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Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction

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Aims High-sensitivity cardiac troponin (hs-cTn) assays provide higher diagnostic accuracy for acute myocardial infarction (AMI) when compared with conventional assays, but may result in increased use of unnecessary coronary angiographies due to their increased detection of cardiomyocyte injury in conditions other than AMI.

Methods and results We evaluated the impact of the clinical introduction of high-sensitivity cardiac troponin T (hs-cTnT) on the use of coronary angiography, stress testing, and time to discharge in 2544 patients presenting with symptoms suggestive of AMI to the emergency department (ED) within a multicentre study either before (1455 patients) or after (1089 patients) hs-cTnT introduction. Acute myocardial infarction was more often the clinical discharge diagnosis after hs-cTnT introduction (10 vs. 14%, $P < 0.001$), while unstable angina less often the clinical discharge diagnosis (14 vs. 9%, $P = 0.007$). The rate of coronary angiography was similar before and after the introduction of hs-cTnT (23 vs. 23%, $P = 0.092$), as was the percentage of coronary angiographies showing no stenosis (11 vs. 7%, $P = 0.361$). In contrast, the use of stress testing was substantially reduced from 29 to 19% ($P < 0.001$). In outpatients, median time to discharge from the ED decreased by 79 min ($P < 0.001$). Mean total costs decreased by 20% in outpatients after the introduction of hs-cTnT ($P = 0.002$).

Conclusion The clinical introduction of hs-cTn does not lead to an increased or inappropriate use of coronary angiography. Introduction of hs-cTn is associated with an improved rule-out process and thereby reduces the need for stress testing and time to discharge.

Clinical Trial Registration Information www.clinicaltrials.gov. Identifier, NCT00470587.

Keywords Myocardial infarction • Coronary artery disease • Angiography • Stress testing • High-sensitivity cardiac troponin

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Introduction

Acute myocardial infarction (AMI) is a major cause of death and disability worldwide. Its rapid and accurate diagnosis is critical for the initiation of effective evidence-based medical management and treatment, but still an unmet clinical need.[1–3] Clinical assessment, the ECG, and cardiac troponin (cTn) testing form the cornerstones of the early diagnosis of AMI. Delayed 'rule-in' increases morbidity and mortality.[4,5] Delayed 'rule-out' prolongs the time spent in the emergency department (ED), delays the recognition and treatment of the actual cause of chest pain, increases patients' uncertainty and anxiety, and causes enormous costs for the health-care system.[6,7]

Recently, high-sensitivity cardiac troponin (hs-cTn) assays have been implemented into routine clinical care in Europe, Canada, Australia, New Zealand, and other countries. These assays overcome some of the limitations of conventional cTn assays, particularly the sensitivity deficit at presentation.[8–14] High-sensitivity cardiac troponin assays provide higher early diagnostic accuracy for AMI when compared with conventional cTn assays.[15–18] However, their clinical introduction has also been associated with challenges, particularly the interpretation of mild elevations.[8–14] Although mild hs-cTn elevations may be due to AMI, also multiple other causes including acute disorders such as arrhythmias, perimyocarditis, hypertensive crisis, takotsubo cardiomyopathy, pulmonary embolism, stroke, and sepsis or even chronic disorders such as heart failure and valvular heart disease may be the underlying aetiology.

Therefore, concern has been articulated that the increased detection of cardiomyocyte injury from ultimately non-ischaemic causes—often incorrectly called 'false-positive' levels—might lead to increased rates of inappropriate coronary angiographies. As this procedure is invasive and associated with rare but potentially fatal complications such as death, stroke, and iatrogenic AMI, as well as substantial costs, we decided to explore in great detail the effect of the clinical introduction of hs-cTn assays on the use of coronary angiography, cardiac stress testing, and time to discharge from the ED in a large multicentre study.

Methods

Study design and population

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international multicentre diagnostic trial, described in details elsewhere.[16–23] Among the recruiting sites, three hospitals clinically switched from conventional fourth generation cTnT to high-sensitivity cardiac troponin T (hs-cTnT) during the study period, while three hospitals continued the clinical use of a less sensitive cTn assay. As the inclusion and exclusion criteria of APACE as well as the general standard operating procedures at the participating hospitals remained unchanged during the whole period, we had the opportunity to compare patients with suspected AMI who were enrolled with the clinical use of conventional cTnT (Phase A) with patients with suspected AMI who were enrolled with the clinical use of hs-cTnT (Phase B) in three hospitals switching to hs-cTnT. As a randomized controlled trial using both methods at the same time in the same institution is not feasible, our methodology may be considered the best possible alternative. For further, exploratory validation of our findings, three hospitals not switching to hs-cTn were used as a control group. In these, the two periods for comparisons were defined by the median of their respective recruitment period.

From April 2006 to June 2013, consecutive patients older than 18 years presenting to the ED with symptoms suggestive of AMI with an onset or peak within the last 12 h were recruited in three hospitals switching from conventional cTnT (fourth generation) to hs-cTnT after informed consent was obtained. In these three institutions, hs-cTnT was clinically introduced at different dates: University Hospital Basel, Basel, Switzerland: Phase A from 21 April 2006 to 17 February 2010, Phase B from 18 February 2010 to 5 June 2013; Hospital del Mar, Barcelona, Spain: Phase A from 28 November 2008 to 31 October 2011, Phase B from 1 November 2011 to 21 November 2012; Bruderholzspital, Bottmingen, Switzerland: Phase A from 11 November 2008 to 3 December 2012, Phase B from 4 December 2012 to 1 March 2013. Thereby, Phase B included the institutions 'learning phase' for hs-cTnT. In parallel, 377 patients were recruited in three hospitals (Kantonsspital Olten, Spital Limmattal Schlieren, Kantonsspital Luzern; all in Switzerland) remaining on a less sensitive cTn assay (Abbott AxSYM Troponin I ADV or Beckman Coulter AccuTnI). Patients presenting with ST-segment-elevation myocardial infarction or with terminal kidney failure requiring regular dialysis were excluded.

