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CME

Undetectable High-Sensitivity Cardiac Troponin T Level in the Emergency Department and Risk of Myocardial Infarction

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CME Objective for This Article: At the conclusion of this activity, the learner will be able to evaluate if an undetectable (<5 ng/l) high-sensitivity cardiac troponin T level, and an electrocardiogram without signs of ischemia can rule out myocardial infarction in the emergency department.

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Undetectable High-Sensitivity Cardiac Troponin T Level in the Emergency Department and Risk of Myocardial Infarction

Objectives This study sought to evaluate if an undetectable (<5 ng/l) high-sensitivity cardiac troponin T (hs-cTnT) level and an electrocardiogram (ECG) without signs of ischemia can rule out myocardial infarction (MI) in the emergency department (ED).

Background Chest pain is a common symptom often associated with benign conditions, but may be a sign of MI. Because there is no rapid way to rule out MI, many patients are admitted to the hospital.

Methods All patients who sought medical attention for chest pain and had at least 1 hs-cTnT analyzed during 2 years at the Karolinska University Hospital, Stockholm, Sweden, were included. We calculated the negative predictive values of an undetectable hs-cTnT and ECG without ischemia for MI and death within 30 days.

Results We included 14,636 patients, of whom 8,907 (61%) had an initial hs-cTnT of <5 ng/l; 21% had 5 to 14 ng/l, and 18% had >14 ng/l. During 30-day follow-up, 39 (0.44%) patients with undetectable hs-cTnT had a MI, of whom 15 (0.17%) had no ischemic ECG changes. The negative predictive value for MI within 30 days in patients with undetectable hs-cTnT and no ischemic ECG changes was 99.8% (95% confidence interval [CI]: 99.7 to 99.9). The negative predictive value for death was 100% (95% CI: 99.9 to 100).

Conclusions All patients with chest pain who have an initial hs-cTnT level of <5 ng/l and no signs of ischemia on an ECG have a minimal risk of MI or death within 30 days, and can be safely discharged directly from the ED. (J Am Coll Cardiol 2014;63:2569–78)

Chest pain is the cardinal symptom of myocardial infarction (MI), and it is one of the most common complaints of patients seeking medical attention in the emergency department (ED), accounting for an estimated 15 to 20 million ED visits per year in Europe and the United States (1–3). Although chest pain is often merely a sign of a completely benign condition, it may indicate that the patient is experiencing a life-threatening disease. As much as 2% of patients with MI are inadvertently discharged directly from the ED, which is associated with a doubling of the risk of death (4). Current guidelines therefore recommend that patients with chest pain who have normal clinical findings, electrocardiograms (ECGs), and cardiac injury markers in the ED should have biomarker testing repeated 3 to 6 h after presentation (2). Commonly, this means that the patient is admitted to the hospital for further evaluation. However, only 10% to 20% of patients admitted for chest pain are diagnosed with MI during hospital stay (4–6).

If MI can be ruled out safely and efficiently, without serial testing or prolonged observation, then hospital admissions, ED overcrowding, and costs could be reduced. Several clinical decision rules have been developed to safely and efficiently exclude MI, which include assessment of pretest probability, biomarker levels, and ECG findings (6–9). However, these algorithms all include serial testing of biomarkers, which may delay patient discharge from the ED.

Recently, high-sensitivity cardiac troponin T (hs-cTnT) has been introduced as a highly sensitive and early biomarker of myocardial damage (10). In 2 prospective cohorts of patients admitted to the hospital for chest pain, undetectable hs-cTnT was found to have a very high negative predictive value for MI (5,11).

We hypothesized that all patients with chest pain who have an initial hs-cTnT level of <5 ng/l and no signs of ischemia on an ECG have a minimal risk of MI or death within 30 days, and can be safely discharged directly from the ED.

Methods

Study population. This study included all patients age >25 years who sought medical attention for chest pain in the ED and had at least 1 hs-cTnT level measured at Karolinska University Hospital, Stockholm, Sweden, from December 10, 2010 to December 31, 2012. This hospital is located at 2 sites that are 22 km apart (Huddinge and Solna), and has a total capacity of 1,610 beds. The annual number of patients presenting to the adult ED is approximately 77,000 in Huddinge and 70,000 in Solna. Coronary angiography and percutaneous coronary intervention (PCI) are available at Huddinge during office hours, and at all times at Solna.

Patients who presented to the ED were identified from the hospitals' register of patients. Archived laboratory data were retrieved to determine which patients had at least 1 hs-cTnT level measured while in the ED. Serum creatinine levels measured in the ED were retrieved to assess renal function, and the time spent in the ED was recorded. Patient data were then sent to the National Board of Health and Welfare to obtain data from the Swedish National Patient Register (12), which includes all patients

hospitalized in Sweden, regarding previous hospital stay for MI, stroke, heart failure, or chronic obstructive pulmonary disease, to determine the background characteristics of the study population. Information about current medications was retrieved from the Swedish Prescribed Drug Register (13). The data were then de-identified and returned to the investigators.

