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HIGH-SENSITIVITY CARDIAC TROPONIN T IN THE EMERGENCY DEPARTMENT: ADMISSIONS, RESOURCE UTILIZATION AND OUTCOMES

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High-Sensitivity Cardiac Troponin T in the Emergency Department: Admissions, Resource Utilization and Outcomes

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund

Patienter som söker akutmottagningen på grund av bröstsmärta utgör 5-10% av alla akuta besök årligen i Europa och USA [1,2]. Bröstsmärta kan vara ett symtom på hjärtinfarkt som kräver omedelbar behandling men 80-85% av alla patienter med bröstsmärta diagnostiseras med helt ofarliga tillstånd. Det är därför oerhört viktigt att snabbt och säkert kunna avgöra vilka patienter som behöver läggas in på sjukhus för undersökning eller kan gå hem direkt från akutmottagningen. För att undersöka om en patient har hjärtinfarkt, görs en klinisk undersökning, EKG tas samt blodprover för att mäta biomarkörer i blodet [3].

Olika biomarkörer har använts sedan 1950-talet för att bekräfta eller utesluta hjärtmuskelskada. På 1990-talet introducerades troponin som den mest hjärtspecifika biomarkören hittills. Riktlinjer har rekommenderat att man ska ta upprepade blodprovsmätningar av troponin efter symtomdebut innan man kan utesluta hjärtinfarkt, vilket ledde till en rädsla för ökade inläggningar på sjukhus för observation [3]. Endast ca 15-20% av patienter som läggs in på sjukhus för bröstsmärta, får slutligen diagnosen hjärtinfarkt. Troponinmetoden har utvecklats och nyligen introducerades så kallat högkänsligt troponin (hs-cTnT) som är känsligare och som kan mäta hjärtmuskelskada i blodet flera timmar tidigare än äldre troponinmetoder [4].

Denna avhandling baseras på fyra studier som utvärderar högkänsligt troponin som analysmetod på akutmottagningen sedan introduktionen i kliniken, dess effekter på handläggning av patienter med bröstsmärta på akutmottagningen samt resursutnyttjande på sjukhus.

Metod och Resultat

I **Studie I** utvärderade vi om ett första omätbart värde på hs-cTnT och ett normalt EKG kunde utesluta hjärtinfarkt direkt på akutmottagningen. Vi inkluderade 14,636 patienter som sökte med bröstsmärta på akutmottagningen på Karolinska Universitetssjukhuset under två år. Resultaten visade att risken för att utveckla hjärtinfarkt var minimal om EKG var normalt och ett första högkänsligt troponinvärde var omätbart.

I **Studie II** undersökte vi om de patienter som skickats hem från akuten i Studie I återkom i högre grad än om de hade lagts in på sjukhus. Efter att vi hade exkluderat de patienter som hade hjärtinfarkt vid besöket, inkluderade vi resterande 13,046 patienter som sökt

akutmottagningen på grund av bröstsmärta på Karolinska Universitetssjukhuset under två år. För patienter med omätbart högkänsligt troponin som lagts in på sjukhus jämfört med de som gått hem direkt från akutmottagningen fann vi en 24% ökad risk för återbesök till sjukhus samt en 3 gånger så hög risk att genomgå kranskärlsröntgen och kranskärlsingrepp.

Studie III studerade trender i inläggning på sjukhus efter introduktionen av högkänsligt troponin. Studien innefattade 15,472 patienter som sökt akutmottagningen på grund av bröstsmärta på Karolinska Universitetssjukhuset i Huddinge under 4 år. Resultaten visade att inläggningar på sjukhus på grund av bröstsmärta minskat med 36% sedan högkänsligt troponin införts som analysmetod.

Studie IV utvärderade överlevnad och resursutnyttjande för 31,904 patienter som sökt på grund av bröstsmärta på akutmottagningen på Karolinska Universitetssjukhuset under 5 år. De första 3 åren när högkänsligt troponin introducerades jämfördes med de 2 föregående åren när konventionellt troponin användes som analysmetod. Resultaten visade en liten minskning i överlevnad samt fler genomförda kranskärlsröntgen och kranskärlsingrepp sedan högkänsligt troponin introducerats.

Slutsatser

Studie I: Patienter som söker på grund av bröstsmärta och har ett första högkänsligt troponinvärde som är omätbart samt ett normalt EKG har en minimal risk att drabbas av hjärtinfarkt och kan säkert skickas hem från akutmottagningen.

Studie II: När patienter som söker akut på grund av bröstsmärta och har ett omätbart högkänsligt troponinvärde läggs in på sjukhus istället för att skickas hem, ökar risken för återbesök till akuten, upprepade inläggningar på sjukhus, kranskärlsröntgen och kranskärlsingrepp.

Studie III: Inläggningar på sjukhus på grund av bröstsmärta minskade med 36% under de första 4 åren efter att högkänsligt troponin införts på akutmottagningen.

Studie IV: Efter introduktionen av högkänsligt troponin observerades en liten minskning i överlevnad samt en ökning av resursutnyttjande. Resultaten bör tolkas med försiktighet.

ABSTRACT

Background
Patients presenting with chest pain in the emergency department (ED) may have myocardial infarction (MI) requiring immediate treatment. High-sensitivity cardiac troponin T (hs-cTnT) was recently introduced as a biomarker that aids in determining whether the patient requires hospital admission or can be safely discharged home. The aim of this thesis was to evaluate the implementation of hs-cTnT in the ED, with respect to hospital admission, resource utilization and patient outcomes.

Methods and Results
Two separate datasets were created by combining administrative information from the ED at Karolinska University Hospital with laboratory data and linking several national health care registers through the National Board of Health and Welfare. The first dataset was used for Studies I and II, while the second dataset was used for Studies III and IV. Cox regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs).

Study I: In total, 14,636 patients with chest pain who presented to the EDs at Karolinska University Hospital, Solna and Huddinge, during 2011 and 2012 were included to evaluate whether a first undetectable (<5 ng/L) hs-cTnT level and an electrocardiogram (ECG) without signs of ischaemia could be used to safely rule out MI in the ED. We identified 15 patients with an undetectable hs-cTnT level and non-ischaemic ECG who were diagnosed with MI within 30 days. The negative predictive value for MI using this strategy was 99.8%, and for death 100%.

Study II: We included 13,046 patients with chest pain who visited the ED at Karolinska University Hospital, Solna and Huddinge, during 2011 and 2012. We calculated HRs at different hs-cTnT levels for the risk of revisits to the ED, readmissions to hospital and resource utilization in terms of whether the patient was discharged or admitted. In patients with a hs-cTnT level of <5 ng/L who were admitted to the hospital compared with discharged home, we observed a 24% increased risk (adjusted HR 1.24, 95% CI 1.05–1.46) of revisiting the ED within 30 days and a three-fold increased risk of coronary angiography or revascularization during follow-up.

Study III: We evaluated trends in admission rates among 15,472 patients with chest pain who presented to the ED at Karolinska University Hospital, Huddinge from 2011 to 2014. Proportions of admitted patients were calculated using each year of the study period (2012, 2013 and 2014) as exposure with year 2011 as reference. We found a 36% relative reduction in hospital admissions. All-cause mortality increased (adjusted HR 1.51, 95% CI 1.18–1.92), but for non-cardiovascular causes only. Coronary angiography significantly increased, but revascularizations remained stable.

Study IV: Survival and resource utilization in 31,904 patients with chest pain were compared during the initial 3 years (2011-2013) when the hs-cTnT assay was implemented to the preceding 2 years (2009-2010) when the conventional troponin (cTnT) assay was in use at Karolinska University Hospital, Solna and Huddinge. Patients who were tested with hs-cTnT had a 15% increase in all-cause mortality (adjusted HR 1.15, 95% CI 1.02–1.29), 13% increase in coronary angiography (adjusted HR 1.13, 95% CI 1.00–1.28) and 18% increase in revascularizations (adjusted HR 1.18, 95% CI 1.01–1.37).

Conclusions
[I] Patients presenting with chest pain, a first undetectable hs-cTnT level and a normal ECG may be safely discharged from the ED because the risk of MI or death is minimal. [II] When patients with chest pain and an undetectable hs-cTnT level are admitted to the hospital instead of discharged home, they have an increased risk of revisits to the ED, recurrent hospital stays, coronary angiography and revascularization. [III] Admissions for chest pain were reduced by 36% during the first 4 years of hs-cTnT use. All-cause mortality increased, but for non-cardiovascular causes only. [IV] After the introduction of hs-cTnT testing in the ED, an increase in mortality, coronary angiography and revascularizations was observed.

LIST OF PUBLICATIONS

I. **Bandstein N**, Ljung R, Johansson M, Holzmann MJ.
Undetectable high-sensitivity cardiac troponin level in the emergency department and risk of myocardial infarction.
Journal of American College of Cardiology 2014;63:2569-78.

II. **Bandstein N**, Ljung R, Holzmann MJ.
Risk of revisits to the emergency department in admitted versus discharged patients with chest pain but without myocardial infarction in relation to high-sensitivity cardiac troponin T levels.
International Journal of Cardiology 2016;203:341-6.

III. **Bandstein N**, Ljung R, Lundbäck M, Johansson M, Holzmann MJ.
Trends in admissions for chest pain after the introduction of high-sensitivity cardiac troponin T.
International Journal of Cardiology 2017, doi:10.1016/j.ijcard.2017.04.028

IV. **Bandstein N**, Wikman A, Ljung R, Holzmann MJ.
Survival and resource utilization in patients with chest pain evaluated with cardiac troponin T compared with high-sensitivity cardiac troponin T.
Submitted.

CONTENTS

LIST OF ABBREVIATIONS

CABG	coronary artery bypass grafting
CI	confidence interval
cTnT	cardiac troponin T
ECG	electrocardiogram
ED	emergency department
eGFR	estimated glomerular filtration rate
HR	hazard ratio
hs-cTnT	high-sensitivity cardiac troponin T
MI	myocardial infarction
NPV	negative predictive value
NSTEMI	non ST-elevation myocardial infarction
PCI	percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction

INTRODUCTION

Patients presenting with chest pain account for 5% to 10% of all visits to the emergency department (ED) [1,2]. Chest pain may be a symptom of myocardial infarction (MI) requiring immediate treatment; therefore, these patients have often been admitted to hospital for observation. But only 10% to 20% of patients who are admitted to hospital because of chest pain, are diagnosed with MI; most patients are diagnosed with non-cardiac conditions [3]. Rapid diagnosis of the cause of chest pain is important to determine whether the patient requires admission to hospital or can be safely discharged home from the ED. The diagnostic tools used to rule out MI are clinical assessment, an electrocardiogram (ECG), and measurement of cardiac biomarkers, commonly troponin. Guidelines have recommended serial measurements of to rule out MI, which often means that patients with chest pain must be admitted to hospital [3].

High-sensitivity cardiac troponin T (hs-cTnT) was recently implemented in the clinical setting. The biomarker has the ability to detect myocardial damage in the blood several hours earlier than previous biomarkers [4]. Introduction of hs-cTnT raised the question of whether hospital admission for repeated measurements of troponin is still necessary [5,6]. The ability to safely and rapidly rule out MI, without serial testing or observation, may lead to reduced hospital admissions and downstream investigations and improved outcomes [7].

The aim of this thesis was to study the clinical impact of implementing hs-cTnT in the ED with respect to hospital admissions, resource utilization and patient outcomes.

BACKGROUND

CHEST PAIN

A key problem in the ED is how to rapidly diagnose patients with MI among all patients with chest pain. Approximately 5% of all patients visiting the ED have chest pain as the main complaint, making it the second most common cause for a visit to the ED; however only 5% of all patients presenting with chest pain are actually diagnosed with MI [1].

The first purpose of evaluation of chest pain is to determine whether it is of cardiac (ischaemic) or non-cardiac origin. The most prominent symptoms (also known as "typical" symptoms) of cardiac ischaemia are retrosternal pain and/or pressure with a radiation to the left arm or jaw that may be persistent for a couple of minutes or occur intermittently [8]. However, radiation to the left arm does not increase the probability of MI [9]. Diaphoresis, nausea or vomiting, back pain, epigastric discomfort, or dyspnoea may also be symptoms of myocardial ischaemia [3].

There is also a high prevalence of symptoms (also known as "atypical" symptoms) that do not primarily raise suspicions of cardiac origin, such as pleuritic knife-like pain and tenderness upon palpation of the thorax. The onset is often random and unrelated to physical activity and can last for seconds, minutes, hours, or all day. Afferent nerve fibres from the heart, lungs, oesophagus, and great vessels carry information to the same thoracic autonomic ganglia. Because of fibre overlap in the dorsal ganglia, a pain stimulus from any of these organs may be experienced in the thoracic region and hence give rise to a number of cardiac and non-cardiac causes of chest pain [10]. However, even patients with "atypical" symptoms may have myocardial ischaemia, which complicates the diagnostic process [3]. Studies have investigated the clinical value of pain severity, facial expressions and symptoms in different ethnic groups during potential MI, but limited diagnostic value for MI has been found [11-13].

Possible differences in the presentation of symptoms of MI between men and women have also been thoroughly investigated [8,14-18]. Guidelines state that "atypical" symptoms of MI are more common in women than men [8]. An important clinical question is whether using sex-specific characteristics of chest pain can improve early diagnosis of MI. Some studies have reported minimal differences in symptoms suggestive of MI between women (more often nausea or jaw pain) and men [14-16]. However, these differences are so small that implementation of sex-specific characteristics is not clinically applicable. Some studies have observed no differences in symptom presentation between the two sexes [17,18].

Apart from myocardial ischaemia, other potentially life-threatening conditions may also be characterized by an onset of chest pain, such as pulmonary embolism or pneumothorax, which presents with an immediate onset of dyspnoea and thoracic aortic dissection, which presents with high-intensity chest pain [19]. These conditions are rare in patients presenting with chest pain but need to be assessed immediately in the ED.

MYOCARDIAL INFARCTION

Incidence of MI

The incidence of MI in Sweden during the last 30 years has decreased markedly, as depicted in FIGURE 1 [20].

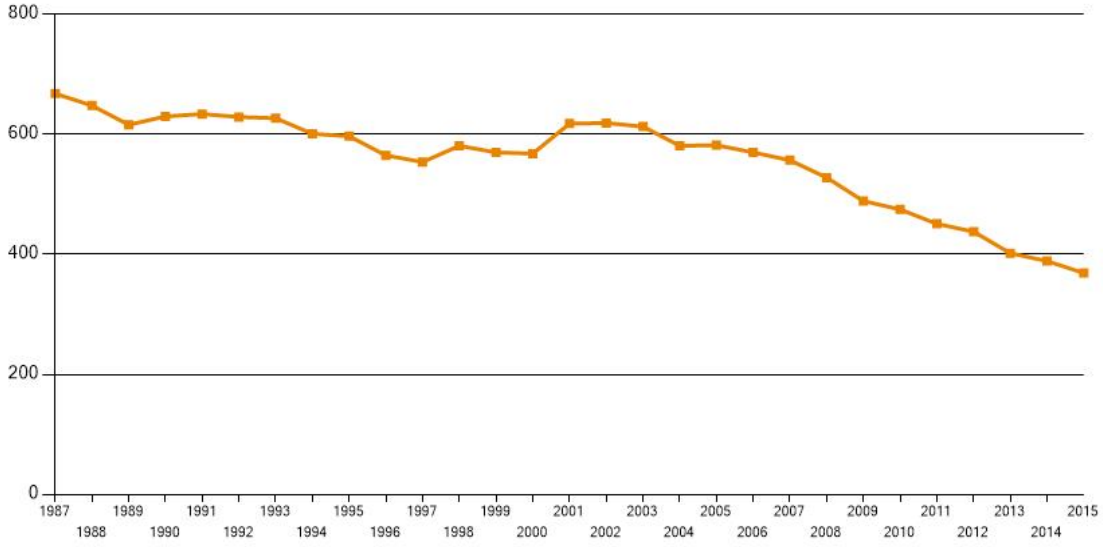


FIGURE 1. Incidence of MI per 100.000 individuals for both sexes, age 20-85 years, during 1987-2015 in Sweden.