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

Routine clinical assessment

All patients underwent a clinical assessment that included medical history, physical examination, 12-lead ECG, pulse oximetry, standard blood test, and chest radiography according to local protocols and in accordance with the most current guidelines of the European Society of Cardiology (ESC) valid at the time of a patient's recruitment.[1,24] The guideline recommendation regarding the use of conventional cTn stayed the same throughout the whole period of patient recruitment. Levels of cTn were measured at presentation and serially thereafter as long as clinically indicated. Using a conventional cTn assay required retesting of cTn after 6 h in most patients with suspected AMI. In contrast, using hs-cTnT allowed retesting of hs-cTnT after 3 h and more rapid rule-out of AMI as indicated for the first time in the 2011 ESC guidelines.[1] As most patients enrolled in Phase B were recruited after the publication of the 2011 ESC guidelines, our study investigates the impact of hs-cTnT mostly used in the context of the 2011 ESC guidelines including the 0 h/3 h algorithm. During the enrolment period (until 2013), no institution applied the 0 h/1 h algorithm, which is recommended in the 2015 ESC guidelines as an additional option.[25] None of the participating EDs had a relevant change in leadership, patient flow, and/or staff to patient ratio during the enrolment period. Treatment of patients was left to discretion of the attending physician. The clinical discharge diagnosis was determined and documented by the clinical team in charge of the individual patient at ED/hospital discharge in the discharge letter. More details on the cardiac workup can be found in the Supplementary material online.

Adjudicated final diagnosis

Details on the adjudication of the final diagnosis can be found in the Supplementary material online.

Statistical analysis

All data are expressed as medians [1st quartile, 3rd quartile] or means (standard deviation) for continuous variables, and for categorical variables as numbers and percentages. Continuous variables were

compared with the Mann–Whitney *U* test or Student's *t*-test, as appropriate, and categorical variables using the Pearson χ^2 test.

In order to adjust for possible confounders between the two time periods, multivariable regression models were used. History of coronary artery disease, known arterial hypertension, and age were used as co-variables in a multivariable model. Interrupted time series analyses were used to test for change in trends over time for duration of stay on the ED and total costs.[26] 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 IBM SPSS Statistiscs for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA), and MedCalc software, version 1 5.4.0 (MedCalc, Ostend, Belgium). More details on statistical analyses and cost calculation can be found in the Supplementary material online.

Results

Baseline characteristics

Of 2544 consecutively enrolled patients in the three hospitals switching to hs-cTnT during the recruitment period, 1455 (57%) patients were enrolled before (Phase A) and 1089 (43%) patients after (Phase B) the introduction of hs-cTnT. Median age was 62 years, 32% were women, and 37% had a history of coronary artery disease (*Table 1*). Some of the baseline characteristics differed between the two periods including age and history of coronary artery disease.

The clinical discharge diagnoses based on all information available at the time of patient discharge including conventional cTn concentrations in Phase A and hs-cTnT concentrations in Phase B differed between the two periods with an absolute increase of 4% and a relative increase of 40% in the prevalence of AMI (10% during Phase A vs. 14% during Phase B, adjusted-$P < 0.001$; Supplementary material online, *Table S1A*), and a corresponding decrease in the prevalence of unstable angina. The adjudicated final diagnoses consistently using serial hs-cTnT levels for patients in Phase A and Phase B overall were similarly distributed (Supplementary material online, *Table S1B*). Acute myocardial infarction was the adjudicated final diagnosis in 420 (17%) of all patients with a comparable prevalence during both periods (17% during Phase A vs. 16% during Phase B, adjusted-$P = 0.211$).

Impact of high-sensitivity cardiac troponin T on coronary angiography

The rate of coronary angiography was similar between the two periods (23% during both phases, adjusted-$P = 0.092$, *Table 2*, *Figure 1*). The extent of coronary atherosclerosis quantified by the number of diseased vessels was comparable in both periods (adjusted-$P = 0.361$), too (*Figure 2*). Furthermore, the percentage of subsequently performed percutaneous coronary interventions and its location remained similar between both periods (rate of interventions 13% in both periods, adjusted-$P = 0.182$). Rates of surgical revascularization using coronary artery bypass grafts were also comparable between the two periods (2% during both phases, adjusted-$P = 0.841$).

