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The epidemiology of myocardial infarction

Trends in incidence, risk factors, severity, treatment and outcomes of myocardial infarction in a general population.

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Summary

Paper 1 and 2 were based on the Tromsø Study, a population-based, prospective cohort study with repeated screenings for cardiovascular risk factors and follow-up with regard to disease incidence and mortality. Paper 3 was based on a local registry of consecutively patients with presumed ST-elevation myocardial infarction who had been given prehospital thrombolytic therapy, and then admitted to the University Hospital in Northern Norway in Tromsø.

In paper 1, we showed that a substantial part of the decline in coronary heart disease mortality in the young and middle-aged population was due to a decreased incidence of myocardial infarction. The study indicates that the population burden of coronary heart disease may be shifting towards women and elderly patients, suggesting that preventive gains have not penetrated equally throughout the population. The severity and case fatality of the disease, however, was declining in all groups.

In paper 2, we found that age- and sex-adjusted incidence of total coronary heart disease decreased by 3% annually over 15 years of follow-up. The decrease was found primarily in reductions in out-of-hospital sudden cardiac death and hospitalized ST-elevation myocardial infarction. Reductions in serum cholesterol accounted for approximately one-third of the event decline, but decreases in smoking, blood pressure, and heart rate and increased physical activity all contributed. Increases in body mass index and diabetes mellitus were associated with modest increases in disease outcomes. Overall, risk factors accounted for 66% of the decline in incidence. Furthermore, the decline in event rates and the decline in

case fatality each explained approximately 50% of the decline in coronary heart disease mortality. This was partly explained by less severe disease in those afflicted, but also by a major improvement in treatment.

In paper 3, we showed that ambulance clinicians with the support of hospital cardiologists could safely and effectively perform prehospital thrombolytic therapy. The implementation of this system was associated with significant reduction in time delays of reperfusion therapy, and reduction in post-infarct systolic heart failure, and high survival rates among ST-elevation myocardial infarction-patients suffering out-of hospital cardiac arrest.

List of publications

This thesis is based on the following three papers, referred to in the text as paper 1, 2 and 3.

Paper 1

Mannsverk J, Wilsgaard T, Njølstad I, Hopstock LA, Løchen ML, Mathiesen EB, Thelle DS, Rasmussen K, Børnaa KH. Age and gender differences in incidence and case fatality trends for myocardial infarction: a 30-year follow-up. The Tromso Study. *Eur J Prev Cardiol.* 2012; 19: 927-934. DOI: 10.1177/1741826711421081.

Paper 2

Mannsverk J, Wilsgaard T, Mathiesen EB, Løchen ML, Rasmussen K, Thelle DS, Njølstad, I, Hopstock LA, Børnaa, KH. Trends in modifiable risk factors are associated with declining incidence of hospitalized and nonhospitalized acute coronary heart disease in a population. *Circulation.* 2016; 133: 74–81. DOI: 10.1161/CIRCULATIONAHA.115.016960.

Paper 3

Mannsverk J, Steigen T, Wang H, Tande PM, Dahle BM, Nedrejord ML, Hokland IO, Gilbert M. Trends in clinical outcomes and survival following prehospital thrombolytic therapy given by ambulance clinicians for STElevation myocardial infarction in rural sub-arctic Norway. *Eur Heart J Acute Cardiovasc Care.* 2019; 1: 8-14. DOI: 10.1177/2048872617748550.

Abbreviations

ACS Acute coronary syndrome

BMI Body Mass Index

CABG Coronary artery bypass graft surgery

CHD Coronary heart disease

CI Confidence interval

CK Creatine kinase

CK-MB Creatine kinase myocardial band isoenzyme

cTn Cardiac troponin

ECG Electrocardiogram

FMC First medical contact

HR Hazard ratio

IQR Interquartile range

LVEF Left ventricular ejection fraction

MI Myocardial infarction

NSTEMI Non-ST-segment elevation myocardial infarction

OHCA Out-of-hospital cardiac arrest

OR Odds ratio

PCI Percutaneous coronary intervention

PHT Prehospital thrombolytic therapy

RCT Randomized controlled trial

SCD Sudden cardiac death

SD Standard deviation

STEMI ST-segment elevation myocardial infarction

UAP Unstable angina pectoris

List of definitions

Acute coronary syndrome - an episode of myocardial ischemia that generally lasts longer than a transient anginal episode that ultimately may lead to myocardial infarction (1).

Atherosclerosis - a thickening and loss of elasticity of the walls of arteries that occurs with formation of atherosclerotic plaques within the arterial intima (1).

Biomarkers - measurable and quantifiable biological parameters (e.g., specific enzyme concentration, specific hormone concentration, specific gene phenotype distribution in a population, presence of biological substances) which serve as indices for health- and physiology-related assessments, such as disease risk, psychiatric disorders, environmental exposure and its effects, disease diagnosis; metabolic processes; substance abuse; pregnancy; cell line development; epidemiologic studies; etc. (1).

Case-control study - a type of observational analytic study. Enrollment into the study is based on presence ("case") or absence ("control") of disease. Characteristics such as previous exposure are then compared between cases and controls (2).

Case fatality rate – the proportion of persons with a particular condition (cases) who die from that condition. The denominator is the number of incident cases; the numerator is the number of cause-specific deaths among those cases (2).

