Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays

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Aims	To examine the diagnostic accuracy of sensitive cardiac troponin (cTn) assays in elderly patients, since elevated levels with sensitive cTn assays were reported in 20% of elderly patients without acute myocardial infarction (AMI).
Methods and results	In this multi-centre study, we included 1098 consecutive patients presenting with symptoms suggestive of AMI, 406 (37%) were >70 years old. Measurement of three investigational sensitive cTn assays [Roche high-sensitive cTnT (hs-cTnT), Siemens cTnI-Ultra, and Abbott-Architect cTnI) and the standard assay (Roche cTnT) was performed in a blinded fashion. The final diagnosis was adjudicated by two independent cardiologists. Acute myocardial infarction was the adjudicated final diagnosis in 24% of elderly patients. Among elderly patients without AMI, baseline cTn levels were elevated above the 99th percentile in 51% with Roche hs-cTnT, in 17% with Siemens TnI-Ultra, and 13% with Abbott-Architect cTnI. The diagnostic accuracy as quantified by the area under the receiver operating characteristic (ROC) curve (AUC) was significantly greater for the sensitive cTn assays compared with the standard assay (AUC for Roche hs-cTnT, 0.94; Siemens cTnI-Ultra, 0.95; and Abbott-Architect cTnI, 0.95 vs. AUC for the standard assay, 0.90; $P < 0.05$ for comparisons). The best cut-offs for the sensitive cTn-assays determined by the ROC-curve in elderly patients differed clearly from those in younger patients. Furthermore, the prognostic value regarding 90-day mortality varied among the sensitive cTn assays.
Conclusion	Sensitive cTn assays have high diagnostic accuracy also in the elderly. Mild elevations are common in elderly non-AMI patients, therefore the optimal cut-off levels are substantially higher in elderly as compared with younger patients. Furthermore, sensitive cTn assays yielded different prognostic value (ClinicalTrials.gov number, NCT00470587).
Keywords	Acute coronary syndromes • Myocardial infarction • New biomarkers • Troponin • Coronary • Artery disease • Elderly • Prognosis

Introduction

Acute myocardial infarction (AMI) is the leading cause of death and morbidity in the elderly population of Europe and the USA.[1] Its rapid and accurate diagnosis is an unmet clinical need. Delayed 'rule in' increases morbidity and mortality.[2,3] Delayed 'rule out' prolongs the time spent in the emergency department (ED), increasing patients' anxiety and causes enormous costs for the health-care system.[4]

New sensitive cardiac troponin (cTn) assays, with a lower limit of detection (LoD), below the 99th percentile of a normal reference population, have recently become available in clinical

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practice.[5,6] These assays improved the early diagnosis of an AMI in unselected patients with acute chest pain.[7,8] However, their diagnostic accuracy in the elderly is uncertain, as elevated levels of cTn were found in up to 22% of persons living in the community who were 70 years of age or older.[9−11]

Therefore, and for other reasons, elderly patients merit particular attention. First, pre-existing heart diseases, risk factors, as well as diseases that potentially cause AMI-like chest pain such as gastritis or pneumonia are more common in the elderly.[12−14] Thus, they are at increased risk for both: AMI, as well as anxiety related to non-cardiac causes of chest pain. Secondly, the interpretation of the 12-lead electrocardiography (ECG) is particularly challenging in elderly patients due to common pre-existing ECG alterations such as a bundle branch block or a pacemaker. In contrast, new ST-segment-elevation is less common in the elderly compared with younger patients.[15] Thirdly, the diagnosis of an AMI is even more challenging in the elderly since they differ from younger patients in perception and presentation of the symptoms.[16,17] Fourthly, due to frequently pre-existing heart diseases and renal failure, cTn levels may also be elevated in elderly patients without an AMI.[18,19] Fifthly, the elderly are more prone to adverse events related to cardiovascular medication, e.g. anticoagulation, as well as to cardiovascular procedures, e.g. coronary angiography, and percutaneous coronary intervention. In this context, an accurate diagnosis of an AMI is mandatory for therapeutic indications.[20−22]

We therefore examined the diagnostic performance of novel sensitive cTn assays for the early diagnosis of an AMI in patients >70 years of age, 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 international multi-centre study designed and co-ordinated by the University Hospital Basel. From April 2006 to June 2009, a total of 1247 consecutive patients presenting to the ED with symptoms suggestive of an AMI with an onset or peak within the last 12 h were recruited. Elderly patients were considered those >70 years of age.

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, the analysis of the data, the preparation of the manuscript, or the 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 presentation 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—the clinical history, findings on physical examination, and results of laboratory tests (including cTn values obtained at the participating hospitals but not those being assessed as part of this study), radiologic testing, ECG, echocardiography, cardiac exercise test, coronary angiography—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 was defined in accordance with current guidelines.[23] In brief, an AMI was diagnosed when there was evidence of myocardial necrosis in association with clinical signs of myocardial ischaemia. Necrosis was diagnosed by a 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%.[5] The following cTn assays were used for the adjudication of the final diagnosis at the 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 an AMI.[5] Unstable angina was diagnosed when a patient had normal cTn levels but new onset or a deterioration of stable angina, positive cardiac exercise testing, coronary artery stenosis of 70% in subsequent cardiac catheterization. Unstable angina was also diagnosed when the diagnosis during hospitalization was uncertain but AMI or sudden cardiac death within 90 days occurred, that was evidently associated with the symptoms described at prior presentation. Further pre-defined diagnostic categories were cardiac but not coronary symptoms (e.g. perimyocarditis or tachyarrhythmias), and non-cardiac causes. If AMI was ruled out at presentation, but no sufficient diagnostic procedures were performed during follow up to establish a definite final diagnosis, symptoms were classified as chest pain of unknown origin.

Investigational cardiac troponin analysis

Blood samples for determination of four investigational cTn assays (three sensitive: Roche High-Sensitive-cTnT, Siemens cTnI-Ultra,[6,24] Abbott cTnI-Architect, and one standard: Roche cTnT[25]) were collected at the time 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 an 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.

