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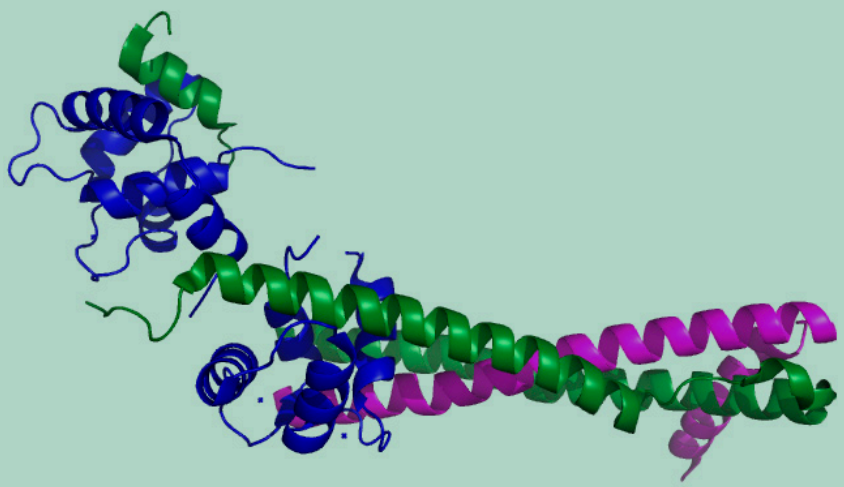

Diagnostic strategies in acute chest pain assessment

- with focus on high-sensitivity cardiac troponin T

Arash Mokhtari

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UNIVERSITY

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Diagnostic strategies in acute chest pain assessment -with focus on high-sensitivity cardiac troponin T

Abstract

Introduction:
Chest pain is a common presenting complaint among patients in the emergency department (ED). The aims of this thesis were to evaluate the diagnostic accuracy of strategies, focusing mainly on high-sensitivity cardiac troponin T (hs-cTnT), for ruling out 30-day major adverse cardiac events (MACE). The goal was to find strategies that could rapidly identify patients with a low enough risk of 30-day MACE that they may be suitable for early discharge without the need for further cardiac testing.

Methods
In two prospective observational cohort studies, ED physicians' assessment of history and ECG, and troponin T values, were collected.

Results
Paper I: The overall clinical assessment was better than its separate components (history, ECG, troponin T) both at ruling in and at ruling out acute coronary syndrome (ACS). Among the components, TnT and ECG were superior to the chest pain history for ruling in ACS, while history was superior for ruling out ACS.
Paper II: An algorithm combining patient history, ECG and 0h and 1h hs-cTnT identified 60% of all patients for rule-out with a negative predictive value (NPV) of 99.5% and a LR- of 0.04 for 30-day MACE. It ruled in 14% of patients with a positive predictive value of 62.3% and LR+ of 12.5.
Paper III: The combination of hs-cTnT <5 ng/L, a non-ischemic ECG, and a non-high risk history was present in 29.2% of patients and yielded a NPV of 99.7% and a LR- of 0.02 for 30-day MACE. The combination with hs-cTnT ≤14 ng/L was present in 66.7% of patients, with a NPV of 98.7% and a LR- of 0.11
Paper IV: The combination of an adapted TIMI score ≤1, a non-ischemic ECG, and either a 0h hs-cTnT <5 ng/L, or a 0h hs-cTnT <12 ng/L combined with a 1h increase <3 ng/L, identified 432 (42.4%) patients as very low risk with a negative predictive value of 99.5% and a negative likelihood ratio of 0.04 for 30-day MACE.

Conclusion
Our results indicate that a combination of history, ECG and hs-cTnT provides a rapid disposition strategy in approximately 75% of ED chest pain patients. With this combination, about 60% of all patients may potentially be discharged without the need for further cardiac assessment, almost half of whom could be identified for rule-out with a single hs-cTnT at presentation, and with the remainder identified by a subsequent 1h hs-cTnT. As an alternative, utilizing a 0h/1h hs-cTnT strategy in conjunction with an adapted TIMI score and ECG also allows safe early discharge of chest pain patients. These strategies could potentially reduce ED crowding, unnecessary admissions, stress testing and costs.

Key words: acute coronary syndrome, chest pain, diagnosis, myocardial infarction, unstable angina, troponin T

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”Medicine is a science of uncertainty and an art of probability”

Sir William Osler

Department of Emergency Medicine and Internal Medicine
Clinical Sciences, Lund
Faculty of Medicine, Lund University
Sweden, Lund

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To my wife and children

Content

List of publications

The present thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I. Arash Mokhtari, Eric Dryver, Martin Söderholm, Ulf Ekelund. Diagnostic values of chest pain history, ECG, troponin and clinical gestalt in patients with chest pain and potential acute coronary syndrome assessed in the emergency department. SpringerPlus. 2015;4:219.

II. Arash Mokhtari, Catharina Borna, Patrik Gilje, Patrik Tydén, Bertil Lindahl, Hans-Jörgen Nilsson, Ardavan Khoshnood, Jonas Björk, Ulf Ekelund. A 1-h Combination Algorithm Allows Fast Rule-Out and Rule-In of Major Adverse Cardiac Events. Journal of the American College of Cardiology. 2016;67(13):1531-1540.

III. Arash Mokhtari, Bertil Lindahl, J. Gustav Smith, Martin J. Holzmann, Ardavan Khoshnood, Ulf Ekelund. Diagnostic Accuracy of High Sensitivity Cardiac Troponin T at Presentation Combined with History and ECG For Ruling Out Major Adverse Cardiac Events. Annals of Emergency Medicine. 2016;68(6):649-658.

IV. Arash Mokhtari, Bertil Lindahl, Alexandru Schiopu, Troels Yndigegn, Ardavan Khoshnood, Patrik Gilje, Ulf Ekelund. A 0h/1h protocol for safe early discharge of chest pain patients. Accepted Manuscript, Academic Emergency Medicine.

Abbreviations

ACS	Acute coronary syndrome
ADP	Accelerated diagnostic protocol
AMI	Acute myocardial infarction
CI	Confidence interval
cTn	Cardiac troponin
CV	Coefficient of variation
ED	Emergency department
ECG	Electrocardiogram
ESC	European Society of Cardiology
Hs-cTnT	High-sensitivity cardiac troponin T
LR	Likelihood ratio
LoB	Limit of blank
LoD	Limit of detection
MACE	Major adverse cardiac event
NPV	Negative predictive value
NSTEMI	Non ST-elevation myocardial infarction
PPV	Positive predictive value
RCV	Reference change value
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction
UA	Unstable angina

Introduction

Chest pain in the emergency department

> "One must be a professional Ulysses in craft and wisdom not sometimes to err in estimating the nature of an attack of severe heart pain. There is no group of cases so calculated to keep one in a condition of wholesome humility."
>
> *Sir William Osler*

Chest pain is the second most common presenting complaint among patients seeking care in the emergency department (ED), accounting for almost 10% of all ED visits,[1] and resulting in 8-10 million annual ED visits in the US alone.[2,3] The primary goal in the evaluation of chest pain patients is to exclude acutely dangerous conditions such as acute coronary syndrome (ACS), aortic dissection and pulmonary embolism, to identify patients with other conditions needing specific management such as perimyocarditis, pneumothorax and pneumonia, and to identify patients where the risk of having a potentially life-threatening condition is very low and who can be safely discharged. Even though the list of differential diagnoses is wide, it is normally the perceived likelihood of ACS i.e. acute myocardial infarction (AMI) or unstable angina (UA) that drives management.

AMI are further classified based on the presence or absence of ST-elevation on the ECG into ST-elevation AMI (STEMI) and non-ST-elevation AMI (NSTEMI). The distinction between NSTEMI and UA is on the other hand primarily based on cardiac troponin (cTn) levels in the blood, where the diagnosis of AMI by definition requires a significant rise or fall of cTn with at least 1 value above the 99th percentile, combined with symptoms or signs of cardiac ischemia.[4] Even though the diagnosis of STEMI is often clear-cut, ruling out NSTEMI and UA can be difficult.

The initial ED assessment relies primarily on the clinical assessment, ECG and troponins. The fear of missing cases with ACS leads to lengthy assessments in the ED and high admission rates,[5-7] constituting 25% of all medical admissions.[7] This contributes to ED and hospital crowding, which results in a worse prognosis for all ED patients.[8,9] Many patients also undergo stress testing and cardiac imaging (referred to as non-invasive testing), which is the approach recommended by the American Heart Association in patients with a negative ECG and biomarkers.[10] Neither routine admission nor non-invasive testing in low risk chest pain patients

have however been shown to improve outcomes,[1,11-13] and may in fact be more harmful than beneficial.[11,13,14] Admissions confer a risk of iatrogenic complications that is not negligible.[15] Among low risk patients who undergo non-invasive testing, few have a positive test[11,16-18] and the majority are false positives,[11,16-18] resulting in further investigations and treatments with consequent risks of complications, radiation exposure, and prolonged hospital stay.[18,19] Further testing has also not been shown to decrease patient anxiety, symptoms, or illness concerns,[20] nor does it reduce further downstream non-invasive testing.[1]

Considering that <15% of all ED chest pain patients and only about 25% of admitted chest pain patients turn out to have ACS,[6,21-24] many of the admissions and investigations are unnecessary, and cause a substantial health care burden.[7] In the US alone, the cost is 10 to 13 billion dollars annually.[1,3] There is thereby room for significant improvement in our assessment of chest pain patients.

The now commonly used high-sensitivity cardiac troponins (hs-cTn), have an improved sensitivity compared to previous generations of cTn, and enable faster rule-out of AMI,[25] and can reduce ED length of stay and costs.[26] Their introduction has also resulted in a decrease in the proportion of patients diagnosed with UA,[26,27] further diminishing the potential gain of non-invasive testing in those identified as low risk.[28] However, many hospitals lack protocols to guide physicians on how to use hs-cTn testing. Unstructured use of hs-cTn in the assessment of ED chest pain patients, without integration within a protocol, has not been shown to confer a large benefit.[29] As many clinicians are uncertain as how to apply hs-cTn in practice, there is a clear need for protocols that can provide a framework for optimal use.

If hs-cTn protocols can be created to rapidly identify a large proportion of chest pain patients suitable for discharge where no further cardiac testing is needed, this may reduce ED and hospital crowding, non-invasive testing, health care costs and benefit both patients and the health care system.

Clinical assessment and ECG

> " The whole is greater than the sum of its parts"
>
> Aristotele

The history and physical examination, the ECG interpretation, and troponin analysis are the cornerstones of the initial evaluation in patients with possible ACS (Figure 1). It has been shown that ED physicians rely heavily on their assessment of the patient history when evaluating chest pain patients,[30] and several studies have evaluated the diagnostic accuracy of the different components of the patient history.[21,31-34] The findings that seem to increase the probability of AMI/ACS the most are: pain radiating to the right arm or both arms,[32-34] vomiting,[31] and the patient

being diaphoretic on examination.[31] The commonly taught findings of radiation to the left arm or the pain being described as crushing/pressure-like on the other hand have a low predictive value.[21,31-34] No single finding in the history is however by itself sufficient to rule out or rule in AMI or ACS.

The ECG is also an important tool, and can identify chest pain patients with a STEMI, enabling timely treatment. The presence of ischemic ST-T changes, especially ST-segment deviation, has a high specificity and increases the probability of ACS.[31,33] However, the absence of such findings also does not rule-out ACS.[31,33]

In routine practice we do not however rely on isolated single findings in the history or the ECG alone, but on our overall clinical assessment or "gestalt" (sometimes referred to as "gut feeling"). Chandra et al. showed that among patients deemed as low risk by physicians using their unstructured clinical assessment, the 30-day MACE event rate was only 2.2%.[35] In a study by Body et al., a physician assessment of non-high risk of ACS, combined with a non-ischemic ECG, lowered the probability of AMI from 17.7% to 5.7%.[36] Even though this level of risk would not be acceptable to allow discharge, it seems clear that a combination of clinical judgement and ECG can identify patients at low risk of ACS. The addition of negative hs-cTn in these patients might then allow a safe rule-out.

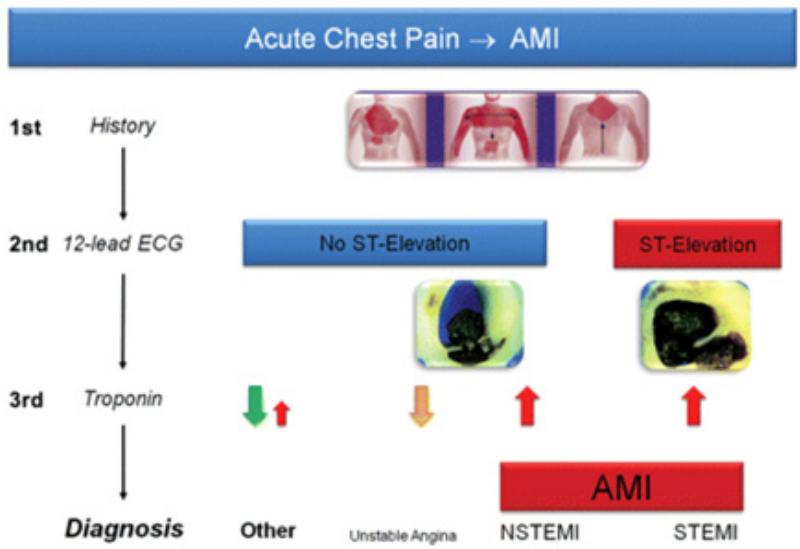

Figure 1.
History, ECG and troponins form the cornerstones of the initial evaluation in patients with possible ACS. Reprinted with permission from Oxford University Press.[37]

Risk scores and accelerated diagnostic protocols (ADPs)

> "Tis with our judgements as our watches, none go just alike,
> yet each believes his own."
>
> *Alexander Pope*

The dichotomous judgement of the patient history (high risk vs non-high risk) by the physician in the assessment of chest pain patients has been shown to have good reproducibility, with a kappa value of 0.75.[22] Nonetheless some physicians are not comfortable relying on a subjective measure such as clinical judgement. There are now several validated scoring systems that do not incorporate clinical judgement, with the Thrombolysis in Myocardial Infarction (TIMI) score being the most extensively studied.[6,38-41] Even though the TIMI score was originally developed as a tool for risk stratifying patients with confirmed ACS,[42] a low score has been shown to identify ED chest patients with a lower risk of ACS.[6,43] An accelerated diagnostic protocol which combines an adapted TIMI score with ECG and hs-cTn at 0h and 2h, the so called modified ADAPT-ADP, has also been shown to accurately identify low risk patients (Figure 2).[38,44]

Patients are ADP negative if they fulfill the following:

Adapted TIMI score* ≤1:

- Age ≥65 years
- ≥3 risk factors for coronary artery disease†
- Use of aspirin in the last 7 days
- Previous coronary stenosis ≥50%
- ≥2 anginal events in last 24 h or persistent discomfort

AND

No signs of acute ischemia on the ECG

AND

Hs-cTn ≤99th percentile at 0 and 2h

Figure 2. The modified ADAPT-ADP.
*The original TIMI score includes ECG and Troponin as variables, but as both are required to be negative in the ADP they are not included in the score here. All score variables are assigned a value of 1. † Risk factors defined as family history of coronary artery disease, hypertension, hypercholesterolemia, diabetes, or current smoking.

