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SOCIOECONOMIC STATUS AND MYOCARDIAL INFARCTION

Influence on Secondary Prevention and Prognosis

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SOCIOECONOMIC STATUS AND MYOCARDIAL INFARCTION
Influence on Secondary Prevention and Prognosis

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Joel Ohm

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Till min familj

ABSTRACT

Background and Aims In the wealth of research undertaken on myocardial infarctions (MIs), secondary prevention is less well studied. Incidence and death from MI have declined substantially in the past decades due to the identification of cardiovascular (CV) risk factors, methods to assess risk in the general population, development of efficient therapies that modify risk factor levels, and the introduction of revascularization therapies used in the acute phase of a MI. Meanwhile, secondary prevention in the large population of MI survivors performs poorly with suboptimal management and low achievement rates of the treatment targets recommended in major prevention guidelines. There is room for improvement. Links between socioeconomic status (SES) and CV risk factors, and first-ever MI have been reported for almost 100 years. Circumstances of contemporary secondary prevention after MI suggest that SES may be an important risk factor. With this thesis, aims were to improve knowledge on SES in secondary prevention care after MI and with regards to prognosis.

Material and Methods This thesis was based a large nationwide cohort of men and women who attended routine revisits in the year after hospitalization for acute MI between 2005 and 2013 and were registered in the Swedish National Quality Registry for cardiac care. Clinical data collected on study participants was linked with data from national registries manged by government agencies on individual-level indicators of SES (disposable income quintiles, educational level, and marital status), claimed drug prescriptions, and recurrent atherosclerotic CV disease events (ASCVD; coronary heart disease death, nonfatal MI, fatal or nonfatal ischemic stroke) during long-term follow-up. Multivariable Cox regression models were used to estimate the association between SES and recurrent ASCVD and between on-treatment blood lipid levels (total cholesterol, low and high density lipoprotein cholesterol [LDL-C and HDL-C], and triglycerides) and recurrent ASCVD. The incremental predictive value of each blood lipid fraction was assessed by addition to a secondary prevention risk score for estimates of differences in C-index and measures of reclassification. The associations between SES and most secondary prevention activities and risk factor treatment targets recommended in major guidelines on secondary prevention were assessed in logistic regression models. Differences in sociodemographic, clinical, and therapeutic characteristics of participants and non-participants in clinical trials after MI were estimated in Poisson regression models and the association between clinical trial participation and recurrent ASCVD was estimated in Cox regression models. Mediation in the association between SES and recurrent ASCVD was assessed using sequential Cox regression models and a method for mathematically consistent estimates of causal mediating effects.

Results Risk for recurrent ASCVD was lower among study participants with higher income, higher educational level, and in marriage. The strongest association with recurrent ASCVD was observed for income and the association was independent of differences in CV risk factor profile. With 97% in the cohort on statin therapy at the 2-month revisit, recurrent ASCVD was weakly associated with achieved levels of LDL-C and strongly associated with levels of triglycerides. The adopted secondary prevention risk score discriminated poorly in the study

cohort (C-index <0.6) and measures of incremental predictive power were inconsistent. Rates of achieved risk factor targets 1 year after MI were overall low and worse in low SES groups. SES was associated with achieving smoking cessation and target levels of blood pressure levels and glycated hemoglobin, but not LDL-C. Correspondingly, rates of participation in programs within comprehensive cardiac rehabilitation were also low overall, and strongly associated with SES. Higher SES was also associated with more lipid profile measurements and intensification of statin therapy during the first year post-MI. Use of risk-modifying drug therapy was high overall. At discharge from initial care, higher SES was associated with receiving dual antiplatelet therapy. One year post-MI, high SES was associated with persistent use of statins, high statin intensity, and renin-angiotensin-aldosterone system inhibitors. The 10% of this cohort who participated in a clinical trial during the first year after MI (compared to those who did not) were more likely to be men, married, have an income in the highest quintile, a post-secondary education, a better risk profile, and their risk for recurrent ASCVD was lower. In the association between SES and recurrent ASCVD, risk attenuated in sequential analysis models, primarily from adjustment for risk factor profile and secondary prevention activities but a 37% higher risk remained in the lowest vs. highest income quintile after full extensive adjustments for plausible risk mediators. Estimated proportions of the excess risk for recurrent ASCVD in the lowest income quintile mediated through risk profile, physical training and patient education within cardiac rehabilitation were significant but small whereas optimal statin therapy was not a mediator of this risk.

Conclusions SES, by proxy disposable income level, may be a better measure than on-treatment lipid levels in the assessment of risk for recurrent ASCVD within the post-MI population. More study is needed to improve secondary prevention risk prediction, for risk-based intensified treatment to those who would likely benefit most. Secondary prevention after MI performs poorly, especially among low-income groups. Observed SES disparities regarding participation in programs within cardiac rehabilitation were mediators for higher long-term risk of recurrent ASCVD events. Hence, interventions for improved cardiac rehabilitation participation in low-income groups may improve health equity. However, the mediating proportions were small and plausible effectiveness of interventions warrant evaluation of efficacy in clinical trials. Awareness of under-representation of low SES individuals among trial participants within the post-MI population must be taken into account in designing such confirmatory trials. Further study on pathways through which low SES is associated with secondary prevention achievements and higher risk for recurrent ASCVD is needed. Adherence to therapies and dietary habits may be important areas to study.

LIST OF SCIENTIFIC PAPERS

I. Joel Ohm, Per H Skoglund, Andrea Discacciati, Johan Sundström, Kristina Hambraeus, Tomas Jernberg, Per Svensson
Socioeconomic Status Predicts Second Cardiovascular Event In 29,226 Survivors of a First Myocardial Infarction
European Journal of Preventive Cardiology, 2018; 25(9): 985-993

II. Joel Ohm, Paul Hjemdahl, Per H Skoglund, Andrea Discacciati, Johan Sundström, Kristina Hambraeus, Tomas Jernberg, Per Svensson
Lipid Levels Achieved After a First Myocardial Infarction and the Prediction of Recurrent Atherosclerotic Cardiovascular Disease
International Journal of Cardiology, 2019; 296: 1-7

III. Joel Ohm, Per H Skoglund, Henrike Häbel, Johan Sundström, Kristina Hambraeus, Tomas Jernberg, Per Svensson
Association of Socioeconomic Status With Risk Factor Target Achievements and Use of Secondary Prevention After Myocardial Infarction
JAMA Network Open, 2021; 4(3):e211129

IV. Joel Ohm, Tomas Jernberg, David Johansson, Anna Warnqvist, Margret Leosdottir, Kristina Hambraeus, Per Svensson
Level A Evidence – For A-Level Patients Only? Association of Clinical Trial Participation After Myocardial Infarction With Socioeconomic Status, Clinical Characteristics, and Outcomes
Submitted

V. Joel Ohm, Ralf Kuja-Halkola, Anna Warnqvist, Henrike Häbel, Per H Skoglund, Johan Sundström, Kristina Hambraeus, Tomas Jernberg, Per Svensson
Mediating Effects of Socioeconomic Disparities in Post-Myocardial Infarction Care on the Risk of Recurrent Major Cardiovascular Outcomes
Submitted

CONTENTS

LIST OF ABBREVIATIONS

ACC/AHA	American College of Cardiolgy / American Heart Association
ASCVD	Atherosclerotic Cardiovascular Disease
ASCVD event	Composite outcome of Coronary Heart Disease death, nonfatal Myocardial Infarction, fatal or nonfatal stroke
CABG	Coronary Artery Bypass Graft(ing)
CV	Cardiovascular
DALY	Disability Adjusted Life-Years
ECG	Electrocardiogram
ESC	European Society of Cardiology
GDP	Gross Domestic Product
HbA1c	Glycated Hemoglobin A_{1c}
HDL-C	High Density Lipoprotein Cholesterol
ICD-10	International Classification of Diagnoses, 10^{th} Edition
LDL-C	Low Density Lipoprotein Cholesterol
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
NSTEMI	Non-ST Segment Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PCSK-9	Proprotein Convertase Subtilisin/Kexin type 9
RAAS	Renin-Angiotensin-Aldosterone System
rASCVD	First recurrent ASCVD event
SES	Socioeconomic Status
STEMI	ST-segment Elevation Myocardial Infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
YLD	Years Lived with Disability
WHO	World Health Organizaton

1 INTRODUCTION

Within a patient population, the individual with the highest risk of an adverse outcome have the greatest need for more intense treatment and will also benefit the most from it.[1] This principle has been the focus of management in primary prevention of incident atherosclerotic cardiovascular disease (ASCVD) events, fatal or nonfatal myocardial infaction (MI) or stroke for decades.[2,3]

Despite concerns regarding the accuracy of risk prediction algorithms and the evidence for use[4,5], application in primary prevention has been successful.[6] Combined with an ageing population and dramatically improved survival of incident ASCVD events, the population with manifest disease in need for secondary prevention has grown large. Risk-based individualized treatment intensity should be provided also after MI.[7] However, assessment and stratification of risk is by comparison absent in the large population in the stable phase after MI[8,9] and overall, secondary prevention management performance is poor.[10,11]

It is well known that low socioeconomic status (SES) is linked to cardiovascular (CV) risk factors and events in primary prevention[12-14], and SES may be considered a "cause of the causes" for ASCVD.[15,16] There is reason to believe that contemporary secondary prevention after MI may amplify the importance of SES as a risk factor for subsequent CV events. Especially in relation to more established CV risk factors that are specifically targeted with efficient risk factor modifying therapies.

The risk for death and worsened burden of disease is most hazardous in the acute phase of a MI. With time, risk levels decline.[9,17] One year after a MI, residual risk for recurrent ASCVD is still elevated compared to the general population but at a stable level. A more stable residual risk is more predictable. Routine revisits after MI are therefore ideal for long-term secondary prevention risk assessment. Furthermore, these are patient – cardiac care provider interactions where decisions on continued, corrected, or intensified treatment are made.

The prerequisites for high-quality registry-based research is good in Sweden. In this thesis, the role of SES in secondary prevention after MI is evaluated, in relation to other CV risk factors and prognosis. Through these studies, this thesis seeks to improve risk assessment for recurrent ASCVD and add to the knowledge on SES among patients with recent MI.

2 LITERATURE REVIEW

2.1 ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

2.1.1 Atherosclerosis

Atherosclerosis is a slowly progressing chronic pathological process of the arterial wall.[18] The process is intricate and involves focal intramural depositions of blood lipid particles, low density lipoprotein cholesterol (LDL-C), and immune system activation. LDL-C particles are oxidized and aggregated in the intramural environment which triggers an innate immune respone and attracts several types of immune cells. Macrophage uptake of aggregated oxidized LDL-C forms foam cells in the artery wall. Further activity from enzymatic, inflammatory, and cell necrosis pathways maintain previous steps and causes vascular smooth muscle cells to transform and proliferate.[19] Smooth muscle cells also migrate from the mid-wall to the subendothelial space. The inner layer of the artery becomes incresingly thickened and in later stages, a collagen-rich fibrous coat is formed that encapsule a core of aggregated foam cells and extracellular necrotic fatty content – an atherosclerotic plaque has formed. By now, the inner lining of the artery is irregular. Large plaques that narrow the lumen considerably may cause symptoms at times when the demand of blood flow and oxygen in downstream tissues increase. In cases of a MI however, the fibrous cap of a plaque has nearly always become thin and ruptured for reasons that are not fully understood.[20] Exposed non-endovascular tissue at the site of rupture triggers adherence, activation, and aggregation of blood platelets as part of normal primary haemostasis and a cascade of circulating coagulation factors of secondary heamostasis. Consequently, a thrombus forms and blood flow is obstructed, causing ischemia and eventually necrosis of downstream dependent tissue.[18]

2.1.2 Myocardial Infarction

A universal definition is used for the diagnosis of an acute MI. The definition was first released in year 2000 and in 2018, the fourth edition was published.[21] Typically, diagnosis requires typical dynamics of serially measured biomarker-levels associated with myocardial necrosis and either symptoms characteristic of myocardial ischemia, ischemic electrocardiogram (ECG) changes, or cardiac imaging evidence such as echocardiographic wall motion abnormalities or evidence from coronary angiography, or autopsy. The vast majority of MIs are the sudden acute pinnacles of decade-long development of atherosclerosis.[20] However, an acute MI, correctly diagnosed according to the criteria, may also be due to non-atherosclerotic mechanisms. These subtypes include MIs caused by coronary interventions, or temporary supply and demand mismatch of oxygen delivery to the myocardium. Additionally, a fairly large proportion of MIs have emerged in recent years parallel to the increasing availability of imaging techniques. Within this heterogeneous group with MI, no obstructed coronary arteries are found by angiographic examination.[21]

2.1.3 Atherosclerotic Cardiovascular Disease

In this thesis, MI and ischemic stroke are referred to as ASCVD events. CV diseases that are manifestations of atherosclerosis also include less prevalent peripheral arterial disease and diseases of the aorta. According to the 2020 WHO Global Health Estimates, ischemic heart disease is by far the overall leading cause of death worldwide accounting for approximately 8.9 million deaths, or 16% of all deaths annualy. The runner up, stroke, was accountable for 11% of world deaths.[22] In 2004, the WHO projected that the incidence of CV diseases would increase in low- and middle-income countries. Furthermore, they projected that economic development in these countries would result in unhealthier lifestyle including physical inactivity, high-fat diets, obesity and diabetes, combined with increased life expectancies. Unfortunately, this prognosis seem to have come true.[22,23]

Myocardial infarction and stroke are also major contributors to global morbidity as measured by an international standardized measure; number of years lived with disability (YLDs), that is weighted for health condition severity. Increasing global trends for YLDs were observed between 1990 and 2019.[24] Countries across the world are urged to reverse these trends through multisectoral interventions of fundamental drivers of ASCVD including socioceonomic status and unequal access to quality health care and prevention.[24]

The economic consequences of ASCVD for society are not easily determined on a global scale because of absent or low quality data. However, direct health care expeditures due to CV disease in Sweden has been estimated to account for more than 10% of total costs and accounted for the largest share of spendings on inpatient care and drugs.[25] Indirect costs for society attributable to CV disease may also be measured. Disease-related loss of productivity may be assessed by adding a measure of premature death (years of life lost) to YLD for disability-adjusted life years (DALYs). Thus, DALYs combine mortality and morbidity and represent years of living with “ideal health” that are lost because of a disease. In 2019, ischemic heart disease remained the leading cause of DALYs in Sweden with roughly 2,000 DALYs per 100,000 Swedish citizens, and was the second leading cause of DALYs worldwide after neonatal conditions.[26] Productivity-loss because of unpaid care by family members remain unaccounted for.

2.1.4 Cardiovascular Risk Factors

In 1913, it was experimentally established that cholesterol-fed rabbits developed coronary atherosclerosis.[27,28] The epidemiological field of CV research and conceptualization of CV risk factors was initiated around 1950. Two cardiologists, sceptics of “the dietary theory” for atherosclerosis[29], launched a case-control study in 1946 that is often referred to as the first CV epidemiological study.[30] In this study, the clinical characteristics in common among 100 young individuals with premature MI were described: male sex, cigarette smoking, family history, elevated levels of cholesterol and blood pressure, and body type.[31,32] The concept of CV risk factors was further established through several longitudinal and observational studies. Among these, the multinational Seven Countries Study and the Framingham Heart

Studies have been particularily recognized.[33] In the Seven Countries Study, one of the important insights was that dietary fat intake and lifestyle was linked to cholesterol levels and ASCVD.[34,35] The Framingham Heart Studies have contributed greatly to the understanding of combinations of risk factors for total risk of CV outcomes and much more.[36] New candidates as risk factors for ASCVD have been evalutated throughout the years, including alternative ways of measuring risk factors, novel biomarkers, and advanced measurements of subclinical atherosclerosis. Although strongly associated with CV outcomes, few have been proven meaningful additions to risk assessment in relation to the risk factors identified decades prior.

Traditional risk factors are those most widely recognized overall. Among the more recent global epidemiological studies that have made a large footprint on what may be considered traditional CV risk factors was INTERHEART.[37] In this large international case-control study published in 2004, nine risk factors (dyslipidemia, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, inadequate consumption of fruits and vegetables, high alcohol consumption, and physical inactivity) were highlighted as being responsible for 90% of all MIs worldwide in both sexes regardless age group. INTERHEARTs results aligned well with risk factors consistently identified in earlier epidemiological studies.

Expert workgroups of the major international CV societies regularly evaluate, summarize, and report the existing evidence in clinical guidelines. The most recent editions on CV prevention, the 2013 American College of Cardiology / American Heart Association (ACC/AHA) Guideline on the assessment of CV risk[3] and the 2016 European Society of Cardiology (ESC) Guidelines on CV disease prevention in clinical practice[38], highlight essentially the same risk factors: age, gender, smoking, dyslipidemia, hypertension, and diabetes. Differences are minor, such as the specification of lipid fractions (hypercholosterolemia and low HDL-C vs. LDL-C and triglycerides) and only the U.S. guideline considers the absence of an intervention, antihypertensive treatment, a risk factor. The European guideline is less selective and additionally emphasizes the importance of physical inactivity and body composition as risk factors as well as previously documentated ASCVD and chronic kidney disease.

WHO and the International Society of Hypertension has published a guideline on the prevention of CV disease as well in which the traditional CV risk factors and their management are addressed one by one in detail.[39] A main application of clinical guidelines is for health care professionals to find recommendations on clinical management according to the best available evidence in real-time. CV risk factors may be classified and viewed upon from a wider perspective than what is sought after in the busy clinical setting.[40] The WHO Commission for Social Determinants of Health presented a conceptual framework for health and health equity improvements in which risk factors are categorized differently: true CV risk factors are all behavioural: unhealthy diet (excessive dietary salt, insufficient fruits and vegetables), physical inactivity, use of tobacco, and alcohol excess. Risk factor that are immediate causes of disease and most regarded in clinical practice: hypertension, hyperlipidemia, diabetes, overweight and obesity are “intermediate risk factors” attributable

to the former. Furthermore, the conceptual framework considers SES a "cause of the causes" for ASCVD that follow globalization, urbanization, and ageing populations. That is, a risk factor shaped by the daily life circumstances and social structures that determine behavioral risk factors, that underly the intermediate risk factors that in turn are measured and acted upon in clinical assessment for ASCVD risk.[15,41,42]

2.2 SOCIOECONOMIC STATUS

In lack of a clear definition, SES may be described as a measure of an individual's position in the hierarchy of a society, according to the opinion of the average member of that society.[13] Many aspects may influence said position. An aspect of SES may be considered more important for a specific setting than another, and two societies may not value the same aspect equal. SES should ideally take into account both resources and prestige-related aspects.[43] The most frequently used and acknowledged indicators of SES are level of income, educational attainment, and occupational status. Other indicators used are wealth, level of social support including marital status, and various neighbourhood characteristics such as rural residency.[44,45]

In research, availability of reliable data influence which SES indicators are used. Sometimes indicators are used alone, in different combinations and sometimes without definition of the indicator(s) used. It is recommended that multiple indicators of SES should be used in research to capture this complex and multifaceted construct.[44,45] In a studied population and setting, the educational level may differ between individuals within a category of occupational status, and differences in occupational status may exist among individuals with the same educational level. It is further recommended that plausible explanatory pathways and mechanisms are considered and that unmeasured indicators of SES may affect findings.[45]

The multiple indicators of SES available, and relevant, should be included in analyses simultaneously.[44] Sometimes, multiple SES indicators are joined into a single SES-index that is convenient for undertaking analyses and for comparisons within the study but this practice is not recommended. First, since the selection of SES indicators used should be determined by the study question and society studied, no SES-index among indices with various compositions is universally applicable to all settings and outcomes. Second, while the inclusion of multiple indicators into a single SES-index make analyses less complex and less sensitive to missing data on single SES indicators, an observed difference in SES-index level may actually compare two different indicators. Third, in interpretation of study findings, reference to a SES-index gives no lead with regards to explanatory pathways.[45]

Plausible pathways in which SES affect outcomes are patient compliance to therapy[46], cognition and health literacy[47], travel distance to health facilities, cost of work-absence for health care visits, ability to pay for medication, and unknown factor affecting access to acute interventions.[48]

2.3 SOCIOECONOMIC STATUS IN CARDIOVASCULAR DISEASE

Abundant support for an inverse relationship between SES and most traditional CV risk factors and first incident CV events is available in the literature since the 1950s.[14,49] It has been suggested that all observations of associations between SES and adverse health outcomes amount to evidence of causality.[16] Even prior to the conceptualization of CV risk factors, an association between SES and atherosclerotic lesions was described at the International Society of Geographical Patology conference in 1934.[33,50]

It is acknowledged in recent major CV prevention guidelines that SES should be considered with regards to risk for morbidity and mortality in primary prevention. However, SES is not only a complex construct. SES is generally considered a non-modifiable risk factor. As such, there is no treatment to prescribe against low SES in the clinical setting. Just as there is no treatment that modifies biological age or gender. Considering the well known association between SES and prevalence of traditional modifiable CV risk factors, management in low SES groups has predominantly been focused on these risk factors.[12]

2.3.1 Wider Perspective

In this thesis, individual-level SES is studied. SES may also be considered at higher levels. Gross Domestic Product (GDP) is a measure of the economic growth and can be used to describe the financial state of a country. The resources available for a health care system in turn determine the quality of care provided to the citizens of a country. For this, and other reasons, initiatives to assess the global burden of CV diseases compare global subregions or low-, middle-, and high-income countries separately.[24] Also within a relatively wealthy continent, Europe, higher-GDP countries have much greater relative and absolute healthcare expeditures than middle-income countries. This is reflected in the utilization of best available therapies for MI as well as incidence of MI, stroke, mortality, and morbidity due to CV disease.[25] Domestic average income-level has also been used as an indicator of SES to compare quality-of-care and long-term outcomes in secondary prevention after MI between European countries.[51] In addition to national economic growth and average income levels, countries differ with regards to the Health Care System used.

