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EARLY DIAGNOSIS AND RISK STRATIFICATION IN PATIENTS WITH SYMPTOMS SUGGESTIVE OF ACUTE CORONARY SYNDROME

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EARLY DIAGNOSIS AND RISK STRATIFICATION IN PATIENTS WITH SYMPTOMS SUGGESTIVE OF ACUTE CORONARY SYNDROME

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background: Chest pain is one of the most common symptoms in patients presenting to the emergency department (ED). Identifying the minority of patients with an acute coronary syndrome (ACS) is a challenge. The introduction of high-sensitivity cardiac troponin (hs-cTn T and I) assays has radically improved the assessment. The aim of this thesis was to evaluate four methods of assessing patients presenting with suspected ACS in the era of hs-cTn.

Methods and results: In Study I, we retrospectively evaluated the value of predischarge exercise ECG testing in 951 chest pain patients in whom myocardial infarction (MI) had been ruled out by means of hs-cTnT. We found no significant differences regarding death or MI between patients with a positive or a negative test, neither at 90 (*n*=1 [1.1%] vs. n=1 [0.2%]), nor at 365 days (*n*=2 [2.1%] vs. n=4 [0.7%]) of follow-up. In total, there were 9 (0.9%) deaths and 10 (1.1%) MIs within 365 days. The one-year rates of death (1.3%) and MI (0.5%) in a matched Swedish population were comparable.

Study II was a retrospective evaluation of the diagnostic sensitivity of an undetectable level of hs-cTnT at presentation, with and without information from the electrocardiogram (ECG), to rule out MI in a non-ST-segment elevation MI (NSTEMI) population presenting early. Twenty-four (2.6%) of the 911 early presenting NSTEMI patients initially had an undetectable level of hs-cTnT. In patients presenting >1–≤2 hours from symptom onset, the sensitivity for MI when combining hs-cTnT and ECG was 99.4% (95% confidence interval [CI] 98.4%–99.8%). In patients presenting ≤1 hour from symptom onset and in patients aged ≤65 years without prior MI, the sensitivity was insufficient. NSTEMI patients presenting with an undetectable level of hs-cTnT were younger but had a similar 30-day outcome to NSTEMI patients presenting with a detectable level of hs-cTnT.

In Study III, we retrospectively evaluated a one-hour hs-cTnT algorithm in 1,091 chest pain patients with a non-elevated hs-cTnT when presenting to the ED and examined early dynamic changes in hs-cTnT. Dynamic one-hour changes (Δ ≥3 ng/L) occurred in 23 patients (2.1%). Fifteen patients (65.2%) in the dynamic group were admitted, compared to 148 patients (13.9%) in the non-dynamic group (p<0.001). Four of the patients admitted (26.7%) in the dynamic and one (0.7%) in the non-dynamic group were diagnosed with an MI (p<0.001). No death or MI occurred within 30 days among those discharged from the ED.

In Study IV, we evaluated the clinical effects of implementing a one-hour hs-cTnT or I algorithm combined with the HEART score in a prospective observational before-after study including 1,233 patients at six centres. The new strategy was associated with a reduction in admission rate (59% to 33%, p<0.001, adjusted odds ratio [95% CI]: 0.33 [0.25–0.42]), median time to discharge (23.2 to 4.7 hours, p<0.001) and median health care-related costs (€1,651 to €1,019, p<0.001). The rates of death and MI were very low.

Conclusions: Rapid hs-cTn algorithms improve the prognostic assessment in patients with suspected ACS, making routine admission and predischarge exercise ECG testing redundant.

LIST OF SCIENTIFIC PAPERS

I. Ljung L, Sundqvist M, Jernberg T, Eggers KM, Ljunggren G, Frick M.
The value of predischarge exercise ECG testing in chest pain patients in the era of high-sensitivity troponins.
European Heart Journal Acute Cardiovascular Care, 2018;7(3):278–84. Epub 2017 Jan 31.

II. Ljung L, Reichard C, Hagerman P, Eggers KM, Frick M, Lindahl B, Linder R, Martinsson A, Melki D, Svensson P, Jernberg T.
Sensitivity of undetectable level of high-sensitivity troponin T at presentation in a large non-ST-segment elevation myocardial infarction cohort of early presenters.
Submitted.

III. Pettersson A*, Ljung L*, Johansson C, Heilborn U, Jernberg T, Frick M, Eggers KM, Lindahl B, Linder R, Martinsson A, Svensson P.
Experiences of a one-hour algorithm in chest pain patients with a nonelevated troponin T at presentation.
*Critical Pathways in Cardiology, 2018;17(1):6–12. *Shared first authorship.*

IV. Ljung L, Lindahl B, Eggers KM, Frick M, Linder R, Löfmark HB, Martinsson A, Melki D, Sarkar N, Svensson P, Jernberg T.
A rule-out strategy based on high-sensitivity troponin and HEART score reduces hospital admissions.
Submitted.

CONTENTS

LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CI	Confidence interval
ECG	Electrocardiogram
ED	Emergency department
EDACS	Emergency Department Assessment of Chest Pain Score
GRACE score	Global Registry of Acute Coronary Events score
HEART score	History, ECG, Age, Risk factors and Troponin score
Hs-cTn	High-sensitivity cardiac troponin
Hs-cTnI	High-sensitivity cardiac troponin I
Hs-cTnT	High-sensitivity cardiac troponin T
ICD-10	International Classification of Diseases
IQR	Interquartile range
LoD	Limit of detection
MACE	Major adverse cardiac event
MACS decision rule	Manchester Acute Coronary Syndromes decision rule
MI	Myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
NPV	Negative predictive value
OR	Odds ratio
PCI	Percutaneous coronary intervention
PPV	Positive predictive value
RCT	Randomized controlled trial
RR	Risk ratio
STEMI	ST-segment elevation myocardial infarction
TIMI score	Thrombolysis in Myocardial Infarction score
UAP	Unstable angina pectoris
ULN	Upper limit of normal
URL	Upper reference limit

1 RESEARCH QUESTION AND RATIONALE

Chest pain is one of the most common symptoms in patients presenting to the emergency department (ED)[1 2]. It is also the most common symptom in patients with an ongoing acute coronary syndrome (ACS), i.e. myocardial infarction (MI) or unstable angina pectoris (UAP)[3]. Traditionally, about 40% of chest pain patients have been admitted to hospital, but only 5–20%, depending on definitions, of those presenting with chest pain, are eventually diagnosed with an ongoing ACS[4-7]. Some patients are diagnosed with other serious conditions such as pulmonary embolism or aortic dissection, but the vast majority are discharged with a benign diagnosis such as non-specific chest pain[3 8]. On the other hand, about 1% of chest pain patients discharged directly from the ED experience a major adverse cardiac event (MACE) within 30 days of follow-up[9].

The introduction of high-sensitivity cardiac troponin (hs-cTn) assays in routine clinical care in 2010 has markedly improved the reliability of early testing in patients presenting with symptoms suggestive of ACS, and several algorithms for early identification of ACS have been developed and validated[10-16]. However, large prospective studies evaluating the algorithms' effect on clinical outcome and health care burden in routine clinical care are scarce. A reliable algorithm for rapid rule-in and rule-out of ACS would enhance assessment of chest pain patients in the ED, enabling an early initiation of treatment for ACS, as well as an early discharge of patients in whom ACS has been ruled out. This would be of great value for the patients and would also optimize the utilization of the health care resources.

The aim of this thesis was to add substantial knowledge to the research field by evaluating different assessment methods in patients presenting with symptoms suggestive of ACS, including a rapid rule-in and rule out algorithm for ACS recently implemented in routine clinical care.

2 INTRODUCTION

2.1 ACUTE CORONARY SYNDROME

ACS is the acute manifestation of coronary artery disease (CAD) and associated with a high morbidity and mortality. It is a major cause of death among both men and women in industrialized countries[17 18]. ACS is divided into the following three categories:

1. UAP, defined as new onset or prompt worsening of previous stable angina pectoris, with symptoms at a low exertion level or at rest, but without any alteration in cardiac biomarker levels[3].
2. Non-ST-segment elevation MI (NSTEMI), defined as an MI without persistent ST-segment elevations on electrocardiogram (ECG) [3].
3. ST-segment elevation MI (STEMI), defined as an MI with persistent ST-segment elevations >20 minutes[3].

2.2 MYOCARDIAL INFARCTION DIAGNOSTICS

2.2.1 Definition of myocardial infarction

In 2000, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) published a consensus document regarding the definition of MI[19]. Until then, the official definition had been the 1979 World Health Organization (WHO) definition, in which MI criteria were considered to have been met in the presence of two out of three of the following: ischemic symptoms (i.e. chest pain or other symptoms suggestive of ACS), elevated cardiac biomarkers and ischemic ECG findings[20]. In spite of the WHO document, the MI definition varied between and even within countries[21]. The consensus document presented in 2000 aimed to state a universal definition of MI. Due to advances in the biomarker area, an alteration of cardiac biomarker levels, preferably cardiac troponin levels, was now made mandatory for an MI diagnosis in routine clinical care[19].

The consensus document has been successively updated[22-24]. Since the 2012 version, MI has been categorized into five different subtypes[23]:

Type 1: Spontaneous MI caused by plaque rupture or erosion with non-occlusive or occlusive thrombus.

Type 2: MI caused by an ischemic imbalance.

Type 3: Sudden death with symptoms suggestive of MI but no biomarkers available.

Type 4: Percutaneous coronary intervention (PCI)-related MI or MI due to stent thrombosis.

Type 5: Coronary artery bypass grafting (CABG)-related MI.

The current universal definition of MI dates from 2018 and includes a dynamic change in cardiac troponin, with at least one value above the 99th percentile of healthy controls' upper reference limit (URL). This must be combined either with ischemic symptoms, new ischemic ECG findings, new pathological Q-waves, imaging evidence indicating recent or ongoing ischemia or identification of an intracoronary thrombus[22].

2.2.2 Troponins as cardiac biomarkers

Cardiac troponins as biomarkers for MI were first presented at the end of the 1980s and introduced into routine clinical care two decades ago[25-29]. Due to their cardiac specificity and high sensitivity to cardiomyocyte injury, they have thereafter successively replaced other MI biomarkers such as creatine kinase MB (CK-MB), creatine kinase (CK) and myoglobin[19 30-33]. Troponins regulate the contraction process of striated muscle (i.e. skeletal and heart muscle). Three subunits of troponin have been identified, troponin C, I and T. Together they form a complex that attaches to the actin filaments in the myocyte, thus initiating the calcium dependent muscle contraction[32 34]. A small part of the troponin subunits also appears free in the cell cytosol[32]. Troponin I and T exist in cardiac isoforms, and are considered to be heart muscle-specific, whereas troponin C presents both in skeletal and heart muscle tissue [32]. Elevated serum levels of troponin I and T indicate cardiomyocyte injury, and their detection and quantification is used in MI diagnostics[25 26]. Analyses are made by immunoassays, either run on automated platforms or by point-of-care tests. Automated platforms are recommended over point-of-care tests due to their higher sensitivity, greater diagnostic accuracy and greater negative predictive value (NPV)[3]. However, point-of-care tests have a shorter turnaround time[3].

Even though elevated troponin levels are considered to be specific for cardiomyocyte injury, they are not specific for MI[35]. There are several other conditions in which elevated troponin levels, as well as dynamic changes in troponin, can be seen[36-38]. Such conditions, are, for example myocarditis, tachyarrhythmia, pulmonary embolism, decompensated heart failure and severe infections.

2.2.3 High-sensitivity cardiac troponin assays

Due to progress in technology in the biomarker area, the sensitivity of cardiac troponin assays has increased successively[39]. Since 2010, a new generation of troponin assays, called hs-cTn assays, has been marketed and is available in routine clinical care. Due to a greater precision in the lower measurement range, with results in the single digit range of nanograms per litre (ng/L) and a coefficient of variation of <10% below the 99th percentile of healthy controls,

they should by definition have the capacity to detect cardiac troponin in >50% of healthy individuals[3 12 37 40]. Until recently, there have been two cardiac troponin assays labelled high-sensitive available on the market, the Elecsys high-sensitivity cardiac troponin T (hs-cTnT) assay (Roche Diagnostics, Basel, Switzerland) and the ARCHITECT *STAT* high-sensitivity cardiac troponin I (hs-cTnI) assay (Abbott Laboratories, Chicago, IL, USA), even though the hs-cTnT assay does not meet the criterion of detection of cardiac troponin in >50% of healthy individuals[41]. The Elecsys hs-cTnT assay has a limit of detection (LoD) of 5 ng/L and a 99th percentile of healthy controls of 14 ng/L[12]. The ARCHITECT *STAT* hs-cTnI assay has an LoD of 1.2 to 1.9 ng/L[42 43]. According to the manufacturer, the single and sex-specific (men/women) 99th percentiles of healthy controls are 26 ng/L and 34.2 /15.6 ng/L respectively. The assays are run on automated platforms. So far, there are no point-of-care tests fulfilling the criteria of a high-sensitivity assay. Studies have shown that the levels of hs-cTn are generally higher in men than in women, and it has been suggested that a single hs-cTn cut-off for men and women might lead to an under diagnosis of MI, especially among women [43-47]. However, the available data are not concordant regarding the benefit of using sex-specific cut-offs for hs-cTnT or hs-cTnI[48-51].

Due to a low threshold of detection and a greater precision in the lower range of values, the hs-cTn assays have made early testing more reliable, and an elevation of hs-cTnT due to MI might be seen as early as within the first hour from symptom onset[3 52 53]. The high-sensitivity assays have also enabled identification of small changes in troponin during serial testing. The diagnostic accuracy of the available hs-cTnT and hs-cTnI assays is considered comparable[52].

The improved sensitivity of the troponin assays has at the same time resulted in a lower specificity for MI. Some patients who would be ruled out of MI with a conventional, non-high-sensitive assay are now identified as patients with a cardiomyocyte injury, even though not all of these patient have an ongoing MI[22 39]. The decision to use the 99th percentile of healthy controls as the cut-off for a non-pathological hs-cTn value has also led to an increased number of patients with a detected cardiomyocyte injury, since this cut-off is considerably lower than prior cut-offs used for MI diagnostics [12 23 54]. Differentiation between a cardiomyocyte injury and an acute MI can be difficult, and a careful clinical examination is needed in order to distinguish between the two[22].