Classification based on mechanism

MI is commonly categorized according to the underlying mechanism, as depicted in TABLE 1 [3]. Type 1 MI constitutes approximately 88% of all MIs in admitted patients according to a recent study [21]. Fewer patients are diagnosed with type 2 MI, approximately 7% of all MIs, and form a more heterogeneous group. Type 3 MI is rare, constituting approximately 3% of all MIs [22].

TABLE 1. Classification of MI.

Type	Mechanism
1	Spontaneous MI caused by atherosclerotic plaque rupture. A thrombus will occlude one or more of the coronary arteries leading to decreased myocardial blood flow and ischaemia.
2	MI secondary to myocardial oxygen supply and demand imbalance, caused by a condition other than atherosclerotic disease, such as sepsis, arrythmias, respiratory failure, hypotension or hypertension.
3	MI caused by presumed myocardial ischaemia leading to cardiac death before biomarkers is obtained.
4a	MI related to coronary angiography or PCI
4b	MI related to stent thrombus
5	MI associated with CABG

Abbreviations: myocardial infarction (MI); percutaneous coronary intervention (PCI); coronary artery bypass grafting (CABG).

Classification based on ECG

The diagnosis of MI is determined by patient symptoms, ECG-findings, and a rise and/or fall of a biomarker, commonly troponin, with one value above the 99th percentile of the upper reference limit [3]. Upon arrival to the ED, a patient presenting with chest pain immediately undergoes ECG recording. A normal ECG-complex is depicted in FIGURE 2. The ST-segment represents the interval between ventricular depolarization and the start of repolarization [3]. When an atherosclerotic plaque in the artery wall ruptures, it may lead to total artery occlusion, causing ischaemia in the myocardium supplied by that artery. The cardiac wall will undergo early repolarization which elevates the ST-segment, as shown in FIGURE 2 [3]. Such patients have developed ST-segment elevation MI (STEMI) and should be rapidly reperfused with coronary angiography and primary PCI at a PCI-capable hospital, or else undergo thrombolysis [23].

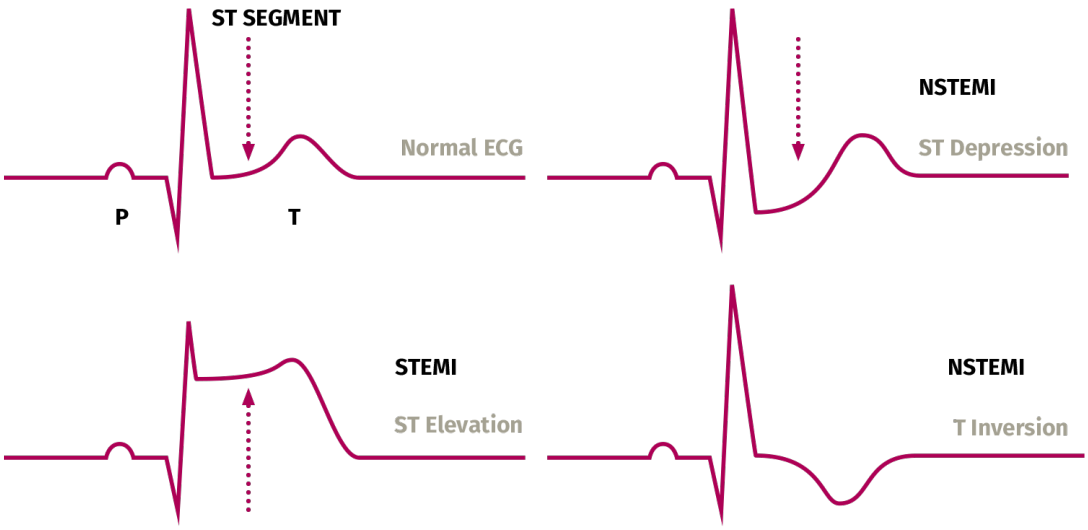


FIGURE 2. The normal ECG complex and ECG during STEMI and NSTEMI. Image reproduced with permission from the publisher.

The ECG is a cornerstone in the diagnosis of STEMI, while ECG findings are normal in more than one-third of all patients with non-ST-segment elevation MI (NSTEMI). During NSTEMI, the ECG may show ST-segment depression or T-wave changes. In the case of partial coronary artery occlusion, an earlier onset of subendocardial repolarization will occur leading to a depression of the ST-segment. A reverse electrophysiological wave will result in an inverted T wave, as depicted in FIGURE 2 [8]. During NSTEMI, the primary goal is to stabilize the patient using nitrates and morphine for the chest pain, beta-blockers, platelet inhibitors, and anticoagulants. Thereafter, the physician decides on conservative therapy or invasive methods, such as coronary angiography with the possibility of revascularization. These decisions are based on the responsiveness to the given therapy, risk stratification, and evaluation of biomarkers [8].

Unstable angina differs from NSTEMI only in that biomarkers are not increased; however the treatment is the same [8].

ASSESSMENT

Clinical judgment

The physicians assessment remains imperative for differentiating MI from other potential causes of disease and should be combined with an ECG and biomarkers to decide whether to admit or discharge patients with suspected MI [24]. Clinical judgment is defined as the use of patient information (history, physical signs and symptoms, laboratory data, and radiologic results) combined with subjective and objective data (best practice or theory) that lead to a conclusion and treatment plan. Clinical judgment is developed through practice and analysis, leading to experience and knowledge. Previous studies have shown improved accuracy when adding clinical judgment to the ECG and biomarker findings in the assessment of patients with chest pain while others have reported inconclusive results regarding clinician assessment [25-27].

Risk factors

A common conception is that the presence of more cardiac risk factors is associated with a higher risk of MI. Several risk factors are associated with increased risk of future MI, including age, male sex, hypertension, hypercholesterolaemia, diabetes mellitus, smoking, family history, obesity, and physical inactivity [28]. These factors may increase the long-term risk of MI, but do not increase the probability of an ongoing MI in the ED in patients with chest pain [29-33].

Scoring systems

Clinical guidelines recommend the use of a scoring system for risk stratification of patients with suspected MI [8] and several studies have shown increased identification of low-risk patients when combining a risk score with troponin measurement [29,34]. However, the implementation of scoring systems in clinical practice and their current use have been poorly investigated [26]. Some of the most common scoring systems are depicted in TABLE 2.

TABLE 2. Common scoring systems and their variables.

Risk score	Year of publication	Score variables
GRACE	2003	Age, Killip class, blood pressure, heart rate, creatinine level, the presence of cardiac arrest on admission, ECG, biomarkers. [35]
TIMI	2000	Age, risk factors, history of coronary artery disease, medication, present angina ECG, biomarkers. [36]
HEART	2008	History, ECG, age, risk factors, troponin (conventional). [34]
MACS	2014	High-sensitivity cardiac troponin T, Heart-type fatty acid binding protein, ischaemic ECG, sweating observed, vomiting, systolic blood pressure <100 mm Hg, Worsening angina, Pain radiating to the right arm or shoulder. [29]
Vancouver chest pain rule	2014	Age, ECG, biomarkers, prior myocardial infarction or nitrate use, physical examination, pain radiation. [37]

Abbreviations: Global Registry of Acute Coronary Event (GRACE); Thrombolysis In Myocardial Infarction score (TIMI); History ECG Age Risk factors Troponin (HEART); Manchester Acute Coronary Syndromes Decision Rule (MACS).

Non-invasive testing

Non-invasive methods for investigating suspected NSTEMI depend on local resources and expertise [26]. The exercise ECG was previously the investigation method of choice and is still widely used in some countries. Current clinical guidelines do not recommend use of exercise ECG for assessment of coronary disease [38]. Stress echocardiography is preferred over the exercise ECG because of its greater diagnostic accuracy and is recommended by guidelines during admission or shortly after discharge [8]. Computed tomographic coronary angiography is indicated in patients with a clinical suspicion of coronary disease, but the clinical outcomes of this test have been debated [39]. In the ED at Karolinska University Hospital, very few or no computed tomographic coronary angiograms are performed. Previous studies have investigated the effectiveness of non-invasive stress testing compared with no testing for reducing the risk of MI and found no difference [40].

TROPONIN

Historic overview

Since the 1950s, several biomarkers have been clinically tested to diagnose suspected MI: aspartate transaminase, lactate dehydrogenase, myoglobin, creatine kinase and the CK isoenzyme MB (FIGURE 3) [41,42]. However, these biomarkers are not cardiac-specific; their levels increase in a variety of pathological conditions and can therefore not be used to distinguish between cardiac or skeletal injury [42]. A breakthrough in the search for a more cardiac-specific biomarker came in the 1990s with troponin. In 1997, troponin was observed to be suitable for detection of myocardial damage in a clinical context, and researchers reported that it would be safe to discharge patients showing negative results on troponin tests [43].

A concern regarding missed diagnoses has accompanied the introduction of troponin as a clinical tool. At the turn of the millennium it was reported that even more specific biomarkers were needed to accurately diagnose myocardial damage and reduce the number of missed diagnoses [44]. In 2000, the First Global Task Force for MI added troponin as part of the recommended diagnostic process for suspected MI, supplementing ECG and physician assessment, and proposed a new definition of MI [45]. The definition of MI was revised a second time in 2007 [46]. In 2012, the definition of MI was updated for the third time in a decade and included high-sensitivity cardiac troponin assays [3].

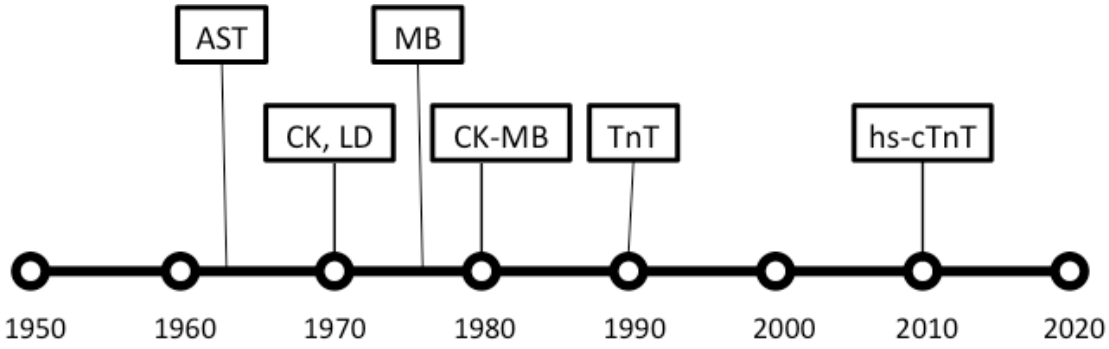


FIGURE 3. Timeline of the development of biomarkers for the diagnosis of MI. Abbreviations: Aspartate transaminase (AST); lactate dehydrogenase (LD); myoglobin (MB); creatine kinase (CK); CK isoenzyme MB (CK-MB); cardiac troponin (TnT); high-sensitivity cardiac troponin T (hs-cTnT).

Structure

Troponin is a protein component of the contractile apparatus of the cardiac muscle cell, the myocyte. The contractile unit of the cardiac muscle cell consists of myosin and actin, tropomyosin, and the troponin complex, as depicted in FIGURE 4. The troponin complex comprises three regulatory subunits: C, I and T, that control the interaction between actin and myosin and therefore control cardiac muscle contraction. Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) have unique isoforms in the cardiomyocyte making them suited for inclusion in immunoassays and diagnostic analyses [47].

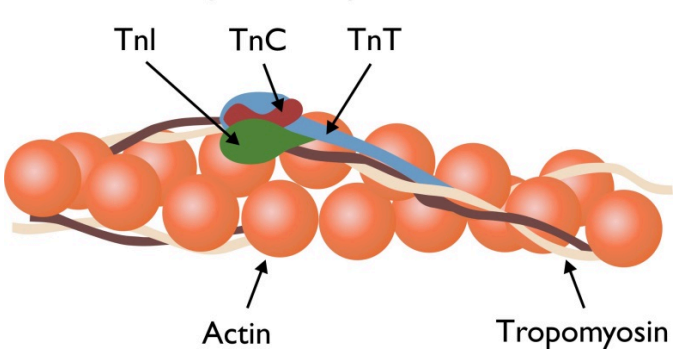


FIGURE 4. The troponin complex structure. Troponin I (TnI); Troponin C (TnC), Troponin T (TnT). Image reproduced with permission from the publisher.

Release mechanism

Troponin is mostly an intracellular protein. Therefore, the presence of troponin in the blood circulation reflects its release from cardiomyocytes. The majority of intracellular troponin is attached to the contractile apparatus and constitutes the structural pool. A minor amount of cardiac troponin, approximately 6% to 8%, is always detectable in the blood, and constitutes the circulating pool. This cytosolic pool is believed to be caused by natural turnover of cardiomyocytes and can be further increased by physiological conditions and physical exercise [48-50].

When damage to a cardiomyocyte occurs, as in ischaemic MI, troponin is believed to be released from small storage areas in the cytosolic pool, followed by a slower release from the contractile apparatus of the cardiomyocyte as it is destroyed. This process results in an increased troponin concentration in the blood for days to weeks

[51,52]. The degree of the troponin increase and the time until its peak concentration is reached are dependent on the underlying cause and mechanism of the troponin release (FIGURE 5) [53]. The mechanism is well described during cardiomyocyte necrosis, but other mechanisms of troponin release that have not been completely clarified may be present (e.g. normal cell turnover, apoptosis, or increased cell membrane permeability) [53-55].

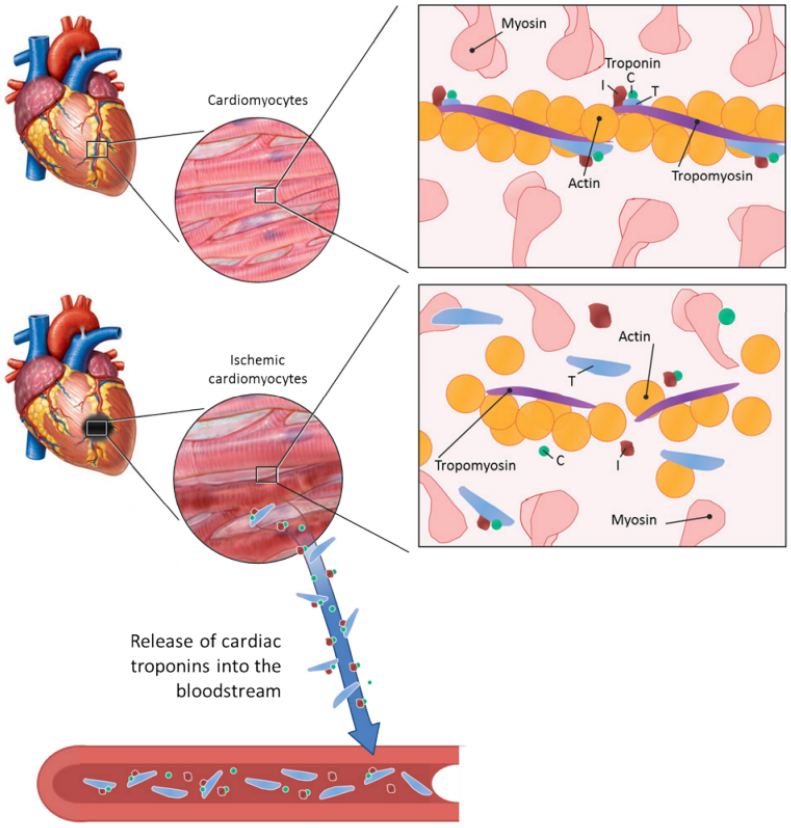


FIGURE 5. The troponin release mechanism. Image reproduced with permission from the publisher.