2.4 SWEDISH PERSPECTIVES

Sweden is a wealthy country with universal health coverage and strong social security. Hence, the conditions for health equity in Sweden are good.[52] Additionally, Swedish health care providers are obliged by law to follow three ethical principles in prioritization for care. The Swedish Healthcare Law (Hälso- och sjukvårdslagen, HSL) states:[53]

The principle of human equality (SFS 2017:30 3 kap. 1 §)	Health care shall be provided with respect for the dignity and equal value of all human beings.
The principle of demand and solidarity (SFS 2017:30 3 kap. 1 §)	Those in greatest need for health care should be given priority to access.
The principle of cost-efficiency (SFS 2017:30 4 kap. 1 §)	Publicly financed health care shall be organized in order to promote cost-efficiency.

Free translation by the author of this thesis

The first principle resembles the first article of the United Nations declaration of human rights.[54] An interpretation is that care should be provided without regard for SES as well as chronological age, gender, lifestyle, societal function, and ability to pay. Further, that high-risk groups should be better identified and that health care providers and decision makers should allocate resources to high-risk individuals. Cost-efficiency is a subordinate healthcare law but importantly points out the necessity of maximizing benefit from common resources at the individual as well as societal level with regard for disease prevalence and severity. However, previous studies on SES in CV disease conducted in regions of Sweden indicated that socioeconomic disparities exist in primary prevention between neighborhood-SES and incident MI[55], in early-phase secondary prevention regarding use of evidence-based drug therapy[56], and for long-term mortality.[57]

2.4.1 Myocardial Infarction Trends in Sweden

MI remains the most common cause of death and disability in Sweden. Almost 30,000 MIs occured in 2013 (383 per 100,000 citizens) according to official statistics. One fifth (18%) died within a day of MI and one out of four (26%) died within a month.[58,59] Among cases hospitalized, the population most relevant for this thesis, the 28-day case fatality was 11%. Among the 5300 individuals who died within a day of the MI, 93% were not admitted to hospital. Although the incidence and fatality-rates are high, remarkable improvements have been achieved in the past years. The incidence of MI decreased by 38% between 2001 and 2014. The 28-day case fatality rate among hospitalized individuals with MI decreased by 50% between 1994 and 2014.[58] The decreasing case-fatality rates after MI started more than 20 years ago. However, further survival gains beyond 1 year seem to be reaching a plateau in the most recent years.[60]

2.5 EVIDENCE-BASED CARDIOVASCULAR MEDICINE

The Swedish Society of Cardiology is part of the ESC, a major international non-profit organization for CV professionals. The existing litterature on CV diseases is extensive and the influx of new findings high. It is a necessity for clinical usefulness, comprehension, and concistency of care that the available research is regularily and systematically reviewed, evaluated for evidence, and condensed into clincial practice guidelines. This work is preferably conducted by experts in the specific field of research and disseminated through an authoritarian and trustworthy professional organization.[61] Swedish cardiac care providers generally follow the clinical practice guidelines issued by the ESC. Numerous guidelines exist that cover areas of different comprehension within CV medicine. Strong recommendations warrant high level of evidence. Just as clinical practice guidelines, meta-analyses and systematic reviews are based on previous original work that is synthesized and provide the highest level of evidence. Among original studies, randomized controlled trials provide the highest level of evidence. This is because the study design allows for elimination of confounding (systematic errors) and determination of causality. Trials are expensive to conduct and require strict inclusion and exclusion criteria during enrollment of study participants. It was recently reported that among recommendations in ESC and counterpart

U.S. guidelines, a very small proportion are supported by large or multiple randomized trials.[62] Better evidence is needed. However, not all hypotheses can be answered by a clinical trial and may not be ethically or financially justifiable. For example, it is not feasible to randomize an individual to a level of SES and it would not be ethical to randomize an individual to take up cigarette smoking. In some instances, a wealth of consistent data from observational data may amount to causal inference.[16] Furthermore, there is an Achilles heel to randomized clinical trials – external validity. Because of the strict selection criteria of the study population (in which an intervention was evaluated), findings may not be generalizable to the population in which an intervention is intended to be used. The selection process of participants to clinical trials may be yet another area of CV disease where SES play a role.

2.6 CARDIOVASCULAR PREVENTION ACHIEVEMENTS

ASCVD prevention may be divided into three phases: primary prevention, acute phase, and long-term secondary prevention. Each phase is characterized by differences in risk mechanism for recurrent ASCVD, level of risk within the population, and available methods for risk assessment that determine management for risk reduction. (Figure 1)

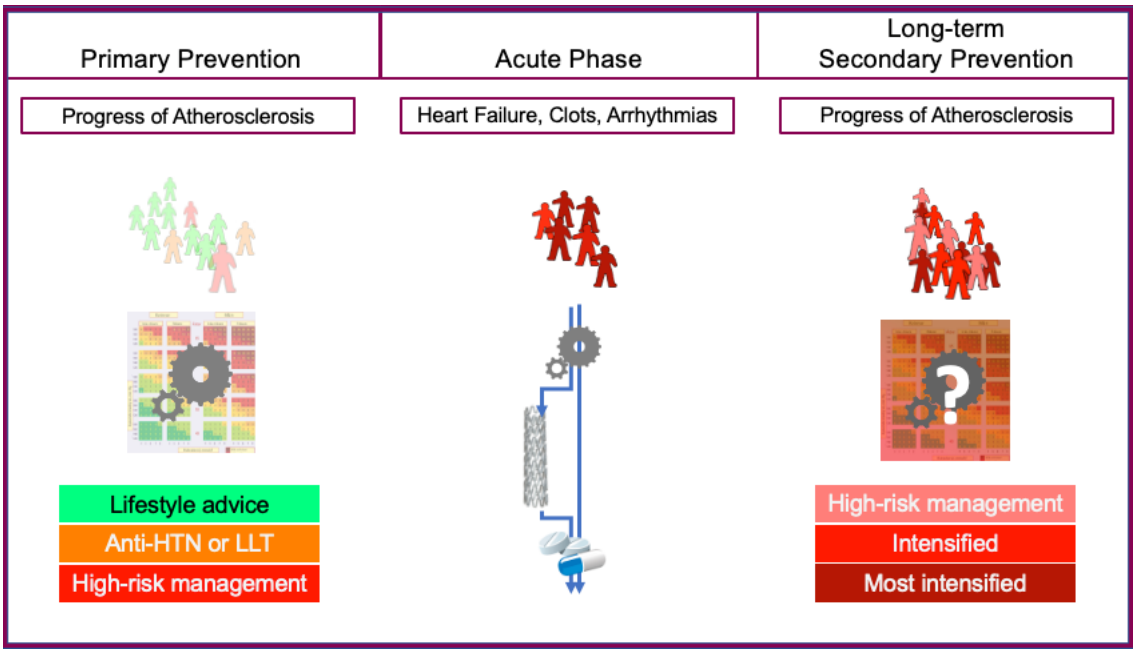


Figure 1. Prevention phases.
Abbreviations: HTN, hypertension. LLT, lipid lowering therapy.

Intense research and development of efficient therapies over the past decades has been a major contributor to the declining MI incidence and mortality in Sweden and other high-income countries. Primary prevention treatment of CV risk factor has been attributed to approximately 50% of the total decline in MI mortality observed in the 1980s and 1990s.[6,63,64]

2.6.1 Improved Primary Prevention

With the advancement of identifying CV risk factors associated with ASCVD, equally important development followed in efficient interventions to modify risk factor levels. Another extension of knowledge was the understanding that the overall risk of ASCVD for an individual was the product of the prevalence, severity, and number of traditional risk factors in that individual. International guidelines advocate that primary prevention treatment takes into account that a person's total CV risk varies widely in the population.[3,38,39,65] Risk assessment tools such as the ESC SCORE, Framingham Risk Scores and New Pooled Cohort Risk Equations generate estimates of the risk for future CV manifestations in an individual based on the prevalence and levels of established CV risk factors with predictive properties.[2,3,66,67] Thereby, decisions on treatment intensity can be individualized and risk-based. Successful broad implementation and a general awareness of CV risk factors in society are also part of the improved primary prevention. Treatment of CV risk factor levels lowers the progression rate of atherosclerosis causing delay or inhibition of acute manifestations.

2.6.2 Introduction of Acute Phase Interventions

Early revascularization of obstruced coronary arteries have been proven time-critial for MI-survival. Systemic treatment with fibrinolytic agents may dissolve an obstructing coronary thrombus but also poses the risk of lethal side effect from bleedning elsewhere. Coronary artery bypass grafting (CABG) has been an option for over 50 years and is the most frequent type of heart surgery procedure worldwide.[68] During CABG, a graft vein is transplanted to the coronary arteries in order to bypass segments of widespread advanced atherosclerosis for blood supply to downstream cardiac tissue. Percutaneous coronary intervention (PCI), was first performed in 1977 and is a minimally invasive endovascular catheter based therapy. Developments of the technique until the new millenia made PCI safe, reliable, and more efficient for improved outcomes. Typically, a catheter is introduced via the radial artery and angiography is performed including identification of the coronary culprit lesion(s). In the same session, a guide wire is passed through the lesion. This allows for a balloon and drug-eluding metal stent to be passed over the wire to the site of the lesion. The stent is then deployed by expanding the balloon whereafter blood flow can be restored. The introduction and further development of PCI has revolutionized acute cardiac care. With growing evidence of efficiency and increasing availability, PCI has become the treatment of choice in STEMI.[69,70] PCI is also recommended for NSTEMI, but may be performed with delay unless the clinical presentation calls for urgency.[71,72] Fairly recent trials have demonstrated superior long-term survival after CABG than after PCI in patients with complex multivessel coronary disease.[73] In Sweden, CABG remains an option in patients with complex coronary disease who are fit for thoracic surgery and recovery in a subacute or elective setting. Systemic thrombolytic therapy remains a rescue treatment in rare cases where transportation to a catheterization lab for PCI would substantially delay revascularization.

2.6.2.1 Acute Phase Risk Scores

The risks of CV events and death peak in the immediate period following a MI, declines sharply within the first few days and more gradually in the following months. In a Swedish cohort of almost 100,000 patients hospitalized for MI between 2006 and 2011, the one-year risk of recurrent MI, stroke or CV mortality was about 18% as compared to approximately 7% in the years following.[17] The risk mechanisms of new MI and death in the populations in acute phase after MI is not primarily progression of atherosclerosis. (Figure 1) Decompensated heart failure may be induced by the loss of viable myocardium, initial stunning of surrounding myocytes or cardiomechanical complications. Infarcted regions of the myocardium are also prone to trigger fatal arrhythmias. Early reinfarctions more likely relate to thrombosis of unstable ruptured plaques or implanted coronary stents.[69]

Every MI is an urgent medical matter but not all MIs are life threatening. Potent therapies available for acute coronary care also carry risk of serious complications. Therefore, the appropriate intensity and urgency of therapies are chosen based on available health care resources and individual risk assessments. The most hazardous MIs are preferably identified by prehospital crews for time-saving transport directly to coronary intervention facilities.[69] Among remaining MI patients, risk level is determined by acute symptoms, measures of MI severity, and other risk factors and comorbidities. Acute-phase risk score algorithms[74,75] are superior to clinical risk assessment and therefore recommended at admission for MI to guide priority to definitive procedures and therapies.[70,71]

2.6.3 Introduction of Efficient Drug Therapies

Drug therapies have constantly been developed and evaluated alongside increasing knowledge about atherosclerosis, underlying causal mechanisms, and CV risk factors. Briefly, the importance of antithrombotic therapy in the acute phase of MI is intuitive considering that the tipping point for manifestation of a ruptured atherosclerotic plaque is thrombus formation. Both platelet inhibition and anticoagulants are used aggressively.[69,71] In addition, antithrombotic therapy is required to prevent clot formation from catheterization during PCI and stent trombosis.[72] Furthermore, antithrombotic therapy prevents new MIs from occurring in the acute phase of MI. Four groups of drugs that are typically initiated in the acute phase of MI are evidence-based therapies also in secondary prevention after MI:

Antiplatelet therapy with acetylsalicylic acid is a cornerstone treatment in acute MI as discussed above and also in the long-term secondary prevention of recurrent MI.[76] A second antiplatelet drug is recommended in addition to acetylsalicylic acid for 12 months after MI. This protects from thrombus formation due to platelet adhesion to coronary stent material until the stent is covered by endothelium. Moreover, the MI induces a highly prothrombotic inflammatory state in itself. Although MIs managed with drugs alone are less likely to receive prolonged dual antiplatelet therapy[77], there is Level A evidence and a Class I recommendation for 12-month dual antiplatelet therapy also for MI patients managed without PCI.[78,79]

Lipid lowering therapy with statins is supported by strong evidence of secondary prevention risk reduction for recurrent ASCVD events.[80] Statin therapy also lowers levels of LDL-C, a key component in the causal pathway of atherosclerosis[81], and may additionally carry pleiotropic effects including anti-inflammatory effects. Statins, lipid lowering, and LDL-C will be discussed in more detail further on in this thesis frame.

Renin-angiotensin-aldosterone system (RAAS) inhibitors are a group of drugs that inhibit an endocrinological system important in regulation of blood pressure and electrolytes. RAAS also affects the reparatory phase during which myocardial scar tissue is formed. The heart is continuously regulated by neurohormonal factors for adequate cardiac output and the ventricular wall is under continuous mechanical strain. These complicating circumstances for repair may initially expand the infarct zone, distort the ventricular shape, cause arrhytmia-prone myocardial hypertrophy surronding the scar, and worsen chronic heart failure. The degree of remodelling is proportional to the size of the infaction and local inflammatory response. RAAS play an important role in post-infarction remodelling. With early initiation of RAAS-inhibition, the reparative response is modulated and outcome improves.[82] Additionally, RAAS-inhibition is beneficial in chronic heart failure, and for CV risk factors hypertension, diabetes, renal disease, or combinations thereof.

Beta blockers target the sympathetic nervous system by inhibiting the effect of catecholamines. Beta blockers have anti-arrhytmic properties, reduce myocardial oxygen demand and improve coronary blood flow. Many trials supporting use in acute MI and secondary prevention were conducted in the 1980s.[83,84] More efficient therapies have evolved since then, in particular revascularization therapies. Alongside decreasing mortality rates, the role of beta blocker therapy in MI has been increasingly questioned. Studies in contemporary populations show lower rates of short-term recurrent MI but no short-term mortality benefit.[85] Treatment among post-MI patients with reduced left ventricular ejection fraction (LVEF) remains a guideline recommendation but epidemiological and longitudinal data on beta blockers in long-term secondary prevention are inconsistent.[86] An ongoing registry-based randomized clinical trial will investigate the efficiency of long-term beta blockers in patient with MI and preserved left ventricular ejection function.[87]

2.7 SECONDARY PREVENTION IN STABLE PHASE AFTER MYOCARDIAL INFARCTION

2.7.1 Population Characteristics

Development of primary prevention and acute cardiac care have strongly contributed to reducing mortality after MI by half over the past decades.[6] As a consequence, the post-MI population living in Sweden has grown large. The ESC and counterpart organizations continuously produce new and updated guidelines on different aspects of cardiac care. However, the most recent guidelines specifically dedicated to secondary prevention was released in 2011.[8] A common denominator among MI survivors is that the first-ever ASCVD event attests to several years worth of systemic atherogenesis prior. Hence, new critical

obstructions and occlusions may occur elsewhere in the arterial system. Indeed, the risk of new ASCVD is elevated in the long-term secondary prevention population compared to in the general population. But lower and settled at a stable level after the first most hazardous months when many of the most frail patients die.[17]

2.7.2 Secondary Prevention Therapies

Months after a MI, the mechanism of CV risk reverts to progressive atherosclerosis again.[9,17] (Figure 1) Hence, post-MI treatment in the stable secondary prevention phase is long-term and a matter of risk factor reduction. The well-established traditional CV risk factors are targeted. Evidence-based drug treatments initiated during the acute phase have been described above. In addition, participation in cardiac rehabilitation is a cornerstone intervention of secondary prevention.[38,88] Cardiac rehabilitation is a multidisciplinary lifestyle intervention. Based on a set of structured programs, comprehensive cardiac rehabilitation is designed to address underlying causes of the traditional risk factors including physical inactivity, health illiteracy, unhealthy diet, mental health[89,90], and smoking[91]. Exercise-based cardiac rehabilitation is particularily important as rates of reinfarction and deaths are reduced from participation.[92] A 2016 Cochrane review found evidence of reduced rates of rehospitalizations and improved quality-of-life, and CV mortality.[93] Exercise-based cardiac rehabilitation is also cost-efficient.[94] Still, referral and participation rates are low.[95] Married post-MI patients are reportedly 2 times more likely to attend cardiac rehabilitation than unmarried[96] Danish researchers have demonstrated that low SES groups are more likely to be non-attendees to cardiac rehabilitation[97], and that attendance rates and secondary prevention target achievements improve if low SES-groups are selectively offered extended cardiac rehabilitation.[98]

2.7.3 Unstratified Risk and Intensity of Therapies

Unlike in primary prevention and short-term follow-up in the acute phase[2,75], no method for risk stratification has been established specifically for the long-term secondary prevention population.[3,8,38] Patients with a previous MI are considered in the ESC prevention guideline.[38] The ESC SCORE algorithm, recommended for assessment and stratification of individual total risk, instructs that patients in stable phase secondary prevention bypass the actual risk algorithm and are stratified to the “very high risk” category by default which is equivalent to an estimated 10-year risk of CV mortality higher than 10%. Recommended management and intensity of therapy is undifferientiated within this risk category (Figure 1). Moreover, patients with other types of manifest ASCVD, type 2 diabetes or type 1 diabetes with organ damage, or chronic kidney disease are also categorized to the “very high risk” group by default.[2] The most recent ESC guideline on chronic coronary disease recommend that caregivers consider regular revisits for patients in stable phase after MI. Risk assessment using unspecified “risk score(s)” for risk stratification are mentioned but without evaluation of evidence or recommendations.[9] Further discussion on secondary prevention risk scores will come later in this thesis frame.

The lack of differentiation by presence, number, and severity of risk factors within the population in stable phase after MI does not align well with the consensus on management based on individual total risk assessments.[1,3,8,38] Thus, patients with the highest risk and greatest need for aggressive treatment within the post-MI population may not be selected for the most intense treatment available. Prophylactic treatment should always balance risks associated with the indication for treatment, potential benefits of treatment, and potential treatment side effects. Highly efficient but expensive drug therapies may be cost-efficient if provided to high-risk patients only. Potential survival benefit may outweigh potential serious side effects. Conversely, potential benefits of a treatment may be outweighed by the side effects in patients with a relatively low risk of a recurrent ASCVD event. Both under- and overtreatment affect cost-efficiency for the individual patient as well as society. There is consequently a need for improved risk prediction in stable phase post MI.