Table 1 Baseline characteristics of patients before and after the introduction of high-sensitivity cardiac troponin T

	All patients ($n = 2544$)	Phase A ($n = 1455$)	Phase B ($n = 1089$)	*P*-value
Age, year, median [q1,q3]	62 [49,75]	64 [51,76]	59 [47,72]	<0.001
Male gender, *n* (%)	1741 (68)	983 (68)	758 (70)	0.272
Risk factors, *n* (%)				
Hypertension	1591 (63)	980 (67)	611 (56)	<0.001
Current smoking	632 (25)	341 (23)	291 (27)	0.064
History of smoking	941 (37)	530 (36)	411 (38)	0.523
Hypercholesterolaemia	1271 (50)	761 (52)	510 (47)	0.006
Diabetes mellitus	447 (18)	283 (20)	164 (15)	0.006
History, *n* (%)				
Coronary artery disease	929 (37)	566 (39)	363 (33)	0.004
Previous myocardial infarction	638 (25)	373 (26)	265 (24)	0.454
Previous revascularization	749 (29)	423 (29)	326 (30)	0.636
Peripheral artery disease	163 (6)	111 (8)	52 (5)	0.004
Previous stroke	151 (6)	93 (6)	58 (5)	0.260
Vital status, median [q1,q3]				
Heart rate, b.p.m.	76 [66,89]	75 [65,88]	78 [68,91]	<0.001
Systolic blood pressure, mmHg	141 [126,158]	142 [127,159]	140 [125,156]	0.072
Diastolic blood pressure, mmHg	82 [71,91]	82 [72,92]	81 [71,91]	0.019
Body mass index, kg/m^2	26.4 [23.9,29.4]	26.4 [23.9,29.4]	26.3 [23.7,29.4]	0.453
Electrocardiographic findings, *n* (%)				
Left bundle branch block	77 (3)	56 (4)	21 (2)	0.007
ST-segment depression	253 (10)	169 (12)	84 (8)	0.001
T-wave inversion	333 (13)	205 (14)	128 (12)	0.084

χ^2 test used for comparison of proportions.

Table 2 Diagnostic workup and management before and after the introduction of high-sensitivity cardiac troponin T

	All patients ($n = 2544$)	Phase A ($n = 1455$)	Phase B ($n = 1089$)	*P*-value	Adjusted *P*-value[a]
Cardiac stress testing, *n* (%)	623 (25)	416 (29)	207 (19)	<0.001	**<0.001**
Cardio SPECT	277 (11)	166 (12)	111 (10)	0.330	0.984
Pathological findings[b]	120 (43)	78 (47)	42 (38)	0.132	0.126
Exercise ECG	346 (14)	250 (17)	96 (9)	<0.001	**<0.001**
Pathological findings[b]	51 (15)	38 (15)	13 (14)	0.697	0.906
Coronary angiographies, *n* (%)	588 (23)	333 (23)	255 (23)	0.754	0.092
Normal vessels[b]	56 (10)	37 (11)	19 (7)	0.586	0.361
Mild sclerosis[b]	32 (5)	16 (5)	16 (6)		
One-vessel disease[b]	114 (19)	65 (20)	49 (19)		
Two-vessel disease[b]	134 (23)	76 (23)	58 (23)		
Three-vessel disease[b]	252 (43)	139 (42)	113 (44)		
Percutaneous coronary interventions, *n* (%)[c]	327 (13)	184 (13)	143 (13)	0.717	0.182
Intervention in left main stem	7 (0.3)	6 (0.4)	1 (0.1)	0.127	0.204
Intervention in LAD	145 (6)	81 (6)	64 (6)	0.739	0.407
Intervention in LCX	105 (4)	66 (5)	39 (4)	0.231	0.520
Intervention in RCA	98 (4)	52 (4)	46 (4)	0.399	0.165
Intervention in CABG	27 (1)	16 (1)	11 (1)	0.827	0.765
Duration of stay					
Outpatients, *n* (%)	1315 (52)	710 (49)	605 (56)	0.001	0.497
Time in the emergency department, min, median [q1,q3]					
All patients	339 [221,490]	377 [226,520]	305 (213,430)	<0.001	**0.046**
Outpatients ($n = 1315$)	305 [215,420]	355 [227,462]	276 (206,345)	<0.001	**<0.001**
Inpatients ($n = 1229$)	396 [235,604]	415 [225,602]	392 (250,625)	0.763	0.099
Overnight stays in the hospital, median [q1,q3]					
All Patients	0 [0,4]	1 [0,5]	0 [0,3]	0.001	0.621
Inpatients only ($n = 1229$)	5 [1,8]	5 [1,9]	4 [1,8]	0.534	0.784

SPECT, single-photon emission computerized tomography; LAD, left anterior descending artery; LCX, left circumlex artery; RCA, right coronary artery; CABG, coronary artery bypass graft.
Values in bold indicate statistical significant of *P*-values.
[a]*P*-value for comparisons between Phase A and Phase B adjusted for age, history of coronary artery disease, and presence of arterial hypertension with the use of a multivariate regression model.
[b]Percentage refers to total number patients undergoing the respective diagnostic exam, not to total number of patients.
[c]Multi-vessel interventions were counted as one percutaneous coronary intervention.

Impact of high-sensitivity cardiac troponin T on cardiac stress testing

In 25% ($n = 623$) of patients, some form of cardiac stress testing to detect myocardial ischaemia was performed. Of these, cardiac single-photon emission computerized tomography (SPECT) was performed in 44% and exercise ECG in the remaining 56% of patients. The rate of SPECT (12% of all patients during Phase A vs. 10% during Phase B, adjusted-$P = 0.984$) was similar during both periods as was the percentage of pathological SPECT findings (47% of all SPECT exams during Phase A vs. 38% during Phase B, adjusted-$P = 0.126$). The rate of exercise ECG was significantly reduced after the introduction of hs-cTnT (17% of all patients during Phase A vs. 9% during Phase B, adjusted-$P < 0.001$), while the percentage of pathological findings remained comparable (15% of all exercise ECG exams during Phase A vs. 14% during Phase B, adjusted-$P = 0.906$).

