause	81 (20)	23 (9)	16 (7)
Unknown	30 (8)	9 (4)	7 (3)

CAD, coronary artery disease.

Table 4 Diagnostic performance of sensitive troponin assays at the 99th percentile; at 10% coefficient of variation for the standard assay (95% CI)

		History of CAD	No history of CAD	*P*-value*
Sensitive troponin assays				
Roche high-sensitive troponin T 99th percentile [0.014 ng/mL (14 ng/L)]	Sensitivity	94 (85–98)	94 (87–98)	0.998
	Specificity	59 (54–65)	81 (78–84)	<0.001
	Negative predictive value	97 (94–99)	99 (97–100)	0.452
	Positive predictive value	35 (29–41)	45 (39–52)	0.137
Siemens troponin I ultra 99th percentile [0.040 ng/mL (40 ng/L)]	Sensitivity	91 (82–96)	89 (81–94)	0.880
	Specificity	85 (80–88)	91 (88–93)	0.007
	Negative predictive value	98 (95–99)	98 (97–99)	0.883
	Positive predictive value	58 (49–67)	62 (53–69)	0.832
Abbott-Architect troponin I 99th percentile [0.028 ng/mL (28 ng/L)]	Sensitivity	83 (73–91)	85 (77–92)	0.918
	Specificity	87 (83–91)	93 (91–95)	0.016
	Negative predictive value	96 (93–98)	98 (96–99)	0.292
	Positive predictive value	61 (51–70)	66 (57–74)	0.719
Standard troponin assay				
Roche troponin T 4th generation 99th percentile (unknown) 10% CV (0.035 ng/mL)	Sensitivity	69 (57–79)	83 (57–77)	0.988
	Specificity	97 (94–99)	95 (96–99)	0.788
	Negative predictive value	93 (90–95)	95 (93–96)	0.417
	Positive predictive value	84 (73–92)	83 (73–90)	0.958

CAD, coronary artery disease; CV, coefficient of variation.
*χ^2 test for comparison of proportions of patients with a history of coronary artery disease and patients without coronary artery disease.

below the 99th percentile was 64% (57–71%) for the Roche hs-cTnT, 65% (60–71%) for the Siemens cTnI-Ultra, and 64% (58–69%), for the Abbott-Architect cTnI assay. In patients without a history of CAD, the negative predictive value was 93% (91–95%), 92% (89–94%), and 91% (88–93%), respectively.

Cardiac troponin levels in patients with recent onset of chest pain

In patients with pre-existing CAD the superiority of the sensitive cTn assays in the diagnosis of AMI was most pronounced among patients with recent onset of chest pain (*Figure 2B*, *Figure 3*, and Supplementary material online, *Table S4A*).

Among CAD patients who presented within 3 h after the onset of chest pain ($n = 167$), the AUCs for the four assays were as follows: Roche hs-cTnT, 0.86 (95% CI: 0.80–0.91); Siemens cTnI-Ultra, 0.96 (95% CI: 0.92–0.98); Abbott-Architect cTnI, 0.93 (95% CI: 0.89–0.97); and the standard assay, 0.76 (95% CI: 0.64–0.88) ($P < 0.01$, $P < 0.001$, $P < 0.001$, respectively, for the comparisons of the sensitive assays with the standard assay). The AUCs of the sensitive cTnI assays, Siemens cTnI-Ultra and Abbott-Architect cTnI, were higher than the AUC of the Roche hs-cTnT assay ($P = 0.012$ and $P = 0.051$, respectively; *Figure 2B* and *Figure 3*).

