Early diagnostic evaluation of patients with possible acute coronary syndrome, with special emphasis on troponin T

Early diagnostic evaluation of patients with possible acute coronary syndrome, with special emphasis on troponin T

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DOCTORAL DISSERTATION

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| The majority of chest pain patients presenting to the emergency department (ED) prove not to have acute coronary syndrome (ACS) and to identify patients without severe disease that may be discharged after minimal testing, is a challenge.  Our first study was a retrospective real life study with the aim to validate the 2011 European Society of Cardiology (ESC) guidelines, which stated that non-ST-elevation acute coronary syndromes (NSTE-ACS) might be excluded with a rapid 3 h high-sensitivity troponin (hsTn) sampling protocol. We found that non ST-elevation myocardial infarction (NSTEMI), but not acute coronary syndrome (ACS), could be ruled out with hsTnT within 3-4 h from ED presentation (NPV 99% and 79%, respectively). We also found that using the standard cut-off (≤ 14 ng/L), hsTnT was unable to rule in ACS, and that hsTnT elevations were very common in patients ≥ 75 years presenting to the ED without ACS. These results were confirmed in paper III where we evaluated if higher cut offs for hsTnT, or a combination of a higher cut off and the early dynamic hsTnT change could improve specificity and PPV for ACS or NSTEMI in patients ≥ 75 years. The combination of a higher cut-off and the hsTnT change resulted in higher specificity and PPV but the diagnostic performance was not improved to an extent likely to be useful in routine clinical care.  In paper II we evaluated if analyses of hsTnT and copeptin in combination could be used to rule out ACS immediately on patient presentation to the ED. We concluded that the combination could rule out NSTEMI at presentation, but not ACS.  In the last paper, we found that a simple and fast diagnostic protocol (the CORE decision rule) could identify patients with a very low risk (< 1 %) for major adverse cardiac events (MACE) within 30 days from presentation.  In conclusion, our studies have important implications for the current chest pain management in the ED. | | |
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*Always pass on what you have learned*

*To my family*

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## List of publications

The thesis is based on the following papers, which will be referred to by their Roman numerals:

#### Paper I:

High-sensitivity troponin T as a diagnostic tool for acute coronary syndrome in the real world: an observational study.

**Catharina Borna**, Johan Thelin, Bertil Ohlin, David Erlinge and Ulf Ekelund European Journal of Emergency Medicine 2014, 21:181–188

#### Paper II:

The combination of high sensitivity troponin T and copeptin facilitates early rule-out of ACS: a prospective observational study.

Johan Thelin, **Catharina Borna,** David Erlinge and Bertil Öhlin.

BMC Cardiovasc Disord. 2013; 13: 42.

#### Paper III:

Predictive role of high sensitivity troponin T within four hours from presentation of acute coronary syndrome in elderly patients. **Catharina Borna**, Katarina Lockman Frostred and Ulf Ekelund BMC Emergency Medicine (2016) 16:1

#### Paper IV:

The clinical objective rule-out evaluation (CORE) allows early rule out of major adverse cardiac events in acute chest pain patients. **Catharina Borna**, Knut Kollberg, Arash Mokhtari, David Larsson and Ulf Ekelund. *Submitted European Journal of Emergency Medicine.*

## Abbrevation list

ACS = acute coronary syndrome

AMI = acute myocardial infarction

CABG = coronary artery bypass surgery

CI = confidence interval

CKD = chronic kidney disease

ECG = electrocardiogram

ED = Emergency Department

EDACS = Emergency Department Assessment of Chest pain Score

HsTnT = high-sensitivity cardiac troponin T

HsTn = high-sensitivity troponin

LBBB = left bundle branch block

MACE = major adverse cardiac event

MI = myocardial infarction

NPV = Negative predictive value

NSTE-ACS = non-ST-elevation acute coronary syndrome

NSTEMI = non ST-elevation myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-elevation myocardial infarction

SWEDEHEART = Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies

ULN = upper limit of normal, 99th percentile of healthy controls

## Abstract

The overall aim of this PhD project was to increase the understanding of the strengths and weaknesses of high-sensitivity cardiac troponin T (hsTnT) as an early diagnostic tool in patients with possible acute coronary syndrome.

The majority of chest pain patients presenting to the emergency department (ED) prove not to have acute coronary syndrome (ACS). Distinguishing patients with ACS among the many patients with chest pain, and to identify patients without severe disease that may be discharged after minimal testing, is a challenge. Rapid and powerful diagnostic tools are needed in order to reduce inconvenience for the patient and costs for the health care system.

In recent years, new high-sensitivity troponin (hsTn) tests have been presented, but their clinical value in routine care has not yet been established. In this thesis, chest pain patients presenting to the ED at the Skåne University Hospital in Lund were studied.

Our first study was a retrospective real life study with the aim to validate the 2011 European Society of Cardiology (ESC) guidelines, which stated that non-ST-elevation acute coronary syndromes (NSTE-ACS) might be excluded with a rapid 3 h hsTn sampling protocol. We found that non ST-elevation myocardial infarction (NSTEMI), but not acute coronary syndrome (ACS), could be ruled out with hsTnT within 3-4 h from ED presentation in our unselected ED patients (NPV 99% and 79%, respectively). We also found that using the standard cut-off (≤ 14 ng/L), hsTnT was unable to rule in ACS, and that hsTnT elevations were very common in patients ≥ 75 years presenting to the ED without ACS. These results were confirmed in paper III where we evaluated if higher cut offs for hsTnT, or a combination of a higher cut off and the early dynamic hsTnT change could improve specificity and PPV for ACS or NSTEMI in patients ≥ 75 years. The combination of a higher cut-off and the hsTnT change resulted in higher specificity and PPV with maintained high sensitivity and NPV, but the diagnostic performance was not improved to an extent likely to be useful in routine clinical care.

In paper II we evaluated if analyses of hsTnT and copeptin in combination could be used to rule out ACS immediately on patient presentation to the ED. We concluded that the combination could rule out NSTEMI at presentation, but not ACS. The combination of hsTnT and copeptin tests at presentation was equivalent to hsTnT analysed at 3-4 h.

In the last paper, we found that a simple and fast diagnostic protocol (the CORE decision rule) could identify patients with a very low risk (< 1 %) for major adverse cardiac events (MACE) within 30 days from presentation.

The first three real life studies in the present thesis are important complements to previous prospective studies performed in less generalisable settings. The findings support that hsTnT and copeptin are useful in the early rule-out of NSTEMI in both unselected and elderly ED patients. In contrast, a single value of hsTnT, or the combination of hsTnT and copeptin, cannot be used to rule in NSTEMI or ACS in unselected ED patients. In elderly patients, the limitations of hsTnT as a rule-in tool are even more pronounced.

The CORE decision rule has the potential to shorten the length of ED stay and in particular, reduce the need of additional investigations and costs.

In conclusion, our studies have led to a better understanding of hsTnT as an early diagnostic tool in patients with possible ACS. The results have important implications for the current chest pain management in the ED.

# Background

## Ischemic heart disease

It is well established that ischemic heart disease (IHD) is a leading cause of death in the western world. In Sweden cardiovascular disease was the underlying cause of death in 36 % of cases in 2014 (*Swedeheart Annual Report 2015*). IHD accounted for 44 % of cardiovascular causes. According to calculations from the Institute for Health Economics in Lund, the total economic cost in 2010 was SEK 61.5 billion including costs of medical care accounting, informal care by family and friends and loss of production.

Several factors account for the increasing burden of cardiovascular disease, including longer average life span, tobacco use, decreased physical activity, and increased consumption of unhealthy food [[1](#_ENREF_1)].

The term *myocardial infarction* (MI) signifies a loss of cardiac myocytes (necrosis) caused by prolonged ischemia. *A*cute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) [[2](#_ENREF_2)].NSTE-ACS is three times more common than STEMI and account for about 1 million hospital admissions yearly in the United States [[1](#_ENREF_1)].

#### Universal definition of myocardial infarction [[3](#_ENREF_3)]

A combination of criteria is required to warrant the diagnosis of AMI; a dynamic change of a biomarker of myocardial necrosis, and at least one of the following:

1. Symptoms of ischemia
2. New ST-T wave changes on ECG
3. Development of Q waves on ECG
4. Imaging evidence of new loss of viable myocardium
5. Intracoronary thrombus

#### Distinguishing type 1 MI from type 2 MI

Type 1 MI occurs after an atherosclerotic plaque rupture resulting in decreased myocardial blood flow. Type 2 MI is a myocardial necrosis due to an imbalance between myocardial oxygen supply and demand. This can be seen in conditions like arrhythmias, heart failure, anemia and respiratory failure [[4](#_ENREF_4)]. It can sometimes be difficult for clinicians to distinguish these two types of MI, and there is a need for clarification in this area to define the frequency and prognosis of type 2 MI. It is also important that appropriate therapy can be administered to the patients with type 1 MI [[5](#_ENREF_5)].

## Emergency Department Assessment of Acute-Onset Chest Pain

Chest pain is a frequent symptom in the ED but the majority of these patients prove not to have ACS [[6](#_ENREF_6), [7](#_ENREF_7)]. About 15 million patients per year in the United States and Europe present to the ED with chest pain or other symptoms suggesting ACS [[8](#_ENREF_8)], i.e. AMI or UA. One challenge in the ED is to safely identify cases without severe disease. A fast and efficient way to identify patients eligible for early discharge is needed to avoid prolonged stays, investigations and unnecessary admissions. It has been estimated that about 6000 SEK (approx. 640 €) could be saved for each patient if patients without ACS could be discharged directly from the ED instead of being admitted [[9](#_ENREF_9)].

### Diagnostic tools to confirm or exclude acute coronary syndrome

The cornerstones in the evaluation of ED patients with possible ACS are the ECG, the symptom history, and blood markers of myocardial necrosis such as troponin [[3](#_ENREF_3)].

#### Symptom history and clinical presentation

Patients with ACS may present with various symptoms but the most common one is chest pain [[3](#_ENREF_3)]. The patients included in this thesis are strictly patients presenting with chest pain and the results can only be applied to this group of patients.

The typical chest pain in ACS is characterized as a retrosternal pressure that sometimes radiate to the left or right arm and that may be intermittent. Atypical symptoms like epigastric pain, dyspnoea or nausea can and often do occur [[3](#_ENREF_3)]. Overall the diagnostic value of chest pain characteristics is limited [[10](#_ENREF_10)] but the presence of chest pain that can be reproduced by external pressure on the chest wall has a relatively high negative predictive value (NPV) for ACS [[11](#_ENREF_11)].

Evaluating elderly patients with suspected ACS is sometimes challenging for the ED physician. Atypical complaints like dyspnoea or nausea are more often reported in the elderly [[3](#_ENREF_3), [12](#_ENREF_12)]. Dementia is more common in this group making the assessment even more difficult.

#### ECG

On the ECG, myocardial ischemia with a risk of AMI can be manifested either as ST segment elevation, ST depression or T-wave inversion. In ED chest pain patients, it is recommended to obtain a 12-lead ECG within 10 min after presentation to exclude persistent ST-segment elevation. Patients with ST-segment elevation in general have a large AMI (STEMI) and need urgent reperfusion therapy [[3](#_ENREF_3)]. Studies have shown that ACS patients with ST depression have a worse outcome than patients with a normal ECG [[13](#_ENREF_13), [14](#_ENREF_14)]. In contrast, isolated T-wave inversion, has not been associated with worse prognosis.

