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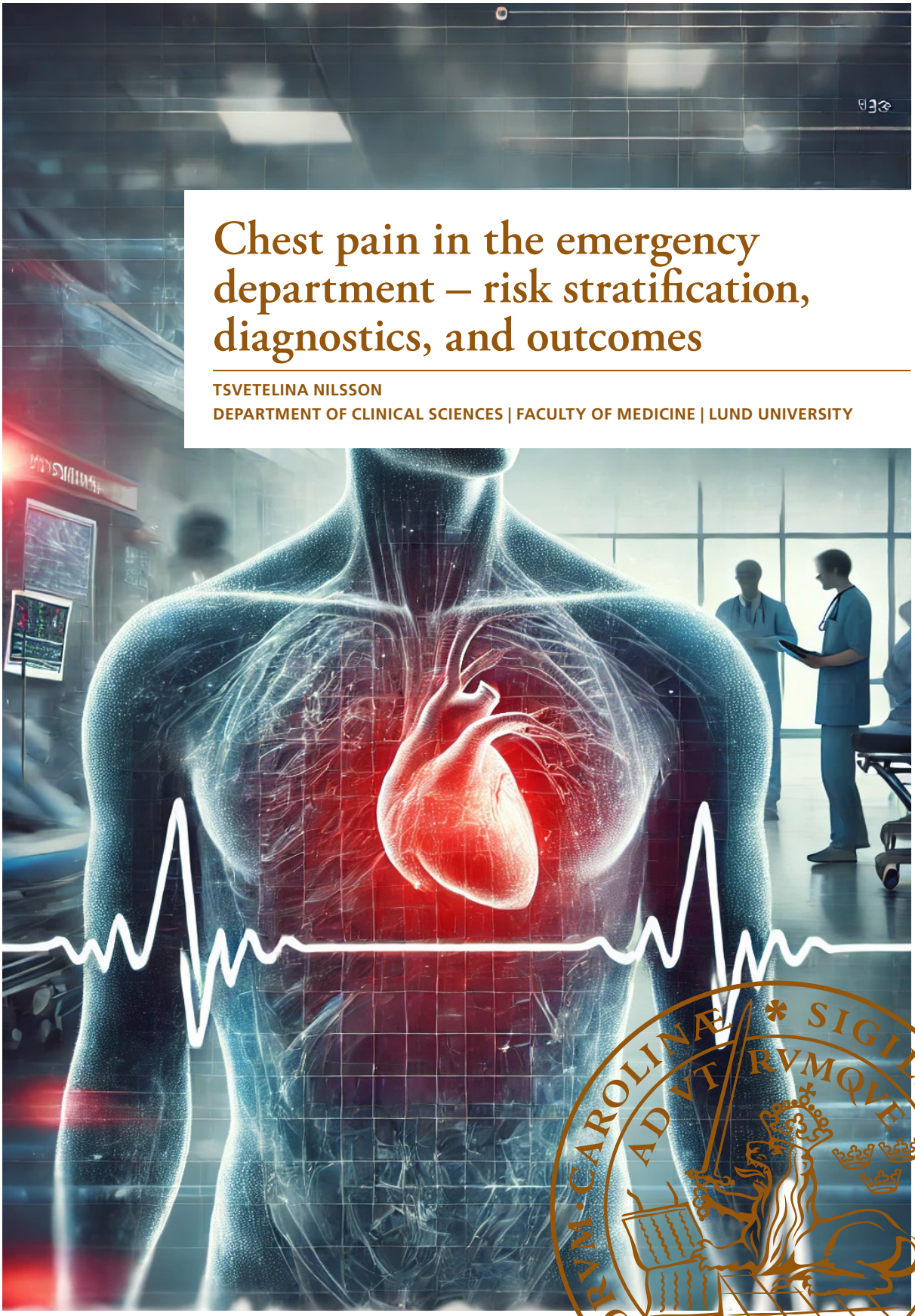
2025

Document Version:
Publisher's PDF, also known as Version of record



Chest pain in the emergency department – risk stratification, diagnostics, and outcomes

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Tsvetelina Nilsson

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on the 8th of May 2025 at 13.00 in Lecture Hall 5 at Skåne University Hospital, Entrégatan 7, Lund

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Organization: Lund University, Faculty of Medicine

Document name: Doctoral Dissertation **Date of issue:** May 8th 2025

Author: Tsvetelina Nilsson **Sponsoring organization:**

Title: Chest pain in the emergency department – risk stratification, diagnostics and outcomes

Abstract:

Chest pain is one of the most common reasons for emergency department (ED) visits. Extensive diagnostic testing is often performed to identify acute coronary syndrome (ACS), but only about 10% of patients ultimately receive an ACS diagnosis. These diagnostic processes are costly, time-consuming, and sometimes invasive, carrying inherent risks. Additionally, most patients with suspected ACS are admitted to the cardiac care unit (CCU) out of concern for serious complications, despite the high costs and limited availability of hospital beds. This highlights the urgent need for improved risk stratification.

The aim of this thesis is to explore novel strategies for enhancing risk assessment and diagnostics in ED chest pain patients to improve patient outcomes and optimize resource utilization.

Study I examined patient characteristics and diagnostic accuracy of the electrocardiogram (ECG) in ED chest pain patients with and without ongoing pain. We found that patients with abated chest pain were older, sicker, and were more often diagnosed with acute myocardial infarction (AMI) and major adverse cardiac events within 30 days. However, the ECG's diagnostic accuracy seemed similar in both groups.

Study II evaluated the diagnostic performance of the HEART and EDACS-ADP scores in combination with the 0-hour/1-hour high-sensitivity cardiac troponin T (hs-cTnT) algorithm. We found that these combined approaches reliably ruled out a significant proportion (approximately half) of ED chest pain patients, allowing for safe early discharge.

Study III investigated the incidence of complications in ED ACS patients and found that merely 6% experienced serious complications, with nearly one-third known already at the ED. Notably, 40% of patients who developed complications were not admitted to the CCU, and nearly half did not undergo coronary angiography.

Study IV compared six established risk scores with a new logistic regression model for predicting complications in ED ACS patients. Our model, based on simple variables available in the ED (e.g., age, vital signs, ECG findings, and basic blood tests like lactate and troponin), outperformed all six existing scores, demonstrating excellent predictive accuracy.

This thesis presents new methods for risk stratification and innovative strategies for the rapid rule-out of low-risk patients. Implementing these findings in clinical practice could improve patient management, reduce unnecessary hospital admissions, and allocate critical resources more effectively to high-risk ACS patients.

Key words: Chest pain, emergency department, acute coronary syndrome, patient characteristics, ECG, troponin, risk score, complications

Language: English **Number of pages**: 98

ISSN and key title: **1652-8220** **ISBN: 978-91-8021-698-2**

Lund University, Faculty of Medicine Doctoral Dissertation Series 2025:45

Signature Date: March 24th 2025

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ISBN: 978-91-8021-698-2
ISSN: 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2025

To my beautiful daughters Vicky and Isabelle…

Stay curious, be nice, work hard and don't forget to smile!

To Henrik…

I wouldn't be here without you!

Table of Contents

Abbreviations

ACS	Acute coronary syndrome
ED	Emergency department
STEMI	ST-elevation myocardial infarction
NSTEMI	Non-ST elevation myocardial infarction
UA	Unstable angina
NSTE-ACS	Non ST-elevation acute coronary syndrome
ECG	Electrocardiogram
CVD	Cardiovascular disease
IHD	Ischemic heart disease
Hs-cTnT	High sensitivity cardiac troponin T
CCU	Cardiac care unit
ICU	Intensive care unit
MACE	Major adverse cardiac events
WHO	World Health Organization
ESC	European Society of Cardiology
ACC	American College of Cardiology
AHA	American Heart Association
(A)MI	(Acute) myocardial infarction
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass graft surgery
NPV	Negative predictive value
PPV	Positive predictive value
LR	Likelihood ratio
IQR	Interquartile range
URL	Upper reference limit
SCA	Sudden cardiac arrest

OHCA	Out-hospital cardiac arrest
IHCA	In-hospital cardiac arrest
MRR	Medical record review
COPD	Chronic obstructive pulmonary disease
TIA	Transitory ischemic attack
ADP	Adenosine diphosphate receptor
ACE/ARB	Angiotensin-converting enzyme/Angiotensin II receptor
PM	Pacemaker
ICD	Implantable cardioverter-defibrillator
LBBB	Left bundle branch block
RBBB	Right bundle branch block
VT	Ventricular tachycardia
VF	Ventricular fibrillation
AHF	Acute heart failure

"Somewhere, something incredible is waiting to be known."
— Carl Sagan

Abstract

Chest pain is one of the most common reasons for emergency department (ED) visits. Extensive diagnostic testing is often performed to identify acute coronary syndrome (ACS), but only about 10% of patients ultimately receive an ACS diagnosis. These diagnostic processes are costly, time-consuming, and sometimes invasive, carrying inherent risks. Additionally, most patients with suspected ACS are admitted to the cardiac care unit (CCU) out of concern for serious complications, despite the high costs and limited availability of hospital beds. This highlights the urgent need for improved risk stratification.

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This thesis presents new methods for risk stratification and innovative strategies for the rapid rule-out of low-risk patients. Implementing these findings in clinical practice could improve patient management, reduce unnecessary hospital admissions, and allocate critical resources more effectively to high-risk ACS patients.

Preface

Millions of people worldwide visit the emergency department (ED) every day due to chest pain, a symptom that often triggers extensive testing out of concern for acute coronary syndrome (ACS). ACS is a serious, potentially life-threatening condition that demands immediate attention. To avoid missed diagnoses and prevent serious complications, many patients are admitted for observation and further evaluation.

However, these admissions place a significant burden on healthcare resources and personnel while also exposing many patients to unnecessary procedures and risks. Although physicians recognize these drawbacks, they often proceed with extensive testing out of fear of missing a critical diagnosis. This pattern of over-diagnostics contributes to ED and hospital overcrowding, delaying care for new patients and, in some cases, postponing life-saving procedures.

Recognizing the inefficiencies and inequities in this system, I decided to dedicate my studies to improving chest pain management in the ED. By developing better risk stratification methods and optimizing workflows, I hope to contribute to a more effective, patient-centered approach that enhances both care quality and resource allocation.

Context of thesis

This thesis examines the process of chest pain management in the ED – from initial assessment to diagnosis and patient outcomes – while exploring new strategies that could enhance both efficiency and patient experience.

My first study aimed to challenge a long-standing practice. In the ED, guidelines recommend repeating an ECG if the first is normal or non-diagnostic, especially if the patient experiences another episode of chest pain. We questioned whether performing an ECG during active chest pain actually improved diagnostic accuracy for ACS diagnosis. While our data included only one ECG per patient, we found no evidence that recording an ECG during active pain improved diagnostic accuracy. As a result, we propose a more streamlined approach: if the initial ECG is inconclusive, clinicians should proceed directly with troponin testing.

The second study focused on the role of troponin testing combined with a validated risk score in assessing chest pain patients. While experienced physicians often rely on clinical judgment, junior doctors may struggle with decision-making and admit patients for further testing out of caution. This practice consumes hospital resources, occupies beds, and exposes patients to unnecessary procedures. By integrating a structured decision-support tool with an established rapid rule-out algorithm, we

aimed to reduce unnecessary admissions, freeing up space for critically ill patients while sparing low-risk individuals from excessive testing. Our algorithms correctly identified nearly half of the chest pain patients as low risk allowing for safe discharge from the ED within 1 hour from arrival.

In recent years, my research has focused on analysing complications in ACS patients diagnosed in the ED. Traditionally, all ACS patients are admitted to the cardiac care unit (CCU) due to concerns about severe complications. However, in reality, only a small fraction experience a life-threatening event. Given the strain on healthcare resources and rising costs, safely reducing CCU admissions could have a significant impact – provided patient safety remains uncompromised – a challenge I sought to address in my final two projects. Our studies aimed to identify high-risk patients and determine factors that could help predict complication risk. We found that only 6 out of every 100 ACS patients in our cohort developed serious complications, many of whom were not admitted to the CCU or treated invasively, despite the latest guideline recommendations. Using basic factors available in the ED, we developed a new prediction model to enhance risk stratification of ED ACS patients and hopefully optimize their management.

Rationale

The driving force behind this thesis is the urgent need to improve chest pain management in the ED. Today, many clinical decisions are influenced by fear – fear of making the wrong call, of missing a serious diagnosis, of potential legal consequences. However, this fear sometimes leads to over-investigation and over-treatment, which can harm patients instead of helping them.

In a busy ED, we frequently witness the consequences of overcrowding. In the past, it was common to see young patients waiting 7-8 hours overnight, only to be sent home with a diagnosis of muscular pain and a simple painkiller. Meanwhile, an infarction patient with pulmonary edema would struggle to breathe on a CPAP machine in the resuscitation room because the CCU beds were occupied by patients with suspected ACS, some of whom likely had no real heart problems but were admitted “just in case”. This is not the way we want to practice medicine today. Unfortunately, in many places this is still how the system works.

Providing the right patient with the right care at the right time is our ultimate goal. Striking a balance between thorough evaluation and efficient resource allocation is the key to achieving the best possible outcomes for all patients.

Ultimately, I hope that the findings in this thesis will contribute to a more precise, sustainable, and patient-oriented approach to chest pain management in the ED.

List of original papers

Study I

Emergency Department Chest Pain Patients With or Without Ongoing Pain: Characteristics, Outcome, and Diagnostic Value of the Electrocardiogram **Nilsson T**., Lundberg G., Larsson D., Mokhtari A., Ekelund *U. Journal of Emergency Medicine 2020;58(6):874-881. First published April 11 2020.*

Study II

Diagnostic accuracy of the HEART Pathway and EDACS-ADP when combined with a 0-hour/1-hour hs-cTnT protocol for assessment of acute chest pain patients **Nilsson T**., Johannesson E., Lundager Forberg J., Mokhtari A., Ekelund U. *Emergency Medicine Journal 2021;38:808-813. First published April 9 2021.*

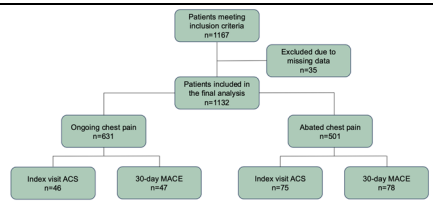
Study III

Complications in Emergency Department Patients with Acute Coronary Syndrome with Contemporary Care **Nilsson T**., Mokhtari A., Sandgren J., Lundager Forberg J., Olsson de Capretz P., Ekelund U. *Cardiology 2024;149(6):523-532. First published April 10 2024.*

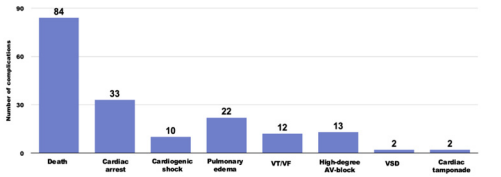
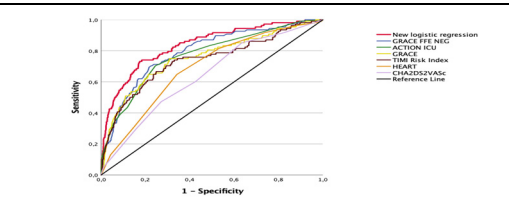
Study IV

Predicting Complications in Emergency Department Patients with Acute Coronary Syndrome – Existing Risk Scores versus a New Logistic Regression Model **Nilsson T**., Strömfors M., Trägårdh A., Mokhtari A., Khoshnood A., Ekelund U. *Submitted manuscript.*

Thesis at glance

	Research Question	Design	Patient cohort	Results	Main Conclusion
I	Is there a difference between patients with ongoing vs abated chest pain in the ED and what is the diagnostic performance of the ECG in these patients?	Observational study using registry data.	1132 consecutive unselected ED chest pain patients		Patients with ongoing pain were younger, healthier and with a significantly lower risk for ACS and 30-day MACE. The diagnostic accuracy of the ECG for ACS did not differ between the two groups.
II	Compare the diagnostic accuracy of the HEART Pathway and the EDACS-ADP combined with 0/1hour hs-cTnT algorithm for ruling out 30-day MACE in ED chest pain patients.	Observational study using registry data.	939 consecutive unselected ED chest pain patients		Combining the HEART Pathway and EDACS-ADP with 0/1h hs-cTnT improves early and safe rule-out for a large proportion of the ED chest pain patients.

	Sensitivity % (95% CI)	NPV (95% CI)
HEART score	94.8 (89.1-98.1)	98.8 (97.4-99.5)
HEART Pathway 0h/1h	99.1 (95.3-99.9)	**99.8** (98.5-100.0)
EDACS ADP 0h/1h-	96.7 (91.4-99.1)	**99.1** (97.8-99.7)

III	Analyze complications in contemporary ED ACS patients and map patient management.	Observational study using registry data; manual chart review for ACS patients with complications.	2463 consecutive ED ACS patients		Complications are rare and around 30% of them are present already in the ED. Treatment and admission decisions could be more selective.
IV	Compare the ability of existing scores to predict complications in ACS patients in the ED and to assess the performance of a new simple risk prediction algorithm.	Observational study using registry data and manual journal review for all ACS patients.	2461 consecutive ED ACS patients		The new logistic regression model based on simple variables available in the ED was an excellent predictor of complications and outperformed six published risk scores.

"The important thing is not to stop questioning.
Curiosity has its own reason for existing."
— *Albert Einstein*

Introduction

Chest pain is one of the most common presenting complaints in the emergency department (ED), accounting for approximately 10% of all ED visits worldwide [1]. Patients with chest pain represent a highly diverse group, with potential diagnoses ranging from benign musculoskeletal or psychosomatic causes to life-threatening conditions such as myocardial infarction, pulmonary embolism, and aortic dissection. Among these concerns, a primary focus in the ED is the identification and management of acute coronary syndrome (ACS).