For patients without a history of CAD, who presented within 3 h to the ED, the three sensitive cTn assays had comparable

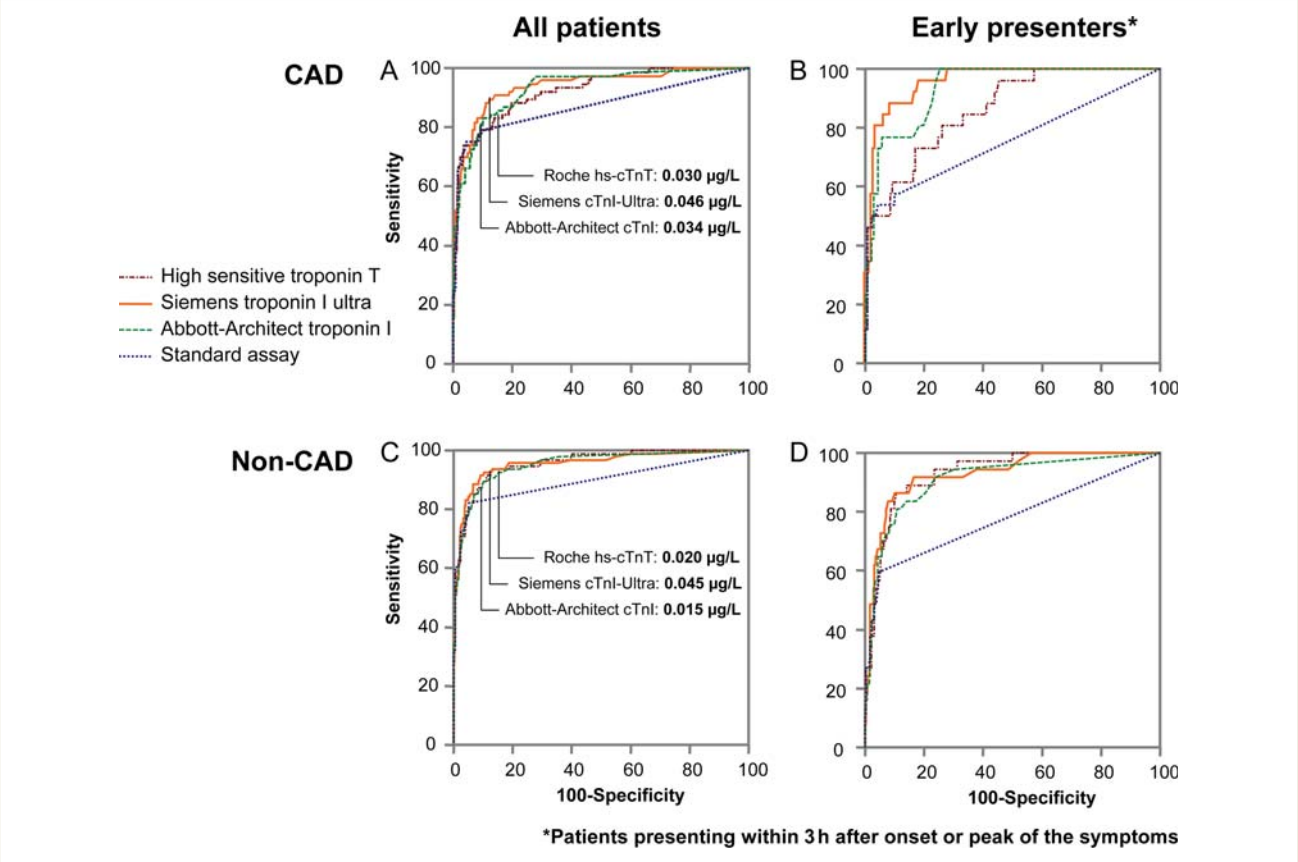

Figure 2 Diagnostic performance of cardiac troponin at presentation. Receiver operating characteristic curves describing the diagnostic performance of different cardiac troponin assays at presentation for the diagnosis of acute myocardial infarction in patients with a history of coronary artery disease (top), and in those without a history of coronary artery disease (bottom). Left side: presenting within 12 h from chest pain onset/maximum. Right side: presenting within 3 h. (*A*) and (*C*) The calculated optimal cut-off values for patients with and without a history of coronary artery disease are defined by the point farthest from the point (0,1) of the graph.

accuracy (AUC for Roche hs-cTnT, 0.93; 95% CI: 0.90–0.96; Siemens cTnI-Ultra, 0.93; 95% CI: 0.90–0.96; Abbott-ArchitectcTnI, 0.91; 95% CI: 0.88–0.94; *Figure 2D* and *Figure 3*).

