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MINI-FOCUS: HIGH-SENSITIVITY TROPONIN

Small Changes in Troponin T Levels Are Common in Patients With Non–ST-Segment Elevation Myocardial Infarction and Are Linked to Higher Mortality

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Objectives The purpose of this study was to examine the extent of change in troponin T levels in patients with non–ST-segment elevation myocardial infarction (NSTEMI).

Background Changes in cardiac troponin T (cTnT) levels are required for the diagnosis of NSTEMI, according to the new universal definition of acute myocardial infarction. A relative change of 20% to 230% and an absolute change of 7 to 9 ng/l have been suggested as cutoff points.

Methods In a clinical setting, where a change in cTnT was not mandatory for the diagnosis of NSTEMI, serial samples of cTnT were measured with a high-sensitivity cTnT (hs-cTnT) assay, and 37 clinical parameters were evaluated in 1,178 patients with a final diagnosis of NSTEMI presenting <24 h after symptom onset.

Results After 6 h of observation, the relative change in the hs-cTnT level remained <20% in 26% and the absolute change <9 ng/l in 12% of the NSTEMI patients. A relative hs-cTnT change <20% was linked to higher long-term mortality across quartiles ($p = 0.002$) and in multivariate analyses (hazard ratio: 1.61 [95% confidence interval: 1.17 to 2.21], $p = 0.004$), whereas 30-day mortality was similar across quartiles of relative hs-cTnT change.

Conclusions Because stable hs-TnT levels are common in patients with a clinical diagnosis of NSTEMI in our hospital, a small hs-cTnT change may not be useful to exclude NSTEMI, particularly as these patients show both short-term and long-term mortality at least as high as patients with large changes in hs-cTnT. (J Am Coll Cardiol 2013;62:1231–8)

When the electrocardiogram (ECG) is inconclusive in patients with signs of acute coronary syndrome, the diagnosis of myocardial infarction (MI) relies largely on the level of the heart damage biomarker cardiac troponin (1). The introduction of high-sensitivity cardiac troponin T (hs-cTnT) assays and the lowering of the diagnostic threshold to the 99th cTnT percentile of 14 ng/l (2) have increased the number of patients presenting with an elevated cTnT level that needs further assessment (3,4). This is especially prevalent among older patients in the emergency department, where 36% to 50% of patients >65 to 70 years of age without MI present with an hs-cTnT level >14 ng/l (5,6). When cTnT is elevated at baseline, the change in the cTnT level is often evaluated during 3 to 6 h and sometimes up to 24 h (1).

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A few hours after cardiac necrosis, the levels of cTnT start to increase and reach a plateau phase after 10 to 15 h, followed by a slow decline (7). Consequently, it is often considered that MI can be excluded if the change in the cTnT level remains below 20% to 50% in patients presenting early after the onset of symptoms (8–11). There are, however, several reports indicating that plaque rupture often occurs days before the patient seeks medical attention (12,13), which is

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Abbreviations and Acronyms

CCU = coronary care unit
CPU = chest pain unit
cTnT = cardiac troponin T
ECG = electrocardiogram
HR = hazard ratio
hs-cTnT = high-sensitivity cardiac troponin T
IQR = interquartile range
MI = myocardial infarction
NCCP = noncardiac chest pain
NSTEMI = non–ST-segment elevation myocardial infarction

in line with the finding that many patients with MI present with elevated troponin levels that remain relatively stable during a 2-h to 6-h evaluation period (4,9,11,14). In addition, it is possible that the problem with stable troponin levels has been underestimated, as a change in the cardiac troponin level is often involved in the diagnosis of MI (1). These findings put the negative predictive power of a small troponin change into question.

To examine this further, we have evaluated hs-cTnT changes in patients with a final diagnosis of non–ST-segment elevation myocardial infarction (NSTEMI) in a clinical setting where the change in hs-cTnT was not mandatory for the diagnosis.

Methods

Study design and populations. Only patients admitted to coronary care unit (CCU) and chest pain unit (CPU) at Sahlgrenska University Hospital during the period December 2009 to January 2012, after the introduction of the hs-cTnT assay (Elecsys [Roche, Germany] hscTnT immunoassay), were included in the study and registered according to the previously described SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) study protocol (15,16). The more than 100 variables in the SWEDEHEART registry comply with the International Cardiology Audit and Registration Data Standards (CARDS) (15). A total of 1,567 patients received the final diagnosis of NSTEMI during the study period. Among these, 241 were excluded because of too few hs-cTnT analyses, and 148 were excluded because of >24 h between symptom onset and the first hs-cTnT sample. The remaining 1,178 patients with a total of 4,467 hs-cTnT measurements were included in the study (Table 1, Online Fig. 1). The time of symptom onset was available for 1,069 of the 1,178 patients who were included. The NSTEMI patients were diagnosed by a cardiologist, by reviewing data from a physical examination, imaging, ECG, and laboratory test results collected during the stay in the CCU/CPU.