Diabetes mellitus was defined as ongoing treatment with any hypoglycemic agent. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula. Chronic kidney disease was defined as an eGFR of <60 ml/min/1.73 m^2. The study protocol complied with the guidelines of the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Stockholm.

The main group of patients studied were those with a first hs-cTnT level of <5 ng/l (undetectable) measured in the ED, combined with no ST-segment changes, indicating myocardial ischemia on the ECG (2). Patients with a first hs-cTnT level of <5 ng/l and initial ECG changes indicating MI were excluded from further analysis. In patients with a first hs-cTnT level of ≥5 ng/l, the ECGs were not reviewed. The hs-cTnT levels were analyzed using the Elecsys 2010 system (Roche Diagnostics GmbH, Mannheim, Germany), which has been available at Karolinska University Hospital since December 10, 2010. This method has a detection limit of 5 ng/l, a limit of blank of 3 ng/l, a 99th percentile cutoff point of 14 ng/l, and a coefficient of variation of <10% at 13 ng/l (14). Patients were categorized into 3 groups according to the first hs-cTnT level: <5, 5 to 14, and >14 ng/l.

Outcome and follow-up. The primary outcome was fatal or nonfatal type 1 MI, which is defined as MI related to atherosclerotic plaque rupture, fissuring, or erosion that leads to an intraluminal thrombus formation, resulting in myocardial ischemia (2) within 30 days of the ED visit. The secondary outcomes were MI within 180 and 365 days of the ED visit, and all-cause mortality within 30, 180, and 365 days of the ED visit. In patients with a first hs-cTnT level of <5 ng/l, the hazard ratio for all-cause mortality was calculated for admitted patients compared with patients discharged directly from the ED.

Patients were followed from the time of the first hs-cTnT level until 30, 180, or 365 days after the ED visit. Data regarding subsequent diagnosis of MI, hospital stays, discharge diagnoses other than MI, and length of hospital

Abbreviations and Acronyms

- **CI** = confidence interval
- **ECG** = electrocardiogram
- **ED** = emergency department
- **eGFR** = estimated glomerular filtration rate
- **hs-cTnT** = high-sensitivity cardiac troponin T
- **MI** = myocardial infarction
- **NSTEMI** = non–ST-segment elevation myocardial infarction
- **PCI** = percutaneous coronary intervention
- **STEMI** = ST-segment elevation myocardial infarction

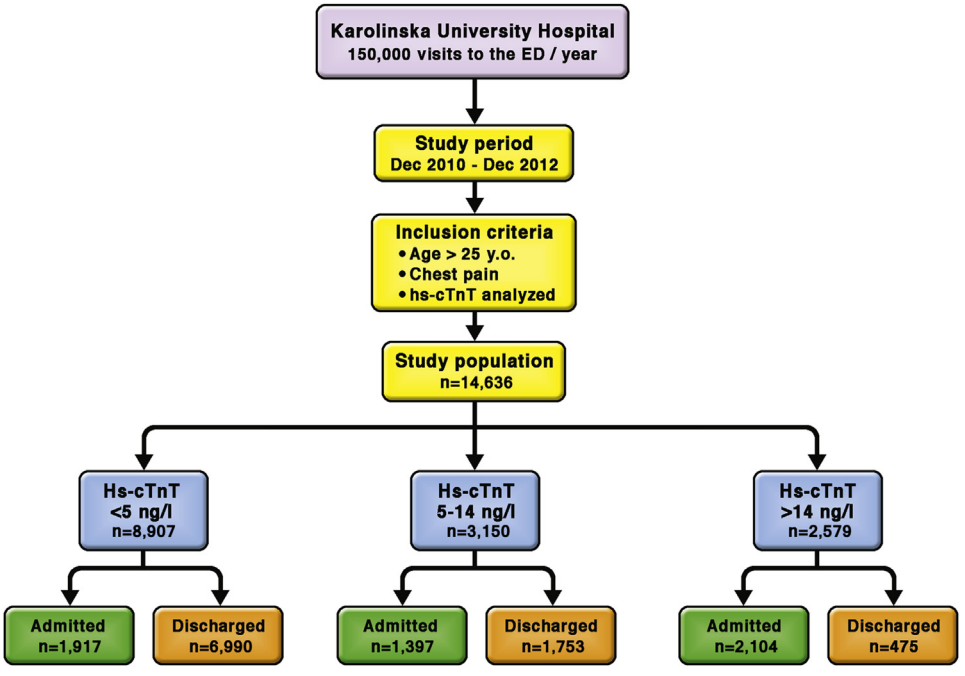

Figure 1 Study Population

The selection of the study population, and number of patients at different levels of high-sensitivity cardiac troponin T (hs-cTnT), which are reported in nanograms per liter. ED = emergency department.

stay were obtained from the Swedish National Patient Register. Causes of death were obtained from the Cause-of-Death Register, which includes all individuals who reside in Sweden at the time of their death.