Case-series - a type of observational descriptive study that follows a group of consecutive patients who have a similar diagnosis or who are undergoing the same procedure over a certain period of time (3).

Cohort study - a type of observational analytic study. Enrollment into the study is based on exposure characteristics or membership in a group. Disease, death, or other health-related outcomes are then ascertained and compared (2).

Coronary angiography - radiography of the vascular system of the heart muscle after injection of a contrast medium (1).

Coronary heart disease - an imbalance between myocardial functional requirements and the capacity of the coronary vessels to supply sufficient blood flow. It is a form of myocardial ischemia (insufficient blood supply to the heart muscle) caused by a decreased capacity of the coronary vessels (1).

Echocardiography - ultrasonic recording of the size, motion, and composition of the heart and surrounding tissues (1).

Electrocardiography - recording of the moment-to-moment electromotive forces of the heart as projected onto various sites on the body's surface, delineated as a scalar function of time. The recording is monitored by a tracing on slow moving chart paper or by observing it on a cardioscope, which is a cathode ray tube display (1).

Epidemiologic studies - studies designed to examine associations, commonly, hypothesized causal relations. They are usually concerned with identifying or measuring the effects of risk factors or exposures. The common types of analytic study are case-control studies; cohort studies; and cross-sectional studies (1).

First medical contact – the time point when the patient is either initially assessed by a physician, paramedic, nurse or other trained emergency medical system personnel who can

obtain and interpret the electrocardiogram, and deliver initial interventions (e.g. defibrillation). First medical contact can be either in the prehospital setting or upon patient arrival at the hospital (e.g. emergency department) (4).

Incidence rate - a measure of the frequency with which an event, such as a new case of illness, occurs in a population over a period of time. The denominator is the population at risk; the numerator is the number of new cases occurring during a given time period (2).

Mortality rate - a measure of the frequency of occurrence of death in a defined population during a specified interval of time (2).

Myocardial infarction - necrosis of the myocardium caused by an obstruction of the blood supply to the heart (coronary circulation) (1).

Myocardial ischemia - a disorder of cardiac function caused by insufficient blood flow to the muscle tissue of the heart. The decreased blood flow may be due to narrowing of the coronary arteries (coronary heart disease), to obstruction by a thrombus (coronary thrombosis), or less commonly, to diffuse narrowing of arterioles and other small vessels within the heart. Severe interruption of the blood supply to the myocardial tissue may result in necrosis of cardiac muscle (myocardial infarction) (1).

Myocardium - the muscle tissue of the heart. It is composed of striated, involuntary muscle cells (myocytes) connected to form the contractile pump to generate blood flow (1).

Necrosis - the pathological process occurring in cells that are dying from irreparable injuries. It is caused by the progressive, uncontrolled action of degradative enzymes, leading to mitochondrial swelling, nuclear flocculation, and cell lysis. It is distinct from apoptosis, which is a normal, regulated cellular process (1).

Non-ST elevated myocardial infarction - a myocardial infarction that does not produce elevations in the ST segments of the electrocardiogram. ST segment elevation of the ECG is often used in determining the treatment protocol (1).

Prevalence - the total number of cases of a given disease in a specified population at a designated time. It is differentiated from incidence, which refers to the number of new cases in the population at a given time (1).

Risk factor - an aspect of personal behavior or lifestyle, environmental exposure, inborn or inherited characteristic, which, on the basis of epidemiological evidence, is known to be associated with a health-related condition considered important to prevent (1).

ST elevation myocardial infarction - a clinical syndrome defined by myocardial ischemia symptoms; persistent elevation in the ST segments of the electrocardiogram; and release of biomarkers of myocardial necrosis (e.g., elevated troponin levels). ST segment elevation in the ECG is often used in determining the treatment protocol (1).

Unstable angina - precordial pain at rest, which may precede a myocardial infarction (1).

1. Introduction of acute myocardial infarction

1.1 Causes, manifestations, and treatments of acute coronary syndrome

Cardiovascular disease is a group of diseases that include both the heart and blood vessels, thereby including coronary heart disease (CHD). The cause of CHD is in most cases stenosis or occlusion of one or more coronary artery branches due to atherosclerosis. The main manifestations of CHD are stable angina pectoris, heart failure, and acute coronary syndrome (ACS), i.e. unstable angina pectoris (UAP), myocardial infarction (MI), and sudden cardiac death (SCD). Central to the pathogenesis of ACS is plaque rupture or erosion with overlying thrombosis and increased tendency to spasm (5). MI occurs when there is cell death (necrosis) due to significant and sustained ischaemia, as measured by a blood test for biomarkers (the cardiac protein troponin T (cTnT) or I (cTnI), and the cardiac enzymes CK and CK-MB).

Based on the electrocardiogram (ECG), two groups of ACS patients can be separated: (1) Patients with acute chest pain and persistent (>20 min) ST-segment elevation. This condition often reflects an acute thrombotic total coronary occlusion, and most patients will develop an ST-elevation myocardial infarction (STEMI). (2) Patients with acute chest pain but no persistent ST-segment elevation. The pathological correlate at the myocardial level is cardiomyocyte necrosis [non-ST-elevation myocardial infarction (NSTEMI)] or, less frequently, myocardial ischaemia without cell death (UAP). UAP and NSTEMI normally result from a partially occluded coronary artery.

