Development of a Prehospital Decision Support Tool

Optimisation of the prehospital triage of patients with chest pain

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“Your eyes can deceive you. Don’t trust them.”

Obi-Wan Kenobi, Jedi master

To Emma, Oliver and Stina

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ABSTRACT

Background: Chest pain is one of the most common symptoms in patients contacting the emergency medical services (EMS). This large group consists of patients with disorders of various causes and severity. Prehospital risk stratification of these patients is warranted in order to identify which patients are in need of prompt advanced hospital care and which could be cared for by for example primary healthcare. Previous research has called for a tool to support EMS personnel in their assessments and decisions when caring for this group of patients.

Aim: To develop a decision support tool for prehospital risk stratification of patients with chest pain.

Methods: Several different methods have been used in this thesis. Paper I is a systematic literature review with semi-quantitative data analysis. It identifies factors associated with a high-risk condition in prehospital patients with chest pain. In Paper II, a content analysis of emergency medical calls is conducted. It explores which symptoms patients with chest pain due to a high-risk condition experience and how these symptoms are described. Paper III uses a quantitative design analysing prospectively collected data. It examines possible associations between prehospitally available variables and outcome in terms of the occurrence of a high- or low-risk condition. In Paper IV, the data collected in Paper III were analysed further. Models were constructed to predict whether the patient's chest pain is due to a low- or a high-risk condition.

Results: Paper I establishes that previous prehospital research is sparse on outcome predictors in EMS patients with chest pain. The level of evidence varies for different predictors. Age, sex, ST-deviation on ECG and vital signs reflecting a compromised circulation are the predictors with the highest level of evidence. In Paper II it was found that patients with chest pain due to high-risk conditions experience a wide range of symptoms which are described in many different ways. Paper III concludes that about 2/3 of all EMS patients with chest pain have a low-risk condition while 16 % have a high-risk condition. There are numerous variables accessible in the EMS setting that predict either low- or high-risk conditions. Several variables were predictive for both low- and high-risk conditions. ST-deviation on ECG, age and Troponin T (TnT) were the strongest predictors for both low- and high-risk conditions. In Paper IV, a few prediction models were developed. The final combined model using nine different variables to predict both low- and high-risk conditions had an ROC-AUC of 0.79 when predicting high-risk conditions and 0.75 when predicting low-risk conditions.

Conclusions: Prehospital research on predictive variables is sparse when assessing EMS patients with chest pain, and more is warranted. EMS patients are a heterogeneous group experiencing a wide range of symptoms. Most patients have a low-risk condition. Without medical risk, they could be referred to less resource-intensive alternatives than transport by ambulance to the emergency department. A decision support tool guiding the EMS in their risk-stratification of patients with chest pain is achievable, using variables readily accessible in the EMS setting. ST-deviation on ECG, age and TnT remain the strongest predictive variables when trying to identify patients with both low- and high-risk conditions. Symptomology has minor value when discriminating patients with low-risk conditions from those with high-risk conditions.

Keywords: Chest Pain, Emergency Medical Services, Signs and Symptoms, Risk Assessment, Triage, Prediction Models

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SAMMANFATTNING PÅ SVENSKA

Bröstsmärta är en av de vanligaste orsakerna till att man kontaktar ambulanssjukvården. Bröstsmärta kan orsakas av mycket allvarliga tillstånd så som hjärtinfarkt eller brusten kroppspulsåder där ett snabbt omhändertagande är av stor vikt. Många, ur medicinsk synvinkel, mindre allvarliga tillstånd, så som oro, ångest och halsbränna kan också ge upphov till bröstsmärta. I många fall hittar man ingen förklaring till patientens bröstsmärta, som då oftast är godartad. Det är en svår uppgift för ambulanspersonalen att avgöra vilken patient som är allvarligt akut sjuk och vem som har en mindre allvarlig orsak till sin bröstsmärta. För att inte riskera att missa någon patient med akut och allvarlig sjukdom så transporteras dessa patienter oftast med ambulans till en akutmottagning för vidare undersökning. Om det var möjligt för ambulanspersonalen att identifiera vilka patienter som är i behov av snabb transport till sjukhus och vilka som skulle kunna stanna kvar hemma, hänvisas till primärvården eller åka annan transport till akutmottagningen än ambulans så skulle detta möjliggöra ett mer effektivt resursutnyttjande och en mer individanpassad vård.

Genom att identifiera patienter med allvarliga tillstånd redan i ambulansen så skulle dessa snabbt kunna transporteras till ett sjukhus eller en sjukhusavdelning som har rätt resurser för att ge patienten adekvat vård. Genom att hänvisa patienter med mindre allvarliga tillstånd till något annat än ambulanstransport till sjukhus så skulle ambulansen bli frigjord tidigare för nya uppdrag, akutmottagningen skulle få ett minskat patientflöde och patienten skulle kunna undvika lång väntan på akuten bara för att få besked om att ingen allvarlig sjukdom föreligger. Ett beslutstöd som bistår ambulanspersonalen i dess arbete med att riskbedöma patienter med bröstsmärta skulle kunna vara ett sätt att möjliggöra detta. Något sådant beslutstöd utvecklat för ambulansanvändning finns inte idag men har efterlysts i flera tidigare studier. Syftet med denna avhandling är att ta fram ett sådant beslutstöd.

För att besvara detta syfte har fyra delstudier genomförts. Studie I var en systematisk litteraturöversikt där tidigare forskning kring identifiering i ambulans av patienter med bröstsmärta orsakad av en högriskdiagnos sammanställdes, kvalitetsgranskades och rådande evidensläge analyserades. Denna studie visade att lite ambulansforskning är gjord kring identifiering av högriskpatienter med bröstsmärta. Gällande ett mindre antal faktorer som predicerar förekomst av akut och allvarlig sjukdom är evidensläget förhållandevis starkt.

I studie II analyserades larmcentralssamtal gällande patienter med bröstsmärta och akut och allvarlig sjukdom för att undersöka vilka symtom patienterna hade utöver sin bröstsmärta samt hur symtomen beskrevs. I studien framkom att patienter med bröstsmärta orsakad av en akut och allvarlig sjukdom kan uppleva en stor mängd olika symtom som involverar hela kroppen och att dessa symtom beskrivs med stor variation.

I studie III samlades uppgifter om bland annat symtom, sjukdomshistoria, EKG och blodprovssvar in för 2917 patienter med bröstsmärta vårdade av ambulanssjukvården. Dessa patienter följdes sedan upp för att se vilka diagnoser som orsakade bröstsmärtan. Syftet var att undersöka vilka symtom, tidigare sjukdomar etcetera som har ett samband med låg- respektive högriskdiagnos hos patienter med bröstsmärta. Studien visar att i 68 % av fallen var bröstsmärtan orsakad av ett lågrisktillstånd medan 16 % hade en medelriskdiagnos och 16 % hade en högriskdiagnos. Det framkom också att ett stort antal faktorer var möjliga att använda för att förutspå förekomst av låg- respektive högriskdiagnoser.

I studie IV bearbetades data insamlad för studie III ytterligare utifrån insikterna i föregående studier för att se hur aktuella faktorer kunde kombineras och viktas för att åstadkomma en så bra träffsäkerhet som möjligt vid identifiering av patienter med låg- respektive högrisktillstånd. I studien togs det fram ett beslutstöd, som kombinerar uppgifter om patientens kön, ålder, hjärtinfarktsblodprov, förekomst av tidigare njursjukdom eller förmaksflimmer, EKG-förändringar, hur länge patienten har haft bröstsmärta samt om patienten är blek. Genom att kombinera dessa uppgifter kunde beslutstödet med god träffsäkerhet redan i ambulansen kunde förutspå om patientens bröstsmärta var orsakad av låg- eller högriskdiagnos.

Avhandlingens slutsats är att tidigare forskning kring vilka faktorer som kan användas för att identifiera vilka ambulanspatienter med bröstsmärta som har en högriskdiagnos är begränsad. Ambulanspatienter med bröstsmärta är en heterogen grupp med varierande symtom som beskrivs på många olika sätt vilket försvårar ambulanspersonalens riskbedömning. De flesta patienterna har en lågriskdiagnos och skulle kunna hänvisas till ett mindre resurskrävande omhändertagande än ambulanstransport till sjukhus. Framtaget beslutstöd skulle kunna användas för att identifiera vilka patienter som har en låg- respektive högriskdiagnos men behöver testas i ytterligare studier innan kliniskt införande.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals:

I. Wibring K, Herlitz J, Christensson L, Lingman M, Bång A. **Prehospital factors associated with an acute life-threatening condition in non-traumatic chest pain patients - A systematic review**. Int J Cardiol. 2016 Sep 15; 219:373-9. doi: 10.1016/j.ijcard.2016.06.066. Epub 2016 Jun 21.

II. Wibring K, Herlitz J, Lingman M, Bång A. **Symptom description in patients with chest pain—A qualitative analysis of emergency medical calls involving high-risk conditions**. J Clin Nurs. 2019 Aug;28(15-16):2844-2857. doi: 10.1111/jocn.14867. Epub 2019 Apr 21.

III. Wibring K, Lingman M, Herlitz J, Amin S, Bång A. **Prehospital stratification in acute chest pain patient into high risk and low risk by emergency medical service - a prospective cohort study.** BMJ Open. 2021 Apr 15:11(4) doi: 10.1136/bmjopen-2020-044938.

IV. Wibring K, Lingman M, Herlitz J, Ashfaq A, Bång A. **Development of a prehospital prediction model for risk stratification of patients with chest pain.** Manuscript.

CONTENTS

ABBREVIATIONS

ALS	Advanced Life Support
AMI	Acute Myocardial Infarction
BLS	Basic Life Support
CCU	Cardiac Care Unit
COPD	Chronic Obstructive Pulmonary Disease
ECG	Electrocardiogram
ED	Emergency Department
EMD	Emergency Dispatch Centre
EMS	Emergency Medical Services
EMT	Emergency Medical Technician
ESC	European Society of Cardiology
LBBB	Left Bundle Branch Block
MACE	Major Adverse Cardiovascular Events
NRS	Numeric Rating Scale
NSTEMI	Non-ST-elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
RETTS	Rapid Emergency Triage and Treatment System
ROC-AUC	Receiver Operating Characteristics – Area Under Curve
RBBB	Right Bundle Branch Block
SIGN	Scottish Intercollegiate Guidelines Network

STEMI	ST-Elevation Myocardial Infarction
TnI	Troponin I
TnT	TnT
VRS	Verbal Rating Scale

1 INTRODUCTION

Since the introduction of prehospital emergency cardiac care in Northern Ireland during the 1960s, remarkable development has taken place across the globe [1]. As early as 1967, Pantridge et al. [2] showed that cardiac arrest could be treated successfully using a mobile intensive care unit. Transmission of electrocardiogram (ECG) from an ambulance to hospital was first described in 1970 [3]. In 1982, Wennerblom et al. [4] stated that improved prehospital identification of patients with acute myocardial infarction (AMI) was called for. The same year they reported that mortality rates in patients with AMI could be lowered by introducing mobile coronary care units [5].

Castaigne et al.[6] showed in 1989 that prehospital thrombolytic treatment of AMI was both safe and feasible. The following year it was shown that prehospital administration of thrombolytics saved time compared with conventional administration after hospital admission [7]. In time, it was also clarified that prehospital thrombolytic treatment reduced mortality rates [8].

In the 1990s, fast tracks for emergency medical services (EMS) patients with ST-elevation myocardial infarction (STEMI) directly to percutaneous cardiac intervention (PCI) were developed. These fast tracks reduced mortality by cutting time from symptom onset to treatment [9].

Since the introduction of PCI fast tracks, the development of prehospital cardiac care has slowed down. The intention of this thesis is to continue in the spirit of elaboration that has characterised prehospital emergency cardiac care for half a century. By using the patient's symptom of chest pain as a starting point instead of the diagnosis of AMI, this thesis has the ambition to widen the scope and hopefully to contribute to the continued development and improvement of prehospital emergency care.

1.1 PREHOSPITAL EMERGENCY CARE

Prehospital emergency care is a concept comprising the delivery of care to the location of the out-of-hospital patient prior to hospital arrival [10]. It is traditionally focused on patient transportation [11]. The organisation and concept of prehospital emergency care differ between countries. They involve a wide range of professions and a mixture of terminology [11 12].

Ambulance services, ambulance emergency services and emergency medical services (EMS) are all terms used to label prehospital emergency care, and may include the emergency medical dispatch centre (EMD) and in some cases the emergency department (ED). In this thesis, the term EMS will be used, not including the ED.

In Sweden, an ambulance has to be staffed with at least one registered nurse [13]. The ambulance is usually staffed with two persons from the following three personnel categories: emergency medical technician (EMT), registered nurse or prehospital nurse with varying levels of specialist education [14].

In an international perspective, the staffing of the ambulance is much more diverse [11 12 15 16]. In many countries, paramedics form the foundation of the staffing. Paramedic is however not a homogeneous definition [11 15 17]. Education varies and there are different subcategories such as paramedic practitioners etc. [18 19]. The use of physicians in the EMS also varies between countries and organisations [15 20]. Besides this variation of professions among the personnel, numerous umbrella terms are also used, for example ambulance clinician, ambulance personnel, EMS provider, EMS crew, EMS staff and various combinations of these terms. In this thesis, the term EMS personnel is used for the persons staffing the ambulance, regardless of their professional title.

It is not only the education of EMS personnel that varies between different countries and organisations, different EMS organisations also commonly use a range of different EMS resources. The two main concepts are basic life support (BLS) and advanced life support (ALS). BLS is usually staffed by EMTs with limited medical resources. ALS is staffed by personnel with a higher level of education, with access to many different medicines and capability for a wide range of medical interventions [11 20]. Beside BLS and ALS, there are different specialised resources such as single responders, helicopters, trauma units, tactical EMS teams etc. [15 20]. In Sweden, all EMS units are to be considered as ALS.

The aspects described above make it difficult to discuss the EMS as a homogeneous entity. The results of research and reports on prehospital emergency care can therefore be hard to transfer and apply to organisations or countries other than where they were conducted. However, patients have, in many aspects, more in common than the healthcare systems caring for them. Therefore, is it sometimes a better approach to start with the patients rather than focusing on which measures are being applied by the organisation caring for them. Therefore, this thesis starts with the patient's experience of chest pain instead of focusing on specific diagnoses related to this symptom.

1.1.1 THE PATIENT'S PATH THROUGH THE EMS SYSTEM

Almost every EMS mission starts with an accident occurring or a patient experiencing a symptom. Thereafter the patient or someone in the patient's vicinity makes an emergency medical call to the EMD centre at 112/999. At the EMD, the telecommunicator carries out a short medical interview to assess the priority of the EMS mission, resulting in an ambulance being dispatched [21 22].

When EMS personnel arrive at the patient, they start to collect information about the patient's situation. This is done by interviewing the patient and witnesses on site about the patient's experience, what has happened, previous medical history etc. Vital signs and symptoms are measured or observed [23-25]. An ECG can also be registered and, if needed, transmitted to personnel with specialist competence who can assist with interpreting it [26]. In some EMS organisations, prehospital blood sample analyses for cardiac biomarkers have been introduced [27].

This information is thereafter used to assess patient care needs and which measures to apply. A decision is taken whether or not the patient needs transportation by ambulance. The alternatives are remaining at the scene or referral to a primary healthcare centre. If EMS transport is needed, appropriate priority and destination are decided upon [23]. In most cases, the patient is transported to the ED but there are also fast tracks bypassing the ED. An example of such a fast track is to transport patients with STEMI directly to a PCI laboratory [28].