Because no published measure of the 99th TnT percentile was available when the hs-cTnT assay was introduced into clinical routine in December 2009, the diagnostic hs-cTnT threshold that was based on the imprecision (coefficient of variation <10%) of the previous fourth-generation cTnT assay of 40 ng/l (17) was kept unchanged during the following 26 months when the study group was recruited. Changes in hs-cTnT levels were assessed but a significant change was not required for the final NSTEMI diagnosis if there was other convincing evidence of an ischemic origin of the hs-cTnT elevation. All hs-cTnT analyses during the period of the hospital stay were obtained from the local clinical chemistry database. Blood samples taken up to 24 h before arrival at the CCU/CPU were included to ensure that no blood samples of interest were missed. The first hs-cTnT analysis during this time period was considered the baseline sample. The attending clinician made all the decisions about when to sample hs-cTnT based on clinical need. The clinical characteristics of patients sampled at different times are shown in Online Table 1. Mortality data were collected from AMDAT, the Västra Götaland County mortality registry. There were 227 deaths in the NSTEMI study group after a median follow-up time of 380 days. No patient underwent coronary artery bypass graft surgery during the hs-cTnT sampling series. The percentage of patients who underwent percutaneous coronary intervention during the hs-cTnT series varied between 0.2% and 14%, depending on the length of the hs-cTnT series. These patients are summarized in Online Table 2.

Table 1 Characteristics of the Study Groups

	NSTEMI (n = 1,178)	NCCP (n = 326)
Age, yrs	74 (64–83)	67 (57–75)
Male	716 (60.8)	205 (62.9)
Diastolic BP, mm Hg	85 (74–99)	85 (76–95)
Systolic BP, mm Hg	150 (130–170)	150 (130–170)
ECG characteristics		
Sinus rhythm	925 (78.5)	325 (99.7)
Atrial fibrillation	159 (13.5)	0 (0)
ST-segment depression	356 (30.2)	29 (8.9)
Q-wave	123 (10.4)	16 (4.9)
Admission hs-cTnT, ng/l	94 (43–269)	8 (6–14)
Maximum hs-cTnT, ng/l	344 (125–973)	9 (6–17)
hs-cTnT change 6 h, %	81 (18–324)	60 (20–117)
hs-cTnT change in hospital, %	141 (34–702)	67 (25–166)
hs-cTnT change 6 h, ng/l	70 (22–233)	3 (2–7)
hs-cTnT change in hospital, ng/l	173 (48–601)	4 (2–11)
Creatinine, μmol/l	86 (71–110)	80 (66–93)
Symptom time, h	3.3 (1.4–6.9)	4 (1.7–7.3)
Risk factors		
Diabetes mellitus	276 (23.4)	49 (15.0)
Hypertension	560 (47.5)	151 (46.3)
Smoker	210 (17.8)	46 (14.1)
Body constitution and lipids		
BMI, kg/m^2	23.5 (26.0–29.3)	26.9 (24.3–29.7)
Total cholesterol, mmol/l	4.7 (4.0–5.6)	5.0 (4.2–5.8)
LDL cholesterol, mmol/l	2.8 (2.1–3.6)	2.9 (2.2–3.7)
Previous cardiovascular disease		
Myocardial infarction	447 (37.9)	75 (23.0)
Chronic heart failure	235 (19.9)	32 (9.8)
Previous PCI	224 (19.0)	51 (15.6)
Stroke	140 (11.9)	21 (6.4)
PCI during hospital stay	452 (38.4)	0 (0)

Values are median (interquartile range) or n (%).
BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; hs-cTnT = high-sensitivity cardiac troponin T; LDL = low-density lipoprotein; NCCP = noncardiac chest pain; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

Changes in the hs-cTnT level were also determined in chest pain patients (n = 326) admitted to the CCU/CPU between December 2009 and January 2012 and for whom a cardiac cause could be excluded (noncardiac chest pain [NCCP]). Patients were excluded if they had diagnoses that could affect the hs-cTnT level, such as heart failure or atrial fibrillation, those who died during the 24 h evaluation period, who underwent coronary angiography or cardiopulmonary resuscitation, or who had an hs-cTnT level either >100 ng/l or <5 ng/l. Of a total of 885 NCCP patients admitted to the CCU/CPU, 524 were excluded. The remaining 326 patients had 881 hs-cTnT measurements. 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.