The ACS model places UAP, NSTEMI, and STEMI at increasingly severe points along a disease continuum (6). Based on the ECG, STEMI and NSTEMI ultimately develop with little crossover into Q-wave and non-Q-wave MI, respectively. The division of MI into Q-wave or non-Q-wave is useful because the presence of Q-waves predicts a lower heart function and a larger MI (7).

The cornerstone of treatment in patients with STEMI is immediate reperfusion, either mechanical by percutaneous coronary intervention (PCI), or pharmacological by thrombolytic therapy (4, 8). In comparison, a routine invasive strategy with coronary angiography and myocardial revascularization is usually recommended within 2-3 days in patients with NSTEMI (9). Coronary artery bypass grafting (CABG) is also a method for coronary revascularization in a subset of the patients (10). Furthermore, the early drug treatment in patients with MI aims to reduce myocardial ischemia (nitroglycerin, β -blockers) and diminish the thrombotic process [aspirin, P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor), and either unfractionated heparin, enoxaparin, or fondaparinux]. Randomized trials provide robust evidence for the impact of pharmacological and interventional treatments in patients with ACS (4, 8, 9).

Many previous studies have found that a large proportion of CHD deaths occur outside of hospitals as SCD (11-15). Classification and disease surveillance of out-of-hospital CHD death is usually deficient because of its sudden onset, lack of witnesses, and low autopsy rates (16). Prospective epidemiological studies can provide more pre event information. Although the immediate mechanism of death is ventricular fibrillation or asystole, CHD is by far the most common underlying etiology (17), accounting for up to 80% of all SCDs (15, 18-20).

Approximately 20% of CHD patients have sudden cardiac death as the first clinical manifestation (14, 21).

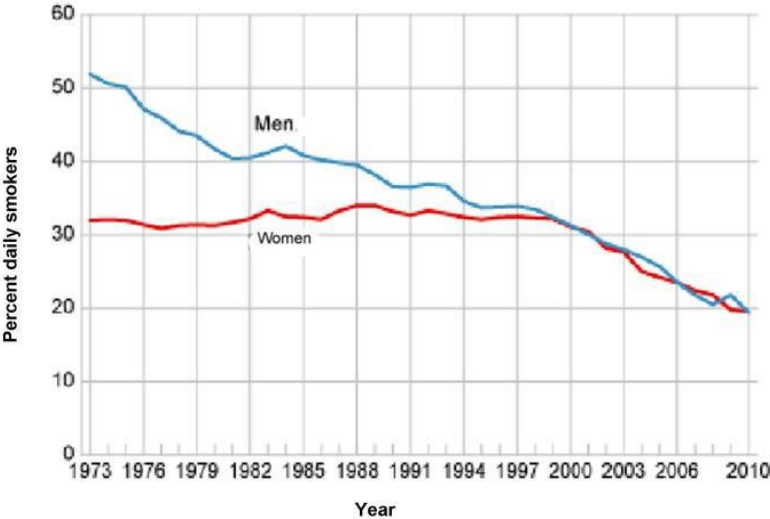
1.2 Cardiovascular risk factors

The lifetime risk for CHD varies depending on the profile of several well-known risk factors. These include age, gender, lipid profile, blood pressure, smoking status, and diabetes. The identification of risk factors and their control through preventive measures has contributed to a reduction in CHD and related mortality in both men and women (22, 23). When all modifiable risk factors are optimal, the lifetime risk of CHD for a 45 year-old is estimated to be <5%, whereas with ≥ 2 major risk factors, it is 50% for men and 31% for women (24). Specific to MI, the INTERHEART Study, a global case-control study across 52 countries (and including 15,152 incident cases of hospitalized MI and 14,820 controls), identified 9 risk factors (smoking, lipids, hypertension, diabetes, obesity, diet, physical activity, alcohol consumption, and psychosocial factors) that accounted for over 90% of the population attributable risk of MI (25). These risk factors were the same in almost every geographic region and racial/ethnic group worldwide, and were similar for men and women. Dyslipidemia and smoking were rated as the most important modifiable risk factors (25). However, the INTERHEART Study has several potential limitations. A case-control design is open to confounding and bias, and the study was limited to survivors. There is a lack of prospective observational studies, which have looked directly at how changes in risk factors correspond to changes in MI incidence, using individual data.

Prevalence of obesity in the United States has increased dramatically in recent decades (as in other Western countries), but, except for diabetes, other risk factors have declined considerably in all body mass index (BMI) groups (26). Using 2008 American Diabetes Association criteria, the prevalence of diabetes was 15.3% during 1988–1994 and 17.5% during 2005–2006 (27). Smoking habits have changed in the United States and Europe in recent decades, with a fall for men and a smaller decline for women (Figure 1) (28, 29).

Figure 1. Percentage of daily smokers according to gender in persons aged 16–74 in Norway from 1973 to 2010. Source: Statistics Norway.

(<https://www.ssb.no/statbank/table/05307/chartViewLine/>)



CHD is more common in men than in women. In the INTERHEART study women experienced their first MI on average 9 years later than men. The difference in age of first MI was mainly explained by the higher risk factor levels at younger ages in men compared to women (30). In both sexes, CHD risk increases with age, and the sex difference persists throughout life, but whereas relative risk estimates diminish with age, absolute differences in risk increase

(31). In a prospective follow-up study from Finland differences in major cardiovascular risk factors explained a substantial part of the sex difference in CHD risk (32). However, in a large, prospective population study in Norway the higher risk of MI in men compared with women could not be explained by differences in established risk factors (31).