The initial 12-lead ECG in ED patients with suspected ACS is diagnostic of injury in only 24% to 60% of patients with a final diagnosis of AMI, indicating that ECG has a limited value for diagnosing ACS without ST elevation (NSTE-ACS) [[15](#_ENREF_15)]. Nor is the ECG very useful for diagnosing NSTE-ACS in patients with paced rhythm or LBBB [[3](#_ENREF_3)]. Interpretation of the ECG mainly relies on direct visual assessment and previous studies have suggested that misinterpretation of the ECG in the ED is relatively common, but the implications of this are still under debate [[16-18](#_ENREF_16)].

#### Diagnostic Biomarkers

A good biomarker should be easily measured and promptly provide meaningful results. The figure shows a variety of biomarkers in AMI and their relationship to various pathophysiological processes.

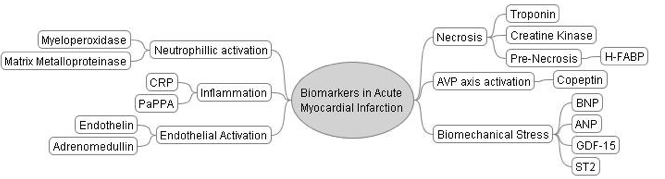


Figure 1

Biomarkers associated with various pathophysiological processes associated with acute myocardial infarction. (Chan and Ng BMC Medicine 2010, 8:34 http://www.biomedcentral.com/1741-7015/8/34)

Two well-known biomarkers in use for diagnosis of AMI are Creatine-Kinase-MB isoform (CKMB) and cardiac Troponin. In 2000, cardiac Troponin replaced CK-MB as the biomarker of choice for diagnosing a myocardial infarction in the western world [[19](#_ENREF_19)].

### Troponin

Cardiac troponins (cTn) are proteins bound to the actin components of the myofibrils of cardiac muscle, and different isoforms (cTnI and cTnT) exist with unique N-terminal sequences that distinguish them from the skeletal muscle isoforms.

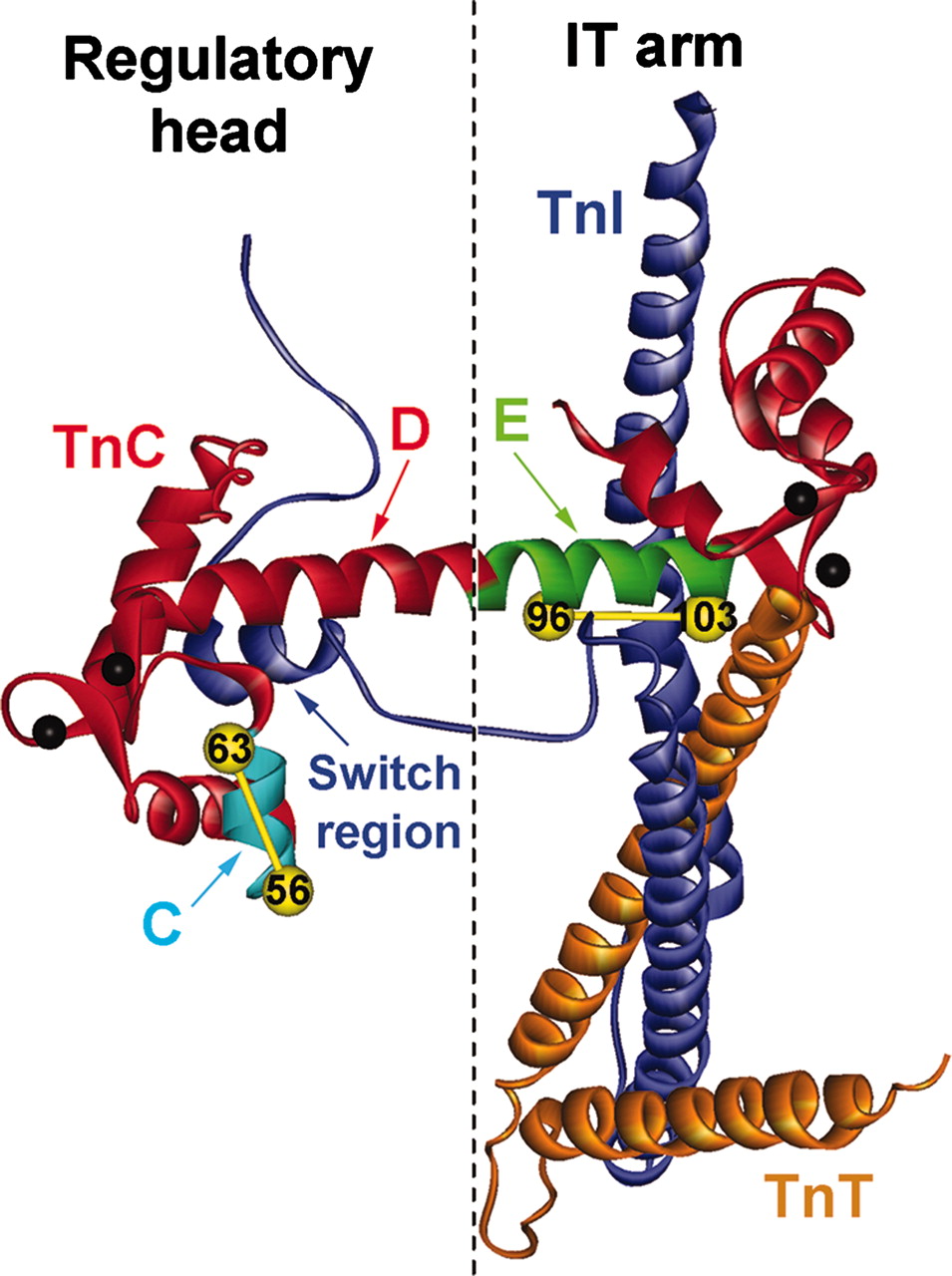


Figure 2

Structure of the core complex of troponin (Copyright © 2016 National Academy of Sciences)

Cardiac troponin is highly specific to cardiac tissue and is released from myocytes into the blood stream when irreversible myocardial infarction occurs. However, there are forms of skeletal muscle disease that could increase circulating levels of cTnT in the absence of cardiovascular disease. This phenomenon has not been described with cTnI [[20](#_ENREF_20)]. In cases of AMI, Troponin levels in the blood peak at 12 hours and stay elevated for 10 days or more [[19](#_ENREF_19), [21](#_ENREF_21)].

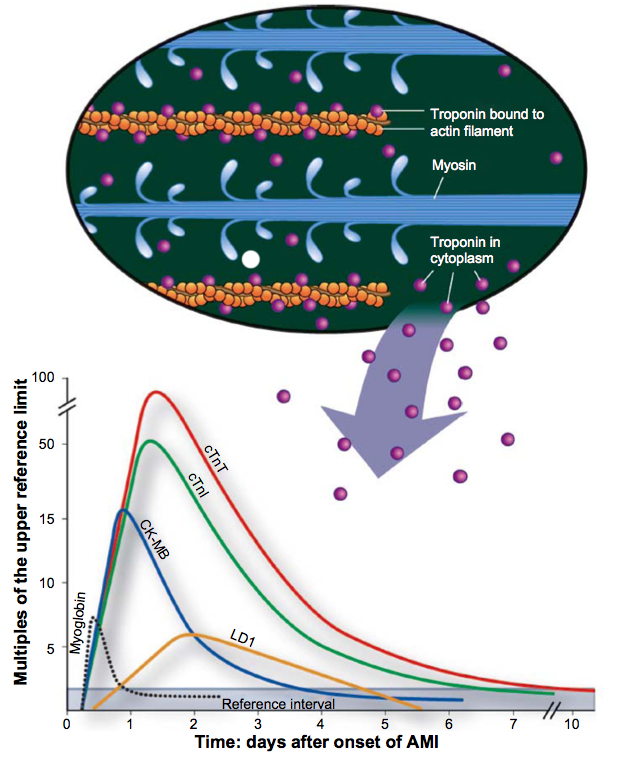


Figure 3

Release of cardiac troponin in acute myocardial infarction.Top: a diagram of a cardiomyocyte releasing biomarkers. Most troponins exists as a complex of C, I and T components that are bound to actin filament. Small amounts of troponins are free in the cytoplasm. Bottom: the pattern of release of different biomarkers based on time after an acute myocardial infarction (AMI) including myoglobin, creatine kinase myocardial band (CKMB), lactate dehydrogenase (LD) and cardiac troponin I (cTnI) and T (cTnT). (Archan et al, Anesthesiology 4 2010, Vol.112, 1005-1012. With permission from Dr Lee A Fleisher)

Since the introduction of blood troponin analysis in the early 1990s, there have been questions about the clinical significance of an elevated troponin. After many years of skepticism, troponins were accepted as the gold standard for patients with chest pain by classifying them into troponin-positive and troponin-negative patients [[22](#_ENREF_22), [23](#_ENREF_23)]. Several studies have found that troponin is an independent prognostic marker for both short-term and long-term outcomes for patients with ACS [[24-27](#_ENREF_24)]. Moreover, low levels of measurable troponin unrelated to ACS have been associated with poor long-term outcome [[28](#_ENREF_28), [29](#_ENREF_29)] and higher levels of troponin T increase the risk of death [[3](#_ENREF_3)]. Even hsTnT levels between the limit of blank (LOB) and limit of detection (LOD) are associated with worse outcomes than concentration below the LOB [[30](#_ENREF_30)].

The recently introduced hsTn assays have improved the accuracy at the lower limit of detection and provide important diagnostic information in the early phase of myocardial infarction [[31](#_ENREF_31), [32](#_ENREF_32)]. These assays measure the upper limit of normal (ULN), the 99th percentile of healthy controls, with a coefficient of variation (CV) of 10%, and permit measurement of cTn concentrations in > 50 % of healthy individuals [[33](#_ENREF_33)]. The use of more specific antibodies, increased sample volume and an optmimised buffert solution have enabled the analytic improvement.

The use of hsTnT assays has resulted in fewer people being classified as having unstable angina (UA) and more people classified as having NSTEMI [[34](#_ENREF_34)]. The 2011 European Society of Cardiology (ESC) guidelines [[35](#_ENREF_35)] stated that NSTE-ACS may be excluded with a rapid 3 h hsTn sampling protocol. However, the underlying trials were not primarily designed to study the optimal time for blood sampling, and included only selected patients [[28](#_ENREF_28), [31](#_ENREF_31), [32](#_ENREF_32), [36](#_ENREF_36)]. In Paper I, we aimed to evaluate the diagnostic and prognostic performance of hsTnT in a real-world setting, i.e. in unselected chest pain patients admitted with possible ACS in routine care.

Increased analytic sensitivity of troponin assays not only increases detection of AMI, but also of the many other conditions with elevated troponin levels such as pulmonary embolism, heart failure, tachycardia and renal failure [[37-41](#_ENREF_37)]. HsTnT has been reported to be less specific than hsTnI for the diagnosis of NSTEMI [[42](#_ENREF_42)]. However, in this study, adjucation of the diagnosis was based on a conventional TnI assay increasing the risk for systematic bias favoring the hsTnI assay.

The daily clinical challenge in using the highly sensitive assays is to interpret the troponin concentrations in patients with concomitant disease. A simple classifying into troponin-positive and troponin-negative patients is no longer an option. Instead we now evaluate hsTn kinetics with serial testing in the clinical evaluation of chest pain patients. However, dynamic changes are not specific for ACS, and other acute conditions leading to myocardial necrosis will also be associated with changes of hsTn [[43](#_ENREF_43)]. The changes of hsTn over time will be determined by the underlying acute cardiac event as well as analytical and biological variation. It is therefore important to establish the reference change values (RCVs) for each biomarker and assay [[44](#_ENREF_44)].

