Determinants and risk factors for early risk stratification and optimal secondary prevention in ischemic heart disease

Maria Sakalaki

Department of Molecular and Clinical Medicine
Institute of Medicine
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG
2024

Determinants and risk factors for early risk stratification and optimal secondary prevention in ischemic heart disease

ISBN 978-91-8069-791-0 (PRINT)
ISBN 978-91-8069-792-7 (PDF)

© 2024 Maria Sakalaki
maria.sakalaki@vgregion.se

Cover illustration: “Med hjärtat i centrum” by Christina Sakalaki

Printed by Stema Specialtryck AB, Borås, Sweden

Στην αγαπημένη και ζεστή μου
Οικογένεια Σακαλάκη Ενγκλοὺντ

To my big, warm family
Sakalaki Englund

ABSTRACT

Background: Ischemic heart disease is the leading cause of death globally. To combat ischemic heart disease and its challenges we must improve secondary prevention for those already affected and prevent its onset in a general population.

Aim: To study risk factors for the incidence of ischemic heart disease and identify determinants of suboptimal secondary prevention.

Methods: In Paper I, a prospective cohort of patients with a first myocardial infarction underwent a structured interview and examinations two years after their myocardial infarction. Papers II and III analyzed data from two cohorts of men from the general Swedish population, the "Study of Men Born In 1913" and the "Study of Men Born In 1943", who had been followed longitudinally from 50 to 70 years of age. In Paper IV, patients with a first myocardial infarction in the Swedish National Inpatient Register were linked to the Prescribed Drug Register to examine the relationship between secondary preventive, pharmacological treatment, and mortality and/or recurrent myocardial infarction.

Results: Secondary prevention two years after a myocardial infarction was suboptimal and multifactorial. The use of pharmacological treatment as secondary prevention decreased in the first years after an acute myocardial infarction and remained low during the follow-up of up to 16 years. The incidence of myocardial infarction has decreased over time among men in Sweden, and in parallel, the risk profile has changed. The addition of the biomarker hs-TNT to risk factors, was able to enhance prediction of ischemic heart disease at an earlier stage in the general population.

Conclusions: Secondary prevention including pharmacological treatment is vital to improve the prognosis in patients with ischemic heart disease, but it remains suboptimal. Despite the reduced incidence of myocardial infarction, it is still challenging to modify risk factors before the onset of an ischemic event. For a better risk stratification, early prediction and detection of ischemic heart disease is crucial.

Keywords: ischemic heart disease, myocardial infarction, secondary prevention, prediction

ISBN 978-91-8069-791-0 (PRINT)
ISBN 978-91-8069-792-7 (PDF)

LIST OF PAPERS

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

I Maria Sakalaki, Salim Barywani, Annika Rosengren, Lena Björck, Michael Fu. Determinants of suboptimal long-term secondary prevention of acute myocardial infarction: the structural interview method and physical examinations.
BMC Cardiovasc Disord. 2019 Nov 6;19(1):243. doi: 10.1186/s12872-019-1238-5

II Maria Sakalaki, Per-Olof Hansson, Annika Rosengren, Erik Thunström, Aldina Pivodic, Michael Fu. Multi-modality biomarkers in the early prediction of ischaemic heart disease in middle-aged men during a 21-year follow-up.
BMC Cardiovasc Disord. 2021 Feb 2;21(1):65. doi: 10.1186/s12872-021-01886-x

III Maria Sakalaki, Aldina Pivodic, Kurt Svärdsudd, Per-Olof Hansson, Michael Fu. Cumulative incidence and risk factors of myocardial infarction during 20 years of follow-up: comparing two cohorts of middle-aged men born 30 years apart.
Clin Res Cardiol. 2023 Sep 27. doi: 10.1007/s00392-023-02308-y

IV Maria Sakalaki, Michael Fu, Aldina Pivodic, Annika Rosengren, Lena Björck. Secondary prevention pharmacological treatment after a first myocardial infarction in Sweden - long-term adherence and association with prognosis.
Manuscript

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Hjärtinfarkt är den vanligaste orsaken till död och sjukdom globalt. För att minska förekomsten av hjärtinfarkt måste vi förebygga nyinsjuknande i sjukdomen och parallellt förbättra sekundärpreventionen för de som redan har drabbats.

Metod

Delarbete I: Är en prospektiv kohortstudie, där patienter med en första hjärtinfarkt identifierades och genomgick en strukturerad intervju, klinisk undersökning och blodprovstagning 2 år efter hjärtinfarkten.

Delarbete II–III: Studien 1913 års män och 1943 års män är två longitudinella kohortstudier som studerar kardiovaskulära riskfaktorer och sjukdomar. Deltagarna följdes prospektivt från 50 till 70 års ålder.

Delarbete IV: Patienter med första hjärtinfarkt identifierades i det Svenska Patientregistret som kopplades till Läkemedelsregistret. Sambandet mellan sekundärpreventiv, farmakologisk behandling och mortalitet och/eller återinsjuknande i akut hjärtinfarkt studerades.

Resultat

Delarbete I: Vi fann att sekundärprevention två år efter en hjärtinfarkt är suboptimal och multifaktoriell.

Delarbete II: Tillägg av biomarkören troponin T till kliniska riskfaktorer var en oberoende signifikant prediktor för ischemisk hjärtsjukdom upptill 20 år senare.

Delarbete III: Insjuknade i hjärtinfarkt har kontinuerligt minskat över tid och riskprofilen har förändrats hos män i den allmänna befolkningen. Riskfaktorer som högt blodtryck, stillasittande livsstil och diabetes mellitus bidrar mer till risken att få en hjärtinfarkt under senare år.

Delarbete IV: Sekundärpreventiv, farmakologisk behandling är associerad med minskad dödlighet och återkommande hjärtinfarkt och är suboptimal.

Slutsatser

Sekundärprevention inklusive farmakologisk behandling är avgörande för att förbättra prognosen hos patienter med hjärtinfarkt, men är fortfarande under önskvärd nivå. Trots den minskade incidensen av hjärtinfarkt är det fortfarande svårt att ändra på riskfaktorer innan att en ischemisk, kardiell händelse uppstår. För en bättre riskstratifiering är tidig förutsägelse och upptäckt av ischemisk hjärtsjukdom avgörande.

CONTENTS

ABSTRACT 5

LIST OF ORIGINAL PAPERS 6

SAMMANFATTNING PÅ SVENSKA 7

ABBREVIATIONS 10

INTRODUCTION 13
- Historical remarks 13
- Pathophysiology 13
  - Atherosclerosis 13
  - Myocardial infarction 14
- Epidemiology 15
- Diagnosis myocardial infarction 15
- Treatment myocardial infarction 15
- Prevention of ischemic heart disease 16
  - Risk factors 16
- Prediction of ischemic heart diseas 19
- Complications and prognosis 19
  - Heart failure 19
  - Mechanical complications 20
  - Recurrent myocardial infarction 20

AIMS 23

PATIENTS AND METHODS 25
- Study population 25
  - Paper I 25
  - Paper II and III 26
  - Paper IV 26
- Measurement variables 27
  - Paper I 27
  - Paper II 27
  - Paper III 28
  - Paper IV 28
- Statistical analyses 29
  - Paper I 29
  - Paper II 29
  - Paper III 30
  - Paper IV 30
- Ethical approvals 30

RESULTS 33
Suboptimal secondary prevention after myocardial infarction 33
Determinants of suboptimal secondary prevention 33
Incidence of myocardial infarction and risk factor profile 35
Prediction of ischemic heart disease 36
Secondary prevention and effects on mortality and recurrent myocardial infarction 37

DISCUSSION 41
Summary of the main findings 41
Paper I 41
Paper II 41
Paper III 41
Paper IV 42
The findings in context 42
Secondary prevention of myocardial infarction 42
Risk factor profile for myocardial infarction 43
Methodological issues 44

CONCLUSIONS 47

FUTURE PERSPECTIVES 49

ACKNOWLEDGEMENTS 50

REFERENCES 53

APPENDIX: PAPER I-IV

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blocker
ATC	Anatomic Therapeutic Chemical
AUC	Area under the curve
ECG	Electrocardiography
HDL	High-density lipoprotein
HbA1c	Glycated hemoglobin
hs-CRP	High-sensitivity C-reactive protein
hs-TNT	High-sensitivity troponin T
IHD	Ischemic heart disease
IL-6	Interleukin-6
IPR	Inpatient Register
LDL	Low-density lipoprotein
LISA	Longitudinell Integrationsdatabas för Sjukförsäkrings- och Arbetsmarknadsstudier (the Swedish Longitudinal Integration Database for Health Insurance and Labor Market Studies)
NT-proBNP	N-terminal pro b-type natriuretic peptide
PAR	Population attributable risk
PCI	Percutaneous coronary intervention
ROC	Receiver operating characteristic
SPDR	Swedish Prescribed Drug Register

Introduction

INTRODUCTION

Historical remarks

Atherosclerosis, defined as thickening and stiffness of the arteries due to an accumulation of plaque, is a disease that may have existed 4000 years ago. In computed tomography scans of 137 mummies from different parts of the world, 34% of them showed signs of atherosclerosis in the form of calcifications (1). This suggests that the perception of atherosclerosis as a disease of recent centuries might be only partly true.

During recent decades many new discoveries have revolutionized the treatment and diagnosis of ischemic heart disease and myocardial infarction. Biomarkers of myocardial infarction have been an important breakthrough in improving the accuracy of and time to diagnosis. The creatine kinase-myocardial band test was introduced in the 1970s and was subsequently used to identify myocardial ischemia within a few hours after the debut of symptoms and thus introduce treatment faster (2). The cardiac troponin T assay was first developed by Hugo Katus at University of Heidelberg, Germany (2). Troponin proteins are a link between myosin and actin in the heart and skeletal muscle and participate in muscle contraction. The high-sensitivity troponin biomarkers were shown to be superior in the detection of myocardial necrosis and are now the biomarkers recommended by the European Society of Cardiology and the American Society of Cardiology in the diagnosis of suspected myocardial infarction (2). High-sensitivity troponins were introduced into Swedish medical care in 2009.

In year 1977 Dr Andreas Grüntzig performed the first coronary angioplasty which would be the start of a revolutionary development in interventional cardiology, resulting in today's percutaneous coronary intervention (PCI) and treating an artery occlusion with a balloon-expandable metal net (3). This intervention has been developed since then and is together with antithrombotic medicine the modern treatment for myocardial infarction today.