A recently published large Scottish study showed that the implementation of hs-cTnI combined with the use of the 99th percentile as cut-off led to a reclassification of 17% of the patients presenting with symptoms suggestive of ACS. However, only one in three of these patients who had a cardiomyocyte injury detected with hs-cTnI but not with a conventional assay, had a final diagnosis of type 1 MI[55]. Furthermore, no difference in subsequent MI or cardiovascular death during one-year follow-up was seen between patients analysed with hs-cTn and a conventional assay. The effect of implementing hs-cTnT in routine clinical care has also been evaluated in a large Swedish registry study. Hs-cTnT was found to increase the ability to adequately identify ACS patients, without admitting a larger number of patients without a final diagnosis of ACS[56]. A second large Swedish registry study showed that the

incidence of MI increased after the introduction of hs-cTn, while the risk of reinfarction decreased during follow-up[57]. A fourth study showed that patients diagnosed with non-specific chest pain after evaluation with hs-cTnT in the ED, experienced fewer MACEs after discharge when compared to patients evaluated with a conventional assay [8].

2.3 TRADITIONAL ASSESSMENT OF PATIENTS WITH SYMPTOMS SUGGESTIVE OF ACUTE CORONARY SYNDROME

2.3.1 Measurement of troponin

The introduction of cardiac troponins two decades ago facilitated the assessment of patients presenting to the ED with symptoms suggestive of ACS. Nevertheless, patients with acute symptom onset were to a great extent admitted to chest pain units in order to verify or rule out an ongoing ACS [58]. In the 2007 ESC guidelines for the diagnosis and treatment of non-ST-segment elevation ACS, an additional measurement of troponin was recommended 6 to 12 hours after admission and again after 6 to 12 hours in case of recurrent pain after admission[59]. Omitting the 12-hour sample was considered safe only if the episode of chest pain occurred more than 12 hours before the baseline sample. Continuous ST-segment monitoring was recommended during the hospital stay.

The 2011 ESC guidelines for the management of ACS in patients presenting without persistent ST-segment elevation presented a quicker way of ruling out MI for centres using hs-cTn assays[17]. In patients with hs-cTn results within the normal reference range 6 hours after symptom onset, further sampling was no longer required to rule out MI. In patients presenting within 6 hours from onset of symptoms who had a baseline hs-cTn below the upper limit of normal (ULN), a second hs-cTn was recommended 3 hours later. In case of a second value below the ULN, MI could be ruled out. These assessment strategies required a careful clinical examination and assessment of the patients' symptoms and medical history.

2.3.2 Risk scores

In order to improve the clinical assessment of chest pain patients in the ED, the value of risk scores has been evaluated. The most frequently recommended scores have been the Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) scores. The GRACE score is developed in patients presenting with an ongoing ACS and estimates in-hospital and 6-month mortality[60]. It is based on findings at admission and includes the variables of age, heart rate, systolic blood pressure, creatinine, Killip class, cardiac arrest at admission, ST-segment deviation on ECG and elevated cardiac biomarkers. The calculation of the score is computerized. Likewise, the TIMI score is developed in an ACS population and predicts 14-day MACE and 14-day mortality [61]. The score variables

collected at admission are age ≥ 65 years, ≥ three risk factors for CAD, prior coronary stenosis of 50% or more, ST-segment deviation on ECG, at least two episodes of angina pectoris within the last 24 hours, the use of aspirin over the last 7 days and elevated cardiac biomarkers. The score can be calculated manually, which is an advantage over the GRACE score. Several studies have compared the discriminative power of the two scores, but the results differ. While some studies found a superiority in discriminative power for the GRACE score[62 63], other studies found the opposite[64 65], and some study results indicate that the two scores are comparable[4]. The scores were developed in ACS populations, but the use of the scores is still recommended so as to facilitate the assessment of chest pain patients in the ED, a population at a much lower risk than the ACS populations[3 17 65-68].

2.3.3 Predischarge exercise ECG testing

Patients admitted to a chest pain unit in whom MI has been ruled out by means of serial measurement of cardiac biomarkers and ECG, have traditionally been recommended stress testing before discharge. Exercise ECG testing has been the most widely used method due to its simplicity to perform, low complication rate and high NPV[17 59 69-73]. At Södersjukhuset Hospital, Stockholm, Sweden, almost a thousand patients admitted to the Department of Cardiology with chest pain during the 18 months 2011–2012 performed a predischarge exercise ECG test in order for the physicians to verify or rule out exercise-induced ischemia[74]. Several studies of exercise testing have been performed during the last decades, the largest including about one thousand patients each[70 71]. Even though there is a slight variation in patient selection between the studies evaluating predischarge exercise ECG testing in chest pain patients, they have shown similar results. About two thirds of the patients have a negative test result (i.e. normal), between zero and 30% a positive test result (i.e. findings indicating ischemia) and the rest an inconclusive test result[69 70]. The sensitivity of the test is limited to about 45–50%[69 72 75]. The NPV is high, which has been a strong argument for the use of the test[69 72]. The incidence of MI and death during follow-up is low, indicating that the populations investigated are low-risk[70 73 76 77]. More recent studies indicate that exercise ECG testing is less useful, due to an uncertain additional value in low-risk populations and a high proportion of inconclusive and false positive test results, which might lead to further redundant non-invasive and invasive testing[77 78]. Imaging stress tests, such as myocardial scintigraphy and stress echocardiography, are preferred due to their higher sensitivity, but these tests are not available at all centres[3 72].

Previous studies have indicated that exercise ECG testing has a lower sensitivity and specificity in women than in men[79]. Exercise-induced ST-segment depressions can occur in middle-aged women without CAD, which has been thought to be due to oestrogen levels[80]. In a study evaluating the prognostic value of exercise ECG testing in women after hospitalization for ACS at the beginning of the revascularization era, isolated exercise-induced chest pain or isolated exercise-induced ST-segment depressions could not predict a recurrent event[81]. However, in other studies, ST-segment depressions during exercise ECG

testing performed shortly after an ACS were shown to be predictive of a recurrent event[82 83]. Evaluation of chest pain populations with exercise ECG testing has so far been recommended in both men and women[72].

2.4 NEW ALGORITHMS FOR ASSESSMENT OF PATIENTS WITH SYMPTOMS SUGGESTIVE OF ACUTE CORONARY SYNDROME

2.4.1 Early rule-out of myocardial infarction in the emergency department

In recent years, studies have questioned the need for admission and further testing in chest pain patients in whom MI has been ruled out in the ED[78 84]. These patients seem to have a very low risk of a future MACE or death, regardless of whether or not they are admitted for further non-invasive or invasive testing. If it were possible to safely rule out MI in the ED and to omit routine admission and further testing, this would have a great impact on routine clinical care.

The high diagnostic and prognostic performances of the hs-cTn assays seem to have made the admission and further testing pathway unnecessary in many cases[56 85]. However, due to the 2011 ESC guidelines recommending 6 hours between chest pain onset and analysis of hs-cTn, or a second sample 3 hours after presentation in patients with a baseline hs-cTn result within the normal reference range to rule out MI, a majority of the chest pain patients have still been admitted in order to avoid a prolonged stay in the ED and new, more rapid algorithms are needed[17].

The hs-cTn assays have enabled more rapid assessment strategies due to the possibility of detecting small changes in troponin in the lower measurement range, thus offering the possibility of earlier testing[12]. The ambition is to radically shorten the time from presentation to diagnosis, while maintaining high patient safety. Several new rapid rule-in and rule-out troponin algorithms have been presented, of which those of most importance for this thesis will be presented here.

2.4.2 Rule-out using an undetectable level of high-sensitivity cardiac troponin at presentation

Body et al. suggested a rule-out algorithm based on a single hs-cTnT value at presentation[10]. The algorithm was first presented in 2011 and validated in a prospective observational study in 2016[11]. The study hypothesis was that a hs-cTnT below the LoD (i.e. hs-cTnT <5 ng/L) at presentation ruled out an ongoing MI. The 2016 study by Body et al. was a prospective multicentre study including 1,282 patients with symptoms suggestive of ACS presenting to the ED within 6 hours from symptom onset[11]. The primary outcome was MI at presentation, and patients were followed for 30 days regarding a MACE. A total of 560 patients had a hs-

cTnT of <5 ng/L at presentation. Four of these patients (0.7%) were diagnosed with an MI at presentation which resulted in a sensitivity of the algorithm of 98.1% (95% confidence interval [CI] 95.3%–99.5%) and an NPV of 99.3 (95% CI 98.2%–99.8%). In order to improve the algorithm, ECG findings were added. In 471 patients with a hs-cTnT <5 ng/L and an ECG without ischemic findings, two (0.4%) had an MI. This resulted in a sensitivity of 99.1% (95% CI 96.7%–99.9%) and an NPV of 99.6% (95% CI 98.5%–100.0%). Altogether 36.7% of the patients in the study could be ruled out of MI at presentation, using the algorithm. These findings have been validated by several other research groups, using hs-cTnT as well as hs-cTnI[86-92].

A short time delay between symptom onset and presentation lowers the sensitivity of the algorithm and increases the risk of missing MI patients however[11 89 90 92]. So far, the number of early presenters evaluated with this algorithm has been modest. It has been suggested that patients presenting with an undetectable level of hs-cTn who develop an MI are at a low overall risk, but there is little data to support that[86]. Moreover, mainly patients without a final diagnosis of MI have been included in the previous studies, and data on early presenting MI patients evaluated by this algorithm is limited[93].

2.4.3 Rule-in and rule-out using a one-hour high-sensitivity cardiac troponin algorithm

A one-hour hs-cTnT algorithm to rule in or out an ongoing MI was presented by Reichlin et al. in 2012[14]. In the study, 872 patients with symptoms suggestive of MI within the last 12 hours were included prospectively. Blood samples for analysis of hs-cTnT were taken at presentation and after one hour and analysed in a blinded fashion. All patients were followed for 30 days regarding a MACE. Patients with STEMI were excluded, since the diagnosis is not based on biomarkers. A total of 436 of the patients included were randomly selected to an algorithm derivation cohort. The algorithm was based on hs-cTnT at presentation and the absolute change in hs-cTnT levels (Δ hs-cTnT) within one hour. The rule-out thresholds were set to allow a 100% sensitivity and NPV for MI. The rule-in thresholds were set using a classification and regression tree (CART) analysis to optimize the rule-in part of the algorithm. The derivation of the algorithm resulted in the following pathways: (1) rule-out if hs-cTnT at presentation <12 ng/L and Δ hs-cTnT<3 ng/L, (2) rule-in if hs-cTnT at presentation ≥52 ng/L or Δ hs-cTnT ≥5 or (3) an observational zone for the remaining patients. The derived algorithm was then validated in the remaining 436 patients included, and the result was as follows: a total of 259 patients (59.4%) were ruled out of MI after one hour, with a sensitivity of 100% and an NPV of 100%. A total of 76 patients were ruled in with the algorithm. Out of these, 64 had a final diagnosis of MI and the specificity and the positive predictive value (PPV) of the algorithm was 97% and 84% respectively. The observational zone included 101 patients, of whom 8 had a final diagnosis of MI. Altogether, a final diagnosis could be set after one hour in 77% of the patients in the validation cohort.

The diagnostic and prognostic performances of the one-hour hs-cTnT algorithm have been evaluated in several prospective observational studies and algorithm thresholds for hs-cTnI have been derived and validated[13 94-98]. In these studies, the sensitivity and NPV for the rule-out cohort has been slightly lower than the 100% set up in the original study. However, data regarding implementation and performance of the algorithm in routine clinical care are lacking, and results may differ when applied to an unselected ED population of chest pain patients.

2.4.4 New guidelines recommending the use of rapid rule-in and rule-out algorithms

In 2015, the current ESC guidelines for the management of ACS in patients presenting without persistent ST-segment elevation were published[3]. As a complement to the assessment strategy presented in 2011, the algorithm using undetectable levels of troponin at presentation and the one-hour troponin algorithm described above were recommended as an alternative in the presence of hs-cTn assays. Due to limited data and inferior performance among early presenters as discussed above, the ESC guidelines recommend at least 3 hours between symptom onset and analysis of hs-cTn in order to apply the algorithms[3]. In addition, the algorithms are recommended together with a detailed assessment of symptoms and ECG[3].

2.4.5 Clinical assessment using the HEART score

Using a risk score is a structured way to clinically assess patients. The History, ECG, Age, Risk factors and Troponin (HEART) score was presented by Six et al. in 2008 and is a risk score developed to assess the risk of an acute MACE in chest pain patients presenting to the ED[65 99 100]. It comprises the five variables of history, ECG, age, risk factors of atherosclerotic disease and troponin. Each variable is rated between zero and two points. The minimum total score is zero points and the maximum is ten points (Table 1). A HEART score of 0–3 points is categorized as a low risk of a MACE, while a score of 4–6 points as an intermediate risk and a score of 7–10 as a high risk[5 60 99 101-103]. The HEART score is developed and validated in a low-risk population of chest pain patients in the ED, in contrast to the GRACE and the TIMI scores which are developed and evaluated in ACS populations[60 61 101 102].

The HEART score has been validated by Backus et al. in both a retrospective and a prospective multicentre validation[101 102]. The prospective study presented in 2013 included 2,388 chest pain patients who were followed for 6 weeks after presentation in the ED[101]. A total of 36.4% of the study population was categorized as low-risk according to the HEART score result and 1.7% of these patients experienced a MACE within follow-up, compared to 16.6% of the patients in the intermediate risk group and 50.1% of the patients in the high-risk group. Similar results were found in a prospective multicentre validation by Poldervaart et al. in 2017[65]. A total of 40.5% of the 1,748 chest pain patients included in this prospective study

had a HEART score of 0–3 points, and 2.0% of these patients experienced a MACE within 6 weeks of follow-up.

Table 1. The HEART score.

History	Highly suspicious	2
	Moderately suspicious	1
	Slightly suspicious	0
ECG	Significant ST-segment depression	2
	Non-specific repolarization disturbance	1
	Normal	0
Age	≥65 years	2
	45–64 years	1
	<45 years	0
Risk factors	≥3 risk factors or history of atherosclerotic disease	2
	1 or 2 risk factors	1
	No risk factors known	0
Troponin	≥ 3 x ULN	2
	>1–<3 x ULN	1
	≤ ULN	0

ECG, electrocardiogram; ULN, upper limit of normal.

The HEART score has also been evaluated retrospectively in a Swedish population[5]. In 410 Swedish chest pain patients, 247 (60.2%) had a HEART score of 0–3 points and of these one patient (0.4%) experienced a MACE within three months of follow-up[5]. Hence, a considerable proportion of the chest pain population in the ED seem to have a HEART score of 0–3 points, which is associated with a very low risk of an acute MACE.