Adjudication of the NSTEMI diagnosis in patients with small hs-cTnT changes. To examine the diagnostic precision among NSTEMI patients with small relative hs-cTnT changes, a random sample of 102 patients with an hs-cTnT change <20% and a matched sample of 100 NSTEMI patients with a 21% to 60% hs-cTnT change were selected. The matching was based on sex, age, and the maximum hs-cTnT level during the hospital stay, the number of hs-cTnT samples analyzed during the hospital stay, and the proportion of patients examined with angiography. Data from medical records, laboratory examinations, angiography, echocardiography, and other medical examinations performed during the hospital stay for the 202 NSTEMI patients were systematically reviewed. In addition, available medical records and hs-cTnT levels involving events before and after the hospital stay were systematically reviewed. In total, 57 separate parameters relevant to the NSTEMI diagnosis were reviewed and evaluated for each patient for whom they were available. Based on these data, each NSTEMI patient was categorized into 1 of 2 categories, in which: 1) the diagnosis of NSTEMI was based on evidence other than elevated hs-cTnT levels and symptoms that supported the diagnosis, such as regional wall motion abnormalities on echocardiography or culprit coronary stenosis identified on angiography (hs-cTnT–independent evidence for NSTEMI); and 2) the NSTEMI diagnosis relied mainly on symptoms and elevated hs-cTnT levels. The results from the adjudication process are presented in Online Tables 3 and 4.

Laboratory methods. The cTnT was measured using the Elecsys hs-cTnT immunoassay on fully automated Modular Analytics E170 and Cobas e602 modules. The within-run,

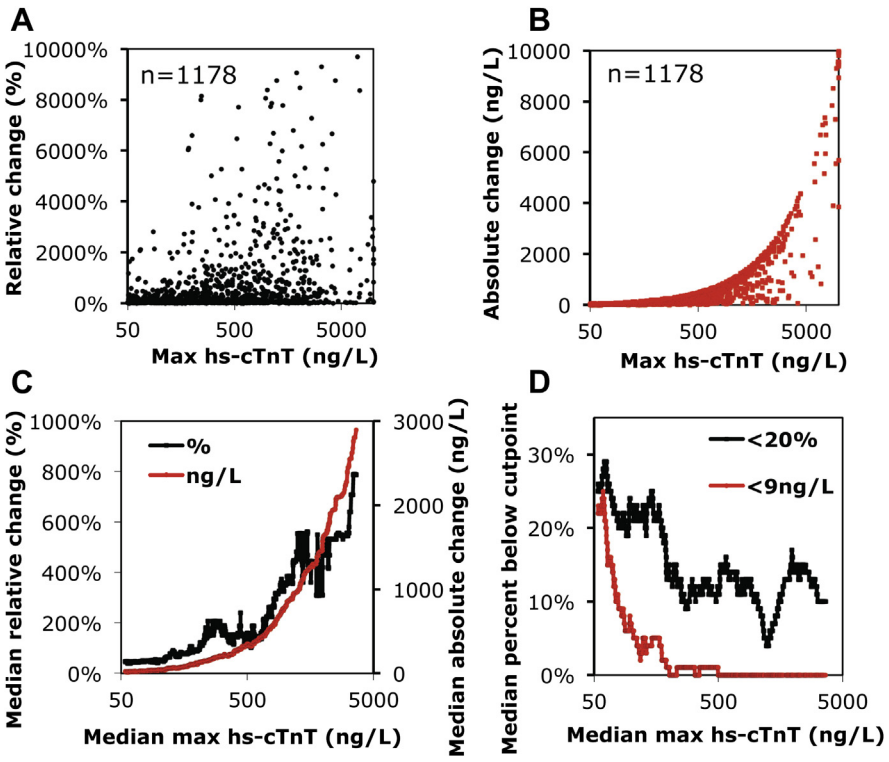

Figure 1 hs-cTnT Change as Function of Maximum hs-cTnT Level Recorded During Hospital Stay of Patients With NSTEMI

Scatter plots of the maximum **(A)** relative and **(B)** absolute high-sensitivity cardiac troponin T (hs-cTnT) change recorded with a median length of the hs-cTnT series of 19.9 h (interquartile range: 9 h to 59 h) in 1,178 patients with non–ST-segment elevation myocardial infarction (NSTEMI), as a function of the maximum (max) hs-cTnT level recorded during the hospital stay. **(C)** Moving-window analysis of the median absolute (ng/l) **(red)** or relative (%) **(black)** hs-cTnT change as a function of the median maximum hs-cTnT level recorded during the hospital stay, calculated from overlapping sets of 100 hs-cTnT NSTEMI patients. **(D)** Moving-window analysis of the percentage of NSTEMI patients with an absolute change below 9 ng/l **(red)** or relative change below 20% **(black)**, as a function of the median maximum hs-cTnT level, calculated from overlapping sets of 100 hs-cTnT NSTEMI patients.

between-run, and long-term coefficients of variation and the performance of the respective reagents and calibrator lots used during the study are summarized elsewhere (5,18). All other laboratory analyses were part of the routine analyses performed at the Sahlgrenska University Hospital Laboratory using the Modular system (Roche Diagnostics, Germany).