1.3 Time trends and burden of coronary heart disease mortality

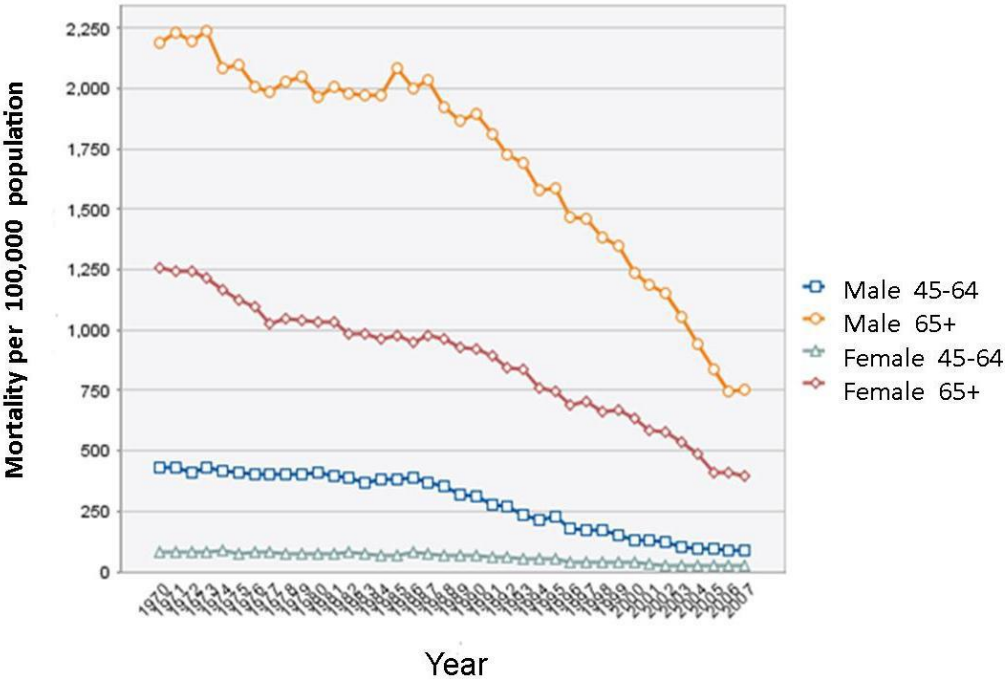
CHD is a major cause of death and disability in developed countries. (33-35). Although age-adjusted CHD mortality rates have declined over the last decades in western countries, CHD remains responsible for about one-third or more of all deaths in individuals over age 35 (34, 35). Mortality data from the Global Burden of Disease Study 2013 showed that the aging and growth of the population have resulted in an increase in global number of cardiovascular deaths, despite a decrease in age-specific death rates in most regions (36, 37). Only in Central Europe and Western Europe did the annual number of deaths from cardiovascular disease actually decline. Globally, CHD has become the leading contributor to the burden of disease as assessed based on disability-adjusted life-years (38).

Acute MI is the major contributor to CHD incidence and mortality. In epidemiological studies, the incidence of MI in a population can be used as a proxy for estimating the CHD burden. Furthermore, MI incidence forms the most relevant indicator for the effect of primary prevention in reducing CHD. If standardized data can be collected on SCD and incident and repeat episodes of MI, then the totality of this burden can be determined (39).

The mortality from MI in Norway has been changing rapidly in both genders since 1970 but with a more marked fall for men (Figure 2).

Figure 2. Mortality from myocardial infarction in men and women over a 37-year period.

Source: Norwegian Institute of Public Health. (<https://www.fhi.no/nettpub/hin/ikke-smittsomme/Hjerte-kar/>)



1.4 Changes in myocardial infarction definition

Evaluating temporal trends in the incidence and outcome of MI is challenging since there have been changes over time in the criteria utilized for the diagnostic confirmation of MI.

The definition of acute MI was introduced by the World Health Organization (WHO) in 1959 (40), followed by reports from American Heart Association (AHA) in 1964, the WHO in 1971,

and the Framingham Study provided further specifications (41-43). The WHO criteria were revised in 1979 (44). The diagnosis of MI was based on the presence of at least two of three criteria: cardiac symptoms, ECG changes, and increase in enzymes indicating myocardial injury. The definitions of the three criteria have varied among researchers, resulting in a lack of comparability among and within studies. This was the background for the WHO multinational MONItoring of trends and determinants in CARdiovascular disease (MONICA) project, which was set up to measure the trends in cardiovascular mortality and incident CHD, classifying the events into five categories (definite, possible, ischemic cardiac arrest, no MI or coronary death, and unclassifiable), related to risk factors (45, 46).

In 2000, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) recommended changing the diagnostic criteria for acute MI to include raised cTn concentrations in addition to ischemic symptoms or ECG changes of ischemia (47). This definition includes only the definite category of MI, which may lead to underestimation of the incidence of MI in epidemiological studies. The ESC/ACC was criticized for changing the definition of MI, first because of problems with comparisons with previous definitions and populations, secondly because of failure of the new definition to cover SCD, and thirdly because the new definition did not include nonfatal cases with missing cTn results (48-51). In 2003 epidemiological researchers published an AHA scientific statement to address the specific needs regarding the definition of MI in population surveillance (16). Later, the ESC, ACC, AHA and World Heart Federation (WHF) published the Universal 2007 definition which addressed several of the weaknesses of the 2000 definition, and included five new categories of MI (52). In addition, some changes were made in the WHO 2009 revision (39) and in the Universal 2012 definition (53).