Recent advances in our understanding of the pathogenesis of ischaemic heart disease confirm that troponin turnover is increased in patients with coronary artery disease and heart failure [56]. These patients are believed to have a larger pool of circulating troponin, possibly due to coronary plaque rupture that cause microinfarctions and chronic troponin leakage. These patients exhibit plasma levels that correlate with the disease burden [57].

THE HIGH-SENSITIVITY CARDIAC TROPONIN T ASSAY

The initial first-generation troponin assays, presently known as conventional assays, exhibited 100% sensitivity for detecting troponin in the blood 6 to 12 hours after the onset of chest pain. Practically, this meant that a patient required a repeated measurement 6 to 12 hours after the first assessment to rule out MI [46]. With conventional assays, the troponin concentration in healthy individuals were below the detection limit. Determination of the upper reference limit was problematic, leading to qualitative assessments and categorization of patients as troponin-positive (detectable) or troponin-negative (undetectable) [58]. The assays were continuously genetically re-engineered to reach an increased analytical sensitivity and were later termed sensitive assays.

Further developments resulted in assays that were able to detect troponin in the blood with higher sensitivity and at a much earlier time point than the previous assays; hence they were termed high-sensitivity assays [4]. The nomenclature negative and positive troponin became useless because hs-cTnT was now detectable even in healthy individuals [59].

Nomenclature

The term "high-sensitivity" reflects the analytical characteristics of the assay. Several terms are present in the literature for more sensitive assays, such as "highly sensitive", "high-sensitive", "high sensitivity", "ultrasensitive", "novel highly sensitive" and "high-performance".

The 99th percentile

An assay must meet two analytical requirements to be considered a high-sensitivity assay. First, the coefficient of variation must be <10% at the 99th percentile in the population. Second, the assay should be able to measure troponin concentrations below the 99th percentile and above the limit of detection for at least 50% of the reference population [47]. The new guidelines recommended using the 99th percentile of a healthy population as the cut-off for the diagnosis of MI [3]. This concept was introduced at a time when conventional assays detected troponin values in <5% of healthy individuals [45,60]. Because high-sensitivity assays are now in

use, more individuals without MI will be found to have normal circulating elevated troponin levels above the 99th percentile (approximately 9% according to a previous study) [59,61]. The 99th percentile is dependent upon the characteristics of the underlying population, and there is an ongoing debate concerning what criteria should be used to define a healthy population. Higher levels of troponin have been observed in male patients, in patients of increasing age, and patients with reduced kidney function as indicated by the estimated glomerular filtration rate (eGFR) [61]. Renal function impacts the troponin concentration, partially because of decreased renal clearance but mostly because of ongoing cardiac damage [62,63]. Age partially reflects the increased remodeling of the myocardium with subsequent cardiomyocyte loss. Several studies have also investigated whether sex-specific [64,65] or age-specific cut-offs should be applied to the diagnosis of MI [61].

Characteristics

Hs-cTnT is superior to previous generations of troponin in many ways, primarily its improved sensitivity and earlier detection (approximately 3 hours) of cardiomyocyte damage [4,66].

The increased sensitivity implies that hs-cTnT detects concentrations of troponin 10 times lower than previous assays, enabling detection of circulating normal troponin concentration in healthy individuals, believed to be the results of natural turnover of cardiomyocytes. Therefore, the troponin concentration should be quantitatively interpreted and has been observed to correlate well with disease severity and the histopathological extent of cardiac injury [67,68]. A higher hs-cTnT level at presentation is associated with a greater risk of MI and death [8]. With the improved sensitivity of these assays, it is imperative for the physician to distinguish between acute and chronic elevations of troponin to determine whether the patient should be admitted, discharged, or undergo further investigations. Causes of acute troponin elevation are associated with a rise and/or fall pattern of a second troponin measurement [3].

With respect to a low or undetectable (<5 ng/L) troponin concentration, several studies have investigated whether a single troponin value is enough to safely rule out

MI [5,6,69]. Current European guidelines recommend discharge of patients who present with chest pain and exhibit a hs-cTnT level of <5 ng/L if the onset of chest pain is persistent for >3h. If the patient has an early onset of chest pain <1 hour before arrival to the ED, a second measurement (delta troponin) is recommended to determine whether the patient should be admitted to hospital or discharged home [8]. The delta troponin is defined as the difference between two troponin values in the same patient, within a specific time interval [70].

The improved sensitivity of current troponin assays has also resulted in decreased specificity for the diagnosis of MI. When sensitive assays were first put into clinical use, an elevated troponin concentration was considered indicative of MI. Recent studies have shown that an elevated troponin level may be associated with multiple pathophysiological conditions such as heart failure, atrial fibrillation, pulmonary embolism, and sepsis [8]. Troponin is thus heart-specific but not disease-specific, and it provides no information about the cause or mechanism of release. The biological variation of hs-cTnT should also be considered when interpreting small troponin increases in healthy individuals [71].

Prognosis

The association between an elevated troponin level and increased long-term mortality in older patients and patients with cardiac disease has been shown in multiple studies [72,73]. A high prevalence of elevated troponin concentrations among seemingly healthy individuals in the general population and increased long-term mortality has also been reported [74]. Hs-cTnT is thus currently regarded as a general prognostic indicator for disease and long-term mortality. How the physician should interpret and evaluate these elevated troponin levels on an individual-patient bases remains unclear. Consequently, when hs-cTnT was first implemented into clinical practice, clinicians were initially concerned that patients would be excessively admitted to hospital for observation and further investigations [70].

Resource utilization

Serial measurements of troponin in many healthy individuals increases the length of stay in the ED, contributes to overcrowding, delays in testing and other

investigations, and lowers patient satisfaction [75,76]. Furthermore, because of the current uncertainty regarding how to handle elevated troponin levels, patients are commonly admitted to hospital, and may undergo investigations that are potentially harmful and unnecessary and have severe economical and health care consequences [40,77-80].

Global use

One existing manufacturer produces the hs-cTnT-assay. First produced in 2010, the Roche Elecsys 2010 system hs-cTnT has been found to be valid in terms of analytical sensitivity, specificity, interference, and precision [4]. This hs-cTnT assay has been used in clinical practice in Europe and Asia. In January 2017, it was also approved for use in the United States with the addition of sex-specific cut-offs. The sales name is Cardiac troponin T (cTnT) because the term "high-sensitivity" is considered to be an analytical term [81].

The use of hs-cTnT was introduced at Karolinska University Hospital on 10 December 2010. From the start of implementation there was a calibration issue of the method which was detected in 2012, when batches of defective reagents were replaced. After the replacement, the method became even more sensitive than before; the Karolinska Laboratory reported that the hs-cTnT level at the 99^{th} percentile was approximately 18% higher [82,83].

AIMS OF THE THESIS

The overall aim of this doctoral thesis was to increase knowledge about how the introduction of the hs-cTnT assay in the ED has affected admissions to hospital, resource utilization, and patient outcomes.

The specific aims were:

Study I To determine whether a first undetectable hs-cTnT level in combination with a normal ECG in patients presenting with chest pain to the ED can safely rule out MI.

Study II To determine whether patients with chest pain and an initial undetectable hs-cTnT level have an increased risk of revisits, readmissions, coronary angiography, or revascularization if they are admitted instead of discharged home directly from the ED.

Study III To describe trends in admission rates of patients presenting with chest pain in the ED during the first 4 years after the introduction of the hs-cTnT assay and investigate outcomes and effects on resource utilization following the ED visit.

Study IV To compare survival and resource utilization between the initial 3 years of hs-cTnT implementation with the preceding 2 years when conventional troponin (cTnT) was in use.

METHODS

OVERVIEW

A summary of study design and outcome for all studies are depicted in TABLE 4.

TABLE 4. Overview of Studies I to IV.

Study	**I** Undetectable	**II** Revisits	**III** Trends	**IV** Survival
Aim	To evaluate if a hs-cTnT level <5 ng/L and a normal ECG can safely rule out MI in the ED.	To assess the effects of discharge vs. admission on resource utilization in patients with low-risk chest pain.	To describe trends in admissions for chest pain after the introduction of hs-cTnT.	To study prognosis and resource utilization in patients evaluated with hs-cTnT compared with cTnT.
Hypothesis	Patients with chest pain, hs-cTnT <5 ng/L and a normal ECG, have a minimal risk of MI or death and can be safely discharged from the ED.	Patients with chest pain, a hs-cTnT <5 ng/L and a normal ECG, have an increased risk of revisits and resource utilization, if they are admitted compared with discharged from the ED.	The proportion of patients admitted for chest pain has been reduced and mortality within 1 year of the ED visit is unaffected.	The implementation of hs-cTnT has improved survival for patients with chest pain in the ED. Resource utilization has not increased.
Study design	Observational cohort study			
Cohort	All patients with a principal complaint of chest pain and a first hs-cTnT level analysed in the ED.	All patients with a principal complaint of chest pain and a first hs-cTnT level analysed in the ED. Patients with MI within 30 days of the ED visit were excluded.	All patients with a principal complaint of chest pain and a first hs-cTnT level analysed in the ED.	All patients with a principal complaint of chest pain and a first troponin level analysed in the ED.
Study setting	Karolinska University Hospital			
	Huddinge, Solna	Huddinge, Solna	Huddinge	Huddinge, Solna
Study period	10 Dec 2010 - 31 Dec 2012		1 Jan 2011- 20 Oct 2014	1 Jan 2009 -31 Dec 2013
No. of patients	14,636	13,046	15,472	31,904
Exposure	hs-cTnT <5 ng/L and a normal ECG	Admitted to hospital	Each year (2012, 2013, 2014) of the study period	hs-cTnT
Reference	N/A	Discharged home	Year 2011	cTnT
Outcomes	1) MI within 30 days 2) MI within 180 or 365 days and all-cause mortality within 30, 180, 365 days	1) revisit to the ED 2) revisit leading to hospital stay, >1 revisit, coronary angiography or revascularization	1) admission rate 2) all-cause mortality, CV-mortality, MI, heart failure or revascularization	1) 1 year all-cause mortality 2) coronary angiography and revascularization within 1 year
Follow up	31 Dec 2012: all-cause mortality, MI, hospital stays	30 June 2014: revisits. 31 Dec 2012 : hospital stays, coronary angiography and revascularization	30 June 2015: all-cause mortality. 31 Dec 2014: CV-mortality. 31 Dec 2013: MI, heart failure, coronary angiography and revascularization.	31 Dec 2014 : all-cause mortality. 31 Dec 2013: MI and CV-mortality.
Statistics	Survival analysis (Cox regression)			
Main findings	Patients with chest pain, a first hs-cTnT <5 ng/L and a normal ECG have a minimal risk of MI and may be safely discharged from the ED.	When patients with hs-cTnT < 5 ng/L are admitted, increased risk of revisit to the ED, coronary angiography and revascularization was seen.	Admissions were reduced by 36% during the first 4 years of hs-cTnT use. Increased mortality and coronary angiography were observed.	After the introduction of hs-cTnT, increased mortality, coronary angiography and revascularization were observed.
Status	*Journal of American College of Cardiology,* 2014.	*International Journal of Cardiology*, 2016.	*International Journal of Cardiology*, 2017.	Submitted.

Abbreviations: Myocardial infarction (MI); emergency department (ED); Not applicable (N/A); high-sensitivity cardiac troponin T (hs-cTnT); cardiac troponin T (cTnT); cardiovascular (CV).

THE DATASET

Two separate datasets were assembled during the course of the thesis and the process of creating each dataset was identical. The ED at Karolinska University Hospital has a local administrative database containing information on the date and time of each visit, reason for the visit, duration of stay in the ED, and several other variables for each patient. Using this database, we identified all patients who presented to the ED with a principal complaint of chest pain. To determine which of these patients had a troponin level analysed at the time of the visit to the ED, we integrated archived laboratory data via the hospital´s Information and Technology Department. The dataset was thereafter sent to the National Board of Health and Welfare, where it was linked with the National Patient Register, the Prescribed Drug Register, and the Cause Of Death register, using each patient´s Swedish personal identity number [84,85]. The complete dataset was anonymized according to regulations and returned to the research group [FIGURE 6].

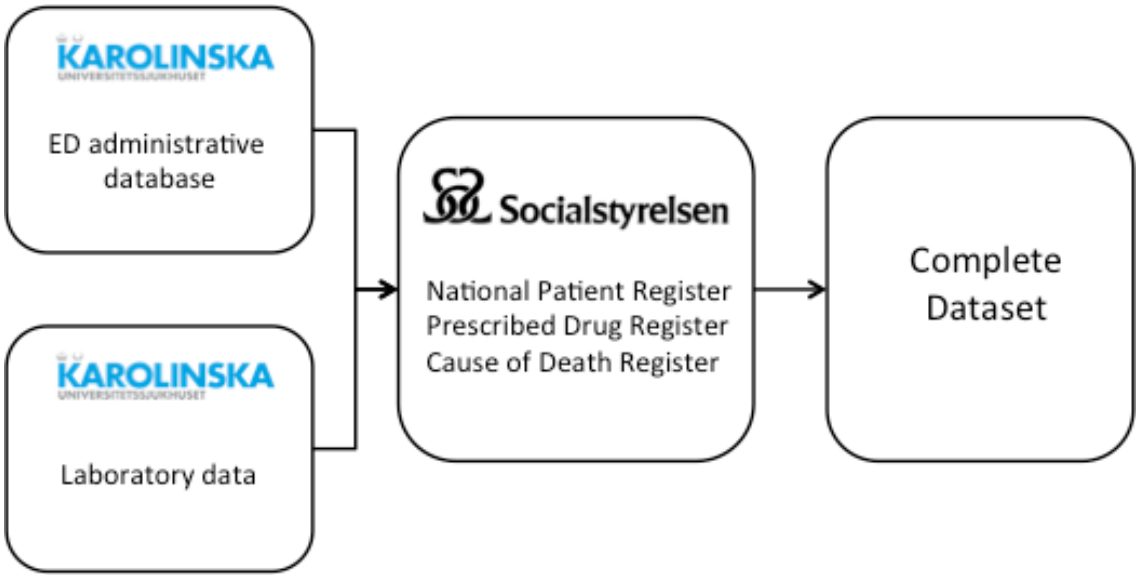


FIGURE 6. Dataset assembly.

REGISTRIES

The **National Patient Register** has had nationwide coverage since 1987 and is maintained by the National Board of Health and Welfare. The register includes data from public and private health care providers regarding outpatient care, admissions and discharges, surgeries, and other procedures. Diagnoses, surgical procedures, and interventions are categorized according to the World Health Organization International Statistical Classification of Diseases and Related Health Problems (ICD) [86]. We extracted data on admissions and discharge diagnoses and interventions such as coronary angiography, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). We also retrieved information on previous hospital stays for MI, stroke, heart failure, chronic obstructive pulmonary disease and other comorbidities. The register has been found to have high validity [84]. It was previously updated annually, but from 30 April 2015, the register has been updated monthly [84,87].

