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Myocardial Infarction as a Risk Factor of Developing Heart Failure

The Tromsø Study

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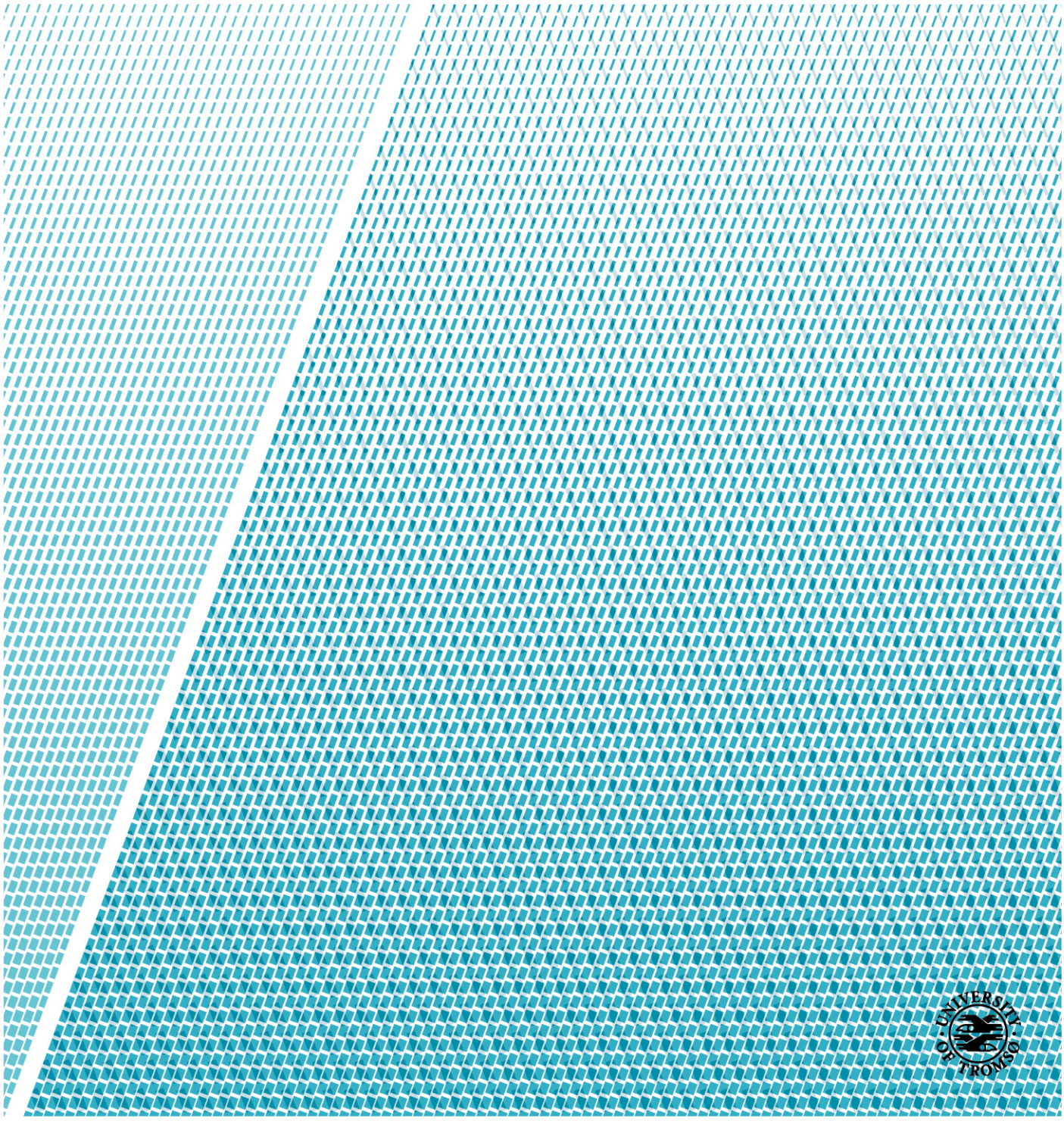

Foreword

The aims for this thesis were to investigate heart failure in relation to myocardial infarction in the Tromsø Study population from 1994 to 1995 and how the trends were in men and women. We investigated several known risk factors for myocardial infarction and heart failure.

I have an interest for public health, life style interventions, prevention of diseases and cardiology. Therefore, I contacted Maja-Lisa Løchen because of her position at the Department of Community Medicine at UiT The Arctic University of Norway. I also remembered her lectures during my medical studies. She had a thesis statement ready together with Tom Wilsgaard from the same department.

I would like to thank my fellow students Hilde Espnes and Ingvild Svanøe-Hafstad for the cooperation when we validated the heart failure diagnosis.

I would like to address a special thanks to my supervisors Maja-Lisa Løchen and Tom Wilsgaard. Thanks for all the good advice, feedback and help during the whole work process and validation of heart failure diagnosis.

June 1st 2018, Sandvika

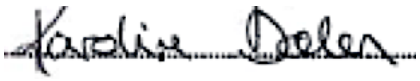

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Table of Contents

List of Tables

List of Figures

Summary

Background and aim: 1-2% suffer from heart failure (HF), and the prevalence increases by age. Lifetime risk for HF is highest among men. Myocardial infarction (MI) is a recognized risk factor for HF while HF is associated with increased mortality.

The aims for this thesis are to investigate how MI affects the risk of subsequent HF in both genders, in different age groups and whether education has an impact on the risk of HF.

Material and method: We followed 26 907 participants ≥25 years of age attending the Tromsø Study from 1994 to1995 for first ever HF (PPV 88%). Mean observation time was 14.7 years. HF diagnoses were collected from the Discharge Diagnosis Registry of the University Hospital of North Norway. HF occurrence was analyzed for the total population, among genders and in different age groups. Cox proportional hazard regressions were used to estimate hazard ratios (HRs) of developing HF. Main exposure variable was MI.

Results: 6.0% of men and 4.4% of women developed HF, a total of 1387 HF diagnoses. Mean age at HF diagnosis was 63.0 years for men, 68.5 years for women. Incidence of HF was highest when aged 66 to 75 years. HR for HF was 2.66 for every 10 years of increased age, and increasing age was a stronger predictor for HF in women. 23.8% men and 10.8% women developed HF subsequent to MI. Multivariable adjusted HR for HF was 3.55 in men and 3.64 in women after MI, but MI was equally associated with HF between genders.

Conclusion: We found that the risk of HF subsequent to MI was similar for both genders. The risk of HF increased markedly with age, especially in women. MI´s effect on risk of HF declined with increasing age. Level of education had no effect on risk of HF.

Abbreviations

ACE	Angiotensin-converting enzyme
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
CVDNOR	Cardiovascular Disease in Norway
DBP	Diastolic blood pressure
EF	Ejection fraction
ICD	International Classification of Diseases
HDL	High-density lipoprotein
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HUNT	The Nord-Trøndelag Health Study
kg	Kilograms
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
LVEDV	Left ventricular end diastolic volume
LVESV	Left ventricular end systolic volume
LVR	Left ventricular remodeling
m	Meters
MI	Myocardial infarction
mmHg	Millimeters of mercury
mmol/l	Millimoles per liter
NSTEMI	Non-ST segment elevation myocardial infarction
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PPV	Positive predictive value
REK	Regional Committee for Medical Research Ethics
SBP	Systolic blood pressure

STEMI	ST segment elevation myocardial infarction
SWEDEHEART	The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
TGF β	Transforming growth factor β
UNN	University Hospital of North Norway
VALIANT	Valsartan in acute myocardial infarction

1 Introduction

1.1 Heart failure (HF) diagnosis and epidemiology

Heart failure (HF) is a clinical syndrome with an underlying cardiac cause in which the metabolic needs of the body are not covered. This cardiac cause could be functional or structural, and lead to either systolic or diastolic dysfunction or both. The presence of certain symptoms like swollen legs, less physical capacity and breathlessness are necessary to diagnose and classify HF. It is possible to have cardiac dysfunction without clinical manifestations, but this is known as precursors to HF. Identification of the cause is important when it comes to choice of treatment (1).

Left ventricular ejection fraction (LVEF or EF) is the percentage of blood in the left ventricle that is pumped forward during systole (contraction) to supply the peripheral circulation. The LVEF is normally between 50 and 70% and is most commonly measured with echocardiography. This measurement results in three types of HF: heart failure with preserved ejection fraction (HFpEF) which implies EF >50%, heart failure with reduced ejection fraction (HFrEF) which implies EF <40%, and heart failure with mid-range ejection fraction (HFmrEF) which implies EF 40 to 49% (1). HF can also be divided into only two categories: HFpEF and HFrEF (2). Heart failure may present itself gradually or acutely. After an acute myocardial infarction (MI), some experience acute HF (1).

The proportion of HF patients with different EF categories seems to have changed over time (3). In hospitalized patients, the trends are that incidence for HFrEF declines while it increases for HFpEF (1). Between 1998 to 1999, 18.0% of HF diagnoses were HFpEF and 48.4% HFrEF according to Desta, L et al. In 2008, the corresponding proportions were 28.8% and 44.4% (3). The same trend was observed in Minnesota in the USA in HF up to 7 days after MI, with 75% HFrEF (EF <50%) in 1990 to 1996 and 62 % in 2004 to 2010. For HFpEF (EF >50%) there was no evidence for a decline in incidence (4). Numbers varying from 22 to 73% are used to describe the proportion of HFpEF. The great variance is due to the definition of EF, the clinical setting, previous MI, age and sex and the year of publication (1). Men suffer from HFrEF rather than HFpEF (proportions respectively 65.4 % and 44.3 % (5). A Swedish study found that the proportion of HFpEF increased from 1998 to 2008, in the same time period as the proportion of women with HF increased from 39 to 46% (3). Patients with HFpEF have less frequently suffered a MI (1) or a valvular disease compared to patients with

HFrEF (5). Furthermore, the patients with HFpEF are usually older, more often women, suffer from hypertension (1, 5), atrial fibrillation (1) and have higher BMI (5). The European Society of Cardiology underline the importance of separating HF patients based on left ventricular function because of underlying different aetiologias, comorbid conditions and response to therapies (1).

As described earlier, the presence of symptoms is necessary to diagnose HF. New York Heart Association (NYHA) has made a classification system due to the severity of symptoms of HF – the NYHA classification, from I to IV, were NYHA I is the least severe degree of HF. This classification does not correlate well with left ventricular function, even though the correlation with prognosis is strong (1). There are several classifications of HF.

In the developed countries, among 1 to 2% of the adult population has HF. The prevalence rises with increasing age. Above 70 years of age, the prevalence is ≥10%. The lifetime risk of developing HF at the age of 55 years is higher among men (33%) than women (28%) (1). Causes of HF are many. Genetic factors, ischemic heart disease, hypertension, toxicity and malignant infiltration could be such factors (1). Coronary heart disease (CHD) and hypertension are the major underlying causes of HF (3). Furthermore, arrhythmias and abnormal loading conditions could lead to HF (1). A patient with MI is at high risk of developing HFrEF because damage of the myocard may give suboptimal systolic function. It has been shown that 5% decrease in LVEF is associated with 29% increase in the risk of HF death or hospitalization due to HF (2). Women with MI have 15% increased risk for HF according to a Swedish study (3). Fewer people die in the acute phase after a MI, but the morbidity due to chronic heart disease has increased in the USA (2). Patients with HF have a 5-years cumulative mortality of 40 to 50%, and frequent readmissions to hospitals (2, 3). Mortality is higher in HFrEF than HFpEF, while hospitalizations more often are due to non-cardiovascular causes in HFpEF patients (1).