The two Roche assays were performed with the use of the Elecsys 2010 system (Roche Diagnostics): for cTnT (fourth generation), the LoD is 0.01 µg/L, the 99th percentile <0.01 µg/L, and the coefficient of variation of <10% (10% CV) is 0.035 µg/L; for hs-cTnT, the LoD is 0.005 µg/L, the 99th percentile 0.014 µg/L, and the 10% CV is 0.013 µg/L.[26] For the Siemens cTnI-Ultra assay, performed with the ADVIA Centaur immunoassay system (Siemens), the LoD is 0.006 µg/L, the 99th percentile 0.04 µg/L, and the 10% CV is 0.03 µg/L, as specified by the manufacturer.[6,7,24] For the Abbott-Architect cTnI assay, performed with the Architect system (Abbott Diagnostics), the LoD is 0.01 µg/L, the 99th percentile 0.028 µg/L, and the 10% CV is 0.032 µg/L, as specified by the manufacturer.

Statistical analysis

Continuous variables are presented as means ($\pm$ SD) or medians [with the inter-quartile range (IQR)], 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 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 an 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.[27] The best cut-off values were determined by the point farthest from the bisector of the ROC curve. For the analysis of the prognostic value of the sensitive cTn assays, we calculated Kaplan−Meier curves, using the log-rank test for comparisons and Cox regression. 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), and MedCalc software, version 10.3.0 (MedCalc).

Results

Patient characteristics

Of the 1247 consecutively enrolled patients, measurement of all four investigational cTn assays were obtained at presentation from 1098 patients, of whom 406 (37%) were older than 70 years. Elderly patients differed from those younger than 70 years of age in several of the baseline characteristics (Table 1). The 90-day follow-up was completed in 100% of patients.

Acute myocardial infarction was the adjudicated final diagnosis in 24% of patients over 70 years when compared with 9% in younger patients (P < 0.001). Other adjudicated diagnoses were unstable angina in 16%, cardiac symptoms from causes other than coronary artery disease in 15%, non-cardiac causes in 34%, and symptoms of unknown origin in 11% of the elderly patients (Table 2).

Cardiac troponin levels at presentation

Among the patients, whose final diagnosis was not an AMI, patients over 70 years old had significantly higher baseline levels of all three sensitive cTn compared with younger patients: median levels in patients aged ≥70 were 0.014 µg/L (IQR: 0.009−0.024), with hs-cTnT; 0.01 µg/L (IQR: 0.004−0.025), with cTnI-Ultra; and 0.003 µg/L (IQR: 0−0.011), with Abbott-Architect cTnI; compared with 0.005 µg/L (IQR: 0.003−0.009), with hs-cTnT; 0.004 µg/L (IQR: 0.001−0.011), with cTnI-Ultra; and 0.000 µg/L (IQR: 0.000−0.002) with Abbott-Architect cTnI in younger patients (P < 0.001 for comparisons). Of the total, 51% of the elderly patients with a final diagnosis other than AMI, had elevated baseline levels of hs-cTnT, 17% had elevated baseline levels of the Siemens cTnI-Ultra, and 13% had elevated baseline levels of Abbott-Architect cTnI above the 99th percentile. Among younger patients, the percentages were significantly smaller with the sensitive cTn assays (14, 8, and 7%; P < 0.001, P = 0.002, and P = 0.004, respectively; Figure 1).

In elderly as well as in younger patients, cTn levels at presentation, as assessed by all the assays, were significantly higher in patients whose final diagnosis was AMI when compared with those with other diagnoses (P < 0.001 for comparisons).

Diagnostic accuracy of cardiac troponin at presentation

In elderly patients, the diagnostic accuracy for an AMI, quantified by the AUC, was significantly higher with the three sensitive cTn assays than that with the standard assay [AUC for Roche hs-cTnT: 0.94; 95% confidence interval (CI): 0.91−0.96; for Siemens cTnI-Ultra: 0.95; 95% CI: 0.93−0.97; and for Abbott-Architect cTnI: 0.95; 95% CI: 0.92−0.97; vs. AUC for the standard assay: 0.90; 95% CI: 0.87−0.93; P = 0.015, P = 0.003, P = 0.006, respectively, for comparisons; Table 3 and Figure 2A]. Overall, among all three sensitive assays, the diagnostic accuracy was similar (P > 0.05). In younger patients, the diagnostic accuracy for an AMI was also significantly higher with the sensitive assays than that with the standard assay (AUC for Roche hs-cTnT: 0.94; 95% CI: 0.91−0.96; for Siemens cTnI-Ultra: 0.95; 95% CI: 0.93−0.97; and for Abbott-Architect cTnI: 0.95; 95% CI: 0.92−0.97; vs. AUC for the standard assay: 0.90; 95% CI: 0.87−0.93; P = 0.015, P = 0.003, P = 0.006, respectively, for comparisons; Table 2 and Figure 2C). Overall, comparing the AUC of the three sensitive assays in elderly vs. younger patients, we found no significant differences (P > 0.4 for all tests).

Best cut-off determined by receiver operating characteristic curve

The best cut-off value to separate AMIs from non-AMIs determined by ROC analysis in elderly patients was nearly four times the 99th percentile for hs-cTnT (0.054 µg/L), but close to the 99th percentile for both sensitive cTnI assays (0.032 µg/L for Abbott-Architect cTnI and 0.045 µg/L for Siemens cTnI-Ultra; see Table 4 and Figure 2A).

In contrast, the best cut-off value to separate AMIs from non-AMIs in younger patients was close to the 99th percentile for hs-cTnT (0.017 µg/L) and for cTnI-Ultra (0.039 µg/L), but less than a third of the 99th percentile for Abbott-Architect cTnI (0.008 µg/L; see Table 5 and Figure 2C).

Cardiac troponin levels in patients with recent onset of chest pain

The accuracy of the sensitive cTn assays was also high among patients with recent onset of chest pain (Figure 2B and D, Figure 3, and Supplementary material online, Table S5A).

Diagnostic performance at the 99th percentile in elderly and younger patients

Overall, at the 99th percentile all cTn assays showed higher sensitivity in elderly when compared with younger patients. The increase in sensitivity in elderly patients was associated with a decrease in specificity, which was particularly pronounced with hs-cTnT (49% in the elderly vs. 86% in younger patients; P < 0.001; see Table 6).

