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INITIAL SYMPTOMS OF MYOCARDIAL INFARCTION – CONSEQUENCES AND METHODOLOGICAL APPROACH

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Initial symptoms of myocardial infarction – Consequences and methodological approach

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Abstract

Survival after acute myocardial infarction (MI) has been improving for decades, but mortality among MI patients who present without chest pain remains high. MI patients presenting without chest pain are more likely to have long treatment delays. Delays can occur because of misrecognition during the first medical contact, as vague or unspecific symptoms can be misinterpreted as benign. Further, non-chest pain MI patients tend to wait longer before seeking help, and when they do, they are more likely to contact general practitioners, medical helplines, or out-of-hours services, instead of calling the emergency number. We currently lack knowledge of what happens during the first medical contact and whether possible prehospital misrecognition contributes to treatment delay and, ultimately, the increased mortality observed among non-chest pain MI patients. As a result, it remains unclear if improved prehospital management of MI patients presenting without chest pain would in fact lead to better outcomes.

The objectives of this thesis was firstly, to investigate the association between symptom presentation and immediate response and survival among MI patients calling for medical assistance at a non-emergency medical helpline (1813) and emergency medical service (1-1-2). Secondly, to investigate whether improved prehospital management of non-chest pain MI patients, assessed by increased emergency ambulance dispatch and prehospital administration of acetylsalicylic acid (ASA), could help reduce mortality among the high-risk non-chest pain patients. The latter required modifying existing statistical methods to allow us to estimate the expected mortality among the exposed under different hypothetical interventions aimed at improving the prehospital management.

In the Capital Region of Denmark inhabitants can dial 1-1-2 for medical assistance for emergencies or 1813 in case of non-emergencies to reach a 24-hour medical helpline (intended as the out-of-hours service of general practitioners). At both medical services the purpose of calls/symptoms and the immediate responses are recorded and information of prehospital care is registered in the electronic prehospital medical record used in ambulances. Using the national Danish registries we linked the preceding calls and prehospital management to hospital admissions of MI patients.

We found that 24% of MI patients were recorded with other primary symptoms than chest pain when calling for help at the 1-1-2 emergency number and 1813-medical helpline. The non-chest pain MI patients were older and had more often called the 1813-medical helpline compared to MI patients with chest pain. In addition, non-chest pain MI patients were less likely to receive emergency ambulances. Among calls to the 1-1-2 emergency number 62% versus 95% of non-chest pain and chest pain patients received emergency ambulances, and among calls to the 1813-medical helpline 17% versus 76% received emergency ambulances. Furthermore, MI patients without chest pain were less likely to be admitted directly to a cardiology ward, received less invasive treatment, and had higher 30-day mortality. Chance of receiving prehospital ASA among ambulance transported MI patients were also found to be lower among non-chest pain MI patients compared to chest pain patients. To investigate whether an unresolved potential existed for improving outcomes among non-chest pain MI patients, we estimated the expected change in outcome among non-chest pain MI patients under two hypothetical interventions, a stochastic and a deterministic, where; (1) non-chest pain MI patients were as likely to receive emergency ambulances/prehospital ASA as observed for chest pain patients, and (2) all non-chest pain MI patients received emergency ambulances/prehospital ASA. To estimate these quantities we defined the parameters and implemented a targeted minimum loss-based estimator. We found no improvement in the expected outcome when hypothetically increasing the emergency ambulance dispatch to non-chest pain MI patients. On the other hand, hypothetically assigning prehospital ASA to all non-chest pain MI patients transported with emergency ambulance was expected to reduce 30-day mortality by 5.3% from 12.8% to 7.4%, but no change was found for a 1-year combined outcome of re-infarct, heart failure admission, and death. The observed 30-day mortality among ambulance transported MI patients with chest pain was markedly lower (3%).

Most MI patients present with chest pain, but the one-fourth presenting with other symptoms are at risk of not being correctly recognised with a an acute life threatening condition when calling for help. Although, this thesis indicate that the 30-day mortality among non-chest pain MI patients could potentially be reduced if the prehospital management was improved, long-term effects appear limited and even under best-case scenarios the mortality remained high compared to the chest pain patients. Importantly, study limitations affects the interpretation of our findings. Confounding is expected to affect our results and prehospital identification of MI patients, especially those presenting without chest pain, is still challenging, limiting real-world application of our findings.

Dansk resumé

Dødeligheden efter akut myokardieinfarkt (AMI) har været faldende i årtier, men den er fortsat høj blandt AMI-patienter, der præsenterer sig uden brystsmerter. De AMI-patienter som ikke oplever brystsmerter er i højere i risiko for at have behandlingsforsinkelser. Forsinkelser opstår til dels, fordi deres symptomer kan fejlfortolkes, når de søger hjælp, men også fordi AMI-patienterne uden brystsmerter venter længere før de søger hjælp og oftere ringer efter hjælp hos almen praksis, lægevagten og akuttelefonen, i stedet for at ringe 1-1-2. På nuværende tidspunkt mangler vi viden om, hvordan sundhedsfaglige håndterer AMI-patienter uden brystsmerter i den første kontakt til sundhedsvæsenet, og om manglende præhospital erkendelse af AMI-patienter uden brystsmerter bidrager til behandlingsforsinkelser og i sidste ende øget dødelighed. Det er derfor uklart, om forbedret præhospital håndtering af AMI-patienter uden brystsmerter faktisk ville føre til bedre overlevelse.

Formålet med denne afhandling var, for det første, at undersøge sammenhængen mellem symptompræsentation og det præhospitale respons og overlevelse blandt AMI-patienter, som ringede efter hjælp hos akuttelefonen 1813 og alarmcentralen 1-1-2. For det andet at undersøge om forbedret præhospital håndtering af AMI-patienter uden brystsmerter, herunder øget brug af akutambulancer og præhospital behandling med acetylsalicylsyre (ASA), kunne bidrage til at reducere dødeligheden for denne højrisikogruppe. Sidstnævnte krævede udvikling af en statistisk metode, som kunne gøre det muligt at estimere den forventede dødelighed blandt AMI-patienter uden brystsmerter under hypotetiske interventioner, som forbedrede den præhospitale håndtering af patienterne.

I tilfælde af en nødsituation kan borgere i Region Hovedstaden ringe 1-1-2, og ved mindre alvorlige situationer kan borgere ringe til akuttelefonen 1813, som er en døgnåben rådgivende sundhedsservice, der primært dækker den tidligere lægevagtsordning. For begge opkaldstjenester bliver formålet med opkaldet/symptomerne registreret sammen med information om, hvilken type hjælp eller rådgivning der blev givet, og hvilket køretøj der blev sendt. Desuden bliver præhospital behandling registreret i den elektroniske præhospitale journal, der anvendes i alle danske ambulancer. Ved brug af de danske nationale registre koblede vi de foregående opkald og den præhospital håndtering

og behandling til hospitalsindlæggelser for AMI-patienter.

Vi fandt, at 24% af AMI-patienter havde andre symptomer end brystsmerter registreret som det primære symptom i deres opkald til 1-1-2 og akuttelefonen 1813. AMI-patienter uden brystsmerter var ældre og havde oftere ringet til 1813 sammenlignet med AMI-patienter med brystsmerter. Derudover var AMI-patienter uden brystsmerter mere tilbøjelige til ikke at få tilsendt en akutambulance. Blandt opkald til 1-1-2 modtog 62% versus 95% af AMI-patienter med og uden brystsmerter akutambulancer, og ligeledes blandt opkald til akuttelefonen 1813 modtog 17% versus 76% akutambulancer. AMI-patienter uden brystsmerter var mindre tilbøjelige til at blive indlagt direkte på en kardiologisk afdeling, de modtog mindre invasiv behandling og havde højere 30-dages dødelighed. Andelen af AMI-patienter, som modtog ASA under ambulancetransporten, var også lavere blandt patienter uden brystsmerter sammenlignet med patienter med brystsmerter. For at undersøge om dødeligheden blandt AMI-patienter uden brystsmerter kunne forventes at blive reduceret, hvis den præhospitale håndtering af patienterne havde været bedre, estimerede vi den forventede ændring i dødeligheden blandt AMI-patienter uden brystsmerter under to hypotetiske interventioner (en stokastisk og en deterministisk), hvor; (1) AMI-patienter uden brystsmerter modtog akutambulancer/præhospital ASA lige så ofte som observeret for brystsmertepatienterne, og (2) alle AMI-patienter uden brystsmerter modtog akutambulancer/præhospital ASA. For at kunne estimere disse effekter definerede vi relevante parametre og tilhørende estimatorer baseret på Targeted Minimum Loss-based Estimation. Vi fandt ingen ændring i den forventede overlevelse, når vi hypotetisk øgede andelen af AMI-patienter uden brystsmerter, som fik tilsendt en akutambulance. Til gengæld faldt 30-dages dødeligheden med 5,3% fra 12,8% til 7,4%, når vi hypotetisk tildelte alle AMI-patienter uden brystsmerter ASA under ambulancetransporten. Vi fandt dog ingen ændring for et 1-årigt kombineret outcome af re-infarkt, indlæggelse med hjertesvigt og død. Den observerede 30-dages dødelighed blandt ambulancetransporterede AMI-patienter med brystsmerter var 3%.

De fleste AMI-patienter har brystsmerter, når de ringer efter hjælp, men den fjerdedel, der oplever andre symptomer, er i risiko for ikke at blive korrekt erkendt med en akut livstruende tilstand. Selvom analyserne i denne afhandling indikerer, at 30-dages dødeligheden blandt AMI-patienter uden brystsmerter potentielt kunne reduceres, hvis den præhospitale håndtering blev forbedret, så fandt vi ikke indikation af forberede langtidsoutcomes. Selv i det bedst scenarie, hvor alle AMI-patienter uden brystsmerter fik behandling, forblev dødeligheden høj i forhold til den observede dødelighed blandt AMI-patienter med brystsmerter. Studierne i denne afhandling har en række metodiske udfordringer som påvirker fortolkningen af vores fund. Vi forventer at confounding påvirker resultaterne, og præhospital identifikation af MI-patienter, og i særdeleshed dem som ikke har brystsmerter, er stadig udfordrende, hvilket begrænser anvendelsen af vores resultater i den virkelige verden.

Thesis Details

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Ph.D. Student:	Amalie Lykkemark Møller
Supervisors:	Christian Torp-Pedersen
	Thomas Alexander Gerds

This thesis was based on the following papers:

[A] Amalie Lykkemark Møller, Elisabeth Helen Anna Mills, Filip Gnesin, Britta Jensen, Nertila Zylyftari, Helle Collatz Christensen, Stig Nikolaj Fasmer Blomberg, Fredrik Folke, Kristian Hay Kragholm, Gunnar Gislason, Emil Fosbøl, Lars Køber, Thomas Alexander Gerds, Christian Torp-Pedersen,"Impact of myocardial infarction symptom presentation on emergency response and survival" *European Heart Journal. Acute Cardiovascular Care*, vol. 10, no. 10, pp. 1150–1159, 2021.

[B] Amalie Lykkemark Møller, Kathrine Kold Sørensen, Julie Andersen, Thomas Alexander Gerds, Christian Torp-Pedersen, Helene Charlotte Wiese Rytgaard "Learning the potential effects of selective health care interventions based on real-world data" In review at *Epidemiology.* Submitted May 2022.

[C] Amalie Lykkemark Møller, Helene Charlotte Wiese Rytgaard, Elisabeth Helen Anna Mills, Helle Collatz Christensen, Stig Nikolaj Fasmer Blomberg, Fredrik Folke, Kristian Hay Kragholm, Freddy Lippert, Gunnar Gislason, Lars Køber, Thomas Alexander Gerds, Christian Torp-Pedersen,"Hypothetical interventions on emergency ambulance and prehospital acetylsalicylic acid administration in myocardial infarction patients presenting without chest pain". In review at *PLoS ONE.* Submitted March 2022

Preface

This thesis has been submitted to the Doctoral School in Medicine, Biomedical Science and Technology at Aalborg University, Denmark. The work has been carried out predominantly at Department of Cardiology, Nordsjællands Hospital and Section of Biostastistics, University of Copenhagen. In addition, I spend 10 months at Section of Preventive Medicine and Epidemiology at Boston University School of Medicine. The PhD project was funded by the Danish Heart Foundation.

I would like to thank my supervisors, Christian Torp-Pedersen and Thomas Alexander Gerds. I truly appreciate the time and effort you have put into this project. Christian, thank you for your encouraging pep talks and optimistic mindset. Thank you for everything you have taught me and for your admirable patience. To Thomas, thank you for teaching me and for the great discussions. Thank you for not letting me take the easy way out. You pushed me to become a better researcher and I am very grateful for that. I would also like to thank Helene Rytgaard for sharing your knowledge and for patiently answering the endless amount of questions I have been asking. Thanks to all of our collaborators at the Copenhagen Emergency Medical Services and Aalborg University for the many great inputs and discussions throughout the years.

I was lucky to enjoy the company of many good colleagues at both Nordsjællands Hospital and Section of Biostatistics at University of Copenhagen. You have all made my time as a PhD student so much more enjoyable. A special thanks to Charlotte Andersson for making my stay in Boston an unforgettable experience. I truly hope that our collaboration in Boston was only the beginning.

Last but not least, I would like to thank my family and friends for their encouragement. To Frederik, thank you for listening, for always believing in me, and for your unconditional support.

Amalie Lykkemark Møller
July 21, 2022

Contents

Part I

Introduction

Introduction

Chest pain is widely considered a cardinal symptom of myocardial infarction (MI), but it is not uncommon that MI patients present with other symptoms.[1,2] MI patients presenting at the hospital without chest pain have been found to be a high-risk population with poor chance of survival.[3–5] Often, the first medical contact for MI patients is a telephone consultation with a general practitioner, a health care center, an out-of-hours medical service, or an emergency medical service.[6–10] The ability to correctly recognize the severity of MI patients' symptoms and refer to treatment during the first medical contact is important to reduce treatment delay and possibly mortality,[11,12] but can be challenging in the absence of chest pain. Prehospital misrecognition and long delays might be an important contributing factor to the observed differences in mortality among MI patients with and without chest pain. Improving the prehospital recognition of MI patients without chest pain is difficult in practice. But assessing the potential benefits of such improvements on patient outcome is an important first step. MI patients presenting without chest pain are typically older and have more comorbidities than patients with chest pain and this can affect chance of survival as well. It is unclear whether patient characteristics or treatment delays are the driving factors of the differences in mortality and as a result we do not know if improved prehospital care would actually reduce the present gap in mortality observed between MI patients with and without chest pain. Existing statistical methods are not suitable for answering this question and new methods need to be developed to be able capture the effect of improving prehospital management of non-chest pain MI patients.

The majority of research investigating symptoms and outcomes among MI patients have used data collected in-hospital or only used data from emergency medical services. In-hospital collection of data can introduce selection bias and previous research indicate that the share of MI patients who contacted the EMS is as low as 25-51%.[6–9] Therefore, results from previous studies might not be representative of the total population of MI patients. In the Capital Region of Denmark, information of symptom or purpose of emergency and non-emergency calls are registered electronically. In combination with the Danish registries this allows us to link calls to later hospitalizations and gain information of what preceded the admission.

1 Objectives

This thesis aimed at providing knowledge on symptom presentation of MI patients in the first medical contact, assess the association between symptom presentation and the prehospital management and mortality, and the impact of improving the prehospital management of non-chest pain MI patients. This was done using data from the emergency and non-emergency medical services in the Capital Region of Denmark. Firstly, we aimed at characterizing the symptoms of MI patients during the first medical contact to a 24-hour medical helpline (intended as an out-of-hours service) and 1-1-2 emergency number, and investigate how the initial primary recorded symptom was associated with emergency response and mortality. Secondly, we aimed at investigating whether hypothetical interventions on the prehospital management of non-chest pain MI patients would in fact lead to improved outcome among these patients. To do so, we needed to define a parameter and estimator that would allow us to identify the potential risk reduction among non-chest pain MI patients under different hypothetical scenarios of improved prehospital management. These aims were divided into the following three papers.

Paper A – Impact of myocardial infarction symptom presentation on emergency response and survival
The aim of this study was to characterize MI patients according to the initial symptom presentation and investigate associations between symptom presentation and the immediate prehospital response, in-hospital procedures, and 30-day mortality across calls to the emergency and non-emergency medical services.

Paper B – Learning the potential effects of selective health care interventions based on real- world data
To estimate the effects of interest in Paper C, we needed to define a target parameter and the corresponding estimator for which we used targeted minimum loss-based estimation (TMLE). This paper aimed at introducing the target parameter and TMLE estimator and illustrate the usability of the proposed method using a real-world case of low-income heart failure patients.