1.2 HF after a MI

Ischemic heart disease is the principal cause of HF, but the development of HF is not that clear (6). The onset and progress of HF are related to infarction size and neurohormonal activation. Percutaneous coronary intervention (PCI) as treatment for MI increased in use in patients with non-ST segment elevation myocardial infarctions (NSTEMIs) and those with left bundle branch block (LBBB) and ST segment elevation myocardial infarctions (STEMIs) between 1996 and 2008 in Sweden. In patients with STEMIs or LBBB, 94% were treated

with thrombolysis in 1996 and 1997, while 91.5% of the reperfusion treatment was primary PCI in the same patient group in 2008. The proportion of patients discharged with medical therapy, such as Angiotensin-converting enzyme (ACE) inhibitors, beta blockers and statins, also increased in the same study (3).

Over time there has been a change in the typical MI patient; with fewer STEMIs, anterior wall MIs and more comorbid diseases (4). Mannsverk, J et al. investigated the trends in risk factors associated with acute CHD from 1995 to 2010 in Tromsø. They observed a 51% decline in incident CHD at the same time as the mean levels of cholesterol, blood pressure (BP), resting heart rate and smoking decreased. The level of physical activity increased. The same did the proportion with overweight and diabetes mellitus. Age- and sex adjusted incidence of total CHD decreased by 3% each year. The incidence of hospitalized STEMIs decreased annually by 4.3% in average during the study period. The NSTEMI hospitalization rate increased from 1995 to 2003 before declining from 2003 to 2010. The increase in incidence of NSTEMI could be explained by more sensitive biomarkers for myocardial damage. Male sex, hyperlipidemia and smoking were more strongly associated with STEMI than NSTEMI and sudden death. Overweight was more associated with STEMI than NSTEMI. In total, the changes in coronary risk factors accounted for 66% (64% in women and 61% in men) of the decline in total CHD. The changes in cholesterol level contributed to 32% of the decline, while BP, smoking and physical activity contributed 14%, 13% and 9%, respectively. The decline in prevalence of smoking and hypercholesterolemia was thought to be the major driving forces for the decline in STEMI incidence. The mortality after a coronary event, age- and sex adjusted, also declined 7.3% each year, both in- and out-of-hospital. 65% of the decline was attributable to the decrease in out-of-hospital sudden deaths. Subjects with sudden death were older, had higher resting heart rates and were less likely to be physically active than those with STEMI and NSTEMI. The authors also claim that the changes in incidence contributed to 43% of the decline in CHD mortality. Decline in age- and sex adjusted incidence of total CHD was driven by decreases in out-of-hospital sudden death and hospitalized STEMI. They also observed that the proportion of patients receiving beta blockers, acetylsalicylic acid and statins at discharge increased over time. The same did the proportion of revascularized patients (7).

Sources report both declining and increasing incidence of HF after MI. Reasons for this could be different definitions of HF, different populations and study designs. The reduced prevalence of HF after MI is thought to be because of improved baseline characteristics and a

decrease in infarct size due to revascularization of the myocardium (3). Primary PCI reduces the infarct size. This decreases the risk of developing HF because of reduced LVEF. On the other hand, other sources claim increased prevalence of HF. Survival after MI has improved, and this might have created a population with greater risk of developing HF. Older population and decrease in sudden deaths due to implantable cardioverter defibrillator might also be a part of the increasing prevalence of HF after MI. HF hospitalization after MI was declining earlier without the primary PCI (8).

HF is associated with poor prognosis, and mortality after discharge is nearly four times higher among those with HF within six months after the first MI than in those without according to a study form 2009 (6). This is also found in more recent studies. After a MI, both known chronic HF and development of HF are associated with worsened outcome on short- and long-term (3). These patients are at higher risk of fatal and nonfatal ischemic events and arrhythmic events than MI patients without HF (9). The anatomical changes post MI changes the conduction system of the heart, and this can predispose for lethal arrhythmias and cardiac arrest. Reduced LVEF is associated with an increased risk of hospitalization (2).

1.3 Left ventricular remodeling (LVR) after MI

Larger ventricular volumes characterize postinfarct left ventricular remodeling (LVR). This happens in about 30% of the MI patients. Both left ventricular end systolic volume (LVESV) and left ventricular end diastolic volume (LVEDV) increase progressively. An increase of minimum 20% in LVEDV from the first imaging after the infarction is usually the definition of ventricular remodeling. This measurement could lead to underestimating the remodeling because the remodeling starts only a few hours after the MI, and the first imaging usually takes place after a few days. LVEF decreases in most cases during LVR. LVR is a negative prognostic factor because it often leads to HF which is associated with increased mortality (2).

Both preload and afterload increase after an MI, and this leads to the remodeling of the ventricles (2). The scar tissue has no contractile qualities, and this area of the myocard will expand (10). The loss of contractile tissue will lead to asynchronous contraction of the ventricular wall and the wall stress will distribute unevenly to the myocard. This results in expansion of the infarcted area and the wall in this area gets thinner. To maintain an overall cardiac function, the healthy tissue becomes hypertrophic (2). The stroke volume can be normal for some time due to the increased preload of the ventricles and increased pressure

produced by the maintaining myocard. This causes an increase in workload for the myocard which contributes to the remodeling. The infarcted myocardial tissue stretches, and this leads to dilatation of the ventricle, thus leading to larger volumes in the left ventricle. The expansion will lead to increased volumes, and the increased volumes will increase the pressure load. Pressure load gives concentric hypertrophy of the myocard and volume overload leads to eccentric hypertrophy of the myocard. According to LaPlace Law, an increase in wall thickness due to concentric hypertrophy will reduce wall stress and thereby afterload. Pressure load can either induce adaptive or maladaptive changes in the myocard. It could seem like the remodeling is beneficial at first, but then disadvantageous as it progresses. Combined pressure and volume overload takes place in the non-infarcted areas. The infarctional changes are therefore a combination between infarct expansion, pressure overload and volume overload. Progressive LVR is crucial in developing heart failure, and the remodeling can take place up to two years after the MI (10).

Dyssynchrony of the left ventricle will affect the hemodynamic conditions of the body; reduced cardiac output, reduced filling velocity, reduced relaxation rates and increased energy demand in the myocard. Shin, S-H et al. suggest "that ventricular dyssynchrony may contribute to adverse prognosis and development of heart failure in the post-MI setting". Abnormal contraction may interfere with the recovery after a MI because of increased work load, but also because of the mitral regurgitation due to the papillary muscle impairment. Resynchronization therapy has positive prognostic effect in HF patients. Hypertension, older age, earlier MI, HF and bundle branch block are associated with dyssynchrony. Shin, S-H et al. had 381 patients from the "Valsartan in acute myocardial infarction" (VALIANT) echocardiography study with EF <35% from echocardiography or <40% from radionucleotide imaging available for dyssynchrony analysis. 26% with the highest degree of dyssynchrony had HF. Patients with dyssynchrony have increased LVEDV, LVESV and mitral regurgitation among other variables. The hospitalization rate for HF and mortality are higher among those with severe dyssynchrony (11).

The remodeling of the myocard also includes an increase in the amount of extracellular matrix as a result of increased fibroblast activity (2). Angiotensin II, for instance, is released from the myocard due to increased wall stress or mechanical load and can stimulate either adaptive or maladaptive myocardial changes depending on the concentration of the molecule. Cardiac fibroblasts increase their synthesis of collagen after stimulus from Angiotensin II, as well as aldosterone and transforming growth factor β (TGF β) (10). This leads to cardiac fibrosis.

The remodeling is proportional with infarct size (10), and infarct size is the best single predictor of developing LVR (2). The infarct size correlates with mortality. The left coronary vessel usually supplies a greater area of the heart than the right coronary vessel. This is why the anterior infarcts tend to be the largest. It has been said that approximately 25% of the left ventricular tissue must be lost to develop HF. Necrosis of the myocard is most severe in the acute phase and during reperfusion. Microvascular obstruction, intramyocardial hemorrhage and mitral regurgitation can also predict ventricular remodeling. The mitral regurgitation is a result of a dysfunctional papillary muscle after an MI and will increase the preload of the left ventricle (2).

Early-onset HF after MI is mainly believed to reflect the myocardial damage and is related to the severity of the infarct. Late-onset HF, on the other hand, is thought to because of the LVR, recurrent MI and subclinical ischemia (4).

1.4 Aims

The aims for this thesis are to investigate how MI affects the risk of subsequent HF in men and women, in different age groups and if level of education has an impact on the risk of HF. The main thesis statement is the same as the title of the thesis; “Myocardial infarction as a risk factor of developing heart failure”.

2 Material and method

2.1 The Tromsø Study and study population

The Tromsø Study is an ongoing prospective cohort study consisting of seven complete surveys (Tromsø 1-7) from 1974 to 2016 (12). In total 45 473 subjects have participated in at least one survey. The participants were enrolled using the official population registry to find the inhabitants in the municipality of Tromsø. Furthermore, the possible participants were invited by a personal letter by mail. The invitation included information about the physical examination and a questionnaire. Some participants in Tromsø 4-7 were invited to a second examination as well. The attendance rates have been high (13). This thesis is based on the fourth survey of the Tromsø Study, which will be referred to as Tromsø 4.

Tromsø 4 took place between 1994 and 1995. The entire population aged 25 years and above was invited, and 27 158 subjects participated. The attendance rate was 77%; 12 865 men (69.6%) and 14 293 women (74.9%) aged 25 to 97 years. The attendance rate at the second visit was 76% (7965 subjects). According to Jacobsen, B et al. the questionnaires covered

among others prevalent cardiovascular diseases and symptoms, diabetes, physical activity, smoking habits, employment, family history of CHD, ethnicity and sosio-economic status (13).

The data set contains 26 907 subjects. 166 of 27 158 did not consent to research. 63 subjects were excluded due to HF diagnosis before the date of Tromsø 4. 22 subjects had moved before the Tromsø 4 examination date and were excluded from the analysis.

2.2 Work process

I contacted Maja-Lisa Løchen in September 2016, and she became my main supervisor. She suggested an idea for a master thesis that had been proposed by Tom Wilsgaard and included him as a statistical supervisor. The protocol was written in October 2016. During the work with the protocol, I searched for relevant literature in PubMed. Unfortunately, I did not write down the search words. The protocol contained background information regarding HF: definitions, pathophysiology and epidemiological data. In collaboration with my main supervisor I also applied to the Tromsø Study Data and Publication Committee for use of the included data.

In June 2017, I started the validation of the HF diagnosis from the Discharge Diagnosis Registry of the University Hospital of North Norway (UNN) in collaboration with my supervisors and two additional medical students. The two other medical students and I used three days each on the validation. Based on validation advice from Henrik Schirmer who supervises another HF project, we performed the validation. The validation was completed in May 2018 by Løchen and Wilsgaard. We validated 77 HF diagnoses. In June 2017, I started the work with the statistical analyses with guidance from Tom Wilsgaard.

During weeks 33-34, August 2017, I was in Tromsø to catch up with my supervisors and to continue the statistical analysis. In September 2017, I sent the first draft to Løchen and Wilsgaard for evaluation and feedback. The draft contained tables and models from the analysis of the data set.