Statistical analysis and calculations. The absolute change was the absolute difference in ng/l between the baseline hs-cTnT level and the hs-cTnT measurement with the maximum deviation from the baseline hs-cTnT level recorded up to the time points in Tables 1 and 2. To calculate the relative change, the absolute change was divided by the baseline hs-cTnT level. To mimic the clinical setting, the maximum change in each patient during the entire hs-cTnT series was considered the maximum change.

Moving-window analysis was used to examine the hs-cTnT change relationship to the maximum hs-cTnT level in Figures 1 and 2. Moving-window analysis is a way to visualize the relationship between 2 parameters over the entire data set. Data are first sorted in ascending order according to 1 parameter. The median of the 2 parameters is then calculated in overlapping "windows" of observations in 1-observation steps in ascending order to generate medians from overlapping data for the entire data set. The resulting medians from the 2 parameters are then plotted as shown in Figures 1C and 1D and Figures 2C and 2D.

The data were divided into quartiles using MedCalc 12.1.4.0. Dichotomous values were compared using exact tests with Monte Carlo estimates, and medians were compared using median tests. Correlations between variables were determined using Spearman's correlation. The Cox proportional hazards model was used for survival analysis, and the variables were included in the multiple models shown in Online Table 4. All statistical analyses were performed using SPSS version 19.0 (SPSS, Inc., Chicago, Illinois) and STATA version 12.0 (StataCorp, College Station, Texas) software. All probabilities were 2-tailed, and p values <0.05 were regarded as significant.

Results

Relative change in hs-cTnT levels in NSTEMI patients. Rising hs-cTnT levels during the hospital stay were observed in 80% of the NSTEMI patients. The median

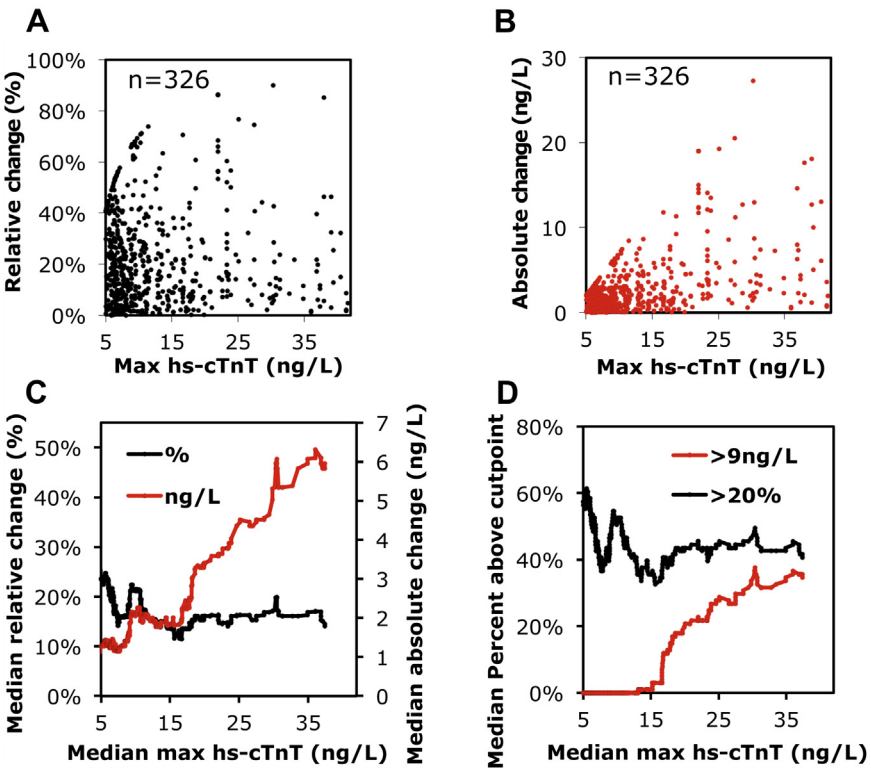

Figure 2 hs-cTnT Change as Function of Maximum hs-cTnT Level Recorded During Hospital Stay in Patients With Noncardiac Chest Pain

