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Decreased admissions and hospital costs with a neutral effect on mortality following lowering of the troponin T cutoff point to the 99th percentile

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Abstract

Background: *The implementation of high-sensitivity cardiac troponin T (hs-cTnT) assays and a cutoff based on the 99th cTnT percentile in the evaluation of patients with suspected acute coronary syndrome has not been uniform due to uncertain effects on health benefits and utilization of limited resources.*

Methods: *Clinical and laboratory data from patients with chest pain or dyspnea at the emergency department (ED) were evaluated before (n = 20516) and after (n = 18485) the lowering of the hs-cTnT cutoff point from 40 ng/L to the 99th hs-cTnT percentile of 14 ng/L in February 2012. Myocardial infarction (MI) was diagnosed at the discretion of the attending clinicians responsible for the patient.*

Results: *Following lowering of the hs-cTnT cutoff point fewer ED patients with chest pain or dyspnea as the principal complaint were analyzed with an hs-cTnT sample (81% vs. 72%, p < 0.001). Overall 30-day mortality was unaffected but increased among patients not analyzed with an hs-cTnT sample (5.3% vs. 7.6%, p < 0.001). The MI frequency was unchanged (4.0% vs. 3.9%, p = 0.72) whereas admission rates decreased (51% vs. 45%, p < 0.001) as well as hospital costs. Coronary angiographies were used more frequently (2.8% vs. 3.3%, p = 0.004) but with no corresponding change in coronary interventions.*

Conclusions: *At the participating hospital, lowering of the hs-cTnT cutoff point to the 99th percentile decreased admissions and hospital costs but did not result in any apparent prognostic or treatment benefits for the patients.* (Cardiol J 2017; 24, 6: 612–622)

Key words: high-sensitivity troponin T, hs-cTnT, 99th percentile, mortality, hospital admissions

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Introduction

When the electrocardiogram is inconclusive, the diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI) relies on the level and the change in heart damage biomarker cardiac troponin [1]. Several reports indicate that the use of high-sensitivity cardiac-specific troponin assays and diagnostic cutoff points based on the 99th troponin percentile value in healthy populations, as advocated by the third universal definition of myocardial infarction (MI), results in improved diagnostic accuracy and an ability to find patients with a poor prognoses who may benefit from intervention [2–7]. Despite this, the implementation of high-sensitivity troponin assays has not been uniform, due, in part, to the suspicion that a lowering of the diagnostic cutoff point will inundate hospitals with patients with no apparent benefit from cardiologic interventions [8].

Due, in part, to this controversy the diagnostic cutoff point for MI, based on the 4th generation cTnT assay imprecision, remained unchanged at 40 ng/L when the high-sensitivity cardiac troponin T (hs-cTnT) assay was introduced in clinical routine at the hospital of this study. For this reason, levels above 40 ng/L were regarded as the diagnostic cutoff point for MI for 25 months, although the clinical hs-cTnT assay was capable of measuring the 99th hs-cTnT percentile of 14 ng/L [9] with a coefficient of variation (CV) below 10% and values down to 5 ng/L were reported to clinicians. After this 25-month period, the diagnostic cutoff point for MI was lowered to the 99th hs-cTnT percentile of 14 ng/L, with the same hs-cTnT assay in use [10], and clinical routines for suspected ischemic coronary disease were changed with hs-cTnT levels down to 5 ng/L reported to the attending clinician.

The aim was to evaluate how lowering of the hs-cTnT diagnostic cutoff point for NSTEMI from 40 ng/L to the 99th hs-cTnT percentile value of 14 ng/L affected 30-day mortality, admission rates and resource utilization in patients with a chief complaint of chest pain or dyspnea in the emergency department (ED).

Methods

Study design and populations

Patients with at least one visit to the EDs at the Sahlgrenska University Hospital (Östra or Mölndal hospitals) with a chief complaint of chest pain or dyspnea between January 2010, and December 2013, were included in the study. Characterization of patients with chest pain from these EDs from another time period has been published before [11]. No exclusion criteria were used (Fig. 1). These ED's did not have any point of care cTn analysis in use during the study period and all cTn evaluations were done using the hs-cTnT assay in the central laboratory.