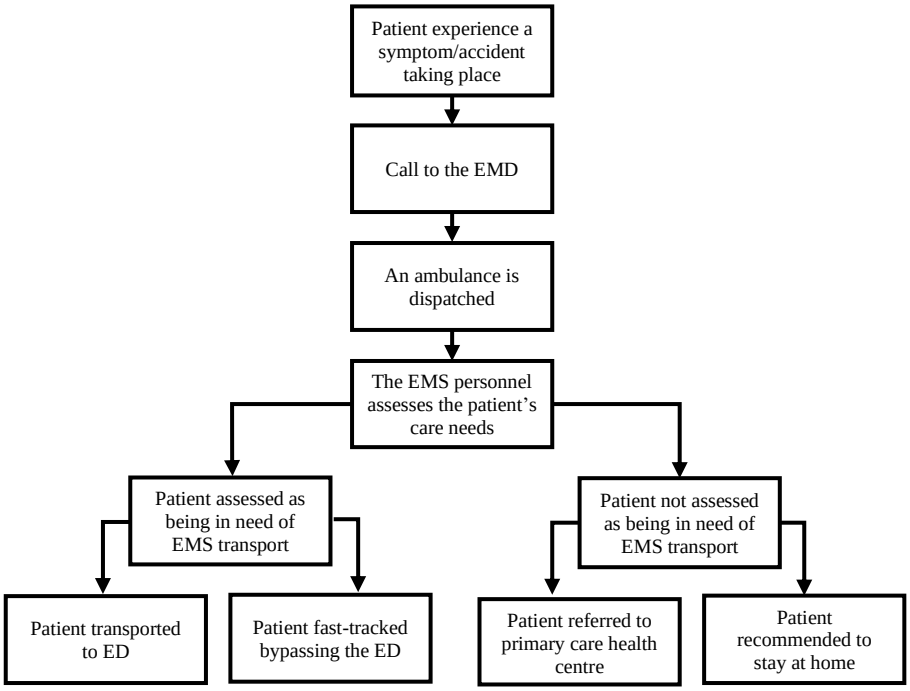

Figure 1. The patient's path through the EMS system

1.2 THE PREHOSPITAL CHEST PAIN PATIENT

Chest pain is one of the most common reasons for contacting the EMS. Patients with chest pain constitute about 10-15 % of all EMS patients [29-31]. EMS missions for patients with chest pain are often dispatched by the EMD with high priority. About 20 % of all EMS missions with the highest priority concern patients with chest pain [32]. Chest pain is thereby the most common complaint among patients assigned the highest priority by the EMD [30].

The proportion of patients with chest pain who arrive at the ED via the EMS has increased [33]. This is in line with international guidelines highlighting the importance of contacting the EMS when experiencing chest pain [34]. Numerous information campaigns have also been conducted to increase public awareness on this subject [35]. However, the increasing number of patients contacting the EMS due to chest pain occurs mainly in the group of patients without AMI [33 36]. In Sweden during the late 1980s, about 28 % of all EMS missions for patients with chest pain concerned patients with AMI [33]. Twenty years later, this proportion was only about 17 % [33]. A few years later the corresponding figure was 12 % [37]. In an international perspective, this figure is reported to be 5-15 % [38 39]. During the last decades there has also been a general increase in EMS utilisation [40-42]. It may be assumed that the increased number of chest pain-related EMS missions is the result of an overall increase in EMS utilisation rather than an increase in EMS contacts due to AMI.

Patients with chest pain are older compared with the typical EMS patient; 80 % are 50 years of age or older [30 37]. The 30-day mortality rate is 2-4 % [31 37 43] which is lower than for non-chest pain patients [31 43]. Comorbidity is very common. A medical history of diabetes mellitus is present in 12-26 % of EMS patients with chest pain. The corresponding figures in previous studies [39 44-47] are 17-70 % for hypertension and 17-30 % for a history of acute coronary syndrome (ACS). The tendency to contact the EMS due to chest pain is independent of sex.

EMS patients with chest pain are older[45 46 48 49] and have a more extensive previous medical history[33 45 48 49] compared with those arriving at the ED by means other than ambulance. EMS patients also differ in terms of symptomology [45 46 49 50], ECG[33 45 49] and vital signs[46 48 50] compared with non-EMS patients in the ED.

1.2.1 THE CHEST PAIN EXPERIENCE

The chest pain experience differs between patients. The mnemonic OPQRST is often used to structure the patients' pain narrative. OPQRST stands for Onset, Palliative/Precipitating factors, Quality, Radiation, Severity, and Time [51].

OPQRST	Example of questions
Onset	How did the pain first occur? Quick or slow debut?
Palliative/Precipitating factors	What is making the pain ease or aggravate?
Quality	Please, describe the quality or character of your pain?
Radiation	Does the pain radiate somewhere?
Severity	How intense is the pain?
Time	When did the pain occur? Is the pain constant or changing over time?

Table 1. Description of OPQRST mnemonic

The onset of pain can be quick, reaching a crescendo in seconds. In other cases, it can be slow, developing over hours. Onset can also be associated with activity, for example eating, moving around or being agitated. Pain can be palliated or aggravated by resting, certain movements, physical contact, taking deep breaths, medication etc. The pain quality can be described as pressuring, stabbing, cramping, burning etc. Pain is often not only located to the chest, but the patient also experiences pain in different parts of the body, such as jaws, arms, back, shoulders etc. The severity of pain can range from very mild to unbearable. Time from onset to medical contact varies between patients. In addition, pain behaviour varies over time in terms of the above-mentioned dimensions. There has been extensive research on trying to describe the pain narrative of patients with chest pain. Most commonly, these studies refer to patients having ACS as the cause of their chest pain [52-61].

Other signs and symptoms are often present along with the chest pain, such as nausea, vomiting, breathlessness, paleness, and clamminess [45 62 63]. Such symptoms are often referred to as associated symptoms [64]. Both associated symptoms and pain experience can vary between patients, but also based on patient characteristics. Sex, age and previous medical history have all been reported to affect patient presentation [34 64].

1.3 CAUSES OF CHEST PAIN

A wide range of diagnoses and conditions can cause chest pain. Some are high-risk conditions, such as myocardial infarction, pulmonary embolism, pneumothorax, aortic dissection or aortic aneurysm rupture [29 65]. Others are relatively harmless such as gastroesophageal reflux disease, musculoskeletal pain, and anxiety and panic disorders [61], although symptoms in some cases may be quite severe.

Most common among high-risk conditions is AMI [37] with its two main sub-groups: non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). NSTEMI constitutes about 2/3 of all AMI [43 66]. This division is based on whether the ST segment on the ECG is elevated or not [34 64]. An elevated ST segment is a sign of transmural infarction [67], and immediate reperfusion therapy is called for, preferably PCI [34].

In total, about 15 % of all patients contacting the EMS due to chest pain are diagnosed with a high-risk condition of which about 2/3 concern patients with AMI [37]. Ten percent of all EMS missions for patients with chest pain end up with the patient remaining at site (non-conveyance) [30 37]. This is often due to being assessed by the EMS personnel as having a low-risk condition and not being in need of further care. However, it is a difficult task to differentiate between those patients in need of prompt hospital care and those for whom acute hospital attendance is unwarranted.

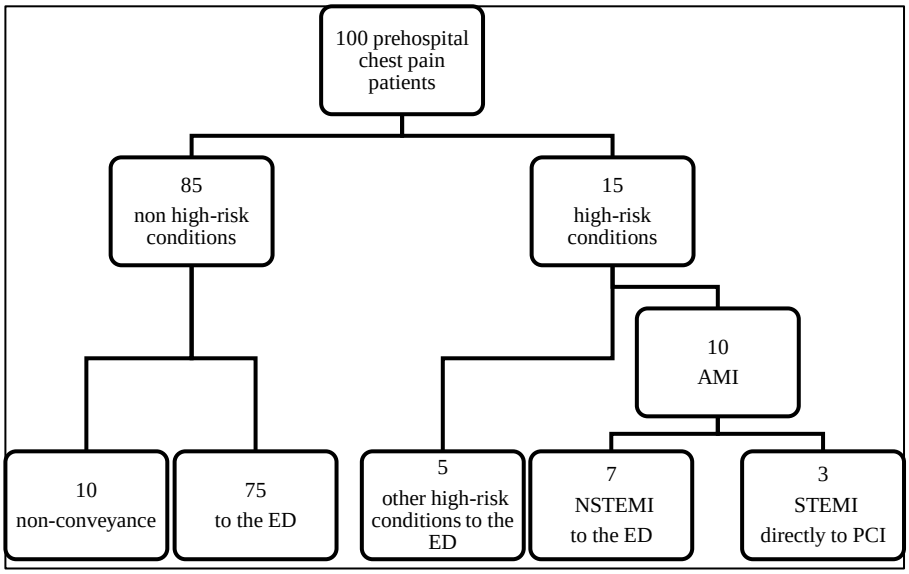

Figure 2. Schematic distribution of patients with chest pain in Scandinavia based on condition and destination

1.3.1 RISK CLASSIFICATION DEFINITIONS

The vast range of conditions within the prehospital chest pain population, ranging from acute life-threatening to harmless conditions, have given rise to a need to define how to risk-classify these conditions. However, defining principles for such a risk classification is difficult. Standardised definitions or terminology do not seem to exist [68].

Herlitz et al. [69] use twenty high mortality diagnoses/conditions to define the term "*life-threatening disease*". This definition is problematic as it does not add any information on appropriate destination for patients with such diseases. One may conclude that most patients defined as having a "*life-threatening disease"* may need hospital care, but this also applies to several other conditions not included in this definition. Furthermore, the definition does not highlight the temporal aspect, i.e. how quickly these patients should receive care, even though one may assume that the intent is that all diagnoses included should be treated without delay. However, there are also life-threatening diagnoses with high mortality for which there is no need of immediate care, such as for example lung cancer. In addition, Herlitz et al. [69] do not use this definition from a strict chest pain point of view, but instead include several different symptoms that could raise suspicion of ACS.

Hagiwara et al. [70] use the similar term *"life-threatening diagnosis"*, which is also based on a number of different diagnoses/conditions, which largely correspond to those used by Herlitz et al. [69]. Therefore the use of "*life-threatening diagnosis"* entails similar problems of clinical utility. Furthermore, *"life-threatening diagnosis"* is even wider in its inclusion as it is meant to be used on all patients cared for by the EMS, not only those complaining of chest pain. The same is true for Magnusson et al.'s. definition of *"time-critical condition"* [71].

Farquharson et al. [72] also start from a wider perspective than patients with chest pain when using the term "*time-critical condition"*. The term is not described in detail, only exemplified by a number of diagnoses for which a minimum of delay before seeking care is vital. Hsiao et al. [73] also use the term *"time-critical condition"*, defining this as a condition requiring care within twelve hours of symptom debut to prevent death. The term is intended to be used in research on low- and middle-income countries and does not originate from a chest pain perspective or a prehospital context.

Salhi et al. [74] use the term *"time-sensitive conditions"* in which STEMI, stroke, cardiac arrest and septic shock are included. The term is not intended to be comprehensive but rather to exemplify conditions that require immediate qualified hospital care. The term is not chest pain-specific and important diagnoses such as NSTEMI and aortic dissection are not included.

Advanced medical life support (AMLS) is an international concept for assessment and treatment of non-trauma patients [75]. AMLS uses the terms *non-emergent*, *non-life-threatening/emergent* and *life-threatening* when categorising how promptly the affected patient needs medical care. AMLS defines the following diagnoses as life-threatening: ACS, pulmonary embolism, aortic aneurysm/dissection, oesophagus rupture, acute pulmonary oedema/heart failure, cardiac arrhythmia, tension pneumothorax and pericardial tamponade. The definition is quite comprehensive and often useful in clinical practice. However, cardiac arrhythmia and heart failure are broad diagnoses including many conditions with low mortality for which immediate care is not necessary.

1.4 PATIENT EVALUATION AND ASSESSMENT

Assessment of patients with chest pain is mainly based on the evaluation of:

- Signs and symptoms
- Previous medical history
- ECG
- Cardiac biomarkers

In the prehospital setting, the EMS personnel are normally dependent on the first three methods for data collection since the prehospital use of cardiac biomarkers is limited.

There is extensive research on risk assessment based on these variables. Most of this research is based on hospital data, not data from the prehospital emergency setting [34 64 76 77]. Furthermore, the primary objective of these studies is in general to identify factors predictive of ACS, and other high-risk diagnoses are not considered.

There are several factors identified as predictive of ACS. The European Society of Cardiology (ESC) states in its guidelines that typical presentation of ACS is central chest pain with a pressuring or heavy character. Radiation to neck, jaw, right, left or both arms is common. Pain usually lasts more than 20 minutes. Nausea, sweating and dyspnoea may also be present. Increase in symptoms during activity and relief while resting are signs of enhanced risk. Pain increase by pressure on the chest wall indicates lower risk for ACS. However, symptoms and signs are not regarded as strong predictors. Risk factors for ACS are male sex, older age, heredity of ACS, and smoking. Previous medical history of diabetes, hyperlipidaemia, hypertension, renal dysfunction, ACS and arteriosclerosis are also risk factors [64]. The strongest predictors of ACS have been reported to be elevation of Troponin biomarkers and ST-elevation or depression on ECG [34 64].

Signs and symptoms

- Central pain
- Pressuring pain
- Heavy pain
- Radiation to:
  - left arm
  - right arm
  - both arms
  - neck
  - jaw
- Pain duration > 20 minutes
- Sweating
- Nausea
- Dyspnoea
- Activity intensifies
- Pain increase by pressure (lowered risk)

Previous history

- Older age
- Male sex
- Family history of ACS
- Diabetes mellitus
- Hyperlipidemia
- Smoking
- Hypertension
- Renal dysfunction
- Previous ACS
- Atherosclerosis

Biochemical markers

- Troponin T
- Troponin I
- CK-MB
- Myosin-Binding protein C
- Copeptin

ECG

- ST-elevation
- ST-depression
- T-wave inversion in multiple leads
- RBBB
- LBBB

Figure 3. Risk factors for ACS according to European Society of Cardiology (ESC) [34] [64]

Overall, EMS personnel's assessment of patient care needs in terms of ED triage level and hospital admission is reported to be deficient [78]. Evidence is insufficient regarding safe non-conveyance by EMS personnel [79]. For patients with chest pain, prehospital and in-hospital diagnostic disagreement is substantial, even in physician-staffed EMS [80].

1.5 DECISION SUPPORT TOOLS

In the prehospital setting, clinical judgement is a dominant aspect in patient assessment. The accuracy of EMS clinical judgement, in terms of identifying the cause of the patient's symptoms, is reported to be fairly imprecise [81 82]. Clinical decision-making is also pointed out as a weakness in EMS care that threatens patient safety [83]. An example is anchoring or if using research methodology terms, confirmation bias. This means that EMS personnel in their decision-making process mainly take into account those clinical findings that support their initial hypothesis and neglect information pointing in other directions. A factor that complicates prehospital emergency decision-making is the diversity of patients and conditions encountered by EMS personnel [23 84]. This diversity and lack of patient case follow-up make it difficult for EMS personnel to accumulate adequate knowledge to support well-founded decision-making in all possible encounters. To improve EMS personnel's clinical decision-making, different decision support tools are commonly used. Examples of such tools are clinical guidelines, checklists, triage and medication protocols [23]. When for example triage tools or early-warning scales are applied in the decision-making process, accuracy is improved [71 85 86]. However, triage tools are often imprecise when assessing patients with chest pain [87-89].

Prehospital risk assessment of patients with chest pain has previously mainly focused on identification of STEMI. However, STEMI accounts for only a few percent of all patients with chest pain [66 90]. It is likely that prehospital assessment of patients with chest pain due to other causes than STEMI can be improved. Both regarding the identification of high- and low-risk patients [71 85 91]. More research is needed on the prehospital risk assessment of patients with chest pain due to other causes than STEMI. A tool for such risk assessment to guide EMS personnel's clinical decision-making has been called for in previous research [92-94].

There are several established tools for assessing patients with chest pain and their likelihood of ACS [95 96]. They have been developed using hospital data for in-hospital use. From a prehospital point of view, this is problematic. Firstly, prehospital and ED patients with chest pain differ in terms of prevalence of high-risk conditions, age, comorbidity and symptomology [45 46 48 97 98]. Secondly, some of these tools use variables that are not available or not readily accessible in the prehospital setting. Thirdly, they use endpoints that neglect high-risk conditions other than ACS. These aspects reduce both utility and validity if applied in the prehospital setting.