Impact of high-sensitivity cardiac troponin T on duration of stay

Duration of stay in the ED among all patients was significantly reduced by 72 min after the introduction of hs-cTnT (median stay 377 min during Phase A vs. 305 min during Phase B; adjusted-$P = 0.046$). Even more pronounced in the subgroup of patients in whom discharge from the ED was feasible (outpatients), median time to discharge was significantly reduced by 79 min (median stay 355 min during Phase A vs. 276 min during Phase B, adjusted-$P < 0.001$, *Figure 3*). A significant change in trends on duration of stay in the ED from a mean increase of 0.63 min per month during Phase A vs. a mean decrease of 3.27 min per month during Phase B could be observed with the use of interrupted time series analyses ($P < 0.001$, *Figure 4*).

Length of hospitalization, quantified by overnight stays, did not differ significantly between the two phases (median overnight

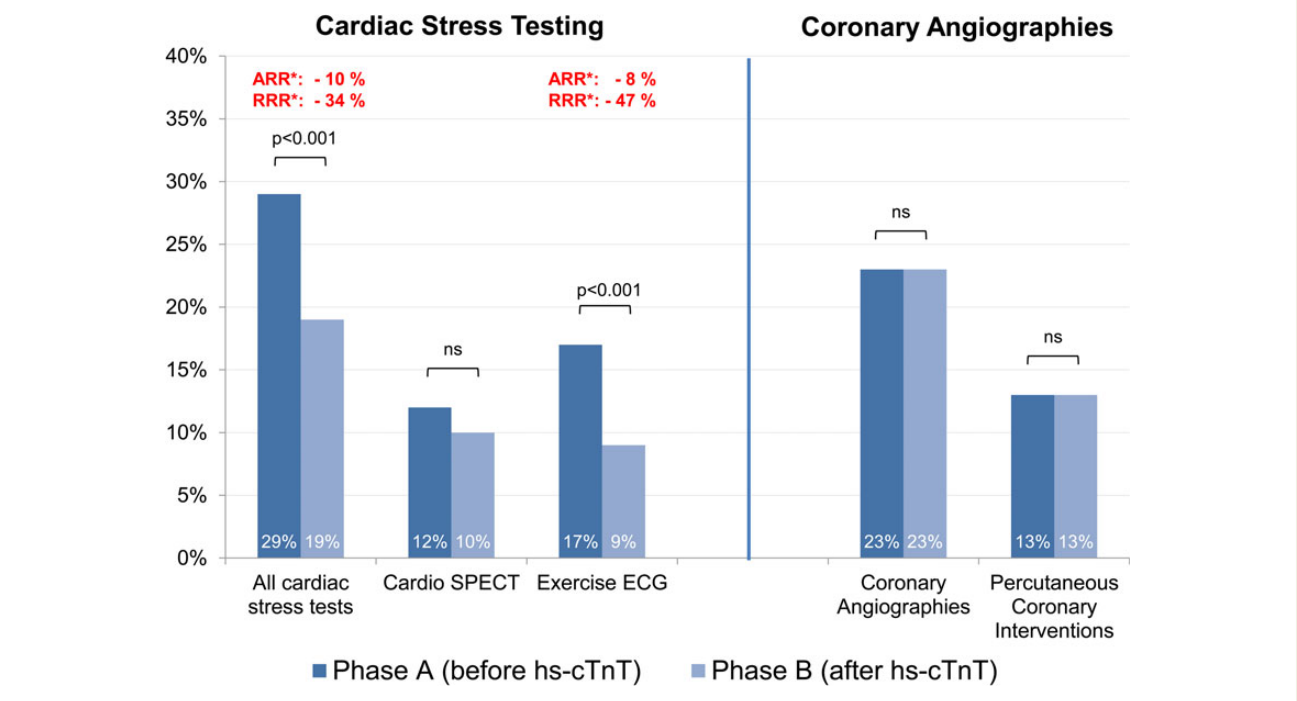

Figure 1 Changes in rates of cardiac stress testing and coronary angiography. Bars represent rates of cardiac stress testing, coronary angiographies, and percutaneous coronary interventions before (Phase A) and after (Phase B) the clinical introduction of high-sensitivity cardiac troponin T. SPECT, single-photon emission computerized tomography; ARR, absolute risk reduction; RRR, relative risk reduction; ns, not significant.