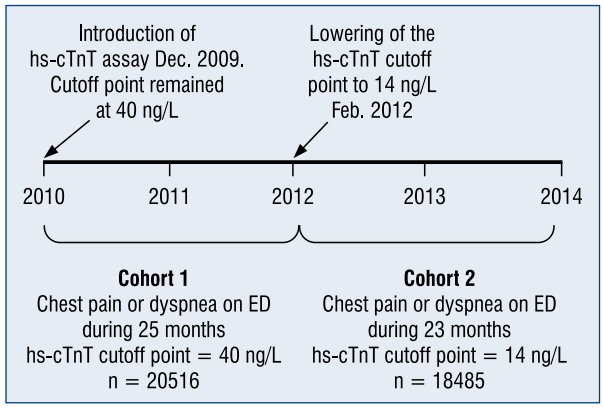

Figure 1. Graphical presentation of the collection of the study group. Cohort 1 was collected using 40 ng/L as the high-sensitivity cardiac troponin T (hs-cTnT) cutoff and Cohort 2 using 14 ng/L as the hs-cTnT cutoff; ED — emergency department.

Study data were retrieved from the hospital's administrative database containing diagnoses, interventions and hospital costs for each admission, from the National Board of Health and Welfare's National Patient Register [12, 13], and Prescribed Drug Register with information on hospital stays and medications [14]. Information on hs-cTnT levels was retrieved from the hospital´s laboratory database.

Data entered in to the local hospital database is used to partition funds within the hospital, thus adding an economic incentive for departments to keep this record complete.

Entry of ordering time and patient identity in the laboratory database is a part of the test ordering procedure and is automatic. It is not possible to obtain a test result from the central lab without a complete registration.

Table 1 (patient characteristics) shows data on diagnoses and medications reported to the Swedish National Board of Health and Welfare between 2010 and 2013. Diagnoses were classified based on ICD-codes. The definition of an "I-diagnose" was having an ICD-10 code beginning with "I". I10 was defined as hypertension, I50 as heart failure, I48 as atrial fibrillation or flutter, J44 as chronic obstructive pulmonary disease (COPD), an ICD-code beginning with "E1" as diabetes and I63 as cerebral infarction.

Medications were classified using ATC-codes. C07 was defined as beta-blockers, C08 as calcium channel blockers, C09A as angiotensin converting enzyme inhibitors, C03DA as aldosterone antagonists, C03C as loop diuretics, B01AC06 as acetylic acid, B01AA as vitamin K inhibitors, C10AA as statins, A10A as insulin and A10B as other glucose lowering medications

Details of the hs-cTnT cutoff change

The 10th of December 2009 the hs-cTnT assay was introduced simultaneously at Östra University Hospital and at the Mölndal Hospital and levels down to 5 ng/L was reported. The previous cutoff based on the 4th generation cTnT assay limit of quantification of 40 ng/L (CV < 10%) was kept unchanged until the end of January 2012.

In February 2012, the hs-cTnT cutoff point for NSTEMI was changed to the 99th percentile of 14 ng/L, as recommended by the European Society of Cardiology, but with continued use of the same hs-cTnT assay. At the same time, local guidelines at Sahlgrenska University Hospital for patients with suspected acute coronary syndrome (ACS) were changed to adapt to the new cutoff point (**translation in supplementary data — see journal website**). The new medical protocol stressed the need for clinical judgment before an hs-cTnT was ordered, especially in patients not considered for chest pain suggesting myocardial ischemia. In addition, the new medical protocol listed alternative conditions other than NSTEMI that could cause hs-cTnT elevations.

Patients with NSTEMI were diagnosed at the discretion of the attending clinician by reviewing available clinical and laboratory data collected during the hospital stay.

The study was approved by the Ethics Committee at the University of Gothenburg, and the study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki.

Laboratory methods

High-sensitivity cTnT was measured using the Elecsys® hs-cTnT immunoassay on a fully automated Modular® Analytics E170. The within-run, between-run and long-term CV have been published previously [15]. During the study Roche, the manufacturer of the hs-cTnT assay, made an error in the calibration routines which resulted in a lowered measure of cTnT concentration, specifically around the 14 ng/L level during the period of January 2011 until May 2012. The local cTnT control based on pooled patient samples had a measured cTnT concentration of 15.8 ng/L in December 2009 when the hs-cTnT assay was introduced into the routine. The same pooled sera gave a measured cTnT concentration of 12.1 ng/L January 2011 and 17.9 ng/L after introduction of appropriate manufacturing routines at Roche May 2012 [10]. After May 2012 there was no observed significant drift of the hs-cTnT assay throughout the rest of the study period. Hs-cTnT values above the limit of quantification (LoQ) of 5 ng/L were reported to clinicians throughout the study. For each patient, all hs-cTnT analyses during the hospital stay were obtained from the local clinical chemistry database. The attending clinician made all decisions about the number of and timing of hs-cTnT sampling, based on clinical need.