There are few ongoing research projects on prehospital decision support tools for risk stratification of patients with chest pain [99-103]. All these projects use Major Adverse Cardiovascular Events (MACE) or ACS as endpoint, thereby not considering other high-risk conditions. Early identification of ACS enables prompt transport to an appropriate destination for these patients. However, not taking other high-risk conditions into account limits the clinical value of these tools in terms of identification of low-risk patients. Therefore, these tools offer little support for clinical decision-making on appropriate care for these patients. For the EMS personnel to be able to recommend a patient non-conveyance, self-transportation or referral to primary care, all high-risk conditions must be excluded in the assessment, not only ACS/MACE.

The above-mentioned projects have evaluated the prehospital use of HEART Score [99 101 103 104] or T-MACS [102], which have been developed for hospital use. None of these projects seems to be investigating whether there are other variables than those included in HEART Score or T-MACS that are relevant in prehospital assessment. Only one study[104] investigated whether any of the variables included in these tools are less important in the prehospital setting. Given the above-mentioned differences between hospital and prehospital patients, it is likely that there are also differences in which variables are important in patient assessment. This was also confirmed by Sagel et al. [104] In some of the projects referred to, it is implied that the tools were to be used on a selected population of patients in whom the EMS personnel suspected ACS. The use of such subjective measures for applying a tool makes it difficult to extrapolate the results to the more heterogeneous group of chest pain patients encountered in the EMS' everyday working situation.

A risk assessment tool may have more clinical value compared with hospital tools for identification of ACS if it:

- has been developed using prehospital data
- is adapted to the prehospital setting
- is to be used on an unselected population of patients with chest pain
- supports decision-making on an appropriate level of care

However, no such tool is available.

If such a tool were available, it is not given that clinical implementation would be unproblematic. Previous research has established that ED physicians consider a missing rate of <0.5-1 % regarding identification of AMI as acceptable for a decision support tool [105]. A study conducted previously showed that five percent of patients with chest pain are discharged from the

ED with AMI wrongly ruled out [106]. Diagnostic accuracy is today probably improved by the introduction of high-sensitive Troponins. However, the results imply that a decision support tool needs a very high level of accuracy to be accepted in clinical care. Improved accuracy compared with clinical judgement is not necessarily sufficient. Three factors that can improve clinical acceptance and adherence are: the quality of the evidence supporting the tool; the format of the tool; and that the tool eases the structuring of information [23]. The tool should preferably be integrated into the regular digital medical record system. The successful implementation of a decision support tool presupposes satisfying these three factors. This may be especially important in the EMS setting since guidelines adherence among EMS personnel is reported to be low [107-109].

On the other hand, the triage tools used today by the EMS do not satisfy all these factors, and neither have they been developed to support decision-making for anything other than determining in which order assessed patients should receive hospital care [86-89 110]. Thus, a new decision support tool offering improvement in one or several of these aspects may be clinically relevant.

1.6 PATIENT SAFETY WHEN CARING FOR PATIENTS WITH CHEST PAIN

Research on patient safety in the EMS setting is limited. This applies also to the specific context of EMS patients with chest pain [83]. Bigham et al.[83] and Hagiwara et al.[84] have identified the following aspects of EMS care as posing a risk to patient safety:

- Clinical judgement and decision-making [83 84]
- Documentation and communication [83 84]
- Transport delay when caring for patients with high-risk conditions [84]
- Deviation from standard care [84]

The use of a clinical decision support tool may reduce patient safety risks in all these aspects [23].

Another threat to patient safety that applies to EMS care is the phenomenon of ED crowding [111 112]. For patients with chest pain, ED crowding is associated with prolonged time until PCI [113] and reduced guidelines adherence [114]. ED crowding is also reported to be associated with an increase of adverse events such as cardiac arrests and arrhythmias for patients with chest pain [115]. Prolonged stay in the ED is also associated with non-cardiac-related complications such as pressure ulcer [116].

ED crowding applies to the EMS in the following ways:

- By referring to non-conveyance or primary care for patients without hospital care needs:
    - the number of patients transported to the ED is reduced. Thereby, the risk of ED crowding is reduced [117]
    - referred patients can avoid the risks associated with attending a crowded ED
- By using fast tracks bypassing the ED, patients with in-hospital care needs can avoid the risks associated with attending a crowded ED and instead reach an appropriate care unit directly.

However, none of these goals can be reached if the appropriate destination or patient management cannot be identified already in the prehospital setting. A decision support tool may offer EMS personnel guidance in their assessment of these aspects. For patients with chest pain this must be done with great accuracy. Misjudgement regarding need of hospital care can have fatal

consequences given that chest pain can be caused by several diagnoses with high mortality. The correct identification of patients with NSTEMI in the prehospital setting and direct referral to a hospital with PCI capabilities seem to make it possible to shorten both time to revascularisation and length of hospital stay [118]. The advantages of early PCI for patients with NSTEMI have been demonstrated [119] and early PCI is also promoted in the ESC guidelines [64].

Other patients seem to benefit instead from being cared for at a primary care centre [120] rather than the ED. It is also reasonable to assume that many patients appreciate avoiding spending time in the ED if possible.

Adequate patient management by the EMS personnel has not only potential benefits for the patient at hand. By referring patients to non-conveyance or self-transportation, EMS resources can be freed earlier. They thus become available for new missions with more urgent care needs. Given that the number of EMS missions is growing [40-42] and EMS response times are increasing [121] [122], this optimisation of EMS utilisation is warranted.

1.7 HEALTHCARE RESOURCE UTILISATION

ED attendances and hospital admissions due to chest pain are associated with high costs [123 124]. A substantial and increasing proportion of all ED patients with chest pain arrive via the EMS [33]. Patients using the EMS thus contribute to a large extent to these costs. Since patients with chest pain account for ten percent of all EMS missions [29 30], it is likely that the EMS costs for caring for this group of patients is also high [99], although no studies on this specific topic can be found. Previous estimations argue that 30-60 % of all patients with chest pain assessed in hospitals could be cared for outside hospitals [125]. Also, among patients cared for by the EMS due to chest pain, a large proportion may be suitable for non-hospital care [37]. Some at least should be identified as such and referred elsewhere than the ED to reduce healthcare costs [126]. Since a large number of patients with chest pain are transported to the ED by the EMS, altered management by the EMS may have considerable economic effects.

Identification of low-risk patients in the prehospital setting may also enable a more effective utilisation of EMS resources. By directing low-risk patients to remain at home or other means of transportation than an ambulance, EMS resources could be released earlier for new missions. EMS utilisation would thereby be optimised. Given the many patients with chest pain, altered care for a few percent may affect a large number of individuals.

The potential economic benefits of prehospital risk stratification and altered care do not only apply to low-risk patients. In the high-risk spectra there may also be possibilities of reducing healthcare costs. Early identification of patients with NSTEMI and direct transport to a hospital with PCI capabilities enable early intervention which may be both beneficial to the patient and cost-effective [99 118 127].

1.8 RATIONALE

A decision support tool may be one way to improve prehospital risk stratification of patients with chest pain. A tool providing guidance on the identification of low- and high-risk patients early on, in the EMS setting, enables differentiated patient management based on patient care needs. This has several potential benefits and clinical applications:

- Improvement of EMS personnel's assessment and clinical judgement to increase the odds for noticing important information and correct decision-making.
- Structuring and improvement of the risk assessment of those patients who today are referred to non-conveyance.
- EMS referral of low-risk patients to primary healthcare or remaining at home allows the patient to avoid unnecessary visits to a crowded ED with long waiting times.
- EMS referral of low-risk patients to primary healthcare or remaining at home reduces ED crowding.
- EMS referral of low-risk patients to primary healthcare or remaining at home reduces hospital costs.
- EMS referral of low-risk patients to primary healthcare, remaining at home or alternative modes of transportation releases limited EMS resources and reduces EMS costs.
- EMS identification of high-risk conditions enables prompt transport to the ED and triage of the patient to receive care before those with less time-sensitive conditions.
- EMS identification of patients with high-risk conditions enables by-passing hospitals without appropriate capabilities such as a PCI laboratory.
- EMS identification of patients with high-risk conditions enables by-passing the ED and transporting the patient directly to the appropriate care unit such as a cardiac care unit, intensive care unit or PCI laboratory.

The ambition of this thesis is to develop a prehospital decision support tool for improving risk stratification of patients with chest pain. By introducing such a tool into clinical care, one or several of the above-mentioned aspects may hopefully be met. This is also in line with the Swedish health and medical services act stating that:

- those with greatest care needs should receive care first
- health and medical services should accommodate the patient's needs of good and safe care
- health and medical services should be organised to promote cost effectiveness

2 AIM

The overall aim of this thesis is to develop a decision support tool for prehospital risk stratification of patients with chest pain.

Specific aims:

Paper I
To identify factors associated with an acute life-threatening condition among patients calling the EMS due to non-traumatic chest pain.

Paper II
To explore the symptom descriptions and situational information provided by patients during ongoing chest pain events caused by a high-risk condition.

Paper III
To describe contemporary characteristics and diagnoses among prehospital patients with high/low risk conditions presenting with chest pain.

To identify factors suitable for the early recognition of:

- patients with time-sensitive conditions in need of immediate care (high-risk conditions)
- patients with no medical need of hospital treatment, suitable for non-conveyance to hospital (low-risk conditions)
- present data that can inform the development of a prediction tool

Paper IV

- To develop a prediction model for optimising identification of patients with low- or high-risk conditions with acute chest pain early in the EMS workflow.

3 METHODS

In this thesis, several different research methods are used. This makes it possible to obtain a more complete picture and capture different aspects of prehospital risk assessment of patients with chest pain.

Paper I describes the results of previous research, portraying the state of knowledge on prehospital risk assessment of patients with chest pain when this project started. Paper II illustrates how patients describe their symptoms during an ongoing chest pain event. In Paper III, focus is on describing the prehospital population of patients with chest pain. Furthermore, Paper III examines which factors may be used for prehospital risk assessment of these patients. Paper IV describes how decision support tools can be constructed and the accuracy of such tools in terms of identification of patients with high- or low-risk conditions.

	Paper I	Paper II	Paper III	Paper IV
Aim	To identify factors associated with an increased risk of acute life-threatening conditions among patients who call the EMS due to non-traumatic chest pain.	To explore how patients describe symptoms and give situational information during ongoing chest pain events caused by a high-risk condition.	To describe contemporary characteristics and diagnoses among prehospital patients with chest pain and identify factors suitable for risk-group prediction.	To develop a prediction model for optimising identification of patients with low- or high-risk conditions in acute chest pain early in the EMS workflow.
Design	Systematic literature review	Qualitative descriptive	Quantitative prospective cohort	Prediction model development study
Data collection	Medical research databases	Emergency medical call recordings	Medical charts with structured symptoms anamnesis	Medical charts with structured symptoms anamnesis. Missing data is imputed.
Population	10 research articles based on prehospital data	56 patients with chest pain diagnosed with a high-risk condition	2,917 EMS missions concerning patients with chest pain	2,578 EMS missions concerning patients with chest pain
Data analysis	Semi-quantitative	Manifest content analysis	Descriptive statistics and regression analyses	Regression analyses and c-statistics
Primary outcome	High-risk condition	High-risk condition	High- or low-risk condition	High- or low-risk condition
Ethical approval	N/A	Regional Ethical Review Board, dno 2016/354	Regional Ethical Review Board in Lund, dno 2017/212	Regional Ethical Review Board in Lund, dno 2017/212
Status	Published 2016	Published 2019	Published 2021	Manuscript.

Table 2. Methodological overview of Papers I-IV

3.1 RISK CLASSIFICATION

In this thesis, low-, intermediate- and high-risk conditions are used to label the applicable risk classification groups. Risk group allocation refers to the diagnosis on discharge from hospital.

- Low-risk relates to diagnoses that are not time-sensitive and can be cared for at home or at a primary healthcare centre. There is no medical need for hospital treatment. Transport by the EMS to hospital is not required.
- Intermediate risk refers to diagnoses that may require hospital care but where the time factor is not crucial.
- High-risk refers to diagnoses requiring prompt emergency care and where rapid transport to hospital is required. The diagnoses included in the high-risk group are diagnoses that are classified as life-threatening by the European Society of Cardiology (ESC) [128] or by the AMLS-concept [75].

The definitions used to constitute these groups are intended to be comprehensive and of clinical relevance when assessing patients with chest pain and their healthcare needs in the prehospital emergency setting. These definitions evade the shortcomings of the definitions used in previous research [68-74].

3.2 PAPER I – A SYSTEMATIC LITERATURE REVIEW

AIM

To identify factors associated with an increased risk of acute life-threatening conditions among patients who call the EMS due to non-traumatic chest pain.

SEARCH METHOD AND SELECTION CRITERIA

A literature search for abstracts or articles published between January 1980 and November 2015 was carried out in the databases listed below:

- CINAHL
- Cochrane Libraries
- PubMed
- Scopus
- Web of Science

The goal of this search was to identify reports recognising factors associated with high-risk conditions in EMS patients with chest pain. The PICO (Population, Intervention, Control, Outcome) approach[129] was used to frame the research question:

P Patients contacting the EMS due to chest pain

I Predictive factors measurable in the EMS setting

C No high-risk condition

O High-risk condition

With assistance from librarians, the search string that follows was constructed:
(chest AND (pain OR discomfort))
AND
(prehospital OR "pre hospital" OR "dispatch center" OR "dispatch centre" OR "emergency medical services" OR EMS OR "emergency medical technician" OR EMT OR paramedic OR paramedics OR ambulance*)

After conducting this search, the first step was to remove all duplicates generated by using multiple databases. Remaining items were manually screened by title, and if there was uncertainty, also by abstract to identify potentially relevant reports meeting the following inclusion criteria:

- Study sample of EMS patients with chest pain
- Providing separate statistics on the association between factors investigated and one or several of the outcome measures listed below:

    - High-risk condition (ACS, cardiac arrest, pulmonary oedema, pulmonary embolism, aortic aneurysm or dissection, myocarditis, endocarditis, pancreatitis, gut perforation, severe arrhythmia or severe heart valve disease).
    - MACE within 30 days, defined as death, myocardial infarction or revascularisation
    - Death within 30 days
- Published in English in a peer-reviewed journal

The references' lists of the items remaining after screening title/abstract along with relevant review articles were screened for further reports. Finally, remaining items were screened in full text to determine whether or not the inclusion criteria were fulfilled.

QUALITY ASSESSMENT

Scottish Intercollegiate Guidelines Network checklists (SIGN) for cohort studies [130] and studies of diagnostic accuracy [131] were then used to rate the quality of reports included. These checklists were modified to include only those elements relevant to the present reports. The modified checklist for cohort studies included eight elements. The checklist for studies of diagnostic accuracy (e.g. studies on biochemical cardiac markers) included 13 elements. Each element could be answered with yes, no, "can't say" or "does not apply". One point was given for each time an element was answered with a yes. For cohort studies, 4-6 points was rated as an "acceptable quality study" (+) and 7-8 points as a "high quality study" (++). For studies on diagnostic accuracy the corresponding figures were 6-9 points and 10-13 points respectively.

DATA EXTRACTION AND ANALYSIS

From each report included, data was extracted on which factors were associated with the outcome studied. If the threshold for significance given in each report was not exceeded, an association between factor and outcome was judged to exist. If no threshold for significance was reported in a study, it was set to $p < 0.05$.

A semi-quantitative synthesis procedure described by Zaal et al. [132] was used to synthesise data obtained. The level of evidence for each reported predictor was assessed using the following criteria:

- number of studies evaluating the factor
- quality of the report(s) according to checklist applied
- consistency between reported results

Level of evidence was defined as follows:

- Strong evidence – association found in ≥75% studies evaluating the predictor, at least 1 high quality
- Moderate evidence – association found in >50% of the studies evaluating the predictor
- Inconclusive evidence – association found in ≤50% of the studies evaluating the predictor
- No evidence – no association found in >75% studies evaluating the predictor

A factor fulfilling the criteria for multiple levels of evidence was assigned the higher of them.

Few of the studies included reported data on the predictive value of biochemical cardiac markers for identification of high-risk conditions. Furthermore, these studies reported data on sensitivity/specificity rather than statistical significance. For these reasons, the semi-quantitative approach described above was not applied to evaluate the level of evidence on biochemical cardiac markers.

3.3 PAPER II – A QUALITATIVE CONTENT ANALYSIS

AIM

To explore the symptom descriptions and situational information provided by patients during ongoing chest pain events caused by a high-risk condition.