1.5 The problems with new sensitive biomarkers

The most complicating factors in many studies of MI trends during the past decades, are the increasing use of cardiac biomarkers and the changing cutoff levels for the laboratory tests used for the diagnosis of MI (52, 54, 55). In the Framingham Heart Study trends in MI incidence were highly dependent on the definition used. ECG-diagnosed MI incidence decreased by 50% between 1960 and 1999, but biomarker-diagnosed MI incidence increased 2-fold (55). Compared with CK and CK-MB, cTns are more sensitive and specific markers of myocyte necrosis. The higher sensitivity allows detection of small amounts of myocardial necrosis that would have gone undetected by CK and its MB fraction. Thus, this biomarker change was predicted to increase the number of smaller MIs, predominantly NSTEMIs, and this increase could obscure declining trends in the incidence of coronary events (56, 57). Given current sensitive biomarkers, the proportion of ACS without necrosis (UAP) has declined to a small fraction ($\approx 7\%$) of ACS presentations. Thus, the hospitalized ACS spectrum is now dominated by MI, composed of STEMI ($\approx 1/3$ of MIs) and NSTEMI ($\approx 2/3$ of MIs), with their differing prognostic and therapeutic implications (58).

There have been a number of studies evaluating the impact of the ESC/ACC 2000 redefinition of MI on the frequency of diagnosis of MI. The increase in the number of MIs due to the increased sensitivity of cTn ranges from 4 % to 195 % (56, 57). In a prospective Minnesota US community study of patients hospitalized with incident MI from 1987 to 2006, 25% of incident MIs met only cTn-based criteria after cTn was introduced. When cases meeting only cTn criteria were included, incidence did not change. When restricted to cases

defined by CK/CK-MB, the incidence of MI declined by 20%. The incidence of NSTEMI increased markedly by relying on cTn, whereas that of STEMI declined regardless of cTn. The severity of infarctions declined regardless of cTn, and the 30-day case fatality improved markedly over time (59). In the Finnish Acute MI (FINAMI) study, the effect of cTns on the incidence of first coronary events tended to be stronger in women and older individuals than in men and younger individuals (60). However, the case fatality trends, with a decline in both sexes in patients aged 35–74 years, were not affected by adjustment for cTns. The redefinition of MI has indeed been shown to identify some patients with ACS who are older and more often female and who have greater comorbidities and worse 6-month and 1-year outcomes who were missed by the old 1979 WHO criteria (61-63).

The clinical acceptance of the new definition, however, was initially incomplete. In one study less than half of the cases identified with the new criteria were documented as MI in the medical record (57). A survey in Scotland in 2002 (64) showed that only one-third of cardiologists made a diagnosis of MI when patients presented with chest pain and elevated cTn levels in the absence of ECG changes or elevated CK or CKMB levels. One study has shown that the new diagnostic criteria for MI were not applied methodically in the hospital studied, and that males with raised cTn T values were more likely to be discharged as having had an MI than females (65).

1.6 Contributors to the fall in CHD mortality

Mortality rates are subject to a number of influences such as changes in risk factors, incidence, disease severity, treatment, and case fatality. Generally, declining CHD mortality

may be driven by reductions in the incidence of coronary events and/or increased survival of those affected. Changes in incidence may reflect the effects of primary prevention with improvements in the levels of population risk factors (46, 66). Changes in case fatality are assumed to be caused by improvements in initial hospital-based treatment and subsequent postdischarge management, while the recurrence rate depends on the success of secondary prevention efforts and treatment of chronic CHD. However, the effects of treatment and prevention may overlap. It is possible that interventions to prevent the initial MI, also can change the case fatality rate after an MI. The severity of incident MI may therefore be influenced by both primary prevention efforts, which might result in less severe events from the earliest stages, and acute care, which might preserve cardiac tissue and function (67). Consequently, improvements in population risk factors would not only prevent an initial MI but also shift the distribution of MIs toward less severe forms.

Epidemiological studies provide an opportunity to examine whether the severity of acute MI differs according to time, place and persons. Indicators of severity can be Killip class (quantifies severity of heart failure in ACS), biomarkers (peak CK, CK-MB or cTn), ECG findings (Q-wave, ST-segment elevation), and case fatality rate. However, evaluating the severity of MI may be difficult (33, 68). The time between symptom onset and presentation to medical care can affect each indicator of severity. Biomarkers and Q-wave can be influenced by treatment, particularly reperfusion, while ST-segment elevation reflect the characteristics of the MI during the first hours and are therefore not affected by treatment. However, the interpretation of the changes in STEMI requires knowledge in the trends in out-of-hospital CHD deaths, since a decline in hospitalized STEMI rates could reflect an increase in those dying out of hospital. Finally, accurate determination of the severity of MI

through biomarker measurement will be affected by the timing and frequency of the biomarker measurements such that the recorded values may not accurately reflect the true peak. However, measurement of cTnT at a single point of time on any of the first 4 days or using the peak value correlates well with infarct mass determined by contrast-enhanced magnetic resonance imaging (69). cTnT serum concentrations show a biphasic curve with one peak on the first day resulting from a release of the cytosolic cTnT pool and a second “plateau” phase 3–4 days after the beginning of chest pain resulting from intramyocardial protein degradation. Compared with cytosolic markers (CK, CK-MB), the second peak of cTnT seems to be almost unaffected by early coronary reperfusion (70).