Review of electrocardiograms and diagnoses of myocardial infarction. All patients with a first hs-cTnT level of <5 ng/l and a diagnosis of MI within 30 days were identified, and their ECGs were retrieved from the medical records. ECGs were also retrieved for 2 control patients per case from the cohort of patients who visited the ED because of chest pain, matched for age, sex, and the first hs-cTnT level, and who were not diagnosed with MI within 30 days. Two independent senior cardiologists, blinded to the study protocol, were asked to review the ECGs and assess whether there was new ST-segment elevation in 2 contiguous leads with cutpoints of ≥0.1 mV in all leads, except for leads V_2 to V_3, where ≥0.2 mV in men ≥40 years of age and ≥0.25 mV in men <40 years of age and ≥0.15 mV in women were applied. These cardiologists also reviewed if there was any significant ST-segment depression, defined as a horizontal or downsloping ST-segment ≥0.05 mV in 2 contiguous leads, or if there was a left bundle branch block present that was new compared with previous ECGs (if there were previous ECGs to compare with) (2). The only data available to the senior cardiologists were the age and sex of each patient, and that the main complaint was chest pain. A third senior cardiologist (M.J.H.) also assessed all the ECGs, and if there was disagreement between the assessments by the 2 independent cardiologists, the assessment by M.J.H. was used for the analyses. At a later stage, the records of all patients with a first hs-cTnT level of <5 ng/l, and no MI within 30 days, were reviewed to determine whether they met the criteria for MI within 30 days according to troponin levels, other laboratory values, coronary angiographic findings, echocardiographic findings, and ECG findings.

Statistical analyses. We stratified patients into 3 groups according to level of hs-cTnT (<5, 5 to 14, and >14 ng/l) and calculated the absolute risks, negative predictive values, and incidence rates with 95% confidence intervals (CIs) for MI and death with a follow-up of 30, 180, and 365 days. The first hs-cTnT level recorded from December 10, 2010 to December 31, 2012 was the starting point of the follow-up for each patient. The Cox proportional hazards model was used to calculate hazard ratios and 95% CIs for the potential association between the exposure not admitted (reference admitted) and the outcome time to death adjusted for age, sex, diabetes mellitus, previous MI, and eGFR. The data management and the calculations for absolute risks, negative predictive values, and incidence rates were conducted using the World Programming System, version 3.0 (World Programming Ltd., Hampshire, United Kingdom). The Cox proportional hazards model was performed using R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics. There were a total of 330,821 visits to the adult ED at Karolinska University Hospital during the study period (Fig. 1). Chest pain was the second most common reason for visiting the ED, accounting for 15,549 (4.7%) patients, of whom 14,636 were aged >25 years and

Table 1 Characteristics of the Study Population According to the First High-Sensitivity Cardiac Troponin T Level

Characteristics	All Patients (N = 14,636)	High-Sensitivity Cardiac Troponin T Level (ng/l)		
		<5 (n = 8,907)	5–14 (n = 3,150)	>14 (n = 2,579)
Percentage of study population	100	61	21	18
Age, yrs	55 ± 19	47 ± 15	63 ± 16	71 ± 15
Female, %	48	53	41	37
eGFR				
>60 ml/min/1.73 m^2, %	88	98	85	57
30–60 ml/min/1.73 m^2, %	10	2.4	15	32
15–30 mL/min/1.73 m^2, %	2.1	0.03	0.74	11
eGFR, ml/min/1.73 m^2	90 ± 25	99 ± 18	82 ± 21	65 ± 28
Diabetes mellitus, %	9.5	4.7	14	21
COPD, %	3.4	1.6	5.0	7.6
Previous MI, %	8.5	4	12	21
Previous stroke, %	4.9	2.1	7	13
Previous hospital stay for CHF, %	5.7	1.4	7.3	19
Aspirin, %	19	9.7	30	40
Beta-blockers, %	23	13	36	47
ACE/ARB, %	24	13	35	46
Statins, %	19	11	28	34

Values are % or mean ± SD.

ACE/ARB = angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker. CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction.

Table 2 Absolute Risks and Negative Predictive Values for Myocardial Infarction or Death at 30, 180, and 365 Days After Discharge From the ED*

Characteristics	High-Sensitivity Cardiac Troponin T Level (ng/l)		
	<5 (n = 8,883)†	5–14 (n = 3,150)	>14 (n = 2,579)
Proportion admitted	1,917 (21)	1,397 (44)	2,104 (82)
Myocardial infarction			
30 days			
No. of events	15	97	676
Absolute risk	0.17 (0.09–0.27)	3.08 (2.48–3.68)	26.2 (24.5–27.9)
Negative predictive value	99.8 (99.7–99.9)	96.9 (96.3–97.5)	73.8 (72.1–75.5)
180 days			
No. of events	33	115	724
Absolute risk	0.37 (0.24–0.54)	3.65 (2.99–4.30)	28.1 (26.3–29.8)
Negative predictive value	99.6 (99.4–99.7)	96.4 (95.7–97.0)	71.9 (70.2–73.7)
365 days			
No. of events	54	134	753
Absolute risk	0.61 (0.45–0.78)	4.25 (3.55–4.96)	29.2 (27.4–31.0)
Negative predictive value	99.4 (99.2–99.5)	95.7 (95.0–96.5)	70.8 (69.0–72.6)
Death			
30 days			
No. of events	2	13	66
Absolute risk	0.023 (0.001–0.054)	0.41 (0.19–0.64)	2.56 (1.95–3.17)
Negative predictive value	100.0 (99.9–100.0)	99.6 (99.4–99.8)	97.4 (96.8–98.1)
180 days			
No. of events	15	66	216
Absolute risk	0.17 (0.083–0.25)	2.09 (1.59–2.59)	8.38 (7.31–9.44)
Negative predictive value	99.8 (99.7–99.9)	97.9 (97.4–98.4)	91.6 (90.6–92.7)
365 days			
No. of events	38	108	342
Absolute risk	0.43 (0.29–0.56)	3.43 (2.79–4.06)	13.3 (12.0–14.6)
Negative predictive value	99.6 (99.4–99.7)	96.6 (95.9–97.2)	86.7 (85.4–88.0)