High-sensitivity cardiac troponin T

Background

> "When troponin was a lousy assay it was a great test, but now that it's becoming a great assay it's getting to be a lousy test"
>
> *Robert Jesse*[45]

Troponin I, Troponin T, and Troponin C are proteins in the contractile apparatus of muscle cells. Troponin T and I have unique isoforms present only in cardiac myocytes, the cardiac troponins (cTn), while troponin C isoforms are also found in skeletal muscle.[46] Cardiac troponins are released into the bloodstream as a result of cellular necrosis.[46] There is also a smaller proportion of cardiac troponin unbound in the cytosole, which is released earlier during myocardial injury and may not signify irreversible damage.[47,48] Tachycardia has for example been shown to induce troponin release in the absence of necrosis.[49]

High-sensitivity cardiac troponin assays are now commonly used. It has been suggested that a high-sensitivity cardiac troponin assay should be defined as an assay that has an analytical precision corresponding to a coefficient of variation (CV) ≤10% at the 99th percentile, and which is able to detect troponin levels above the limit of detection (LoD) in at least 50% of a healthy population.[50] These assays thereby meet the universal AMI guidelines criteria which recommend the use of assays with a CV ≤10% at the 99th percentile cut-off value, as to improve the detection of significant change between serial troponins.[4]

There are several hs-cTnI assays and one hs-cTnT assay in clinical use.[51] The assay primarily evaluated in this thesis is the hs-cTnT.

Characteristics of hs-cTnT

> "What if we called it "low specificity troponin" instead of "high sensitivity troponin"? Would that knock some sense into people?"
>
> Joe Lex

Hs-cTnT has a limit of blank of 3 ng/L, a LoD of 5 ng/L and a CV of 10% at a value of 13 ng/L, thereby achieving the guideline-recommended ≤10% CV at the 99th percentile upper reference limit (URL) of 14 ng/L.[50]

Hs-cTnT levels however seem to be higher among men and the elderly,[52] and it is currently unclear whether sex-specific cut-offs should be used instead of 14 ng/L as a cut-off for all. Shah et al. have shown that using a hs-cTnI assay with sex

specific cut-offs increases the number of women diagnosed with AMI with about 40%.[53] This suggests that the use of a generic cut-off for both men and women, instead of using sex-specific cut-offs, would lead to underdiagnosis of AMI in women. Studies evaluating the use of sex specific cut-offs for hs-cTnT, using a cut-off of 9 ng/L for women and 16 ng/L for men, have however not been able to confirm these results.[54-56] There are therefore currently no general recommendations to use sex-specific cut-offs with hs-cTnT.[55] The Food and Drug Administration (FDA) have however recently approved hs-cTnT for use in the US, but with a cut-off of 22 ng/L for men and 14 ng/L for women, meaning the US will use this assay with different cut-offs than the rest of the world.[57] There are also currently no general recommendations for the use of age-specific cut-offs, and it is uncertain as to whether the higher hs-cTnT levels in the elderly are normal or are a sign of underlying cardiac disease.

Hs-cTnT has both higher analytical and diagnostic sensitivity than the previous generation cTnT (fourth generation).[25] The analytical sensitivity refers to the lowest measurable level of cTn by the assay, while the diagnostic sensitivity refers to the proportion of patients with the condition we are trying to diagnose that are identified as positive by the test. Due to differences in assay calibration, values cannot however easily be converted between the hs-cTnT and the previous generation cTnT, with the 30 ng/L cutoff of the fourth generation cTnT being equivalent to about 50 ng/L with the hs-cTnT.[50] Due to the higher analytical sensitivity the time interval before an elevated troponin can be detected has been reduced, allowing earlier detection of AMIs.[25] Additionally, significant change can be detected using shorter sampling intervals,[58-60] allowing a rapid rule-out of AMI in the ED.[59,60] However, this increase in diagnostic sensitivity comes at the expense of a lower specificity of the hs-cTnT assay compared to the fourth generation cTnT.[25]

This lower specificity causes difficulties in the ED as we now observe mildly elevated hs-cTnT levels in a large proportion of ED patients.[61] An elevated troponin level signifies myocardial injury, which can be seen in many non-AMI conditions such as myocarditis, pulmonary embolism, heart failure and renal failure (Figure 3).[27] With the higher analytical sensitivity, elevated hs-cTnT in these conditions are now more commonly detected. Also, the 99th percentile URL has been derived in a healthy population without cardiovascular disease,[50] while ED patients are rarely completely healthy, with a high prevalence of conditions such as heart and renal failure. As a result, most ED chest pain patients with elevated hs-cTnT do not have an AMI.[62] It is however important to remember that even though these are false positive for AMI, they are true positive for myocardial injury, and that these patients generally have a worse prognosis.[46,48,63]

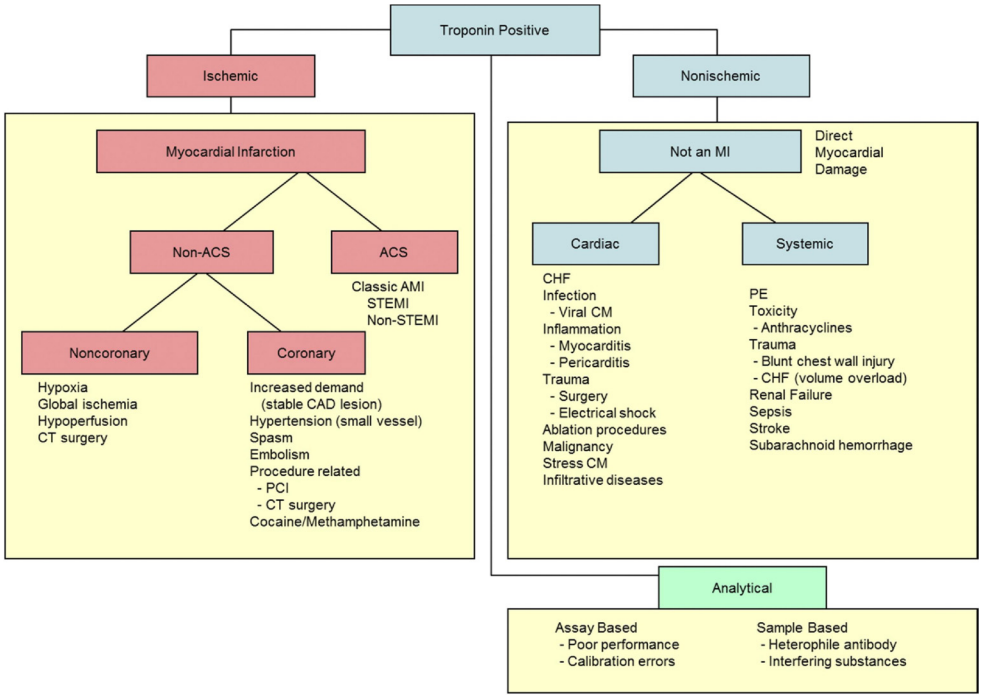

Figure 3.
Differential diagnoses of troponin elevation. Reprinted with permission from Elsevier.[64]

This reduced specifity presents a challenge to both ED physicians and cardiologists. There is also considerable uncertainty regarding the optimal protocol to identify patients for safe discharge. The solution to these issues requires an understanding of a number of concepts, namely 1) the importance of pre-test probability, 2) the test threshold approach, 3) quantitative interpretation of hs-cTnT, 4) the delta approach, and 5) the performance of different hs-cTnT sampling intervals.

The importance of pre-test probability

> "…a diagnostic test can be only as good as its interpretation. Expecting the test to provide all the answers without including the proper clinical context can lead to erroneous diagnoses."
>
> *George A. Diamond and Sanjay Kaul*[65]

When interpreting a test result, it is important to consider that a test does not tell you if the patient has a disease or not, but merely changes the probability of the condition in question.[66] The probability of the condition after the test is performed is referred

to as the post-test probability, while the probability of the condition prior to the test is the pre-test probability. The post-test probability is highly dependent on the pre-test probability, and in accordance with Bayes theorem the post-test odds is equal to the product of the pre-test odds and the likelihood ratio (LR) of the test.

In troponin studies, the pre-test probability is usually the AMI prevalence in that studied population. As an example one can consider the results of the landmark study by Reichlin et al.[25] where an elevated hs-cTnT yielded a post-test probability of 50% for the outcome of AMI, i.e. the test had a positive predictive value of 50%, a number commonly cited in the literature. However, the AMI prevalence (pre-test probability) in this study was 17%. In a separate study with an AMI prevalence of 9%, the post-test probability of an elevated hs-cTnT was only 30%,[62] while in yet another study with an AMI prevalence of 2%, the post-test probability was only 11%.[67] The test characteristics of hs-cTnT were similar (sensitivity around 90-95% and specificity around 80-85%) in all studies, which illustrates the impact of the pre-test on the post-test probability.

In routine care, patients also undergo clinical assessment and ECG testing, which significantly alters the probability of AMI from the overall ED prevalence of AMI. The results of strategies based on troponin alone may therefore be misleading as they do not consider the true pre-test probability. As an example, the ED AMI prevalence in Lund is about 7%. Among those with a hs-cTnT >14 ng/L, 23% have AMI (Figure 4A). However, if the patient history is assessed as high risk and/or the ECG has signs of acute ischemia, the patient's probability of AMI changes from 7% to 33% (Figure 4B). In this setting, a hs-cTnT >14 ng/L yields a post-test probability of 53%. On the other hand, if the history is assessed as non-high risk, and the ECG as non-ischemic, the patient's probability of AMI is only 2% (Figure 4C). With this pre-test probability, a hs-cTnT >14 ng/L yields a post-test probability of only 8%.

Hs-cTnT should therefore always be interpreted in the proper clinical context, and this is also recommended by guidelines (Figure 5).[64] Initiating invasive assessment or ACS treatment in all patients with hs-cTnT elevation without consideration of the pre-test probability will expose a large number of patients to unnecessary risks.

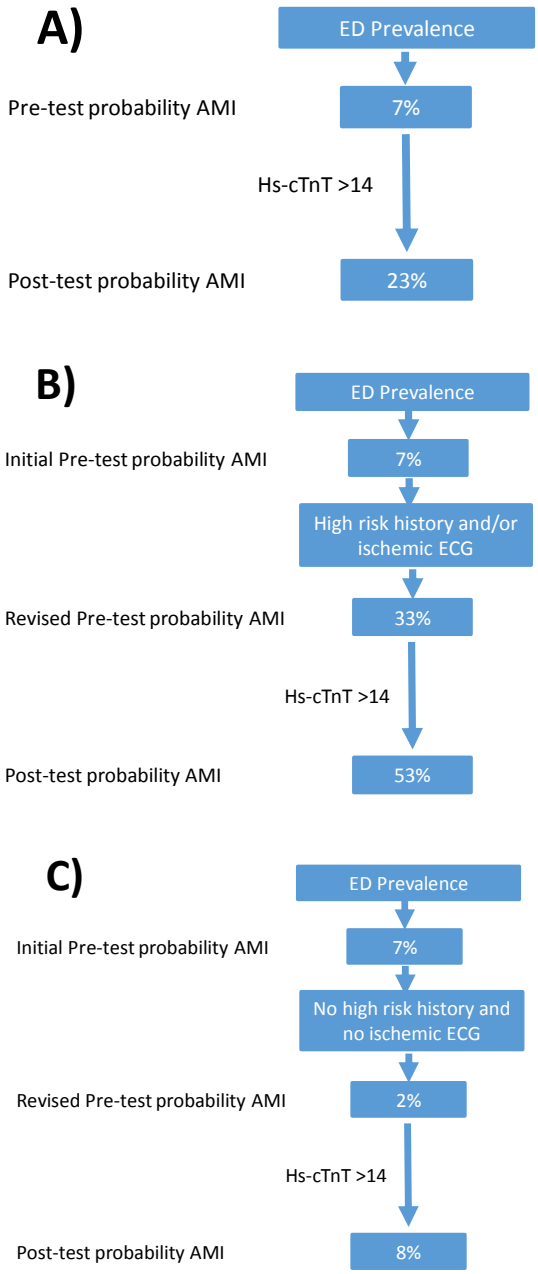

Figure 4.
Differences in pre- and post-test probabilities when history and ECG are also considered (Mokhtari et al. unpublished data). Panel A) shows the post-test probability resulting from a hs-cTnT >14 ng/L when the ED prevalence is used as the the pre-test probability. Panel B) shows the post-test probability resulting from a hs-cTnT >14 ng/L in patients with a high-risk history and/or ischemic ECG. Panel C) shows the post-test probability resulting from a hs-cTnT >14 ng/L in patients with a non-high risk history and non-ischemic ECG.