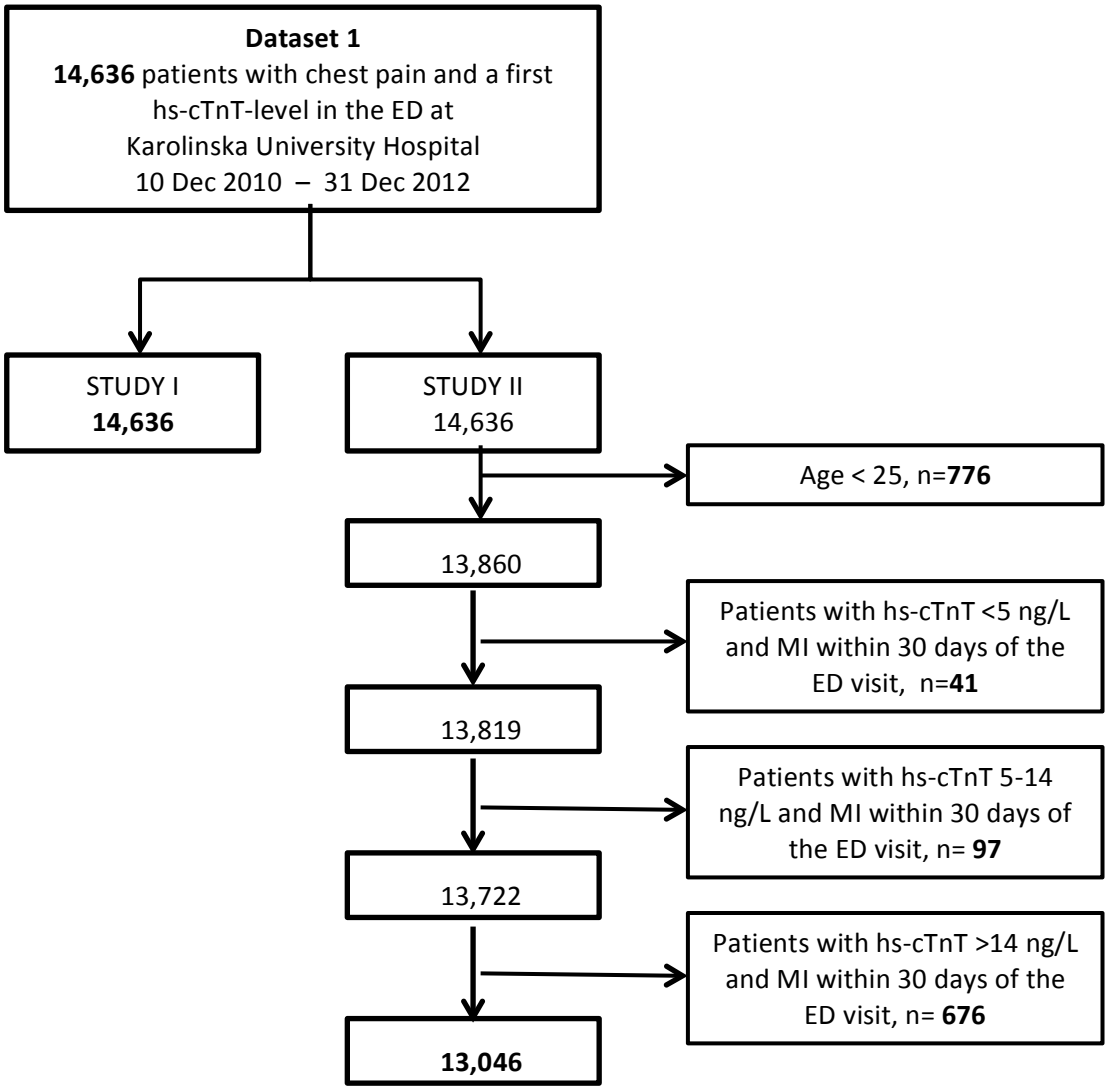
The **Prescribed Drug Register** contains data on drugs prescribed for individuals and dispensed prescriptions at pharmacies since 1 July 2005. The register is maintained by the Swedish National Board of Health and Welfare, and the number of prescriptions exceeds 100 million each year. The register is updated monthly [85].

Since 1961, the **Cause of Death Register** has been maintained by the National Board of Health and Welfare. The register holds data on all deceased Swedish residents, including age, time of death, and cause of death according to the ICD. The register is updated annually [88].

STUDY DESIGN AND POPULATION

Dataset 1 was created at the start of Study I, used in Studies I and II, and includes data from the ED at both sites, Huddinge and Solna, of Karolinska University Hospital from 12 December 2010 to 31 December 2012.

Dataset 2, was created at the start of Study III, used in Studies III and IV, and includes data from the ED at both sites, Huddinge and Solna, of Karolinska University Hospital from 1 January 2009 to 20 October 2014. When choosing study population for Study III, we included only patients from the Huddinge site, from 1 January 2011 to 20 October 2014. A description of Datasets 1 and 2 is provided in FIGURE 7.



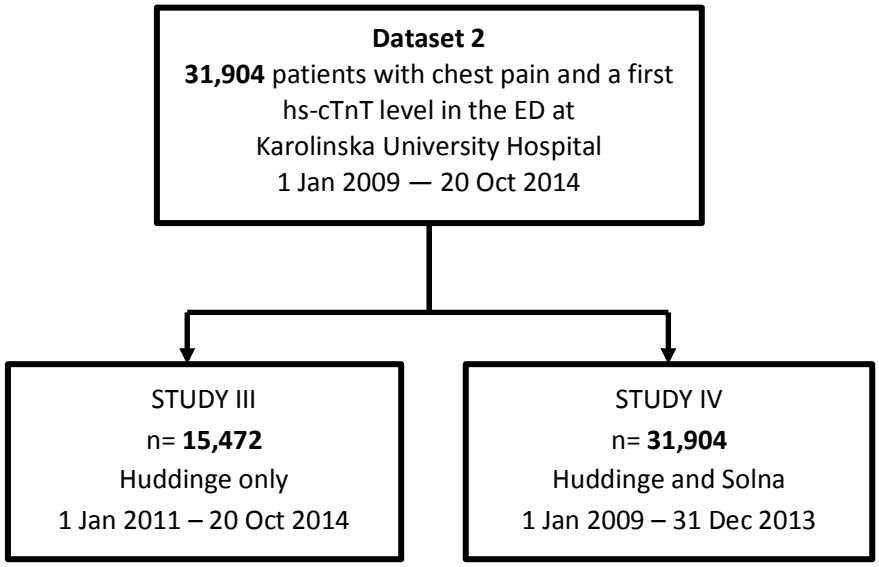


FIGURE 7. A description of Datasets 1 and 2, the study population and exclusion criteria for all studies.

Study I

From Dataset 1, we included all patients who presented to the ED with a principal complaint of chest pain and had a first hs-cTnT level analysed during the visit to the ED, (defined as the index date) from 10 December 2010 to 31 December 2012. Patients were categorized according to the first hs-cTnT level analysed: <5, 5-14 and >14 ng/L. The exposure was a hs-cTnT level of <5 ng/L and an ECG with no ischaemic changes.

For patients identified with a first hs-cTnT of <5 ng/L and a diagnosis of MI within 30 days of the visit to the ED, we retrieved the ECGs from their medical records. For each case we also retrieved the ECGs for two control patients, matched for age, sex and first hs-cTnT level. Two senior cardiologists who were blinded to the study protocol, assessed the ECGs. Medical records were also screened for all patients with a first hs-cTnT level of <5 ng/L and a diagnosis of MI within 30 days, to validate the diagnosis of MI according to the troponin levels, and coronary angiography and/or echocardiography findings and to evaluate the patient´s characteristics and history.

Study II

Patients were included from the same dataset used in Study I, from 10 December 2010 to 31 December 2012. The inclusion criteria were all patients ≥25 years, who presented to the ED with a principal complaint of chest pain and had a hs-cTnT level

analysed during the visit to the ED, (defined as the index date). The exclusion criteria were patients <25 years (n=776) and MI within 30 days of the visit to the ED (total, n=814) as depicted in FIGURE 7. Patients were categorized by their admission or discharge status and according to the first hs-cTnT level analysed: <5, 5-14 or >14 ng/L. The exposure was to be admitted to hospital, while the reference was to be discharged home from the ED.

Study III

A second dataset was created using an identical process as for Dataset 1. From this dataset, we included patients aged ≥25 years who presented with chest pain to the Huddinge ED and who had a hs-cTnT level analysed during the visit, from 1 January 2011 to 20 October 2014. For descriptive reasons, patients were categorized according to the first hs-cTnT level analysed in the ED: <5, 5-14 and >14 ng/L. The exposure was defined as each year (2012, 2013, and 2014) of the study period. The first year, 2011, when the hs-cTnT method was introduced, was defined as reference.

Study IV

Study IV was based on the same dataset used in Study III. From Dataset 2, we included all patients aged ≥25 years who presented to the ED with a principal complaint of chest pain and had a hs-cTnT level analysed during the visit at both sites, Huddinge and Solna, from 1 January 2009 to 31 December 2013. Depending on the time of the ED visit, patients were analysed with either cTnT or hs-cTnT. At the Karolinska Laboratory, the fourth-generation troponin cTnT assay was in use from 1 January 2009 to 9 December 2010 and this period was defined as the reference. From 10 December 2010 to 31 December 2013, hs-cTnT was used and was defined as the exposure under study.

BIOMARKERS

The fifth-generation hs-cTnT assay, (Roche Diagnostics) was introduced at the Karolinska University Hospital Laboratory on 10 December 2010 and was used to analyse hs-cTnT in Studies I to IV. The method has a limit of detection of 5 ng/L and a limit of blank of 3 ng/L. The 99th percentile cut-off is 14 ng/L, and the assay has a coefficient of variation of <10% at 13 ng/L [4].

The fourth-generation cardiac troponin cTnT assay was in use at the Karolinska University Hospital Laboratory until 9 December 2010. The method has a limit of detection of 0.01 mikrog/L, a 99th percentile cut-off at <0.01 and a coefficient of variation of 10% at 0.03 mikrog/L [89].

OUTCOME AND FOLLOW UP

Study I

The primary outcome was fatal or non-fatal type 1 MI within 30 days of the ED visit. The secondary outcomes were MI within 180 and 365 days and all-cause mortality within 30, 180 and 365 days after the ED visit. The patients first hs-cTnT level on the index date initiated the follow up period, which ended on 31 December 2012 for hospital stays, MI, and all-cause mortality.

Study II

The primary outcome was a revisit to the ED, regardless of cause. The secondary outcomes were a revisit to the ED within 30, 90, 180, and 365 days; a revisit to the ED leading to a hospital stay, >1 revisit to the ED, and coronary angiography or revascularization (defined as PCI or CABG). The patients first hs-cTnT level on the index date initiated the follow up period, which ended 30 June 2014 for revisits and 31 December 2012 for hospital stays, coronary angiography, and revascularization.

Study III

The primary outcome was the admission rate since the introduction of hs-cTnT. The secondary outcomes were all-cause mortality, cardiovascular and non-cardiovascular mortality, and major adverse cardiac events (MI, heart failure, or revascularization) within 1 year of the visit to the ED.

The proportions of admitted patients with chest pain were calculated each year during the study period (2011, 2012, 2013, and 2014). The proportions of patients admitted for abdominal pain and dyspnoea were also calculated for comparison. Moreover, proportions of patients with chest pain who underwent coronary angiography and revascularization within 1 year of the visit to the ED were also calculated.

Patients were included on their first visit to the ED with a principal complaint of chest pain and followed up until (a) the outcome under study occurred (MI, heart failure, or revascularization), (b) the patient died, (c) a new visit to the ED with a principal complaint of chest pain occurred or (d) 1 year had passed since the first visit to the ED (index visit). If the patient presented to the ED with chest pain within 1 year or any outcome had occurred, a new follow-up period was initiated. Patients were followed until 30 June 2015 for all-cause mortality, 31 December 2014 for cause-specific mortality and 31 December 2013 for the outcome MI, heart failure, coronary angiography and revascularization.

Study IV

The primary outcome was 1-year (a) all-cause mortality, (b) coronary angiography, and (c) revascularization defined as PCI or CABG. Follow-up started at the index visit and ended 1 year after the ED visit, at the time of death or at the end of the study. The end of the study was 31 December 2014 for all-cause mortality and 31 December 2013 for MI and cause-specific death. If a patient revisited the ED because of chest pain and had a concurrent troponin measurement, a new follow-up period started. It was therefore possible for the same patient to first be exposed to the cTnT method and later to the hs-cTnT method.

STATISTICAL ANALYSIS

Data management and statistical analyses were conducted using the World Programming System, version 3.0 (World Programming Ltd., Hampshire, UK). A Cox proportional hazards model was performed using R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Study I

We stratified patients into categories according to their first hs-cTnT-level: <5, 5 to 14, and >14 ng/L and calculated the absolute risk, negative predictive value (NPV) and incidence of MI and death with a follow-up of 30, 180 and 365 days. In addition, Cox proportional hazards model was used to calculate hazard ratios (HRs) with 95% confidence intervals (CI) for the potential association between the exposure (not

admitted with the reference admitted) and the outcome (time to death). In the Cox model, we adjusted for age, sex, diabetes, prior MI, and eGFR.

Study II

Patients were stratified by their first hs-cTnT-level: <5, 5–14, and >14 ng/L and by their admission or discharge status. Within each of the six strata, the absolute risk and incidence per 1000 person-years with 95% CI were calculated for the primary and secondary outcomes. Also, Cox proportional hazard models were used to calculate the HRs with 95% CI for the possible association between admitted versus discharged patients and the primary and secondary outcomes stratified by the three hs-cTnT categories (<5, 5–14, and >14 ng/L). This estimation was conducted for three models: 1) crude; 2) adjusted for age and sex; and 3) adjusted for age, sex, eGFR, diabetes, prior MI, prior stroke, chronic obstructive pulmonary disease, and heart failure. Age and eGFR were defined as continuous variables. A total of 122 patients had missing eGFR and were excluded from the Cox proportional regression models. We calculated cumulative survival and constructed a survival curve using the Kaplan-Meier method.

Study III

HRs with 95% CIs for the outcomes all-cause mortality, cardiovascular or non-cardiovascular mortality, and major adverse cardiac events (MI, revascularization, or heart failure) within 1 year of the ED visit for chest pain were estimated using Cox proportional hazard models. HRs were adjusted for age, sex, eGFR, prior stroke, prior MI, chronic obstructive pulmonary disease, or heart failure (defined as primary discharge diagnosis from hospital stay before study onset), and diabetes (defined as ongoing medication with any hypoglycaemic agent).

Study IV

Cox regression models were used to calculate HRs with 95% CIs for all-cause mortality, cardiovascular mortality, coronary angiography and revascularization during 1 year of follow-up after the visit to the ED. In addition, HRs with 95% CIs were calculated in the following subgroups: 1) patients who were discharged directly from the ED 2) patients who were admitted, but did not have MI, and 3) patients who were admitted and diagnosed with MI. The estimation was made for three models: 1) crude 2) adjusted for age and sex, and 3) adjusted for age, sex, eGFR, prior MI, prior stroke,

heart failure, chronic obstructive pulmonary disease, diabetes, prior revascularization, and ongoing medication with aspirin, statins, beta-blockers, or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

ETHICAL CONSIDERATIONS

Studies I to IV

All studies adhered to the guidelines of the Declaration of Helsinki. Approval of the study protocols was granted by The Regional Ethical Review Board in Stockholm. Personal information was handled according to regulations in the Personal Data Protection Act [90]. All data were analysed and saved in anonymized form according to regulations that protected the integrity of the patients. Personal identification numbers were replaced by consecutive numbers to prevent identification of single individuals in the dataset. In general, large register-based studies containing anonymized information, have a minimal risk of single individuals being exposed to a violation of personal integrity.