*According to the first high-sensitivity cardiac troponin T level, in 14,612† patients who sought medical attention for chest pain at Karolinska University Hospital from December 2010 to December 2012. †Twenty-four patients with a first high-sensitivity cardiac troponin T level of <5 ng/l were excluded because they had electrocardiographic changes suggestive of myocardial infarction at the time of presentation to the emergency department. Absolute risks and negative predictive values are given as percentage (95% confidence interval).

had at least 1 hs-cTnT level measured. Laboratory results showed that 61% of these patients had a first hs-cTnT level of <5 ng/l, 21% had a first hs-cTnT level of 5 to 14 ng/l, and 18% had a first hs-cTnT level of >14 ng/l (Table 1). Patients with a first hs-cTnT level of <5 ng/l were younger; were less likely to have chronic kidney disease, chronic cardiovascular disease, or diabetes mellitus; and were less likely to be taking medications for secondary prevention of cardiovascular disease (Table 1). With increasing levels of hs-cTnT, patients were older, more often men, and had more comorbidities.

Admissions, second high-sensitivity cardiac troponin T levels, and discharge diagnoses. A total of 5,418 (37%) patients were admitted to the hospital, of whom 35% had a first hs-cTnT level of <5 ng/l (Table 2, Fig. 1). The hospital stay rate was 21% in patients with a first hs-cTnT level of <5 ng/l, 44% in patients with a first hs-cTnT level of 5 to 14 ng/l, and 82% in patients with a first hs-cTnT level of >14 ng/l (Table 2). Among patients with a first hs-cTnT level of <5 ng/l, 1,704 (89%) had a second hs-cTnT level measured, which was <5 ng/l in 1,362 (90%) patients, 5 to 14 ng/l in 111 (7.3%) patients, and >14 ng/l in 44 (3.0%) patients. Patients with a first hs-cTnT level of <5 ng/l and no MI within 30 days were admitted to the hospital for a total of 3,262 days, with a mean duration of hospital stay of 1.5 ± 3.0 days; 1,482 (77%) of these patients were discharged on the same or next day. The most common discharge diagnoses in patients with a first hs-cTnT level of <5 ng/l were nonspecific chest pain (50%), atrial fibrillation or supraventricular tachycardia (5.6%), and angina (5.1%) (Table 3). A diagnosis of MI was unusual (2.0%) in patients with a first hs-cTnT level of <5 ng/l, but was more common with higher hs-cTnT levels (26%) in patients with a first hs-cTnT level of >14 ng/l (Table 3). Among patients with a first hs-cTnT level of <5 ng/l, the time spent in the ED was similar for those who were discharged compared with those who were admitted to the hospital (208 ± 101 min vs. 203 ± 111 min). Time in the ED in relation to level of troponin and final diagnosis of MI is described in Online Table 1.

Myocardial infarction and death. A total of 746 (14%) patients were discharged from the index hospital stay with a diagnosis of MI. Forty-four patients with a first hs-cTnT level of <5 ng/l were diagnosed with MI within 30 days. No patient was diagnosed with type 2 MI in the group with

Table 3 The 12 Most Common Discharge Diagnoses for Patients Admitted to Hospital, According to the First High-Sensitivity Cardiac Troponin T Level

High-Sensitivity Cardiac Troponin T Level (ng/l)					
<5 (n = 1,917)		5–14 (n = 1,397)		>14 (n = 2,104)	
Chest pain, %	50.0	Chest pain	34.0	MI	26.0
A-fib/SVT, %	5.6	Angina	8.1	Chest pain	13.0
Angina, %	5.1	A-fib/SVT	7.5	Heart failure	8.7
Abdominal pain, %	2.8	MI	3.0	A-fib/SVT	7.2
Myalgia, %	2.4	Unstable angina	3.2	Angina	4.2
MI, %	2.0	Heart failure	3.1	Pneumonia	4.1
Pneumonia, %	1.8	Pneumonia	2.3	Unstable angina	2.4
Syncope, %	1.8	Syncope	1.9	Myocarditis	1.6
Hypertension, %	1.6	Myalgia	1.7	PE	1.2
Unstable angina, %	1.5	Hypertension	1.4	Syncope	1.2
PE, %	1.3	PE	1.3	Aortic stenosis	1.1
Palpitations, %	1.0	Dyspnea	1.2	Hypertension	0.9

