

Symptoms, prehospital delay and long-term survival in men vs. women with myocardial infarction

A combined register and qualitative study

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No one knows what he can do till he tries

Pubilius Syrus

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Abstract

The general aim of this thesis was to study symptoms, prehospital delay and time trends in long-term survival in men and women with myocardial infarction (MI). The study was based on quantitative and qualitative data collections. Study **I** was based on The Northern Sweden MONICA Myocardial Infarction Registry, 1989-2003, including 5072 men and 1470 women with a confirmed MI. Symptoms and prehospital delay were described and trends over time according to sex and age were studied. Typical pain was present in 86% of the men and 81% of the women and typical symptoms were more common among younger persons than older persons. Up to the age of 65 no gender differences were seen in the prehospital delay. In the oldest age group (65–74 years) time to hospital was longer than among the younger group, especially among women. Study **II** was based on individual interviews with 20 men with a first confirmed MI, representing the age range 65-80 years, about their experiences during the prehospital phase. The interviews were analyzed using qualitative content analysis. The interviewed older men described how the symptoms developed from diffuse ill-being, to a cluster of severe symptoms. The men had difficulties to relate to the experienced symptoms, which did not correspond to their expectations about an MI, and about whether they should seek medical care. By using different strategies the participants initially tried to understand, reduce, or treat the symptoms by themselves, with a desire to maintain an ordinary life. As the symptoms evolved to a persistent and alarming chest pain, the men realized the seriousness in the perceived symptoms, that all strategies were inefficacious and they came to the decision to seek medical care. Study **III** was based on individual interviews with 20 women with a first confirmed MI, representing the age range 65-80 years, about their experiences during the prehospital phase. The interviews were analyzed using qualitative content analysis. The interviewed older women described how the symptoms were perceived as a stepwise evolvment from intangible and bodily sensations to a more distinct, persistent and finally overwhelming chest pain. The women struggled against the symptoms and used different strategies, by downplaying and neglecting the symptoms in order to maintain control over their ordinary lives and maintain the social responsibilities. As the symptoms evolved to a

persistent and overwhelming chest pain the women realized the seriousness in the perceived symptoms, they were not able to struggle against them anymore and they came to the decision to seek medical care. Study **IV** was based on The Northern Sweden MONICA Myocardial Infarction Registry which was linked to The Swedish National Cause of Death Registry for 6762 men and 1868 women, 25 to 64 years of age, with a first MI during 1985-2006. Also deaths before admission to hospital were included. Follow-up ended on August 30, 2008. Between 1985 and 2006 long-term survival after a first MI increased in both men and women. Over the whole 23-year period women showed a 9 percent higher survival than men. This slight difference was due to lower risk for women to die before reaching hospital, and during the last period similar rates of long time survival were noted in men and women.

In conclusion there were no major differences between men and women in symptoms, prehospital delay or long-term survival. However, older patients had fewer typical symptoms and longer prehospital delay, especially among women. The prehospital phase was found to be multifaceted with experiences difficult to interpret in both men and women, with a dynamic development of symptoms, conceptions and expectations while the participants strove to maintain the ordinary and familiar life. The symptoms experienced presented a more heterogeneous and complex picture in both men and women than is usually described in the literature. Women under the age of 65 have a slightly higher age-adjusted long-term survival than men. Over a 23-year period long-term survival has improved similarly in both men and women.

Keywords: myocardial infarction, symptoms, prehospital delay, men and women, long-term survival, time trend, experiences.

Sammanfattning/Swedish summary

Det övergripande syftet med avhandlingen var att beskriva symtom, prehospital fördröjning och långtidsöverlevnad hos män och kvinnor med hjärtinfarkt. Studien baserades på kvantitativa och kvalitativa datainsamlingar. Delstudie **I** baserades på data från hjärtinfarktregistret vid The Northern Sweden MONICA Study under åren 1989-2003, inkluderande 5072 män och 1470 kvinnor, med fastställd hjärtinfarkt. Symtom och tid från symtomstart till medicinsk vård beskrevs och tidstrender relaterades till kön och ålder. Resultatet visade att typisk smärta förelåg hos 86% av männen och 81% av kvinnorna och att typiska symtom var mer förekommande hos de yngre. Upp till 65 års ålder fanns inga könsskillnader mellan symtomstart och tid till medicinsk vård. I den äldsta åldersgruppen (65-74 år) var tiden till sjukvård längre, främst hos kvinnor. Delstudie **II** baserades på individuella intervjuer med 20 män, mellan 65 och 80 år som drabbats av sin första hjärtinfarkt, om hur de upplevde den prehospitalla fasen. Intervjuerna analyserades med hjälp av kvalitativ innehållsanalys. Männen beskrev hur symtomen utvecklades från ett diffust illabefinnande, till ett kluster av svåra symtom. De hade svårt att relatera till de upplevda symtomen som inte motsvarade deras föreställningar om hur symtom på hjärtinfarkt tar sig uttryck, och hade svårt att veta om de skulle söka vård. Deltagarna vidtog olika strategier för att försöka förstå, minska eller behandla symtomen på egen hand, i en strävan att få livet att fortgå som vanligt. När symtomen utvecklats till en alarmerande och ihållande bröstsmärta insåg männen allvarlighetsgraden i symtombilden och att strategierna för att hantera symtomen var verkningslösa och beslutade att söka vård. Delstudie **III** baserades på individuella intervjuer med 20 kvinnor, med sin första hjärtinfarkt i åldern 65-80 år, för att få en djupare förståelse för hur de upplevde den prehospitalla fasen. Intervjuerna analyserades med hjälp av kvalitativ innehållsanalys. De äldre kvinnorna beskrev hur symtomen stegvis utvecklades från ogripbara och kroppsliga förmimmelser, mot en mer distinkt, ihållande och slutligen överväldigande bröstsmärta. Kvinnorna kämpade mot symtomen och använde olika strategier, som att tona ner och negligera symtomen för att behålla kontrollen över livssituationen och upprätthålla det sociala ansvarstagandet. När symtomen utvecklades till en ihållande och överväldigande bröstsmärta

insåg kvinnorna allvarlighetsgraden i symtombilden, att de inte kunde kämpa mot symtomen längre och beslutade att söka vård. Delstudie **IV** inkluderade patienter med en första hjärtinfarkt mellan åren 1985 och 2006 validerade i hjärtinfarktregistret vid The Northern Sweden MONICA Study i Norr- och Västerbotten som följdes upp i dödsorsaksregistret tom 30 augusti, 2008. Totalt 6762 män och 1868 kvinnor i åldern 25-64 studerades. Även patienter som avled före sjukhusvård inkluderades. Resultatet visade att mellan 1985 och 2006 förbättrades långtidsöverlevnaden efter en första hjärtinfarkt hos både män och kvinnor. Över hela 23-års perioden hade kvinnor 9 procents högre åldersjusterad överlevnad jämfört med män. Denna skillnad berodde på lägre risk för kvinnor att avlida innan de nådde sjukhuset. Under den sista tidsperioden var långtidsöverlevnad lika hos både män och kvinnor.

Sammanfattningsvis visar denna studie inga stora skillnader mellan män och kvinnors symtom, prehospitla fördröjning eller långtidsöverlevnad. Dock hade äldre patienter färre typiska symtom och längre prehospitla fördröjning, särskilt hos kvinnor. Den prehospitla fasen var en mångfasetterad och svårtolkad upplevelse hos både män och kvinnor, med en dynamisk utveckling av symtom, föreställningar och förväntningar, samtidigt som deltagarna strävade efter att upprätthålla det vardagliga och välbekanta livet. Symtomen vid hjärtinfarkten var en mer heterogen och komplex upplevelse hos både män och kvinnor än vad som vanligtvis beskrivs i litteraturen. Över en 23-års period har långtidsöverlevnaden efter en första hjärtinfarkt förbättrats hos både män och kvinnor. Kvinnor under 65 år har en något högre långtidsöverlevnad jämfört med män.

Definitions

The terms used in this thesis are mainly collected or revised from Miquel Porta (Ed), *A Dictionary of Epidemiology*, International Epidemiological Association, Oxford University Press, New York 2008.

Adjustment for age: The crude specific rates are recalculated by statistical methods to what they would have been in the study population, if that population had the same age distribution as the standard population.

Case fatality: The proportion of cases that is fatal within a specified time.

Cohort: A group of subjects who have shared a particular time together during a particular time span.

Confidence interval: Quantifies the uncertainty in measurement. It is usually reported as 95% CI, which is the range of values within which we can be 95% sure that the true value for the whole population lies.

Coronary heart disease: Initially silent and progressive disease that eventually can be manifested as MI.

Cox regression: A method for investigating the effect of several variables upon the time it takes a specified event takes to happen. For the outcome of death this is known as Cox regression for survival analysis.

Fatal event: Defined in the MONICA Project defined as all subjects who die within 28 days from the onset of the MI.

Hazard ratio: In survival analysis the effect of an explanatory variable on the hazard or risk of an event.

Incidence: A measure of disease that allows us to determine a person's probability of being diagnosed with a disease during a given period of time. Therefore, incidence is the number of newly diagnosed cases of a disease. In the MONICA myocardial infarction registry the term incidence refers to first-ever MI.

Kaplan Meier: Also known as the product limit estimator; estimates the survival time from life-time data.

Mortality: The number of deaths in a population.

Non-fatal: In the MONICA Project, all MI in individuals surviving the first 27 days after the onset are counted as non-fatal.

Population: All the inhabitants of a given country or area considered.

Population survey: An investigation in which information is systematically collected, but in which an experimental method not is used. Within the MONICA project, risk factors for cardiovascular disease in randomly selected people have been examined in a defined population.

Primary prevention: Inhibiting the development of disease before it occurs.

P-value: Indicates the probability that the result obtained is due to chance rather than to a true relationship between measures.

Secondary prevention: The identification and interdiction of diseases that are present in the body, but that have not progressed to the point of causing signs, symptoms, or dysfunction. These preclinical conditions are most often detected by disease screening and follow-up of the findings.

Total cholesterol: The total amount of cholesterol in the blood.

Trend: Method of time series data analysis involving comparison of the same item over a significantly long period to detect a general pattern of relationship between associated factors or variables, and to project the future of this pattern.

Validation: The process of establishing that a method is sound.

Variable: A quantity that varies. Any attribute, phenomenon or event that can have different values.

Abbreviations

CCU	Coronary Care Units
CHD	Coronary Heart Disease
CI	Confidence Interval
ECG	Electrocardiogram
GP	General Practitioner
HR	Hazard Ratio
MI	Myocardial Infarction
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
NSTEMI	Non ST-Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PIN	Personal Identification Number
STEMI	ST-Elevation Myocardial Infarction
WHO	World Health Organisation

Original papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals, I-IV.

I. Isaksson RM, Holmgren L, Lundblad D, Brulin C, & Eliasson M. (2008). Time trends in symptoms and prehospital delay time in women vs. men with myocardial infarction over a 15-year period. The Northern Sweden MONICA Study. *European Journal of Cardiovascular Nursing*. 7:152-158.

II. Isaksson RM, Brulin C, Eliasson M, Näslund U, & Zingmark K. Prehospital experiences of older men with a first myocardial infarction: a qualitative analysis within the Northern Sweden MONICA Study. Resubmitted.

III. Isaksson RM, Brulin C, Eliasson M, Näslund U, & Zingmark K. Older women's prehospital experiences of their first myocardial infarction: a qualitative analysis within the Northern Sweden MONICA Study. In manuscript.

IV. Isaksson RM, Jansson JH, Lundblad D, Näslund U, Zingmark K, & Eliasson M. (2011). Better long-term survival in young and middle-aged women than in men after a first myocardial infarction between 1985 and 2006. An analysis of 8630 patients in the Northern Sweden MONICA Study. *BioMedCentral Cardiovascular Disorders*. 11:1.

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Introduction

In this thesis, I write about men and women and their journey through myocardial infarction (MI); their symptoms, their prehospital delays, and their long-term outcomes. For people who suffer from a serious and life-threatening condition such as MI, life comes to a crisis point; the significance of the heart emerges in a new way, and death looms as a possibility. The patient suddenly faces an unexpected, foreign, frightening, and unexpected situation. The more time that passes, the more of the heart that dies, and the worse the prognosis becomes. Individuals who wait before seeking care for a MI risk permanent heart damage, and in the worst case, their lives. Each minute is significant, yet for a variety of reasons many delay seeking care when the symptoms of MI arise.

I have worked as a nurse for 20 years, mainly in a cardiology ward, where I met and cared for many patients who suffered an MI. I have seen that the urgent onset of cardiac illness appears to encompass more than the medical concept of myocardial infarction. I often wondered what it was like for patients before they arrived at the hospital. For the past few years, I have worked as a research nurse at the Northern Sweden MONICA Myocardial Infarction Registry, where I began this thesis.

Background

Myocardial infarction and its symptoms

Myocardial infarction is defined as myocardial necrosis secondary to interruption of coronary blood supply caused by ischemia [1]. As a consequence of ischemia, necrosis occurs first in the sub-endocardial myocardium, beginning as early as 15–20 minutes after coronary artery occlusion. When the myocardium is injured, it releases biochemical markers such as troponins, which can be detected by their elevation in the blood. An MI can also be described in terms of what an electrocardiogram (ECG) shows: ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI). A STEMI is a more severe type of MI where the coronary artery is completely blocked off, as opposed to an NSTEMI, where the artery is only partly occluded [2].

The ischemia is usually the cause of the symptoms of an MI, although other mechanisms such as hypotension or spasm are possible [3]. The most common symptom of MI is acute severe chest pain. The chest pain may also be characterized by pressure, burning, or aching. The pain can radiate toward the jaw, neck, arms, or back and usually lasts more than 15 minutes. These are typical described symptoms [4-6]. Symptoms other than chest pain that may occur in those suffering an MI include weakness and fatigue [7, 8], shortness of breath [9, 10], nausea, cold sweat, and dizziness [6, 9].

Symptoms in men vs. women with myocardial infarction

Both quantitative (e.g. prospective or retrospective medical record studies and surveys) and qualitative (interviews) studies have compared men and women for symptoms of MI with various results. There is some evidence that men are more likely to present with chest pain during an MI [8, 11-14]; however, there is also evidence showing no differences in reports of chest pain between men and women [4, 6, 15-18]. Regardless, chest pain is the most commonly reported symptom among both men and women [4, 11-13, 15, 17-26].