The level of hsTn change considered significant is under debate, and changes between 20 and 200% have been proposed to indicate AMI in previous studies [[36](#_ENREF_36), [45-47](#_ENREF_45)]. The Study Group on Biomarkers in Cardiology in 2012 suggested that a rise of 50% from the baseline value at low concentrations of hsTnT [[4](#_ENREF_4)] was significant while values over the 99th percentile only required a rise or fall of 20 %. However, different troponin assays and different patient populations make this a very complex question and several studies have shown that absolute changes in blood troponin concentrations have a higher diagnostic accuracy for AMI than relative changes [[45-47](#_ENREF_45)]. In the latest ESC guidelines [[3](#_ENREF_3)] it is proposed that elevations beyond 5-fold the ULN have a high positive predictive value for AMI type 1, but the guidelines fail to provide a reference for this statement. This is an area where current guidelines are not sufficient.

#### Troponin and renal insufficiency

Cardiovascular disease is the most common cause of death in patients with renal insufficiency. Cardiac troponins can be elevated in some patients with renal failure but the interpretation of an elevated troponin is controversial. Most of the large-scale trials of patients with ACS exclude patients with elevated serum creatinine [[48](#_ENREF_48)]. The underlying mechanisms of elevated troponin in patients with renal insufficiency are not completely understood. On-going subclinical micro-infarctions and myocardial hypertrophy have been suggested as causes. Decreased clearance by the failing kidney has also been proposed but this is less likely since the free cTnT is a relatively large molecule (37 kDa) similar to albumin making it improbable that troponin is cleared by the kidney. Furthermore, the majority of studies have failed to show a relationship between serum creatinine levels and the degree of troponin elevation [[48](#_ENREF_48)].

Patients with chronic kidney disease (CKD) are thus more likely than those without it to have elevated troponin levels. Studies of patients with CKD have shown that chronically elevated troponin levels are associated with increased risk for cardiovascular morbidity and mortality. Whether asymptomatic patients with CKD and elevated troponin levels should be treated differently from those with normal levels is unclear [[48](#_ENREF_48)].

Patients in hemodialysis (HD) often demonstrate elevated hsTnT values. In one study hsTnT was elevated ≥ 14 ng/l in 30-85% of asymptomatic HD patients [[49](#_ENREF_49)]. Specificity and PPV for AMI have been described to be very low, 12 and 3 % respectively [[50](#_ENREF_50)].

#### Troponin and age

The prevalence of symptomatic ischemic heart disease increases with age. In the United States, elderly patients represent the majority of cardiovascular patients and about 21% of men and 11% of women aged 60–79 years had ischemic heart disease in 2012 [[51](#_ENREF_51)].

The ULN of hsTnT has been determined by analysis on apparently healthy subjects [[52](#_ENREF_52)]. In this study by Saenger et al., mean age was 37 years and there were no women > 70 years. No statistically significant decade specific difference could be identified for either sex but there was a significant difference in the trends from the lowest to the highest decade of age.

Concerns have been raised that the introduction of hsTn assays decreases the diagnostic value of troponin for AMI in elderly patients [[53-57](#_ENREF_53)].

Previous studies have shown that false-positive results for hsTnT are very common, especially in the elderly where conditions like pulmonary embolism, heart failure, tachycardia and renal failure are more frequent [[3](#_ENREF_3), [37](#_ENREF_37), [38](#_ENREF_38), [58-60](#_ENREF_58)].

In Paper III we aimed to evaluate if the diagnostic performance of hsTnT for ACS up to 3-4 h after presentation in elderly patients could be improved.

#### Troponin and gender

Circulating concentrations of cardiac troponins seem to be higher in men than in women. In an international multicenter validation study of a Roche hsTnT assay, the ULN of hsTnT in men was 15.5 ng/l and in women 8.9 ng/l [[52](#_ENREF_52)].

In a study from 2012 where all high-sensitivity cardiac troponin assays were tested, ULN for males were 1.2 to 2.4 times higher than those for females [[61](#_ENREF_61)]. In a study including 13 000 patients the 99th percentile for hsTnT in men > 65 years was 31ng/l [[57](#_ENREF_57)].

There are studies suggesting that troponins predict cardiovascular risk differently in men and women [[62-65](#_ENREF_62)]. In a study by Cullen et al. sex-specific cut-offs recommended by the manufacture were compared to overall cut-offs in 2000 patients. There were only small differences in outcome after one year. Whether implementation of sex specific diagnostic thresholds of high sensitivity troponin assays will improve outcomes through more aggressive therapy for coronary heart disease is still unclear [[63](#_ENREF_63)]. At this time, there is insufficient data to recommend gender-specific cut-offs.

#### Rule-in and rule-out

Several studies have tried to develop a three-zone strategy; rule-in, observational and rule-out based on either a 1 h or 3 h protocol after patient presentation together with clinical data and ECG findings [[3](#_ENREF_3), [66-68](#_ENREF_66)]. With these strategies, the overall NPV for MI in the rule-out group has been >98%, but in the rule-in group up to 25% of the patients will not have AMI, indicating that hsTnT has substantial limitations as a rule-in tool [[3](#_ENREF_3)]. Even if the three-zone strategy is theoretically appealing, there will be substantial difficulties in actually implementing this rather complicated strategy.

### Copeptin

Cardiac troponins are released after myocardial cell disintegration and are markers of cell necrosis. This may be the reason for the relative weakness in diagnostic performance in patients presenting early after chest pain onset. Many additional biomarkers have been suggested to be useful in the diagnosis of ACS, but very few have been shown to be clinically useful [[19](#_ENREF_19)]. Among the many tested, copeptin is one of few additional biomarker that seems to have clinical relevance [[3](#_ENREF_3)].

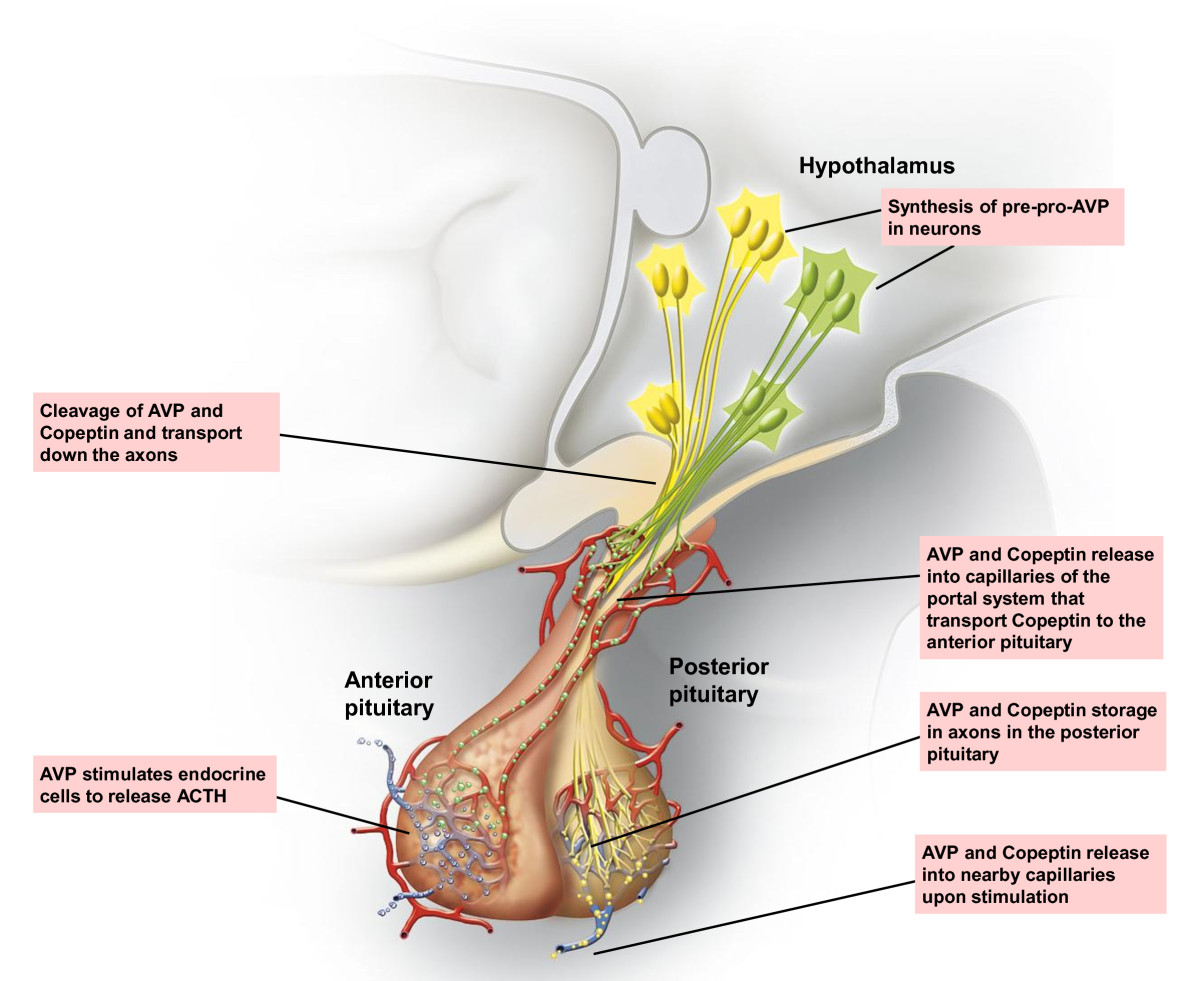


Figure 4

Synthesis and release of AVP and copeptin in hypothalamus and pituitary. Pro-AVP is processed in the hypothalamus, followed by two distinct release-mechanisms for the anterior and posterior pituitary. During stress, a drop in blood pressure, or a change in osmotic pressure, AVP is released into the circulation. ACTH: adrenocorticotropic hormone; AVP: arginine vasopressin. (© Nickel et al; licensee BioMed Central Ltd.2012)

The antidiuretic hormone arginin-vasopressin is secreted by the neurohypophysis and controls osmotic hemostasis. Copeptin is the c-terminal of the vasopressin precursor hormone and is co-secreted with the hormone [[69](#_ENREF_69)]. Copeptin blood levels therefore directly reflect vasopressin release but have a longer half-life than vasopressin, which makes it easier to detect and analyse. Vasopressin, and thereby copeptin, is released by endogenous stress and increase immediately after chest pain onset [[69](#_ENREF_69), [70](#_ENREF_70)]. The combination of a marker of endogenous stress and a marker of cell necrosis has been suggested to improve the diagnostic performance in ED chest pain patients [[71](#_ENREF_71), [72](#_ENREF_72)].

Some publications address the potential benefit of the combination of troponins and copeptin to safely rule out ACS already at presentation [[71-76](#_ENREF_71)]. However, these studies have included few patients and used the conventional troponin assays [[72](#_ENREF_72)], have included STEMI patients [[71-73](#_ENREF_71)] in which biomarkers are of less value, or has only ruled out AMI and not the entire ACS population including UA [[72](#_ENREF_72), [73](#_ENREF_73), [75](#_ENREF_75), [76](#_ENREF_76)]. In Paper II we evaluate the combination of hsTnT and copeptin in an early rule-out strategy for ACS.