Scatter plots of the **(A)** relative and **(B)** absolute high-sensitivity cardiac troponin T (hs-cTnT) change calculated from 881 hs-cTnT measurements in 326 cardiac care unit/chest pain unit (CCU/CPU) patients with the final diagnosis of noncardiac chest pain and a median length of the hs-cTnT series of 8 h (interquartile range: 5.9 h to 11.6 h), as a function of the maximum hs-cTnT level recorded during the stay in the CCU/CPU. **(C)** Moving-window analysis of the median absolute (ng/l) **(red)** or relative (%) **(black)** hs-cTnT change as a function of the median hs-cTnT level, calculated from overlapping sets of 50 hs-cTnT change measurements. **(D)** Moving-window analysis of the percentage of hs-cTnT change measurements with an absolute change above 9 ng/l **(red)** or relative change above 20% **(black)**, as a function of the median hs-cTnT level, calculated from overlapping sets of 50 hs-cTnT change measurements.

Table 2 Change in hs-cTnT Levels in Patients With NSTEMI at Different Times After Baseline Sample

Time After Baseline Sample (h)*	3 h	6 h	11 h	22 h
n	553	593	438	351
Actual length of cTnT series (h)†	3.0 (3.0–3.1)	6.0 (5.9–6.2)	11.1 (9.6–12.7)	21.6 (18.3–26.5)
Relative change percentiles, %‡	2/10/36	4/18/79	6/26/128	10/35/159
Absolute change percentiles, ng/l‡	2/12/38	4/21/68	6/35/133	12/54/208
Proportion with different change in hs-cTnT level§				
Change <20%‖	37%	26%	19%	13%
Change <60%¶	59%	47%	39%	33%
Change >60%	41%	53%	61%	67%
Change <9 ng/l#	19%	12%	7%	3%
Change <30 ng/l**	43%	32%	23%	15%
Change >30 ng/l	57%	68%	77%	85%
Proportion with different relative change if <20% change in hs-cTnT level at 3 h††				
n	207	135	63	40
Change <20%	100%	71%	40%	30%
Change <60%	100%	96%	87%	75%
Change >60%	0%	5%	13%	25%
Proportion with different change if maximum hs-cTnT level <100 ng/l‡‡††				
n	112	125	88	53
Change <20%	46%	37%	31%	21%
Change <60%	72%	67%	59%	58%
Change >60%	28%	33%	41%	42%
Change <9 ng/l	45%	31%	23%	8%
Change <30 ng/l	85%	74%	67%	55%
Change >30 ng/l	15%	26%	33%	45%

Values are n, median (interquartile range), or %. *Time in hours between sample and baseline troponin T sample. †Median (interquartile range). ‡5th/25th/50th percentiles. §Highest change recorded in each patient until the stated sampling time was used. ‖Recommended cutoff point based on analytical precision (8). ¶Upper normal value of relative high-sensitivity cardiac troponin T (hs-cTnT) change in hospitalized patients without myocardial infarction (5). #Area under the curve optimized cutoff at 6 h (9). **Upper normal value of absolute hs-cTnT change in hospitalized heart failure patients without myocardial infarction (5). ††Highest hs-cTnT level recorded during the hospital stay. ‡‡Arbitrary level below the median hs-cTnT level chosen to allow inclusion of sufficient number of patients for analysis.

NSTEMI = non–ST-segment elevation myocardial infarction.

relative hs-cTnT change was 128%, and the median hs-cTnT level during the hospital stay was 346 ng/l (Table 1). The proportion of patients with a small relative change (<20%) was 26% 6 h after baseline. Small relative hs-cTnT changes were even more prevalent among NSTEMI patients in whom the maximum hs-cTnT levels remained low (low level arbitrarily set to 100 ng/l) during the hospital stay (Table 2).

The relative hs-cTnT change was positively correlated with the maximum hs-cTnT level during the hospital stay (Figs. 1C and 1D). The relative hs-cTnT change was weakly

Table 3 Total Mortality* in Relation to Relative hs-cTnT Change Stratified by Sampling Time,† Maximum hs-cTnT During Hospital Stay, or Baseline hs-cTnT Level

	hs-cTnT Change <20%	hs-cTnT Change >20%	p Value	hs-cTnT Change <60%	hs-cTnT Change >60%	p Value
Sampling time						
3 h	24/77 (31%)	76/467 (16%)	0.003	43/191 (22%)	57/353 (16%)	0.082
6 h	23/76 (30%)	90/506 (18%)	0.013	46/200 (23%)	67/382 (18%)	0.12
11 h	18/48 (37%)	75/378 (20%)	0.007	39/125 (31%)	54/301 (18%)	0.003
22 h	5/32 (16%)	53/306 (17%)	1.00	17/94 (18%)	41/244 (17%)	0.87
Maximum hs-cTnT‡						
hs-cTnT <median	29%	16%	0.001	23%	14%	0.012
hs-cTnT >median	28%	20%	0.13	25%	19%	0.12
Baseline hs-cTnT						
hs-cTnT <median	35%	15%	0.001	21%	16%	0.18
hs-cTnT >median	26%	21%	0.21	25%	19%	0.10