The data are equivocal for other symptoms also. In a number of studies, men more often reported sweating [4, 6, 12, 27] and women more often reported nausea [6, 12, 15, 28-30], indigestion [15, 28-30], dyspnoea [12, 13,

15, 27-29], arm pain [12], back pain [12, 13, 15, 17], and neck and jaw pain [12, 17]. Other studies show no sex differences for sweating [13, 15, 18], nausea [20], epigastric discomfort [4, 12, 13, 18, 20], dyspnoea [18, 20], arm pain [6, 13, 15, 18], back pain [18, 21], neck pain [15, 20], and jaw pain [15, 18, 20]. Reviews of the literature found that while chest pain was common among women, they also reported more associated symptoms such as back pain, nausea, and shortness of breath, than men did [31, 32].

It has been reported that men and women may experience diffuse symptoms before the acute onset. These so-called prodromal symptoms are defined by McSweeney et al. [30] as intermittent symptoms that increase in frequency and/or severity before the MI and disappear afterwards. In a review, the most common prodromal symptoms reported in both men and women were chest pain, dyspnoea, and fatigue [33]. Data on prodromal symptoms are sparse, but they have been reported to be most common among women [30]. However, it has also been reported that prodromal symptoms may predict the severity of MI symptoms [30, 34].

It has been claimed that men use different language from women to describe their symptoms. Men are more likely to use short descriptive terms, and women to include broad descriptive accounts of their symptoms [35, 36]. A study of patients presenting to an emergency department with an MI found that, although men and women were equally likely to present with chest pain, women were more likely to describe the pain as pressure, heaviness, or tightness and less likely to describe the pain as located in the centre or left of the chest [15, 30]. The verbal interaction between patient and physician might influence how chest pain is described and understood [35, 36].

Symptoms are the signals that lead people to seek medical care [37]. However, the process of perceiving symptoms and deciding to seek care for an MI has been found to be complex. In 1976, the first qualitative study was published describing the course of patients who had suffered an MI, from their first perceived symptoms through to their decision to call for medical assistance [38]. Cowie [38] noted that an MI is often not immediately recognizable to those experiencing it. Initial symptoms (e.g. chest pain, heartburn, sweating) are often “normalized” by attributing them to indigestion or exertion. Patients only sought medical care when the severity of chest pain increased so much that non-serious complaints were ruled out. Patients in his study reviewed their past lives in an attempt to “explain” their MI; these explanations included hard physical and/or mental work, strenuous activity, past health problems, warnings such as earlier chest pain,

ageing, smoking, stress, and the idea that the heart attack “built up” through strain over a long period. Cowie’s account is valuable for having pointed out important issues for further studies in this area. However, his study was criticised by Clark et al. [39] for including only married respondents and very few women.

Qualitative studies of patient experiences of having an MI began to increase in the early 1990s and most commonly included both men and women. Thomas [40] was the first to use an exclusively female sample in 1994, and by the late 1990s almost all studies were conducted with female-only samples. This move mirrors the belated recognition in the 1990s that women had long been excluded from research on MI [32].

Acute medical treatment and prehospital delay

The primary goal of acute medical treatment in patients with MI is to relieve symptoms, minimize myocardial damage, and prevent life-threatening coronary events [2, 41, 42]. In the late 1980s it was discovered that an intravenous thrombolytic agent given in the early stage could reduce mortality in men and women with a threatening STEMI. When this treatment was given within the first hour after the onset of symptoms, mortality was reduced by 50%. This resulted in the formulation of “the golden hour” [3].

The acute medical treatment of patients suffering from MI has changed dramatically over the last two decades, leading to significant improvements in MI outcomes. Prompt and effective reperfusion therapy (restoration of flow in the coronary arteries), using thrombolysis or, preferably, percutaneous coronary intervention (PCI), is the cornerstone of the treatment, particularly in patients with STEMI [42, 43]. It is extremely important to initiate reperfusion as quickly and effectively as possible, to ensure the greatest efficacy of the treatment. Thrombolysis and PCI greatly reduce damage to the cardiac muscle, recurrence of MI and mortality [44].

The elapsed time between the onset of symptoms and reperfusion is a critical determinant of the clinical course of patients with MI. The earlier thrombolytic therapy is given, the greater the reduction in infarct size and subsequent disability and mortality [45, 46]. Although thrombolytic therapy may be effective if administered up to 12 hours after symptom onset, the greatest benefit is derived when therapy is initiated within 1–2 hours of symptom onset. Patients treated within 90 minutes of symptom onset have 50–80% lower mortality rates and a 50% reduction in infarct size compared

with those treated later [45, 47]. In fact, every 30 minutes of delay increases the 1-year mortality risk by 7.5% [48].

Slightly fewer than one-third of all patients suffering an MI die outside hospital [27, 49] secondary to ventricular fibrillation [27]; two-thirds of these have the cardiac arrest in their home (34). These fatalities most often occur within the first hour of onset of symptoms [50, 51] and it has been reported that they are preceded by symptoms such as chest pain and shortness of breath for longer than 15 minutes in 70% of the patients [52].

Because the effect of medical treatment is time dependent, it is crucial to explore the causes of delays in seeking care for MI symptoms. Causes of prehospital delay may include geographical factors, cultural factors, or patient factors such as gender and age. A study of 18 928 patients carried out in the United States, showed that the prehospital delay was not significantly reduced between the early 1990s and the early 2000s [53]. In the literature, the prehospital delay in the context of cardiac care is usually defined as the time from onset of symptoms to arrival at hospital [10]. The prehospital phase can be further divided into two major parts; the patient decision phase and the transportation phase [54].

The patient decision phase

This phase involves the patient assessing and interpreting symptoms and then finally deciding to seek medical care [34]. Figure 1 shows that the patient decision phase in the literature has been found to be the greatest part of the delay, accounting for up to 75% of prehospital time after the onset of symptoms [55]. This phase includes thoughts and actions taken by the patient in response to symptoms. For example, the patient may decide to seek medical care at once, to wait and periodically evaluate or self-treat the symptoms, or to seek advice from family and friends. Patient decision times still remain unacceptably long in Sweden and in other countries, with times of greater than 4 hours for 40% or more of patients with an MI [56, 57].

The transportation phase

This phase is defined as the interval from calling the emergency service number to the arrival of the ambulance at hospital. Transportation time is usually of minor significance in non-rural areas. For private transportation, this phase is defined as the interval from the decision to go to hospital to arrival at the hospital [56].

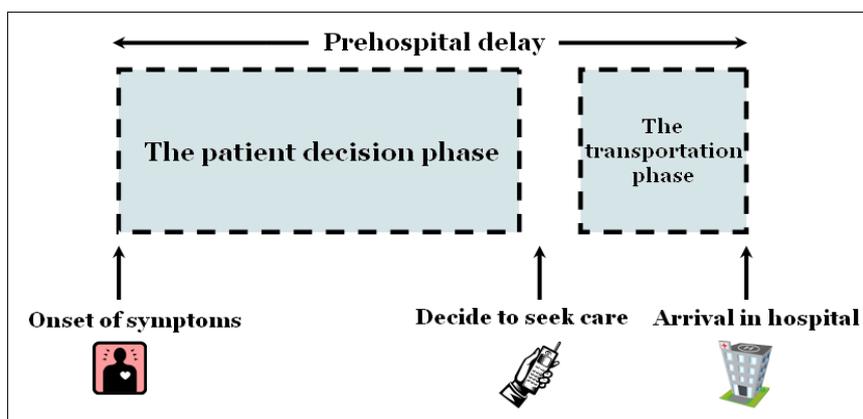


Figure 1. The temporal window between the onset of symptoms and arrival at hospital.

Since the time window in prehospital delay has not undergone any significant changes over the recent decades [53] it seems obvious there is still a need to explore how symptoms of MI differ between men and women and how this may lead to delays in seeking medical care.

Prehospital delay in men vs. women with myocardial infarction

Research on patients' symptom-perception as a determinant of care seeking indicates that symptoms have a key role in the initiation of the patient's decision process. How patients interpret their symptoms, and judge the seriousness of their symptoms and their need for medical care, have a major impact on their decision to seek care [57, 58, 59]. Incorrect interpretation of symptoms has been found to be a critical factor in lengthening the prehospital phase [60-62], while one of the most important factors in shortening it is the recognition by the patient and others that the symptoms are related to the heart [63, 64]. When there is a mismatch between patients' expectations or knowledge about MI and the symptoms they experience, it is even more difficult for them to decide to call for medical care immediately, because they do not interpret the symptoms as originating in the heart [65, 66].

To understand the phenomenon of prehospital delay in MI, researchers also have attempted to identify characteristics predictive of increased patient delay in response to MI symptoms by using both quantitative and qualitative

methods. The results have been contradictory. Some researchers have found that women delay seeking care longer than men [4, 67, 68], while others have not found no such differences [44, 54, 69-72]. However, according to Moser and Dracup [72], the question of sex and gender differences in prehospital delay are important. Responses such as thinking that the pain will disappear or not recognizing the importance of the symptoms result in hesitation about seeking medical care [61, 73, 74]. Women have been found to hesitate to seek medical care for reasons including their perception of MI as a “male” problem, their preference to self-medicate, and their wish to identify a non-cardiac origin of their chest pain [75]. Others have found that women do not want to bother others, including doctors, and often place the welfare of others before their own needs [76, 77]. A review of the qualitative literature found that the influence of social roles is important: many female patients have difficulties reconciling family responsibilities and medical advice, while male patients worry about being absent from work [32]. Many diseases change their clinical manifestation over time. Because the spectrum of symptoms and prehospital delays in MI may have undergone great changes due to changes in medical care and awareness in the public, population- based registry studies in this area are very important.

The WHO MONICA study

The multinational MONItoring of trends and determinants in Cardiovascular disease (MONICA) study is the base for this thesis. MONICA was initiated by the World Health Organization (WHO) in 1982 in 39 centers in 26 countries (Figure 2) with the aim of measuring trends in cardiovascular risk factors in parallel with cardiovascular endpoints [78]. Sweden participated in the project with two centers, one in the south (Gothenburg area) and one in the two northernmost counties, including Norrbotten and Västerbotten. [79].

In the early 1980s, when WHO initiated the MONICA project, official mortality statistics showed that people in the northern part of Sweden had a more than 30% higher mortality from both coronary heart disease (CHD) and stroke than the national average [80]. In 1984, the County Councils of Norrbotten and Västerbotten decided to jointly take part in the MONICA Project, combining their populations to meet the MONICA minimum of 500 000. Two MONICA secretariats were established, one in Norrbotten and one in Västerbotten. In Norrbotten, all MI events for both counties were registered, and in Västerbotten all stroke events were registered [81]. The

WHO MONICA project was closed in 1995, but the work at the centers has proceeded as a local project in northern Sweden [79].

The MONICA project included two types of research design, regular population surveys and continuous event registrations of acute myocardial infarctions (MONICA myocardial infarction registry) and stroke.

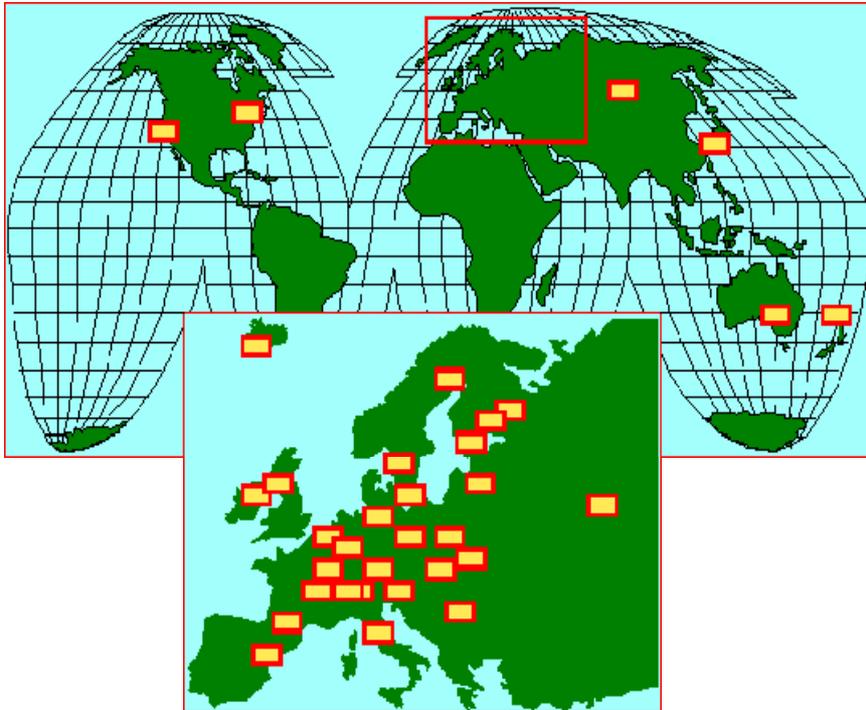


Figure 2. Centers collaborating in the WHO MONICA Project.

Event registrations started on 1 January 1985 in Norrbotten and Västerbotten counties [81]. All medical records with CHD as a diagnosis at discharge and all death certificates were screened for acute cardiovascular events. The MONICA Project was a population-based project, which means that all acute events were included, not only those in patients treated in hospital [81]. Initially, subjects from 25 to 64 years of age were included, and from the year 2000 subjects aged 65–74 years were also included [79].

In the WHO MONICA registry explicit and extensive criteria were used to validate medical history, clinical symptoms, electrocardiograms (ECG), and cardiac enzymes, for both fatal and non-fatal events. Trained nurses, supervised by the register's physicians, registered the MI cases [79]. Originally, MI diagnoses were based on typical chest pain, cardiac enzymes,

and ECG findings. In the late 1990s, troponins were introduced to diagnosis of MI, and since 2000, they have been the biomarker used by all hospitals in northern Sweden [79].

Since 2000, MI diagnoses in the MONICA registry have been based on typical chest pain and biomarkers. When only one of these parameters was positive, ECG analysis was included to decide the final diagnosis. Based on these parameters, survivors were diagnosed having had a definite MI or as non-MI patients. Subjects who died within 28 days of onset of MI were recorded as fatal cases. These included prehospital deaths, patients who died in hospital and patients who were discharged alive, but died outside hospital within 28 days. An event was considered the first ever MI for the patient if the patient's history was free of any previous clinically recognized MI, otherwise the event was considered recurrent. "Total events" describe all events whether or not the patients had a previous event. For fatal events, both definite and possible infarctions were included. For this purpose, information was also obtained from death certificates and autopsy reports when available [78].