DESIGN

A qualitative descriptive approach was applied. Manifest content analysis was used to analyse emergency medical calls to an EMD concerning patients with chest pain.

SETTING

The current EMD centre is operated by telecommunicators answering the emergency medical calls. They use a criteria-based index to guide them when determining whether an ambulance needs to be dispatched and with which priority. If the telecommunicator is in doubt, the call can be transferred to a registered nurse supporting their decision-making [21 22]. The telecommunicators use a digital support tool as guidance when interviewing the caller. This tool is based on index nodes, where chest pain is one of many. This tool suggests specific questions for each such node. Examples of questions in the chest pain index node is: Can you try to describe your pain? Is your breathing affected? Where in your chest do you have pain? Are you in pain all the time?

SAMPLE

Stratified purposive sampling [133] was used to attain recordings of emergency medical calls representing severely ill patients with chest pain. Patients who contacted the EMD due to chest pain and who were later diagnosed with a high-risk condition at hospital discharge were included.

Inclusion criteria

- A diagnosis at hospital discharge included in any of ICD-10 groups mentioned below (i.e. having a high-risk condition):
    - I20.0, I21 and I22 – Unstable angina pectoris or myocardial infarction
    - I26 – Pulmonary embolism
    - I71 – Aortic aneurysm/dissection
    - J93.0 and J93.1 – Spontaneous pneumothorax
- Patient being cared for by the EMS (i.e. emergency medical call available)
- Patient mentioning having chest pain during the emergency medical call
- Emergency medical call in Swedish

Exclusion criteria

- Caller to the EMD identified as a nurse or a physician

This sampling approach was applied to enable the creation of preconditions for the saturation of data in terms of symptoms described by patients with chest pain due to a high-risk condition. All patients in Halland with a diagnosis at hospital discharge corresponding to the high-risk conditions listed above during the first six months of 2016 were identified. Related EMS records were screened for inclusion and exclusion criteria until fifteen patients were identified for each of the high-risk conditions of interest. For those high-risk conditions where fifteen patients could not be identified during these six months, the period was expanded until those fifteen patients were identified.

Seventeen calls were excluded due to not mentioning chest pain in the emergency medical call or call being made by a nurse or a physician. Excluded calls were once more replaced by expanding the search for appropriate calls, adding 13 calls. In total, 56 emergency medical calls were included. Calls included lasted for a median time of close to four minutes, generating just over four hours of emergency medical call recordings.

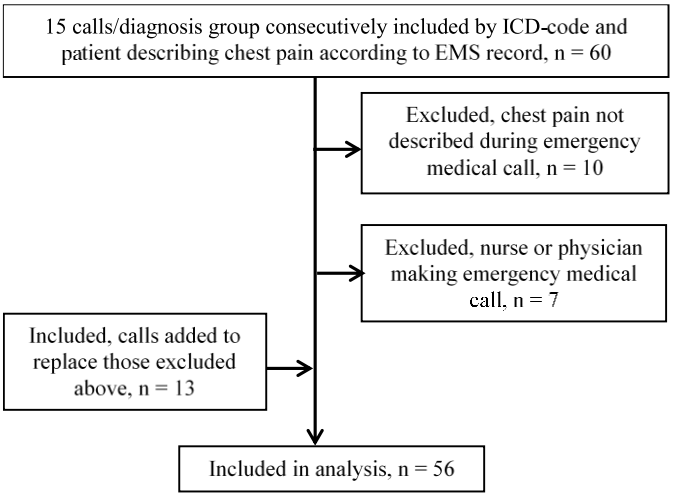

Figure 4. Flow chart of inclusion process for Paper II

DATA ANALYSIS

All recordings were first listened to and then transcribed verbatim. This allowed researchers to get familiar with the data in its original form [134]. Thereafter a manifest content analysis was carried out [135]. The manifest approach was applied to describe what the callers actually said, without paying attention to subtle aspects or trying to interpret between the lines. The ambition was to stay close to the actual words of the caller i.e. content analysis rather than meaning analysis.

The emergency medical call transcripts were read through to get an overall picture. Thereafter, the transcripts were read through again and relevant words and passages (i.e. meaning units) were highlighted. This process was repeated until no new information was observed. The meaning units were then condensed into codes. These codes were then grouped into subcategories and finally merged into categories based on their similarities and differences.

The codes were thereafter backtracked to the emergency medical call transcripts to ensure that the initial meaning had not been lost during the analysis process. It was also double-checked that the codes were sorted into the correct subcategory. During this step, a few categories were altered or merged to describe the data better. Finally, the transcripts, meaning units, codes and categories were gone through several times, back and forth. This was done to ascertain that the categories were representative of what was being said in the calls and that the categories captured all relevant aspects given the aim of the study.

3.4 PAPERS III AND IV – A PROPSPECTIVE COHORT STUDY

AIM

Paper III

To describe contemporary characteristics and diagnoses among prehospital patients with high/low risk conditions presenting with chest pain.

To identify factors suitable for the early recognition of:

- patients with time-sensitive conditions in need of immediate care (high-risk conditions)
- patients with no medical need of hospital treatment, suitable for non-conveyance to hospital (low-risk conditions)
- present data that can inform the development of a prediction tool

Paper IV

- To develop a prediction model for optimising identification of patients with low- or high-risk conditions with acute chest pain early in the EMS workflow.

STUDY POPULATION

During 2018, all EMS missions in the county of Halland concerning patients, ≥18 years old, with a chief complaint of non-traumatic chest pain were eligible for inclusion. In total, 3,121 such EMS missions were carried out. Of these 2,917 missions were included after excluding patients lost to follow up or declining to participate.

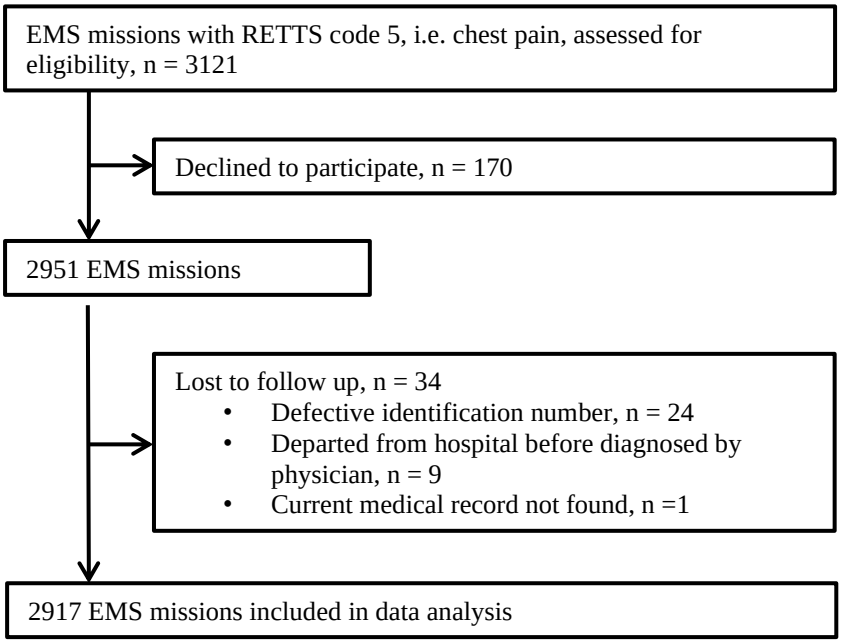

Figure 5. Flow chart of inclusion process for Papers III/IV

HEALTHCARE SYSTEM

In 2018, the county of Halland had 329,000 inhabitants, covering an area of 5,500 km^2. There are two emergency hospitals, of which one has PCI capabilities. There are eight EMS stations with 19 ambulances during daytime and 12 during the night. Approximately 30,000 patient-related EMS missions are carried out each year (inter-hospital transfers excluded). Each ambulance is staffed with a nurse working together with an EMT or another nurse. In most cases the ambulance is staffed by two nurses.

DATA COLLECTION

Each patient was tracked through the acute healthcare chain by using the unique personal identity number assigned to all inhabitants in Sweden. Each patient was tracked from EMS contact to hospital discharge. Patients were also tracked for 72 h readmission to hospital and 30-day mortality.

A questionnaire with fifteen items regarding patient symptoms was developed and integrated in the digital EMS record system. The questionnaire was developed using the results of Papers I and II along with results and methodology of several other reports concerning symptoms and symptom descriptions of patients with chest pain. Both the EMS record and the questionnaire were accessible bed-side using tablets during the entire EMS mission.

The questionnaire consisted mainly of items focusing on the patients' pain experience, for example onset, intensity, localisation, provocation/palliation, duration and quality. Pain intensity was evaluated using the Numerical Rating Scale (NRS) ranging from 0-10[136] or a Verbal Rating Scale (VRS) ranging from "no pain" to "unbearable pain"[137]. If the VRS was applied, the answers were recoded into NRS values [138]. Besides items on pain narrative, the questionnaire also covered associated symptoms such as dyspnoea, nausea, vomiting, clamminess and paleness.

Data on vital signs was obtained from the EMS record. Data regarding diagnosis at hospital discharge along with data on previous medical history was collected from primary care and hospital medical records.

A blood sample was obtained during the EMS mission. On hospital arrival, this blood sample was analysed for high-sensitive Troponin T (TnT), detecting values ≥ 5 ng/L. Pathological cut-off was set to >14 ng/L. To stipulate data on TnT as it would have been presented if the EMS personnel had used Roche's device Cobas h 232 for bedside TnT analysis, TnT values obtained were also converted to the following intervals: ≤50, 51-100, 101-1000 and >1000 ng/L.

A pre-set ECG interpretation template was used to interpret the ECGs retrieved. In cases of uncertainty, interpretation was discussed within the research group until consensus was reached.

With exception for data on ECG and diagnosis at hospital discharge, all data was automatically extracted using digital software. The automatically extracted data was extensively checked against the original medical records without finding any inconsistencies. Diagnosis at hospital discharge, according to ICD 10, was collected by manual medical record follow-up.

SAMPLE SIZE

Originally the sample size was set to 1,500 EMS missions. With 1,500 EMS missions included, an absolute difference of 9 % and a relative difference of 64 % would be statistically detected for a variable present at 10 % of the

observations. An absolute difference of 7 % and a relative difference of 49 % would be detected for a variable present at 20 % of the observations. These calculations were based on a 15 % incidence rate of high-risk conditions, 80 % power and a significance level of 5 % (two-sided). The originally planned data collection time frame was expanded to increase sample size. The sample size increase was applied to compensate for high rates of missing data on specific variables that were seen during the initial inclusion process.

ENDPOINT

Patients included were classified as having either a low-, intermediate- or high-risk condition as the cause of their chest pain. Risk condition classification was based on diagnosis made by the physician responsible at hospital discharge.

- Low-risk refers to conditions that are not time-sensitive and can be cared for at home or at a primary healthcare centre. There is no medical need for hospital treatment. Transport by the EMS to hospital is not required. This group also included patients who were left at site by the EMS, who did not visit the ED within 72 hours and who did not die within 30 days.
- Intermediate-risk refers to conditions that may require hospital care but where the time factor is not crucial.
- High-risk refers to a time-sensitive condition with an increased risk of death, requiring prompt emergency care and where rapid transport to hospital is required.

This risk-classification was based on strictly medical grounds based on hospital diagnosis. Other, non-medical reasons for hospital care or EMS transport were not taken into account. High- and low-risk classification were used as the primary endpoint.

STATISTICAL ANALYSIS

Each variable was analysed twice using univariate logistic regression to test association with high-risk respectively low-risk conditions. A p-value <0.05 was considered statistically significant.

For Paper IV, missing data was imputed using the MissForest algorithm [139]. In this way, a new data set was provided with complete data on all 2,917 EMS missions originally included. Thereafter, EMS missions including patients with strongly deviating vital signs (red vital signs according to National Early Warning Score 2, NEWS 2) [140] or ST-elevation on ECG were excluded given the already well-established pathways for these patients. This reduced the

utility of further risk assessment. After excluding these EMS missions, 2,578 missions remained for regression analyses and prediction model development.

The prediction model development was carried out in two separate processes, one for high-risk prediction and one for low-risk prediction:

- Step 1. Models were generated using moderately restricted p-value thresholds for variable entry and removal in stepwise forward multivariate analyses.
- Step 2. P-value thresholds were further constricted to reduce prediction model size.
- Step 3. Manual variable selection was applied to reduce model size further. This manual selection of variables was based on a high predictive value and a low p-value. Furthermore, the variable independence of patient narrative was considered to ease clinical use and reduce the impact of patient subjectivity.
- Step 4. The variables from both high- and low-risk models were combined into a common model for both high- and low-risk prediction.

The high-risk models from each step were tested with a 50 % endpoint probability as cut-off for assigning a risk classification group. The corresponding figure for low-risk models was 90 %.

3.5 ETHICS

Informed consent is a cornerstone in research involving humans, as described in the Declaration of Helsinki, the Nuremburg Code and the Belmont Report [141]. In the prehospital emergency setting, obtaining informed consent is often problematic. Informed consent means that the study participant is informed about the background and aim of the study along with information on potential risks and benefits. Furthermore, the participant must be informed that participation is voluntary and can be withdrawn at any time. They must also be provided with information on how the data collected is handled in terms of confidentiality and data protection. This information must be presented both in written form and orally. Informed consent obtained from the study participant should preferably be confirmed in writing [142].

The prehospital setting is characterised by limited personnel resources since most ambulances are manned by only two personnel. These two personnel need to handle patient care, bystanders, documentation, driving, radio communication etc. Furthermore, time is sometimes short due to caring for a severely ill patient in need of immediate care and rapid transport. Patients are also often emotionally affected due a stressful situation, being in pain etc. These conditions often make it difficult to carry out a process of obtaining informed consent in the EMS setting [143 144]. This also applies to parts of this project.

3.5.1 PAPER I

Paper I is a review study only using data from previously conducted studies. Therefore, the ethical aspects that need to be considered are limited.

3.5.2 PAPER II

The study described in Paper II was approved by the Ethical Review Board in Lund (dno 2016/354). For this study no informed consent was obtained from the patients included in the study. Obtaining informed consent prospectively was not judged to be possible. It was impossible to identify patients for inclusion or obtain informed consent during the emergency call since inclusion criteria were based on diagnosis at hospital discharge. Trying to obtain informed consent from all potential participants (i.e. all patients with chest pain) would have resulted in a delay of patient care in potentially time-sensitive conditions. Furthermore, many emergency medical calls are stressful with the caller being in great distress, making it even more inappropriate to address the issue of informed consent during the emergency medical call. It was not either

possible to present written information on the study to the potential participants in conjunction with the emergency medical call.

To contact the potential participants in retrospect was not judged as being justified. Such contact could be seen as an intrusion that might have revived a traumatising event. It was deemed unethical to do this for a study that could be carried out without the patients' attention. Furthermore, obtaining informed consent in retrospect would not be possible for those patients who were deceased. This would result in excluding the most severely ill patients (i.e. those whose high-risk condition caused death) who are of utmost interest given the study's aim. In summary, obtaining informed consent was not judged to be feasible or ethically motivated.

This study entails patient integrity intrusion due to investigating emergency medical recordings and medical records. However, data collection was conducted by only one person and data was anonymised before being presented to the other researchers involved or starting the data analysis. The extent of this integrity intrusion was thus minimised. Furthermore, all data was presented on a group level (except carefully anonymised citations) thus reducing the risk of participant identification. When applying these measures, it was judged that the possibility to improve patient care for future patients with chest pain exceeded the integrity intrusion associated with conducting this study. Therefore, this integrity intrusion was deemed ethically justified.

3.5.3 PAPERS III AND IV

Papers III and IV are based on the same study, approved by the Ethical Review Board in Lund (dno 2017/212). For this study, informed consent was not obtained either. This was motivated as follows:

- No patients were put at risk since conducting the study did not affect patient care.
- Some patients suffered from diagnoses where the time was crucial. Trying to obtain informed consent under such circumstances is problematic since this may put the patient's health at risk [141 143 145 146].
- The physical state of the patient can have negative impact on the process of obtaining informed consent, for example having severe pain or an altered level of consciousness [143 146].
- Patients cared for by the EMS are often stressed and emotionally upset, making it difficult to receive and interpret information. This also impairs the conditions for informed decision-making [141 145 146].