Statistical analyses and calculations

The absolute hs-cTnT change during hospital stay was calculated as an absolute value of the difference between baseline hs-cTnT level and hs-cTnT level deviating the most from the level recorded during hospital stay. The hs-cTnT relative change during hospital stay was calculated as an absolute hs-cTnT change divided by baseline hs-cTnT level recorded during hospital stay multiplied by 100.

Dichotomous values were compared using exact tests with MonteCarlo estimates. Medians were compared using median tests and means using independent sample t-tests.

All statistical analyses were performed using SPSS version 21. All probabilities were two-tailed, and p values < 0.05 were regarded as significant.

Results

Study population

The study cohort comprised of 21576 unique patients who were accountable for 39001 visits to the ED, and had in total 58524 hs-cTnT levels analyzed during the study period. During 2010 until the end of January 2012, when hs-cTnT cutoff point for NSTEMI was kept at 40 ng/L, a total of 13215 unique patients had 20516 visits for chest pain or dyspnea to the ED and 32167 hs-cTnT levels analyzed (Cohort 1). After the lowering of the hs-cTnT cutoff point in February 2012, and the change to the medical protocol for suspected ACS, 11185 unique patients were analyzed with 26357 hs-cTnT analyses at 18485 visits during February 2012 to December 2013 (Cohort 2).

Characteristics of the study cohorts before and after hs-cTnT cutoff point change

After lowering of hs-cTnT cutoff point (Fig. 1), there was no change in age and gender distribu-

Table 1. Characterization of patients with chest pain or dyspnea as principal complaint on the emergency department before (Cohort 1) or after (Cohort 2) lowering the high-sensitivity cardiac troponin T (hs-cTnT) cutoff.

	Cohort 1	Cohort 2	P
Number of emergency department visits	20516	18485	
Demographics			
Age [years]	67 (51–80)	68 (51–80)	0.46
Male sex	49.1%	49.9%	0.11
Dyspnea	38.0%	36.2%	< 0.001
Diagnoses#			
I-diagnoses*	69%	69%	0.39
Hypertension	44%	45%	0.0089
Heart failure	26%	24%	< 0.001
Atrial fibrillation or flutter	25%	25%	0.13
Chronic obstructive pulmonary disease	19%	18%	0.0087
Diabetes mellitus	18%	17%	0.013
Cerebral infarction	6%	7%	0.0005
Drugs#			
Beta-blockers	58%	59%	0.057
Calcium channel blockers	33%	35%	0.0013
ACE inhibitors	34%	36%	0.0044
Aldosterone antagonists	14%	13%	0.065
Loop diuretics	41%	39%	< 0.001
Acetylic acid	49%	47%	0.015
Vitamin K antagonists	16%	18%	< 0.001
HMG CoA reductase Inhibitors	41%	44%	< 0.001
Insulin	10%	9%	0.02
Other glucose lowering therapy	12.5%	12.4%	0.73

#Data between 2010 and 2013 from the Swedish National Board of Health and Welfare; *ICD-10 code beginning with "I"; ACE — angiotensin--converting enzyme

tion among patients in the ED with a primary complaint of chest pain or dyspnea (Table 1). There were some small but statistically significant differences in cohorts before and after the cut-off change: 1. Proportion of patients with dyspnea decreased slightly (38% vs. 36%, $p < 0.001$). 2. Small increases or decreases were also observed in the frequency of heart failure, diabetes mellitus, COPD, cerebral infarction and use of medications relevant for heart disease. There was however, no overall change in frequency of patients with diagnoses related to cardiovascular disease (ICD-10 I--diagnoses).

Overall changes after lowering the hs-cTnT cutoff point

After lowering of hs-cTnT cutoff point admission frequency decreased (58.8% vs. 52.8%, $p < < 0.001$; Table 2). After the lowering of the hs-cTnT cutoff point, fewer patients were analyzed with an hs-cTnT sample (81% vs. 72%, $p < 0.001$). However, admissions also decreased among patients who were analyzed with an hs-cTnT sample in the ED, despite increases in baseline hs-cTnT levels and increased frequency of slightly elevated baseline hs-cTnT levels (14–40 ng/L). The frequency of return to the ED within 30 days (Tables 2–4) and frequency of MI among returners increased (Cohort 1: 0.51%, Cohort 2: 0.69% MI among patients who returned within 30 days, $p = 0.021$).

There was no overall change in the frequency of NSTEMI (4.0% vs. 3.9%, $p = 0.72$) or unstable angina pectoris diagnoses (Table 2). However, the NSTEMI diagnoses increased among patients with a baseline hs-cTnT between 14 ng/L and 40 ng/L (Fig. 2B). Coronary angiographies increased (2.8% vs. 3.3%, $p = 0.004$) with no corresponding increase in percutaneous coronary interventions (1.3% vs. 1.2%, $p = 0.60$).