Comparisons of the HEART, GRACE and TIMI scores have been performed. The HEART score has been shown to have at least as good precision as the TIMI score and better precision than the GRACE score in identifying low-risk patients, with a higher proportion of patients classified as low-risk patients, but the results vary somewhat between studies[4 64 65 104]. In a recent study, the HEART score was superior in discriminating for a MACE when compared to the other scores[65]. The HEART score has also been compared to exercise ECG testing in chest pain patients presenting to the ED. In a small prospective study (*n*=248), no significant additive value of exercise ECG testing could be shown in patients who had already been assessed using the HEART score [77].

These data support the use of the HEART score in routine clinical care. However, when implemented as a rule-in and rule-out algorithm in a large stepped-wedge, cluster-randomized trial, the assessment strategy was shown to be safe, but no significant effect on utilization of health care resources was seen[103]. This was thought to be due to nonadherence to the HEART

score algorithm and might be explained by the fact that clinicians did not rely on a rule-out strategy that only included a risk score. Moreover, in a recent meta-analysis, 3.3% of patients with a HEART score of 0–3 points experienced a MACE during follow-up[105].

2.4.6 Rapid rule-in and rule-out algorithms evaluated in routine clinical care

While the rapid hs-cTn algorithms described in Chapters 2.4.2 and 2.4.3 have not yet been evaluated in routine clinical care, several other new algorithms in addition to the HEART score algorithm have. The algorithms of importance for this thesis will be presented here. However, even though they have been evaluated in routine clinical care and compared in reviews, direct comparisons between these algorithms are lacking[106].

2.4.6.1 Troponin combined with copeptin

In a large multicentre randomized controlled trial (RCT) presented in 2014, Möckel et al. compared the combination of a single measurement of troponin and copeptin at presentation with the rule-out strategy presented in the 2011 ESC guidelines[107]. Copeptin is a marker of acute stress that has been shown to rise promptly in MI patients[108]. The combination was shown to be as safe as the traditional strategy but, when using hs-cTn assays instead of conventional troponin assays, copeptin did not provide any additional diagnostic information[107 109].

2.4.6.2 A two-hour hs-cTn I algorithm combined with the TIMI score

An algorithm based on measurement of hs-cTnI at presentation and after two hours combined with a modified TIMI score was evaluated in a single-centre randomized, parallel-group trial by Than et al. in 2014[110]. To classify a patient as low risk according to the modified TIMI score, all variables of the score had to be negative. The two-hour algorithm was compared to a traditional assessment strategy that included measurement of hs-cTn 6–12 h after symptom onset and often included admission. It showed that 19.3 % of patients in the two-hour algorithm group, compared to 11.0% in the traditional assessment group, were discharged within 6 hours and without experiencing a MACE within 30 days of follow-up.

2.4.6.3 The HEART pathway

In this small single-centre RCT (n=282) by Mahler et al. presented in 2015, patients evaluated with a three-hour algorithm using conventional troponin combined with the HEART score were compared to patients receiving standard care according to the 2007 ACC/American Heart Association (AHA) guidelines recommending serial troponin measurement and objective cardiac testing before discharge[67 111]. With this new strategy, the admission rate decreased from 78% to 61% and the length of stay in the hospital was reduced from 21.9 to 9.9 hours, without any increase in MACE during the 30-day follow-up.

In a small multicentre RCT (*n*=105) by Frisoli et al. presented in 2017, patients ruled-out of MI by the HEART pathway were randomized either to a direct discharge from the ED, or to non-invasive stress testing[112]. By using the HEART pathway, the length of stay was reduced from 25.9 to 6.3 hours and the total costs from $9,616 to $2,950. No MACE occurred in any of the groups during the 30-day follow-up.

2.4.6.4 The EDACS accelerated diagnostic pathway

In a single-centre RCT by Than et al., the newly developed and validated Emergency Department Assessment of Chest Pain Score (EDACS) was compared to the modified TIMI score[6 110 113]. The EDACS was developed to be applied in an unselected chest pain population in the ED and includes the variables of age, sex, risk factors for CAD or established CAD, and symptom characteristics. Patients in both groups were assessed according to routine clinical care including measurement of hs-cTnI at presentation and after two hours. There was no difference in the proportion of patients who were discharged within 6 hours and without experiencing a MACE within 30 days of follow-up (32.3% in the EDACS group vs. 34.4% in the modified TIMI score group), indicating that the EDACS could be implemented in routine clinical care. The same research group recently showed that the implementation of such accelerated diagnostic pathways in routine clinical care increases the number of early discharged patients and with very low risk[114].

2.4.6.5 Shared decision making in the ED

In this large multicentre RCT by Hess et al., standard care was compared to shared decision making where patients were informed of their calculated risk of ACS and, together with the physician, decided whether they should be admitted for further testing or discharged and followed-up in an outpatient setting[115]. The admission rate decreased from 52.1% among patients assessed according to standard care to 37.3% among patients in the shared decision-making group. The proportion of patients who underwent stress testing within 30 days decreased from 45.6% to 38.1%. None of the patients who were directly discharged from the ED experienced a MACE within 30 days.

2.4.6.6 The MACS decision rule

In a small, single-centre pilot RCT (*n*=138) by Body et al. presented in 2017, patients assessed according to the Manchester Acute Coronary Syndromes (MACS) decision rule were compared to patients receiving standard care[116]. The MACS decision rule is based on measurement of hs-cTnT, heart type fatty acid binding protein and blood pressure at presentation combined with ECG findings and symptom characteristics. A total of 26% of the patients assessed according to the MACS decision rule were discharged within 4 hours, compared to 8% of the patients in the standard care group. None of these patients experienced a MACE within 30 days.

2.5 MEASUREMENTS OF DIAGNOSTIC TESTS

Measurements of diagnostic tests are discussed throughout this thesis. To facilitate reading, they are briefly explained here.

2.5.1 Sensitivity

Sensitivity is the proportion of individuals with a certain disease that are correctly identified by a pathologic diagnostic test (e.g. an MI patient identified by an elevated troponin level)[117]. The sensitivity should be high in diagnostic tests where the aim is not to miss any individuals with the disease. Sensitivity is not affected by the prevalence of the disease.

2.5.2 Specificity

Specificity is the proportion of individuals without a certain disease that are correctly identified by a non-pathologic diagnostic test (e.g. a chest pain patient without MI who turns out to have a non-elevated troponin level)[117]. The specificity should be high in diagnostic tests where the aim is to detect a disease in a population. Specificity is not affected by the prevalence of the disease.

2.5.3 Positive predictive value

PPV is the proportion of individuals with a pathological test result that are correctly diagnosed (e.g. a patient with an elevated troponin who turns out to have an MI)[117]. PPV is affected by the prevalence of the disease. The higher the prevalence, the higher the PPV and in a population where the prevalence of a certain disease is high, the PPV of a diagnostic test will be high by default.

2.5.4 Negative predictive value

NPV is the proportion of individuals with a normal test result that are correctly diagnosed (e.g. a patient with a non-elevated troponin and without an MI)[117]. NPV is affected by the prevalence of the disease. The lower the prevalence, the lower the NPV and in a population where the prevalence of a certain disease is low, the NPV of a diagnostic test will be low by default.

2.5.5 Efficacy vs. safety

When choosing a rule-in and rule-out algorithm to implement in routine clinical care, there is a trade-off between efficacy (i.e. the algorithm's capacity to classify patients as rule-in or rule-out) and safety (i.e. the algorithm's capacity to correctly rule out patients). Using a hs-cTn algorithm alone seems to improve the efficacy compared to a combined hs-cTn and risk score algorithm while the latter seems to improve the safety[118]. Increased safety could increase the clinicians' adherence rate. In addition, a hs-cTnT algorithm cannot identify UAP patients while combined algorithms might. There is no general recommendation for the sensitivity for ACS or MI of a rule-in and rule-out algorithm, but it seems impossible to obtain a sensitivity of 100% in routine clinical care without admitting all presenting patients. However, redundant admittance of patients is not always good for the patients and also leads to an ineffective utilization of health care resources. In routine clinical care, a sensitivity at or above 99% is often the aim among clinicians. In a survey performed among1,029 ED physicians in New Zealand, Australia, USA and Canada, about 40% of the participants were willing to accept a miss-rate of a MACE of 1% and 55% a miss-rate of 0.5%[119].

3 AIMS

The overall aim of this thesis was to evaluate four methods of assessing patients presenting with symptoms suggestive of ACS in the era of hs-cTn, including a new assessment strategy for these patients recently implemented in routine clinical care in Stockholm and Uppsala, Sweden.

The specific aims of the individual studies were:

Study I To evaluate the value of predischarge exercise ECG testing in chest pain patients in whom MI had been ruled out by means of hs-cTnT.

Study II To evaluate the diagnostic sensitivity of using an undetectable level of hs-cTnT at presentation, with and without information from the ECG, in order to rule out MI in a NSTEMI population presenting early after onset of symptoms.

Study III To evaluate the use of a one-hour measurement of hs-cTnT in routine clinical care in an ED population of chest pain patients with a non-elevated hs-cTnT at presentation and to examine early dynamic changes in hs-cTnT.

Study IV To evaluate whether the clinical implementation of a one-hour hs-cTnT or I algorithm combined with the HEART score would reduce admission rates and affect the time to discharge, health care-related costs and outcome.

4 METHODS

4.1 ETHICAL CONSIDERATIONS

The studies were conducted according to the principles of the Declaration of Helsinki[120] and approved by the Regional Ethical Review Board in Stockholm (Study I approval number 2013/841-31/2, Study II approval number 2017-331/31, Study III approval number 2016/744-31/4 and Study IV approval number 2013/621-31/4).

Study I–III were retrospective studies, and the possible harm for the participating patients was considered to be negligible.

Study IV was a prospective observational study conducted according to Good Clinical Practice Guidelines[121], and written informed consent was obtained from all participants. The patients participating received the same clinical assessment as patients outside the study. Additional blood samples were taken from the participants, both for instant analysis and for bio banking. Blood sampling may lead to complications such as bleeding, haematomas or infections, but these complications are very rare. The amount of blood obtained could not lead to anaemia.

The data used were made anonymous before analysis and presentation in all studies and could not be connected to specific patients. The aim was to design clinically relevant studies with adequate research questions. It would then be possible for the patients participating in the studies to benefit from the study results in the future. If the studies improved the assessment of patients presenting with symptoms suggestive of ACS, the positive effect would outweigh the minimal risks that the participating patients were exposed to.

4.2 STUDY I

4.2.1 Study design, setting and participants

In this retrospective study, all patients who underwent predischarge exercise ECG testing while admitted to the Department of Cardiology, Södersjukhuset Hospital, Stockholm, Sweden from January 1, 2011 to June 30, 2012 were screened for inclusion. Consecutive patients admitted due to symptoms suggestive of ACS in whom MI had been ruled out by means of hs-cTnT before the exercise ECG test were included if they had a Swedish identity number and were registered in the County of Stockholm from the inclusion date to the end of the follow-up. Patients could only be included once in the study.

4.2.2 Data sources and variables

Baseline and presentation characteristics and exercise ECG test data were retrieved from the hospital's medical records. All baseline ECGs were assessed. The exercise ECG test data were assessed and categorized as negative (i.e. normal), positive (i.e. pathological) or inconclusive. If no classification could be made based on the given data, the continuous ECG-registration was reviewed. Follow-up data were retrieved from the hospital's medical records, the Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART) registry[122] and the Public Healthcare Services Committee Administration of the Stockholm County Council. All diagnoses were coded according to the International Classification of Diseases (ICD-10)[123]. Study endpoints were death, MI, death and MI combined and post-discharge revascularization within 90 and 365 days respectively. Data from Statistics Sweden and the National Board of Health and Welfare were used to calculate the one-year risk of death and MI in an age, gender and calendar time-matched Swedish population.

4.2.3 Statistical methods

Categorical variables were presented as numbers and percentages and continuous data as medians with interquartile ranges (IQR). The chi-square test or Fisher's exact test were used to evaluate differences in proportions between the exercise ECG test outcome groups. The Mann-Whitney U test was used to compare continuous variables. All statistical analyses were performed using IBM SPSS Statistics version 22, Armonk, North Castle, NY, USA.

4.3 STUDY II

4.3.1 Study design, setting and participants

This retrospective study was conducted after the introduction of hs-cTnT in the County of Stockholm, Sweden in December 2010. All patients admitted to five centres in Stockholm from January 1, 2011 to December 31, 2015 presenting $\leq$2 hours from symptom onset and receiving a final diagnosis of NSTEMI were identified through the SWEDEHEART registry. These inclusion criteria were verified in the hospitals' medical records. Analysis of hs-cTnT at presentation was mandatory for inclusion, and patients with cardiac arrest prior to presentation, as well as patients with a prior participation in the study, were excluded.

4.3.2 Data sources and variables

Data regarding presentation, symptom onset, results of hs-cTnT measurements and NSTEMI diagnosis were retrieved from the hospitals' medical records. All ECGs in patients presenting

with an undetectable level of hs-cTnT (i.e. <5 ng/L) were assessed. The SWEDEHEART registry provided all other baseline and outcome data. The diagnostic sensitivity for MI when using an undetectable level of hs-cTnT at presentation to rule out MI was calculated separately in patients presenting ≤2 hours, >1 hour to ≤2 hours and ≤1 hour from symptom onset. The additive value of a non-ischemic ECG was calculated. Patients aged ≤65 years without prior MI were analysed separately. NSTEMI patients with and without a detectable level of hs-cTnT at presentation were compared regarding baseline and in-hospital characteristics and revascularization and death at 30 days.

4.3.3 Statistical methods

Sensitivity for MI with the exact Clopper-Pearson 95% CI for the observed proportion was calculated. Categorical variables were given as numbers and percentages and continuous data as medians (IQR). The chi-square test or Fisher's exact test were used to evaluate differences in proportions. The Mann-Whitney U test was used to compare continuous variables. All statistical analyses were performed using IBM SPSS Statistics version 23, Armonk, North Castle, NY, USA or MedCalc version 18.2.1, MedCalc Software, Ostend, Belgium.

4.4 STUDY III

4.4.1 Study design, setting and participants

This retrospective study was conducted after the introduction of a new algorithm combining measurement of hs-cTn at presentation and after one hour with calculation of the HEART score in routine clinical care. The algorithm is described in Chapter 4.5.1. Screening for eligible patients was made through the Karolinska University Hospital Database (KARDA) which consists of data from the hospital's medical records. All patients with a registered chief complaint of chest pain presenting to the ED of Karolinska University Hospital, Solna, Sweden, from December 1, 2014 to September 14, 2015 who had a Swedish identity number and two hs-cTnT measurements obtained during the ED visit with a time period between the first and second sample of >30–≤90 minutes were included. Patients with STEMI or ventricular tachycardia were excluded. Patients could only be included once, and one of the visits during the study period was randomly chosen.