Although both diagnostic methods and treatment of ischemic heart disease have developed dramatically in recent decades, physicians still need to focus much more on preventing the disease and seeking methods to predict who will develop it in many years beyond. Continuous research is of utmost importance to update clinicians on the optimal prevention of ischemic heart disease and to refine the identification of the associated risk factors in good advance.

Pathophysiology

Atherosclerosis

The artery wall consists of three layers, the inner layer called *tunica intima* is build up by a layer of endothelial cells covering the luminal side of the vessel together with elastic fibers and collagen. The second layer, *tunica media*, consist of smooth muscle cells, but also collagen and elastic fibers and finally the third layer *tunica*

externa is an external wall of connective tissue (4). The development of coronary heart disease starts with the process of atherosclerosis. Atherosclerosis is a progressive condition that leads to a slow narrowing of a blood vessel lumen due to the accumulation of fats and other substances in and around the artery wall.

One of the early events of atherosclerosis is damage of the endothelial cell barrier, starting a gradual accumulation of other blood cells and lipids forming what is known as the fatty streak. The fatty streaks grow bigger with time due to lipid deposits and proliferation of smooth muscle and fibrotic tissue in the artery wall, partly mediated by inflammation. Later in the process, calcium salt and lipids in the plaque form hard calcifications making arteries rigid and non-resilient. The growth of the plaque eventually affects the lumen of the arteries, reducing blood flow and the capacity for oxygen delivery. Acute restriction of blood flow can occur if the atherosclerotic plaque ruptures, exposing its lipid core, activating platelets, and creating a thrombus in the coronary artery (5)(Figure 1).

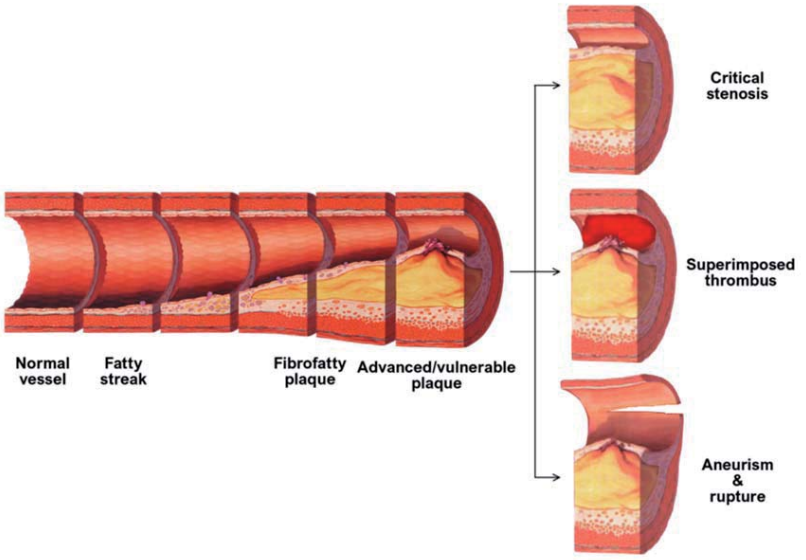

Figure 1. Progression of atherosclerosis. Licensed under Creative Commons CC BY 4.0. https://commons.wikimedia.org/wiki/File:Late_complications_of_atherosclerosis.PNG.

Myocardial infarction

Myocardial infarction is usually the result of a thrombotic occlusion of a coronary artery, depriving the heart muscle of oxygen which is necessary for the heart muscle cell to remain alive. Initially, the infarcted area becomes filled with blood from local blood vessels, which eventually start to leak fluid and instead create an edematous heart muscle; heart muscle cells with no cellular metabolism will swell and die within a few hours (6). Myocardial infarction can also be caused by other factors than acute thrombosis in a coronary artery, if the oxygen demand of the myocardial muscle is not met.

Epidemiology

Cardiovascular disease is the leading cause of death, responsible for approximately 17.8 million deaths per year globally (7). Ischemic heart disease causes most deaths in this group and accounts for about 16% of all deaths worldwide (8); these numbers are expected to increase due to an ageing and growing population. In 2019, the incidence of ischemic heart disease was lower among women than men in European countries. The median age-standardized incidence was twice as high in middle-income countries than in high-income countries. Simultaneously, in 2018, high-income countries spent approximately four times more on health care compared to middle-income countries (7).

As in many other high-income countries, cardiovascular disease mortality has decreased in Sweden, (9), mostly because of lifestyle modifications related to major risk factors such as cholesterol and smoking (10, 11).

Diagnosis myocardial infarction

The initial step in the diagnosis of myocardial infarction is to assess the clinical presentation, often chest pain, described as pressure and heaviness, which can be spread to the arms, neck and back. A physical examination is supplemented by diagnostic tools such as electrocardiography (ECG), biomarkers, such as cardiac troponins, and echocardiography (12).

According to the fourth universal definition of myocardial infarction, it is present when there is a rise and/or fall of cardiac troponin values and one of the following is found: symptoms related to myocardial ischemia, new ischemic ECG changes, imaging evidence of damaged heart muscle, and identification of a thrombus in the coronary artery (13).

Treatment myocardial infarction

Antithrombotic therapy is one of the cornerstones in treatment of myocardial infarction. Aspirin and P2Y12-receptor inhibitors are recommended as first treatment. The time of initiation, choice of medicine, and duration are individualized to minimize ischemic events and bleeding risk as well as co-morbidities.

Reperfusion therapy of coronary occlusion is determined according to disease complexity and other co-morbidities, and there is a choice between PCI and coronary artery bypass graft surgery. Other considerations are the overall risk of a heart surgery, the mechanical complications of the myocardial infarction, and the feasibility of PCI (12).

The long term treatment of a myocardial infarction includes several components, such as: 1) promoting a healthy lifestyle, 2) maintaining optimal medical treatment including anti-thrombotic agents and lipid-lowering medications, and 3) reaching and upholding targets for specific risk factors, such as blood pressure, cholesterol, and blood glucose levels (12).

Prevention of ischemic heart disease

Ischemic heart disease is a constellation of disorders in which myocardial ischemia is the underlying mechanism from the obstruction of coronary artery blood flow by coronary atherosclerosis.

Primary and secondary prevention describe actions taken to prevent ischemic heart disease from developing or reoccurring, respectively. This is mainly achieved by treating and eliminating risk factors for atherosclerosis.

Risk factors

Smoking and Smokeless tobacco

The connection between smoking cessation and decreased cardiovascular disease mortality is well established (14) and smoking cessation should be advocated in all patients with ischemic heart disease. About 20% continue to smoke after a myocardial infarction or reperfusion therapy (PCI or coronary artery bypass graft surgery) and most of the persistent smokers do not attempt to quit after their hospital stay (15). Quitting smoking remains a challenge and repeated counseling, nicotine replacement therapy, and medication to facilitate cessation should be encouraged (Figure 2).

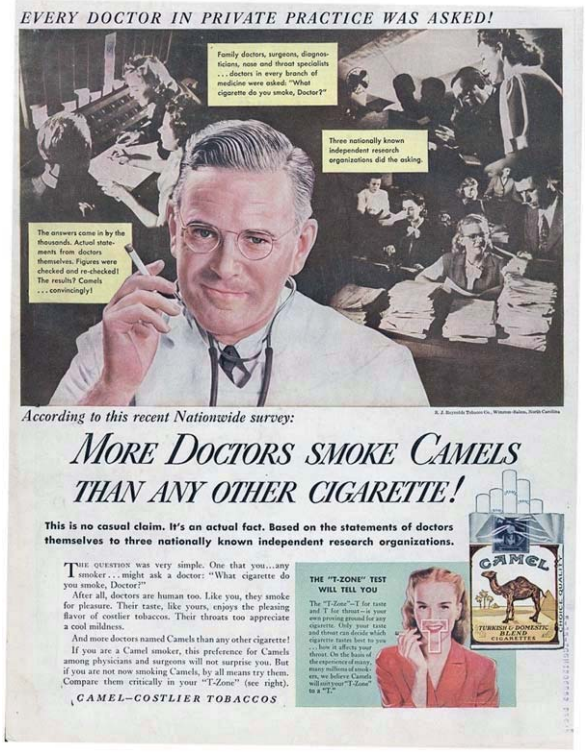

Figure 2. Cigarette advertisement, published in 1946. Image source: From the collection of Stanford University (tobacco.stanford.edu). March 2024.

The use of e-cigarettes is increasing, especially among adolescents and young adults. Long-term cohort studies on the cardiovascular outcomes of e-cigarettes are currently lacking; however, the current understanding of e-cigarettes and nicotine suggests that e-cigarettes should not be considered safe regarding cardiovascular effects (16).

Swedish snus is a moist, smokeless tobacco placed between the lips and the gums, used mainly in northern countries in Europe. Snus has been shown to be associated with an increased risk of cardiovascular mortality (17, 18). Although these data have not been consistent, it is known that nicotine can have multiple effects on the arterial wall, such as endothelial dysfunction, predisposing for cardiovascular disease (19, 20).

Cholesterol

Several clinical and genetic studied have found a causal relationship between low-density lipoprotein (LDL) cholesterol and the development of atherosclerotic cardiovascular disease (21). A reduction in LDL levels decreases the risk of cardiovascular events, even in populations with lower risk of major vascular events (22), and the European guidelines encourage continuous risk assessment and treatment in specific risk groups (23).

The treatment goal of LDL-lowering drugs is determined by two factors: LDL levels and total cardiovascular risk in each individual, which is based on several risk assessment tools, for example, the Systemic Coronary Risk Evaluation (SCORE). Based on the SCORE result and/or presence of other risk conditions (such as diabetes or chronic kidney disease), four risk categories (low, moderate, high, and very high risk) are defined. A very high-risk patient, such as after a myocardial infarction, should strive for a goal of LDL cholesterol below 1.4 mmol/L (23).

Hypertension

The definition of hypertension is blood pressure consistently at or above 140/90 mmHg taken in the clinic (23). However, this definition is changing, and some health care professionals define hypertension as blood pressure consistently at or above 130/80 mm Hg (24).