Table 2. Characteristics of patients with chest pain or dyspnea as principal complaint at the emergency department before (Cohort 1) or after (Cohort 2) lowering the high-sensitivity cardiac troponin T (hs-cTnT) cutoff.

	Cohort 1	Cohort 2	P
Admission	58.8%	52.8%	< 0.001
Hospital cost among admitted (mean DRG weigh/chest pain or dypnea patient visit)	0.46	0.25	< 0.001
Admission if hs-cTnT analyzed on ED	71.3%	66.3%	< 0.001
Admission time (days ± SD)	4.2 ± 4.8	4.1 ± 4.5	0.11
hs-cTnT sampling frequency	80.9%	71.7%	< 0.001
Median baseline hs-cTnT level [ng/L]	6 (3–22)	9 (5–22)	< 0.001
Baseline hs-cTnT level 14–40 ng/L among analysed on ED	19.7%	23.5%	< 0.001
Return to emergency department within 30 days	25.9%	30.2%	< 0.001
NSTEMI diagnosis†			
NSTEMI	4.0%	3.9%	0.72
NSTEMI if baseline hs-cTnT 14–40 ng/L	4.9%	7.4%	< 0.001
NSTEMI if baseline hs-cTnT > 40 ng/L	24.2%	23.1%	0.40
Primary or secondary diagnosis†			
Unstable AP	1.1%	1.0%	0.58
Stable AP	4.9%	4.4%	0.048
Heart failure	6.2%	5.4%	< 0.001
Interventions			
Coronary angiography	2.8%	3.3%	0.004
Percutaneous coronary intervention	1.3%	1.2%	0.56
All cause mortality			
30 day	3.9%	3.9%	0.98
180 day	9.6%	10.1%	0.13
All cause mortality if not analyzed with hs-cTnT			
30 day	3.8%	5.8%	< 0.001
180 day	11.7%	16.4%	< 0.001

†Only patients that were admitted; AP — angina pectoris; DRG — diagnosis related group, a way to assess the hospital coast related to different diagnosis group; ED — emergency room; NSTEMI — non-ST-segment elevation myocardial infarction

All-cause mortality was unchanged in the entire cohort. However, the mortality increased among patients who were not analyzed with an hs-cTnT sample (Table 2, Fig. 2C). Patients who were not analyzed with an hs-cTnT sample were older (Cohort 1:65 years, Cohort 2:68 years, $p < 0.001$) and had more comorbidity (≥ 2 of heart failure, atrial fibrillation, COPD or stroke: Cohort 1: 29%, Cohort 2: 33%, $p < 0.001$). The mortality decreased among patients who were analyzed with at least one hs-cTnT level in the ED (30 day mortality 3.9% vs. 2.9%, $p < 0.001$).

Subgroup analysis of ED patients with chest pain or dyspnea

In addition to overall changes, subgroup analysis of chest pain patients showed decreased frequency of NSTEMI if baseline hs-cTnT was above 40 ng/L in cohort 2 (Table 3, Fig. 2B).

Patients with dyspnea were older, had higher baseline hs-cTnT levels, were more often admitted, had higher frequencies of heart failure and higher mortality, compared with chest pain patients (Table 4). After lowering the hs-cTnT cutoff point, the hs-cTnT sampling frequency decreased by over a third in dyspnea patients (Fig. 2A) together with a borderline significant decrease in the NSTEMI frequency (Table 3).

The non-sampled patient group was older and had more comorbidity after lowering the hs-cTnT cutoff (Fig. 2C, D, Table 4). The increase in 30-day mortality among patients not analyzed with an hs-cTnT was especially prominent among dyspnea patients (Table 3, Fig. 2C).

Table 3. Characteristics of patients with chest pain as principal complaint on the emergency department before (Cohort 1) or after (Cohort 2) lowering the high-sensitivity cardiac troponin T (hs-cTnT) cutoff.