Paper C – Hypothetical interventions on emergency ambulance and prehospital acetylsalicylic acid administration in myocardial infarction patients presenting without chest pain
We aimed at exploring whether there exists a potential for improving outcomes (30-day mortality and a 1-year combined outcome) among non-chest pain MI patients if hypothetical their chance of receiving emergency ambulances and prehospital acetylsalicylic acid (ASA) was increased using method introduced in Paper B.

Background

2 Myocardial infarction

An MI occurs when the blood supply to the heart muscle is reduced due to a partly or fully blockage of the coronary artery. Insufficient blood supply can cause damage to the part of the heart muscle supplied by the occluded artery. If the blood flow is not restored in time the heart muscle can be permanently damaged possibly leading to a fatal outcome.[13] The diagnosis of MI is typically determined by testing for elevation of cardiac troponin in the blood, a cardiac marker for heart muscle cell damage, and by electrocardiography (ECG). The diagnosis of MI diagnosis is often divided into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) according to presences and absences of an elevation in the ST-segment on the ECG.[14,15] The type of MI can affect both the symptom presentation and patients outcomes including mortality. STEMI patients typically have higher short-term mortality whereas NSTEMI patients have higher long-term mortality.[16–19]

2.1 Recommended prehospital management of myocardial infarction patients

Regardless of the type of infarction, MI patients should seek medical attention as soon as possible after symptom onset to reduce the time to diagnosis and treatment. The total prehospital delay, that is time from symptom onset to hospital arrival, is typically divided into two categories: a decision delay, the time from symptom onset to first medical contact, and a transportation time, which covers the time from the first medical contact to hospital arrival.[6,20] Ideally, the decision delay would be short and MI patients would call the emergency medical services (EMS) promptly to receive acute help. As stated in the European Society of Cardiology guidelines, dispatching mobile intensive care units to myocardial infarction patients is a critical part of the prehospital management, not only in order to reduce transport time, but also because it is a central part of improving chance of early diagnosis, fast triage, and timely initiation of treatment.[15] It is recommended that ambulances are equipped with

12-lead ECG systems that allows paramedics to perform ECG's during ambulance transport and forward these to cardiologists at hospitals.[21] As a result, STEMI can be determined even before hospital arrival. If paramedics find ST-elevation on the prehospital ECG then patients are directly referred to primary percutaneous coronary intervention (PCI) centers. The use of prehospital ECG to enable direct transfer of STEMI patients to PCI centers have been found to reduce total time to treatment among these patients.[22–24] Additionally, due to low risk and possible large benefits, administration of ASA as soon as possible is recommended acute prehospital treatment for both STEMI and NSTEMI patients in the absence of contraindications.[21,25] Additional prehospital treatment can include other antiplatelets, anticoagulants, anti-anginal drugs, and fibrinolytics depending on whether the patients is diagnosed with STEMI or not and whether the patients is expected to undergo catherterization or PCI.[21]

3 Symptom presentation of myocardial infarction and associated outcomes

Chest pain is the most frequent clinical presentation of MI, but far from all MI patients present with this symptom. MI patients presenting without chest pain can experience symptoms including dyspnea, weakness, fatigue, abdominal pain, back pain, vomiting, nausea, syncope, dizziness, diaphoresis and cold sweat, anxiety, jaw or neck pain, and malaise.[2,5,9,26–28] The literature suggests that the prevalence of MI patients presenting without chest pain is between 8% and 44% depending on the selection of MI patients.[1,2,4,29–33] Previous studies have indicated that symptom presentation varies according to type of MI, where absence of chest pain have been found more common for NSTEMI, where 23% to 44% presented without chest pain,[4,28,30] whereas symptom presentation without chest pain among STEMI patients is somewhat less common (13% and 27%).[4,29,31]

Advancement in treatment during the past decades has contributed to a considerable reduction in mortality after MI.[34–36] Despite these reductions the chance of survival remains low among MI patients presenting without chest pain.[3–5] The 30-day mortality among MI patients presenting without chest pain have been estimated to 7-31%, whereas the equivalent mortality among chest pain MI patients was 2-9%.[3,29,33] A similar pattern was found for long-term mortality where the 1-year mortality was estimated to 4-17% and 15-23% in MI patients with and without chest pain.[3,28,30] Overall, previous findings indicate that the mortality risk is two to three times higher among non-chest pain MI patients compared to chest pain patients.

4 Suggested pathways between symptom presentation and mortality among MI patients

Currently, we do not fully understand the underlying causes of why MI patients who present without chest pain have such increased mortality risk, but previous research have identified several pathways that could explain parts of the variation in mortality observed between chest pain and non-chest pain MI patients.

4.1 Differences in patient characteristics

Some patient characteristics have been found to differ according to symptom presentation in MI patients. Comorbidities including type 2 diabetes, and in some studies hypertension and heart failure, seems to be more common among MI patients presenting without chest pain.[1,4,28,32,37] Additionally, elderly and females have been found to be more likely to present without chest pain.[3,28,37,38] On the other hand, some patient characteristics have been found to be more common among MI patients with chest pain. These include being younger, being male, having a family history of coronary artery disease, having hypercholesterolemia/dyslipidemia, and smoking.[1,28,33,37] These factors could contribute to the observed differences in mortality between MI patients with and without chest pain.

4.2 Prehospital misrecognition and treatment delay

As previously described, prehospital delays in MI patients must be minimized to improve chance of timely treatment and thereby reduce mortality risk.[11,12,15] Studies have suggested that absence of chest pain in MI patients is linked to prehospital delay through misrecognition during the first medical contact, possibly affected by non-chest pain MI patients often choosing non-emergency rather than emergency services, and decision delay in seeking medical attention.[20,31,39,40] MI patients first medical contact is often a telephone consultation with a general practitioner, a health care center, an out-of-hours medical service, or an emergency medical service.[6–9] Although little information is available on health care providers ability to accurately recognize non-chest pain MI patients during the first medical contact, one study found that acute coronary syndrome patients presenting without chest pain when calling the EMS were more likely to be triaged to a non-life threatening response than those presenting with chest pain.[41] MI patients seeking medical attention at a non-emergency service, either primary health care center or general practitioner, were more likely to have longer total prehospital delay compared to patients calling the EMS or showing up directly at the emergency department.[7,39,40,42] At the same time, patients contacting non-emergency services have also been found to be more likely to present without chest pain.[7] Lastly, a range of patient

related factors have been found to be associated with increased prehospital delay including long decision time. Such factors included perceiving symptoms as benign, mismatch between expected and experienced symptoms of MI, vague symptoms, and gradual symptom onset instead of fast onset.[20,39,43–47] The discrepancy between expected and experienced symptoms was largest among non-chest pain patients.[43] Overall, research indicates that MI patients presenting without chest pain are more likely to misinterpret their own symptoms, not seeking help at emergency medical services, and being misrecognized in EMS consultations leading to lower dispatch. All these factors can contribute to prolonging the prehospital delay and specifically increasing time to diagnosis and treatment.

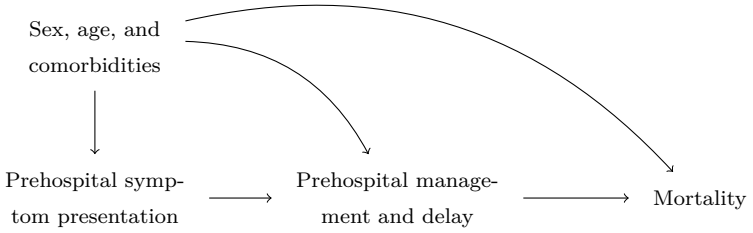
5 Methodological considerations and gap in existing knowledge

The majority of previous studies have investigated the symptom presentation of MI patients from registrations upon arrival at the emergency department or during the hospital admission.[1–4,27–31,48] In some studies data on prehospital symptoms and care seeking behaviour or prehospital delay was collected from hospitalized MI patients by interviews or using a self-administered questionnaire.[5,7,9,27,49] The symptom presentation at hospitals is therefore relatively well documented, but as symptoms can develop during the time span between the first medical contact and hospital admission, the symptom presentation recorded at the hospital might not align with the initial symptoms. An additional limitation of the studies that collected data by interviewing patients, is that they are prone to select survivors of MI. As the mortality is expected to be higher among non-chest pain MI patients, such studies could underestimate the proportion of patients presenting without chest pain. To our knowledge only few studies have investigated the symptoms of MI (or acute coronary syndrome) patients as they were reported during the first medical contact.[41,50] For these studies, only contacts to an emergency medical service were included. Recent research indicate that 50% or more of the MI patients seek medical attention at other services than the emergency medical services.[6,7,9] As a result, it is currently unknown whether the existing information on symptom presentation of MI patients actually is representative of the symptoms reported during the first medical contact.

In summary, previous studies have determined that non-chest pain symptom presentation (as recorded in-hospital or at emergency medical services) is associated with (1) sub-optimal prehospital management including longer prehospital delay and low chance of receiving highest priority emergency dispatch, and (2) increased risk of short- and long-term mortality. The symptom presentation itself is not expected to directly affect the mortality, but instead affect mortality through the sub-optimal prehospital management or be associated

with mortality through patient characteristics as sex, age, and comorbidities. A simplified directed acyclic graph illustrating the assumed causal structure is shown in Figure 1.

Fig. 1: A simplified directed acyclic graph illustrating the pathways between symptom presentation and mortality



Currently, we do not have evidence to support that improved prehospital management of non-chest pain MI patients, would in fact lead to lower mortality. Although it seems reasonable to believe in such a scenario, we cannot rule out that the high mortality among non-chest pain MI patients is predominantly driven by the higher age or differences in comorbidity burden observed for this patient group, rather than the sub-optimal prehospital management. Due to lack of options to effectively identify non-chest pain MI patients in the first medical contact, the possibility of setting up a clinical trial is very limited. If initiated, we would expect that patients not suffering from an MI would be included too. Instead we suggest starting by investigating if a possible unfulfilled potential for reducing the mortality among non-chest pain MI patients exist by hypothetically improving the prehospital management of these patients using observational data. This requires designing a study that investigates the potential reduction in mortality among non-chest pain patients had we hypothetically been better at recognizing them during the first medical contact and treated them according to guidelines.

Some existing methods could be considered when aiming at identifying an effect of modifying an intermediate variable, in this case prehospital management, but these methods have some limitations. Firstly, the natural indirect effect [51] has been a common choice of parameter when investigating how changing an intermediate variable impact an outcome. [52] Identifying indirect effects require intervening on not only the intermediate, but also the exposure, and are typically identified among the total population, i.e. all MI patients, rather than the target population of non-chest pain MI patients alone. Our exposure is a symptom, which must be considered not directly manipulable, and potential outcomes based on interventions on non-manipulable exposures is typically not considered to have meaningful interpretations. [52] As a result, and even though indirect effects have been defined among the exposed, [53] indirect effects are

likely not meaningful for our particular case. A different approach could be to estimate the average causal effect,[54] also known as the average treatment effect, of optimal prehospital management among the subpopulation of MI patients presenting without chest pain. In such analysis we would compare the scenarios where all non-chest pain MI patients versus none received optimal prehospital management. This comparison might again not be ideal, as we do expect at least some of the non-chest MI-patients to receive appropriate prehospital management.

In this thesis, we propose a method, which allows us to identify the expected mortality among MI patients presenting without chest pain, under two hypothetical interventions: (1) a stochastic intervention, where non-chest pain MI patients were as likely to receive optimal prehospital management as observed for chest pain MI patients, and (2) a deterministic intervention, where all non-chest pain MI patients received optimal prehospital management. The expected mortality under the stochastic and deterministic interventions are compared to the expected mortality without intervention, where non-chest pain MI patients' chance of receiving optimal prehospital management was as observed. The difference between the expected outcome with and without intervention equals the expected change in mortality if hypothetically the prehospital management provided to non-chest pain MI patients was improved. We will refer to the stochastic and deterministic interventions as selective interventions as they describe effects that are identified among the high risk subpopulation, e.g. non-chest pain MI patients, rather than the total population. We propose estimating the described target parameters using TMLE where nuisance parameters are estimated using super learning.[55,56]

Part II

Methods

Methods

This thesis is based on three papers. Paper A and C are cohort studies investigating outcomes of MI patients according to prehospital recording of their symptoms, whereas Paper B is a methodological paper introducing a parameter and estimator for deriving effects of the selective interventions including a real-world example of hypothetical interventions targeting low-income heart failure patients. All three papers use Danish registry data and in the following section we describe the danish health care system, the general setting of all three papers, and the prehospital setting of the Capital Region, the specific setting of Paper A and C. Table 1 provides an overview of all three papers.

Table 1: An overview of the papers included in this thesis

	Paper A	**Paper B**	**Paper C**
Aim	To characterize MI patients according to the initial symptom presentation and investigate associations between symptom presentation and the immediate prehospital response and 30-day mortality, respectively	To introduce the proposed parameter and TMLE estimator for selective interventions and illustrate the use of the method by estimating the expected effect of improving treatment initiation among low-income heart failure patients	To investigate whether there exists a potential for improving outcomes among non-chest pain MI patients if hypothetically their chance of receiving emergency ambulances and prehospital ASA was increased using the methods described in Paper B
Study population	Primary diagnosis of MI or MI as cause of death up to 72 hours after a call to 1813-medical helpline or 1-1-2 emergency number, age>30	Newly diagnosed heart failure patients who had an MI within 3 months before the heart failure diagnosis, 40< age >80	Primary diagnosis of MI up to 24 hours after a call to 1813-medical helpline or 1-1-2 emergency number, age>30
Inclusion period	2014 – 2018	2005 – 2016	April 2015 – 2018
Exclusion criteria	Patients suspected dead at the time of call. First call for each MI within the 72 hours was kept for analysis	Patients not living in Denmark at the time of diagnosis, missing information of income or education, prior diagnosis of mental illness, dementia, cancer, bradyarrhythmias, chronic kidney disease, and dialysis treatment	No/non-informative symptom, unconscious or suspected dead at time of call, terminal disease, living in nursing home or received palliative treatment up to 5 years prior to call. For the analysis of prehospital ASA, patients with contraindications of ASA were also excluded.
Exposure	Recorded symptom: Chest pain, atypical symptoms, no recorded or non-informative symptoms, and unconscious	Average yearly income	Recorded symptom of chest pain and non-chest pain
Intermediate		Initiation of treatment with β-blockers and RASi	Emergency ambulance dispatch and prehopsital ASA
Outcome	Emergency response, 30-day mortality, and in-hospital management	1-year mortality	30-day mortality and a 1-year combined outcome of re-infarct, heart failure admission, and mortality

RASi=Renin-angiotensin system inhibitors, ASA=Acetylsalicylic acid

6 Setting

The Danish health care system is funded predominantly through taxes and health care including hospital treatment, prehospital services, and primary health care is available without any out-of-pocket expenses to all Danish residents.[57–59] Medication provided to patients in-hospital is also free of charge, but co-payment is required after discharge and for any medication prescribed at general practitioners or specialists. The amount the patients need to pay is determined by the accumulated pharmaceutical expenses for each patient during the past 12 months. Patients pay the full amount up to an expense limit of 1,020 DKK / 137 EUR (2021 thresholds). Here after, patients are reimbursed 50% which gradually increases to 85% of the price of the pharmaceutical products up until the patients co-payments exeeds 4,320 DKK / 581 EUR (2021 thresholds) after which the patient is reimbursed 100% of the price.[59–61] Danish citizens are assigned a personal civil registration number, which is registered for contacts to the public authorities. This unique id enables linkage between public registries and databases including registries of in-hospital procedures and prehospital contacts.[57,62,63] There is five administrative regions in Denmark. Each region administrates health care services including hospitals, emergency medical services, and out-of-hours medical services of their area. While the hospital setting is relatively similar across the different regions, some variations exist in the structure of the prehospital services including the emergency medical services and out-of-hours medical services.[57]

6.1 Prehospital organization of the Capital Region

In the case of an urgent need of medical assistance, inhabitants of the Capital Region can contact their general practitioner, call 1813 to reach a 24-hour medical helpline, or call 1-1-2 to reach the emergency medical services. The 1813-medical helpline is predominantly operating as an out-of-hours service as it covers out-of-hours of general practice which is from 16.00 in the afternoon to 8.00 in the morning on weekdays and all 24 hours of the day on holidays. In the Capital Region, the 1813-medical helpline and the emergency medical service share location and administration and the combined service is called the Copenhagen Emergency Medical Services.[57] Importantly, referral to emergency departments is required, therefore, inhabitants should contact their general practitioner or call 1813 or 1-1-2 in order to schedule an emergency department visit before showing up. However, it is still possible to receive treatment at emergency departments without prior referral.[57]

1813-medical helpline

The 1813-medical helpline is a regional medical service covering all the 1.8 mil. inhabitants of the Capital Region.[57] The 1813-medical helpline was initiated in January 2014 and replaced the previous decentralized system of local

general practitioner cooperatives covering the out-of-hours service and holidays of general practitioners in the region. General practitioner cooperatives are still used in other Danish regions.[57] The 1813-medical helpline is staffed by predominantly trained nurses (∼80%), but also medical doctors. Nurses can either consult or pass on the call to a medical doctor on call if in doubt of medical condition or optimal triage.[64,65] The nurses (and to some extent the medical doctors) at the 1813-medical helpline use a computerized decision support system that was developed locally for this helpline specifically. This decision support system guides the call-taker in deciding on the most appropriate triage according to presented symptoms and condition of the patients.[66] The call-takers can choose to provide advise over the telephone, refer to consultation, home visits by nurses or physicians, or emergency departments, and dispatch ambulances.[65] The 1813-medical helpline and the emergency medical service (reached by dialing 1-1-2) shares software systems which enables call-takers at the 1813-medical helpline to use services linked to the emergency medical service and vice versa.