- EMS care is characterised by urgency with several examinations being conducted, numerous questions being posed to the patient and multiple treatments being initiated during a limited amount of time. Under these circumstances it is not suitable to ask the patient for informed consent. This would increase an already heavy workload for the EMS personnel and might raise patient stress levels when their focus needs to be elsewhere.
- The patient is in a position of being dependent on the EMS personnel on site. Thus, the voluntariness of informed consent obtained in such circumstances can be questioned.

These problems associated with obtaining informed consent in the prehospital setting are previously known. Therefore, literature on the subject argues that waiving informed consent when conducting research in the EMS setting is often justified as long as the patients are not put at risk and the benefits exceed potential disadvantages [141] [143] [146]. Therefore, instead of obtaining traditional informed consent, an opt-out procedure was carried out for this study [147]. An mail was sent to all eligible patients asking them to respond in four weeks if they did not accept study participation. No reason for opting out was needed. In total five percent of eligible patients opted out. Most patients spontaneously motivated this with a fear of the data collected ending up in the wrong hands.

The data collected was stored digitally without the patients' social security number. Code numbers were used instead for patient-tracking. Access to the medical record system was needed to connect a code number to a specific patient.

The patient integrity intrusion associated with this study in terms of extracting data from the patients' medical records was deemed to be exceeded by the potential benefits of the results. Therefore, this integrity intrusion was justified from an ethical point of view.

4 RESULTS

4.1 SUMMARY OF RESULTS

Paper I points out that prehospital research on risk prediction in patients with chest pain is sparse. Predictors of high-risk conditions with strong evidence are among others: old age, male sex and ST-deviation on ECG.

Paper II shows that patients with chest pain due to a high-risk condition present with a wide range of symptoms described in variety of ways.

Paper III highlights that there are numerous factors predicting a low- or high-risk condition in a patient. Some of these predictive factors are new. On the contrary, other predictive factors presented previously did not show any predictive value in this study.

Paper IV presents several models varying in construction and accuracy for both low- and high-risk prediction. Even limited models with few variables have acceptable predictive accuracy. However, some patients with a high-risk condition are wrongly classified as low-risk. ST-deviation on ECG, TnT and age are the strongest predictors in prehospital prediction of both low- and high-risk conditions.

4.2 PAPER I

4.2.1 STUDY IDENTIFICATION

The database search generated 3,512 items. When removing duplicates, 1,243 items remained. When screening by title/abstract 1,192 items were excluded. When cross-checking the references' lists of the remaining 51 reports along with relevant review articles, two additional reports were added. Screening these 53 reports in full text resulted in excluding 41 reports, mostly due to failing to fulfil the inclusion criteria regarding a study sample consisting of EMS patients. Beyond this, two reports were excluded due to reporting similar data based on the same study sample. In the end, ten reports were included and quality-assessed.

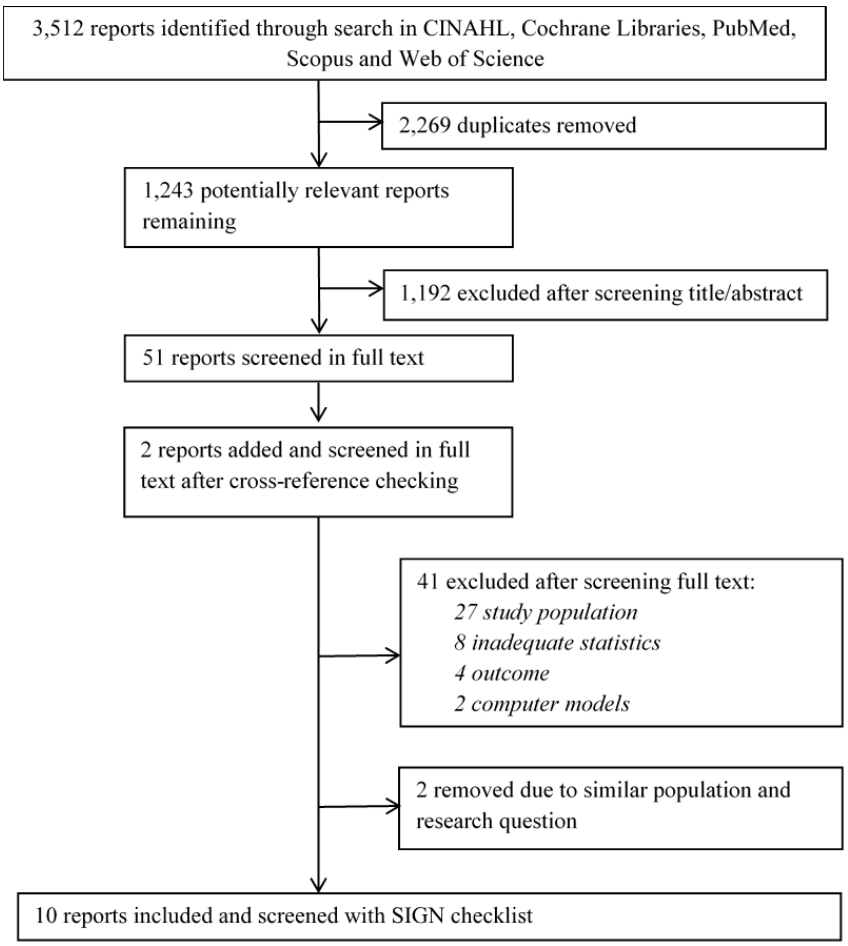

Figure 1. Screening process for Paper I

4.2.2 STUDY CHARACTERISTCS AND QUALITY

Of the studies included, seven evaluated whether factors such as symptoms, signs and previous medical history were associated with having a high-risk condition [62 148-153]. Together these seven studies evaluated associations between high-risk conditions and 56 different factors. Of these, 20 were evaluated in more than one study.

Three studies evaluated the diagnostic accuracy of biochemical markers when applied in the prehospital setting [154-156]. These biochemical markers were Troponin I (TnI), Troponin T (TnT), Myoglobin, Creatine Kinase-Myocardial Band (CKMB) and CardioDetect®. TnT was the only biochemical marker studied in two studies. These two studies reported a specificity of 98 % [155] and 97 % [156] and a sensitivity of 25 % [155] and 18 % [156] for AMI prediction.

In general, the studies included were conducted on relatively small cohorts, with a median of 394 study participants. Two studies included more than 2,000 patients [151 152]. Six studies used myocardial infarction as the outcome measure [148 152-156], two used a combined outcome measure of different high-risk conditions [149 150] and two used short-term survival rate as the outcome [62 151]. Two studies [148 152] were rated as high-quality studies when assessed using the SIGN checklist.

4.2.3 LEVEL OF EVIDENCE

The semi-quantitative synthesis and analysis of study data extracted resulted in the following evidence rating for the factors studied and their association with high-risk conditions:

Strong evidence

- Increasing age
- Male sex
- Elevated heart rate
- Low systolic blood pressure
- ECG – ST-elevation
- ECG – ST-depression

Moderate evidence

- Previous medical history of myocardial infarction
- Previous medical history of angina pectoris
- ECG – Pathologic Q-wave
- ECG – Left bundle branch block

Inconclusive evidence

- Dyspnoea
- Cold sweat/paleness
- Nausea/vomiting
- Previous medical history of congestive heart failure
- Smoking
- ECG – T-wave inversion
- ECG – Right bundle branch block

No evidence

- Severity of pain
- Previous medical history of diabetes mellitus
- Previous medical history of hypertension

A few factors were reported to be associated with high-risk conditions but were only evaluated in a single report:

- history of coronary artery by-pass graft operation [152]
- chronic medication with [150]:
    - beta-blockers
    - nitrates
    - anti-diabetic drugs
    - psychopharmacological drugs (reduced risk of high-risk condition)
- heredity of cardiovascular disease [148]
- oxygen saturation [62]
- breathing rate [62]

	High quality		Acceptable quality			
Factor evaluated	**Association**	**No association**	**Association**	**No association**	**No. of studies**	**Level of evidence**
Age*	[152]	[148]	[149 151 62]		5	Strong
Male*	[148 152]		[151 62]	[149]	5	Strong
Sign/symptom:						
Elevated heart rate	[152]		[62]		2	Strong
Low systolic blood pressure**	[152]		[62]		2	Strong
Dyspnoea			[62]	[149]	2	Inconclusive
Cold sweat/ Paleness			[62]	[149]	2	Inconclusive
Nausea/ Vomiting			[62]	[149]	2	Inconclusive
Strong pain		[148]		[149 62]	3	No evidence
History of:						
Myocardial infarction	[152]		[150]	[62]	3	Moderate
Angina pectoris	[152]		[150]	[62]	3	Moderate
Congestive heart failure		[152]	[62]	[150]	3	Inconclusive
Smoking	[148]			[150 62]	3	Inconclusive
Hypertension		[148]		[150 62]	3	No evidence
Diabetes mellitus		[148]		[150 62]	3	No evidence
ECG:						
ST-elevation	[152]		[153 62]		3	Strong
ST-depression	[152]		[153 62]		3	Strong
Q-wave	[152]		[62]	[153]	3	Moderate
Left bundle branch block	[152]		[62]	[153]	3	Moderate
Right bundle branch block			[62]	[153]	2	Inconclusive
T-wave inversion	[150]			[153 62]	3	Inconclusive

*Data from reference **[150]** excluded due to same data as reference **[149]**.
Data from reference **[151] excluded, reporting no association regarding systolic blood pressure >150, other studies reporting on low systolic blood pressure.

Table 3. Overview of reports evaluating each factor and level of evidence

4.3 PAPER II

The median age of patients included was 74 years old, ranging from 18-96 years old. Two-thirds of the patients were male. In 38 %, the calls to the EMD were made by the patient her-/himself. In an additional 17 % of the calls the patient did not initiate the call but took an active part. Half of the calls were made by a significant other such as friend, partner or relative.

	All n=56	**ADA n=15**	**PE n=15**	**ACS n=15**	**PT n=11**
Age of patient, years					
Median	74	76	59	79	67
Range	18-96	54-91	22-90	56-94	18-96
Male patient n (%)	38 (68)	11 (73)	10 (67)	10 (67)	7 (64)
Caller n (%)					
Patient	21 (38)	3 (20)	10 (67)	7 (47)	1 (9)
Significant other	28 (50)	11 (73)	4 (27)	7 (47)	6 (11)
Home care or institution staff	7 (13)	1 (7)	1 (7)	1 (7)	4 (36)
Patient taking active part in call	31 (55)	8 (53)	10 (67)	10 (67)	3 (27)
Caller on site	55 (98)	14 (93)	15 (100)	15 (100)	11 (100)
Duration of call, min					
Median	03:53	03:45	04:41	04:10	03:47
Range	2:04-11:17	2:04-07:12	2:33-8:41	02:33-11:17	02:12-06:30

ADA = Aortic dissection or aneurysm
PE = Pulmonary embolism
ACS = Acute coronary syndrome
PT = Pneumothorax

Table 4. Characteristics of patients and calls

During the analysis of the emergency medical calls, seven categories emerged: 1) Pain narrative, 2) Affected breathing, 3) Bodily reactions, 4) Time, 5) Bodily whereabouts, 6) Fear and concern, 7) Situation management. These categories comprised seventeen subcategories.

Main category	Subcategory				
Pain narrative	Pain throughout the body	Diverse locations around the chest	Chest pain expressions	Severe pain	Pain behaviour
Affected breathing	Difficulties breathing	Pain when breathing			
Bodily reactions	General weakness	Skin and temperature	Sickness and dizziness	Loss of body control	
Time	How it started	Symptoms changing and lasting	Previous illness and experiences		
Bodily whereabouts					
Fear and concern					
Situation management	Difficulties handling a perceived emergency	Reasoning about cause	Self-care		

Table 5. Overview of categories and subcategories

PAIN NARRATIVE

The experience of pain was dominating when describing patient symptomology during the emergency medical calls. The pain narrative included descriptions of the quality of the pain, where it was located in the chest and if the patient experienced pain in other parts of the body than the chest. It also included descriptions of how the pain behaved in terms of persistency and variance over time. This category contained five subcategories: *Chest pain expressions; Severe pain; Diverse locations around the chest; Pain throughout the body* and *Pain behaviour*.

AFFECTED BREATHING

In many of the emergency medical calls included, the breathing of the patient was described as affected. The patients stated that they felt breathlessness, that it was hard to breath, etc. They also described that breathing was associated with the intensity of the pain. Two subcategories constitute this category: *Pain when breathing* and *Difficulties breathing*.

BODILY REACTIONS

Several other bodily reactions were reported besides symptoms of pain and affected breathing. These were reactions not directly associated with the affected organs of the thorax, such as heart and lungs, but rather comprising

other organs and body systems. Patients described that they experienced a loss of energy and feeling tired. They also lost control over the body, felt that their body started to move involuntarily or that certain parts of their body lost their functionality. Changes in body temperature and the look of the patients' skin were also reported, along with experiences of nausea and dizziness. The Bodily reactions category consisted of four subcategories: *Skin and temperature, Loss of body control, Sickness and dizziness,* and *General weakness.*

TIME

A central aspect of the patients' experience was time, forming a category with the following subcategories: *Previous illness and experiences, How it started* and *Symptoms changing and lasting.* These subcategories contained descriptions of the symptoms debut, how long the symptoms had lasted and how they changed over time. The current patient experience was also put in the context of the patient's previous experiences both in the recent past and a more distant one.

BODILY WHEREABOUTS

The callers sometimes stated the location of the patient, for example if the patient waited *outside* or was *lying down on the floor.* Information on what the patient was doing physically was also provided, for example if the patient was *lying down* or *sitting up*. Sometimes the patient was described as unable to sit or lie down or had to be constantly moving around. Symptoms could also be provoked/palliated through certain positions, activities or movements.

FEAR AND CONCERN

A few callers described the mental and emotional dimension of their experience of illness. Words like *scared, nervous, worried* or *concerned* were used to describe this psychological aspect of the illness perceived.

SITUATION MANAGEMENT

The callers described different strategies they had used to try to manage the situation. This included resting, trying different medications, measuring the patients' physical state using vital signs etc. Statements reflecting an inability to handle the situation on their own and being in need of help were pronounced. There were also callers providing their own thoughts on the cause of the symptoms experienced. The subcategories *Self-care, Difficulties handling a perceived emergency* and *Reasoning about cause* illustrate these coping strategies.

4.4 PAPERS III AND IV

4.4.1 DESCRIPTION OF THE COHORT

In total, 2,917 EMS missions representing 2,352 unique patients were included. The median age of patients included was 72 years old (Q25-Q75, 58-82), and the sexes were equally represented.

Of the EMS missions included, 63 % were assigned priority 1 (highest priority) by the EMD centre. These priority 1 missions concerning patients with chest pain thereby constitute 11 % of all priority 1 EMS missions. On sight, the EMS personnel triaged ten percent to the highest priority and four to the lowest priority when applying the Rapid Triage and Treatment System (RETTS) [85] [110].