	Chest pain		
	Cohort 1	Cohort 2	P
Number of ED visits	12714	11794	
Age [years]	61 (47-76)	63 (47-75)	0.007
Male sex	51.4%	52.5%	0.086
Dyspnea	NA	NA	NA
Admission	51.1%	45.1%	< 0.001
Hospital cost among admitted (mean DRG weigh/patient visit)	0.33	0.18	< 0.001
Admission if hs-cTnT analyzed on ED	52.1%	45.9%	< 0.001
Admission time (days ± SD)	3.2 ± 4.1	3.2 ± 3.6	0.65
hs-cTnT sampling frequency	90.1%	88.4%	< 0.001
Median baseline hs-cTnT level [ng/L]	3 (3–13)	8 (4–16)	< 0.001
Baseline hs-cTnT level 14–40 ng/L among analysed on ED	14.5%	20.3%	< 0.001
Return to ED within 30 days	23.4%	28.8%	< 0.001
NSTEMI diagnosis†			
NSTEMI	5.0%	5.1%	0.79
NSTEMI if baseline hs-cTnT 14–40 ng/L	8.1%	9.7%	0.098
NSTEMI if baseline hs-cTnT > 40 ng/L	42.5%	33.6%	< 0.001
Primary or secondary diagnosis†			
Unstable AP	1.6%	1.5%	0.539
Stable AP	7.2%	6.4%	0.008
Heart failure	2.0%	1.7%	0.066
Interventions†			
Coronary angiography	4.0%	4.5%	0.039
Percutaneous coronary intervention	2.0%	1.8%	0.28
All cause mortality			
30 day	1.1%	1.1%	0.95
180 day	3.6%	4.2%	0.037
All cause mortality if not analyzed with hs-cTnT			
30 day	0.6%	0.9%	0.39
180 day	2.8%	5.0%	0.004

†Only patients that were admitted; AP — angina pectoris; DRG — diagnosis related group, a way to assess the hospital coast related to different diagnosis group; ED — emergency room; NA — not applicable; NSTEMI — non-ST-segment elevation myocardial infarction

Subanalysis of patients with NSTEMI

There was no overall change in NSTEMI diagnoses after lowering the hs-cTnT cutoff. Median hs-cTnT levels among patients with NSTEMI were lower after implementation of 14 ng/L as the hs-cTnT cutoff point (Table 5) and more often remained below 40 ng/L throughout hospital stay (Fig. 3). The mortality among patients with NSTEMI was unchanged (Table 5).

Discussion

After lowering the hs-cTnT diagnostic cutoff point from 40 ng/L to the 99th hs-cTnT percentile of 14 ng/L, hs-cTNT sampling frequency and admissions decreased with a neutral effect on overall mortality and NSTEMI frequency among patients visiting the ED with suspected ACS at this hospital. However, increased mortality was observed among

Table 4. Characteristics of patients with dyspnea as principal complaint on the emergency department before (Cohort 1) or after (Cohort 2) lowering the high-sensitivity cardiac troponin T (hs-cTnT) cutoff.

	Dyspnea		
	Cohort 1	**Cohort 2**	**P**
Number of ED visits	7802	6691	
Age [years]	76 (63–84)	76 (64–85)	0.95
Male sex	45.3%	45.3%	0.97
Dyspnea	NA	NA	NA
Admission	71.3%	66.3%	< 0.001
Hospital cost among admitted (mean DRG weigh/patient visit)	0.67	0.39	< 0.001
Admission if hs-cTnT analyzed on ED	73.7%	70.2%	0.002
Admission time (days ± SD)	5.4 ± 5.2	5.3 ± 5.1	0.15
hs-cTnT sampling frequency	66.0%	42.2%	< 0.001
Median baseline hs-cTnT level [ng/L]	19 (6–42)	22 (9–44)	< 0.001
Baseline hs-cTnT level 14–40 ng/L among analysed on ED	31.4%	36.7%	< 0.001
Return to ED within 30 days	29.9%	32.7%	< 0.001
NSTEMI diagnosis†			
NSTEMI (%)	2.3%	1.8%	0.046
NSTEMI if baseline hs-cTnT 14–40 ng/L	1.7%	2.8%	0.052
NSTEMI if baseline hs-cTnT > 40 ng/L	10.3%	10.3%	1.000
Primary or secondary diagnosis†			
Unstable AP	0.1%	0.1%	0.44
Stable AP	1.0%	1.0%	1.000
Heart failure	13.0%	12.0%	0.074
Interventions†			
Coronary angiography	0.9%	1.1%	0.11
Percutaneous coronary intervention	0.2%	0.3%	0.48
All cause mortality			
30 day	8.4%	8.7%	0.49
180 day	19.3%	20.4%	0.091
All cause mortality if not analyzed with hs-cTnT			
30 day	5.3%	7.6%	< 0.001
180 day	16.0%	20.4%	< 0.001

†Only patients that were admitted; AP — angina pectoris; DRG — diagnosis related group, a way to assess the hospital coast related to different diagnosis group; ED — emergency room; NA — not applicable; NSTEMI — non-ST-segment elevation myocardial infarction

patients that were not analyzed with an hs-cTnT sample. This study is a service report and therefore, it is not possible to prove a cause and effect relationships. It is however, speculated that a lower hs-cTnT cutoff point resulted in a sampling bias so patients at high risk of non-specific hs-cTnT elevations were sampled less frequently after lowering the cutoff. This could result in bias toward older patients with several comorbidities that resulted in higher mortality in the non-sampled group.