Serial cardiac troponin levels

During serial sampling, the AUC for all cTn assays increased in patients over 70 years (Supplementary material online, Table S5B). Absolute values of changes in cTn levels from presentation

Table 1 Baseline characteristics

	All patients (n = 1098)	Patients >70 years (n = 406)	Patients ≤ 70 years (n = 681)	P-value*	Patients >70 years		P-value
					Acute myocardial infarction		
					Yes (n = 98)	No (n = 308)	
Male gender, n (%)	756 (67)	218 (54)	511 (75)	<0.001	63 (64)	155 (50)	0.016
Age (years)							
Median	64 (51–75)	78 (74–82)	54 (46–63)	<0.001	79 (75–85)	78 (74–85)	0.093
Risk factors, n (%)							
Hypertension	693 (63)	330 (81)	360 (53)	<0.001	83 (85)	247 (80)	0.320
Dyslipidaemia	492 (45)	210 (52)	282 (41)	0.001	52 (53)	158 (51)	0.761
Diabetes	217 (20)	110 (27)	107 (16)	<0.001	31 (32)	79 (26)	0.244
Current smoking	265 (24)	36 (9)	224 (33)	<0.001	12 (12)	24 (8)	0.179
Prior smoking	391 (36)	154 (38)	236 (35)	0.235	39 (40)	115 (37)	0.675
History, n (%)							
Prior coronary artery disease	401 (37)	212 (52)	189 (27)	<0.001	56 (57)	156 (51)	0.262
Prior myocardial infarction	271 (25)	146 (36)	125 (18)	<0.001	42 (43)	104 (34)	0.102
Prior revascularization	296 (27)	140 (35)	155 (23)	<0.001	33 (34)	107 (35)	0.847
PCI	254 (23)	116 (29)	137 (20)	0.001	24 (25)	92 (30)	0.304
Surgery	111 (10)	68 (17)	43 (6)	<0.001	18 (18)	50 (16)	0.622
Peripheral artery disease	76 (7)	53 (13)	23 (3)	<0.001	13 (13)	40 (13)	0.943
Impaired kidney function	115 (11)	90 (22)	25 (4)	<0.001	28 (29)	62 (20)	0.080
Prior stroke	64 (6)	51 (13)	13 (2)	<0.001	17 (17)	34 (11)	0.101
	All patients (n = 1098)	**Patients >70 years (n = 406)**	**Patients ≤70 years (n = 692)**	**P-value***	**Patients >70 years**		**P-value**
					Acute Myocardial Infarction		
					Yes (n = 98)	No (n = 308)	
Vital status, median (IQR)							
Heart rate (b.p.m.)	75 (66–89)	75 (64–90)	76 (66–89)	0.086	81 (71–100)	73 (62–88)	<0.001
Systolic blood pressure (mmHg)	142 (127–160)	145 (127–164)	142 (127–158)	0.097	136 (119–161)	146 (130–164)	0.011

Continued

Table 1 Continued

	All patients	Patients >70 years	Patients ≤ 70 years	P-value*	Patients >70 years Acute myocardial infarction		P-value
	(n = 1098)	(n = 406)	(n = 681)		Yes (n = 98)	No (n = 308)	
Diastolic blood pressure (mmHg)	84 (74–93)	79 (70–88)	86 (78–95)	<0.001	78 (70–90)	79 (69–88)	0.501
Body mass index	26 (24–30)	26 (24–29)	27 (24–30)	0.14	26 (24–29)	26 (24–29)	0.448
ECG, n (%)							
Potential ischaemic ECG changes	247 (23)	118 (29)	129 (19)	0.003	54 (55)	64 (21)	<0.001
ST segment depression	131 (12)	66 (16)	65 (9)	0.001	34 (35)	32 (10)	<0.001
Abnormal Q-wave	112 (10)	59 (15)	53 (8)	<0.001	14 (14)	45 (15)	0.937
Left bundle branch block	42 (4)	27 (7)	15 (2)	<0.001	14 (14)	13 (4)	<0.001
T-wave inversion	147 (13)	72 (18)	75 (11)	0.001	29 (30)	43 (14)	<0.001

*Comparison of patients >70 years and ≤70 years.

to 1 and 2 h had similar diagnostic accuracy as the baseline cTn levels. The combination of baseline levels plus early changes did slightly improve the performance of the baseline level for all cTn assays. This increase in accuracy was statistically significant for the hs-cTnT assay and the Siemens cTnI-Ultra assay with the combination of the baseline levels and the change already within the first hour after presentation ($P = 0.013$ and $P = 0.017$, respectively). For the Abbott-Architect cTnI assay, the improvement in accuracy was only significant with the combination of the baseline level and the change within the first 2 h after presentation ($P = 0.014$; Supplementary material online, *Table S5C*). The diagnostic performance of the standard cTn was significantly improved by the measurement of early changes in cTn levels after 2 h as well as by the combination of baseline levels plus early changes at 1 h and at 2 h ($P < 0.05$; see Supplementary material online, *Table S5C*).

Cardiac troponin in the diagnosis of unstable angina and acute coronary syndromes

In elderly patients, the sensitive cTn assays had very poor accuracy for differentiating unstable angina from non-cardiac causes of chest pain (AUC for Roche hs-cTnT: 0.62; 95% CI: 0.55–0.69; for Siemens cTnI-Ultra: 0.58; 95% CI: 0.51–0.65; for Abbott-Architect cTnI: 0.59; 95% CI: 0.52–0.66). The diagnostic accuracy for differentiating unstable angina from non-cardiac causes of chest pain was significantly higher in younger patients than in elderly with Roche hs-cTnT (AUC: 0.74; 95% CI: 0.69–0.80; P = 0.019 for comparison). Within the group of younger patients and within the group of elderly patients the diagnostic accuracy of all sensitive cTn assays was similarly low (P > 0.2 for comparisons). However, the diagnostic performance among sensitive assays was still significantly greater than that of the standard assay (AUC for the standard assay 0.52 in elderly as well as in younger patients, P < 0.001 for comparisons of the standard assay with the sensitive assays among elderly and younger patients).