According to the MONICA criteria, symptoms of a coronary event are classified as typical, atypical, other, or insufficient data.

- Typical symptoms are coded when chest pain is present and characterized by duration of more than 20 minutes. Any synonym for pain such as pressure, discomfort, and ache, is acceptable.
- Atypical symptoms include one or more of atypical pain, acute left ventricular failure, shock, and, syncope. Atypical pain is of short duration or intermittent, with each bout lasting for less than 20 minutes; at an unusual site; or in the upper abdomen, arms, jaw, or neck.
- Other symptoms are those that are well described but do not satisfy the criteria for typical or atypical MI symptoms.
- Insufficient data is coded if descriptive information on the presence or character of symptoms or other data is inadequate to allocate the case to any other code.
- Onset is the onset of the acute symptoms of the coronary event.
- Medical presence is the time at which skilled medical care for the patient first becomes available, either in the form of a medical practitioner or a specially trained and equipped team of paramedics. The time delay between onset of symptoms and medical presence is expressed in hours and minutes.

Trends in risk factors

The MONICA registry provides a unique opportunity for the important study of trends over time. The registry can illustrate the dynamics of the changing nature of CHD due for example to the lower proportion of STEMI, but it also reflects how care and treatments develop over time. Because cardiovascular diseases are undergoing rapid changes in presentation, demographics and treatment, new data are needed based on current study populations.

Generally, in the Western world the decreased mortality from CHD is due to a combination of declining incidence and improved survival [82]. From the results of the MONICA population survey it was concluded that decreases in the classical risk factors for CHD – smoking, high cholesterol, and high blood pressure – explain a great part of the decline in CHD. The declining trends in northern Sweden in these major cardiovascular risk factors are shown in Figures 3, 4 and 5 [83]. In addition, changes in coronary care and secondary prevention have contributed substantially to lower CHD mortality [82, 84].

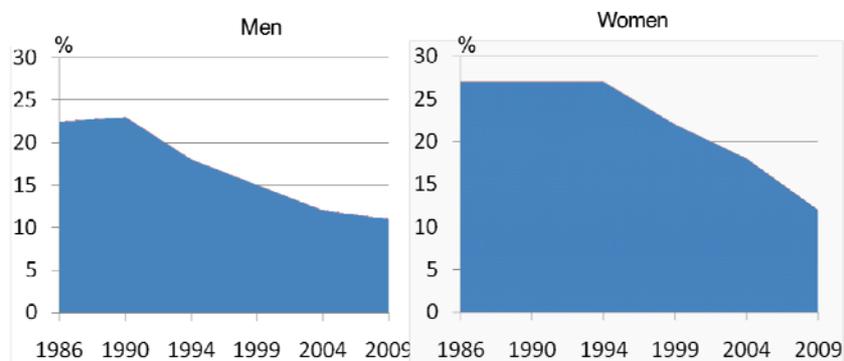


Figure 3. Regular smokers in men and women aged 25-74 years in the northern Sweden MONICA population survey.

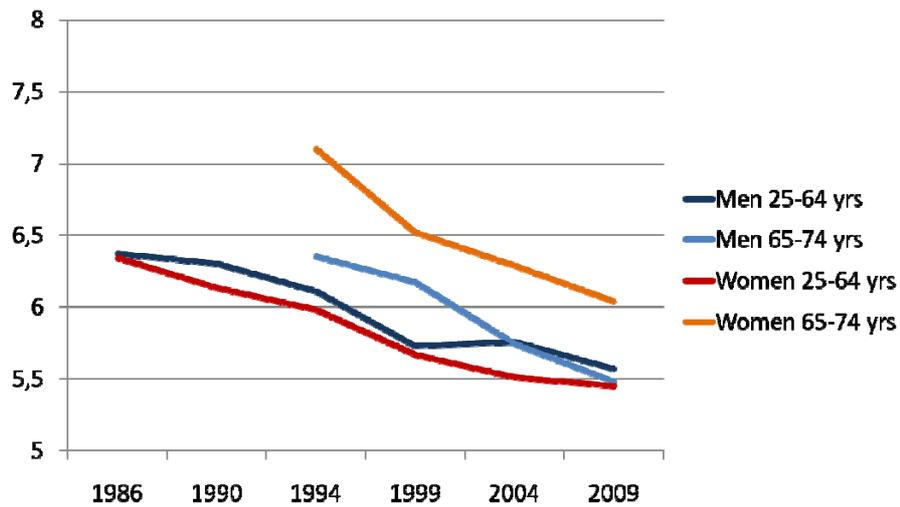


Figure 4. Total cholesterol levels in men and women aged 25-74 years in the northern Sweden MONICA population survey.

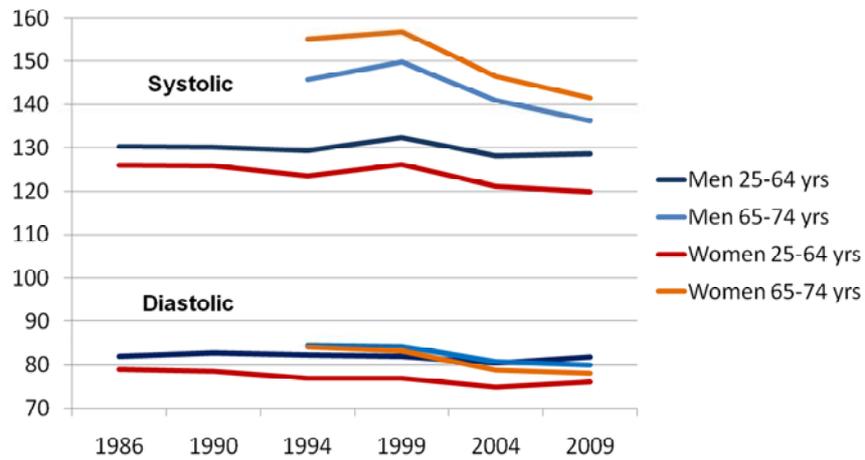


Figure 5. Blood pressure in men and women aged 25-74 years in the northern Sweden MONICA population survey.

Incidence and survival of MI

In 2008, 29 676 people (12 494 women and 17 182 men) had an MI in Sweden. However, incidence and mortality rates of CHD have decreased

substantially over the last few decades, and this trend seems likely to continue. Figure 6 illustrates the risk of mortality from CHD over the past fifty years in Sweden. Among women, cardiac mortality has continuously declined since the early 1960s, however among men, mortality increased from the 1950s until the early 1980s and only then declined [85].

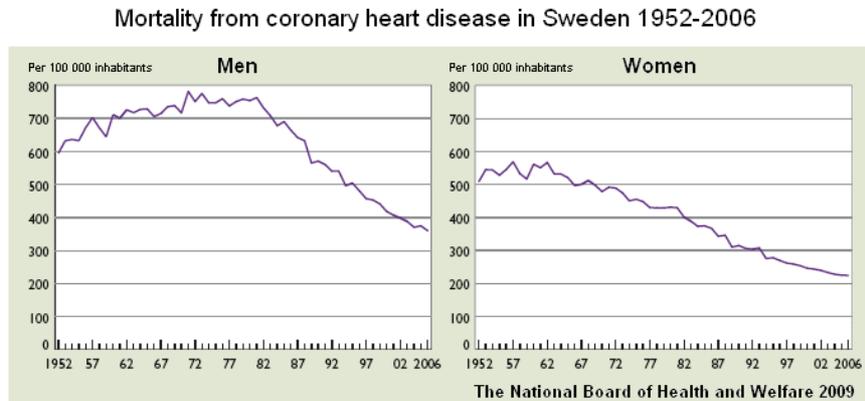


Figure 6. Risk of mortality from CHD over the past 50 years in Sweden. Data from the National Board of Health and Welfare 2009.

Despite these declines however, CHD remains the leading cause of death in Sweden, most Western European countries and the United States. [86-88]. For those under 55 years of age, the risk of CHD among men is almost four times that of women [88]. Women's risk of CHD increases after menopause, and on the average, the disease manifests itself about ten years later in women than in men [88, 89]. Among women under the age of 65 the risk of a first MI has not declined, but the risk of recurrence and death has declined in both men and women [79, 89, 90].

At the start of the MONICA project in 1985 the incidence of, and mortality due to, MI in the two northernmost counties in Sweden were the highest in the country [80]. However, these counties have gradually approached the national average, indicating a faster reduction of risk in northern Sweden than in the rest of the country [79]. The downwards trends in first MI, recurrent MI, and mortality have been particularly strong in men, whereas the respective declines in women have been less impressive [49, 79]. The total event trends in MI in men and women are shown in Figure 7.

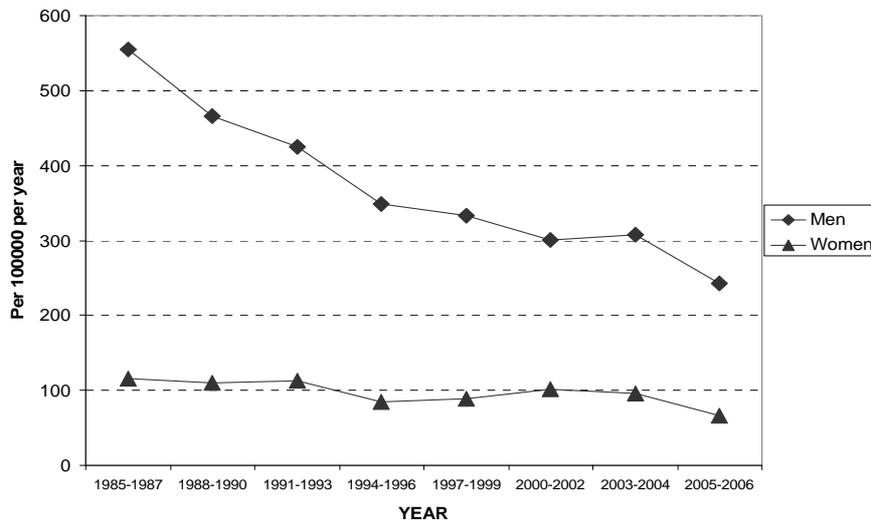


Figure 7. Total event trends in myocardial infarction in men and women aged 25-64 years in the Northern Sweden MONICA Myocardial Infarction registry.

Long-term survival in men vs. women with myocardial infarction

Most studies of long-term survival after an MI have had a follow-up time 5 years or less [19, 91-94]; only a few have had a longer period [95-98]. Also, only a few studies have documented the impact of sex in long-term survival after an MI [19, 94, 98, 99]. Two of these studies from the 1990s [19, 94] included first and recurrent MIs, had a short perspective, and found no sex differences in 30-day to 1-year mortalities. A Scottish study of 201 114 patients with a first MI during the years 1986–1995, including out-of-hospital deaths, showed that women did not fare worse than men when age was taken into account [99]. In an American 6-year follow-up study of 12 331 patients with both first and recurrent MIs, long-time survival was also similar between the sexes [98].

No studies have investigated sex-specific time trends in long-term mortality in patients with a first MI. As there are important sex differences in mortality before admission to hospital and men have been shown to fare worse [99], such data must be included to give the true picture of the total mortality burden of MI.

Rationale for the thesis

During planning for this thesis in 2007, studies were available regarding symptoms, pre-hospital delay, and long-term survival in patients with MI. However, a thorough search of the literature revealed contradictory results that were therefore not entirely comprehensible. Furthermore, the majority of the studies were carried out in the United States, and because of cultural and healthcare differences the results were not directly transferable to a Swedish context. At that time, Swedish media often reported that women misunderstood their symptoms of MI and as a result delayed seeking care: it was speculated that care was often less effective for women, who presumably did not receive modern drugs and reperfusion therapies.

Few international studies and no Swedish studies had focused on the effects of sex, age, and time trends in symptoms and prehospital delay in a well-defined population. Many diseases change their clinical manifestation over time, thus the spectrum of symptoms in MI could possibly have undergone great changes due to changes in medical care and public awareness. It was therefore worthwhile to study these potential differences in a large Swedish population.

Also lacking in this research field are accounts of the patients' own experiences of their symptoms and delay in seeking care during the prehospital phase. Uncertainty and differences in how men and women perceive their symptoms of an MI can be crucial to when they decide to seek medical care, which in turn will affect both their medical treatment and their risks of mortality. We found no study focused solely on older men's or older women's experiences of symptoms and how these experiences may influence delay in seeking care for a first MI. Most studies in the field included both men and women. Despite the fact that most patients affected by MI are older, the studies that included only women were not stratified for age, nor did they differentiate between first and recurrent MIs.

Over the last two decades differences in MI outcome between men and women have been increasingly highlighted. Still, the evidence regarding sex-specific outcome and prognosis after MI is contradictory. Only a few studies of long-term survival after an MI have had a follow-up time longer than 5 years, and these have also included both first and recurrent MIs. No studies have investigated sex-specific time trends in long-term mortality in patients

with a first MI. To clarify whether implementation of evidence-based preventive initiatives and treatment of MI have had the same impact on both men and women it was important to analyze time trends in long-term survival after onset of a first MI and evaluate whether differences could be found between the sexes. This thesis was designed to fill gaps in our knowledge of patients' symptoms, prehospital delays, and long-term survival after a first MI.

Aim

The overall aim of this thesis was to study symptoms, prehospital delay and time trends in long-term survival in men and women with MI.

Specific aims for the papers

- | | |
|-----------|--|
| Paper I | To describe symptoms and time between onset and medical presence in men vs. women with MI and to analyze trends over a 15-year period. |
| Paper II | To explore older men's prehospital experiences of their first MI. |
| Paper III | To explore older women's prehospital experiences of their first MI. |
| Paper IV | To analyze sex-specific survival of patients for up to 23 years after a first MI in northern Sweden and to describe time trends. |

Method

This thesis includes four interconnected studies. Study I was based on data from the MONICA myocardial infarction register in northern Sweden which was initially aimed to describe time trends in symptoms and prehospital delay in men and women with MI. In Studies II and III patients with their first MI were interviewed to add to the results of Study I to gain a deeper understanding of how men and women experience their symptoms and how they think and act with respect to seeking medical care. It was therefore important to use the personally narrated experiences of these men and women and analyze them using qualitative methodology. Study IV was based on data from the MONICA myocardial infarction register and analyzed time trends in order to evaluate whether there were differences between men and women with respect to long-term survival after a first MI.