Values are n or %. Number of deaths/total number of patients fulfilling the stated criteria. Percentage who died shown inside brackets. *Total mortality during median follow-up of 380 days. †Patients with the stated relative high-sensitivity cardiac troponin T (hs-cTnT) change until a sampling time of 3, 6, 12, or 22 h after baseline sample. ‡Maximum hs-cTnT level during the evaluation period of 24 h after the baseline sample.

correlated both with the evaluation time ($r = 0.17$, $p < 0.001$) and the number of hs-cTnT samples during the hospital stay ($r = 0.22$, $p < 0.001$).

The independent adjudication of the NSTEMI diagnosis in a subsample of patients indicated that the proportion of patients with a diagnosis of NSTEMI, relying on evidence independent of hs-cTnT level, did not differ among patients with a <20% or 20% to 60% relative hs-cTnT change (79% and 83%, respectively; $p = 0.47$). Significant differences between hs-cTnT change groups were that patients with a hs-cTnT change <20% more often presented with primary symptoms other than chest pain and were less likely to undergo percutaneous coronary intervention or coronary artery bypass graft surgery (Online Table 3).

Among NSTEMI patients with low hs-cTnT levels (maximal hs-cTnT <100 ng/l), a smaller proportion had a diagnosis relying on evidence independent of hs-cTnT level (62% and 69%, respectively; $p = 0.52$). In this low hs-cTnT level subgroup, the patients with a <20% hs-cTnT change also had a higher prevalence of comorbidity and more often displayed ventricular arrhythmias during continuous ECG monitoring (Online Table 4).

Small relative hs-cTnT changes during the hospital stay were associated across quartiles with higher age ($p < 0.001$), presenting with a primary symptom other than chest pain, longer symptom duration ($p = 0.001$), lower blood pressure ($p < 0.001$), and higher long-term mortality ($p = 0.002$). The 30-day mortality was similar across quartiles of hs-cTnT change (Online Table 5).

The long-term mortality remained significantly elevated in patients with a <20% relative hs-cTnT change recorded during an observation time of 3 h, 6 h, and 11 h, but not 22 h after the baseline sample. Total mortality was significantly associated with low hs-cTnT changes among patients with an admission or maximum hs-cTnT level below but not above the cohort median (Table 3). The link between small relative hs-cTnT changes and long-term mortality remained statistically significant in a multivariate analysis of the entire cohort (hazard ratio [HR]: 1.61 [95% confidence interval [CI]: 1.17 to 2.21], $p = 0.004$), in male patients (HR: 1.81 [CI: 1.20 to 2.73], $p = 0.005$) but not among female NSTEMI patients (HR: 1.25 [95% CI: 0.74 to 2.11], $p = 0.399$) (Online Table 6). However, the difference in HR between males and females was insignificant when tested using an interaction variable ($p = 0.229$).

A follow-up 50 days (interquartile range [IQR]: 37 to 72 days) after the event of 94 NSTEMI patients yielded a median hs-cTnT level of 15 ng/l (IQR: 7 to 30 ng/l) and 90% had hs-cTnT levels <44 ng/l. The median long-term hs-cTnT change was 4,520% (IQR: 1,489% to 17,271%) and 90% had a long-term hs-cTnT change of >398% (Online Table 7).

Absolute change in hs-cTnT levels in NSTEMI patients. Absolute hs-cTnT change was greater among patients with high hs-cTnT levels (Fig. 1C). After 6 h of observation, the proportion of NSTEMI patients with a small absolute hs-cTnT change (<9 ng/l) was 12% in the entire cohort and 31% among NSTEMI patients with hs-cTnT levels <100 ng/l during the hospital stay (Table 2). However, all patients with a maximum hs-cTnT level >160 ng/l had an absolute hs-cTnT change >9 ng/l (Fig. 1D). The absolute hs-cTnT change was not associated with mortality (Online Table 5).