ACS encompasses a spectrum of clinical presentations resulting from the disruption of myocardial blood flow, typically due to the rupture of an atherosclerotic plaque leading to thrombus formation and subsequent ischemia and necrosis of heart tissue [2]. The severity of ACS varies, with presentations including unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI) [3, 4]. ACS is a serious condition that requires rapid and effective management.

According to current guidelines and clinical practice, the initial assessment of a chest pain patient in the ED involves a structured approach, including a thorough patient history, physical examination, and measurement of vital signs (Figure 1). An electrocardiogram (ECG) should be performed within 10 minutes of arrival, and cardiac biomarkers, particularly troponins, should be measured at repeated intervals to detect myocardial injury [5]. To mitigate the risk of life-threatening complications such as malignant arrhythmias and cardiac arrest, patients are typically placed under continuous cardiac monitoring.

Concerns about missing an ACS diagnosis often lead to excessive testing and prolonged observation in many chest pain patients [6], despite the fact that only a small proportion (approximately 10%) are ultimately diagnosed with ACS [7]. Moreover, recent studies have shown no clear benefit of urgent non-invasive or invasive testing in low-risk patients [8]. This highlights the urgent need for improved strategies to rapidly identify low-risk patients who may be safely discharged without unnecessary cardiac evaluations. Extensive research has been going for years in search for new improved methods for risk stratification and rapid diagnosis of chest pain patients in the ED [9-11].

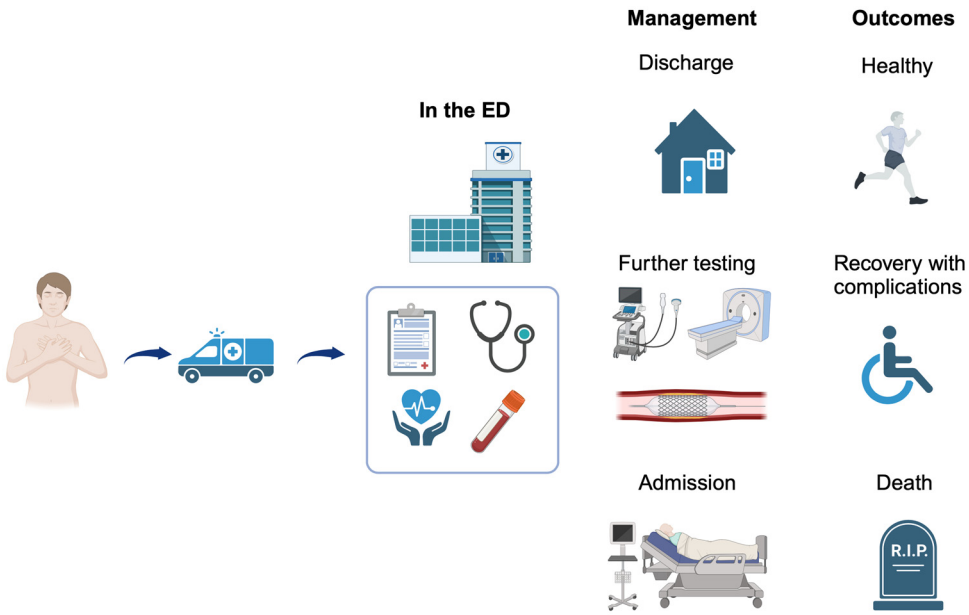


Figure 1. Management of a chest pain patient and outcomes

Current recommendations advise that all ACS patients be admitted to a coronary care unit (CCU), intensive care unit (ICU), or a ward with cardiac monitoring for at least 24 hours due to the risk of complications [12]. However, these admissions are costly and often constrained by bed shortages. More efficient risk stratification is essential to ensure that high-risk patients receive appropriate care while optimizing resource utilization.

Advances in revascularization strategies, particularly percutaneous coronary intervention (PCI), have significantly improved outcomes in STEMI and NSTEMI patients. However, ongoing research continues to refine the optimal timing for PCI, particularly in NSTEMI, where decision-making is more complex due to varying degrees of ischemia [13-15]. The influence of patient age and comorbidities on treatment decisions is a frequently debated topic. Studies are currently evaluating the benefits of early invasive intervention versus conservative management in elderly patients with NSTEMI, with mixed findings so far [16-20].

Patients with myocardial infarction, whether STEMI or NSTEMI, remain at risk for complications such as heart failure, arrhythmias, and sudden cardiac death. Ongoing research has been dedicated for many years to developing strategies for the early identification of high-risk patients and exploring innovative approaches to prevent complications, with the ultimate goal of improving long-term outcomes [21].

Definitions and pathophysiology

The first definition of acute myocardial infarction (AMI) occurred in the 1950s to 1970s, when working groups from the World Health Organization (WHO) established a primarily ECG-based definition of AMI intended for epidemiological use [22]. In the beginning of 21st century, with the introduction of more sensitive cardiac biomarkers, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) collaborated to redefine MI using a biochemical and clinical approach, and reported that myocardial injury detected by abnormal biomarkers in the setting of acute myocardial ischemia should be labelled as MI [23].

Pathophysiologically, AMI is defined as cardiomyocyte death resulting from prolonged ischemia due to an acute imbalance between oxygen supply and demand [24]. The primary cause of ACS is the disruption of an atherosclerotic plaque [25]. Atherosclerosis in the coronary arteries begins as early as adolescence and progresses over time at a rate influenced by factors such as lifestyle, diet, genetics, and comorbidities. The American Heart Association (AHA) classifies atherosclerotic lesions into six types (Figure 2), with types IV and V being the most clinically significant [26]. Any injury to the fibrous cap of the atherosclerotic plaque, such as erosion or rupture, triggers the activation of pro-thrombotic proteins and factors, leading to thrombus formation within the coronary artery, ultimately causing myocardial ischemia and infarction [27].

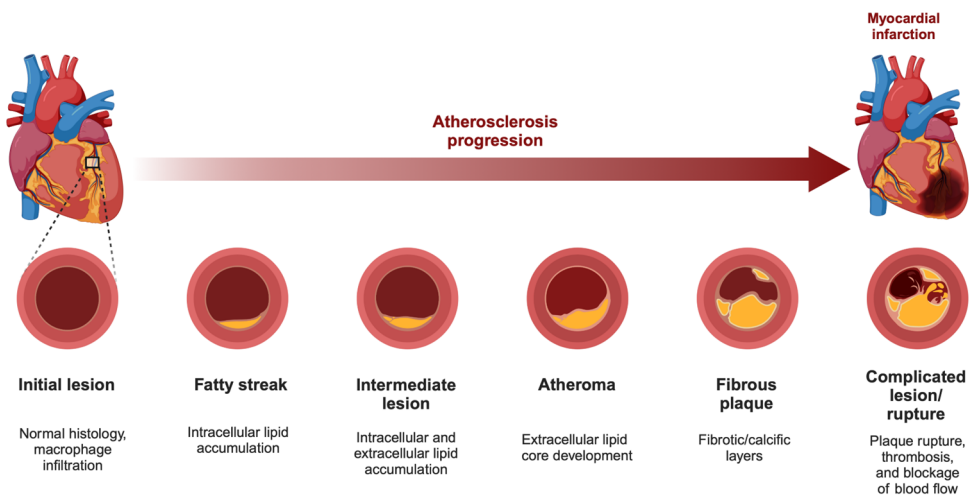
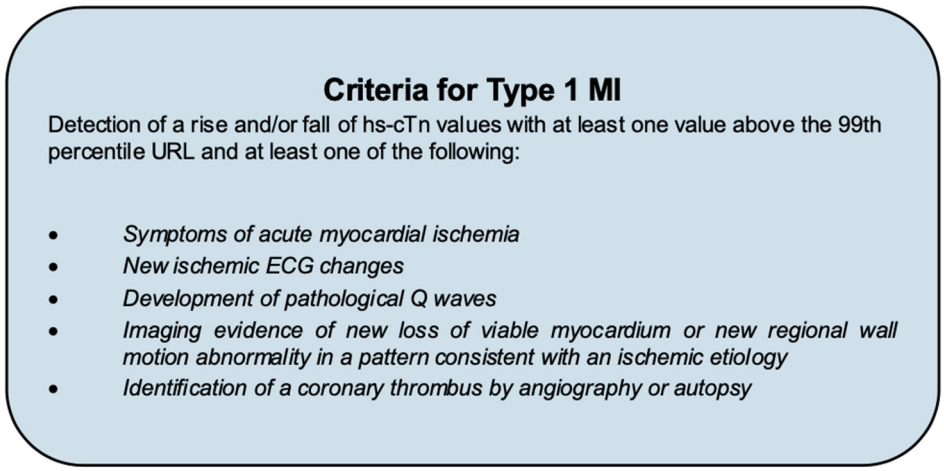


Figure 2. Atherosclerosis progression

According to the Fourth Universal Definition of AMI [28], myocardial injury is characterized by cardiac troponin levels surpassing the 99th percentile of the upper reference limit (URL). Myocardial injury can be classified as acute (indicated by a rise and/or fall in troponin levels), or chronic, with minimal variation (≤20%) in troponin levels. It can occur in various contexts, including postprocedural settings (e.g., after coronary intervention) and in association with both cardiovascular and non-cardiovascular conditions. When acute myocardial injury occurs in the setting of acute myocardial ischemia, it is defined as acute myocardial infarction.

The different types of myocardial infarction (MI) are classified as follows:

- **Myocardial infarction type 1** is caused by acute atherothrombotic coronary artery disease, typically triggered by atherosclerotic plaque disruption, leading to a reduction in myocardial blood supply. This is the most common form of MI.
- **Myocardial infarction type 2** results from an imbalance between myocardial oxygen supply and demand due to stressors unrelated to acute coronary thrombosis. It is commonly seen in critically ill patients or those with stable coronary artery disease and comorbidities experiencing an acute exacerbation.
- **Myocardial infarction type 3** occurs in patients who suffer cardiac death with symptoms suggestive of acute myocardial ischemia, accompanied by new ischemic ECG changes, but die before biomarker testing can be performed.
- **Myocardial infarction type 4a** is defined as a PCI-related increase in cardiac troponin exceeding five times the 99th percentile URL from a normal or, if elevated, stable pre-procedural baseline. Diagnosis requires evidence of new myocardial ischemia on ECG or cardiac imaging, or complications leading to reduced coronary blood flow.
- **Myocardial infarction type 4b** is caused by acute myocardial ischemic injury due to stent thrombosis.
- **Myocardial infarction type 4c** is associated with acute myocardial ischemic injury resulting from stent restenosis.
- **Myocardial infarction type 5** occurs following coronary artery bypass graft (CABG) surgery, with a troponin increase exceeding ten times the 99th percentile URL from a normal or, if elevated, stable pre-procedural baseline. Diagnosis requires evidence of new myocardial ischemia or loss of myocardial viability.



This classification offers a structured framework for diagnosing and distinguishing the various mechanisms of MI. However, in recent years, its validity has been debated, with some experts arguing that the definitions are overly complex. As a result, alternative classifications have been proposed, categorizing infarctions as arising spontaneously, secondary to another condition or as a complication from a cardiac procedure [29]. A new universal definition of MI is expected to be introduced in 2026.

STEMI, NSTEMI and UA

Although STEMI, NSTEMI and UA all fall under the umbrella of ACS, they differ in severity, clinical presentation, pathophysiology, and management. Understanding these distinctions is essential for accurate diagnosis, effective treatment, and the prevention of adverse outcomes. The primary differences between these conditions lie in the extent of myocardial injury, ECG findings and biomarker elevations (Figure 3).

STEMI is a clinical syndrome including chest pain, myocardial ischemia, and ECG changes in form of ST elevations in specific leads. It results from complete or near-complete occlusion of a coronary artery, leading to transmural myocardial ischemia and subsequent injury or necrosis. If untreated, the infarcted area can expand, leading to significant damage to the heart muscle, electrical disturbances, and reduced cardiac output. STEMI is the most severe form of ACS and carries the highest risk of life-threatening complications, including cardiogenic shock, ventricular arrhythmias, and cardiac arrest. Without immediate treatment, these complications can lead to irreversible myocardial damage and death.

NSTEMI occurs when a coronary artery is partially occluded by a thrombus, resulting in myocardial ischemia and injury though without full-thickness damage as seen in STEMI. NSTEMI is also referred as subendocardial infarction. Unlike

STEMI, NSTEMI does not show significant ST-segment elevation on ECG, though changes like ST-depression or T-wave inversion may be present. Biochemical markers, such as cardiac troponins, are elevated in both NSTEMI and STEMI, indicating myocardial damage. Although the myocardial damage is less severe, NSTEMI still carries a significant risk of adverse outcomes, including heart failure and arrhythmias, especially if ischemia is prolonged.

UA is characterized by chest pain or discomfort occurring at rest or with minimal exertion due to reduced coronary blood flow but without myocardial necrosis (i.e., troponins remain normal). It is considered a warning sign of potential infarction. Typically, it is caused by atherosclerotic plaque rupture and partial thrombosis, leading to transient coronary obstruction. Unlike STEMI and NSTEMI, UA does not cause permanent myocardial damage. The ECG in patients with UA is often normal but may show non-specific ST-segment or T-waves deviations. Currently, there is no strong evidence suggesting that patients with UA have an increased long-term risk of serious complications compared to those with NSTEMI or STEMI. However, UA remains a high-risk condition for short-term adverse events, as it may progress to NSTEMI or STEMI if untreated.

The ACS diagnosis requires an integrated approach that includes clinical evaluation, ECG findings, cardiac biomarkers, and imaging studies. The combination of these tools allows for accurate risk stratification and timely management. While coronary angiography remains the gold standard for assessing coronary anatomy and guiding intervention, the use of cardiac biomarkers and ECG plays a pivotal role in the early diagnosis and differentiation of the ACS subtypes. Early recognition and appropriate management of ACS are critical in improving outcomes and reducing mortality associated with these conditions.

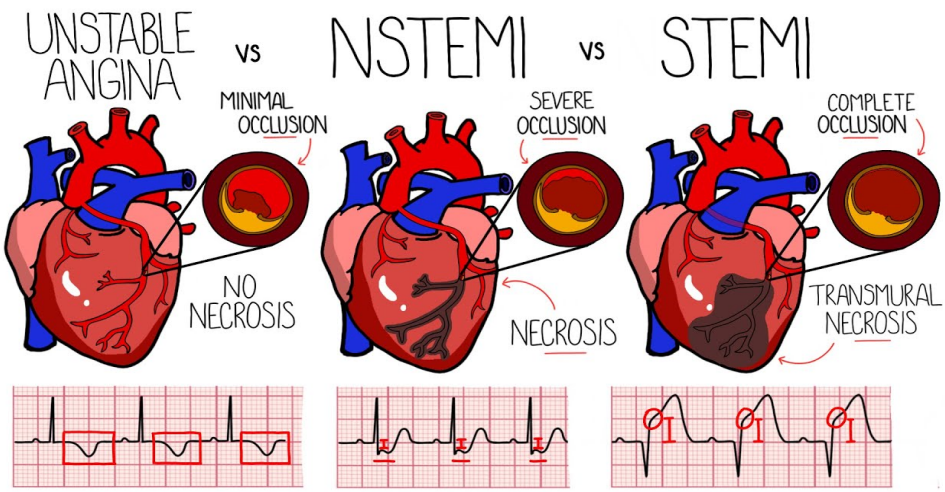


Figure 3. Pathophysiological changes and ECG in ACS subtypes

The patient history

Chest pain is a hallmark of ACS, but its characteristics can vary significantly among patients and ACS subtypes. Recognizing key features of ACS-related chest pain is essential for timely diagnosis and appropriate management.

Using the **MAPLES OPQRST** framework, chest pain in ACS is typically described as follows:

- **O (Onset):** Pain may develop suddenly without a clear trigger or occur during physical exertion, emotional stress, or after heavy meals. It may also occur at rest, especially in UA.
- **P (Provocation):** Typically worsens with exertion and does not improve with nitroglycerin (in most MI cases). Unlike musculoskeletal pain, it is not influenced by body position, breathing, or movement.
- **Q (Quality):** Often described as diffuse, dull, tight, pressing, or a crushing/squeezing sensation.
- **R (Region/Radiation):** Primarily retrosternal, frequently radiating to the left arm, back, neck, or jaw. Some patients, particularly older adults and women may report discomfort in the upper abdomen.
- **S (Severity):** Generally severe and distressing, often accompanied by a sense of impending doom and anxiety, particularly in STEMI.
- **T (Timing):** Cardiac chest pain is persistent, lasting several minutes or longer, and does not resolve quickly.

It is important to recognize that chest pain characteristics can vary widely depending on factors such as the subtype of ACS, patient demographics, comorbidities, and the presence of atypical symptoms.

- In STEMI, chest pain is typically more severe and often accompanied by significant anxiety or distress. Patients commonly describe it as intense retrosternal pain, resembling a heavy weight or tight band around the chest. The pain is persistent, lasting 30 minutes or more, and does not improve with nitroglycerin. STEMI is frequently associated with shortness of breath, profuse sweating (diaphoresis), nausea, and vomiting, further contributing to patient discomfort and distress.
- In NSTEMI, chest pain is usually less intense, and patients are less likely to experience severe vegetative symptoms such as nausea, vomiting, and diaphoresis. The pain typically lasts longer than a few minutes but is often shorter than in STEMI and may occur intermittently over several hours or days before worsening.

- In UA, chest pain is variable and often unpredictable, occurring suddenly at rest or, more commonly, during or after physical activity. While typically more severe than stable angina, it is less intense than STEMI or NSTEMI. The discomfort is often described as mild to moderate but may progressively worsen, become more frequent, or occur with decreasing levels of exertion.