Setting

The studies in this thesis were based on the population of Norrbotten and Västerbotten, the two northernmost counties in Sweden. The area is sparsely populated with just over 500 000 inhabitants in an area of 154 300 km², where the majority live in cities near the coast [90].

The population consisted of MI patients in the defined geographical area who were registered in the Northern Sweden MONICA Myocardial Infarction Registry.

An overview of the different papers' participants, data collection procedures, and analytic methods are presented in Table 1.

Table 1. Characteristics of studies presented in papers I–IV.

Paper	Participants	Data sources	Analyses
I	n = 6542 5072 men 1470 women	The Northern Sweden MONICA myocardial infarction registry	Descriptive statistics, Chi 2 test for trends
II	n = 20 20 men	Interviews	Qualitative content analysis
III	n = 20 20 women	Interviews	Qualitative content analysis
IV	n = 8630 6762 men 1868 women	The Northern Sweden MONICA myocardial infarction registry, The Swedish National Cause of Death Registry	Descriptive statistics, Kaplan meier, Cox regression, Hazard ratio

Participants

Study I

The participants were all patients aged from 25 to 64 years who were registered from 1 January 1989 to 31 December 2003. Since the year 2000, subjects from 65 to 74 years of age were also included for 8254 cases that fulfilled the MONICA criteria for MI. Only cases classified as definite events were included. Both first and recurrent MIs were included.

Subjects classified “dead out of hospital” (1712 cases) were excluded. Subjects were classified dead out of hospital if no decision on management could be taken because the patient was already dead or in cardiac arrest when seen by a doctor. People with the time variable coded as “not known, probably 24 hours” (367 cases) were also excluded. A final total of 6542 participants, 5072 men and 1470 women, were included in this study. The mean age for the participants was 55.6 for men and 56.6 for women, with an overall range of 25–64 years.

Studies II and III

Twenty men (II) and twenty women (III), 65–80 years of age, at three hospitals in northern Sweden, with a confirmed first MI validated according to the criteria of the WHO MONICA manual, participated in the studies. Patients with unstable circulation, more serious complications, confusion, or dementia were excluded. Potential participants with a previous history of MI or angina pectoris were excluded to ensure that this event was a new experience for all in the study groups. The participants were all healthy and physically active before the MI. The participants were asked to participate by the nurses in the order they arrived at the hospital. All of the eligible invited men (II; n = 20) agreed to participate and provided written informed consent. Three of the invited women (III) declined to participate, so three other women were asked and agreed to participate (n = 20). The background characteristics, diagnoses, and prehospital delays of the patients are shown in Table 2.

Study IV

In this study, only first MIs in subjects 25–64 years of age were included. During the study period from 1 January 1985 to 31 December 2006, a total of 12 635 patients who fulfilled the MONICA criteria and had been diagnosed with a definite MI were registered in the MONICA myocardial infarction registry, 8630 of these had not had a previous MI and so were included in the study. The population at risk in the study area was 258 576 (31 December 2009). Mean age of the study cohort was 55.5 years for men and 56.4 years for women. Clinical characteristics are shown in Table 3.

Table 2. Background characteristics, diagnoses and prehospital delays of the participated men in Study II and women in Study III.

Characteristics	Study II Men (n=20) n	Study III Women (n=20) n
Age (years)		
Mean	70.9	73.0
Range	65-80	65-80
Marital status (n)		
Married/cohabiting	18	10
Single	2	10
Surroundings at onset (n)		
At home	15	14
Not at home	5	6
Alone	3	9
Not alone	17	11
Distance to hospital (n)		
< 10 km	5	8
> 10 km	15	12
Clinical history (n)		
Hypertension	6	8
Diabetes mellitus	3	0
Hyperlipidemia	2	0
Current smoker	0	1
Delay time (n)		
< 1 hour	12	8
1-4 hours	2	5
> 4 hours	6	7
Range (time)	15 min – 4 d	15 min – 3 d
Transportation mode to hospital (n)		
Ambulance	12	8
Self-transportation	8	12
Initiative to seek care (n)		
Own initiative	8	10
Wife's / husband's or cohabitant's	3	1
After consultation with wife/husband or cohabitant	4	1
After consultation with other	5	8

Table 3. Clinical characteristics at baseline of men and women with a first myocardial infarction during four consecutive time periods from 1985 to 2006.

		1985-1988	1989-1994	1995-2000	2001-2006	1985-2006
Men	N	1463	1927	1711	1662	6763
	Survived (%)	408 (27.8)	903 (46.9)	1092 (63.8)	1296 (78.0)	3697 (54.7)
	Mean age	55.6	55.3	55.3	55.7	55.5
	IHD (%)		355 (30.1)	520 (31.3)	412 (25.3)	1287 (28.8)
	Hypertension (%)		782 (42.6)	531 (33.4)	598 (36.9)	1911 (37.9)
	Diabetes (%)		221 (11.6)	242 (14.2)	262 (15.9)	725 (13.8)
	Regular smoking (%)		683 (38.2)	545 (43.0)	516 (38.2)	1744 (39.6)
Women	N	350	509	495	514	1868
	Survived (%)	101 (28.9)	230 (45.2)	338 (68.3)	401 (78.0)	1070 (57.3)
	Mean age	57.1	56.5	55.9	56.2	56.4
	IHD (%)		86 (27.5)	138 (29.0)	127 (25.2)	351 (27.2)
	Hypertension (%)		247 (50.9)	196 (42.4)	231 (47.2)	674 (46.9)
	Diabetes (%)		82 (16.3)	71 (14.4)	97 (18.9)	250 (16.6)
	Regular smoking (%)		231 (49.1)	218 (57.7)	233 (55.7)	682 (53.9)

Data collection and analysis

Study I

This study was based on cases registered in the MONICA myocardial infarction registry in northern Sweden. Descriptive statistics were used and data are presented with mean values, proportions, and p-values. Because this study was population-based and included all MIs within the age range, there was no random sample and thus no tests of significance were used for differences between the groups. To test for significant trends over time, the Chi² test was used. All analyses were carried out using the statistical computer programme SPSS version 13.0.

Separate groups were constructed for men and women to test for different types of symptoms and for time between onset and medical presence for each group. Time-periods of MI onset were grouped in 3-year cohorts: 1989–1991, 1992–1994, 1995–1997, 1998–2000, and 2001–2003. Finally, a separate group was created for the oldest age group, 65–74 years, to test for relationship between age, sex, symptoms, and time between onset and medical presence during the years 2000–2003.

It should be noted that in this study we used the MONICA definition of prehospital delay: from onset of symptoms until skilled medical care first became available (“medical presence”), in the form of either a medical practitioner or a specially trained and equipped team of paramedics. Thus, prehospital delay could – by definition – end in the ambulance, in the district health care center, or at the hospital.

Studies II and III

In these studies, prehospital delay was defined as “patient decision time”, which involves assessing and interpreting one’s own symptoms and deciding to seek medical care [34].

Based on the aim of the study, individual interviews were chosen as the method of data collection. The interviews were conducted to gain knowledge of how the participants experienced the prehospital phase of their first MI. Before starting the interview study, I conducted pilot interviews (not included in the results) with two people in my vicinity in order to evaluate the interview guide and practise how to use the technical equipment and how to create secure and stimulating interplay during the actual interviews.

I informed all staff in the relevant departments at the hospitals about the study and its purpose. Interviews were then conducted at cardiac care units

(CCU) in three different hospitals in Norrbotten and Västerbotten. The interviews were conducted after three days of hospital care to ensure that the participants were physiologically stable and pain-free, but retained the experience of the MI clearly in their minds. The interviews were held in an undisturbed private room in the hospital. They lasted 20–70 minutes and were recorded either by tape recorder or by digital voice recorder.

I began the interviews with a brief introduction about the interview, its purpose, and the use of the recorder, and asked if the interviewee had any questions before the interview began. I recorded necessary background information, such as age and distance to hospital, in the introduction to each interview. The interviews were semi-structured, with distinct question areas within which spontaneous narrative was encouraged.

The interview guide (appendix 1) used to support the interview process, was based on a literature review and my own experiences as a cardiac care nurse. The interview questions were slightly modified based on the results of the pilot interviews. The main purpose of the questions was to prompt the participants to describe their symptoms, their thoughts, and the actions they took during their first MI. I attempted to establish good rapport by listening attentively and showing interest, understanding, and respect for what the interviewees said. The interview opened with the question “Where were you when you became ill?” The next question was “What happened?” This question often prompted spontaneous and detailed descriptions of the entire prehospital phase. Other questions included; “Can you describe the symptoms?”, “Do you know how long it took from the time the symptoms started until you decided to seek care?”

Follow-up questions were asked to encourage the interviewee to clarify, provide nuances, and go into greater depth in the narrative. According to Kvale [100], interviewees’ statements can be ambiguous and understood in different ways, so follow-up questions are particularly important to ensure that the results are based on the interviewees’ detailed statements and the viewpoint of the interviewee, rather than on the researcher’s perspective or interpretation. Examples of follow-up questions included; “Can you tell me more?”, “How do you mean?”, “How did that feel?” and “What did you think then?” The interviews ended with “I have no more questions. Is there anything more you would like to discuss or to ask me before we conclude the interview?” This question gave the interviewees an additional opportunity to raise any questions or make any final explanations they may have thought of during the interview.

Data were collected over the course of one year and I conducted 29 of the 40 interviews. I did not conduct all of the interviews because long distances in the geographic area (up to 300 km one way) combined with short hospitalization times sometimes made it impossible for me to reach the hospital before the patient was discharged. Consequently six of the interviews were conducted by one of my supervisors, two by another supervisor, and three by doctoral students who were in the vicinity of the relevant hospital. I transcribed all 40 interviews word for word shortly after each interview. I tried to reproduce the interviewees' responses as accurately as possible in the interview transcripts, noting pauses, sighs, silence, laughter, and crying. Before, during, and after the transcription process I listened to the interviews on several occasions.

To achieve the aim of the studies, qualitative content analysis was used to analyze the data. Graneheim and Lundman [101] provide an overview of concepts and suggestions for the stepwise procedure for the analysis that has guided me through the data analysis.

The interviews of men (II) and women (III) were analyzed separately in the following steps. First, all interviews were read through several times to gain a sense of the material as a whole. The interview text was sorted into content areas, i.e. specific explicit areas related to symptoms and prehospital delay such as progression of symptoms or strategies to deal with the symptoms. The interview text was then divided into meaning units related to the research question. The meaning units could consist of words, sentences, or paragraphs that related to each other. The meaning units were condensed through shortening the text while still preserving the core. The condensed meaning units were abstracted, i.e. described and interpreted on a higher level, and labelled with a code. The codes described the content of the meaning units. All coded material within each content area was then compared, abstracted, and sorted into sub-themes and themes. A sub-theme can be defined as a thread of meaning running through the condensed text, while the formulated themes can be considered as a thread of underlying meaning that embraces the content of the related sub-themes on a more abstract and interpretative level. A theme may also be seen as an expression of the latent content of the text.

Throughout the analysis, the first and last authors compared and contrasted the codes, sub-themes and themes with the original text. This involved readings back and forth between the whole text and text segments to ensure stringent and trustworthy analysis.

The results of the studies are presented based on themes and sub-themes and are illustrated with quotations from the interviews. Parts of the text that did not answer the research question, such as references to the weather or narratives about the lives of other people, were excluded from the text. In Study II an illustration of the findings was created to provide a comprehensive and more in-depth understanding of the analysis.

Study IV

Data from the Northern Sweden MONICA myocardial infarction registry was linked with data from the Swedish National Cause of Death Register. It is estimated that 93% of all deaths are reported to Statistics Sweden within 10 days and 100% within 30 days using the unique personal identification number (PIN) assigned to every Swedish citizen. The two registries (MONICA and the Cause of Death Register) were linked through patients' PINs [102]. The endpoint studied was death from any cause, i.e. all cause mortality.

Descriptive statistics for baseline characteristics are presented with means and proportions. Separate groups according to age at onset were constructed to achieve groups of similar size: 25-50 years, 51-56 years, 57-60 years and 61-64 years for both men and women. The patients were separated into four cohorts representing their year of onset of MI: 1985-1988, 1989-1994, 1995-2000 and 2001-2006. Survival time was calculated as the number of days between the date of the MI and the date of death, or 30 August, 2008. Because this study was population based and included all MIs within the age range there was no random sample upon which to apply tests of significance for differences between the groups

Survival times were computed with the Kaplan-Meier product limit estimate. Hypothesis testing of no difference in survival was calculated using Cox regression analysis, presented as hazard ratios adjusted for age. For explanatory reasons, a sensitivity analysis was performed by omitting those who had died out of hospital; 95% confidence intervals are given. All analyses were carried out using the statistical computer program PASWStatistics 18.

Ethical considerations

Studies I, IV

The Research Ethics Committee, Umeå University (dnr 09-041M) and the national Computer Data Inspection Board (dnr 96–154) approved the study and the data handling procedures. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Before being recorded in the MONICA myocardial infarction registry, the patients, or relatives of the deceased patients, received a personal letter explaining the purpose of the registry and asking them to report to the MONICA secretariat if they did not wish to give consent to their personal data being recorded with identifying information. Over the years, 0.4% of the myocardial patients did not wish to be identified and their data were recorded without personal identification [81].

Studies II, III

The studies were approved by the Ethics Committee at Umeå University (dnr 07-113M). The patients who met the inclusion criteria received oral and written information about the study from regular nurses at the CCUs. Those patients who were interested were provided with an information letter, which my supervisors and I formulated, with an invitation to participate in the study. When the patient consented orally and in writing, the nurse at the ward contacted me. The nurse and patient agreed on the best time for the interview and the nurse informed me by telephone of the appointment. I then went to the hospital and interviewed the patient. The researchers had no relationship to the participants and were not involved in any decisions about the participants' care.

Ethical principles cannot be considered only at a given point in time or during a certain situation; rather, for me they have been important guidelines throughout the research process. I have endeavoured to achieve ethical awareness while adhering to good research ethics. Ethics were taken into account at all stages of preparations for the studies, during the interviews and analyses, when describing and publishing the results, and when storing research and work materials to prevent unauthorized access.