Study I

In the first study (DNR 2013/843-31/3 and 2013/1512-32), medical records were screened to validate the diagnosis of MI and evaluate the medical history and risk factors. During the review, only relevant non-personal information was recorded. However, there may have been a potential ethical issue concerning creation of the overview, which described each of the patient´s signs and symptoms during the episode, because very few patients presented with a first hs-cTnT level of <5 ng/L and MI within 30 days.

The patient records were screened on computers located at Karolinska University Hospital. No records were saved or printed outside the hospitals computer system. During interpretation of ECGs, all records were anonymized and personal identification numbers were replaced with consecutive numbers. The process took place in a locked room at Karolinska University Hospital in Huddinge and no records left this room. Therefore, confidentiality and anonymity were ensured during the data processing.

Study III

In the third study (DNR 2015/1903-32), we reviewed the medical records of 100 randomly chosen patients from 2013 to 2014 for information on risk assessment and the use of any scoring system. Again, the screening process was performed on computers located in a locked room at Karolinska University Hospital in Huddinge.

RESULTS AND METHODOLOGICAL DISCUSSIONS

STUDY I

Results

Patient characteristics

In total, 14,636 patients with chest pain were included and 61% (n = 8,907) of these presented with a first hs-cTnT level of <5 ng/L (FIGURE 8). Patients with undetectable hs-cTnT were younger and less likely to have diabetes or chronic cardiovascular disease. With increasing levels of hs-cTnT, patients were older, more often men, and had more comorbidities (TABLE 6).

Primary outcome measure

Of the 8,907 patients with a first hs-cTnT level of <5 ng/L, only 44 patients were diagnosed with MI within 30 days. Some patients were excluded from further analysis; 2 had periprocedural MI, 3 did not meet the current criteria for MI [3], and 24 had initial ECG changes. The remaining 15 patients were older and more often men with cardiovascular disease (FIGURE 9). A first hs-cTnT level of <5 ng/L in combination with a normal ECG showed a 99.8% NPV for MI within 30 days (CI 99.7-99.9) and a 0.17% absolute risk for MI (CI 0.09-0.27) (TABLE 7).

Secondary outcome measures

A total of 39 patients with hs-cTnT <5 ng/L developed MI 30 to 365 days after discharge from the ED, resulting in an incidence rate of 7.36 (CI 5.55-9.58) per 1,000 person-years.

The NPV for death within 30 days for patients with a first hs-cTnT level of <5 ng/L was 100% (CI 99.9-100.0). During the first 365 days after discharge from the ED, 38 deaths ocurred; only 2 deaths had cardiovascular causes (TABLE 7). Among patients with a first hs-cTnT <5 ng/L, there was no difference in the risk of death within 365 days between those who were admitted to hospital or those who were discharged home (HR 0.73, 95% CI 0.48-1.12).

TABLE 6. Characteristics of patients in the study population of Study I.

		hs-cTnT (ng/L)		
	All patients	<5	5-14	>14
Number of patients, (%)	14,636	8,907 (61)	3,150 (22)	2,579 (18)
Age, years	55 (19)	47 (15)	63 (16)	71 (15)
Female sex, (%)	48	53	41	37
eGFR 15–30 mL/min/1.73 m^2, (%)	2,1	0,03	0,74	11
Diabetes mellitus, (%)	9,5	4,7	14	21
Prior MI, (%)	8,5	4	14	39
Prior hospitalization for CHF, (%)	5,7	1,4	8,2	22

Age and GFR are given as means with standard deviations. Abbreviations: high-sensitivity cardiac troponin T (Hs-cTnT); estimated glomerular filtration rate (eGFR); myocardial infarction (MI); congestive heart failure (CHF).

TABLE 7. Absolute risk of MI or death in association with hs-cTnT levels.

	hs-cTnT (ng/L)		
	<5	**5-14**	**>14**
Myocardial infarction			
30 days Number 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)
NPV	99,8 (99,7-99,9)	96,9 (96,3-97,5)	73,8 (72,1-75,5)
Death			
30 days Number of events	2	13	66
Absolute risk	0,023 (-0,0087-0,054)	0,41 (0,19-0,64)	2,56 (1,95-3,17)
NPV	100 (99,9-100)	99,6 (99,4-99,8)	97,4 (96,8-98,1)
365 days Number 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)
NPV	99,6 (99,4-99,7)	96,6 (95,9-97,2)	86,7 (85,4-88,0)

Absolute risks and negative predictive values are given as percentages with 95% confidence intervals in brackets. Abbreviations: negative predictive value (NPV); high-sensitivity cardiac troponin T (hs-cTnT).

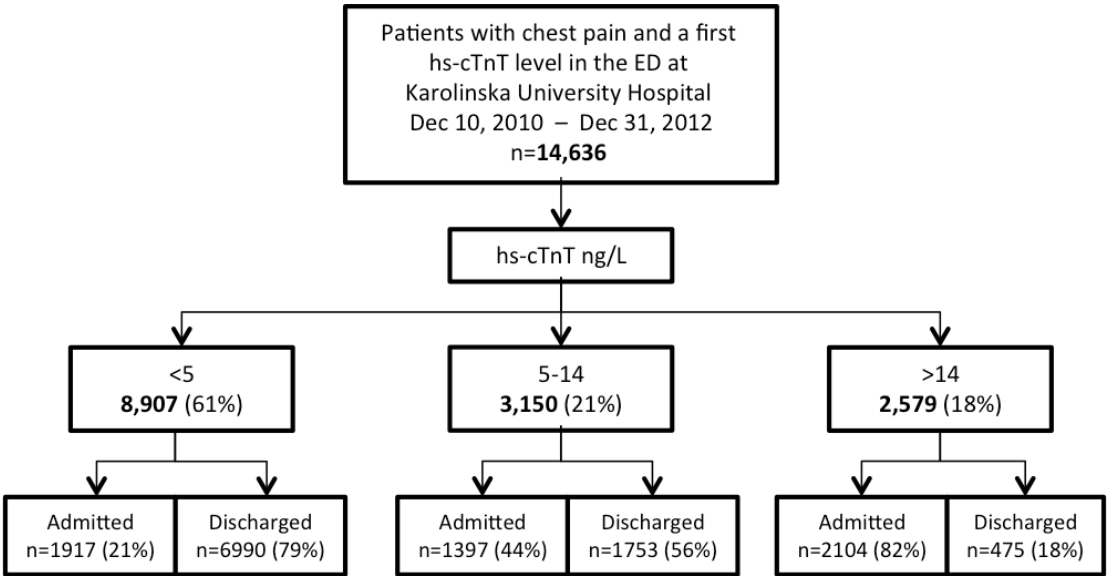


FIGURE 8. The study population of Study I. Abbreviations: emergency department (ED), high-sensitivity cardiac troponin T (hs-cTnT).

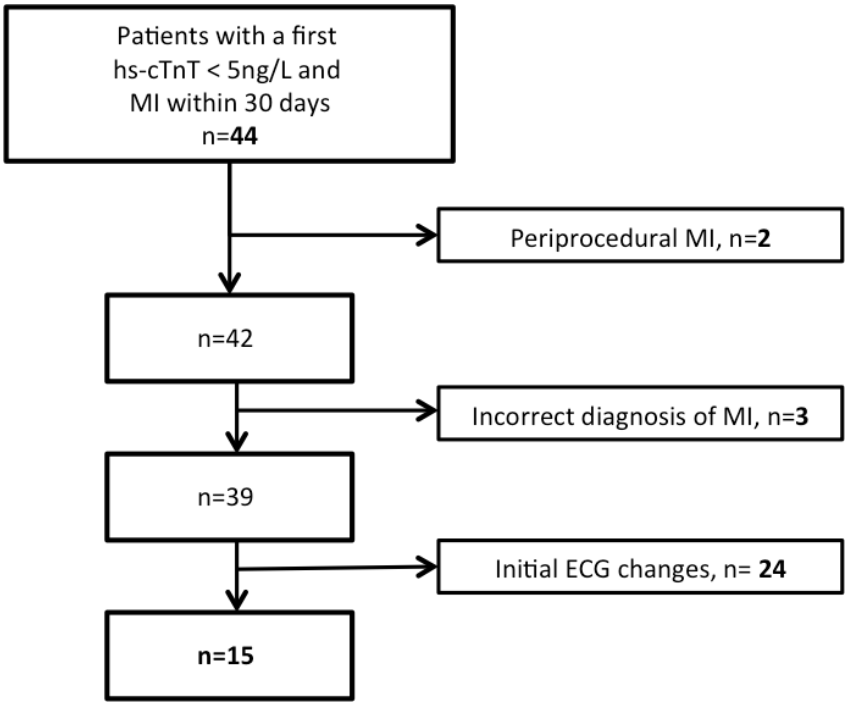


FIGURE 9. Patients with a first undetectable hs-cTnT and MI within 30 days. Abbreviations: high-sensitivity cardiac troponin T (hs-cTnT); myocardial infarction (MI).

Discussion

This study showed that a first single undetectable hs-cTnT level in combination with a non-ischaemic ECG can be used to safely rule out MI in the ED.

The major strength of the study was the large unselected study population comprising patients with chest pain which is representative of many EDs globally in similar health care settings.

A main limitation of the study is that we had no clinical information on signs and symptoms upon arrival to the ED. Additionally, we had no information on whether any risk scoring system had been used during the evaluation of the patient. Another limitation is that we were unable to perform a sex- or age-stratified analysis because of the small number of patients (n = 15) with MI and no ECG-changes. These patients´ ages ranged from 39 to 72 years and only 4 of the 15 patients were women.

STUDY II

Results

Patient characteristics

Among 13,046 included patients, 34% were admitted to hospital. In total, 22% (n = 1,825) of all patients with a first hs-cTnT level of <5 ng/L were admitted. Among patients with undetectable hs-cTnT levels, those who were admitted were older, predominantly men, and more likely to have diabetes, MI or prior revascularisation compared with those who were discharged (TABLE 8).

Primary outcome measure

A total of 59% of all patients revisited the ED at least once during a mean follow-up of 516 days. The likelihood of a revisit in patients with a hs-cTnT level of <5 ng/L increased by 12% during follow-up (adjusted HR 1.12, 95% CI 1.04–1.20) for those who were admitted to the hospital compared with those who were discharged from the ED. Patients with hs-cTnT levels of >14 ng/L showed a trend toward fewer revisits by 11% if admitted (adjusted HR 0.89, 95% CI 0.79–1.00), as shown in TABLE 9. The unadjusted risk of revisits was increased in patients with a hs-cTnT level of ≤14 ng/L and decreased in those with a hs-cTnT level of >14 ng/L throughout the follow-up period (FIGURE 10).

Secondary outcome measures

A total of 13% of patients revisited the ED within 30 days. Patients with a hs-cTnT level of <5 ng/L who were admitted had a 24% higher risk of revisits (adjusted HR 1.24, 95% CI 1.05–1.46) compared with patients who were discharged at the first ED visit (TABLE 10). The likelihood of a revisit leading to a hospital stay was almost doubled (HR 1.84, 95% CI 1.59–2.12) in patients with a hs-cTnT level of <5 ng/L who were admitted versus discharged at the first visit (TABLE 11). The likelihood of undergoing coronary angiography or revascularization was more than three-fold higher in patients with a hs-cTnT level of <5 ng/L who were admitted to hospital than discharged from the ED (HR 3.39, 95% CI 2.52–4.56 and HR 3.34, 95% CI 2.11-5.29 respectively) (TABLE 12).

TABLE 8. Characteristics of patients in the study population of Study II.

	hs-cTnT (ng/L)					
	< 5		5-14		> 14	
	Discharged	Admitted	Discharged	Admitted	Discharged	Admitted
Number of patients	6,360	1,825	1,691	1,288	467	1,415
Age (SD), years	47 (14)	56 (13)	62 (16)	68 (13)	73 (15)	73 (15)
Female sex, n (%)	54	51	42	41	43	40
Diabetes mellitus (%)	4,0	8,3	12	16	20	24
Prior MI (%)	2,4	9,0	9.0	17	19	23
Prior revascularisation	2,8	10	10	19	21	19

Abbreviations: high-sensitivity cardiac troponin T (hs-cTnT); standard deviation (SD); myocardial infarction (MI).

TABLE 9. Revisits to the ED associated with admission to hospital compared with discharge home and hs-cTnT level.

	hs-cTnT (ng/L)					
	< 5		5-14		>14	
	Discharged	Admitted	Discharged	Admitted	Discharged	Admitted
Revisit to the ED						
No cases/no patients	3,259/6,360	1,089/1,825	984/1,691	848/1,288	386/467	1,128/1,415
HR, adjusted *full model	Referent	**1.12** (1.04–1.20)	Referent	1.09 (0.99–1.20)	Referent	**0.89** (0.79–1.00)

Abbreviations: hazard ratio (HR); number (No); high-sensitivity cardiac troponin T (hs-cTnT).
*Multivariable adjustment in the full model was made for age, sex, diabetes, chronic obstructive pulmonary disease, prior myocardial infarction, heart failure, or stroke, and estimated glomerular filtration rate.

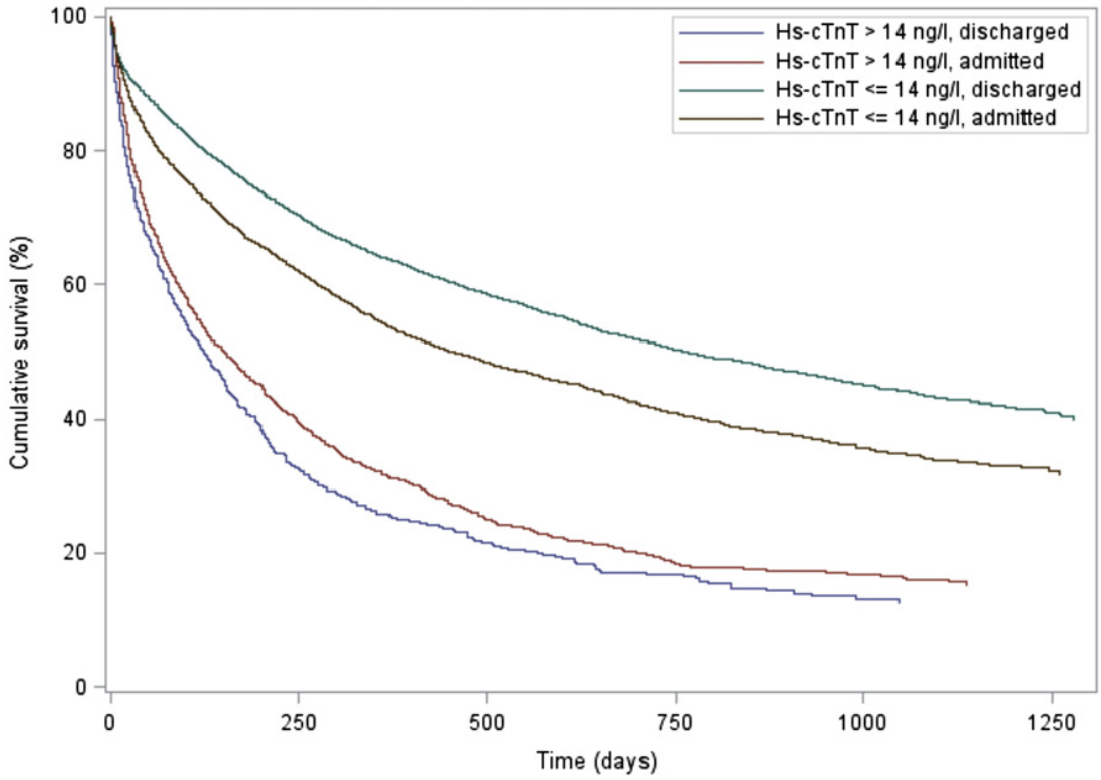


FIGURE 10. Survival free of revisit to the emergency department in patients who were admitted to hospital or discharged home at the index visit, stratified for the first hs-cTnT level analysed. Abbreviations: high-sensitivity cardiac troponin T (hs-cTnT).