4.4.2 Data sources and variables

Baseline data were retrieved from the KARDA. Outcome data were retrieved from the KARDA with a linkage to the Swedish population register. All diagnoses were coded according to ICD-10[123]. In patients with a main diagnosis of MI, the diagnosis and MI type (1 or 2) was adjudicated. All patients with a baseline hs-cTnT value of ≤14 ng/L were followed for 30 days regarding the following endpoints: admission, readmission, MI and death. Patients with a dynamic one-hour change in hs-cTnT (i.e. Δ≥3 ng/L) were compared to those with a non-dynamic change in hs-cTnT (i.e. Δ<3 ng/L). The HEART score was calculated retrospectively in the subgroup of patients with a dynamic one-hour change in hs-cTnT levels and in those with an ACS diagnosis but without a dynamic one-hour change in hs-cTnT.

4.4.3 Statistical methods

Categorical variables were presented as numbers and percentages. Continuous data were presented as mean with standard deviations or medians (IQR) or minimum and maximum (min– max) range as appropriate. The chi-square test or Fisher's exact test were used to evaluate differences in proportions. Comparisons of continuous variables were made with the Student's t-test for normally distributed variables and with the Mann-Whitney U-test for other continuous variables. All statistical analyses were performed using STATISTICA version 12 (2014) (Stat Soft Inc., Tulsa, OK, USA) and Microsoft Excel (Microsoft Office 2008) (Microsoft Corp., Redmond, WA, USA).

4.5 STUDY IV

4.5.1 Study design, setting and participants

The Fast ASsessment of Thoracic pain in the Emergency department using high-Sensitive Troponins and a simple risk score (FASTEST) study was a prospective observational study conducted at six centres in Stockholm and Uppsala, Sweden. The study was divided into two phases, before and after the implementation of a new algorithm for patients presenting to the ED with symptoms suggestive of ACS. During phase 1 (June 4, 2013– September 2, 2014), patients were assessed according to local guidelines based on recommendations from the ESC and ACC/AHA. During phase 2 (January 27, 2015– May 20, 2016), patients were assessed according to the new algorithm which applied a modified one-hour hs-cTn algorithm in combination with calculation of the HEART score (Figure 1). In patients with a baseline hs-cTnT or I within the ULN, a one-hour change in hs-cTnT <3 ng/L or hs-cTnI <6 ng/L and a HEART score ≤3, ACS was considered unlikely. In patients with a baseline hs-cTnT or I within the ULN, a one-hour change below these cut-offs and a HEART score ≥4, MI was considered unlikely, but the risk of an ACS was considered elevated. In patients with a

baseline hs-cTnT or I within the ULN, a one-hour change in hs-cTnT ≥3 or hs-cTnI ≥6 ng/L, an ongoing MI should be considered regardless of the HEART score. Inclusion criteria were symptoms suggestive of ACS, symptom duration of ≥10 minutes and onset of last episode ≤12 hours. Patients presenting with ST-segment elevation or new left bundle branch block on ECG were excluded.

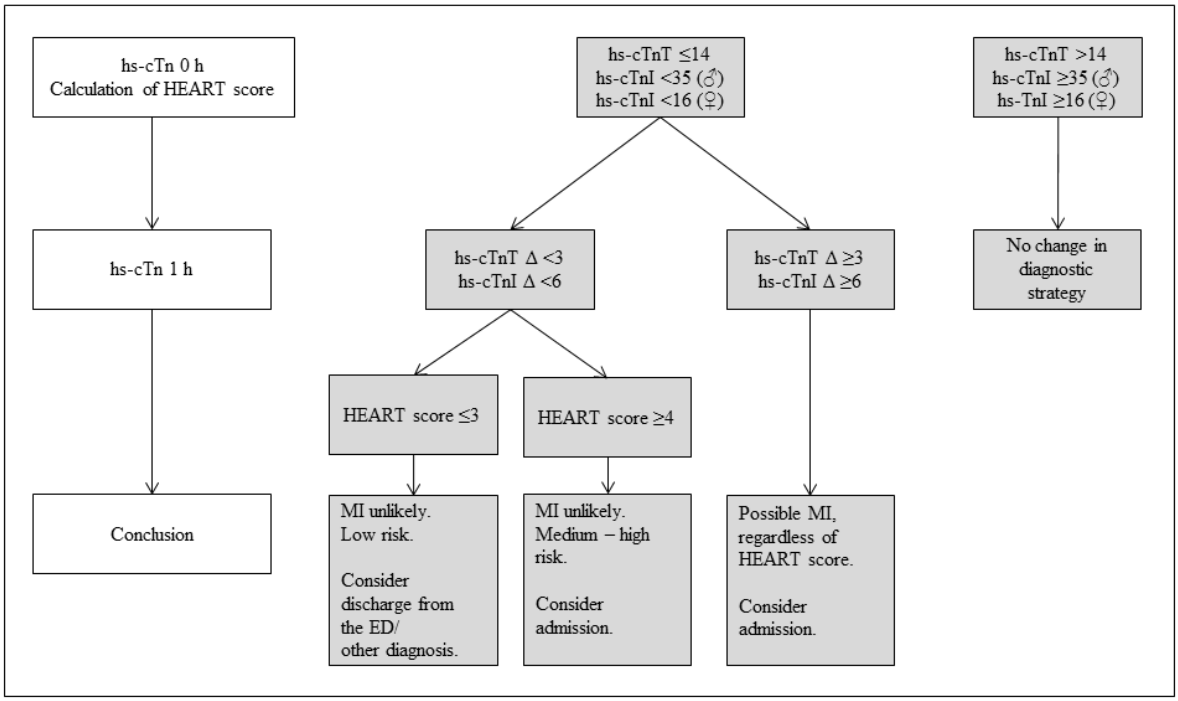

Figure 1. The new algorithm. The new algorithm included measurement of hs-cTn at presentation and after one hour, combined with the HEART score. To be considered "low risk" hs-cTn needed to be within the normal reference range at baseline, i.e. the HEART-score for troponin=0."

Hs-cTn levels are expressed in nanograms/litre.

♂ indicates men; ♀ indicates women; Δ indicates delta; ED, emergency department; h, hour, hs-cTn; high-sensitivity cardiac troponin; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction.

4.5.2 Data sources and variables

All data collection was performed by a research assistant who entered the data onto a web-based case report form. Patients were followed by a telephone call at the end of a 30-day follow-up, and by the hospitals' medical records if necessary. All study cases with an elevated troponin level during the index visit or readmission to hospital were adjudicated regarding whether or not the MI criteria were fulfilled[23]. The primary endpoint of the study was admission rate, defined as the rate of patients admitted to an in-patient ward. Secondary endpoints were time to discharge from the hospital, health care-related costs and clinical

outcomes defines as new presentation to the ED, readmission to the hospital, unplanned revascularization, MI or death.

4.5.3 Statistical methods

The power calculation for the primary endpoint was based on an expected admission rate of 45% during phase 1 and 35% during phase 2. In order to detect a reduction in admission rate of 10% with a power of 0.90 and an alpha-value of 0.05, a total of 524 patients were required in each phase. Categorical variables were presented as numbers and percentages and continuous data as medians (IQR). The chi-square test or Fisher's exact test were used to evaluate differences in proportions between phase 1 and 2 according to the intention-to-treat principle. The risk ratio (RR) with 95% CI was calculated. The Mann-Whitney U test was used to compare continuous variables. A logistic regression analysis was performed to adjust for differences in baseline characteristics between phase 1 and 2. A sensitivity analysis was performed in order to adjust for an index diagnosis of MI vs. non-MI. All statistical analyses were performed using IBM SPSS Statistics version 23, Armonk, North Castle, NY, USA.

5 RESULTS

5.1 STUDY I

5.1.1 Study population

A total of 951 patients were included in the analysis. The median (IQR) age was 62 (51–70) years and 428 (45.0%) of the patients were women. The presentation ECG was normal in 658 patients (69.2%). A total of 909 patients (95.6%) had more than one hs-cTnT sample taken during the hospital stay and 820 (86.2%) had a peak level of hs-cTnT ≤14 ng/L. In total, 111 patients (11.7%) were initially treated for a suspected ACS, but the diagnosis was ruled out before the exercise ECG test. In 585 patients (61.5%), the exercise ECG test was negative, in 94 (9.9%) positive and in 272 (28.6%) inconclusive. In comparison with patients with negative tests, patients with positive or inconclusive tests were older, more often male, had more risk factors, were more often being treated with beta-blockers and had more often a peak level of hs-cTnT >14 ng/L or a pathological ECG.

5.1.2 Main findings

Ninety-five patients (10.0%) underwent coronary angiography during their hospital stay (Table 2). A total of 46 (4.8%) patients were revascularized before discharge and an additional 39 (4.1%) during the one-year follow-up. Overall, there were 3 (0.3 %) and 9 (0.9 %) deaths and 4 (0.4%) and 10 (1.1%) MIs within 90 and 365 days, respectively. In an age, gender and calendar time-matched Swedish population the one-year rate of death was 1.3% and the one-year rate of MI 0.5%.

Patients with a positive exercise ECG test were more likely to undergo coronary angiography and subsequent PCI in hospital, as well as revascularization after discharge when compared to patients with a negative test (Table 2). There were no statistically significant differences regarding death or MI between patients with a positive or a negative test, neither at 90 (1.1% vs. 0.2%) nor at 365 days (2.1% vs. 0.7%) of follow-up. Patients with an inconclusive test had a worse prognosis than patients with a negative test and were more likely to reach the combined endpoint death or MI during follow-up. A total of 445 patients with a normal ECG at presentation and a hs-cTnT peak level of <5 ng/L were analysed separately. Only two deaths and one MI occurred in this cohort within 365 days of follow-up.

Table 2. Outcome at 90 and 365 days. Patients were divided into groups based on the predischarge exercise ECG test result.

***n* (%)**

	All patients (*n*=951)	**Negative exercise ECG test (*n*=585)**	**Positive exercise ECG test (*n*=94)**	**Inconclusive exercise ECG test (*n*=272)**
Coronary angiography before discharge	95 (10.0)	12 (2.1)	45 (47.9) ***	38 (14.0) ***
Significant stenosis before discharge	51 (5.4)	4 (0.7)	29 (30.9) ***	18 (6.6) ***
Revascularization before discharge	46 (4.8)	4 (0.7)	28 (29.8) ***	14 (5.1) ***
Imaging stress test performed after discharge but before any coronary angiography	154 (16.2)	58 (9.9)	23 (24.5) ***	73 (26.8) ***
Positive imaging stress test	20/154 (13.0)	7/58 (12.1)	4/23 (17.4)	9/73 (12.3)
Death due to any cause ≤90 days	3 (0.3)	1 (0.2)	0 (0.0)	2 (0.7)
Myocardial infarction ≤90 days	4 (0.4)	0 (0.0)	1 (1.1)	3 (1.1) *
Any revascularization after discharge ≤90 days	18 (1.9)	1 (0.2)	8 (8.5) ***	9 (3.3) ***
Death or myocardial infarction ≤90 days	7 (0.7)	1 (0.2)	1 (1.1)	5 (1.8) *
Other cardiovascular readmission ≤90 days	33 (3.5)	8 (1.4)	8 (8.5) **	17 (6.3) ***
Death due to any cause ≤365 days	9 (0.9)	2 (0.3)	0 (0.0)	7 (2.6) **
Myocardial infarction ≤365 days	10 (1.1)	2 (0.3)	2 (2.1)	6 (2.2) *
Any revascularization after discharge ≤365 days	39 (4.1)	7 (1.2)	16 (17.0) ***	16 (5.9) ***
Death or myocardial infarction ≤365 days	19 (2.0)	4 (0.7)	2 (2.1)	13 (4.8) ***
Other cardiovascular readmission ≤365 days	87 (9.1)	28 (4.8)	20 (21.3) ***	39 (14.3) ***

*=p<0.05, **=p<0.01, ***= p<0.001 when compared to patients with a negative exercise ECG test.

ECG, electrocardiogram.

5.1.3 Gender differences

The median (IQR) age among men and women was 60 (51–69) and 62 (53–70) years respectively and 170 (32.5%) of the men and 65 (15.2%) of the women had a history of ischemic heart disease. Men and women had to a similar extent a normal ECG at presentation (69.2% and 70.1% respectively). Altogether 281 (53.7%) of the men and 301 (70.3%) of the women had a maximum hs-cTnT <5 ng/L, and 157 (30.0%) of the men and 81 (18.9%) of the women had a maximum hs-cTnT of 5–14 ng/L. The exercise ECG test outcome in men was 58.5% negative tests, 13.6% positive tests and 27.9% inconclusive tests (Table 3). Among women, 65.2% of the tests were negative, 5.4% positive and 29.4% inconclusive (Table 4).

Table 3. Outcome at 90 and 365 days in men. Patients were divided into groups based on the predischarge exercise ECG test result.

***n* (%)**

	All patients (*n*=523)	**Negative exercise ECG test (*n*=306)**	**Positive exercise ECG test (*n*=71)**	**Inconclusive exercise ECG test (*n*=146)**
Coronary angiography before discharge	63 (12.0)	7 (2.3)	36 (50.7) ***	20 (13.7) ***
Revascularization before discharge	33 (6.3)	3 (1.0)	23 (32.4) ***	7 (4.8) *
Death due to any cause ≤ 90days	3 (0.6)	1 (0.3)	0 (0)	2 (1.4)
Myocardial infarction ≤90 days	2 (0.4)	0 (0)	1 (1.4)	1 (0.7)
Any revascularization after discharge ≤90 days	15 (2.9)	1 (0.3)	7 (9.9) ***	7 (4.8) **
Death or myocardial infarction ≤90 days	5 (1.0)	1 (0.3)	1 (1.4)	3 (2.1)
Death due to any cause ≤365 days	7 (1.3)	2 (0.7)	0 (0)	5 (3.4)*
Myocardial infarction ≤365 days	4 (0.8)	1 (0.3)	1 (1.4)	2 (1.4)
Any revascularization after discharge ≤365 days	29 (5.5)	4 (1.3)	12 (16.9) ***	13 (8.9) ***
Death or myocardial infarction ≤365 days	11 (2.1)	3 (1.0)	1 (1.4)	7 (4.8) *

*=p<0.05, **=p<0.01, ***= p<0.001 when compared to patients with a negative exercise ECG test.