The knowledge about how and if the traditional CV risk factors actually predict recurrent ASCVD events is weak.[8,99] These risk factors were epidemiologically identified and established for primary prevention to assess the risk of a first clinical manifestation of CV disease.[33] Therefore they cannot simply be extrapolated to apply to the population with established CV disease. The post-MI population is further differentiated in a high-income country affording the resources to provide modern health care. In theory, and logically, the predictive value of an untreated traditional risk factor level diminishes as an intended result of the risk factor modifying drugs and lifestyle interventions routinely used post-MI. If such a shift in relative predictive importance take place, other less established risk factors, such as SES, may play a larger role for risk of subsequent events in the post-MI setting. LDL-C and hypertension are causally linked to atherosclerosis and important to treat.[38,100,101] Regardless of being ideal risk factors that are convenienty measured and suitable for monitoring as levels respond reliably to pharmacological treatment intensity, LDL-C and blood pressure levels may not be appropriate for secondary prevention risk assessments in the stable post-MI patient.

2.7.4 Room for Improvement

The implementation of secondary prevention according to ESC guidelines[38] is evaluated periodically. EUROpean Action on Secondary Prevention through Intervention to Reduce Events (EUROASPRIRE) are cross-sectional surveys based on respondents to interviews conducted 6-36 months after a coronary event or intervention and a retrospective review of their medical records. The purpose is to chart patient CV risk factor levels and to evaluate whether secondary prevention management after coronary events or interventional procedures adheres to the guideline recommendations. EUROASPIRE was first conducted in 1994 by inititative from the ESC, the European Atherosclerosis Society, and the European Society of Hypertension and has since been repeated four times. The report of EUROASPIRE IV[11] was discouraging. 7,998 patients from 24 European countries were interviewed between 6 and 36 months after a coronary event or intervention. Among these, 49% of smokers continued and only 19% of them had been advised behavioral intervention

or pharmacological support. Obesity was reported in 38% and diabetes by 27%. 60% reported physical inactivity, 51% were advised participation in a cardiac rehabilitation program but only 41% attended. Guideline target levels for blood pressure and lipids was achieved in 57% and 19%, respectively.

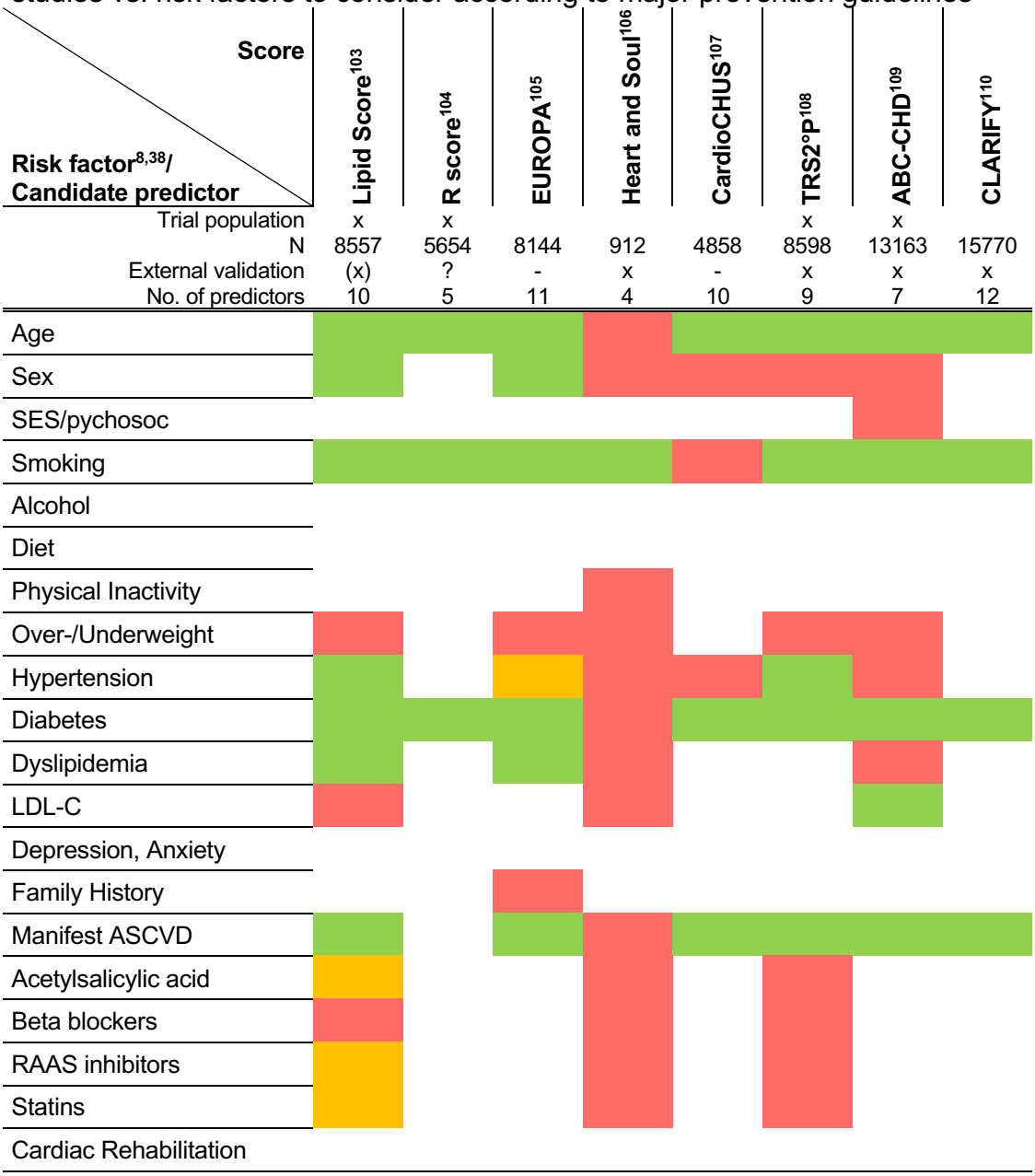
In absence of a method for risk stratification post-MI, therapy should at least be provided to each generic post-MI patient as recommended by current guidelines. Whether the 1-year survivors after MI with the highest CV risk achieve targets and received recommended therapies to a greater or lesser extent than average is unknown.

2.7.5 Review of Secondary Prevention Risk Prediction Studies

The state of knowledge on CV risk factors with predictive importance in secondary prevention after MI for recurrent ASCVD events was assessed in preparation for the half-time seminar of this thesis in November 2018. The PubMed and Web of Science databases were searched using combinations of relevant Medical Subject Headings (MeSH) keywords for secondary prevention risk prediction studies published between 2001 and 2018. Citations within retrieved articles were followed for additional references. Study samples, time between indexing event, inclusion and assessment, methods of predictor selection, and time-to-event predicted varied considerably. For sensible comparison with the post-MI cohort of this thesis, studies on populations with an indexing coronary event or procedure that were estimating risk for an ASCVD event outcome were selected for evaluation (n=8).

Table 1 reports the qualifying predictors of each secondary prevention risk prediction study by CV risk factors recommended management according to the major international guidelines on CV prevention.[3,38] Notably, neither hypertension nor LDL-C were clearly predictive of recurrent CV events in secondary prevention after a coronary event or procedure. Conversely, conformity was observed between guidelines and assessed predictive values for risk factors age, smoking status, diabetes, and previous manifestations of ASCVD across selected studies. Availability of candidate predictors were limitations of both trial- and registry-based samples. For instance, very few studies considered psychosocial factors or cardiac rehabilitation as candidate predictors. None of the selected secondary prevention prediction studies included participation in cardiac rehabilitation, a well-documented risk-modifying intervention after MI[93,102], as a candidate predictor.

Table 1. Qualifying predictors of secondary prevention prediction/risk score studies vs. risk factors to consider according to major prevention guidelines



Abbreviations: SES, socioeconomic status; LDL-C, low density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; RAAS, Renin-angiotensin-aldosterone system.
Green indicates a risk factor qualified to to the final prediction model
Orange indicates a risk factor may have qualified statistically, but was not chosen to the final prediction model or did not qualify statistically but was chosen.
Red indicates a risk factor assessd that did not qualify statstically as a predictor and was not included in the final prediction model.
Blank indicates a risk factor was not considered a potential predictor in the analysis.

2.8 RISK FACTORS WITH POTENTIAL IMPORTANCE IN SECONDARY PREVENTION

The transition from primary to secondary prevention does not reset the abundance of evidence for, sometimes causal, associations between the traditional CV risk factors and further progression of atherosclerosis. These risk factor need aggressive management also in secondary prevention. Nonetheless, the CV risk factors currently used in secondary prevention risk assessment need reevaluation. SES may better separate high- from low-risk individuals within the secondary prevention population after MI.

2.8.1 LDL-C – the Dominant Established Risk Factor

Evidence of efficient prevention of incident fatal and nonfatal ASCVD events from cholesterol lowering was first shown in 1994 by the Scandinavian Simvastatin Survival Study (4S)[111] Since then, new generations of statins have been developed, each more potent than the former with regards to both lipid lowering effect and reduction of CV events.[112] Several hypotheses on the underlying mechanisms through which lipid lowering therapies act are still debated.

The statin hypothesis suggest what the 4S Study and subsequent major statin trials were evident of; that CV risk reduction is proportional to statin therapy intensity. Proponents of the LDL-C hypothesis instead suggest that it is the achieved lower level of LDL-C that exerts an effect proportional to CV risk reduction. The LDL-C hypothesis has covered ground in recent years alongside emerging confirmatory evidence of a causal role of LDL-C for atherosclerosis based on genetic, epidemiological, and clinical studies.[81] Some advocates even suggest that effective LDL-C lowering alone may eliminate coronary disease.[32] With stronger focus on LDL-C levels in CV care overall, LDL-C has also gained a status of importance for residual CV risk assessment post-MI and for decisions on continued treatment intensity. LDL-C has become a surrogate marker of adverse outcomes. Recent examples are the first trials targeting further reduction of LDL-C on top of statins using monoclonal antibodies, proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitors. In FOURIER and ODYSSEY-OUTCOMES[113,114], LDL-C levels were reduced by half on top of high-intensity statin therapy but neither provided evidence of mortality benefits in the treatment arm. Potential benefical pleiotropic effects from statins[115], such as an anti-inflammatory[116], may have been underestimated.

The inflammatory hypothesis of atherosclerosis is far from rejected. Contrary, findings from the 2017 CANTOS-trial rather sparked interest. Another monoclonal antibody was evaluated in this trial. Canakinumab neutralizes interleukin-1ß of the innate immunity system and treatment efficiently reduced recurrent ASCVD events in patients with recent MI without interference of lipid levels.[116] Similarily, the anti-inflammatory mechanisms of a substance used by humans for millennia, colchicine[117], improve CV outcomes in patients with acute MI according to findings of a recent trial.[118] Importantly, a 2020 randomized clinical trial evaluating low-dose colchicine treatment among patients in stable phase secondary prevention after MI was also efficient for risk of recurrent ASCVD.[119,120].

Lipid level treatment targets have been used in secondary prevention of manifest ASCVD since the 1990s.[121] Initial focus on total cholesterol levels transitioned via multiple measures of dyslipidemia to LDL-C in the early 2000s.[122] Since then, the LDL-C target level has periodically been lowered in guideline recommendations.[123-125] To date, no trial has evaluated two LDL-C target levels against each other for evidence of morbidity or mortality benefit. The recommended LDL-C target levels used in clinical practice are arbitrary and based on post-hoc analyses of clinical trials and can therefore be questioned.[126]

2.8.2 Socioeconomic Status – Amplified Importance in Secondary Prevention?

2.8.2.1 Why SES may be an important risk factor in secondary prevention after MI

The mutual prognostic significance among established CV risk factors may not remain the same before and after initiation of routine secondary prevention therapy. Increasingly more aggressive management of a risk factor, such as LDL-C, will lower the on-treatment risk factor level. Hypothetically, if all measurable traditional CV risk factors in all individuals of the post-MI population were treated to normal levels, the risk for recurrent ASCVD events would decrease but still remain elevated compared to risk for incident ASCVD in the general population. Lowering CV risk factor levels may also reduce the residual prognostic importance of the risk factors. In this hypothetical framework, the prognostic importance of unmodified risk factors would increase relative to the modified traditional CV risk factors.

SES has consistently been associated with incident MI in primary prevention, independent of prevalence of traditional risk factors. SES has been put forward as an emerging non-traditional CV risk factor and suggested to be incorporated into primary prevention risk score algorithms.[13] The 2012 Joint ESC Guideline on CV disease prevention did describe SES as a risk factor.[123] The current 2016 version of the guideline categorizes SES to "other risk markers" and is highlighted as a risk modifier with potential to reclassify borderline low total risk estimated with ESC SCORE.[38]

2.8.2.2 Adherence

A major problem for health care in general is that adherence to drug treatment among patients with chronic diseases is approximately 50%.[127,128] Patient adherence is a major hurdle to overcome for improvement of secondary prevention after MI.[129] Many factors that affect adherence negatively have been identified and include the need of breaking long-standing habits, treatment of asymptomatic conditions, complex drug regimens, total number of pills[130], long duration of treatment, actual or plausible treatment side effects, low health literacy, lack of involvement in the treatment-decision process, lack of transportation, lack of social support, high medical costs, and more.[129,131]

The expectations on post-MI patients are very high with regards to adherence to the recommendations provided with CV prevention guidelines. ASCVD is a disease of the elderly and key components of secondary prevention is usually complete lifestyle change regarding diet, physical activity, alcohol and tobacco. Furthermore, risk factor-modification requires multiple pills daily that have potential side effects. Most interventions are intended for life and target asymptomatic risk factors. Although Swedish health care is heavily subventioned for the individual, secondary prevention is not free of charge.

Hence, secondary prevention after MI is a textbook example of a setting with prerequisites for poor population adherence. Many reasons for non-adherence correlate to SES and the association has been demonstrated.[46,132,133]

2.9 BACKGROUND SUMMARY

MIs are common and major contributors to overall morbidity and mortality in Sweden and globally. Several decades of considerable research efforts has improved knowledge about the underlying pathological processes, atherosclerosis, and risk factors associated with progression. Efficient therapies have been developed for risk factor modification as well as management in the acute phase of an MI. As a result, MI mortality has steadily declined over the past quarter of a century in Sweden and other high-income countries while the population with manifest ASCVD grows larger.

A less extensive scientific literature exists about the secondary prevention population in stable phase after MI. A strategy of extrapolating the risk factors, methods, and priorities of primary prevention to the secondary prevention population is ongoing. However, this practice is failing in spite of regular introduction of ever more efficient risk-factor modifying therapies. The continuous decline of 1-year mortality seem to be reaching a plateau.[60] Current approaches to secondary prevention risk factor management performs poorly with regards to achievements of stipulated treatment targets. Moreover, existing reports on the predictive values of the established CV risk factors in this population are inconsistent.

The issue of adherence may contribute to the poor performance of secondary prevention in addition to deficient understanding about the relative risk contribution from risk factors in the secondary prevention setting. SES may be considered a “cause of the causes”. That is, a determinant of health through which the established CV risk factors develop. There are strong and well established links between SES and adherence, SES and traditional CV risk factors, and between SES and CV outcomes. Hence, SES may be an underestimated risk factor in secondary prevention after MI. Relatively well-managed traditional CV risk factors such as LDL-C may receive disproportionate focus. Meanwhile, risk factors that are managed by non-physicians, including physical activity and other behavioral interventions, may also be underestimated.

The studies of this thesis targeted the knowledge gap about risk factors in secondary prevention after MI and the role of SES in this population. Through improved knowledge on these areas, high-risk individuals within a large patient population may be better identified for more individualized and risk-based treatment intensity. Moreover, health care costs-efficiency and the allocation of resources may improve.

3 RESEARCH AIMS

The overall aim of this thesis was to improve the knowledge about risk factors of importance in secondary prevention among patients in stable phase after myocardial infarction, with special focus on socioeconomic status and prognosis.

Specifically, the aims were:

- To assess the association between both established risk factors, achieved blood lipid levels, as well as a less established risk factor, socioeconomic status, and recurrent major atherosclerotic cardiovascular disease events.

- To study underlying mechanisms of risk, whether socioeconomic disparities within secondary prevention were modifiable risk mediators for subsequent cardiovascular events.

- To elucidate ways in which socioeconomic status is associated with available evidence and the recommendations found in guidelines on prevention after myocardial infarction.

4 MATERIALS AND METHODS

A large nationwide population of MI survivors was studied in retrospective cohort studies using prospectively collected data. The studies were made possible by the existence of multiple Swedish national registries and the means to link the wealth of individual-level data they collect.

4.1 DATA SOURCES

Several government agencies collect a variety of individual-level data in Sweden for purposes including national official statistics and taxation. The Swedish Tax Agency (Skatteverket) manages the Swedish Population Register which gathers birth and death certificate data. In 1947, Sweden was the first country in the world to assign each and every person residing for 1 year or more in the country a unique personal identification number to facilitate the tasks of the Swedish Tax Agency. This unique 10-digit number enables for linkage between national registries.[134] Sweden also boasts a strong tradition of numerous certified National Quality Registries that are sanctioned and partially financed by the state.[135,136] National Quality Registries collect individual-level data concerning a health issue with the purpose of nationwide health care development including the opportunity of continuous benchmarking between hospitals, and ultimately to improve the outcomes for patients. Registry-based research in Sweden requires approval by Swedish Research Ethics Committees before access to specified data requests may be granted by the central personal data controller of the registry.[136] Multiple registries were used for the studies of this thesis. The National Board of Health and Welfare collected each dataset, linked the datasets using the personal identification number, and pseudonymized the data before it was handed over to the researchers for further statistical management and merging.