Almost 90 % of the EMS missions included resulted in the patient being transported to hospital. Of these about 50 % were admitted to a hospital ward. Ten percent remained at site and less than one percent were transported directly to a primary healthcare centre.

	n (%)
All	2917 (100)
Mean age (SD)	69 (17)
Median age (Q1-Q3)	72 (58-82)
Priority by EMD	
Priority 1	1836 (62.9)
Priority 2	1049 (36.0)
Priority 3	32 (1.1)
Priority by EMS-personnel	
Priority 1	311 (10.7)
Priority 2	1969 (67.5)
Priority 3	325 (11.1)
Priority 4	10 (0.3)
Did not convey	302 (10.4)
Priority according to RETTS by EMS-personnel	
Red	290 (9.9)
Orange	1628 (55.8)
Yellow	887 (30.4)
Green	112 (3.8)
Transport from primary healthcare centre	508 (17.4)
Transport to primary healthcare centre	15 (0.5)
Transported to hospital	2600 (89.1)
Admitted to hospital (missing = 1)	1409 (48.3)
EMS response time (minutes)	
Median EMS dispatch to scene arrival (Q1-Q3)	10 (6-15)
Median EMS time at scene (Q1-Q3)	25 (18-31)
Median transportation time (Q1-Q3)	25 (13-34)
Median total EMS time (Q1-Q3)	95 (73-118)

Table 6. Description of study sample Paper III

Most EMS missions concerned patients with a low-risk condition (68 %). The remaining 32 % were evenly distributed between intermediate- and high-risk conditions. The 30-day mortality rate was 2.9 % for the unique 2,352 patients included in the study. For high- and low-risk patients this figure was 8.9 % and 0.5 %. respectively

All % (n)	100 (2917)
High-risk conditions	16.0 (467)
NSTEMI	6.7 (194)
STEMI	4.3 (127)
Unstable angina pectoris	2.1 (60)
Pulmonary embolism	0.8 (24)
Undefined AMI	0.4 (11)
MINCA/MINOCA	0.2 (7)
Aortic dissection/aneurysm	0.2 (7)
Severe arrhythmias and conducting disorders	0.2 (7)
Takotsubo	0.2 (5)
Sepsis	0.1 (4)
Stroke/TIA	0.1 (4)
Gastric ulcer with perforation/bleeding	0.1 (4)
Pulmonary oedema	0.1 (2)
Other, high risk	0.4 (11)
Intermediate-risk conditions	15.6 (455)
Atrial fibrillation/flutter	3.8 (112)
Heart failure (without pulmonary oedema)	2.1 (60)
Pneumonia	1.8 (52)
Myocarditis, pericarditis, endocarditis	1.1 (31)
Syncope and collapse	0.6 (18)
Aortic valve stenosis	0.6 (17)
Tumour	0.6 (17)
Chronic obstructive pulmonary disease (COPD)	0.5 (14)
Infection, intermediate risk	0.5 (14)
Supraventricular tachycardia	0.4 (13)
Cholelithiasis	0.4 (13)
Pancreatitis	0.3 (9)

Electrolyte disturbance	0.2 (7)
Convulsions and seizures	0.2 (6)
Diverticulitis	0.1 (4)
Other, intermediate risk	2.3 (67)
Low-risk conditions	68.4 (1995)
Chest pain, unspecified	41.5 (1211)
Did not convey (No related ED visit in 72 h or death within 30 days)	9.5 (276)
Angina pectoris (unstable and spasm-induced angina excluded)	3.1 (90)
Abdominal and pelvic pain	2.1 (62)
Infection, low risk	1.6 (47)
Gastritis/Gastro-oesophageal reflux disease	1.4 (41)
Dyspnoea and coughing	1.4 (40)
Palpitation and benign arrhythmias	1.2 (35)
Anxiety and other mental disorders	0.9 (25)
Other pain	0.7 (19)
Anaemia	0.5 (16)
Vertigo	0.5 (14)
Back pain	0.3 (10)
Orthostatic hypotension	0.3 (10)
Hypertension	0.3 (10)
Mental and behavioural disorders due to alcohol	0.3 (10)
Headache	0.2 (6)
Other, low risk	2.5 (74)

Table 7. Diagnoses and risk classification distribution

A wide variety of diagnoses were represented by the cohort. Unspecified or musculoskeletal pain were the most common. AMI was the second most common. Of the EMS missions included, the patient was given a diagnosis of AMI in twelve percent of the cases. Other relatively common diagnoses were atrial fibrillation/flutter (3.8 %), stable angina pectoris (3.1 %), unstable angina pectoris (2.1 %), heart failure (2.1 %), and unspecified abdominal pain (2.1 %). In almost ten percent of the EMS missions, the patient was not conveyed to the ED and did not have a related ED visit within 72 hours.

Patients included presented with varying symptomology in all risk classification groups. They most commonly described central chest pain about the size of a palm, pressuring in character and accompanied by pain in left arm and affected breathing. Such "classical" myocardial infarction symptoms were commonly reported both in the high- and low-risk group. Strongly deviating vital signs were uncommon. In general, the patients included were old and had a substantial comorbidity. Hypertension (58%), psychiatric disorder (39%), ACS (29%) and atrial fibrillation/flutter (26%) were the most common diagnoses in the patients' previous medical history.

4.4.2 PREDICTIVE VARIABLES

In the univariate analyses of the data observed, 25 variables showed significantly increased odds ratios and 16 variables showed significantly decreased odds ratios of having a high-risk condition (Appendix I).

When predicting low-risk conditions, 11 variables showed significantly increased odds ratios for a low-risk condition whereas 36 variables showed a significant increase in the ability to predict the absence of a low-risk condition (Appendix II).

When executing the same analyses on imputed data regarding high-risk prediction, nine variables were added. One variable was withdrawn. For low-risk prediction the corresponding figures were six and one variable respectively.

4.4.3 PREDICTION MODELS

In general, high-risk prediction models were more accurate in terms of Receiving Operating Characteristics – Area Under Curve (ROC-AUC), compared with models predicting low-risk conditions. High- and low-risk models 1 (full models) included 20 and 22 variables respectively. These models were also the most accurate of all models in terms of ROC-AUC (0.83 respectively 0.80).

	p-value	Odds ratio
Male sex	<0.001	1.72
Age group ≤50 years (reference)	<0.001	
Age group 51-64 years	0.001	2.78
Age group ≥65 years	<0.001	5.67
Previous history of chronic obstructive pulmonary disease (COPD)	0.015	0.52
Previous history of angina pectoris	0.047	0.68
Previous history of kidney disease	0.002	0.46
Previous history of atrial fibrillation/flutter	<0.001	0.29
ECG - ST-depression	<0.001	3.75
Paleness	<0.001	2.15
Pain intensity according to Numeric Rating Scale >8	0.011	2.19
Time elapsed since pain onset >3 hours	0.002	0.62
Pain debut during activity	<0.001	2.26
Pain debut while sleeping	0.037	0.61
Constant pain	0.001	1.60
Pain in right shoulder	0.009	2.68
Pain in left arm	0.026	1.58
Pain in right arm	0.006	2.29
Tingling/stinging pain	0.022	0.23
Central chest pain	0.003	1.58
Right-sided chest pain	0.047	0.33
Prehospital TnT ≤50 ng/L (reference)	<0.001	
Prehospital TnT 51-100 ng/L	<0.001	4.97
Prehospital TnT 101-1000 ng/L	<0.001	19.44
Prehospital TnT >1000 ng/L	0.001	30.33

Table 8. Variables included in high-risk model 1 (full model)

	p-value	Odds ratio
Male sex	<0.001	0.67
Age group ≤50 years (reference)	<0.001	
Age group 51-64 years	<0.001	0.48
Age group ≥65 years	<0.001	0.25
Previous history of angina pectoris	0.001	1.59
Previous history of heart failure	0.018	1.42
Previous history of kidney disease	0.001	1.84
Previous history of atrial fibrillation/flutter	<0.001	2.37
ECG - without abnormalities	<0.001	2.07
ECG - atrial fibrillation/flutter	<0.001	0.38
ECG - ST-depression	<0.001	0.23
ECG - Q-wave	0.001	2.57
Paleness	<0.001	0.48
Vomiting	0.045	0.64
Affected breathing	<0.001	0.61
Time elapsed since pain onset >3 hours	0.022	1.29
Pain debut during activity	0.009	0.70
Pain debut, sudden, within seconds	0.004	1.42
Constant pain	0.002	0.71
Pain in right shoulder	0.002	0.40
Pain in right arm	<0.001	0.38
Pain in right leg	0.042	4.83
Pressuring pain	<0.001	0.64
Prehospital TnT ≤50 ng/L (reference)	<0.001	
Prehospital TnT 51-100 ng/L	<0.001	0.28
Prehospital TnT 101-1000 ng/L	<0.001	0.08
Prehospital TnT >1000 ng/L	0.144	0.23

Table 9. Variables included in low-risk model 1 (full model)

By reducing the number of variables and combining them into a model predicting both low- and high-risk condition (Combined model) clinical feasibility was improved. This reduced prediction model accuracy, but the ROC-AUC remained above 0.7 for both low- and high-risk condition prediction.

	High-risk prediction		Low-risk prediction	
	p-value	**Odds ratio**	**p-value**	**Odds ratio**
Male sex	<0.001	1.59	0.001	0.72
Age group ≤50 years (reference)	<0.001		<0.001	
Age group 51-64 years	0.001	2.59	<0.001	0.49
Age group ≥65 years	<0.001	4.13	<0.001	0.29
Prehospital TnT ≤50 ng/L (reference)	<0.001		<0.001	
Prehospital TnT 51-100 ng/L	<0.001	5.37	<0.001	0.26
Prehospital TnT 101-1000 ng/L	<0.001	20.17	<0.001	0.08
Prehospital TnT >1000 ng/L	<0.001	32.92	0.050	0.16
Previous history of kidney disease	<0.001	0.38	<0.001	2.19
Previous history of atrial fibrillation/flutter	<0.001	0.29	0.002	1.47
ECG - ST-depression	<0.001	3.34	<0.001	0.25
Paleness	<0.001	2.19	<0.001	0.41
ECG - without abnormalities	0.143	0.80	<0.001	2.03
Time between pain onset and EMS arrival >3 hours	<0.001	0.55	0.004	1.35

Table 10. Variables included in combined prediction model

	High-risk model 1 (full model)	**Low-risk model 1 (full model)**	**Combined model, high-risk prediction**	**Combined model, low-risk prediction**
Number of variables in model	20	22	9	9
Probability cut-off, %	50	90	50	90
Sensitivity, %	31	33	26	21
Specificity, %	98	94	98	95
Positive predictive value, %	74	94	70	92
Negative predictive value, %	91	33	90	30
ROC-AUC	0.83	0.80	0.79	0.75
High-risk patients classified as low-risk, n (%)	-	16 (0.6)	-	10 (0.4)

Table 11. Prediction models' characteristics and accuracy

Age, ST-depression on ECG and TnT were the strongest predictors in all prediction models. This was true for both low- and high-risk prediction. Of all patients with a high-risk condition, 40 % had a TnT value >50 ng/L. If high-sensitive TnT analyses was accessible in the EMS setting, enabling the use of >14 ng/L as threshold for pathological TnT value, 78 % of all patients with a high-risk condition would pass this threshold. This means that 38 % of all high-risk patients have TnT value between 15 and 50 ng/L.

5 DISCUSSION

5.1.1 NEW STUDIES ON PREDICTIVE VARIABLES

After the submission of Paper I in April 2016, a few more reports on the subject have been published, using prehospital data. They present results on the association between the following factors and an outcome measure in line with the inclusion criteria of Paper I.

- Male sex [43 63]
- Older age [39 43 63]
- Previous medical history of:
    - AMI/ACS [39 63 157]
    - PCI [63]
    - CABG [63]
    - Hyperlipidaemia [63]
    - Hypertension [39 63]
    - Anxiety/panic attacks (negative association) [63]
    - Congestive heart failure (negative association) [43]
    - Chronic obstructive pulmonary disease (COPD) (negative association) [43]
- Medication with aspirin, clopidogrel or statins [39]
- Central/retrosternal chest pain [39 157]
- Severe pain [39 157 158]
- Continued pain [39]
- Radiation
    - Any radiation [39 43]
    - Arm [63]
    - Jaw [63]
- Clamminess/Nausea [43 63]
- Dyspnoea [43]
- Pain increasing by position change or taking breaths (negative association) [39]

The results of these studies strengthen the level of evidence for several of the factors examined when added to the results of Paper I. However, one should be aware of that no association was reported for several of the factors evaluated in Paper I in these recently published reports. This may weaken the level of evidence for these factors. For example, Pedersen et al.[43] reported no association regarding previous medical history of AMI or diabetes mellitus. Rawshani et al. [157] stated no association concerning increase of pain when moving or taking deep breaths, and the same was true for nausea/vomiting.

Frisch et al. [63] did not find any association regarding vital signs, previous medical history of diabetes mellitus, congestive heart failure or nausea/vomiting.

The number of reports published on the subject since the submission of Paper I highlight that more knowledge on risk assessment of EMS patients with chest pain is warranted. The sometimes contradictory results and the low level of evidence for several factors also stress that more research is needed.

5.1.2 SYMPTOMS IN EMS PATIENTS WITH CHEST PAIN

Paper II shows that patients with chest pain due to a high-risk condition present with a wide range of symptoms. Paper III also highlights that symptoms vary widely, in patients both with and without a high-risk condition. This is partly explained by the variety of outcome diagnoses included in both Papers II and III. However, symptoms also vary substantially between patients with the same diagnosis of their chest pain. This underlines how problematic it is to reason in terms of typical high-risk chest pain presentation, or even typical AMI presentation.

Most patients in Paper III (and also Paper II) have one or several typical AMI symptoms [64] such as: central chest pain, pressuring pain, pain in left arm, experiencing affected breathing or area affected by pain the size of a palm [159]. However, this is true for patients with both low- and high-risk conditions. This thesis does not provide any answers as to why such symptoms are so common. One may assume that the general idea among laymen on how an AMI presents is in line with above-mentioned "classical" symptoms. Such symptoms therefore trigger them to contact the EMD to a greater extent than other types of chest pain and chest pain-related symptoms.

The variety of symptoms along with typical AMI symptoms also being so frequent in patients with low-risk conditions stresses how difficult it is to risk-assess patients with chest pains based on symptoms presentation. This highlights the challenging task that EMS personnel and especially EMD personnel encounter in their clinical everyday life. The latter are almost exclusively directed to making their assessments based on symptoms descriptions. These difficulties are further exacerbated by subjectivity in both symptom experience and description. What one patient means when describing a cramping pain radiating to the left shoulder with a sudden onset may differ from another one using the same wording but describing another sensation or experience. It is important for EMS personnel to be aware of these difficulties and take them into account in their patient assessments.

However, one should not neglect the fact that several symptoms (not least several typical AMI symptoms) have a predictive value in the identification of high-risk conditions, both in univariate and multivariate analyses. For example, central chest pain, pressuring pain, paleness, intense pain, pain debut during activity, constant pain and pain in left or right arm increase the odds ratios for having a high-risk condition.

Regarding the identification of patients with low-risk conditions based on symptoms presentation, this seems even harder compared with the identification of high-risk conditions. This is especially the case since few symptoms are associated with increased odds ratios for low-risk conditions in, above all, the multivariate analyses but also the univariate ones.

5.1.3 THE PREDICTIVE VALUE OF VITAL SIGNS

In the vast majority of the EMS missions described in Paper III, the vital signs are fairly normal in patients with both low- and high-risk conditions. High breathing rate and low oxygen saturation were the only vital signs predicting high-risk conditions. On the contrary, all the vital signs studied showed association with low-risk conditions. Thus, elevated breathing rate, low oxygen saturation, elevated heart rate, decreased level of consciousness and elevated body temperature all had a negative predictive value in the identification of low-risk conditions. Deviating vital signs seem therefore to be of most interest when ruling out low-risk conditions.

Paper I concludes that few reports have investigated the predictive value of vital signs in prehospital patients with chest pain. Furthermore, it should be pointed out that the predictive value of vital signs can be difficult to clarify. This is due to a number of different reasons. One is the relative rareness of deviating vital signs, and this affects the preconditions for providing significant results in statistical analyses. Furthermore, the predictive impact can vary depending on which cut-offs are set to define what is a deviating vital sign. In addition, many vital signs can deviate in two directions. For example, both a very low and very high heart rate are pathological. The same is true for body temperature, breathing rate and blood pressure. This complicates how vital signs should be managed in prediction model development analyses. Instead, one may argue that a strongly deviating vital sign is, in itself, reason enough for prompt hospital transport and not referral to self-care, self-transportation or primary care. This line of action is supported by the results of Paper III, showing that strongly deviating vital signs reduce the odds ratios for having a low-risk condition. This is also the reason why patients with strongly deviating

signs are excluded from the prediction model development analyses in Paper IV.

5.1.4 ECG IN PREHOSPITAL PATIENTS WITH CHEST PAIN

Several ECG abnormalities were predictive of high-risk conditions in the univariate analyses. Most of them turned out to be non-significant in the multivariate analyses, probably due to association between ECG changes and old age. ST-elevation was by far the strongest predictor of a high-risk condition among the ECG variables studied. Given the already strong evidence for the use of fast-tracks for patients with ST-elevation [34], EMS missions covering patients with ST-elevation were excluded from the multivariate analyses.