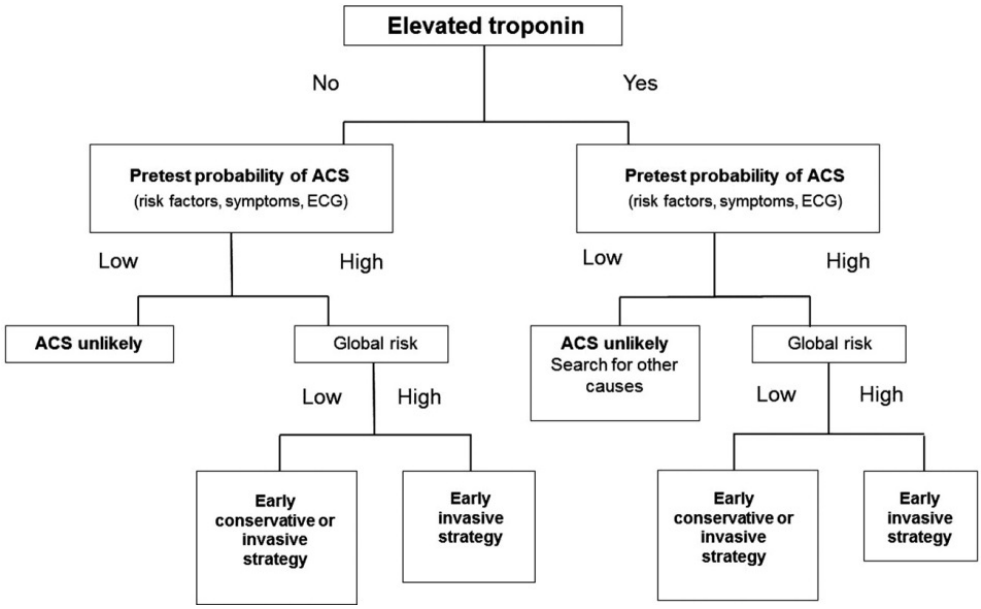

Figure 5.
Proposed algorithm for interpretation of troponin values. Reprinted with permission from Elsevier.[64]

The test threshold approach

> "Absolute certainty in diagnosis is unattainable, no matter how much information we gather, how many observations we make, or how many tests we perform. . . . Our task is not to attain certainty, but rather to reduce the level of diagnostic uncertainty enough to make optimal therapeutic decisions."
>
> *Jerome Kassirer*[68]

When considering if a diagnostic strategy enables safe discharge, one needs to determine what level of risk would be considered "safe". As no tests have a 100% sensitivity and specificity, there will always be false positives and false negatives. The approach suggested by Pauker-Kassirer suggests that testing should only be performed in patients whose probability of disease is above the so-called test threshold, but below the so called treatment threshold (Figure 6).[68]

Patients with a probability of disease below the test threshold are more likely to be harmed than to benefit from additional testing. For ACS, the test threshold has been calculated to be about 2%.[14] Testing in patients below this threshold will yield few positive results, and in those with a positive results, most will be false positives leading to unnecessary antithrombotic treatment, and radiation exposure and possible complications from coronary angiographies or radionuclide imaging.[11,14] The end result will thus be more harm than good to our patients.

Above the treatment threshold, the probability of disease is so high that the benefit of initiating treatment exceeds that of further testing. An example is patients with chest pain and ST elevation on ECG, where we immediately initiate treatment, and do not await test results such as troponins.

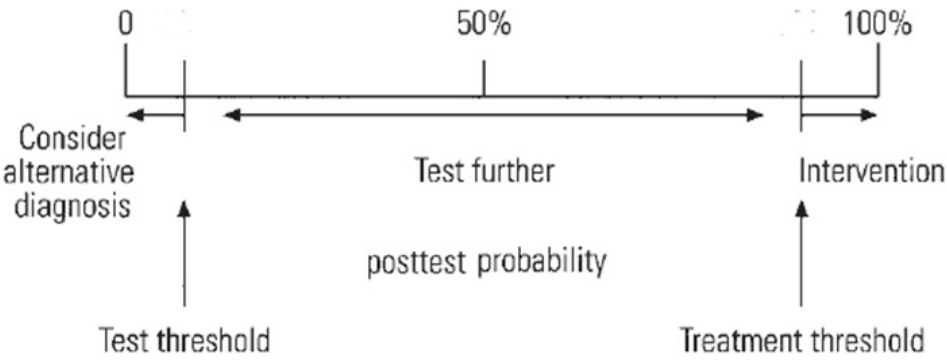

Figure 6.

Depicting proability of disease from 0 to 100% and the concepts of test threshold and treatment threshold, and the probability in between where furter testing is needed. Reprinted with permission from Elsevier.[69]

Even though the test threshold for ACS is about 2%, it has been shown that most ED physicians will not feel comfortable discharging patients unless their risk of serious 30-day events such as AMI and death is <1% (preferably ≤0.5%).[70] For any decision tool to be useful, it should therefore identify patients with a <2% risk of ACS, ensuring a risk of ACS below the test threshold, and a <1% risk of serious 30-day MACE.

In the end, the patient also needs to be comfortable with the level of risk, and shared decision-making is therefore recommended. It has been shown that ED chest pain patients often overestimate their risk of ACS,[71] and when informed of their low risk they often prefer outpatient follow-up.[72]

Interpreting hs-cTnT quantitatively

> "Any troponin is worse than no troponin.
> More troponin is worse than less troponin"
>
> *Judd Hollander*[73]

Hs-cTnT should be interpreted quantitatively and not dichotomously (negative vs positive), as the probability of AMI increases with increasing hs-cTn levels (Figure 7).[59] Among ED chest pain patients with a small hs-cTn elevation <50 ng/L, only about 20% have an AMI, while a majority of those with a hs-cTnT >50 ng/L have

AMI.[59,60] The PPV of a hs-cTnT >60 ng/L has been shown to be >80%, and does not improve with the addition of kinetic changes on serial sampling.[74] The recent ESC guidelines on NSTE-ACS also suggest that a hs-cTn value >5 times the URL (70 ng/L for hs-cTnT), in the proper clinical context, may be used alone to establish the diagnosis and proceed with invasive management.[27] The actual troponin level thus needs to be taken into account in the management of chest pain patients.

This is also true in patients with a normal hs-cTnT, where a hs-cTnT below the LoD (<5 ng/L) has a much higher negative predictive value (NPV) for AMI than a hs-cTnT of 5-14 ng/L.[75-80]

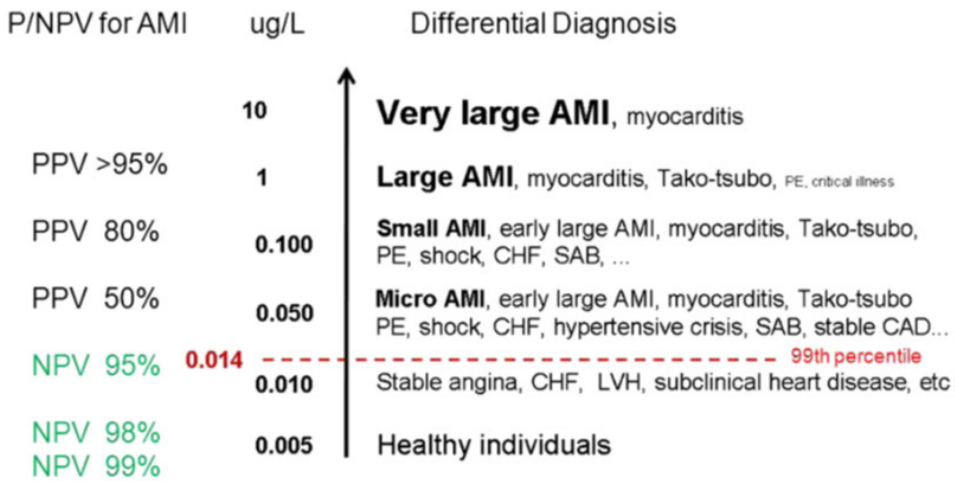

Figure 7.
Illustrating the increasing PPV with increasing hs-cTnT values, and the increasing NPV with decreasing hs-cTnT levels. Reprinted with permission from Elsevier.[81]

The delta approach

> "Sometimes change is what we need"
>
> *Unknown*

An elevated troponin signifies myocardial injury, and the presence of a significant rise or fall indicates acute myocardial injury. A significant change in the troponin level (delta), can thereby help distinguish between chronic hs-cTnT elevations, such as in heart or renal failure, and acute elevations such as in AMI. Taking significant change into account raises the specificity and PPV of hs-cTnT for the diagnosis of AMI, but at the cost of a decrease in sensitivity.[82] Acute myocardial injury can however also be seen in other conditions such as pulmonary embolism and does not automatically equal AMI, which also requires clinical evidence of acute myocardial

ischemia. A very large change is however suggestive of AMI,[27] and the delta should thus also be interpreted quantitatively.

The absence of a significant change consequently increases the sensitivity and NPV, and when combined with hs-cTnT levels ≤14 ng/L identifies patients with a very low risk of AMI.[83]

There are currently uncertainties as to what signifies a significant change, and whether a relative or absolute delta is superior. The change criteria are also dependent on the time interval between samples. The ESC biomarker group recommend using a 20% change in a 3h sample in patients with a 0h hs-cTnT >14 ng/L, and an absolute delta of >7 ng/L in those with a 0h hs-cTnT ≤14 ng/L (Figure 8).[84]

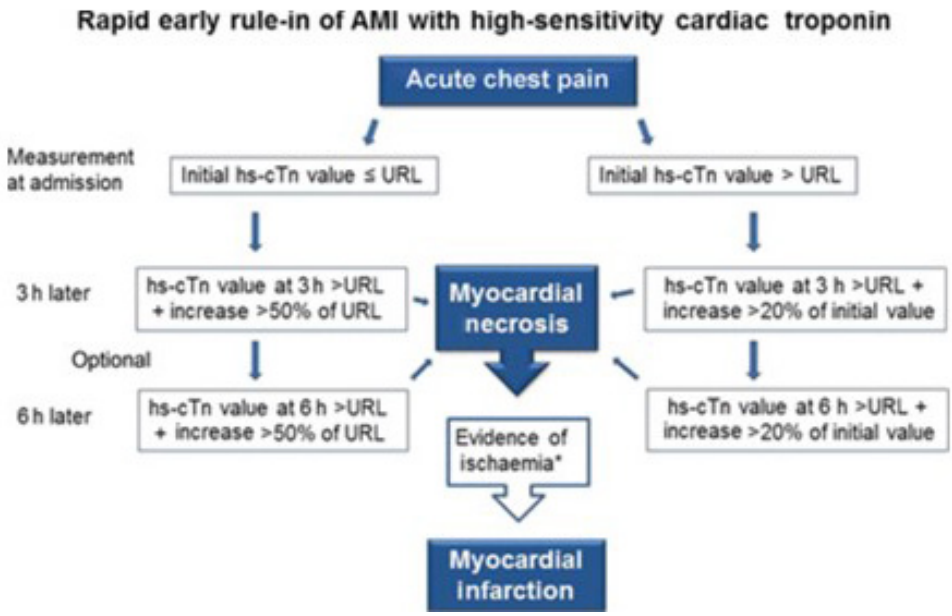

Figure 8.
The ESC biomarker group recommendations on what constitutes a significant delta. Reprinted with permission from Oxford University Press.[84]

In patients with hs-cTnT at or below the 99th percentile, some recommend using the reference change value (RCV) as a change metric, which takes into account both biological and analytical variation.[48] For hs-cTnT the RCV is about 50%.[48]

Several studies have suggested that an absolute change may be superior to a relative change.[85,86] The currently suggested optimal change values are absolute changes >7ng/L at 2-3h, or ≥9 ng/L at 6h.[85-87] Absolute changes do not however take the degree of troponin elevation into account, and the use of such small absolute deltas in patients with clearly elevated values may seem odd. For instance, a 0h hs-

cTnT of 1000ng/L and a 3h hs-cTnT of 1010 ng/L would be classified as a significant change. Indeed, one reason for the superiority of an absolute change may be the increased identification of AMIs in plateu phase who may not exhibit a 20% change, but may still have a small absolute change.[86] This concept of a lacking significant change on serial troponins in AMI patients is important and often overlooked. Several studies have shown that about 25% of AMI patients do not exhibit a significant change on serial troponin sampling.[61,83,84] The reason is that cTn reaches a plateu phase 10-18h after symptom onset, and late presenters may therefore not show a significant change.[61,88]

0h/3h hs-cTnT

> ”Delay is preferable to error.”
>
> *Thomas Jeffersson*

ESC has been recommending a 0h/3h hs-cTnT protocol since 2011.[89]
According to this protocol, patients can be considered ruled out if they have a 0h hs-cTnT ≤14 ng/L and no significant change in the 3h sample, or if the 0h hs-cTnT is ≤14 ng/L and analyzed ≥6h from symptom onset. Patients are considered ruled in if they have elevated values combined with a significant change, or a hs-cTnT >70 ng/L in a proper clinical context (the latter criteria added in the 2015 version). This protocol is however largely based on expert opinion and before 2016, the evidence for this approach was scarce. Two studies evaluating this protocol have been published during 2016. In the first study, a significant change was defined according to ESC biomarker group recommendations (i.e. change >7 ng/L if 0h hs-cTnT is ≤14 and change >20% if 0h hs-cTnT is >14 ng/L) and the rule-out arm had a NPV of only 98.7%.[90] In comparison, a strategy of hs-cTnT <14 ng/L at 0 and 3h (without incorporating a delta) had a NPV of 99.0%. The PPV for AMI was 72%, but the strategy failed to identify 46.2% of AMIs for rule-in.

In the other study, only the rule-out approach was evaluated. A 0h hs-cTnT ≤14 ng/L analyzed ≥6h from symptom onset combined with a GRACE score <140 and the patient being painfree had a NPV of 99.8%, while a 0h and 3h hs-cTnT ≤14 ng/L (without incorporating a delta) had a NPV of 99.9%.[91]

0h/1h hs-cTnT

> "Fast is fine, but accuracy is everything"
>
> *Wyatt Earp*

In the most recent ESC guidelines on non-ST-elevation ACS, a 0h/1h algorithm has received a class 1 recommendation (Figure 9).[27]

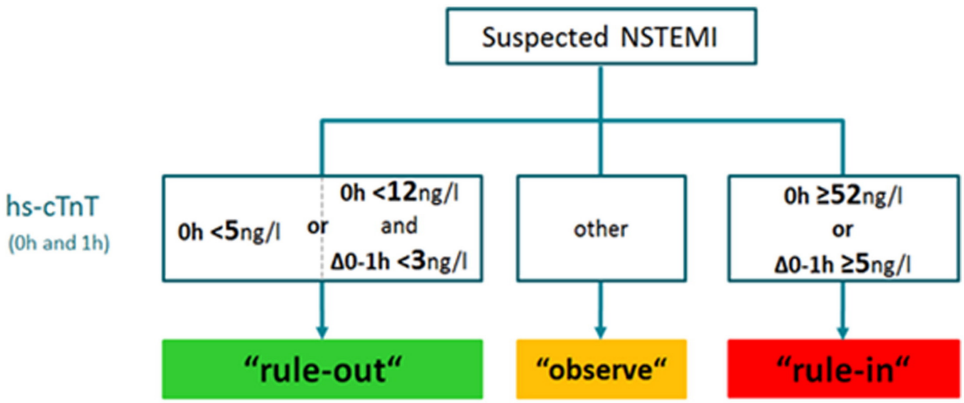

Figure 9.
The European Society of Cardiology 0h/1h algorithm. Reprinted with permission from Elsevier.[92]

According to this algorithm, AMI is considered ruled out if hs-cTnT is <5 ng/L at presentation, and in those with a 0h hs-cTnT <12 ng/L combined with a 0 to 1h change <3 ng/L. AMI is ruled in with a 0h hs-cTnT ≥52 ng/L, or a 0 to 1h change ≥5 ng/L.[27]

Most studies have however only evaluated either the 0h hs-cTnT <5 ng/L component separately,[75,76,78] or the 1h component (the algorithm without 0h hs-cTnT <5 ng/L) which is often referred to as the 1h algorithm.[60] In this thesis, the term 1h algorithm or 1h hs-cTnT strategy is used to refer to the algorithm without the 0h <5 ng/L component, 0h hs-cTnT strategy for referring to 0h <5 ng/L, 0h/1h algorithm for referring to the complete algorithm depicted above, and "extended algorithm" when referring to the algorithm evaluated in Paper II, which consists of the 1h algorithm supplemented with history and ECG assessments.