In elderly patients, for the diagnosis of acute coronary syndromes (AMI or unstable angina), the negative-predictive value of a negative assay result, defined as a value below the 99th percentile with a level of imprecision of <10%, was 64% (57–71%) for Roche hs-TnT, 65% (60–71%) for Siemens cTnI-Ultra, 64% (58–70%) for Abbott-Architect cTnI, and 61% (56–66%) for the standard assay. In younger patients, the negative-predictive value was 86% (83–89%), 86% (82–88%), 84% (81–87%), and 82% (78–85%), respectively.

Prognostic value of sensitive cardiac troponin assays

The 90-day follow-up was completed in 100% of patients. Elevated levels of hs-cTnT and Siemens cTnI-Ultra above the 99th percentile at presentation in patients who had a final diagnosis other than AMI strongly predicted death within 90 days, while elevated levels of Abbott-Architect cTnI had no predictive value (*Figure 4*). Accordingly, in a Cox regression model, adjusted for age >70 years, hs-cTnT, and Siemens TnI-Ultra levels above the 99th percentile represented independent predictors for death within 90

Table 2 Final diagnoses, *n* (%)

	All patients (*n* = 1098)	Patients >70 years (*n* = 406)	Patients ≤70 years (*n* = 692)	*P*-value*
Acute myocardial infarction	173 (16)	**98 (24)**	**75 (11)**	**<0.001**
ST-segment-elevation	41 (4)	21 (5)	20 (3)	0.054
Non-ST-segment-elevation	132 (12)	**77 (19)**	**55 (8)**	**<0.001**
Unstable angina	152 (14)	66 (16)	86 (12)	0.076
Cardiac cause, but not CAD	146 (13)	59 (15)	88 (13)	0.394
Non-cardiac cause	518 (48)	**140 (34)**	**388 (56)**	**<0.001**
Unknown	98 (9)	43 (11)	55 (8)	0.138

*Comparison of patients >70 years and ≤70 years.

days among patients whose final diagnosis was other than AMI (HR: 4.7; 95% CI: 1.2–18.6; *P* = 0.027 for Roche hs-cTnT; and HR: 3.6; 95% CI: 1.2–11.0; *P* = 0.027 for Siemens cTnI-Ultra). Regarding AMI within 90 days, none of the sensitive cTn assays had predictive value (all *P* > 0.05).

Discussion

This prospective multi-centre study involving consecutive patients >70 years of age examined the diagnostic performance of new sensitive cTn assays for the early diagnosis of AMI. We report seven major findings that have important clinical implications for 'rule in' and 'rule out' AMI:

First, among elderly patients with a final diagnosis other than AMI, the percentage of patients with a baseline level of sensitive cTnI and hs-cTnT above the 99th percentile was high and differed largely among the three sensitive cTn assays, ranging from 13 to 51%. Clinically, the high incidence of elevated cTn levels in the elderly challenges the application of the 99th percentile as the decision limit for the diagnosis of AMI as suggested in current guidelines. Careful clinical assessment is essential to separate AMIs from a variety of acute and chronic disorders also associated with low-level myocardial necrosis, especially in elderly patients, since rhythm disorders, heart failure, and impaired renal function are common in them.[19]

In addition, the substantial difference between the sensitive cTnI assays and the hs-TnT assay, regarding the incidence of cTn levels above the 99th percentile in patients without AMI, might indicate a variation of release of cTnI and cTnT in these non-AMI settings. The hypothesis of a difference in the release between cTnI and cTnT is supported by recent data indicating a higher prevalence of hs-cTnT levels above the 99th percentile than of cTnI levels above the 99th percentile in elderly patients without symptoms or signs of AMI.[9,10]

Secondly, despite the above findings, the diagnostic accuracy was similarly high already at presentation for all three sensitive cTn assays in elderly (AUC: 0.94–0.95) as well as in younger patients (AUC: 0.94–0.96) and significantly higher than that of the standard assay.

Thirdly, although the AUC of sensitive cTn assays did not differ significantly comparing elderly and younger patients, the best
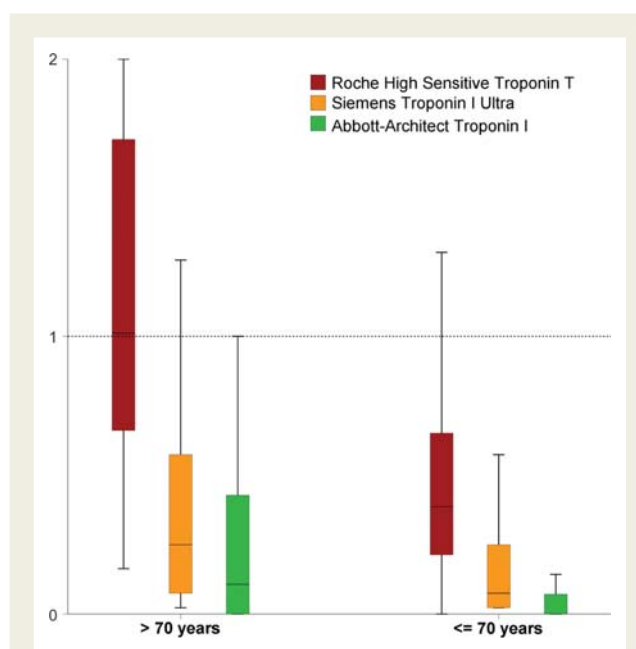

Figure 1 Baseline levels of sensitive troponin at presentation. Troponin levels at presentation to the emergency department displayed as multiples of the 99th percentile in patients whose adjudicated final diagnosis was other than acute myocardial infarction. Boxes represent inter-quartile ranges, while whiskers display ranges (without outliers further than 1.5 inter-quartile ranges from the end of the box). Left side: patients, >70 years of age. Right side: patients, age 70 years or younger.