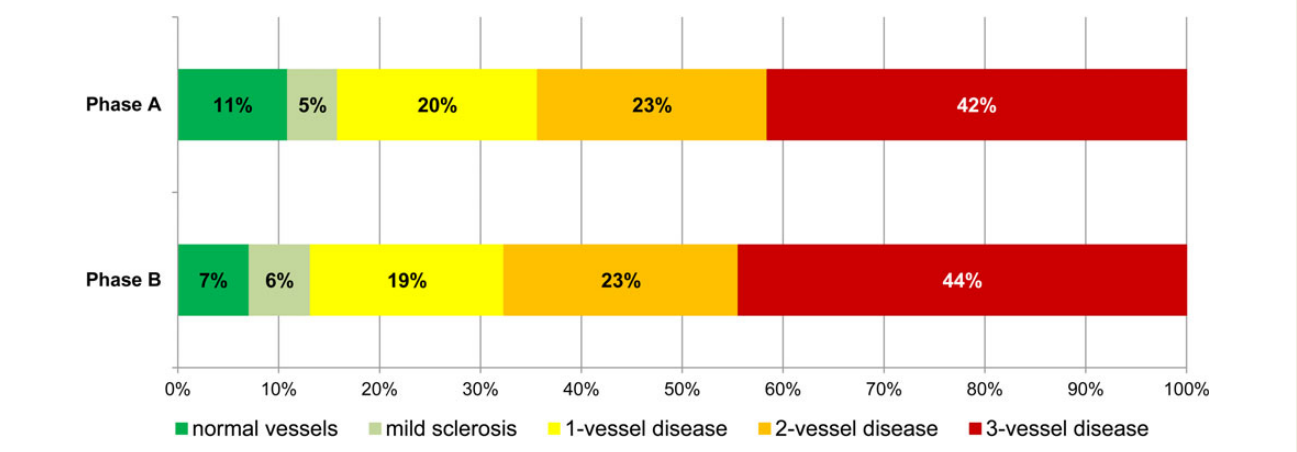

Figure 2 Relative distribution of coronary angiography findings before and after the introduction of high-sensitivity cardiac troponin T. Relative distribution of coronary angiography findings performed in acute chest pain patients before (Phase A) and after (Phase B) the introduction of a high-sensitivity cardiac troponin T assay.

stays, 1 night [0,5] during Phase A vs. 0 night [0,3] during Phase B, adjusted-$P = 0.621$).

Impact of high-sensitivity cardiac troponin T on discharge diagnoses and their distribution among different cardiac workup strategies

While the number of patients discharged with AMI significantly increased from 10% during Phase A to 14% during Phase B in hospitals switching to hs-cTnT, the prevalence of unstable angina decreased in parallel from 14 to 9%, respectively. In total, the prevalence of acute coronary syndrome remained stable during both periods (24 vs. 23%, respectively, adjusted-$P = 0.322$). Overall, rates of coronary angiographies remained stable during both phases (23% during both phases). However, among all patients undergoing invasive testing, the percentage of patients discharged with AMI increased by 44% from 36 to 52% during Phase B (adjusted-$P < 0.001$), while the percentage of patients discharged with unstable angina decreased by 44% from 39 to 22% (adjusted-$P < 0.001$,

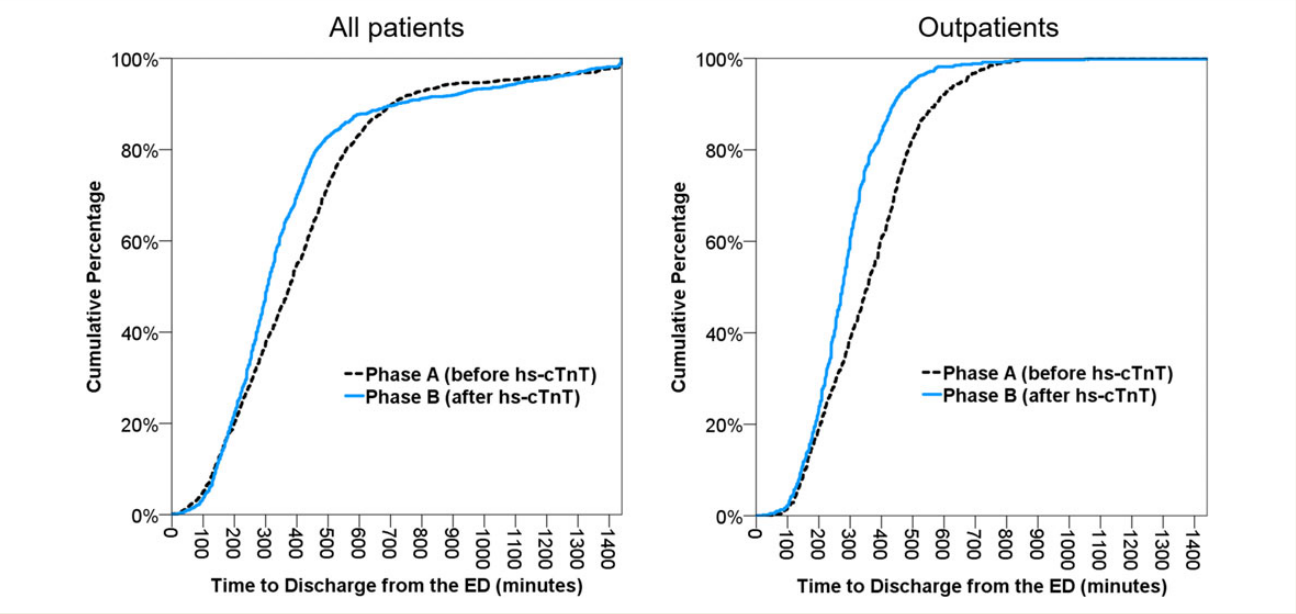

Figure 3 Cumulative distribution of time to discharge from the emergency department before and after the introduction of high-sensitivity cardiac troponin T.

Supplementary material online, *Figure S1*). During both periods, three-fourths of all patients undergoing invasive testing were discharged with acute coronary syndrome (75 vs. 74%, $P = 0.673$).

In contrast, the prevalence of patients discharged with chest pain of unknown origin significantly decreased after the introduction of hs-cTnT by 21% from 48 to 38% (adjusted-$P < 0.001$). Among all patients undergoing cardiac stress testing, the prevalence of patients discharged with chest pain of unknown origin decreased by 17% from 59 to 49% after the introduction of hs-cTnT (adjusted-$P = 0.011$, Supplementary material online, *Figure S2*).