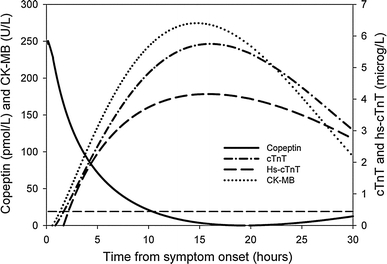


Figure 5

Temporal release pattern of copeptin versus CK-MB, cTnT, and hs-cTnT. The *dashed horizontal line* represents the upper limit of normal (99th percentile) for copeptin. (Yolan et al; Clin Res Cardiol. 2011 Dec; 100(12): 1069–1076)

## Increasing diagnostic accuracy using decision supports

Decision support tools are meant to add more objectively estimated probabilities to the common practice in order to predict the risk of serious outcome events [[77](#_ENREF_77)]. When designing a decision support for the ED it is critical to understand clinicians’ working conditions. Most of the time, working pace is high with frequent interruptions due to the demands of constant availability. Speed and usability are therefore of paramount importance when decision supports are to be integrated with practice. A decision support that delivers several alternatives is seldom useful; simple directions are preferable [[78](#_ENREF_78)].

To be adopted by professionals the decision support must improve patient outcomes and the cost effectiveness of care. Validation studies are important because the performance is often not as good as in the original studies when applied to new individuals [[79](#_ENREF_79)] in routine care.

Models for risk stratification are usually developed using logistic regression analysis but risk scores based on complex algorithms and computer supports have been less accepted by clinicians.

#### Risk scores for patients with ACS and chest pain

Many risk scores have been developed with the intention to help clinicians to identify the chest pain patient´s level of risk for adverse outcomes in the short term. These scores typically include examination findings and the patient’s history as well as the results of diagnostic tests.

The GRACE and TIMI risk score were originally designed as prognostic assessment tools for patients with established ACS [[80-82](#_ENREF_80)]. Newer scores like HEART [[83-86](#_ENREF_83)], EDACS [[87](#_ENREF_87)] and the Vancouver rule [[88](#_ENREF_88)] were specifically developed for unselected chest pain patients the ED, and have tried to identify chest pain patients eligible for early discharge. These scores and have a high sensitivity for important endpoints (usually death and/or MI). The EDACS-ADP developed by Than et al. [[87](#_ENREF_87)] has shown great potential (sensitivity 100%, specificity 50-59%) but is like the HEART-score hard to use without electronic assistance, which is a great limitation and makes them both less likely to be accepted by clinicians.

According to current European guidelines, simple risk scores like TIMI are preferred due to its few variables, its additive scoring system and a binary outcome.

#### GRACE

Variables used in the GRACE 2.0 risk calculation include age, systolic blood pressure, pulse rate, serum creatinine, Killip class at presentation, cardiac arrest at admission, elevated cardiac biomarkers and ST deviation on the ECG. The score is highly driven by age and were originally designed for patients with established ACS and not for unselected ED chest pain patients [[89](#_ENREF_89)].

#### TIMI

The TIMI risk score uses seven variables in an additive system: age ≥65 years, three or more coronary artery disease (CAD) risk factors, known CAD, aspirin use in the past 7 days, severe angina (two or more episodes within 24 h), ST change ≥0.5 mm and a positive cardiac blood marker. As with the GRACE score, TIMI risk score was originally designed for risk assessment in patients with established ACS [[81](#_ENREF_81)]. However, it is recommended before other scores by the current European guidelines due to its simplicity and existing validation [[3](#_ENREF_3)]. Disadvantages with the TIMI risk score include the highly subjective variable of “≥ 2 episodes of severe angina within the last 24 h”, and also the variable “aspirin use within 7 days” which many clinicians find counterintuitive. In a metaanalysis from 2010 including 17 000 patients it was stated that TIMI was insufficiently sensitive to identify ED patients for early discharge. Conventional biomarkers were used in these studies [[90](#_ENREF_90)].

#### HEART

HEART is a risk score with five variables; patient history, ECG abnormalities, risk factors, age and elevated troponin. It is complicated, hard to use without electronic assistance and include subjective variables [[91](#_ENREF_91)].

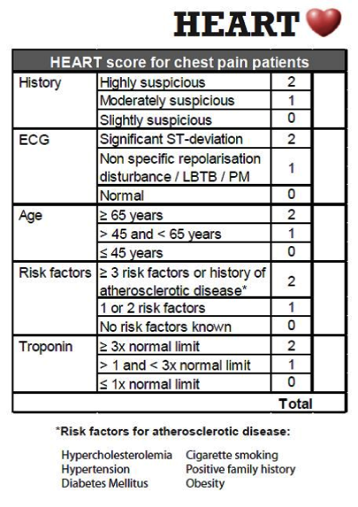


Figure 6

HEART (http://www.heartscore.nl/score/)

#### EDACS

EDACS is an advanced risk score that needs computer support. The score does not include ECG findings but several subjective parameters [[87](#_ENREF_87)].

Table 1

EDACS risk calculator

|  |  |
| --- | --- |
| **a) Age (Please Circle SINGLE Best Answer)** |  |
| **18–45** | +2 |
| **46–50** | +4 |
| **51–55** | +6 |
| **56–60** | +8 |
| **61–65** | +10 |
| **66–70** | +12 |
| **71–75** | +14 |
| **76–80** | +16 |
| **81–85** | +18 |
| **86 +** | +20 |
| **b) Male sex (Please circle if true)** | +6 |
| **c) Aged 18–50 years and either:**  **(i) known coronary artery disease or**  **(ii) ≥3 risk factors** | +4 |
| **d) Symptoms and signs (Circle each if present)** |  |
| **Diaphoresis** | +3 |
| **Radiates to arm or shoulder** | +5 |
| **Pain occurred or worsened with inspiration** | −4 |
| **Pain is reproduced by palpation** | −6 |

Overall, the clinical use of the chest pain scores has been limited due to complexity and lack of utility. Ideally, a diagnostic score or clinical decision rule should be simple to use and include few subjective variables such as interpretation of the ECG and assessment of chest pain characteristics.

In Paper IV we aimed to evaluate a clinical decision rule for rapid exclusion of major cardiac events (MACE) within 30 days from presentation by using the clinical objective rule-out evaluation (CORE) rule, a simplified risk score including age, known arteriosclerosis disease and history of hypertension or diabetes mellitus.

# Aims of the study

1. To evaluate the diagnostic and prognostic performance of hTnT tests in a real-world setting, i.e. in unselected chest pain patients admitted with possible ACS in routine care. (Paper I)
2. To examine the ability of a combination of copeptin and hsTnT to rule out ACS in patients presenting with chest pain, and to compare the diagnostic performance to hsTnT alone. (Paper II)
3. To evaluate if the diagnostic performance of hsTnT for ACS up to 3-4 h after presentation in elderly patients could be improved. (Paper III)
4. To evaluate a simple and objective decision rule for ruling out major adverse cardiac events within 30 days from presentation in unselected ED chest pain patients. (Paper IV)

# Methods

## Study site

The Skåne University Hospital in Lund is the primary hospital for 300 000 inhabitants. The hospital has a cardiac intensive care unit with 19 beds and an observation unit with 20 beds with ECG monitoring. Percutaneous coronary intervention and coronary artery bypass grafting (CABG) are available 24 h a day. Some 65 000 patients present to the ED per year. Of these, about 6000 present with acute chest pain. A prehospital ECG system is in operation with ambulance ECGs sent to a cardiologist on call. If a STEMI is identified, the patient is transported directly to the angiography laboratory, bypassing the ED.

## Inclusion of patients

All patients included in this thesis had non-traumatic chest pain as their main complaint and were older than 18 years. Data were collected from 2010 to 2011 (papers I-III) and from 2013 to 2014 (Paper IV). In Paper I and III, data were retrospectively collected while Paper II and IV were prospective studies. In Papers I-III patients were included in the study database if they were admitted to the cardiac ICU or the observation unit after the initial ED assessment. Patients discharged home directly from the ED were not included. In Paper IV both outpatients and inpatients were included.

All patients with missing blood samples, STEMI, cardiac arrest at the ED or living outside the region were excluded from the studies.

## Clinical assessment

All patients underwent routine assessment in the ED including physical examination, 12-lead ECG and laboratory analyses including hsTnT. After admission to the observation or the cardiac ICU, all the patients included were subjected to continuous ECG monitoring, pulse oxymetry and noninvasive blood pressure measurements. In paper I-III blood samples for hsTnT analysis were collected at admission and thereafter at the discretion of the attending physician, but mainly after 3–4 and 6–7 h from presentation according to the general practice at the hospital.

In Paper IV, clinical data and physician assessments were collected by research assistants (final year medical students supervised senior physicians) using a standardized questionnaire created in accordance with guidelines on chest pain study methodology [[92-94](#_ENREF_92)]. The physician assessed whether the ECG had signs of acute ischemia or not. Blood samples for hsTnT analysis were collected at admission and after 2 h from presentation and thereafter at the discretion of the attending physician.

Further diagnostic testing and treatment were performed at the discretion of the treating physician.

## High-sensitivity troponin T assay

The hsTnT analyses were performed with the use of the Elecsys 2010 system (Roche Diagnostics) with a LOD of 5 ng per liter, a 99th-percentile cutoff point of 14 ng per liter, and a coefficient of variation of less than 10 % at 13 ng per liter. The imprecision at the levels between 3.4-10 ng per liter is reported to be 5-37 % [[52](#_ENREF_52)]. In a healthy population, values over the LOD were reported in 61 % [[95](#_ENREF_95)].

The assay was also used in routine care during the study periods. The assay employs two monoclonal antibodies specifically directed against human cardiac troponin T. Total duration of assay is 18 minutes. Falsely low results are obtained when using samples with hemoglobin concentrations > 0.1 g/dL. Except for the occurrence of haemolysis, clinically significant interferences are rare.

## Copeptin (Paper II)

Blood samples drawn at admission were collected and troponin T was determined directly, while copeptin samples were frozen and analysed later. Copeptin were analysed using the BRAHMS copeptin kryptor assay, with a limit of detection of 4.8 pmol/L, a measuring range of 4.8 to 1200 pmol/L and an interassay CV <15% for values <20 pmol/L and <8% for values >50 pmol/L. A copeptin value of <14 pmol/L was used as diagnostic cut-off point in accordance with previous studies [[71](#_ENREF_71), [72](#_ENREF_72)] and the manufacturer’s recommendation.

## The Clinical Objective Rule-out Evaluation (CORE) (Paper IV)

In paper IV we evaluated a simple objective rule, *t*he Clinical Objective Rule-out Evaluation (CORE). This rule is based on hsTnT sampled at 2 h after ED presentation and a simplified risk score consisting of four objective parameters; age ≥65 years, known arterial disease or history of hypertension or diabetes mellitus.

The components of the risk score were based on previous studies [[81](#_ENREF_81), [87](#_ENREF_87), [91](#_ENREF_91)] and clinical experience. We only included objective variables in order to minimize the risk of different results depending on the physician. To make the protocol as user-friendly as possible, we designed the stratification system with scores 0 or 1, with the score being the simple arithmetic sum of all variables.

Patients younger than 65 years were considered as low risk. This assumption was based on the TIMI and HEART-scores [[81](#_ENREF_81), [91](#_ENREF_91)] for risk stratification of chest pain patients. Based on available literature and clinical experience we included the following previous conditions in the score: hypertension, diabetes mellitus type 1 and 2 (currently treated), AMI, PCI, CABG, significant stenosis of a coronary, cerebral or abdominal artery or peripheral arterial disease. We chose not to include smoking and family history of coronary artery disease since these risk factors are not easily classified. We did not include hyperlipidemia since this is seldom known at the ED if the patient is not on lipid-lowering medications. If so, the patient will in most cases have a history of IHD, hypertension and/or diabetes [[96](#_ENREF_96)].