A 0h hs-cTnT <5 ng/L has in multiple studies been shown to have a NPV ranging between 99 and 100% for index visit AMI.[62,75-77,79,80,93-95] The NPV for this strategy is even higher if combined with a non-ischemic ECG.[75,76,78]

The 1h algorithm was originally derived by Reichlin et al. in a cohort with an ACS prevalence of about 30%.[59] In this study with 872 patients they found that the 1h algorithm could identify 60% of patients for rule-out with a NPV for AMI of

100%, and 17% of patients for rule-in with a PPV of 84%. The remaining patients were placed in the so called observational zone, and would need further investigation.

ED physicians are interested in a high NPV to be able to safely rule out AMI with few false negatives, while cardiologists are interested in a high PPV to accurately rule in AMI with a low proportion of false positives. By using 2 different cutpoints for baseline hs-cTnT and delta values, the 1h algorithm is able to fulfill both these needs. This algorithm also takes into account that hs-cTnT and delta values should be interpreted quantitatively, and that absolute deltas seem superior. It also provides clear directives for what signifies significant kinetics which reduces the uncertainties in using hs-cTnT.

Several multicenter studies have been able to confirm its excellent performance (Table 1).

Table 1.

Summary of studies evaluating the 1h algorithm

Study	N	Outcome	NPV (%)	Proportion "ruled out" (%)
Reichlin et al.[59]	872 (multicenter)	AMI	100	60
Reichlin et al.[60]	1320 (multicenter)	AMI	99.9	60
Mueller et al.[96]	1282 (multicenter)	AMI	99.1	63
Pickering et al.[97]*	2222 (multicenter)	AMI	99.5	64

* Evaluated the combined 0h/1h strategy

Key Messages

- Hs-cTnT has a higher analytical and diagnostic sensitivity compared to the previous generation cTnT, but a lower specificity.
- Elevated hs-cTnT levels in the ED are common.
- An elevated troponin signifies myocardial injury.
- Many conditions other than AMI can cause elevated troponin levels, such as pulmonary embolism, heart failure, renal failure and myocarditis.
- Similarly, a significant cTn change signifies acute myocardial injury, which does not automatically equal an AMI.
- Hs-cTnT should always be interpreted in relation to the clinical context, ie the pre-test probability.
- The diagnosis of AMI requires the presence of acute myocardial injury combined with a proper clinical context ie history, ECG and/or imaging supportive of myocardial ischemia.
- In late presenters with a high pre-test probability for AMI, the AMI diagnosis can be made in the presence of an elevated troponin without significant change.
- Absolute delta cTn has been shown to be superior to the relative delta for AMI diagnosis.
- A rule-out strategy should identify patients whose risk of having a 30-day MACE (primarily AMI and death) is <1%, while their risk of having ACS is <2%.
- Hs-cTnT <5 ng/L identifies patients at a low risk of AMI.
- In serial sampling, 0h and 1h hs-cTnT is likely a safe alternative to 0h and 3h hs-cTnT for ruling out AMI.

Aims

The aims of this thesis were to evaluate the diagnostic accuracy of strategies, focusing mainly on hs-cTnT, for ruling out 30-day MACE in ED chest pain patients. The goal was to find strategies that could rapidly identify patients with a low enough risk of 30-day MACE that they may be suitable for early discharge without the need for further cardiac testing.

The specific aims of the different papers are summarized below.

Paper I: To determine the diagnostic value of the ED physician's overall clinical assessment of ACS likelihood, and the values of the main diagnostic modalities underlying this assessment, namely the chest pain history, the ECG and the initial troponin result.

Paper II: To evaluate the diagnostic accuracy of the 1h algorithm supplemented with patient history and ECG for predicting a 30-day MACE, and to compare it with the algorithm based on hs-cTnT alone.

Paper III: To evaluate the diagnostic accuracy of a hs-cTnT <5 ng/L or ≤14 ng/L at ED presentation, combined with the ED physician's assessment of the history and ECG, for ruling out MACE within 30 days.

Paper IV: To evaluate the diagnostic accuracy of the guideline recommended 0h/1h hs-cTnT strategy when used as part of the modified ADAPT-ADP for ruling out 30-day MACE.

Methods

This section provides a summary of the methods and results of Paper I-IV. For further details, please refer to each individual paper.

Setting

All patient enrollment took place in the ED of Skåne University Hospital at Lund, which is a tertiary care teaching hospital. Percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) are available 24 hours a day. Patients with ST-elevation myocardial infarction (STEMI) who are identified via ambulance ECGs as a rule bypass the ED and are taken directly to the angiography suite. The ED is staffed mainly by emergency physicians. Physicians making the initial assessments in the studies were interns, residents, or attending physicians.

Study population

Paper I: This was a prospective observational cohort study. Patients aged over 18 years who presented with non-traumatic chest pain to the Lund ED during June 12th - October 8th 2009 were enrolled in the study. Patients were excluded if the history was unreliable due to e.g. alcohol intoxication or dementia, if they were transferred to another hospital, if they refused admission for inpatient evaluation, or if data were missing.

Papers II-IV: These were also prospective observational cohort studies, all using the same patient material. Consecutive patients aged 18 years or older, with a primary complaint of nontraumatic chest pain, and for whom hs-cTnT was ordered at presentation (0 hours) were enrolled during weekdays between 9 AM and 9 PM from February 2013 to April 2014. We did not enroll patients with severe communication barriers, eg, not speaking Swedish or English, or with dementia, and other patients who were unable to provide written informed consent. We also did not enroll patients with STEMI because this diagnosis is not based on biomarkers. Patients with STEMI at the index visit who were erroneously enrolled were

excluded. We also excluded those with missing data required for evaluating index tests, and those with significant hemolysis (H-index ≥100) in presentation (0h) hs-cTnT samples (Paper II-IV) or 1h samples (Paper II and IV) because this can cause falsely low hs-cTnT results.

Data collection

Paper I: The physicians' assessment of the chest pain history, ECG and their overall clinical assessment regarding the probability of ACS were recorded on a specific study form. Physicians were asked to categorize the chest pain history as typical of AMI, typical of UA, nonspecific for ACS, or not suspicious of ACS. The physicians also noted the presence or absence of ECG changes, and finally they recorded their composite assessment of the likelihood of ACS among four ACS likelihood levels: Obvious ACS, Strong suspicion of ACS, Low suspicion of ACS, and No suspicion of ACS.

The troponin assay used in this study was Elecsys troponin T, which has a 99th percentile cutoff of 0.01 μg/L, and with 0.03 μg/L reported as the lowest concentration with a coefficient of variation ≤10%. This was thereby not a high-sensitivity assay. The first cTnT test result was retrieved from the electronic patient records, with values ≥0.05 μg/L considered indicative of ACS.

Papers II-IV: Clinical data including TIMI score variables and physician assessments were collected by research assistants using a custom-made data form. The research assistants also collected the 1h hs-cTnT samples, using timers to achieve accurate timing, with sample times rounded to the nearest 10-minute mark in accordance with practice at our central laboratory. ED physicians assessment of the likelihood of acute coronary syndrome according to the patient history (high, intermediate, low, or very low risk) and ECG (showing signs of acute ischemia or not) were also obtained.

Samples for hs-cTnT, which was the assay in clinical use during the study period, were collected in lithium heparin tubes and analyzed with the Roche Cobas e602 (Roche Diagnostics, Basel, Switzerland), as in routine care. This assay has a limit of blank of 3 ng/L and a limit of detection of 5 ng/L, and the coefficient of variation is less than 10% at the 99th percentile cutoff point of 14 ng/L.[98]

Index test

Paper I: The evaluated index tests were the physicians overall clinical assessment of ACS likelihood, and the values of the main diagnostic modalities underlying this assessment, namely the chest pain history, the ECG and the initial troponin result.

Paper II: The primary evaluated index tests were the 1h algorithm proposed by Reichlin et al.[59] (Figure 10, in this paper referred to as the "troponin algorithm") and the troponin algorithm supplemented with the ED physician's assessment of patient history and ECG (Figure 11, in this paper referred to as the "extended algorithm"). The troponin algorithm rules out patients with a 0h hs-cTnT level <12 ng/l and a hs-cTnT change <3 ng/l from 0 to 1 h (1h delta). Patients are ruled in when the 0h hs-cTnT level is ≥52 ng/l or the 1h delta is ≥5 ng/l. The remaining patients are placed in an "observational zone." In the extended algorithm, rule-out also required a history assessed as non–high risk (intermediate, low, or very low risk) and the absence of acute ischemia on ECG. We further added a variable to the rule-in arm, allowing rule-in of patients with a 0h or 1h hs-cTnT >14 ng/l if combined with either a high-risk history and/or an ischemic ECG. The rationale was that in these patients with a high pretest probability, hs-cTnT >14 ng/l should have a positive predictive value sufficient for rule-in. This approach is in accordance with the American College of Cardiology Foundation expert consensus document.[64]

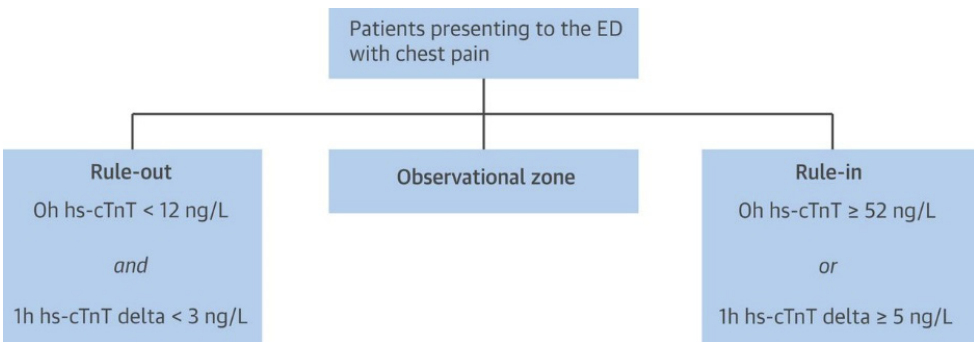

Figure 10. The troponin algorithm.
This algorithm used only high-sensitivity cardiac troponin T (hs-cTnT) testing at presentation (0 h) and 1 h for rule-out and rule-in of emergency department (ED) patients presenting with chest pain.

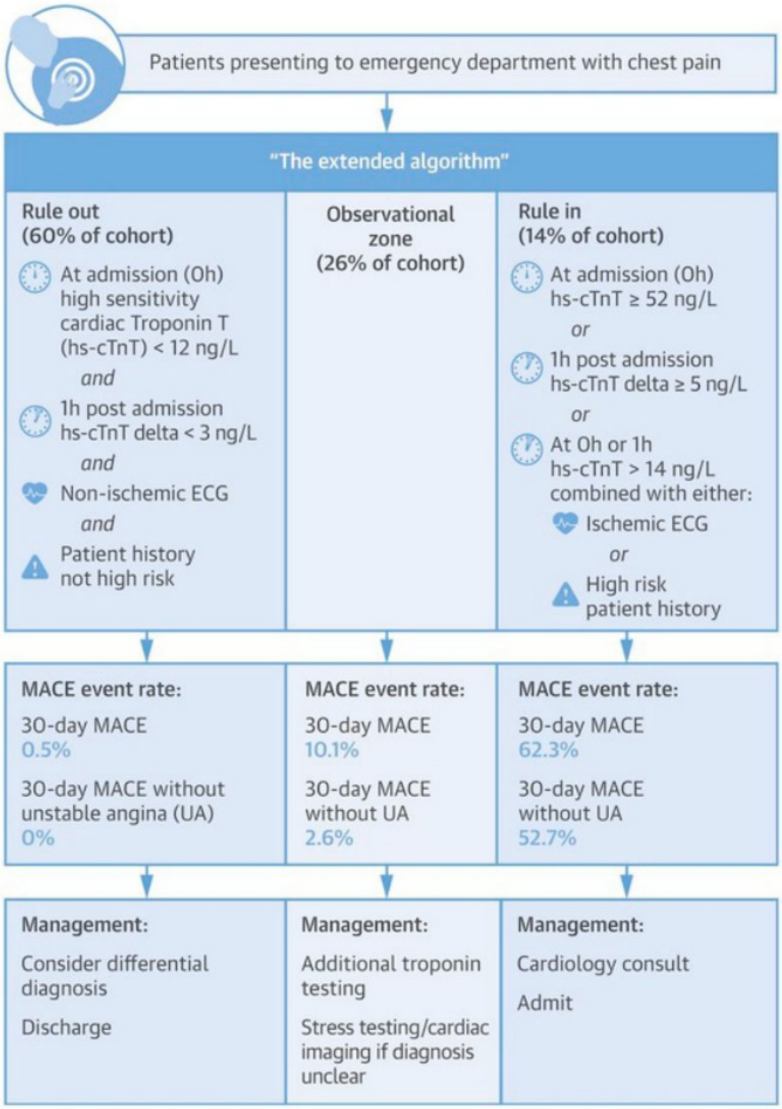

Figure 11. The extended algorithm.
For patients presenting to the emergency department (ED) with chest pain, the extended algorithm combines high-sensitivity cardiac troponin T (hs-cTnT) testing at 0 h and 1 h with the patient history and electrocardiogram (ECG) to predict the risk of a 30-day major adverse cardiac event (MACE) with and without unstable angina (UA). Rule-out, rule-in, and observational zone arms are shown, together with suggested courses of action.

Paper III: The 2 index tests were hs-cTnT <5 ng/L and ≤14 ng/L at ED presentation, combined with a physician assessment of a non-ischemic ECG result and a non-high risk history (history assessed as intermediate, low, or very low risk of acute coronary syndrome). We also evaluated an isolated 0h hs-cTnT <5 ng/L or

≤14 ng/L, and when combined with only a non-ischemic ECG result. Additionally, we studied a presentation hs-cTnT level in the setting of a high pretest probability, defined as either an ischemic ECG and/or a high-risk history.

Paper IV: The evaluated index test was the 0h/1h hs-cTnT rule-out strategy used as part of the modified ADAPT-ADP (Figure 12) where patients were identified as very low risk if they had an adapted TIMI score ≤1, no signs of acute ischemia on the ECG, and either 0h hs-cTnT <5 ng/L *or* 0h hs-cTnT <12 ng/L with a 1h increase <3 ng/L.