TABLE 10. Revisit to the ED associated with admission compared with discharge home in relation to hs-cTnT level.

	hs-cTnT (ng/L)					
	< 5		**5–14**		**>14**	
	Discharged	Admitted	Discharged	Admitted	Discharged	Admitted
30 days						
Revisits (%)	566 (8.9%)	221 (12%)	211 (12%)	198 (15%)	122 (26%)	313 (22%)
HR, 95% CI	Referent	**1.24** (1.05-1.46)	Referent	1.21 (1.00-1.48)	Referent	0.86 (0.70-1.06)

Abbreviations: high-sensitivity cardiac troponin T (hs-cTnT); hazard ratio (HR); confidence interval (CI). Hazard ratios were adjusted for age, sex, diabetes, chronic obstructive pulmonary disease, prior myocardial infarction, revascularisation, heart failure, or stroke, and estimated glomerular filtration rate.

TABLE 11. Revisit to the ED leading to admission, and >1 revisit to the ED associated with admission to hospital compared with discharge home in relation to hs-cTnT level.

	hs-cTnT (ng/L)					
	< 5		5-14		>14	
	Discharged	Admitted	Discharged	Admitted	Discharged	Admitted
Revisit to the ED leading to admission						
No cases/no patients	500/6,306	327/1,802	289/1,680	394/1,277	177/463	643/1,396
HR, adjusted *full model	Referent	**1.84** (1.59-2.12)	Referent	1.54 (1.32-1.79)	Referent	1.12 (0.94-1.32)
More than 1 revisit to the ED						
No cases/no patients	1,876/6,306	723/1,802	653/1,680	587/1,277	308/463	859/1,396
HR, adjusted *full model	Referent	1.22 (1.12–1.33)	Referent	1.09 (0.97–1.22)	Referent	0.88 (0.78–1.00)

Abbreviations: high-sensitivity cardiac troponin T (hs-cTnT); number (No); emergency department (ED); hazard ratio (HR); confidence interval (CI); *Multivariable adjustment in the full model was made for age, sex, diabetes, chronic obstructive pulmonary disease, prior myocardial infarction, revascularisation, heart failure, or stroke, and estimated glomerular filtration rate. Absolute risks, hazard ratios and incidence rates are given with 95% confidence intervals in brackets.

TABLE 12. Likelihood of undergoing coronary angiography or revascularization if admitted to hospital compared with discharged home in relation to hs-cTnT level.

	hs-cTnT (ng/L)					
	<5		5–14		>14	
	Discharged	Admitted	Discharged	Admitted	Discharged	Admitted
Coronary angiography						
No cases/no patients	85/6,306	98/1,802	70/1,680	90/1,277	33/463	106/1,396
HR, adjusted *full model	Referent	**3.39** (2.52–4.56)	Referent	1.41 (1.03–1.94)	Referent	1.04 (0.70–1.54)
Revascularization						
No cases/no patients	34/6,306	42/1,802	35/1,680	50/1,277	20/463	56/1,396
HR, adjusted *full model	Referent	**3.34** (2.11-5.29)	Referent	1.54 (1.00–2.38)	Referent	0.90 (0.54–1.50)

Abbreviations: high-sensitivity cardiac troponin T (hs-cTnT); number (No); hazard ratio (HR); confidence interval (CI); *Multivariable adjustment in the full model was made for age, sex, diabetes, chronic obstructive pulmonary disease, prior myocardial infarction, heart failure, or stroke, and estimated glomerular filtration rate. Hazard ratios are given with 95% confidence intervals in brackets

Discussion

Patients with low-risk chest pain, who were admitted to the hospital instead of discharged home, revisited the ED more often than if they were discharged. They also underwent coronary angiography and revascularization to a greater extent than did discharged patients.

After being discharged directly from the ED, patients may have visited other hospitals in the Stockholm area or elsewhere in the country. However, this information was not known to us and was the main limitation of the study. Another limitation was the lack of information on the patients´medical history, lifestyle factors, and clinical signs suggestive of MI (e.g., diaphoresis, vomiting, or radiating chest pain), which possibly influenced the likelihood of admission to the hospital. Even so, it seems less likely that the clinical presentation at the first visit influenced their likelihood of a revisit to the ED after discharge. It is thus unlikely that this lack of information would have confounded the results. Unknown residual confounding that we could not adjust for might have been present. However, we do not believe that these potential unknown comorbidities led to an increased likelihood of clinical investigations. Additionally, we had no information on whether non-invasive tests such as exercise ECG or stress echocardiography was performed before coronary angiography and whether it may have influenced the increased likelihood of invasive testing. Finally, the study lacked information on the patient´s coronary angiography and revascularization findings, which may have contributed to a more complete understanding of the study results.

STUDY III

Results

Patient characteristics

The clinical characteristics of the study population were stable over time, but the proportion of patients with a hs-cTnT level of <5 ng/L changed significantly from 62% in 2011 to 42% in 2014 (TABLE 13).

Primary outcome measure

A relative 36% decrease in admissions for chest pain was observed during the first 4 years of using the hs-cTnT assay (FIGURE 11). The total hospital admission rate, irrespective of complaint, was stable, and admissions for abdominal pain and dyspnoea, remained virtually unchanged (FIGURE 11). The largest relative increase in discharges was found in patients with a hs-cTnT level of >14 ng/L, (15% to 32%) (FIGURE 12).

Secondary outcome measures

Within 1 year of the ED visit, the absolute risk of death increased from 2.8% to 3.9%. The risk of all-cause mortality significantly increased, from 26% (adjusted HR 1.26, 95% CI 1.00-1.58) to 51% (adjusted HR 1.51, 95% CI 1.18-1.92) but for non-cardiovascular deaths only, the risk increased from 34% (adjusted HR 1.34, 95% CI 1.00-1.80) to 85% (adjusted HR 1.85, 95% CI 1.34-2.55) (TABLE 14). There was a significant 6.8% to 9.6% increase in coronary angiography performed within 1 year of the visit for chest pain (TABLE 15), and this was most prominent in patients with a hs-cTnT level of 5-14 ng/L (8.2% to 11%) and >14 ng/L (15% to 20%). In patients with undetectable hs-cTnT levels, the number of coronary angiographies decreased from 4.2% to 2.8%. Parallel to this finding was a slight overall increase in revascularizations (4.6% to 5.2%), which was most prominent in patients with a hs-cTnT level of 5-14 ng/L (TABLE 15).

TABLE 13. Characteristics of patients in the study population of Study III.

	2011	2012	2013	2014‡
Number of patients	4,120	4,199	3,937	3,216
Number of visits	4,921	4986	4,623	3,707
Age, years, mean (SD)	59 (17)	58 (17)	58 (17)	58 (17)
Men, %	2,597 (53)	2,581 (52)	2,496 (54)	1,962 (53)
eGFR <60 ml/min</1.73 m^2, %	4,240 (86)	4,254 (85)	3,985 (86)	3,196 (86)
*Prior MI, %	762 (16)	731 (15)	731 (16)	548 (15)
*Prior heart failure, %	471 (10)	481 (10)	443 (10)	310 (8)
*Diabetes, %	637 (9)	617 (12)	593 (13)	519 (14)
Hs-cTnT < 5 ng/l, %	3,069 (62)	2,295 (46)	1,761 (38)	1,571 (42)
Hs-cTnT 5–14 ng/l, %	913 (19)	1,635 (33)	1,760 (38)	1,277 (34)
Hs-cTnT > 14 ng/l, %	939 (19)	1,056 (21)	1,102 (24)	859 (23)
†MI during hospital stay, %	281 (6)	235 (5)	244 (5)	-

Abbreviations: standard deviation (SD); estimated glomerular filtration rate (eGFR); high-sensitivity cardiac troponin T (hs-cTnT); myocardial infarction (MI). *Data available until 2013, †Data not available for 2014. ‡Data available until 20 October 2014.

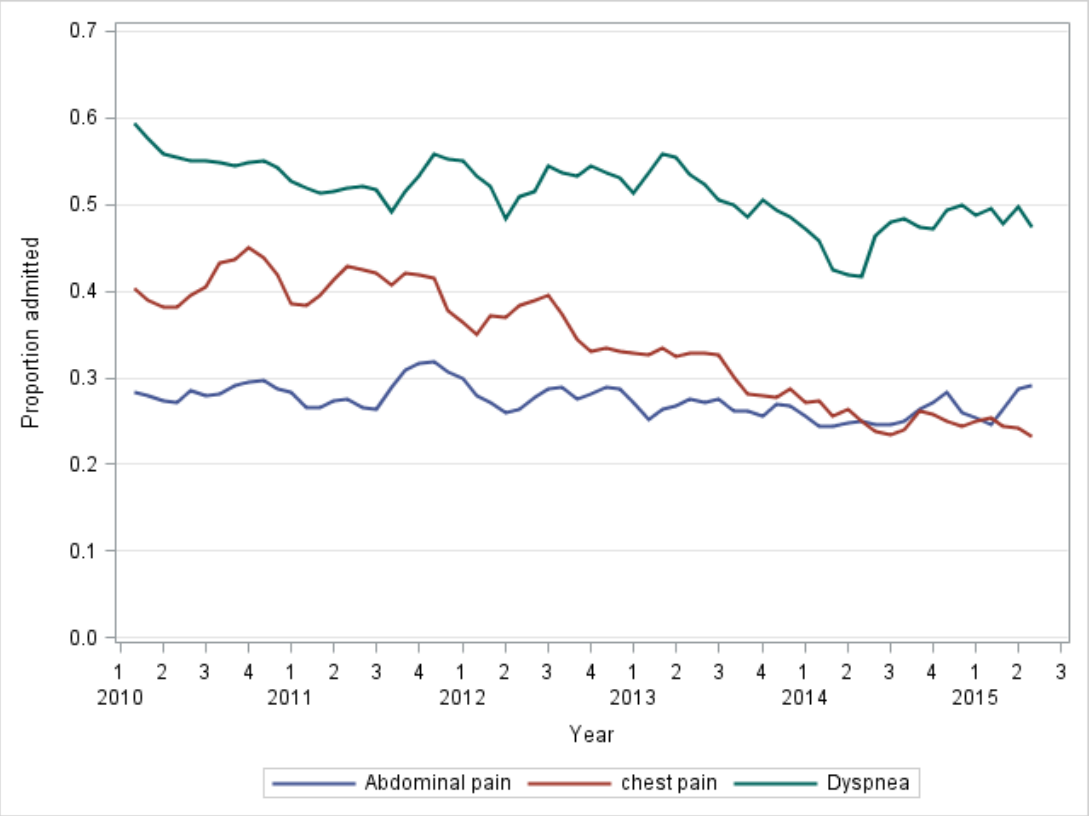


FIGURE 11. Admission rates for abdominal pain, chest pain, and dyspnoea from 2011 to 2014.

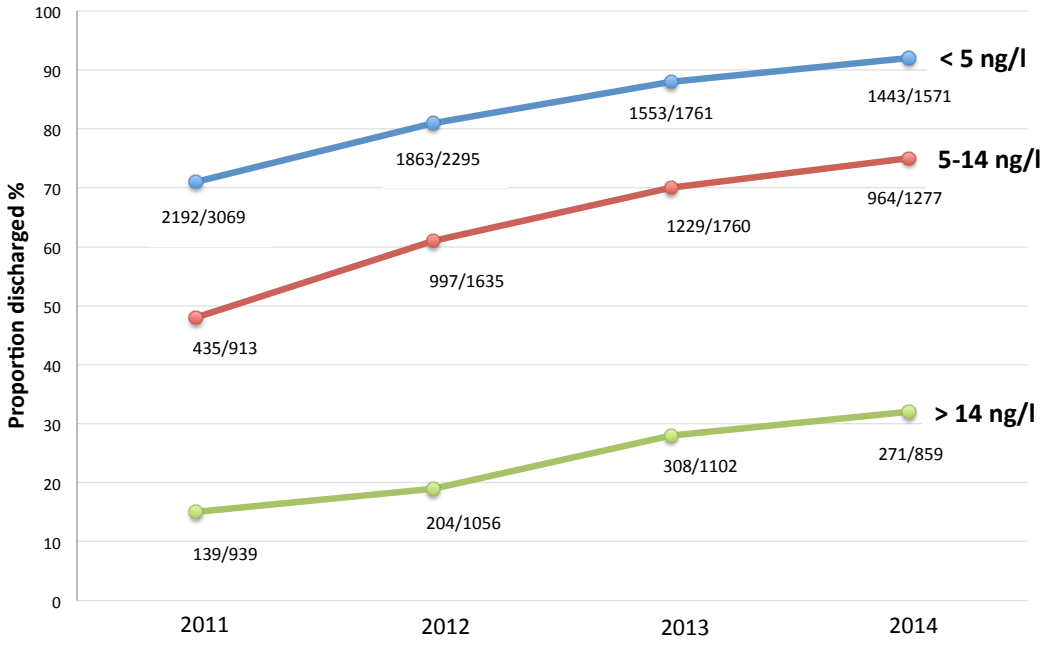


FIGURE 12. Proportion of discharged patients with chest pain from 2011 to 2014 in association with high-sensitivity cardiac troponin T- levels.

TABLE 14. HRs for mortality within 1 year of the visit to the ED for all patients with chest pain.

	2011	**2012**	**2013**	**2014***
All patients	4921	4986	4623	3707
All-cause mortality				
Deaths, n (%)	140 (2.8)	165 (3.3)	138 (3.0)	143 (3.9)
HR, 95% CI, crude	Referent	1.14 (0.91-1.44)	1.00 (0.79-1.27)	1.29 (1.01-1.64)
HR, 95% CI, adjusted	Referent	**1.26** (1.00-1.58)	1.17 (0.92-1.49)	**1.51** (1.18-1.92)
Cardiovascular mortality				
Deaths, n (%)	57 (1.2)	64 (1.3)	62 (1.3)	34 (0.92)
HR, 95% CI, crude	Referent	1.01 (0.78-1.60)	0.99 (0.68-1.14)	0.94 (0.61-1.45)
HR, 95% CI, adjusted	Referent	1.12 (0.78-1.60)	1.15 (0.80-1.68)	1.09 (0.70.1.69)
Non-cardiovascular mortality				
Deaths, n (%)	83 (1.7)	101 (2.0)	76 (1.6)	73 (2.0)
HR, 95% CI, crude	Referent	1.23 (0.99-1.63)	0.99 (0.72-1.36)	1.63 (1.18-2.25)
HR, 95% CI, adjusted	Referent	**1.34** (1.00-1.80)	1.13 (0.83-1.55)	**1.85** (1.34-2.55)

Abbreviations: hazard ratio (HR); confidence interval (CI); myocardial infarction (MI). Hazard ratios were adjusted for age, sex, eGFR, prior stroke, MI, COPD, heart failure and diabetes. *Last patient was included October 20, 2014, and information for MI, heart failure, and revascularization was not available for 2014.

TABLE 15. Trends for coronary angiography and revascularization within 1 year of the ED visit.