Some ACS patients (older patients, women, diabetics) present with atypical symptoms such as chest discomfort rather than pain (described as tightness or pressure in the chest), pain in areas other than the chest (epigastrium, upper back, or left shoulder/arm). Older patients commonly complain of fatigue, nausea, or indigestion. The absence of classic chest pain might delay the diagnosis and lead to misinterpretation of the symptoms as non-cardiac in origin. While certain pain characteristics can influence the likelihood of ACS, symptom overlap among ACS subtypes is significant, and no single symptom or combination of symptoms is sufficient to rule it out [30, 31].

In STEMI, patients typically present with persistent chest pain, while those with non-ST elevation ACS (NSTE-ACS, including NSTEMI and UA) may seek medical attention after the pain has subsided. However, even STEMI patients can occasionally present without ongoing chest pain. Patients experiencing continuous chest pain are generally considered at the highest risk for cardiovascular emergencies and are highly prioritized in triage systems (Figure 4) [32-34]. Nonetheless, patients with suspected NSTE-ACS whose pain has abated still face a risk of serious complications. Therefore, all chest pain patients with a history suggestive of ACS should be highly prioritized, regardless of their current pain status.

Prio	Criteria
1	Ongoing chest pain with simultaneous vegetative symptoms ST-elevation in the ECG
2	Ongoing typical cardiac chest pain Chest pain with recorded loss of consciousness Transient chest pain with vegetative symptoms within the last 24 hours Previous heart surgery (including PCI) within the last three months Chest pain with new onset left or right bundle branch block Ongoing or transient chest pain with signs of ischemia in the ECG
3	Other ongoing or transient chest pain
4	None of the symptoms or signs mentioned above

Figure 4. RETTS criteria for triage of chest pain patients [35]

The ECG

The ECG is the most widely used diagnostic test to identify acute myocardial ischemia/infarction [36]. It is cheap, non-invasive, and easily accessible and the results are usually easy to interpret for medical professionals. Table 1 outlines the ECG criteria for identifying new signs of ischemia, as specified in the most recent ESC guidelines [5].

Table 1. ECG criteria showing new ischemic changes according to the latest ESC guideline

ECG Feature	Definition
ST-Segment Elevation	New ST elevation at the J-point in any two contiguous leads ≥1.0 mm Accept V2-3 where: ≥2.5 mm in men <40 years ≥2.0 mm in men ≥40 years ≥1.5 mm in women
ST-Segment Depression	Horizontal or down-sloping ST depression ≥0.5 mm in two contiguous leads
T-Wave Inversion	T-wave inversion ≥1.0 mm in two contiguous leads
Pathological Q Waves	Q waves ≥0.04 seconds in duration and ≥25% of the R-wave amplitude in the same lead in two contiguous leads
New Left Bundle Branch Block (LBBB)	Prolonged QRS duration greater than 120 ms QS or rS complex in V1 Broad, often notched, or slurred R waves in I, aVL, V5 or V6 Absence of Q waves in V5 or V6
New Right Bundle Branch Block (RBBB)	Prolonged QRS duration greater than 120 ms rsr', rsR', or rSR' pattern ("M-shaped") QRS complex in V1 and V2 Wide slurred S wave in I, aVL, V5 or V6 ST-segment depression and T-wave inversion may be seen in V1–V3

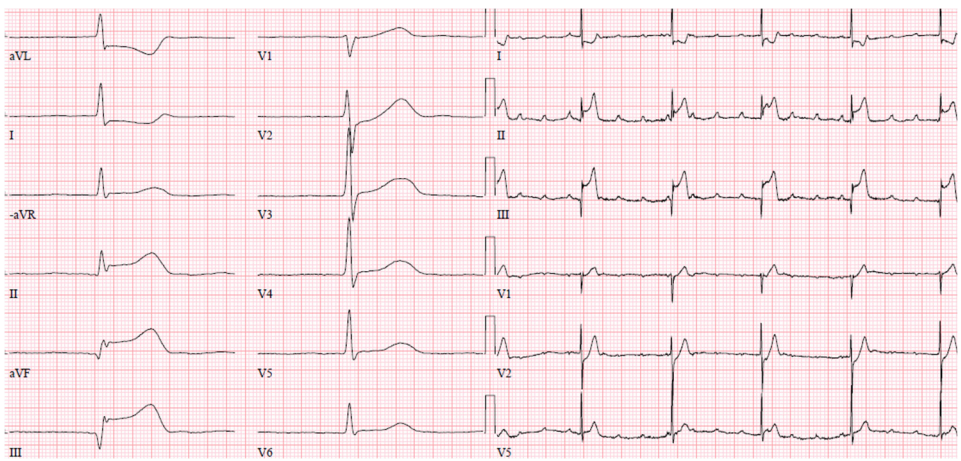
An ECG within 10 minutes of arrival is recommended for all patients with acute chest pain who present to the ED. The ECG is the gold standard for diagnosing STEMI (Picture 1). However, it has low sensitivity, and many NSTE-ACS patients might present with normal or nonspecific ECG changes. Studies suggest that up to 60% of NSTEMI cases have non-diagnostic ECGs at presentation [37-39]. If the diagnosis is unclear or if a new chest pain episode occurs, the guidelines recommend an extra ECG recording [5]. Ischemic ECG abnormalities can be transient and may resolve before recording, potentially leading to false reassurance. This is why serial ECGs or stress testing are often necessary for a more accurate assessment. It is believed that serial ECGs or continuous monitoring can capture transient ischemic events that may not be evident on the initial recording.

In clinical practice, if a patient experiences a new episode of chest pain while in the ED, protocol dictates that a repeat ECG should be performed to capture any dynamic

changes. However, due to ED crowding and staff shortages, timely repeat ECGs are not always feasible. As a result, emergency physicians often have to make critical management decisions based on a single ECG, regardless of whether the patient is experiencing pain at the time. Previous studies in cardiological clinics, along with clinical guidelines suggest that an ECG taken during ongoing chest pain is more likely to detect ischemic changes than one recorded after symptom resolution [40-43]. While this may hold true for cardiology patients, there is no strong evidence supporting its reliability in unselected chest pain patients in the ED.

The skills of ED physicians in interpreting ECGs can vary. In general, experienced clinicians are quite good at recognizing STEMI on an ECG, but they may be less accurate at diagnosing NSTEMI or unstable angina, especially if the ECG appears normal or shows subtle changes. Several factors can influence accuracy, including experience, time pressure, patient demographics (e.g., age, comorbidities), and the presence of confounding factors such as previous ECG abnormalities or non-cardiac causes of chest pain. Comparing the current ECG with a previous one can be helpful in identifying changes. However, a prior ECG may not always be available. The sole use of computerized ECG interpretation in clinical practice has been long discussed but so far not been recommended [44].

In recent years, integrating artificial intelligence (AI) and machine learning into the diagnostic process has been proposed as a way to assist physicians by flagging potentially concerning ECG findings that might be overlooked in time-sensitive settings [45]. AI systems trained on large datasets could serve as a second review layer to enhance accuracy and reduce human error. In the future, these systems may even evolve into primary interpretation tool, with physician oversight reserved for ambiguous or complex cases.



Picture 1. ECG showing Inferior STEMI with 3rd degree AV block

The troponins

Troponins are a group of three regulatory proteins (troponin C, I, and T) essential for cardiac and skeletal muscle contraction [46]. Troponin C is found in both skeletal and cardiac muscle, making it less useful in clinical practice. In contrast, troponin I (TnI) and troponin T (TnT) are exclusive to cardiac tissue and are now considered the gold standard for diagnosing ACS [47, 48]. These proteins are released into the bloodstream following myocardial injury, particularly due to necrosis of cardiac muscle cells. However, elevated troponin levels are not exclusive to ACS and may also be observed in conditions such as myocarditis, arrhythmias, post-cardiopulmonary resuscitation (CPR), and traumatic injuries [49]. In ACS, cardiac troponin levels are used to detect minor myocardial damage, stratify patients, estimate infarct size, and assess treatment efficacy [50].

Recent technological advances have enabled the measurement of cardiac troponins with high-sensitivity assays (hs-cTnI and hs-cTnT) [51]. These assays detect even very low troponin levels, allowing for earlier ACS identification, faster coronary intervention, and potentially improved patient outcomes [52-54].

Both the ESC and the ACC recommend high-sensitivity cardiac troponins (hs-cTnT and hs-cTnI) for ACS diagnosis [55, 56]. The current guidelines endorse a 0-hour/1-hour hs-cTn protocol for ruling out AMI [5]. According to this protocol, patients with an hs-cTnT level below 5 ng/L at presentation (0h) or an hs-cTnT level below 12 ng/L at 0h with a 1-hour change of less than 3 ng/L can be ruled out with high negative predictive value (NPV).

A significant rise in cardiac troponin – more than three times the normal value – or a dynamic increase within one hour, alongside clinical signs of ischemia, confirms the diagnosis of AMI. However, interpreting troponin results in patients with impaired kidney function or chronic heart failure can be challenging, as these conditions may lead to persistently elevated troponin levels. Studies show that troponin rise in patients with chronic kidney disease is related to cardiac pathology and indicate that troponin T is a strong predictor of short-term prognosis in ACS patients, regardless of creatinine clearance, and remains the preferred biomarker for ACS diagnosis [57, 58].

Cardiac troponins continue to be a major focus of research, with numerous studies evaluating the safety and efficacy of high-sensitivity troponin algorithms in clinical practice [59-64]. Integrating these assays with clinical assessment and ECG has significantly reduced time to diagnosis and hospital discharge, enhancing overall patient management. The implementation of hs-cTn point-of-care testing has been shown to further reduce ED length of stay without compromising safety. A recent study reported that the use of a high-sensitivity troponin point-of-care assay within a structured accelerated diagnostic pathway significantly decreased ED stay compared to traditional laboratory assays [65].

The risk scores

Risk scores are formula-based tools designed for quantitative risk assessment, providing a rank-order of individuals based on their likelihood of experiencing a specific outcome (or combination of outcomes) within a defined timeframe [66, 67]. These tools are integral to risk stratification, enabling clinicians to estimate the probability of adverse events and tailor treatment decisions accordingly. In the context of ACS, patients identified as high-risk may benefit from early invasive interventions, while those at lower risk might be better suited for more conservative approach. Precise risk assessment is crucial for optimizing the balance between the benefits and potential risks of therapeutic strategies.

Several risk scores are available for assessing chest pain patients, aiding in the diagnosis and prognosis of ACS. Well-established scores such as HEART, EDACS, GRACE, and TIMI are widely recognized in the literature, with numerous validation studies and systematic reviews supporting their utility [68-74]. Some studies suggest that risk scores may not significantly outperform clinical gestalt in experienced physicians [75]. While experienced clinicians may rely on their expertise for risk assessment, these scoring systems can be particularly valuable for less-experienced doctors, who may still be refining their skills in history-taking and diagnostic interpretation. The risk scores serve as a cognitive aid, guiding junior doctors through complex clinical reasoning and even boosting their self-confidence in decision making. By streamlining the diagnostic process, risk scores may allow for quicker triage, improving ED flow and efficiency.

In this thesis, we utilized the following risk scoring systems for chest pain patients: Thrombolysis in Myocardial Infarction (TIMI) risk index, Global Registry of Acute Coronary Events (GRACE) and GRACE Freedom From Events (GRACE FFE), History, ECG, Age, Risk Factors, and Troponin (HEART), Emergency Department Assessment of Chest Pain Score (EDACS), Acute Coronary Treatment and Intervention Outcomes Network (ACTION) ICU, and CHA2DS2VASc.

TIMI

Invented in the late 1990s, the TIMI score is a widely used tool for predicting the risk of adverse cardiovascular events, including AMI, the need for urgent revascularization, and death. It was originally designed for risk stratification in NSTE-ACS and separately, STEMI [76]. A TIMI score of 0-2 indicates low risk, 3-5 represents intermediate risk, and a score of 6 or 7 signifies high risk. Additionally, TIMI Risk Index is a separate scoring system applicable to all ACS patients, providing a 30-day mortality estimate [77].

Due to its simplicity and reliance on readily available clinical parameters, the TIMI score is particularly useful in ED settings allowing for rapid bedside calculation and aiding in early triage and management decisions. Studies have demonstrated that the

TIMI risk score is significantly more effective in diagnosing ACS compared to ECG and biomarker evaluation alone [78]. Furthermore, research indicates a strong correlation between TIMI scores and findings on coronary angiography, with higher scores being associated with a greater likelihood of severe culprit lesions [79]. Therefore, the TIMI score's greatest utility lies in its ability to guide the management of patients presenting with signs of NSTE-ACS, aiding in risk stratification, and informing treatment decisions.

HEART

The HEART score (Supplement Table 1) is a widely used risk stratification tool in the ED for assessing the short-term risk of MACE in patients presenting with chest pain. It evaluates five key components: History, ECG, Age, Risk factors, and Troponin, with a total score ranging from 0 to 10. Patients are categorized into three risk groups: low (0-3 points), intermediate (4-6 points), and high (7-10 points).

Designed to simplify and expedite the diagnostic process, the HEART score predicts the 6-week risk of MACE, including acute AMI, the need for revascularization (PCI or CABG), and death [80]. A low HEART score indicates a minimal likelihood of a serious cardiac event, allowing for safe discharge or outpatient monitoring. Conversely, a high HEART score suggests a significant risk, often warranting hospital admission, further diagnostic testing, or urgent intervention.

Due to its simplicity, practicality, and strong predictive value, the HEART score is one of the most used chest pain risk assessment tools in everyday ED practice.

The HEART score relies solely on the 0-hour hs-cTn value for risk assessment. In contrast, the HEART Pathway (Supplement Table 2) integrates the HEART score with serial troponin testing to improve identification of low-risk patients who may be safely discharged [81, 82].

GRACE and GRACE FFE

The GRACE score is one of the most extensively validated risk stratification tools for predicting both in-hospital and long-term (6-month) mortality in ACS patients and is currently guideline-recommended for risk assessment in NSTE-ACS [5, 83]. Unlike some risk scores that are specific to certain ACS subtypes, GRACE can be applied to patients with STEMI, NSTEMI, and UA. The score ranges from 1 to 363, with higher values indicating a greater risk of adverse outcomes [84]. GRACE is particularly useful in identifying high-risk patients who may benefit from early invasive management, such as PCI or CABG. Patients with a GRACE score above 140 (for in-hospital risk) are advised to undergo urgent coronary angiography, while those at intermediate risk (GRACE score 109 to 140) may also require early intervention based on clinical presentation and additional risk factors.

Compared to TIMI and HEART scores, GRACE offers superior long-term prognostic accuracy and is especially effective in predicting mortality in NSTE-ACS patients [85]. However, the GRACE score is more complex and requires a software calculator. It also includes laboratory results, which can delay risk assessment. While it excels in long-term risk prediction, it may be less practical for rapid ED decision-making compared to the HEART score [86]. Some studies suggest that GRACE may overestimate mortality in low-risk patients, potentially leading to unnecessary hospital admissions and additional testing [87].

The GRACE Freedom from event (FFE) score is based on GRACE and predicts the likelihood of remaining free from adverse in-hospital event (myocardial infarction, arrhythmia, congestive heart failure or shock, major bleeding, stroke, or death) in patients with NSTEMI or UA [88]. By assessing various clinical factors, the GRACE FFE score helps healthcare providers determine which patients might be suitable for treatment in less resource-intensive environments, such as general medical wards, rather than intensive care units [89, 90]. High GRACE FFE score equals low risk of adverse in-hospital events.

Table 2 compares the GRACE, TIMI, and HEART scores, each tailored for specific clinical applications. The GRACE score is highly effective for predicting in-hospital and long-term mortality, making it valuable for guiding long-term management decisions. The TIMI score is particularly useful for identifying patients who may benefit from early revascularization. The HEART score, by contrast, is specifically designed for rapid risk stratification in the ED, aiding in the safe and efficient rule-out of low-risk chest pain patients [86].

Table 2. Comparison between GRACE, TIMI and HEART score

Feature	GRACE Score	TIMI Score	HEART Score
Purpose	Mortality prediction	Risk of events (MI, death, urgent PCI)	Risk of major cardiac events (MACE)
Target patient category	STEMI, NSTEMI, UA	STEMI/ NSTEMI, UA	Chest pain in ED
Risk Factors	8 clinical + lab variables	7 clinical variables	5 clinical + ECG + Troponin
Prediction Time Frame	In-hospital & 6 months	30 days	6 weeks
Best For	Long-term mortality	Short-term ischemic risk	ED chest pain stratification

EDACS

The EDACS is a clinical tool used to assess the risk of MACE in chest pain patients in the ED, with the primary goal of identifying low-risk individuals who can be safely discharged without the need for further diagnostic testing or admission. The EDACS has been shown to effectively identify nearly 50% of chest pain patients as low-risk, providing acceptable sensitivity for predicting MACE [91]. According to EDACS-Accelerated Diagnostic Protocol (EDACS-ADP) (Supplement Table 3), patients with EDACS score <16, an ECG showing no signs of acute ischemia and negative serial troponins are considered low-risk, eligible for discharge [92].

ACTION ICU

The ACTION ICU score was developed to assess the risk of complications requiring ICU admission in initially stable NSTEMI patients, based on variables available at hospital admission [93]. These complications include cardiac arrest, cardiogenic shock, high-grade atrioventricular (AV) block, respiratory failure, stroke, or death. A score of ≤2 indicates a very low risk (<5%) of clinical deterioration necessitating ICU care, while a score of ≥12 corresponds to a >30% risk of requiring ICU admission.

While the ACTION-ICU score effectively identified nearly 50% of ACS patients as low risk for severe complications requiring ICU care, its complexity makes manual calculation challenging, often necessitating an electronic tool. Additionally, its external validation remains limited, requiring further studies to confirm its reliability in broader populations.

CHA2DS2-VASc

CHA2DS2-VASc is a score that was developed for and is widely used to determine the need for anticoagulants in patients with atrial fibrillation. Studies have shown that CHA2DS2-VASc score could also effectively predict in hospital mortality and MACE events in ACS patients [94, 95].