1.7 The IMPACT model

Researchers have used mathematical models which include data on major risk factor levels in the population and data on the use of medical treatments and interventions to try to explain the observed decline in CHD mortality (71). The IMPACT CHD mortality model is a cell-based model originally developed by Capewell and colleagues in 1996 (72). Using a MS EXCEL spreadsheet, this aggregate model combines data from many sources on patient numbers, treatment uptake, treatment effectiveness, and risk factor trends to model CHD mortality. The model is used to estimate the proportion of a mortality decline (or increase) over a certain time span that might be attributed to specific treatments or to risk factor changes. The validity of the model has been checked by comparing the estimated fall in CHD deaths with the observed fall in specific age and sex categories. Based on this model it has been suggested that risk factor improvements explain more of the mortality decline than treatments, ranging from 40% to 75% (73-81). More than half of the CHD mortality decrease

in Sweden between 1986 and 2002 was attributable to reductions in major risk factors, mainly a large decrease in total serum cholesterol (81). Adverse trends were seen for diabetes and overweight, but not so much as in US (78). Medical and surgical treatments explained nearly 40 % of the mortality reduction. The largest reduction came from the use of secondary-prevention medications after MI, followed by initial treatment for MI and UAP and treatments for heart failure.

These studies based their estimates on ecological data and mathematical modeling of aggregate data. Studies based on aggregate data are often referred to as an ecological design. The association found with aggregate data may not apply to individuals (ecological fallacy). We found only two studies that have looked directly at how changes in risk factors in a cohort correspond to changes in MI incidence using individual data (82, 83), and these two studies were limited to population subgroups and did not study out-of-hospital CHD or subtypes of MI. However, there are very few populations in the world where it is possible to do such studies. The Tromsø Study is unique here.

1.8 Cardiovascular registers and population-based epidemiological studies

Randomized trials provide robust evidence for the effects of pharmacological and interventional treatments in patients with MI, and such studies may influence practice guidelines depending on their quality and generalizability. To improve quality of care and ensure adherence to guidelines, registries in various countries have been developed (84-87).

In Norway, nationwide studies on MI incidence have not been possible due to lack of relevant registries and databases. The Norwegian Cardiovascular Disease Registry (NCVDR)

has been operating since December 2012 and is a national person-identifiable health register that does not require the consent of the registered patient. The register consists of a basic register containing data from the Norwegian Patient Register and the Cause of Death Register, and currently has eight associated national medical quality records. NCVDR therefore provides information on all patients admitted for acute MI in the entire country, their individual baseline characteristics, the use of evidence-based treatments, and the short- and long-term outcome.

Cardiovascular disease registries have provided important contributions to our understanding of outcomes in MI. However, the inability to quantify or characterize the underlying populations from which their patients are drawn limits their usefulness in studying disease incidence and the potential effectiveness of primary prevention efforts (54). Population-based epidemiologic data, such as that from the Tromsø Study, provide the best evaluation of the risk factors that contribute to the development of CHD and to the way CHD evolves, progresses, and terminates. Additionally, these data are less restricted by the unavoidable selection bias of clinical trials data. Therefore, population-based studies on trends in MI have been the principal source of knowledge in the understanding of MI epidemiology. However, existing literature assessing recent temporal trends in the incidence of MI is relatively sparse, and studies often lack sufficient power and diversity (54).

1.9 Recent trends in myocardial infarction epidemiology and unresolved issues

Several studies have examined temporal trends in the incidence of MI. Interpreting and comparing the studies is difficult because of geographic differences in patient populations,

temporal changes in the criteria used to diagnosis MI, and differences in study methodology. However, the overall body of literature suggests that the incidence of MI has declined significantly over the past decades (88). Trends in the incidence rate of MI in the United States may have changed from relatively stable rates in the 1980s and 1990s (89, 90) to significant declines in the new millennium (6, 55, 59, 91-93). Since 1987, the adjusted incidence rate of hospitalization for acute MI or fatal CHD in the United States has declined by 4 to 5% per year (94). In Seattle, the age- and sex-adjusted incidence rates of out-of-hospital cardiac arrest with ventricular fibrillation from 1980 to 2000 declined by 56%, and the incidence of all treated arrests declined by 34% (95). Numerous publications have documented improvements in the in-hospital or short-term case-fatality rate (6, 55, 59, 89, 92, 93, 96). One-year postdischarge death rates decreased between 1997 and 2005 for patients with STEMI and NSTEMI (6). In the Framingham Study, 1- and 5-year mortality among adults who had an MI decreased by 65% and 64%, respectively, during the period from 1960 to 1999 (55).

Recent publications from the Nordic (97-101) and other European countries (83, 102, 103) have also reported decreases in MI incidence and case fatality rates. Both hospitalized case-fatality and out-of-hospital mortality have been reported to decrease over time (11, 102, 104-107). Autopsy data have reported a reduced prevalence of anatomic CHD over time in both the general population and military personnel (108, 109).