Patients with 0 p was considered to be at low risk and eligible for an early discharge from the ED without further investigations.

Table 2

*T*he Clinical Objective Rule-out Evaluation (CORE)

For the patient to be classified as low risk, all criterias have to be met.

a. Age <65 years

b. No history of arterial disease

c. No history of hypertension

d. No history of diabetes mellitus

e. hsTnT ≤ 14 ng/l at 0 or 2 h

## Recording of patient diagnosis and endpoints

In paper I-III the primary combined endpoint was a MACE within 60 d. The MACE was defined as AMI or UA at the index visit, new AMI or UA, non-elective CABG, non-elective PCI or death of all causes. In paper IV the primary endpoint was a MACE defined as AMI, UA, cardiac arrest, cardiogenic shock, ventricular arrhythmia requiring intervention, atrioventricular block requiring intervention, or death of a cardiac or unknown cause within 30 d including the index visit.

The final discharge diagnosis was recorded into the database from the discharge summary written by the ward physician and reviewed for quality by the responsible specialist ward physician. The diagnostic criteria for ACS, AMI or UA used at the hospital during the study were those recommended by the ESC, the American College of Cardiology and the American Heart Association [[97](#_ENREF_97), [98](#_ENREF_98)].

In paper I-III the authors reviewed all diagnoses. In paper IV the final diagnosis was decided by independent reviews of two cardiologists and, in case of disagreement, by a third cardiologist. With the exception of Paper II where the authors were blinded for copeptin, the adjudicated diagnoses were based on all available clinical information.

AMI was defined according to the universal definition requiring a significant rise or fall of hsTnT with at least one value above the 99th percentile combined with symptoms of cardiac ischemia, ischemic ECG changes, or imaging evidence of myocardial ischemia [[98](#_ENREF_98)]. The adjudication process differed between study I-III and IV since recommendations were changed concerning significant changes of hsTnT during the study period [[4](#_ENREF_4), [22](#_ENREF_22), [98](#_ENREF_98)]. In paper I and III a diagnosis of AMI was adjudicated only if there was a 50% increase or decrease in hsTnT when hsTnT elevation was greater than 14 ng/l but less than 50 ng/l,. In patients with an hsTnT greater than 50 ng/l, a 20% increase or decrease was considered sufficient for an AMI diagnosis. In paper III, above 14 ng/l a 20% increase or decrease was needed for an AMI diagnosis. In paper IV all reviewers were provided with the following definitions of significant hsTnT dynamics: An absolute change of > 7 ng/L at 2-3 h, or ≥ 9 ng/L at 6 h [[47](#_ENREF_47), [99-101](#_ENREF_99)], and/or an increase on a 2-6 h sample of > 50 % of the upper reference limit of the assay (which equals > 7 ng/L for hsTnT) if the 0 h hsTnT was < 15ng/L, or a change > 20 % of the initial value if the 0 h hsTnT was ≥ 15ng/L (17). In all papers an AMI diagnosis could also be determined in the absence of a significant hsTnT rise or fall the patient presented late with clearly elevated hsTnT and a history consistent with AMI.

The UA diagnosis required normal or elevated hsTnT levels without a significant rise or fall and deterioration of previous stable angina, typical chest pain at rest, or a positive cardiac stress test or a stenosis ≥ 70 % on coronary angiography.

## Follow-up

In Region Skåne, all hospitals use the same computerized patient record system, and we thereby had access to charts for patients seeking care at any hospital in the region. Deaths and causes of death were obtained from the registers at the Swedish National Board of Health and Welfare. In paper IV we also obtained data from the National Patient Register where all admissions to in-hospital care in Sweden are registered.

## Statistical analysis

Continuous variables are presented as medians (with interquartile range) and were compared using the Mann–Whitney U-test.

For patient characteristics, categorical variables were compared using the Pearson Chi-square test.

In the assessment of the time-dependent diagnostic and prognostic performance, sensitivity, specificity, negative predictive values (NPV) and positive predictive values (PPV) with 95% confidence intervals (CI) were calculated. Sensitivity and specificity were compared with McNemar test in Paper II.

IBM SPSS Statistics 18 (IBM, New York, New York, USA) and Microsoft Excel software was used for all statistical analyses, and a P value less than 0.05 was considered statistically significant.

# Results

## Diagnostic performance of hsTnT for ACS in real life

#### (Paper I)

A total of 792 chest pain patients were admitted to the cardiac intensive care unit or the observation unit, and 773 were included in the final analysis.

A complete series of tests at 0, 3-4 and 6-7 h were obtained in 278 patients. ACS was more common in this selected population compared to the total group (28% vs 23%), as was hypertension and previous coronary artery disease. The fraction of males and patients ≥ 75 years, and the GRACE score median, were similar.

Figure 7 describes the diagnostic performance of hsTnT ≤ 14 ng/L for ACS at presentation, at 3-4 h and at 6-7 h. Sensitivity for ACS at 6-7 h was only 81 %. Analysis of AMI alone, as compared to ACS, increased the sensitivity on admission from 68 to 80 %, and at 3-4 h from 79 to 97 %. The NPV on admission increased from 85 to 93 %, and at 3-4 h from 89 to 99 %. Patients with ACS and no elevation of hsTnT after 6-7 h (n=15) were patients with UA in all cases but one*.* The UA patients underwent CABG more often than those with NSTEMI indicating more frequent multi-vessel disease in the UA group.

At 60 days, 13 of the 773 patients had died. None of these patients had a normal hsTnT at presentation. Fourteen (1.8 %) of the 773 patients had an endpoint after the initial hospital stay but within 60 days. Eight of these patients re-presented to the ED with ACS, and none died.



|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Sens | Spec | PPV | NPV | Accur | LR+ | LR- |
| Admission | 0.68 | 0.69 | 0.46 | 0.85 | 0.69 | 2.19 | 0.46 |
| 3-4 h | 0.79 a | 0.65 b | 0.47 | 0.89 | 0.69 | 2.27 | 0.32 |
| 6-7 h | 0.81 c | 0.65 d | 0.47 | 0.90 | 0.69 | 2.28 | 0.30 |

a p < 0.012 vs sensitivity at admission   
b p < 0.039 vs specificity at admission  
c p > 0.5 vs sensitivity at 3-4 h  
d p > 0.5 vs specificity at 3-4 h

Figure 7.

Diagnostic performance of hsTnT for ACS during hospital stay in 278 patients at admission, at 3-4 and at 6-7 h.

PPV, positive predictive value; NPV, negative predictive value; Accur, accuracy, LR+, positive likelihood ratio; LR-, negative likelihood ratio.

## Diagnostic performance for ACS in the elderly

#### (Papers I and III)

In paper I, we evaluated the diagnostic performance of hsTnT in a subgroup of elderly patients. Two hundred and forty (31 %) patients were ≥ 75 years. Of these, 59 patients (24 %) had ACS during the hospital stay and among these, 13 patients had UA. As seen in Figure 8, the sensitivity of hsTnT ≤ 14 ng/L on admission for ACS was higher in patients ≥ 75 years compared to patients < 75 years (n=533). However, the specificity on admission was significantly lower in those ≥ 75 years (41 %) than in those < 75 years (79 %). Among patients ≥ 75 years, 150 patients (63 %) had a hsTnT > 14 ng/L on admission, but only 59 (39 %) of these had an ACS during the initial hospital stay.



|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Sens** | **Spec** | **PPV** | **NPV** | **Accur** | **LR+** | **LR-** | **n** |
| **Patients ≥ 75 years** | | | |  |  |  |  |  |
| **Admission** | 0.80 | 0.41 | 0.31 | 0.86 | 0.51 | 1.35 | 0.49 | 234 |
| **3-4 h** | 0.87 | 0.34 | 0.30 | 0.89 | 0.47 | 1.33 | 0.38 | 154 |
| **6-7 h** | 0.86 | 0.36 | 0.35 | 0.86 | 0.50 | 1.34 | 0.40 | 121 |
| **Patients < 75 years** | | | |  |  |  |  |  |
| **Admission** | 0.66 \* | 0.79 \*\* | 0.47 | 0.89 | 0.76 | 3.14 | 0.43 | 523 |
| **3-4 h** | 0.79 | 0.81 | 0.56 | 0.92 | 0.80 | 4.05 | 0.26 | 357 |
| **6-7 h** | 0.77 | 0.78 | 0.54 | 0.91 | 0.78 | 3.52 | 0.30 | 257 |

\* p= 0.07 vs sensitivity at admission in patients ≥ 75 years   
\*\* p = 0.001 vs specificity at admission in patients ≥ 75 years

Figure 8.

Diagnostic performance of hsTnT for ACS at 0, 3-4 and 6-7 h from admission in patients < 75 and ≥ 75 years.

PPV, positive predictive value; NPV, negative predictive value; Accur, accuracy, LR+, positive likelihood ratio; LR-, negative likelihood ratio.

In paper III, 477 patients ≥ 75 years with suspected ACS were studied. Twenty-seven percent of the patients had ACS and 21 % AMI during the hospital stay. Twenty-five patients (5 %) were considered to have type 2 AMI. One hundred and forty-three patients (30 %) had a MACE within 2 months. Six patients were diagnosed with ACS and twelve patients died after the initial stay but within 2 months. The causes of death were not registered.

There were no significant differences in prior cardiovascular disease between patients with and without ACS. Male sex was significantly more common and warfarin treatment significantly less common in the ACS group. Average age was similar in patients with and without ACS, but GRACE score was significantly higher in the group with ACS. Only 49 of the patients with ACS (38 %) presented with ECG changes not known to be old.

In Table 3, panel a, it can be seen that with the cut-off 14 ng/L, the sensitivity for ACS was 88 % at 3-4 h, with a specificity of 38 %. Analysing for NSTEMI alone (panel b) gave a sensitivity and NPV of 100 % but did not improve specificity and PPV. When diagnostic performance for all AMI (NSTEMI and Type 2 AMI) was analysed (panel c), sensitivity and NPV again reached 100 % but specificity remained low at 41%. Using the cut-offs 20 and 30 ng/L decreased sensitivity and increased specificity for all endpoints.

Table 3

Diagnostic performance for ACS (a), NSTEMI (b), all AMI (c) and MACE after 2 months (d) of HsTnT analysed at 3-4 h.