The number of people with hypertension has doubled from 1990 to 2019, despite a stable prevalence globally (25). The Prospective Urban Rural Epidemiology (PURE) study investigated the awareness, the treatment, and the control of hypertension in high- to low-income countries worldwide. The overall awareness of the diagnosis was less than 50% and treatment suboptimal, although the benefits of lowering high blood pressure were well known (26). Current guidelines recommend a lower blood pressure target (<130/80 mm Hg) for adults at high risk of cardiovascular events (23).

It is important to stress that the treatment of hypertension involves lifestyle changes in addition to drug treatment, which also adds far more health benefits.

Diabetes mellitus and overweight

The prevalence of diabetes mellitus at hospitalization for myocardial infarction has been stable in Sweden in recent years and was 23% in 2023 (27). Similarly, the percentage of people with overweight and obesity has been stable, with some decrease among men and an increase among women. However, a worrying long-term trend of increasing diabetes mellitus and obesity has been seen and may generate a new challenge for future prevention of coronary artery disease (28).

Lifestyle interventions to reach or maintain a low body weight and prevent the development of diabetes mellitus are cornerstones in the prevention of cardiovascular disease. In the most recent guidelines, the target level for long-term blood sugar (glycated hemoglobin, HbA1c) is <53 mmol/mol, to decrease the risk of cardiovascular disease and other organ damage among patients with established diabetes mellitus (23) (Figure 3).

Figure 3. An AI generated picture of the “Healthy diet”, generated by www.bing.com, Copilot. Question: “Create a image of a healthy diet according to the Swedish Food Agency”. August 2024.

Physical activity and diet

Almost all parts of the prevention of cardiovascular disease include radical changes in lifestyle. Therefore, it is strongly recommended to offer continuous counseling with realistic goals and exercise-based cardiac rehabilitation. Nowadays, all patients with a myocardial infarction are invited to participate in this kind of rehabilitation and educational program in Gothenburg.

Physical activity should include moderate-intensity exercise daily or vigorous exercise weekly, and efforts should be made to decrease sedentary time during the day (23). A nationwide Swedish study showed that participation in exercise-based cardiac rehabilitation decreased mortality (29), and that being physically active one year after a myocardial infarction decreased the risk of a nonfatal cardiovascu-

lar event, irrespective of increasing or decreasing activity, compared to not being physically active at all (30).

A healthy diet is also one of the most important lifestyle changes in the prevention of cardiovascular disease, for example by increasing plant-based products and decreasing animal-based ones.

Prediction of ischemic heart disease

Today, there are no validated tools for early prediction in the general population for ischemic heart disease; it develops over a long time, usually decades, and often with previous subclinical atherosclerosis (31). Such a tool would be invaluable for initiating preventive measures at an early stage.

Previous tools in risk stratification have been mainly focused on clinical risk factors. The *Framingham Risk Score* is a well-established algorithm estimating 10-year risk of cardiovascular death or nonfatal myocardial infarction, ranging from low risk (<6%), intermediate risk (6–20%), and high risk (>20%) based on data from the Framingham Heart study conducted in the United States (32). This risk scale is based on a 12-year follow-up and includes risk factors such as age, total cholesterol, high density lipoprotein (HDL), systolic blood pressure, smoking, and diabetes mellitus. However, physical activity, body mass index (BMI), and biomarkers are not included. Similarly, the SCORE scale is based on well-established risk factors and predicts the 10-year risk of death from cardiovascular disease (33). The SCORE 2 is an updated model that estimates total cardiovascular events for low-, moderate-, high-, and very-high-risk regions of Europe (23).

However, when calculating future risk of cardiovascular death or non-fatal ischemic events today, it is desirable to also account for the changes in risk factors that have occurred in modern times, such as reduced smoking, lower cholesterol, lifestyle changes and more prevalent overweight and obesity (34). In fact, we have witnessed cardiovascular risk factors continuously changing in recent decades (28, 35). Several biomarkers, including troponin, natriuretic peptides, and inflammatory biomarkers have been shown to have a high prognostic value for ischemic heart disease (36, 37). However, it is unclear whether these biomarkers can predict at an early stage the risk of developing the disease and in particular decades beyond. Biomarkers together with clinical risk factors can be a valuable approach in this direction to increase the possibility and precision of early identification of people at risk of ischemic heart disease.

Complications and prognosis

Heart failure

Myocardial infarction remains the most frequent cause of heart failure, and heart failure can occur at the onset of a myocardial infarction event, during hospitalization or after discharge. From 1996 to 2008, Sweden witnessed a decrease in the

in-hospital (19% to 13%), 30-day (23% to 17%), and one-year mortality (36% to 31%) for patients with acute myocardial infarction and clinical heart failure symptoms, possibly due to improved pre-hospital care and the widespread use of reperfusion therapies and secondary prevention. This is evidenced by the parallel decrease in the incidence of in-hospital heart failure caused by myocardial infarction, from 46% in the thrombolytic era to 28% later in the PCI era. Still, the long-term adjusted mortality in patients with heart failure was double that of those without heart failure (38).

The incidence of heart failure is highest during the months after an acute myocardial infarction hospitalization and continues at a frequency of 1.3–2.2% per year afterwards. Clinical risk factors for developing heart failure after an acute myocardial infarction are, among others, higher age, diabetes mellitus, hypertension, female sex, new-onset atrial fibrillation, and previous myocardial infarction (39).

Mechanical complications

Mechanical complications after an acute myocardial infarction include ventricular septal defect, acute mitral regurgitation secondary to papillary muscle rupture, and wall rupture. Fast intervention and reperfusion with PCI have made it possible to reduce the ischemia duration and improve outcome. The prevalence of ventricular septal defect is estimated to be 0.17–0.21%, papillary muscle rupture 0.05–0.26%, and freed wall rupture 0.01–0.52%, and mortality remains high (40). Early diagnosis, clinical stabilization, and a multidisciplinary team for decisions about possible therapeutic treatment are essential in the care of these patients (41).

Recurrent myocardial infarction

Patients who have survived from an index myocardial infarction are at high risk of recurrent events or death, and the incidence of myocardial infarction recurrence increases with time after the first event (42). Recurrent myocardial infarction constitutes almost a third of the annual myocardial infarction cases (43). Although all-cause mortality has decreased in recent years, myocardial infarction patients have an increased relative risk for all-cause mortality compared with persons with no myocardial infarction (44), in particular for patients with risk factors such as older age, smoking, diabetes mellitus, and hypertension (45).

Aims

AIMS

The overall aim of this thesis is to study predictors and risk factors that can identify early the future risk of ischemic heart disease in the general population and the determinants of suboptimal secondary prevention in a cohort of patients who have suffered from a myocardial infarction.

The specific aims of the separate papers were:

Paper I To assess determinants of suboptimal secondary prevention two years after an acute myocardial infarction.

Paper II To investigate the predictive value of biomarkers to identify the future risk of ischemic heart disease in middle-aged men.

Paper III To describe the incidence and risk factor profile for myocardial infarction among middle-aged men born 30 years apart and followed for 20 years.

Paper IV To study adherence to evidence-based drug treatment as part of secondary prevention after myocardial infarction and the association between adherence and the prognosis.

Patients and Methods

PATIENTS AND METHODS

Study population

Paper I

Paper I was based on the prospective secondary prevention of acute myocardial infarction (SEPAT) study. The cohort consisted of patients aged between 18–85 years who had been hospitalized with acute myocardial infarction in the period July 2010 to December 2011. All patients who were still alive two years after the myocardial infarction event and lived in the Gothenburg catchment area were identified retrospectively and invited to participate. In total, 200 patients were included and underwent a structured interview, physical examinations, and laboratory analysis (Figure 4). The interview included questions about smoking habits, marital status, education, medication, and physical activity.

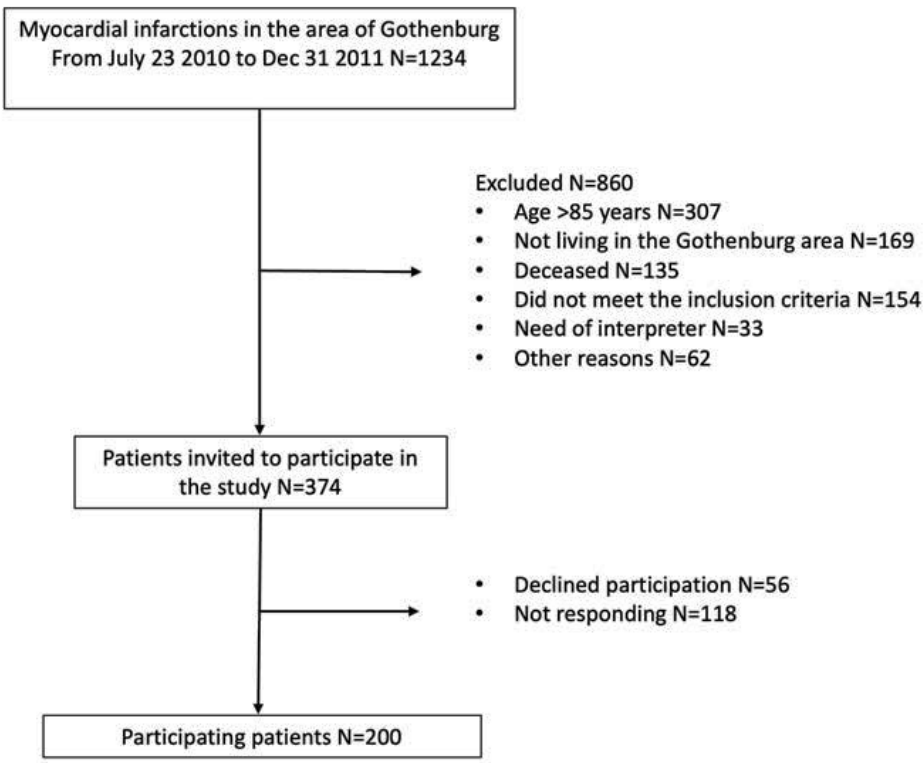

Figure 4. Study flow chart (46). With permission.

Paper II and III

Papers II and III were based on two longitudinal cohorts, the "*Study of Men Born In 1913"* and the *"Study of Men Born In 1943"*, which have previously showed dramatically decreased all-cause and coronary artery disease death during 20 years of follow-up (Figure 5).