1-1-2 emergency number

In Denmark the universal emergency number is 1-1-2 for fire, police, and medical emergencies. In the Capital Region, the Copenhagen fire brigade answers emergency calls and forward calls regarding medical emergencies to the emergency medical coordination center at the Copenhagen Emergency Medical Services, where paramedics and nurses handles the calls. The call-takers assess the urgency of the situation using a criteria-based dispatch protocol called Danish Index for Emergency care, which is a translation of the Norwegian Index for Medical Emergency Assistance.[67,68] The Danish Index consists of 37 main symptom or complaint groups which each are divided into levels of urgency ranging from highest urgency (A) indicating that the call is regarding a life-threatening or potentially life-threatening situation to lowest urgency (E) indicating no need for an ambulance/other transport.[57,67,69]

General practitioners

During the normal day time working hours, 8:00 to 16:00, patients can also seek medical advice at their general practitioner. Services available at the general practitioner includes telephone, e-mail, and face-to-face consultations. The general practitioner can prescribe medication, refer to specialists and emergency departments, and request ambulances through the emergency medical coordination center.[57] Information on patients symptoms or the purpose of consultations is not collected systematically at general practitioners and data from this service is not used in this thesis.

Ambulance service

The Danish ambulance service is administered at the regional level but must live up to requirements stated in national law.[70] In Denmark, ambulances are typically staffed by ambulance assistants, paramedics, and paramedics with additional competencies, who work under the delegation of a physician. The most basic ambulance response would include an ambulance with two health professionals where at least one is a trained paramedic. As a supplement to the basic ambulance response, paramedics with special competences and prehospital anesthesiologists can be called to the scene in either rapid response vehicles or mobile intensive care units.[57] Ambulances are dispatched for urgency level A, B and C. The emergency medical coordination center also dispatches non-emergency transports including non-emergency ambulances and other non-acute transportation typically ordered by general practitioners or hospital wards. These are typically categorized at urgency level D. Since 2015, all Danish ambulances have used an electronic prehospital medical record from which data can be forwarded to hospitals. In this prehospital record the ambulance personnel register clinical data including observations of the patients, vital measures, and prehospital treatment etc.[57,69,71]

7 Study populations

7.1 Paper A

For Paper A we considered calls for all patients above age 30 who had called the 1813-medical helpline or 1-1-2 emergency number between January 1st 2014 and December 31st 2018. We defined calls to be regarding an MI, if the calls considered patients who were registered with a primary diagnosis of MI (International Classification of Diseases version 10 (ICD-10): I21) or MI as cause of death within up to 72 hours after the call. For both Paper A and C the type of MI was defined as: STEMI (ICD-10: I210B, I211B, I213), NSTEMI (ICD-10: I210A, I211A, I214), Unknown/Other (ICD-10: I210, I211, I219, I219A).[10] As the 1813-medical helpline receive calls for inquests, it is in fact possible that patients were dead at the time of call. To reduce risk of inclusion of patients who had already passed at the time of call, we excluded patients who had registrations of inquest or descriptions indicating that the patients had passed. If multiple calls were identified for the same patient within the 72 hours prior to the MI diagnosis, we included only the first. Sensitivity analyses of the choice of call can be found in Table 5 in the Supplementary material of Paper A.[10]

7.2 Paper B

For Paper B we included all first time heart failure patients from 2005 to 2016 who were between 40 and 80 years and who had an MI diagnosis up to 3 months

prior the heart failure diagnosis.[72] The heart failure diagnosis was defined by either an in-hospital diagnosis with any of the following ICD-10 codes: I110, I420, I426, I50, or J819, or a combination of an outpatient visit with a registration of heart failure and a claimed loop-diuretic (Anatomical Therapeutic Chemical Classification System (ATC) code: C03C) up to 90 days prior to the visit. Exclusions included patients who had a prior diagnosis of heart failure, patients living abroad, patients with missing information of income or education, patients with prior diagnosis of bradycardia (ICD-10: I441-I443, I495), cancer (ICD-10: C00-C96 (excluding C619)), dementia (ICD-10: F00-F03, F051, G30), mental illness (ICD-10: F20-F22), and chronic kidney disease (ICD-10: N18) or patients in dialysis treatment (procedure codes: BJFD, KKAS). Furthermore, we excluded patients who died during the first 90 days after the heart failure diagnosis, and patients who had redeemed β-blockers (ATC: C07A) or renin-angiotensin system inhibitors (RASi) (ATC: C09) 180 days before the heart failure diagnosis.[73] Further details on the populations can be found in previous publication by Andersen et al. 2021.[73]

7.3 Paper C

For Paper C we included patients above age 30 who had called the 1813-medical helpline or 1-1-2 emergency number between April 1st 2015 and December 31st 2018. The time period was chosen such that we had data from the prehospital electronic patient record which was introduced in the beginning of 2015.
For this study, we defined calls to be related to an MI if the patient was hospitalized with a primary diagnosis with MI (ICD-10: I21) within up to 24 hours after the call.[74] The type of MI was defined as described in Section 7.1. Patients with missing recording of symptom or recordings not informative of the patients condition were excluded.[10] Further information of these calls can be found in Section 9.1. Additionally, patients registered as unconscious or suspected dead at time of call were excluded. Finally, we excluded patients living in nursing home and patients who had received palliative treatment up to 5 years prior to call.[74] In the analysis considering prehospital ASA administration, we excluded all patients with a allergy or a contraindication of ASA. A patient was defined with allergy if a notation of allergy to ASA was registered in the allergy tab of the patient record and contraindication of ASA was defined if any of the following words were mentioned in the prehospital electronic patient record: *aneurysm*, *blood*, *bleeding*, or *ulcer*.[74]

8 Data sources

8.1 Copenhagen Emergency Medical Services

Data on the medical service which the patient had called (either the 1813-medical helpline or the 1-1-2 emergency number), the criterion assigned by the

call-taker (which has information on the symptom/purpose of calls), and the vehicle assignment was drawn from Computer Aided Design (CAD) systems at The Copenhagen Emergency Medical Services. In addition information of treatment assigned during patient transportation in ambulances were defined using the electronic prehospital patient record. [10,57,74]

Recorded symptoms (Paper A and C)

Call-takers at the 1813-medical helpline and 1-1-2 emergency number register a single criterion describing the primary purpose or symptom of the patient for each call. Although the two services use similar software, two different protocols are used to guide the call-takers. For the 1813-medical helpline a locally developed electronic decision support system is used and at the 1-1-2 emergency number the Danish Index is used. Both protocol systems are criteria based with a hierarchically ordering of the symptoms, such that symptoms are grouped according to the primary symptom or complaint followed by sub-symptoms. [10,67,74] The assigned criterion is used for registration as well as assigning of appropriate vehicle if needed. [57]

Emergency response (Paper A and C)

For each call at the Copenhagen Emergency Medical Services the call-takers register the immediate action that follows calls (including ambulance dispatch, watch-full waiting, self-care, self-transport to hospital etc.). These actions will be referred to as the emergency response.

Prehospital electronic patient record (Paper C)

For each ambulance transportation the ambulance personnel record data in the prehospital electronic patient record. The recorded data typically consists of observations of the patient, including description of the patients symptoms and overall condition, relevant allergies, and any treatment given to the patient. [57]

8.2 National registries

The Danish Civil Registration System (Paper A-C)

The Danish Civil Registration System is a national register of Danish inhabitants who has a civil registration number, including current and previous residents of Denmark (since 1968) and Greenland (since 1972). The register contains information including name, address, civil status, migration, date of birth, sex at birth, and time of death. [75]

The Register of Causes of Death (Paper A)

The Register of Causes of Death includes information from death certificates issued by medical doctors for all deaths occurring in Denmark. The register includes data on time, place, manner, and causes of death.[76]

The Danish National Patient Register (Paper A-C)

The National Patient Register contains information on hospital admissions to somatic departments since 1977, and information of admissions to psychiatric wards, out-patient contacts, and emergency department visits since 1995. The register contains information of start and end of hospital visits, diagnosis, treatment, surgeries, and information of place including the hospital and hospital departments. ICD-10 codes have been used since 1994 and before then ICD-8 was used.[77]

The Danish National Prescription Registry (Paper A-C)

Since 1995, information of prescriptions redeemed at any community pharmacy in Denmark has been collected in The Danish National Prescription Registry. The registry includes information on product name, ATC code, defined daily doses per package, tablet/units per package and strength (per tablet/unit). Drugs not registered at community pharmacies include drugs used during hospital admissions, drugs used by some institutionalized people e.g. with psychiatric illnesses, and drugs directly supplied to hospitals including e.g. chemotherapeutic agents.[78]

The Population Education Register (Paper A-C)

In the Population Education Register the highest completed level of education for people who attained a degree in Denmark or self-reported their education. The register contains an 8-digit code describing the education, which can be transformed into International Standard Classification of Education (ISCED) codes. The register has non-missing information of 97% of ethnic Danish people and 85-90% of immigrants born 1945 to 1990.[79]

The Danish Integrated Database for Labour Market Research (Paper B)

Since 1981, information on Danish citizens' employment and unemployment, occupation, work experience, and income has been collected in The Danish Integrated Database for Labour Market Research. The registry is updated on a yearly basis.[80]

9 Definition of variables

9.1 Exposures

Two exposures were considered for this thesis. In Paper A and C we assess the primary symptom recorded for patients who called the Copenhagen EMS and in Paper B we assess the average yearly income of heart failure patients.

Recorded primary symptom (Paper A and C)

The criteria from the 1-1-2 emergency number and 1813-medical helpline was combined in order to enable analysis across the two systems and all criteria were grouped prior to analysis predominantly using the main chapter or primary complaint. For these studies the assigned criterion is considered to reflect the primary symptom of the patient considered in the call and we will refer to the assigned criterion as the recorded symptom. [10,74]

For some calls the criterion was missing (referred to as no recorded symptom). Missing registrations were largely contributed to medical doctors not always using the registration system, which had been made mandatory for other health professionals at the 1813-medical helpline including the nurses. For other calls the chosen criteria was did not contain information of the symptom presented by the patient (referred to as non-informative symptoms). At the 1-1-2 emergency number the non-informative symptoms were mostly orders of vehicles including ambulances e.g. by other health care institutions, and at the 1813-medical helpline the non-informative symptoms were most often calls from patients located in other Danish regions not covered by the service or calls where no one was answering (e.g. because the patient had left the phone). [10]

For Paper A, the symptom categories were re-classified into four categories: chest pain, atypical symptoms (abdominal/back/urinary, breathing problems, CNS symptoms, other atypical symptoms, other cardiac symptoms, and unclear problem), unconscious, and no recorded or non-informative symptoms. [10] The category 'other atypical symptoms' included symptom categories for which less than 100 calls were identified. These categories included: eyes, complication after treatment, ear-nose-throat, skin, cramps, bleeding, psychiatry/abuse, medication/prescription, infection/fever, complication of known disease, musculoskeletal, and trauma/ exposure. [10] In Table 2, examples of the original criteria and assigned symptom categories are shown.

A simpler categorization of symptoms were considered for Paper C. Here, criteria were categorized according to whether chest pain was the primary recorded symptom, and thus, the symptom categories consisted of the primary symptoms; chest pain and non-chest pain. [74]

Table 2: Examples of criteria codes and texts with assigned symptom category

Symptom category	Medical service	Criteria code	Criteria text
Breathing problems	1-1-2 emergency number	A.28.13	Breathing problems, Recently underwent surgery and suddenly got breathing problem
		A.28.99	Breathing problems, No suitable criterion
		B.28.01	Breathing problems, Patient is known with COPD, which is getting worse despite use of medication
		B.28.02	Breathing problems, Other acute breathing difficulty, which is gradually worsening
	1813-medical helpline	SS.01.04	Infections Adults, Cough / Respiratory difficulties
		SS.04.02	Heart and lungs, Breathing problem
Chest pain	1-1-2 emergency number	A.10.03	Chest pain - heart disease, New onset of central pain in the chest lasting more than 5 min
		A.10.06	Chest pain - heart disease, Chest pain or chest discomfort and - pale, clammy skin
		B.10.02	Chest pain - heart disease, Irregular heartbeats and feeling unwell
		C.10.01	Chest pain - heart disease, Pain (not severe) and patient feels ok
	1813-medical helpline	SS.04.01	Heart and lungs, Pain/discomfort in chest
Other atypical symptoms	1-1-2 emergency number	A.33.02	Accident, Possible serious injury
		B.11.02	Diabetes, Impaired consciousness/lethargy and has measured /suspicion of low blood sugar
	1813-medical helpline	SS.01.01	Infections Adults, Fever primary symptom >38
		SS.02.02	Motor apparatus without trauma, Symptoms from the neck without trauma
		SS.40.04	Request a prescription / medicine, Reaction to medication

The criteria shown in this table is a small sample of all the criteria identified for MI patients. An exhaustive list of the symptom categories, the criteria codes, and descriptions for the MI patients is available in the supplementary material of Paper A.[10]

Income (Paper B)

For Paper B, the exposure of interest was high versus low income. The income considered for this paper included wages, transfer payments, returns of investments, and pension payouts. The individual income was constructed based on the total household income which was weighted according to the number of people with permanent address in the household. The Organization for Economic Co-operation and Development (OECD) scale was used, such that the total household income for a household with only one adult would be divided with 1, but a household with two adults would be divided by 1.5.[81] All income was inflation adjusted to 2015. As income might vary from one year to another, we used a 5-year average of the individual income weighted according to household size including the 5 years preceding the heart failure diagnosis,

but not including the year of the diagnosis.[73] Finally, the average weighted income was categorized into approximate quartiles. We considered two definitions of low income; below 200.000 DKK (~1st quartile) and below 250.000 DKK (~2nd quartile). High income was defined as income above 400.000 DKK (~3rd quartile). The quartiles refers to the distribution of income within the study population of heart failure patients.[72]

9.2 Intermediate variables

In Paper B and C, we investigated interventions on a total of three intermediate variables, treatment initiation (Paper B) and emergency ambulance dispatch and prehospital ASA assignment (Paper C).

Treatment initiation (Paper B)

In Paper B, we investigated hypothetical interventions on the intermediate variable; initiation of treatment with β-blockers and RASi. Heart failure patients were defined as treatment initiators if they had redeemed at least one prescription of β-blockers (ATC: C07A) and at least one prescription of RASi (ATC: C09), during the first 90 days after the heart failure diagnosis.[72,73]

Emergency ambulance dispatch and prehospital ASA (Paper C)

For Paper C, we assessed the impact of hypothetical interventions targeting two intermediate variables; dispatch of emergency ambulance and prehospital ASA administration. The dispatch of emergency ambulances were defined as all dispatches of type A, which is emergency ambulances (mobile intensive care units) with lights and sirens. All remaining emergency responses including lower priority ambulances, no dispatch of vehicle, self-transport etc. was categorized as no emergency ambulance. Prehospital ASA treatment was defined as any type of ASA registered in the medicine tab of the electronic prehospital medical record. The majority of the assigned ASA was by oral administration but we also included intravenous administration.[74]

9.3 Outcomes

The outcomes considered for the three papers including emergency response and invasive procedures (Paper A), mortality (Paper A-C), and a combined 1-year outcome (Paper C) is described in the following.