4.1.1 SWEDEHEART

The National Quality Registry for cardiac care is Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) which is managed by Uppsala Clinical Research Center (UCR). As a National Quality Registry, Swedish law sanctions patient registration without active consent but patients need to be informed about registration and their right to opt-out or to have their data erased at any time upon request. Opt-out is however extremely rare. Launched in 2009, SWEDEHEART is a registry for Swedish cardiac care in its entirety with direct online data entry by local health care professionals. The web-based case report of each patient provides a convenience when patient are transfered between units and hospitals. Hundreds of variables on each individual with MI may be collected to SWEDEHEART throughout the course of care.[137] Biannual monitoring visits to each Swedish hospital is performed to ensure data consistency through random sample comparison between registry data and hospital health records. A recent application of SWEDEHEART and UCR has become to serve as a platform for registry-based randomized clinical trials (RRCTs).[138] The following SWEDEHEART sub-registries were used in this thesis:

4.1.1.1 RIKS-HIA

Registry of Information and Knowledge about Swedish Heart Intensive care Admission (RIKS-HIA), the initial care sub-registry of SWEDEHEART, was initiated in 1991, rapidly spread to new hospitals, and developed into a certified National Quality Registry in 1995. Since 2008, all cardiac care hospitals throughout Sweden reports to RIKS-HIA.[137] Detailed clinical data on previous risk factors and comorbidities, from admission, during inpatient care, and at hospital discharge are collected. In 2013, coverage was 92% of all patients aged <80 years who were hospitalized with MI (according to the 10th edition of the international classification of diseases, code I21) as the main diagnosis.[10]

4.1.1.2 SEPHIA

SEcondary Prevention after Heart Intensive care Admission (SEPHIA) was founded in 2005 as a secondary prevention complement to RIKS-HIA. Since start, the purpose has been to improve the treatment targets of secondary prevention after MI in Sweden through systematic monitoring of risk factor levels, provided care, and outcomes including risk factor target achievements.[137] Data was collected to SEPHIA at routine clinical revisits, preferably 6-10 weeks and 12-14 months after MI, in this thesis referred to as the 2-month and 1-year revisits. If a physical visit was not feasible, SEPHIA data collection was also possible via phone call and supplementary biometric and biochemical data acquired through primary health care visits at the recidency of the study participant. A SEPHIA registration was trigged by default for all patients aged ≤75 years discharged from a coronary care unit with a MI (type 1) diagnoisis in whom the RIKS-HIA-report is completed. It was optional for cardiac care centers to register older age groups. Data was collected on risk factor levels based on biometrics, blood samples, lifestyle factors, and questionaire scores, patient reported symptoms and quality of life, as well as interventions and drug therapies that were ongoing, planned, quit or completed. If a second MI occurred in an individual within the first year, it was registered as a readmission, not a new SEPHIA registration. 70 out of 72 (97%) cardiac care units in the country were reporting to SEPHIA by 2014. Completeness was 81% of eligible patients younger than 75 years attending the 1-year visit after hospital care for MI. Participants lost to follow-up were at the group-level more likely to have a history of ASCVD (and secondary prevention efforts) than SEPHIA-attendees. Agreement between registry and health record data was around 95%.[10,135]

4.1.1.3 SCAAR

Swedish Coronary Angiography and Angioplasty Registry (SCAAR) was founded in 1998 by merging national registries on angioplasty and angiography and was incorporated into SWEDEHEART in 2008.[137] SCAAR is the sub-registry on procedual interventions and collects data related to angiographies and PCIs. In 2014, 26 centres throughout Sweden performed coronary angiography and PCI.[10]

4.1.2 Statistics Sweden

Statistics Sweden (Statistiska centralbyrån, SCB) is the government agency responsible for the official statistics of Sweden including demographics. One of the registries managed is the database Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA). In the LISA database, labour market, educational, and social sector data is collected annualy on all citizens aged over 16 years.[139]

4.1.3 The National Board of Health and Welfare

The National Board of Health and Welfare (Socialstyrelsen, SoS), a government agency under the Department of Social Affairs, is responsible for collecting and managing national health data including births, deaths, hospital discharges, and prescribed drugs.[140] The following national health data registries were used in this thesis:

4.1.3.1 The National Patient Register

Since 1987, the National Board of Health and Welfare gathers data on inpatient diagnoses from all hospitals throughout Sweden. Diagnoses are coded according to the international classification of disorders (ICD). Since 2001, diagnoses registered at public and private outpatient care facilities, except primary care, were added to the registry. The National Inpatient Register is the subregistry covering diagnoses of patients hospitalized and discharged. Coverage for inpatient care is almost 100% complete.[141]

4.1.3.2 The Cause of Death Register

In Sweden, all causes of all deaths in the population has been recorded since 1911. The Cause of Death Register was managed by the Statistics Sweden until 1994 when responsibility was transfered to the National Board of Health and Welfare. Swedish law mandates that certified deaths are reported to the Swedish Tax Agency and that a separate cause of death-report is sent within three weeks to the National Board of Health and Welfare. In case a cause of death cannot be establish with reasonable certainty, autopsy is warrented. Causes of deaths reported are coded according to the International Classification of Diseases (ICD) together with personal identification data, relevant dates, geographic location, and underlying comorbidities and diseases contributing to death. Coverage of deaths is near complete and even though rates of autopsies have declined in recent year, 96% of deaths have a sufficiently specified underlying cause recorded.[142]

4.1.3.3 The Prescribed Drug Register

All drugs prescribed and dispensed at any pharmacy throughout Sweden is registered in the national Prescribed Drug Register since 2005. Data collected includes patient identification data, brand name and pharmacological substance categorized according to Anatomical Therapeutic Chemical (ATC) classification system, formulation, quantity, intended dosage regimen, and relevant dates.[143] Data on over-the-counter drugs and drugs dispensed to hospitals for inpatient care are not collected.

4.2 PARTICIPANTS

Eligible study cohort participants of this thesis were registrered in SWEDEHART at the 2-month or 1-year revisit between 1 January 2005 and 31 December 2013. The optionally higher age limit than mandatory for inclusion post-MI in the registry allowed for setting the upper age limit to 76 years or younger and the specified time intevals between index MI and the revisits were expanded to 4-14 weeks and 11-15 months, respectively. To study a cohort naïve of previous exposure to cardiovascular secondary prevention, eligible participants with previous MI, stroke, PCI or stroke were excluded.

In Study I, III, and V, only participants surviving to attend and be registered at the 1-year revisit were included for a study samples in stable phase of coronary heart disease. Baseline visits prior to January 1, 2006 were excluded for bias-minimized data on the primary indicator of SES, disposable income. In Study I, a lower age limit of 40 years was used.

In Study II, the 2-month visit was used as baseline. Two months is a sufficient time period after initiation of statin therapy to evaluate treatment effect on lipid levels[144] and for decisions on continued lipid management in clinical practice.

In Study IV, the study question required a cohort more representative of the population eligible for clinical trial participation after MI. Therefore, patients with previous history of nonfatal ASCVD or invasive cardiac interventions who survived until the 1-year visit were included. Only patients attending their revisit from 2008 were included as study participants because of when the exposure variable was introduced in SWEDEHEART.

4.3 EXPOSURES

4.3.1 Socioeconomic Status

The relative importance of different indicators of SES vary with the population and outcome studied. Therefore, multiple indicators were chosen and mutually adjusted. Besides gaining knowledge on their relative importance in secondary prevention after MI, an intent was to improve chances of findings that would be comparable to similar studies. Two well established indicators of SES in CV research, levels of income and education[44], were chosen in this thesis. Use of novel or less established indicators of SES are also recommended.[44] Owing to the importance of social support for CV disease, marital status was added as an indicator of SES.

4.3.1.1 Income level

The mean disposable income per household consumption unit was chosen to measure disposable income level. This measure accounts for each study participant's household size and composition. It is calculated by dividing the sum of the disposable income of all family members with the total household consumption weight (the sum of weighted consumption by age of each family member).[139] Data acquired in the year preceding that of the index MI was used for income levels that were unaffected by sick leave due to the MI. The income levels

were categorized by quintiles into calendar year-specific fifths to correct for inflation throughout study years, because of a proportionally higher SES in the initial years after SWEDEHEARTs secondary prevention sub-registry was founded, and for more intuitive and useful comparison than between figures of the actual earning. Due to lower median income among women than among men, the proportion of women classified to low SES by proxy of disposable income quintile was disproportional. Therefore, in Study III and V, the income quintiles were categorized into quintiles for men and women separately and then combined for gender- and calendar year-specific income levels.

4.3.1.2 Educational level

The highest educational attainment at the baseline visit was chosen and categorized according to thresholds of the current educational system in Sweden: ≤9 years, 10-12 years, and >12 years equivalent of compulsory education (primary and lower secondary education), upper secondary education, and ≥1 semester of post-secondary education including postgraduate education, respectively.

4.3.1.3 Marital status

Marital status at the baseline visit was categorized as married (including registered partnership) and not married (further subcategorized into unmarried, divorced, and widowed).

4.3.2 Blood Lipid Levels

In Study II, levels of total cholesterol, LDL-C, HDL-C, and triglycerides were used as measures of exposure. Lipid levels registered in the secondary prevention sub-registry of SWEDEHEART were from blood samples drawn in close proximity (±2 weeks) to the first revisit after MI. The principal method for obtaining levels of LDL-C was by calculation using the Friedewald forumla: LDL-C = total cholesterol – (triglycerides x 0.45) – HDL-C in millimoles per liter.[145] In cases where use of the Friedewald formula was invalid, for example if the level of triglycerides was higher than 4.5 mmol/L, or if data on non-LDL-C lipid fractions were unavailable, a direct measurement of LDL-C was used if available. Each lipid fraction was categorized into quintiles. LDL-C was also categorized by thresholds used in guidelines and clinical practice[124]: <1.8 mmol/L, 1.8 to <2.6 mmol/L, 2.6 to <4.0 mmol/L, and ≥4.0 mmol/L.

4.3.3 Clinical Trial Participations

Exposure of Study IV was clinical trial participation (no, yes). The original SWEDEHEART variable was introduced in 2007 for data collection at the 2-month and 1-year revisits and affirmative responses had the options: yes – lipid lowering therapy trial or yes – other clinical trial.[137]

4.4 OUTCOMES

4.4.1 Recurrent Atherosclerotic Cardiovascular Disease Events

In 2013, the ACC/AHA replaced the Framingham Risk Score with the New Pooled Cohort Risk Equations as the recommended primary prevention risk algorithm. As a consequence, the predicted outcome changed from composite MI or coronary heart disease death to a new primary composite outcome, "first hard ASCVD event" which was defined as first occurrence of nonfatal MI, coronary heart disease death, or fatal or nonfatal stroke. The new composite outcome was chosen because of greater clinical relevance for patients and providers.[3]

The primary outcome in Study I, II, IV, and V, rASCVD, mimics the outcome of the New Pooled Cohort Risk Equations and the prefix *r* indicates "first recurrent". Apart from clinical relevance of chosen events, rASCVD also resembles the composite outcomes used in many outcomes trials that shape evidence and guideline recommendations after MI. Events were defined as nonfatal MI, coronary heart disease death, fatal or nonfatal ischemic stroke. Codes for corresponding main discharge and death diagnoses according to ICD-10 were collected from the National Inpatient and Cause of Death registries. (Table 2) Events of rASCVD were collected from study baseline visit until the first event within the follow-up time frame or censoring due to study end or death from other cause.

Table 2. Definition of ASCVD

Outcomes			ICD-10 code	Registry
ASCVD	Nonfatal MI		I210-I214 & I219, I220-221, I228-I229	Inpatient
	CHD Death	Fatal MI	I210-I214 & I219, I220-221, I228-I229	Cause of Death
		Sudden Cardiac Death	I461, I469	Cause of Death
	Fatal Ischemic stroke		I630-I635, I638-I639	Cause of Death
	Nonfatal Ischemic Stroke		I630-I635, I638-I639	Inpatient

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; ICD-10, international classification of diseases, 10th edition; MI, myocardial infarction; CHD, coronary heart disease.

4.4.2 Secondary Outcomes

In Studies I and II, secondary outcomes were fatal or nonfatal MI (ICD-10: I21.0-4, 9 and I22.0-1, 8-9), fatal or nonfatal ischemic stroke (ICD-10: I63.0-9), and all cause death. In Study V, CV mortality (defined as ICD-10: I00-99) and all cause death were secondary outcomes.

4.4.3 Secondary Prevention Activities and Treatment Target Achievements

In Study III, relevant major CV prevention guidelines were consulted for the selection of study outcomes.[8,38] SWEDEHEART variables were available for most risk factor targets and secondary prevention activities recommended while some were not. For example, no data was available to assess the targeted lifestyle change to a mediterranean diet and no variable existed for administration of annual influenza vaccination.

Risk factor target outcomes were assessed at the 1-year revisit and included achievement of:

- Smoking cessation. Estimated among study participants that were current smokers at admission for the index MI.
- Physical activity. Based on self-reported activity on leisure time during the week prior to the revisit. Defined by the achievement of the recommended minimum activity level of at least 5 sessions a week of moderate exertions lasting 30 minutes or more.
- LDL-C. Achievement was defined in relation to target levels applicable in Sweden during the study period: <2.5 mmol/L before 2012 and <1.8 mmol/L after 2012.
- Blood pressure. Thresholds were set for systolic blood pressure to <140 mmHg and for diastolic blood pressure to <90 mmHg.
- Glycated Hemoglobin (HbA1c). A threshold was set at <53 mmol/mol and assessed among study participants with a diabetes diagnosis at the index MI.

Secondary prevention activities utilized throughout the first year after MI included:

- Participation in programs within comprehensive cardiac rehabilitation registered at either the first or second follow-up visit:
    - Physical training program. Defined as structured individualized physical exercise including both cardiorespiratory and weight training led by a physiotherapist for 3 months or more.
    - Patient educational group sessions (Hjärtskola). Interactive program during which MI patients and their family members are educated on coronary artery disease and consequences, CV risk factors, healthy diet, tobacco use, psychosocial factors, physical activity and exercise for risk factor control and drug therapies. Information routinely provided during inpatient care, at discharge and at revisits not included.
    - Stress management group session. Structured behavioural program led by a person with competence in techniques for stress relief. Estimated in study participants with self reported symptoms of anxiety or depression screened for at the 2-month visit using the EQ-5D standardized questionaire.[146]
    - Smoking cessation program. Structured program or counseling arranged by the hospital, primary care or private initiatives. Estimated in study participants smoking at admission for the index MI.
    - Dietary course. Program on healthy dietary habits intended for patients with coronary disease.

- Monitoring of risk factor levels:
    - Glycated Hemoglobin (HbA1c) monitoring. Monitoring was considered adequate in study participants with diagnosed diabetes if there were ≥2 measurements recorded out of the three patient-health care interactions at discharge from initial care, and the two revisits.
    - Lipid level monitoring. Adequate monitoring was set to registration of a blood sample drawn for a lipid panel including total cholesterol, LDL-C, HDL-C, and triglycerides at ≥1 of the two revisits.
    - Statin therapy intensification. Whether statin therapy was intensified between the two follow-up visits was estimated using data from the National Prescribed Drugs Register on the dosages and statin-types of the claimed statin prescriptions. Statin therapy intensity was stratified according to the 2013 ACC/AHA Blood Cholesterol Guideline[122,147] and the statin intensity (high, moderate, low) prescribed at each routine revisit was compared.
- Drug treatments initiated at discharge and persistent use at the 1-year visit:
    - Dual antiplatelet treatment. Assessed at discharge but not at the 1-year (12 to 14-month) revisit because planned period of use was expected to be shorter according to guideline recommendation.
    - Acetylsalicylic acid
    - Statins
    - High-intensity statin therapy. According to the high-intensity definition of the 2013 ACC/AHA Blood Cholesterol Guideline[147] by using data from the National Prescribed Drug Register on statin type and dosage prescribed at discharge from the index MI and the 1-year revisit.
    - RAAS inhibitor. Including use of either angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Use was assessed in study participants with indication for treatment including hypertension, diabetes, or LVEF ≤40% during initial care.
    - Beta blockers. Assessed in study participants with indication for use; LVEF≤40% during initial care.

4.5 COVARIATE MANAGEMENT

4.5.1 Clinical Data Management of Variables Used in Analyses

A large number of clinical variables were used for cohort description and analyses in the studies of this thesis. The covariates included in analysis models are reported in Table 3 and the data definitions and management were as follows: Smoking status (current, never, or former defined as cessation >1 month prior) was self-reported at MI and at 2-month and 1-year visits. Body mass index (kg/m^2) was calculated by dividing weight (kg), measured at revisits, with height (m), measured at MI, squared and used as a continuous variable or categorized according to WHO thresholds (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2). Diabetes (yes, no) collected at admission was defined as dietary or pharmacological treatment of the

disease, while variables collected at revisits were oral treatment for diabetes (yes, no) and insulin treatment for diabetes (yes, no) and were used separately or joined into a diabetes (yes, no)-variable. Hypertension (yes, no) was based drug treatment for hypertension at admission, or on dichotomization (systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg) of continuous measurements at revisits. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[148] using serum or plasma Creatinine measured at initial care and a mean value if more than one data input was recorded. Unless continuous values, chronic kidney disease staging (>90, 60-89, 30-59, 15-29, <15 ml/min/1.73m^2) thresholds were used. Heart failure (yes, no) was based on a previously documented left ventricular dysfunction (for example by echocardiography examination) at admission. Symptoms of anxiety or depression (yes, no) was collected at revisits, based on the EQ-5D-3L questionnaire[146], and dichotomized by joining categories mild and tangible as affirmative. Hyperlipidemia (yes, no) was collected at MI admission and indicated ongoing drug treatment. Total cholesterol, LDL-C, HDL-C, and triglycerides were continuous measurements in mmol/L. Previous stroke, MI, PCI, and CABG were dichotomous variables collected during initial care. Peripheral artery disease (yes, no) was created using the National Inpatient Register by combining ICD-10 codes I702, I702A, I702C, I702X, I739, and I739B diagnosed prior to the 2-month revisit to match the definition used in the TRA2°P-TIMI50-trial.[108] Main complaint (chest pain, other) at MI admission was dichotomized by joining dyspnea, cardiac arrest, and other primary presenting symptoms. ECG ST deviation (STEMI vs. NSTEMI) was created using a variable on MI type (STEMI vs. NSTEMI) determined at coronary care unit discharge using formal criteria and clinical judgement. In cases where the discharge infarction type data was missing, available admission ECG data on ST deviation for STEMI (defined as ST elevation of (i) ≥1 mV amplitude in leads I, II, III, aVF, aVL, V5 and V6 or (ii) ≥2 mm in leads V1, V2, V3 and V4, in ≥2 adjacent leads), NSTEMI (defined as 0,05 mV ST depression in ≥2 adjacent leads) or QRS annotation of pathological Q-waves (defined as (i) ≥30 ms duration and (ii) a 25% R/Q-ratio) or left bundle branch block (defined as (i) QRS duration >120 ms (ii) monophase R-wave in leads I, V5, and V6, (iii) absent Q-waves in leads V5 and V6) was used. ECG rhythm (sinus, non-sinus) collected during initial care and at the 1-year revisit were used with atrial flutter/atrial fibrillation and other rhythms joined to the non-sinus category. Angiographic findings (myocardial infarction with non-obstructive coronary arteries, 1-vessel, 2-vessel, 3-vessel or left main disease) was a created by re-categorizing the more detailed original variable on significant lesions and their location as assessed by the angiographer. Troponin max (quintiles) was created using data on cardiac injury biomarker type (troponin T, troponin I, or high-sensitivity troponin T) and biomarker maximum levels (µg/L, µg/L or ng/L). The maximum troponin levels were categorized into quintiles by biomarker type and the highest biomarker quintile measurement of a study participant was selected. LVEF (≥50%, 30-49%, <30%) or (≥50%, <40-49%, <40%) categorizations were used for assessments obtained during initial care. PCI if angiographic pathology (yes, no) was created by dichotomizing the angiographic findings-variable and a variable on types of PCIs performed, and then combining the two. Dual antiplatelet therapy (yes, no) was defined as simultaneous use of

Table 3. Covariates included in analyses by thesis study

	Study I	Study II	Study III	Study IV	Study V
Age	C	C/P	C	C	C
Gender	C	C	C	C	C
Calendar year of baseline visit	C	C	C	C	C
Income level	E		E	C	E
Educational level	E		(E)	C	(E)
Marital status	E		(E)	C	(E)
TRADITIONAL RISK FACTORS	S2	S1		S2	MI
Smoking status	C	P		C	M
Body mass index	C			C	M
Diabetes (dietary, oral or insulin treatment)	C	P		C	M
Hypertension treatment at MI	C				M
Systolic blood pressure	C		[O]	C	
Glomerular filtration rate at MI	C	P		C	M
History of congestive heart failure at MI		P			M
Symptom of anxiety or depression at S1				C	
Hyperlipidemia treatment at MI					M
Lipid levels	S2	S1		S2	
Total Cholesterol	C	E		C	
LDL-C	C	E	[O]	C	
HDL-C	C	E		C	
Triglycerides	C	E		C	
Coronary disease and symptoms					
Previous MI	N/A	N/A	N/A	C	N/A
Previous stroke	N/A	N/A	N/A	C	N/A
Previous PCI	N/A	N/A	N/A	C	N/A
Prior CABG	N/A	N/A	N/A	C	N/A
Peripheral artery disease at S1		P			
Main complaint					M
ECG ST deviation					M
ECG rhythm	MI C			S2 C	MI M
Angiographic findings					M
Troponin max	C				M
Left ventricular ejection fraction	C			C	M
INITIAL THERAPIES AND SECONDARY PREVENTION					
PCI if angiographic pathology					M
Dual antiplatelet therapy					M
Planned procedure					M
Lipid profile monitoring			O		M
Statin therapy intensification			O		M
Screening for depression or anxiety					M
Participation in clinical trial				E	
Cardiac rehabilitation program participation	S2			S2	S1+2
Physical training program			O	M	M
Patient educational session	(C)		O	M	M
Dietary course	(C)		O	M	M
Smoking cessation program			O	M	M
Stress management group session			O	M	M
Evidence-based drug therapies at S2			S1+2		
Acetylsalicylic acid			O	M	M
Statins	(C)		O	M	M
Beta blockers			O	M	M
RAAS inhibitors.			O	M	M

Abbreviations: C=potential confounding factor. P=predictor according to TRS2°P prediction model.[108] E=study exposure. M=mediator. N/A=variable used for sample exclusion criteria. O=Outcome variable. [O]= dichotomized version of variable used as outcome. MI=variable collected at admission or discharge from initial care of the index MI. S1=variable collected at 2-month visit. S2=variable collected at 1-year visit.
Parentheses indicates that the variable was not part of the main analysis

acetylsalicylic acid and another antiplatelet inhibitor at discharge from initial care. Planned procedure (yes, no) was created from three variables indicating whether a referral was written by the time of initial care discharge for angiography, PCI, and sub-acute CABG, respectively. Screening for depression or anxiety (yes, no) was defined as yes if a data was registered and no if data was missing. The remainder of variables listed in Table 3 are described separately in the Exposures and Outcomes sections.