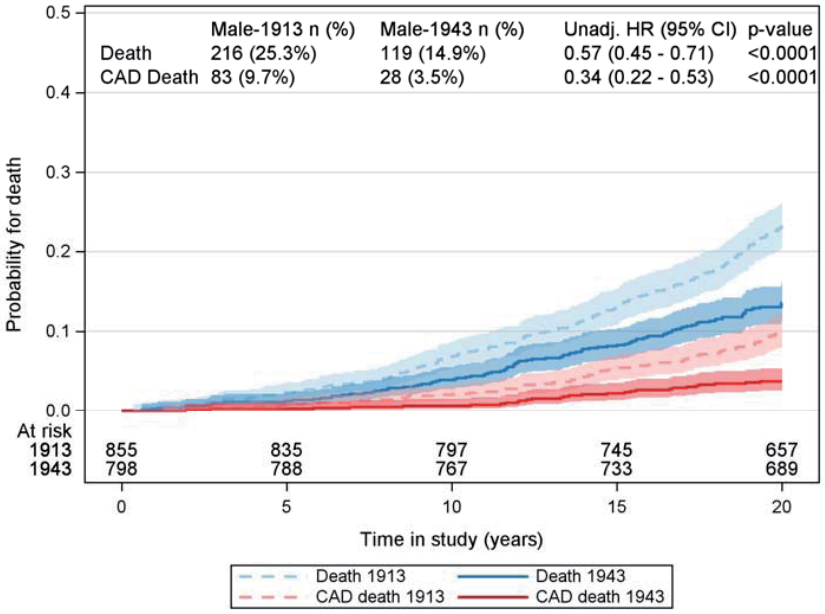

Figure 5. All-cause mortality and coronary artery disease death over a 21-year period in 50-year-old men from cohort 1913 and cohort 1943. (47) With permission.

The first cohort was taken from the Swedish population register consisting of all men born in 1913 on a day divisible by 3 (e.g. the third and the ninth of each month). The second cohort was a random sample of fifty percent of all men who were born in 1943. All participants fulfilled the criterion of living in the city of Gothenburg or catchment area.

Both cohorts were randomly collected from the general population and followed prospectively from 50 years of age for 21 years. All examinations followed the same study protocol for both cohorts.

Paper IV

Paper IV was based on data extracted from the Swedish National Inpatient Register (IPR), consisting of patients aged 18–84 years and hospitalized with a first recorded myocardial infarction between January 2006 and December 2022. The patient's social security number was used to link data from every individual with

the Swedish Prescribed Drug Register, the National Cause of Death Register, and the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) register.

Registers

The IPR is part of the Swedish National Patient Register that was launched by the National Board of Health and Welfare in 1987. The IPR holds information from hospital discharges in Sweden and contains diagnoses and medical procedures performed during the hospital stay. The IPR was used to identify individuals with myocardial infarction and other co-morbidities. The general positive predictive value of diagnoses in the IPR is estimated to be 85–95%, but is higher for the diagnosis myocardial infarction with a positive predictive value of 98–100% (48).

The LISA register holds data on social variables such as marital status, country of birth, income, and education for individuals above the age of 16 years registered in Sweden. This register has been updated yearly since 1990 (49).

The National Cause of Death Register holds data on deaths in the Swedish population since 1961 (50).

The Swedish Prescribed Drug Register contains information on dispensed medication This register was established in July 2005 and includes the social security number of every individual, allowing data on dispensed drugs to be linked with information from other registers (51). Drugs in the register are categorized according to the Anatomic Therapeutic Chemical (ATC) classification.

Measurement variables

Paper I

The secondary prevention goals that were included were: blood pressure <140/90 mmHg, LDL <1.8 mmol/L, HbA1c <48mmol/mol, regular physical activity that causes sweating at least twice a week, BMI <25 kg/m^2 and non-smoking, including those that had never smoked and quit smoking.

The structural interview was led by a research nurse at a minimum of two years after the acute myocardial infarction event. The physical examination included body height, body weight, waist circumference, ECG, blood pressure, and laboratory analyses included, among others, hemoglobin, total triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, glycated hemoglobin (HbA1c), and blood glucose.

Paper II

Ischemic heart disease was defined as a new fatal or non-fatal myocardial infarction event, hospitalized unstable angina, or intervention with either PCI or coronary artery bypass graft surgery from the first examination in 1993 to August 30,

2014. To confirm the diagnoses, medical records were also collected and studied retrospectively. Each participant's data file was also matched against the Swedish National Patient Register and the National Cause of Death Register.

Fasting venous blood samples were taken before each clinical examination. A panel of biomarkers was analyzed from blood samples drawn at the visit in 1993 and kept frozen (- 70 °C) until analysis in year 2014. Biomarkers included high-sensitivity troponin T (hs-TNT), interleukin- 6 (IL-6), high-sensitivity C-reactive protein (hs-CRP) and N-terminal pro b-type natriuretic peptide (NT-proBNP). The definition of the multimodality biomarkers included hs-CRP >1 mg/L, NT-proBNP >100 pg/mL, hs-TNT >10 ng/L and IL-6 >8 ng/L and the number of biomarkers ranged between 0 and 4.

Paper III

Myocardial infarction was defined as first fatal or non-fatal myocardial infarction that required admission to hospital. The information on myocardial infarction was taken at each re-examination and from medical records that were studied to identify and verify diagnoses for both cohorts. Data from the Swedish Hospital Discharge Register complemented the myocardial infarction discharge diagnosis for the 1943 cohort and data from the National Cause of Death Register for both cohorts. Diagnoses were found by the International Classification of Diseases codes I21 (ICD 10) and 410 (ICD 8 and 9).

The 1913 cohort was followed from January 1,1964, until the study endpoint, date of death, or censoring on January 1, 1984. The 1943 cohort was followed from January 1, 1994, until the study endpoint, date of death, date of visit in 2014, or January 1, 2014.

Paper IV

The study subjects were identified through the IPR by referring to the following ICD codes for myocardial infarction: 410 (ICD-9) and I21 (ICD-10). Drugs in the register are categorized according to the ATC classification. Four classes of drugs were analyzed in this study (Table 1).

Marital status was divided into five categories: married/cohabiting, unmarried, divorced, widowed, and unknown. Income was the annual household income and was stratified into quintiles, from Q1 (lowest) to Q5 (highest). Country of birth was divided into two groups: Nordic countries and non-Nordic countries. Educational level had three categories: less than 10 years, 10 to 12 years, and more than 12 years.

Continuation with prescribed drugs for pharmacological treatment after a myocardial infarction was defined as retrieving a prescription for the drugs studied within a period of six months.

Table 1. ATC codes for the four drug classes studied in Paper IV.

Drug class	ATC code
Lipid-lowering therapy	
Statins	C10AA
	C10BA02
	C10BA05
Ezetimibe	C10AX09
PCSK9 inhibitors	C10AX13
	C10AX14
Antiplatelet and anti-coagulant therapy	
Antiplatelet	B01AC
Warfarin	B01AA
Eliquis, Xarelto, Lixiana	B01AF
Pradaxa	B01AE07
ACE inhibitorARB	C09
Betablocker	C07, excl
	C07AA07

(ACE=angiotensin-converting enzyme,ARB=angiotensin receptor blocker, ATC=Anatomic Therapeutic Chemical, PCSK9=proprotein convertase subtilisin/kexin type 9)

Statistical analyses

The analyses in Paper I were performed using SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA), USA). In Papers II–IV the statistical analyses and graphs were created using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Paper I

Categorical variables are presented as percentages and continuous variables as the mean ± SD. Univariable and multivariable logistic regression analyses were used to study the association between achieved secondary prevention goals and baseline characteristics. The variables with a p-value <0.25 from the univariable models were subsequently analyzed in multivariable models. The odds ratios (ORs) from logistic regression analysis were presented with 95% confidence intervals (CIs).

Paper II

The impact of clinical risk factors and biomarkers on the first incidence of ischemic heart disease were studied using univariable Cox proportional hazards models. The effect size was presented as the hazard ratio (HR) with 95% CI, and the

strength of association of the variable's impact was ranked through standardized HR. The Framingham 10-year risk score was calculated in this cohort for comparison (52).

Risk factor models were created for predicting ischemic heart disease. Model A included the cohort´s calculated Framingham 10-year risk score. Model B included known clinical risk factors for ischemic heart disease that were significant in the univariable analysis. These were: total cholesterol, HDL cholesterol, hyperlipidemia, systolic blood pressure, diastolic blood pressure, hypertension, and smoking.

Further, model C included significant factors from the univariable analyses of glucose, BMI, physical activity and biomarkers. Likelihood ratio test was used to study the improvement of model C vs model B. The probability of experiencing ischemic heart disease from the age of 50 and during 21 years of follow-up was calculated using each model, and the models´ discriminative ability was described by the area under the receiver operating characteristic (ROC) curve. An area under the ROC curve (AUC) of >0.70 is considered acceptable.

Paper III

The impact of risk factors on the incidence of myocardial infarction were studied using univariable time-updated Cox's proportional hazards models and HRs were presented as effect measurement together with the 95% CI. The significance of impact of variables on myocardial infarction between the two cohorts was studied by calculating the interaction effect.

Population attributable risk (PAR) was assessed by calculating the difference between the incidence of myocardial infarction in the exposed versus non-exposed group for a specific risk factor.

Paper IV

The Mantel-Haenszel chi-square trend test was used when two groups were tested, the chi-square test was used for non-ordered categorical variables, and the Mann–Whitney U test for continuous variables.

Time-to-events analyses were performed using time-updated Cox's regression and showed by the HR and 95% CI. P-values <0.05 were considered significant.

Ethical approvals

All studies were conducted in accordance with the 1964 Declaration of Helsiniki (53) and ethical approval is available for all studies in this doctoral dissertation. The study protocols were approved by the Regional Ethical Committee, Gothenburg, *Paper I* DNR: 325-12, *Papers II and III* DNR: 886-13 and *Paper IV* DNR: 262-17.

In the initial processing, the data files contained social security numbers, which were replaced with a code number during the statistical analysis. In Paper IV, the social security number was replaced with a code number, and the code key was stored at the National Board of Health and Welfare for three months and thereafter destroyed.

Results

RESULTS

Suboptimal secondary prevention after myocardial infarction

In Paper I, only 10.5% of all participants successfully achieved all six secondary prevention goals of optimal blood pressure, HbA1c, LDL levels, BMI, regular physical activity, and not smoking. Results demonstrated that only 53% achieved a blood pressure <140/90 mmHg, 18.5% a LDL level of <1.8 mmol, and 45.5% regular physical activity. In this cohort, 77.4% did not smoke before the index myocardial infarction event, and 87.5% did not smoke two years later.