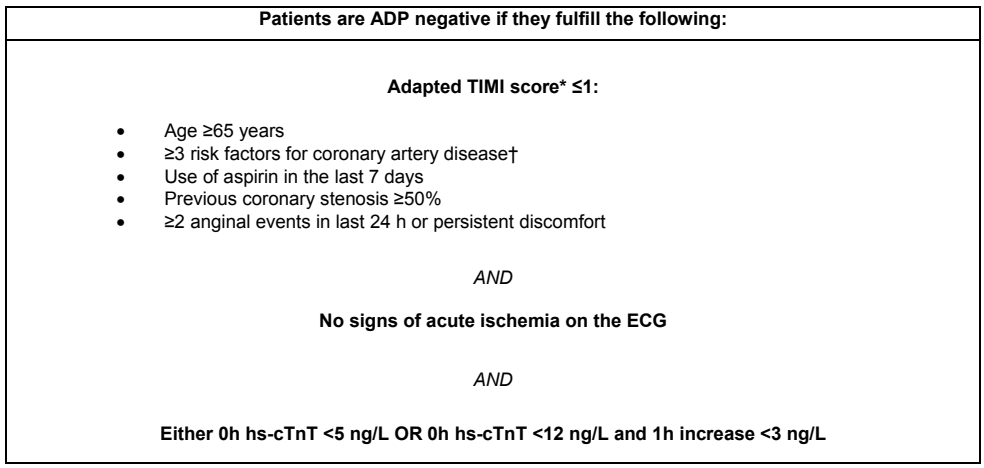

Figure 12. The modified ADAPT-ADP incorporating 0h/1h hs-cTnT.
*The original TIMI score includes ECG and Troponin as variables, but as both are required to be negative in the ADP they are not included in the score. All variables are assigned a value of 1. † Risk factors defined as family history of coronary artery disease, hypertension, hypercholesterolemia, diabetes, or being a current smoker. ADP = Accelerated Diagnostic Protocol; ECG = electrocardiogram; hs-cTnT = high-sensitivity cardiac troponin T; TIMI = Thrombolysis In Myocardial Infarction.

Outcomes and reference standard

Paper I: The primary outcome was a discharge diagnosis of ACS or a cardiac death during the index visit or within 30 days of ED presentation.

Papers II-IV: The primary outcome was a MACE within 30 days, including the index visit. Major adverse cardiac events were defined as an adjudicated diagnosis of AMI, UA, cardiac arrest, cardiogenic shock, ventricular arrhythmia requiring intervention, high-degree atrioventricular block requiring intervention, or death from a cardiac or unknown cause. The secondary outcome was MACE without UA within 30 days (Paper II and III).

The reference standard was a final adjudicated diagnosis of 30-day MACE, as decided by independent reviews by 2 cardiologists, and in case of disagreement, by

a third cardiologist. The cardiologists were blinded to the data form and the 1h hs-cTnT. For the adjudication they had access to all available clinical information from all hospitals in Sweden within 60 days from the index visit, including complete medical records, results of blood samples and radiologic investigations, ECGs, echocardiograms, stress tests and coronary angiographies. Deaths and causes of death were obtained from medical records, the Swedish population registry, and the national cause-of-death registry.

Adjudicators were provided with definition criteria for MACE events in accordance with guidelines and published standardized data definitions,[4,99] with AMI defined according to the universal definition requiring a significant rise and/or fall of hs-cTnT levels with at least one value above the 99th percentile, combined with symptoms or signs of cardiac ischemia.[4] Significant hs-cTnT change was defined as: an absolute change >7 ng/L within 2-3 h or ≥9 ng/L within 6 h,[84-87] and/or a change >20% if the 0 h hs-cTnT was >14 ng/L.[84] To avoid misclassification of patients presenting in a troponin plateau phase, an AMI diagnosis could still be adjudicated in patients with elevated hs-cTnT levels in the absence of a significant rise or fall, if considered to be the most likely diagnosis based on all available information.[4,61]

The diagnosis of UA required normal or slightly elevated hs-cTnT levels without a significant rise or fall, *and* a history consistent with UA defined as rest angina, new-onset angina of Canadian Cardiovascular Society class ≥3, or increasing angina, *and* at least one of the following: stenosis ≥70% in a vessel on coronary angiography, positive stress test if no angiography was performed, or new ischemic ECG changes in patients managed without stress test or angiography. An UA diagnosis could also be adjudicated in patients who were discharged after AMI was ruled out and were subsequently diagnosed with AMI or suffered death of cardiac or unknown cause within 30 days from the index visit.

The other components of the 30-day MACE outcome were defined according to published standardized data definitions.[99]

Statistical analyses

Papers I-IV: For descriptive data, continuous variables were described with mean and SD or median with interquartile range, and categorical variables described with proportions. Sensitivity, specificity, negative predictive values (NPVs), negative likelihood ratios (LR–), positive likelihood ratios (LR+), and corresponding 95% confidence intervals (CIs) were calculated for the different diagnostic strategies.

Comparisons between groups were performed by using Pearson's chi-square and Fisher exact tests for categorical variables, and independent Student t-test and 1-way analysis of variance for continuous variables, as appropriate based on test

assumptions (Papers II and IV). Comparisons of sensitivity and specificity were performed using McNemar's test (Paper II). All tests were 2-tailed and $P<.05$ was considered significant.

Analyses were made using IBM SPSS (version 19; IBM, Armonk, NY) and Microsoft Excel 2007 (Paper I) and IBM SPSS (version 21; IBM, Armonk, NY) and MedCalc Statistical Software (version 14.8.1; MedCalc Software bvba, Ostend, Belgium) (Papers II-IV).

Ethics

All included patients (paper I-IV) gave written informed consent and the studies were approved by the Regional Ethics Review Board in Lund.

Results

Diagnostic values of chest pain history, ECG, troponin and clinical gestalt in patients with chest pain and potential acute coronary syndrome assessed in the emergency department (Paper I)

AIM: To determine the diagnostic value of the ED physician's overall clinical assessment of ACS likelihood, and the values of the main diagnostic modalities underlying this assessment, namely the chest pain history, the ECG and the initial troponin result.

Baseline characteristics

1222 patients were included in the study. Seventy-one patients were excluded based on predefined criteria, leaving 1151 patients in the final analysis (Figure 13). The mean age was 61 years, 29% had a history of coronary artery disease (CAD), and 15% had diabetes. Fifty-four per cent of the patients were admitted for inpatient care but only 23% of these had ACS. In the entire study population, 13% had a final diagnosis of ACS (97 AMI, 49 UA) during the index visit or within 30 days.

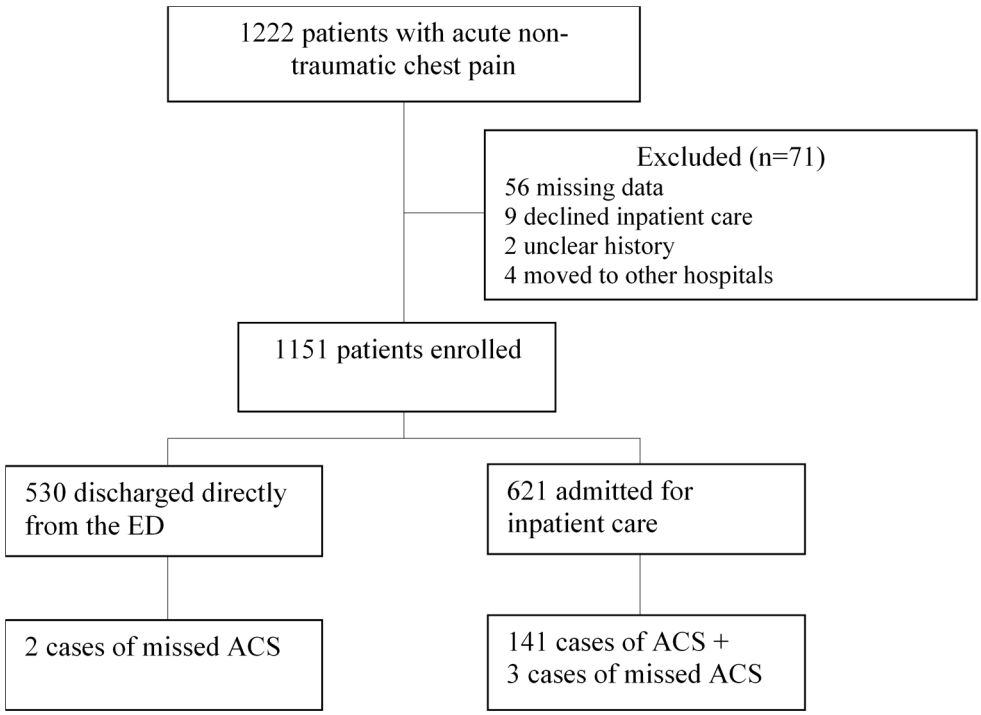

Figure 13.
Flow diagram of enrolled and excluded patients

Main results

As seen in Table 2, the clinician's overall assessments of obvious or strong suspicion of ACS clearly raised the probability of ACS (LR 29 and 4.8), whereas no suspicion of ACS markedly lowered the probability (LR 0.01). Among the modalities underlying this assessment, a chest pain history judged by the physician as typical of AMI or UA increased the probability of the disease (LR 4.9 and 5.6 respectively), while symptoms assessed as nonspecific or not suspicious of ACS lowered the probability (LR 0.3 and 0.02 respectively). However, when evaluating only patients with no ischemic ECG changes and negative initial troponins, chest pain history deemed typical of AMI had only a small impact on the likelihood of AMI (LR 1.6). Symptoms suspicious of UA however retained its predictive ability (LR 4.7). The presence of any ischemic ECG changes or an elevated TnT both increased the probability of ACS markedly (LR 7.6 and 24.9 respectively), while their absence only had a minimal effect (LR 0.6 and 0.7).

Table 2.
Diagnostic performance of physician assessments in percent (95% CI) for ACS within 30 days

	Sensitivity	Specificity	LR+	LR-
Chest Pain History				
Typical of ACS	86 (80-91)	80 (77-82)	4.3 (3.8-5.0)	0.2 (0.1-0.3)
Typical of AMI*	47 (38-57)	90 (88-92)	4.9 (3.7-6.5)	0.6 (0.5-0.7)
Typical of UA†	73 (60-84)	87 (85-89)	5.6 (4.5-7.1)	0.3 (0.2-0.5)
Nonspecific for ACS	87 (80-92)	39 (36-42)	0.3 (0.2-0.5)	1.4 (1.3-1.5)
Not suspicious of ACS	99 (96-100)	41 (38-44)	0.02 (0.00-0.12)	1.7 (1.6-1.8)
ECG				
ST-elevation	11 (7-17)	99 (99-100)	15.7 (6.6-37.6)	0.9 (0.8-0.9)
ST-depression	20 (14-27)	98 (97-99)	11.7 (6.6-20.8)	0.8 (0.8-0.9)
T-wave inversion	8 (5-14)	98 (97-98)	3.6 (1.8-7.1)	0.9 (0.9-1.0)
Non-Ischemic‡	39 (31-47)	95 (94-97)	0.6 (0.5-0.7)	7.6 (5.5-10.6)
TnT				
Positive initial TnT	42 (34-50)	98 (97-99)	24.9 (15.0-41.5)	0.7 (0.5- 0.7)
Overall suspicion of ACS				
Obvious ACS	12 (7-18)	100 (99-100)	29 (10-86)	0.9 (0.8-0.9)
Strong suspicion	71 (63-77)	85 (83-87)	4.8 (4.0-5.8)	0.4 (0.3-0.4)
Low suspicion	82 (75-88)	41 (38-44)	0.4 (0.3-0.6)	1.4 (1.3-1.5)
No suspicion	100 (98-100)	44 (41-47)	0.01 (0.00-0.12)	1.8 (1.7-1.9)

It should be notet that some of the sensitivity and specificities presented in the table in the original article are erroneous. The table above contains the true values.

A 1-h Combination Algorithm Allows Fast Rule-Out and Rule-In of Major Adverse Cardiac Events (Paper II)

AIM: To evaluate the diagnostic accuracy of the 1h hs-cTnT algorithm supplemented with patient history and ECG for predicting a 30-day MACE and to compare it with the algorithm based on hs-cTnT testing alone.

Baseline characteristics

We enrolled 1167 patients in this study, with 129 excluded due to STEMI, hemolysis or missing data, leaving 1038 patients in the final analyses (Figure 14).

A 30-day MACE was adjudicated in 121 patients (11.7%) and 30-day MACE without UA in 84 (8.1%). The number of subjects with each component of the MACE outcome are shown in Table 3.

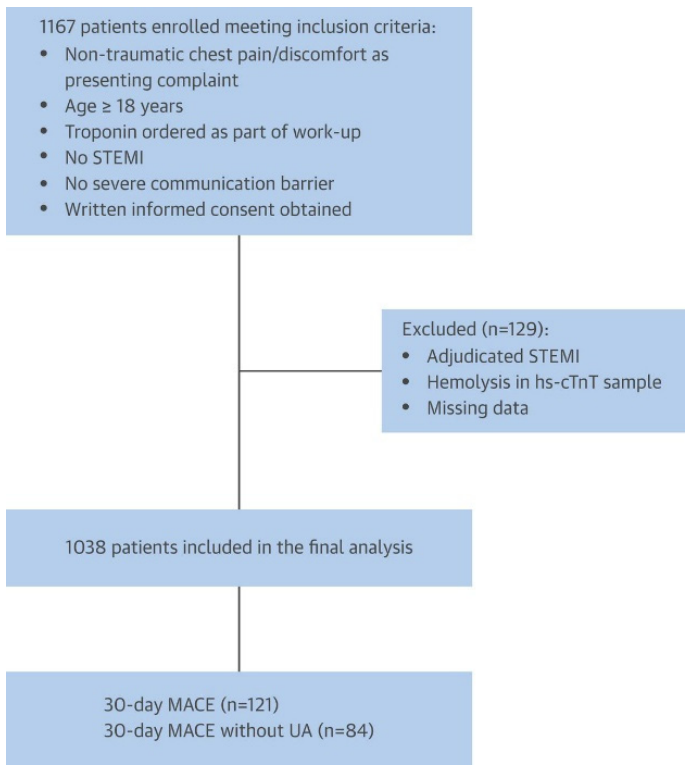

Figure 14.
Patient flow.