Emergency response (Paper A)

For Paper A the emergency response was divided into four groups. The first category, *No referral for treatment*, included referring the patient to a general practitioner and watchful waiting, which means that the patient was asked

to wait it out and monitor symptom progression. The second category *Non-ambulance and self-transport/home visits* included patients who arranged transportation to the hospital themselves, patients receiving non-emergency transport i.e. transportation with other vehicles than ambulances, and patients who was seen by health care personnel in their own home. *Non-urgent dispatch* included a dispatch of a non-emergency ambulances, that is mobile intensive care units predominantly of type B but also C. The political service aim for type B ambulances in the Capital Region is that 90% arrives within 25 min, and the aim of type C is that 90% arrives within 2 hours. Lastly, *emergency dispatch* was a dispatch of an emergency ambulance driving with lights and sirens. The emergency ambulances are mobile intensive care units of type A and the political aim is that 90% arrives at the patient within 13 min. [10,71]

In-hospital management (Paper A)

As a secondary outcome we investigated differences in the in-hospital management by assessing (1) the time from hospital arrival to entry at a cardiology department and (2) the use of invasive procedures within the first 7 days after the call. The invasive procedures included coronary angiography (CAG) (UXAC40, UXAC85, UXAC85A-D, UXAC90, UXUC85-87, UFYA20) and PCI (KFNG00, KFNG02, KFNG02A, KFNG05, KFNG05A, KFNG10, KFNG12, KFNG20, KFNG22, KFNG30, KFNG40, KFNG96, KZFX01). [10]

Mortality (Paper A-C)

For Paper A and C, 30-day mortality was defined as any death occurring between time of MI diagnosis and 30 days after. For Paper B, 1-year mortality was defined as any death occurring between 90 days after the heart failure diagnosis and 1-year after that date.

Combined 1-year outcome (Paper C)

For Paper C a combined outcome of health events was defined. Patients were considered having the combined outcome if they were registered with either (1) death, or (2) a hospitalization with a re-infarct or (3) a hospitalization with heart failure within 1 year of the MI diagnosis. Diagnosis of MI and heart failure that were registered during the same hospital admission as the MI for which the patient was included in the study, were not considered for this outcome. [72]

9.4 Covariates

For all papers we included age (continuous, and also categorized for Paper A), sex (female, male), ethnicity (categorized as Danish, Immigrant, and Descendent of immigrant or Danish and Immigrant/Descendent of immigrant),

educational level categorized by ISCED codes (0–2: basic, 3–4: intermediate, and 5–8: advanced), and hypertension (patients claiming two types of antihypertensive drugs) and diabetes (patients claiming hypoglycemic medication), both within 180 days before the call/heart failure diagnosis, and following comorbidities: ischemic heart disease, chronic obstructive lung disease (COPD), and atrial fibrilation.[10,72,74] For Paper A and C we additionally defined claimed prescription of Non-Steroidal Anti-Inflammatory Drugs (NSAID) and opiods within 180 days before the call, medical service receiving call (1813-medical helpline and 1-1-2 emergency number) and previous MI, congestive heart failure, cancer, and moderate/severe renal disease.[10,74] For Paper B we additionally included occupation status (Employed/self-employed, unemployed, other/unknown, retired early, retired), cohabitation status (living alone or with a partner), claimed loop-diuretics and statins within 180 days before the heart failure diagnosis, and finally, chronic kidney disease and peripheral vascular disease.[72] The definition of covariates for each of the three papers are summarized in Table A1 in the Appendix. For analyses and tables only shown in the manuscript of the papers (and not in this thesis), some additional covariates were used. These are described in detail in the papers and their supplementary material.[10,74] The ATC-codes used to define hypertension align with previous work by Olesen et. al[82] and can be found in the supplementary material for both Paper A and C.[10,74]

10 Analyses

This section includes an overview of the methods used in the analyses of Paper A – C. For all papers, results were presented as proportions, absolute risks, and absolute risk differences and 95% confidence intervals were used throughout.

10.1 Standardized mortality

In Paper A, we estimated the standardized 30-day mortality for each symptom category (Chest pain, atypical symptoms, unconsciousness, and no recorded/non-informative symptoms), to enable comparison between the symptoms groups for which the distributions of especially age and comorbidities differed. We used model-based standardization to derive the standardized 30-day mortality for each subgroup. We standardized to the distribution of age, sex, COPD, prevalent diabetes, previous heart failure, previous MI, and educational level for the standard population which was the total population included in the study. MI patients with missing information of the educational level was excluded for this analysis. We used a logistic regression model to fit the probability of 30-day mortality and derived the 95% confidence interval using bootstrap with replacement.[10]

Standardization is often used in causal inference as a tool to achieve conditional

randomization,[83,84] but for this analysis standardization was merely used as an epidemiological tool for comparing subpopulations.[85] Thus, the differences between MI patients with and without chest pain should not be interpreted as the causal effect of the symptom presentations.

10.2 Stochastic and deterministic interventions among the exposed

In Paper B we define and introduce the target parameters and estimators that was needed to estimate the desired quantities in Paper C. Beside introducing the statistics in Paper B, we also illustrated the use of the suggested parameter and estimator using clinical case of low-income heart failure patients. In the following, we will introduce the target parameters and estimators using the clinical cases from both papers. In the first part, we define the parameters for each of the two papers without using mathematical notation. Thereafter, we introduce the mathematical notation to be able to derive the identifiability assumptions needed for a causal interpretation and the TMLE estimator. We are aware that this is a technical section. To improve readability the most essential information including a description of the target parameters and the causal assumptions has been comprised in Table 3 and 4 and a step-by-step guide to the TMLE estimator is available in Figure 2.

Target parameters

The target parameters are defined as the difference in expected outcome among the exposed patients with versus without a hypothetical intervention on the intermediate variable. Two different types of interventions are considered; a stochastic and a deterministic intervention. We will describe the two types of interventions for Paper B and C, respectively, in the following. An overview of the defined interventions and parameters for the two papers is available in Table 3.

For Paper B, we considered two definitions of the exposure low-income (income below 200,000 DKK and below 250,000 DKK), one intermediate variable (treatment initiation), and one outcome (1-year mortality). Low-income is used jointly for the two exposures in the following. The first target parameter is the expected change in 1-year mortality among low-income heart failure patients if hypothetically low-income patients had the same chance of initiating medical treatment as observed for the high-income heart failure patients conditional on covariates. The second target parameter is the expected change in 1-year mortality among low-income heart failure patients if hypothetically all low-income patients had initiated treatment conditional on covariates (See Table 3).[72]

For Paper C, we considered one exposure (non-chest pain), two intermediates (emergency ambulance and prehospital ASA), and two outcomes (30-day

mortality and a 1-year combined outcome). The target parameters described in the following were defined for both of the intermediate variables for each of the two outcomes. The first target parameter was defined as the expected change in outcome (30-day mortality/1-year combined outcome) among non-chest pain MI patients if they hypothetically had the same chance of receiving emergency ambulances/ASA as observed for chest pain MI patients conditional on covariates. The second target parameter was the expected change in outcome (30-day mortality/1-year combined outcome) among non-chest pain MI patients if hypothetically all non-chest pain patients had received emergency ambulances/ASA conditional on covariates (See Table 3).[74]

Table 3: An overview of the interventions and parameters for Paper B and C

Parameter	**Paper B**		**Paper C**	
	Stochastic intervention	Deterministic intervention	Stochastic intervention	Deterministic intervention
Expected outcome under intervention	The expected 1-year mortality among low-income heart failure patients if they hypothetically had the same chance of initiating treatment as observed for high-income patients	The expected 1-year mortality among low-income heart failure patients had they all initiated treatment	The expected outcome among non-chest pain MI patients if they hypothetically had the same chance of receiving emergency ambulance/ASA as observed for chest pain patients	The expected outcome among non-chest pain MI patients had all non-chest pain patients received emergency ambulances/ASA
Expected outcome without intervention	The expected 1-year mortality among low-income heart failure patients if low-income patients' chance of treatment initiation was as observed		The expected outcome among non-chest pain MI patients if non-chest pain patients' chance of emergency ambulances/ASA was as observed	
Risk difference	The expected change in 1-year mortality if low-income heart failure patients were as likely as observed for high-income patients to initiate treatment	The expected change in 1-year mortality had all low-income patients initiated treatment	The expected change in outcome if non-chest pain MI patients were as likely as observed for chest pain patients to receive emergency ambulances/ASA	The expected change in outcome had all non-chest pain MI patients received emergency ambulances/ASA

This table is a modified version of a Table 1 from Paper B, Learning the potential effects of selective health care interventions based on real-world data, by Møller et al. Submitted May 2022.[72] The outcomes for Paper C were 30-day mortality and a 1-year combined outcome of re-infarct, heart failure admission, and mortality. ASA=Acetylsalicylic acid.

Notation

Here, we introduce a simple data structure, where we let A be a binary variable of the exposure (non-chest pain or low-income), and $A = 1$ indicates being exposed (having non-chest pain or low-income) and $A = 0$ represents unexposed. The binary variable Z is an indicator of the intermediate variable (treatment initiation, emergency ambulance, or prehospital ASA), where $Z = 1$ indicate that the patient received the treatment and $Z = 0$ indicates the that the patient did not. Finally, we have a binary variable Y indicating the outcome (30-day mortality, 1-year mortality, or 1-year combined outcome). Here, $Y = 1$ indicates that a patients had the outcome, and $Y = 0$ indicates that the patient did not have the outcome. W denote a covariate set of potential confounders. Importantly, for present setup we assume that we have no right-censoring, whereby we have followed all patients for 30 days and 1 year, respectively.[72]

As stated previously, we are interested in defining a target parameter which describes the expected change in outcome risk we would observe under two different hypothetical interventions that modify the intermediate variable. Regardless of which of the interventions is considered the parameters are defined using the counterfactual framework.[83] The stochastic intervention among the exposed is described in detail in Paper B[72] but this intervention will also be described briefly in the following. However, the deterministic intervention, which is a more simple static intervention, was not given much attention in the paper, and we will provide more details of that intervention here.

Stochastic intervention among the exposed

We here introduce the stochastic intervention targeting the intermediate variable Z. We aim at identifying the change in outcome we would expect under the stochastic intervention where the distribution of Z among the exposed is changed to the distribution of Z observed among the unexposed conditional on the covariates. Mathematically, the difference in the expected outcome with versus without the stochastic intervention can be defined as follows:

$$\psi = \psi_0 - \psi_1 = \mathbb{E}[Y^{\gamma^0} \mid A = 1] - \mathbb{E}[Y \mid A = 1].$$

Here, Y^{γ^0} is the counterfactual outcome variable under the stochastic intervention where the distribution of Z among the exposed followed the distribution γ^0, and similarly, $\psi_0 = \mathbb{E}[Y^{\gamma^0} \mid A = 1]$ is the expected outcome we would have observed had all exposed patients' distribution of Z followed γ^0. We define γ^0 as:

$$\gamma^0(z \mid w) = P(Z = z \mid A = 0, W = w), \text{ for } z = 0,1.$$

This means that under the stochastic intervention of interest the observed distribution of Z among the exposed is changed to γ^0 which is equal to the

distribution of Z observed among the unexposed ($A = 0$) conditional on covariates W. Finally, $\psi_1 = \mathbb{E}[Y \mid A = 1]$ denotes the expected outcome among the exposed if their distribution of Z was as observed i.e. the observed expected outcome among the exposed.[72]

Deterministic intervention among the exposed

We now consider a deterministic intervention under which all exposed individuals have a fixed probability of the intermediate variable Z.[72] For this deterministic intervention, we define a counterfactual variable, Z^{γ^*}, which is simply defined as $\gamma^* = P(Z^{\gamma*} = 1)$. Hereby, Z^{γ^*} is the counterfactual distribution of the intermediate variable we would have observed had we fixed the exposed patients' chance of $Z = 1$ to a specific static level. In our applications, the probability γ^* is fixed to 100%, indicating that all the exposed patients had $Z = 1$, but this framework allows the user to choose any probability between 0% and 100%. The parameter $\psi_0^{\gamma^*} = \mathbb{E}[Y^{\gamma^*} \mid A = 1]$ is the expected outcome among the exposed, had all exposed patients' chance of $Z = 1$ followed γ^*. Again, we wish to compare this to the expected outcome ψ_1 which is defined above. The target parameter is the difference between $\psi_0^{\gamma^*}$ and ψ_1, where ψ^{γ^*} is the difference in expected outcome among the exposed with versus without the deterministic intervention:

$$\psi^{\gamma^*} = \psi_0^{\gamma^*} - \psi_1 = \mathbb{E}[Y^{\gamma^*} \mid A = 1] - \mathbb{E}[Y \mid A = 1].$$

Identifiability assumptions

To identify the target parameters in observed data, we need assumptions including exchangeability, positivity, and consistency. In Table 4 an overview of the assumptions needed for a causal interpretation is listed for the stochastic and deterministic intervention, respectively. We will in the following shortly describe the assumptions and provide some examples using the studies from Paper B and C. In the Section 17.2, we return to these assumptions as we discuss why a causal interpretation of the results in Paper B and C is not possible due to violations of especially the consistency and exchangeability assumptions.

First of all, for the stochastic intervention we need positivity for A and Z meaning that there must be a non-zero probability of being exposed $A = 1$ and unexposed $A = 0$ for all levels of the covariates, and similarly for receiving the intermediate $Z = 1$ and not receiving it $Z = 0$. For the deterministic intervention, we only need positivity for Z among the exposed $A = 1$. Secondly, for both interventions consistency is needed of the counterfactual outcome variable (Y^{γ^0} and Y^{γ^*}).[72] In the context of Paper C, this implies that there must not be different versions of receiving an emergency ambulance or prehospital ASA that would affect the outcome, 30-day mortality/1-year combined outcome, in different ways.[86] Lastly, we need exchangeability of Y^{γ^0} or Y^{γ^*} and the intermediate variable Z. This requires the counterfactual outcome variable Y^{γ^0} or

Y^{γ^*} and the observed Z to be conditionally independent given the exposure A and covariates W.[72] Returning to the clinical case from Paper C, conditional exchangeability between $Y^{\gamma^0}$and Z would imply that after conditioning on the symptom presentation and confounders the 30-day mortality risk among the patients who did not receive an emergency ambulance ($Z = 0$) would have been the same as the 30-day mortality risk among the patients who did receive an emergency ambulance ($Z = 1$) had they just received the ambulance.[83]

Table 4: An overview of the identifiability assumptions for the stochastic and deterministic interventions among the exposed

Intervention	**Assumptions**
Stochastic intervention	Conditional exchangeability between the counterfactual Y^{γ^0} and Z
	Consistency of the counterfactual Y^{γ^0}
	Positivity for A
	Positivity for Z
Deterministic intervention	Conditional exchangeability between the counterfactual Y^{γ^*} and Z
	Consistency of the counterfactual Y^{γ^*}
	Positivity for Z among $A = 1$

Table A1 from the Supplemental Digital Content for Paper B, Learning the potential effects of selective health care interventions based on real-world data, by Møller et al. Submitted May 2022.[72]

Targeted Minimum Loss-based Estimation

We have chosen to estimate our parameters using TMLE, a minimum-loss based substitution estimation procedure that can generally be used for estimation of causal effects from observational or randomized studies.[55] The TMLE for both the stochastic and deterministic intervention are implemented as an R-package available at `https://github.com/amalielykkemark/tmleExposed`. In Figure 2 we have described the estimation steps for the expected outcome under the stochastic and deterministic intervention, respectively, and the expected outcome under no intervention.

TMLE is a two-step procedure including an initial estimation step (1a-c in Figure 2) which is later updated in the targeting step (2 and 2a-c in Figure 2) to improve the bias-variance trade-off and to achieve valid inference.[55] The first part of the estimation involves modelling the distribution of the exposure, intermediate variable, and outcome as shown in Figure 2 in step 1a-c. The conditional distribution of the exposure is denoted $\pi(a \mid W) = P(A = a \mid W)$, the conditional distribution of the intermediate variable is denoted $\gamma(z \mid a, W) = P(Z = z \mid A = a, W)$, and finally, the conditional expectation of the outcome is denoted $Q(a, z, W) = \mathbb{E}[Y \mid A = a, Z = z, W]$, where the conditional expectation of the outcome among the exposed is $Q(1, z, W) = \mathbb{E}[Y \mid A = 1, Z = z, W]$.[72]

Different algorithms can be chosen for modelling of the above mentioned quantities. We will return to that when describing the super learner in the next section. In the targeting step, the estimators from step 1a-c are updated such that they solve the efficient influence function sufficiently well (see step 2 and 2a-c in Figure 2). The parameters for the stochastic and deterministic intervention, and the parameter under no intervention, can now be estimated using the updated TMLE estimators shown in Figure 2 step 3a-c.