The only ECG abnormality that remained in the high-risk models after introducing TnT as a predictor was ST-depression. This was one of the strongest predictors along with old age and TnT. ST-elevation and ST-depression seem therefore to be the only ECG abnormalities that are of interest when predicting high-risk conditions in patients with chest pain in the prehospital emergency setting. However, one should take into account that rare ECG abnormalities such as atrioventricular block III and ventricular tachycardia by themselves constitute high-risk conditions.

An ECG with sinus rhythm and none of the ECG abnormalities studied increased the odds ratios for having a low-risk condition. A "normal" ECG therefore indicates that the patient is less in need of acute hospital care. However, it is important that EMS personnel are aware that in the cohort studied, about a quarter of all patients with a high-risk condition had an ECG showing a sinus rhythm without any abnormalities.

5.1.5 THE PREVIOUS MEDICAL HISTORY OF EMS PATIENTS WITH CHEST PAIN

In the univariate analyses in Paper III, a previous medical history of COPD, atrial fibrillation/flutter or psychiatric diagnoses all reduced the odds ratios for a high-risk condition, while hypertension and diabetes mellitus increased the odds. A previous medical history of hypertension, heart failure, stroke, kidney disease, cancer and COPD lowered the odds ratios for a low-risk condition. Being previously diagnosed with a psychiatric disease increased the odds for having a low-risk condition.

Previous medical history is strongly associated with age and sometimes also sex. Therefore, the associations between previous medical history and outcome indicated by the univariate analyses reported in Paper III are quite uncertain.

The multivariate analyses in Paper IV (high-risk model 1) show that none of previous medical history variables increased the odds ratios for having a high-risk condition. Odds ratios for having a high-risk condition were reduced if there was a previous medical history of COPD, angina pectoris or atrial fibrillation/flutter. One may assume that in EMS missions concerning patients with these chronic diagnoses, the chest pain experienced by the patient is often caused by their chronic disease and not by a new event.

Previous history of kidney disease became predictive first after introducing TnT to the model. Renal insufficiency may result in elevated TnT levels without any myocardial damage being present [64]. Therefore, it may be so that previous medical history of kidney disease is a confounder affecting TnT levels and thereby the predictive value of TnT, rather than having a true negative association with high-risk conditions. This is strengthened by ad hoc analyses showing an association between previous kidney disease and elevated TnT levels.

5.1.6 TROPONINS IN THE EMS SETTING

TnT turned out to be one of the strongest predictors in all models in which it was included. TnT analyses can therefore contribute substantially to prehospital risk assessment and triage.

Thirty-eight percent of all patients with a high-risk condition had a pathological TnT value detectible with high-sensitive analyses but not with today's prehospital TnT analysis equipment. This result implies that by making high-sensitive analyses accessible in the EMS setting, prehospital risk prediction could be improved further. Unfortunately, bed-side high-sensitive TnT analyses are not available at present but remain to be developed.

TnI is, just like TnT, a biochemical cardiac marker that can be used to detect myocardial damage. For TnI there are already handheld devices for bed-side use that provide more sensitive analyses detecting lower levels of Troponins compared with the corresponding products for TnT analyses [160 161]. Therefore the use of prehospital TnI analyses can already be one way to improve the risk assessment of patients with chest pain. However, it is of great value that the EMS uses the same Troponins as the hospital(s) to which they transport the patients. Then the value obtained by the EMS can be used as reference for continued Troponin sampling at the hospital.

5.1.7 DIFFERENCES COMPARED WITH PREVIOUS STUDIES

This thesis shows that there are numerous variables that can be used to predict low- or high-risk conditions in EMS patients with chest pain. The predictive value of some variables strengthens the results of previous research, while other are contradictory compared with previous findings.

For example, several of the symptoms with a predictive value regarding the identification of high-risk conditions, as shown in Papers III and IV, are not stated as predictors of ACS according to the ESC. Examples of such variables are paleness and highly rated pain intensity. On the contrary nausea and pain in jaw or neck are symptoms that according to ESC predict AMI but did not turn out as high-risk predictors in Paper III/IV. Regarding negative predictors of high-risk conditions, right-sided or low chest pain and a small area affected by pain all reduced the odds ratios for a high-risk condition according to Papers III/IV but not according to the ESC guidelines [64].

These differences may be explained by the use of a wider outcome measure (i.e. including more diagnoses in the high-risk group) in this thesis compared with previous research including the ESC guidelines [64], generally focusing on AMI prediction. Even if AMI constitutes the majority in the high-risk group, the inclusion of other diagnoses ought to affect the predictive value of the variables studied.

Another factor that may explain these differences is that the cohort studied is fairly unselected. For Papers III/IV, all adult patients with a chief complaint of chest pain were included, not considering what the EMS personnel judged as being the cause of the patient's chest pain. This should be compared with many previous studies in which inclusion is based on a suspicion of AMI/ACS or on excluding patients severely affected by their illness, e.g. with impaired circulation.

Furthermore, the results presented in this thesis are based on the analyses of data collected in the prehospital setting. In contrast, the ESC guidelines [64] are based on studies conducted in the hospital setting. EMS patients with chest pain are older [45 46 48 49 97], have more comorbidity [45 48-50 97], differ in symptomology [33 45 46 49 97], differ in vital signs [46 48 50], are examined closer to symptom onset [49 97] and more commonly have an AMI [33] compared with ED patients. All these differences may have an impact on the predictive value of the variables studied.

Quite surprisingly, premature atrial contractions (PAC) turned out to be a high-risk predictor in the multivariate analyses based on complete cases in Paper III.

This may, once again, be explained by the inclusion of other diagnoses than AMI in the high-risk endpoint. This is strengthened by ad hoc analyses using AMI as the endpoint and in which PAC did not turn out as a predictor. However, PAC was not included in any of the prediction models based on the set of cases used in Paper IV (imputed data). Therefore, one can reason that this finding in Paper III might be a chance finding. More research is needed to clarify this finding.

Neither LBBB nor RBBB turned out to be high-risk predictors in the predictions models developed. In the ESC guidelines, both RBBB and LBBB are stated as AMI predictors (however weak) in patients with a high suspicion of AMI [64]. This discrepancy may, as previously mentioned, be explained by the unselected inclusion of patients with chest pain, not only patients with a high suspicion of AMI, and the use of high-risk conditions as endpoint instead of AMI. Furthermore, whether the LBBB/RBBB on the prehospital ECG was new or old was taken into consideration in this thesis.

The results in Paper IV indicate that previous medical history does not seem to increase the odds ratio for having a high-risk condition. This is quite surprising and in contrast to the ESC guidelines [64] which state that diabetes mellitus, hypertension, renal dysfunction and previous manifestations of coronary artery disease all increase the risk of NSTEMI in patients with suspected AMI. Once again, this may be due to this thesis not using AMI as endpoint. It is also possible that the comorbidity was so extensive in the cohort studied that statistical prerequisites for risk prediction based on previous medical history were altered. This means that EMS patients with chest pain have so much comorbidity that risk stratification based on previous medical history is somewhat distorted.

That previous medical history of ACS did not increase the odds ratios for having a high-risk condition neither in univariate nor multivariate analyses was especially unexpected. Both the ESC guidelines [64] and several prehospital studies [39 63 157] state that previous ACS increases the risk of adverse outcome in patients with chest pain. However, there are also some prehospital studies reporting no such association [43 62]. This discrepancy may be explained both by different studies using different definitions of previous history of ACS and using differing endpoints. One may conclude that the predictive value of previous ACS in EMS patients with chest pain is not clear and needs to be studied further.

The ESC guidelines [64] state that renal dysfunction is a risk factor in patients with acute chest pain. Thang et al. [62] and Pedersen et al. [43] report no association

between kidney disease and cardiovascular complications or in-hospital death in EMS patients with chest pain. The results of this thesis show that kidney disease lowers the risk for having a high-risk condition. Renal dysfunction and kidney disease are vast concepts and reported differences may very well be due to using different definitions. One should also not ignore the risk that this may be a chance finding, or, as discussed earlier, that kidney disease is a confounder affecting TnT levels.

Paper I shows that the predictive value of previous medical history when assessing EMS patients with chest pain in general is quite poorly investigated and that the evidence is inconclusive. When adding the results from studies published after Paper I to the findings in Papers III/IV, it becomes even clearer that more research is needed to clarify the role of the patient's previous medical history in EMS risk assessment.

5.1.8 COMPARISION WITH OTHER PREDICTIVE TOOLS

Previous studies on predictive tools for prehospital risk stratification are focused on applying HEART Score in the EMS setting [101] [162-164]. When comparing the results of these studies and the combined prediction model presented in Paper IV, one can observe that the c-statistics are equivalent. However, one should keep in mind that these studies use MACE as the endpoint and not the risk group classification used in this thesis. They therefore do not consider several other high-risk diagnoses. Both Ishak et al. [164] and Cooper et al. [162] also point out that some patients with high-risk conditions are misclassified in their studies as low-risk. Compared with HEART Score, the combined prediction model developed in Paper IV has the advantage of containing fewer variables, which eases clinical use.

Both Cooper et al. [162] and Stopyra et al. [101] use TnI instead of TnT. Furthermore, Stopyra et al. [101] use TnI obtained in-hospital rather than in the prehospital setting. Van Dongen et al. [163] use prehospitally analysed TnT but in their study they had access to prehospital analysis equipment with a limit of TnT detection of 40 ng/L instead of 50 ng/L as applied in the prediction models in Paper IV. When contacting the manufacturer Roche Diagnostics, they state that the equipment used by van Dongen et al. [163] is not accessible in the Nordic countries. This is the reason why Stengaard et al. [118] [165] also use 50 ng/L as the lower detection limit in their studies on the use of prehospital TnT in Denmark. These differences regarding Troponin analyses make it slightly more difficult to compare the results of these studies with the findings in Paper IV. One may assume that both using a lower detection limit like van Dongen et al. [163] or using TnI obtained later on, after hospital arrival, like Stopyra et al. [101] result

in improved accuracy. Therefore, it is likely that the prediction models developed in this thesis would be further improved by applying such Troponin fundamentals instead.

As argued in this thesis, it is not unproblematic to apply prediction models developed for hospital use in the EMS setting. Firstly, prediction model endpoints appropriate for hospital decision-making are not always as relevant in the prehospital emergency setting. For example, EMS personnel have little guidance in their decision-making on non-conveyance, self-transportation cases, appropriate receiving healthcare unit and transportation urgency, by assessing the risk of MACE in 30/45 days as provided by HEART Score. The reason is that this does not rule out other diagnoses requiring acute care. Instead, assessing the probability of the patient having a high- or low-risk condition causing her or his chest pain would be of greater clinical value and provide better support for EMS clinical decision-making.

Secondly, the hospital and prehospital chest pain population differ in several clinical characteristics [33 45 46 48-50 97]. These differences may affect the predictive value of such variables and how an optimal prediction model should be constructed. One example of this is the predictive value of the patient's previous medical history. In HEART Score, previous medical history is just as important as ECG findings and age. Paper IV implies that in EMS patients with chest pain, previous medical history is of less importance, especially when adjusting for age, while ST-depression on ECG and age are stronger predictors. It may be so that HEART Score, when applied in the prehospital setting, overrates the predictive value of previous comorbidities.

Today, the EMS often use more general assessment tools such as RETTS [85] or early warning scores [166] in their decision-making, also when assessing patients with chest pain. One may assume that by applying more specific tools when assessing the large population of EMS patients with chest pain, prediction accuracy could be improved. For example, in Paper III, only 4 % were assessed at the lowest priority according to RETTS. Given that 68 % of all EMS missions included patients with a low-risk condition, one may suppose that more refined and specific tools may improve identification of patients with low-risk conditions. This is also strengthened by the results of Paper IV and previous studies on low-risk prediction using HEART Score [162 163]. Ad hoc analyses imply that prediction models that have been developed outperform RETTS not only in low-risk prediction but also regarding high-risk identification accuracy.

5.1.9 CLINICAL CONSIDERATIONS

When conducting research, potential clinical application and real-world feasibility should be taken into account. Therefore, as mentioned earlier, applied endpoint definitions in terms of high- and low-risk classification were decided upon to ensure clinical relevance.

When considering which variables to include in the prediction models, it is important to take clinical feasibility into account. For example, symptoms are subjective and differ between patients both in terms of experience and description. Signs such as paleness are subjective to the observer. Two EMS colleagues may assess paleness differently. Regarding previous medical history, this can sometimes be hard to pinpoint in the prehospital setting. Patients are not always able to recollect relevant comorbidities and diagnosis classification may differ over time and between clinicians. The impact of such subjectivity and related shortcomings can be limited by providing explicit definitions of variables included or by reducing the use of particularly problematic variables. In the combined prediction model in Paper IV, this is done by reducing the number of symptom variables and to a large extent relying on more objective variables such as age, sex, troponin and ECG findings.

Prediction model development in Paper IV was based on an unselected cohort of EMS patients with chest pain. This improves the prerequisites for generalisation of the results. But above all, the unselected inclusion of patients with chest pain eases the identification of patients where the prediction would be applied if implemented in clinical care. This means that the prediction model is valid for all EMS patients with chest pain, given that the need of prompt hospital care is not obvious in terms of ST-elevation on ECG or strongly deviating vital signs. This should be compared for example with the studies by Cooper et al. [162] and van Dongen et al. [163] in which inclusion was based on the EMS personnel's subjective suspicion of ACS. The use of chest pain as the basis for inclusion instead of the clinical suspicion of certain conditions is also more in line with standard EMS working methods. They are, for obvious reasons, focused on symptoms rather than diagnoses.

One goal of the prediction models developed in this thesis was to identify patients with low-risk conditions enabling safe referral to less resource-intensive venues, not to identify all patients suitable for such referral. One should also keep in mind that if the prediction model classifies a patient as low-risk, this does not mean that ambulance transport to hospital is by definition inappropriate. The intention of the prediction models developed is to guide the

EMS personnel in their decision-making, not to replace clinical judgement. Furthermore, ambulance transport to hospital can also be motivated by other reasons than the calculated risk of adverse medical outcome. Examples are physiological factors, frailty, social factors or the patient needing analgesics during transport. All these aspects need to be considered if implementing any of the models in clinical care.

It is also important to consider the risks entailed by wrongly classifying a patient with a high-risk condition into the low-risk group. These risks can be limited if the patients classified as low-risk are referred to primary healthcare or self-transportation to the ED rather than waiting at home. However, the latter approach will only be beneficial for the EMS organisation and will not spare low-risk patients from unnecessary ED attendances or reduce ED crowding. Wrongly classifying low-risk patients as high-risk is less likely to harm the patient but may entail unnecessary utilisation of in-hospital resource-intensive procedures. Before initiating clinical testing of the prediction models developed, these aspects of potential risks and benefits regarding patients and healthcare resource utilisation should be thoroughly reflected upon. Which decisions should the prediction model support? What are the risks? What will be gained? Will the benefits outweigh the risks?

5.2 METHODOLGICAL CONSIDERATIONS

This thesis is about prehospital risk stratification of patients with chest pain. There is no consensus on how to risk-classify different conditions in prehospital care [68]. For this thesis, a three-part risk classification (low-, intermediate- and high-risk) is used. However, the definition of these risk classification groups is not consistent throughout the papers included. In Paper I, the following diagnoses are regarded as high-risk conditions: ACS, cardiac arrest, pulmonary oedema, pulmonary embolism, aortic aneurysm or dissection, myocarditis, endocarditis, pancreatitis, gut perforation, severe arrhythmia or severe heart valve disease. In Papers III and IV, myocarditis, endocarditis and pancreatitis are not considered as high-risk conditions. These differences between the papers are due to the ongoing discussion on the most clinically useful definition of the risk classification groups during the work of this project. This discussion needs to be continued among researchers and clinicians in order to create conditions for valid research on prehospital risk assessment as suggested by Wibring et al. [68].

For this thesis, the difference in the definition of high-risk conditions between Papers I and III/IV does not affect the results as no studies analysed in Paper I included the disjunctive diagnoses (i.e. myocarditis, endocarditis or pancreatitis) as part of their endpoints.

5.2.1 PAPER I

Paper I includes studies based on data collected both at the EMD and after EMS patient arrival. These wide inclusion criteria complicate clinical utility since it is difficult to comprehend how the results apply to the specific clinical setting of interest. On the other hand, the limited number of studies included indicates that narrower inclusion criteria may result in too few studies being included to allow any aggregation and analysis.