The treatment

The initial treatment of ACS aims to relieve chest pain, restore blood flow to the heart, and prevent complications such as heart failure, arrhythmias, or sudden cardiac death. Time to treatment for symptoms of ACS can be a matter of life and death [96]. The primary treatment involves a multi-faceted approach, starting with rapid diagnosis and stabilization, followed by antiplatelet therapy, anticoagulation, and, when appropriate, reperfusion strategies such as PCI or thrombolysis. Figure 5 presents the main approaches in the initial as well as long-term treatment of ACS.

Initial stabilisation

Upon presentation to the ED, the first step in managing ACS is to stabilize the patient. Patients are typically started on oxygen therapy if their oxygen saturation is low, nitroglycerin is often used to relieve chest pain, while morphine may be given to alleviate pain and reduce anxiety.

Pharmacological Management

Immediate pharmacological treatment aims to alleviate ischemia, prevent thrombus propagation, and reduce myocardial oxygen demand. Antiplatelet agents, including aspirin and P2Y12 inhibitors, are administered to inhibit platelet aggregation. Anticoagulants, such as unfractionated heparin or low-molecular-weight heparin, are used to prevent further thrombus formation. Beta-blockers may be prescribed to decrease heart rate and myocardial oxygen consumption, provided there are no contraindications. The 2023 European Society of Cardiology guidelines emphasize the importance of tailoring pharmacological therapy to individual patient profiles to optimize outcomes [5].

Reperfusion Strategies

For STEMI patients, prompt reperfusion therapy is critical. Primary PCI is the preferred method when it can be performed in a timely manner, ideally within 90 minutes of first medical contact. If PCI is not available within this timeframe, fibrinolytic therapy should be considered, especially if administered within 12 hours of symptom onset. For NSTEMI patients, the timing of invasive strategies is guided by risk assessment, with high-risk individuals undergoing early angiography and revascularization (within 24h of presentation). Studies have shown that earlier reperfusion decreased significant the incidence of severe complications in ACS patients [97].

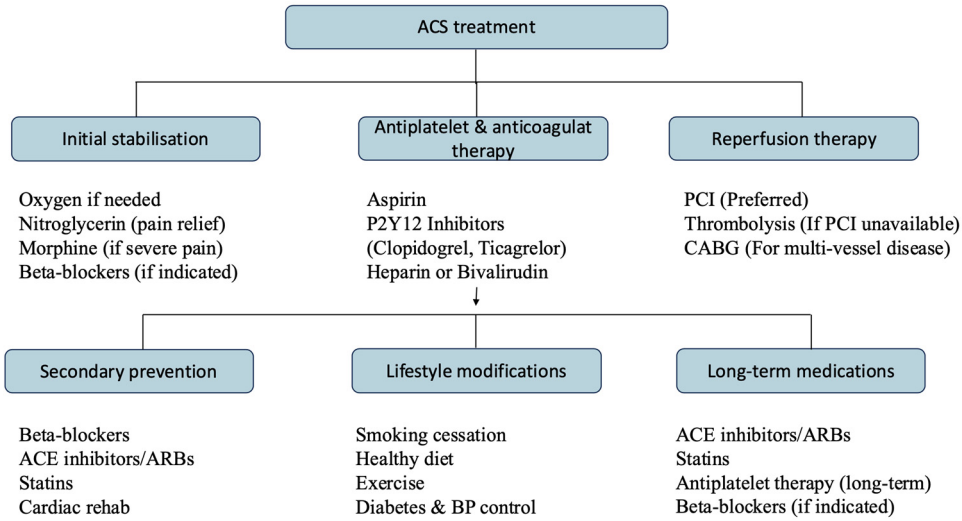


Figure 5. ACS treatment

The long-term management of ACS patients involves a combination of pharmacologic therapy, lifestyle modifications, comorbidity management, cardiac rehabilitation, and regular follow-up. Additionally, psychosocial support and planned endovascular procedures, when necessary, play a crucial role in optimizing outcomes and reducing the risk of future cardiovascular events.

The complications

If not promptly addressed, ACS could precipitate severe complications such as ventricular arrhythmias and cardiogenic shock leading to cardiac arrest and death if untreated (Figure 6). Acute heart failure (AHF) is a common complication in ACS, associated with high morbidity and mortality [98]. Mechanical complications, such as ventricular septal defects (VSD), papillary muscle rupture, or cardiac tamponade due to free-wall rupture, can also arise if ACS is not promptly treated or detected. These complications further exacerbate the patient's condition and require immediate medical interventions. If left untreated, they can lead to irreversible damage and potentially death.

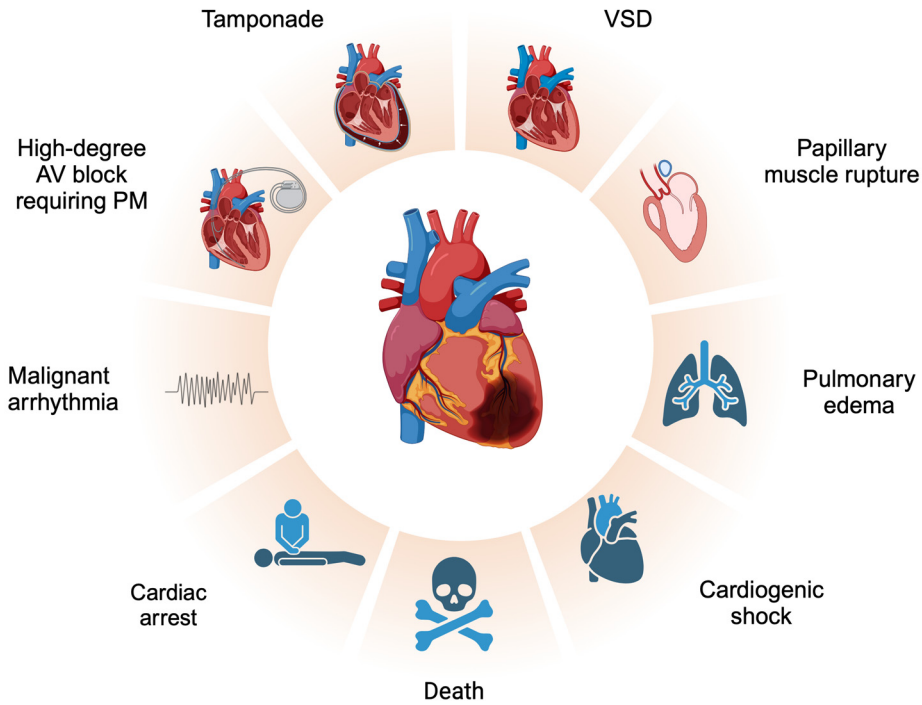


Figure 6. Common ACS complications

The pathophysiology of complications

Myocardial damage in ACS triggers a cascade of physiological responses that can lead to various complications. The most critical complications arise from myocardial dysfunction, electrical instability, and systemic inflammatory and neurohormonal responses. Figure 7 illustrates the key pathophysiological mechanisms underlying the most common complications of ACS.

Extensive MI leads to loss of contractile function, reducing cardiac output and tissue perfusion, leading to cardiogenic shock. In response, the heart compensates with increased sympathetic activation, causing vasoconstriction and increased heart rate, which further elevate myocardial oxygen demand, and exacerbate ischemia. Rising LV filling pressures contribute to pulmonary congestion and pulmonary edema, leading to hypoxia and, in severe cases, multi-organ failure. Diastolic dysfunction, particularly in hypertensive or elderly patients, further impairs ventricular filling, worsening hemodynamic instability.

Ischemia-induced disruption of normal electrical conduction creates areas of slowed conduction and re-entry circuits, predisposing the heart to ventricular tachycardia

(VT) and ventricular fibrillation (VF) – the leading cause of sudden cardiac arrest (SCA) and death in ACS. Additional factors such as heightened catecholamine release and electrolyte imbalances (e.g., hypokalemia, hypomagnesemia) further destabilize cardiac rhythm.

Infarction of the right coronary artery (RCA), which supplies the sinoatrial (SA) and atrioventricular (AV) nodes, can result in sinus bradycardia, AV blocks, or junctional rhythms. Increased vagal tone (Bezold-Jarisch reflex) during inferior MI further exacerbates bradycardia and hypotension.

Prolonged ischemia weakens myocardial structures, particularly in transmural infarctions, and could lead to serious mechanical complications. Papillary muscle rupture leads to severe mitral regurgitation, causing pulmonary edema and cardiogenic shock. Ventricular septal rupture creates a left-to-right shunt, increasing pulmonary blood flow and causing acute heart failure. Free wall rupture results in cardiac tamponade, leading to obstructive shock and rapid hemodynamic collapse.

If left untreated, these complications lead to profound cardiac dysfunction, cardiac arrest, and a high risk of death. While cardiac arrest is a sudden, reversable loss of heart function causing circulation to stop, death is irreversible cessation of all vital functions, including brain and heart activity. If cardiac arrest is not promptly and successfully treated, it results in biological death, leaving no possibility of recovery.

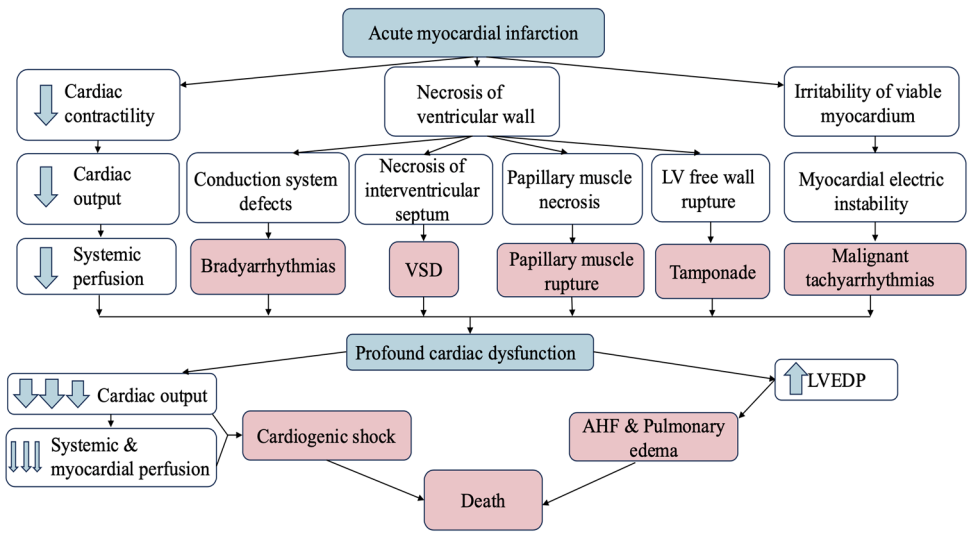


Figure 7. Pathophysiological mechanisms underlying the most common complications in ACS

Death

Despite advances in the prevention and treatment of cardiovascular disease (CVD), ischemic heart disease (IHD) continues to be the leading cause of death globally [99]. In 2021, CVD was responsible for nearly 20 million deaths worldwide [100].

In-hospital mortality rates for ACS patients are influenced by multiple factors, including the type of ACS, patient demographics, and comorbidities. Accurate identification of mortality predictors is essential for effective risk stratification and optimizing patient management. Over recent years, extensive research has sought to identify key factors that predict both short- and long-term mortality in ACS patients. Some of these factors include advanced age, reduced left ventricular ejection fraction (LVEF), elevated serum creatinine levels, increased heart rate, chronic obstructive pulmonary disease (COPD), elevated blood glucose levels, lack of revascularization procedures (e.g., PCI or CABG), low hemoglobin levels, and peripheral artery disease [83, 101, 102]. Among the numerous risk scores tested, the GRACE score has consistently shown the highest predictive accuracy.

Furthermore, recent studies have turned to advanced methodologies, such as machine learning, to enhance mortality prediction in ACS patients. Machine learning models have shown promising potential, offering improved accuracy in mortality risk assessment by integrating a wide range of clinical variables and patient data [103, 104].

Cardiac arrest

Cardiac arrest is a severe and life-threatening complication that can arise from ACS. The actual incidence of SCA in the setting of ACS is unknown [105]. Studies have reported that cardiogenic shock occurs in approximately 3% to 13% of ACS cases [106]. About half of these patients experience cardiac arrest, and two-thirds of those who suffer cardiac arrest subsequently develop cardiogenic shock [107]. This overlap underscores the critical nature of these complications and the necessity for prompt medical intervention. The prognosis for ACS patients who suffer cardiac arrest remains grim.

Recent studies have investigated the incidence of out-of-hospital-cardiac-arrest (OHCA) in ACS patients. One study reported that approximately 10% of ACS events result in OHCA; however, this study focused exclusively on individuals younger than 50 years, which may limit its generalizability to the broader ACS population [108]. Another study found that the incidence of SCA was 17.5% among all ACS patients and 23.6% specifically in those with STEMI [109]. These findings underscore the critical need for improved early detection of ACS, particularly outside of healthcare settings, to reduce premature deaths related to coronary artery disease.

In a large cohort study of STEMI patients, the incidence of in-hospital cardiac arrest (IHCA) was reported to be 2.2%. The study identified several predictors of IHCA,

including age ≥75 years, female sex, non-smoking status, history of diabetes mellitus, prior renal failure, occurrence of OHCA, heart rate >100 beats per minute, systolic blood pressure <90 mm Hg, and Killip class IV at presentation [110].

Given the high morbidity and mortality associated with cardiac arrest in the setting of ACS, early recognition and rapid treatment are imperative. Strategies such as timely PCI, effective management of cardiogenic shock, and post-resuscitation care are essential components in improving patient outcomes. Ongoing research continues to explore optimal therapeutic approaches and interventions to mitigate the risks associated with this critical complication.

Cardiogenic shock and AHF

Cardiogenic shock, a severe early ACS complication associated with a high mortality rate of up to 50% despite advances in medical care [111, 112]. This condition typically results from extensive myocardial infarction (involving more than 40% of the heart muscle), leading to a significant loss of contractile function [113]. The subsequent decline in cardiac output causes hypotension, impaired organ perfusion, and multi-organ dysfunction. Immediate revascularization of the occluded artery has been shown to reduce mortality [114].

AMI is known to be a leading cause of AHF (clinically presenting as pulmonary edema) and cardiogenic shock [115]. An observational study of over 14,000 ACS patients across 14 countries found similar incidences of AHF in STEMI (15.6%) and NSTEMI (15.7%), while patients with unstable angina had a lower incidence (8.2%) [116]. Both AHF and cardiogenic shock carry a poor prognosis, requiring intensive treatment strategies such as invasive and non-invasive mechanical ventilation, vasoactive medications (vasopressors and inotropes), and circulatory support devices like intra-aortic balloon pumps (IABP) and percutaneous ventricular assist devices (e.g., Impella). Given the severity of these conditions, they are strong indications for admission to the CCU/ ICU [117].

Malignant cardiac arrhythmias

Arrhythmias are a frequent early complication of ACS, occurring in both STEMI and NSTEMI patients. These range from benign to life-threatening, including ventricular arrhythmias such as VT and VF, as well as high-degree AV block. VT/VF are particularly common within the first 48 hours of AMI and have significant prognostic implications. Approximately 6-10% of STEMI patients develop serious arrhythmias, primarily polymorphic VT, which often degenerates into VF during the early in-hospital phase [118]. In contrast, NSTEMI patients experience fewer early sustained ventricular arrhythmias (<2%), but studies continue to indicate increased mortality at one-year follow-up due to arrhythmia-related complications [119, 120]. Although the incidence of ventricular arrhythmias has declined during the hospital phase of ACS due to timely revascularization and optimal medical therapy, up to 6% of ACS patients still develop VT and/or VF

within the first few hours of symptom onset [121]. The presence of ventricular arrhythmias in ACS is associated with higher in-hospital mortality and worse outcomes [122, 123], making it a key indication for CCU/ICU admission and continuous cardiac monitoring.

Recent studies suggest a decreasing incidence of high-degree AV block in ACS patients [124]. Despite this trend, in-hospital mortality for those who develop high-degree AV block remains significantly elevated, underscoring the severity of the underlying ACS [125, 126]. Studies have found that the incidence of high-degree AV block is higher in older patients, more often diagnosed with STEMI [127, 128]. Early identification of precipitating factors predictive of high-degree AV block, ideally upon presentation in the ED, is crucial and warrants further investigation.

Malignant arrhythmias, including both bradyarrhythmias and tachyarrhythmias, are associated with poorer outcomes in ACS patients and are a major concern driving CCU admissions. However, these complications occur in fewer than 10% of ACS cases, making routine CCU admission for all ACS patients impractical. Therefore, accurately identifying patients at high risk for malignant arrhythmias is a clinical priority. Ongoing research is essential to refining risk stratification and improving early detection, ensuring that intensive care resources are allocated appropriately.

Mechanical complications

Post-MI mechanical complications are uncommon and are more often associated with STEMI (0.27%) than NSTEMI (0.06%), but mortality rates for patients with mechanical complications remains very high (42.4% after STEMI and 18.0% after NSTEMI) [129]. In a recent large Spanish cohort, the prevalence of post-MI mechanical complications was 0.35% [130]. Among the various post-AMI mechanical complications, VSD remains the most common complication with an estimated prevalence of up to 0.91%, while the prevalence of papillary muscle rupture and free wall rupture is less than a half percent [131]. Delayed presentation and treatment have long been recognized as significant risk factors for these complications. The advent of reperfusion therapies, particularly PCI, has led to a notable decrease in the incidence of mechanical complications post-STEMI, thereby contributing to improved survival rates. Recent studies indicate that patients who develop mechanical complications tend to be older, female, have a history of heart failure or chronic kidney disease, and often present with their first AMI [132-134].