HsTnT, high-sensitivity troponin T; AMI, acute myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction. All AMI includes NSTEMI and Type 2 AMI. MACE, NSTEMI, non-elective PCI, non-elective CABG and death within 2 months.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **a) ACS prediction at 3-4 h**  **n= 77** | **Sensitivity**  **(95% CI)** | **Specificity**  **(95% CI)** | **NPV**  **(95% CI)** | **PPV**  **(95% CI)** |
| **HsTnT** |  |  |  |  |
| **> 14** | 88  (78-94) | 38  (32-44) | 90  (83-95) | 32  (26-35) |
| **> 20** | 81  (70-88) | 58  (52-65) | 90  (84-90) | 39  (31-47) |
| **> 30** | 77  (65-85) | 75  (69-80) | 91  (86-94) | 50  (41-59) |
| **b) NSTEMI prediction at 3-4 h**  **n= 61** |  |  |  |  |
| **HsTnT** |  |  |  |  |
| **> 14** | 100  (93-100) | 39  (33-45) | 100  (95-100) | 28  (22-35) |
| **> 20** | 93  (83-98) | 59  (53-65) | 97  (93-99 | 36  (28-44) |
| **> 30** | 90  (79-96) | 75  (69-80) | 97  (93-99) | 47  (37-56) |
| **c) All AMI prediction at 3-4 h**  **n= 81** |  |  |  |  |
| **HsTnT** |  |  |  |  |
| **> 14** | 100  (94-100) | 41  (35-48) | 100  (95-100) | 36  (32-43) |
| **> 20** | 94  (85-98) | 63  (56-69) | 97  (92-99) | 45  (37-53) |
| **> 30** | 90  (80-95) | 80  (73-84) | 96  (92-98) | 58  (49-67) |
| **d) MACE prediction at 3-4 h**  **n= 86** |  |  |  |  |
| **HsTnT** |  |  |  |  |
| **> 14** | 91  (83-96) | 39  (33-46) | 93  (85-97) | 35  (29-42) |
| **> 20** | 83  (73-90) | 60  (54-66) | 91  (85-95) | 42  (35-51) |
| **> 30** | 77  (66-85) | 77  (70-81) | 90  (85-94) | 53  (44-63) |

In an attempt to improve specificity and PPV for NSTEMI, a single hsTnT value at presentation was combined with the absolute hsTnT change from 0 to 3-4 h. Figure 9 shows that area under the ROC curve was larger for absolute than for relative hsTnT changes from 0 to 3-4 h.

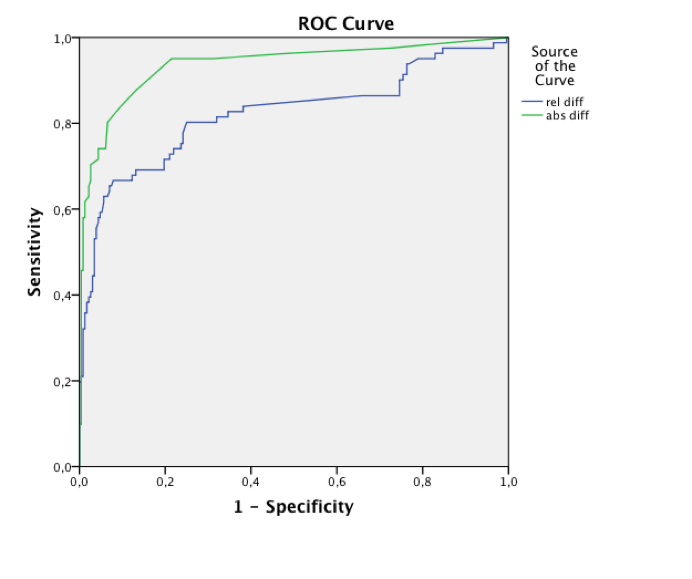


Figure 9. ROC curves for AMI prediction of absolute and relative HsTnT changes from presentation to 3-4 h.

Areas under the curves: 0.94 (95% confidence interval 0.899-0.972) for absolute HsTnT change and 0.82 (95% confidence interval 0.759-0.885) for relative change.

The diagnostic performance for the combination of hsTnT at presentation and the absolute hsTnT change from 0 to 3-4 h is shown in Table 4. Combining hsTnT at presentation > 30 ng/L and/or a change > 5 ng/L gave a 63 % specificity and a PPV of 46 %, a 99 % sensitivity and a NPV of 99 % for NSTEMI. On the assumption that 98 % sensitivity is acceptable in routine care, these criteria would allow NSTEMI to be ruled out at 3-4 h in 47 % of the patients with a sensitivity of 99%.

Increasing the cut-offs for the initial hsTnT or the absolute change decreased the sensitivity to less than 98%.

Table 4

Diagnostic performance for NSTEMI with analysis at single time points and/or changes.

HsTnT, high-sensitivity troponin T; NSTEMI, non-ST-elevation myocardial infarction; abs Δ to 3-4 h, absolute change TnT from admission to 3-4 hours. A sensitivity of ≥ 98 % are considered acceptable rule out levels. Best diagnostic performance is marked with grey.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Sensitivity  (95% CI) | Specificity  (95% CI) | NPV  (95% CI) | PPV  (95% CI) |
| HsTnT at presentation | > 14 |  |  |  |  |
| and/or abs Δ to 3-4 h | > 5 | 99  (93-100) | 30  (25-36) | 99  (94-100) | 30  (25-35) |
|  | >7 | 98  (92-100) | 32  (27-38) | 98  (92-100) | 30  (25-36) |
|  | >9 | 96  (89-99) | 32  (27-38) | 96  (90-99) | 30  (25-35) |
| HsTnT at presentation | > 20 |  |  |  |  |
| and/or abs Δ to 3-4 h | > 5 | 99  (93-100) | 46  (41-52) | 99  (96-100) | 36  (30-43) |
|  | >7 | 98  (92-100) | 49  (43-54) | 99  (95-100) | 37  (31-44) |
|  | >9 | 96  (89-99) | 49  (43-54) | 97  (93-99) | 37  (31-43) |
| HsTnT at presentation | > 30 |  |  |  |  |
| and/or abs Δ to 3-4 h | > 5 | 99  (93-100) | 63  (57-68) | 99  (96-100) | 46  (40-54) |
|  | >7 | 97  (90-99) | 66  (60-72) | 98  (95-100) | 48  (41-56) |
|  | >9 | 94  (87-98) | 67  (61-72) | 97  (94-99) | 48  (41-56) |
| HsTnT at presentation | > 40 |  |  |  |  |
| and/or abs Δ to 3-4 h | > 5 | 95  (88-98) | 70  (64-76) | 98  (94-99) | 51  (43-59) |
|  | >7 | 91  (82-96) | 75  (70-80) | 96  (92-98) | 54  (46-62) |
|  | >9 | 88  (80-94) | 76  (70-81) | 95  (91-98) | 54  (46-63) |

HsTnT at presentation was pathological in more than 50 % with the patients not having ACS. Elevated hsTnT levels were very common in patients with pneumonia, pulmonary embolism and heart failure. All patients with type 2 AMI had clinical conditions that made in-hospital care necessary regardless of the hsTnT value.

## Diagnostic performance of high sensitivity troponin T and copeptin for early rule-out of ACS

#### (Paper II)

In this study, 478 patients were included and 107 patients (22%) were diagnosed with ACS during the hospital stay. Of these, 69 patients (14%) had NSTEMI and 37 patients (8%) had UA. As seen in Table 5, the combination of hsTnT >14 ng/L or copeptin ≥14 pmol/L at presentation identified ACS, NSTEMI and UA with a higher sensitivity than hsTnT alone. Sensitivity and NPV for ACS and UA was low for both hsTnT alone and for the combination of hsTnT and copeptin.

Table 5

Diagnostic performance for ACS, NSTEMI and UA for hsTnT alone and the combination of hsTnT and copeptin at presentation. Sensitivity, Specificity, NPV and PPV are given with corresponding 95% confidence interval. NPV: negative predicitive value; PPV: positive predicitive value; ACS: acute coronary syndrome NSTEMI: non ST-elevation myocardial infarction; UA: unstable angina.

|  |  |  |  |
| --- | --- | --- | --- |
|  | hsTnT ≤14 ng/L | hsTnT ≤14 ng/L and Copeptin <14 pmol/L | p-value |
|  | (n= 478) | (n= 478) |  |
| ACS |  |  |  |
| Sensitivity | 69 (59-77) | 83 (74-89) | <0,001 |
| Specificity | 70 (65-75) | 50 (45-55) | <0,001 |
| NPV | 89 (84-92) | 91 (86-94) |  |
| PPV | 40 (33-47) | 32 (27-38) |  |
|  |  |  |  |
| NSTEMI |  |  |  |
| Sensitivity | 87 (76-93) | 96 (86-98) | 0,031 |
| Specificity | 69 (65-74) | 49 (44-54) | <0,001 |
| NPV | 97 (94-98) | 99 (95-99) |  |
| PPV | 32 (26-40) | 24 (19-30) |  |
|  |  |  |  |
| UA |  |  |  |
| Sensitivity | 35 (20-52) | 59 (42-74) | 0,004 |
| Specificity | 61 (56-66) | 43 (38-48) | <0,001 |
| NPV | 92 (88-95) | 93 (87-95) |  |
| PPV | 7 ( 4-12) | 8 (5-12) |  |
|  |  |  |  |

In Table 6 it can be seen that sensitivity and NPV for a repeated hsTnT analysed 3-4 hours after presentation was equal to the combination of hsTnT and copeptin at presentation for all endpoints. Specificity and PPV were lower with the combination compared to hsTnT alone.

Table 6.

Diagnostic performance for ACS, NSTEMI and UA for hsTnT analysed 3 to 4 hours after presentation and the combination of troponin and copeptin at presentation. Sensitivity, Specificity, NPV and PPV are given with corresponding 95% confidence interval. NPV: negative predicitive value; PPV: positive predicitive value; ACS: acute coronary syndrome NSTEMI: non ST-elevation myocardial infarction; UA: unstable angina.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **hsTnT≤14 ng/L and Copeptin<14 pmol/L at presentation** | **hsTnT≤14 ng/L after 3-4 hours** | **p-value** |
|  | (n=309) | (n=309) |  |
| **ACS** |  |  |  |
| **Sensitivity** | 86 (74-92) | 77 (65-86) | 0,031 |
| **Specificity** | 50 (44-56) | 68 (62-74) | <0,001 |
| **NPV** | 92 (85-96) | 91 (86-95) |  |
| **PPV** | 33 (26-40) | 41 (32-50) |  |
|  |  |  |  |
| **NSTEMI** |  |  |  |
| **Sensitivity** | 98 (87-100) | 98 (87-100) | 1 |
| **Specificity** | 49 (43-55) | 68 (62-73) | <0,001 |
| **NPV** | 99 (95-100) | 99 (96-100) |  |
| **PPV** | 25 (19-32) | 35 (27-44) |  |
|  |  |  |  |
| **UAP** |  |  |  |
| **Sensitivity** | 61 (39-80) | 35 (17-57) | 0,031 |
| **Specificity** | 42 (37-48) | 57 (51-63) | <0,001 |
| **NPV** | 93 (87-97) | 92 (86-95) |  |
| **PPV** | 8 (5-13) | 6 (3-12) |  |
|  |  |  |  |

## The Clinical Objective Rule-out Evaluation (CORE)

#### (Paper IV)

There were 751 patients included in this study. A MACE within 30 days occurred in a total of 90 (11.9%) patients within 30 days. NSTEMI was the most common MACE (63 %) and twice as common as UA (31 %).

In Table 7, the diagnostic accuracy for the CORE rule, combining the simplified risk score and hsTnT are shown. The CORE rule identified 248 (33%) of patients as low risk of with a sensitivity of 98.9% and a negative predictive value (NPV) of 99.6% for MACE. There was only one (0.4%) patient identified as low risk who had a MACE within 30 days. This patient was a previously healthy 60-year-old male who presented after 2 h of chest pain, and was eventually diagnosed with UA. During the index visit the patient had a stress test and echocardiography before an emergency CABG was performed.

A strategy including only hsTnT and ECG, identified 504 (67%) patients as low risk but with an unacceptably low sensitivity. As it can be seen in the table, sensitivity was 88.9% and NPV was 98%. Adding the ED physician’s interpretation of the ECG to CORE did not improve diagnostic performance.

Table 7

Diagnostic accuracy of ECG, hs-cTnT and three different diagnostic strategies.