4.5.2 Covariate Determination

In all studies of this thesis, bias-minimized analysis models were built using causal diagrams, Directed Acyclic Graphs.[149] This is a graphical method in which analytic covariates and their relationships are drawn according to a set of rules. Assumptions on the causal direction of relationships are introduced in this method. These assumptions were based on the collective experience of the research group from clinical work within cardiac care and registry-based research and literature review. The causal diagram then guide decisions on appropriate statistical management for bias-minimized analyses by determining measurable confounding and mediating factors. Age, gender, and calendar year of inclusion were potential confounders. That is, analytic covariates presumed to be causal in their relationship with both the exposure and the outcome. Circumstances considered were the upper age limit for SWEDEHEART inclusion, higher median age at incident ASCVD manifestations among women than among men, changes in clinical management taking place during the study period, and less representable data during initial years after the SWEDEHEART secondary prevention sub-registry was founded.

In Study I, two approaches to the relationship between covariates were considered. In the alternative approach, both SES and CV risk factors were presumed to be determined by unknown and unmeasured factors in common which suggested that CV risk factors were confounders. In Study II, both an explanatory and a prediction modelling approach was used. Confounding was considered in the former while causal relationships and confounding are irrelevant for prediction models. In Study IV and V, groups of variables in the association between the respective exposure and rASCVD were determined to be confounders and mediators. In Study V, relationships between covariates were thoroughly rethought with special consideration for the risk factors and therapies recommended in major international guidelines and for the chronological order in which variables were collected.

4.6 STATISTICAL ANALYSES

Patient characteristics were reported as means and standard deviations (Study I, III, IV, V) or medians and interquartile ranges (Study II) for continuous data and as frequencies and percentages for categorical data. Differences between study group characteristics were compared using Student's t-test for continuous data and chi2-test for categorical data in studies with predefined hypotheses on the matter (Study III and IV).

Study II used the 2-month revisit as baseline and remaining studies identified the cohort at the 1-year revisit. In studies with time-to-event analyses (Study I, II, IV, V), participants were

followed from the date of the study baseline visit until the first occurrence of an event, death due to other causes, or study end on December 31, 2013 (Study I and II) or on December 31, 2018 (Study IV and V). Crude incidence rates of rASCVD by exposure category were calculated as the number of events per 1000 person-years and Kaplan-Meier curves were generated to visualize crude cumulative occurrence of rASCVD. Multivariable Cox proportional-hazards models were used to estimate cause-specific hazard ratios (HRs) and 95% confidence intervals (CIs) in order to assess the associations between the study exposure and rASCVD. The proportional hazards assumption was assessed by means of scales of Schoenfeld's residuals. No evidence of departure from this assumption was observed.

Data management, calculations and statistical analyses were performed using Stata versions 14, 15, and 16 (StataCorp, College Station, TX, USA) and R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) for mediation analyses in Study V and for rendering Forest Plots in Studies III and IV.

4.6.1 Study I

Two Cox regression models were created. Model I included the three SES indicators and confounders sex, baseline age and calendar-year. Based on the idea of existing unknown and unmeasured factors that determine both SES and CV risk factors, model II was further adjusted for selected risk factors considered relevant in secondary prevention management (smoking status, diabetes, lipid levels, systolic blood pressure, hypertension treatment, body mass index, eGFR, LVEF, maximum troponin level, and heart rhythm). A third model, additionally adjusted for treatment variables collected at baseline was added by suggestion during the publishing review process in order to evaluate whether received secondary prevention treatment affected the associations between SES and rASCVD. Furthermore, gender subgroup analysis on the association between the SES indicators and rASCVD was performed. Missing data were imputed at the time of the baseline visit using last observation carried forward if previous measurements existed (that is, either during the 2-month revisit or during initial care). Remaining missing values were included in the models as a separate category.

4.6.2 Study II

In an etiological (or explanatory) modelling approach, group level associations between each of the lipid fractions and rASCVD were estimated using two Cox regression models. Model I was crude, reflecting the basis for decisions on lipid lowering therapy in clinical practice. Model II was bias-minimized and adjusted for age, gender, and year of the 2-month revisit. A prediction modelling approach was also used. Model III was built on 9 variables that had been identified and selected among numerous candidate clinical indicators of ASCVD risk in an externally validated secondary prevention risk prediction study.[108,150,151] The four lipid fractions were then added to model III, one at a time, and the predictive performance was measured by calculating differences in Harrell's C index[152] with standard errors calculated using the jackknife estimator.[153] The incremental predictive model performance from adding

the four lipid fractions was additionally assessed by estimating differences in integrated discrimination improvement (IDI) and continuous net reclassification improvement (cNRI).[154,155]

In a sensitivity analysis, the robustness of model II findings was assessed by comparing estimates of the association between lipid levels and rASCVD in subgroups with and without high-intensity statin therapy. A second sensitivity analysis evaluated the potential confounding from intensification of lipid lowering therapy after the baseline visit among patients with high LDL-C levels. This was done by adding an adjustment factor accounting for any change in statin treatment intensity (none, decrease, increase) after the 2-month revisit to model II. In a third sensitivity analysis, HDL-C and triglycerides were both entered into model II in order to evaluate covariation between levels the two lipid fractions. There were negligible numbers of missing data for variables included in analytic models I-III and therefore no imputation of data was performed.

4.6.3 Study III

Associations with the outcomes were estimated using multivariable logistic regression models including the disposable income quintiles, age, sex, and calendar year of the baseline visit. Estimates were presented as odds ratios (ORs). Robust sandwich estimators were used to estimate standard errors and 95% CIs were reported. Educational level and marital status were added as covariates in separate analysis for estimates of associations with the outcomes in which SES-indicators were mutually adjusted. No missing values were imputed because of few missing values. The characteristics of participants with and without complete outcome data were reported separately.

4.6.4 Study IV

Univariate Poisson regression models with robust standard errors were used to estimate risk ratios (RRs) and 95% CIs in the associations between clinical trial participation and each sociodemographic, clinical and therapeutic characteristic. Clinically relevant thresholds were chosen for continuous outcome variables (LVEF <30%, eGFR <60 ml/min/1.73 m2, systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, body mass index ≥30 kg/m2, non-HDL-C ≥2.6 mmol/L, LDL-C ≥1.8 mmol/L, HDL-C <1.0 mmol/L in men and <1.2 mmol/L in women, triglycerides ≥1.7 mmol/L. SES indicators were dichotomized: highest vs. lowest disposable income quintile, highest vs. lowest educational level and married vs. not married.

Four multivariable Cox regression models were developed to estimate the association between clinical trial participation and rASCVD. Model I was adjusted for potential confounders (age, sex, and calendar year). Sequential models added potential risk mediators. Model II was further adjusted for traditional risk factors including previously ASCVD manifestations (previous MI, stroke, or heart surgery), LVEF and eGFR at discharge from initial care, and heart rhythm, smoking status, diabetes (with oral and/or insulin treatment), systolic blood pressure, body mass index, symptoms of anxiety or depression, and achieved

lipid levels (total cholesterol, LDL-C, HDL-C, and triglycerides) at the 1-year revisit. Model III was further adjusted for use of secondary prevention therapies including evidence-based drugs (acetylsalicylic acid, statins, beta blockers, and RAAS inhibitors) and participation in comprehensive cardiac rehabilitation (physical training program, interactive patient educational sessions, dietary advice course, smoking cessation program or counseling, and stress management group sessions). Model IV was further adjusted for SES (disposable income, educational level, and marital status). Missing values were included in the models as a separate category.

4.6.5 Study V

Five Cox regression models were developed. The base model included disposable income as proxy for SES and age, gender, and calendar year that were considered confounding factors. Then, clusters of covariates were added in sequential models by chronological order of participant exposure. Risk attenuation attributable to each added cluster was intended to be interpreted as a mediating effect. Clusters were (i) CV risk factor accumulated prior to the index MI, (ii) measures of MI presentation and severity, (iii) initial therapies including procedural interventions and discharge drugs, and (iv) secondary prevention utilization including comprehensive cardiac rehabilitation participation, lipid management, screening for anxiety or depression during follow-up, and evidence-based drug therapies used at the 1-year revisit.

Risk mediation was additionally assessed on time-to-event data to allow for mathematically consistent interpretation of causal mediation.[156,157] For this analysis, four potential mediators were selected: risk profile through the metabolic syndrome, participation in physical training program, participation in patient educational sessions, and optimal statin management (statin intensity increase during first year after MI or high-intensity statin therapy at the 1-year revisit). Estimates of proportional causal natural indirect direct (NIE), i.e. mediated through a potential mediator, and natural direct effects (NDE) between the highest and lowest income quintile on rASCVD were calculated for selected potential mediators. A Cox regression base model was used for the primary outcome and logistic regression models were used for the selected potential mediators. The proportion of the total excess probability attributed to the NIE for a potential mediator was calculated. 95% bootstrap intervals based on 1000 resamplings were calculated around the estimate.

In a sensitivity analysis assessing the robustness of using disposable income as proxy for SES, three sequential Cox regression models were repeated adding educational level and marital status to the models for estimates of the association with rASCVD for mutually adjusted indicators of SES. For variables with higher percentages of missing values (body mass index, admission ECG ST-deviation, angiographic findings, maximum troponin level, and LVEF), missing values were included in the models as a separate category and this imputation strategy was evaluated in a complete case analysis.

4.7 ETHICAL CONSIDERATIONS

The Helsinki declaration is a set of ethical principles for medical research involving human subjects that was first adopted by the World Medical Association General Assembly in 1964.[158] As required, studies of this thesis were approved by a Research Ethics Committee, the Ethical Review Board in Stockholm.

Focusing on SES, an overall theme relates to the first article of the United Nations declaration on human rights adopted in 1948[54], which reads: "All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood." Acknowledging the existence of widespread disparities in secondary prevention after MI, in a country with universal health care, provides incentives for further exploration on underlying causal mechanisms and study on efficient measures to improve health equity.

According to the Helsinki declaration, the forseeable benefits of conducting a study must outweigh risks and burdens to the research subjects. From this ethical aspect, ASCVD is a chronic disease and the most common cause of mortality and morbidity both in Sweden and globally. New knowledge based on relevant hypotheses, sound scientific methods, and high quality data have the potential for real-world improvements. However, the study participants are unlikely to benefit directly from study findings. This thesis was registry-based in its entirety. Although SWEDEHEART data is collected prospectively, the design of the studies of this thesis were retrospective. Consequently, many participants were not even alive by the time of data analyses. Unlike experimental study designs, observational studies poses no risk of physical harm for participants.

General principles of the Helsinki declaration state that the well-being, rights, dignity, integrity, confidentiality of personal information, and privacy of the individual research subjects must always exceed the interests and goals of science and society. Several legal ethical measures were undertaken in addition to applications for ethical approvals; A confidentiality agreement was established between Karolinska Institutet and agencies that manage the National Registries used. The dataset used for this thesis was created in compliance with the Personal Data Act (personuppgiftslagen). Before the data was made available to the researchers, the National Board of Health and Welfare had pseudonymized the linked dataset. A deciphering key was kept at the government agency for a predetermined time period until destruction. During this time period, requests for complementary data extracts were only considered after amendment approval by Regional Ethical Review Boards. Thereby, the research group were never directly handling sensitive information that was traceable to individual identities. Furthermore, the cohort size was sufficiently large to make identification through combination of individual-level data highly unlikely.

Infringement of personal integrity is possible in a retrospective registry-based study. The degree of such violations are dependent on subjective sense of harm as well as more objective plausible or actual consequences. The individual-level data used in this thesis not only

contains extensive sensitive information on personal health but also on socioeconomic indicators. If all data used in this thesis was made freely available, in particular if identities were deciphered, misuse could take many forms. For instance, personal health data on morbidities and risk factors for morbidities and preterm death as well as personal data on SES could lead to discrimination. Assumptions on risk derived from personal health data have major plausible consequences for insurance policies, employment and career opportunities.

Informed consent is another ethical cornerstone of the Helsinki declaration. Swedish registry-based research is typically approved by Swedish Research Ethics Committees even though it is debatable whether all requirements for informed consent are met. The first article of the Helsinki declaration states that the declaration applies to medical research involving "identifiable human material and data". Apart from the initial collection of data to SWEDEHEART, one may claim that the researchers involved in this thesis project only access pseudonymized data. However, a deciphering key does exist. One may question what measures have been taken to keep such deciphering keys safely stored away from unauthorized access considering the continuous digitalization of society and increasing demands for data safety. In theory, the mere existence of a deciphering key for our pseudonymized dataset in fact means our data is traceable to individuals, i.e. identifiable human data, and the Helsinki declaration should apply. The Helsinki declaration further declares that there may be "exceptional situations", where informed consent is "impossible or impracticable to obtain", where research may be conducted if a Research Ethics Committee first reviews, considers and approves such research. It was not feasible to contact each study participant of our cohort because of (i) pseudonymization, (ii) the retrospective design with occuring deaths prior to analyses, and (iii) the large sample size.

Article 13 of the Helsinki declaration states that "Groups that are underrepresented in medical research should be provided appropriate access to participation in research." Registries with nationwide coverage provide an opportunity for insights on misrepresented groups. Although exclusion criteria also applies for registration in SWEDEHEART, data representability for real-world patients is better than in many other types of research. For example, participation bias of clincial trials was possible to elucidate in Study IV.

With the privilege of access to Swedish registry data for research, ethical obligations on another level follows. Swedish registry-based research has a high international reputation because the unique prerequisites for high-quality research has been well managed. SWEDEHEART-based studies are frequently published in high-impact medical journals. Other countries without comparable population and health registries, but with similarities regarding for example demography, wealth, and health infrastructure, are likely to assimilate Swedish registry-based research findings and apply them on their respective populations. Therefore, the high quality of the registry data must be matched by the research conduct including hypotheses of importance and high-quality methods for reliable results.

In contemporary research, significant positive results are more likely to be published. Unfortunately, this publishing practice may lead to ethically unjustifiable selective reporting,

adaptations of research questions, methods, or in worst case, the underlying data. Counteractively, many medical journals have made it a condition of consideration for publication that the analysis plan of a clinical trial must be made publicly available in advance of trial conduct. No such demands apply to observational studies. Voluntary prospective public registration of analysis plans for non-trial studies are even sometimes discouraged by medical journals. Therefore, the ethical and moral responsibility not to deviate from a predefined hypothesis towards data-driven results is high within registry-based research.

In conclusion of this research ethics reflection, the potential benefits of conducting the studies of this thesis by far exceeded potential risks for individual study participants. Furthermore, registry-based research is associated with an ethical obligation towards study participants to manage the data they made available with care and respect.

5 RESULTS

Main results are summarized in this section. For detailed reports of results, the reader is referred to the full manuscripts appended at the end of this thesis.

5.1 STUDY I

29,226 study participants were studied. Mean (SD) age was 63.1 (8.1) years and 26.9% were women. Higher income was associated with higher educational level and being married. Lower SES was associated with female sex, smoking, depressed LVEF, treatment for diabetes, body mass index, and lower eGFR. Higher SES groups were more likely to use statin therapy and participate in patient educational sessions and diet courses, and less likely to use diuretics.

During the mean 4.1-year follow-up, there were 2284 (7.8%) rASCVD. All three SES indicators were associated with rASCVD and the strongest association was observed for disposable income (Figure 2). In multivariable Cox regression analysis with mutually adjusted indicators of SES (Figure 3), adjustments for clinically relevant CV risk factors in model II attenuated risk estimates, whereas further adjustment for identified differences in secondary prevention therapy did not.

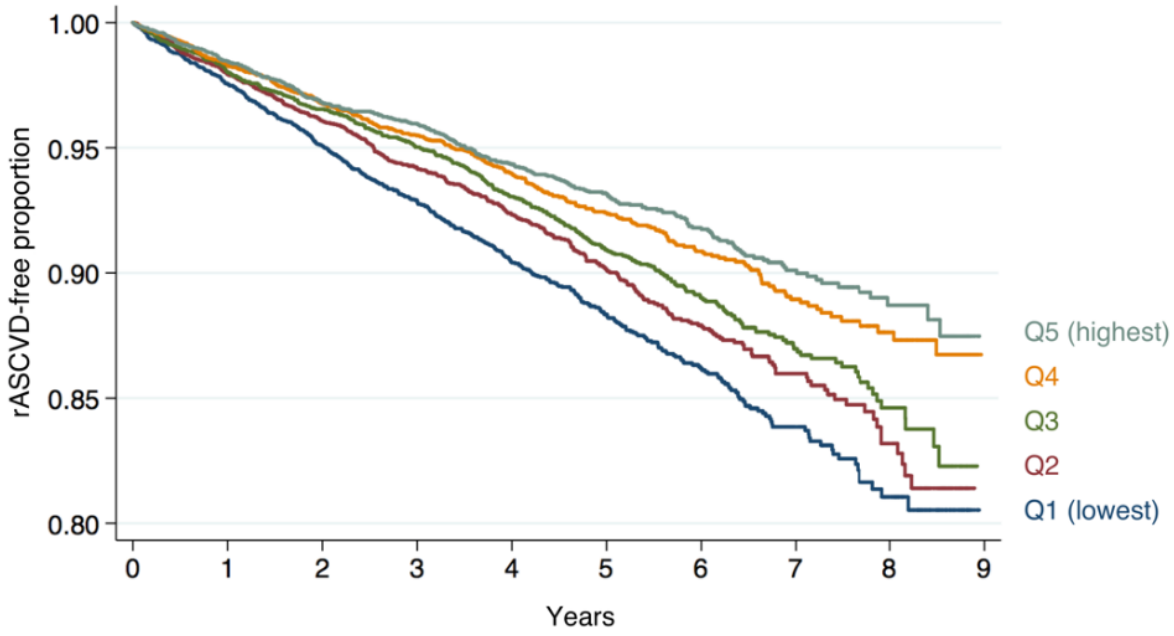


Figure 2. Kaplan Meier estimate depicting the rASCVD-free proportion by disposable income quintile.
Abbreviations: rASCVD, first recurrent atherosclerotic cardiovascular disease event. Q, quintile.
Ohm J, Skoglund PH, Discacciati A, et al. Socioeconomic status predicts second cardiovascular event in 29,226 survivors of a first myocardial infarction. Eur J Prev Cardiol. 2008;25(9):985-993, by permission of Oxford University Press.