I have tried to apply research ethics at all times and I have also tried to describe the most central reflections and decisions made during the course of the research.

Men and women participated in the interview studies voluntarily and wanted to share their experiences. Prior to and in conjunction with the interviews the interviewees were fully informed about the study and their rights to refuse or withdraw from participation with no consequence to their care, both in writing and in person. When narratives or quotations were used in the results, I removed any identifying information so that the passages could not be traced to or harm the person who provided them. This was done to protect the dignity of the interviewees. Similarly, material that was reviewed at seminars for doctoral students or on other occasions was de-identified.

When the recorder was turned off and the interview concluded, all interviewees expressed their appreciation of having the opportunity to participate. They said it felt good to have someone take the time to listen to everything they had to say about becoming ill. This may be seen as an example of how the narrative interviews may be of benefit to the respondent [103]. The interviewees were all extremely engaged, asked many questions about my project, and said they were glad to be able to contribute to the research.

Results

The results from the four papers are presented separately.

Study I: Time trends in symptoms and prehospital delay time in women vs. men with myocardial infarction over a 15 year period. The Northern Sweden MONICA Study

The aim of this quantitative study was to describe symptoms and time between onset and medical presence in men vs. women with MI over a 15-year period. The results showed no major sex differences in type of symptoms according to the MONICA criteria. As shown in Table 4, typical symptoms, i.e. chest pain, or synonyms for pain such as pressure, discomfort and ache, for 20 minutes or more, were somewhat more common in men than in women. Out of 5072 men, 86.3% had experienced typical symptoms and of 1470 women the corresponding value was 80.8%. Among men, the proportion of typical symptoms decreased over time while it decreased among women. Atypical symptoms, i.e. atypical pain for less than 20 minutes, at an unusual site, or in the upper abdomen, arms, jaw, or neck, or other symptoms, i.e. symptoms that do not satisfy the criteria for typical or atypical, were common in both sexes, but slightly more in women. Insufficiently reported symptoms were unchanged over time in men while in women they decreased.

When symptoms were stratified for age and sex (Table 5) the results showed that younger people, especially men, were more likely than older people to have typical symptoms. For women, typical symptoms were similar in all age groups except the oldest, 65-74 years, where typical symptoms were modestly decreased.

Table 6 shows the time between onset of symptoms of MI and medical care during 3-year blocks from 1989 to 2003. The results show that up to the age of 65, no sex differences were seen in prehospital delay. The time trend analysis revealed that a prehospital delay of 24 hours or more, increased through the study period for both men and women.

Table 4. Trends in symptoms 1989-2003. Men and women aged 25-64 years in the Northern Sweden MONICA infarction registry.

			1989-1991		1992-1994		1995-1997		1998-2000		2001-2003		Total	
			n	%	n	%	n	%	n	%	n	%	n	%
Male	Symptoms	Typical	1004	87.4%	915	87.4%	835	85.9%	798	84.6%	825	85.8%	4377	86.3%
		Atypical, other	98	8.5%	101	9.6%	95	9.8%	103	10.9%	72	7.5%	469	9.2%
		Insufficient data	47	4.1%	31	3.0%	42	4.3%	42	4.5%	64	6.7%	226	4.5%
Female	Symptoms	Typical	244	78.2%	231	81.3%	197	78.5%	248	83.2%	268	82.5%	1188	80.8%
		Atypical, other	43	13.8%	40	14.1%	38	15.1%	36	12.1%	40	12.3%	197	13.4%
		Insufficient data	25	8.0%	13	4.6%	16	6.4%	14	4.7%	17	5.2%	85	5.8%

Table 5. Proportion of men and women with different symptoms, ages 25-64 years during 1989-2003. (Patients aged 65-74 years were only included in 2000-2003).

			Male		Female		n	%
			n	%	n	%		
25-34	Symptoms	Typical	40	93.0%	9	81.8%	49	90.7%
		Atypical, other	2	4.7%	1	9.1%	3	5.6%
		Insufficient data	1	2.3%	1	9.1%	2	3.7%
35-44	Symptoms	Typical	276	87.1%	65	82.3%	341	86.1%
		Atypical, other	26	8.2%	7	8.9%	33	8.3%
		Insufficient data	15	4.7%	7	8.9%	22	5.6%
45-54	Symptoms	Typical	1 352	88.9%	293	80.7%	1 645	87.3%
		Atypical, other	116	7.6%	53	14.6%	169	9.0%
		Insufficient data	53	3.5%	17	4.7%	70	3.7%
55-64	Symptoms	Typical	2 709	84.9%	821	80.7%	3 530	83.9%
		Atypical, other	325	10.2%	136	13.4%	461	11.0%
		Insufficient data	157	4.9%	60	5.9%	217	5.2%
65-74	Symptoms	Typical	1 017	79.8%	512	78.0%	1 529	79.2%
		Atypical, other	182	14.3%	89	13.6%	271	14.0%
		Insufficient data	75	5.9%	55	8.4%	130	6.7%

Table 6. Trends in time between onset and medical presence 1989-2003. Men and women aged 25-64 years in the Northern Sweden MONICA infarction registry.

		Time	1989-1991		1992-1994		1995-1997		1998-2000		2001-2003		Total	
			n	%	n	%	n	%	n	%	n	%	n	%
Male	Time	< 2 hours	423	38.6%	412	39.9%	417	45.5%	373	41.9%	352	40.5%	1977	41.2%
		< 4 hours	244	22.3%	210	20.3%	170	18.5%	179	20.1%	168	19.3%	971	20.2%
		4-24 hours	340	31.0%	304	29.5%	230	25.1%	249	28.0%	210	24.2%	1333	27.7%
		> 24 hours	89	8.1%	106	10.3%	100	10.9%	89	10.0%	139	16.0%	523	10.9%
Female	Time	< 2 hours	109	36.9%	120	43.6%	112	46.5%	118	42.6%	105	37.1%	564	41.1%
		< 4 hours	60	20.3%	51	18.5%	38	15.8%	61	22.0%	62	21.9%	272	19.8%
		4-24 hours	101	34.2%	77	28.0%	65	27.0%	74	26.7%	83	29.3%	400	29.2%
		> 24 hours	25	8.5%	27	9.8%	26	10.8%	24	8.7%	33	11.7%	135	9.8%

Table 7. Proportion of men and women in different time intervals between onset of symptoms and medical presence, ages 25-64 years during 1989-2003. (Patients aged 65-74 years were only included in 2000-2003).

			Male		Female		n	%
			n	%	n	%		
25-34	Time	< 2 hours	18	42.9%	3	33.3%	21	41.2%
		< 4 hours	3	7.1%	2	22.2%	5	9.8%
		4-24 hours	14	33.3%	3	33.3%	17	33.3%
		> 24 hours	7	16.7%	1	11.1%	8	15.7%
35-44	Time	< 2 hours	137	45.1%	40	53.3%	177	46.7%
		< 4 hours	58	19.1%	14	18.7%	72	19.0%
		4-24 hours	77	25.3%	18	24.0%	95	25.1%
		> 24 hours	32	10.5%	3	4.0%	35	9.2%
45-54	Time	< 2 hours	616	42.8%	150	44.1%	766	43.1%
		< 4 hours	277	19.2%	67	19.7%	344	19.3%
		4-24 hours	390	27.1%	87	25.6%	477	26.8%
		> 24 hours	156	10.8%	36	10.6%	192	10.8%
55-64	Time	< 2 hours	1 206	39.9%	371	39.2%	1 577	39.8%
		< 4 hours	633	21.0%	189	20.0%	822	20.7%
		4-24 hours	852	28.2%	292	30.8%	1 144	28.8%
		> 24 hours	328	10.9%	95	10.0%	423	10.7%
65-74	Time	< 2 hours	460	41.1%	210	38.4%	670	40.2%
		< 4 hours	237	21.2%	99	18.1%	336	20.2%
		4-24 hours	284	25.4%	168	30.7%	452	27.1%
		> 24 hours	138	12.3%	70	12.8%	208	12.5%

The prehospital delay was also stratified for age and sex (Table 7). It was found that older patients had longer prehospital delay. In the oldest age group, 65-74 years, the delay in seeking medical care for symptoms of MI was longer than in the younger groups, especially in women. In the oldest age-group, delays between 4 and 24 hours were seen in 25% of men and 30.5% of women.

Study II: Prehospital experiences of older men with a first myocardial infarction: a qualitative analysis within the Northern Sweden MONICA Study

The aim of this qualitative study was to explore older men's prehospital experiences of their first MI. The prehospital phase was found to be complex. The results consist of three themes and nine sub-themes. The themes are "from uncertainty to conviction", "an effort to maintain an ordinary life" and "a negotiation with conceptions and expectations". The themes and sub-themes are presented in Table 8.

Table 8. Older men's prehospital experiences of their first MI.

Themes	From uncertainty to conviction	An effort to maintain an ordinary life	A negotiation with conceptions and expectations
Sub-themes	Intangible feelings of not being well	Behaving as usual	Not believing oneself to be at risk
	Significant symptoms with different characteristics	Attempting to treat the symptoms	Not expecting that MI would feel like this
	Persistent and alarming chest pain	Trying to trigger the symptoms and test the limits	Convincing oneself that the symptoms will go away

The theme **from uncertainty to conviction** encompassed men's experiences of a range of symptoms of varying degree and duration. This theme was developed from three underlying sub-themes: "intangible feelings

of not being well”, “significant symptoms with different characteristics”, and “persistent and alarming chest pain”. The participants described symptoms of diffuse ill-being as a part of their prehospital experiences. The indistinct symptoms were experienced several days or weeks before the MI and were described in expressions such as *“I was out of sorts”*. However, the men did not interpret the symptoms as precursors to an MI. For some, these became clear retrospectively, often during the interviews. Some participants experienced a cluster of significant symptoms that covered a wide area of the body and included the left arm or both arms, the back, shoulders, neck, throat, and stomach. Various sensations in the chest were the most common, but only a few men described them as their main symptom. In addition, the men used a variety of terms other than “chest pain” or the word “heart” to describe their symptoms. Instead, they talked about their ribcage, breastbone and chest to locate the symptoms. The characters of the symptoms were described as discomfort, stitch, ache, pain, tightness, pressure, numbness, cramping, or burning and were often described as intermittent. During the progression of the symptoms, the men experienced how the intensity and duration of pain changed nature and became more intense, persistent and alarming, until it was finally a well-defined chest pain *“It was still there in the middle of my chest and also like squeezed out through my back”*.

While symptoms evolved the participants became aware that something serious was happening to them. Most of the men explained that it was because of the changing nature of symptoms and increased pain *“When I felt that really tight belt across my chest, it wasn’t hard to understand what was going on”*. Due to the intense and persistent pain the men came to a point when the situation became intolerable and they had to seek medical care.

The theme **an effort to maintain an ordinary life** concerned how the participants tried to maintain an ordinary life during the prehospital phase by dealing with their symptoms in different ways. This theme was developed from three underlying sub-themes “behaving as usual”, “attempting to treat the symptoms” and “trying to trigger the symptoms and test the limits”. The participants described how despite their symptoms they tried to spend time on daily chores in the hope that the symptoms would disappear. They also tried to rest or sleep in order to relieve the symptoms, but their strategy did not work. Some tried to treat their symptoms by themselves through different kinds of self-care activities like massage or stretching and some

participants described how they challenged the symptoms with physical activity in order to know the limits of their perceived ill-being.

The theme **a negotiation with conceptions and expectations** concerned the participants' thoughts and reasoning about their symptom experiences during the prehospital phase. This theme was developed from three underlying sub-themes: "not believing oneself to be at risk", "not expecting that MI would feel like this", and "convincing oneself that the symptoms will go away". The men were involved in a negotiation with previous conceptions and expectations of MI symptoms in relation to their actual experiences of ill-being. The men described how they dealt with their conceptions about MI symptoms. They had ideas of what MI symptoms should feel like and these were not consistent with their own experienced symptoms, which they expected to disappear. Their perceived symptoms therefore misled them in their decisions about further action. Some expressed frustration about the ambiguous symptoms. There was also a tendency to negotiate away from the option that the symptoms could be related to the heart, along with a conviction that the symptoms would go away, resulting in the decision to wait until the next day before taking any measures *"It'll will go away, in most cases it does – toothache or whatever.*

An illustration of the findings was created (figure 8) to provide a comprehensive and more in-depth understanding of the findings.

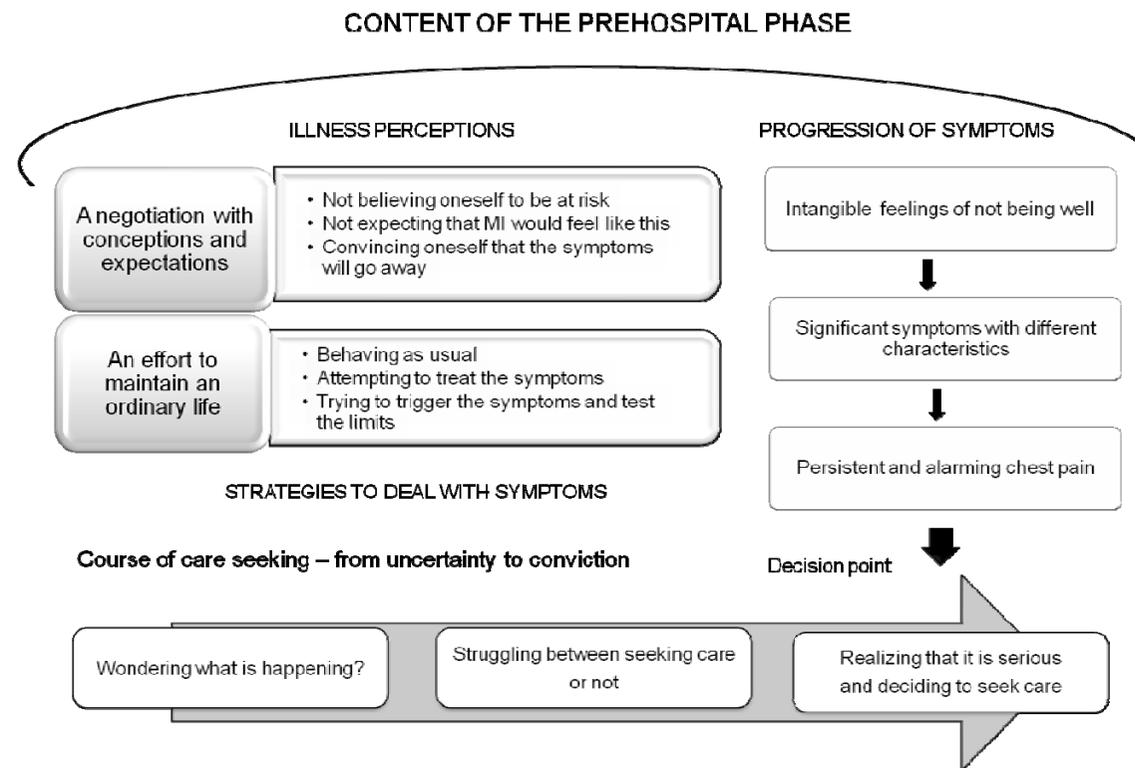


Figure 8. The content of the prehospital phase in older men with a first myocardial infarction.