The estimators for the target parameters are derived as the difference between the estimators of the parameters with and without intervention.[72] For the stochastic intervention the estimator of the target parameter is:

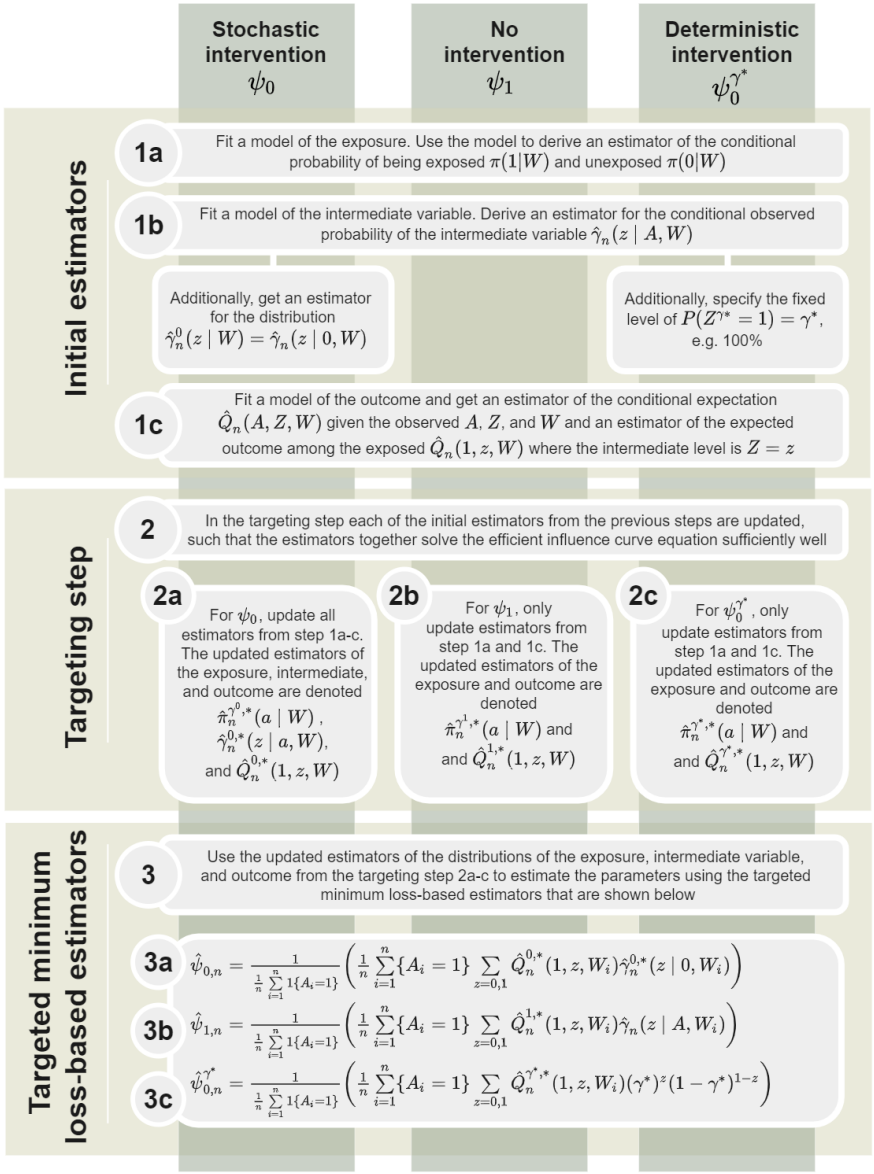
$$\hat{\psi}_n = \hat{\psi}_{0,n} - \hat{\psi}_{1,n},$$

and similarly, for the deterministic intervention the estimator of the target parameter is:

$$\hat{\psi}_n^{\gamma^*} = \hat{\psi}_{0,n}^{\gamma^*} - \hat{\psi}_{1,n}.$$

For all estimators, the standard errors can be derived using the efficient influence functions.

Fig. 2: A step-by-step guide to the estimation of the expected risk difference under the stochastic and deterministic interventions among the exposed using TMLE



This figure comprises the statistical estimation of the stochastic intervention which is also described in Paper B. Learning the potential effects of selective health care interventions based on real-world data, by Møller et al. Submitted May 2022. [72]

Super Learner

For the initial estimators of the distribution of the exposure, intermediate variables, and outcome described in 1a-c in Figure 2 logistic regression can be applied, but a range of other algorithms could be considered to minimize risk of model misspecification. We suggest using the so-called super learning [56] to choose the optimal algorithm for each of the three underlying models for the TMLE. In short, super learning is a method that allows the researcher to identify one optimal algorithm (discrete super learning) or an optimal weighted combination of algorithms (the super learner estimator) based on a pre-specified library of algorithms, often referred to as the super learner library. [56] The super learner library can contain a range of algorithms including regression models with and without interactions and machine learning algorithms as neural network and random forest, just to mention some. The super learner uses V-fold cross-validation to identify the best performing algorithm (or weighted combination of algorithms) in terms of lowest cross-validated risk. For the papers included in this thesis, we apply discrete super learning. Super learning is thereby used to identify the algorithm in the pre-specified super learner library with the best fit. In the R package the user can choose to use discrete super learning as well as the super learner estimator. Further details of the statistical procedure of the super learner is available in (van der Laan et al. 2007) [56] along with introductions to the super learner package in (Polley et. al 2011) [87] and step-by-step descriptions for applied researchers (Naimi and Balzer, 2018) [88] and (Rose, 2013) [89].

Specification of underlying models for Paper B and C

In both Paper B and C we used discrete super learning to select the optimal algorithm for the initial estimators described in Figure 2 step 1a-c.

In Paper B we let the super learner library consist of a least absolute shrinkage and selection operator (LASSO), elastic net, and logistic regression model. All models were adjusted for sex, age, cohabitation status, occupation, year of heart failure diagnosis, type-2 diabetes, and COPD. Further, the models considered as candidates for the exposure (income) model were also adjusted for level of education. The models considered for the intermediate variable (treatment initiation) were adjusted for level of education, atrial fibrillation, peripheral artery disease, loop-diuretics, and previous statin use. Finally the models considered for the outcome (1-year mortality) was also adjusted for atrial fibrillation. [72]

In Paper C the models included in the super learner library were logistic regression models. For each exposure/intermediate variable/outcome model we let the super learner choose between two logistic regression models; one with main terms including a broad selection of variables and one including main terms and in some cases second order interactions selected based on clinical

knowledge. All models were adjusted for sex, age, level of education, choice of medical service (1813-medical helpline or 1-1-2 emergency number), COPD, type-2 diabetes, heart failure, previous myocardial infarction, and opioid use. We also considered immigration, cancer, and ischemic heart disease in the adjustment set for some models. Finally, we also adjusted for type of infarct in the models of the outcome (30-day mortality/1 year combined outcome).[74]

Sensitivity analyses

For Paper C, we hypothesized that STEMI patients would benefit more of receiving emergency ambulances and prehospital ASA administration compared to NSTEMI patients, as STEMI patients more often have an acute complete occlusion of a coronary blood vessel. Likewise we expected a smaller benefit among NSTEMI patients as they are more likely to have a narrowing rather than occlusion of the vessel, and thus, their condition is considered less acute.[9,14,15] Finally, large variations in the proportion of patients who were correctly recognized and received the highest dispatch priority were observed across the two medical services (the 1813-medical helpline and the 1-1-2 emergency number).[10] Further, we expect that the severity of symptoms is worse among calls to the 1-1-2 emergency number and that symptom severity is possibly linked to severity of the patients condition. It would be reasonable to believe that the effect of the proposed interventions would differ between the two health care services given the expected differences in severity of symptoms and MI across the two services. Thus, to investigate whether the expected risk change caused by the hypothetical interventions differed across subpopulations, the target parameters described in Section 10.2 were also estimated in subgroups of STEMI patients, NSTEMI patients, and 1-1-2 emergency calls. The sensitivity analyses were adjusted for the same set of variables as the main analyses in Paper C although omitting type of infarction in the analyses of STEMI/NSTEMI and choice of medical service in the analyses of 1-1-2 calls.

Part III

Results

Results

11 Paper A – Impact of myocardial infarction symptom presentation on emergency response and survival

11.1 Background and objectives

MI patients often seek medical attention for their symptoms by calling for help.[7,9] Diagnosing MI in telephone consultations is challenging and patients presenting with atypical symptoms might be at risk of treatment delay caused by misrecognition. The extent to which MI patients present with atypical symptoms when calling for help is not well elucidated and it remains unclear how the initial symptom presentation is related to the prehospital management of the patients. In this study, we aimed at characterizing the initial symptom presentation of MI patients and assess the associations between the symptom presentation and the immediate prehospital response, in-hospital procedures, and 30-day mortality for calls to the emergency and non-emergency medical services.

11.2 Main results

Between January 1st 2014 and December 31st 2018, we identified 1,958,319 calls to the 1813-medical helpline and 326,040 calls to the 1-1-2 emergency number for individuals with information on civil registration number. Patients who were suspected to be dead at the time of call were excluded and the first call for each MI (if multiple calls existed) were extracted. The final population consisted of 8,336 calls for MI patients from the Capital region of Denmark who had called either the 1813-medical helpline or the 1-1-2 emergency number up to 72 hours prior to an in-hospital diagnosis of MI or MI as cause of death.[10] In Table 5 characteristics of the MI patients according to symptom presentation is shown.

Table 5: Characteristics of MI patients according to the symptom recorded at the 1813-medical helpline and 1-1-2 emergency number

Variable	Level	Chest pain N=5,219	Atypical symptoms N=1,713	Uncon-scious N=290	Non-infor-mative/no recorded symptom N=1,114	Total N=8,336
Call type	1-1-2 emergency number n(%)	3,508 (67.2)	900 (52.5)	280 − 290	180 − 190	4,880 (58.5)
	1813-medical helpline n(%)	1,711 (32.8)	813 (47.5)	≤ 15	925-935	3,456 (41.5)
Sex	Female n(%)	1,681 (32.2)	762 (44.5)	79 (27.2)	425 (38.2)	2,947 (35.4)
Age	Median [IQR]	67.5 [56.6, 77.1]	73.6 [62.5, 82.9]	73.2 [63.1, 83.0]	67.7 [56.1, 77.7]	68.9 [57.7, 78.8]
Ischemic heart disease	n(%)	1,710 (32.8)	422 (24.6)	70 (24.1)	272 (24.4)	2,474 (29.7)
Previous MI	n(%)	1,175 (22.5)	269 (15.7)	36 (12.4)	173 (15.5)	1,653 (19.8)
Heart failure	n(%)	649 (12.4)	263 (15.4)	54 (18.6)	119 (10.7)	1,085 (13.0)
Diabetes (Type 2)	n(%)	777 (14.9)	325 (19.0)	54 (18.6)	180 (16.2)	1,336 (16.0))
Hypertension	n(%)	1,809 (34.7)	641 (37.4)	114 (39.3)	360 (32.3)	2,924 (35.1)
COPD	n(%)	410 (7.9)	262 (15.3)	27 (9.3)	90 (8.1)	789 (9.5)
NSAID/ opioid	n(%)	1,305 (25.0)	564 (32.9)	79 (27.2)	276 (24.8)	2,224 (26.7)
Educational level	Basic n(%)	1,566 (31.2)	645 (39.4)	103 (36.9)	338 (31.9)	2,652 (33.2)
	Intermediate n(%)	2,233 (44.5)	659 (40.3)	135 (48.4)	427 (40.3)	3,454 (43.2)
	Advanced n(%)	1,215 (24.2)	333 (20.3)	40 − 50	290 − 300	1,883 (23.6)
	missing n	205	76	≤ 15	50 − 60	347

A modified version of Table 1 from Paper A, Impact of myocardial infarction symptom presentation on emergency response and survival. European Heart Journal. Acute Cardiovascular Care, 10(10):1150–1159, December 2021, by Møller et al.[10] COPD=Chronic Obstructive Pulmonary Disease, NSAID=Non-Steroidal Anti-Inflammatory Drugs, IQR=Inter Quartile Range. Data cells with fewer than 15 observations were set to ≤ 15 to protect the identity of the patients.

Overall, 58.5% (4,880/8,336) had contacted the 1-1-2 emergency number and 41.5% had called the 1813-medical helpline prior to their MI, 35.4% were female, and median age 68.9 IQR[57.7;78.8]. We identified 7,222 MI patients with informative data on symptoms. Among these, the most common symptom was chest pain which 72% (5,219/7,222) of the MI patients had been recorded with. A total of 24%(1,713/7,222) were recorded with atypical symptoms among which breathing problems was identified as the most common of the atypical symptoms (8% (556/7,222)). Previous cardiovascular diseases (is-

chemic heart disease and myocardial infraction) were most prevalent among chest pain patients compared to patients with atypical symptoms (32.8% and 22.5% versus 24.6% and 15.7%). Patients with atypical symptoms had a higher prevalence of type 2 diabetes (19%), COPD (15.3%), and were more likely to have picked up opiods or NSAID during the past 180 days (32.9%) compared to chest pain MI patients (Table 5).[10]

The proportion of MI patients recorded with chest pain were unevenly distributed across sex and age groups as well as across the two medical services. Younger MI patients were more likely to have been recorded with chest pain at the time of call compared to elderly patients as were male patients compared to females and patients who had called the 1-1-2 emergency number rather than the 1813-medical helpline. Among the 7,222 MI patients who had information on recorded symptom, male patients aged 30–59 who had called the 1-1-2 emergency number were identified as the subgroup most often recorded with chest pain (85%). On the other hand, elderly females (age above 79) who had called the 1813-medical helpline were the least likely to have been recorded with chest pain (49%). We found breathing problems to be most prevalent among elderly females who had called the 1-1-2 emergency number (age above 79: 13% and age 70-79: 15%) and patients older than 79 who had called the 1813-medical helpline (females: 12% and males: 13%). Figure 2 in Paper A illustrates the distribution of the recorded symptoms in subgroups of sex and age.[10]

In total, 7,875 of the MI patients were hospitalized. Details of the in-hospital management of these patients, including time from admission to arrival at cardiology ward and invasive procedures are available in Table 6. The time from admission to arrival at a cardiology department was generally longer for MI patients presenting with atypical symptoms than chest pain. Patients who were unconscious or had presented with chest pain were the most likely to arrive directly at the cardiology ward (59% and 52%). This was true for only a third of the MI patients with atypical symptoms. Similarly, PCI and CAG procedures were more common for chest pain and unconscious patients (CAG: 79% and 75%, PCI: 54% and 55%) compared to patients with atypical symptoms (CAG: 58% and PCI: 32%) (Table 6).[10]

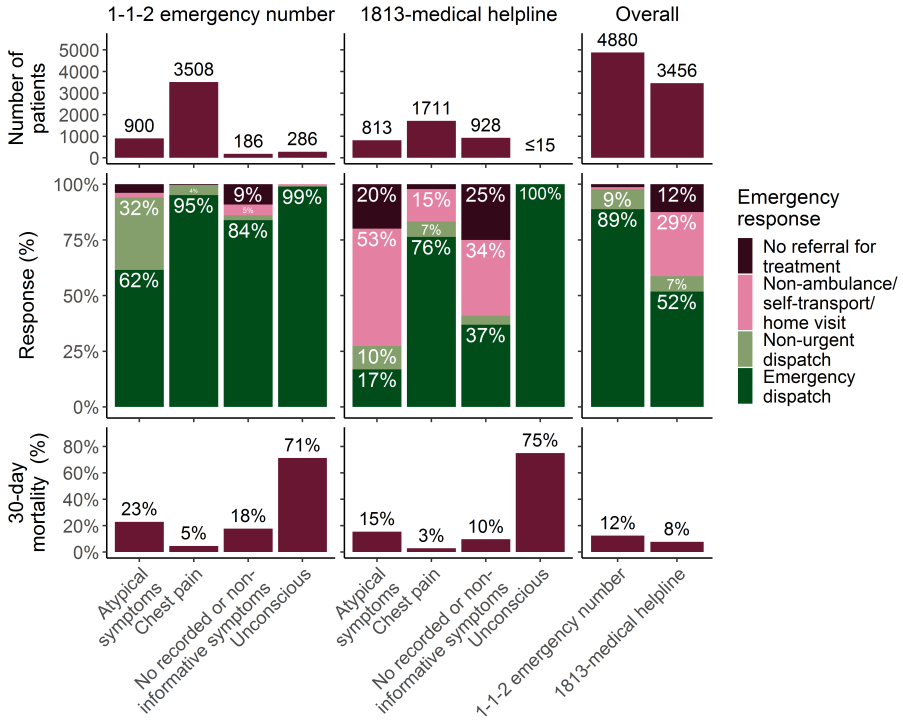
Table 6: In-hospital management of 7,875 myocardial infarction patients hospitalized within 72 hours after a call the the 1813-medical helpline or 1-1-2 emergency number

Variable	Level	Chest pain (N=5,156)	Atypical symptoms (N=1,556)	Unconscious (N=112)	No recorded or non-informative symptoms (N=1,051)	Total (N=7,875)
Admitted to cardiology ward during admission	Yes	5,054 (98.0)	1,466 (94.2)	104 (92.9)	1,014 (96.5)	7,638 (97.0)
Time from hospital arrival to cardiology ward	Directly to cardiology	2,634 (52.2)	470 (32.2)	61 (59.2)	367 (36.3)	3,532 (46.4)
	<2 hours	956 (19.0)	291 (19.9)	25 (24.3)	235 (23.2)	1,507 (19.8)
	2 to 4 hours	768 (15.2)	236 (16.2)	≤ 15	179 (17.7)	$1,180 - 1,190$
	4-12 hours	389 (7.7)	214 (14.7)	≤ 15	135 (13.4)	$740 - 750$
	>12 hours	295 (5.9)	249 (17.1)	≤ 15	95 (9.4)	$640 - 650$
	missing	114	96	≤ 15	40	$250 - 260$
PCI within 7 days of call	Yes	2,793 (54.2)	496 (31.9)	62 (55.4)	496 (47.2)	3,847 (48.9)
CAG within 7 days of call	Yes	4,075 (79.0)	897 (57.6)	84 (75.0)	764 (72.7)	5,820 (73.9)

Selected information from Table 3 from Paper A, Impact of myocardial infarction symptom presentation on emergency response and survival. European Heart Journal. Acute Cardiovascular Care, 10(10):1150–1159, December 2021, by Møller et al.[10] CAG=Coronary angiography, PCI=Percutaneous coronary intervention. Data cells with fewer than 15 observations were set to ≤ 15 to protect the identity of the patients.