cut-off values to separate AMIs from non-AMIs varied substantially. Among elderly patients, the best cut-off values to separate AMIs from non-AMIs were around the 99th percentile with the sensitive cTnI assays, but nearly four times the 99th percentile with hs-cTnT. In contrast, the best cut-off values in younger patients were close to the 99th percentile for hs-cTnT and for cTnI-Ultra, but less than a third of the 99th percentile for Abbott-Architect cTnI. These findings highlight the clinical need to develop test-specific algorithms that fine tune the application of these novel tests for the diagnosis of patients with acute chest pain.[9,11]

Table 3 Diagnostic performance of cardiac troponin in elderly patients at presentation (n = 406)

	Sensitivity (95% CI)	Specificity (95% CI)	Negative-predictive value (95% CI)	Positive-predictive value (95% CI)
Sensitive troponin assays				
Roche high-sensitive troponin T				
Limit of detection (0.005 µg/L)	100 (96–100)	1 (0–3)	100 (40–100)	24 (20–29)
99th percentile (0.014 µg/L)[a]	98 (93–100)	49 (44–55)	99 (95–100)	38 (32–44)
Siemens troponin I-Ultra				
Limit of detection (0.006 µg/L)	99 (94–100)	30 (25–35)	99 (94–100)	31 (26–36)
99th percentile (0.040 µg/L)[a]	92 (85–96)	83 (79–87)	97 (94–99)	64 (55–72)
Abbott-architect troponin I				
Limit of detection (0.010 µg/L)	94 (87–98)	72 (67–78)	97 (94–99)	52 (45–60)
99th percentile (0.028 µg/L)	89 (81–94)	87 (83–91)	96 (93–98)	69 (60–77)
10% CV (0.032 µg/L)	88 (80–94)	88 (84–92)	96 (93–98)	70 (62–78)
Standard troponin assay				
Roche troponin T fourth generation				
99th percentile (unknown)				
Limit of detection (0.010 µg/L)	83 (74–90)	90 (86–93)	94 (91–97)	72 (62–80)
10% CV (0.035 µg/L)	76 (57–79)	96 (93–98)	93 (89–95)	86 (77–93)

[a]Criterion of 10% variation coefficient (10% CV) fulfilled at the 99th percentile.

Table 4 Diagnostic performance of sensitive troponin assays in elderly patients (>70 years old) at the best cut-off determined by the receiver operating characteristic curve (95% confidence interval)

	Best cut-off ROC		Best cut-off ROC	99th percentile	P-value*
Sensitive troponin assays					
Roche high-sensitive troponin T, 99th percentile (0.014 µg/L)	**0.054 µg/L**	Sensitivity	79 (69–86)	98 (92–100)	**<0.001**
		Specificity	96 (93–98)	49 (44–55)	**<0.001**
		Negative-predictive value	93 (90–96)	99 (95–100)	**0.042**
		Positive-predictive value	86 (77–92)	38 (32–44)	**<0.001**
Siemens troponin I-Ultra, 99th percentile (0.040 µg/L)	**0.045 µg/L**	Sensitivity	92 (85–96)	92 (85–96)	1
		Specificity	88 (84–91)	83 (79–87)	0.458
		Negative-predictive value	97 (94–99)	97 (94–99)	0.997
		Positive-predictive value	71 (62–79)	64 (55–72)	0.643
Abbott-Architect Troponin I, 99th percentile (0.028 µg/L)	**0.032 µg/L**	Sensitivity	88 (80–94)	89 (81–94)	0.976
		Specificity	88 (84–91)	87 (83–91)	0.934
		Negative-predictive value	96 (93–98)	96 (93–98)	0.984
		Positive-predictive value	70 (62 –78)	69 (60–77)	0.970

*Comparisons among elderly patients.

Fourthly, the accuracy of sensitive cTn assays was also very high among elderly patients with a recent onset of chest pain. Improvement in the early diagnosis of AMI offers the opportunity to minimize myocardial damage by extending early treatment options to AMI patients without ST-segment-elevation.[1,2] Our findings highlight that the 'rule in' benefits of sensitive cTn assays can be confirmed in the high-risk group of elderly patients.[1,2,23] The cost savings associated with increased sensitivity already at presentation might be substantial.[4] On the other hand, the lower specificity increases the incidence of patients with elevated cTn levels not having an AMI, which may trigger additional costly investigations

to identify the cause of myocardial necrosis. Detailed cost analyses need to be performed to define the net economic effect of the clinical application of the sensitive cTn assays.[28]

Furthermore, the distinction between an AMI and other medical conditions associated with cTn elevations including myocarditis, tako-tsubo cardiomyopathy, and heart failure will still require full clinical evaluation. Also, the ECG remains an indispensable tool to immediately identify patients with ST-segment-elevation AMI.[2–6]