Table 3.
30-day MACE

Outcomes	All Patients N = 1,038	Extended Algorithm		
		Rule-out n = 625	Observational Zone n = 267	Rule-in n = 146
30-day MACE*	121 (11.7)	3 (0.5)	27 (10.1)	91 (62.3)
AMI during index visit	78 (7.5)	0 (0)	5 (1.9)	73 (50.0)
AMI during follow-up†	3 (0.3)	0 (0)	1 (0.4)	2 (1.4)
UA	39 (3.8)	3 (0.5)	21 (7.9)	15 (10.3)
Cardiogenic shock	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac arrest	1 (0.1)	0 (0)	0 (0)	1 (0.7)
Ventricular arrhythmia‡	0 (0)	0 (0)	0 (0)	0 (0)
High-grade AV block‡	1 (0.1)	0 (0)	1 (0.4)	0 (0)
Cardiac death	4 (0.4)	0 (0)	1 (0.4)	3 (2.1)
Death of unknown cause	0 (0)	0 (0)	0 (0)	0 (0)
30-day MACE without UA	84 (8.1)	0 (0)	7 (2.6)	77 (52.7)

Main results

As seen in Table 4, both the extended algorithm and the troponin algorithm categorized a clear majority of patients for rule-out or rule-in (74% and 75%, respectively). The extended algorithm identified somewhat fewer patients for rule-out than the troponin algorithm (60.2% vs. 65.7%; 95% confidence interval [CI]: 4.0 to 7.0; $p < 0.001$). The rule-out arm of the extended algorithm however had a markedly higher sensitivity than the troponin algorithm for 30-day MACE (97.5% vs. 87.6%; 95% CI: 4.0 to 15.8; $p < 0.001$), missing only 3 patients with UA compared with 1 AMI and 14 UA patients missed by the troponin algorithm. Among patients identified for rule-out with the extended algorithm, the 30-day MACE rate was 0.5% versus 2.2% with the troponin algorithm.

The rule-in arm of the extended algorithm was also more sensitive than that of the troponin algorithm (75.2% vs. 56.2%; 95% CI: 10.5 to 27.5; $p < 0.001$) but had a slightly lower specificity (94.0% vs. 96.4%; 95% CI: 1.4% to 3.4; $p < 0.001$). The proportion of patients in the observational zone was not significantly different between the 2 algorithms (25.7% vs. 24.6%; 95% CI: –0.8 to 3.1; $p = 0.28$).

Table4.
Algorithmic Diagnostic Accuracy for 30-day MACE

	Troponin Algorithm % (95% CI)	Extended Algorithm % (95% CI)	p Value
Rule-out	n = 682	n = 625	
Sensitivity	87.6 (80.4-92.9)	97.5 (92.9-99.5)	<0.001
Specificity	72.7 (69.7-75.6)	67.8 (64.7-70.9)	<0.001
NPV	97.8 (96.4-98.8)	99.5 (98.6-99.9)	
LR	0.17 (0.11-0.27)	0.04 (0.01-0.11)	
Rule-in	n = 101	n = 146	
Sensitivity	56.2 (46.9-65.2)	75.2 (66.5-82.6)	<0.001
Specificity	96.4 (95.0-97.5)	94.0 (92.3-95.5)	<0.001
PPV	67.3 (57.3-76.3)	62.3 (53.9-70.2)	
LR	15.6 (10.8-22.6)	12.5 (9.5-16.5)	
Observational Zone	n = 255	n = 267	
PPV	14.9 (10.8-19.9)	10.1 (6.8-14.4)	
LR	1.3 (1.0-1.8)	0.9 (0.6-1.2)	

For the outcome of 30-day MACE without UA (Table 5), there were no significant differences in sensitivity in the rule-out arms between the extended algorithm and the troponin algorithm (100% vs. 98.8%; 95% CI: –1.2 to 3.5; p = 1.00). For both the extended and the troponin algorithm, NPV (100% vs. 99.9%) and LR (0 vs. 0.02) were excellent.

Table 5.
Algorithmic Diagnostic Accuracy for 30-day MACE without UA

	Troponin Algorithm % (95% CI)	Extended Algorithm % (95% CI)	p Value
Rule-out	n = 682	n = 625	
Sensitivity	98.8 (93.5-100)	100 (95.7-100)	1.0
Specificity	71.4 (68.4-74.2)	65.5 (62.4-68.5)	<0.001
NPV	99.9 (99.2-100)	100 (99.4-100)	
LR	0.02 (0.00-0.12)	0.00 (0.00-0.07)	
Rule-in	n = 101	n = 146	
Sensitivity	78.6 (68.3-86.8)	91.7 (83.6-96.6)	0.001
Specificity	96.3 (94.9-97.4)	92.8 (90.9-94.3)	<0.001
PPV	65.4 (55.2-74.5)	52.7 (44.3-61.1)	
LR	21.4 (15.2-30.2)	12.7 (10.0-16.1)	
Observational Zone	n = 255	n = 267	
PPV	6.7 (3.9-10.5)	2.6 (1.1-5.3)	
LR	0.8 (0.5-1.3)	0.3 (0.2-0.6)	

Diagnostic Accuracy of High Sensitivity Cardiac Troponin T at Presentation Combined with History and ECG For Ruling Out Major Adverse Cardiac Events (Paper III)

AIM: To evaluate the diagnostic accuracy of a hs-cTnT <5 ng/L or ≤14 ng/L at ED presentation, combined with the ED physician's assessment of the history and ECG, for ruling out MACE within 30 days.

Baseline characteristics

The same cohort of 1167 patients used in Paper II was used for this study, with 1138 patients included in the final analyses (Figure 15). A final diagnosis of 30-day MACE was adjudicated for 125 patients (11%), and 30-day MACE without unstable angina for 87 patients (7.6%). Of the 80 patients with an index visit AMI, 14 had a 0 h hs-cTnT measured ≤2 h from symptom onset of whom 3 had an initial hs-cTnT between 5-14 ng/L.

Among patients assessed as having a non-ischemic ECG, 8.1% had a MACE within 30 days and among those with both a non-high risk history and a non-ischemic ECG, 3.4% had a 30-day MACE.

Patients assessed as having a non-high risk history were generally younger, more often female and hade less often a history of previous AMI or cardiac risk factors. They also less often described their pain as similar to previous ischemia, radiating to the left or right arm, or worse with exertion, while more often as pleuritic.

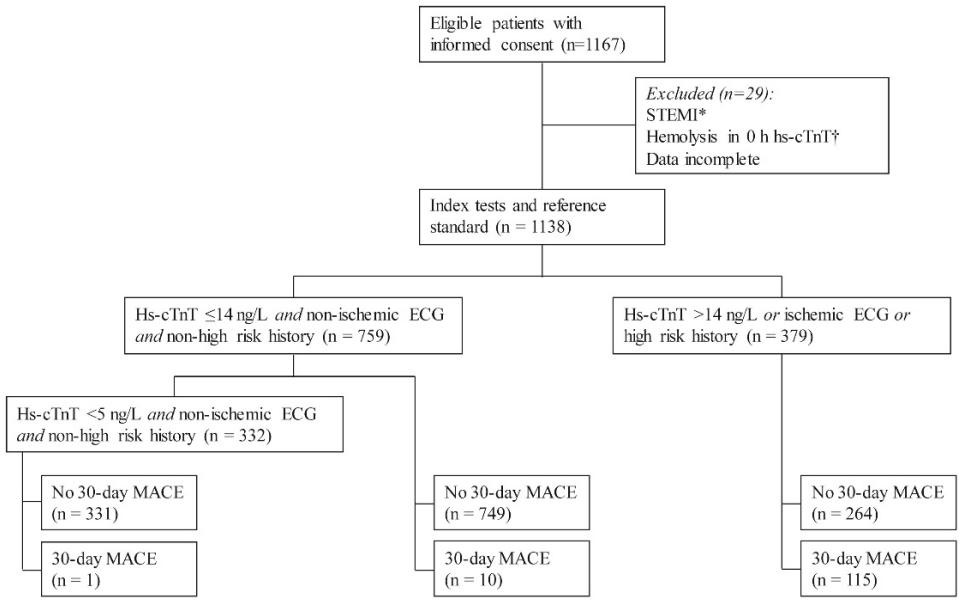

Figure 15.
Flow diagram of patient inclusion and exclusion.

Main results

With a rule-out criterion of hs-cTnT <5 ng/L, 343 (30.1%) of all patients were identified for rule-out, and when a non-ischemic ECG result and a non-high risk history were added, 332 (29.2%) were ruled out. Among patients with a hs-cTnT <5 ng/L, 1.2% had a 30-day MACE, with the strategy missing 2 AMIs and 2 UAs (Table 6). When supplemented with a non-ischemic ECG, the resulting 30-day MACE event rate in ruled out patients was 0.9% (missing 1 AMI and 2 UA cases). When a non-high risk history was further added, the strategy identified patients with a 30-day MACE rate of 0.3%, missing only a single case of unstable angina.

Table 6 also shows that for the outcome 30-day MACE without UA, a hs-cTnT level <5 ng/L combined with ECG and history resulted in a sensitivity and NPV of 100%, thereby not missing a single patient with this outcome.

Eleven patients had hs-cTnT <5 ng/L, combined with a high pretest probability (acute ischemia on ECG and/or a high-risk history). Among these patients, 3 had a MACE (2 AMI and 1 UA) within 30 days (NPV 72.7%), all at the index visit.

Table 6.
Diagnostic accuracy of hs-cTnT <5 ng/L at presentation in combination with ECG and history

	Sensitivity % (95% CI)	**Specificity** % (95% CI)	**NPV** % (95% CI)	**LR-** (95% CI)
30-day MACE				
Hs-cTnT <5 ng/L (n=343)	96.8 (92.0 – 99.1)	33.5 (30.6 – 36.5)	98.8 (97.0 – 99.7)	0.10 (0.04 – 0.25)
Hs-cTnT <5 ng/L + negative ECG* (n=340)	97.6 (93.2 – 99.5)	33.3 (30.4 – 36.3)	99.1 (97.4 – 99.8)	0.07 (0.02 – 0.22)
Hs-cTnT <5 ng/L + negative ECG* and history† (n=332)	99.2 (95.6 – 100)	32.7 (29.8 – 35.7)	99.7 (98.3 – 100)	0.02 (0.00 – 0.17)
30-day MACE without UA				
Hs-cTnT <5 ng/L	97.7 (91.9 – 99.7)	32.5 (29.6 – 35.4)	99.4 (97.9 – 99.9)	0.07 (0.02 – 0.28)
Hs-cTnT <5 ng/L + negative ECG*	98.9 (93.8 – 100)	32.3 (29.4 – 35.2)	99.7 (98.4 – 100)	0.04 (0.01 – 0.25)
Hs-cTnT <5 ng/L + negative ECG* and history†	100 (95.9 – 100)	31.6 (28.8 – 34.5)	100 (98.9 – 100)	0.00 (0.00 – 0.15)

As shown in Table 7, hs-cTnT level was ≤14 ng/L at presentation in 839 patients (73.7%). This strategy identified patients with a risk of 30-day MACE of 3.8%. When hs-cTnT ≤14 ng/L, a non-ischemic ECG result, and a non-high risk history were combined, 759 patients (66.7%) were identified for rule-out, with a 1.3% 30-day MACE rate, missing 10 patients with 30-day MACE.

For the outcome 30-day MACE without UA, patients with a hs-cTnT ≤14 ng/L combined with a non-ischemic ECG and a non-high risk history had an event rate of 0.7%.

Table 7.
Diagnostic accuracy of hs-cTnT ≤14 ng/L at presentation in combination with ECG and history

	Sensitivity % (95% CI)	**Specificity** % (95% CI)	**NPV** % (95% CI)	**LR-** (95% CI)
30-day MACE				
Hs-cTnT ≤14 ng/L (n = 839)	74.4 (65.8 – 81.8)	79.7 (77.1 – 82.1)	96.2 (94.7 – 97.4)	0.32 (0.24 – 0.43)
Hs-cTnT ≤14 ng/L + negative ECG* (n = 811)	79.2 (71.0 – 85.9)	77.5 (74.8 – 80.0)	96.8 (95.3 – 97.9)	0.27 (0.19 – 0.38)
Hs-cTnT ≤14 ng/L + negative ECG* and history† (n = 759)	92.0 (85.8 – 96.1)	73.9 (71.1 – 76.6)	98.7 (97.6 – 99.4)	0.11 (0.06 – 0.20)
30-day MACE without UA				
Hs-cTnT ≤14 ng/L	86.2 (77.2 – 92.7)	78.7 (76.1 – 81.1)	98.6 (97.5 – 99.3)	0.18 (0.10 – 0.30)
Hs-cTnT ≤14 ng/L + negative ECG*	89.7 (81.3 – 95.2)	76.3 (73.6 – 78.9)	98.9 (97.9 – 99.5)	0.14 (0.07 – 0.25)
Hs-cTnT ≤14 ng/L + negative ECG* and history†	94.3 (87.1 – 98.1)	71.7 (68.9 – 74.5)	99.3 (98.5 – 99.8)	0.08 (0.03 – 0.19)

A 0h/1h protocol for safe early discharge of chest pain patients (Paper IV)

AIM: To evaluate the diagnostic accuracy of the guideline recommended 0h/1h hs-cTnT strategy when used as part of the modified ADAPT-ADP for ruling out 30-day MACE.

Baseline characteristics

The same cohort of 1167 patients used in Paper II-III was used for this study. Of these, 147 were excluded, leaving 1020 for the final analysis (Figure 16). There were no important differences with regard to age, sex, baseline characteristics or 30-day MACE prevalence between included patients and those excluded due to missing data.

The median time from ED presentation to 0h hs-cTnT sampling was 32 minutes (IQR: 19 – 54), and the median time between the 0h and 1h sample was 60 minutes (Range: 30 – 90; IQR: 60 - 60).

MACE within 30 days occurred in 119 (11.7%) patients. Most cases of MACE were index visit AMI (n=77; 7.5%), and UA (n=38; 3.7%). All UA patients had either a significant stenosis on angiography (n=35), and/or pathological provocative testing (n=11), and/or ECG signs of acute ischemia (n=11).