ECG, electrocardiogram.

A total of 63 (12.0%) of the men underwent coronary angiography before discharge, and 33 (6.3%) were revascularized, compared to 32 (7.5%) and 13 (3.0%) of the women (Table 3 and 4). In men, there were overall 3 (0.6%) deaths and 2 (0.4%) MIs after 90 days and 7 (1.3%) deaths and 4 (0.8%) MIs after 365 days of follow-up. In women, there were no deaths but 2 (0.5%) MIs after 90 days and 2 (0.5%) deaths and 6 (1.4%) MIs after 365 days of follow-up. None of the men or women with a positive exercise ECG test died during follow-up and there was no statistically significant difference in the proportion of MIs between those with a positive and a negative exercise test. Both men and women with a positive exercise test were revascularized to a significantly greater extent during the 365-day follow-up when compared to those with a negative test.

Table 4. Outcome at 90 and 365 days in women. Patients were divided into groups based on the predischarge exercise ECG test result.

***n* (%)**

	All patients (*n*=428)	**Negative exercise ECG test (*n*=279)**	**Positive exercise ECG test (*n*=23)**	**Inconclusive exercise ECG test (*n*=126)**
Coronary angiography before discharge	32 (7.5)	5 (1.8)	9 (39.1) ***	18 (14.3) ***
Revascularization before discharge	13 (3.0)	1 (0.4)	5 (21.7) ***	7 (5.6) **
Death due to any cause ≤ 90days	0 (0)	0 (0)	0 (0)	0 (0)
Myocardial infarction ≤90 days	2 (0.5)	0 (0)	0 (0)	2 (1.6)
Any revascularization after discharge ≤90 days	3 (0.7)	0 (0)	1 (4.3)	2 (1.6)
Death or myocardial infarction ≤90 days	2 (0.5)	0 (0)	0 (0)	2 (1.6)
Death due to any cause ≤365 days	2 (0.5)	0 (0)	0 (0)	2 (1.6)
Myocardial infarction ≤365 days	6 (1.4)	1 (0.4)	1 (4.3)	4 (3.2) *
Any revascularization after discharge ≤365 days	10 (2.3)	3 (1.1)	4 (17.4) ***	3 (2.4)
Death or myocardial infarction ≤365 days	8 (1.9)	1 (0.4)	1 (4.3)	6 (4.8) **

*=p<0.05, **=p<0.01, ***= p<0.001 when compared to patients with a negative exercise ECG test.

ECG, electrocardiogram.

5.2 STUDY II

5.2.1 Diagnostic sensitivity for MI

Altogether 911 NSTEMI patients presenting ≤2 hours from symptom onset were included in the study. Twenty-four (2.6%) presented with an undetectable level of hs-cTnT. The diagnostic sensitivity for MI when using an undetectable level of hs-cTnT at presentation with and without information from the ECG is shown in Table 5. The sensitivity was higher in patients presenting in the second hour (i.e. >1 hour to ≤2 hours) from symptom onset compared to patients presenting within the first hour (i.e. ≤1 hour). The lowest sensitivity was found in the subgroup of patients aged ≤65 years without prior MI presenting within one hour. The sensitivity improved in all cohorts when ECG was added to the algorithm.

Table 5. Diagnostic sensitivity for MI. Sensitivity when using an undetectable level of hs-cTnT at presentation, with and without information from the ECG, to rule out MI in a NSTEMI population presenting ≤2 hours from symptom onset.

	Presentation ≤1 hour from symptom onset	**Presentation >1–≤2 hours from symptom onset**	**Presentation ≤2 hours from symptom onset**
Sensitivity (95% CI) (n/d) for hs-cTnT at presentation			
All patients (*n*=911)	94.6 (91.0–97.0) (243/257)	98.5 (97.2–99.3) (644/654)	97.4 (96.1–98.3) (887/911)
Patients ≤65 years, no prior MI (*n*=282)	86.0 (76.9–92.6) (74/86)	96.9 (93.5–98.9) (190/196)	93.6 (90.1–96.2) (264/282)
Sensitivity (95% CI) (n/d) for hs-cTnT and ECG [a] at presentation			
All patients (*n*=911)	95.7 (92.5–97.8) (246/257)	99.4 (98.4–99.8) (650/654)	98.4 (97.3–99.1) (896/911)
Patients ≤65 years, no prior MI (*n*=282)	89.5 (81.1–95.1) (77/86)	98.5 (95.6–99.7) (193/196)	95.7 (92.7–97.8) (270/282)

[a] Normal ST-T-findings were defined as the absence of an ST-segment elevation >1 mm (>2 mm in lead V2–V3), of an ST-segment depression >1 mm in two leads and of a T-wave inversion >1 mm.

CI, confidence interval; d, denominator; ECG, electrocardiogram; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; n, nominator; NSTEMI, non-ST-segment elevation myocardial infarction.

5.2.2 Baseline and outcome comparisons

Compared to NSTEMI patients with a detectable level of hs-cTnT at presentation, patients presenting with an undetectable level of hs-cTnT were younger (median age 56 vs. 69 years), to a comparable extent male (70.8 vs. 68.9%), less often had a history of MI (12.5 vs. 36.4%) and more often presented within the first hour from symptom onset (58.3 vs. 27.4%). A total of 62.5% of the patients presenting with an undetectable level of hs-cTnT had a non-ischemic admission ECG, compared to 42.6% of the patients presenting with a detectable level, but this difference was not statistically significant.

NSTEMI patients with an undetectable level of hs-cTnT at admission reached a similar peak level of hs-cTnT when compared to patients with a detectable level of hs-cTnT at admission (median 182 vs. 200 ng/L). No statistically significant difference was seen in the proportion of in-hospital coronary angiographies (95.8 vs. 79.7%), revascularization (62.5 vs. 63.2%) or death (4.2 vs. 1.6%). Patients in the two groups were to a similar extent discharged with acetylsalicylic acid, P2Y12 inhibitors, beta-blockers and lipid lowering drugs. At the 30-day follow-up, a total of 95.8% and 62.5% of the patients who presented with an undetectable level of hs-cTnT had undergone coronary angiography and revascularization respectively, compared to 80.3% and 63.5% respectively of those who presented with a detectable level. The 30-day cumulative incidence of death was 4.5 and 3.2% respectively.

5.2.3 Gender differences

Seventeen men (2.7%) and seven women (2.5%) presented with an undetectable level of hs-cTnT. Out of these, thirteen men (76.5%) and five women (71.4%) were 65 years or younger and did not have a history of MI. The diagnostic sensitivity for MI in men presenting in the second hour from symptom onset was 99.5% (95% CI 98.4%–99.9%) (Table 6). In men ≤65 years without prior MI presenting in the second hour from symptom onset, the sensitivity was 99.3% (95% CI 96.1%–100.0%). In women, the sensitivity for MI among those presenting in the second hour from symptom onset was 99.1% (95% CI 96.7%–99.9%) (Table 7). In women ≤65 years without prior MI presenting in the second hour from symptom onset the sensitivity was 96.3% (95% CI 87.3%–99.6%).

Table 6. Diagnostic sensitivity for myocardial infarction in men. Sensitivity for MI when using an undetectable level of hs-cTnT at presentation, with and without information from the ECG, to rule out MI in a NSTEMI population presenting ≤2 hours from symptom onset.

	Presentation ≤1 hour from symptom onset	**Presentation >1–≤2 hours from symptom onset**
Sensitivity (95% CI) (n/d) for hs-cTnT at presentation		
All patients (*n*=628)	94.2 (89.8–97.1)	98.6 (97.1–99.5)
	(178/189)	(433/439)
Patients ≤65 years, no prior MI (*n*=213)	85.9 (75.6–93.0)	97.9 (94.0–99.6)
	(61/71)	(139/142)
Sensitivity (95% CI) (n/d) for hs-cTnT and ECG [a] at presentation		
All patients (*n*=628)	95.8 (91.8–98.2)	99.5 (98.4–99.9)
	(181/189)	(437/439)
Patients ≤65 years, no prior MI (*n*=213)	90.1 (80.7–95.9)	99.3 (96.1–100.0)
	(64/71)	(141/142)

[a] Normal ST-T-findings were defined as the absence of an ST-segment elevation >1 mm (>2 mm in lead V2–V3), of an ST-segment depression >1 mm in two leads and of a T-wave inversion >1 mm.

CI, confidence interval; d, denominator; ECG, electrocardiogram; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; n, nominator; NSTEMI, non-ST-segment elevation myocardial infarction.

Table 7. Diagnostic sensitivity for myocardial infarction in women. Sensitivity for MI when using an undetectable level of hs-cTnT at presentation, with and without information from the ECG, to rule out MI in a NSTEMI population presenting ≤2 hours from symptom onset.

	Presentation ≤1 hour from symptom onset	**Presentation >1–≤2 hours from symptom onset**
Sensitivity (95% CI) (n/d) for hs-cTnT at presentation		
All patients (*n*=283)	95.6 (87.6–99.1) (65/68)	98.1 (95.3–99.5) (211/215)
Patients ≤65 years, no prior MI (*n*=65)	86.7 (59.5–98.3) (13/15)	94.4 (84.6–98.9) (51/54)
Sensitivity (95% CI) (n/d) for hs-cTnT and ECG [a] at presentation		
All patients (*n*=283)	95.6 (87.6–99.1) (65/68)	99.1 (96.7–99.9) (213/215)
Patients ≤65 years, no prior MI (*n*=65)	86.7 (59.5–98.3) (13/15)	96.3 (87.3–99.6) (52/54)

[a] Normal ST-T-findings were defined as the absence of an ST-segment elevation >1 mm (>2 mm in lead V2–V3), of an ST-segment depression >1 mm in two leads and of a T-wave inversion >1 mm.

CI, confidence interval; d, denominator; ECG, electrocardiogram; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; n, nominator; NSTEMI, non-ST-segment elevation myocardial infarction.

5.3 STUDY III

5.3.1 ED and study population

During the study period, 3,581 patients visited the ED with a chief complaint of chest pain. Hs-cTnT was analysed in 3,169 of these patients. A second sample of hs-cTnT was obtained in 1,973 patients out of which 1,397 (70.8%) had the second sample obtained within >30–≤90 minutes and were included in the study. A total of 1,091 of these patients had a baseline hs-cTnT level of ≤14 ng/L and were followed 30 days regarding clinical outcomes. In these 1,091 patients, the median (IQR) value of the first as well as the second hs-cTnT sample was <5 (<5 to 7) ng/L. Altogether, 23 patients (2.1%) had a dynamic one-hour change in hs-cTnT. The incidence of an index MI among included patients with a baseline level of hs-cTnT of ≤14 ng/L was 0.5%, compared to 4.2% in all included patients regardless of the baseline level of hs-cTnT (*n*=1397) and 4.4% in all screened patients who were analysed with hs-cTnT (*n*=3169).

5.3.2 Main findings

A total of 65.2% of the patients with a dynamic one-hour change in hs-cTnT were admitted to hospital, compared to 13.9% of the patients with a non-dynamic change (Table 8). Four (26.7%) of the patients admitted in the dynamic group had an index diagnosis of MI, compared to one patient (0.7%) in the non-dynamic group. In addition, nine of the patients admitted (6.1%) in the non-dynamic group were diagnosed with UAP. Eight patients (34.8%) in the dynamic group were discharged directly from the ED, but none was diagnosed with ACS or readmitted during follow-up and no death occurred. In these eight patients, the one-hour change in hs-cTnT varied between 3 and 5 ng/L. No ACS or death occurred in the 920 patients (86.1%) in the non-dynamic group who were discharged directly from the ED. The median (min– max range) HEART score value among patients discharged with a dynamic change and among those admitted and diagnosed with ACS without a dynamic change was 1 (0–4) and 5 (4–7) respectively.

A total of 621 patients with an undetectable level of hs-cTnT at presentation were analysed separately. Six patients (1.0%) had a dynamic one-hour change in hs-cTnT. None of the 621 patients had an index diagnosis of MI and no MI, death or readmission occurred during follow-up. One patient (1.6%) in the non-dynamic group had an index diagnosis of UAP. Thus, in total, one of the 621 patients (0.2%) with an undetectable level of hs-cTnT at presentation was diagnosed with ACS.

Table 8. Comparisons of the non-dynamic and dynamic groups with a baseline value of ≤14 ng/L. A second value was obtained within a time period of >30 to ≤90 minutes, *n*=1091.

Variable	Δ<3 (*n*=1068)	Δ≥3 (*n*=23)	p
Age (years)	51.8 ± 16 [1062]	59.8 ± 14.2	0.018
Male gender	594 (55.6%)	10 (43.5%)	0.240
Systolic BP (mmHg)	147 ± 25 [1059]	148 ± 27 [22]	0.787
Diastolic BP (mmHg)	82 ± 12 [1050]	86 ± 17 [22]	0.091
Heart rate (bpm)	77 ± 16 [1054]	91 ± 27 [22]	<0.001
eGFR (mL/min/1.73 m^2)	93 ± 23 [1059]	85 ± 19	0.095
NT-proBNP (ng/L)	105 (38–221) [123]	147 (60–968) [8]	0.436
Time in the ED (min)	240 (194.5–309)	267 (182–355)	0.487
Time until attended by physician (min)	75 (38–143) [1058]	30 (21–71)	0.001
Admitted	148 (13.9%)	15 (65.2%)	<0.001
Myocardial infarction *(ICD I21–I22)*	1 (0.7%)	4 (26.7%)	<0.001
Unstable angina pectoris *(ICD I20.0)*	9 (6.1%)	0	1.000
Angina pectoris *(ICD I20.8–9)*	12 (8.1%)	1 (6.7%)	1.000
Atrial fibrillation *(ICD I48)*	8 (5.4%)	1 (6.7%)	0.590
Supraventricular tachycardia *(ICD I47.1)*	2 (1.4%)	1 (6.7%)	0.252
Unspecified chest pain *(ICD R07.4)*	70 (47.3%)	6 (40%)	1.000
Other diagnoses	46 (31.1%)	2 (13.3%)	0.234
Death within 30 days	1 (0.7%)	0	NS
Readmission within 30 days due to myocardial infarction, unstable angina pectoris or angina pectoris	0	0	NS
Readmission within 30 days due to any diagnosis	7 (4.7%)	0	0.502
Discharged directly from the ED	920 (86.1%)	8 (34.8%)	<0.001
Death or readmission within 30 days due to myocardial infarction or unstable angina pectoris	0	0	NS
Readmission within 30 days due to angina pectoris	1 (0.1%)	0	NS
Readmission within 30 days due to any diagnosis	11 (1.2%)	0	0.756

Data are presented as mean ± standard deviation or median (IQR) or sum and % of the total/ [amount of group].