Serial cardiac troponin levels

During serial sampling the AUC for all cTn assays increased (Supplementary material online, *Table S4B*). Absolute values of changes in high-sensitive cTn levels from presentation to 1 and 2 h alone had similar diagnostic accuracy as the baseline high-sensitive cTn levels. The combination of baseline levels plus early changes improved the performance of the baseline level for all cTn assays. With the hs-cTnT assay and the Siemens cTnI-Ultra assay this increase in accuracy was statistically significant for the combination of the baseline level and the change already within the first hour after presentation ($P = 0.032$ and $P = 0.039$, respectively); with the Abbott-Architect cTnI assay this increase was only significant for the combination of the baseline level and the change within 2 h after presentation ($P = 0.02$; Supplementary material online, *Table S4C*).

With the standard assay the diagnostic performance of the combination of baseline levels plus early change at 2 h was superior to that of the combination of baseline levels and early change at 1 h. The diagnostic performance of the combinations was higher than that of early changes alone, and superior to the single measurement at presentation (all *P*-values < 0.05; see Supplementary material online, *Table S4C*).

Prognostic value of sensitive cardiac troponin assays

Median follow-up was 379 days (IQR: 107–721) days. Among the whole cohort, 58 patients died and 53 patients sustained an AMI during follow-up. Cumulative survival rates for patients with pre-existing CAD were 0.88 at 1 year vs. 0.98 in patients without a history of CAD (log-rank test: $P < 0.001$). In patients with AMI, survival rates at 1 year were 0.82 vs. 0.97 in patients with other diagnoses than AMI (log-rank test: $P < 0.001$). In patients with elevated levels of Roche hs-cTnT, Siemens cTnI-Ultra, and Abbott-Architect cTnI above the 99th percentile, survival rates were 0.87, 0.83, 0.85 vs. 0.99, 0.98, 0.97 in patients with cTn levels below the 99th percentile (all comparisons by log-rank test <0.001; for details see Supplementary material

Table 5 Diagnostic performance of sensitive troponin assays in patients with pre-existing coronary artery disease at the optimal cut-off determined by the receiver operating characteristic curve (95% CI)

	Optimal cut-off ROC	Corresponding cTn values[a]		Optimal cut-off ROC	99th percentile	*P*-value*
Sensitive troponin assays						
Patients with pre-existing coronary artery disease						
Roche high-sensitive troponin T 99th percentile [0.014 ng/mL (14 ng/L)]	0.030 ng/mL (30 ng/L)	0.025–0.035	Sensitivity Specificity	83 (73–91) 86 (82–89)	94 (85–98) 60 (54–65)	0.008 <0.001
Siemens troponin I ultra 99th percentile [0.040 ng/mL (40 ng/L)]	0.046 ng/mL (46 ng/L)	0.034–0.083	Sensitivity Specificity	88 (79–95) 89 (85–92)	91 (82–96) 85 (80–88)	0.500 <0.001
Abbott-Architect troponin I 99th percentile [0.028 ng/mL (28 ng/L)]	0.034 ng/mL (34 ng/L)	0.020–0.061	Sensitivity Specificity	83 (73–91) 90 (86–93)	83 (73–91) 87 (83–91)	1 0.008
Sensitive troponin assays						
Patients without pre-existing coronary artery disease						
Roche high-sensitive troponin T 99th percentile [0.014 ng/mL (14 ng/L)]	0.020 ng/mL (20 ng/L)	0.016–0.025	Sensitivity Specificity	91 (83–96) 88 (86–91)	94 (87–98) 82 (79–85)	0.250 <0.001
Siemens troponin I ultra 99th percentile [0.040 ng/mL (40 ng/L)]	0.045 ng/mL (45 ng/L)	0.029–0.066	Sensitivity Specificity	89 (80–94) 93 (90–95)	89 (80–94) 91 (89–93)	1 0.016
Abbott-Architect troponin I 99th percentile [0.028 ng/mL (28 ng/L)]	0.015 ng/mL (15 ng/L)	0.010–0.024	Sensitivity Specificity	90 (82–95) 90 (87–92)	85 (77–92) 93 (91–95)	0.125 <0.001

*Comparisons among patients by McNemar χ^2 test.
[a]cTn values that correspond to the 95% confidence interval of the sensitivity at the ROC-derived optimal cut-off.