Effective management of patients with mechanical complications following acute myocardial infarction necessitates a multidisciplinary heart team approach to ensure timely recognition, accurate diagnosis, and appropriate intervention for complex hemodynamic conditions, thereby optimizing patient outcomes [135]. Early and precise risk stratification upon hospital arrival is vital, admission to the CCU/ICU is imperative for continuous monitoring and advanced therapeutic support for these patients.

Aims

The primary aim of this thesis is to characterize ED chest pain patients with suspected ACS, evaluate their diagnostics, management, and outcomes, identify complication risks, and develop improved risk prediction algorithms to enhance patient outcomes and optimize resource utilization.

Specific Objectives:

- To compare patient characteristics and assess the diagnostic performance of the ECG in ED patients with ongoing vs. abated chest pain. **(Study I)**

- To evaluate the diagnostic accuracy of the HEART Pathway and EDACS-ADP when combined with a 0-hour/1-hour hs-cTnT protocol for ruling out MACE within 30 days in ED chest pain patients. **(Study II)**

- To analyze the types and number of complications in contemporary ED ACS patients and to map patient management, including admission wards, treatment strategies and interventions. **(Study III)**

- To compare the ability of existing risk scores to predict complications, and to assess the performance of a new simplified risk prediction model in ED ACS patients. **(Study IV)**

Materials and methods

To analyse the characteristics and management of ED chest pain patients, we used prospectively collected registry data (SCORE and ESC TROP cohorts) from two separate trials conducted within our research group [56, 136]. This data provided the foundation for the four observational studies included in this thesis.

Study setting

In **study I and II**, we included patients who visited the ED at the Skåne University Hospital in Lund. This tertiary care centre operates 24/7, receiving approximately 65,000 patients annually, and is primarily staffed by emergency physicians. The hospital features a state-of-the-art CCU with 22 beds, with at least one cardiologist available at all times. It also provides 24-hour access to a catheterization lab (cath lab) and serves as the only regional unit admitting STEMI patients outside regular working hours. In our region (Skåne), STEMI patients identified via ambulance ECG are transported directly to the cath lab and subsequently admitted to the CCU, bypassing the ED.

For **study III and IV**, we included patients from five EDs across Region Skåne, Sweden – Lund, Malmö, Ystad, Kristianstad, and Helsingborg. This selection comprises two large academic tertiary care EDs, two urban community EDs, and one small rural community ED. Each hospital has a CCU with varying admission criteria. The most unstable cardiac patients are typically transferred to the CCU in Lund, given its advanced resources and specialized capabilities.

Study design

We conducted four observational studies utilizing registry data for all studies, and additional manual chart review for study III and IV. The study populations, timeframes and primary outcomes are summarized in Table 3.

In **study I and II** we included consecutive chest pain patients that visited the ED in Lund on weekdays during daytime from February 2013 to April 2014.

Study III and IV were secondary analyses of prospectively collected data from the ESC TROP trial [56], which included all chest pain patients presenting to one of five EDs in Region Skåne, between February 1st to November 30th in both 2017 and

2018. Our studies focused specifically on ACS patients within this cohort. ACS patients with complications were identified using predetermined diagnoses (ICD-10) and intervention codes (KVÅ). A retrospective manual chart review was then conducted to gain deeper insight into the circumstances surrounding the patient visits, treatment decisions and outcomes. In study III, the chart review was performed only for patients with complications, whereas in study IV, we reviewed all ACS patients' charts.

Table 3. Study populations

	Cohort	Study participants	Time frame	Outcomes
Study I	SCORE	1132	February 2013 – April 2014 9AM-9PM weekdays	ACS index visit 30-day MACE
Study II	SCORE	939	February 2013 – April 2014 9AM-9PM weekdays	30-day MACE 30-day MI
Study III	ESC TROP	2463	February – November 2017 and 2018	30-day MACE
Study IV	ESC TROP	2223	February – November 2017 and 2018	30-day MACE

Inclusion and exclusion criteria

All studies included patients aged 18 and older who presented to the ED with a chief complaint of non-traumatic chest pain.

Study I and II included consecutive chest pain patients where at least one hs-cTnT was ordered. The studies did not include patients with adjudicated STEMI diagnosis, as well as patients with severe communication barriers such as dementia, or other cognitive disorders, patients who did not speak Swedish or English or those who were unable to sign a written informed consent.

In **study I** we included patients with a documented ECG and chest pain status. Patients with missing data for ECG interpretation or chest pain status were excluded from the final analyses.

In **study II** we excluded patients with missing or inconclusive data where the HEART and EDACS scores could not be calculated as well as patients with haemolysis in either 0h or 1h hs-cTnT blood sample.

Study III and IV included consecutive ACS adult patients. Data from all ACS patients in the population was analysed in **study III**. There were no exclusion criteria.

After comprehensive manual chart review of all patient charts, the patients with chief complaint other than chest pain or a no-ACS diagnosis as well as missing data were excluded from **study IV**. For the final analysis we excluded patients with hemodynamic instability in the ED, those who suffered a complication prior to admission as well as patients with palliative care from the ED. Patients with procedural complications were not included in the complications cohort since these complications are hard to predict from the ED.

Data collection

In **Study I and II**, research assistants collected clinical data and troponin samples immediately after patient presentation to the ED, with an additional sample taken at 1 hour for hs-cTnT measurements. Data was recorded in real time using a standardized study form during the initial patient assessment. Each patient provided a description of their chest pain characteristics, while the attending physician documented their interpretation of the patient's history and ECG findings. The chest pain descriptions were later used to calculate HEART and EDACS scores in Study II, based on predefined criteria (detailed in Supplement Table 1 and 3). Follow-up data was gathered from electronic medical records and national patient registries.

Study III and IV used data from the ESC TROP database which integrates information from regional electronic medical records and multiple quality registries, including SWEDEHEART, the Swedish emergency care register (SVAR), and the Swedish National Patient Register [137-139]. Patients diagnosed with ACS and complications were identified using predetermined International classification of diseases, 10th Revision codes (ICD-10) and intervention (KVÅ) codes and subsequently included in the analyses (Supplement Table 4 and 5).

Complications were defined as: death, cardiac arrest, cardiogenic shock, pulmonary edema, high-degree AV block requiring pacemaker (PM), ventricular arrhythmias, and mechanical complications such as VSD, cardiac tamponade and papillary muscle rupture. In **study IV** additional complications included PM or implantable cardioverter-defibrillator (ICD) implantation and the use of a circulatory assist devices such as intra-aortic balloon pump (IABP), percutaneous ventricular assist device (Impella pump) or extracorporeal membrane oxygenation (ECMO). Manual chart review of all ACS patients with complications **(study III)** and further, the entire ACS cohort **(Study IV)** was conducted by the author of this thesis, with the help of one more physician, a medical student and several research assistants. Data from this review was used to calculate six established risk scores.

Study endpoints

The primary outcome in **study I** was adjudicated diagnosis of ACS at index visit. The secondary outcome was 30-day MACE including the index visit. MACE was defined as an adjudicated diagnosis of AMI or UA, cardiac arrest, cardiogenic shock, ventricular arrhythmia requiring intervention, high-degree AV block requiring intervention and death of cardiac or unknown origin.

The primary endpoint in **Study II** was MACE within 30 days of the index visit, using the same MACE definition as in study I. The secondary outcome was index visit AMI.

The primary endpoint in **study III and IV** was the occurrence of any complication (as defined above) within 30 days of index visit.

Statistics

Most statistical analyses in this thesis were conducted using IBM SPSS (versions 21-29) and MedCalc statistical software.

For categorical data we used frequencies and percentages. For continuous data – mean and standard deviation (SD) for normally distributed data and median with interquartile ranges (IQR) for skewed distributions.

Differences in proportions were assessed using the Chi-square and Fisher's exact test, and continuous variables were compared using the Mann-Whitney U test.

For diagnostic accuracy, sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and likelihood ratios were calculated with corresponding 95% confidence intervals (CI) (**study I, II and IV**).

In **study III**, odds ratios were used to compare complication rates across different subgroups in the study population.

In **study I and IV** logistic regression analyses were performed. In **study IV**, the predictive accuracy of the different risk scores and the logistic regression model was evaluated using the area under the receiver operating characteristic (AUROC) curve.

Diagnostic testing

Diagnostic tests are essential for distinguishing between individuals with and without a specific disease. Many conditions have a gold standard test for diagnosis; however, these tests often come with significant limitations, such as being invasive, time-consuming, or costly. Developing new diagnostic methods that overcome these challenges is a key focus of ongoing research. The primary aim when introducing new diagnostic tests is to achieve improved diagnostic performance compared to the existing gold standard. Table 4 outlines the key statistical measures used to evaluate diagnostic accuracy.

Table 4. Measures of diagnostic accuracy

	Disease status		
	Sick	**Healthy**	
Test outcome			
Test positive	True positive (A)	False positive (B)	Positive Predictive Value A/(A+B)
Test negative	False negative (C)	True negative (D)	Negative Predictive Value D/(C+D)
	Sensitivity A/(A+C)	Specificity D/(B+D)	Total

Sensitivity measures a test's ability to correctly identify individuals with a disease (true positives). A highly sensitive test is positive in almost all affected individuals, making it particularly useful for ruling out disease when the result is negative. For example, if a test has 99% sensitivity, this means that out of 100 individuals with the disease, 99 will test positive, while only one will incorrectly test negative (false negative). A negative result from such a test strongly suggests the absence of disease.

Specificity measures a test's ability to correctly identify healthy individuals (true negatives). A highly specific test is negative in almost all unaffected individuals, making it useful for confirming disease when the result is positive. For example, if a test has 98% specificity, this means that out of 100 healthy individuals, 98 will test negative, while two will incorrectly test positive (false positives). A positive result from such a test strongly indicates the presence of disease.

Choosing a test depends on what the priority for the results is. In screening studies, where detecting the majority of diseased individuals is critical, a test with high sensitivity is preferred. When confirming a diagnosis, a test with high specificity is more appropriate. However, in clinical practice, we only see test results and must determine the likelihood that a patient truly has or does not have the disease. This is where predictive values come into play.

Negative Predictive Value (NPV) measures the probability that an individual with a negative test result truly does not have the disease.

Positive Predictive Value (PPV) measures the probability that an individual with a positive test result actually has the disease.

Both NPV and PPV are influenced by disease prevalence, meaning their reliability varies depending on how common the condition is in a given population.

Ethical concerns

Ethical concerns in observational studies primarily focus on safeguarding patient privacy, ensuring transparency, obtaining informed consent, addressing potential biases in data collection, and maintaining the trust of vulnerable populations. When conducting registry-based research it is important to understand how the data has been generated and at all times follow the obvious confidentiality restrictions for all kinds of personal data [140].

Obtaining informed consent in observational registry studies presents a grey area. Since data is usually collected retrospectively, patients may not have the chance to provide direct consent for the use of their medical records in research. Depending on the study design and jurisdiction, researchers may request a waiver of consent, but this raises ethical challenges, as patients may be unaware that their data is being used. All patients in **Study I** and **II** signed informed consent upon inclusion. In the ESC TROP trial (database used in **Study III** and **IV**), patients were included by default and informed through leaflets distributed in the triage area and around the ED. They were also given the option to revoke access to their data at any point by contacting the study administrator via phone or email. All studies were approved by the regional ethics board.

For **study III** and **IV**, we conducted manual chart reviews. The most significant ethical issue in medical chart review studies is maintaining patient privacy and ensuring that medical information remains confidential. Unauthorized access or misuse of data could result in breaches of confidentiality and compromise patient privacy. Our chart review was strictly limited to predefined endpoint parameters, and no unplanned data was accessed or extracted. Although observational studies do not intervene in patient care, there may do indirect harm. For instance, patients may feel anxious or uncomfortable knowing their medical data is being reviewed for research purposes, especially if sensitive issues are involved. No sensitive patient information (e.g. socioeconomic status, ethnicity, mental health, substance abuse etc) was analysed or presented in our studies. The researchers followed strict protocols for chart review, using monitored accounts with limited access to only the essential clinical information. The manual chart review was approved by the regional ethics board.

Medical chart reviews often rely on pre-existing records, which may be incomplete, inaccurate, or inconsistent. This can introduce biases, such as selection or

information bias, which could affect the validity and generalizability of the findings. Ethical concerns arise if these biases are not addressed appropriately, potentially leading to misinterpretation of patient outcomes or treatments. In our chart review, two authors independently reviewed most of the cases and discussed their findings and interpretations. In instances of uncertainty, the main project supervisor had the final say. We believe that involving several experienced consultants and having access to the complete patient medical history helped ensure that our interpretations were as accurate as possible.

In our projects, we adhere to the principle of delivering the right care for the right patient at the right time. For certain low-risk patients this could mean providing less interventions than usual. This idea raises a few ethical concerns – first, even lower risk patients could experience some complications and doing less could prolong the time to recognition of deteriorating conditions, potentially leading to worse outcomes. The duty of care requires that each patient receives appropriate medical attention based on their needs and not statistical probabilities.

Patients should have a say in their care decisions. If hospitals reduce monitoring or interventions for low-risk patients without informing them, this undermines patient autonomy. Ethical implementation would require clear communication, shared decision-making, and an opportunity for patients to express concerns or request additional care.

Patients trust that hospitals will provide optimal care, regardless of risk level. If they perceive that they are receiving reduced attention due to resource constraints, trust in the healthcare system may erode. A lack of transparency in how risk levels are determined and acted upon could further increase scepticism and dissatisfaction.

On the other hand, if reducing care for low-risk patients allows for better allocation of resources to critically ill patients, there could be a strong argument in favor of this approach. However, safeguards must be in place, such as: rigorous, evidence-based risk assessment models to ensure safe classification, rapid escalation protocols for low-risk patients whose condition worsens and patient education and involvement in decision-making about their care level.

Results

Study I

In study I we compared the patients' characteristics and the diagnostic accuracy of the ED physician's ECG interpretation in 1132 consecutive chest pain patients with ongoing vs abated chest pain (Figure 8). The main patient characteristics are presented in Table 5. We found that the patients with abated chest pain (n=501) were in general older, sicker and had twice as often ACS at index visit (15%) or MACE within 30 days (15.6%) compared to the ones with ongoing chest pain (n=631, ACS 7.3%, 30-day MACE 7.4%). Almost all MACE occurred during index visit with AMI and UA diagnosis being the most common. There were a total of 5 deaths in the cohort (2 patients with ongoing chest pain and 3 patients with abated chest pain). The patients with abated chest pain had significantly more often signs of acute ischemia on their ECG (8% vs 4.6%, p=0.018).

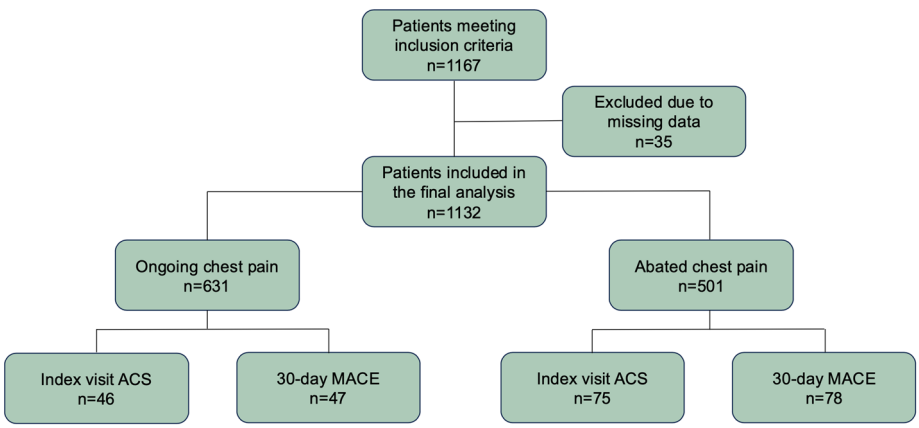


Figure 8. Flow chart of patients included in study I

Table 5. ED chest pain patient characteristics

	Ongoing chest pain n=631	Abated chest pain n=501	p-value
General information			
Age, years (median, IQR)	60.2 (46.4-71.2)	66.5 (52.9-77.0)	
Male sex	323 (51.2%)	294 (58.7%)	0.012
History of			
Heart failure	62 (9.8%)	65 (13.0%)	0.095
Previous AMI	121 (19.2%)	106 (21.2%)	0.408
Diabetes mellitus type 1 or 2	72 (11.4%)	86 (17.2%)	0.006
Hypercholesterolaemia	129 (20.4%)	131 (26.1%)	0.023
Hypertension	240 (38.0)	257 (51.3%)	0.000
Current medications			
Aspirin/ADP-inhibitor	158 (25.0%)	183 (36.5%)	0.000
ACE/ARB-blocker	173 (27.4%)	180 (35.9%)	0.002
Beta-blocker	177 (28.1%)	169 (33.7%)	0.039
Nitroglycerin	140 (22.2%)	124 (24.8%)	0.311
Statins	173 (27.4%)	169 (33.7%)	0.022
Insulin	23 (3.6%)	37 (7.4%)	0.005
Physician assesment			
ECG showing signs of acute ischemia	29 (4.6%)	40 (8.0%)	0.018
Physian's level of education			0.173
Intern	240 (38.0%)	164 (32.7%)	
Resident	257 (40.7%)	225 (44.9%)	
Specialist	134 (21.2%)	112 (22.4%)	
Index visit diagnosis of ACS	46 (7.3%)	75 (15.0%)	0.000
Final diagnosis of AMI	32 (5.1%)	48 (9.6%)	0.003
Final diagnosis of UA	14 (2.2%)	27 (5.4%)	0.005
MACE within 30 days			
Total MACE (including UA)	47 (7.4%)	78 (15.6%)	0.000
Death – cardiac or unknown cause within 30 days	1 (0.2%)	3 (0.6%)	0.215
All-cause death within 30 days	2 (0.3%)	3 (0.6%)	0.478

Table 6 summarizes the diagnostic performance of the ECG for index visit ACS in patients with vs. without ongoing pain. The ECG demonstrated low sensitivity (24% vs. 38%) but high specificity, approaching 97%. However, there was no statistically significant difference between the two groups. Even after adjusting for confounders, no significant difference was observed in the ECG's diagnostic performance for index visit ACS in patients with ongoing versus abated chest pain.