Values are %. Chest pain was defined as *International Classification of Diseases, 10th Revision* codes R07.4, R07.3, Z03.4, or Z03.5; atrial fibrillation (A-fib) as I48.9; supraventricular tachycardia (SVT) as I47.1; myalgia as M79.1; syncope as R55.9; hypertension as I10.9; unstable angina as I20.0; pulmonary embolism (PE) as I26.9; palpitations as R00.2; pneumonia as J18.9; abdominal pain as R10.4, K29.7, or K85.9; dyspnea as R06.0; aortic stenosis as I35.0; myocarditis as I40.9; and myocardial infarction (MI) as I21.4, I21.9, or I21.1.

undetectable troponin levels. Two of these patients had a periprocedural MI, and 3 did not meet the current criteria for MI (2).

These 5 patients were excluded from further analysis. Twenty-four of the remaining patients had significant ECG changes, of whom 15 (62%) were diagnosed with ST-segment elevation myocardial infarction (STEMI) and 9 (38%) who were diagnosed with non–ST-segment elevation myocardial infarction (NSTEMI) (Fig. 2). No patient had a left bundle branch block on the ECG.

In 15 of the remaining 39 patients, there were no significant changes on the first ECG performed in the ED

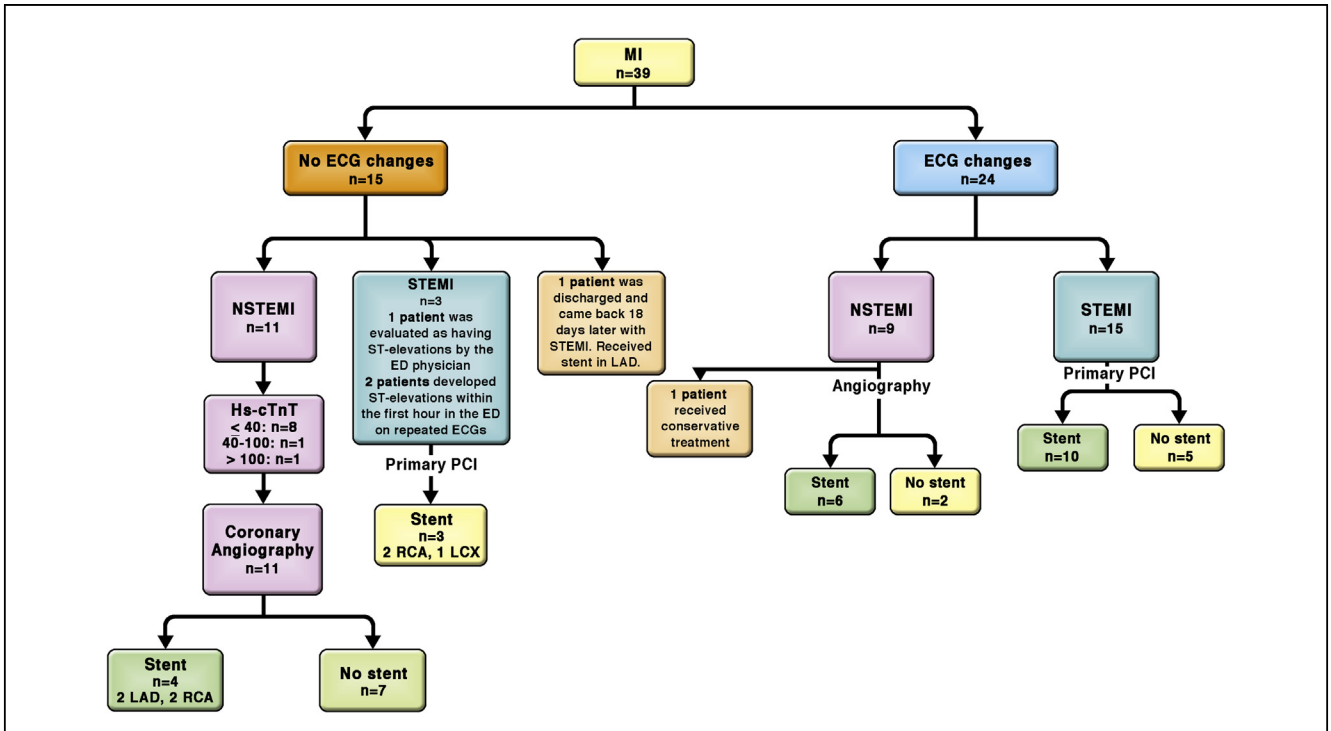

Figure 2 Patients With Undetectable High-Sensitivity Cardiac Troponin T and Myocardial Infarction Within 30 Days

All 39 patients with an initial high-sensitivity cardiac troponin T (hs-cTnT) <5 ng/l and an electrocardiogram (ECG) without ST-segment elevation or depression, but myocardial infarction (MI) within 30 days of follow-up. LAD = left anterior descending artery; LCX = left circumflex artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; other abbreviations as in Figure 1.