Overall, 52% of calls to the 1813-medical helpline and 89% of calls to the 1-1-2 emergency number resulted in an emergency dispatch with an emergency ambulance of type A. Mostly, calls for patients recorded with chest pain resulted in an emergency dispatch (1-1-2 emergency number: 95%, 1813-medical helpline: 76%). This was less common for patients with atypical symptoms where on average 62% had received an emergency dispatch at the 1-1-2 emergency number and 17% at the 1813-medical helpline. The prevalence of other types of emergency responses can be found in Figure 3.[10]

Fig. 3: Distribution of the emergency response and 30-day mortality according to the recorded symptom for 8,336 myocardial infarction patients who had called the 1813-medical helpline or 1-1-2 emergency number. The 'Overall' column shows the summarized distributions for all calls to the 1813-medical helpline and 1-1-2 emergency number, respectively.



A modified version of Figure 3 from Paper A, Impact of myocardial infarction symptom presentation on emergency response and survival. European Heart Journal. Acute Cardiovascular Care, 10(10):1150–1159, December 2021, by Møller et al. [10]

The 30-day mortality was standardized to the distribution of age, sex, educational level, previous MI, COPD, heart failure, and diabetes of the total MI population. Patients with missing information of education was excluded (N=347) leaving 7,989 patients for this analysis. The standardized 30-day mortality was 4.3% for chest pain patients, 15.6% for atypical symptoms, 11.9% for no record/non-informative symptoms and 64.9% for unconscious patients. The variation in mortality across symptoms was slightly higher for the observed 30-day mortality (chest pain: 3.9%, atypical symptoms: 19.1%, no record/non-informative symptoms 11.0% and unconsciousness 71.3%). The observed mortality according to recorded primary symptom and medical service is available in Figure 3. [10]

12 Paper B – Learning the potential effects of selective health care interventions based on real-world data

12.1 Background and objectives

The target parameter and estimator presented in Paper B was described in details in Section 10.2. We will in this section focus on the application of the developed method in general and illustrate the use by estimating effects of hypothetical interventions aimed at improving the medical treatment initiation among low-income heart failure patients.

The goal of selective interventions is to reduce risk of adverse health outcomes in high-risk populations. Populations or subpopulations with increased risk can be identified by shared features such as race, low income, or previous disease. These features are typically not considered to be directly intervenable, meaning that it is difficult (if not impossible) to imagine a real-world intervention that could modify these features of the population in a meaningful way. As a result, public health interventions often target an intervenable intermediate factor affected by the high-risk feature and which itself affects the health outcome of interest. Such intermediate factors could be access to quality treatment or health behaviour which are factors that could meaningfully be targets of real-world interventions. Selective public health interventions can therefore improve outcomes in high-risk populations by intervening on these intermediate factors.[90] We demonstrate how the potential effects of selective interventions can be estimated from real-world data using a clinical case of low-income heart failure patients.[72]

RASi and β-blockers are central therapies in the medical treatment of heart failure patients with reduced ejection fraction and adherence is important to reduce mortality and adverse outcomes.[91,92] Previous research have indicated that heart failure patients of lower socioeconomic status/income have lower use of evidence-based therapies, including RASi and β-blockers, and increased mortality compared to the patients of higher socioeconomic status/income.[93–98] It is possible that the lower use of medical therapies among low-income heart failure patients is a contributing factor to the observed differences in mortality between patients with low versus high income.[72]

12.2 Main results

We defined two hypothetical interventions, a stochastic and a deterministic, that could contribute to elucidate the impact of improving chance of treatment initiation on the mortality among low-income heart failure patients. For the hypothetical stochastic intervention the target parameter was the expected

change in 1-year mortality among low-income heart failure patients had they had the same chance of initiating medical treatment as observed for the high-income patients conditional on covariates. For the deterministic intervention, the target parameter was the expected change in mortality among low-income patients if all low-income patients had initiated medical treatment.[72]

For this study, we included 3,399 heart failure patients who were diagnosed at a Danish hospital between 2005 and 2016. We identified the low-income heart failure patients by considering two cut-offs for the average yearly income. For the lowest cut-off (average yearly income below 200.000 DKK) we identified 817 heart failure patients and for the higher cut-off (average yearly income below 250.000 DKK) we identified 1,536 patients (Figure 4). Finally, 833 of the heart failure patients had an average yearly income above 400,000 DKK and were considered high-income patients.[72]

Fig. 4: The expected 1-year mortality among low-income heart failure patients under the stochastic and deterministic intervention and under no intervention. The median and inter quartile range of the probability of initiating treatment among low-income patients is shown for each intervention on the right hand side.

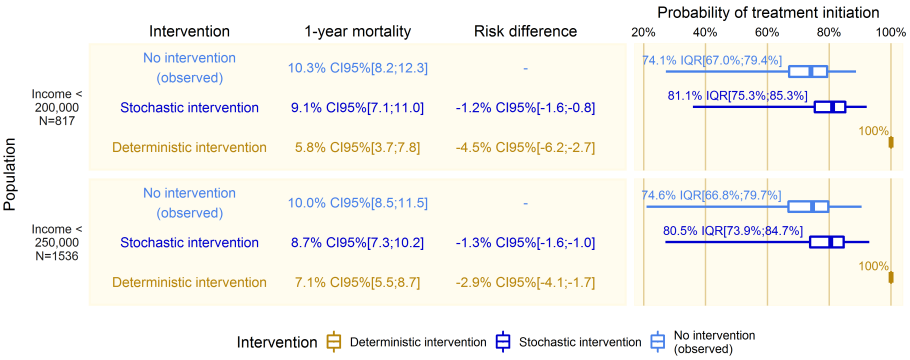


Figure 1 from Paper B, Learning the potential effects of selective health care interventions based on real-world data, by Møller et al. Submitted May 2022.[72] IQR=Inter Quartile Range.

Under the stochastic intervention, where low-income heart failure patients hypothetically had the same chance of initiating treatment as observed for high-income patients, the potential reduction in 1-year mortality was 1.2% CI95%[0.8;1.6] (income below 200.000 DKK) and 1.3% CI95%[1.0;1.6] (income below 250.000 DKK). For the deterministic intervention, where all low-income hear failure patients initiated treatment, the reduction in 1-year mortality among low-income patients was 4.5% CI95%[2.7;6.2] (income below 200,000 DKK) and 2.9% CI95%[1.7;4.1] (income below 250,000 DKK). The estimated absolute 1-year mortality and the distribution of the probability of the treatment initiation for low-income heart failure patients with and without inter-

vention is available in Figure 4.[72]

13 Paper C – Hypothetical interventions on emergency ambulance and prehospital acetylsalicylic acid administration in myocardial infarction patients presenting without chest pain

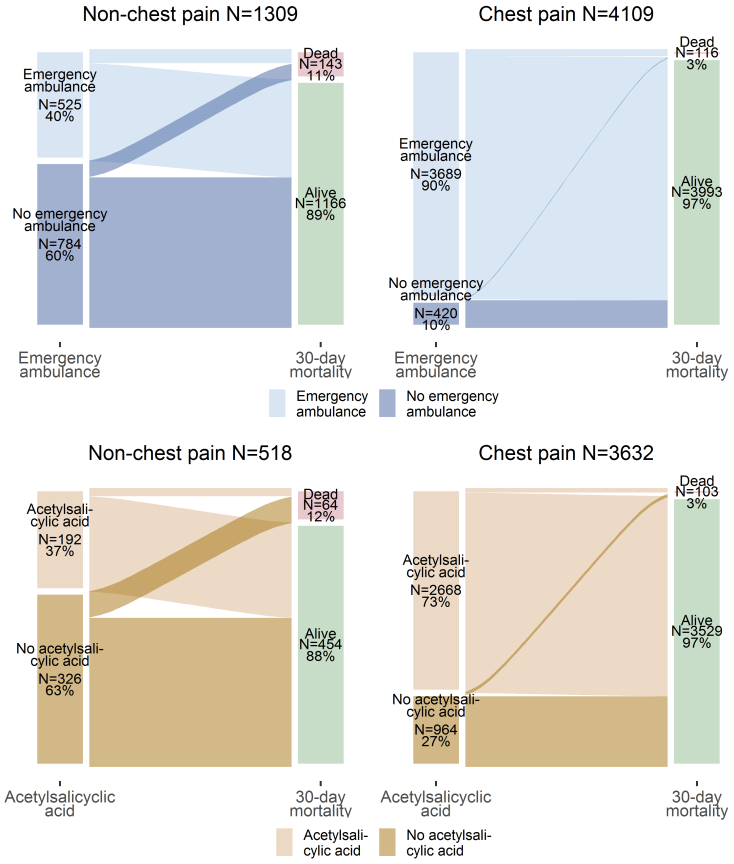
13.1 Background and objectives

MI patients who present without chest pain receive less-optimal prehospital management, have longer prehospital delays, and higher mortality compared to MI patients with chest pain.[3,4,10,39,44] Still, it remains unclear whether improving the prehospital management of non-chest pain MI patients could in fact contribute to improving their outcomes. We aimed at elucidating if a possible unresolved potential for reducing mortality among non-chest pain MI patients existed. To investigate this, we analyzed the expected outcome under two hypothetical interventions intended at improving the prehospital management among non-chest pain MI patients. Specifically, we analysed the expected outcome among non-chest pain MI patients under a stochastic intervention where hypothetically they received emergency ambulances and prehospital ASA with the same probability as observed for similar chest pain patients, and secondly, the expected outcome among non-chest pain MI patients under a deterministic intervention where they all received emergency ambulances and ASA.[74]

13.2 Main results

We included 5,418 calls regarding hospital diagnosed MI patients who had called the 1813-medical helpline or 1-1-2 emergency number within 24 hours before their MI diagnosis between April 2015 and December 2018. Calls were categorized based on primary recorded symptom of chest pain (76%) and non-chest pain (24%). In the subgroups the prevalence of non-chest pain was 17%(292/1,685) for STEMI patients, 25%(590/2,358) for NSTEMI patients, and 20%(713/3,526) for MI patients who had called the 1-1-2 emergency number. In total, 90% (3,689/4,109) of chest pain and 40% (525/1,309) of non-chest pain patients received emergency ambulances. Among the 4,150 MI patients who received an emergency ambulance and did not have any contraindications of ASA, 73% (2,668/3,632) of chest pain and 37% (192/518) of non-chest pain patients were administered prehospital ASA (See Figure 5).[74]

Fig. 5: The number and proportion of MI patients who received emergency ambulance dispatch and prehopsital acetylsalicyclic acid (ASA) according to symptom presentation of chest pain and non-chest pain. Only emergency ambulance transported MI patients with no contraindication of ASA was included in the lower two plots.



A modified version of Figure 2 from Paper C, Hypothetical interventions on emergency ambulance and prehospital acetylsalicylic acid administration in myocardial infarction patients presenting without chest pain, by Møller et al. Submitted March 2022.[74]

The expected change in 30-day mortality and the 1-year combined outcome among non-chest pain MI patients under the hypothetical interventions can be found in Figure 6. In the figure, *As chest pain* refers to the stochastic intervention where non-chest pain MI patients were as likely to receive emergency ambulances/ASA as observed for the chest pain patients, and *All* refers to the deterministic intervention where all non-chest pain MI patients received emergency ambulances/ASA.[74]

A small, but not significant, increase in the expected outcome were found when

increasing chance of receiving emergency ambulance among non-chest pain MI patients (30-day mortality: 1.5% CI 95%[-0.6%; 3.6%] and 2.1% CI 95%[-0.7%; 4.8%], 1-year combined outcome: 1.3% CI 95%[-1.4%;4.0%] and 1.6% CI95%[-1.9%;5.1%]). For the subgroup analyses of both STEMI patients and calls to the 1-1-2 emergency number the expected change in outcome when increasing emergency ambulance dispatch were very close to null with increases in 30-day mortality/1-year combined outcome ranging between 0.4% CI95%[-1.3%;2.2%] and 0.9% CI95%[-1.9%;3.8%] (Figure 6).[74]

Prehospital administration of ASA to all emergency ambulance transported non-chest pain MI patients was expected to reduce 30-day mortality by 5.3% CI95%[1.7%;9.0%] from 12.8% to 7.4%. The expected reduction was 3.3% CI95%[1.4%;5.2%] (from 12.8% to 9.5%) had emergency ambulance transported non-chest pain MI patients had the same chance of receiving ASA as observed for similar chest pain patients. In comparison, we found that observed 30-day mortality among emergency ambulance transported chest pain patients was 3%. The impact of increasing prehospital ASA administration on 30-day mortality were largest among the subgroup of STEMI patients. Assigning ASA to all non-chest pain STEMI patients resulted in a mortality reduction of 6.7% CI95%[2%;11.4%] and assigning ASA with the same probability as observed for chest pain patients led to a reduction of 4.5% CI95%: [1.4%;7.6%]. For the subgroup of NSTEMI patients, the number of 30-day mortality events was to small to enable analysis of increasing prehospital ASA administration. No significant reduction was found for the 1-year combined outcome when increasing ASA administration for the main population (1.5% CI95%[-1.4%;4.4%] and 2.6% CI95%(-2.9%;8.1%)) or any of the three subgroups (Figure 6).[74]

Fig. 6: The expected change in 30-day mortality and 1-year combined-outcome among MI patients recorded without chest pain under hypothetical interventions on emergency ambulance dispatch and prehospital acetylsalicylic acid.

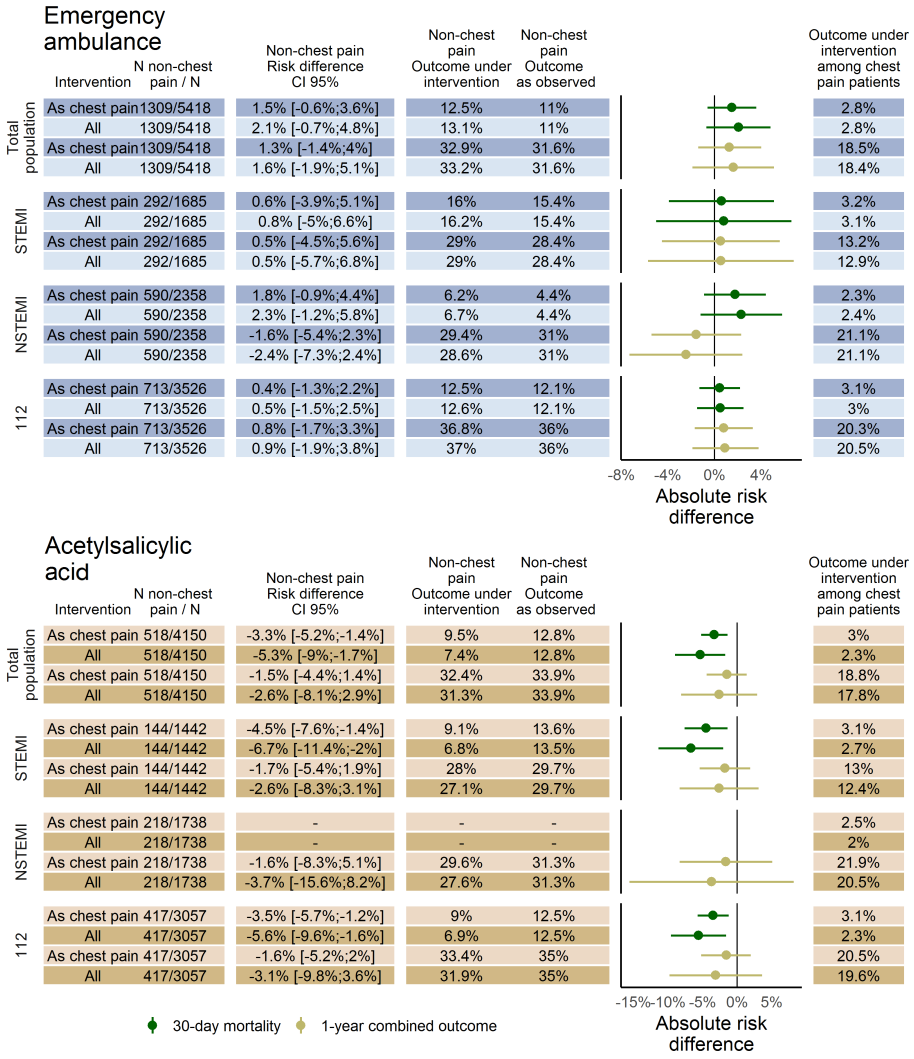


Figure 3 from Paper C, Hypothetical interventions on emergency ambulance and prehospital acetylsalicylic acid administration in myocardial infarction patients presenting without chest pain, by Møller et al. Submitted March 2022.[74] The 1-year combined outcome is composite outcome of re-infarction, heart failure admission, or mortality occurring within 1 year of the MI diagnosis.