Sensitivity, Specificity, NPV and PPV are given with corresponding 95% confidence interval. NPV: negative predicitive value; PPV: positive predicitive value; hsTnT: high-sensitivity cardiac troponin; ECG: electrocardiogram; CORE: the clinical objective rule-out evaluation.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | ECG alone | HsTnT alone | HsTnT + ECG | CORE rule (score + HsTnT) | CORE rule + ECG |
| Sensitivity  (95% CI) | 32.2  (23.0–43.0) | 86.7  (77.5–92.6) | 88.9  (80.0-94.3) | 98.9  (93.1–99.9) | 98.9  (93.1 – 99.9) |
| Specificity  (95% CI) | 97.1  (95.4–98.2) | 77.0  (73.6–80.1) | 74.7  (71.2-78.0) | 37.4  (33.7–41.2) | 36.9  (33.2 – 40.7) |
| NPV  (95% CI) | 91.2  (88.8–93.2) | 97.7  (95.9–98.7) | 98.0  (96.3-99.0) | 99.6  (97.4–100) | 99.6  (97.4 - 100) |
| PPV  (95% CI) | 60.4  (45.3-73.9) | 33.9  (27.9-40.5) | 32.4  (26.7-38.7) | 17.7  (14.6-21.4) | 17.6  (14.4–21.3) |

# Discussion

The overall aim of this PhD project was to increase the understanding of the strengths and weaknesses of hsTnT and copeptin as early diagnostic tools in patients with possible acute coronary syndrome.

There are five major findings in this thesis. First, a single hsTnT analysis at 3-4 h from presentation can exclude NSTEMI in unselected ED patients with excellent accuracy. Second, the combination of hsTnT and copeptin can exclude NSTEMI already at presentation and the diagnostic performance is equivalent to hsTnT alone analysed at 3-4 h. Third, current biomarkers alone cannot exclude ACS at 3-4 hours from presentation. Fourth, diagnostic performance for hsTnT alone and for the combination of hsTnT and copeptin as a rule in tool for ACS is poor. Fifth, a simple and objective decision rule can identify patients with a very low risk (< 1 %) for MACE within 30 days from presentation.

### A single hsTnT at 3-4 h can exclude NSTEMI in unselected ED patients

The 2011 European Society of Cardiology guidelines state that ACS may be excluded with a rapid 3 h hsTnT sampling protocol. Since the underlying trials [[28](#_ENREF_28), [31](#_ENREF_31), [32](#_ENREF_32), [36](#_ENREF_36)] were not primarily designed to study the optimal time for blood sampling we wanted to evaluate the diagnostic performance of hsTnT in unselected chest pain patients admitted with possible ACS in routine care. We found that NPV for NSTEMI of hsTnT ≤ 14 ng/l at 3-4 h was 99 % for all ages and 100 % for patients > 75 years. In patients > 75 years NSTEMI could be excluded by a hsTnT value ≤ 20 ng/l at 3-4 h with a NPV of 97%.

Our data confirm that prolonged testing with biomarkers after 3-4 h is no longer needed when using a high sensitive assay. A hsTnT value ≤ 14 ng/l at 3-4 h practically rules out AMI and the finding is in line with previous studies [[28](#_ENREF_28), [31](#_ENREF_31), [32](#_ENREF_32), [36](#_ENREF_36), [53](#_ENREF_53), [56](#_ENREF_56), [58](#_ENREF_58), [102](#_ENREF_102)].

ACS however, cannot be excluded with the rapid 3 h hsTnT sampling protocol, see below under “ACS cannot be excluded by biomarkers alone”.

### Diagnostic accuracy for rule out of NSTEMI of hsTnT and copeptin at presentation is equivalent to hsTnT analysed at 3-4 h

Cardiac troponins are released after myocardial cell disintegration and are markers of cell necrosis. This may be the reason for the relative weakness in diagnostic performance in patients presenting early after chest pain onset. Our studies indicate that NSTEMI can be excluded with excellent precision using either the combination of hsTnT and copeptin at presentation or by a second sample with hsTnT after 3 hours. In paper I-III, NPV for ruling out NSTEMI was as high as 99% and this is in line with several other studies on hsTnT alone [[45](#_ENREF_45), [47](#_ENREF_47), [66](#_ENREF_66)] and the combination of hsTnT and copeptin [[71-74](#_ENREF_71), [76](#_ENREF_76)]. By using the combination of hsTnT and copeptin at presentation instead of a repeated hsTnT test, three hours of observation could theoretically be spared per patient. This must however be set against the difficulties and costs for implementation of a new biomarker assay. In addition, the lower specificity for the combination of hsTnT and copeptin compared to hsTnT alone is a considerable shortage.

### ACS cannot be excluded by current biomarkers alone

An important dimension for all papers in this thesis is that UA were included in all endpoints. Most studies on both hsTnT alone [[45](#_ENREF_45), [47](#_ENREF_47), [66](#_ENREF_66)] and the combination of hsTnT and copeptin [[71-74](#_ENREF_71), [76](#_ENREF_76)] focus on AMI and not the entire ACS population. Even in the era of high-sensitivity cardiac troponin assays, patients with UA have a significant risk of AMI or death [[103](#_ENREF_103)] and to our knowledge; no study has shown that patients with UA can safely be discharged from the ED without further investigation and treatment.

For hsTnT alone the sensitivity for ACS was low at all time points compared to the sensitivity for NSTEMI alone. The ESC rapid rule-out protocol for NSTEMI failed to identify 20 % of the patients with ACS in our study, even at 6-7 h after presentation. The present findings highlight the inherent problem with using a marker of myocardial necrosis to rule out acute coronary disease.

The combination of hsTnT >14 ng/L or copeptin ≥14 pmol/L at presentation identified ACS with a sensitivity of 83 % and a NPV of 91 %. These results are in accordance with previous studies from Keller and Reichlin [[71](#_ENREF_71), [72](#_ENREF_72)]. Keller et al. [[71](#_ENREF_71)] reported a NPV of 80% for ACS when combining a conventional troponin T test and copeptin in a very small study population. Ours is the first larger study using the combination of hsTnT and copeptin for ruling out ACS and not only NSTEMI. Based on the combination of hsTnT and copeptin alone, 18 out of 107 patients (9 %) with ACS would have been misdiagnosed as non-ACS in our study and our conclusion is that current biomarkers alone are unable rule out ACS.

Reichlin et al [[72](#_ENREF_72)] reported no significant difference in copeptin concentration between UAP patients and patients with other diagnoses than ACS and attributed this to that UAP does not cause sufficient endogenous stress for vasopressin release.

In study III, we found that the sensitivity for ACS in the elderly was higher than for the general population in study I, but sensitivity still did not exceed 90 %. In elderly patients it is even more difficult to achieve a robust diagnosis of ACS (UA) since elderly patients often do not undergo coronary angiography due to the inherent risks. We therefore also evaluated the diagnostic performance of hsTnT for MACE within 2 months. Sensitivity and NPV for 60-day MACE were similar to those for ACS during the index visit indicating that excluding NSTEMI at the ED is not sufficient for optimal care, even if the 2-month follow-up in this study was quite generous.

### Diagnostic performance for hsTnT and copeptin as a rule in tool for ACS is poor.

In all studies in the thesis, a considerable number of patients presented with a hsTnT value > 14 ng/L unrelated to ACS, especially among patients ≥ 75 years. We found a lower specificity of hsTnT for AMI than the studies referred to in the ESC guidelines [[28](#_ENREF_28), [31](#_ENREF_31), [32](#_ENREF_32), [36](#_ENREF_36)]. The low specificity in our studies could be explained by an older population with more comorbidities, and that the exclusion criteria were few, as in routine care.

Like in previous studies [[53](#_ENREF_53), [56](#_ENREF_56), [104](#_ENREF_104)], we found a positive hsTnT to be very common among elderly patients; 63 % of those ≥ 75 years had elevated hsTnT levels on admission. Further, less than one third of these positive tests were true positive (PPV 31%). Elderly patients are common in all EDs, and in our unselected material 31 % of the patients were ≥ 75 years.

These patients could be at risk for unnecessary admission to in-hospital care, over-investigation and over-treatment with anticoagulant and antiplatelet drugs for ACS. In paper III we further wanted to evaluate the diagnostic performance of hsTnT in the elderly. In this study we hypothesised that either adjusted cut-offs, or a combination of adjusted initial hsTnT results and the change from 0 to 3-4 h could improve diagnostic performance for rule in. We found that hsTnT cannot be used to rule in NSTEMI during the initial 3-4 h using either standard or adjusted cut-offs, or a combination of the initial hsTnT result and the change from 0 to 3-4 h.

Using the standard cut off 14 ng/L, the ability of a single hsTnT to rule in both NSTEMI and all AMI was poor, since specificities and PPVs were below 50 %. This low specificity of hsTnT for AMI (and ACS) confirms previous results by Bahrmann [[53](#_ENREF_53)] and Olivieri et al. [[58](#_ENREF_58)], and is also well described in the meta-analysis by Sethi et al [[60](#_ENREF_60)]. The initial hsTnT was > 14 ng/L in all patients with pneumonia or pulmonary embolism, and in almost all patients with heart failure or atrial fibrillation. Taken together with the considerable biological variation in the hsTnT level over time [[44](#_ENREF_44)], this can explain why the diagnostic yield of the hsTnT change during the initial hours for rule-in was limited in patients ≥ 75 years.

Increasing the cut off values for single hsTnT tests improved specificity but resulted in a low sensitivity. HsTnT as a single analysis in the elderly thus has similarities with the d-dimer test where a positive result is not useful to rule in thrombosis due to its low specificity and PPV [[105](#_ENREF_105)].

We also evaluated a combination of a higher hsTnT cut-off at presentation and a low hsTnT change up to 3-4 h in order to reduce the number of false positive tests. In this way, patients without AMI but with an elevated baseline troponin level were not classified as AMI, while AMI patients with low baseline hsTnT values could still be identified by the hsTnT change.

With the combined criteria specificity and PPV improved, but it seems unlikely that they will improve clinical care. With combined criteria, PPV still did not reach more than 46 % when aiming at a sensitivity of ≥ 98%. We agree with Rains et al. that it is not possible to assign a working diagnosis of AMI using only troponin in the elderly [[51](#_ENREF_51)].

### Low risk patients can be identified with the Clinical Objective Rule-out Evaluation (CORE)

One important issue for the emergency physician is to identify patients without serious conditions suitable for early discharge with no need of further investigation. As we stated above, biomarkers alone cannot rule out ACS in unselected chest pain patients. The Clinical Objective Rule-out Evaluation (CORE)evaluates not only the risk of AMI but also the risk of a MACE within 30 days. One-third of all chest pain patients were identified as having a very low 30-day risk of MACE with the CORE decision rule and these patients may potentially be discharged from the ED without additional investigation for ACS. The CORE rule thereby has the potential to shorten the length of ED stay and in particular, reduce the need of additional investigations and costs.

Another finding in this study was that adding the ECG to CORE did not improve sensitivity or NPV for MACE. It is known that many ACS patients have a non-ischemic ECG [[67](#_ENREF_67), [103](#_ENREF_103)], and it is reasonable to believe that this has become even more common after the introduction of high sensitivity troponins. Only a third of the MACE cases in this study had an ischemic ECG at the ED (sensitivity 32 %). The specificity of the ECG has probably also decrease over time since pathological ECGs are most likely more frequent due to the ageing population and improved cardiac care. In addition, misinterpretation of the ECG is relatively common [[16-18](#_ENREF_16)].