The prehospital phase in older men was found to be a complex and extended journey entailing the areas; progression of symptoms, illness perceptions, strategies to deal with symptoms and course of care seeking. On the way from the initial perception of ill-being to the final decision to seek medical care, an internal negotiation took place about the progression of symptoms experienced and whether to seek care or not. At the same time different time-consuming strategies were undertaken to deal with the symptoms and maintain an ordinary life. Eventually, as the symptoms evolved to persistent and alarming and strategies to deal with them were found to be futile, a final decision point emerged. At this decision point, the nature of the pain and insight into the seriousness of the symptoms and the real threat against their lives, provoked the participants to seek medical care.

Study III: Older women’s prehospital experiences of their first myocardial infarction: a qualitative analysis within the Northern Sweden MONICA Study

The aim of this qualitative study was to explore older women’s prehospital experiences of their first MI. The prehospital phase was found to be complex. The results consist of two themes and seven sub-themes. The themes are “undergoing increasing discomfort and pain” and “struggling against intrusive symptoms to maintain control and responsibility”. The themes and sub-themes are presented in Table 9.

Table 9. Older women’s prehospital experiences of their first MI

Themes	Undergoing increasing discomfort and pain	Struggling against intrusive symptoms to maintain control and responsibility
Sub-themes	Early indistinct physical sensations	Downplaying and doubting perceived ill-being
	Warning distinct ill-being	Neglecting the seriousness of perceived symptoms
	Persistent and overwhelming chest pain	Putting others’ well-being in front
		Giving in to symptoms

The theme **undergoing increasing discomfort and pain** concerned how the women experienced a stepwise development of symptoms, from indistinct to alarming. The experiences of discomfort and pain were described in all stages as unfamiliar and strange. This theme was developed from three underlying sub-themes “early indistinct physical sensations”, “warning distinct ill-being”, and “persistent and overwhelming chest pain”.

Initially, the participants experienced indistinct physical sensations. For some these symptoms became clear retrospectively, often during the interviews, while for others the symptoms remained unnoticed until pointed by relatives. These early symptoms were experienced days, weeks and even months before the MI. In this early stage the symptoms were usually perceived as an unusual fatigue with non specific discomfort in different parts of the body, described as unusual or unpleasant malaise or fatigue. Sensations in the chest were common and described by the women as stitches, tightness or pressure. Shortness of breath and symptoms from the stomach area were also experienced.

The indistinct physical sensations became more distinct, increasing, intermittent, and variable. In this warning stage the symptoms were more worrying with distinctive signals of ill-being and were unlike anything the women had experienced before. Even so, though, the participants found it difficult to understand the origin of the symptoms, and they did not associate them with the heart.

Eventually, the warning symptoms became acute and alarming. In this final stage, chest pain came to dominate the event and was experienced by all the women. Describing the pain most of the participants referred or pointed to their chest with the hand how the pain was located in the middle of the chest. The women experienced how the chest pain increased rapidly, within seconds, minutes or hours, and in such degree that it was extremely distressing. The pain was persistent and overwhelming and described as terrible, crushing, tightening, gripping and stabbing “*My pain was so deep and so terrible*”. The pain could also occur in the back, in the left arm or in both arms with or without heaviness or squeezing sensations behind the shoulders. Some described how radiating pain could start in the chest and travel to one arm or through both arms.

The theme **struggling against intrusive symptoms to maintain control and responsibility** concerned how the women despite evolving symptoms were striving to live their daily life as usual and household responsibilities were, through all symptom stages, considered essential. This theme was developed from four underlying sub-themes “downplaying and

doubting perceived ill-being”, “neglecting the seriousness of perceived symptoms”, “putting others well-being in front” and “giving in to symptoms”.

The participants described how, even during the early phase of indistinct physical sensations they felt that something was not right. In this early symptom stage some decided to seek medical care, usually on the advice of relatives, but they were all sent home again without any testing, like ECG, or diagnosis which made them feel ignored and discounted. The women began to doubt themselves and started to wonder if they had only imagined their symptoms. This self-doubt was sometimes increased by comments from health care professionals such as, “*You’re just out of condition*”.

Though the symptoms progressed the participants did not think of them as possible symptoms of MI, even though many of them thought that they knew about MI symptoms. They wanted to find more natural or normal explanations for their symptoms, such as indigestion due to something they had eaten. Contributing to this wish to search for a natural explanation was the fact that their symptoms differed considerably from those the women imagined would signal an MI, which presented a confusing picture for them. Some women associated MI with more crushing chest pain radiating to the left arm and not with the slow onset and sometimes intermittent symptoms as they experienced.

All participants tried to self-manage the symptoms, which delayed them seeking medical care while they waited to see whether their home interventions were effective. Many tried to sleep and some took painkillers. The participants expressed the desire to get along on their own and their unwillingness to let others make decisions for them. They openly acknowledged that they did not like to ask others for help.

Despite growing symptoms the women wanted to carry on as usual with their lives and therefore distanced themselves from their symptoms. The symptoms seemed to create a feeling of shame in the participants, who did not wish to be seen or to think of themselves as weak. The women described how they did not want to let others see that they were not as strong and capable of taking care of their homes and responsibilities as they used to be.

Eventually, the severe pain overwhelmed the women but still they attempted to carry on with their daily lives as usual. The participants described how they tried to wait out severe symptoms by trying to cope with them on their own. Many participants eventually sought medical care not when the pain was most intense, but when they felt that the timing was right; putting the needs of others before their own needs for medical care. Women

felt the need to meet social responsibilities before seeking medical care and worried that they might disappoint others: *"I put off calling [for medical care] because I didn't want to disrupt my daughter's holiday with her family"*. The women viewed their own health as a low priority compared with the interests of their family members or friends and they placed more importance on the health and well-being of others than on their own. *"When you are busy taking care of your husband, your children, your grandchildren, it is easy to forget about yourself"*.

The participants seemed caught between a desire to maintain control and the realization that there might be something seriously wrong with them requiring medical care. Despite experiencing strong and intense pain, the participants were still uncomfortable about seeking medical care. Previous negative health care experiences in the early symptom stage were for some described as barriers to seeking medical care for women who feared being embarrassed by seeking medical care for what could be false alarm.

However, when the women reached a point of unbearable pain and/or the timing seemed right, they finally took the decision to seek medical care. But they still had worries about where to go and how to get there. They did not know whether they should call or go to the medical center, call directly to the emergency department, or call for an ambulance. Calling an ambulance seemed too drastic and embarrassing because they did not consider themselves "sick enough". To the very end, women had difficulties in putting themselves first, and instead continued to think of others: *"I thought it best that we take the car instead of an ambulance, for how would my husband get home otherwise?"*.

Study IV: Better long-term survival in young and middle-aged women than in men after a first myocardial infarction between 1985 and 2006. An analysis of 8630 patients in the Northern Sweden MONICA Study

The aim of this quantitative study was to analyze sex-specific survival of patients for up to 23 years after a first MI in northern Sweden and to describe time trends. A total of 8630 subjects, 6762 men and 1868 women, with a first MI between 1985 and 2006, were included. Median follow-up was 85 months (7.1 years). During the follow-up, 3066 (45.3%) of the men and 798 (42.7%) of the women died. Among men, 959 (14.2%) died before admission to hospital and among women 205 (11.0%) died before admission.

Mean age for those who died before reaching hospital was 56.0 years for men and 57.1 years for women.

In a Cox regression analysis, the hazard ratio (HR) for all-cause mortality, after adjustment for age, was 1.09 (95 % confidence interval [CI] 1.010-1.18, $P = 0.025$) for males vs. females, *i.e.* 9 % higher rate of survival in women than in men. After excluding subjects who died before reaching hospital, the difference in mortality was no longer significant, (HR 1.017 95%CI = 0.93-1.11, $P = 0.7$).

Median survival for men was 187 months (95% CI 179-194) and for women 200 months (95% CI 186-214) (Figure 9). In Table 10, the proportions of those who were alive at 7 days, 28 days, 1, 3, 5, 10 and 20 years after their MI are presented, stratified for age. For any duration of follow-up, a higher proportion of women were alive, irrespective of age group. As the median follow-up was 7.1 years, figures on 5-year survival will include most subjects. Five years after a first MI 75.3% of men and 77.5% of women in the younger age groups (25-55 years) were still alive. In the age group 56-64 years the corresponding survival rates were 65.5% for men and 66.3% for women. After excluding subjects who died before reaching hospital, median survival for men was 225 months (95 % CI = 217-233) and for women was 222 months (95 % CI = 207-236).

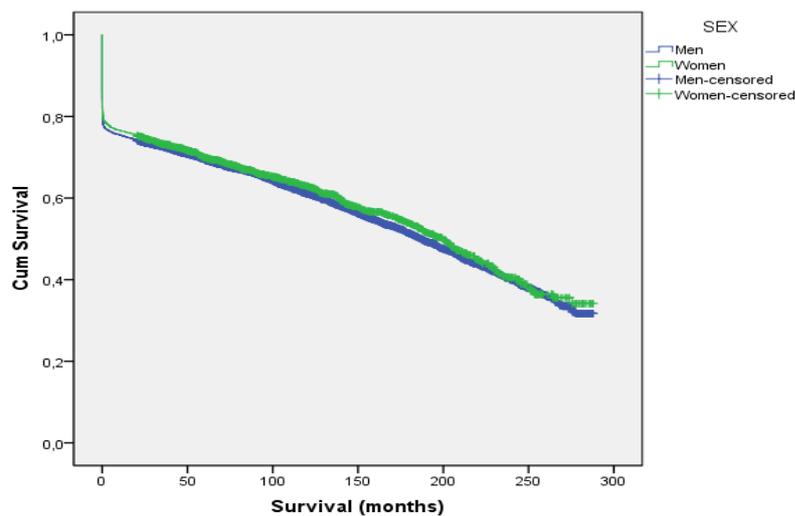


Figure 9. Median survival after a first myocardial infarction according to sex.

Table 10. Proportion of men and women surviving after a first myocardial infarction stratified for age

Time after MI	Survival (%) at different times after MI			
	Men		Women	
	Age 25-55 years	Age 56-64 years	Age 25-55 years	Age 56-64 years
7 days	82.2	77.6	85.2	79.1
28 days	81.2	74.9	82.9	76.9
1 years	79.2	72.3	81.4	73.5
3 years	77.3	68.9	79.3	69.9
5 years	75.3	65.5	77.5	66.3
10 years	71.0	58.0	75.1	59.8
20 years	63.9	48.9	69.7	51.2

In each age group, women had a longer median survival than men (Figure 10). Survival was shorter with higher age.

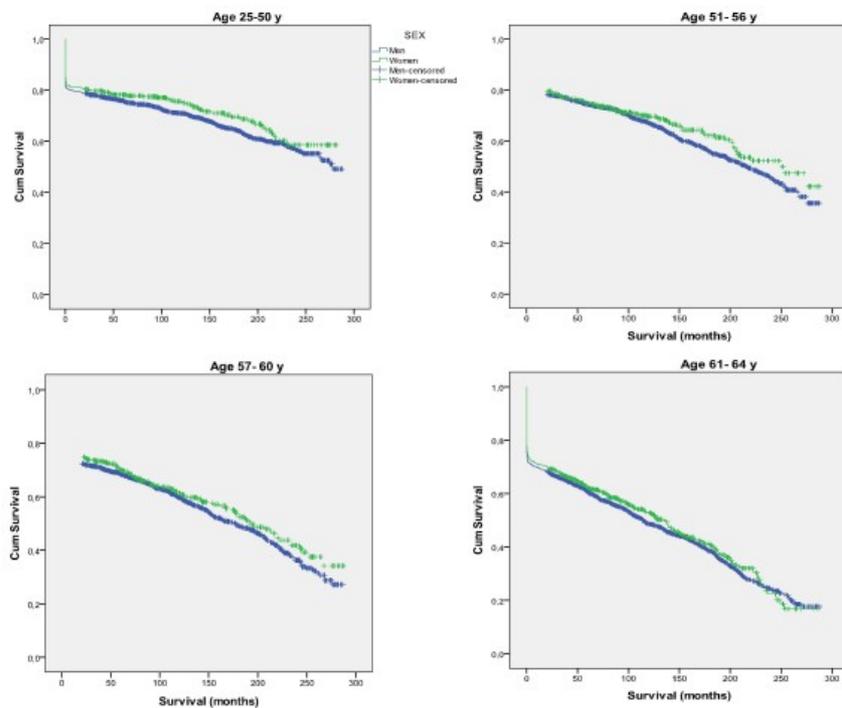


Figure 10. Survival after a first myocardial infarction according to sex and age group

With each succeeding cohort survival increased (Figure 11). During the first and third periods, survival in women exceeded that of men, while the reverse was true for the second period, and no difference was seen during the last period (Figure 12).