Part IV

Discussion

Discussion

14 Summary of findings

Overall, this thesis underpin that MI patients presenting without chest pain are a high-risk population. They often do not receive the appropriate emergency response, they are less likely to have ASA administered prehospital, and have high mortality compared to MI patients with chest pain.

To investigate whether improved prehospital management of non-cheat pain MI patients could potentially reduce mortality, we assessed the impact of hypothetical interventions increasing chance of emergency ambulance dispatch and prehospital ASA among non-chest pain MI patients. We formalized two target parameters allowing us to derive the quantities of interest, namely the change in outcome had all non-chest pain MI patients (1) been as likely to receive emergency ambulance/prehospital ASA as observed for chest pain patients and (2) all received emergency ambulance/prehospital ASA, and developed a TMLE estimator to estimate these parameters.

We found no indication of reduction in 30-day mortality and 1-year combined outcome of re-infarct, heart failure admission, and mortality when hypothetically increasing non-chest pain MI patients chance of receiving emergency ambulance dispatch. Increasing prehospital ASA administration led to a reduction in 30-day mortality but not for the 1-year combined outcome. Regardless of the interventions considered, the 30-day mortality among non-chest pain MI patients remains high compared to the MI patients recorded with chest pain.

15 What does this thesis add?

As concluded in the introduction, knowledge was sparse on (1) what symptoms were recorded in the first medical contact of MI patients, especially for non-emergency medical services, (2) the immediate response provided to MI patients according to symptom presentation, and (3) the expected effect of improving the prehospital management of non-chest pain MI patients. We believe that this thesis have provided important insights to the symptom presentation

of MI patients during the first medical contact by sourcing the information on symptoms directly from the prehospital registrations at both emergency and non-emergency medical services. Similarly, we were able to link data from calls directly to the immediate response and treatment registered in the prehospital electronic patient record. This enabled us to describe the prehospital management of MI patients with and without chest pain. A causal interpretation of the effect of the hypothetical interventions on prehospital management investigated in Paper C is difficult to achieve as discussed later in Section 17.2. Still, we believe that trying to investigate the change in the expected outcome under a relevant change in the distribution of the prehospital management provides insights more relevant for clinicians than assessing associations between the presented symptoms and the prehospital management and outcomes, respectively. Lastly, we have developed methods that can be used to quantify effects of hypothetical interventions targeting high-risk populations and illustrated the applicability using two real-world cases. The R-codes implementing the TMLE estimator have been made publicly available and we hope that the estimator can be of relevance to other researchers.

16 Discussion of findings and comparison with existing literature

16.1 Prevalence of non-chest pain among MI patients

In both Paper A and C we found that 24% of all MI patients presented without chest pain, although the two studies considered slightly different populations. Further, in Paper C we found that 25% of NSTEMI and 17% of STEMI patients presented without chest pain. In recent research the proportion of non-chest pain patients were found to be 11% - 21% in studies of MI/MI undergoing PCI,[2,33] 13%-38% for NSTEMI/NSTEMI undergoing PCI,[9,28,30] and 11% - 14% for STEMI/STEMI undergoing PCI patients.[9,29,31] The prevalence of non-chest pain for NSTEMI alligned with the literature, but our study found slightly higher prevalences for STEMI and for MI overall. Several differences between our and recent studies might explain this. First of all, the symptoms were registered in-hospital in other studies whereas we included the symptom registered during the first medical contact. It is plausible that patients experienced other symptoms than chest pain during the first medical contact, but then developed chest pain in the time span from first medical contact to hospital admission. Secondly, differences in inclusion criteria, study periods, populations, and health care system might also explain some of the differences in non-cheat pain prevalences.

In Paper A, we estimated that 8% (556/7,222) of MI patients had breathing problems, which was equivalent to 32% (556/1,713) of the non-chest pain patients with available information on symptom.[10] Other studies have similarly

estimated this proportion to 25% to 49% depending on the population.[2,3,28,32] Breathing problems must be considered a dominating symptom among those presenting without chest pain, especially among elderly patients as shown in Paper A, possibly deserving greater attention in the prehospital setting.

16.2 Mortality according to symptom presentation among MI patients

The observed 30-day mortality following MI was 4% and 19% for patients with and without chest pain in Paper A and equivalently, 3% and 11% in Paper C. Few studies have reported the observed 30-day mortality for comparable populations and therefore direct comparison of our findings to previous studies is difficult. A recent study, including patients in Japan from 2013-2014, reported the observed 30-day mortality for in-hospital diagnosed MI patients undergoing PCI to 3% and 13% with and without chest pain.[33] A Swedish study including hospitalized MI patients between 1996 and 2010 reported 30-day mortality to 6% (1.9% <age 65, 8.7% >age 65) and 15% (7% <age 65, 16% >age 65) for patients with and without chest pain.[3] The 30-day mortality of chest pain MI patients is relatively high in the Swedish study compared to findings from this thesis, but the variations in inclusion periods could explain these differences. The 30-day mortality of 19% for non-chest pain MI patient found in Paper A, is high compared to findings from other studies and Paper C. For this study we included MI patients based on both MI diagnosis and MI as cause of death. MI patients identified based on death certificates were more likely to have been recorded without chest pain, and thus, these patients contribute relatively more to the mortality among non-chest pain MI patients, than chest pain patients. To our knowledge, no other study have included MI patients based on death certificates.

16.3 Prehospital management of MI patients

Overall, previous studies have suggested that MI patients are generally dispatched to high priority and transported with emergency ambulances.[9,50] Clawson et al. found that 90% of MI patients who had called an emergency medical service (9-1-1) received emergency ambulances.[50] Thylén et al. found that 98% of STEMI patients who had called the emergency medical services and 78-83% of patients contacting a primary health care center or Swedish healthcare district were transported to the hospital in ambulance.[7] We found that 89% of MI patients calling the 1-1-2 emergency number received an emergency ambulance dispatch and that 98% (emergency dispatch: 89% and non-urgent dispatch: 9%) received any type of ambulance, which aligns with the previous findings indicating that MI patients who seek medical attention at the emergency medical services are generally managed according to guidelines. Nevertheless, the proportion of patients transported by any type of ambulance was 59% (emergency dispatch: 52% and non-urgent dispatch: 7%) among calls to the 1813-

medical helpline. This was considerably lower, also in comparison with findings from the Swedish study, and this indicates that almost half of the MI patients seeking medical attention at the non-emergency medical service do not receive the optimal response. These patients were either asked to contact their general practitioner or call back in case of aggravation of symptoms, received time slot at emergency department (self-transport), or received non-ambulance patient transport to hospital, possible causing unnecessary treatment delay.

Additionally, MI/ACS patients with chest pain have been found to be more likely to receive high priority dispatch when calling the emergency medical services[41] and have shorter delays[39,99] compared to non-chest pain patients. The results from Paper A and C support these findings and highlight the magnitude of the differences in the prehospital management of MI patients with and without chest pain. At the 1-1-2 emergency number 95% versus 62% of MI patients with and without chest pain received an emergency dispatch. Equivalent proportions for calls to the 1813-medical helpline was 76% versus 17%. Similarly, twice as many of the emergency transported MI patients with chest received ASA compared to the non-chest pain patients.[10,74]

16.4 Improving the prehospital management of non-chest pain MI patients

As described in Section 3 and 4, several studies have investigated and documented the association between symptom presentation and prehospital/treatment delay and symptom presentation and mortality. However, to our knowledge, no previous study have examined the effect of hypothetical interventions targeting the prehospital management of non-chest pain MI patients. With Paper C, we added new insights to the existing literature on the potential change in outcome we could expect under a relevant hypothetical intervention.

Emergency ambulances

We found no improvement in expected outcome risk under the two hypothetical interventions where non-chest pain MI patients chance of receiving an emergency ambulance was increased. On the contrary, we found a small increase in the risk of 30-day mortality and 1-year combined . It is unlikely to believe that dispatching ambulances to more MI patients would have an adverse impact on patient outcomes. Instead, we expect that patients with more severe infarcts are more likely to receive an emergency ambulance. Therefore, our findings are expected to be biased as we were not able to effectively adjust for the severity of the MI. However, we did investigate the same hypothetical interventions in subgroups of STEMI, NSTEMI, and 1-1-2 emergency calls, which are all expected to be indicators of the severity of the infarct or reported symptoms. For the subgrops of STEMI patients and calls to the 1-1-2 emergency number the change in outcome risk was very close to null, indicating that increasing chance

of receiving emergency dispatch had no effect on outcomes.

In general, the distances to hospitals are short in Denmark. Only 3% have more than 50 km and more than a third of the population has less than 10 km.[100] The distances are even shorter in the Capital Region where this study was conducted. In Paper C we estimated the differences in time from call to hospital arrival of non-chest pain MI patients who did and did not receive emergency ambulance. We found that the difference in the median time was only 10 minutes (emergency ambulance: 51.5 min, no emergency ambulance: 61.6 min) (See Supplementary Table S5 in Paper C).[74] It is possible that the differences in prehospital delay are too small to impact the outcomes considered in this thesis. We cannot rule out that increasing dispatch of emergency ambulances to non-chest pain MI patients in other regions or countries would lead to very different results, especially in areas with long driving distances to nearest hospital.

Prehospital administration of acetylsalicylic acid

The observed differences in the prehospital administration of ASA to MI patients with and without chest pain were large (73% vs 37%). Increasing the chance of receiving prehospital ASA among emergency ambulance transported non-chest patients was found to reduce the 30-day mortality by 3-5%, depending on the intervention, but no significant reductions were found for the long-term outcome.[74] The reduction in the 30-day mortality was large considering that the distances to hospitals are expected to be short and that most emergency transported non-chest pain patients did not have a STEMI. Thus, the anticipated gain on survival of reducing time to treatment was expected to be smaller. We believe that our results are at least partly affected by other associated factors. As MI must be suspected in patients who were given ASA, such patients would likely have been diagnosed using prehospital ECG. Prehospital diagnosis of MI would likely trigger fast triage to cardiology departments or PCI centers, which would reduce time to in-hospital treatment. Unfortunately, we did not have data on the obtained prehospital ECGs and could therefore not determine if the estimated effects are caused by early diagnosis or ASA.

Secondly, the effect of administrating ASA prehospital versus in-hospital is uncertain, especially among NSTEMI patients.[21] A previous observational study indicated that prehospital versus in-hospital administration of ASA to MI patients could reduce 30-day mortality,[101] but to our knowledge, no clinical studies have investigated the effect of administrating ASA in the prehospital setting, and thus, current recommendations for early ASA treatment rely predominantly on the Second International Study of Infarct Survival (ISIS-2) trial.[21,102]

Some non-chest pain MI patients had contraindication of ASA. These patients were excluded from the analysis to reduce risk of structural positivity vio-

lations. We searched for contraindication listed in the prehospital electronic patient record, but we cannot rule out that contraindications for some patients were never listed or that they were missed in the search. In addition, assessing the risk of adverse effects including risk of bleeding was beyond the scope of this thesis, but such investigations are warranted if ASA administration was in fact to be increased in a real-world setting.

16.5 Other factors affecting mortality in MI patients

The prehospital management is important to reduce overall ischemic time, but the management and treatment provided to MI patients in-hospital could have a bigger impact on outcomes. In alignment with findings from Paper A, previous studies have indicated that non-chest pain MI patients are less likely to receive medical treatment and invasive procedures, including CAG, PCI, and coronary artery bypass graft surgery during their hospitalization.[1,3,28] It is reasonable that interventions targeting the in-hospital management would lead to greater risk reductions among non-chest pain MI patients, than the interventions considered in this thesis. Additionally, MI patients with concomitant acute non-cardiac conditions, as pneumonia, gastrointestinal bleeding, stroke, and sepsis, are also less likely to receive evidence based in-hospital treatment for MI and have high mortality.[103] Although not directly assessed in previous studies, we cannot rule out that the lower chance of treatment and high mortality in non-chest pain MI patients is at least partly affected by their state of health before the MI and possibly concomitant severe disease also requiring acute treatment. Finally, the decision delay, i.e. the time from symptom onset to first medical contact, have been found to be longer among patients presenting without chest pain.[6] Even though MI patients often seek help fast, some patients can have symptoms for days or even weeks before seeking medical attention.[39] Given the magnitude of the decision delay, at least for some patients, it is reasonable that reducing the time from the first medical contact to hospital arrival with possibly 10-30 min would not have a major impact on mortality.

17 Limitations and methodological considerations

17.1 Limitations

In this section we will discuss limitations of this thesis, including assessing risk of different sources of bias. In addition, we will discuss the interpretation of our findings in Paper B and C considering the causal assumptions needed to identify the target parameter and finally, evaluate the generalizability of our findings.

Misclassification of symptoms and MI diagnosis

For Paper A and C we used the criteria registered at the 1813-medical helpline and 1-1-2 emergency number as proxy of the primary symptom of the MI patient. At the two medical services the call-takers choose one primary criteria and can add sub-criteria from a list. Using this data source provides systematic data on a very large amount of calls, but some uncertainty of the registration of symptoms exists. First of all, the registered criteria represents the call-takers perception of the symptoms and not the patients. It is likely that the patients and the call-taker disagree on whether symptoms are present or not, and which symptoms are the most important. Secondly, the criteria based system is divided into chapters, where each chapter represents a symptom, disease, condition, or purpose of call. Some symptoms, as e.g. chest pain, have their own chapter whereas other symptoms, as syncope or palpitations, are listed as sub-chapters or share a chapter with other symptoms. The structure of the criteria based system used at these organizations thereby affects our ability to categorize the symptoms. As a result, some symptoms, especially more vague or unspecific symptoms, are very difficult to identify from this data source and might be misclassified. Lastly, we cannot rule out that a patient categorized with breathing problems also experienced chest pain, but that this symptom for some reason was listed secondary or not listed at all. This occurs partly because the call-taker decides that breathing problems was the symptom that most accurately described the patients condition, but also because of the structure of the criteria based system described above. Although some misclassification of the symptom presentation is expected, our primary symptom of interest, chest pain, is ranked as an important symptom in the criteria based system and patients calling with chest pain would typically be registered with a criteria from the chapter *Chest pain*. We believe that the data from the Copenhagen Emergency Medical Services enables researchers to answer important questions regarding how health care personnel perceive the symptoms of the patients and react to them during the first medical contact.

We used the Danish National Patient Registry, and for Paper A also the Register of Causes of Death, to define patients with an MI. Some misclassification must be expected when using registry data to define MI. Previous studies indicate overall high validity of the definition of MI using the Danish National Patient Registry (positive predictive values for first time MI and recurrent MI was 99% and 88%), but somewhat lower when using the Danish Register of Causes of Death (positive predictive value of 62% to 86%).[104,105] Thus, we can not rule out that some patients included based on death certificates actually suffered other diseases. However, the vast majority (94% in Paper A and 100% in Paper C) were included based on MI diagnosis registered in the Danish National Patient Registry.

Selection bias

Patients can experience an MI without receiving a diagnosis, either because the infarction was small or because it was not registered. We do not have data that would allow us to identify patients with MI's not diagnosed in-hospital (or on death certificates), and thus, inclusion of such patients was not possible. Our population of MI patients must be expected to consist MI's requiring treatment and thereby the more 'severe' MI's.