	2011	2012	2013
Coronary angiography			
All patients, %	6.8%	9.0%	9.6%
<5 ng/L	4.2%	3.8%	2.8%
5-14 ng/L	8.2%	12%	11%
>14 ng/L	15%	17%	20%
PCI or CABG			
All patients, %	4.6%	5.5%	5.2%
<5 ng/L	2.1%	2.2%	1.4%
5-14 ng/L	5.6%	7.0%	6.7%
>14 ng/L	13%	11%	9.2%

Abbreviations: coronary artery bypass grafting (CABG); emergency department (ED); percutaneous coronary intervention (PCI).

Discussion

The results of this study showed a 36% relative decrease in admission rates during the first 4 years of hs-cTnT use in clinical practice in the ED. The greatest decrease in admissions was found in patients with a hs-cTnT level of >14 ng/L, who are often older and have more comorbidities than patients with lower hs-cTnT levels. The increased mortality in parallel with the reduced admission rate for patients with a hs-cTnT level of >14 ng/L is of great concern and needs more attention. The aim of the study was to evaluate trends in admissions and not to report prognosis, hence mortality rates must be interpreted with caution. HRs varied during the study period and sometimes independently of the decreasing number of admissions.

The proportion of patients with a hs-cTnT level of <5 ng/L was 62% in 2011 and decreased to 42% in 2014. This is explained by the increased sensitivity of the hs-cTnT assay after the change of faulty batches of reagents, which were replaced in April 2012 [82,83]. Another limitation of the study is that other unknown external factors may have influenced the decreased admission rate of patients with chest pain. Equally, we had no information from other hospitals that may have allowed for comparison with our results.

STUDY IV

Results

Patient characteristics

During the 5-year study period, 31,904 patients with chest pain visited the ED. Their clinical characteristics were nearly unchanged, as shown in TABLE 16. The proportion of patients with a troponin level above the 99th percentile was 6,8% in 2009 and 6,5% in 2010 and increased after the introduction of the hs-cTnT assay to 20%, 21%, and 23% in 2011, 2012, and 2013 respectively. The incidence of MI decreased slightly despite the increased sensitivity of the troponin assay (TABLE 16).

Primary outcome measure

The risk of all-cause mortality increased by 15% in patients analysed with hs-cTnT (adjusted HR 1.15, 95% CI 1.02–1.29) compared with those who underwent testing with cTnT (TABLE 17); however cardiovascular mortality was stable (HR 1.13, 95% CI 0.93–1.39). The likelihood of undergoing coronary angiography and revascularization during the hs-cTnT testing period was increased by 13% (adjusted HR 1.13, 95% CI 1.00–1.28) and 18% (adjusted HR 1.18, 95% CI 1.01-1.37), respectively (TABLE 17).

The reasons for undergoing revascularization during the two time periods changed as shown in TABLE 18. Initially, 31% of patients underwent revascularization for MI and 32% for unstable angina. During the later period, when hs-cTnT was in use, 49% of patients underwent revascularization for MI and 17% for unstable angina (TABLE 18).
Among patients with chest pain who were admitted to the hospital, but were not diagnosed with MI, the all-cause mortality rate was increased by 22% (adjusted HR 1.22, 95% CI 1.05–1.42) (TABLE 19).

When analyses were restricted to patients tested with batches of reagents that were not affected by the calibration issue from 25 April 2012 to 31 December 2013, the results showed that these patients had a 22% increased risk of all-cause mortality (adjusted HR 1.22, 95% CI 1.06-1.39) and a 31% increased risk of cardiovascular mortality (adjusted HR 1.31, 95% CI 1.04-1.66). The associations between being tested with hs-cTnT from 8 December 2010 to 24 April 2012 and the risks of all-cause and cardiovascular mortality were not statistically significant (TABLE 20).

TABLE 16. Characteristics of patients in the study population of Study IV.

Year	2009	2010	2011	2012	2013
Number of patients	5029	6159	6963	6929	6824
Number of visits	5765	7149	8202	8131	7967
Admitted, n (%)	3379 (59)	4287 (60)	5259 (64)	4811 (59)	4222 (53)
Age (years)	58.7 (17)	59.0 (17)	58.1 (17)	57.4 (17)	57.3 (17)
Men (%)	3024 (52)	3815 (53)	4411 (54)	4253 (52)	4267 (54)
eGFR >60 ml/min/1.73 m^2, %	4714 (82)	6007 (85)	6961 (85)	6852 (85)	6785 (86)
Prior MI*, %	773 (13)	1063 (15)	1160 (14)	1102 (14)	1147 (14)
Prior heart failure, %	572 (9.9)	675 (9.4)	773 (9.4)	714 (8.8)	707 (8.9)
cTnT > 0.03 µg/L, %	393 (6.8)	463 (6.5)	N/A	N/A	N/A
Hs-cTnT > 14 ng/L, %	N/A	N/A	1676 (20)	1712 (21)	1808 (23)
Prior revascularization, %	774 (13)	1067 (15)	1138 (14)	1141 (14)	1124 (14)
MI during hospital stay**	302 (5.2)	364 (5.1)	424 (5.2)	362 (4.4)	372 (4.7)

Abbreviations: estimated glomerular filtration rate (eGFR); myocardial infarction (MI); cardiac troponin T (cTnT); high-sensitivity cardiac troponin T (hs-cTnT). *Includes only MI as a primary diagnosis.
** Includes MI as discharge diagnoses in any position (primary, secondary etc).

TABLE 17. HRs for all-cause mortality, cardiovascular mortality, coronary angiography and revascularization during 1 year after the visit to the ED for all patients with chest pain from 2009 to 2013.

	Biomarker assay	
	cTnT	**hs-cTnT**
Total, n	12,485	24,729
All-cause mortality*		
No. of events	457	828
HR (adjusted full model)	Referent	**1.15 (**1.02-1.29)
CV mortality**		
No. of events	164	270
HR (adjusted full model)	Referent	1.13 (0.93-1.39)
Coronary angiography		
No. of events	412	731
HR (adjusted full model)	Referent	1.13 (1.00-1.28)
Revascularization		
No. of events	269	484
HR (adjusted full model)	Referent	1.18 (1.01-1.37)

Adjusted full model: age, sex, comorbidities (defined as prior MI, stroke, heart failure, chronic obstructive pulmonary disease, estimated glomerular filtration rate (eGFR) , diabetes, prior revascularization, and ongoing medication with aspirin, statins, betablockers, or angiotensin converting enzyme inhibitor/angiotensin receptor (ACE/ARB).
Abbreviations: myocardial infarction (MI); cardiac troponin T (cTnT); high-sensitivity cardiac troponin T (hs-cTnT); hazard ratio (HR).
* Follow-up for all-cause mortality ends 14-12-31.
**Follow-up for cardiovascular mortality ends December 31, 2013.

TABLE 18. Discharge diagnoses for patients undergoing revascularization within 1 year after the visit to the ED because of chest pain from 2009 to 2013.

	Biomarker assay	
Diagnoses	**cTnT**	**hs-cTnT**
Total, n	269	484
MI, n (%)	83 (31)	239 (49)
Unstable angina, n (%)	85 (32)	83 (17)
Angina, n (%)	81 (30)	111 (23)
Other, n (%)	20 (7)	51 (11)

Abbreviations: myocardial infarction (MI); cardiac troponin T (cTnT); high-sensitivity cardiac troponin T (hs-cTnT).

TABLE 19. HRs for all-cause mortality for patients with chest pain from 2009 to 2013.

	Biomarker assay	
	cTnT	**hs-cTnT**
Total, n	12,367	24,568
Discharged		
No. of visits, N	7,152	15,469
Proportion discharged, N/n (%)	58	63
No. of events (%)	121 (1.69)	217 (1.40)
HR (adjusted full model)	Referent	1.03 (0.83-1.30)
Admitted, non-MI		
No. of visits	4,573	7,947
No. of events (%)	261 (5.71)	513 (6.46)
HR (adjusted full model)	Referent	**1.22** (1.05-1.42)
Admitted, MI		
No. visits	642	1,152
No. of events (%)	75 (11.7)	98 (8.51)
HR (adjusted full model)	Referent	0.96 (0.71-1.31)

Adjusted full model: age, sex, comorbidities defined as prior MI, stroke, heart failure, COPD, eGFR, diabetes, prior revascularization, and ongoing medication with aspirin, statins, betablockers, or ACE/ARB.
Abbreviations: myocardial infarction (MI); chronic obstructive pulmonary disease (COPD); estimated glomerular filtration rate (eGFR); cardiac troponin T (cTnT); high-sensitivity cardiac troponin T (hs-cTnT); hazard ratio (HR); angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACE/ARB).

TABLE 20. HRs for all-cause mortality, cardiovascular mortality, coronary angiography and revascularization during 1 year after the visit to the ED for all patients with chest pain from 2009 to 2013.

	Biomarker assay		
	cTnT 1 Jan 2009 - 7 Dec 2010	**hs-cTnT** 8 Dec 2010 - 24 April 2012	**hs-cTnT** 25 April 2012 - 31 Dec 2013
Total, n	12,485	11,222	13,507
All-cause mortality*			
HR, 95% CI, Adjusted full model	Referent	1.09 (0.95-1.25)	**1.22** (1.06-1.39)
CV mortality**			
HR, 95% CI, Adjusted full model	Referent	1.00 (0.79-1.26)	**1.31** (1.04-1.66)
Coronary angiography			
HR, 95% CI, Adjusted full model	Referent	1.14 (0.99-1.31)	1.13 (0.98-1.31)
Revascularization			
HR, 95% CI, Adjusted full model	Referent	1.17 (0.98-1.39)	1.19 (1.00-1.43)

Adjusted full model: age, sex, comorbidities defined as prior MI, stroke, heart failure, COPD, eGFR (continuous variable), diabetes, prior revascularization and ongoing medication with aspirin, statins, betablockers, or ACE/ARB. Abbreviations: myocardial infarction (MI), cardiovascular (CV), cardiac troponin T (cTnT), high-sensitivity cardiac troponin T (hs-cTnT), hazard ratio (HR), Revascularization means percutaneous coronary intervention or coronary artery bypass grafting. * Follow-up for all-cause mortality ends 14-12-31. **Follow-up for cardiovascular mortality ends 13-12-31, or on the last date when the cause-of-death register is updated.

Discussion

The transition from conventional cTnT to hs-cTnT was associated with increased mortality and more frequent coronary angiography and revascularization.

After the change of faulty batches in 2012, which led to an increased sensitivity of the hs-cTnT assay, we noted a decrease in the proportion of patients with a hs-cTnT level of <5 ng/L and a parallel increase in the proportion of patients with a hs-cTnT level of 5-14 ng/L. The proportion of patients with a hs-cTnT >14 ng/L was virtually unchanged; this has also been reported in previous studies [83,91].

Several factors were unknown to us and must count as limitations of the study. As discussed previously, an elevated hs-cTnT level may originate from conditions other than MI, causing the patient to be admitted to the hospital. Additionally, whether any advancements ocurred in practice for non-cardiac diagnoses that may have affected the long-term mortality of the admitted patients remains unknown. Finally, we had no information regarding the decision on whether to admit or discharge a patient, such as clinical symptoms.

DISCUSSION

METHODOLOGICAL CONSIDERATIONS

Internal validity

Internal validity refers to the extent to which a test measures what we think it is measuring. Epidemiologic studies are subject to several errors, mainly systematic errors and random errors, that decrease the accuracy of the study results.

Study design

Because it is impossible to study complete collections of anything, one must define a sample from which to draw conclusions. A study begins by defining a background population and choosing an epidemiological study design, usually an interventional (such as randomized controlled trial) or observational design. Observational studies can be further divided into longitudinal and cross-sectional studies, which in turn comprise case-control, cohort, and ecological studies. The present thesis contains cohort studies.

In a cohort study, outcomes between an exposed population and non-exposed population are compared. If the study is retrospective and based on thorough registries, an immediate evaluation of outcomes of diseases or deaths can be performed. However, more details concerning patients signs and symptoms can be difficult to track because of the retrospective nature of the study. Numerous registries with high validity in Sweden facilitate retrospective cohort studies.

Systematic error

Systematic errors, or bias, arise due to short-comings in the study design and occur when measures divert from the true value in a systematic way. Observational studies are not randomized with even allocation of subjects to each group. Therefore, it is fundamental to consider other explanations that may affect the results, such as systematic errors. A systematic error is not dependent on the size of the study population; thus it is not possible to increase the number of subjects to avoid systematic errors. Different types of bias affect the internal validity of a study. A

study with complete absence of systematic errors is considered to have high validity. Three types of systematic errors are mainly discussed: selection bias, information bias, and confounding bias (or simply confounding) [92].

Selection bias arises when there is a difference between the participants chosen for the study and the background population that the study population is thought to represent. This type of bias is common in case-control studies, when the probability of being selected as a case or control is associated with the exposure status. In retrospective cohort studies, selection bias can arise if the study population is not well defined or the material from which the cohort was retrospectively defined was incomplete or excluded individuals before the beginning of follow-up, possibly because of death or emigration [92].

In Studies I to IV, the broad inclusion of unselected patients visiting the ED reduced the risk of selection bias with respect to which patients were included in the study. In prospective studies, patients in the ED have commonly been selected to participate in the study and have thus been found to have a higher risk of MI than unselected real-world patients. This leads to a non-representative population sample of patients with chest pain. For example, in previously reported prospective studies, the incidence of prior MI was reportedly 25%; in contrast it was 14% in our retrospectively collected cohort [93]. Likewise, the reported rate of prior revascularization is approximately 30% while it was 14% in our cohort [93]. If any differences were present between the retrospectively enrolled patients in our studies, these differences were randomly included in both the exposed and non-exposed patient groups.
A risk of selection bias may have been present in Studies III and IV, because older patients with more comorbidities are more likely to be admitted to the hospital for observation than fairly healthy patients, who are discharged to a greater extent. However, to control for this, we adjusted for differences in characteristics between admitted and discharged patients.

Information bias occurs when information gathered from or about the study participant is incorrect. Studies I to IV relied upon diagnoses previously evaluated to have high validity in national registries. The diagnosis of MI was reportedly correct

in 98% to 100% of cases [84].

One example of information bias is misclassification, which occurs when study participants are assigned to the wrong category. In Studies I to IV, the troponin analysis for each patient was performed in the laboratory, which was blinded to the patient´s status.

The outcome mortality is difficult to misclassify because it is an irreversible state and virtually no information concerning death is missing. Although the national registries are of high quality, there may have been some patients suffering misclassified MIs, leading to bias in our results.

During Study III, the rate of autopsies was very low. Therefore, subgrouping mortality into cardiovascular and non-cardiovascular causes may have been associated with misclassification. Misclassification may also have occurred because all studies evaluate time periods associated with the low-end shift of hs-cTnT. One study revealed that about 8% of patients visiting for chest pain were at risk of misdiagnosis [83].

Information bias can also be introduced when patients with missing values are excluded from a study. In Study II, 122 patients had missing information on eGFR and were excluded from the Cox proportional regression models.

Confounding bias is another type of systematic error. A confounder is a factor that is associated with both the exposure and the outcome. Three conditions must be fulfilled for confounding to arise: 1) it is associated with the exposure, 2) it is an independent risk factor for the disease, and 3) it is not part of the causal link from exposure to outcome (FIGURE 13).