Δ indicates delta; *n*, total number of patients in the group; BP, blood pressure; bpm, beats per minute; eGFR, estimated glomerular filtration rate; ng/L, nanograms/litre; NT-pro BNP, N-terminal prohormone of brain natriuretic peptide; ED, emergency department; ICD, international classification of diseases; NS, not significant.

5.4 STUDY IV

5.4.1 Study population

A total of 1,233 patients were included in the study. The 612 patients in phase 1 had a median age of 64 years and 57% were male. The 621 patients in phase 2 had a median age of 63 years and 54% were male. The two groups were similar with regard to most risk factors and comorbidities, but prior angina pectoris and revascularization was more common in patients included during phase 1. The median time from symptom onset to presentation was 2.8 (1.2–5.6) and 3.0 (1.6–5.3) hours during phase 1 and 2 respectively. A total of 93% and 91% of the patients in phase 1 and 2 had a normal ECG at presentation and 75% and 77% respectively had a baseline troponin level within the ULN. The median (IQR) HEART score was 3 (2–5) during phase 2. The incidence of an index MI in the study population was 10%. The absolute number of MIs was higher during phase 1 (*n*=83) compared to phase 2 (*n*=44) but the proportion of MIs among patients admitted was comparable between the two phases (23% and 22% respectively).

5.4.2 Admission rate

In the study, the admission rate decreased from 59% during phase 1 to 33 % during phase 2 (risk ratio [RR] [95% CI]: 0.55 [0.48–0.63]) (Table 9). After adjustment for differences in baseline and presentation characteristics, the odds of being admitted were still lower during phase 2 (odds ratio [OR] [95% CI]: 0.33 [0.25–0.42]). The difference in admission rate remained significant after also adjusting for index MIs (OR [95% CI]: 0.33 [0.25–0.44]). The adherence rate to the new algorithm was 87%, and 269 of 308 patients determined as low-risk patients during phase 2 were discharged directly from the ED.

5.4.3 Secondary objectives

The median (IQR) length of hospital stay decreased from 23.2 (4.3–48.2) hours during phase 1 to 4.7 (3.5–24.7) hours during phase 2 ($p<0.001$) (Table 9). This was mainly explained by the difference in admission rates between the two phases. The median (IQR) estimated median health care costs related to each hospital visit decreased from €1,651 (1,019–5,334) to €1019 (1,019–2,312) during phase 2 ($p<0.001$). The reduction was mainly caused by fewer admissions and fewer procedures, such as exercise ECG tests and coronary angiographies. A total of 3 (0.5%) and 3 (0.5%) patients had an MI after discharge in phase 1 respectively, and 2 (0.3%) and 0 (0%) patients died after discharge in phase 1 and phase 2 respectively. Two of the MIs in both phases occurred in patients discharged directly from the ED. No death occurred in patients discharged directly from the ED.

Table 9. In-hospital and 30-day outcome (*n*=1233).

	Phase 1		Phase 2				
	(*n*=612)		(*n*=621)		**RR**	**95% CI**	**p**
Admission to hospital	362	(59)	202	(33)	0.55	(0.48–0.63)	<0.001
Time to discharge (h)	23.2	(4.3–48.2)	4.7	(3.5–24.7)	–	–	<0.001
Health care-related costs (€)	1,651	(1,019–5,334)	1,019	(1,019–2,312)	–	–	<0.001
New presentation to the ED	78	(13)	81	(13)	1.02	(0.77–1.37)	0.876
Readmission to hospital	44	(8.0)	36	(6.0)	0.75	(0.49–1.14)	0.175
Unplanned revascularization [a]	3	(0.5)	6	(1.0)	1.97	(0.50–7.85)	0.506
Myocardial infarction after discharge	3	(0.5)	3	(0.5)	0.99	(0.20–4.86)	1.000
Death after discharge	2	(0.3)	0	(0)	–	–	0.246
Persistent chest complaints	212	(39)	214	(37)	–	–	0.481
Rating of own health (0–100)	75	(50–85)	75	(50–85)	–	–	0.819
Confidence in management (0–100)	90	(80–100)	95	(80–100)	–	–	0.012

Data are presented as median (IQR) or *n* (%).

[a] Defined as a new presentation to the ED followed by admission and revascularization.

CI, confidence interval; ED, emergency department; h, hours; IQR, interquartile range; RR, risk ratio.

5.4.4 Gender differences

Men and women were analysed separately regarding the main outcomes of the study (Table 10). In both men and women, the admission rate, as well as the time to discharge and the health care-related costs, were significantly lower during phase 2, compared to phase 1. Men seemed to have a somewhat longer stay in the hospital and somewhat higher health care-related costs during both phases compared to women. The numbers of deaths and MIs after discharge were very low in both men and women.

Table 10. In-hospital and 30-day outcome in men and women (*n*=1230).

	Phase 1		**Phase 2**		
Men (*n*=677)	(*n*=346)		(*n*=331)		**p**
Admission to hospital	210	(61)	115	(35)	<0.001
Time to discharge (h)	25.0	(4.6–51.2)	4.6	(3.4–27.4)	<0.001
Health care-related costs (€)	1,920	(1,019–6,465)	1,105	(1,019–3,823)	<0.001
New presentation to the ED	46	(13)	44	(13)	0.999
Readmission to hospital	24	(8.0)	23	(7.2)	0.711
Unplanned revascularization [a]	1	(0.3)	5	(1.5)	0.116
Myocardial infarction after discharge	1	(0.3)	3	(0.9)	0.363
Death after discharge	2	(0.6)	0	(0)	0.500
Women (*n*=553)	(*n*=264)		(*n*=289)		**p**
Admission to hospital	151	(57)	87	(33)	<0.001
Time to discharge (h)	10.4	(4.2–30.4)	4.7	(3.5–14.4)	<0.001
Health care-related costs (€)	1,522	(1,019–3,030)	1,019	(1,019–2,038)	<0.001
New presentation to the ED	32	(12)	37	(13)	0.809
Readmission to hospital	20	(8.0)	13	(4.6)	0.103
Unplanned revascularization [a]	2	(0.8)	1	(0.3)	0.608
Myocardial infarction after discharge	2	(0.8)	0	(0)	0.227
Death after discharge	0	(0)	0	(0)	–

Data are presented as median (IQR) or *n* (%).

[a] Defined as a new presentation to the ED followed by admission and revascularization.

ED, emergency department; h, hours; IQR, interquartile range.

5.4.5 Patients with a baseline troponin level within normal reference range

Altogether 461 (75%) of the patients during phase 1 and 476 (77%) of the patients during phase 2 had a baseline troponin level within the normal reference range. Fourteen (3.0%) of the patients during phase 1 and ten (2.1%) of the patients during phase 2 had an index diagnosis of MI (RR [95% CI]: 0.69 [0.31–1.54]). The primary and secondary outcomes of this subgroup are shown in Table 11. Of the 363 patients who were sent home from the ED during phase 2, two (0.6%) had a subsequent MI of which both had an elevated hs-cTn and a HEART score above 3.

Table 11. In-hospital and 30-day outcome in patients with a baseline troponin level within the normal reference range (*n*=937).

	Phase 1 (*n*=461)		**Phase 2** (*n*=476)		**p**
Admission to hospital [a]	229	(50)	113	(24)	<0.001
Time to discharge (h)	7.5	(3.8–27.9)	4.3	(3.3–6.8)	<0.001
Health care-related costs (€)	1,388	(1,019–2,657)	1,019	(1,019–1,862)	<0.001
New presentation to the ED	51	(11)	51	(11)	0.864
Readmission to hospital	29	(7.0)	20	(4.4)	0.091
Myocardial infarction after discharge	3	(0.7)	2	(0.4)	0.682
Death after discharge	0	(0)	0	(0)	–
Persistent chest complaints	167	(41)	158	(37)	0.167
Rating of own health (0–100)	75	(60–85)	75	(60–85)	0.927
Confidence in management (0–100)	90	(80–100)	95	(85–100)	0.011

Data are presented as median (IQR) or *n* (%).

[a] Risk ratio (95% confidence interval): 0.48 (0.40–0.58)

ED, emergency department; h, hours; IQR, interquartile range.

6 DISCUSSION

The introduction of hs-cTn assays in routine clinical care has considerably improved the assessment of patient presenting with symptoms suggestive of ACS. Due to the low threshold of detection and high precision in the lower measurement range, the time from presentation to diagnosis has been radically shortened[3 12 59]. The high diagnostic and prognostic performances of these assays have improved the assessment of prognosis in patients diagnosed with an MI, as well as in chest pain patients discharged directly from the ED[8 56 57]. However, biomarkers alone are not enough to rule out an ongoing ACS. Patient history and ECG still play an important role, especially in UAP patients where no alteration of cardiac biomarkers is seen[124]. To structure the clinical assessment, clinical risk scores are recommended and new scores focusing on low-risk chest pain patients have been validated[3 101 113 125]. Due to the progress in assessment seen during the last years, the need for admission and further testing in chest pain patients now seems unnecessary in many cases[77 78 84].

However, there is still limited evidence regarding the new assessment strategies that have been developed as a consequence of the new conditions discussed above. With the studies presented in this thesis, we aimed to add substantial knowledge to the research field by evaluating four approaches to assess patients presenting with symptoms suggestive of ACS in the era of hs-cTn.

6.1 THE VALUE OF PREDISCHARGE EXERCISE ECG TESTING

In the first study of this thesis, we evaluated the value of predischarge exercise ECG testing in chest pain patients in whom MI had been ruled out by means of medical history, ECG and hs-cTnT. The main findings were as follows: no statistically significant difference was seen regarding death or MI at 90 or 365 days when comparing patients with a positive and a negative predischarge exercise ECG test. In addition, the chest pain cohort studied had a very low risk of death and MI during 365 days of follow-up, a risk that was actually comparable to that of an age, gender and calendar time-matched cohort from the Swedish population. When analysing men and women separately, the findings in outcome were similar.

The study evaluated predischarge exercise ECG testing as performed in routine clinical care. We included a large cohort of chest pain patients equivalent in size with other large-scale exercise ECG testing studies, and the distribution between negative, positive and inconclusive test results was comparable with previous findings, even though some variation was seen, probably depending on differences in baseline characteristic of the cohorts[70 71 73 76 77].

Our results confirm the relatively high proportion of false positive tests seen in previous studies[69 71]. Out of the 94 patients (9.9%) with a positive predischarge exercise test, less than

fifty percent performed a coronary angiography before discharge and 28 (29.8%) were revascularized. This suggests that the clinicians did not entirely rely on the test result. No increase in death or MI as a consequence of omitting routine invasive evaluation in the positive exercise ECG group was seen when compared to the negative exercise test group, either at 90 or at 365 days. However, patients with a positive exercise test were to a greater extent revascularized when compared to patients with a negative test, both before and after discharge. This is expected since it is recommended by current guidelines. Our study cannot answer the question of whether the patients' symptoms prior to revascularization were due to CAD or whether revascularization in this non-MI population prevented death or MI[72].

Predischarge exercise ECG testing has been recommended as a rule-out strategy in chest pain patients as it is simple to perform and has a low complication rate, but also due to its high NPV[17 59 69-73]. In our study, only 4 (0.7%) of the patients with a negative exercise test died or had an MI within 365 days, indicating a high NPV. But, since the patient cohorts evaluated with predischarge exercise ECG testing mainly consists of low-risk patients with a very low risk of subsequent death [70 73 76 62], a high NPV is expected and the pre-test probability of having a positive test result is very low. The same low-risk pattern was seen in our study. The low incidences of death and MI were not restricted to patients with a negative test, only 7 out of 951 patients (0.7%) in the study cohort died or had an MI within 90 days of follow-up.

In our study, we found that the proportion of false positive tests was high. Moreover, more than one quarter of the patients had an inconclusive test result which left the clinician without guidance for further assessment. Moreover, there were no statistically significant differences in mortality or incidence of MI between patients with a negative and positive test result at 90 or 365 days of follow-up. Finally, the cohort of chest pain patients had a very low risk of subsequent death or MI comparable to the one-year risk of death and MI of a matched Swedish population.

Even though we cannot exclude the possibility of some prognostic impact of variations in coronary revascularization rates between patients with a negative and a positive test, our data suggest that routine predischarge exercise ECG testing does not provide additional information in a chest pain population where MI has been ruled out and the predischarge exercise ECG test may, therefore, be unnecessary. Further testing may be considered in selected patients but, considering the substantial risk of a misleading exercise ECG test result, other non-invasive methods or coronary angiography may be considered. Finally, since most hospitals do not provide exercise ECG testing at night and during weekends, this strategy could shorten the hospital stay thus reducing the costs.

6.1.1 Limitations

This was a retrospective study reflecting clinical practice. The decision to refer a patient to a predischarge exercise ECG test was not made according to a study protocol, but by the attending clinician. The classification of the test result in the study was based on the written

clinical conclusion, and the continuous ECG registration was not systematically reviewed. A prospective randomization to predischarge exercise ECG testing or a direct discharge, as well as the use of a study protocol to analyse the exercise ECG tests prospectively, would have provided more reliable results. However, this study reflects the assessment of chest pain patients in routine clinical care with its value and limits. The single-centre design may have reduced the generalizability of the results. The study was performed prior to the 2013 ESC guidelines on the management of stable coronary artery disease recommending risk stratification with pre-test probability, and it is possible that some of the exercise tests performed would have been omitted after the introduction of these guidelines [72]. Left ventricular function and the use of beta-blockers on the day of the test may have had an impact on the exercise test outcome, but these factors were unknown in the study. We classified tests without any sign of exercise-induced ischemia at a heart rate of ≥80% of the age-predicted maximum as negative, although a cut-off of 85% is conventional[69 70]. However, the 85% cut-off has never been validated and previous data suggest that the cut-off could be lowered to 80% of the age-predicted maximum heart rate[69 70]. The incidences of death and MI were low and a larger population might be required to identify differences between patients with a negative and a positive exercise ECG test. Still, the number of patients included in the study was equivalent to the number of patients in other large-scale exercise ECG test studies and the findings regarding outcome were similar. The registry follow-up was only performed within the County of Stockholm and clinical events occurring elsewhere during follow-up might have been missed.