Table 6. Diagnostic performance of the ECG

	Ongoing Chest Pain	Abated chest pain	Adjusted p-value
Sensitivity, %	23.9 (12.6-38.8)	34.7 (24.0-46.5)	0.064
Specificity, %	96.9 (95.2-98.2)	96.7 (94.6-98.2)	0.805
PPV, %	37.9 (20.7-57.7)	65.0 (48.3-79.4)	0.050
NPV, %	94.2 (92.0-95.9)	89.4 (86.2-92.0)	0.586
LR+	7.77 (3.91-15.46)	10.55 (5.78-19.25)	
LR-	1.27 (1.08-1.50)	1.48 (1.25-1.75)	

Study II

In study II we analyzed the diagnostic performance of two established risk scores (HEART and EDACS) combined with 0-hour/1-hour high sensitivity troponin T protocol for the assessment of 939 ED chest pain patients. One hundred and sixteen patients in the cohort (12.4%) had MACE within 30 days. Of them 75 patients had index visit AMI and 38 patients were diagnosed with index visit UA. The HEART score alone identified 501 patients (53.3%) as low risk, the HEART 0-hour/1-hour Pathway ruled out 468 patients (49.8%) and the EDACS 0-hour/1-hour-ADP – a total of 466 patients (49.6%).

The diagnostic accuracies of the different scores are presented in Table 7. The score with the highest diagnostic performance was the HEART 0-hour/1-hour Pathway which correctly identified 467 patients (49.7%) as low risk and missed only 1 patient with UA. The EDACS 0-hour/1-hour-ADP correctly identified 462 low risk patients (49.2%). The score missed one patient with AMI and 3 patients with UA within 30 days. The HEART score alone identified 495 true low risk patients (52.7%) but missed 6 patients with MACE within 30 days – 4 patients with AMI, one with UA and one that suffered cardiac arrest.

However, due to the notable overlap in the confidence intervals, no statistically significant difference was observed between the scores.

Table 7. Diagnostic accuracy of the HEART, HEART 0h/1h Pathway and EDACS 0h/1h-ADP

	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV (95% CI)	LR- (95% CI)
30-day MACE				
HEART score	94.8 (89.1-98.1)	60.2 (56.7-63.5)	98.8 (97.4-99.5)	0.09 (0.04-0.19)
HEART 0h/1h Pathway	99.1 (95.3-99.9)	56.7 (53.3-60.2)	99.8 (98.5-100.0)	0.02 (0.00-0.11)
EDACS 0h/1h ADP	96.7 (91.4-99.1)	56.1 (52.7-59.6)	99.1 (97.8-99.7)	0.06 (0.02-0.16)
Index visit MI				
HEART score	94.7 (86.9-98.5)	57.5 (54.2-60.9)	99.2 (98.0-99.7)	0.09 (0.04-0.24)
HEART 0h/1h Pathway	100.0 (95.2-100.0)	54.2 (50.8-57.5)	100.0 (99.2-100)	0.00 (0-NaN)
EDACS 0h/1h ADP	98.7 (92.8 -100.0)	53.8 (50.4-57.2)	99.8 (98.5-100.0)	0.02 (0.00-0.17)

Study III

In Study III we mapped the complications and management of 2463 ED ACS patients. A total of 151 (6.1%) patients experienced at least one complication within 30 days of their index visit. Patients with complications were older (79.2 vs 69.4 years, $p<0.001$), often elderly – above 80 years of age (OR 5.29), and more frequently female (OR 1.34) compared to those without complications. These patients were more likely to be admitted to the CCU/ICU (OR 2.51), less likely to undergo coronary angiography (OR 3.60) and less likely to be revascularized (OR 2.03) compared to patients without any complications.

We divided the patients into subgroups based on ACS subtype (STEMI, NSTEMI and UA), admission ward (CCU/ICU and other wards), age (>80 years old), sex (males vs. females) and analyzed the differences in management. The complications and management details based on admission ward are presented in Table 8. Patients admitted to the CCU/ICU were more likely to be diagnosed with STEMI (OR 2.5), more often underwent coronary angiography (OR 18.0) and had a lower 30-day mortality (OR 0.16) than the patients admitted to other wards. Mortality rates were significantly higher in the medical/geriatric wards than in cardiology units or the CCU.

Table 8. Complications and management of ED ACS patients based on admission ward

	All ACS patients n=2463	Patients with complications within 30 days		
		All patients n=151	Admitted to CCU/ICU n=88	Not admitted to CCU/ICU n=63
Complication Type				
Death	84 (3.4%)	84 (55.6%)	34 (38.6%)	50 (79.4%)
Death during index visit	53 (2.1%)	53 (35.0%)	23 (26.1%)	29 (46.0%)
Cardiac arrest	33 (1.3%)	33 (21.9%)	29 (33.3%)	4 (6.3%)
Cardiogenic shock	10 (0.4%)	10 (6.6%)	8 (9.1%)	2 (3.2%)
Ventricular arrhythmia	12 (0.5%)	12 (7.9%)	12 (13.6%)	0
High-degree AV block	13 (0.5%)	13 (8.6%)	8 (9.1%)	5 (7.9%)
Pulmonary edema	22 (0.9%)	22 (14.5%)	16 (18.1%)	6 (9.5%)
VSD	2 (0.1%)	2 (1.3)	2 (2.3%)	0
Cardiac tamponade	2 (0.1%)	2 (1.3)	2 (2.3%)	0
Time from ED arrival to first complication				
0-12h	65 (2.6%)	65 (43.1%)	48 (54.5%)	17 (27.0%)
12 to 24h	12 (0.5%)	12 (7.9%)	8 (9.1%)	4 (6.3%)
after 24h	74 (3.0%)	74 (49.0%)	32 (36.4%)	42 (66.7%)
Situation at complication				
Present in ED	41 (1.7%)	41 (27.2%)	29 (33.0%)	12 (19.0%)
Before planned coronary angiography	38 (1.5%)	38 (25.2%)	34 (38.6%)	4 (6.3%)
During coronary angiography	17 (0.7%)	17 (11.3%)	16 (18.2%)	1 (1.6%)
Admission level				
CCU	874 (35.5%)	79 (52.3%)	79 (89.8%)	0
ICU	10 (0.4%)	9 (6.0%)	9 (10.2%)	0
Cardiology ward with telemetry	764 (31.0%)	18 (11.9%)	0	18 (28.6%)
Telemetry ward	433 (17.6%)	15 (9.9%)	0	15 (23.8%)
Medical/geriatric ward	379 (15.4%)	27 (17.9%)	0	27 (42.8%)
ED	3 (0.1%)	3 (2.0%)	0	3 (4.8%)

Treatment Strategy				
Invasive	1416 (57.5%)	78 (51.7%)	68 (77.3%)	10 (15.9%)
PCI	1202 (48.8%)	51 (33.8%)	44 (50.0%)	7 (11.1%)
CABG	228 (9.3%)	11 (7.3%)	10 (11.4%)	1 (1.6%)
Conservative treatment	1041 (42.3%)	67 (44.4%)	19 (21.6%)	48 (76.2%)
Palliative treatment	6 (0.2%)	6 (4.0%)	1 (1.1%)	5 (7.9%)
ACS diagnosis				
STEMI	279 (11.3%)	62 (41.1%)	44 (50.0%)	18 (28.6%)
NSTEMI type 1	1318 (53.5%)	71 (47.0%)	37 (42.0%)	34 (54.0%)
NSTEMI type 2	u/a	10 (6.6%)	3 (3.4%)	7 (11.1%)
Unstable angina	866 (35.2%)	2 (1.3%)	1 (1.1%)	1 (1.6%)
Others	u/a	6 (4.0%)	3 (3.4%)	3 (4.8%)

We observed variations in complication rates based on ACS subtype – 22% in STEMI patients, 5.4% in NSTEMI and just 0.2% in UA patients. The types of complications also differed – cardiac arrest and cardiogenic shock were more common in STEMI cases, while pulmonary edema and high-degree AV block were more prevalent in NSTE-ACS patients. Additionally, patients with STEMI in our study population tended to develop complications earlier, typically within the first 12 hours, whereas complications in NSTEMI patients were more likely to occur after 24 hours.

Study IV

In Study IV we evaluated the ability of six published risk scores to predict complications in 2223 ED ACS patients and compared their performance to a new logistic regression model. After conducting a manual chart review, we identified 164 patient (7.4%) who suffered at least one serious complication, with many patients having multiple complications (Figure 9). Patients with complications were, on average, older, sicker, and more likely to have a signed Do-Not-Resuscitate (DNR) order compared to the patients without complications.

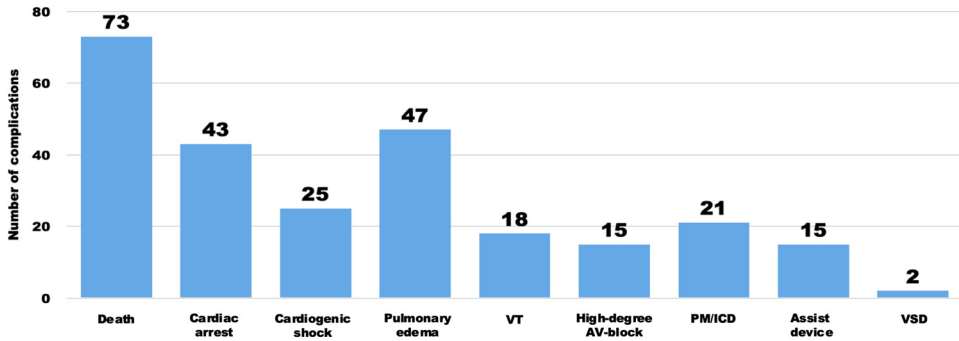


Figure 9. Number and types of complications in 2223 ED ACS patients

Our logistic regression analysis identified several statistically significant predictors of complications, including age (OR 1.04), STEMI (OR 2.02), higher troponin at arrival (OR 1.80), elevated initial lactate (OR 11.62), shock index (OR 3.85,), Killip class (OR 2.24 for class II; OR 6.48 for class III), and new ECG changes (OR 2.11). The AUROC for both the published scores and our logistic regression model is presented in Figure 10. Our logistic regression model demonstrated excellent predictive ability (AUROC 0.84) and outperformed all existing risk scores – GRACE FFE (0.79), ACTION ICU (0.77), GRACE (0.76), TIMI (0.74), HEART (0.69) and CHA2DS2-VASc (0.64).

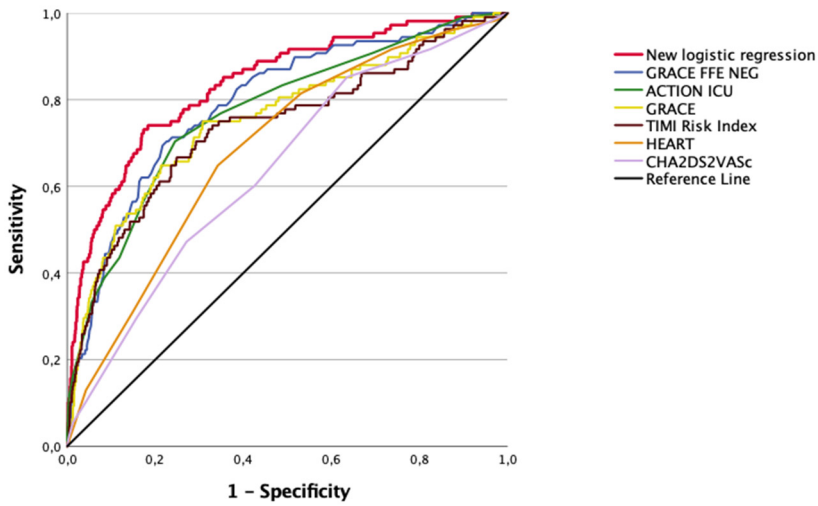


Figure 10. ROC curves of published risk score compared to a new logistic regression model

The corresponding cutoff values along with the accuracy of the different risk scores are shown in Table 9. With a set sensitivity of 90%, our logistic regression model could correctly identify 98 patients with and 1007 patients without complications, providing the highest specificity of 52% and NPV of 99.0% compared to the published risk scores.

Table 9. Cut-offs and accuracy of the risk scores for complications in ED ACS patients, n=2056

Score	AUROC	95% CI	Cut-off	Sensitivity	Specificity
New logistic regression	0.837	0.796 - 0.879	0.022	90.7%	51.7%
GRACE FFE (neg)	0.792	0.748 - 0.837	-260.5	90.7%	43.4%
ACTION ICU	0.772	0.724 - 0.820	2	90.7%	30.7%
GRACE	0.756	0.703 - 0.809	80.8	90.7%	24.4%
TIMI	0.739	0.683 - 0.794	16.6	90.7%	21.3%
HEART	0.687	0.638 - 0.736	5	91.7%	26.3%
CHA2DS2VASc	0.640	0.588 - 0.692	1	91.7%	17.6%

Discussion

Extensive research has focused on improving the management of ED chest pain patients, with an emphasis on rapidly ruling out low-risk patients while minimizing unnecessary testing and hospital admissions. However, optimizing the disposition and monitoring of ACS patients remains a significant challenge for ED physicians, particularly given the persistent shortage of hospital beds and resources. The primary aim of this thesis is to identify factors that enhance risk stratification, improve diagnostic accuracy, and refine the management of chest pain patients in the ED. This thesis presents multiple key findings.

Ongoing vs abated chest pain in the emergency department

In **Study I**, we found that patients whose chest pain had abated upon ED arrival were generally older, with more comorbidities, and were at a higher risk of ACS and MACE compared to those with ongoing chest pain. Unlike the carefully selected cardiology patients, the ED cohort includes a diverse range of conditions, and our findings demonstrate that ongoing chest pain is not a reliable indicator of disease severity. Contrary to the recommendations of certain triage systems [32, 35], our results suggest that patients with resolved chest pain should not automatically be assigned lower priority than those with persistent symptoms.

While STEMI patients frequently present with ongoing chest pain, NSTE-ACS patients more often report one or multiple episodes of chest pain that have subsided by the time they reach the ED. Given these findings, we emphasize the importance of obtaining a thorough patient history during triage. Patients with a typical chest pain history but no ST-elevations on ECG should be prioritized equally regardless pain status to ensure timely and appropriate care.

Diagnostic accuracy of the ECG in patients with and without ongoing chest pain

The diagnostic value of ECG in detecting NSTE-ACS is known to be limited, as a normal ECG does not rule out the diagnosis [141]. Previous studies on patients with known cardiovascular disease suggest that ECG recorded during ongoing chest pain has greater diagnostic performance, as ischemic changes may be present during pain

but disappear once symptoms subside [142]. However, the correlation between chest pain characteristics and ischemic ECG changes is weak [143, 144], and in some ACS patients, ischemia and myocardial necrosis can occur without chest pain. Therefore, obtaining an ECG even in the absence of ongoing symptoms remains a reasonable approach.

There is no firm evidence that ECG performance is consistent across all ED chest pain patients. Recent studies indicate that the diagnostic accuracy of ECG criteria for ACS in the ED setting is low [145]. To our knowledge, **Study I** was the first to assess the diagnostic accuracy of ECG in ED patients with and without ongoing chest pain. We found that ECG sensitivity was low and specificity was high in both groups, in accordance with previous research [146]. After adjusting for potential confounders, we were unable to demonstrate a significant difference in ECG accuracy between the two groups. Therefore, we recommend that if the ECG is normal or inconclusive, regardless of pain status, the evaluation should continue with the troponin testing and further clinical assessment. The role of repeated ECGs warrants further investigation.

Diagnostic accuracy of the HEART Pathway and EDACS-ADP when combined with 0-hour/1-hour hs-cTnT algorithm

In **study II** we assessed the diagnostic accuracy of the HEART and EDACS-ADP scores combined with 0-hour/1-hour hs-cTnT algorithm for ruling out MACE within 30 days in ED chest pain patients. Our findings demonstrated that all tested strategies identified a substantial proportion of low-risk patients, with a NPV exceeding 98%. Notably, HEART 0-hour/1-hour Pathway and EDACS 0-hour/1-hour-ADP achieved an NPV above 99.5% for ruling out index visit AMI, a commonly accepted threshold for defining an effective chest pain rule-out strategy [147]. There were no statistically significant differences between the scores, suggesting that their application in clinical practice is reasonable. The choice of score may be left to individual physician preference, depending on familiarity and comfort with its use.

Several previous studies have recommended the use of high-sensitivity troponins in conjunction with the 0-hour/2-hour hs-cTnI and 0-hour/3-hour hs-cTnT algorithms alongside the HEART score [148-150] and EDACS-ADP [92]. Our study is the first to propose using the 0-hour/1-hour hs-cTnT algorithm with the HEART Pathway and EDACS-ADP, thereby reducing the time required for rule-out. Our results align with existing literature, confirming that the HEART Pathway and EDACS-ADP can safely rule out MACE in a large cohort of ED chest pain patients.

While the 0-hour/1-hour hs-cTnT algorithm alone has been shown to effectively rule out AMI [136] it does not reliably exclude 30-day MACE including unstable

angina. Thus, the algorithm should be used in conjunction with a comprehensive clinical assessment.

Our study contributes to the growing body of evidence supporting the safety of the HEART Pathway and EDACS-ADP [150-152] and shows that these risk scores can be effectively integrated with a guideline-approved algorithm. This combination has the potential to enhance patient management and streamline clinical decision-making.