There are a number of key features for user-friendliness that need to be present for a clinical decision rule [[78](#_ENREF_78)]. The rule should be simple, intuitive and fast to use. An additive scoring system and a binary outcome are preferred [[3](#_ENREF_3)], as well a clear recommendation for action as opposed to providing the likelihood of adverse events [[77](#_ENREF_77), [79](#_ENREF_79)]. In order to decrease interpersonal variation in management decisions a decision support tool should also be as objective as possible [[35](#_ENREF_35)], since this will increase the generalisability. The CORE rule has a binary outcome, is simple, fast to use, free from subjective variables and should be reasonably intuitive to the clinician.

Other risk scores that have been evaluated for their ability to identify low risk chest pain patients are e.g. the TIMI [[82](#_ENREF_82), [106](#_ENREF_106), [107](#_ENREF_107)], HEART [[83-86](#_ENREF_83)] and EDACS [[87](#_ENREF_87)] scores. These scores have a high sensitivity for selected endpoints and have all accurately identified between 10-40 % of patients as low risk for death and/or AMI. The TIMI risk score was originally designed for patients with established ACS whereas newer scores like HEART, EDACS and the Vancouver rule were specifically developed for unselected ED chest pain patients [[83-88](#_ENREF_83), [91](#_ENREF_91)]. These scores have potential disadvantages in routine care and none of them are widely used in clinical practice. The HEART-score and the EDACS-ADP are both hard to use without electronic assistance and include subjective variables [[83](#_ENREF_83), [85](#_ENREF_85), [91](#_ENREF_91)] [[87](#_ENREF_87)]. The Vancouver Chest Pain Rule is only recommended for patients aged 25 to 49 and will therefore probably only have a limited effect on the total number of patients discharged [[88](#_ENREF_88), [108](#_ENREF_108)]. The TIMI score has an additive scoring system and a binary outcome, but includes the subjective variable “≥ 2 episodes of severe angina within the last 24 h”, and also “aspirin use within 7 days”, which many clinicians find counterintuitive as a risk factor.

The CORE decision rule seems to have the requirements needed for a clinical setting. In this study CORE was evaluated in the ED but the decision rule could also be tested and validated prospectively in individuals suspected of having ACS in a primary care setting. Further, it would be interesting to evaluate a point of care analysis of hsTnT within the CORE rule.

Before clinical implementation of the CORE rule, prospective validation in routine care is needed.

# Conclusion and future directions

The first three real life studies in this thesis are important complements to previous prospective studies in less generalisable settings [[31](#_ENREF_31), [32](#_ENREF_32), [56](#_ENREF_56), [71](#_ENREF_71), [72](#_ENREF_72), [102](#_ENREF_102)]. The findings support that hsTnT is useful in the early rule out of NSTEMI in both unselected and elderly ED patients. In combination with copeptin, hsTnT can exclude NSTEMI but not ACS already at presentation. In contrast, a single value of hsTnT, or the combination of hsTnT and copeptin, cannot be used to rule in NSTEMI or ACS in an unselected ED population. In elderly patients, a higher cut off or a combination of a higher cut-off and the early hsTnT change improves specificity and PPV but not to a clinically valuable extent. Our simple decision rule CORE can correctly identify one third of chest pain patients in the ED as needing no further investigation for acute coronary disease.

In conclusion, our studies have led to a better understanding of the strengths and weaknesses of hsTnT as an early diagnostic tool in patients with possible ACS.

It is important to highlight that results from this study are restricted to patients with chest pain as their main complaint. However, it is well known that elderly ACS patients often have atypical symptoms such as shortness of breath or fatigue [[109](#_ENREF_109)].

The hsTnT assay was introduced at our university hospital in 2010. The sensitivity of the method permits measurement of cTn concentrations even in a significant number of healthy individuals. This creates problems in the real life management of unselected chest pain patients. Clinicians have to learn how to deal with the high sensitive assays and the introduction of hsTn has increased the responsibility of the clinician to interpret the test in clinical context. There is no doubt that the new hsTn assays have shortened the hospital stay for a number of patients, but due to its low specificity patients will be at risk of harmful and unnecessary investigations and treatments. These risks are most apparent for elderly patients.

Many ED patients without chest pain as their main complaint will have a hsTnT test taken as a part of standard care. The diagnostic accuracy in this setting is not evaluated in this thesis and the value of introducing hsTnT under these circumstances needs to be clarified.

For optimal use of hsTn, there are some major questions that have to be answered. Is it possible to introduce age- and sex-specific upper reference limit cut-offs? Does a specific change of hsTn exist for ruling in AMI or ACS? If not, we must look for a new biomarker that is specific for the etiology of cardiac cell death in ACS, i.e. acute myocardial ischemia.

Does hsTn assays in routine clinical practice improve patient outcome? In a study by Sanchis et al. hsTnI was compared to a conventional TnI. HsTnI simplified chest pain management by reducing non-invasive tests but led to longer hospitalization and more invasive procedures with no impact on 6-month outcome [[110](#_ENREF_110)]. To our knowledge, potential benefits with hsTnT such as earlier diagnosis, more adequate monitoring and shorter times to invasive treatment, leading to reduced morbidity and mortality have not been demonstrated in any study, despite a considerable number of published papers.

The management of chest pain patient is the subject of intense research. New biomarkers will be developed and evaluated, and hopefully some of them will be more specific for ACS. If not, this author believes that the separation of type 1 and typ 2 AMI should be deleted from future terminology. A type 2 AMI is not *one* condition but several and they only have one thing in common; myocardial cell death. It is the underlying condition that should be the primary target for treatment and not the heart.

Decision rules like the CORE rule have the potential to improve acute chest pain management, but in the end prediction models will only improve the quality and the cost-effectiveness of care when the provided information improves the physician’s decision-making. This needs to be analysed in prospective studies in routine care.

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# Populärvetenskaplig sammanfattning

Hjärtkärlsjukdom är den vanligaste dödsorsaken i västvärlden och en stor kostnad för samhället. Förekomsten av hjärtkärlsjukdom ökar och detta har flera förklaringar, bla en ökad medellivslängd, rökning, minskad fysisk aktivitet och ohälsosamma matvanor.

Instabil kranskärlssjukdom omfattar två begrepp, akut hjärtinfarkt och instabil kärlkramp (angina). Tillståndet beror på förändringar i hjärtats kranskärl och resulterar i hastigt försämrad blodcirkulation till hjärtmuskeln.

Varje år söker ca 15 miljoner människor i USA och Europa vård pga bröstsmärta, ett vanligt symptom vid akut hjärtinfarkt. Hjärtinfarkt är ett allvarligt tillstånd som varje läkare måste kunna diagnostisera. Eftersom endast ca 10% av patienter med bröstsmärta visar sig ha hjärtinfarkt, ligger svårigheten i att hitta de patienter som har hjärtinfarkt bland alla de som söker. Följden blir att många patienter måste stanna på sjukhus för observation och ibland genomgå riskfyllda och dyra undersökningar i onödan. Det finns ett stort behov av enkla och säkra verktyg för att tidigt identifiera de patienter som drabbats av hjärtinfarkt men också att hitta de patienter som inte behöver ytterligare utredningar. Skulle vi lyckas med detta kommer många patienter slippa långa vistelsetider på akutmottagningar och sjukhusavdelningar.

Under 2010 introducerades ett nytt blodprov för hjärtinfarktdiagnostik, sk högsensitivt troponin (hsTnT) på Skånes Universitetssjukhus. Troponin är ett ämne som finns bundet i hjärtmuskeln och som frisätts i samband med en hjärtmuskelskada. HsTnT är en utveckling av en tidigare metod som använts under flera år. Nackdelen med den äldre metoden är att precisionen i blodprovet är mindre exakt vid lägre koncentrationer, ex i tidigt skede av en hjärtinfarkt. Detta medför att det kan ta flera timmar innan en diagnos kan ställas. Den nya metoden ger en högre precision vid lägre koncentrationer i blodet och det i sig möjliggör en tidigare diagnos. Införandet av den nya metoden medför dock att även många patienter utan hjärtinfarkt uppvisar förhöjda koncentrationer i blodet.

I vår första studie ville vi säkerställa att den Europeiska kardiologföreningens rekommendationer för att utesluta instabil kranskärlssjukdom (The 2011 European Society of Cardiology (ESC) guidelines) gällde även för våra patienter vid vår akutmottagning. Rekommendationerna innebar att det var tillräckligt att följa blodprover upp till tre timmar efter ankomsten till sjukhus, att jämföra med sex till tolv timmar med den äldre metoden. I vår studie fann vi att tre timmar var tillräckligt för att utesluta en manifest hjärtinfarkt men inte förstadiet till en infarkt, sk instabil kärlkramp. I samma studie gjorde vi en separat analys på patienter över 75 år och såg då att förhöjda koncentrationer av hsTnT var mycket vanligt hos äldre patienter. Det var så vanligt att majoriteten av de patienter som hade förhöjda värden inte hade någon hjärtinfarkt. Med anledning av detta fynd gjorde vi en fördjupad studie av de äldre patienterna där vi försökte optimera diagnostiken med hsTnT på olika sätt. Vi analyserade bla om ett högre tröskelvärde kunde minska andelen patienter som felaktigt definierades som sjuka utan att missa någon patient med instabil kranskärlssjukdom. Det visade sig att tillåtandet av ett högre tröskelvärde riskerade att missa patienter med en pågående hjärtinfarkt. Vi provade då att kombinera ett högre ankomstvärde med olika nivåer av koncentrationsförändringar mellan ankomst till sjukhus och efter tre timmars observationstid. Denna strategi minskade andelen friska patienter som felaktigt definierades som sjuka men fortfarande var denna andel betydande vilket medförde avsevärda svårigheter att korrekt diagnostisera en hjärtinfarkt hos äldre patienter.

För att se om vi ytterligare kunde förkorta observationstiden på akutmottagningen analyserade vi en metod som kombinerade provtagning för hsTnT med copeptin i samband med ankomst till sjukhus. Copeptin är ett hormon som frisätts från hypofysen i samband med att kroppen utsätts för någon form av stress. Återigen fann vi att det gick utmärkt att utesluta en manifest hjärtinfarkt men inte förstadiet instabil kärlkramp. Att analysera hsTnT tillsammans med copeptin vid ankomst visade sig vara lika bra som enbart hsTnT efter tre timmar för att utesluta hjärtinfarkt. Nackdelen var att det blev en ännu större andel friska patienter som felaktigt definierades som sjuka.

Eftersom det inte gick att säkert identifiera alla patienter med instabil kranskärlssjukdom enbart med hjälp av blodprov, undersökte vi om en enkel analys av riskfaktorer för hjärtinfarkt i kombination med hsTnT kunde användas för att fånga alla patienter med instabil kranskärlssjukdom Vi kallade vårt beslutstöd för *CORE* *(The Clinical Objective Rule-out Evaluation).* Med hjälp av detta beslutsstöd blev risken att missa en patient med allvarlig hjärtsjukdom mindre än en procent.

Sammanfattningsvis är det svårt att med hjälp av hsTnT och copeptin säkert *påvisa* en hjärtinfarkt. Inom detta område krävs ytterligare forskning.

Däremot visar avhandlingen att såväl hsTnT som copeptin är effektiva verktyg för att tidigt kunna *utesluta* akut hjärtinfarkt. Med hjälp av beslutsstödet *CORE* kan även instabil kärlkramp uteslutas och detta kan möjliggöra förkortad vistelsetid på akutmottagningen, minskat lidande för patienter och ett mer effektivt resursutnyttjande.

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