Impact of high-sensitivity cardiac troponin T on management in patients with and without acute myocardial infarction

Among patients discharged with AMI ($n = 295$), the number of cardiac stress tests performed remained stable during Phases A and B, while the number of coronary angiographies increased during Phase B (81 vs. 90%, respectively, adjusted-$P = 0.021$) with no significant change in coronary interventions (Supplementary material online, *Table S2A*). Time of observation in the ED was longer during Phase B (217 vs. 289 min, respectively, adjusted-$P = 0.009$).

In contrast, among patients with a discharge diagnosis other than AMI ($n = 2249$), use of cardiac stress testing decreased significantly (30 vs. 20%, adjusted-$P < 0.001$) while the number of coronary angiographies remained stable (16 vs. 13%, respectively, adjusted-$P = 0.411$, Supplementary material online, *Table S2B*). The number or coronary interventions tended to be lower in Phase B compared with Phase A without reaching level of significance (7 vs. 4%, adjusted-$P = 0.054$). Time of observation on the ED (390 vs. 310 min, respectively, adjusted-$P = 0.006$) and median overnight stays were significantly reduced during Phase B.

Levels of high-sensitivity cardiac troponin T among different cardiac workup strategies

In hospitals switching to hs-cTnT, median levels of hs-cTnT determined in study blood samples obtained directly at presentation to the ED remained comparable during both periods (median 9.4 vs. 8.0 ng/L, $P = 0.263$, Supplementary material online, *Table S7*). However, with the clinical introduction of hs-cTnT during Phase B, median levels of hs-cTnT in patients undergoing no further cardiac diagnostic examinations significantly decreased from 9.0 to 6.0 ng/L ($P < 0.001$) while median levels of hs-cTnT significantly increased in patients undergoing coronary angiography (20.3 vs. 27.0 ng/L, respectively, $P = 0.032$) or coronary intervention (21.8 vs. 35.3 ng/L, respectively, $P = 0.037$).

In contrast, in hospitals not switching clinically to hs-cTnT, no change in distribution of median hs-cTnT levels could be observed among the different workup strategies.

Observations in hospitals not switching to high-sensitivity cardiac troponin

In the three hospitals not switching to hs-cTn, the diagnostic workup and its change over time was analysed in 377 patients presenting with symptoms suggestive of AMI. Similarly to the main cohort, a trend towards younger age and lower prevalence of cardiovascular risk factors was observed during Phase B (Supplementary material online, *Table S3*). Distributions of the clinical discharge diagnoses and the adjudicated final diagnoses were comparable between the two periods (Supplementary material online, *Table S4A and B*).

The rate of coronary angiography and subsequent percutaneous coronary interventions was stable between the two periods