Complications in ED ACS patients

In **studies III** and **IV**, we investigated complications in ED ACS patients. Our findings revealed that complications occurred in approximately 6-7% of all ACS patients, with nearly one-third already present upon ED arrival. **Study III** mapped complication types and management strategies, revealing that a significant proportion of ACS patients with complications were not admitted to the CCU/ICU, and did not receive invasive treatment, despite current guideline recommendations. This raises important questions about admission and treatment criteria.

Interestingly, mortality and severe complication rates were significantly lower than in previous studies [153-155], potentially due to more advanced cardiac care, a lower STEMI prevalence, and a higher proportion of UA patients in our population. However, the potential influence of additional factors (such as comorbidities, socioeconomic conditions, and variations in treatment approaches) remains uncertain but cannot be ruled out.

CCU/ICU admission for ACS patients aims to monitor for life-threatening complications like malignant arrhythmias and cardiogenic shock. However, modern care has reduced the incidence of severe arrhythmias [156] potentially leading to CCU overutilization [12, 157]. A recent study found that while ACS patients comprise up to 56% of CCU admissions, only about 5% required intensive treatment beyond monitoring [158]. Our findings support this: only 1.3% of ACS patients experienced cardiac arrest or cardiogenic shock, and 2% had malignant arrhythmias requiring intervention, leaving over 96% of ACS patients free from any significant rhythm or circulatory disturbances. These findings suggest that continuous ECG and advanced circulatory monitoring should be reserved for truly high-risk patients rather than applied universally to all ACS cases.

The variation in complication types and timing across ACS subtypes highlights the need for a more individualized management approach to optimize resource use and outcomes. Current guidelines advocate for uniform admission strategies for AMI patients [159], but our findings question their effectiveness. Few NSTEMI patients developed complications, typically after 24 hours, challenging the recommendation for routine short-term (up to 24h) monitoring. Given the low complication rates in

NSTE-ACS patients, universal CCU/ICU admission may not be the most efficient approach. Prioritizing high-risk patients could help alleviate CCU overcrowding.

More than half of ACS patients with complications were over 80 years old, and most deaths occurred in this group. Advanced age is a known risk factor for increased mortality in ACS [160]. **Study IV** showed that approximately 64% of elderly patients (aged 75 and above) had a signed DNR order, suggesting that many in the complication group had a limited life expectancy. In these cases, telemetry monitoring is not indicated, and less intensive approach may be more appropriate. Frailty and comorbidities significantly impact outcomes in the elderly and are key considerations in treatment decisions [161]. However, there remains no clear consensus on whether invasive treatment consistently improves outcomes in this population. Recent studies argue that invasive approach in frail elderly doesn't improve clinical outcomes and advise on a more individualized treatment plan for these patients [18, 162]. Based on our results, individualized plans for elderly ACS patients seem reasonable, without routine CCU/ICU admissions and coronary interventions.

In our study population, just over half of ACS patients underwent revascularization within 30 days of admission. More than 20% of the patients underwent coronary angiography but did not receive PCI due to factors like complex anatomy, insignificant stenosis, or significant comorbidities. Despite this, complication rates remained low, suggesting that a more conservative approach to ACS management may be appropriate in selected cases.

In **Study III**, approximately one-third of patients with complications already had them at admission, yet 12 patients (7.9%) were not admitted to the CCU/ICU, indicating that factors beyond complication risk influence admission decisions.

Our findings highlight that, in real-world clinical practice, complications in ACS are less frequent than expected and patient selection for CCU/ICU admission is not strictly based on guideline recommendations but involves more nuanced decision-making. This underscores the need for improved risk stratification, potentially supported by a decision-assist algorithm, to enhance consistency and optimize patient care. Developing a simple risk score that can be quickly calculated in the ED to identify low-risk patients could benefit both ED physicians and cardiologists.

In **study IV,** we developed a new risk prediction algorithm using logistic regression analysis, incorporating age, vital signs, basic blood tests, and ECG findings. This model outperformed six published scores, demonstrating excellent predictive ability. Many of its key predictors, such as blood pressure, heart rate, Killip class, STEMI, and larger infarction (presented by high troponin levels), are well-established risk factors [135, 163-166]. Notably, lactate, typically associated with impaired circulation and infections [167-170], emerged as a predictor of complications even in initially stable ACS patients – a novel finding that suggests lactate measurement could enhance early risk assessment in ED ACS patients.

Although most risk scores assess similar variables, none of the previously published scores performed well in predicting 30-day complications in ACS patients. This is not entirely surprising, as most of these scores were not specifically designed to predict the broad range of complications we examined in our population. Additionally, some of these scores were created for specific patient populations. For instance, the HEART score is intended to predict 6-week risk of AMI and mortality in unselected chest pain patients in the ED, while the ACTION ICU score is designed to predict complications requiring ICU admission in NSTEMI patients, and the CHA2DS2-VASc score is primarily used to assess the need for anticoagulation in patients with newly diagnosed atrial fibrillation. Our new model demonstrated the highest specificity, accurately identifying 49% of ACS patients as low risk at a fixed sensitivity of 90%. This tool could help ED physicians reduce unnecessary CCU/ICU admissions, allowing cardiologists to focus resources on truly high-risk patients. Further research is needed to refine risk stratification and optimize the management of ACS patients in the ED, ensuring that high-risk individuals receive appropriate intensive care while avoiding overcrowding the CCU.

Limitations

Several methodological limitations should be considered when interpreting the results of this thesis.

The choice of study design has its limitations. In **all four studies** we analysed patient registry data – a widely used approach in epidemiological research [171]. Patient registries enable the prospective collection of observational and clinical data, allowing for large-scale analyses, diverse populations, and efficient data collection at a lower cost than randomized controlled trials [172]. Moreover, registries provide real-world data and include complete study populations, reducing the risk of selection bias. However, registry data often suffer from variable quality due to missing or incomplete information, administrative errors, discrepancies between different registries, lack of active follow-up, and limited clinical detail.

To enhance data accuracy, in **study III and IV** we performed a medical record review (MRR), also known as a retrospective chart review. MRR studies, which use pre-recorded patient data, are commonly employed in emergency medicine research, accounting for approximately 25% of recent publications in the field [173]. One advantage of MRR is that data collection has already occurred, making it a relatively quick method compared to prospective studies. In some cases, the quality of MRR data is comparable to prospectively collected data. For instance, ECG findings indicative of AMI remain unchanged whether documented retrospectively or recorded in real time. Additionally, retrospective data collection may provide a more accurate representation of clinical practice, as prospective studies risk introducing observation bias, where patient management may be altered simply

because it is being studied. For these reasons, a registry study combined with a chart review was deemed the most appropriate design for our research questions.

Despite these advantages, MRR studies have known limitations, particularly regarding retrospective and source-dependent data collection. Medical records primarily serve as clinical documentation rather than research tools, increasing the risk of missing data and misinterpretation of findings. Missing data can introduce nonresponse bias if the omitted cases differ significantly from the rest of the study population. This issue is particularly relevant to chart reviews, where clinically non-essential information may be omitted, or certain records may be inaccessible.

By comparing the findings from **Study III** and **IV**, we recognized the limitations of our registry data. Future studies addressing similar research questions should incorporate medical record reviews more frequently to enhance data quality and ensure the accuracy of results and conclusions.

Future directions

Despite extensive research on ED chest pain management and numerous risk stratification algorithms for identifying low-risk patients eligible for early discharge, the optimal approach for intermediate-risk patients remains unclear. Further studies are needed to refine their management, as current clinical guidelines often lead to unnecessary testing and admissions, highlighting the uncertainty surrounding the best course of action.

An ongoing Swedish project is addressing this gap by studying intermediate-risk chest pain patients (HEART score >3) without myocardial infarction [174]. This multicenter study is evaluating early coronary computed tomography angiography (CCTA) as a non-invasive alternative to traditional testing. If widely implemented, CCTA could offer a rapid, efficient assessment option directly from the ED, provided the necessary hospital infrastructure is in place.

Age-related differences in ACS complications suggest that more targeted research within specific age groups could provide valuable insights into their unique risk profiles and management needs.

The development of a new risk score based on our logistic regression model to predict 30-day complications in ED-diagnosed ACS patients is currently underway and will soon be presented. Multicenter observational studies are essential for validation, and if successful, a randomized controlled trial assessing the safety of step-down unit admissions for low-risk ACS patients based on this model would be highly valuable.

If step-down unit strategy proves to be safe, it may prompt a broader discussion about whether ambulatory coronary angiography for select ACS patients – such as those with minimal MI or UA receiving appropriate medical therapy – is merely an ambitious vision or an emerging clinical reality.

With advancements in artificial intelligence and machine learning, integrating these technologies with clinical evaluations for ED chest pain risk assessment could enhance accuracy and improve patient outcomes in the future.

"It always seems impossible until it’s done."
− *Nelson Mandela*

Conclusion

Efficient diagnostics and accurate risk stratification for ED patients with acute chest pain are critical, yet there remains significant potential for improvement in their management. This thesis primarily addresses two key challenges in the ED: accurately identifying low-risk chest pain patients eligible for rapid and safe rule-out and recognizing high-risk patients who require advanced care.

Our findings indicate that patients presenting with ongoing chest pain in the ED tend to be younger, healthier, and at a lower risk for ACS and MACE within 30 days. Additionally, the diagnostic performance of ECG during active chest pain is not superior to its interpretation after symptom resolution.

The use of risk stratification tools such as HEART and EDACS-ADP, in combination with the validated 0-hour/1-hour high-sensitivity troponin algorithm, enables emergency physicians to safely discharge a substantial proportion of ED chest pain patients.

Among ACS patients diagnosed in the ED, serious complications occurred in only 6-7% of cases, with more than a third of these complications already evident at the time of presentation. Furthermore, four out of every ten ACS patients with complications were not admitted to the CCU/ICU, and nearly half were not managed invasively, contrary to current guideline recommendations.

In an era of limited resources and hospital bed shortages, accurate patient selection and precise risk assessment are increasingly important. Our study demonstrated that a logistic regression model incorporating simple variables available in the ED, such as age, vital signs, ECG findings, and basic blood tests (including lactate and troponin at arrival), was excellent in predicting complications and outperformed six established risk scores.

The management of acute coronary syndromes in the ED is a dynamic and evolving field. Timely assessment, risk stratification, and initiation of appropriate therapies are paramount to improving patient outcomes. While significant progress has been made, continued research is essential to address existing challenges and enhance the quality of care for patients with ACS.

Summary

This thesis focuses on diagnosis and risk assessment of chest pain patients coming to the emergency department (ED). Every day, many people show up at the ED with chest pain, often worried they might be having a heart attack. However, only about one in ten of these patients are actually diagnosed with acute coronary syndrome (ACS), which includes conditions like unstable angina (threatening heart attack) and heart attack. Sometimes it takes a lot of time to confidently rule out a heart attack. Right now, diagnosing ACS in the ED is not as accurate as it could be, leading to many unnecessary tests. About three-quarters of patients admitted with suspected ACS end up being fine, which wastes resources and does not offer the best care for our patients. When the ED gets crowded, it can be hard to give everyone the attention they need in a timely manner. This thesis focuses on creating tools to quickly and accurately identify patients having a heart attack, so people who are not at risk can safely be sent home without the long wait. The thesis also looks at factors that can help predict which heart attack patients might get really sick and need advanced treatment.

When it comes to diagnosing chest pain, three things are key: the patient's history (what they tell us), the ECG (a short recording of the heart's electrical activity that could show signs of heart attack), and the troponin level (a blood test showing damage to the heart muscle).

The patient's history is critical, but it is also one of the trickiest parts because it is based on what the patient shares, and how the doctor interprets it. This can be subjective, depending on the doctor's experience. To help with the clinical decisions, we use tools called risk scores, which help standardize the process and can make it more reliable. These tools ask important yes/no questions, looking at details from the patient, the ECG, and the initial troponin test. Based on the answers, a score is given that helps predict the likelihood of a heart attack.

As for the ECG, doctors often say, "If the patient has chest pain again, take a new ECG!" The idea is that if the pain is still there, the ECG will clearly show if a heart attack is happening. However, we do not know if this is true for all chest pain patients in the ED . In our first study, we looked at all chest pain patients in the ED and their ECGs and found that patients with ongoing chest pain were younger, healthier, and had half the rate of ACS compared to patients whose pain had already gone away. We could not prove that taking the ECG under active chest pain was

better. Now, we recommend: "Take an ECG, and if it is normal or you cannot decide, move on to the troponin test."

In the past, there used to be a routine that a second troponin test should be done at least 3 hours after the first one to check if the patient has a heart attack, which meant patients had to stay in the ED for a very long time. Now, we have shortened that wait to just 1 hour after the first test, which allows us to quickly identify the sick ones. In our second study, we looked at whether combining two well-known risk scores with the troponin values from the first test and one hour later could help us determine which patients could safely go home without missing any heart attacks. We found that this combination can safely send home almost half of chest pain patients within just one hour of arriving at the ED, making the process faster and helping reduce the pressure on the department.

Patients suspected of having ACS are often connected to heart monitors and admitted to the cardiac care unit (CCU) – a ward in the hospital where the medical staff monitors the heart patients 24/7. This is mostly done to keep a close eye on potential life-threatening complications like dangerous arrhythmias (when the heart beats like crazy), which can lead to cardiac arrest (when the heart stops beating) and death. While CCU admission ensures patients are closely monitored and reduces the risk of missing any serious issues, there are limited CCU beds, and often there are not enough beds for all patients with suspected ACS. Not only is the diagnosis of ACS less common than initially suspected, but many ACS patients also never experience complications. In our studies III and IV, we aimed to understand which patients are more likely to experience complications and identify key factors that can help predict who is at higher risk. In Study III, we found that only 6 out of every 100 ACS patients have complications, and these patients tend to be older, sicker, and often treated only with medications in general medical wards without undergoing coronary angiography (a test which allows the doctor to see inside the blood vessels of the heart). In Study IV, we developed a new risk prediction model using simple factors like vital signs, blood tests, and ECG results, which are already available in the ED. We demonstrated that our model was better at predicting complications than six widely used algorithms.

Improving how we assess risk could help us take better care of chest pain patients by making better use of CCU beds, monitoring, and hospital resources around the world. It could also reduce unnecessary tests and admissions for low-risk patients. The findings from this research could lead to better care for all chest pain patients in the emergency department.

Populärvetenskaplig sammanfattning

Den här avhandlingen handlar om hur vi kan diagnostisera och bedöma risker hos patienter med bröstsmärta på akutmottagningen. Varje dag kommer många personer med bröstsmärta till akuten och är oroliga över att de ska ha fått en hjärtinfarkt. Emellertid är det bara ungefär en av tio som får diagnosen akut koronart syndrom (AKS), som inkluderar både instabil angina (hotande hjärtinfarkt) och akut hjärtinfarkt. Problemet idag är att det tar tid att utesluta hjärtinfarkt med säkerhet. Den initiala diagnostiken av AKS är idag inte av optimal kvalitet. Patienterna måste genomgå många långdragna utredningar, och cirka tre av fyra av de som läggs in på sjukhus för misstänkt AKS visar sig inte ha det. Det här belastar sjukvården och innebär låg kvalitet på vården för patienterna. Ibland kommer många patienter samtidigt till akuten, vilket gör att vi inte alltid hinner ge alla snabb och bra vård. Därför vill vi skapa ett verktyg som hjälper oss att snabbt och säkert identifiera de patienter som verkligen har en hjärtinfarkt, så att de som är hjärtfriska kan snabbt och tryggt skickas hem från akuten. Vi vill också hitta faktorer som kan hjälpa till att förutsäga vilka hjärtinfarktpatienter som kan bli allvarligt sjuka och behöva avancerad vård.

Tre faktorer hjälper oss att bedöma patienter med bröstsmärta: patientens anamnes (vad patienten berättar), EKG-et (några sekunders inspelning av hjärtats elektriska aktivitet, som visar om hjärtmuskeln är skadad) och troponinvärdet (ett blodprov specifikt för hjärtat som visar hjärtmuskelskada).

Anamnesen, dvs vad patienten berättar om sina symtom och tidigare sjukdomar, är en viktig del av bedömningen, men läkarens tolkning kan vara väldigt subjektiv och beror mycket på läkarens erfarenhet. Därför finns det några riskbedömningsverktyg, så kallade risk scores, som gör det lättare att standardisera bedömningen. De baseras på ja/nej-frågor om patientens historia, EKG och det första troponinvärdet. Beroende på svaren får patienten poäng och vi kan förutsäga om risken för hjärtinfarkt är hög.

När det gäller EKG, brukar vi läkare säga: ”Om patienten får ont i bröstet igen, ta ett nytt EKG!” Man tror att EKG under pågående bröstsmärta bättre visar om det handlar om hjärtinfarkt. Det är en väldigt gammal tradition, men vi vet inte om det stämmer för alla patienter på akuten. I vår första studie tittade vi på alla bröstsmärta patienter på akuten och deras EKG och vi kunde visa att patienter med pågående bröstsmärta på akuten var yngre och friskare och oftare inte hade AKS än de vars

smärta hade avklingat. Vi försökte, men kunde inte bevisa att den gamla rutinen med EKG under pågående bröstsmärta förbättrade vårt arbete. Därför säger vi nu istället: ”Ta ett EKG, och om det är normalt eller du kan inte bestämma något konkret, gå vidare med troponinprover.”

Tidigare var rutinen att ett nytt troponinprov skulle tas minst 3 timmar efter det första för att se om patienten har en hjärtinfarkt, vilket innebar att patienterna fick vänta länge på akuten. Nu har vi kortat ner tiden till bara 1 timme, vilket gör att vi snabbare kan upptäcka dem som faktiskt har en hjärtinfarkt. I vår andra studie tittade vi på möjligheten att kombinera två kända risk scores med troponinvärden vid ankomst och efter 1 timme för att bedöma vilka patienter som kan gå hem direkt utan att missa någon hjärtinfarkt. Våra resultat var lovande och visade att denna kombination kan tryggt skicka hem nästan hälften av bröstsmärta patienterna redan efter en timme på akuten, vilket skulle göra vårt arbete mer effektivt och kan minska belastningen på akuten.