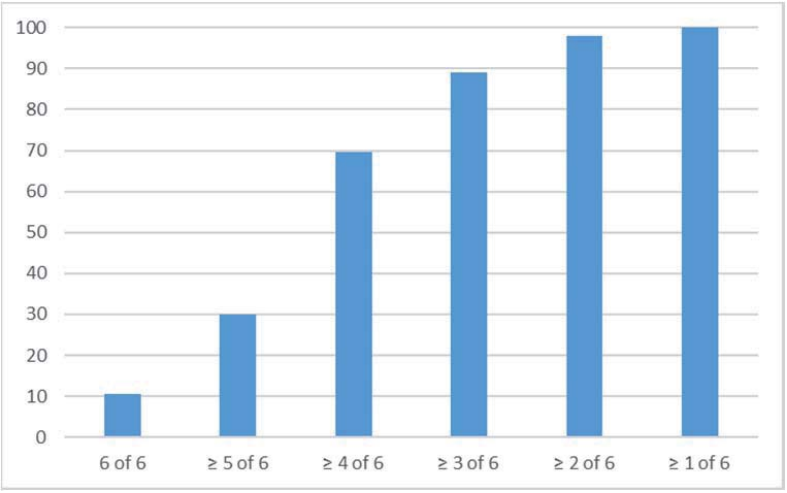

Figure 6. Percentage of achieved secondary preventive goals two years after acute myocardial infarction. Reprint from Paper I.

Pharmacological treatment for secondary prevention decreased the first years after new-onset myocardial infarction and remained on a similar level during the study follow-up of up to 16 years (Paper IV).

Determinants of suboptimal secondary prevention

In Paper I, we could not find a common determinant for the participants who failed to achieve all six secondary prevention goals. Younger (under 65 years) and unemployed individuals were more likely to be smokers, and being native was associated with not reaching a LDL <1.8 mmol/L. Furthermore, having diabetes and walking difficulties was associated with not achieving optimal BMI, while living alone was associated with being physically active regularly. Men were less likely to achieve blood pressure <140/90 mmHg, but patients with heart failure were more likely to accomplish this secondary prevention goal, Table 2.

Table 2. Independent predictors of achievement of different secondary preventive goals after acute MI

	Odds ratio (95% CI)	P-value
Non-smoking		
Sex, male	0.17 (0.02-1.34)	0.093
Age ≤ 65 years	0.24 (0.07-0.74)	0.013
Unemployed	0.23 (0.06-0.82)	0.023
LDL <1,8 mmol/L		
Overweight	0.52 (0.24-1.12)	0.096
Native (born in Sweden)	0.28 (0.12-0.63)	0.002
HbA1c < 48mmol/mol		
Sex, male	0.46 (0.18-1.18)	0.106
BMI	0.91 (0.82-1.02)	0.095
Regular physical activity		
Sex, male	1.95 (0.93-4.09)	0.078
Living alone	1.94 (1.02-3.69)	0.044
Achieved BMI <25 kg/m²		
Living alone	0.45 (0.20-1.00)	0.050
Diabetes type1/type2	0.21 (0.04-0.98)	0.046
Walking difficulties	0.23 (0.07-0.71)	0.011
Blood pressure <140/90 mmHg		
Diabetes type1/type2	1.86 (0.61-5.62)	0.271
Heart failure after admission, ≤ 45%	2.77 (1.05-7.31)	0.040
Left ventricular hypertrophy	1.40 (0.57-3.48)	0.466
Age >65 years	1.49 (0.70-3.20)	0.301
Sex, male	0.36 (0.13-0.97)	0.043

BMI=body mass index, LDL=low-density lipoprotein, HbA1c=glycated hemoglobin) Adapted from Paper I.

The results from Paper IV showed that several socio-economic factors were associated with treatment discontinuation; in particular, low income was associated with increased risk of discontinuing lipid-lowering treatment and antiplatelets/oral anticoagulants. Comorbidities, such as kidney failure, increased the risk of discontinuing ACE inhibitor/ARB treatment.

Incidence of myocardial infarction and risk factor profile

During follow-up, men born in 1943 had a 34% lower risk of myocardial infarction [HR 0.66, 95% CI (0.50–0.88), p = 0.0051] than men in the 1913 cohort (Figure 7). In total, 119 of the men born in 1913 had a myocardial infarction (14.1%, event rate 8.04 per 1000 person-years [95% CI 6.72–9.62]), compared to 77 men in the 1943 cohort (9.8%, event rate 5.4 per 1000 person-years [95% CI 4.30–6.72]).

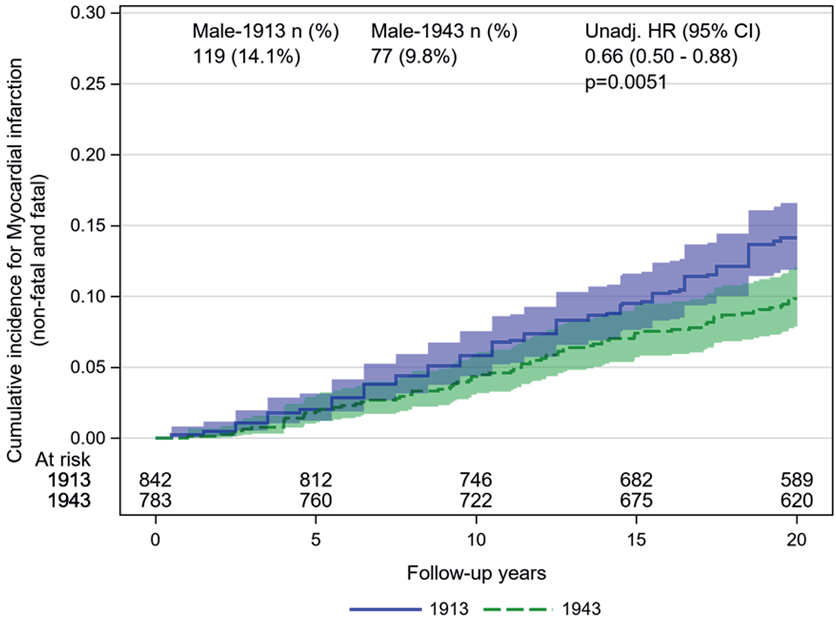

Figure 7. Cumulative incidence for myocardial infarction in men born 1913 and 1943. (HR = hazard ratio.) Reprint from Paper III.

Furthermore, the risk factors for myocardial infarction for the two cohorts of men born 30 years apart were compared. Figure 8 shows that elevated systolic blood pressure and diastolic blood pressure and being treated with blood-pressure-lowering medication were associated with increased risk of myocardial infarction in both cohorts. Hypertension was significantly associated with increased myocardial infarction risk only in the 1943 cohort.

Smoking was almost equally associated with risk of myocardial infarction in both cohorts. However, the proportional hazard assumption was not fulfilled in the 1913 cohort. A sedentary lifestyle was associated with an increased risk for myocardial infarction in the 1943 cohort. Cholesterol had a similar association with myocardial infarction in the two cohorts but was only statistically significant in

the 1913 cohort. The impact of diabetes mellitus and BMI on developing myocardial infarction was not significant in both cohorts.

Furthermore, the interaction analysis showed that hypertension had a significantly higher impact on the risk of myocardial infarction in men born 1943 compared to men born in 1913. A similar finding was observed for sedentary lifestyle but did not reach statistical significance (p = 0.053), Figure 8.

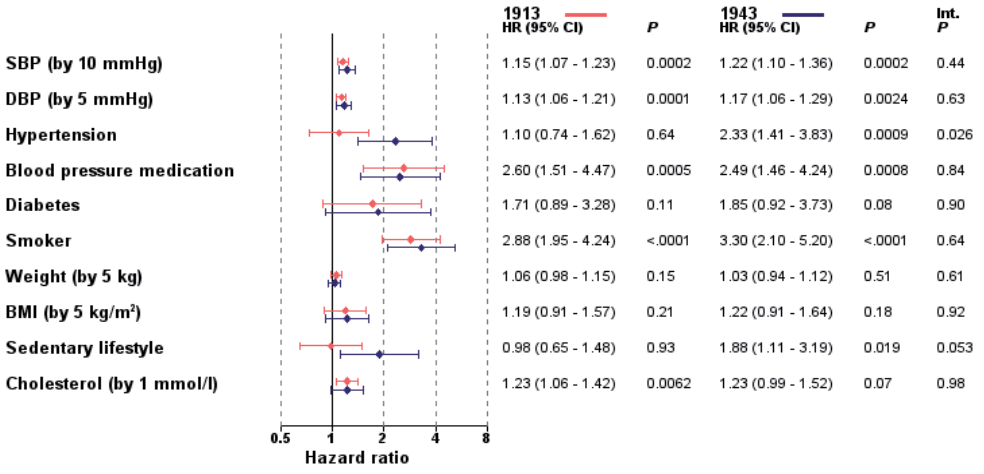

Figure 8. Univariable Cox proportional hazards models for the myocardial infarction risk and the interaction effect of risk factors among the 1913 and 1943 cohort. (SPB = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index.) Reprint from Paper III.

The analysis of the population attributable risk (PAR) in Paper III showed that hypertension contributed 2.5-fold more to the risk of myocardial infarction in the 1943 cohort compared to those born 30 years before. The risk factor diabetes mellitus contributed most to the incidence of myocardial infarction in the 1943 cohort and second most in the 1913 cohort. PAR was higher for smoking and total cholesterol in men born 1913 compared to those born in 1943, while a sedentary lifestyle contributed more to the risk of myocardial infarction in men born in 1943.

Prediction of ischemic heart disease

In Paper II, prediction models were developed to assess the risk of myocardial infarction, exploring the role of biomarkers. Model A included only the Framingham risk score. Model B included lower HDL cholesterol, higher total cholesterol and hypertension, based on a stepwise regression among recognized risk factors that increase the risk of ischemic heart disease. In Model C, hs-TNT (categorized as ≤3, 3–10, and >10 ng/L) was also added as a significant predictor.

Model C provided significantly better prediction than model B, when tested by the likelihood ratio test (p = 0.033). The discriminative ability of prediction of ischemic heart disease of the three models was measured by the AUC, which was 0.69 (95% CI 0.63–0.74) for model A, 0.71 (95% CI 0.66–0.77) for model B, and 0.72 (95% CI 0.67–0.78) for model C, as illustrated in Figure 9. There was no statistically significant difference between the three ROC curves.