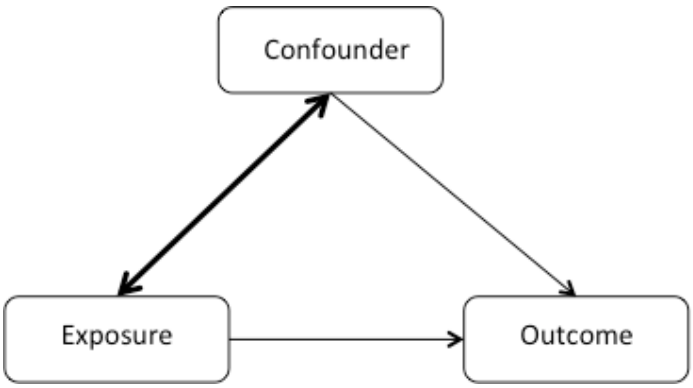


FIGURE 13. A confounder is associated with the exposure and the outcome, but is not part of the causal link.

As an example, age can be regarded as a confounder in determining the association between physical activity and MI. The distribution of age may differ among subjects in the physical activity group. Younger subjects tend to be more physically active and have a lower risk of MI. Age is thus associated with both physical activity and MI but it is not causally linked to the development of MI. Adjusting for age would allow for a fair estimation of the effect between physical activity and MI (FIGURE 14).

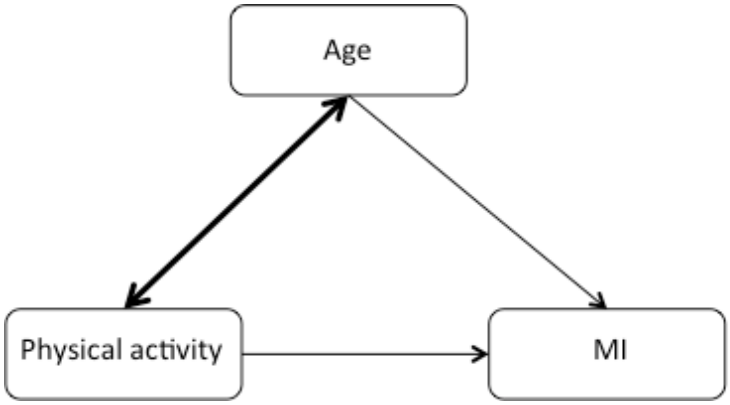


FIGURE 14. Age as a confounder for physical activity and myocardial infarction (MI).

Multivariable regression models were used and stratifying analysis were performed to reduce confounding in all studies in this thesis. Adjustments were made for the most important risk factors, such as age, sex, and comorbidities that may have been associated with MI, death, or the investigations performed. Other methods of handling confounding during data selection include restriction, matching and randomization, (which also resolves the problem of unknown confounders).

Confounders may still be present, even after stratification; these are known as residual confounders. All studies in this thesis may have been influenced by residual confounding factors unknown to us.

Random error and precision

Random error is the result of chance and affects the precision of the estimate. Random error is dependent on the sample size; increasing the sample size decreases random error and thereby increases precision. Absolute precision is achieved in the absence of random error. Case-control studies involve a sampling process, whereas cohort studies often do not.

Low precision in an epidemiological study may lead to misclassification of individuals regarding a disease or exposure, which causes a greater uncertainty in the results. It may be more difficult to find true associations; i.e., differences between healthy and sick individuals may be difficult to identify even if such differences exist in reality.

Confidence intervals were used in all studies of this thesis, both presenting a range in which the true value is likely included and describing the precision of our observations. The interval was set at 95%, meaning that there was a 95% likelihood that the true value was included within this interval. The p value can also be used to increase precision; this value indicates the probability that the observed value is based on chance. A 95% CI and p value of <0.05 are commonly used in medical research [92].

External validity

External validity or generalizability is the ability to apply the results of a study to another cohort in other countries or settings other than where the study was conducted. For Studies I, II and IV, which included both sites of Karolinska University Hospital, we believe that the generalizability is high and that the patients were representative of ED patients found in countries with a level of health care similar as that in Sweden. A limitation in Study III was its single-centre setting. There were small differences in characteristics among patients presenting with chest pain to each of the two sites at Karolinska University Hospital, which is why we believe that the characteristics of the Study III site are similar to those of other EDs in Sweden and EDs in other countries with a standard of health care similar to that of Sweden.

INTERPRETATION OF FINDINGS

Study I

Single measurement

The hypothesis of the first study was derived from the clinical experience that patients with chest pain and a hs-cTnT level of <5 ng/L who were admitted never seemed to be diagnosed with MI. We were aware of few publications before conducting this study [5,6,94]. In 2011, one study reported that an undetectable hs-cTnT level seemed to have a high NPV and may be suited to rule out MI more safely and rapidly without serial testing [5]. Shortly thereafter, another study observed that measuring hs-cTnT at presentation and 1 hour later (delta troponin), allowed for both safe rule-in and rule-out for MI [94]. The next year, another study compared 4 troponin assays and concluded that an undetectable hs-cTnT-level provided a high NPV for MI [6]. These previous studies included prospectively recruited patients who were admitted to hospital. In comparison, our study was performed on a large unselected cohort of patients in the ED independent of risk factors, age, sex, pretest probability, duration of symptoms and timing of measurement [5,6]. Several studies have since repeated a similar strategy to test a single measurement approach using hs-cTnT [69,95].

Early measurement of hs-cTnT

In 11 of the 15 patients with MI, who had a first hs-cTnT level of <5 ng/L and a normal ECG, the first hs-cTnT level was measured <2 h after the onset of chest pain. If a second hs-cTnT measurement would have been obtained 3 to 4 h after the onset of symptoms, it would likely have been elevated. When we measured a second hs-cTnT level in admitted patients with an initial concentration of <5 ng/L, an increased hs-cTnT level was found in only 10% of patients. In addition, 100 medical records were randomly screened during the study period to determine the average time to ED arrival after chest pain onset. This time was found to be 2.5 hours, which has also been reported in previous larger studies [96,97].

Mortality

If some of the patients with a first hs-cTnT level of <5 ng/L who were discharged from the ED had instead been admitted to the hospital, they might have had a hs-cTnT level of >14 ng/L and thus been diagnosed with MI. When we estimated the risk of death within 1 year of the ED visit for patients who were admitted compared with those who were discharged, we found no difference in mortality.

Only two cardiovascular deaths occurred among patients with an undetectable hs-cTnT level and a normal ECG during the 1 year of follow-up. This finding shows that an undetectable troponin level indicates a low baseline risk for MI and cardiovascular mortality and can be used as a prognosticator for long-term mortality. This has also been reported previously [74].

Small elevations of hs-cTnT and PCI

After the final exclusion, 5 of the remaining 11 patients had a maximum hs-cTnT level of <30 ng/L. It is important to determine whether patients with a small elevation in their hs-cTnT level would benefit from a diagnosis of MI and the downstream investigations and complications that this diagnosis may imply. MI associated with PCI has a worse prognosis than PCI without MI [98]. Using the older generations of troponin assays, these patients would not have been diagnosed with MI [4].

Clinical implications

Chest pain is the second most common reason that patients seek medical attention in the ED, and is therefore a considerable global health care burden. Using the results of this study, it may be possible to safely discharge a larger proportion of patients with chest pain from the ED. Discharging patients instead of admitting them will preserve patients´ quality of life and save health care resources. The study results were implemented in the ESC 2015 guidelines for diagnostic use of hs-cTnT in the ED [8].

Study II

Admission of patients with a hs-cTnT level of <5 ng/L

The hypothesis for the second study originated in the aftermath of Study I. A question arose regarding whether patients who were discharged home would revisit the ED

more often than if they had been admitted to the hospital for observation. We found that when healthy patients with chest pain and a hs-cTnT level of <5 ng/L were admitted instead of discharged, their risk of revisits to the ED increased, which in turn may have contributed to further ED overcrowding. Our results also showed a concurrent increased risk of hospital admissions in association with the revisit to the ED in these patients.

Investigating patients with a lower risk for disease may have multiple effects. A common conception among clinicians is that patients request admission to hospital for additional testing and investigations and that they will be reassured and less anxious by finally receiving a normal test result [99]. In contrast, recent studies [80,100-102] have revealed increased anxiety and impaired quality of life long-term in patients after investigations despite normal results. Hence, when low-risk individuals are exposed to admission, non-invasive stress testing, or echocardiographies it may lead to anxiety and worry about illness rather than reassurance [80,100,101]. Clinicians may be reassured by a normal test result, but many patients may still remain uncertain if given a negative or inconclusive test result. Although current guidelines recommend non-invasive cardiac imaging to prevent future cardiovascular events, no available evidence indicates that non-invasive stress testing in patients with low-risk chest pain reduces the future risk of MI or cardiovascular death compared with a more conservative approach [8,40,103]. Such investigations may also further increase anxiety in patients and reduce their quality of life.

Resource utilization

Patients who were admitted had a more than three-fold higher risk of undergoing coronary angiography and revascularization than did discharged patients. Prior studies have shown that low-risk patients with chest pain and no MI do not benefit from undergoing coronary angiography or revascularization [104]. There is always a risk of adverse complications during investigations, such as potential MI during PCI or nosocomial infections related to hospital admission. Therefore, unnecessary investigations may harm instead of help patients [40,77]. Performing extensive investigations also has consequences for the ED, because of an increased length of stay, which contributes to overcrowding, causes delays in testing and investigations, and lowers patient satisfaction [75,76]. Additionally, overall resource utilization increases with severe economic and health care consequences [78-80].

Admission of patients with a hs-cTnT level of >14 ng/L

Interestingly, patients with a hs-cTnT level of >14 ng/L who were admitted to hospital, had a reduced risk of revisits and readmissions. These patients were older and more likely to have diabetes or cardiovascular disease. This finding is consistent with previous studies in which elderly patients were reported to benefit from admission to hospital for medical optimization [105].

Clinical implications

Early discharge from the ED instead of admission to hospital seems to be beneficial in patients with chest pain and undetectable hs-cTnT levels. This strategy may avoid potentially harmful unnecessary investigations, reduce overcrowding in the ED, and sustain patients quality of life. Admitting elderly ill patients appears to prevent future revisits to the ED, thus reducing readmissions and preserving health care resources.

Study III

Admissions to hospital

The clinical introduction of high-sensitivity assays, raised concerns among clinicians globally that an increased proportion of patients with elevated troponin concentrations may lead to increased admission rates [106,107]. Our aim was to evaluate admission rates after the introduction of hs-cTnT at our hospital and results showed a 36% decrease in admissions during the first 4 years of hs-cTnT use.

Several recent studies have investigated the impact of the introduction of high-sensitivity assays into the clinical setting [93,108-110]. Only one study evaluated changes in admission rates during the first year after introducing a high-sensitivity assay and the admission rates did not decrease a few months after introduction of the hs-cTnT assay [108].

Several potential reasons could explain a decrease in admission rates for chest pain, such as cut-backs in available hospital beds, new guidelines for the care of patients with chest pain, novel research that may affect the way patients with chest pain are assessed in the ED, or organizational changes in the ED. We were unable to identify

any of these factors as potential explanations for the marked decrease in admissions for chest pain in our study other than the introduction of the hs-cTnT assay itself and the effect it had on the assessment of patients with chest pain in the ED. Additionally, overall hospital admissions and admissions for abdominal pain, the most common reason for visiting the ED, remained virtually unchanged.

Mortality

The primary aim of this study was to report trends in admission rates for chest pain; assessment of prognosis was only a secondary aim. Some studies have reported contradictory results concerning prognosis during hs-cTnT implementation [108,110,111]. In our study, the largest relative increase in discharges was found in patients with a hs-cTnT level of >14 ng/L (from 15% to 32%). In parallel, all-cause mortality was increased by 51% in 2014 compared with 2011, but for non-cardiovascular deaths only. When patients were stratified according to their hs-cTnT level, only patients with a hs-cTnT level of >14 ng/L had significantly increased mortality. Our findings indicate that the observed increased mortality rate may have been related to the strong reduction in admissions among patients with a hs-cTnT level of >14 ng/L. The safety of discharging such a large proportion of patients with a hs-cTnT level of >14 ng/L, indicating a high risk of adverse outcomes, is questionable. We strongly believe that these patients should be admitted and investigated more thoroughly than is commonly done today.

Resource utilization

Conflicting results have also been reported regarding the effects of the clinical introduction of high-sensitivity assays on resource utilization [93,108-110]. These conflicting results may be due to differences in study populations because the cohorts comprised selected high-risk patients with elevated troponin levels. Our results obtained from a cohort of completely unselected patients with chest pain, showed a significant increase in coronary angiography, but only a small increase in revascularization. The marked decrease in hospital stays for chest pain outweighed these findings in terms of resource utilization. Because the increase in coronary angiography was not paralleled by a similar increase in revascularization it is likely that a large proportion of the additional coronary angiography procedures was normal.

Clinical implications

Our results suggest that the introduction of hs-cTnT has led to markedly decreased admission rates for patients with chest pain. It appeared safe to discharge 92% of patients with undetectable hs-cTnT levels where no increase in adverse events was found. In contrast, our results showed a worse prognosis in patients with a hs-cTnT level of >14 ng/L; we strongly believe that these patients should be admitted and more thoroughly investigated than what is done today.

Study IV

Incidence of MI

After observing trends in admission rates in Study III, we aimed to evaluate outcomes and resource utilization since the use of the hs-cTnT assay commenced. Previous reports have shown that the incidence of MI has slightly increased since the introduction of hs-cTnT [93,110]. However, we observed a slight decrease in the incidence of MI during patients hospital stay, possibly because of inherent variation or reluctance among physicians to diagnose patients with MI when exhibiting small increases in troponin levels that would have been undetected by the previous troponin assays.

Mortality

Several studies have reported outcomes when transitioning from conventional troponin assays to high-sensitivity assays in clinical practice and report conflicting results. Some studies [108-110,112] reported unchanged prognoses and one study indicated increased patient survival [111]. Our results showed a 15% increased risk of all-cause mortality in patients tested with hs-cTnT compared with cTnT. However, cardiovascular mortality was unchanged. This finding needs to be interpreted cautiously because of potential residual confounding, which may have changed the association with mortality to non-significant if known. We observed a significant reduction in admissions for chest pain in parallel with the increase in mortality. The patients admitted were older and had more comorbidities; consequently, they probably had a higher risk of death. Despite adjustments for comorbidities, eGFR and ongoing

medication in our statistical models, some confounders that we could not account for may still have been present and might explain the associations found.

Resource utilization

Our results also demonstrated an increased use of coronary angiography and revascularization during the hs-cTnT period, which has been reported in previous studies [109,113] while others observed unchanged practice [93,108,112]. It is important to identify the underlying study population characteristics, as it reflects the need for coronary angiography and revascularization. Patients admitted to cardiac care units undergo coronary angiography more often and have been previously revascularized to a greater extent compared with our unselected patient population in the ED [114].

Clinical implications

This study analysed two large patient cohorts tested with either the conventional cTnT or hs-cTnT assay and revealed slightly increased mortality, coronary angiography and interventions in the cohort tested with hs-cTnT. However, the results of increased mortality must be interpreted cautiously.

CONCLUSIONS

Study I Patients with a hs-cTnT level of <5 ng/L and a normal ECG have a minimal risk of MI or death and may be safely discharged from the ED.

Study II When low-risk patients with chest pain and a hs-cTnT level of <5 ng/L were admitted to the hospital instead of discharged from the ED, we observed increased risk of revisits to the ED, recurrent hospital stays, coronary angiography and revascularization.

Study III There was a 36% reduction in admissions for chest pain during the first 4 years after the implementation of hs-cTnT. All-cause mortality and coronary angiography increased slightly while revascularization remained stable.

Study IV After the introduction of hs-cTnT, there was a slight increase in all-cause mortality, coronary angiography and revascularization.

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