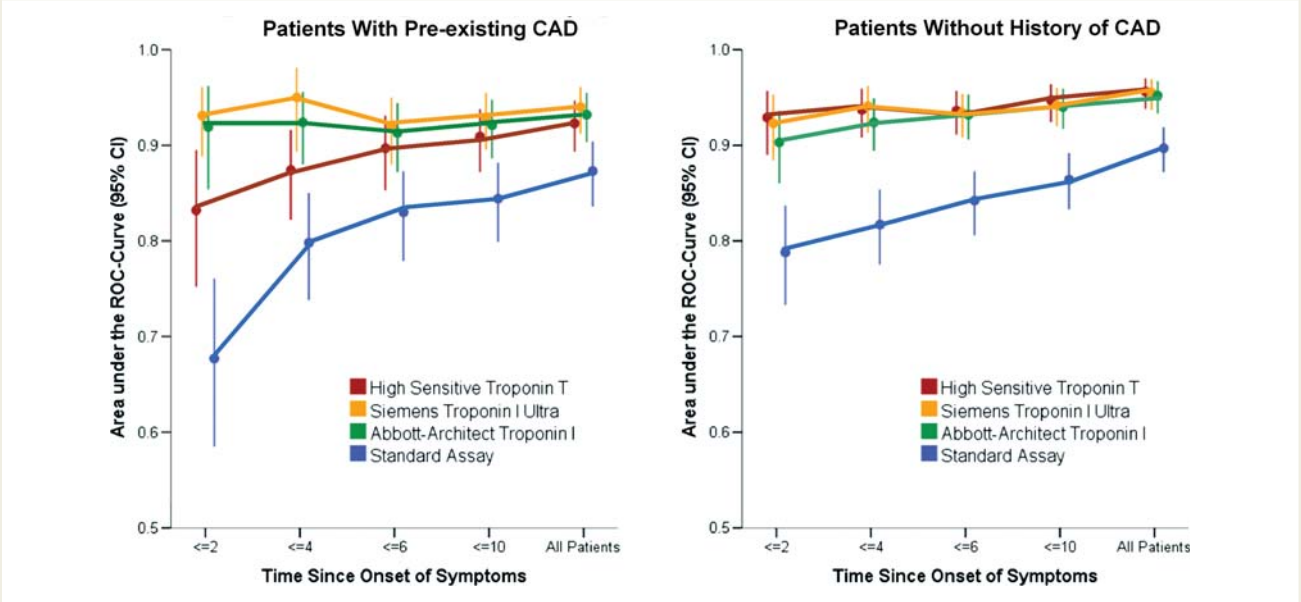

Figure 3 Diagnostic accuracy at presentation according to chest pain onset. Area under the receiver operating characteristic curves and 95% confidence intervals for the different cardiac troponin assays at presentation in the diagnosis of acute myocardial infarction according to the time from the onset of chest pain. Left: patients with a history of coronary artery disease. Right: patients without a history of coronary artery disease.

online, *Table S5A* and *B* in the Supplementary material online, Appendix).

Elevated levels of Roche hs-cTnT as well as Siemens cTnI-Ultra above the 99th percentile strongly predicted mortality independent of the presence of pre-existing CAD, age, sex, arterial hypertension, and diabetes in all patients (HR: 2.3, 95% CI: 1.1–5.1, $P = 0.034$; HR: 2.3, 95% CI: 1.2–4.4, $P = 0.009$; respectively).

In Cox regression analyses, adjusting for pre-existing CAD, age, sex, arterial hypertension, and hypercholesterolaemia, none of the sensitive cTn assays predicted AMI during follow-up (all *P*-values not significant).

Discussion

In this prospective multicentre study, we address important issues related to the clinical application of sensitive cTn assays and examined the impact of pre-existing CAD on their diagnostic and prognostic accuracy. We provide seven important findings with impact on their best possible use in the early diagnosis of AMI:.