Relatively few population-based studies have examined recent temporal trends in the incidence of MI by type, i.e. NSTEMI, STEMI and SCD. The grouping of these individual

conditions into the single category of MI may be misleading, because these MI subtypes to some extent have different treatments, and impose different burdens on patients, physicians, and health care systems. Furthermore, we are not aware of prospective studies of predictors of the three MI subtypes, i.e. studies that compared premorbid characteristics /risk factors. Because the clinical history of patients with these individual conditions may differ, cross-sectional data collected from medical records at the time of the event may not reflect premorbid characteristics. We know that there is a consistent pattern for STEMI to be relatively more common in younger than in older people, and more common in men than in women (6, 110-113). Compared to NSTEMI patients, those with STEMI are less likely to have a prior history of several comorbidities (6, 111). In addition, STEMI patients are more likely to receive effective cardiac medications and PCI (6).

Despite large falls in MI rates differences continue to exist across population subgroups: the decline in incidence may not have happened equally in men and women, the young and the elderly and across socioeconomic groups. Most studies report overall age-standardized rates, and data on age-specific trends are sparse. In young adults flattening of the decline and even increases in AMI incidence have been observed (96, 97, 114). Furthermore, falls in MI incidence have been reported to be greater in men than women (114-118). Emerging trends in coronary risk factors support these observations (29, 119,120). In a 2009 report that used National Health and Nutrition Examination Survey (NHANES) data, MI prevalence in the US was compared by sex in middle-aged individuals (35–54 years) during the 1988–1994 and 1999–2004 time periods (119). The study found a higher prevalence of MI in men compared with women in the two periods, but prevalence tended to decline in men over time, whilst the opposite trend was found in women. More contemporary assessments of

epidemiology of MI are needed to help assess the effectiveness of primary prevention and treatment and identify areas for potential improvement (54).

1.10 Treatments of ST-segment elevation myocardial infarction

Although recent population-based studies indicate a reduction in incidence, STEMI is still a major health issue worldwide (6, 59, 92). In a recent study describing the current situation in 30 European countries, the annual incidence for hospital admissions for STEMI varied between 44 and 142 cases per 100 000 inhabitants (121). Primary PCI and thrombolysis have been proven to preserve left ventricular function and lower infarct size and mortality (122, 123). Randomized clinical trials have shown that, if delay to treatment is similar, primary PCI is superior to thrombolysis in reducing mortality, reinfarction, or stroke (123). Therefore, primary PCI is preferred over thrombolytic therapy in acute STEMI, but only if PCI is performed in a timely fashion, i.e. within 90 to 120 min from first medical contact (FMC) (4, 8). Both randomized studies and registries have indicated that long delays to primary PCI are associated with worse clinical outcomes.

Generally, thrombolysis is more widely available and can be started earlier than primary PCI. In settings where primary PCI cannot be performed in a timely fashion, thrombolysis should be considered, particularly if it can be given in a pre-hospital setting (e.g. in the ambulance) (124-128) and within the first 120 min of symptom onset (129-132). The pharmaco-invasive strategy combining prehospital thrombolytic therapy (PHT) and rapid transfer to planned PCI within 3-24 hours in stable patients, and rescue PCI for failed thrombolysis, is an efficient reperfusion strategy for STEMI patients (4, 8, 133-136). Randomized trials comparing such

PHT strategy with primary PCI in patients who present early show no difference in 30-day mortality or re-infarction (124, 128).

An early study showed that the benefits of aspirin and thrombolytics (i.e. streptokinase) were additive (137). Clopidogrel added to aspirin will further reduce the risk of cardiovascular events and overall mortality in patients treated with thrombolysis (138).

Parenteral anticoagulation should preferably be given until revascularization (if performed), and the net clinical benefit favored enoxaparin over unfractionated heparin in the ASSENT 3 trial (139). Weight-adjusted i.v. tenecteplase, aspirin, and clopidogrel given orally, and enoxaparin i.v. followed by s.c. administration until the time of PCI (revascularization), comprise the antithrombotic cocktail most extensively studied as part of a pharmacoinvasive strategy (4).

If trained medical or paramedical staff are able to analyze the ECG onsite or to transmit the ECG to the hospital for interpretation, it is recommended to initiate thrombolytic therapy in the pre-hospital setting. The aim is to start thrombolytic therapy within 30 min from FMC (8) [(within 20 min in the latest guidelines from 2017 (4)]. However, only limited information is available on the speed of implementation of this new treatment strategy and its association with morbidity and mortality in real-life health care (140).

1.11 Predictors of outcome with ST-segment elevation myocardial infarction

Thrombolytic therapy is associated with a small but significant excess of cerebral hemorrhage (141). In the latest trials, intracranial bleeding occurred in 0.9–1.0% of the total

population studied (128). Left ventricular (LV) systolic dysfunction is a complication following MI and can be transient (i.e. myocardial stunning) or persistent due to cell loss (MI), depending on the duration of ischemia and completeness of reperfusion. LV systolic dysfunction is a powerful independent predictor of mortality (142, 143). LV dysfunction may be clinically silent or cause clinical heart failure, and the diagnosis is made by clinical and imaging techniques, most frequently echocardiography, with estimating of the LV ejection fraction (LVEF). LVEF is the ratio of blood ejected during systole (stroke volume) to blood in the ventricle at the end of diastole (end-diastolic volume), i.e. a percent measurement of how much blood the left ventricle pumps out with each contraction. A normal heart's LVEF may be between 50% and 70%. Trials in both the pre- and the post-thrombolytic era have shown that an LVEF of 40% is the break point separating patients at relatively low, versus higher, mortality risk (144-146). Heart failure is the most frequent complication and one of the most important prognostic factors in patients with STEMI (147, 148). Cardiogenic shock is defined as persistent hypotension (systolic blood pressure <90mmHg) despite adequate filling status with signs of hypoperfusion. It complicates 6–10% of all cases of STEMI and remains a leading cause of death, with in-hospital mortality rates $\geq 50\%$ (149).