6.2 EVALUATION OF A RULE-OUT ALGORITHM IN EARLY PRESENTERS

This is so far the largest study examining the diagnostic performance of the undetectable hs-cTnT at presentation algorithm in early presenters with a final diagnosis of NSTEMI. There has been some uncertainty regarding the safety of using the algorithm within 2–3 hours from symptom onset due to the lack of early presenters with MI in previous studies[3 11 93]. With the second study of the thesis we aimed to clarify this uncertainty. There is no consensus on acceptable sensitivities for MI, even though a sensitivity at or above 99% is often aimed at in routine clinical care, as discussed previously in this thesis[119]. Furthermore, little is known about the prognosis in NSTEMI patients presenting with an undetectable level of hs-cTnT. The main findings of the study were as follows:

An undetectable level of hs-cTnT at presentation alone did not result in an acceptable sensitivity for MI in patients presenting within 2 hours from symptom onset. However, combined with a non-ischemic ECG, the diagnostic sensitivity was as high as 99.4% (95% CI 98.4%–99.8%) in patients presenting in the second hour (i.e. >1 hour to ≤2 hours) from symptom onset, indicating that the algorithm might be applied in this population. These findings remained when analysing men and women separately. Previous studies have

suggested a minimum delay of 2 to 3 hours between symptom onset and presentation when applying the algorithm, due to a decreased diagnostic sensitivity for MI found in patients presenting earlier[11 86 89 90]. Our large cohort of early presenters with NSTEMI enabled a much more detailed analysis, as well as the possibility of dividing patients into those presenting within the first hour (i.e. ≤1 hour) and those presenting in the second hour.

An undetectable level of hs-cTnT at presentation combined with a non-ischemic ECG did not, however, result in a sufficient sensitivity for MI in patients presenting within the first hour from symptom onset (sensitivity 95.7%, 95% CI 92.5%–97.8%). We considered this to be due to the fact that the time interval was too short to expect an alteration of hs-cTnT levels and serial testing is preferred in this population[3 38 52].

Interestingly, we found a decreased diagnostic sensitivity for MI in the subgroup of patients aged ≤65 years without prior MI (sensitivity 98.5%, 95% CI 95.6%–99.7%), in patients presenting in the second hour from symptom onset. Our findings contradict results of previous studies where a similar or improved algorithm sensitivity was reported (similar among patients <70 and ≥70 years[91], improved among patients <65 years[11] and among patients with a non-high risk history, including younger patients and patients who less often had a history of MI [88]). The different results might partly be explained by the fact that these studies were not restricted to early presenters. The shorter the time interval from symptom onset to presentation, the higher the risk of a false negative hs-cTnT result, and elderly patients are in general more likely to present with a hs-cTnT above the LoD which lowers their risk of being missed by the undetectable hs-cTnT at presentation algorithm[11 86 91 126]. Another explanation might be the low number of NSTEMI patients in these studies when compared to our study. In a study focusing on early presenters (<3 hours), the diagnostic sensitivity for MI was above 99% when combining an undetectable hs-cTnT at presentation with a TIMI score of 0 points (which includes age <65 years)[87]. However, as in the other studies referred to, the number of patients with a final diagnosis of NSTEMI was low compared to our study, 269 patients had a MACE during follow-up.

The diagnostic sensitivity for MI among women aged ≤65 years without prior MI presenting in the second hour was decreased. However, when analysing men separately, a sensitivity of 99.3% (95% CI 96.1%–100.0%) was noted. Even though the CI is moderately broad, these finding indicate that the algorithm might be applied in men aged ≤65 years without prior MI presenting in the second hour from symptom onset. These findings could partly be explained by the fact that men in general have higher levels of hs-cTnT, as discussed in Chapter 2.2.3, which would then reduce their risk of being missed by undetectable hs-cTnT at presentation algorithm.

Finally, we found that NSTEMI patients admitted with an undetectable level of hs-cTnT at presentation were younger but had a similar 30-day outcome to those admitted with a detectable level. The peak levels of hs-cTnT and the incidence of revascularization were comparable. These findings indicate the importance of identifying NSTEMI presenting with an undetectable level of hs-cTnT.

6.2.1 Limitations

This was a retrospective study with a relatively high exclusion rate. A total of 700 patients identified as eligible in the SWEDEHEART registry were excluded during the screening process in the medical records due to the fact that data regarding time from symptom onset to presentation could not be verified. Altogether, 89 patients were excluded due to a type 2 MI or a myocardial injury. Since the MI diagnoses in the study were set by the clinicians and not all patients underwent coronary angiography, it is possible that some MIs were incorrectly classified. However, the validity of MI diagnoses set in routine clinical care in Sweden has been reported to be high[127]. The time of taking blood samples may deviate somewhat from that stated in the medical records, since the time used was the time when the electronic referral for analysis of the sample was sent to the laboratory. For this reason, we chose to use the time from symptom onset to presentation to the hospital in the inclusion criteria and the analysis of the results. We evaluated the diagnostic performance of the algorithm by calculating sensitivity. Specificity, PPV or NPV could not be calculated, since only cases with MI were included in the study. However, the aim was to evaluate the safety of the algorithm and sensitivity is then considered to be the most important measurement. In spite of our large sample of early presenting NSTEMI patients, only 24 presented with an undetectable level of hs-cTnT. Since we only included patients admitted, we might have missed some NSTEMI patients with an undetectable level of hs-cTnT discharged directly from the ED. If these patients presented again, they would then present with a detectable level of hs-cTnT, which falsely may have increased the calculated diagnostic sensitivity for MI in our study. It is also possible that such patients chose not to present again or died before presentation. Unfortunately, neither the SWEDEHEART registry, nor the Swedish patient registry could provide data on reinfarction within 30 days, which is why this information is missing in the study. Regarding mortality data, a larger population would have been needed in order to compare differences in mortality between the groups.

6.3 EXPERIENCES OF A ONE-HOUR ALGORITHM IN ROUTINE CLINICAL CARE

The third study of the thesis evaluated some of the consequences of the use of a one-hour hs-cTnT algorithm when implemented in routine clinical care. The patient population consisted of an unselected ED population of chest pain patients with a non-elevated hs-cTnT at presentation, which contrasts with several previous studies where the focus has been a more selected chest pain population at a higher risk of ACS[13 94 96] . The main findings of the study were the following: in chest pain patients presenting with a non-elevated hs-cTnT, dynamic one-hour changes in hs-cTnT were uncommon but were associated with a higher rate of admission and of MI. No death or MI occurred among patients discharged directly from the ED during follow-up.

Dynamic one-hour changes in hs-cTnT occurred in 23 (2.1%) of the patients, while 97.9% of the patients had a non-dynamic change. The explanation for the low proportion of patients with dynamic changes is partly the fact that we included a large proportion of all patients presenting to the ED with chest pain, which also reflects the situation in routine clinical care. Even more important is the fact that only patients presenting with a non-elevated hs-cTnT were included in the final analysis. This led to a higher proportion of patients in the non-dynamic group when compared to prior one-hour algorithm studies that included patients regardless of the baseline level of hs-cTnT[13 94 96].

The difference in admission rate between the dynamic and non-dynamic groups was significant (65.2% vs. 13.9%) and suggests that the algorithm was applied by the clinicians. The low proportion of admitted patients in the non-dynamic group probably reflects assessment with both the one-hour hs-cTnT algorithm and the HEART score, even though the HEART score was not systematically evaluated in this study. There was also a significant difference in the rate of MI among patients admitted (26.7% vs. 0.7%) when comparing the dynamic and the non-dynamic groups. Altogether, 17.4% of all patients presenting to the ED with dynamic one-hour changes in hs-cTnT had a final diagnosis of MI, compared to 0.1% of the patients presenting with a non-dynamic change. These findings suggest that the algorithm could be both useful for rapid rule-in of MI as well as safely applied for rule-out of MI in an ED chest pain population, a population with a traditionally high admission rate. In our study, the total incidence of MI among those presenting with a hs-cTnT of ≤14 ng/L was low, 0.5%, and it has been discussed whether a single presentation value of hs-cTnT of ≤14 ng/L would be enough to rule out an ongoing MI. This has, however, been shown to be insufficient[92]. Also, the results of the FASTEST study support further evaluation in chest pain patients presenting with a hs-cTnT of 14 ng/L, since 24 of the 937 patients (2.6%) presenting with a non-elevated troponin had a final diagnosis of MI (Chapter 5.4.5).

Compared to previous studies evaluating the original one-hour hs-cTn algorithm, the incidence of MI was markedly lower in our study[13 14 94 96]. We consider this due to the fact that we included an unselected ED chest pain population and only included patients presenting with a non-elevated hs-cTnT. The latter reduced the incidence of MI from 4.2% in our study population, to 0.5% in the patients included in the final analysis. The MI incidence within 30 days of follow-up was only slightly higher (5.4%) in another study focusing on an unselected chest pain population in the ED[86].

The majority of patients with dynamic one-hour changes in hs-cTnT were not diagnosed with ACS and the release of, as well as dynamic changes in, hs-cTnT, were considered to be due to diagnoses other than a type 1 MI, which has also been shown in earlier studies[12 36 37 128]. In the non-dynamic group, nine of the patients admitted had a final diagnosis of UAP which formally goes without an elevation in hs-cTnT levels[124]. However, the median HEART score value for these patients and for the one patient with MI was elevated (5 points). This suggests not only that patients at an acute risk of a MACE could be identified by the HEART score, but also that a careful clinical assessment is needed in patients presenting with chest pain.

Finally, none of the 920 patients (86.1%) in the non-dynamic group who were discharged directly from the ED died or had an MI during the 30-day follow-up.

In conclusion, we found that it was possible to implement a one-hour measurement of hs-cTnT in chest pain patients presenting with a non-elevated value in routine clinical care. Moreover, even though early dynamic changes in hs-cTnT were uncommon, the one-hour measurement improved the assessment when compared to a single baseline value of ≤14 ng/L. Finally, a one-hour measurement of hs-cTnT may facilitate an early rule-out of MI in chest pain patients, thus reducing the proportion of patients admitted without a final diagnosis of MI. However, troponins cannot replace a careful clinical assessment, e.g. with the HEART score, especially not in those ACS patients where dynamic one-hour changes in hs-cTnT cannot be seen.

6.3.1 Limitations

This was a single-centre, retrospective study. The single-centre design may have influenced the generalizability of the results. The decision to include all patients presenting with a chief complaint of chest pain reduced the proportion of patients with high risk of an ACS and an evaluation of the algorithm in a more selected population might be of clinical value. However, since the population included reflected the patients presenting to the ED in routine clinical care, our results could provide results that are more representative of the one-hour algorithm when implemented in clinical practice, when compared to previous controlled studies. A relatively high proportion of the patients screened had no or only one hs-cTnT analysed in the ED. Again, this indicates that the study population was a low-risk population. The decision to omit the second sample could be in accordance with the present guidelines (e.g. long duration since pain onset, undetectable baseline hs-cTnT, admission without further assessment)[3]. Due to the difficulties of obtaining a blood sample after precisely one hour in routine clinical care, a time interval of >30–≤90 minutes was accepted. Even though a small proportion of the second samples were obtained ≤60 minutes, no MACE occurred in patients discharged from the ED. Another challenge in routine clinical care is that the time from obtaining the blood sample to the end of the analysis often exceeds one hour. Therefore, it is likely that in a large proportion of the patients in the study the result of the first hs-cTnT sample was not known when the second sample was obtained. Even though the one-hour algorithm was implemented together with the HEART score at the study centre, the HEART score was not systematically documented and could therefore not be evaluated in this study. Both the incidence of dynamic one-hour changes in hs-cTnT and that of MI was low, and a larger population would be needed to evaluate the rule-in part of the algorithm as well as to verify the safety of the algorithm. Nevertheless, the excellent safety of the one-hour algorithms has been validated in several previous studies[13 96 97].

6.4 EVALUATION OF A ONE-HOUR ALGORITHM AND A RISK SCORE COMBINED

In this prospective observational multicentre study, the combination of a one-hour hs-cTn algorithm and the HEART score was evaluated for the first time in routine clinical care. Our main findings in this fourth study of the thesis were the following: the new algorithm was associated with a reduction in admission rates, shorter hospital stays and reduced health care-related costs, with very low rates of 30-day MACEs. The adherence rate to the algorithm was high, 87%. No major differences were seen when analysing men and women separately.

After the implementation of the algorithm in routine clinical care, the admission rate decreased from 59% to 33%. This finding remained after adjusting for differences in baseline and presentation characteristics and the number of index MIs between the two study phases (OR [95% CI]: 0.33 [0.25–0.44]). The significant decrease in admission rate also remained (50% to 24%) when analysing patients presenting with a troponin level within the normal reference range, i.e. in those affected by the new algorithm. A previous small single-centre RCT using a three-hour measurement of conventional troponin combined with the HEART score showed a similar positive effect[111]. The HEART score alone was recently compared to standard care in a large, multicentre RCT. In this study, no reduction in admission rate was seen, which might be explained by a lower adherence rate (82%) to the HEART score strategy in low-risk patients but also to differences in study size and design[103].

The median time to discharge was significantly reduced from 23.2 to 4.7 hours. In the above-mentioned small RCT, the time to discharge was reduced from 21.9 to 9.9 hours[111]. The shorter hospital stays seen in our study might be explained by the use of hs-cTn assays, which enabled a shorter sample interval. The combination of a two-hour hs-cTn algorithm and a modified TIMI score or the EDACS has been shown to significantly increase the number of patients discharged within 6 hours without any increase in MACE[6 110 114]. A similar positive effect was seen in a small study combining hs-cTn at presentation with the MACS decision rule[116]. However, direct comparisons between the new algorithms are limited.

The reduction in admission rate did not result in longer stays in the ED or an increase in tests and examinations after discharge. On the contrary, the proportion of non-invasive tests and coronary angiographies was significantly lower during the second phase of the study. A similar pattern was noted in a study evaluating the transition from conventional troponin to hs-cTn assays in routine clinical care[129].

The estimated median (IQR) health care costs related to each hospital visit decreased from €1,651 (1,019–5,334) to €1,019 (1,019–2,312) during the second phase of the study. The reduced costs were attributed to the lower admission rate and the reduction in diagnostic procedures. In the large multicentre RCT evaluating the HEART score, costs were calculated over 3 months, which is why we cannot make a direct comparison with our study. However,

in the latter study, no cost reduction was seen in the group of patients assessed with the HEART score[103].

The study was not powered to detect a difference in MACE. However, the rates of MI, death, new presentation to the ED, readmission to the hospital and unplanned revascularization after discharge were very low in both study phases. No death occurred among patients discharged directly from the ED. Two patients (0.8%) in the first phase and two (0.5%) in the second had an MI after being sent home from the ED. However, both patients in the second phase had an elevated delta troponin and a HEART score above 3, i.e. not considered suitable for rule-out according to the algorithm.