The present findings differ from previous studies of ED patients following the implementation of a lower cTn cutoff point where an increased NSTEMI frequency [16–18] and lower mortality [16] were found. These studies only included ED patients who were analyzed with a cTn sample [16, 19] or admitted as high risk patients [17, 18]. In this study, all patients who came to the ED with chest pain or dyspnea were included. This allowed for an examination of whether a different cohort was sampled when the hs-cTnT cutoff point was lowered.

In agreement with previous studies, it was also found that the NSTEMI frequency increased

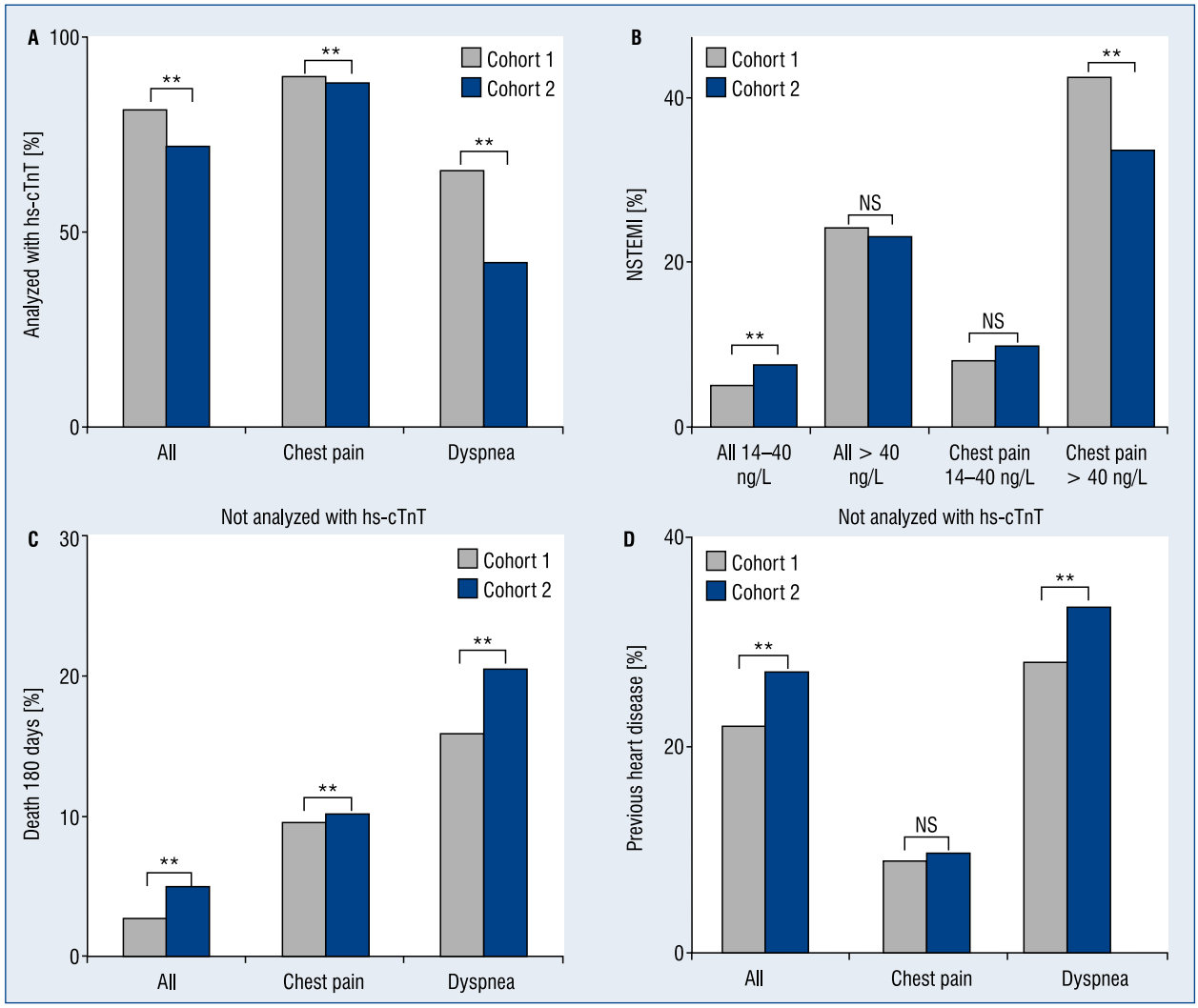

Figure 2. Graphical representation of selected data before (Cohort 1) and after (Cohort 2) lowering of the high-sensitivity cardiac troponin T (hs-cTnT) cutoff point from 40 ng/L to 14 ng/L; **A.** The percentage of all, chest pain or dyspnea patients analyzed with at least one hs-cTnT sample on the emergency department (ED); **B.** Non-ST-segment elevation myocardial infarction (NSTEMI) frequency among patients with baseline hs-cTnT level 14–40 ng/L or above 40 ng/L. Data from all patients or chest pain patients are shown; **C.** All cause death at 180 days after the ED visit; **D.** Recorded heart diagnosis except for hypertension among patients that were not analyzed with hs-cTnT during the ED visit or hospital stay. Data for all patients, chest pain patients and dyspnea patients are shown; **p < 0.01; NS — not significant.

and mortality decreased among admitted patients analyzed with at least one hs-cTnT sample after lowering the hs-cTnT cutoff point. When both sampled and non-sampled patients were analyzed, no change in NSTEMI frequency or mortality was found. This agrees with other studies that did not find an effect on mortality following introduction of a more sensitive cTn assay in clinical routine [20, 21].