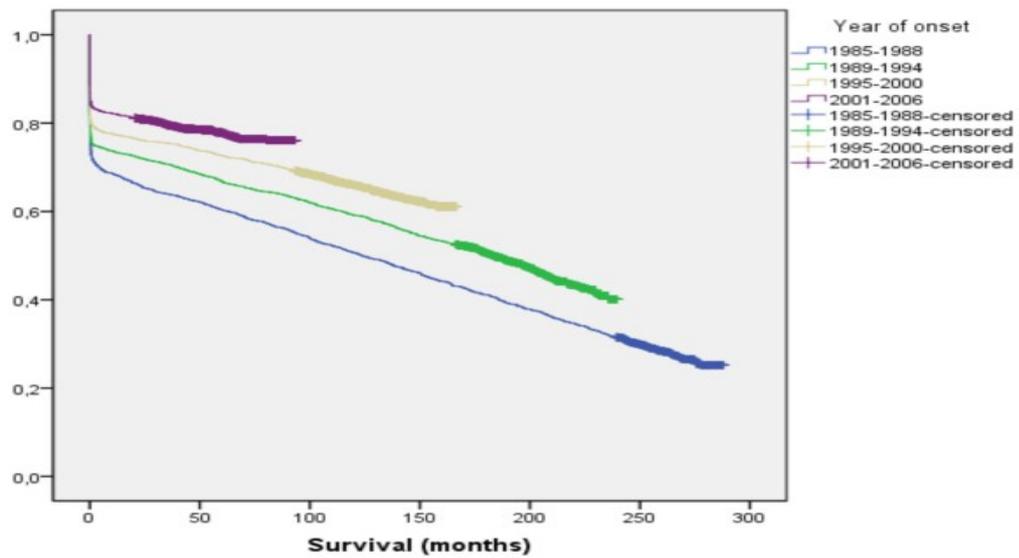


Figure 11. Survival after a first myocardial infarction according to year of onset

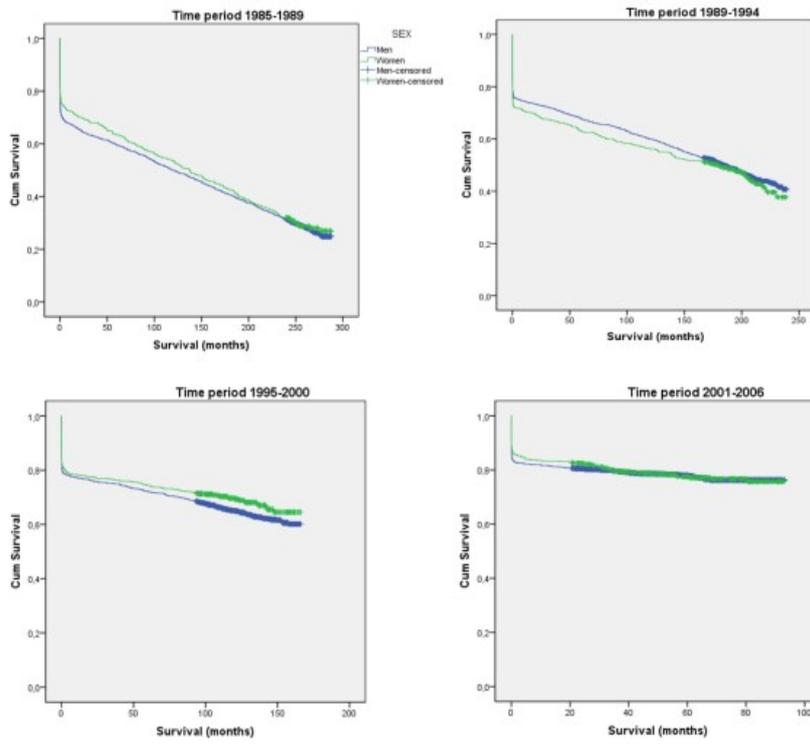


Figure 12. Survival after a first myocardial infarction according to sex and year of onset.

Discussion of main results

The main findings in this thesis show that on the whole there were more similarities than differences between men and women in symptoms, prehospital delay, and long-term survival.

Symptoms and prehospital delay in men and women

In Study I, from a quantitative perspective, typical symptoms, i.e. chest pain, or synonyms for pain such as pressure, discomfort or ache, for more than 20 minutes, were the most common symptoms in more than 80% of both men and women, which accords with previous studies [4, 11, 12, 15, 19, 21, 22]. But several studies have also found that women present with atypical symptoms more often than do men. A review by DeVon and Zerwic [104] showed that women with MI had more back pain, neck pain, nausea and dyspnoea than men. Men on the other hand, had more chest pain and diaphoresis. Our data confirmed that typical pain was somewhat more common in men, and atypical symptoms somewhat more common among women. However, findings in previous studies have been remarkably inconsistent, probably because they have included different populations and methods, based for example on interventional studies and/or including patients with angina [22]. However, gender differences in symptoms of MI have received attention in the media and may unfortunately have led women to believe that they will not experience typical symptoms if they suffer an MI.

In line with our findings, in a recently published Swedish study [22] in 225 patients, aged 25 to 74 years, reported chest pain as the most common presenting symptom in both men and women. However, even when women had chest pain, similar to that in men, they also displayed a greater number of diverse symptoms such as nausea, back pain, dizziness and palpitations. This result also accords with a recent review by Canto [31]. The authors of both studies [22, 31] suggested that the presence of a greater number of symptoms could lead the physician to misdiagnose a musculoskeletal, gastrointestinal, or neurological cause of the complaints. These misinterpretations may delay medical treatment and thereby lead to worse outcomes.

All men and almost all women initially experienced a wide array of diffuse symptoms from different parts of the body, so-called prodromal symptoms [30]. This is an interesting finding as prodromal symptoms have previously

been reported as typical among women with MI [23, 30]. Even more notable is that this became obvious to our participants only in retrospect. As people grow older they tend to accept having several diverse symptoms as a part of life, as has been shown in a previous Swedish study of men and women with MI [105]. Perhaps the participants in our studies (II, III) did not link their symptoms to any kind of disease, but instead perceived them as the “normal” aches and pains of aging or minor ailments and therefore did not pay any particular attention to them. The discussion of prodromal symptoms is interesting and can be carried one step further. What exactly are prodromal symptoms? Are they really a sign of angina or potential MI or are they things like fatigue and listless that come and go normally for everyone, and do not necessarily signal an upcoming MI. These questions could not be answered within the framework of our studies but they do deserve further attention and research.

The development of symptoms was quite similar between men and women. In men (Study II) the symptoms were perceived as evolving from intangible feelings of not being well to persistent and alarming symptoms with chest pain. In women (Study III) the symptoms were perceived as evolving from indistinct bodily sensations to persistent and overwhelming chest pain. Symptom recognition (or lack there of) is the first of several important factors that cause delay when it is important to seek care. The slow onset of symptoms presented a confusing picture to participants of both genders and probably contributed to delays in seeking care.

The most important findings in Studies II and III were that both men and the women experienced a prehospital period that was clearly influenced by their conceptions and expectations about MI symptoms. Symptoms of an MI were commonly perceived as limited to an acute and crushing chest pain, and were not expected to include the slow onset of symptoms that both men and women experienced. Based on our findings, I agree with Berg et al. [22] and Canto et al. [31] that it is important to emphasize in public education and to health care workers at all levels that an MI can present in many different ways and that atypical symptoms can occur in both men and women.

Of particular note, in Study I almost all of the men and women experienced “typical” symptoms, while in Studies II and III almost all of the participants experienced atypical symptoms, at least initially. Symptoms reflect the patient’s personal subjective experience, which is then interpreted, subjectively, by health professionals [106]. Not surprisingly,

there is disparity between patients' assessments of symptoms and those of nurses and physicians.

In Study I symptoms were identified from medical records, which for various reasons do not always provide a complete picture of a patient's symptoms and may be imprecise in describing the presence and nature of symptoms. When the patient arrives at the emergency department with an acute MI there is no time for the physician or nurse to ask the detailed questions about symptoms that may be asked during a more formal and unhurried interview. Nor does the patient in the midst of an MI have time to describe the symptoms in depth. It is also possible that the physicians' document the symptoms they consider important and do not document all the symptoms the patient describes. Previous conceptions and expectations about MIs in men and women may thus affect not only the patient, but also the nurses and attending physicians.

The verbal interaction between patient and health care professionals may also influence how symptoms are understood [36]. According to Albarran [35] the language or metaphors patients use, such as "stabbing", "burning" and "like a belt tightening across my chest", can reflect the quality and intensity of their experience of chest pain and often encompass a sensory or emotive component [35]. This also highlights the importance of nurses' and physicians' awareness about how to ask questions about symptoms. Health care professionals need to ask questions about nonspecific symptoms when meeting patients with a suspect MI and not focus solely on typical chest pain. The patients should be invited to describe their symptoms freely.

In Study I we found that delay in seeking medical care was more common, especially among women, in the oldest age group, 65-74 years. Gender differences in prehospital delay have been demonstrated in previous studies, but have also been conflicting. Some researchers found that women delayed longer than men [4, 63, 67, 68], while others documented no such differences [69, 71, 107-108]. Our findings are in agreement with those studies [109-110] who found that women and older people delay longer than men and younger people.

The findings in the qualitative studies (II and III) showed complex interactions between symptom progression, illness perceptions, physical manifestations of pain, and response to symptoms in older men and women. That symptoms have a key role in the decision-making process in both men and women is clearly evident. We found that the idea of an MI as an acute strong chest pain did not prepare either the men or the women, to interpret less dramatic symptoms as a possible MI. Therefore they initially ruled out

the possibility of an MI and thereby lengthened their prehospital delay. This result shows that highlighting gender differences in symptoms of MI may cause men to ignore symptoms that are traditionally framed as “feminine”, because they feel they should have the typical MI symptoms, and conversely may cause women to ignore symptoms traditionally framed as “masculine”, because they feel they should have the publicized atypical MI symptoms.

Identifying in the interviews the time of onset of symptoms was more difficult than expected. In a recently published Swedish study [111] of men and women with a recent MI, the researchers also found it difficult to obtain unambiguous answers from the patients regarding the time of symptom onset. Although neither the men nor the women in our studies had difficulties in defining the time of onset it may be important to consider what kind of symptoms they referred to. We cannot be sure whether our participants referred to the start of the diffuse symptoms or to the start of the persistent chest pain. In our studies (II, III) the patients perceived the patients' delay more difficult to estimate than I expected from the literature. Only when symptoms persisted and became worse did both the men and women realize that the situation was serious. This point probably corresponds to what most of the patients estimate, and emergency room staff may incorrectly consider as the “onset of symptoms”. It is of great clinical importance to take this into account as acute medical treatment is time dependent. Our findings further reveal the importance for nurses and physicians to obtain in-depth information from patients about symptoms in order to determine as accurately as possible the time of onset of symptoms.

The phenomenon of prehospital delay can be described and understood in different contexts. Different models, such as the health-belief model [112] and the self-regulatory model of illness behavior [113] are examples of theoretical perspectives of illness perceptions and health behavior that focus on the relationship between the unique experiences, interpretation of symptoms, and the coping responses to the symptom representation of the individual. The self-regulatory model proposes that three stages regulate the behavior seen in response to a health threat. The first stage, cognitive representation of the health threat, includes identifying the symptoms and labeling the threat, potential cause(s), and possible consequences of the threat. The second stage is the action plan or coping stage in which a plan of action is formulated and initiated. The motivation to engage in coping actions is self-generated in response to the individual's representation of the health threat and individual potential for coping, and the relationship between the coping strategies and the threat. In the third stage the individual

appraises the success of his or her coping actions, and if progress seems insufficient, the representation of the problem and the plans to cope with it are reassessed and may be changed.

In Study II the men had difficulty making the final decision to seek medical care and strived to maintain an ordinary life. They initially tried to understand, reduce, or treat the symptoms by themselves. In study III the women struggled against the symptoms by downplaying, and neglecting the seriousness of perceived symptoms. They used different kind of strategies to effect their strong desire to maintain control. Social responsibilities took priority over concerns about their own health. The findings of Study III might be better understood in the context of a model based on women's social concerns. For example, recognition of the problem as a possible MI may be delayed when symptoms are not considered serious or not attributed to the heart. Even when the symptoms are recognized as a potentially serious health threat related to the heart, the emotional concerns about troubling others, and fear of either embarrassment or the consequences of seeking help may lead to an initial decision not to seek medical attention, which may subsequently be appraised as an unsuccessful action plan. The plan may then be revised and help is sought.

No model can grasp every aspect of this complex process of care-seeking by patients afflicted by an MI. Aside from their obvious aims, our results can also be understood within theoretical frameworks of masculinity and femininity, norms, and gender [114]. Help-seeking behaviors in both men and women are purported to be closely tied to stereotypical and traditional ideals of masculinity and femininity [115, 116], such as the expectation that men will have a high threshold for pain and discomfort and enjoy being challenged, while women are typically viewed as primary care givers and reluctant to bother with others with their problems [115, 116].

Many aspects of the results in our studies do in fact fit within the stereotypical patterns of masculine and feminine gender in the context of care-seeking behavior, but several participants also reported responses that were not typical of their gender. The men in Study II described displaying a high threshold for pain and discomfort and dismissing any need for help, which may be related to the hegemonic concept of masculinity. However, several women in Study III also reported struggling against severe pain for as long as they were ever able. In the interviews it was also shown how strongly the women wanted to remain in control and were accustomed to be seeing as strong, active and independent of others, qualities that could be interpreted and understood as typically masculine [117]. Many men also

reported responses that would more commonly be associated with women, most often in accounts of feelings, such as vague experiences of unease, or behaviors such as arranging for practical things and avoiding worry for family or friends before calling for medical care.

As a whole men and women in our studies had a similar decision making pattern. However, in women we found that the prehospital delay was strongly influenced by the broader context of their social responsibilities. This is in line with a Canadian study [118] among women with symptoms of potential cardiac illness, where the primary reasons for care seeking were influenced by the context of women's lives as mothers, daughters, and wives, and secondly, by their interpretations and conclusion about their symptoms were secondary. The women in our study (III) have probably grown up with the notion that women's primary responsibilities are to the family and the home. The responsibilities, for family and home are, I hope, now more equitably divided between the genders, and thereby no longer a great contributor to women's prehospital delay. However, I agree with Galdas et al [119] that men's and women's behavior when deciding to seek care may sometimes vary, but cannot be easily parsed into distinct gender patterns.

Long-term survival in men and women

In study IV we found that between 1985 and 2006 long-term survival after a first MI had increased in both men and women between 25 and 64 years of age in northern Sweden. Over the whole period women showed a 9% higher survival rate than men. We proposed that the difference was due to the lower risk for women of dying before reaching hospital, and from year 2000 similar rates were noted in both men and women.