Patienterna med misstänkt AKS läggs ofta in på hjärtintensiven (HIA) – en avdelning där man är uppkopplad på monitor och övervakas hela tiden för att se om hjärtat slår som det ska, eftersom vi är oroliga att de kan få allvarliga komplikationer, som livshotande störningar i hjärtats elektriska aktivitet som kan leda till hjärtstopp och död. Att vara på HIA innebär att man är under noggrann övervakning och minskar riskerna att missa någon komplikation, men platser på HIA är begränsade och räcker inte till för alla. Många patienter med AKS får inga komplikationer alls.

I studierna III och IV försökte vi kartlägga vilka patienter som faktiskt får komplikationer och vilka de vanligaste komplikationerna är. Vi undersökte även viktiga faktorer som kan hjälpa oss att förutsäga vilka patienter som har hög risk för allvarliga komplikationer. I Studie III visade vi att endast 6 av 100 patienter med AKS får komplikationer, och dessa patienter är ofta äldre och sjukare. En del av dessa patienter behandlas enbart med mediciner på vanliga avdelningar och genomgår inte kranskärlsröntgen. I studie IV presenterade vi en ny metod för att förutsäga komplikationer, där vi använder enkla faktorer som vitala parametrar, blodprover och EKG, som redan är kända när patienten kommer till akuten. Vi visade att vår nya metod var bättre på att förutsäga komplikationer än sex tidigare publicerade risk scores.

En förbättrad riskbedömning skulle göra det möjligt att använda sjukhusresurser som övervakning och sängplatser mer effektivt och minska onödiga inläggningar och tester för patienter med låg risk. Fynden som beskrivs i denna avhandling kan därför leda till bättre vård för alla patienter med bröstsmärtor på akuten.

AI statement

OpenAI’s ChatGPT-4 was used in this thesis exclusively for English language review, focusing solely on grammar, syntax, and language clarity. The AI tool played no role in any other aspect of the dissertation's creation. After using ChatGPT-4, the author carefully reviewed and edited the content to ensure accuracy, coherence, and overall quality.

My journey

The heart has always been an important part of my life. As a child, whenever I played doctor, my toys inevitably ended up with heart problems. When I was a teenager, I would always buy the heart-shaped necklaces. In medical school, the heart was the most interesting organ in anatomy class. My first job was at the National Cardiology Hospital in Sofia. Even today, I find heart patients the most intriguing, and myocardial infarction remains one of my favourite conditions to study. It felt natural that my research would also focus on the heart.

I enjoy working with chest pain patients. Meeting these patients presents an exciting challenge – figuring out the underlying problem is like solving a puzzle. I have cared for all kinds of patients, from those experiencing anxiety to critically ill individuals in cardiogenic shock due to a massive myocardial infarction, where every second counts. The ED is a unique place, bringing together people with vastly different needs. A big part of my job is to prioritize correctly, ensuring that each patient receives the right tests and treatment.

One of the biggest challenges in the ED today is overcrowding. Patients sometimes wait for hours to see a doctor, get an X-ray, or be admitted to a ward. For someone with a suspected infarction, these delays can be life-threatening – time can literally mean the difference between life and death. We are constantly discussing how to improve. After working closely with chest pain patients and seeing the daily struggles first-hand, I felt compelled to investigate the problem further and develop something meaningful that could improve both our workflow and patient care.

I met my supervisor, Ulf Ekelund, a few weeks after I started working in the ED in Lund during the summer of 2015. I knew he had a big research group focused on ACS and chest pain, and I felt that I had to reach out. I still remember the day I asked him if I could get involved in a project – he looked at me suspiciously but quickly agreed to give it a try. At the time, I was new to Sweden, learning the language, adjusting to a different healthcare system, and just starting my career while aiming for a residency spot. Ulf and I decided it would be best to start small. And now, nearly 10 years later, I'm here writing this thesis. It has been an incredible journey – full of ups and downs, countless hours wrestling with statistical software, and endless presentation-practice sessions in front of the mirror. But I made it through.

At first, I was eager to dive straight into the data. But I quickly ran into my first obstacle – I had no idea where to start. I spent hours watching YouTube tutorials and asking my friends for help. I remember chasing my co-supervisor, Ardavan, down the hallway, begging him to show me how to run a Chi-square test in SPSS. Despite the steep learning curve, I managed to write an abstract and present it at the annual SWEdish Emergency medicine Talks (SWEETs) conference in Stockholm in 2016. Looking back, I do not think I had any idea of what I was talking about at the time. Balancing night shifts and clinical rotations slowed down my first publication, but eventually, the paper was published. Just as it was going to print, discussions about an official PhD position began. And then it was 11th of January 2020 when the email came that I was finally accepted to the PhD program and my world changed.

Over the years, I have had the privilege of meeting brilliant researchers from around the world, reading hundreds of fascinating papers, and attending numerous conferences. Ulf often jokes that I am the "conference lady" because I try to attend as many as possible. But I genuinely believe these experiences have provided me with invaluable knowledge and inspiration.

Public speaking has always been a challenge for me. I vividly remember my first international presentation at the EUSEM conference in Lisbon in 2021. I prepared my talk a month in advance and rehearsed it at home. Poor Henrik had to listen to me every single day. On the day of the presentation, I walked 10 km just to calm my nerves. Sitting in the lecture hall moments before my turn, I checked my watch and saw my heart rate skyrocketing – during the talk, it shot up to 150 beats per minute (talk about prio1-criteria here!). But once it was over, the first thing I said to Ulf was, "When can I do it again?!" That moment gave me the confidence to push forward. Since then, I've presented at multiple conferences, and my preparation time has decreased significantly. For my latest presentation, I finished my slides just the day before and practiced for only a few hours – I call this improvement.

Over the past few months, I dedicated myself to preparing this thesis. Despite the sleepless nights and weary eyes, I could feel myself growing with every word I wrote. I am grateful for the opportunity to present my work and sincerely hope it sparks the same questions that drove me at the beginning. And perhaps, one day, it will contribute to meaningful change for the better.

In my future career, I hope to continue working with chest pain patients while expanding my research projects, perhaps even establishing my own research group one day. I aspire to inspire others to embark on the journey of research, exploring a world of limitless knowledge and opportunities for innovation. Just as Ulf has guided me throughout the years, I hope to mentor and support others in their pursuit of discovery and progress.

Acknowledgements

This thesis would not have been possible without the unwavering support and help I have received over the years from many important people in my life. I would like to express my deepest appreciation to the following:

First and foremost, my main supervisor, **Ulf Ekelund**. Words cannot fully express how grateful I am for your guidance throughout these years. Your patience, humility, and exceptional expertise have had a profound impact on my journey. I truly could not have done this without you. You have been an incredible mentor – always teaching, encouraging, and challenging me to grow. Your generosity in sharing your knowledge has meant the world to me, and I am beyond grateful to have had you by my side. I will never stop learning from you. I am truly honoured to have worked with you and I look forward to more exciting projects with you in the future.

To my co-supervisors, **Arash Mokhtari**, **Ardavan Khoshnood** and **Jakob Lundager Forberg** – I am deeply grateful for your guidance, expertise, and support. **Arash**, your brilliant mind and insightful ideas have been invaluable, and whenever I need cardiological advice, you will always be the first person I call. **Ardavan**, thank you for your encouragement, for teaching me the chi-square test and how to navigate Endnote, and for all the laughter through the years. You are a highly valued friend. **Jakob**, our collaboration has been enriching and inspiring, and your thoughtful advice has been truly indispensable. Working with each of you has been an absolute privilege.

To our research nurse **Mahin Akbarzadeh** - for all your hard work and essential help with data collection and distribution, and for the moral support in Barcelona.

Malin Strömfors, Alicia Trägårdh, Mahin Akbarzadeh and **David Sell** thank you for your help with the chart reviews. I would still be reading journals if it wasn't for you.

To my dear friend, college, and travel companion **Alexandra Ringqvist**. We may have met just a few years ago, but it feels like a lifetime. Thank you for all the support, for listening to my presentations wherever we were, and for all your ideas and advice on how I could grow and improve. Your friendship has been a true gift, bringing countless moments of joy and laughter. I am so grateful to have you by my side.

To my colleges and fellow PhD students, **Eric Dryver** and **Pontus Olsson de Capretz**, I am grateful for all the stimulating scientific discussions and ideas you have shared. And thank you Eric for all help to organise this dissertation. Without your checklist, I would probably have missed half of the deadlines.

To statisticians, **Jenny Sandgren** and **Helene Jacobsson**, thank you for your outstanding statistical support. I am deeply appreciative of how patiently you answered all my questions, no matter how trivial they seemed.

Ardavan Khoshnood, Helen Olofsson and **Johanna Holme**, I appreciate you taking the time to read through my thesis and provide fantastic comments and suggestions for improvement.

To **Line Hård af Segerstad** for standing by my side in Lisbon during my first international presentation and one of my most anxiety-filled moments. They say the first is always the hardest, and you were there for me. You might not even remember it, but I will never forget it. Sometimes, the smallest gestures leave the deepest impact, and yours meant the world to me.

A heartfelt thanks to **Nicolina Carlsson, Emelie Lincoln and all my colleges** from the ED in Lund for your support and all that you have taught me over the past 10 years. You made me feel like a part of the community and I would have never ended up where I am today without you.

I would like to thank the current heads of the Department of Emergency Medicine at Skåne University Hospital in Lund, **Jan Gebel** and **Anna Gislén,** for the support and freedom they have given me to pursue my projects. Special thanks to the former head of the Emergency Department, **Ulrika Pahlm** – when I first shared my idea of pursuing a PhD, you believed in me without hesitation. Your unwavering belief gave me the confidence to take the leap, and I will always be grateful for that conversation.

A huge thank you to **Susanne Vesterlund** for your standing support and for always sorting out the scheduling chaos I created over the years. I appreciate your help immensely!

Thanks to my mother **Valentina Ribnishka** for giving me my life and guiding me through it, for believing in me and helping me during the difficult moments. Only you know how much this journey has cost me, but I am here now, and I couldn't be happier. / Благодаря на моята майка, Валентина Рибнишка, че ми даде живот и ме напътства през него, че вярваше в мен и ми помагаше в трудните моменти. Само ти знаеш колко много ми е струвало това пътуване, но сега съм тук и не бих могла да бъда по-щастлива. Обичам те!

Special thanks to my grandparents **Tsvetanka and Metodi Ribnishki** for taking care of me when I was a child and guiding me through my first years in school. You taught me how to study and you laid the foundation for the road that led me to this

day today. / Специални благодарности на моите баба и дядо Цветанка и Методи Рибнишки, че се грижеха за мен, когато бях дете и ме напътстваха през първите ми години в училище. Вие ми показахте как да уча и зададохте основите на пътя, който ме доведе до този ден днес. **Баба Цвети и дядо Методи**, обичам ви безкрайно много!

Thank you to my beautiful daughters **Vicky and Isabelle** for giving my life true meaning. Thank you for all the hugs when I was stressed, for the coffee in bed in the morning when I was tired and didn't want to get up, and for not hating me for all the time I spent at work and in front of the computer. I will always love you!

And last but also most importantly, to my husband **Henrik Nilsson**, thank you for always being there for me. From the moment we met, you held my hand and never let it go. Thank you for giving me the freedom to grow and bloom while standing beside me, supporting me every step of the way. Thank you for the most wonderful family I could ever imagine. This graduation would mean nothing without you. I love you!

Supplement

Supplement Table 1 HEART Score

HEART Score		
History	Highly suspicious	2
	Moderately suspicious	1
	Slightly or nonsuspicious	0
ECG	Acute ischemia	2
	LBBB, RBBB, LVH, PM	1
	No signs of acute ischemia	0
Age	≥ 65 years	2
	45 – 65 years	1
	≤ 45 years	0
Risk factors	≥ 3 risk factors, or history of atherosclerotic disease	2
	1 or 2 risk factors	1
	No known risk factors	0
Troponin T	> 42 ng/L	2
	15-42 ng/L	1
	≤ 14 ng/L	0
RULE-OUT REQUIRES:	**HEART Score ≤3 points**	

*Risk factors = family history of premature CAD, hypercholesterolemia, diabetes mellitus, hypertension and current or recent (<30 days) smoker

Supplement Table 2 HEART 0-hour/1-hour Pathway

HEART Score		
History	Highly suspicious	2
	Moderately suspicious	1
	Slightly or nonsuspicious	0
ECG	Acute ischemia	2
	LBBB, RBBB, LVH, PM	1
	No signs of acute ischemia	0
Age	≥ 65 years	2
	45 – 65 years	1
	≤ 45 years	0
Risk factors*	≥ 3 risk factors, or history of atherosclerotic disease	2
	1 or 2 risk factors	1
	No known risk factors	0
Troponin T	> 42 ng/L	2
	15-42 ng/L	1
	≤ 14 ng/L	0
RULE-OUT REQUIRES:	**HEART Score ≤3 points** ***And*** **0h hs-cTnT < 5 ng/L,** ***Or*** **0h hs-cTnT < 12 ng/L with a 1h increase < 3 ng/ L**	

*Risk factors = family history of premature CAD, hypercholesterolemia, diabetes mellitus, hypertension and current or recent (<30 days) smoker

Supplement Table 3 EDACS 0-hour/1-hour ADP

EDAC Score	
Male sex	+6
Age	
18-45	+2
46-50	+4
51-55	+6
56-60	+8
61-65	+10
66-70	+12
71-75	+14
76-80	+16
81-86	+18
86+	+20
Aged 18-50 years and either	
known CAD or ≥ 3 risk facrtors*	+4
Symptoms and signs	
Diaphoresis	+3
Radiates to arm or shoulder	+5
Pain worsened with inspiration	-4
Pain is reproduced by palpation	-6
RULE-OUT REQUIRES:	**EDACS < 16 points** **AND** **No sign of acute ischemia on the ECG** **AND** **Hs-cTnT ≤ 14 ng/L at 0 h and 1 h**

*CAD defined as previous AMI, CABG or PCI; risk factors = family history of premature CAD, hypercholesterolemia, diabetes mellitus, hypertension and current smoker

Supplement Table 4 ICD-10 codes used to define complications in study III and IV

International Classification of Diseases, 10th Revision (ICD-10) codes	
I46.9	Cardiac arrest, unspecified
I46.0	Cardiac arrest with successful CPR
I46.1	Sudden cardiac death
R96.0	Instant death
R96.1	Death within 24 hours of onset of symptoms that cannot be explained in any other way
R98; R98.9	Unwitnessed death
R99; R99.9	Other incompletely defined and unspecified causes of death
R57.0	Cardiogenic shock
I47; I47.2	Paroxysmal ventricular tachycardia
I49.0	Ventricular fibrillation and ventricular flutter
I44.1; I44.2	Atrioventricular block, total
I44.1B	AV block grade II/Möbitz type II
I44.1	Atrioventricular block, second degree
J81.9	Pulmonary edema
I23.0	Hemopericardium as a complication of acute myocardial infarction
I23.5	Rupture of papillary muscle as a complication of acute myocardial infarction
I23.1	Atrial septal defect as a complication of acute myocardial infarction
I23.2	Ventricular septal defect as a complication of acute myocardial infarction
I23.3	Rupture of the heart wall without hemopericardium as a complication of acute myocardial infarction
I23.4	Rupture of the chordae tendineae as a complication of acute myocardial infarction
I23.6	Thrombosis in the atrium, auricle or chamber as a complication of an acute heart attack
I23.8	Other specified complications of acute myocardial infarction

Supplement Table 5 Swedish Intervention (KVÅ) codes used to define complications in study III and IV

Swedish healthcare intervention codes (KVÅ)	
DF005	Insertion of intra-aortic balloon pump
DF012	Chest compressions
DF013	External, transthoracic pacing
DF017	Mechanical chest compression, no manuell compressions (LUCAS)
DF025	Electrocardioversion/defibrillation of ventricular arrhythmia
DF028	Cardio-pulmonary resuscitation (CPR)
FNA, FNB, FNC, FND, FNE, FNF, FNG	Revascularisation (PCI, CABG)
FPE00	Insertion of transvenous pacemaker with ventricular electrode
FPE10	Insertion of transvenous pacemaker with atrial electrode
FPE20	Insertion of transvenous pacemaker with atrial and ventricular electrode
FPE26	Insertion of transvenous pacemaker with biventricular electrode
TFP00	Temporary use of transvenous or epicardial pacemaker
ZXG40	Insertion of a transvenous pacemaker
DG017 & DG018	Tracheal intubation
DG001	Initiation of emergency treatment with airway counterpressure CPAP or BilevelPAP
FEA00	Closed external drainage of the pericardium
FEB10	Decompression and drainage of the pericardium

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About the author

TSVETELINA NILSSON is a dedicated clinician, an emerging researcher, and a travel enthusiast. Born and raised in Sofia, Bulgaria, she earned her medical degree from the Medical University of Sofia. Her heart led her to Sweden, where she built a wonderful family and pursued her career in Emergency Medicine. She completed her residency at Skåne University Hospital in Lund and now works as an attending physician at the Department of Emergency Medicine in Lund, Sweden.

Tsvetelina's primary interests include cardiology, global cultures and exploring the world. Throughout her PhD journey, she has traveled to over 15 countries across four continents – many of these trips driven by her research and professional pursuits. According to Tsvetelina, the best way to do research is in the shade of a palm tree, with the sound of the ocean in the background and a reliable internet connection.

Printed by Media-Tryck, Lund 2025 NORDIC SWAN ECOLABEL 3041 0903

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FACULTY OF MEDICINE

Department of Clinical Sciences

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2025:45
ISBN 978-91-8021-698-2
ISSN 1652-8220