The present interpretation is that decreased hs-cTnT cutoff point may have resulted in a more restrictive selection of patients to assess hs-cTnT levels in order to limit false positive results. This may have resulted in sampling bias, with the selection of younger patients with fewer comorbidities. The new medical protocol that was implemented when hs-cTnT cutoff was lowered to the 99th percentile stated that the only indication of a hs-cTnT test is suspicion of acute cardiac damage [22] and alerted the attending physician to the fact that old age [6, 15], decreased kidney function [23–25] and heart failure [26, 27] can result in false positive hs-cTnT results. This could be an explanation behind decreased hs-cTnT sampling frequency

Table 5. Characteristics of chest pain or dyspnea patients with non-ST-segment elevation myocardial infarction (NSTEMI) diagnosis and baseline high-sensitivity cardiac troponin T (hs-cTnT) sample analyzed in the emergency department before (Cohort 1) or after (Cohort 2) lowering the hs-cTnT cutoff.

	Cohort 1	Cohort 2	P
Number of NSTEMI patients	741	648	
Age [years]	78 (67–87)	76 (65–86)	0.014
Dyspnea	21.7%	16.4%	0.012
Male sex	57.2%	54.3%	0.28
Hospital cost (mean DRG weight ± SD)	1.16 ± 0.49	1.03 ± 0.44	< 0.001
hs-cTnTn levels			
Baseline hs-cTnT [ng/L]	79 (35–223)	51 (25–151)	< 0.001
Max hs-cTnT [ng/L]	239 (104–599)	156 (62–438)	< 0.001
Interventions			
Coronary angiography	24.2%	33.0%	< 0.001
Percutaneous coronary intervention	13.1%	14.8%	0.39
All cause mortality			
30 day	8.1%	6.2%	0.18
180 day	17.5%	13.9%	0.066

DRG — diagnosis related group, a way to assess the hospital coast related to different diagnosis group