Absolute and relative hs-cTnT changes in CCU/CPU patients with noncardiac chest pain. In CCU/CPU patients with a final diagnosis of NCCP (Table 1), the relative hs-cTnT change did not show any clear correlation with the hs-cTnT level (5) (Figs. 2A and 2C) and overlapped significantly with the relative hs-cTnT change in the NSTEMI cohort (Online Figs. 2A and 2B). In contrast, the absolute hs-cTnT change in the NCCP cohort was positively associated with the maximum hs-cTnT level during the stay in the CCU/CPU. As a consequence, the percentage of NCCP patients with an absolute change >9 ng/l increased with increasing hs-cTnT levels and overlapped with the absolute hs-cTnT change observed in NSTEMI patients with low hs-cTnT levels (maximum hs-cTnT <100 ng/l) (Online Figs. 2C and 2D).

Discussion

Our findings suggest that a small relative change in the hs-cTnT level may not be useful to rule out NSTEMI, as many NSTEMI patients presenting <24 h after symptom onset have a small cardiac troponin change, as reported by others (4,9,11,14,19–21). More than a quarter of the NSTEMI patients had a <20% hs-cTnT change during a 6-h observation time. In a previous study, we showed that the upper normal value (the 97.5 percentile) for the relative hs-cTnT change is 60% in CCU/CPU patients without MI (5). Similar to previous reports (9,14), we found, after 6 h of observation, that almost one-half of the NSTEMI patients in our study and two-thirds of the NSTEMI patients with low hs-cTnT levels during the hospital stay (<100 ng/l) displayed hs-cTnT changes within the range that can be seen in CCU/CPU patients without MI.

Small absolute hs-cTnT changes were less common in the NSTEMI cohort, as previously reported (9,21). However, the logic behind evaluating the hs-cTnT change is to provide evidence independent of hs-cTnT level of acute myocardial damage, which is most important when hs-cTnT is only moderately elevated. The relative hs-cTnT change fulfills this criterion, as the relative hs-cTnT change is not related to the hs-cTnT level in patients without MI (Fig. 2C) (5). In contrast, because the absolute hs-cTnT change increases with the hs-cTnT level (Fig. 2C) (5), evaluation of absolute hs-cTnT changes using a single cut-off point such as 9 ng/l (9) does not provide information independent of hs-cTnT level, resulting in a risk of over-diagnosing at high hs-cTnT levels and missing NSTEMI patients with low hs-cTnT levels. For example, the proportion of NCCP patients with an absolute hs-cTnT change above 9 ng/l approached 40% at a hs-cTnT level of 30 ng/l (Fig 2D), cTnT levels sometimes encountered in patients of old age (5)

with kidney failure (22,23) or heart failure (24). Conversely, nearly one-third of the NSTEMI patients with low hs-cTnT levels (<100 ng/l) had an absolute change below 9 ng/l during 6 h of evaluation (Table 2, Fig. 1D), resulting in an overlap with the hs-cTnT change observed in the NCCP cohort (Online Fig. 2D). This is unfortunate, as evaluation of the hs-cTnT change has its greatest diagnostic value when the hs-cTnT level is only moderately elevated. As discussed before (9), hs-cTnT level–dependent cutoff points must be applied to generate sufficient diagnostic precision when the absolute hs-cTnT change is used.

An important question is why small relative hs-cTnT changes were so common in NSTEMI patients. One possibility is that most patients with stable hs-cTnT elevations had other hs-cTnT–elevating conditions like myocarditis, renal failure, or heart failure, as the NSTEMI cohort was recruited in a clinical setting where a change in the hs-cTnT level was not mandatory for the diagnosis. We find this possibility unlikely for several reasons. First, a majority of the NSTEMI diagnoses in the low-change group was supported by hs-cTnT–independent evidence, indicating that most of the stable hs-cTnT elevations found in this study were due to MI. Second, patients in our study were diagnosed using a high hs-cTnT cutoff point of 40 ng/l that result in a 2-fold-higher positive predictive value compared with the use of the 99th hs-cTnT percentile of 14 ng/l (3). Third, most of the characteristics among patients with insignificant (<20%), and small but significant (20% to 60%) hs-cTnT changes were similar. Last, our finding is not unique. Several studies report that small relative troponin changes are common in patients with NSTEMI (4,9,11,14,19–21). In most of these studies, the troponin change was only monitored during a few hours. Our data, however, show that patients with a <20% hs-cTnT change during the first 3 h of observation are twice as likely to remain in the low hs-cTnT-change group (Table 2). This finding indicates that the frequency of stable troponin elevations found in previous short-time evaluations is likely to concur with our findings.

Instead, our data suggest that many patients with a small hs-cTnT change present late in the infarction process when hs-cTnT levels are close to their maximum. The hypothesis that a small change was due to long ischemic time was supported by correlations across quartiles, where long symptom duration, presenting with primary symptoms other than chest pain, presenting with basal rales, and not being sent directly to the angiography laboratory from the ambulance, indicating less acute symptoms, all correlate with a small relative hs-cTnT change (Online Table 5).