(Table 4, Fig. 2). These patients were older, more often men (73%), and had previous cardiovascular disease (20%) more frequently than patients with hs-cTnT <5 ng/l and no MI. In addition, they were often active smokers (40%). The first hs-cTnT level was measured within 2 h of the onset of symptoms in 11 (73%) patients, and >3 h after the onset of symptoms in 2 (13%) patients. One patient was discharged directly from the ED and was readmitted with a diagnosis of STEMI after 18 days. In 2 patients, a second ECG within 1 h of the first ECG showed ST elevation, and in another patient, the ED physician judged the ECG to be consistent with a diagnosis of STEMI. These 4 patients underwent primary PCI. In the 11 patients who did not undergo immediate cardiac catheterization, the maximum hs-cTnT level ranged from 18 to 157 ng/l. In 5 (45%) of these 11 patients, the maximum hs-cTnT level was <30 ng/l (Table 4).

A first hs-cTnT level of <5 ng/l in combination with no signs of ischemia on the ECG had a negative predictive value for MI of 99.8% (95% CI: 99.7 to 99.9) and an absolute risk for MI of 0.17% (95% CI: 0.09 to 0.27) (Table 2). MI occurred in 39 patients with a first hs-cTnT level of <5 ng/l at 30 to 365 days after discharge from the ED, which is an incidence of 7.36 (95% CI: 5.55 to 9.58) per 1,000 person-years. In patients with a first hs-cTnT level of 5 to 14 ng/l, the absolute risk of MI within 30 days was 3.1%, and the negative predictive value for MI within 30 days was 96.9%. In patients with a first hs-cTnT level of >14 ng/l, the absolute risk of MI within 30 days was 26.2%, and the negative predictive value for MI within 30 days was 73.8% (Table 2).

In patients with a first hs-cTnT level of <5 ng/l and no signs of ischemia on the ECG, the negative predictive value for death within 30 days was 100% (95% CI: 99.9 to 100.0) (Table 2), and there were 38 deaths during the 365 days after discharge from the ED. The underlying cause of death was cardiovascular disease in 2 (5%) patients, cancer in 32 (84%) patients, and another cause in 4 (11%) patients.

Among patients with a first hs-cTnT level of <5 ng/l, there was no significant difference in the risk of death within 365 days between those who were discharged directly from the ED and those who were admitted to the hospital after adjustment for age, sex, diabetes mellitus, previous MI, and eGFR (hazard ratio: 0.73; 95% CI: 0.48 to 1.12).

Discussion

In a large cohort of 14,636 consecutive patients who sought medical attention for chest pain in the ED, we found that a first hs-cTnT level of <5 ng/l combined with no signs of ischemia on the ECG had a 99.8% negative predictive value for MI and a 100% negative predictive value for death within 30 days.

Cardiac troponins have been used as a cornerstone of diagnosis of MI, together with clinical assessment and ECG findings, for more than 15 years (15). However, a limitation of former generations of troponin assays have been that they required at least 6 h from the onset of symptoms before they would be detectable (14). Repeated testing was often required, leading to unnecessary hospital stays for investigation of chest pain. Recently, high-sensitivity cardiac troponins have been introduced into clinical practice (10,16). They increase diagnostic accuracy by identifying a larger proportion of patients with MI at the time of presentation to the ED. Because elevation of high-sensitivity cardiac troponin levels are detectable at a much earlier stage than earlier generations of troponin assays (10,14,16), they have been suggested to have the potential to rule out MI at an earlier stage (5–8,10,11,16).

Two recent studies investigated the negative predictive value of an initial undetectable hs-cTnT for MI (5,11). In both of these studies, patients were recruited prospectively at the discretion of the ED physician, serial hs-cTnT levels were measured, and only patients admitted to the hospital were included. In another study, a second troponin measurement was taken 1 h after the first, and was used to rule out patients with MI (8). In all 3 studies, the negative predictive value for MI was almost 100% if hs-cTnT was undetectable. In contrast to these 3 studies, the present study included all patients who presented to the ED with a main complaint of chest pain, and used the first hs-cTnT level and ECG findings to rule out MI, without assessment of the pretest probability of MI and without serial measurements of hs-cTnT levels. This simple strategy confirmed the findings of the 2 previous studies—that an undetectable first hs-cTnT level rules out MI with almost 100% accuracy.

Chest pain was the second most common reason for presentation to the ED during the study period, and 61% of patients with a main complaint of chest pain had a first hs-cTnT level of <5 ng/l. Hospital stay occurred in 21% of these patients, accounting for one-third of all patients admitted to the hospital because of chest pain. This indicates that 594 patients with a first hs-cTnT level of <5 ng/l would have to be admitted to detect 1 additional MI. More than two-thirds of the patients with a first hs-cTnT level of <5 ng/l who were admitted to the hospital were discharged on the same day or the next day, and 50% had a discharge diagnosis of nonspecific chest pain. Although some of these patients may have had other conditions requiring hospital stay such as heart failure, atrial fibrillation, or pulmonary embolism, we believe that hospital stay could have been avoided in the majority of these patients, resulting in an annual decrease of 600 to 700 admissions to our hospital, which corresponds to a 20 to 25% reduced admission rate of patients with chest pain. Considering that an estimated 15 to 20 million patients seek medical attention at an ED for chest pain every year in Europe and the United States, the potential savings for healthcare providers are enormous (1–3).