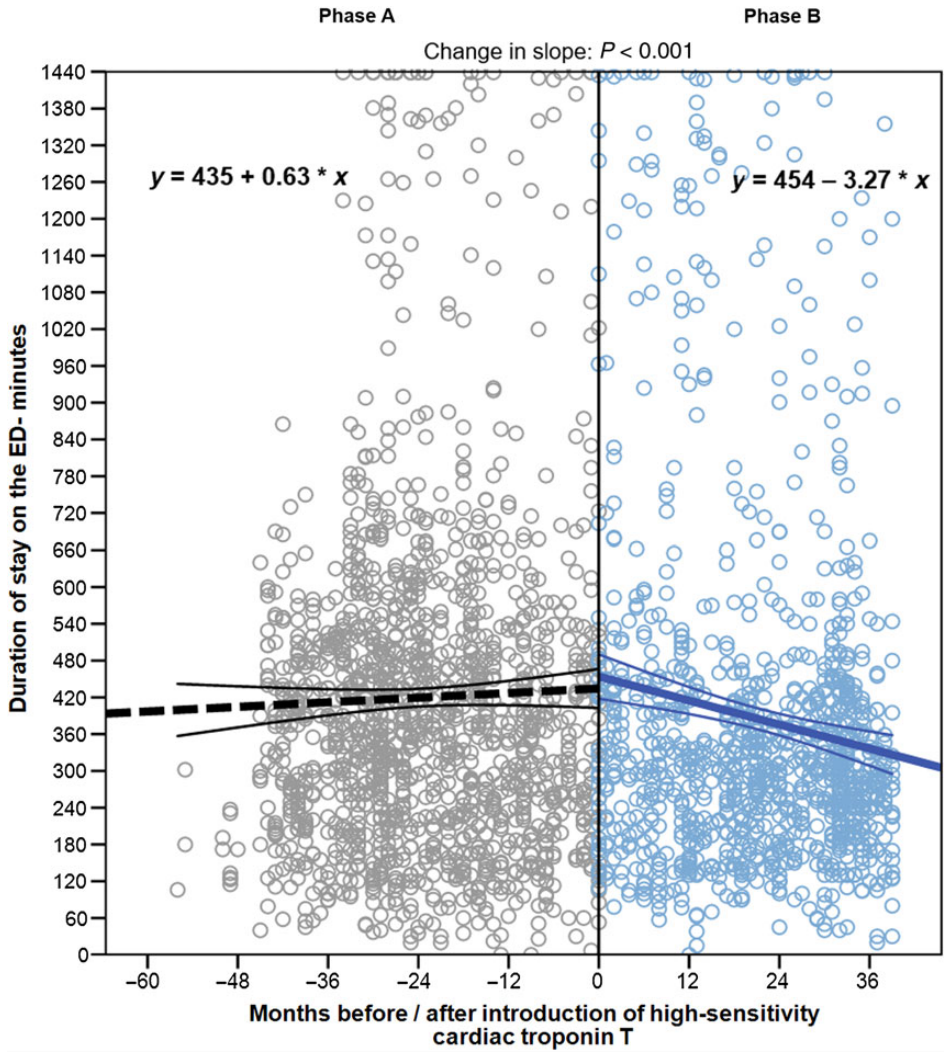

Figure 4 Change in trends of duration of stay on the emergency department before and after the introduction of high-sensitivity cardiac troponin T. Scatter plot depicting the duration of stay on the emergency department for each patient with respect to months before (Phase A, grey) and after (Phase B, blue) the introduction of high-sensitivity cardiac troponin T. Interrupted time series analyses were used to analyse for trends during both phases and to compare for change in slopes.

(24 vs. 24% and 16 vs. 15% during Phases A and B, respectively, adjusted-*P*-values 0.974 and 0.976, respectively; Supplementary material online, *Table S5* and *Figure S3*). The extent of coronary atherosclerosis quantified by the number of diseased vessels was comparable in both periods (adjusted-*P* = 0.288, Supplementary material online, *Figure S4*).

In contrast to the main cohort, rates of cardiac stress testing were comparable in the two phases (35% during Phase A vs. 29% during Phase B, adjusted-*P* = 0.167) in hospitals that did not switch to hs-cTn.

Duration of stay in the ED among all patients increased during Phase B when compared with Phase A by 97 min (adjusted-*P* = 0.012, Supplementary material online, *Figure S5*). In the subgroup of patients, in whom discharge from the ED was feasible (outpatients), time to discharge remained unchanged (adjusted-*P* = 0.427) while among inpatients, median duration of stay at the ED significantly increased by 81 min (adjusted-*P* = 0.044). Interrupted time series analyses revealed no significant change in trends comparing Phases A and B (*P* = 0.250, Supplementary material-online, *Figure S6*).

Cost calculation

Interrupted time series analyses revealed a significant change in trend on total costs from a mean increase of €5.05 per month during Phase A to a mean decrease of €12.12 per month during Phase B (*P* = 0.012, Supplementary material online, *Figure S7A*) while mean total costs remained similar in the overall population during both phases. In outpatients, a mean reduction of 20% in total costs could be observed (Supplementary material online, *Table S6A and B*; mean total costs €782 vs. €626, adjusted-*P* = 0.002). In hospitals not switching to hs-cTnT, total costs remained similar for the overall population as well as for the subgroup of patients managed as

outpatients. Interrupted time series analyses revealed no significant change in trend on total costs (Supplementary material online, *Figure S7B*).

Discussion

This analysis compared the use of coronary angiography, cardiac stress testing, and time to discharge from the ED in 2544 patients with suspected AMI enrolled in a multicentre study with identical inclusion and exclusion criteria before and after the clinical introduction of hs-cTnT testing. We report six major findings.

First, the clinical introduction of hs-cTnT was neither associated with an increase in the rate of coronary angiography, nor the rate of potentially unnecessary coronary angiographies as quantified by the rate of coronary angiographies showing normal coronary arteries, nor the rate of coronary revascularization procedures. *Second*, hs-cTnT testing was, associated with a reduction in the need for cardiac stress testing by >30%. This reduction was seen exclusively in the rate of exercise ECG, the stress modality that is usually applied in low-to-moderate risk patients. *Third*, the availability of more precise biomarker information in the lower range as offered by hs-cTnT was associated with improved allocation of patients to further diagnostic cardiac testing: low-risk patients as identified by very low levels of hs-cTnT to no further cardiac testing and high-risk patients as identified by elevated levels of hs-cTnT to coronary angiography. *Fourth*, in patients who were candidates for discharge from the ED, the use of hs-cTnT was associated with a significant reduction in time to discharge by nearly 80 min, related to more rapid rule-out of AMI. Interrupted time series analyses documented a significant change in trends on duration of stay in the ED from a mean increase of 0.63 min per month during Phase A vs. a mean decrease of 3.27 min per month during Phase B. *Fifth*, in parallel, total costs were also reduced by 20% in patients managed as outpatients. Again, interrupted time series analyses revealed a significant change in trend on total costs from a mean increase of €5.05 per month during Phase A to a mean decrease of €12.12 per month during Phase B, while mean total costs remained similar in the overall population during both phases. *Sixth*, the reduction in stress testing and the reduction in time to discharge from the ED were not observed in a control group of patients recruited during the same time period in three hospitals not switching to hs-cTnT. In contrast, time-to-discharge increased in the control group.

These findings corroborate and extend prior studies highlighting the increased diagnostic accuracy achieved with hs-cTnT, recent studies exploring the best possible application of hs-cTnT, as well as recent modelling performed to estimate its cost-effectiveness.[15–23,27–30] The substantial improvements in patient pathway characteristics are even more impressive when considering that Phase B included the clinical 'learning phase' regarding hs-cTnT at the switching hospitals.

Our findings also extend observations made in a pilot study including rather selected patients (patients presenting with chest pain with a low likelihood to be of coronary origin (e.g. musculoskeletal or pleuritic chest pain), also showing a reduction of cardiac stress testing, but an increased use of coronary angiography and revascularization after the introduction of hs-cTnT in a Spanish single-centre study.[31] Potential reasons for the different findings regarding coronary angiography include inclusion criteria, which more closely reflect 'real life' and the recommended clinical application of hs-cTn in APACE, the extent of teaching during clinical implementation, the threshold to order an invasive test, as well as personal or institutional incentives (positive or negative) to perform coronary angiography.