In conclusion, the adding of the HEART score to the one-hour hs-cTn algorithm improved the assessment of patients presenting to the ED with symptoms suggestive of an ACS.

6.4.1 Limitations

This was a prospective observational before-after study where patients were not randomized to one of the two assessment strategies. This design implies an elevated risk of bias due to differences between the two cohorts that may not be identified and adjusted for, which may be associated with the study outcome. There was an imbalance regarding recruitment to the two phases of the study. The recruitment rate was low, especially during the second phase, which increases the risk of selection bias. Patients in the second phase had a history of cardiovascular disease and revascularization somewhat less often and the proportion of index MIs was lower during the second phase. Even though adjustments for these differences were made in a logistic regression analysis and in a sensitivity analysis, there might still be residual confounders that may weaken the association between the study phases and the study outcomes. For example, we were not able to adjust for the bed occupancy in the hospitals participating. An RCT would have improved the reliability of the results and minimized the problem with residual confounders. Conclusions about causality instead of association could have been made. However, there is a risk that the assessment strategy in one group would influence the assessment in the other group and thereby affect the difference in outcome between the two phases. Another, preferable, option would have been a stepped-wedge, cluster-randomized trial, but the risk of influence between the two groups would remain since our study was performed in a limited geographical region. A second advantage with a stepped-wedge cluster-randomized design would be that overall patient consent for the site could be obtained, instead of an informed consent from each study participant. This might reduce the risk of selection bias at inclusion. However, such a selection bias would most probably be non-differential, since it would be the same for the two phases and would hence not affect the outcome.

In addition to the logistic regression analysis, several measures were taken in order to minimize the time-dependent differences in the study. The new assessment strategy was introduced and implemented immediately after the completion of the first phase of the study,

and the second phase started as soon as the new assessment strategy was considered implemented. We also analysed patients with a baseline troponin level within the normal reference range and with no difference in the proportion of patients with an index MI separately.

The presence of a research assistant in the ED might have increased the clinicians' adherence to the new algorithm, hence leading to a higher adherence rate inside compared to outside the study. The study was not powered to detect a difference in MACE, but the safety of the one-hour hs-cTnT algorithm and the HEART score has been validated in several previous studies[13 65 96 97 103].

6.5 PATIENTS WITH AN UNDETECTABLE LEVEL OF HIGH-SENSITIVITY CARDIAC TROPONIN

In three of the studies we evaluated patients with an undetectable level of hs-cTnT, either at presentation or as a peak value before discharge. In the study evaluating predischarge exercise ECG testing, 445 (46.8%) of the 951 patients included had a peak value of hs-cTnT of <5 ng/L combined with a non-ischemic ECG at presentation. This group had an excellent prognosis, with only three (0.7%) of the patients reaching the combined endpoint of death or MI within a year. In the study evaluating a one-hour hs-cTnT algorithm in the ED the findings were similar. In total, one (0.2%) of the 621 patients presenting with an undetectable level of hs-cTnT had a final diagnosis of UAP. These findings are supported by previous studies evaluating an undetectable level of hs-cTnT or I at presentation and according to present guidelines further evaluation of these patients might be omitted after a careful clinical assessment[1 3 11 86 90 91]. However, our study including 24 early presenting NSTEMI patients with an undetectable level of hs-cTnT at presentation showed that, even though they were younger, these NSTEMI patients had a similar 30-day outcome as NSTEMI patients presenting with detectable levels. It is, therefore, important to identify patients with an undetectable level of hs-cTnT and an elevated risk of a MACE.

In chest pain patients without a final diagnosis of ACS, there seems to be a graded relationship between the levels of hs-cTnT and cardiovascular morbidity and all-cause mortality. The risk seems to increase already in patients presenting with a hs-cTnT of 5–14 ng/L[126 130-135].

6.6 PRESENT AND FUTURE PERSPECTIVES

In this thesis we evaluated different methods of assessing patients presenting with symptoms suggestive of ACS in the era of hs-cTn. The findings of the studies suggest that a more rapid

assessment than the ones recommended in the ESC guidelines would be possible. The current ESC guidelines suggest predischarge stress testing (exercise ECG testing if stress imaging testing is not available) in patients with a pre-test probability of CAD of 15–85% after rule-out of MI[72]. The results of our first study indicate that routine predischarge exercise ECG testing is unnecessary in such a population. Furthermore, due to limited data, the ESC guidelines advise against using the undetectable level of hs-cTn at presentation algorithm or the original one-hour hs-cTn algorithm within three hours from symptom onset[3]. The findings of our second study suggest that a time interval of one hour from symptom onset to presentation would be sufficient to apply the undetectable level of hs-cTn at presentation algorithm. In the fourth study of this thesis, 50% of the patients assessed with the one-hour hs-cTn algorithm combined with the HEART score presented within three hours from symptom onset. Finally, the study population in our third study was an unselected ED chest pain population, a patient population at a lower risk than the patients included in previous one-hour hs-cTn algorithm studies, which contributes valuable information about the algorithm when applied in routine clinical care.

The studies of this thesis were observational. To evaluate the research questions in an RCT would improve the reliability of the results and enable conclusions about causality. This would increase the possibility of impacting guidelines.

Several new algorithms have been developed in recent years and direct comparisons, both between hs-cTn algorithms and the newly developed risk scores would be of great value. A prospective comparison between the HEART score and a simplified version, the HET score including medical history, ECG and troponin, would also be of interest. A previous, retrospective study found that these three variables were independent predictors of a MACE, while age and risk factors were not[5]. In the second study of this thesis, we found that younger patients with fewer risk factors of atherosclerotic disease were at a higher risk of being missed by the undetectable hs-cTnT at presentation algorithm, which also supports an evaluation of the HET score.

The new hs-cTn algorithms have shown an excellent sensitivity, thus enabling a safe rule-out of MI at an early stage. However, the specificity of the hs-cTn algorithms is lower and patients ruled in by the algorithms might eventually be discharged without an MI diagnosis. This is partly due to the high sensitivity of hs-cTn assays to cardiomyocyte injury, and partly to the decision to use the 99th percentile of healthy controls as a cut-off for a non-pathological hs-cTn value. New assessment strategies are needed for patients presenting with a discrete elevation of hs-cTn but without other findings indicating an MI.

Measurement of hs-cTn should be combined with a careful clinical examination in order to identify ACS patients without elevation of hs-cTn. Further development of safe and easily used clinical risk scores would improve the assessment of these patients.

7 CONCLUSIONS

Routine predischarge exercise ECG testing had no prognostic value in chest pain patients admitted in whom MI had been ruled out by means of medical history, ECG and hs-cTnT.

An undetectable level of hs-cTnT at presentation combined with a non-ischemic ECG may be used to safely rule out MI in patients presenting as early as in the second hour from symptom onset. Patients aged ≤65 years without a history of MI should be assessed with caution. NSTEMI patients presenting with an undetectable level of hs-cTnT were younger than those presenting with a detectable level but had a similar 30-day outcome.

Early dynamic changes in hs-cTnT were uncommon in an unselected ED population of chest pain patients presenting with a non-elevated hs-cTnT, but a one-hour hs-cTnT algorithm identified MI patients and facilitated an early rule-out of MI in this population.

The structured implementation of a one-hour hs-cTn T or I algorithm combined with the HEART score in routine clinical care was associated with a reduction in admission rate, time to discharge and health care-related costs in patients presenting to the ED with symptoms suggestive of an ACS, with very low rates of death and MI after discharge.

In conclusion, the diagnostic pathways for patients with suspected ACS have been radically shortened with the introduction of hs-cTn in routine clinical care. Our findings support the use of early rule-out protocols in the ED based on a single baseline value of undetectable hs-cTn or a one-hour hs-cTn algorithm, preferably combined with a simple risk score. Furthermore, our findings support the fact that routine admission, as well as routine predischarge exercise ECG testing, can be omitted in this population, a measure that could shorten hospital stays and reduce health care-related costs.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING

Bröstsmärta är en av de vanligaste sökorsakerna vid sjukhusens akutmottagningar. Det är också det allra vanligaste symtomet vid akut koronart syndrom (AKS), dvs. hjärtinfarkt eller instabil kärlkramp. Traditionellt har ungefär 40 % av bröstsmärtepatienterna som söker akut lagts in på sjukhus för vidare utredning men bara 5–20 % av alla sökande får diagnosen AKS. Ett fåtal av dem som läggs in får andra allvarliga diagnoser såsom blodpropp i lungan eller skada på stora kroppspulsådern, men den stora majoriteten kan skrivas ut med en helt godartad diagnos. Å andra sidan visar studier att ungefär 1 % av bröstsmärtepatienterna som skickas hem direkt från akutmottagningen drabbas av en allvarlig hjärt- och kärlhändelse inom 30 dagar.

År 2010 introducerades en känsligare mätmetod för att upptäcka hjärtinfarkt vid blodprovstagning. Blodprovet kallas högkänsligt troponin och finns i två likvärdiga former: högkänsligt troponin T och I vilka frisätts från hjärtmuskeln vid hjärtinfarkt. Istället för att som tidigare vänta tre till sex timmar efter att bröstsmärtan startade, kan man nu göra blodprovsanalysen redan efter någon timme. Detta har medfört att nya rutiner för handläggning av bröstsmärtepatienter har utvecklats, i syfte att så tidigt som möjligt i förloppet ställa rätt diagnos. Genom att tidigt bekräfta eller utesluta AKS möjliggörs ett förbättrat omhändertagande av bröstsmärtepatienter vid sjukhusens akutmottagningar, där behandling för dem med AKS kan sättas in snabbt och patienter utan AKS eller annan allvarlig diagnos kan skickas hem direkt från akutmottagningen. Detta är positivt för patienterna och optimerar samtidigt utnyttjandet av hälso- och sjukvårdens resurser.

Syftet med denna avhandling har varit att bidra med ny kunskap inom detta forskningsområde genom att utvärdera fyra olika rutiner för handläggning av patienter med misstänkt AKS efter införandet av högkänsligt troponin i den kliniska vardagen.

I den första studien utvärderade vi värdet av arbetsprov på träningscykel inför utskrivning från hjärtkliniken vid Södersjukhuset i Stockholm, från januari 2011 till juni 2012 för bröstsmärtepatienter där hjärtinfarkt uteslutits med symtombeskrivning, EKG och högkänsligt troponin T. Arbetsprov har länge varit en rutinundersökning för dessa patienter men nya studier talar för att resultatet ofta är felaktigt eller svårtolkat, vilken kan leda till onödig utredning av patienter som i slutänden visar sig vara friska. I vår studie, med 951 patienter, förelåg ingen signifikant skillnad i antalet dödsfall eller hjärtinfarkter under tolv månaders uppföljning när vi jämförde patienter med patologiskt arbetsprovsresultat med dem med normalt arbetsprovsresultat. Vi jämförde även alla studiepatienter oavsett arbetsprovsresultat med en matchad svensk kohort. Risken för död och hjärtinfarkt inom ett år var jämförbar mellan dessa båda grupper.

I den andra studien undersökte vi huruvida ett icke mätbart värde av högkänsligt troponin T (dvs. under detektionsgränsen för mätmetoden) vid ankomst i kombination med ett normalt

EKG kunde utesluta akut hjärtinfarkt hos patienter som sökte vård inom två timmar från symtomdebut. Via register- och journalgenomgång fann vi 911 patienter som vårdats pga. hjärtinfarkt vid fem akutsjukhus i Stockholm 2011–2015, och som sökt vård inom två timmar från symtomdebut. Studien visade att man för flertalet patienter med icke mätbart högkänsligt troponin T och normalt EKG med hög säkerhet kunde utesluta hjärtinfarkt redan efter en till två timmar efter symtomdebut. Däremot var säkerheten otillräcklig för dem som sökte vård inom en timme och för yngre patienter utan tidigare hjärtinfarkt. Studien visade också att de som vårdades pga. hjärtinfarkt hade en likvärdig 30-dagarsprognos, oavsett mätbart eller icke mätbart värde av högkänsligt troponin T vid ankomst.

I den tredje studien utvärderade vi införandet av entimmesmätning av högkänsligt troponin T vid akutmottagningen vid Karolinska Universitetssjukhuset Solna i Stockholm. Den nya arbetsrutinen gällde alla patienter som sökte pga. bröstsmärta och som hade ett första värde av högkänsligt troponin T inom normalreferensen. Dessa fick lämna ytterligare ett blodprov efter en timme. Vi inkluderade 1091 patienter från december 2014 till september 2015 och följde dem i 30 dagar. Studien visade att det var ovanligt med ett stigande värde (>2 enheter) av högkänsligt troponin T i denna patientgrupp, men att det var associerat med en ökad risk dels för sjukhusinläggning, dels för hjärtinfarktdiagnos. Ingen av dem som skickades hem direkt från akutmottagningen efter införandet av den nya arbetsrutinen avled eller drabbades av hjärtinfarkt under uppföljningstiden.

I den fjärde studien utvärderade vi effekten av införandet av entimmesmätning av högkänsligt troponin T eller I kombinerat med ett enkelt riskvärderingsformulär (HEART score). Studien genomfördes vid sex akutmottagningar i Stockholm och Uppsala och var uppdelad i två faser, före (juni 2013– september 2014) och efter (januari 2015– maj 2016) införandet av den nya rutinen. De två faserna jämfördes med varandra. Totalt inkluderades 1233 patienter vilka följdes under 30 dagar. Studien visade att den nya rutinen var associerad med en signifikant minskning av antalet sjukhusinläggningar, vårdtid och sjukvårdsrelaterade kostnader. Ett mycket litet antal hjärtinfarkter men inget dödsfall inträffade bland de patienter som skickades hem direkt från akutmottagningen efter införandet av det nya arbetssättet.

Sammantaget har denna avhandling bidragit med ny och viktig kunskap om omhändertagandet av patienter med misstänkt AKS efter införandet av högkänsligt troponin. Vi har visat att arbetsprov inte tillför någon prognostisk information efter att hjärtinfarkt uteslutits. Vidare har vi visat att hjärtinfarkt kan uteslutas med ett icke mätbart värde av högkänsligt troponin och ett normalt EKG redan efter en till två timmar efter symtomdebut. Slutligen har vi visat att entimmesmätning av högkänsligt troponin, gärna i kombination med ett enkelt riskvärderingsformulär, förbättrar tidig diagnostik av hjärtinfarkt vilket i sin tur kan leda till ett minskat antal sjukhusinläggningar och minskade hälso- och sjukvårdskostnader.

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