Only 15 of all patients who presented to our ED during the study were diagnosed with MI despite having an undetectable first hs-cTnT level combined with no signs of ischemia on the initial ECG. The first hs-cTnT level was measured <2 h after the onset of symptoms in 11 of these

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Table 4 Details of 15 Patients With Chest Pain and a First High-Sensitivity Cardiac Troponin T Level of <5 ng/l Combined With No Signs of Ischemia on an Electrocardiogram, Who Had a Final Diagnosis of Myocardial Infarction

Sex	Age, yrs	Previous Medical History	Current Medical History	Time from Onset of Symptoms to 1st, 2nd and 3rd hs-cTnT Level	ECG Assessment by the ED Physician	Clinical Course
Male	48	This patient had COPD, never smoked, and had a BMI of 31 kg/m^2.	Sudden onset of chest pain and tachycardia in the morning.	<1 h: <5 ng/l 6–7 h: 33 ng/l 12–13 h: 23 ng/l	SR, 108 beats/min, no signs of ischemia.	Coronary angiography was performed on day 3, and a stent was placed in the LAD. The final diagnosis was NSTEMI.
Female	52	This patient had hypertension, was an ex-smoker, and had a BMI of 22 kg/m^2.	Sudden onset of chest discomfort in the morning.	2–3 h: <5 ng/l 8–9 h: 18 ng/l 14–15 h: 9 ng/l	SR, 97 beats/min, nonspecific ST-segment changes in leads V_4–V_6.	Coronary angiography on day 4 was normal. The final diagnosis was NSTEMI.
Male	39	This patient had hypertension, was an ex-smoker, and had a BMI of 28 kg/m^2.	Sudden onset of chest pain and nausea during physical activity.	1–2 h: <5 ng/l 7–8 h: 1,930 ng/l	SR, 55 beats/min, ST-segment elevation in leads II and aVF.	Primary PCI was performed, and a stent was placed in the RCA. The final diagnosis was STEMI.
Male	64	This patient was a previously healthy smoker and had a BMI of 28 kg/m^2.	Sudden left-sided stabbing sensation in the chest.	<1 h: <5 ng/l	SR, 85 beats/min, no signs of ischemia.	This patient was discharged from the ED, but returned after 18 days with STEMI, which was treated with primary PCI with stenting of the LAD.
Male	57	This patient had a previous CABG, never smoked, and had a BMI of 25 kg/m^2.	Sudden onset of chest pain and nausea in the morning.	1–2 h: <5 ng/l 7–8 h: 0.16 ng/l* 13–14 h: 0.34 ng/l*	SR, 63 beats/min, Q-wave in lead III.	Coronary angiography was performed on day 3, and a stent was placed in the RCA. The final diagnosis was NSTEMI.
Male	59	This patient had hypertension, was a current smoker, and had a BMI of 27 kg/m^2.	Sudden onset of chest pain during the night.	1–2 h: <5 ng/l 7–8 h: 81 ng/l 13–14 h: 149 ng/l	SR, ST-segment depression in leads I and aVL.	Coronary angiography was performed on day 3, and a stent was placed in the RCA. The final diagnosis was NSTEMI.
Male	62	This patient was a nonsmoker and had a BMI of 28 kg/m^2.	Sudden onset of recurrent chest pain.	1–2 h: <5 ng/l 7–8 h: 21 ng/l 13–14 h: 21 ng/l	SR, 107 beats/min, no signs of ischemia.	Coronary angiography was performed on day 2, and a stent was placed in the LAD. The final diagnosis was NSTEMI.
Female	72	This patient was a current smoker and had a BMI of 22 kg/m^2.	Sudden onset of left-sided chest pain in the morning.	<1 h: <5 ng/l 6–7 h: 4,560 ng/l	SR, 45 beats/min, no signs of ischemia.	A second ECG performed 1 h after the first ECG showed ST-segment elevation in the inferior leads. Primary PCI was performed, and a stent was placed in the LCX. The final diagnosis was STEMI.
Male	68	This patient had hypertension, was a nonsmoker, and had a BMI of 31 kg/m^2.	Sudden onset of chest pain, diaphoresis, nausea, and dyspnea.	2–3 h: <5 ng/l 8–9 h: 18 ng/l 14–15 h: 15 ng/l	SR, 110 beats/min, no signs of ischemia.	Coronary angiography was performed on day 4, and was normal. The final diagnosis was NSTEMI.
Male	64	This patient was a current smoker and had a BMI of 31 kg/m^2.	Sudden onset of chest pain and diaphoresis at noon.	1–2 h: <5 ng/l 7–8 h: 158 ng/l 13–14 h: 888 ng/l	SR, 60 beats/min, T-wave inversion in leads V_1 and V_2.	A second ECG performed 30 min after the first ECG showed ST-segment elevation in the inferior leads. Primary PCI was performed, and a stent was placed in the RCA. The final diagnosis was STEMI.