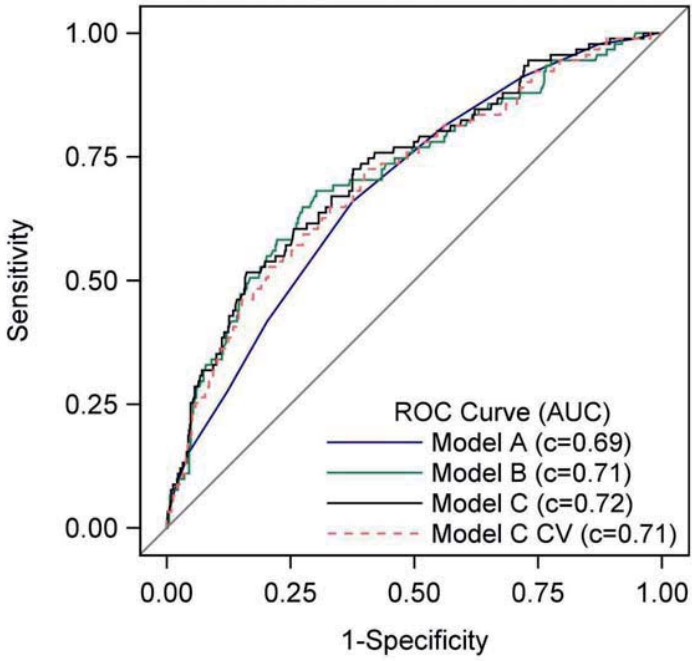

Figure 9. ROC curve showing the predictive ability for models A, B, and C for ischemic heart disease. Model A: Framingham risk score. Model B: risk factors (hypertension, cholesterol, HDL); Model C: risk factors + hs- TNT; Model C CV: cross-validation model for Model C. Reprint from Paper II. (ROC = receiver operating characteristic, AUC = area under the curve.)

Furthermore, by using univariable Cox hazard models, several factors were found to be associated with an increased risk of ischemic heart disease. Among the biomarkers, decreasing HDL and the number of biomarkers (hs-CRP >1 mg/L, NT-proBNP >100 pg/mL, hs-troponin-T >10 ng/L, IL-6 >8 ng/L) with elevated levels had the highest predictive ability for the incidence of ischemic heart disease (Paper II).

Secondary prevention and effects on mortality and recurrent myocardial infarction

In Paper IV, treatment with antiplatelets/oral anticoagulants, lipid-lowering therapy, and ACE inhibitors/ARBs was associated with decreased all-cause mortality or recurrent myocardial infarction after the initial myocardial infarction, HR

0.76 [95% CI 0.74–0.78], p <0.0001, HR 0.68 [95% CI 0.67–0.70], p <0.0001, and HR 0.81 [95% CI 0.79–0.83], p <0.0001, respectively. However, medication with betablockers had a marginally increased relative risk for all-cause mortality or recurrent myocardial infarction, HR 1.04 [95% CI 1.02–1.07], p <0.0001.

Furthermore, Paper IV studied the importance of cumulative adherence to medications for mortality and recurrent myocardial infarction risk and showed that the risk was decreased with time when treated with antiplatelets or oral anticoagulants. The results from longer adherence with lipid-lowering medication or ACE inhibitors/ARBs varied, and longer use of betablockers mainly had an increasingly, higher risk for all outcomes except recurrent myocardial infarction.

Discussion

DISCUSSION

This thesis focused on optimal prevention of ischemic heart disease by studying adherence to secondary prevention goals and pharmacological treatment after a myocardial infarction, as well as investigating determinants of suboptimal secondary prevention.

In addition, this thesis investigated possible predictors for ischemic heart disease decades beyond and changes in the risk factor profile during recent decades, in order to explore ways for the early detection of individuals at risk of this serious illness.

Summary of the main findings

Paper I

- Secondary prevention two years after an acute myocardial infarction remains suboptimal.
- The cause of suboptimal secondary prevention is probably multifactorial and no specific determinants were found for achieving all guideline-recommended preventive goals.
- When addressing specific preventive goals, several determinants were identified for each goal.

Paper II

- Several factors were found to be associated with an increased risk of ischemic heart disease. Among the biomarkers, decreasing HDL and the number of biomarkers (CRP, TNT, NT-proBNP, and IL-6) with elevated levels, had the highest predictive ability for incidence of ischemic heart disease.
- The discriminative ability of three models for the prediction of ischemic heart disease was tested. Model C, combining clinical factors (hypertension, higher total cholesterol, lower HDL cholesterol) and the biomarker hs-TNT, had the best predictive ability, with an AUC of 0.72 (95% CI 0.67–0.78).

Paper III

- There was a lower incidence of myocardial infarction among men born in 1943 compared to men born in 1913.
- The risk factors hypertension, diabetes mellitus, and a sedentary lifestyle have become increasingly more important among men born in 1943 compared to men born in 1913.
- Hypertension contributed 2.5-fold more to the risk of myocardial infarction among men born in 1943 compared to men born in 1913.

Paper IV

- The medication groups antiplatelets/oral anticoagulants, ACE inhibitors/ARBs, and lipid-lowering medication decreased the risk of all-cause mortality or recurrent myocardial infarction.
- Treatment with betablockers slightly increased the risk of all-cause mortality or recurrent myocardial infarction, and cardiovascular mortality.
- Pharmacological secondary prevention after an acute myocardial infarction decreased in the first years after hospitalization and remained low during long-term follow-up.
- Socioeconomic factors such as low income were associated with discontinuation of pharmacological treatment after a myocardial infarction.

The findings in context

Secondary prevention of myocardial infarction

The overall cardiovascular risk remains high after a myocardial infarction, which requires long-term management for an optimal secondary prevention follow-up (54). In Paper I we demonstrated that long-term secondary prevention after an acute myocardial infarction is suboptimal, with just 10.5% achieving all six predefined secondary prevention goals. Although this study was based on a small cohort, goal achievement was still very low two years after a myocardial infarction. Data collection in Paper I was conducted during 2010–2011. The latest report from the national Swedish registry SWEDEHEART shows that one year after acute myocardial infarction, the proportion of patients reaching treatment targets for systolic blood pressure, LDL cholesterol, and physical activity has improved in the last two decades.The proportion of smokers who had quit smoking one year after a myocardial infarction was approximately 50–55% and remained the same throughout the period 2007–2023 (27).

The European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) has also reported improved blood pressure and lipid treatment after an acute myocardial infarction, with a median follow-up time below two years in the period 1999-2013 (55). This thesis contributes with a longer follow-up of secondary prevention, which is especially demonstrated in Paper IV, with a follow-up of up to 16 years. The use of pharmacological treatment as secondary prevention was high shortly after hospitalization for an acute myocardial infarction but decreased during the first years and remained low during the 16-year follow-up. This sheds light on secondary prevention in the long term and emphasizes the importance of continuous and intensive support from the health care system to the patients.

The reasons for suboptimal secondary prevention are many and are often mistakenly believed to be mainly patient-related; this is explained further in a thorough

WHO report focusing on adherence to long-term therapies, stating that adherence is also related to the health system, socioeconomic factors, and medicine-related factors (56). As similarly discussed in Paper I and IV, the cause of suboptimal secondary prevention seems to be multifactorial and dependent on socioeconomic factors and comorbidities. In Paper IV, determinants such as low income and kidney failure were associated with discontinuation of some medication groups prescribed after an acute myocardial infarction. Other studies have previously shown similar associations with socioeconomic factors (57-59), underlining the importance of supporting these patient groups.

Risk factor profile for myocardial infarction

The incidence of myocardial infarction has decreased in western countries (60, 61) and similar findings were shown in Paper III. The group of men born in 1943 had a 34% lower risk of first myocardial infarction compared with men born in 1913. Nevertheless, ischemic heart disease is still the primary cause of death in the world according to WHO (62). Better risk factor control and primary prevention are of importance to decrease the number of deaths caused by ischemic heart disease.

However, with new insights and improved treatment, the profile of risk factors for myocardial infarction changes over time and needs to be updated to target those specific populations with disproportionately high burdens of morbidity and mortality due to ischemic heart disease. In this thesis, the risk factor profile was compared between two cohorts 30 years apart, and hypertension was found to have had a higher impact on the risk of myocardial infarction in the 1943 cohort than 30 years before. Meanwhile, diabetes mellitus and a sedentary lifestyle have contributed more to the risk of myocardial infarction in the modern era. In recent decades the rapidly increasing prevalence of obesity and diabetes mellitus signals that more resources are need to combat these challenges (63, 64). This thesis highlights how the different risk factors have changed over a period of 30 years and how the health system could be strengthened to improve the delivery of health care service and improve health outcomes. The optimal control of any disease is to prevent its onset. An earlier prediction of ischemic heart disease will provide tremendous opportunities for better risk stratification and closer monitoring and guidance for individuals at most risk.

The addition of biomarkers in addition to conventional risk factors for ischemic heart disease might improve prediction. Paper II demonstrates how the number of elevated biomarkers (hs-CRP >1 mg/L, NT-proBNP >100 pg/mL, hs-troponin-T >10 ng/L, IL-6 >8 ng/L) predicted the risk of ischemic heart disease in an apparently healthy population of individuals of 50 years of age, which suggests that ischemic heart disease can be predicted at an early stage. The question of using several biomarkers as predictive markers for ischemic heart disease needs to be further addressed, including aspects of cost-effectiveness, clinical implementation, and ethics.

Methodological issues

With greater resources we could have extended the population size and the catchment area in Paper I to create a more representative study group covering the general population. The study design would also be improved if the same methodology was used for data intake at baseline and at the two-year follow-up, making this information more comparable.

Ideally, the study population in Paper II would also have included female participants to widen the representation of the general population and the group with ischemic heart disease. In our study we were able to investigate the importance of biomarkers for the prediction of ischemic heart disease 20 years later. However, the atherosclerotic process develops over a long period and the study question might have been better answered with an even longer follow-up time.

Concerning Paper III, it would have been interesting to include and compare study groups of participants born in more recent years, to give a more up-to-date description of the risk factor profile for myocardial infarction. The risk factor analysis could also have been improved by including waist measurements as a complement to BMI and to give an objective approximation of physical fitness.