First, the prevalence of elevated sensitive cTnI and hs-cTnT levels above the 99th percentile in CAD patients with a final diagnosis other than AMI was high and differed largely among the three novel cTn assays, ranging from 13 to 40%. Clinically, the high incidence of elevated cTn levels in CAD patients challenges the application of the 99th percentile for the decision limit for the diagnosis of AMI, as suggested in current guidelines. Careful clinical assessment and thoughtful differential diagnosis are required to separate AMI from a variety of acute and chronic disorders also associated with low-level myocardial necrosis.[24] In addition, the difference regarding the incidence of cTn levels above the 99th percentile in CAD patients without AMI might indicate the presence of important differences in the release of cTnI and cTnT in these non-AMI settings, which is further supported by recent data.[11,12] An alternative explanation for the difference regarding the incidence of elevated cTn levels is the fact that the 99th percentiles for the three sensitive assays were not determined in the same reference population.

Second, for all three sensitive cTn assays, the diagnostic accuracy at presentation was nevertheless significantly higher than with the standard assay in CAD patients as well as in patients without a history of CAD.

Third, the ROC-derived optimal cut-off levels for CAD patients tended to be higher than in patients without a history of CAD, although the AUC of sensitive cTn assays did not differ significantly comparing CAD and non-CAD patients. All cTn assays showed higher sensitivity but lower specificity in CAD patients when compared with patients without a history of CAD, reflecting the higher baseline levels in CAD patients without AMI. These findings highlight the clinical need to develop test-specific algorithms that fine tune the application of these novel tests in patients with acute chest pain.[12]

Fourthly, the superiority of the sensitive cTn assays was most pronounced among CAD patients with a recent onset of chest pain, offering the opportunity to minimize myocardial damage by extending early treatment options to AMI patients without ST-segment elevation.[1,2]

Fifthly, the sensitive cTnI assays seemed to outperform the hs-cTnT assay in early presenters.

Sixthly, the accuracy of sensitive cTn assays to diagnose ACS (AMI or UA) was significantly lower in patients with pre-existing CAD when compared with patients without pre-existing CAD. Further research is necessary to identify biomarkers that reliably detect myocardial ischaemia irrespective of necrosis, particularly in patients with pre-existing CAD.[25]

Seventhly, the Roche hs-cTnT and the sensitive Siemens cTnI-Ultra assay predict mortality independent of age, sex, pre-existing CAD, and cardiovascular risk factors. Our findings extend the results of previous studies, investigating the mortality of apparently healthy subjects with elevated levels measured with sensitive cTnI assays.[11,26,27]

The following limitations of the current study merit consideration. First, we evaluated three sensitive cTn assays. We hypothesize that our findings can be generalized to other cTn assays with similar sensitivity and precision. However, additional studies need to confirm this hypothesis. Secondly, in this ongoing prospective study, the subgroup analysis of patients with pre-existing CAD was not predefined at the time of the initial protocol written in 2005. It was added while we were still blinded to the results in 2009, with regard to recent investigations, challenging the diagnostic accuracy of sensitive cTn assays in CAD patients.[11,12] Therefore, e.g. our analysis of the assay-specific ROC-derived optimal cut-off values to differentiate AMI from other causes of acute chest pain should be considered exploratory and requires confirmation in additional studies. Third, this observational study cannot quantify exactly the clinical benefit associated with the increase in early diagnostic accuracy. To add this important information, intervention studies seem warranted. Fourth, the first 800 blood samples for the hs-cTnT assay were collected into tubes containing serum, while all other blood samples were collected into tubes containing potassium EDTA, which might lead to slightly different concentration values. Fifthly, some of the patients with positive sensitive cTn values classified as non-AMIs might have had small AMIs below the decision value of conventional cTn. Presumably, this contributed to the reduced specificity of the sensitive assays.

In conclusion, sensitive cTn assays introduce diagnostic improvements as well as challenges. The excellent diagnostic performance of sensitive cTn assays in the early diagnosis of AMI can be extended to patients with pre-existing CAD. However, elevated cTn levels at presentation are common also in CAD patients with diagnoses other than AMI, challenging differential diagnosis. Accordingly, the accuracy to diagnose ACS was lower in patients with pre-existing CAD when compared with patients without pre-existing CAD and optimal cut-off levels tend to be higher. Sensitive cTn assays have prognostic value in patients with a final diagnosis other than AMI.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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