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Table 4 Continued

Sex	Age, yrs	Previous Medical History	Current Medical History	Time from Onset of Symptoms to 1st, 2nd and 3rd hs-cTnT Level	ECG Assessment by the ED Physician	Clinical Course
Male	56	This patient was a current smoker and had a BMI of 20 kg/m^2.	Sudden onset of chest pain during physical activity.	1–2 h: <5 ng/l 7–8 h: 29 ng/l 13–14 h: 56 ng/l	SR, no signs of ischemia.	Coronary angiography was performed on day 5, and was normal. The final diagnosis was NSTEMI.
Female	68	This patient had 3 previous MIs and a previous CABG, was an active smoker, and had a BMI of 17 kg/m^2.	Sudden onset of left-sided chest pain during physical activity.	>3 h: <5 ng/l >9 h: 40 ng/l	SR, 60 beats/min, no signs of ischemia.	Coronary angiography was performed on day 2 and showed no significant stenosis. The final diagnosis was NSTEMI.
Female	56	This patient was an active smoker and had a BMI of 27 kg/m^2.	Sudden onset of chest pain during the night.	<1 h: <5 ng/l 6–7 h: 19 ng/l	SR, 76 beats/min, no signs of ischemia.	ECG later on the day of admission showed ST-segment elevation. Coronary angiography showed no significant stenosis. The final diagnosis was STEMI.
Male	54	This patient had hypertension, was an ex-smoker, and had a BMI of 26 kg/m^2.	Sudden onset of chest pain in the morning.	1–2 h: <5 ng/l 7–8 h: 157 ng/l 13–14 h: 92 ng/l	SR, nonsignificant ST-segment elevation in leads V_3–V_6.	Coronary angiography was performed on day 3 and showed no significant stenosis. The final diagnosis was NSTEMI.
Male	72	This patient had a previous stroke, was a nonsmoker, and had a BMI of 24 kg/m^2.	Sudden onset of chest pain during the night.	>3 h: <5 ng/l >9 h: 12 ng/l > 15 h: 29 ng/l	SR, no signs of ischemia.	Coronary angiography was performed on day 3 and showed no significant stenosis. The final diagnosis was NSTEMI.

*This patient had cardiac troponin I analyzed after he was admitted to the cardiac care unit.

BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; hs-cTnT = high-sensitivity cardiac troponin T; LAD = left anterior descending artery; LCX = left circumflex artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; RR = respiratory rate; SR = sinus rhythm; STEMI = ST-segment elevation myocardial infarction.

patients. If a second hs-cTnT level would have been obtained 3 to 4 h after onset of symptoms, most likely it would have been significantly elevated in most of these patients.

Because chest pain is 1 of the most common symptoms in patients seeking medical attention in the ED, our strategy may help to reduce overcrowding of the ED. However, our results did not show that low-risk patients who are admitted to the hospital spend more time in the ED than those who are discharged directly from the ED.

There were only 2 cardiovascular deaths in patients with undetectable hs-cTnT levels during the year that followed the visit to the ED. This indicates that hs-cTnT may not only be a predictor of early, but also long-term, prognosis (17).

There may have been several patients among those with undetectable levels of hs-cTnT who were discharged from the ED, who, if they were admitted to the hospital, would have had elevated hs-cTnT levels subsequently. We calculated the risk of death within the year after the visit to the ED for patients who were admitted compared with patients who were discharged directly from the ED and found no difference.

It is very important to determine whether patients with a very small elevation of the first hs-cTnT level benefit from being diagnosed with MI. There were two procedure-related MIs in patients with undetectable hs-cTnT levels. Because MI after PCI has a worse prognosis than PCI without MI (18), a diagnosis of MI based on a very small elevation of the hs-cTnT level may increase the risk to the patient. In almost half of the patients diagnosed with MI who had a first hs-cTnT level of <5 ng/l combined with no signs of ischemia on the ECG, the maximum hs-cTnT level was <30 ng/l. With earlier generations of troponin assays, these patients would probably not have been diagnosed with MI (14).

To the best of our knowledge, this is the first study of such a large cohort of consecutive patients (n = 14,636) who sought medical attention for chest pain, and had information on hs-cTnT levels at an ED over a 2-year period. Patient follow-up was complete because follow-up data were obtained from national registers.

Conclusions

We found that a first hs-cTnT level of <5 ng/l combined with no signs of ischemia on ECG ruled out MI with nearly 100% accuracy, regardless of previous disease, timing of measurement of the hs-cTnT level, age, sex, or other risk factors for MI.

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Key Words: chest pain ■ emergency department ■ high-sensitivity troponin ■ myocardial infarction.

APPENDIX

For a supplemental table, please see the online version of this article.