Fifthly, the overall diagnostic accuracy of the sensitive assays at the 99th percentile, quantified by the AUC for the sensitive
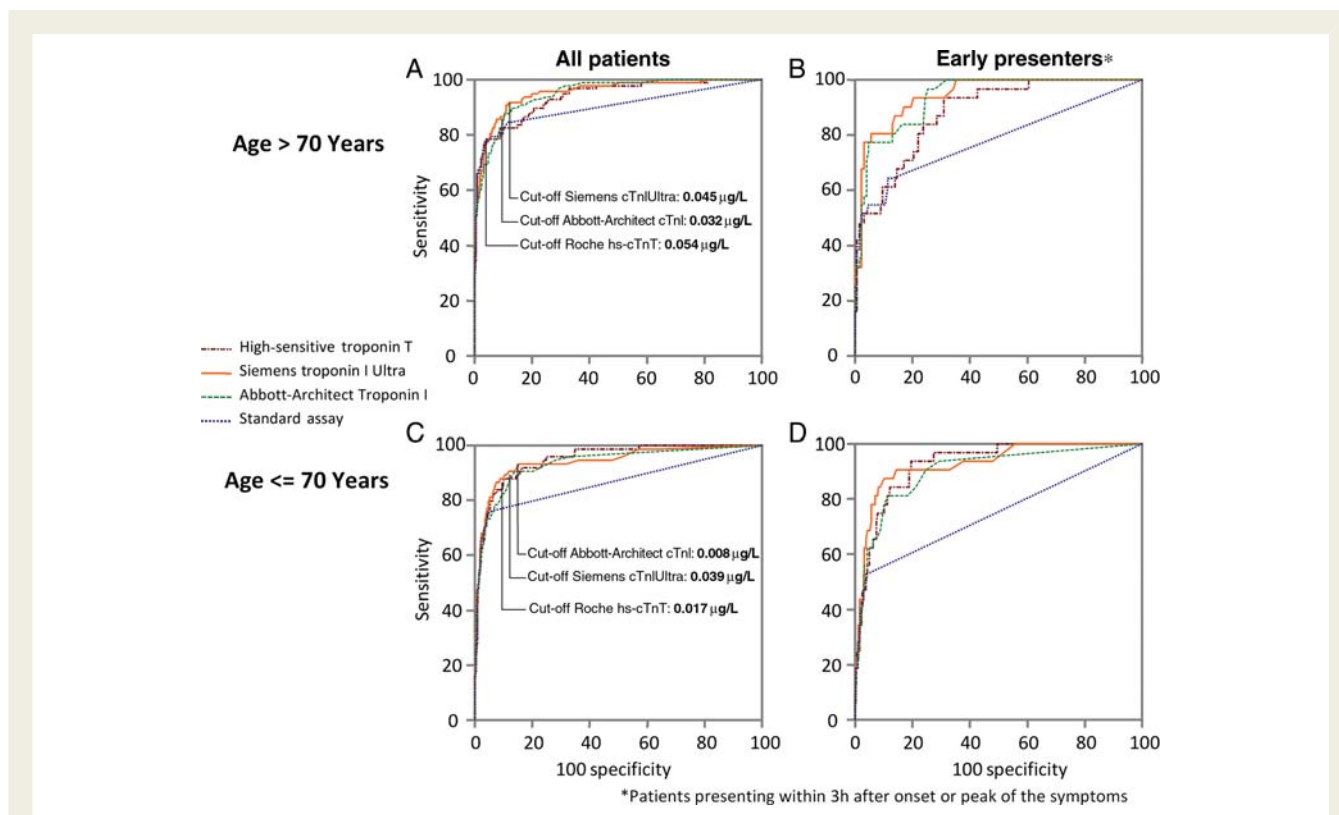
Figure 2 Diagnostic performance of cardiac troponin at presentation. Receiver operating characteristic curves describing the diagnostic performance of different cardiac troponin assays at presentation for the diagnosis of acute myocardial infarction in patients >70 years of age (top), and in those, aged 70 years or younger (bottom). Left side: presenting within 12 h from chest pain onset. Right side: presenting within <3 h of chest pain onset. (*A* and *C*): the calculated best cut-off values for elderly and for younger patients are defined by the point farthest from the bisector of the receiver operating characteristic curves.

Table 5 Diagnostic performance of sensitive troponin assays in younger patients (70 years or younger) at the best cut-off determined by the receiver operating characteristic curve (95% confidence interval)

	Best cut-off ROC			**Best cut-off ROC**	**99th percentile**	*P*-value*
Sensitive troponin assays						
Roche high-sensitive troponin T, 99th percentile (0.014 μg/L)	**0.017 μg/L**		Sensitivity	88 (78–94)	88 (78–94)	1
			Specificity	90 (87–92)	86 (83–89)	0.215
			Negative-predictive value	98 (97–99)	98 (97–99)	0.997
			Positive-predictive value	51 (42–60)	44 (36–52)	0.527
Siemens troponin I-Ultra, 99th percentile (0.040 μg/L)	**0.039 μg/L**		Sensitivity	87 (77–93)	87 (77–93)	1
			Specificity	92 (90–94)	92 (89–94)	0.979
			Negative-predictive value	98 (97–99)	98 (97–99)	1
			Positive-predictive value	57 (47–66)	56 (47–72)	0.989
Abbott-Architect troponin I, 99th percentile (0.028 μg/l)	**0.008 μg/L**		Sensitivity	91 (82–96)	79 (68–87)	0.125
			Specificity	85 (82–88)	93 (91–95)	**<0.001**
			Negative-predictive value	99 (97–99)	97 (96–98)	0.256
			Positive-predictive value	43 (35–51)	57 (47–67)	0.065

*Comparisons among younger patients.

assays did not differ significantly in elderly and younger patients. However, regarding the diagnostic parameters in detail, the sensitivity and specificity of the sensitive cTn assays diverged in the elderly compared with younger patients, especially with hs-TnT.

All cTn assays showed higher sensitivity but lower specificity in elderly when compared with younger patients, reflecting the higher incidence of baseline levels above the 99th percentile in elderly patients with a final diagnosis other than AMI.
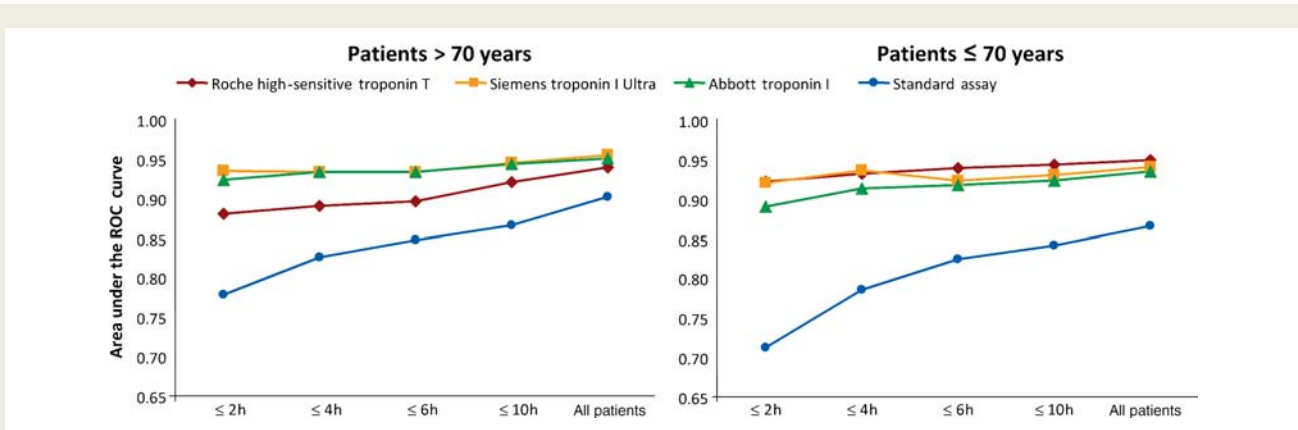
Figure 3 Diagnostic accuracy at presentation according to chest pain onset. Area under the receiver operating characteristic curves for the different cardiac troponin assays at presentation in the diagnosis of acute myocardial infarction according to the time since chest pain onset. (A): patients, >70 years of age. (B): patients, age 70 years or younger.