Additionally, for Paper A and C we only considered MI patients who had a call to the 1813-medical helpline and 1-1-2 emergency number up to 72 or 24 hours before the MI diagnosis. This selection of patients does not include those who sought medical attention at (1) their general practitioner, or (2) directly at the emergency department without calling the 1813-medical helpline in advance. The share of MI patients having a visit at the primary health care center was estimated to 9-14% in Swedish studies [7,9]. Unfortunately, we did not have data on symptoms or purpose of contact for these patients and therefore we could not include these. The 1813-medical helpline was launched in January 2014, and before then inhabitants of the Capital Region did not need to call in advance before entering the emergency department. In January and February 2014, the patient had showed up without calling in advance in 36-39% of all emergency department visits, but in 2016, this proportion was reduced to 20%. [106,107] We do not know the share of MI patient showing up at emergency departments without calling in advance, but the proportions listed above indicate that we could be missing patients, especially in the first period after 2014. The patients showing up at emergency departments without calling in advance do not have a prehospital contact, and thus, investigating the prehospital management of these patients is not relevant given the particular questions considered in this thesis. However, this is a relatively large patient group and research investigating the symptoms and reasons for not calling for help among these patients is needed to fully understand the help-seeking behavior of MI patients, an important step in order to increase the use of the emergency number among MI patients.

To identify the MI patients of interest we had to condition on the MI diagnosis given 24/72 hours after the call, as we currently are not able to diagnose MI patients in the telephone consultations. In consequence, the MI population can not be identified at the time of call, which limits the applicability of our findings in a real-world setting. However, prehospital recognition during the ambulance transportation is often possible with the use of prehospital ECG, [21,24] although the use and effectiveness for identifying non-chest pain MI patients is unclear.

Residual and unmeasured confounding

For all three papers included in this thesis bias caused by residual and unmeasured confounding is a concern. Firstly, residual confounding might be a concern in our studies as we defined comorbidities by registry data, which might not capture the true comorbidity burden of the patients. Further, controlling for confounding using binary or categorized variable as we did for educational level, comobidities etc. might not fully capture the confounding of that variable, and thus, leading to residual confounding. The same problem would occur if we misspecified the functional form of a confounder or had other types of model misspecifications. Additionally, some confounders were unmeasured, and as a result, omitted from the analyses. Such confounders include lifestyle factors such as smoking, diet, physical activity and obesity. Further, as mentioned previously in the discussion, it is reasonable to believe that the symptoms reported by the MI patients could be associated with the severity of their infarct. In such a scenario, we could have that increased mortality among non-chest pain MI patients was caused by more severe infarcts rather than prehospital misrecognition and treatment delays. In Paper C, we tried to discriminate between the severity of the MI by repeating the analysis in subgroups STEMI and NSTEMI patients, but for one fourth this differentiation was not possible due to missing information of infarct type. Categorization according to STEMI and NSTEMI is very common in the literature[4,7,9,29–31], but vital parameters at the time of call could have improved our ability to differentiate between severe and less severe MI's which is expected to be an important unmeasured confounder. Previous studies have indicated that symptom presentation without chest pain is more common among those with NSTEMI. As NSTEMI usually have better short term survival than STEMI patients, we would expect such bias to reduce the difference in the 30-day mortality between MI patients with and without chest pain. On the other hand, patients with type 2 infarcts have been found to be more likely to present without chest pain and to have higher mortality.[108,109] Such bias would likely increase the difference in mortality between MI patients with and without chest pain. Thus, it is not obvious in which direction or to what extent the estimation of the effect is biased.

17.2 Methodological considerations

As shown in Table 5 the patients presenting without chest pain are different from those with chest pain in several ways. The median age is 6 years higher than for chest pain patients, they suffer a greater burden of comorbidities including heart failure, COPD, and diabetes, and a third of the non-chest pain patients have claimed prescribed opioid or NSAID within 180 days before the call to the medical service.[10] Even though, all patients included in our study are suffering form an MI, it seems unlikely that MI patients with and without chest pain are in fact comparable (even after conditioning on covariates). If these patients had been comparable, we would still not be able to imagine an inter-

vention that would enable us to change the symptom presentation of non-chest patients to chest pain and vice versa. Similar challenge exists for the example of low-income heart failure patients, where low- and high-income patients are expected to have very different characteristics, and thus, not only differ in terms of income, and again, actual interventions changing income are difficult to define. As a result, estimating the effect of changing the symptom or income is likely not very relevant for clinical practice. Recent publication by Moreno-Bentacur et al. 2021 emphasizes the importance of defining effects mapped to a target trial with a well defined hypothetical intervention, that can in fact be emulated with the observational data at hand, especially in relation to mediation analysis which historically has focused on pathway discovery rather than quantifying effects of interventions targeting the mediator.[110] To improve the clinical relevance of the study, we aimed at quantifying the expected change in outcome if we hypothetically had intervened on the prehospital management of non-chest pain patients and treatment initiation among low-income heart failure patients, which are in fact modifiable variables.

We chose to estimate the effects of two different interventions, (1) a stochastic intervention under which the exposed patients were as likely to receive treatment as observed for the unexposed patients, and (2) a deterministic intervention for which all exposed patients received treatment. We chose these two interventions, as intervention (2) represent the best case scenario under which all patients were managed according to guidelines. Such scenario could be criticised for not being realistic in real-world settings, and thus we added the stochastic intervention (1) as we believe that increasing treatment to what was observed among the unexposed would be a more realistic best case scenario.

Interpretation of estimates

As described in Section 5 existing methods were not ideal for deriving the parameter of interest. Thus, we designed the target parameter, and since the estimator, that allowed us to estimate the effect of an intervention targeting only the non-chest pain patients. In this way, a causal interpretation of the effect of a relevant intervention on the prehospital management could be achieved under less strict assumptions. Although our proposed parameter allows us to relax the assumption of exchageability for the exposure-mediator relationship, exchageability of the mediator-outcome relationship, consistency, and positivity is still needed for a causal interpretation as described in Section 10.2. In the following, we discuss why such assumptions are difficult to meet in the analyses in Paper B and C.

Consistency

Whether real-world interventions would in fact lead to the effects estimated in thesis are of cause debatable. Ideally researchers should specify the target

trials in such detail that treatments would be sufficiently well defined as ill defined interventions can lead violations of consistency under which the potential outcome, and thus, the causal effect estimate becomes ill defined too.[83,111] For example 'prehospital ASA' might not be sufficiently well defined to ensure that the assigned treatment is actually the same for all patients, for example we could imagine that the two versions 'ASA and fast-tracked to PCI center', and 'ASA and not fast-tracked to PCI center' would have different impact on mortality. Further, the administration (intravenous/oral) and timing should have been specified too. Additionally for the low-income heart failure case, we could imagine several versions of claiming the prescribed medication, which was our proxy of treatment initiation, that could have (at least) two versions with very different expected effect, (1) claiming prescribed medication and adhere to treatment, versus (2) claiming prescribed medication and not adhere. In consequence, we expect violations of consistency of the counterfactual outcome in our studies.

Exchangeability

Although exchangeability between the exposure and mediator is not required, we still need exchangeability between the counterfactual outcome Y^{γ^0} and Y^{γ^*} and the observed intermediate given the exposure and covariates.

Returning to our discussion of possible unmeasured confounding from Section 17.1, the infarct type or severity of the patients condition could be an import unmeasured confounder, as we suspect that patients in with worse vital parameters would be more likely to receive emergency ambulance, and would also have increased risk of mortality. Additionally, we can not rule out that other unmeasured confounders including lifestyle factors, such as smoking and obesity, could possibly affect chance of the intermediate variable and outcome in a similar way. These unmeasured confounders are expected to bias the effect estimate. Similar challenges exist for the heart failure case. We tried to reduce risk of bias caused by low eject fraction, which is an indication of treatment also associated with poor outcome, by restricting the population to patients with a recent infarction.[72,73] But we cannot rule out that bias is introduced by other unmeasured confounders.

Positivity

We investigated if all observations in our data had a non-zero probability of being exposed and unexposed, i.e. having non-chest pain/chest pain, and receiving treatment and not receiving treatment. For the analyses in both Paper B and C some observations' probability of presenting with non-chest pain/having low income was close 0 or 1 for several analysis. Although no actual violations were identified, near violations could be problematic. For the deterministic intervention, where all received emergency ambulance/ASA/initiated treatment,

positivity was only required for the intermediate variable among the exposed (non-chest pain /low-income patients), and this did not seem to be violated.

In conclusion, a direct causal interpretation of the results from Paper B and C is not possible due to violations of the causal assumptions. However, we still believe that our studies can contribute to understanding how interventions on an intermediate variable could affect the outcome, and thus, provide a currently best suggestion of the impact of improving the prehospital management of non-chest pain MI patients.

17.3 Why use TMLE?

As described in Section 10.2 the defined target parameters for Paper B and C does not rely on a specific estimator and therefore other estimators could have been considered. So why choose TMLE? TMLE has many appealing properties that can make this estimator advantageous to other estimators.[55] Firstly, TMLE is a double robust estimator. That is, an estimator that use two different models, typically an exposure model and an outcome model, to estimate the effect of an exposure (or intervention). An advantage of such estimators is that they can provide an unbiased estimation of the causal effect if either the model of the exposure or the outcome is correctly specified.[112] In practice, this means that even if one of models is misspecified, e.g. because a confounder was omitted, the estimator still provides an unbiased result as long as the other model is correctly specified. Secondly, with TMLE the underlying models of the exposure, intermediate, and outcome can be modelled using super learning. Super learning allows the user to select the one most optimal algorithm or an optimal weighted combination of algorithms, and enable use of machine learning. Including machine learning algorithms among the candidate algorithms might be beneficial in terms of reducing reliance on parametric modelling assumptions as well as improving the final algorithms ability to identify complex or high order interactions and nonlinear relationships that are difficult to model using regression models.[89]

17.4 Generalizability of findings

The prehospital health care systems, and health care systems in general, vary in coverage and setup across countries. In some countries the emergency medical services and out-of-hours medical service are not covered by a universal health care system. In such settings patients' health care seeking behavior might be different from described in this thesis. The prehospital setting in the Capital Region is of Denmark is somewhat unique regarding the use of the centralized 1813-medical helpline. The applicability of the findings in this thesis to other countries, or even other regions within Denmark, will require thorough evaluation and comparison of the health care systems as countries often have several different prehospital health care systems, as it is the case in Denmark.

During the past decade European and OECD countries have generally moved towards centralization of the out-of-hours primary care and most OECD countries have implemented new technologies including telephone triage system and advice lines, which could be similar to the setup considered in this thesis. [113,114]

Additionally, it should be noted that the Danish population is predominantly ethnic Danish which also could affect the generalizability of the findings to other populations.

18 Conclusion

This thesis aimed at providing knowledge of the initial symptoms reported by MI patients during the first medical contact, how the reported symptoms affected the immediate response, and if improved prehospital management of the high-risk non-chest pain MI patients could potentially help reduce mortality. To be able to identify the effects of improving the prehospital management, we proposed a target parameter capturing the change in expected outcome under a stochastic and deterministic intervention on an intermediate variable.

We found that a fourth of the MI patients presented with another primary symptom than chest pain when calling for help at a non-emergency medical helpline and emergency medical service in the Capital Region of Denmark. Though, MI patients with chest pain are generally managed according to guidelines, non-chest pain MI patients often do not receive high priority dispatch and prehospital ASA. Increasing chance of receiving prehospital ASA among emergency ambulance transported non-chest pain MI patients was found to be associated with a lower 30-day mortality risk, but we did not find evidence supporting a long-term effect of the interventions. The risk of 30-day mortality and a combined outcome of re-infarct, heart failure hospitalization, and mortality within one year remained high among non-chest pain MI patients regardless of the hypothetical interventions considered.

Our findings must be interpreted in the light of several limitations. Importantly, unmeasured and residual confounding is expected to affect our results, particularly, the severity of the infarction is assumed to be an important unmeasured confounder. Additionally, effective identification of MI patients during the first medical contact is currently not possible limiting the real-world application of our findings. However, with the limitations in mind our findings contribute to the current literature with important descriptions of the prevalence of chest pain and the management of MI patients across emergency and non-emergency medical services. By considering hypothetical interventions, we believe that we provide a currently best guess of the expected effect of improving the prehospital management of non-chest pain MI patients. A question that is difficult to investigate in clinical trials given the current challenges of

identifying MI patients, and especially those presenting without chest pain, in the prehospital setting.

19 Future perspectives

The overall mortality of MI is low, but it remains high among those presenting without chest pain. To further reduce overall mortality among MI patients, those at substantial higher risk must be considered an important target. Earlier diagnosis could be a key to reduce delays and improve timely prehospital treatment, which, as shown is this thesis, is currently low. This thesis showed that close to half of MI patients seek help at the non-emergency medical service. These patients often present without chest pain and are very difficult to recognize with an acute life threatening disease in the prehospital setting. We advocate that future studies assess the possibility of improving early recognition of non-chest pain MI patients for both emergency and non-emergency medical services. However, the findings of this thesis suggests that even though non-chest pain MI patients are less likely to receive emergency ambulance dispatch and prehospital ASA, it is not well documented that improved prehospital management would in fact lead to better long-term outcomes for these patients. The true causal link between the symptoms, management, and outcomes of MI patients is currently not well understood. We warrant future research determining the underlying cause of the high mortality among non-chest pain MI patients and assessing the impact of prehospital diagnosis and treatment, separately. An important distinction, that was not possible to make in the present work.

With this thesis we have shown the usability of our proposed TMLE for two clinical scenarios, but more scenarios likely exist. We envision that our suggested parameter could be relevant for many future studies especially within the area of health disparities, where assessments of the effects of modifying an intermediate variable affected by a non-intervenable exposure are common. The method has been made available to other researchers as an R-package at github `https://github.com/amalielykkemark/tmleExposed`. The method, as it is currently implemented, is only designed for binary exposures, intermediates variables and outcomes. For many studies, it would be necessary to extend the method for other scenarios including continuous outcomes and intermediates and time-to-event settings.

Finally, testing the performance of using machine learning algorithms in combination with super learning was beyond the scope of this thesis. We applied super learning in a relatively simple form, i.e. discrete super learning considering a super learner library of different simple models. But future users could choose to add machine learning algorithms to the super learner library and apply the super learner estimator instead of the discrete super learner as

described in Section 10.2. It is possible that the accuracy of the estimation in Paper B and C could have been improved had we had more time to work on optimizing the fitting of the super learner. It is my hope, that I will be able to continue working and learning about TMLE, super learning, and machine learning and gain further insights to real-world applications of these tools during my postdoc.

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Appendix

Table A1: An overview of covariates and their definitions for Paper A-C

Data source	Paper A and C	Paper B
The Danish Civil Registration System	Age, sex (female, male), ethnicity (Danish, Immigrant, and Descendent of immigrant or Danish and Immigrant/Descendent of immigrant)	
The Population Education Register	Educational level was categorized by ISCED codes (0–2: basic, 3–4: intermediate, and 5–8: advanced)	
The Danish Integrated Database for Labour Market Research	Occupation (Employed/self-employed, unemployed, other/unknown, retired early, retired). Cohabitation status (living alone or with partner)	
The Danish National Prescription Registry	Type 2 diabetes: claimed hypoglycemic medication (ATC: A10). Hypertension: at least two different classes of antihypertensive drugs (α adrenergic blockers, diuretics, vasodilators, β-blockers, calcium channel blockers, and RASi).[82] Both within 180 days before the call/heart failure diagnosis	
	Use of NSAID (ATC: M01A) and opioids (ATC: N02AA01, N02AA03-5, N02AA55, N02AB02-3, N02AE01, N02AG02, N02AX02, N02AX06, N07BC02, R05DA04) during the 180 days before the call.	Use of loop-diuretics (ATC: C03C) and statins (ATC: C10AA) up to 180 days before the heart failure diagnosis.
Copenhagen Emergency Medical Services	Medical service receiving call (1813-medical helpline and 1-1-2 emergency number)	
The National Patient Register*	Myocardial infarction (ICD-10: I21) Ischemic heart disease (ICD-10: I20, I22-25) Congestive heart failure (ICD-10: I11.0, I13.0, I13.2, I42.0, I42.6-9, I50.0-3, I50.8-.9) Moderate/severe renal disease (ICD-10: I12-3, N00-N05, N07, N11, N14, N17-N19, Q61) COPD (ICD-10: J44) Cancer (ICD-10: C00-C96 (excluding C61.9)) Arterial fibrillation (ICD-10: I48)	Peripheral vascular disease (ICD-10: I70-4, I77) Ischemic heart disease (ICD-10: I20-25) Chronic kidney disease (ICD-10: N18) Atrial fibrillation (ICD-10: I48) COPD (ICD-10: J44)

*ICD-10 codes registered up to 10 years before index (Paper A) and 5 years before index (Paper C) were included. COPD=Chronic obstructive lung disease.

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