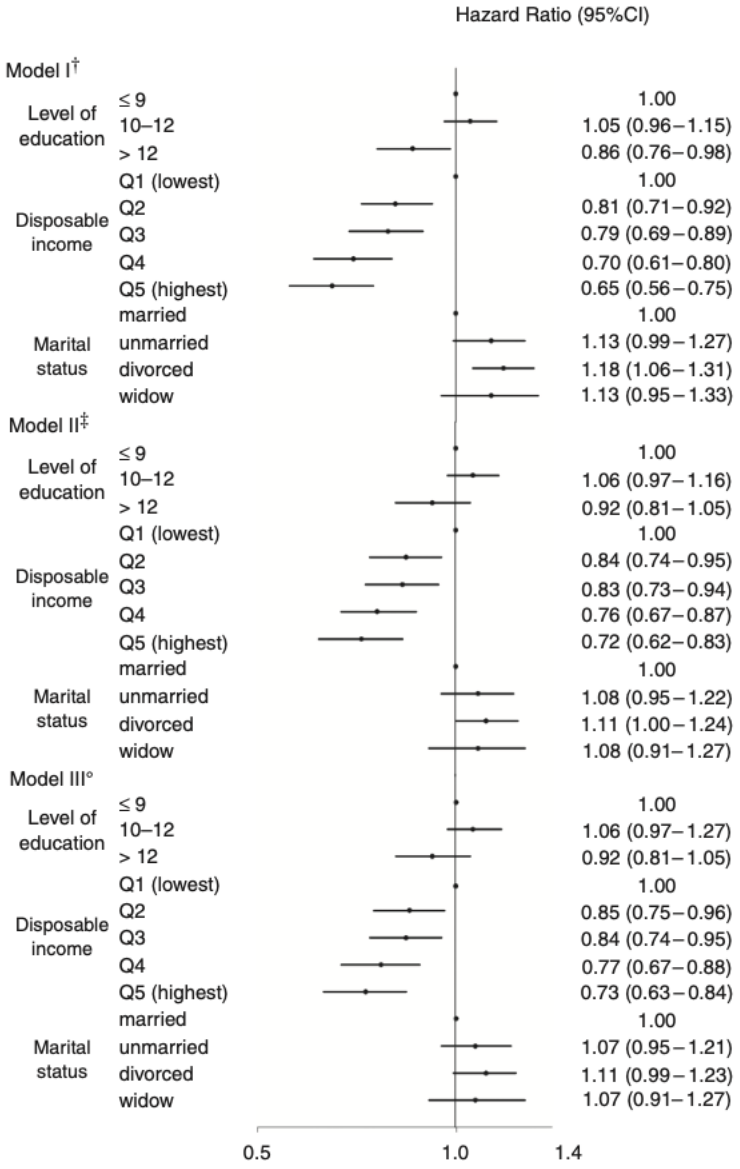


Figure 3. Estimates of the associations between SES-indicators and rASCVD by analysis model depicted with Forest plots.
Model I was adjusted for age, sex, and calendar year. Model II was adjusted for multiple CV risk factors. Model III added treatment with statins and diuretics, particiaption in patient educational session and dietary advice course.
Ohm J, Skoglund PH, Discacciati A, et al. Socioeconomic status predicts second cardiovascular event in 29,226 survivors of a first myocardial infarction. Eur J Prev Cardiol. 2008;25(9):985-993, by permission of Oxford University Press.

In subgroup analysis by sex, the proportion of rASCVD was higher among women (8.2% vs. 7.7% among men). No association between SES and rASCVD was detected in the female subgroup. Sex interactions was observed in the association between disposable income and rASCVD which indicated greater effect on risk among men ($p<0.05$). Sex interaction was also observed in the association between marital status and rASCVD which indicated that unmarried men but married women were at higher risk ($p=0.01$ for unmarried status).

5.2 STUDY II

In the final study cohort (n=25,643), median (IQR) age was 63.3 (56.4, 68.8) years, 27% were women, and 96.9% were on statin therapy at the 2-month revisit according to data on claimed drug prescriptions from the National Prescribed Drugs Register. Study participants with lower LDL-C levels were typically older, men, non-smoking, obese, and were treated for hypertension and diabetes. Lower levels of LDL-C was associated with claiming prescriptions for more intense statin therapy and use of RAAS inhibitors. Levels of total cholesterol and triglycerides but not HDL-C were clearly correlated with level of LDL-C.

During a mean 4.1-year follow-up, rASCVD occurred in 8.5% of study participants (n=2173). Achieved levels of LDL-C and total cholesterol were associated with a moderate risk of rASCVD, but only in the highest vs. referent lowest quintile and weaker for LDL-C than for total cholesterol. (Figure 4) Achieved levels of HDL-C in the third to fifth quintiles vs. the lowest were associated with lower risk of rASCVD and the greatest risk reduction was observed in the median quintile. For achieved levels of triglycerides, increasingly strong associations with rASCVD was observed from the third to the fifth quintiles vs. the lowest.

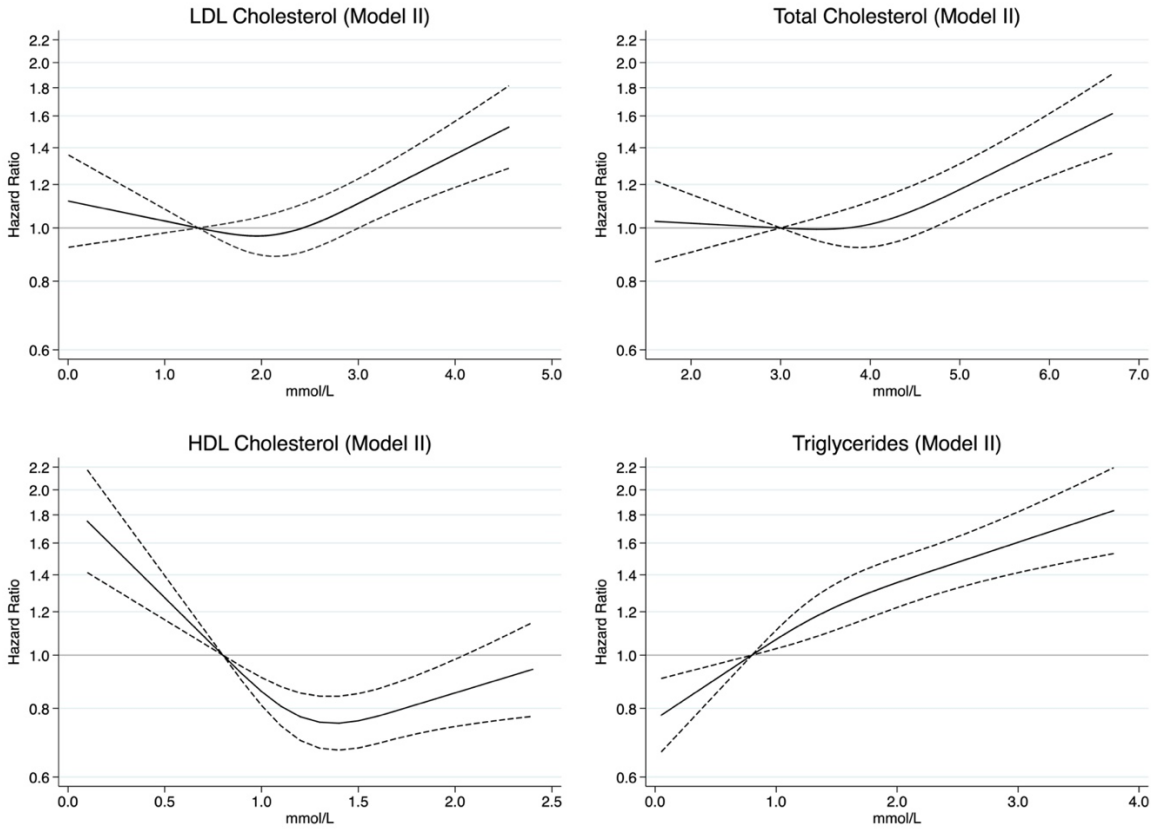


Figure 4. Association between continuous lipid fraction levels modelled with restricted cubic splines and rASCVD. The median lipid level in the lowest quintile of each lipid fraction was set as the referent value.
Abbreviations: LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; rASCVD, first recurrent atherosclerotic cardiovascular disease event.
Solid line represent the hazard ratio and dotted line represents the 95% confidence interval boundaries.

The discriminatory capacity of the TIMI Risk Score for secondary prevention[108], derived from a trial cohort, was poor (C-index <0.6) when applied to the study sample. Addition of each lipid fraction, including LDL-C, to the prediction model improved measures of predictive accuracy significantly, but changes were negligibly small.

In a complementary Cox regression analysis, the acknowledged secondary prevention treatment target for lipid levels, LDL <1.8 mmol/L, was used as the referent category. Only 621 study participants with LDL-C ≥4.0 mmol/L were associated with higher risk of rASCVD. (Figure5)

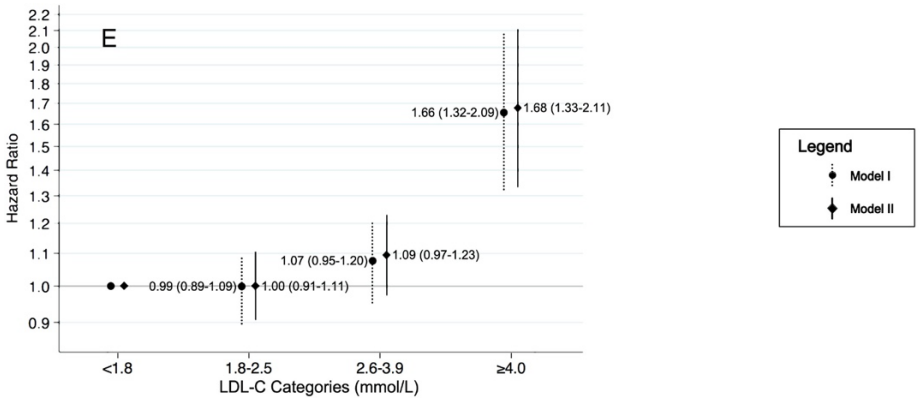


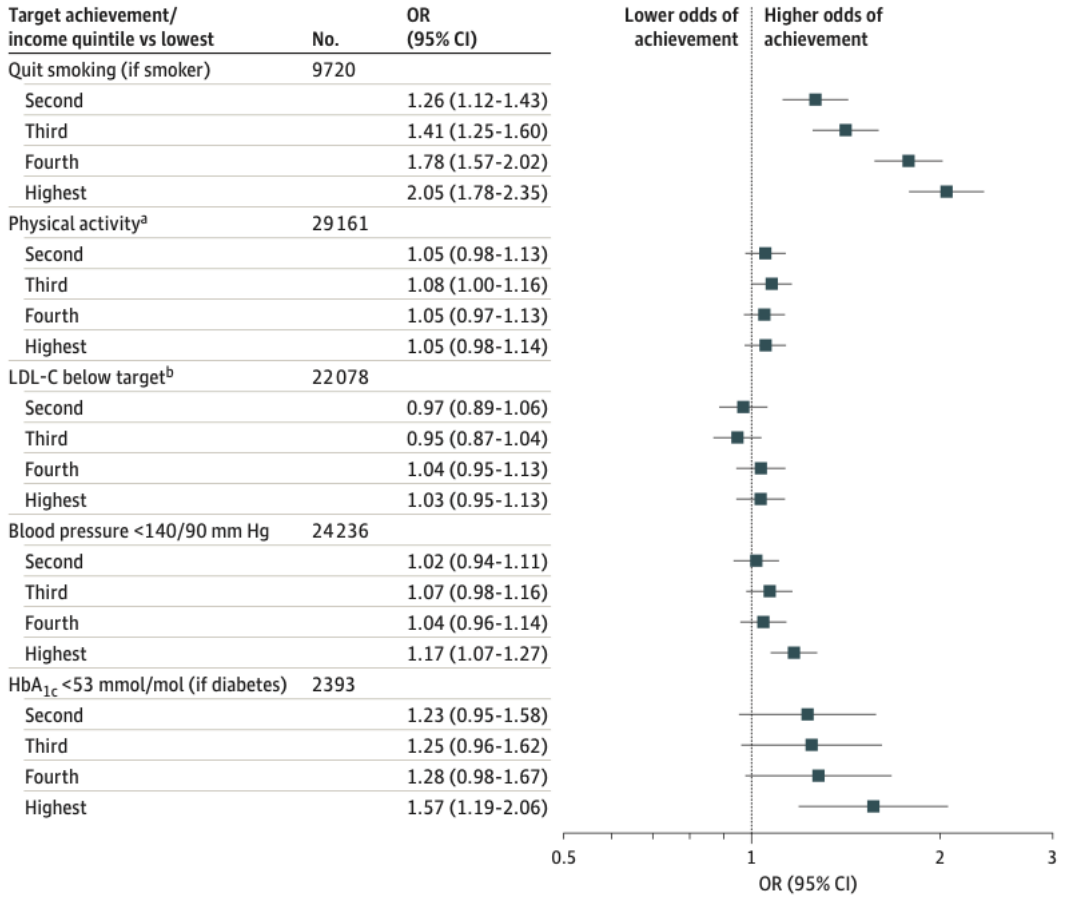
Figure 5. Forest plot depicting hazard ratios and 95% CIs using the recommended treatment target, LDL-C <1.8 mmol/L as the referent category. Model I was crude. Model II was adjusted for age, sex, and calendar year.

Analysis in the subgroup treated with high-intensity statins (n=6907), neither LDL-C or total cholsterol were associatiated with rASCVD while attenuated associations remained for triglycerides and HDL-C. Additional adjustment for changes in statin therapy intensity after basline did not appear to affect main results, except that no associations with rASCVD was observed between the lowest and higher levels of LDL-C. In secondary outcome analyses, associations were overall similar, except that no associations were observed between levels of LDL-C and fatal or nonfatal stroke and that higher quintiles of LDL-C were associatied with lower risk of all cause death.

5.3 STUDY III

A final sample of 30,191 study participants was identified. Mean age (SD) was 63.0 (8.6) years and 27.1% were women. Co-indicators of SES were strongly associated with one other. Mean age and frequencies of previous hypertension, dyslipidemia, and congestive heart failure, eGFR, and STEMI were similar across income quintiles. Lower income quintiles were associated with smoking, obesity, diabetes, the metabolic syndrome, non-sinus admission ECG, atypical presenting symptoms, and more extensive coronary disease with higher peak troponin levels, obstruction of more coronary vessels, and more depressed LVEF. Higher income quintiles were associated with more frequent angiography, PCI in cases of angiographic indication, and primary PCI in cases of STEMI.

The proportion achieving risk factor targets was typically low and worse in lower income groups. Higher ORs in the highest vs. lowest income quintile were observed for achieving smoking cessation, target levels of blood pressure and glycated hemoglobin (HbA1c) (Figure 6). Associations between indicators of SES and achieved LDL-C target and weekly physical activity were inconsistent.



JAMA Network Open. 2021;4(3):e211129. doi:10.1001/jamanetworkopen.2021.1129

Figure 6. Tabulation and Forest plot of the associations between disposable income and secondary prevnetion treatment targets.
[a] ≥ moderate exertion ≥ 5 times lasting 30 minutes.
[b] LDL-C target according to changed recommendation in 2012 from LDL-C <2.5 to <1.8 mmol/L.

Frequencies of secondary prevention utilization were typically high for evidence-based drug therapies, low for participation in cardiac rehabilitation programs and patient monitoring activities, and better in higher income quintiles. Associations with participation in comprehensive cardiac rehabilitation was observed for all indicators of SES. The highest vs. lowest income quintile was strongly associated with participation in physical training programs, patient educational sessions, and stress management group sessions, and moderately associated with participation in dietary advice courses. (Figure 7) The highest vs. lowest income quintile was associated with more frequent lipid profile measurements, intensification of statin therapy after revisits, use of statins, and use of high-intensity statins at the 1-year revisit. Associations were observed between higher SES and discharge with dual antiplatelet therapy, statins and RAAS inhibitors. At the 1-year revisit, higher SES was associated with using statins, high-intensity statin therapy and RAAS inhibitors.

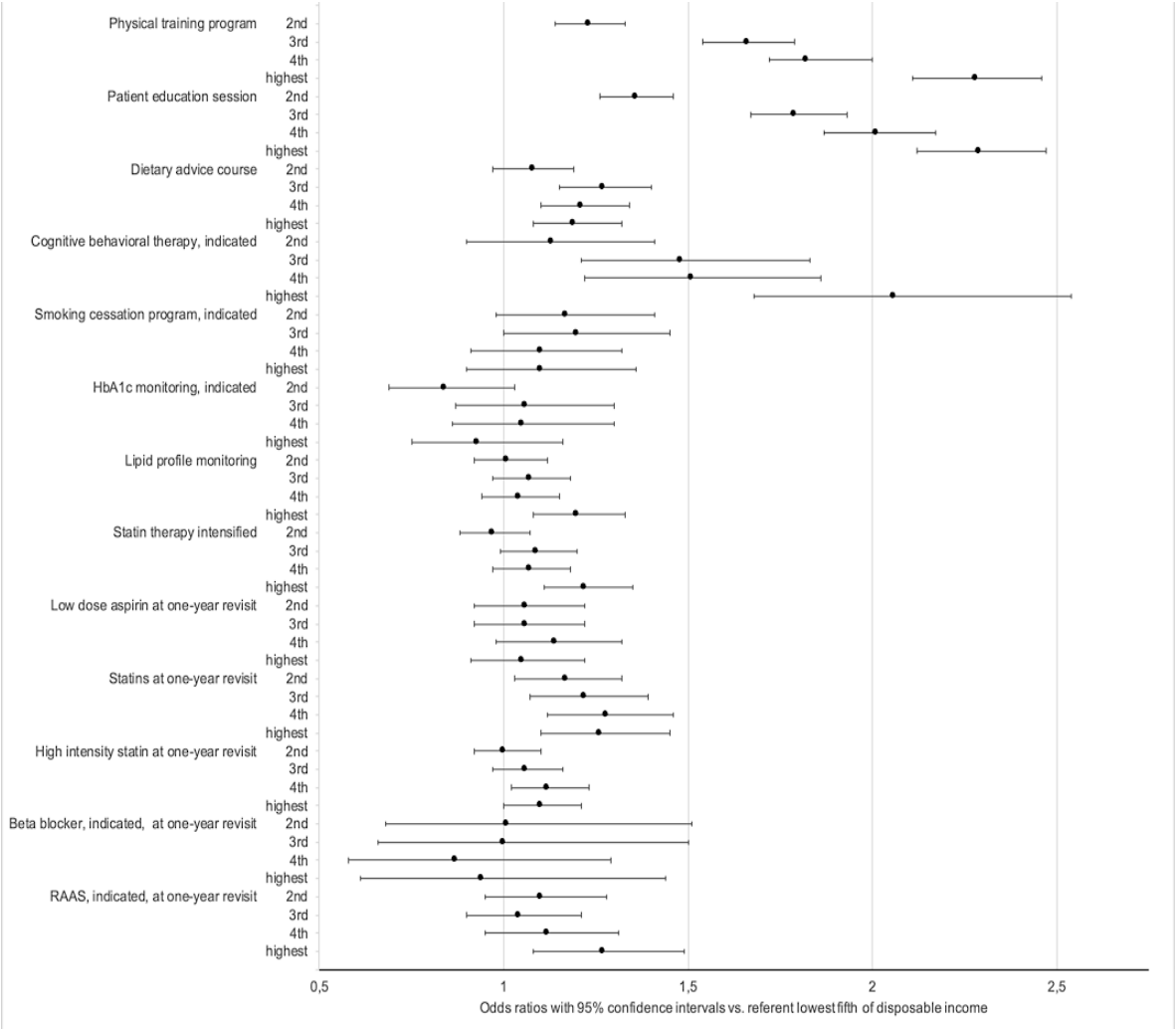


Figure 7. Forest plot depicting estimates of the association between disposable income and secondary prevention activities throughout the first year after myocardial infarction.

Associations between disposable income risk factor targets and secondary prevention utilization were similar among men and women. However, the odds of achieving blood pressure target was stronger among women than men in the highest income quintile and the odds of statin use at the 1-year revisit was stronger among men than women in the highest vs. lowest income quintile.

5.4 STUDY IV

The final study cohort comprised 31,792 individuals. There were 2,941 trial participants and 28,851 individuals who had not participated in a clinical trial after the index MI. Between the groups, mean age was similar. Trial participation was associated with male sex, higher income, higher educational level, and being married. Non-participation in a trial was associated with a history of stroke and MI, smoking, symptoms of anxiety and depression, reduced LVEF, low eGFR, worse mean lipid levels, and non-sinus rhythm at the 1-year visit. Prevalence of diabetes and mean values of blood pressure and body mass index were similar between groups (Figure 8). Trial participation was associated with use of acetylsalicylic acid and RAAS inhibitors, participation in physical training and patient educational programs within cardiac rehabilitation whereas non-participantion was associated with use of diuretics, nitrates and oral anticoagulants.