During the winter, I have worked with, and finished the statistical analyses. In January 2018, Wilsgaard found an error in the data set. Participants with HF coded as more than one ICD code, were counted as more than one single participant in the data set. Therefore, I received a new version of the data set from Tromsø 4. I performed all the analyses one more time with the correct information.

From March through May 2018, I have worked almost daily with the thesis. My supervisors have continuously given me feedback.

2.3 The variables

The data set from Tromsø 4 contained results from physical examinations, non-fasting blood samples, self-reported health and lifestyle habits. We chose known common risk factors for cardiovascular disease and in particular for HF from the available list of variables (table 1).

After 2 minutes of rest, systolic blood pressure (SBP) was measured three times in a sitting position separated by 1-minute intervals using an automated device (Dinamap Vital Signs Monitor; Critikon, Tampa, Florida, USA). The value used in this paper is the mean value of reading two and three. Diastolic blood pressure (DBP) and resting heart rate are included in the same way. The unit for BP was millimeters of mercury (mmHg) and the unit for SBP in the Cox regression is 15 mmHg. Weight was measured in kilograms (kg) while height was measured in centimeters. From this, body mass index (BMI) was calculated: m/h^2 were m is mass in kg and h is height in meters (m).

Non-fasting blood samples were taken, and the lipid levels were analyzed. The data set contains information about time since last meal, but we have not considered this in the analysis.

The rest of the data is based on the self-reported questionnaires. Yes or no questions were asked: “Do you have, or have you had a heart attack?”, “Do you have, or have you had angina pectoris?”, “Do you have, or have you had a cerebral stroke/brain hemorrhage?”, “Do you have, or have you had diabetes?”. The alternatives to the question “Do you use blood pressure lowering drugs?” were 1) currently, 2) previously, but not now or 3) never. Smoking habits were separated in cigarettes, cigarillos and cigars, and three questions were asked: “Do you smoke cigarettes/cigarillos/cigars/pipe daily?”. If the answer was yes to one or more of these three questions, the participant was considered to be a smoker in this thesis. The question for alcohol consumption was: “How many times a month do you normally drink alcohol?”. The categories made were 1) zero times a month, 2) 1-7 times a month and 3) eight or more than eight times a month. We also included the subjects with missing values in the new alcohol variable because of a great number of missing alcohol values. Because of this, we made a separate variable for the missing alcohol values (missing yes/no). Two questions were asked about physical activity. How many hours each week had the participants done hard

(perspiring and/or out of breath) and light (not perspiring and/or not out of breath) physical activity during leisure time on average the last year? Both questions had four alternatives: 1) none, 2) less than one, 3) 1-2 or 4) 3 or more. The answers were recoded into a single variable with the categories 1) sedentary, 2) low, 3) moderate or 4) high level of physical activity (table 2). The highest level of education completed was reported and organized in the categories 1) 7-10 years primary/secondary school, modern secondary school, 2) Technical school, middle school, vocational school, 1-2 years senior high school, 3) High school diploma (3-4 years), 4) College/university, less than 4 years and 5) College/university, 4 or more years. Alternative 4 and 5 were considered as higher education (college/university) while the rest were considered as lower in this thesis.

For some variables, there were missing values. Since these accounted for a small part of the data set, except from the alcohol variable described earlier, they were not expected to influence the result.

2.4 Ascertainment and follow up of HF

Participants with a prevalent HF diagnosis in the Tromsø 4 were excluded from the study. The Discharge Diagnosis Registry of the UNN (included outpatient clinic diagnoses) was used to identify participants who reached the clinical endpoint of the thesis, namely HF with diagnostic codes from the International Classification of Diseases (ICD). The HF codes used were code 428 from ICD-9 and code I50 from ICD-10. The patients with these diagnoses were linked to the participants of Tromsø 4. UNN is the only hospital in Tromsø, and it is likely that the majority of participants were admitted here when in need of hospital medical care because of the long distance to other hospitals (13).

2.5 Validation of HF diagnosis

Two other medical students and I received an extract of patients who had participated in Tromsø 4 with HF diagnosis at hospital discharge or at the outpatient clinic. Our co supervisor gave us 77 randomly selected subjects among the Tromsø 4 participants who also had an echocardiographic examination in the study. The selection of participants with an echocardiographic examination was necessary because the validation will be included in other studies as well in the future. The extract contained the unique five-digit code which is part of the national identification number for Norwegian citizens, name and date for HF diagnosis.

Along with our main supervisor, we read through all the 77 patient journals to investigate if the patient actually had HF. After 2000, the journals were electronic. We first searched for case history or medical record from the date of HF from the extract. We looked for blood sample answers, x-ray reports and echocardiographic examination results to ensure that HF existed. Furthermore, we used the Norwegian search words for HF, failure of the left ventricle, diastolic failure, the HF diagnostic codes, echocardiography and dyspnea. We searched through 20 paper patient journals from before 2000. We could confirm that 68 of 77 had definite HF. This gives a positive predictive value (PPV) of 88%. 9 patients did not have HF. Instead 3 patients had dyspnea due to respiration failure, 2 had CHD without HF, 1 had an aortic stenosis surgery without HF, 1 had been referred with suspected HF but this was disproven and 2 had no sign of heart- or lung disease or dyspnea at all.

2.6 Statistical analysis

The statistical analysis was performed with IBM Statistical Package for the Social Sciences (SPSS; IBM Corporation, Armonk, NY, USA) statistics, version 24.0. Categorical variables are presented as numbers and percent while continuous variables are presented as means with associated standard deviation.

Incidence of HF was analyzed for the total population, among men and women separately, and in different age groups.

Cox proportional hazard regression analysis was used to estimate hazard ratios (HRs) of developing HF with 95% confidence intervals (CIs). All subjects were followed from the date of the examination in 1994-95 until the date of first ever HF, the date of emigration from Tromsø, the date of mortality, or end of follow-up December 31st 2012, whichever came first. The main exposure variable was self-reported MI at baseline, and the following risk factors and were included as covariates: age, SBP, BMI, total cholesterol, triglycerides, HDL, smoking, education, physical activity and alcohol. Missing alcohol values yes/no were also included as a covariate in the model (HRs not presented in table 6) to get a real linear correlation over the categorical variable. We analyzed the HRs of developing HF in the same way, but without the named covariates, in 3 separate age groups. The stratified Cox model was used to plot survival curves for those with MI vs those without MI. The proportional hazard assumption was assessed by graphical inspection of log minus log of the survival curves. P-value <0.05 was considered statistically significant.

Tests of interactions by sex was performed by including a cross-product term between sex and each assessed independent variable in the age adjusted Cox model.

2.7 Ethics and permission

The Tromsø Study is approved by the Regional Committee for Medical Research Ethics (REK) and has a license from the Norwegian Data Protection Authority. Access to the depersonalized data file with the described variables was received after approval from the Data and Publication committee of the Tromsø Study. This study is covered by this approval. All included subjects provided written informed consent and could at any time withdraw their consent.

3 Results

3.1 Baseline characteristics

Mean age at baseline was approximately 47 years for both genders (table 3). Out of 26 907 subjects 52.6% were women. SBP was 136.8 mmHg for men without HF compared to 131.1 mmHg for women without HF. The total cholesterol levels where equal between men and women without HF. Women were less physically active than men. Men reported greater consumption of alcohol than women. More women than men reported to have completed the lowest level of education possible in Tromsø 4 (table 1).

In total 5.2% (1387 subjects) were identified in the discharge registries from UNN Tromsø with a HF diagnosis. 55.1% were men. The incidence of HF was higher among men; 6.0%, compared to 4.4% among women. Mean observation time for HF subjects was 10.1 years (±5.0). The mean age for subjects with HF was 65.5 years in total, 63.0 years for men and 68.5 years for women, compared to 45.5 years for men without HF and 46.1 years for women without HF (table 3). Mean SBP was 148.2 mmHg for men with HF compared to 157.7 mmHg for women with HF. Total cholesterol was 6.6 mmol/L among men with HF and 7.1 mmol/L among women with HF. The difference in the levels of triglycerides and HDL was less. There were more smokers among men with HF (34.0%) than among women with HF (27.8%). In percent, more men and women smoked without having HF. Among both genders, the majority of the subjects with HF were more sedentary than the subjects without HF. More subjects with HF did not drink alcohol compared to those without HF. When it comes to education, the majority of the subjects with HF in both genders had the lowest level (table 1).

The incidence of HF was highest between 65-74 years (table 3). 40.1% of women with HF were in this age group.

3.2 Impact of MI on the risk of future HF

23.8% men and 10.8 % women developed HF subsequent to MI during the observation time. 88.6% of women and 75.8% of men had not suffered MI before development of HF. 2.8% of men with no HF had earlier self-reported MI, while the number was 1.1% among women with no self-reported MI. 20.2% of women with HF and 23.2% of men with HF reported angina pectoris (table 1).

The HR of developing HF after a MI was 13.55 (95% CI 11.8-15.6) times higher than for those without MI. Adjusted for age and sex, the HR of developing HF after a MI was 3.59 (95% CI 3.1-4.1) (table 4). Multivariable adjusted HR for HF after MI was 3.55 (95% CI 3.0-4.3) for men and 3.64 (95% CI 2.8-4.6) for women (table 6). HR for HF between those with self-reported MI yes vs no did not vary between men and women, p-value for sex by MI interaction was 0.97. Therefore, there was no evidence that MI was more associated with HF among women than men. HR for HF between those with self-reported MI yes vs no did vary with age, p-value for age by MI interaction was <0.0001 (95% CI 0.5-0.7). Therefore, we analyzed the risk of HF subsequent to MI and three separate age groups (table 5). The HR for the effect of MI on HF decreased by increasing age (table 5) while the risk of HF increased by increasing age (table 6).

Significant predictors of HF in both genders were age, MI, SBP, BMI, smoking habits and physical activity (table 6). Age, SBP, total cholesterol and level of education as predictors of HF, adjusted for age and MI, had different effect among men and women (p-value for predictor by sex interaction respectively <0.0001, 0.047, 0.002 and 0.002). The rest of the interaction analysis (predictor by sex interaction) for the predictors BMI, triglycerides, HDL, smoking, physical activity and alcohol were not significant. Total cholesterol levels were significantly associated with HF in total and among men. Physical activity per unit over 4 levels was significantly inversely associated with HF in both sexes. Increase in HDL-levels were inversely associated with HF, but this was not significant (borderline significant in men). Other variables without statistical significant association with HF were triglycerides among both genders and in total, education among both genders and in the total population, total cholesterol levels among women and alcohol in the total population and in men (table 6).

Mean observation time was 14.7 years (±5.4). At this time the probability of no HF subsequent MI was approximately 0.95 while it was 0.99 if no MI (figure 1).

4 Discussion

In the present study we tested and confirmed that in both men and women, previous MI was significantly and independently associated with an increased risk of future HF. This association was similar in both sexes. 5.2% of the subjects in Tromsø 4 developed HF during the long observation period. Increasing age was a statistically significant predictor for HF following a MI. The effect of MI on future HF decreased by age.