An extended inclusion of clinical data, such as blood samples and other comorbidities, would have been of interest to further interpret the results in Paper IV. Second, classification and description of the myocardial infarction, but also secondary consequences such as heart failure and arrythmias, might add clinical value to the findings about betablockers, which have been shown to be of importance in earlier studies.

Conclusion

CONCLUSION

This thesis shows that secondary prevention after a myocardial infarction, including adherence to clinical prevention goals and pharmacological treatment, is suboptimal and needs to be improved. Treatment with lipid-lowering medication, antiplatelets/oral anticoagulants and ACE inhibitors/ARBs after a myocardial infarction were associated with decreasing risk for all-cause mortality, recurrent myocardial infarction, and cardiovascular mortality. The cumulative incidence of myocardial infarction has decreased over time and, in parallel, the risk factor profiles have changed, with hypertension, a sedentary lifestyle, and diabetes mellitus contributing more to the risk of myocardial infarction in more recent years.

Using biomarkers, such as hs-TNT, in addition to conventional risk factors improves the early prediction of ischemic heart disease in a general population. Further studies need to be conducted to better understand the value of biomarkers in addition to conventional risk factors on the long-term risk assessment of ischemic heart disease and tailored optimal primary and secondary prevention of ischemic heart disease.

Future perspectives

FUTURE PERSPECTIVES

The increasing prevalence of obesity and diabetes mellitus illustrates the continuous changes in risk factors for ischemic heart disease and emphasizes the importance of monitoring and following these temporal trends to better combat this disease. The concept of the "*Study of men born in 1943*" was also applied in 1953 and 1963, in studies that included both women and men. These, together with the ongoing Swedish CArdioPulmonary bioImage Study (SCAPIS) allow further follow-up of risk factors for ischemic heart disease over time. One of the goals of SCAPIS is to predict who is at risk of suffering a heart attack, stroke or chronic obstructive pulmonary disease in a national, population-based cohort study with the objective to predict and prevent these diseases (65). Understanding how temporal trends and evolving outcomes develop over time can offer profound insights for a more cost-effective decision-making to promote better health and well-being.

Undoubtedly, the decrease in coronary death and recurrent myocardial infarction over recent decades is at least partly attributable to widespread reperfusion therapy and secondary prevention. But long-term secondary prevention remains suboptimal. Further research is warranted to understand how to help and support patients to make important lifestyle changes. New technical solutions and phone applications could support patients in this effort and monitor their progress. These tools could be an extension to specialized outpatient clinics, which have proven success in this area, in times when clinical staff and resources are insufficient.

Early identification of risk factors is vital to help prevent disease onset and moderate the disease course. However, ischemic heart disease is clearly a multifactorial disease with factors that are modifiable, such as blood pressure, cholesterol level, glucose level, living style, and smoking, as well as factors that are not modifiable such as age, ethnicity, and family history of cardiovascular disease. In this context, the increasing collection of individual health data and the concept of precision medicine might in the future enable a more personal prediction of the disease at an earlier stage in its development. Furthermore, harnessing the potential of artificial intelligence will intensify the power of the data analysis and might reveal patterns not fully visible with today's methods. This is an exciting aspect of future research in preventive medicine that needs further investigation and refinement.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to the people who have been part of this thesis project and supported me in different ways over the years.

Professor Michael Fu, my main supervisor. I admire you as a researcher, cardiologist and human being. I have always looked up to you and I am grateful that you have been my tutor. Thank you for all the great discussions, your generosity and always putting your younger colleagues to the fore. You have taught me so much and I will always be grateful for that. I hope that our work together will continue for many years more, because a cannot imagine a better mentor. Once again, thank you.

Docent Lena Björck, my co-supervisor. It has been a pleasure to work with you. Thank you for making epidemiology more understandable and always answering emails, SMS, and phone calls even on your vacation! Writing our fourth paper and exploring the world of registers has been very exciting and educational; thank you for sharing your knowledge.

Salim Barywani, my co-supervisor. Thank you for your support and kindness. Even if we do not see each other as often as before, you are always there to give advice and encouragement when I have needed it.

Per-Olof Hansson, my colleague and co-author. Your enthusiasm and support in this thesis have been priceless. You offered to help me and spent many hours doing so, without any personal gain. I will remember you for your kindness, humility, and great intelligence. Thank you for always being a supportive colleague and a good person, you will always be in our hearts.

Professor Annika Rosengren, *Professor Kurt Svärdsudd*, my special thanks to you as co-authors who invested your time and knowledge to achieve the best result for the papers in this thesis. Your comments and input have been invaluable, and we have created manuscripts that I have felt very proud of.

Aldina Pivodic, co-author and statistician in papers II–IV. Thank you for all your clear explanations of statistics and your patience in helping me understand it all. You are an incredible statistician and I admire your intelligence and work ethic. I am glad that we have got to know each other better during these years and I look forward to following you in your career at APNC Statistics in Life Science.

Sofia Ekdahl head of the Internal Medicine, Geriatric and Emergency Medicine Department at Sahlgrenska University Hospital/Östra. Thank you for ensuring a stimulating research environment and prioritizing research studies, although it has not always been easy in our tough clinical working milieu.

Erik Thunström, head of the Department of Cardiology at Sahlgrenska University Hospital/Östra. Thank you for encouraging research and all my other side projects that I somehow end up in. I appreciate all the opportunities you have given me for further education as a cardiologist and for introducing me to the Swedish Society of Cardiology.

Helen Sjöland, former head of the Department of Cardiology at Sahlgrenska University Hospital/Östra and former head of the Research and Development Unit. Thank you for always believing in me and boosting my confidence. I look forward to exploring and participating in the development of innovation in medical care together!

Ulrica Forslund-Granheden, thank you for your expertise and for helping me navigate the administration of being a Ph.D. student. You always have the answer and never say no to giving support in any way! *Eva Thydén*, thank you for our chats all the way from Karlstad and your incredible work on the layout of this thesis.

To my colleagues and friends *Christina Karazisi, Lotta Magnusson, Felicia Toska, Maria Wideqvist, Carmen Basic*, and *Maria Fedchenko*. Thank you for all the discussions, support, and just social chats at "plan 2". I always look forward to going to work!

All colleagues at the Internal Medicine, Geriatric and Emergency Medicine Department at Sahlgrenska University Hospital/Östra for making it an amazing and developing workplace.

To my innovative colleagues and friends, in particularly *Peter Kelly*, for teaching me that the sky is the limit and helping me reach it, and *Sara Hansson* for always encouraging me and giving me perspective. Maternity leave was one of the best times in my life and I am happy that I shared it with you.

To my friends *Hanna Söderström, Rebecka Henriksson*, and *Ellenor Mattelin*. Thank you for always being there and always saying the right things. Our chats and messages are part of my daily routine and I couldn't be without them. You are the best!

"The Gang", my best friends from medical school. Thank you for being the kindest and warmest family of friends ever! Thank you for all the trips and laughs and for letting me be part of all your memorable moments in life. Although 12 years have passed since graduation, we are still the same!

To my mom and dad, *Labriani* and *Konstantinos Sakalakis*, thank you for creating a secure, warm place called home that I can always come back to. For your endless love, always being there, and putting us first. By being generous, kind, and humble, you have taught me great moral values that I will carry with me in all my achievements. You are my rock!

Στους αγαπημένους μου γονείς, *Λαμπριανή* και *Κωνσταντίνο*,
Σας ευχαριστώ, που δημιουργήσατε ένα ασφαλές, ζεστό μέρος που ονομάζεται σπίτι στο οποίο μπορώ πάντα να επιστρέφω, που είσαστε πάντα στο πλευρό μας γεμίζοντας μας με την αστείρευτη αγάπη σας και που μέσω της γενναιοδωρίας και της καλοσύνης σας μου δείξατε τις πραγματικές αξίες της ζωής που πάντα θα έχω μαζί μου σε κάθε μου βήμα. Σας αγαπώ πολύ.

To my sister, *Christina Sakalaki*, thank you for your support and endless love, especially for Einar. You have rescued us many times, making it possible for me to be able to focus on my research work when necessary. I am happy that Einar has such a wonderful "nona" and my only concern is that he will be spoiled! Love you!

To my second family, the *Englunds*, thank you for the love you give us and Einar, and for always being ready to help when needed. I am so glad to be able to extend my family with so many beautiful people.

To my big, fat *Greek family*, I would not be me without you. Thank you for the unconditional love, kindness and happy cheering along the way. I am happy to have you and be embraced by your big, warm family hug.

To nona and nonos, *Magda Nerantzaki* and *Georgios Bouroutzakis*, thank you for always following me in all my stages and achievements in life. Thank you for the kindness you show me and my family. Nona, I am glad that we became the good friends my father anticipated that we would be.

To my life partner, *Robert Englund*, thank you for creating the best team with me and for always listening. Life is easier, funnier and so much better with you, and I am very excited to see what more it has to bring. I love you always.

To my son, *Einar Konstantinos*, the meaning of life, my everything. You make me so happy and proud, showing me every day what really matters. I love you unconditionally.

This work was supported by funding from the Swedish Medical Research Council, the Swedish Heart and Lung Association, the Gothenburg Society of Medicine, the Swedish agreement between the government and the county councils concerning economic support for providing an infrastructure for research and education of doctors (the ALF agreement), and the Regional Development Fund, Västra Götaland County, Sweden (FOU-VGR).

REFERENCES

1. Thompson RC, Allam AH, Lombardi GP, Wann LS, Sutherland ML, Sutherland JD, et al. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. Lancet. 2013 Apr 6;381(9873):1211-22.

2. Hajar R. Evolution of Myocardial Infarction and its Biomarkers: A Historical Perspective. Heart Views. 2016 Oct-Dec;17(4):167-72.

3. Tan C, Schatz RA. The History of Coronary Stenting. Interv Cardiol Clin. 2016 Jul;5(3):271-80.

4. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, et al. Pathophysiology of Atherosclerosis. Int J Mol Sci. 2022 Mar 20;23(6).

5. Guyton & Hall, (2006), Medical Physiology, (11th edition), Elsevier Saunders, pages 848-850.

6. Guyton & Hall, (2006), Medical Physiology, (11th edition), Elsevier Saunders, pages 253.

7. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018 Nov 10;392(10159):1736-88.