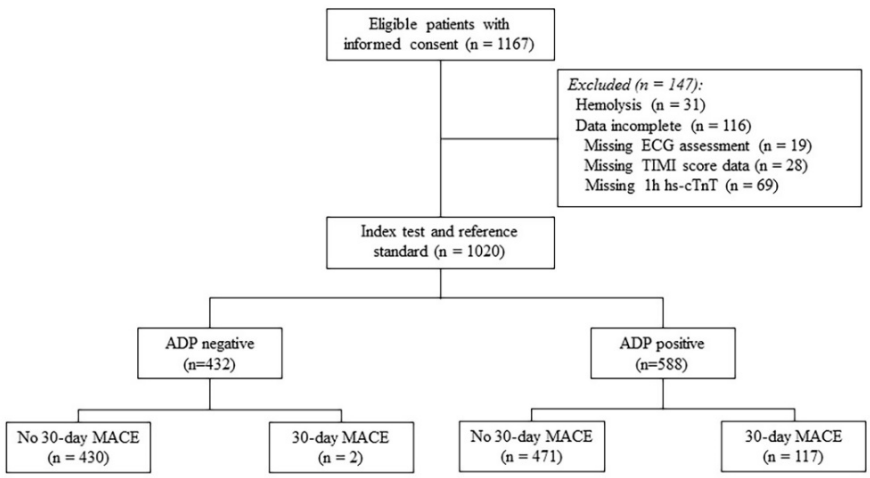

Figure 16.
Patient flow chart

Main results

Table 8 and Figure 17 describe the performance of the ADP using the guideline-recommended 0h/1h hs-cTnT strategy. The combination of an adapted TIMI score ≤1, a non-ischemic ECG, and either a 0h hs-cTnT <5 ng/L, or a 0h hs-cTnT <12 ng/L combined with a 0 to 1h increase <3 ng/L identified 432 (42.4%) patients as very low risk with an excellent NPV and LR-. Among ADP-negative patients 0.5% had a 30-day MACE, with the ADP missing only 2 patients with UA.

The ADP with only 0h hs-cTnT <5 ng/L identified 268 (26.3%) patients for potential immediate discharge with a risk of 30-day MACE of 0.4%, missing a single patient with UA.

Using only the 1h hs-cTnT component in the ADP identified 428 (42.0%) patients as very low risk, with a 30-day MACE risk of 0.5%, missing the same 2 patients with UA as with the complete 0h/1h strategy above.

Table 8.
Diagnostic accuracy of the ADP using 0h/1h hs-cTnT for 30-day MACE

	Sensitivity % (95% CI)	**Specificity** % (95% CI)	**NPV** % (95% CI)	**LR-** (95% CI)
TIMI ≤1 AND Negative ECG* AND				
0h hs-cTnT <5 ng/L OR 0h hs-cTnT <12 ng/L with 1h increase <3 ng/L (n=432)	98.3 (94.1 – 99.8)	47.7 (44.4 - 51.0)	99.5 (98.3 – 99.9)	0.04 (0.01 – 0.14)
0h hs-cTnT <5 ng/L (n=268)	99.2 (95.4 – 100)	29.6 (26.7 – 32.7)	99.6 (97.9 – 100)	0.03 (0.00 – 0.20)
0h hs-cTnT <12 ng/L with 1h increase <3 ng/L (n=428)	98.3 (94.1 – 99.8)	47.3 (44.0 – 50.6)	99.5 (98.3 – 99.9)	0.04 (0.01 – 0.14)

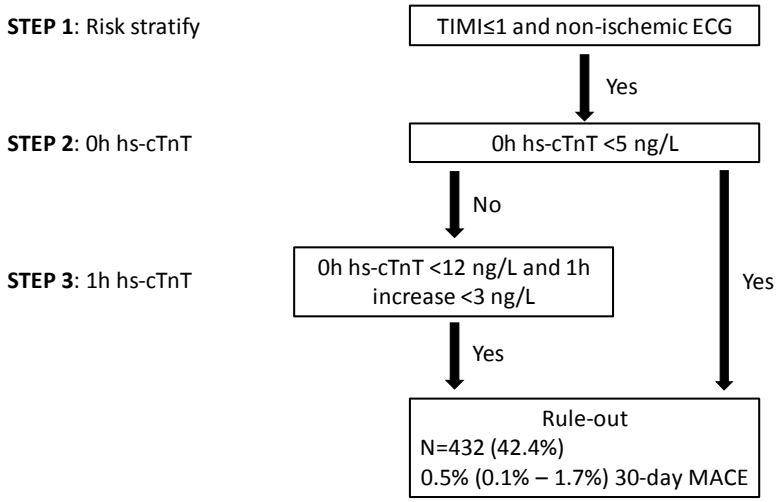

Figure 17.
Stepwise approach to identifying very low risk patients

As seen in Table 9, not incorporating the TIMI score resulted in a larger proportion of patients being identified for rule-out; 679 (66.6%) with 0h/1h hs-cTnT alone and 658 (64.5%) with the addition of the ECG. The event rates in ruled out patients were however higher, with a 2.4% MACE rate with the 0h/1h hs-cTnT alone strategy (2 missed AMIs, 14 missed UAs) and 2.0% MACE rate with the 0h/1h hs-cTnT + ECG strategy (1 missed AMI, 12 missed UAs). Among the 247 patients who met the 0h/1h hs-cTnT rule-out criteria but had a higher pre-test probability (adapted TIMI score >1 and/or ischemic ECG) 5.7% had a 30-day MACE.

In a sensitivity analysis, the 0h/1h hs-cTnT strategy alone had a sensitivity of 97.4% (95% CI: 90.9 – 99.7) and a NPV of 99.7% (95% CI: 98.9 – 100) for an outcome of index visit AMI, while the ADP had a sensitivity of 100% (95% CI: 95.3 – 100) and a NPV of 100% (95% CI: 99.2 – 100).

Table 9:
Diagnostic accuracy of the 0h/1h hs-cTnT strategy ± ECG but without TIMI score for 30-day MACE

	Sensitivity % (95% CI)	**Specificity** % (95% CI)	**NPV** % (95% CI)	**LR-** (95% CI)
0h hs-cTnT <5 ng/L OR 0h hs-cTnT <12 ng/L and 1h increase <3 ng/L (n=679)	86.6 (79.1 – 92.1)	73.6 (70.6 – 76.4)	97.6 (96.2 – 98.7)	0.18 (0.12 – 0.29)
+ Negative ECG* (n=658)	89.1 (82.0 – 94.1)	71.6 (68.5 – 74.5)	98.0 (96.7 – 98.9)	0.15 (0.09 – 0.26)

Discussion

The aims of this thesis were to evaluate the diagnostic accuracy of strategies, focusing mainly on hs-cTnT, for ruling out 30-day MACE in ED chest pain patients. The goal was to find strategies that could rapidly identify patients with a low enough risk of 30-day MACE that they may be suitable for early discharge without the need for further cardiac testing.
The main findings in this thesis are:

I) A combination of history, ECG and 0h and 1h hs-cTnT provides a rapid disposition strategy in approximately 75% of ED chest pain patients.

II) Using this combination about 60% of all patients may potentially be discharged without the need for further cardiac assessment, almost half of whom could be identified for rule-out with a single hs-cTnT at presentation, and with the remainder identified by a subsequent 1h hs-cTnT.

III) An alternative strategy utilizing 0h and 1h hs-cTnT in conjunction with TIMI score and ECG also allows safe early discharge of chest pain patients.

We have thereby identified strategies that hold great promise for use in ED routine care, and could potentially reduce ED crowding, unnecessary admissions, stress testing and costs.

History, ECG and troponin T (Paper I)

The main tools used to determine the likelihood of ACS in the ED are the history, the ECG and troponins. The predictive values for ACS of these diagnostic methods have been extensively analyzed,[32-34,100] but most studies have focused on each component separately.

Paper I confirmed the value of history, ECG, troponins, and the physician's overall clinical assessment based on all three, in the risk stratification of chest pain patients. In this study, the overall clinical assessment outperformed its individual components both at ruling in and ruling out ACS. Among the three components, the

history seemed superior for identifying patients at a lower risk, while TnT and ECG were better for ruling in ACS.

History, ECG and 0h and 1h hs-cTnT (Paper II and III)

Several studies have indicated that a single hs-cTnT result <5 ng/L at ED presentation, or the use of the 1h algorithm could accurately rule out AMI with a high NPV.[59,60,75,76,80] The use of these hs-cTnT strategies consequently received a Class I recommendation in the 2015 ESC guidelines for non-ST-elevation ACS.[27] The management of chest pain patients with suspected ACS in routine care is however not based on hs-cTnT alone, but also on an assessment of the patient history and ECG. Accordingly, the ESC guidelines included a caveat stating that these hs-cTnT strategies should only be used in combination with a full clinical assessment. In Paper II and III we were the first to evaluate these hs-cTnT strategies in conjunction with clinical risk stratification, which we believe provides important information for those considering to implement these guideline-recommended strategies in real world practice.

Our results showed that the combination of a history, ECG and 1h hs-cTnT identified about 60% of patients for rule-out with a mere 0.5% risk of MACE within 30 days, missing only three patients with UA. The combination with hs-cTnT <5 ng/L also performed well, and identified about 30% of patients for rule-out with a risk of 30-day MACE of only 0.3%, missing just a single patient with UA. Both strategies were thereby able to identify patients with a very low risk of risk of 30-day MACE that was below both the test threshold (<2%) as well as the threshold acceptable to most emergency physicians (<1%).

Patients identified for rule-out by 0h hs-cTnT <5 ng/L or the 1h algorithm, without incorporating history and ECG assessment, had on the other hand a much higher risk of a 30-day MACE, consisting primarily of missed UAs. This indicates that this approach is not sufficient for identifying patients for safe discharge, in contrast to what has previously been implied.[59,101] Further, among patients with hs-cTnT <5 ng/L and a high pre-test probability (high risk history and/or ischemic ECG) a large proportion had a 30-day MACE. Our results thus emphasize the importance of interpreting hs-cTnT in conjunction with other clinical information, and discharging patients based on these hs-cTnT strategies only if they have a low pre-test probability.

In Paper III we also evaluated if combining a non-high risk history and a non-ischemic ECG with a hs-cTnT ≤14 ng/L would be sufficient for a safe rule-out. This however resulted in a higher miss rate than the strategy using hs-cTnT <5 ng/L, and we were consequently unable to validate the previous findings of Body et al. who reported a NPV of 100% with this combination for ruling out AMI.[36] Our results

were instead more comparable to those of Freund et al.[102] who found a 1% risk of AMI in patients with hs-cTnT ≤14 ng/L and a low to moderate pre-test probability based on clinical assessment and ECG.

The results from Paper II and III thus suggested that a hs-cTnT <5 ng/L combined with a non-high risk history and a non-ischemic ECG result could allow safe discharge of approximately 30% of ED chest pain patients after a single hs-cTnT result at presentation, while an additional 30% could be discharged at the return of the 1h hs-cTnT test. The extended algorithm also identified patients at a high risk of 30-day MACE who should be admitted, thus providing an early disposition strategy in approximately 75% of patients.

TIMI Score, ECG and 0h/1h hs-cTnT (Paper IV)

In Paper II and III we combined 0h and 1h hs-cTnT strategies with the physician assessment of the patient history and ECG. Even though we believe this to more accurately reflect real life practice where we commonly rely on unstructured assessments of the history and ECG in our risk stratification, some clinicians may hesitate to use these strategies because of fear of lacking objectivity. As to provide an alternative, we therefore evaluated using the 0h/1h hs-cTnT strategy in combination with the ECG and TIMI score, as per the so called modified ADAPT-ADP. The TIMI score is both objective and relatively easy to use, and it is already used for risk stratification as part of routine care at some EDs.[38,44,103]

Our results showed that the combination of 0h/1h hs-cTnT, ECG and adapted TIMI score was able to identify patients with only a 0.5% risk of 30-day MACE, missing just two patients with UA and no patients with AMI or other forms of MACE. This protocol could thereby allow safe early discharge in about 40% of ED chest pain patients.

The 0h/1h hs-cTnT strategy alone identified more patients for rule-out than when the ECG and adapted TIMI score were also incorporated, but missed more patients with 30-day MACE. Those missed were mostly patients with UA, while the NPV for AMI was high and on par with previous studies.[59,60,96] The sensitivity for AMI was however only about 97%, which is similar to what was shown by Pickering et al.[97] Further, among patients who met the 0h/1h hs-cTnT rule-out criteria but who had a higher pre-test probability (adapted TIMI score >1 and/or ischemic ECG), the 30-day MACE rate was unacceptably high. Combining 0h/1h hs-cTnT with a low adapted TIMI score and a negative ECG on the other hand, increased sensitivity and NPV for 30-day MACE and AMI, and this strategy did not miss a single AMI. Our results thus again emphasize the importance of interpreting hs-cTnT together with ECG and clinical risk stratification for identification of patients suitable for early discharge. In this regard, the recent NICE guidelines state that a 0h hs-cTnT <5 ng/L

should be combined with a low TIMI score for identifying low risk patients.[104] Paper IV was the first to evaluate this combination and showed that this approach is indeed safe.

Unstable angina in the hs-cTn era

Most studies that have evaluated the 0h hs-cTnT <5 ng/L and the 1h algorithm, have only assessed their performance for an outcome of index visit AMI.[59,60,75,76,80] We included UA in the primary outcome in all our studies in this thesis. It might be argued that this is not useful as some have suggested that UA is no longer existent in the era of high-sensitivity troponins, and should be excluded from the ACS spectrum.[105] Studies using hs-cTn have however shown that the prevalence of UA is still quite high,[59,106,107] and that these patients have a significant 30-day risk of AMI and death.[108]

Our studies showed that patients ruled out by the 0h and 1h hs-cTnT strategies, without incorporating clinical risk stratification, could still have UA. This is important to have in mind when applying these strategies in routine care, as no studies have shown that UA patients can safely be discharged from the ED and left untreated. We therefore believe it is important to identify patients with UA since this condition changes management. We also believe that omission of UA in the outcome may even introduce bias in an observational study, as UA patients commonly receive treatment as part of routine care, which may in turn prevent other MACE outcomes such as AMI and death.[109]

0h and 1h hs-cTnT limitations

Despite the class 1 recommendation in the ESC guidelines, the use of 0h and 1h hs-cTnT strategies in clinical practice is controversial.[90,110-112]

The most important critique is that these strategies may miss AMI patients who present very early after symptom onset. The definition of a very early presenter is however also controversial, where some have defined it as those with a 0h sample measured <2h from symptom onset,[111] while others have defined it as <1h[27] or <3h from symptom onset.[113] The number of very early presenters among AMI patients have in all studies been low,[110] and as such there is no way of currently knowing that these strategies will be safe in these patients. Additionally, in subgroup analyses, the NPV has consistently been lower among very early presenters. In a study by Shah et al. evaluating a hs-cTnI strategy, the NPV was only 97.6% among those with hs-cTnI sampling ≤2 hours from symptom onset, and 99.8% in the

remaining patients. Similarly, in a study by Body et al. the hs-cTnT <5 ng/L strategy had a NPV of only 98.7% among very early presenters (<2h), compared to a NPV of 100% among late presenters (≥2h),[78] and in a study by Rubini Gimenez et al. the NPVs were 96.4% (<3h) vs 99.5% (≥3h).[101] Therefore, until larger studies or a meta-analysis have proven the safety of 0h and 1h hs-cTnT strategies in very early presenters, this author believes that we should perform additional hs-cTnT testing at 3h in patients with a 0h hs-cTnT sampling ≤2h from symptom onset due to the potential risk of false negative tests.