Table 6 Diagnostic performance of sensitive troponin assays at the 99th percentile; at 10% coefficient of variation for the standard assay (95% confidence interval)

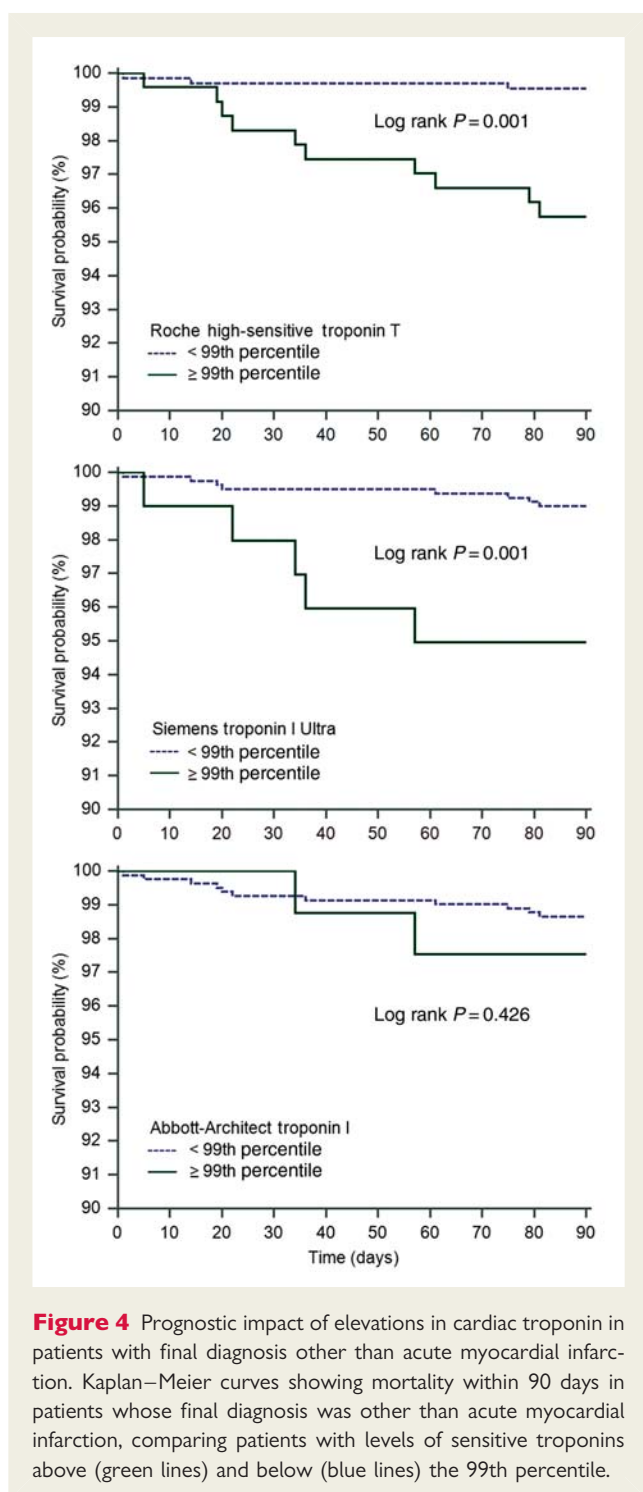|		>70 years	≤70 years	P-value*
Sensitive troponin assays				
Roche high-sensitive troponin T, 99th percentile (0.014 μg/L)	Sensitivity	**98 (92–100)**	88 (78–94)	**0.019**
	Specificity	**49 (44–55)**	86 (83–89)	**<0.001**
	Negative-predictive value	99 (95–100)	98 (97–99)	0.984
	Positive-predictive value	38 (32–44)	44 (36–52)	0.288
Siemens troponin I-Ultra, 99th percentile (0.040 μg/L)	Sensitivity	92 (85–96)	87 (77–93)	0.394
	Specificity	**83 (79–87)**	92 (89–94)	**<0.001**
	Negative-predictive value	97 (94–99)	98 (97–99)	0.370
	Positive-predictive value	64 (55–72)	56 (47–65)	0.253
Abbott-Architect troponin I, 99th percentile (0.028 μg/L)	Sensitivity	89 (81–94)	79 (68–87)	0.109
	Specificity	**87 (83–91)**	93 (91–95)	**0.008**
	Negative-predictive value	96 (93–98)	97 (96–98)	0.481
	Positive-predictive value	69 (60–77)	57 (47–67)	0.088
Standard troponin assay				
Roche troponin T fourth generation, 99th percentile (unknown) 10% CV (0.035 μg/L)	Sensitivity	**76 (57–79)**	59 (47–70)	**0.028**
	Specificity	96 (93–98)	98 (97–99)	0.135
	Negative-predictive value	93 (89–95)	95 (93–97)	0.152
	Positive-predictive value	86 (77–93)	79 (66–88)	0.351

*Comparison of patients >70 years and ≤70 years.