4.1 HF and age

In this study 59.4% of the subjects in the cohort who developed HF were 66 years or older. The mean age in HF subjects was almost 20 years higher than in the non-HF group. The multivariable adjusted hazard ratio for HF increased 2.66 times for every 10 years (table 6). Increasing age was a stronger predictor in women. Still, self-reported MI´s effect on future HF decreased with age. Ezekowitz, J et al. followed an elderly population (≥65 years) in Canada from 1994 to 2000 and found that 76% developed HF subsequent to MI. 70.6% developed HF within 5 years after their first MI when aged 65-69 years. In subjects older than 75 years, 76.8% developed HF (6). This study cannot directly compare with our results because of the study population which consists of MI patients only, 65 years or older, whereas our study includes subjects from the general population of Tromsø, 25 years or older. Despite this, the high incidence of HF subsequent to MI supports our finding of age as a stronger predictor of HF following a MI. The same study suggests several possible explanations for increased risk of HF in elderly MI patients such as increasing age and comorbidity, improved revascularization and better management of MI, as well as oral medical treatment for cardiovascular disease that delay the HF syndrome. Ezekowitz, J et al. rise the hypothesis that improved MI treatment and thereby reduced MI mortality are the drivers behind claimed increased HF incidence (6). Sulo, G et al. studied a large MI cohort (n=69 372) from the "Cardiovascular Disease in Norway" (CVDNOR) registry. 21.3% developed HF within one year from MI hospitalization. The proportion with HF was greater in patients 70-84 years than 25-69 years (14). A large Swedish MI cohort study found that the risk of HF increased for every additional year in age by 5% (3). Another large Swedish MI cohort study by Shafazand, M et al. (n=175 216 subjects) found that every additional year of age increased the 3-year incidence of HF by 6% (15).

4.2 Occurrence of HF and sex aspects

Studies show both declining and increasing incidence of HF after MI with numbers varying from 20 to 75% depending on study design. According to Shafazand, M et al. the majority show a decline, and their study found that 25% developed HF within three years after the MI (15). Two studies based on the same population-based health survey, The Nord-Trøndelag Health Study (HUNT), in Norway from 1995 to 1997 investigated association between alcohol consumption and incident HF (n=60 655) and insomnia and the risk of future HF (n=54 279). They found a HF incidence of 2.6% during follow up of 11.2 years (16), and a HF incidence of 2.6% during follow up of 11.3 years (17), respectively. This Norwegian study population can compare with our study population due to invitation of the whole population >20 years of age with attendance rate of 69%, and exclusion of previous HF patients. Our study and the two HUNT studies are conducted in the same time period in Norway. Our study found a HF incidence of 5.2%. A possible explanation for this is that the two HUNT studies included HF as main diagnosis only while we also included HF as secondary diagnosis which can explain the different incidence numbers. The HUNT studies have not considered MI in relation to HF.

Desta, L et al. studied 199 851 MI patients from 1996 to 2008 in Sweden. They found a marked decrease in the incidence of in-hospital HF following MI, which they claim to be consistent with the majority of population-based studies. The proportion with HF in 1996 to 1997 >75 years was 61%, 39% between 50 and 75 years and 17% <50 years. In 2008 the corresponding numbers were, 41%, 18% and 11% respectively. The HF diagnosis was not based on ICD codes in patient's journals, but rather on clinical signs of HF. Women with MI had increased risk of developing HF across the study period (3), while we found no sex difference for risk of HF following MI in our study. The Swedish study suggests that an increase in HFpEF might reflect the increasing proportion of women with HF and that HFpEF has developed due to comorbidities, for example hypertension (5). In our study we did not have available data to differentiate between the types of HF because the hospital discharge diagnoses do not have such information. Furthermore, reasons for the reduced incidence of HF after MI is thought to be reduced infarct size due to more sensitive MI diagnostic, effective treatments and secondary prevention and changes in burden of risk factors (3, 15).

Shafazand, M et al. found that women had 6% higher incidence of HF than men independently of age, year of MI or comorbidities like diabetes mellitus, atrial fibrillation, valvular disease and stroke. Between 2002 and 2004, 11.1% men and 12.8% women aged 35

to 64 years were diagnosed with HF. In the same time period, when aged 65 to 84 years 26.6% men were diagnosed with HF while the proportion with HF diagnosis was 29.6 % in women. The authors suggest that the explanations partly are that men had higher mortality after MI than women, and that they might have died before they developed HF (15). Our study found higher incidence of HF among men in the whole cohort (6.0%) and among subjects with MI (23.8%) than women in total (4.4%) and women with MI (10.8%), and no sex difference in risk of HF following MI as described before.

Although our study did not show any sex difference in risk of HF subsequent to MI, there were several other factors that did. Adjusted for the listed variables in table 6, age had significantly different effect in men and women for predicting HF with 2.63 times increased risk in men and 2.78 times in women. On average, men were diagnosed with HF subsequent MI at 63.0 years of age while women were 68.5 years. 30.8% of women and 16.3% of men were above 76 years old at the time of HF diagnosis. 33.8 % of men and 40.1 % of women were aged 66-75 years when diagnosed with HF. Between 76 to 85 years 14.9 % men and 27.4 % women received the HF diagnosis.

In our study, level of education had a statistically significant different effect in men and women on the risk of HF when adjusted for age and MI. The multivariable adjusted HRs for HF showed 7% reduced risk for HF in men and 27% reduced risk for HF in women for the highest level of education (yes versus no). Still, the risk reducing effects were not statistically significant in men and women when adjusting for the listed covariates (table 6). In a systematic review of 11 articles Damiani, G et al. found that level of education had no effect on the risk of readmission to hospital for HF or MI in patients >65 years with HF or MI (18). The review did not compare effect between genders. Still, we have not considered risk of readmissions to hospital like Damiani, G et al., as HF is our only outcome, in contrast to MI and HF combined. Therefore, this study is not compatible with our finding, but documents another dimension considering HF and level of education.

SBP as a predictor for HF showed statistically significant different effect in men and women when adjusted for MI and age in our study. For every 15 mmHg increase in SBP, men had 8% increased risk for HF and women 12% increased risk for HF when adjusted for several listed variables (table 6). SBP was a stronger predictor for HF among women. On average, women´s SBP were 157.7 mmHg and men´s SBP were 148.2 mmHg while approximately 26% in both genders reported to use anti-hypertensive medication at baseline (table 1). Recent studies have

shown that women are less likely to achieve treatment goals for secondary prevention than men (19, 20), and fewer women use beta blockers and ACE-inhibitors than men (20). The proportion of MI patients with hypertension increased from 32.5% to 47.0% in Sweden between 1996 and 2008. Hypertension at admission for MI increased the risk for HF during hospitalization by 7%. Hypertension is associated with HFpEF which is increasing compared to HFrEF, and this is thought to reflect the increasing proportion of women with such a comorbidity (3). HF is more likely to complicate MI in people with comorbidities like hypertension according to Hung, J et al. As in Sweden, the proportion of MI patients with hypertension increased from 44.0% between 1996 and 1998 to 54.1% between 2005 and 2007 while the mean age and sex mix of patients remained the same. In Australia, MI patients who developed HF were more likely to be older and female, and hypertension was a predictor of HF within a year after MI (21). Hopstock, LA et al. studied two MI cohorts in Tromsø, Norway where MI-cohort I was selected from the same Tromsø Study survey as ours. They reported that 35% of women and 52% of men achieved BP <140/90 mmHg (or 130/80 mmHg if diabetic) between 1994 and 1995 compared to 50% women and 54% between 2007 and 2008. The trend was that women had higher SBP, less decrease in BP over the observation time and lower achievements of the treatment targets. Suggested explanations for this were that women suffered MIs later in life than men, and that secondary prevention less frequently was offered to the elderly (19). Hopstock, LA et al. did not consider HF in their study of MI patients and BP. Still, they found interesting sex differences that can support our findings of SBP-sex interaction on SBP´s effect on HF when adjusted for age and MI. As presented earlier, the proportion of HFpEF is increasing compared to HFrEF, and this might partly be due to the trend presented in the Norwegian study by Hopstock, LA et al (19). Control of hypertension will delay onset of HF (1). The fact is that women do not reach treatment goals for secondary prevention after MI which make them vulnerable for developing HFpEF later in life.

The effect of total cholesterol level on HF, when adjusted for age and MI, depends on whether you are a woman or man in our study. Women with HF in Tromsø 4 had mean total cholesterol levels of 7.1 mmol/L (±1.3) while men with HF had 6.6 (±1.2) mmol/L (table 1). Another study on MI patients from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry found that there were sex differences in the use of statins among other pharmacological treatments post MI, and that women used less

statins than men (88.2% vs 92.2%), and that there were sex differences regarding cholesterol treatment target post MI. This study also found that women were at higher risk for readmission to hospital due to cardiac events than men post MI (20). We have no data on use of pharmacological treatment other than self-reported antihypertensive medication or not. Therefore, it is interesting that the Swedish study report sex differences in use of such preventive medicines in MI patients. In our multivariable regression model, the total cholesterol levels were only significantly related to risk of HF in men and in total with 17% increased risk in men with each mmol/L increase in total cholesterol. The European Society of Cardiology state that statins can prevent or delay onset of HF. Furthermore, aspirin, antiplatelet agents or revascularization have been shown to reduce the risk of developing HF or mortality in patients with stabile coronary artery disease (1).

4.3 HF and other life style factors

Obesity is a known risk factor for HF, but it is unknown how treatment for obesity affects the development of HF (1). Compared to men with HF, women with HF had higher BMI in our study (27.6 vs 26.7 kg/m^2), but we must make allowances for women´s age. For each unit increased BMI, the risk of HF in the multivariable adjusted model was 5% higher in women, and 6% in men. The effect of BMI on risk of developing HF showed no significant difference depending on sex (BMI-sex interaction p=0.054) when adjusted for MI and age. Obesity has been found more commonly in HFpEF than HFrEF. Weight loss has not been proved to be beneficial in HF patients but rather to worsen symptom status and quality of life (1).

Alcohol can affect the risk of HF. According to Doran, KS et al. the lowest risk of developing HF in men is with an alcohol consumption up to 7 drinks each week. Greater consumption than this can lead to toxic cardiomyopathy which illustrates an U-shaped relationship between total alcohol intake and HF (22), and this finding was also referred to by the European Society of Cardiology in their HF guidelines (1). A suggested explanation for this relationship is that a moderate alcohol consumption is associated with less MIs (22). Another HUNT study from 1995 to 1997 (n=60 665) investigated correlation between alcohol consumption and HF. This study followed their participants until first ever HF (n=1588) and found that frequently drinking (>5 times each month) with light-to-moderate consumption (>3 drinks, <6 drinks each week) gave decreased risk of HF in their low-drinking population. MI, for instance, could not explain the association. The association between alcohol consumption and HF were not influenced by sex among other possible modifying factors (16). Not all sources report this benefit of moderate alcohol consumption (22). In our study, only 2.1% of women with HF

drank alcohol >8 times a month while 11.4% of men with HF did the same. More HF subjects were teetotalers than subjects without HF. >8 times a month was our highest category of consumption, and this cannot directly compare with the measurement "up to 7 drinks each week". Alcohol consumption had significant effect on development on HF among women in our study with 23% reduced risk for HF with each increased unit of alcohol while no effect could be seen in men. However, the different effect in men and women was not statistically significant (sex-alcohol interaction p=0.449, adjusted for age and MI). The similar effect between genders is consistent with the mentioned HUNT study. In total, our multivariable model showed a non-significant risk reducing effect of alcohol consumption in relation to HF while the HUNT study found a significant risk reducing effect.