The improvement in survival rates shown in our study is probably a combination of better treatment by paramedics before admission to hospital, improvements in the acute coronary care and secondary prevention. Over the study period there was an increasing use of evidence-based medical treatments and coronary artery revascularisation at the onset of MI both of which have been shown to reduce cardiac morbidity and mortality [120]. Secondary prevention programmes and patient activities have become routine in the follow-up of patients with MI in Sweden. Since the early 1990s all cardiac patients have been called and invited for individual counselling by cardiologists or nurses.

Over the last two decades there has been an ongoing debate about the differences in terms of treatment and outcome between men and women

suffering from MI [121, 122]. Our results do not support the contention that the outcome of a first MI in women is worse than in men. On the contrary, we found women had a slightly longer median survival and a higher probability of being alive during long-term follow-up in accordance with recent large studies [97-99].

Reasons for the slight difference in long-term outcome between men and women are unclear and explanations to a great extent are speculative. We had no data on the severity of the MIs, which may be a link in the causal chain leading to somewhat better prognosis for women. Still, the sex-differences shown in the results of Study IV underscore the importance of recognizing the potential effects of sex and gender on all parts of the MI-journey, including symptom representation and recognition, reasons for delay, diagnosis, treatment and long-term outcome.

Discussion of methods

A quantitative and qualitative approach was combined in this thesis to give a more comprehensive picture of the phenomenon studied. Each approach has its strength and weakness.

The quantitative studies (I, IV)

Validity is the capability of a study to measure what it is supposed to measure according to a certain criterion. Validity is usually discussed in terms of internal and external validity. Internal validity shows how well results from the study population reflect the true situation of the study base. External validity shows the generalizability of the results of the study, i.e. whether the results can be applied to other populations.

The internal validity of our findings is strengthened by the strict and uniform use of the MONICA criteria over the whole period. To insure a complete registration, computer-based lists of discharge diagnoses from hospitals and nursing homes were screened annually for cases. All reported events were re-evaluated using MONICA methodology [79]. The large database, the internal and external quality control, and the stability of personnel involved in the MONICA Myocardial Infarction Registry ensure the reliability of the data. During the first 10 years, a central quality assurance program was performed at the MONICA Data Centre in Helsinki and the data from Northern Sweden maintained a good quality score [123].

For external validity it is essential that our study population represents the larger population. The studies presented in Papers I and IV were based on data from the Northern Sweden MONICA myocardial infarction registry, which covers the total population aged 25-64 years in the Northern Sweden MONICA area. From the year 2000, the registry has included those aged up to 74 years. Thus, all patients with MI are included and thus the risk of selection bias is removed. It is reasonable to assume that our findings are representative of Swedish patients with MI, but care should be taken before extrapolating these results to populations in other countries.

The major strength of Studies I and IV was the large number of patients studied over a long period - up to 23 years in study IV. When analyzing mortality from MI it is not enough to analyze in-hospital mortality. A

considerable proportion of deaths from MI occur outside hospital, and unpublished data from the Northern Sweden MONICA Study show that between 10% and 15% of all those suffering an MI before the age of 65 die before reaching hospital.

The MONICA registry includes deaths before admission to hospital therefore our description of the total burden of the disease is accurate and provides a more relevant presentation from a public health of view. It is also important to be noted that Studies I and IV are not based on a random sample from the entire population, as the registry includes all those who suffered an MI in the defined geographical area.

The main limitation is the fact that only patients under 65 years of age were registered before the year 2000. When the WHO MONICA project was initiated in the early 1980s, the focus was on what was then regarded as premature cardiovascular disease. This was seen primarily as a health problem in the middle-aged, and it was not clearly understood to have any essential public health impact in people over 60 years of age. Therefore, the upper age limit for the initial study was set at 65 years. It was soon evident, however, that the MONICA project did not capture the most important age groups for MI, especially in women. Better primary and secondary prevention and treatment have also caused the mean age at onset of MI to shift upwards. To reflect these changes, since the year 2000 the age group 25–74 years has been recorded in the MONICA myocardial infarction registry, but our results cannot be applied to older age groups or to the total population without some reservation.

A limitation in Study I was that the MONICA registry was based on medical records and thus was a retrospective study. It is highly probable that a prospective study with a standardized questionnaire would give a more detailed and balanced picture. That might also reduce the bias introduced by symptom presentation being filtered through the preconceived conceptions of the mostly young and inexperienced physicians in the emergency room, who also are those who document cases in the medical records.

Another limitation of Study I was that both subjects with first and recurrent MI were included. It is very probable that suffering a first MI leads to patients learning how to describe their symptoms in a way that fits the expectations of physicians and nurses. Restricting the sample to only patients with first MI would perhaps have given a clearer picture of patients' experiences and understanding, which is the major reason we included only subjects with first MI in the qualitative studies.

A limitation in Study IV is the introduction of troponins in the 1990s as markers of myocardial injury. These markers were not included in the early 1980's MONICA criteria for validation and classification of events. This means that MI definitions before and after the year 2000 differ to some extent and patients with less myocardial damage than before were included after 2000 than before. This in turn means that cases that previously diagnosed as angina or unstable angina would later show signs of myocardial injury in blood samples and therefore more appropriately be given diagnosis of MI. Because of this clinically milder cases are included in Study IV, however, it does not thereby imply that those prognoses are less severe. This situation is complex and difficult to reconcile, especially since all the hospitals in Sweden changed their diagnostic markers during this period and stopped using the older biomarkers that were described in the original MONICA project. The switch to measurements by troponins, however, would not affect the large proportion of subjects dead before hospital, nor would the effect be likely to differ between the sexes and thus invalidate our findings.

It is also important to be noted that studies I and IV are not based on a random sample from the population, as the registry includes all those who suffered an MI in the defined geographical area and therefore hypothesis testing with statistical methods was not needed.

Data from the Cause of Death Register was used in Paper IV. The register covers all Swedish residents, whether the person in question was a Swedish citizen or not, and irrespective of whether the death occurred. The coverage is high, since the Cause of Death Register is annually linked to the official population statistics. It is estimated that 93% of all deaths are reported to Statistics Sweden within 10 days and 100% within 30 days using the unique PIN assigned to every citizen in Sweden [102].

The qualitative studies (II, III)

The qualitative studies gave us the opportunity to gain an insight into how the patients experienced the prehospital phase. We considered it important to include only patients with a first MI and to exclude those who may have learned to report "expected symptoms" from a previous MI or from living with angina pectoris. We judged that 20 men and 20 women would be large enough samples to allow for sufficient variation of experiences, but small enough to permit a deep analysis of the data [124].

Validity and reliability are not appropriate concepts to use when discussing trustworthiness in studies with a qualitative design. In qualitative content analysis credibility, dependability, and transferability are markers most usually discussed in relation to trustworthiness [101, 124]. Credibility refers to how well the constructed themes reflect the participants' experiences as expressed in the interviews. In these studies (II & III), credibility was established by showing representative quotations from the transcribed text and by a dialogue among the research group. Dependability concerns how well the research process and the analysis can be followed. This was established by open discussion within and among the research group and fellow researchers, in order to minimize inconsistencies and achieve a logical and clear documentation. The development of themes was discussed within the whole research group until consensus was reached. Transferability describes to what extent the findings are transferable to other illnesses or other populations. This was facilitated by providing a description of participants, the data collection and the process of analysis together with appropriate quotations. Presenting relevant quotations along with our findings also allow the reader to judge the authenticity of our interpretations.

Reflections about the interviews

Working with interviews during my dissertation project has been both interesting and rewarding. The atmosphere of the interviews was consistently relaxed. One reason was the interviewees' candour and positive attitude towards being interviewed. Kvale [100] notes that a qualitative research interview can be a positive and enriching experience for the interviewee, and that is consistent with the reactions of the interviewees in these studies. All the participants talked openly and in rich detail about their experiences, which contributed to very comprehensive interviews.

The interviewer learns how to interview by interviewing [125], which is consistent with my own experiences. I practiced my sensitivity as I went along, and learned to bring up important themes in the answers and to wait out silences. I also learned to probe and to stimulate narrative with follow-up questions. I can truly see how I was able to grow and improve as an interviewer over the course of the dissertation project.

In my experience, interviewing men was not the same as interviewing women. This is an observation that I have not found mentioned in the literature regarding qualitative studies in cardiovascular disease. Men stayed on topic throughout the interview and their descriptions of their experiences

were extremely revealing and vivid. Women's descriptions of their experiences were as detailed as the men's, but they did not adhere to the subject in the way the men did and they tended to speak more in circles touching on many other things, including their husbands, children, grandchildren, the weather, and other ancillary topics. Consequently, on many occasions with women interviewees I had to try to steer the conversation back to the focus of the interview.

Interviews conducted by different interviewers can sometimes provide different results due to the interviewers' varying sensitivity and knowledge about the subject [100], however, I considered such a risk to be low in the current studies, because all of the interviewers were highly experienced, familiar with the subject, and provided with the same interview guide.

Pre-understanding

When conducting these qualitative studies I had a pre-understanding from many years' experience as a registered nurse working at a cardiac ward. My knowledge of concepts within cardiac care and of the context as a whole helped me in the research process. Throughout the process, I tried to be aware of my pre-understanding of clinical experience. I consider it a strength that I was familiar with meeting and caring for patients with MI: nevertheless, it is important to reflect upon how this might have influenced the research process. I have tried to be as open-minded as possible and to avoid influencing the interpretations. My pre-understanding of the context could, however, also be a weakness, had I taken any statements for granted or neglected to probe. Despite this possibility, I consider that my pre-understanding was more helpful than biasing during the interviews, as my previous experience and knowledge of patients who have suffered an MI facilitated my ability to create a safe atmosphere and establish rapport with the participants.

Because the men and women were interviewed in the order they were admitted to the hospital, I had the same pre-understanding for each when collecting the data through the interviews. During the analysis of the women's interviews, however, I was aware of the results of the interviews with the men, although I tried to distance myself from this pre-understanding during the analysis of the interviews of women.

Clinical implications

In order to shorten the prehospital phase, it is important to provide accurate information to both men and women at risk of CHD, about MI symptoms and the importance of responding to symptoms as rapidly as possible in order to improve their chances of survival. Textbook descriptions of MI symptoms are often based on medical care from 20 to 30 years ago, and patients' interpretations of symptoms are very likely influenced by societal factors and media coverage. We need to rewrite the books and publish accurate data and symptom descriptions for both men and women.

The general public should be made aware of the variability of MI symptoms and understand that not all MIs are manifested by chest pain. Atypical symptoms and mild chest discomfort are common, especially in the early stages. The varying nature of the symptoms should be highlighted.

All health care professionals, throughout the whole chain of care, including those in primary and secondary care settings as well as those providing health care information and telephone counselling, can more promptly and accurately diagnose and treat MI if they are aware of the various symptoms of MI. They need to ask questions about nonspecific symptoms and not focus solely on the presence or absence of typical chest pain, especially in older patients of either gender who are feeling vaguely, but disturbingly, unwell. The patients should be invited to describe their symptoms freely.

The findings in this thesis can be used to develop educational and clinical interventions to help both men and women, especially the older, recognize MI symptoms and reduce their prehospital delay. Empirical and recent data on how men and women actually feel, think, and act in these situations should provide the basis for new, more effective interventions, especially in older patients.

Patient education and interventions should be individualized to specific patients and delivered to them face-to-face by a nurse or a clinician who can personalize the message and emphasize the importance of recognizing MI symptoms and seeking immediately medical care. This message should also include specific warnings about the coping responses that tend to be associated with delays and how to recognize and deal with these responses.

I hope that thesis may serve as an inspiration for health care systems to develop more effective ways to help both men and women to achieve better outcomes in the event of an MI by raising public awareness of the different types of MI symptoms and the importance of immediate medical attention.

Implications for further research

Delay in seeking medical care for an MI is still a problem and is more prominent among older patients. Further qualitative studies including close relatives of patients with CHD (e.g. in-depth interviews or focus groups) are needed to better understand the relations between age and gender both in symptoms of MI and in the patient decision-making process. Interventions studies should test the effect of further information on the multi-faceted presentation of MI and the dangers of lingering at home instead of seeking prompt medical care.

More studies among patients with MI in Europe and Scandinavia are needed, because our health care systems and social systems differ from those in United States, from where much research is reported. Differing aspects of social and health care systems may influence results, thus it is important to conduct more local research.

Conclusions

Typical symptoms of myocardial infarction were most common in both men and women. Typical symptoms were more common in younger versus older patients. Older patients, especially women, had longer prehospital delay **(I)**.

In older men the the prehospital phase was a complex experience that was obviously influenced by their conceptions and expectations about myocardial infarction symptoms. The symptoms developed dynamically from diffuse ill-being to persistent and alarming chest pain. The decision to seek medical care evolved at the same time from uncertainty to conviction, while the men tried to understand, reduce, or treat the symptoms by themselves **(II)**.

In older women the prehospital phase was a complex experience that, as in men, was clearly influenced by their conceptions and expectations about myocardial infarction symptoms. The symptoms evolved from indistinct physical sensations to a persistent and overwhelming chest pain. The women struggled against the symptoms by downplaying and neglecting their seriousness and struggling to remain in control. Social responsibilities took priority over concerns about their own health **(III)**.

Age-adjusted long-term survival after a first myocardial infarction has improved markedly and equally in both men and women over a 23-year period. Women showed a slightly higher survival rate than men, due to the lower risk for women to die before reaching hospital. **(IV)**.

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It is with both joy and sadness that I realize that my time as a doctoral student is soon coming to an end. This period has meant more to me than I can described in mere words. Beyond all the words and the pages are my memories, my perceptions, and my experiences that have no place in the dissertation, but that I will cherish in my heart. I am about to leave my postgraduate education behind me to embark upon a new phase.

I try to linger a while longer as a doctoral student, reluctant to leave such an exciting and enlightening episode in my life. Writing a thesis is a creative process that I truly enjoyed, but it has also been extremely hard work; at times I both doubted and despaired. The process is long—writing, proofreading, rewriting, having others proofread the text, rewriting—with the ultimate goal of approval and publication. In addition to the thesis was the host of courses that had to be completed to deepen my knowledge. But we can handle far more than we would ever believe possible.

Taken together, this has become a personal journey for me, which enabled me to grow and develop. My perspective has broadened and I now see phenomena from a new point of view. I am extremely grateful for all I experienced. Moving forward, I hope this thesis will make a difference not only to me, but also, by providing knowledge about men and women with myocardial infarction, to those who will read and share the results of my research.

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Appendix 1

Dissertations from Department of Nursing