8. WHO. The top 10 causes of death. February 2024. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

9. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. N Engl J Med. 2015 Apr 2;372(14):1333-41.

10. Bjorck L, Rosengren A, Bennett K, Lappas G, Capewell S. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. Eur Heart J. 2009 May;30(9):1046-56.

11. Mortality per 100 000 persons in ischemic heart disease (ICD I20-I25) in Sweden. https://sdb.socialstyrelsen.se/if_dor/resultat.aspx. February 2024.

12. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023 Oct 12;44(38):3720-826.

13. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019 Jan 14;40(3):237-69.

14. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA. 2003 Jul 2;290(1):86-97.

15. Kotseva K, De Backer G, De Bacquer D, Rydén L, Hoes A, Grobbee D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol. 2019 May;26(8):824-35.

16. Kavousi M, Pisinger C, Barthelemy JC, De Smedt D, Koskinas K, Marques-Vidal P, et al. Electronic cigarettes and health with special focus on cardiovascular effects: position paper of the European Association of Preventive Cardiology (EAPC). Eur J Prev Cardiol. 2021 Dec 20;28(14):1552-66.

17. Byhamre ML, Araghi M, Alfredsson L, Bellocco R, Engström G, Eriksson M, et al. Swedish snus use is associated with mortality: a pooled analysis of eight prospective studies. Int J Epidemiol. 2021 Jan 23;49(6):2041-50.

18. Arefalk G, Hambraeus K, Lind L, Michaëlsson K, Lindahl B, Sundström J. Discontinuation of smokeless tobacco and mortality risk after myocardial infarction. Circulation. 2014 Jul 22;130(4):325-32.

19. Titova OE, Baron JA, Michaëlsson K, Larsson SC. Swedish snuff (snus) and risk of cardiovascular disease and mortality: prospective cohort study of middle-aged and older individuals. BMC Med. 2021 May 7;19(1):111.

20. Rohani M, Agewall S. Oral snuff impairs endothelial function in healthy snuff users. J Intern Med. 2004 Mar;255(3):379-83.

21. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017 Aug 21;38(32):2459-72.

22. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012 Aug 11;380(9841):581-90.

23. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021 Sep 7;42(34):3227-337.

24. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun;71(6):e13-e115.

25. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021 Sep 11;398(10304):957-80.

26. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013 Sep 4;310(9):959-68.

27. SWEDEHEART. Annual report 2023. https://www.ucr.uu.se/swedeheart/. May 2024.

28. Rosengren A, Eriksson H, Hansson PO, Svardsudd K, Wilhelmsen L, Johansson S, et al. Obesity and trends in cardiovascular risk factors over 40 years in Swedish men aged 50. J Intern Med. 2009 Sep;266(3):268-76.

29. Ekblom Ö, Cider Å, Hambraeus K, Bäck M, Leosdottir M, Lönn A, et al. Participation in exercise-based cardiac rehabilitation is related to reduced total mortality in both men and women: results from the SWEDEHEART registry. Eur J Prev Cardiol. 2022 Mar 25;29(3):485-92.

30. Lönn A, Börjesson M, Hambraeus K, Ekblom Ö. Changes in Physical Activity and Incidence of Nonfatal Cardiovascular Events in 47 153 Survivors of Myocardial Infarction. Journal of the American Heart Association. 2023 Oct 17;12(20):e030583.

31. McGill HC, Jr., McMahan CA, Zieske AW, Tracy RE, Malcom GT, Herderick EE, et al. Association of Coronary Heart Disease Risk Factors with microscopic qualities of coronary atherosclerosis in youth. Circulation. 2000 Jul 25;102(4):374-9.

32. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008 Feb 12;117(6):743-53.

33. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003 Jun;24(11):987-1003.

34. Zhong Y, Rosengren A, Fu M, Welin L, Welin C, Caidahl K, et al. Secular changes in cardiovascular risk factors in Swedish 50-year-old men over a 50-year period: The study of men born in 1913, 1923, 1933, 1943, 1953 and 1963. Eur J Prev Cardiol. 2017 Apr;24(6):612-20.

35. Arnett DK, McGovern PG, Jacobs DR, Jr., Shahar E, Duval S, Blackburn H, et al. Fifteen-year trends in cardiovascular risk factors (1980-1982 through 1995-1997): the Minnesota Heart Survey. Am J Epidemiol. 2002 Nov 15;156(10):929-35.

36. Daniels LB, Laughlin GA, Clopton P, Maisel AS, Barrett-Connor E. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. J Am Coll Cardiol. 2008 Aug 5;52(6):450-9.

37. Jorgensen PG, Jensen JS, Appleyard M, Jensen GB, Mogelvang R. Plasma pro-brain natriuretic peptide and electrocardiographic changes in combination improve risk prediction in persons without known heart disease. Int J Cardiol. 2015 Dec 15;201:104-9.

38. Desta L, Jernberg T, Löfman I, Hofman-Bang C, Hagerman I, Spaak J, et al. Incidence, temporal trends, and prognostic impact of heart failure complicating acute myocardial infarction. The SWEDEHEART Registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies): a study of 199,851 patients admitted with index acute myocardial infarctions, 1996 to 2008. JACC Heart Fail. 2015 Mar;3(3):234-42.

39. Jenča D, Melenovský V, Stehlik J, Staněk V, Kettner J, Kautzner J, et al. Heart failure after myocardial infarction: incidence and predictors. ESC Heart Fail. 2021 Feb;8(1):222-37.

40. Mahtta D, Mohammed I, Elgendy IY. Overview of prevalence, trends, and outcomes of post myocardial infarction mechanical complications. Ann Cardiothorac Surg. 2022 May;11(3):322-4.

41. Damluji AA, van Diepen S, Katz JN, Menon V, Tamis-Holland JE, Bakitas M, et al. Mechanical Complications of Acute Myocardial Infarction: A Scientific Statement From the American Heart Association. Circulation. 2021 Jul 13;144(2):e16-e35.

42. Li S, Peng Y, Wang X, Qian Y, Xiang P, Wade SW, et al. Cardiovascular events and death after myocardial infarction or ischemic stroke in an older Medicare population. Clin Cardiol. 2019 Mar;42(3):391-9.

43. Lee SH, Jeong MH, Ahn JH, Hyun DY, Cho KH, Kim MC, et al. Predictors of recurrent acute myocardial infarction despite successful percutaneous coronary intervention. Korean J Intern Med. 2022 Jul;37(4):777-85.

44. Norgaard ML, Andersen SS, Schramm TK, Folke F, Jørgensen CH, Hansen ML, et al. Changes in short- and long-term cardiovascular risk of incident diabetes and incident myocardial infarction--a nationwide study. Diabetologia. 2010 Aug;53(8):1612-9.

45. Johansson S, Rosengren A, Young K, Jennings E. Mortality and morbidity trends after the first year in survivors of acute myocardial infarction: a systematic review. BMC Cardiovasc Disord. 2017 Feb 7;17(1):53.

46. Ergatoudes C, Thunström E, Rosengren A, Björck L, Bengtsson Boström K, Falk K, et al. Long-term secondary prevention of acute myocardial infarction (SEPAT) - guidelines adherence and outcome. BMC Cardiovasc Disord. 2016;16(1).

47. Fu M, Rosengren A, Thunström E, Mandalenakis Z, Welin L, Caidahl K, et al. Although Coronary Mortality Has Decreased, Rates of Cardiovascular Disease Remain High: 21 Years of Follow-Up Comparing Cohorts of Men Born in 1913 With Men Born in 1943. Journal of the American Heart Association. 2018;7(9).

48. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

49. Statistics Sweden. Logitudinal integrated database for health insurance an labour market studies (LISA). https://www.scb.se/vara-tjanster/bestall-data-och-statistik/bestalla-mikrodata/vilka-mikrodata-finns/longitudinella-register/longitudinell-integrationsdatabas-for-sjukforsakrings--och-arbetsmarknadsstudier-lisa/. February 2024.

50. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017 Sep;32(9):765-73.

51. Wallerstedt SM, Wettermark B, Hoffmann M. The First Decade with the Swedish Prescribed Drug Register - A Systematic Review of the Output in the Scientific Literature. Basic Clin Pharmacol Toxicol. 2016 Nov;119(5):464-9.

52. Framingham Heart Study. The Framingham Risk Score. https://frami nghamheartstudy.org/fhs-risk-functions/hard-coronary-heart-disease- 10-year-risk/. February 2024.

53. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov 27;310(20):2191-4.

54. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: Nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J. 2015;36(19):1163-70a.

55. Kotseva K, De Bacquer D, Jennings C, Gyberg V, De Backer G, Rydén L, et al. Time Trends in Lifestyle, Risk Factor Control, and Use of Evidence-Based Medications in Patients With Coronary Heart Disease in Europe: Results From 3 EUROASPIRE Surveys, 1999–2013. Global Heart. 2017;12(4):315-22.e3.

56. WHO report Adherence to long-term therapies: evidence for action. https://iris.who.int/handle/10665/42682. May 2024.

57. Nachshol M, Lurie I, Benyamini Y, Goldbourt U, Gerber Y. Role of psychosocial factors in long-term adherence to secondary prevention measures after myocardial infarction: a longitudinal analysis. Ann Epidemiol. 2020;52:35-41.

58. Jin H, Tang C, Wei Q, Chen L, Sun Q, Ma G, et al. Age-related differences in factors associated with the underuse of recommended medications in acute coronary syndrome patients at least one year after hospital discharge. BMC Cardiovasc Disord. 2014 Sep 24;14:127.

59. Lauffenburger JC, Robinson JG, Oramasionwu C, Fang G. Racial/Ethnic and gender gaps in the use of and adherence to evidence-based preventive therapies among elderly Medicare Part D beneficiaries after acute myocardial infarction. Circulation. 2014;129(7):754-63.

60. Kesteloot H, Sans S, Kromhout D. Dynamics of cardiovascular and all-cause mortality in Western and Eastern Europe between 1970 and 2000. Eur Heart J. 2006 Jan;27(1):107-13.

61. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010 Jun 10;362(23):2155-65.

62. WHO. Global Health Estimates: Leading causes of death. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death, May 2024.

63. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017 Jul 6;377(1):13-27.

64. International Diabetes Federation Diabetes Atlas. https://diabetesatlas.org/data/en/world/. May 2024.

65. The SCAPIS study. https://www.scapis.org/. August 2024.