Physical activity decreased the risk of developing HF in both genders (13% in men and 11% in women) with no significant interaction between level of activity and sex. The European Society of Cardiology also claims that this inverse relationship exists (1), and several observational cohort studies have shown the same (23). Norwegian guidelines recommend both endurance training and weight training in stable HF patients, that is NYHA class I-III. The effect of physical activity has documented effect on decreasing risk of hospitalizations and mortality due to HF, and increased quality of life in HF patients (24). Endurance training is recommended 3 to 5 times a week, with moderate to high intensity over 20 to 60 minutes. Weight training is recommended 2 to 3 times a week, 40 to 60% of one-repetition-maximum and 8to 15 repetitions, but has to be individually adjusted (25). The American Heart Association guidelines recommend $\geq$150 min/week of moderate-intensity aerobic to reduce the risk of CHD. At the same time, some studies claim that the level of physical activity needed to reduce the HF risk might differ from the level necessary to reduce risk of CHD. There seems to be a dose-response-relationship between level of physical activity and risk of HF, and higher level of physical activity is needed to reduce the risk of HF than the level required to the reduce risk of CHD because of the activity´s effect on different physiological factors related to CHD and HF. Pandey, A et al. found that the risk of HF was 30% lower for the highest level of physical activity compared to the lowest level. There was also a risk reduction effect with moderate or light levels of physical activity compared with lowest level. The authors claim that the association between the highest level of physical activity and HF risk was similar across sexes (23). This is consistent with our finding. Still, we have considered a population cohort consisting of a heterogenous Tromsø population while Pandey, A et al. have considered published prospective cohort studies (53.5% women,

n=370 360) that reported associations between baseline physical activity levels and incident HF (n=20 203).

Furthermore, Pandey, A et al. refers to studies that have shown age-related decline in left ventricular compliance and thereby diastolic dysfunction and the development of HF, especially HFpEF. A recent study have shown that high levels of life time exercise were associated with favorable ventricular compliance while the association was not clear with lower level of physical activity (23).

4.4 When does HF occur after the MI?

Studies suggest that the risk of HF following MI is highest the first year after the MI. After a MI, the cumulative incidence of HF hospitalization was 4.4% per year and then was reduced to about 1.0% per year from 1 to 5 years following the MI (8). Ezekowitz, J et al. found that 36.6% were diagnosed with HF during hospitalization for the MI, and that the incidence of HF diagnosed at a hospital from 1994 to 2000 increased absolutely by 7.9 % or relatively by 25.1%. The majority (53.0%) developed HF within the first year after the MI (6). Sulo, G et al. found that 17.1% of MI patients from the CVDNOR registry developed HF during MI hospitalization while 5.4% of 47 673 patients discharged alive without HF developed HF within the first year after MI. The overall change in risk of HF occurring at any time within the follow-up for one year was not statistically significant. Still, the odds of HF during MI hospitalization increased by 2.3% each year while the risk of HF within one year after discharge declined by 6.3% each year. The increased odds for HF during hospitalization could be because of the decline in out-of-hospital coronary deaths in Norway. Observed age differences in the in-hospital HF group could be because of different baseline characteristics (14). HF within the first year is associated with increased risk for hospitalization due to HF beyond 1 year (8). According to Shafazand, M et al. studies consistently show that HF in relation to MI develops during hospitalization for the MI or within the first few months, and they found that 25 % had developed HF within 3 years of admission for their first MI (15). Our study has considered self-reported MI yes/no, and no data were available for an analysis of time from MI to HF.

4.5 Validity of HF diagnosis

McCormick, N et al. reviewed 19 articles published between 1999 and 2009 which considered HF and had reported on the validity of the HF diagnosis using codes for HF in administrative data. In the majority of the studies, the specificity was $\geq$95% and PPV was $\geq$87% while the

sensitivity for HF was ≤69%. Still, the authors concluded that "most HF diagnosis in administrative databases do correspond to true HF cases", and a patient was 52 times more likely to actually have HF if coded as HF than someone without HF code. To identify more cases, they suggested searching for laboratory data and prescription medication data, and to conduct a broader search for both hospitalized patients and outpatient patients. The authors claim that many HF patients do not get a HF code because of less severe HF, or that the HF syndrome did not prolong their hospital stay, and for that reason the broader search should be conducted. The authors refer to North American databases with PPV as high as >90% for HF, and point out the prevalence of a disease and its effect on PPV (and negative predictive value as well) (26). Since we have considered a randomly selected extract from the population-based Tromsø 4 and we conducted a broader search resembling the search suggested by McCormick, N et al., our validated PPV of 88% is satisfactory. We had echocardiographic data available, and results from this investigation are often used to identify HF, even though it is a clinical syndrome.

4.6 Possible implications of the results

MI was already a known risk factor for subsequent HF. We wanted for the first time to investigate if this finding could be confirmed in the Tromsø population. The risk of HF subsequent to MI was similar in women and men. This confirms that other factors than MI, such as BP and age, contributes to the known sex differences in the different types of HF. The high PPV of the HF diagnosis from UNN strengthens our findings and can lead to use of these diagnoses in other studies with good certainty.

4.7 Limitations

Our data on MI and other factors were collected through self-report. This might have led to under- or overestimation of MI, level of physical activity, smoking habits, use of anti-hypertensive medication and level of education among other variables within the cohort. We did not have access to detailed data on prescribed drugs which may have influenced the development of HF subsequent to MI and may have had different effect on HF in women and men. In our long follow-up, changes in medical therapy or comorbidities could have influenced the risk of incident HF. We have no data on EF, and can therefore not compare our findings with other studies when it comes to sex and type of HF. We have not considered number of previous MIs which might lead to greater myocardial damage and increased risk of HFrEF, or type of MI. No data were collected on severity of HF. Exclusion of 251 subjects reduced the sample size somewhat and may have resulted in loss of subjects with HF,

although there were not many subjects without the needed data. Some subjects with MI may have developed HF without being diagnosed during follow-up. We did not consider non-HF patient journals to check for possible missed HF diagnoses when validating the HF diagnosis.

4.8 Strengths

We performed our study in a large population-based cohort including both sexes 25 years or older, with high attendance rates and long follow-up. Previous studies on HF subsequent to MI have usually used MI patient cohorts (3, 4, 6, 8, 9, 14, 15, 21), often with shorter follow-up time. We have validated 77 HF diagnoses.

5 Conclusion

MI is a known risk factor for developing HF, and we confirmed this finding. The risk of HF subsequent to MI was similar for women and men. The risk of HF increased markedly with age, and the risk was higher for elderly women. MI´s effect on risk of HF declined with increasing age. Higher level of education has no impact on the development of HF.

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7 Tables

Table 1. *Baseline characteristics of men and women with and without subsequent heart failure. The Tromsø Study.*

	Total n=26907 *With HF* n=1387 (5.2)							
	Men n=12759 (47.4)				*Women* n=14148 (52.6)			
	Heart Failure n=764 (6.0)		*No Heart Failure* n=11995 (94.0)		*Heart Failure* n=623 (4.4)		*No Heart Failure* n=13525 (95.6)	
Age, years	63.0	± 12.2	45.5	± 14.0	68.5	± 10.5	46.1	± 15.0
Systolic BP, mmHg	148.2	± 22.2	136.8	± 16.8	157.7	± 25.9	131.1	± 21.8
Diastolic BP, mmHg	85.6	± 12.8	79.7	± 11.6	85.7	± 15.1	76.0	± 12.5
Resting heart rate, bpm	72.4	± 13.5	71.5	± 12.2	75.7	± 13.5	75.3	± 12.0
BMI, kg/m^2	26.7	± 3.8	25.5	± 3.3	27.6	± 5.4	24.7	± 4.1
Total cholesterol, mmol/L	6.6	± 1.2	6.0	± 1.2	7.1	± 1.3	6.0	± 1.4
Triglycerides, mmol/L	2.0	± 1.2	1.8	± 1.2	1.9	± 1.2	1.3	± 0.9
HDL, mmol/L	1.3	± 0.4	1.3	± 0.4	1.6	± 0.4	1.6	± 0.4
Myocardial infarction	182	(23.8)	338	(2.8)	67	(10.8)	145	(1.1)
Angina pectoris	177	(23.2)	404	(3.4)	126	(20.2)	367	(2.7)
Stroke	45	(5.9)	177	(1.5)	29	(4.7)	154	(1.1)
Diabetes	51	(6.7)	169	(1.4)	50	(8.0)	203	(1.5)
Anti-hypertensive medication								
Yes	194	(26.4)	584	(4.9)	161	(25.8)	704	(5.2)
Previously	39	(5.1)	250	(2.1)	47	(7.5)	344	(2.5)
Never	529	(69.2)	11126	(92.8)	413	(66.3)	12439	(92.0)
Daily smoking	260	(34.0)	4510	(37.6)	173	(27.8)	4969	(36.7)
Physical activity								
Sedentary	114	(14.9)	984	(8.2)	159	(25.5)	1278	(9.4)
Low	282	(36.9)	4746	(39.6)	266	(42.7)	5795	(42.8)
Moderate	324	(42.3)	5162	(43.0)	183	(29.4)	5888	(43.5)
High	42	(5.5)	1092	(9.1)	12	(1.9)	553	(4.1)
Alcohol								
0 times per month	191	(25.0)	1817	(15.1)	216	(34.7)	3544	(26.2)
1-7 times per month	359	(47.0)	7594	(63.3)	126	(20.2)	7019	(51.9)
≥ 8 times per month	87	(11.4)	1532	(12.8)	13	(2.1)	805	(6.0)
Education								
Lower education	639	(83.2)	8067	(67.3)	586	(94.1)	9560	(70.7)
College/university	122	(16.0)	3896	(32.5)	33	(5.3)	3903	(28.9)

Data are presented as mean ± SD or number (%).

BP=blood pressure, mmHg=millimeters of mercury, bpm=beats per minute, BMI=body mass index, kg=kilograms, m=meters, mmol/L=millimoles per liter, HDL=high-density lipoprotein

***Table 2**. Development of new variable on physical activity from the original variables for light and hard physical activity. How many hours each week have you spent doing hard and light physical activity on average each week the last year? 1= none, 2=less than 1, 3=1-2, 4=≥3. New categories were 1) Sedentary, 2) Low level of physical activity, 3) Moderate level of physical activity and 4) High level of physical activity*

		Hard physical activity			
		1	*2*	*3*	*4*
Light physical activity	*1*	Sedentary	Low level	Low level	Moderate level
	2	Low level	Low level	Low level	Moderate level
	3	Low level	Low level	Moderate level	Moderate level
	4	Moderate level	Moderate level	Moderate level	High level

Table 3. *Age distribution of men and women in the total population and in subjects with heart failure (HF) according to age groups at baseline. The Tromsø Study.*

	Men		*Women*		*Total*	
Mean age	*Total*	*With HF*	*Total*	*With HF*	*Total*	*With HF*
	46.6 (±14.5)	63.0 (±12.2)	47.1 (±15.5)	68.5 (± 10.5)	46.8 (± 15.0)	65.5 (±11.8)
Age groups (years)	*n (%)*	*With HF, n (%)*	*n (%)*	*With HF, n (%)*	*n (%)*	*With HF, n (%)*
25-34	3051 (23.9)	13 (1.7)	3575 (25.3)	5 (0.8)	6626 (24.6)	18 (1.3)
35-44	3321 (26.0)	53 (6.9)	3515 (24.8)	9 (1.4)	6836 (25.4)	62 (4.5)
45-54	2894 (22.7)	115 (15.1)	2917 (20.6)	50 (8.0)	5811 (21.6)	165 (11.9)
55-64	1700 (13.3)	200 (26.2)	1702 (12.0)	117 (28.8)	3402 (12.6)	317 (22.9)
65-74	1257 (9.9)	258 (33.8)	1525 (10.8)	250 (40.1)	2782 (10.3)	508 (36.6)
75-84	478 (3.7)	114 (14.9)	800 (5.7)	171 (27.4)	1278 (4.8)	285 (20.5)
85-90+	54 (0.4)	11 (1.4)	114 (0.8)	21 (3.4)	168 (0.6)	32 (2.3)
Total	12755 (47.4)	764 (6.0)	14148 (52.6)	623 (4.4)	26903 (100.0)	1387 (5.2)