As most patients enrolled in Phase B were recruited after the publication of the 2011 ESC guidelines, our study investigated the impact of hs-cTnT mostly used in the context of these guidelines including the use of the 99th percentile and the hs-cTn 0 h/3 h algorithm with retesting for hs-cTnT at 3 h. It is therefore important to acknowledge these additional factors beyond the assay that changed. Accordingly, similar improvements may be possible with other cTn assays as long as they can detect accurately the 99th percentile (='sensitive' assays). In addition, there may have been differences that cannot be accounted for. Four considerations argue against the hypothesis that the reduction in time to discharge observed were the consequence of perfection of the diagnostic process due to general insights gained during previous scientific work in this setting by the investigators. First, if this would be the case, hospitals not switching to hs-cTn should have had the same reduction in time to discharge in outpatients. This was not observed. Second, all participating institutions applied the clinical practice guidelines of the ESC, which remained unchanged during the enrolment period for the use of conventional cTn assays.[1,24] Third, interrupted time series analyses documented a significant change in trends on duration of stay (and costs) at the time of the clinical introduction of hs-cTnT. Fourth, most of the insights gained from our previous work in APACE are specific to the use of hs-cTn.[16–23]

In addition to the cTn assay itself, the respective cut-off levels selected for clinical use may impact on management decisions and resource utilization. The clinical cut-off levels for the fourth-generation cTn assay used during Phase A (40 ng/L) is the 10% CV level and was recommended by guidelines and experts at that time.[2,13] In the meantime, some hospitals mainly in the USA, where hs-cTn assay are still not available, have lowered the cut-off level from 40 to 10 ng/L in order to better reflect the 99th percentile without fulfilling the criteria of 10% CV. For hospitals using a clinical decision level lower than the one used in Phase A (40 ng/L), any concerns about a systematic detrimental effect regarding coronary angiography should be even smaller. However, also the beneficial effects on time to discharge and exercise testing could be smaller than observed in our trial.

Rates of patients referred to coronary angiography in our data set are similar to those observed in a recent international diagnostic chest pain study performed on three continents including sites in the USA investigating the diagnostic accuracy of a 0 h/1 h algorithm to rule-out and rule-in AMI (rates of coronary angiography, 23% in both trials).[32] This finding further supports the generalizability of the findings from the APACE study.

The following limitations of the current study merit consideration. *First*, we evaluated the effects of the clinical introduction of hs-cTnT. It is unknown whether our findings can be extrapolated to the clinical introduction of other hs-cTn assays with similar diagnostic accuracy.[8,9,23,27] We hypothesize that hs-cTnI assays with similar diagnostic accuracy should result in similar resource use as seen with hs-cTnT. Of course, these hypotheses require

confirmation or rejection in future studies. *Second*, our findings relate to the use of hs-cTnT in experienced centres applying the 2011 ESC guidelines and accompanied by a dedicated educational campaign. We cannot comment on the possible impact of hs-cTnT in other settings. *Third*, our data confirm the increased attendance of younger patients to the ED seen in prior studies. This trend required adjustments for age. Future studies are warranted to quantify this effect. *Fourth*, we cannot comment on the impact of the clinical introduction of hs-cTnT among patients with terminal kidney failure requiring dialysis, since such patients were excluded from our study. *Fifth*, some lots of the hs-cTnT assay used clinically in the management of patients in Phase B were affected by the low-end shift.[33–36] According to several recent studies, the low-end shift nearly exclusively affected concentrations below 14 ng/L (the 99th percentile) and thereby seemed to have had no relevant impact on the clinical diagnosis of AMI.[33–36] *Sixth*, the findings from our cost analyses must be interpreted carefully. While we adjusted for multiple differences observed between the two phases such as age, history of coronary disease, and presence of arterial hypertension, there may have been differences that cannot be accounted for. No propensity-score matching was performed. Findings from cost analyses *per se* are not necessarily generalizable to other healthcare systems than observed in this trial due to potential differences in costs.

In conclusion, when introduced in experienced centres accompanied by a dedicated educational campaign and in combination with a strategy of lowering the diagnostic cut-off value for AMI (to the 99th percentile as recommend in the ESC guideline), the clinical introduction of hs-cTnT was not associated with an increased or inappropriate use of coronary angiography. High-sensitivity cardiac troponin T was associated with an improved rule-out process and thereby helped to substantially reduce the need for cardiac stress testing and time to discharge.

Supplementary material

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

Authors' contributions

R.T. and C.M. performed statistical analysis. R.T., M.R.G., T.R., S.O., and C.M. handled funding and supervision. R.T., C.J., M.R.G., K.W., T.R., T.N., J.B., K.G., C.P., B.M., G.P., N.S., I.C., K.R., S.S., and C.M. acquired the data. R.T., M.R.G., K.W., T.R., J.B., I.C., K.R., S.S., and C.M. conceived and designed the research. R.T. and C.M. drafted the manuscript. R.T., C.J., M.R.G., K.W., T.R., T.N., J.B., K.G., C.P., B.M., G.P., N.S., I.C., K.R., S.S., S.O., and C.M. made critical revision of the manuscript for key intellectual content.

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