It has also been suggested that a small subset of AMI patients may be so called "late risers" who do not develop an elevated hs-cTnT level until >6h after ED presentation.[114] These patients risk being missed by the rapid rule-out strategies. On the other hand, they will likely also be missed by the recommended alternative, the 0h/3h hs-cTnT strategy.

Further, the 1h algorithm has been criticized for its use of small deltas, since these changes could be caused by the assays analytical imprecision alone, especially if older equipment is used for the analysis.[111,115] Reichlin et al. however argue that the algorithm was developed using a data driven approach, and that the theoretical concerns above are less relevant, as the algorithm has consistently been shown to perform well.[116]

The safety of 0h and 1h hs-cTnT strategies have also been questioned as several studies have shown that they have <99% sensitivity,[80,96,97,101] which has caused some controversy as to whether this is adequate for a diagnostic strategy aiming to rule out AMI.[97,112]This can however, as shown in Paper II-IV, be remedied by combining these strategies with ECG and clinical risk stratification.

Studies to date have only included patients presenting with chest pain. There are therefore uncertainties as to the performance of these strategies if implemented in routine ED care, and applied to patients with other presenting complaints such as dyspnea. As the prevalence of ACS is lower among patients with other primary complaints, the negative predictive values of these strategies would be expected to be even higher in this setting, while the positive predictive values on the other hand will be lower. This could thereby result in the rule-in aspect of the 1h algorithm, and specifically the 0h hs-cTnT ≥52 ng/L criteria, identifying a large proportion of patients as "ruled in", who do not have ACS.[110]

Additionally, some have questioned the use of an algorithm without sex-specific cut-offs.[111] The cut-off of <12 ng/L used in the 1h algorithm is however about mid-way between the proposed sex-specific cutoffs for men (16 ng/L) and women (9 ng/L).

There are also uncertainties regarding patients neither identified for rule-out nor rule-in, the so called "observational zone". This constitutes about 20-25% of patients in the different studies,[59,60,96] and even though some have tried to study this group specifically,[92] the optimal management of these patients is currently unclear.

In Paper III, patients aged ≥65 years ruled out by a combination of hs-cTnT <5 ng/L, a non-ischemic ECG and non-high risk history still had a 3.3% risk of 30-day MACE. These patients were few and the confidence interval very wide, and since this was a subgroup analysis it should only be seen as hypothesis generating. Nonetheless, these results are in line with the findings of Body et al. who showed that 4.3% of patients aged ≥65 years with a hs-cTnT <5 ng/L and a non-ischemic ECG had a 30-day MACE.[78] Whether hs-cTnT <5 ng/L strategies should be utilized in those aged ≥65 years is therefore unclear.

Putting it all together

Chest pain is the second most common presenting complaint among patients seeking care in the ED, yet many hospitals lack protocols to guide physicians on how to use hs-cTn testing. Unstructured use of hs-cTn in the assessment of ED chest pain patients, without integration within a protocol, does not confer a large benefit,[29] and many clinicians feel uncertain as how to apply hs-cTn in practice. Hospitals should therefore have clear protocols that can provide a framework for optimal hs-cTn use and provide guidance on how chest pain patients should be managed. This is highlighted by the Australian guidelines with a 1A level of recommendation. Such a protocol should incorporate not only hs-cTnT, but also formal risk stratification using the ECG and other clinical information, such as clinicians' clinical judgement or a risk score to identify patients with a low vs a high pre-test probability which is in line with guideline recommendations[64] and the results of the studies in this thesis.

A possible approach for such a protocol is that those with a low pre-test probability (non-ischemic ECG and either a non-high risk history or a low TIMI score) in combination with a hs-cTnT <5ng/L or a 0h h-cTnT <12ng/L combined with a 1h delta <3 ng/L are considered "ruled out", if the 0h hs-cTnT is measured >2h after symptom onset. This approach is in line with our results and the current ESC guidelines.[27] A sampling interval of 2-3h instead of 1h can be used, and these are also recommended by the ESC. Using 1h sampling and the 1h algorithm however has the advantage of being more rapid, providing clear directives for hs-cTnT kinetics, and risk stratifying all patients instead of identifying only low risk patients. In this author's opinion, those identified for rule-out who do not have another condition requiring admission, should be discharged with no further cardiac testing, as further testing would likely cause more harm than benefit. Such low risk patients do not benefit from hospital admission[13] and often prefer outpatient follow-up when informed of their low risk.[72] Providing discharge information recommending patients to return if their symptoms worsen or do not resolve will likely also catch the few patients with UA that are missed, and prevent harm.

Chest pain patients with a hs-cTnT >14 ng/L in combination with a high risk history, those with a hs-cTnT ≥52 ng/L, a 1h delta ≥5 ng/L, as well as those with a clear ischemic ECG, should be admitted, preferably to a cardiology ward, as their risk of having a MACE is high. After admission, additional hs-cTnT testing would be warranted in some cases, and echocardiography and coronary angiography in most cases.

Patients not identified for neither rule-out or rule-in will consist primarily of those with a mildly elevated hs-cTnT between 15 and 51 ng/L combined with a low pre-test probability and a 1h delta <5 ng/L, and those with a high-risk history but a non-ischemic ECG and negative 0h and 1h hs-cTnT. These patients have an intermediate risk of 30-day MACE. In patients with an elevated hs-cTnT in this risk group, other potential causes of troponin elevation such as pulmonary embolism, renal failure and heart failure need to be considered, as well as an AMI in plateau phase. The medical records should be reviewed to evaluate if there are previous hs-cTnT measurements for comparison. Additional hs-cTnT testing at 3h should be performed in most patients, and echocardiography and other cardiac testing should be considered. Finally, among patients with a high risk history but negative hs-cTnT and non-ischemic ECG, non-invasive testing should be considered to exclude UA.

Future directions

In recent years, there has been an aboundance of publications in the field of hs-cTn, which has considerably increased our knowledge on the optimal use of these assays. Unfortunately, almost all studies have been observational, and although the 0h and 1h hs-cTnT strategies as well as the 0h and 3h strategies have performed well, physicians in routine care might not find them sensible, consider them too complicated, or may not feel comfortable discharging patients in accordance with their recommendations. The true safety and efficacy of these strategies when implemented in routine care is thereby unknown. Prospective clinical trials are therefore desperately needed to clarify this issue.

Additionally, there are currently several protocols for the management of chest pain patients, with different risk stratification and troponin algorithms. The most optimal approach for risk stratification, whether by clinical assessment (“gestalt”) or the use of a formal risk score such as the TIMI score, as well as the optimal timing of serial troponin testing is currently unclear. Ideally, the different diagnostic strategies should be compared in clinical trials.

When using the 0h/1h algorithm, a considerable proportion of patients are placed in the “observational zone”. How these patients should be further managed also needs further elucidation.

The safety of rapid rule-out protocols in very early presenters (≤2h) is currently unclear as well. Optimally this should be studied in a meta-analysis.

Even though the 0h/1h protocol has performed well in the different studies, they have only looked at patients with a primary complaint of chest pain. The value of these protocols in patients with other complaints are unclear and needs further studying.

Guidelines, such as those from the AHA, recommend routine non-invasive testing in low risk chest pain patients. However, observational data indicate that admission and non-invasive testing in these patients is likely more harmful than beneficial. In low risk patients, the time has come to test an approach of outpatient management with no further cardiac testing in a clinical trial.

Limitations

Paper I

This study had several limitations. It was performed at only one university hospital which limits the generalizability of the results, but the ACS prevalence was however comparable to that in other studies of unselected ED chest pain patients.[22,23,117,118]

Our reference standard was discharge diagnoses, and since we aimed to study diagnostic value in routine care, we did not review the diagnoses for accuracy. We cannot exclude that adjudication of diagnoses would have changed the results to some extent.

A diagnosis of ACS within 30-days was obtained from our hospital records, and we may have missed a small number of patients presenting to other hospitals. However, we believe such misclassifications were probably few and unlikely to significantly affect the results.

Suggested definitions of the different levels of ACS suspicion were present on the study forms, and although they left considerable room for judgment, other (or no) definitions may have led to somewhat different results. Additionally, although the physicians were instructed to disregard ECG and TnT when evaluating the symptoms, we cannot exclude that ECG and TnT results influenced the symptom assessment in some cases.

As TnT was used in the gestalt assessment as well as in deciding the final diagnosis, incorporation bias could have been present. This was however probably limited by the fact that the emergency physicians only had access to the initial TnT, whereas the discharge diagnoses were most often based on repeated TnT analyses to assess for a significant rise or fall.

Many of our results also had broad confidence intervals suggesting that some of the analyses were somewhat underpowered.

Finally, we did not have data regarding physician level of experience. Previous studies have however shown that differences in the diagnostic accuracy of the gestalt depending on experience are small.[119]

Paper II-IV

We did not enroll patients during all hours of the day or during weekends, and the study population was from a single university hospital. There were, however, no important differences between included patients and patients seeking care outside of inclusion hours. Our AMI and UA prevalences were also similar to that in previous studies with a continuous patient inclusion at our ED,[24] suggesting that there was no significant selection bias and that the present sample was representative of our entire ED chest pain population. Furthermore, our AMI prevalence was similar to that at several other centers,[22,23,117,118] and our ACS prevalence was similar to the reported average ED ACS rate.[21]

Patients with missing data were excluded. This might introduce a risk of selection bias, but as these cases were few (Paper III) and as there did not seem to be any important differences between those included and those excluded due to missing data (Paper II and IV), any such bias is likely to be of limited importance.

We only evaluated patients with a primary complaint of chest pain and used the Roche hs-cTnT assay. Whether similar results would be obtained in patients with other primary complaints such as dyspnea and with the use of hs-cTnI assays is unknown. However, both single troponin rule-out strategies as well as 1h strategies with hs-cTnI have also been shown to perform well,[101,120] and it seems reasonable to believe that combining hs-cTnI with clinical risk stratification will yield results similar to those obtained with hs-cTnT.

ED physicians were not blinded to the 1h hs-cTnT, but they were unaware of the study hypotheses. The adjudicating cardiologists were blinded to the 1h hs-cTnT, and the final diagnosis of AMI was therefore independent of these samples, which minimized the risk of incorporation bias in the assessment of 1h hs-cTnT strategies. The adjudicators were however not blinded to the 0h hs-cTnT level, which introduces a risk of incorporation bias in the assessment of 0h strategies. This is difficult to avoid as troponins are obligatory for the AMI diagnosis.[4] The AMI diagnoses in our study were, however, usually based on a significant hs-cTnT increase or decrease in a proper clinical context and on all clinical information within 60 days.

As in routine care, not all patients underwent stress testing/cardiac imaging and, despite careful adjudication, a few cases of UA might have been missed. If so, however, these cases had an uneventful 60-day follow-up.

The 1h hs-cTnT samples were collected to achieve precise timing. In routine care, the 1h sample will likely in some cases be collected later than in this study. This is however unlikely to adversely affect the sensitivity and NPV of the 1h strategy as there will be more time to detect a potential hs-cTnT rise.[97,121]

Conclusion

- The combination of patient history, ECG and a 0h hs-cTnT <5 ng/L identified about 30% of ED chest pain patients at a very low risk of 30-day MACE who may be suitable for early discharge.

- The addition of patient history and ECG to the 1h algorithm improved its performance, and could allow a rapid safe rule-out in about 60% of patients, while identifying about 15% of patients who have a high risk of 30-day MACE and who should be admitted.

- A combination of history, ECG and 0h and 1h hs-cTnT thereby provided a rapid disposition strategy in approximately 75% of ED chest pain patients

- Using this combination about 60% of all patients may potentially be discharged without further cardiac assessment, almost half of whom could be identified for rule-out with a single hs-cTnT at presentation, and with the remainder identified by a subsequent 1h hs-cTnT

- An alternative strategy utilizing 0h and 1h hs-cTnT in conjunction with TIMI score and ECG also also identified patients with a very low risk of 30-day MACE, and could potentially allow safe early discharge of about 40% of ED chest pain patients.

Populärvetenskaplig sammanfattning

En av de vanligaste sökorsakerna på akutmottagningen är bröstsmärta, för vilket hundratusentals patienter söker vård årligen. En stor andel av patienterna blir inlagda för att utesluta hjärtinfarkt samt s.k. instabil kärlkramp, ett tillstånd som kan beskrivas som ”hotande hjärtinfarkt”. Båda dessa tillstånd orsakas av syrebrist i hjärtat.

För att utesluta hjärtinfarkt tar man idag ett särskilt blodprov som kallas troponin. Provet tas vid ankomst till akuten, samt tre till sex timmar senare. Det tar ungefär en timme att få utsvarat. Om båda proverna är normala kan man med hög sannolikhet utesluta hjärtinfarkt. Vid instabil kärlkramp kan däremot normala nivåer av detta prov ses. De flesta blir därför inlagda för ytterligare blodprovstagning samt ställningstagande till annan utredning för att med säkerhet utesluta även instabil kärlkramp. Sammantaget är det mindre än 15% av alla som söker med bröstsmärta som visar sig ha hjärtinfarkt eller instabil kärlkramp. De allra flesta lider istället av godartade tillstånd som exempelvis smärtor från muskulaturen.

Om man kan identifiera ett sätt att snabbt och säkert utesluta hjärtinfarkt och instabil kärlkramp redan på akuten, skulle man kunna förhindra inläggningar och utvidgad utredning.

I studierna som ingår i denna avhandling har vi tittat på olika strategier för att snabbt och säkert kunna identifiera patienter med bröstsmärta som har en så pass låg risk för hjärtinfarkt och instabil kärlkramp att de kan skickas hem. Våra studier visar att mätning av troponin vid ankomst samt redan efter en timme kan vara tillräckligt för att utesluta hjärtinfarkt. Om man kombinerar ovanstående provtagning med EKG och den enskilda patientens sjukhistoria kan man med mycket hög sannolikhet utesluta även instabil kärlkramp. Om ovanstående strategi hade införts hade upp till 60% av alla som söker på grund av bröstsmärta på akutmottagningen kunnat skickas hem redan inom två timmar efter ankomst, varav hälften redan inom en timme. Detta är inte av värde enbart för patienter som söker för bröstsmärta utan även för övriga patientgrupper. Resultatet skulle kunna bli att vi sparar vårdplatser samt kan minska handläggningstiderna på akuten.

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