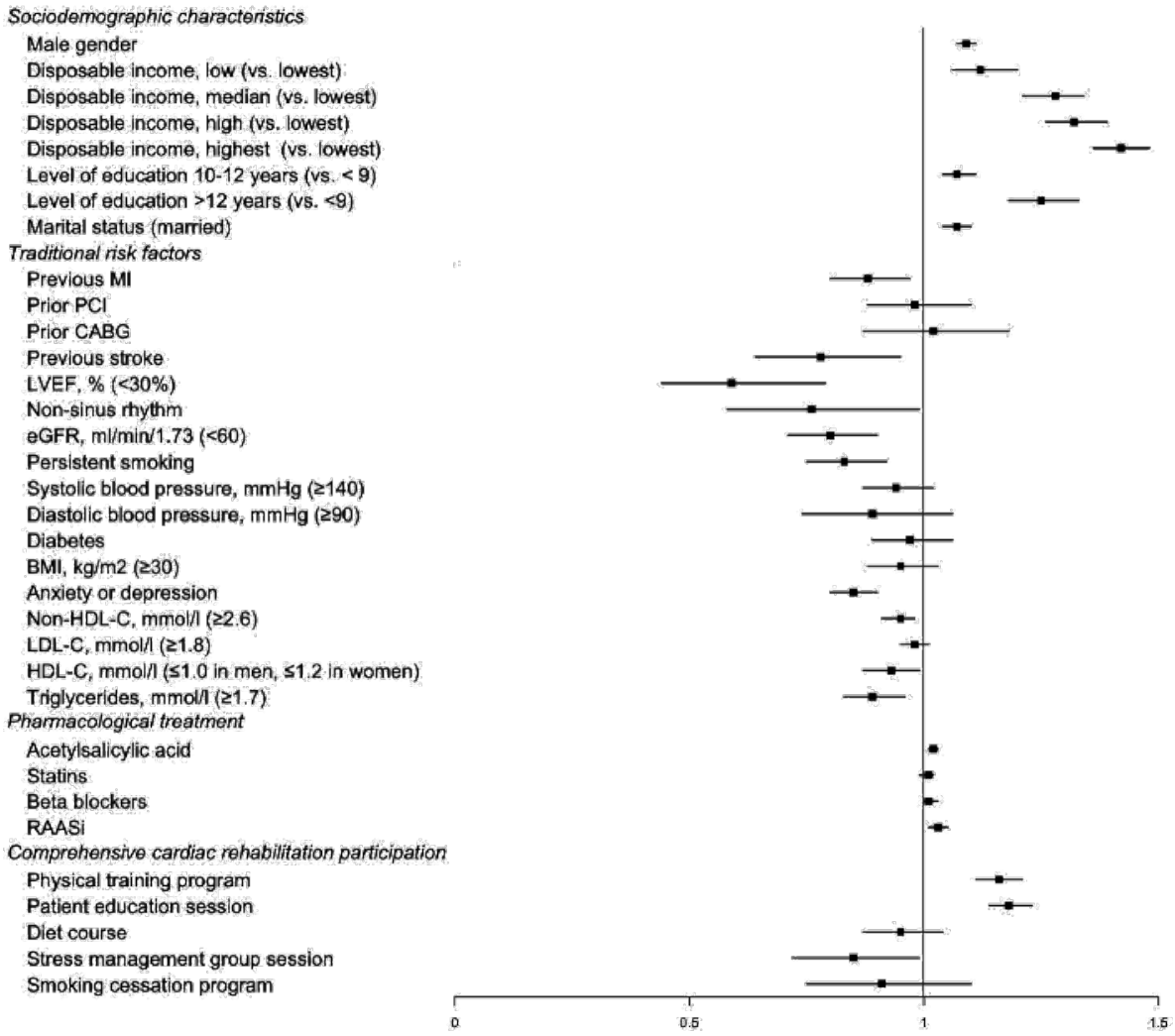


Figure 8. Forest plot depicting the risk ratios with 95% CIs estimated with Poisson regression between participants and non-participants in clinical trials after myocardial infarction.
Abbreviations: MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol. RAASi, renin-angiotensin-aldosterone system inhibitor.

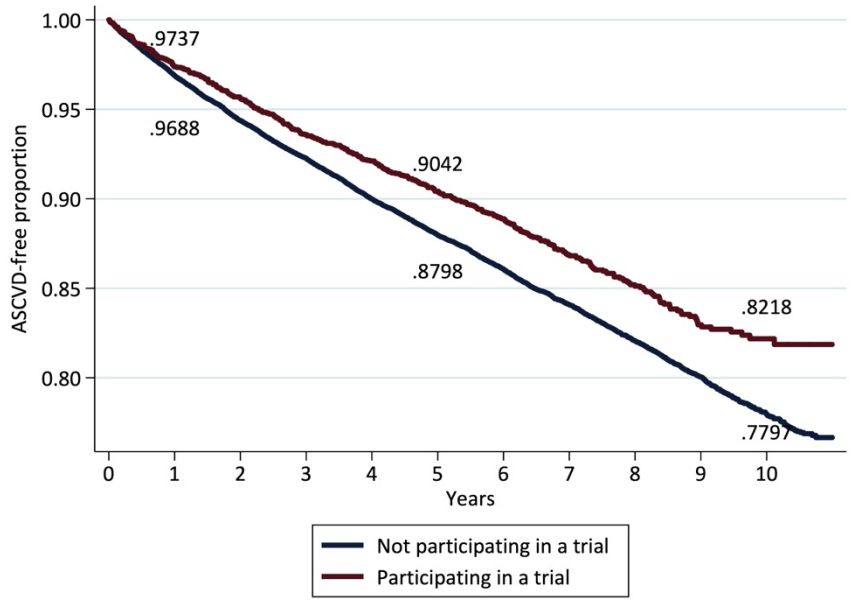


Figure 9. Kaplan Meier estimate of ASCVD event-free proportion between participants and non-participants in clinical trials after myocardial infarction during long-term follow-up.

During a mean 6.7-year follow-up, rASCVD occurred in 16.4% individuals in the study population. The 10-year absolute difference in rASCVD-free proportion between groups was 4.2% (Figure 9). Trial participation was associated with lower crude risk of rASCVD that was independent of adjustments for age, gender, and calendar year. Further adjustment for clinical risk factors and comorbidities, but not secondary prevention use, attenuated the association between trial participation status and rASCVD. Final model adjustments for SES indicators attenuated the association further. However, a lower risk in trial participants remained that was unattributed for.

5.5 STUDY V

The study cohort was the same as in Study III. Summarized descriptive results and comparisons between disposable income levels and co-indicators of SES, CV risk factors, variables related to MI presentation and severity, initial therapies, and secondary prevention use are reported above.

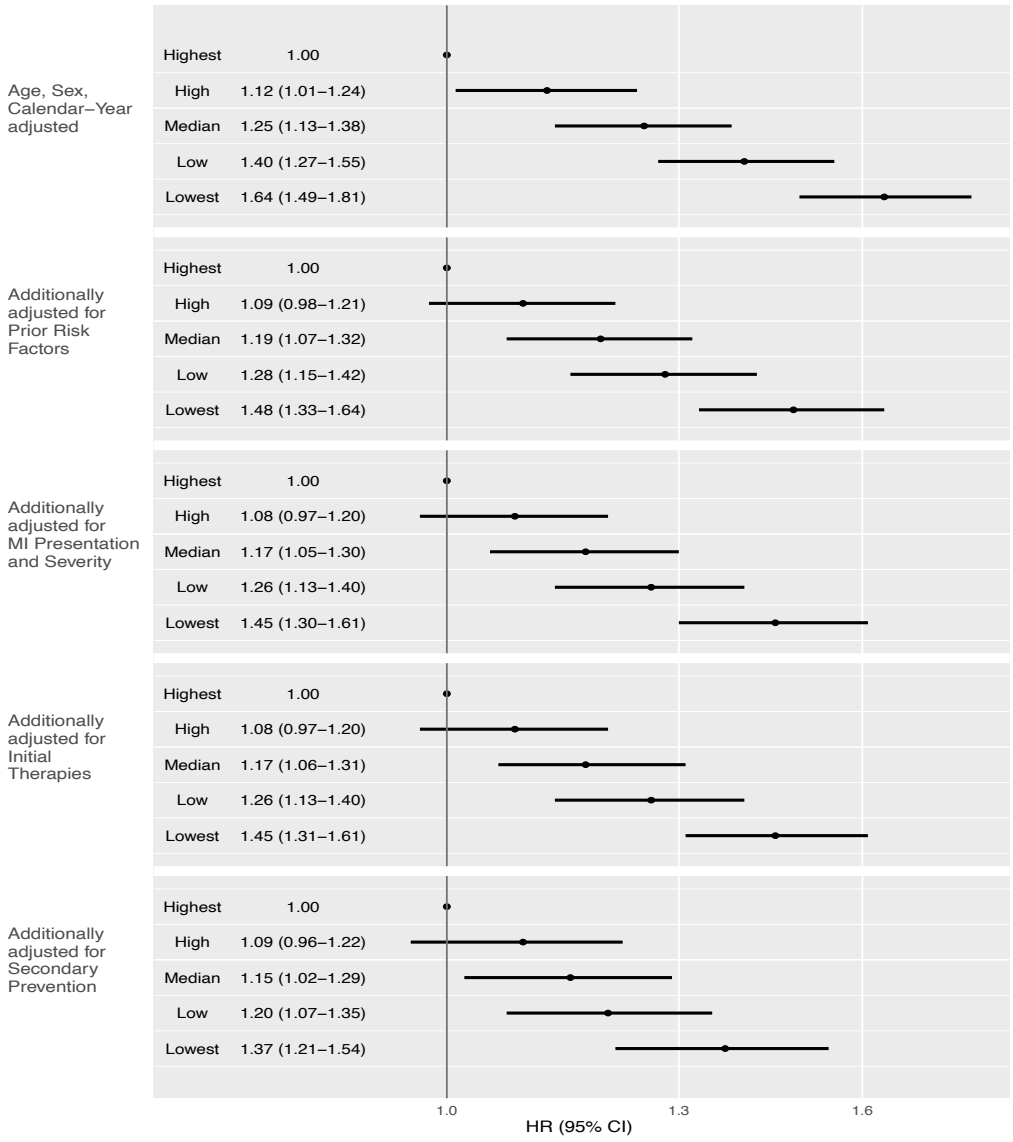


Figure 10. Association between disposable income quintiles and rASCVD estimated in five sequential models for hazard ratios with 95% CIs presented as forest plots.

During a mean 7.4-year follow-up, rASCVD occurred in 14.2% of the 31,191 study participants. The lowest vs. highest income quintile was strongly associated with rASCVD in a bias-minimized model adjusted for age, gender, and calendar year (Figure 10). In sequential models, excessive risk in the lowest income quintile was attenuated by adding traditional risk factors, but not substantially by additional adjustment for acute presentation, infarct severity, and initial therapies. Further attenuation was observed in the final model that was additionally adjusted for secondary prevention activities.

Participation in physical training programs and patient educational sessions within cardiac rehabilitation, and the metabolic syndrome each mediated excess rASCVD risk in the lowest

vs. highest income quintile whereas optimal statin management did not. The proportion of excess rASCVD risk in the lowest income quintile through a potential mediator by follow-up year is presented in Figure 11. Estimated mediating proportions were small.

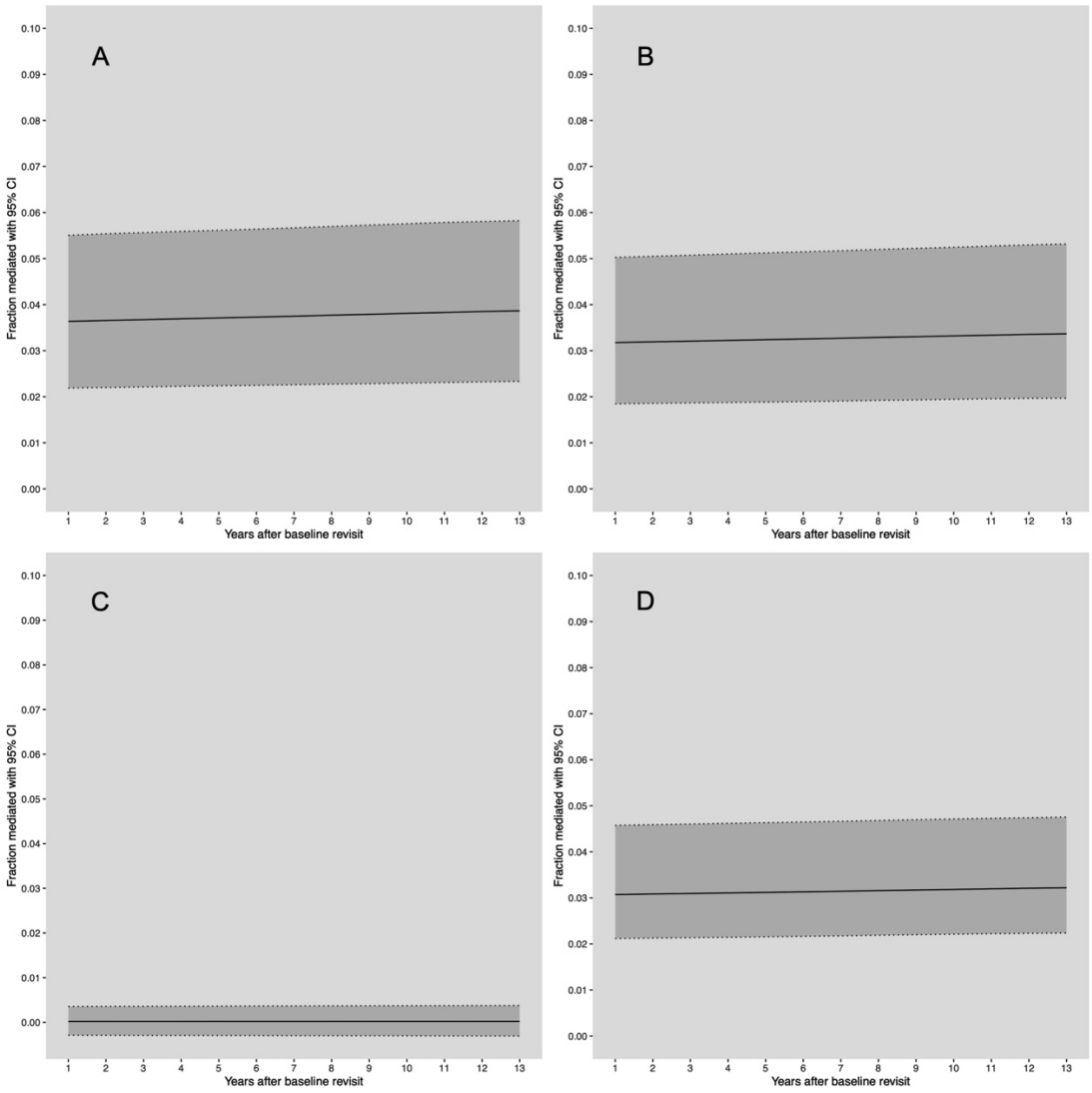


Figure 11. Proportion of the total excess probability of rASCVD due to income in the lowest quintile mediated through a plausible mediator. In Panels A-D, the plausible mediator was participation in physical training program, participation in patient educational sessions, optimal statin therapy, and the metabolic syndrome, respectively. The mediating proportions were the excess probability of rASCVD associated with an income in the lowest quintile attributed to its estimated mediating natural indirect effect for a potential mediator. The total risk was the complement of the survival function and was based on a model adjusted for age, sex, and calentar year. The plausible mediator was assessd in logistic regression.

In sensitivity analyses with mutually adjusted indicators of SES, associations between disposable income and rASCVD were attenuated but remained strong. The associations between marital status and rASCVD was moderately strong and independent of all adjusting factors. Educational level was the weakest SES indicator for rASCVD. Complete case analysis estimates were similar to results in the full cohort.

Secondary outcomes CV death and all-cause death during mean 7.9 years of follow-ups occurred in 4.5% and 12.4% study participants, respectively. The risk gradients by disposable income quintile were stronger for secondary outcomes than for rASCVD. In sequential model analysis, prior risk factor accumulation and secondary prevention activities, but also MI presentation and severity, attenuated estimates of excess risk in lower income quintiles.

6 DISCUSSION

In this thesis, the importance of risk factors in secondary prevention after MI and the role of SES in this population was studied in order to improve knowledge. A less established risk factor for CV risk assessment after MI, SES, was strongly associated with rASCVD in Study I. Between disposable income, educational level, and marital status, associations were the strongest for disposable income. Study II demonstrated that the association between achieved on-treatment levels of LDL-C, an established measure for risk assessment, and rASCVD was weak and that lipid levels carried a minimal predictive value for long-term risk. Plausible mediation in the association between SES and rASCVD during the first year of secondary prevention was then assessed in Study III. Socioeconomic disparities were observed regarding use of therapies, monitoring, and risk factor target achievements that are recommended in clinical practice guidelines on CV prevention. Associations between SES and participation in cardiac rehabilitation programs intended for lifestyle modification were the strongest. There is room for improvements in secondary prevention after MI in general, and preferably through evidence-based recommendations. Study IV found that patients participating in clinical trials after MI were a highly selected group with higher SES, female under-representation, fewer CV risk factors, and better long-term prognosis. Hence, trial findings derived from the post-MI population may contribute with high-level evidence but at the expense of poor generalizability to low-SES groups, and the real-world post-MI population overall. In Study V, a mediating effect on excess risk for rASCVD in low SES was observed for cardiometabolic risk profile (the metabolic syndrome). Similar mediating effect sizes were observed for participation in cardiac rehabilitation programs (physical training programs and patient educational sessions), whereas optimal statin management did not mediate excess risk for rASCVD in low SES.

6.1 RISK FACTORS WITH IMPORTANCE IN SECONDARY PREVENTION

Conclusions from Study I and II were that SES, by proxy disposable income level, may be a better measure than on-treatment lipid levels in the assessment of risk for rASCVD within the post-MI population.

6.1.1 Lipid Levels

In Study II, on-treatment levels of LDL-C were weakly associated with rASCVD and the predictive value was negligable. The findings question whether the arbitrary LDL-C target level used in clinical practice[38,124,125,159,160] can discriminate high-risk individuals from low-risk individuals at revisits two months after MI for decisions on continued treatment intensity. The 2013 ACC/AHA guideline on the treatment of blood cholesterol abandoned LDL-C targets in lack of evidence.[147] A study based on post-MI trial samples suggested that percentage LDL-C reduction was more predictive than achieved LDL-C levels for rASCVD.[161] Study V align with findings from a meta-analysis comparing intensive vs. less intensive lipid lowering therapy in which there was evidence of increased mortality risk among patients with baseline LDL-C >2.6 mmol/L only[162] and the ODYSSEY-OUTCOMES

trial in which results were driven by outcomes in the prespecified subgroup with LDL-C >2.6 mmol/L.[163] Study V findings do not question that LDL-C is a key causal component of atherosclerosis[164], that there is overwhelming evidence in support of lipid lowering therapy with statins for reduction of ASCVD risk[112,126], or that LDL-C is excellent for measuring baseline-risk in the general population. However, causal properties of a risk factor are irrelevant for risk prediction.[165] However, in a secondary prevention population where virtually all post-MI patients are treated with potent statins, LDL-C is not a surrogate measure for adverse outcomes.[166]

Shortly after the landmark trials on PCSK-9 inhibitors were published[114,167], the 2019 ESC guideline on dyslipidemia recommended continued use of LDL-C target levels and that it should be lowered from <1.8 mmol/L to <1.4 mmol/L.[125] A simulation study estimated that half of the Swedish post-MI population, even if all were treated with high-intensity statin therapy plus ezetimibe, would be eligible for PCSK-9 inhibition according to the guideline recommendations. Adding a PCSK-9 inhibitor would increase cost of lipid lowering treatment by thousands of percent, an increase from around €30 to €4500 a year for each eligible post-MI patient.[168] The cumulative cost would be a considerable financial burden for the Swedish tax-financed health care system. Whether low-income groups would be disadvantaged remains for future research. In Study III, the highest (vs. lowest) income level was not associated with LDL-C target achievement at the the 1-year revisit.