Data are presented as mean ±SD or number (%)

Table 4. *Hazard ratios (HRs) of heart failure developing after myocardial infarction in the total population, in men and women. HRs are unadjusted and adjusted for age and sex in the total population, adjusted for age in men and women. The Tromsø Study*

	Men						*Women*						*Total*					
	Unadjusted			Adjusted by age			Unadjusted			Adjusted by age			Unadjusted			Adjusted by age and sex		
	HR	95% CI	p	HR	95% CI	P	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Myocardial Infarction	12.35	10.4-14.6	<0.0001	3.83	3.2-4.6	<0.0001	14.72	11.4-19.0	<0.0001	3.36	2.6-4.3	<0.0001	13.55	11.8-15.6	<0.0001	3.59	3.1-4.1	<0.0001

Table 5. *Hazards ratios (HR), adjusted by age, for heart failure subsequent to myocardial infarction in men and women. Adjusted for sex as well in the total population. The Tromsø Study.*

	Men			*Women*			*Total*		
Age groups (years)	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
25-54	7.98	5.0-12.7	<0.0001	13.55	4.2-43.8	<0.0001	8.13	5.3-12.5	<0.0001
55-74	3.91	3.2-4.8	<0.0001	4.19	3.0-5.8	<0.0001	3.98	3.3-4.8	<0.0001
75-90+	2.38	1.6-3.5	<0.0001	2.30	1.5-3.5	<0.0001	2.35	1.8-3.1	<0.0001

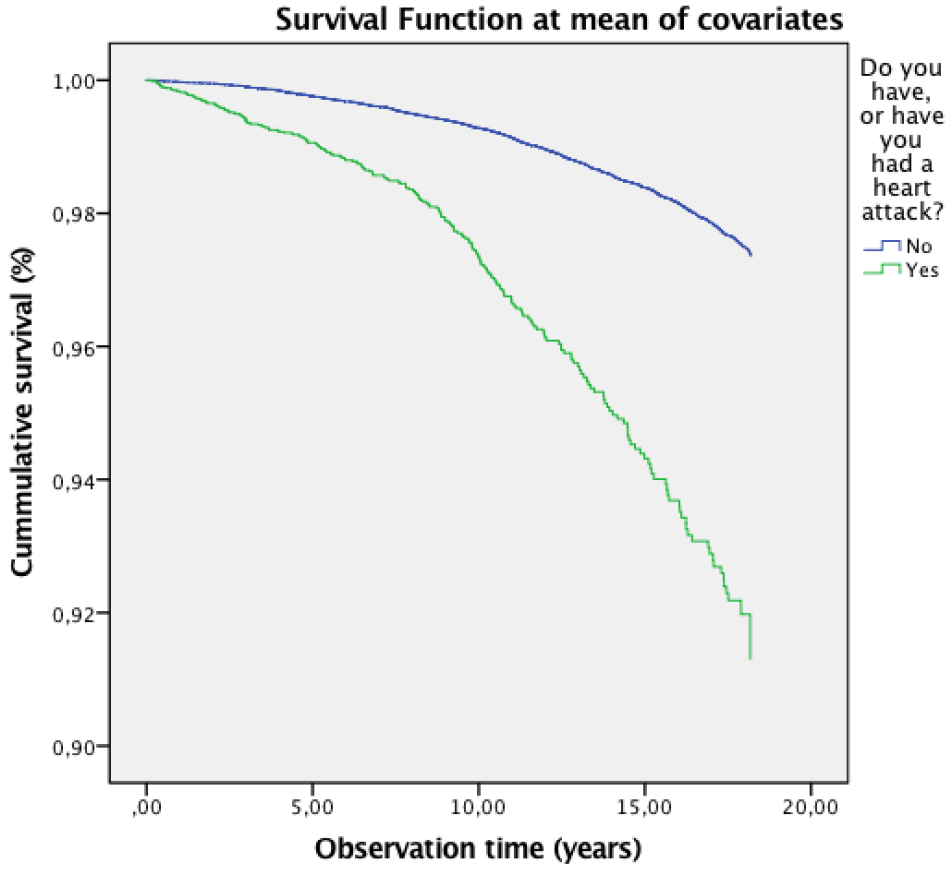
Table 6. *Multivariable adjusted hazard ratios[1] (HR) for heart failure in men and women and the total population. The Tromsø Study*

	Men			*Women*			*Total*		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age, 10 years	2.63	2.4-2.8	<0.0001	2.78	2.5-3.0	<0.0001	2.66	2.5-2.8	<0.0001
Sex, man							1.94	1.7-2.2	<0.0001
Myocardial infarction, yes/no	3.55	3.0-4.3	<0.0001	3.64	2.8-4.6	<0.0001	3.56	3.1-4.1	<0.0001
Systolic blood pressure, 15 mmHg	1.08	1.0-1.1	0.005	1.12	1.1-1.2	<0.0001	1.11	1.1-1.1	<0.0001
BMI, 1 kg/m^2	1.06	1.0-1.1	<0.0001	1.05	1.0-1.1	<0.0001	1.06	1.0-1.1	<0.0001
Total cholesterol, 1 mmol/l	1.17	1.1-1.2	<0.0001	0.97	0.9-1.0	0.401	1.07	1.0-1.0	0.003
Triglycerides, 1 mmol/L	1.03	1.0-1.1	0.460	1.04	0.9-1.1	0.453	1.04	1.0-1.1	0.212
HDL, 1 mmol/L	0.80	0.6-1.0	0.066	0.98	0.8-1.3	0.975	0.90	0.8-1.1	0.197
Daily smoking, yes/no	1.40	1.2-1.6	<0.0001	1.84	1.5-2.2	<0.0001	1.54	1.4-1.7	<0.0001
College/university education, yes/no	0.93	0.8-1.1	0.482	0.73	0.5-1.1	0.091	0.88	0.7-1.1	0.163
Physical activity, per unit over 4 levels	0.87	0.8-1.0	0.003	0.89	0.8-1.0	0.028	0.87	0.8-0.9	<0.0001
Alcohol, per unit over 3 levels	0.99	0.9-1.1	0.881	0.77	0.6-0.9	0.008	0.92	0.8-1.0	0.103

[1] All HRs were mutually adjusted for all listed variables.

8 Figures

Figure 1. *Cumulative probability of no heart failure according to follow-up time from Cox proportional hazard regression model stratified by heart attack (myocardial infarction) and adjusted for age and sex. The Tromsø Study*



9 GRADE

Reference: Ezekowitz J, Kaul P, Bakal J, Armstrong P, Welsh RC, McAlister FA. Declining In-Hospital Mortality and Increasing Heart Failure Incidence in Elderly Patients With First Myocardial Infarction Reply. J Am Coll Cardiol. 2009;55(1):81-.

Design: Cohort study	
Level of documentation	2b
Grade: Quality of evidence	C

Aims

Examine the long-term incidence of HF in elderly patients with MI.

Conclusion

HF developed in 75% of the patients in the 5 years after their first MI. Subsequent HF usually happens the first year. The proportion with HF increased over time. New-onset HF significantly increases the mortality risk among these.

Land

Alberta, Canada

Year of data collection

April 1, 1994- March 31, 2000

Material and method

Source data: N=7,733 patients. "The Alberta Elderly Cohort" created by linking 5 separate databases in Alberta, Canada. Recruitment of participants: From regional registry

Inclusion criteria: ≥ 65 years hospitalized (n=11,479) with a first MI (ICD-9, 410.x) without prior history of HF.

Exclusion criteria: prior admission for MI or HF in the last year. N=2,523 (HF), n=1,688 (MI)

Definitions of the cohort: Follow-up 5 years or until death, end of follow up April 1, 2005.

Variables: Concurrent HF: HF developing as a complication of the index MI. Subsequent HF: hospitalization or physician claim for HF (ICD-9-CM 428.x). Time to HF: the time of discharge if the HF occurred as a complication of the index MI or the time of subsequent admission for subsequent hospitalizations.

Statistical methods: continuous baseline variables: compared using mean (SD) and t-tests or medians with interquartile tests and Wilcoxon tests. Count data: compared with percentages, relative risks and chi-square tests. Temporal trends: Cochrane-Armitage test. Multistate model (if univariate analysis p<0.20) with the purpose to model transition from MI to HF or death. Results presents as ORs, RRs, HRs with 95% CI. P<0.05 significant.

Results

Table 1. Baseline Characteristics of All Patients at Index Myocardial Infarction

Variable	At Index Myocardial Infarction: No HF	At Index Myocardial Infarction: Developed HF	Relative Risk for Developing HF During the Index Hospitalization	p Value
n (%)	4,902 (63.4%)	2,831 (36.6%)		
Age, yrs, median (IQR)	74.5 (69.7–80.3)	75.5 (70.5–81.1)		<0.001
Female	41.3	37.8	0.86 (0.78–0.95)	0.0022
Diabetes	16.7	23.2	1.51 (1.35–1.70)	<0.0001
Hypertension	35.3	42.3	1.40 (1.27–1.54)	<0.0001

- Median age 75 y. 60.0% men
- MI n=7733 → HF n=5871 → death n=2316
  → death n=771

During hospitalization for index MI:

- 36.6% were diagnosed with HF during MI hospitalization.
- Incidence of in-hospital HF among survivors increased, RR 25.1% (AR 7.9% regnet ut selv). P=0.001
- Patients with HF at the index MI were more likely to have undergone PCI (13.9% vs 10.6%, p<0.001), but less likely to have received beta blocker (49.6% vs 58.7%, p<0.001)
- 28.1% relative reduction in mortality (p=0.01) during index hosp. from 1994 through 2000. (Mortality 18.1% 1994, 13.0% 2000 → absolute risk reduction 5.1% (har jeg regnet ut))
- Additional 71% among hospital survivors without earlier HF developed HF within 5 years. 64% occurred the first year. In total, *76% who survived developed HF over 5 years.*

Long-term follow up:

- 70.8% of the 4291 MI survivors developed subsequent HF after discharge. 53.0% of these did so within the first year.
- 65-69 y: 70.6% HF in the 5 y following MI
- 70-75 y: 75.1% HF in the 5 y following MI
- >75 y: 76.8% HF in the 5 y following MI. P for all < 0.0001
- Users of betablockers after index MI were less likely to develop HF (HR 0.83 95% CI 0.79-0.89). same for statins (HR 0.91 95% CI 0.83-0.99). These 2 + ACE-inhib were associated with reduced mortality.
- PCI with stent and development of HF (HR 1.08, 95% CI 0.98-1.19). Mortality in the same group (HR 0.59 95% CI 0.47-0.73). Mortality after PCI but no HF (HR 0.75 95% CI 0.46-1.24)

Discussion/comments

Check list:
Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? **Ja, alle har MI**
Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? **Ja**
Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon? **Ja**
Var studien prospektiv? **Ja**
Ble eksposisjon og utfall målt likt og pålitelig i de to gruppene? **Ja**
Ble mange nok personer i kohorten fulgt opp? **Ja**
Er det utført frafallsanalyser? **Nei**
Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? **Ja**
Er det tatt hensyn til viktige konfunderende faktorer i design/gjennomføring? **Ja**
Er den som vurderte resultatene (endepunktene) blindet gruppetilhørighet? **Kommer ikke frem**

Strengths: multistate model that modelled the competing risks of HF development against death in a survival model for those who developed HF.