In addition, hs-cTnT measurement in a small subset of patients at 6-week follow-up after the event showed that the long-term hs-cTnT change was >4,000% in most patients, whereas there was a median hs-cTnT change during the hospital stay of 166%, indicating that many NSTEMI patients present close to the plateau phase of hs-cTnT release. Furthermore, it is a clinical observation that NSTEMI patients have often had repeated episodes of chest pain during the days before admission, making it difficult to use symptom duration to estimate the ischemia time.

The possibility that a large proportion of NSTEMI patients present late is also in line with what we know about the pathophysiology of MI. Close to 50% of the thrombi extracted from coronary arteries in patients with myocardial infarction show histological signs of being several days old (12,25), and 75% of all ruptured coronary plaques assigned as the culprit lesion show signs of earlier rupture (26). In addition, a large portion of myocardial infarctions found in prospective studies are silent, most likely because of nonspecific symptoms (27,28) that can be explained by the observation that many ischemic events detected by ECG do not result in chest pain (29).

We also found higher long-term mortality among NSTEMI patients with a small hs-cTnT change that remained significant after multivariate analysis using a model with possible covariates found in the quartile analysis. The association with mortality was the strongest among NSTEMI patients with an insignificant (<20%) hs-cTnT change and low admission or maximum hs-cTnT levels. This finding indicates that NSTEMI patients with hs-cTnT levels and hs-cTnT changes analogous to what is often observed in patients with heart failure, renal failure, and old age is a high-risk group important to identify. In addition, NSTEMI patients with low hs-cTnT levels were more likely to be in the low hs-cTnT change group (Table 2), indicating that the proportion of NSTEMI patients with stable hs-cTnT elevations is likely to increase when the 99th hs-cTnT percentile of 14 ng/l is implemented as the cutoff point.

Taken together, the findings presented in this and previous reports (4,9,20,21) challenge the use of a small hs-cTnT change recorded during the hospital stay as a way to rule out NSTEMI in patients with elevated hs-cTnT levels. Other studies indicate that this problem is also evident when using troponin I assays (11,14,19). It is possible that the hs-cTnT change evaluated at an outpatient checkup a week or so after the event could be an alternative way to confirm or exclude the diagnosis in patients where the clinical suspicion of myocardial infarction is low or moderate, the in-hospital hs-cTnT levels are only minimally to moderately elevated, and the hs-cTnT change is small. In these instances, the NSTEMI diagnosis could remain tentative until a large relative hs-cTnT decrease can be recorded at the outpatient checkup. If these patients, as appropriate after evaluation of the bleeding risk, were started on the same secondary prevention scheme as patients with a firm NSTEMI diagnosis, this procedure would add diagnostic precision with little risk to the patient. We are currently evaluating some aspects of this procedure, and a first analysis indicates that the long-term hs-cTnT change is >400% in most NSTEMI patients 6 weeks after the event (Online Table 7).

Study limitations. First, it is a retrospective study in which the NSTEMI diagnosis was based on clinical routine and not adjudicated using a study protocol. Therefore, the diagnostic

precision is likely to be variable as patients in this study were diagnosed using different combinations of investigations and hs-cTnT sampling protocols, as commonly seen in clinical routine practice. For this reason, it cannot be excluded that in some patients with stable hs-cTnT levels had other conditions as the main cause of the hs-cTnT elevation. To establish the true distribution of hs-cTnT change in NSTEMI patients, a prospective study must be performed where all patients are subjected to angiography, imaging, and functional examinations to obtain hs-cTnT–independent evidence of myocardial damage of ischemic origin. Second, although most patients were sampled at 3-h or 6-h intervals, the hs-cTnT sampling did not follow a predefined protocol and was left to the discretion of the attending clinician. Third, the diagnostic cutoff point used was not the 99th cTnT percentile, and that is likely to affect both the hs-cTnT levels and the hs-cTnT change in the NSTEMI cohort. Last, we only analyzed total mortality and have not been able to apply reliable data to cardiovascular mortality.

Conclusions

In summary, we find that a large proportion of patients with a clinical diagnosis of NSTEMI in our hospital have hs-cTnT changes within the normal range, most probably because of long ischemic time. These findings question the use of in-hospital hs-cTnT changes as a way to exclude NSTEMI.

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Key Words: mortality ■ non–ST-segment elevation myocardial infarction ■ troponin T change.

APPENDIX

For supplementary figures and tables, please see the online version of this article.