6.1.2 Socioeconomic Status

SES is generally not considered to be a modifiable risk factor. As a risk factor on the individual-level, SES cannot be improved by health care professionals by any means. According to the WHO conceptual framework[15,41], political economy, social policies and politics are a wider set of forces – a system – that shape "the circumstances in which people are born, grow up, live, work and age, and the system put in place to deal with illness." These life circumstances rule the SES of an individual and encompass economic stability, social and community support, access and quality of education and health care, housing and neighborhood conditions. Individual life circumstances and SES in turn determine lifestyle and behavioral factors that determine levels of blood pressure, blood lipids, abdominal adiposity, and blood sugar - the most proximal causes of ASCVD. Our limited resources and efforts should not be too heavily focused on treating the "consequences of the consequences". Instead, SES should be considered a fundamental, causal and modifiable risk factor.[16,40]

An individual or family may change SES actively. For example by moving away from adverse elements of life circumstances, by pursuing education to migrate on the socioeconomic gradient over a life course, and SES may change through professional careers and marriages. For improvements of socioeconomic health equity, elimination of SES from society is not feasible. However, disparities of the life circumstances can be diminished through health policies and strategies, legislation, and resource allocation at national, regional and local levels of society and health care.[169] For example, political actions such as prevention of active and passive smoking[170], adverse dietary habits[171] and promotion of youth

sports activities[172] may reduce socioeconomic health disparities for future generations. In Sweden, the Public Health Agency (Folkhälsomyndigheten, FOHM) is responsible for this important work, alongside other major tasks.[173] At the level of the healthcare system and clinical practice, focus may need to be stronger on lifestyle interventions. Further knowledge gains on secondary prevention risk mediation are warranted for efficient allocation of resource.

In these studies, disposable income was the strongest indicator of SES when mutually adjusted for educational level and marital status. Disposable income was associated with utilization of secondary prevention, treatment targets, rASCVD and secondary outcomes. The data does not explain why these associations were observed. Healthcare services and prescription drugs are expensive but virtually fully covered by the Swedish tax-financed healthcare system. Nontheless, a low-income individual may be less willing to spend any amount of money on prescription drugs and health promoting activites such as fees for access to organized physical training. Low income may also affect the option of buying healthier food.[171,174] Disposable income level, if long-standing, has also been suggested to be the best SES-indicator of material resources and living standards.[175] With higher material standards, car ownership is more likely which in turn may improve access to cardiac rehabilitation and other health promoting facilities.[176] Beneficial psychological effects from self-sufficiency is another plausible aspect. A limitation of using disposable income as indicator of SES is that income level may changes due to an event such as MI. Therefore, income levels collected in the year prior to baseline was used in all studies.

Study I, III, IV, and V suggest that disposable income level carries information that is clinically relevant. Although frequently used as proxy for SES in research, income and other indicators of SES are often considered sensitive information. Patients and care providers may feel uncomfortable by the thought of discussing something that may be considered an intrusion of privacy.[13,45,177] However, these hesitations are based on assumptions of the feelings of others and may be degradable boundaries set by social structures and culture. The same type of social forces that determine SES. Individual-level income was measured in this thesis, but income was categorized into fifths for study of group-level SES. As a reflection SES and life circumstances. The clinical relevance of our findings encourages clinical use of disposable income level as a measure to identify high-risk individuals post-MI eligible for specific or intensified therapy.

6.2 SECONDARY PREVENTION IN STABLE PHASE AFTER MYOCARDIAL INFARCTION

Study I findings generated hypotheses for Study III and V and a final conclusion that increased rates of participation in cardiac rehabilitation among low-SES groups may reduce long-term risk of recurrent ASCVD events and improve health equity.

6.2.1 Secondary Prevention Therapies

It is well established that lowering of CV risk factor levels is associated with a reduction of ASCVD events.[6,38] Use of lipid lowering therapies and anti-hypertensive drugs are evidence-based in primary as well as secondary prevention[83,84,112], although efficacy of beta blockers need reevaluation in the revascularization era population.[86] In long-term secondary prevention, also platelet inhibitors are evidence-based.[76] These therapies are cornerstones of secondary prevention management. Frequencies of usage among study participants in the thesis cohort were high overall. However, as reported in Study III, reported use of statins and RAAS inhibitors was lower among low-SES individuals 1 year after MI. Interventions for better drug therapy adherence in low SES may improve health equity.[131,132,178] For example, the use of polypills has been suggested in order to simplify drug administration.[7]

Interventions for lifestyle change may be crucial for achieving further overall reductions of recurrent ASCVD in Sweden. Just as secondary prevention drug therapies, cardiac rehabilitation is associated with improved outcomes and is evidence-based.[92,93,179,180] Although rates of participation in cardiac rehabilitation in Sweden are higher overall than in many other countries, few post-MI patients complete three months of physical training program.[181] Therefore, a great potential for improvements remains to be achieved from lifestyle interventions through increased uptake of cardiac rehabilitation.[94] In low SES, strong face-to-face endorsement for participation by the hospital physician appears to be effective but does not necessarily increase rates of completion.[182,183] Cost of transportation and parking may affect attendance and home-based interventions may be effective and cost less.[13,183] Additionally, cardiac rehabilitation need better standardization, quality control, and work routines at centers throughout the country. Identification of cardiac rehabilitation components that matter most for prognosis has been warranted[184] and Study V may contribute with some guidance. However, the mediating effects observed for participation in physical training program and patient educational sessions were small and interventions may not improve socioeconomic health equity substantially. In Study V, a small mediating effect was also observed for a cardiometabolic risk profile. Similar findings were reported in a recent primary prevention study on a lifestyle factor-index as a mediator between SES and CV outcomes.[185] Hence, strengthening of primary prevention may reduce both incident and recurrent ASCVD in low SES.

Study III reported that participation in cardiac rehabilitation programs was strongly associated with SES. Only 34% in the lowest income quintile participated in exercice based cardiac rehabilitation compared to 54% in the highest income group. In Study III, the association between SES and participation in stress mangement group sessions was also strong and self-reported symptom of depression and anxiety were more frequent among low-SES individuals. These symptoms are associated with non-compliance after MI[90,186] as well as with worse outcomes.[187] Overlapping between SES and psychosocial factors may be explanatory for differences in participation in cardiac rehabilitation and long-term outcomes.[187]

6.2.2 Room for improvement

As reported in the literature review of this thesis, the 2016 EUROASPIRE IV survey on CV risk factor target achievements and guideline adherence in secondary prevention after coronary events or interventions was discouraging.[11] The 2019 EUROASPIRE V survey, on 8,261 secondary prevention respondents from 27 European countries was not indicating any improvement.[188] Risk factor levels and management adherence to guidelines varied between countries and were likely overestimated in general because of the major limitation of EUROASPIRE, participation-bias due to low rates (≈ 50%) interviewed. The secondary prevention sub-registry of SWEDEHEART represents the population of origin better than the multinational European sample of EUROASPIRE-respondents. According to SWEDEHEART, approximately 80% of all individuals hospitalized for MI who are under 75 years attend the 1-year follow-up in Sweden. In comparison between attendants and the proportion lost to follow-up, non-attendants are higher-risk individuals who more frequently have a history of previous CV events than registered participants.[10,181] Representability of SWEDEHEARTs secondary prevention registry has improved further in recent years. Since 2018, 100% of cardiac care hospitals throughout Sweden are reporting and the upper age-limit has been raised to 80 years of age. SWEDEHEART evaluates secondary prevention quality in detail. Four secondary prevention targets, besides registry completeness, are considered to be particularily important in assessment of quality of care and are assessed at the 1-year revisit: targets for blood pressure level and LDL-C, participation in physical training program within cardiac rehabilitation, and smoking cessation. Smoking cessation has been achieved in approximately 55% of smokers in annual follow-ups during the past decade whereas the proportion achieving blood pressure targets and LDL-C targets continuously improve.[181] In 2014, only 16% of Swedish 1-year survivors of MI achieved all four targets.[10] Between 2014 and 2019, the proportion participating in a physical training program after MI increased marginally but has stagnated at approximately 20%.[181] Epidemiological studies are fundamental for better understanding of secondary prevention circumstances and the SWEDEHEART secondary prevention sub-registry serves as a unique platform. An extension of the continuous efforts of developing SWEDEHEART is higher potential of deriving epidemiological studies that may further improve secondary prevention care.

6.3 METHODOLOGICAL CONSIDERATIONS

Logistic regression was used in Study III and as part of mediation analysis of Study V. Logistic regression describes the association between an exposure and a dichotomous outcome as odds ratios.[189]

Poisson regression was used for in Study IV for estimates presented as risk ratios that are more intuitively interpreted than odds ratios. Poisson regression is a linear model on the log-scale. That is, the method applies a logarithm transform and is used for outcomes that are counts distributed by the Poisson distribution. Proportional risk rate and constant risk rate over time is assumed.[190]

Kaplan-Meier estimates were used to visualize associations between exposures and outcomes over follow-up time. Kaplan-Meier is a descriptive method to display time-to-event analysis. An assumption of the method is that censoring is independent of time. That is, migration or competing risks are not accounted for.[190]

Cox proportional-hazards regression analyses were used in used Studies I, II, IV, and V. Cox regression is a flexible and popular method for time-to-event analysis that is based on Poisson regression but does not require constant hazard rate during observation time. Compared to Kaplan-Meier estimates, Cox regression handles censoring. There is no assumption of constant hazard rate, however that hazard rate between compared groups is proportional throughout the observation time. This was verified by means of scales of Schoenfeld's residuals.[190]

Harrell's C-index (or C-statistic or the area under the curve plotted from sensitivity by the complement of specificity) is frequently used to estimate predictive performance or accuracy. C-index evaluate the discriminatory capacity of a test. That is, how well a test separates cases from non-cases.[152] A weakness is that significant differences in absolute risk may render small changes of C-index, in particular when the base model used for evaluation of a candidate predictor includes powerful predictors.[154]

continuous Net Reclassification Index (cNRI) and **Integrated Discrimination Improvement (IDI)** are tests of reclassification that complement discrimination testing. Reclassification tests evaluate how well a model classifies individuals to different (clinically relevant) risk-strata. For example, NRI calculates whether cases are more likely to be recategorized to a higher risk strata and non-cases are more likely to be recategorized to lower risk strata when a candidate predictor is added to the model. Reclassification tests used in Study II were non-categorical (that is, cNRI calculates the proportion of cases in whom risk is increased, and the proportion of non-cases in whom the risk level is decreased, compared with the reference prediction model. IDI indicates the proportion explained variation[154,155]. The reclassifications have been criticized for overestimating model performance.[191]

Causal mediation analysis was performed in Study V using an advanced method for mathematically consistent causal interpretation of causal mediation on observational data. The method combines multivariable time-to-event analysis with logistic regression data for estimates on causal natural indirect (i.e. mediating) and direct effects through a candidate mediator in the association estimated with time-to-event data.[156,157] Mediation analysis is a growing field in epidemiology and biostatistics. Several types of bias may arise including backdoor path bias, non-collapsability of hazard ratio, and intermediate confounding. The method used in Study V was based on the counterfactual framework which is considered to improve validity. Method assumptions on temporal ordering were satisfied.[192]

6.4 LIMITATIONS

6.4.1.1 Study design

All studies in this thesis were registry-based observational retrospective cohort studies. Major limitations of the observational study designs include risk of residual confounding and incompatability with making causal inferences. Retrospective use of registry-data limited control of variable choice. In Study II, data on lipid levels at admission for the index MI were not available. At the time of data extraction, no variable existed that accounted for dietary habits.

Neither patient-reported use, records of physician prescriptions, or pharmacy claims of prescriptions reveal whether drug therapies actually enter the blood stream of a patient. In studies on SES after MI, where adherence to drug is likely important, such data would have been desirable. SWEDEHEART collects data on drug therapies reported before MI, at discharge from initial care, and at the 2-month and 1-year revisits after MI. In Study II, III, and V, further detailed data on drug therapy intensity was added through linkage from the National Prescribed Drug Register. However, there was no way to account for patient adherence to medication.

6.4.1.2 Erroneous data

Even though SWEDEHEART data were entered directly on site by health care professionals, entry was manually and occasional human error is inevitable. This may introduce random erroneous data that is more or less obvious (for example, body mass index 92 instead of 29 vs. body mass index 32 instead of 23). Bias may be introduced from variable definitions that differ from clinical interpretation (for example, definitions for ECG annotation data entry). Smoking cessation program and dietary advice course were not options at all cardiac rehabilitation sites throughout the country and were available as variables for registration for a limited period only. Hence, participation status may be unrelated to SES and findings regarding these variables in Study III and V should be interpreted with caution. Variables may also be *not missing at random* which introduces bias that is difficult to account for in retrospect. Furthermore, in the process of merging datasets, selecting variables, and other parts of data management, errors may have been introduced. Throughout the thesis, work was performed in close cooperation with statisticians tied to the project in order to minimize errors in data management and analyses.

6.4.1.3 Exposures

Data from Statistics Sweden was near complete on indicators of SES. However, disposable income may be biased for many reasons. For example, individuals of a household where one spouse earn enough to provide for the other would be misclassified. We handled this bias by choosing a type of disposable income that account for household income, size, and composition. Inevitably, misclassification would persist in plausible high-income households with the incitement of reporting low annual incomes to evade taxation.

Despite having chosen three indicators of SES for Study I, comparison to the findings of other studies on SES is a difficulty in research on SES. For example, a recent meta-analysis of 1.7 million study participants investigated the associations between SES and CV risk factors, and mortality. However, a European classification of occupational status was used as proxy for SES.[169] Indicator selection and the number of indicators used to measure SES affect usability of findings. Occupational status was available but actively not chosen when this doctoral project was initiated because of difficulties categorizing occupations that undergo changes in societal status over time.

A potential limitation of restricting the choice of SES indicators to the individual-level is that neighborhood or regional socioeconomic circumstances may carry information relevant to underlying mechanisms to the association between SES and rASCVD. For example, driving distance to health care facilities is associated with attendance to cardiac rehabilitation[176] as pointed out in Study III. This information has potential importance for decisions on resource allocations.

The trial participation variable used in Study IV was near complete with missing values reported for less than two percentages of eligible study participants attending the 1-year visit after MI. A limitation was that no information was available on reasons for non-participation in a clinical trial. For example, whether a study participant had been made the offer to participate in a clinical trial.

6.4.1.4 External validity

Representability is discussed as a strength of all studies in this thesis, with good reason, and was hypothesis generating for Study IV. Therefore, a reflection in this thesis discussion is that extrapolation of SWEDEHEART-based findings also warrant caution. SWEDEHEART completeness is high. However, 20% of eligible post-MI patient are lost to follow-up. This population have a worse CV risk profile and there is good reason to believe that they have lower SES considering the established associations between SES and adherence and CV risk profile. Furthermore, registry coverage or completeness refers to the number of patients that are eligible for inclusion. The upper age limits for SWEDEHEART inclusion and the fact that only individuals hospitalized for MI were eligible must be considered in interpretation of study findings of this thesis. A considerable proportion of all MIs occurring in the country are unaccounted for. Our findings may not apply to individuals with an advanced age, who have severe comorbidities or are most frail for other reasons. Since data extraction, representability has improved.[181]

7 CONCLUSIONS

7.1 STUDY I

SES was strongly associated with rASCVD among patients in stable phase after first-ever MI in a large Swedish cohort with nationwide representation. The strongest indicator of SES was disposable income, and the association with rASCVD was independent of most traditionally considered CV risk factors. Hence, SES should be considered in risk assessment post-MI for clinical decisions on secondary prevention intensity.

7.2 STUDY II

LDL-C achieved 2 months after a first-ever MI was the routinely measured lipid fraction with the weakest association with rASCVD. The strongest association was observed for level of triglycerides. Furthermore, lipid levels carried minimal incremental predictive value on top of other traditional CV risk factors in a secondary prevention prediction model. Consequently, our data questions the use of LDL-C levels achieved at the 2-month revisit for risk assessment and decisions on continued treatment intensity.

7.3 STUDY III

Among 1-year survivors after MI in the tax-financed health care system of Sweden, lower SES was associated with worse utilization of target-oriented secondary prevention activities including patient monitoring, participation in cardiac rehabilitation programs for lifestyle change, and use of evidence-based drug therapies. Lower SES was also associated with worse achievements of 1-year risk factor targets. The observed socioeconomic disparities were indicating a causal chain and a plausible explanatory mechanisms for higher long-term risk of rASCVD in lower SES.

7.4 STUDY IV

Among patients surviving 1 year after MI, those who took part in a clinical trial were more often male, had higher SES, a healthier risk factor profile, were more likely to recieve recommended secondary prevention therapies, and had better prognosis than those who did not take part in a clinical trial. Additional unmeasured participation bias was implied. External validity of post-MI trials is questionable. In particular risk factor profile and SES should be carefully considered in application of clinical trial findings on real-world patients.

7.5 STUDY V

Socioeconomic disparities regarding CV risk profile and utilization of secondary prevention were explanatory factors for worse prognosis in low SES after first-ever MI. Participation in core cardiac rehabilitation programs during the year after MI were identified as risk mediators. Therefore, improved cardiac rehabilitation uptake in lower SES may improve health equity. Findings were also indicating that improved primary prevention management of the metabolic syndrome in low SES may reduce the risk for recurrent ASCVD.

7.6 OVERALL CONCLUSIONS

The overall aim of this thesis was to improve the knowledge about risk factors with importance in secondary prevention among patients in stable phase after MI, with special focus on prognosis and SES. Risk assessments based on SES, measured by disposable income level, may be preferable over achieved levels of LDL-C for the identification of high-risk individuals after MI. Low SES was associated with worse achievements of guideline-directed treatment targets and use of target-oriented secondary prevention activities. SES disparities regarding participation in physical training program and patient educational sessions within cardiac rehabilitation programs and the metabolic syndrome risk profile were identified as mediators in the association between SES and rASCVD. Although the observed mediating effects were small, these findings provide modifiable targets for action to improve health equity after MI. Specific interventions must be evaluated in clinical trials. These trials should take into consideration that SES was a contributor to the participation bias of clinical trials conducted post-MI.

8 POINTS OF PERSPECTIVE

Observation of a strong associaton between SES and rASCVD, and a weak association between achieved LDL-C levels and rASCVD, may be useful to better identify high-risk individual at revisits after MI in Sweden. Regardless, risk prediction post-MI remains an area of secondary prevention research in need for improved methods.[7] Existing secondary prevention risk scores are often derived from highly selected trial samples or heterogenoeous populations.[108,193,194] Unless externally validated among post-MI patients with adequate predictive performance, useability is uncertain. A risk prediction score for the well-defined population that attend routine revisits after MI should be developed. At these revisits, the risk levels for rASCVD are elevated and have stabilized, several treatment options at different intensities exist to choose from, and the organization and resources are at hand for individualized risk-based interventions. SWEDEHEART and other national registries provide unique opportunities for the purpose of risk prediction modelling post-MI which should be pursued.[134,137,141]

From a long-term perspective, stretching over generations, much can be, and is being done at the political level for improvements of public health and health equity after MI.[173] Focus may need to be stronger on actions further up in the hierarchical chain of causality described by the WHO. At the clinical level, even stronger focus may be required on lifestyle than more easily measured secondary CV risk factors.[38] Further study is needed to pinpoint causal pathways in the associations between SES and rASCVD. Although a mediating effect in the association between income and rASCVD was observed for cardiac rehabilitation programs and the metabolic syndome, the effects were small and need experimental confirmation. Regional differences in SES as well as cardiac rehabilitation content and accessibility may add information that is important for decisions on resource allocation. Other mediating pathways must be further explored, such as plausible differences in adherence to post-MI drug therapies.[131,132,178] Interventions for cardiac rehabilitation uptake among low-SES individuals may improve secondary prevention achievements and health equity. An obstacle of designing and conducting trials post-MI regarding interventions on risk mediators in the association between SES and rASCVD may be the under-representation of women[195,196] and lower-SES individuals. Further investments in conducting novel registry-based randomized clinical trials[138] may improve generalizbility of trial findings to lower-SES groups.

Further study is warranted on the predictive value of on-treatment LDL-C and whether LDL-C target level should be used. For example, a randomized clinical trial comparing two LDL-C target levels. Unclarity of the evidence is demonstrated by the changing and conflicting recommendations from major professional organizations.[38,124,125,147,159,160] Many LDL-C target recommendations are accompanied by an relative LDL-C level reduction.[161] If Study II was to be redone, data on lipid levels at admission should be acquired to enable additional analysis assessing the associations between relative LDL-reduction reduction and recurrent ASCVD events.

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