Limitations: Consent to the database and recruitment. Results reported as RR only, not AR. No validation of HF diagnosis. STEMI not separated from NSTEMI → underestimated the risk of HF in high-risk patients because of inclusion of lower-risk patients. No troponin measures in diagnostics may underestimate the MI frequency. Lack of information on eligibility for thrombolytic therapy for STEMI patients.

Discussion: Are improvement of MI care and reduced mortality the drivers of increased HF incidence? This study reported higher post-MI HF than other studies. Prior analysis in Alberta among all ages: 22% developed HF during index MI hosp, 7% during 32 months follow up but the mean age in the study was almost a decade younger. No further data on subsequent long-term HF incidence. Possible reasons for increased incidence of HF and risk of HF post-MI: increased comorbidity and age of patients presenting with their first MI, improved application of revascularization, and improved chronic oral therapies for cardiovascular disease that delay but do not cure the disease. Patients who underwent revascularization at the index hospitalization did not have a reduced incidence of HF, but if it developed, they had a lower mortality risk.

Reference: Hung J, Teng THK, Finn J, Knuiman M, Briffa T, Stewart S, et al. Trends From 1996 to 2007 in Incidence and Mortality Outcomes of Heart Failure After Acute Myocardial Infarction: A Population-Based Study of 20 812 Patients With First Acute Myocardial Infarction in Western Australia. Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease. 2013;2(5):e000172.	**Design: Cohort Study**	
	Dokumentasjonsnivå	2b
	Grade:	C

Aims	Material and method	Results	Discussion, comments
Investigate sex-specific trends in incidence of HF with an index MI in patients aged 40-84 years. Explore clinical predictors of concurrent and late-onset HF after MI. Determine if short-term and 1-year mortality with HF after first MI has changed oved decades. **Conclusion** Decline in the incidence of HF complicating MI, but still high mortality. Need for increased attention in these high-risk patients because of the lack of improvement in their long-term prognosis. **Land** Australia, Western Australia (WA) **Year of data collection** 1996-2007	**Source data:** National registries. Linked health data between Hospital Morbidity Data and Mortality Registry **Inclusion criteria:** codes 410x (ICD-9-CM), I21x (ICD-10-AM). WA resident, first MI admission when aged 40-84 years **Exclusion criteria:** HF history **Definitions of the cohort:** *first MI*: a patient without a hospital admission for MI among the 21 discharge diagnosis for the previous 10 years. *HF history*: any HF hospitalization in the 10 years before the MI admission. *Concurrent HF*: HF during MI admission. *Late-onset HF:* within 1 year after discharge. *HF:* ICD codes 428x, 402.01, 402.11, 402.91, 404.1, 404.3, 425x, 518.4, 514, 391.8, and 398.91 (ICD-9-CM) and I50x, I11.0, I13.0, I13.2, I42x, J81, and I01.8 (ICD-10-AM). Follow-up until death or 1 years after MI hospitalization. **Variables:** comorbidities: principal or secondary diagnose within the 5 years before admission for MI, defined ICD-codes in the article. **Statistical methods:** 28-day survival analysis for all, 1-year survival analysis for admission 1996-2006 (only those who survived >28 days). Categorical variables are presented as proportions and continuous variables as means±SD or medians and interquartile ranges. The Pearson chi-square test: test for differences in categorical variables. ANOVA, the t test, or the nonparametric Mann–Whitney test for continuous variables. Cochran–Armitage trend test. Age- and sex-adjusted logistic and multivariable regression models to determine ORs, 95% CI	- See table 2 for baseline characteristics - N=20812 (29.6% women) - Stable mean age and sex mic over time, increasing frequency of hypertension, diabetes and ischemic heart disease (excluding MI), p<0.001 for all. Decrease in occurrence of peripheral vascular disease and cerebrovascular disease (p<0.001) - PCI performed increased from 17.4% in 1996-97 to 43.2% in 2006-2007 p<0.001 - **Decrease in overall HF up to 1 year post MI, from 28.1% 1996-97 to 16.5% in 2006-08 p<0.001** (*ARR=11.6%, RRR=58.7%)*, **largely because of decline in concurrent HF (75% of incident HFcases in total)** - **1996-2007: OR (age and sex adjusted) of developing HF within 1 year was 0.50 (95% CI 0.44-0.55 p<0.001)** - 90.8% of HF cases occurred within 90 days of the initial MI, 95.0% within 6 months. - HF patients were more likely to be female and older than no HF patients. - Hypertension was a predictor for concurrent HF	**Check list** Er formålet med studien klart formulert? **Ja** Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? **Ja. alle som er valgt ut har tidligere MI, fra WA og mellom 40-84 år** Ble personenere rekruttert til kohorten på en tilfredsstillende måte? **Ja** Ble eksponeringen presist målt? **Ja, ICD-kode der diagnose har blitt validert.** Ble utfallet presist målt? **Ja. ICD-koder, validert** Har forfatterne identifisert alle konfunderende faktorer? **Ja** Er det tatt hensyn til konfunderende faktorer i design? **ja** Ble mange nok fulgt opp, og ble de fulgt opp lenge nok? **Delvis. 1 år oppfølging for alle dersom de ikke døde.** Presise resultater? **Ja. p<0.001 og smale CI** Er det utført frafallsanalyser? **Nei** Kan resultatene overføres til praksis? **Ja** Var studien prospektiv? **Ja** Er den som vurderte resultatene (endepunktene) blindet gruppetilhørighet? **Uklart** **Discussion:**Confirmation that HF is more likely to complicate AMI in older persons, in women, and in people with added comorbidities including diabetes, hypertension, renal failure, and peripheral vascular disease. Patients with prior IHD (excluding AMI) were less likely to develop HF - because they were more likely to be on cardioprotective medications at onset of AMI? 1/5 had an HF diagnose within 1 year after MI. Most cases occurred in the acute relation to the MI. Declining incidence of HF may be because of pharmalogical therapy following MI. Increase in MI diagnosis of less severe MI may have contributed to reduced OR for HF. **Strengths:** Large cohort. Exclusion of prior HF. Validated HF (PPV 92.4%) and MI diagnosis. **Limitations:** No distinction between type of infarct. Diagnostic criteria for MI changed over the study period (HF incidence may be related to detection of smaller infarcts). Not adjusted for severity of HF.

Reference: Desta L, Jernberg T, Löfman I, Hofman-Bang C, Hagerman I, Spaak J, et al. Incidence, Temporal Trends, and Prognostic Impact of Heart Failure Complicating Acute Myocardial Infarction: The SWEDEHEART Registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies): A Study of 199,851 Patients Admitted With Index Acute Myocardial Infarctions, 1996 to 2008. JACC: Heart Failure. 2015;3(3):234-4

Design: Cohort study	
Level of documentation	2a
Grade	C

Aims

Examine temporal trends in the incidence and outcome of in-hospital post-AMI HF over a time period of 13 years.

Conclusion

Marked decrease in the incidence of in-hospital HF complicating AMI between 1996 and 2008. HF worsen the prognosis of AMI. The mortality is decreasing over time.

Land

Sweden

Year of data collection

1996-2008

Material and method

Source data: SWEDEHEART/RIKS-HIA registry which enrolls all patients with symptoms of coronary heart syndromes. *N=199851*. Mortality data: Swedish population register. Previous diseases/diagnosis: National Patient Register.

Inclusion criteria: Patient with first AMI, admitted between 1996 and 2008.

Exclusion criteria: On request (all patients were informed that they were enrolled in the database)

Definitions of the cohort: HF: pulmonary rales, administration of intravenous (IV) diuretic agents, continuous positive airway pressure, or the use of IV inotropic drugs, Killip classification for severity

Variables: age, sex, hypertension, diabetes, prior HF, prior myocardial infarction, prior coronary artery bypass grafting, and prior medication (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers, calcium antagonists, digoxin, and diuretic agents) and time period

Statistical methods: Data reported as proportions, mean ± SD, and median. Cohorts of patients admitted over 2-years periods were compared. Chi-square test for trend with the linear-by-linear model. Logistic regression: identify predictors of HF and death. Cox regression model: independent association between acute HF and subsequent long-term mortality.

Results

Background factors:

- Mean age increased from 70.0 to 70.9 years. Approximately 35.0% to 37.1% women. *HT increased from 32.5% to 47.0%.* Patients with history of AMI from 18.4% to 10.6%. Patients with history of congestive HF from 11.7% to 9.7%.

Table 2. Proportion of Patients With HF in Different EF Categories Over the Years

Variable	1998–1999 (n = 2,338)	2000–2001 (n = 8,148)	2002–2003 (n = 11,902)	2004–2005 (n = 16,675)	2006–2007 (n = 19,673)	2008 (n = 10,273)
EF ≥50%	175 (18%)	696 (21.4%)	1,016 (23.1%)	1,440 (25.6%)	1,662 (28.8%)	825 (30.1%)
EF 40%–49%	327 (33.6%)	1,098 (33.7%)	1,354 (30.8%)	1,468 (26.1%)	1,451 (25.1%)	696 (25.4%)
EF <40%	470 (48.4%)	1,462 (44.9%)	2,027 (46.1%)	2,726 (48.4%)	2,666 (46.1%)	1,216 (44.4%)
Total new HF/period	972 (100%)	3,256 (100%)	4,397 (100%)	5,634 (100%)	5,779 (100%)	2,737 (100%)

HF during index MI

- HF incidence declined from 46 % to 28% ($p<0.001$), but more pronounced among STEMI with LBBB (50-28%) than in NSTEMI (42-28%) $p<0.001$.
- Proportion of women with HF from 39% to 46%
- 1996-97 proportion with HF 61% >75 years, 39% 50-75, 17% <50 y. 2008 corresponding numbers for the respective ages were 41%, 18% and 11%.
- Every additional year in age increased the risk for HF (OR 1.054, 95% CI 1.05-1.06)
- Women with AMI had increased risk of developing HF across the study period (OR 1.15 95% CI 1.12-1.19).
- Risk factors for clinical HF during hospitalization for index AMI: history of AMI (OR 1.21, 95% CI 1.16-1.26), diabetes mellitus (OR 1.33, 95% CI 1.29-1.37), hypertension (OR 1.07, 95% CI 1.05-1.09), history of chronic HF (OR 2.2, 95% CI 2.1-2.3)

AMI treatment

- See table 1. Increased use of PCI. Increased use of medical therapy at discharge, but also when admitted.