The outcome measure of the studies included varies. However, most of them uses an ACS-related endpoint. This makes it difficult to determine to what extent the results apply to high-risk conditions other than ACS.

The diagnostic criteria for ACS, EMS workflow and the prehospital chest pain population have changed over time. The inclusion of older studies therefore complicates the evaluation of the results when applied to EMS care of today. However, once again, further limiting inclusion criteria would not be feasible.

The studies included were assessed using SIGN to provide an objective and validated score of study quality. These checklists had to be adjusted to comply with the design of the studies included since several checklist items did not apply. This adjustment may have reduced the quality of the assessment. Furthermore, the checklists do not take sample size into account. The results of very small studies and studies based on larger sample sizes are therefore valued equally. This is problematic since small sample sizes may leave true statistical associations undetected.

A meta-analysis of pooled data would have been preferable. However, differences between the studies included in terms of outcome, patient inclusion criteria, applied statistics and data availability prevented the execution of such a meta-analysis.

5.2.2 PAPER II

The methodological approach used in Paper II was chosen to obtain and present data on which symptoms and situational information are described close to illness onset by patients with chest pain due to a high-risk condition. The use of recorded emergency medical calls to provide data on patients' experiences is quite rare, particularly in studies on patients with chest pain. Emergency medical calls differ substantially compared with the data provided by in-depth interviews that is often used when studying patient experiences in qualitative research. The nature of the data in terms of short duration and question-response conversations provided quite succinct descriptions which also characterise the results.

Due to the ambition to stay close to the original data and the nature of the calls, an analysis on a manifest level was carried out [167]. This resulted in categories with a lower degree of abstraction compared with analysing latent data and applying a deeper interpretation [133 167]. This may be considered a weakness. However, the ambition of the study was to identify statements in the patient narrative that could be used when developing the questionnaire for Paper III. Therefore, this is rather a strength, making the results more useful for the project.

This study included patients with several chest pain-related high-risk conditions, not only ACS, which is the case in many previously conducted qualitative studies on symptom descriptions [52-57 61 168]. Furthermore, emergency medical call recordings were analysed instead of using retrospective interviews. This was done to avoid excluding deceased patients or patients who

were too severely ill to take part in an interview. Using emergency calls instead of retrospective interviews also eliminates the effect of recall bias.

The results presented in Paper II confirm previous findings to a large extent. One may therefore assume that the effect of using emergency medical call recordings instead of retrospective interviews and including more diagnoses than ACS was somewhat more limited than had been understood. However, the results of this study provide a more detailed and extensive picture of patients' symptoms descriptions than previous reports.

The nature of the calls was dependent on how the telecommunicator structured the call. Most calls were characterised by the telecommunicator asking a question and the caller answering this question. The type of question asked therefore greatly influenced the information provided by the caller. Given the extensive and varied results, one may conclude that this interviewer effect did not hinder the callers from providing a rich description of the situation.

5.2.3 PAPERS III AND IV

For the data collection, a new questionnaire was developed. This was designed by using the results of Papers I and II along with the design and results of numerous previously conducted studies on chest pain symptom description and assessment. Initially, more than twenty items were included. This number was reduced to ensure clinical functionality and protocol compliance. A draft of the questionnaire was also sent to all EMS personnel in Halland asking them to comment on the items included and the functionality in clinical EMS care.

The items in the questionnaire are to some extent focused on ACS identification. Items more related to other high-risk conditions were also included, but the priority of the questionnaire was to ensure ACS identification, knowing that ACS is by far the most common high-risk condition in the population. To include items on for example long-term inactivity or the use of birth control pills in the hope of identifying patients with pulmonary embolism was not deemed statistically motivated, since such items would probably only apply to a very few patients. Also, the low incidence of pulmonary embolism especially in the prehospital chest pain population did not justify its inclusion.

The data used in Papers III and IV is quite unique since it provides a detailed and comprehensive description of a large cohort of EMS patients with chest pain. Data is presented on demographics, vital signs, biochemical cardiac markers, ECG and a large number of symptoms. However, some variables have high rates of missing data. Given the prehospital nature of the study, this problem with missing data is not surprising. Data collection in the prehospital

setting is known to be challenging. Reasons for this are low protocol compliance among EMS personnel [144] [169], an often stressful situation and limited personnel resources, which taken together make it difficult to obtain the information requested.

Given these preconditions, one may argue instead that the rate of missing data is quite low. This can probably be explained by:

- Using a questionnaire integrated in the ordinary EMS journal and including items resembling those of interest in an ordinary anamnesis
- Including EMS personnel in the design of the questionnaire
- A research question of clinical relevance for EMS personnel
- Project manager clinically active in the current EMS organisation
- Providing continuous feedback and encouragement to the EMS personnel on the data inclusion progress
- Using opt-out for patient inclusion instead of obtaining informed consent on site

The rates of missing data were higher for certain variables, for example pain radiation, pain intensity and pain quality. This is probably partly explained by the fact that these variables were collected using free text fields in the questionnaire instead of multiple-choice options. These higher rates of missing data may also be due to difficulties in obtaining this information from the patient. If that is the case, one should be careful about including such variables in a prediction model as it may reduce clinical feasibility.

In general, missing data was somewhat more common in EMS missions concerning patients with low-risk conditions. This is probably partly explained by the fact that almost all patients remaining at site had a low-risk condition. For these patients, no TnT blood sample was obtained (given the use of in-hospital TnT analysis). Furthermore, the questionnaire was filled in to a lesser extent for these patients. However, this slight bias in missing data distribution was not deemed to have any substantial impact or to influence the clinical relevance of the results, especially given the use of imputed data for model development.

In all research, potential bias should be considered. Selection bias is always a risk in cohort studies, i.e. that the participants selected are not representative of the patient population of interest [170]. The unselective approach of including all patients with chest pain within the current EMS organisation should limit the risk of such selection bias. However, the inclusion of participants was based

on the EMS personnel assessing the patient as having a chief complaint of chest pain. It is possible that the EMS personnel sometimes made this assessment also for patients without chest pain, due to willingness to include patients in the study or suspecting a cardiovascular event in patients without chest pain. One example is patients with abdominal pain or dyspnoea who have ECG findings indicating a cardiac origin. It is not possible to determine if this was sometimes the case. However, the number of patients assessed as having a chief complaint of chest pain did not differ in 2018 compared with previous or following years, suggesting that this did not occur in any larger extent.

Other types of bias are observer bias and misclassification bias. Observer bias refers to different observers making different assessments concerning how to classify data [170]. For example, various EMS personnel might assess patient paleness differently. Since the data of the study was collected by close to 200 EMS personnel, with different experiences and education, it is quite certain that observation bias is a factor. This reflects a problem also existing in real-life EMS care and that will also be present if applying the prediction models developed in clinical care. It is difficult to compensate for this, and may not be appropriate either if wanting to provide results that are valid for real-world clinical care.

Misclassification bias refers, for instance, to assigning a data point in the wrong way [170]. Examples are ticking the wrong box in a questionnaire or writing down a wrong number when extracting data from a medical journal. The use of computerised data extraction from patient medical records reduced the risk of misclassification bias when putting the data set together. Unfortunately, this makes no difference if the data extracted was already misclassified in the original source.

Altogether, these and other kinds of bias may have a negative impact on the validity and reliability of the study results. The biases that this study struggles with often also constitute problems in the real world. Thus, one may assume that the results are quite representative for real-world EMS clinical care.

For Papers III and IV, many analyses were carried out due to the many potentially predictive variables and using two different endpoints (low- and high-risk conditions). When conducting multiple analyses, the risk of chance findings (type I error) increases. There are different statistical approaches to handle this problem. One is to use the Bonferroni correction method. However, Bonferroni may be criticised for being too conservative when carrying out many tests and thereby producing false negatives (type II error) [171 172]. Another way to reduce the risk of chance findings is by simply setting a lower threshold

for assessing statistical significance, i.e. lowered p-value. However, this approach also increases the risk of false negatives.

Given the unique data set and the lack of research on predictive factors/models based on prehospital data, a permissive approach in terms of statistical significance was applied. This approach decreases the risk of potential predictors being wrongly rejected. In the prediction model developing process, using multivariate regression analyses, stricter p-value thresholds were applied. The aim was to improve the chance of retained accuracy of the models when applied to another cohort, i.e. to improve generalisability.

The prediction models developed in Paper IV need to be validated on another out-of-sample data set. This type of validation study may also make it possible to identify potential chance findings. Another way to validate prediction models is to divide the data set into two parts before carrying out any analyses. One part is then used for prediction model development and one for prediction model validation. For this project, no such validation methodology was used, since it reduces the sample size available for predictive variable identification, thereby increasing the risk of the study becoming under-powered. As mentioned before, it was deemed important not to risk wrongly rejecting true predictors but instead to discover as many potential predictors as possible. Prediction model validation is instead intended to be conducted in a future study using a new set of data.

6 CONCLUSIONS

Prehospital research on predictive variables when assessing EMS patients with chest pain is sparse. The results of available research are sometimes contradictory and not always in line with previous findings based on hospital data. EMS patients constitute a heterogeneous group. They experience a wide range of symptoms and describe them in many different ways. Typical AMI symptoms are common in patients both with and without a high-risk condition. Vital signs are often within the normal range. Previous medical history is often extensive. Altogether, this makes the EMS personnel's task of risk-assessing these patients very complicated and it should therefore be done with great care and humbleness.

The prehospital risk assessment of patients with chest pain can be assisted by using a decision support tool for the identification of patients with low- and high-risk conditions respectively. The decision support tool developed in this thesis seems accurate enough to provide support in clinical decision-making. The model developed is equivalent in prediction accuracy to HEART Score, but has the advantages of being developed on a more unselected patient cohort, including fewer variables and predicting a more clinically relevant endpoint. The variables included also differ from those used in HEART Score.

ECG ST-deviation, age and TnT are the strongest predictive variables when trying to identify patients with both low- and high-risk conditions, while symptoms have minor value when discriminating patients with low-risk conditions from those with high-risk conditions. This indicates that prehospital Troponin analyses contribute substantially to the risk assessment of EMS patients with chest pain. However, a more sensitive prehospital TnT analysing method is warranted.

7 FUTURE PERSPECTIVES

The prediction model developed in this thesis shows promising results. It seems possible to provide prediction models accurate enough to be supportive in the EMS personnel's decision-making. However, before clinical implementation, the prediction model needs to be tested on an independent cohort. It is also important to decide in which clinical decision-making the prediction model should be applied. To enable clinical use, the model should preferably be integrated into the EMS digital medical record system, and possible to use bed-side, or at least as a separate application in a mobile device. It would be desirable for this model automatically also to render a risk prediction and a suggestion as to appropriate care and destination, when EMS personnel enter data into the patient's medical record, during patient examination.

A digitally integrated decision support tool such as this would allow the use of much more complex and hopefully more precise prediction models compared with the semi-analogue, rule-based ones conventionally used today [173]. This would also allow the prehospital use of machine learning algorithms which show promising results regarding both ED triage[174] and ACS prediction, [175-178] outperforming both conventional triage tools and risk scores. One step in this direction is the planned development of a machine learning risk prediction algorithm based on the data collected for Papers III and IV in this thesis.

Data for Papers III and IV in this thesis was to a large extent retrieved from patient medical records using data extraction software. Adapting medical journal software to facilitate such data extraction along with developing data extraction techniques would allow outcome prediction research on larger samples with better quality. Not least, research would benefit from the possibilities of applying machine learning algorithms in the prehospital setting. This would also reduce the ethical issue of integrity intrusion entailed by reading medical records for research data extraction, since automated data extraction makes it possible to collect, compile and present data anonymously without anyone actually reading the patient's medical record. A prerequisite for this is the possibility to follow the patient automatically from EMS (or EMD) contact to hospital discharge and preferable even further.

By applying machine learning at the EMD, it seems feasible to improve both cardiac arrest identification[179 180] and dispatch prioritisation [173]. Using the data collected for this thesis to develop a prediction model based on symptoms, medical history and patient demographics would be one step in trying to

improve EMD prioritising of patients with chest pain, since this most commonly is the only data available to EMD personnel.

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APPENDIX I – UNIVARIATE ANALYSES, HIGH-RISK PREDICTORS

Increased odds ratio of a high-risk condition	p-value
Male sex	<0.001
Older age	<0.001
Previous history of hypertension	0.016
Previous history of diabetes mellitus	0.027
Breathing rate ≥25 breaths/min	0.001
Oxygen saturation ≤91 %	0.001
Pale	<0.001
Clammy	<0.001
Increased pain intensity	<0.001
Pain debut during activity	<0.001
Quick debut, within minutes	0.001
Constant pain	<0.001
Pain between scapulars	0.014
Pain in left arm	<0.001
Pain in right arm	<0.001
Pressuring pain	0.031
Central chest pain	<0.001
Increased TnT level	<0.001
ECG - ST-elevation	<0.001
ECG - ST-depression	<0.001
ECG - T-wave inversion	<0.001
ECG - Premature Ventricular Contraction, PVC	0.016
ECG - Premature Atrial Contractions, PAC	0.002
ECG - Right Bundle Branch Block, RBBB	0.007
ECG - Increased QRS-duration	<0.001

Lowered odds ratio of a high-risk condition	p-value
Previous history of chronic obstructive pulmonary disease	0.021
Previous history of atrial fibrillation/flutter	<0.001
Previous history of psychiatric diagnosis	<0.001
Pain debut while resting	0.010
Pain debut while sleeping	0.012
Slow pain debut, within hours	0.031
Fluctuating pain	0.001
Stabbing pain	0.001
Pain in left side of chest	0.001
Pain in right side of chest	0.013
Pain in lower part of chest	0.026
Pain area of two-inch diameter	<0.001
Palpation tenderness	0.001
Pain affected by movement	0.003
Pain affected by breathing	<0.001
ECG - Sinus rhythm without abnormalities	<0.001

Variables with p-value <0.05 in univariate regression analyses on observed data, high-risk prediction

APPENDIX II – UNIVARIATE ANALYSES, LOW-RISK PREDICTORS

Lowered odds ratio of a low-risk condition	p-value
Male sex	<0.001
Older age	<0.001
Previous history of chronic obstructive pulmonary disease	0.039
Previous history of hypertension	<0.001
Previous history of heart failure	<0.001
Previous history of stroke	0.041
Previous history of kidney disease	0.013
Previous history of atrial fibrillation/flutter	0.016
Previous history of cancer	<0.001
Breathing rate ≥25 breaths/min	<0.001
Oxygen saturation ≤91 %	<0.001
Heart rate ≥131 beats/min	<0.001
Systolic blood pressure ≤90 mmHg	0.003
Decreased level of consciousness or new confusion	0.001
Body temperature >38.0	<0.001
Pale	<0.001
Clammy	<0.001
Vomiting	0.001
Affected breathing according to patient	<0.001
Increased pain intensity	0.004
Quick debut, within minutes	0.012
Constant pain	<0.001
Right arm	<0.001
Pressuring	0.011
Central pain	<0.001
Entire chest	0.001
Increased TnT level	<0.001
ECG - Sinus tachycardia	<0.001
ECG - Atrial Fibrillation/Flutter, AF	<0.001

ECG - ST-elevation	<0.001
ECG - ST-depression	<0.001
ECG - T-wave inversion	<0.001
ECG - Premature Atrial Contractions, PAC	0.014
ECG - Left Bundle Branch Block, LBBB	0.001
ECG - Right Bundle Branch Block, RBBB	<0.001
ECG - Increased QRS-duration	<0.001

Increased odds ratio of a low-risk condition	**p-value**
Previous history of psychiatric diagnosis	<0.001
Pain debut while sleeping	0.047
Sudden debut, within seconds	0.017
Fluctuating pain	0.002
Stabbing pain	0.015
Tingling/Stinging pain	<0.001
Pain in left side of chest	<0.001
Pain area of two-inch diameter	0.002
Palpation tenderness	0.001
Pain affected by movement	0.002
ECG - Sinus rhythm without abnormalities	<0.001

Variables with p-value <0.05 in univariate regression analyses on observed data, low-risk prediction.