Sixthly, sensitive cTn assays seemed not helpful in the diagnosis of unstable angina in elderly patients and had only little value in younger patients. Further research is necessary to identify biomarkers that reliably detect myocardial ischaemia without necrosis.[8,29]

Seventhly, elevated levels of Roche hs-cTnT and Siemens TnI Ultra in patients with a final diagnosis other than AMI were strongly related to all-cause mortality within 90 days. This association was not seen for the Abbott-Architect cTnI. Further investigations are required to specify the prognostic capabilities of sensitive cTn assays for short- and long-term prognosis and to illuminate potential explanations for differences among sensitive cTn assays and outcomes. Our findings extend the results of previous studies, investigating the long-term mortality of apparently healthy subjects with elevated levels measured with sensitive cTnI assays.[11,30] Further, we found that none of the sensitive cTnI assays predicted an AMI within 90 days.[11,30]

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 aged >70 years was not pre-defined at the time of the initial protocol written in 2005. It was added while we were still blinded to the results in 2008,[8] with regard to recent investigations, showing that up to

Figure 4 Prognostic impact of elevations in cardiac troponin in patients with final diagnosis other than acute myocardial infarction. Kaplan–Meier curves showing mortality within 90 days in patients whose final diagnosis was other than acute myocardial infarction, comparing patients with levels of sensitive troponins above (green lines) and below (blue lines) the 99th percentile.

21% of elderly, presumably healthy patients had elevated levels of sensitive cTn.[9–11] Thirdly, this observational study cannot quantify exactly the clinical benefit associated with the increase in early diagnostic accuracy. To add this important information, interventional studies seem warranted. Fourthly, 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. Fifthly, in this study, we found discrepant

prognostic performance among the sensitive cTnI assays. Further analyses are necessary to evaluate possible explanations for these differences.

In conclusion, the excellent diagnostic performance of sensitive cTn assays in the early diagnosis of AMI can be confirmed in elderly as well as in younger patients. However, elevated cTn levels are common in elderly patients with diagnoses other than AMI and challenge differential diagnoses and currently recommended cut-off levels in the elderly, particularly with hs-cTnT, highlighting the clinical need to develop test-specific algorithms for patients with acute chest pain.

Supplementary material

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

References

1. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE II, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* 2007;**116**:e148–e304.
2. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;**28**:1598–1660.
3. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;**284**:835–842.
4. Forberg JL, Henriksen LS, Edenbrandt L, Ekelund U. Direct hospital costs of chest pain patients attending the emergency department: a retrospective study. *BMC Emerg Med* 2006;**6**:6.

5. Apple FS, Jesse RL, Newby LK, Wu AH, Christenson RH. 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–e355.

6. Apple FS, Smith SW, Pearce LA, Ler R, Murakami MM. Use of the Centaur TnI-Ultra assay for detection of myocardial infarction and adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. *Clin Chem* 2008;**54**:723–728.

7. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Frohlich M, Sinning CR, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, Tiret L, Lackner KJ, Munzel TF, Blankenberg S. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;**361**:868–877.

8. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;**361**:858–867.

9. Eggers KM, Lind L, Ahlstrom H, Bjerner T, Ebeling Barbier C, Larsson A, Venge P, Lindahl B. Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects. *Eur Heart J* 2008; **29**:2252–2258.

10. Eggers KM, Lind L, Venge P, Lindahl B. Will the universal definition of myocardial infarction criteria result in an overdiagnosis of myocardial infarction? *Am J Cardiol* 2009;**103**:588–591.

11. Zethelius B, Johnston N, Venge P. Troponin I as a predictor of coronary heart disease and mortality in 70-year-old men: a community-based cohort study. *Circulation* 2006;**113**:1071–1078.

12. Faisal MA, Russell RM, Samloff IM, Holt PR. Helicobacter pylori infection and atrophic gastritis in the elderly. *Gastroenterology* 1990;**99**:1543–1544.

13. Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH, Gottdiener J, Fried LP. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Arch Intern Med* 2002;**162**:2333–2341.

14. Majumdar SR, Kim N, Colman I, Chahal AM, Raymond G, Jen H, Siminoski KG, Hanley DA, Rowe BH. Incidental vertebral fractures discovered with chest radiography in the emergency department: prevalence, recognition, and osteoporosis management in a cohort of elderly patients. *Arch Intern Med* 2005;**165**:905–909.

15. Alexander KP, Roe MT, Chen AY, Lytle BL, Pollack CV Jr, Foody JM, Boden WE, Smith SC Jr, Gibler WB, Ohman EM, Peterson ED. Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;**46**:1479–1487.

16. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, Van de Werf F, White HD, Weaver WD, Naylor MD, Gore JM, Krumholz HM, Ohman EM. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation* 2007;**115**:2549–2569.

17. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, Montalescot G. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest* 2004;**126**:461–469.

18. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**(2 Suppl. 1):S1–S266.

19. Tsutamoto T, Kawahara C, Yamaji M, Nishiyama K, Fujii M, Yamamoto T, Horie M. Relationship between renal function and serum cardiac troponin T in patients with chronic heart failure. *Eur J Heart Fail* 2009;**11**:653–658.

20. Pfisterer M, Buser P, Osswald S, Allemann U, Amann W, Angehrn W, Eeckhout E, Erne P, Estlinbaum W, Kuster G, Moccetti T, Naegeli B, Rickenbacher P. Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: one-year results of the randomized TIME trial. *JAMA* 2003;**289**:1117–1123.

21. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;**279**: 1200–1205.

22. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. *Br J Clin Pharmacol* 2004;**57**:121–126.

23. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernandez-Aviles F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N. Universal definition of myocardial infarction. *Circulation* 2007;**116**:2634–2653.

24. Melanson SE, Morrow DA, Jarolim P. Earlier detection of myocardial injury in a preliminary evaluation using a new troponin I assay with improved sensitivity. *Am J Clin Pathol* 2007;**128**:282–286.

25. McCann CJ, Glover BM, Menown IB, Moore MJ, McEneny J, Owens CG, Smith B, Sharpe PC, Young IS, Adgey JA. Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponin T. *Eur Heart J* 2008;**29**: 2843–2850.

26. 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**:254–261.

27. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;**44**:837–845.

28. Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D, Scholer A, Christ M, Perruchoud AP. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. *Arch Intern Med* 2006;**166**:1081–1087.

29. Staub D, Nusbaumer C, Zellweger MJ, Jonas N, Wild D, Pfisterer ME, Mueller-Brand J, Perruchoud AP, Mueller C. Use of B-type natriuretic peptide in the detection of myocardial ischemia. *Am Heart J* 2006;**151**:1223–1230.

30. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med* 2009;**361**: 2538–2547.