Discussion/comments

Check list:
Er formålet med studien klart formulert? **Ja**
Ble personenere rekruttert til kohorten på en tilfredsstillende måte? **Ja**
Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? **Ja, alle har AMI som utgangspunkt.**
Ble eksponeringen presist målt? **Hvertfall likt målt, data fra register**
Ble utfallet presist målt? **HF som klinisk diagnose**
Har forfatterne identifisert alle konfunderende faktorer? **Ja**
Er det tatt hensyn til konfunderende faktorer i design? **ja**
Ble mange nok fulgt opp, og ble de fulgt opp lenge nok? **Ja**
Presise resultater? **Ja.**
Er det utført frafallsanalyser? **Nei**
Var studien prospektiv? **Ja**
Er den som vurderte resultatene (endepunktene) blindet gruppetilhørighet? **Uklart**

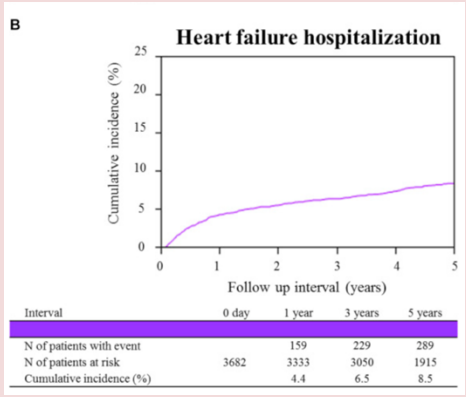
Discussion: Major decrease in the incidence of HF following AMI regardless of sex, age and infarct type. Declined incidence of AMI despite more sensitive diagnostic methods. This could contribute to reduced risk of HF as HF is related to infarct size. The decline in the incidence of HF did not show an abrupt change after the new diagnosis criteria for AMI in 2001. The decline must rather be because of effective treatments and changes in the burden of risk factors. There was a greater decrease in post STEMIs than in NSTEMIs HF incidence, so the decline could not just be because of detection of smaller infarcts. Proportion with HFpEF increasing (increased proportion of women, often with HT)

Strengths: Large observational study. Long follow up of mortality. Different findings than Ezekowitz study; could be because this study is in-hospital only, while Ezekowitz also reports from primary health care system

Limitations: Only in-hospital HF. HF on admission not distinguished from HF during hospital stay. Different sampling schedules over the long period of observation. Use of clinical HF diagnosis, decompensated, not ICD from patient´s records. Other clinical definitions of HF may lower specificity.

Referance: Taniguchi T, Shiomi H, Morimoto T, Watanabe H, Ono K, Shizuta S, et al. Incidence and Prognostic Impact of Heart Failure Hospitalization During Follow-Up After Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction. The American Journal of Cardiology. 2017;119(11):1729-39.

Design: Cohort study	
Level of documentation	2b
Grade:	C

Aims	Material and method	Results	Discussion/comments
Evaluate incidence of HF hospitalization and its impact on long-term outcomes in contemporary patients with STEMI after primary PCI **Conclusion** HF hospitalization within 1 year was independently associated with a higher risk for all-cause death and HF hospitalization beyond 1 year. **Land** Japan **Year of data collection** Jan 2005- Des 2007	**Source data:** The Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto), Kyoto Acute Myocardial Infarction Registry. 5429 patients. Study population for 1-year landmark analysis n=3458 **Inclusion criteria:** STEMI and primary PCI within 24 h of symptoms and discharged alive (n=3682) **Exclusion criteria:** Refusal to participate (n=9). CABG surgery after the index AMI (n=195). NSTEMI (n=789). PCI beyond 24 h after onset (n=494). Died during hospitalization (n=260). Died or lost follow-up within 1 year (n=224). **Definitions of the cohort:** *HF hospitalization (n=125)*: due to worsening HF requiring iv drug therapy. **Variables:** Age, previous MI, HF at STEMI, left ventricular dysfunction, anterior AMI, onset-to-balloon time > 3h, use of betablocker, nonuse of statin at discharge. Outcome measures: all-cause deaths and HF hosp. **Statistical methods:** Continuous variables:t-test or a Wilcoxon rank-sum test. Categorical variables: Chi-square test and Fisher´s exact test for. Kaplan-Meier: estimate cumulative incidens. Log rank test: estimate differences. Cox proportional hazard models: identify predictos associated with HF hosp with 95% CIs. Multivariable Cox proportional hazards.	- Mean age 67.0 (±12.2). 75% men. 2% with a HF history, 27% HF.9% with prior MI. - N=125 with HF hospitalization within 1 year, - The incidence of HF hospitalization was 4.4%/year during the first year after the index STEMI. Then 1.0%/year beyond 1 year to 5 years with the median follow-up period of 1,956 days. - Risk factors associated with HF hosp. Within 1 year after STEMI: Age ≥75 (HR 1.64 95%CI 1.05-2.57, p=0.03). Men (HR 0.73 95%CI 0.47-1.14, p=0.16). Prior MI (HR 2.07 95%CI 1.18-3.47, p=0.01). - Subjects with HF hosp. <1 year were older, had more frequent LVEF ≤ 40%, previous MI. Anterior MI was more often seen in HF hosp < 1 year, bigger infarcts. - After one year, the cumulative incidence HF hospitalization up to 5 years after STEMI were significantly higher in patients with HF hospitalization within 1 year of STEMI than in patients without. (40.4% vs 4.3%, p <0.001). - HF hospitalization within 1 year was associated with a higher risk for HF hospitalization beyond 1 year (HR 5.72, 95% CI 3.46-9.22, p <0.001) - Delay from symptom onset to reperfusion was independently associated with higher risk for HF hospitalization within 1 year (HR 5.9, CI 3.6-11.0 vs HR 2.4, CI 1.1-5.0, p < 0.001) 	**Check list:** Er formålet med studien klart formulert? **Ja** Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? **Ja.** Ble personenere rekruttert til kohorten på en tilfredsstillende måte? **Ja** Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? **Ja** Var studien prospektiv? **Ja** Ble eksponeringen presist målt? Ja Ble utfallet presist målt? Nei. Ble mange nok personer i kohorten fulgt opp? **Ja** Er det utført frafallsanalyser? **Nei** Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? **Ja** Er det tatt hensyn til viktige konfunderende faktorer i design/gjennomføring? **Ja** Er den som vurderte resultatene (endepunktene) blindet gruppetilhørighet? **Uklart** **Strengths:** Big cohort. 5 years follow up. **Limitations:** HF hospitalization influenced by judgement of phycicians. No data from less severe HF in outpatient settings. Differences in baseline characteristics might limit the comparability of the groups. Follow-up are conducted through secondary data collection, not in person and data might have been lost. No data on troponin and BNP. Medical therapy at discharge was not optimal from the current standard. **Discussion:** In high-risk patients for HF, severe HF often occurs relatively early after STEMI, if it does occur.Focus on HF hosp prevention after discharge in high-risk HF patients because this might lead to reduction in long-term mortality.

Reference: Sulo, G., et al. (2017). "Trends in the risk of early and late-onset heart failure as an adverse outcome of acute myocardial infarction: A Cardiovascular Disease in Norway project." European Journal of Preventive Cardiology **24**(9): 971-980.	**Design: Cohort study**	
	Dokumentasjonsnivå	2a
	Grade:	C

Aims	Material and methods	Results	Discussion/comments
Investigate the risk factors of developing HF among patients hospitalized with an acute MI. HF leads to poor prognosis, and it is a serious complication following an acute MI. **Conclusions** HF occurring during acute MI hospitalization (early-onset) accounts for the majority of HF cases. HF rates after discharge declined over the study period. The risk of early-onset HF increased over time, while the risk of late-onset HF declined, leading to a 'null effect' on the overall risk of HF occurring within a year of AMI hospitalization. **Land** Norway **Year of data collection** 2001-2009	**Source data:** Data were collected from the "Cardiovascular Disease in Norway" (CVDNOR). 69372 patients nationwide aged 25-84 years with a first AMI were followed until HF. **Inclusion criteria:** Aged 25-84 years hospitalized with an incident AMI as principal diagnosis. **Exclusion criteria:** previously HF and patients discharged alive within 24 h of AMI hospitalization. **Definitions of the cohort:** Early-onset-HF: during hospitalization for the MI. Late-onset-HF: within one year of discharge from the MI hospitalization. Age groups: younger 25-69 years and older (70-84 years) **Variables:** HF: ICD-10 code I50.x in any discharge diagnosis field. Independent variable: AMI year. Analyzed in two models; as a categorical variable and as a continuous variable. Adjustment: gender, age, CHD, DM, HT, renal failure, COPD, valvular heart disease and AF. **Statistical methods:** The risk trends were explored separately in the early and late-onset-HF by using logistic regression. Results presented as ORs and 95% CIs. Time trends of late-onset HF were explored using competing risk regression models with death as competing event. Results: subhazard ratios, 95% CI.	- Mean (SD) age 66.4 (12.3) years. Men 68.4% of study population. - Early-onset-HF: 17.1% had HF (25-69 years: 11.6 % HF. 70-84 years 23.5% HF). OR 1.023, 95 % CI 1.015-1.031. Increased odds of HF by 2.3% each year. This increased odds was influenced by an increase of 5.9% (OR = 1.059; 95% CI: 1.046–1.073) among 25-69 years, older patients did not experience significant changes over time (OR = 0.999; 95% CI: 0.989–1.010) - Late-onset-HF: 47,673 were discharged without early-onset-HF and alive. 5.4% experienced HF, 2.6% of younger and 9.4% of older. It was a statistically significant decline in overall risk of HF by 6.3% per year (subhazard ratio = 0.937; 95% confidence interval: 0.921–0.954). 6.8% (SHR = 0.932; 95% CI: 0.802–0.963) per year among younger and 5.9% (SHR = 0.941; 95% CI: 0.922–0.960) per year among older. - HF at any time: 60,234 with AMI 2001-2008→12,839 (21.3%) HF within one years from AMI hospitalization. It was not a statistically significant change in the overall risk of HF occurring at any time in the follow up. Still, the risk increased by 3.3% (SHR = 1.033; 95% CI: 1.020–1.046) per year among younger and declined by 1.5% (SHR = 0.985; 95% CI: 0.976–0.993) per year among older.	**Check list:** Er formålet med studien klart formulert? **Ja** Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? **Ja** Er personene rekrutterte på en tilfredsstillende måte? **Ja** Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon? **Ja** Var studien prospektiv? **Ja** Ble eksponeringen presist målt? **Ja** Ble utfallet presist malt? **Ja, ICD-kode. Ikke validert** Presise resultater? Ble mange nok fulgt opp, og ble de fulgt opp lenge nok? **Ja** Er det utført frafallsanalyser? **Nei** Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? **Ja** Er det tatt hensyn til viktige konfunderende faktorer i design/gjennomføring? **Ja. Kjønn, alder, CHD, diabetes, hypertensjon, nyresvikt, KOLS, klaffesykdom, atreiflimmer.** Er den som vurderte resultatene (endepunktene) blindet gruppetilhørighet? **Uklart** **Strengths:** Big nationwide cohort without age or gender restrictions. All patients with first AMI are included. Retrospective search to exclude high probability of previous episodes of AMI and HF. Trends investigate early-onset and late-onset HF. Non-significant results presented. **Limitations:** No information on lifestyle indicators or the disease severity. No info on prescription of from outpatient clinics or GPs were not included. The cohort consists of only AMI patients. Only ICD-10 code I50.x. Little info on other variables than age. **Discussion:** Risk of early-onset HF increased (reduced of out-of-hospital coronary deaths (2001-09). The risk of late-onset-HF declined, reduction the incidence of the same – probably reflects the increase of revascularization. These opposite direction changes results in no significant changes in the risk of developing HF at any time during follow-up. Observed age-group differences in the early-onset-HF might be because factors influencing the risk of early-onset-HF operate differently in younger and older. Causes can be trends in risk factors for HF and use of cardio-protective drugs. SBP and DBP levels declined from 1995-08.