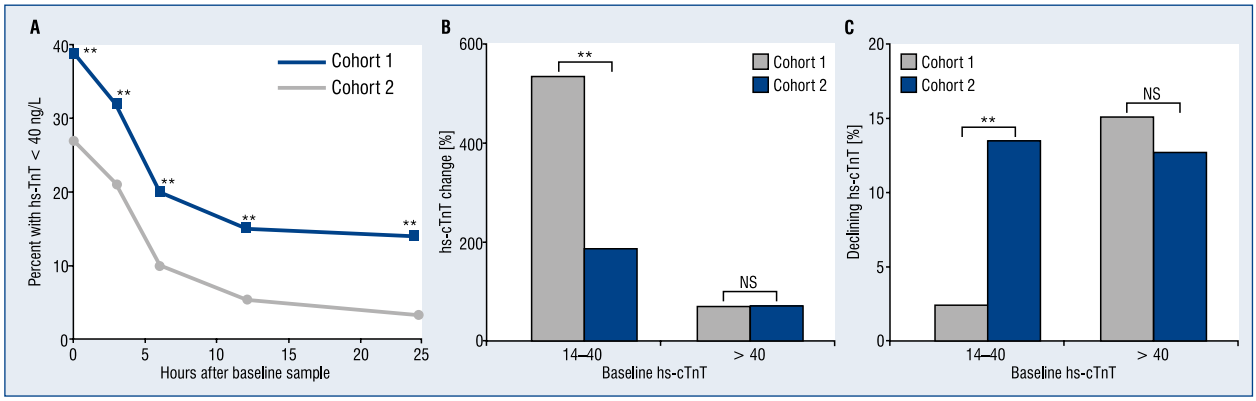

Figure 3. Analysis of non-ST-segment elevation myocardial infarction (NSTEMI) patient data before (Cohort 1) and after (Cohort 2) lowering high-sensitivity cardiac troponin T (hs-cTnT) cutoff point from 40 ng/L to 14 ng/L; **A.** Frequency of patients with NSTEMI with hs-cTnT levels below 40 ng/L after different times of hs-cTnT sampling; **B.** Median relative change in hs-cTnT levels during 24 h in patients with NSTEMI with baseline hs-cTnT levels between 14 ng/L and 40 ng/L or above 40 ng/L; **C.** Percentage of patients with NSTEMI with in-hospital hs-cTnT levels below baseline hs-cTnT levels (declining pattern) in patients with baseline hs-cTnT levels between 14 ng/L and 40 ng/L or above 40 ng/L;**p < 0.001; NS — not significant.

especially among patients with dyspnea, who more often present with comorbidities and at older age. The more restrictive use of hs-cTnT sampling and admissions resulted in a decrease in hospital costs with a neutral effect on overall mortality, also when patients who were sent home from the ED were analyzed separately (data not shown).

On the other hand, an increased mortality was observed among patients who were not analyzed with a hs-cTnT sample, a higher return to the ED within 30 days in combination with a slight increase in MI frequency among patients that did return. This can potentially be explained by the fact that non-sampled patients were older and had more comorbidities after lowering the hs-cTnT cutoff. It is therefore unclear if these patients would benefit from more sampling and intervention. This is the subject of future studies from the present group.

Thus, this experience underscores the importance of a predefined protocol on how to deal with unspecific troponin elevation unrelated to MI [28, 29] before implementing the 99th cTnT percentile as the diagnostic cutoff point.

This data also show indirect evidence that patients with NSTEMI with low and stable hs-cTnT levels were more often missed in Cohort 1, when 40 ng/L instead of 14 ng/L was used as a diagnostic cutoff point.

Firstly, the frequency of patients with NSTEMI with low hs-cTnT levels increased following the introduction of 14 ng/L as a diagnostic cutoff point.

Secondly, when 14 ng/L was used as a cutoff point, patients with NSTEMI more often had baseline hs-cTnT levels below 40 ng/L with stable or declining hs-cTnT levels. In contrast, these patients were rare when the cutoff point was 40 ng/L, possibly because patients with NSTEMI having stable or declining hs-cTnT levels below 40 ng/L were more often missed when 40 ng/L was used as a cutoff.

On the other hand, it was also observed that the frequency of NSTEMI among chest pain patients with a baseline hs-cTnT above 40 ng/L decreased, possibly due to more restrictive use of NSTEMI diagnosis, as dictated by the altered medical protocol. This reciprocal change, with an increased NSTEMI frequency among patients with low hs-cTnT levels and a decreased NSTEMI frequency when baseline hs-cTnT levels were high, is likely the reason behind the unchanged overall NSTEMI frequency after lowering the hs-cTnT cutoff point.

Limitations of the study

This study has several limitations. It was a service evaluation of retrospective data and not designed to examine only the effect of implementation of the 99th hs-cTnT percentile. During the 4 year study, clinical routines changed, as described in Materials and Methods, and it is not possible to attribute all the effects in hospital and laboratory statistics to lowering of hs-cTnT cutoff point. In addition, the NSTEMI diagnosis was in many cases a clinical diagnosis and not carried out according to a predefined protocol to provide hs-cTnT-independent evidence of myocardial damage of ischemic origin. No adjudication of NSTEMI diagnoses were done. In addition, there was a drift in the hs-cTnT assay calibration resulting in an underestimation of hs-cTnT levels a year before and 4 months after lowering the hs-cTnT cutoff. It is unclear if this might have affected clinical judgements [30]. The study also does not include important prognostic variables like metabolic syndrome, body mass index, waist circumference, serum cholesterol levels and family history of important diseases. However, the large sample size and the use of the same hs-cTnT assay in clinical routines both before and after the lowering of hs-cTnT cutoff point offered a unique possibility to assess the implications of a lowered hs-cTnT cutoff point down to the 99th percentile in a real clinical situation.

Conclusions

In summary, our service report indicates that, after implementation of the 99th cTnT percentile as the diagnostic cutoff point for MI, hs-cTnT sampling routines changed, admission rates decreased, 30-day mortality and NSTEMI frequency was unchanged.

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