The mortality in STEMI patients is influenced by many factors, among them advanced age, heart failure, time delay to treatment, presence of emergency medical system (EMS)-based STEMI networks, treatment strategy, history of MI, diabetes mellitus, renal failure, number of diseased coronary arteries, and LVEF (4). Several recent studies have observed a fall in acute and long-term mortality following STEMI in parallel with greater use of reperfusion therapy, primary PCI, modern antithrombotic therapy, and secondary prevention (86, 150-152). Reported 1-year mortality among STEMI patients in angiography registries is

approximately 10% (153, 154). Overall, NSTEMI patients appear to have lower short-term mortality compared with STEMI individuals, while at 1- or 2-years follow-up the mortality rates become comparable. This is likely due to differences in baseline characteristics, including older age and a greater prevalence of co-morbidities in the NSTEMI population (113, 155).

2. Aims of the thesis

The main aim of the thesis was to describe recent trends in incidence, risk factors, severity, treatment and outcome of MI in a general Norwegian population during the time period 1974 -2012.

More specifically, our main focus has been:

1. To examine gender- and age-specific trends in incidence, case fatality and the severity of first MI over a 30-year follow-up.
2. To study trends in the rates of out-of-hospital SCDs, and the incidence, treatment, and outcome of hospitalized STEMI and NSTEMI, and the impact of changes in coronary risk factor levels on event rates.
3. To study clinical results following implementation of a decentralized PHT-system combined with improved availability of 7/24 invasive diagnosis and treatment-service in consecutive patients with presumed STEMI in a single center over an 11-year period.

3. Methods

3.1 Study population and follow-up used in paper 1-2

The rapid increase of CHD mortality in Northern Norway during 1951–1970, and the higher CHD mortality figures in this region than in the rest of the country, led the University of Tromsø, established in 1972, to start a study to identify the major operating cardiovascular risk factors in this population. The Tromsø Study is a single-centre, population-based, prospective health study conducted in the municipality of Tromsø (156, 157). Tromsø is the regional centre and the largest city in Northern Norway. Tromsø had about 40,000 inhabitants in 1974, whereas the population in 2018 is about 75,000. The University Hospital of Northern Norway in Tromsø (UNN Tromsø) is the only hospital in the area. The Tromsø Study consists of seven repeated health surveys (Tromsø 1: 1974, Tromsø 2: 1979-80, Tromsø 3: 1986-87, Tromsø 4: 1994-95, Tromsø 5: 2001-02, Tromsø 6: 2007-08 and Tromsø 7: 2015-16). Both total birth cohorts and random samples of Tromsø inhabitants were invited by written mail-sent invitations. The overall participation rate ranged from 65-85 %. Women were included in the 1979 survey and onwards. An overview over the Tromsø Study sample is given in table 1.

No national registry of cardiovascular diseases existed in Norway until 2012. Therefore, the Tromsø study had to establish its own disease registry covering incident MI, and later on also stroke, venous thromboembolism, atrial fibrillation, and diabetes.

Table 1. Overview of the Tromsø study 1974–2016.

Year	Survey	Participants	Age (years)	Attendance ^a
1974	Tromsø 1	6595 men	20-49	83 %
1979-80	Tromsø 2	16,621 men and women	20-54	85 %
1986-87	Tromsø 3	21,826 men and women	12-67	81 %
1994-95	Tromsø 4	27,158 men and women	25-97	77 %
2001-02	Tromsø 5	8130 men and women	30-89	79 %
2007-08	Tromsø 6	12,984 men and women	30-87	66 %
2015-16	Tromsø 7	21,083 men and women	40-99	65 %

^a Of eligible population (adjusted for deaths and emigration from Tromsø).

Paper 1 is a follow-up study of gender- and age-specific trends in incidence, case fatality and the severity of first MI among all participants from the first five surveys (Tromsø 1-5: 1974-2002). They were followed from the date of first attendance at the population health screening until date of first-ever fatal or non-fatal MI, emigration from Tromsø, death from other causes or 31st December 2004, whichever came first. All analyses were stratified by sex and age (35–49 years, 50–64 years, 65–79 years and 80 years and older). To ensure valid trends with stable average age within each age group, we had to take into account that the oldest birth cohorts were recruited later than the younger ones (Table 1). Therefore, for men, age-specific trend analyses for the age groups 35–49 years, 50–64 years and 65 years

and older could be performed for the time periods 1974–2004, 1988–2004 and 1995–2004, respectively. For women, age-specific trend analyses for the age groups 35–49 years, 50–64 years and 65 years and older could be carried out for the time periods 1979–2004, 1993–2004 and 1995–2004, respectively. A total of 31,323 participants were included in the analysis, 15,566 men and 15,757 women.

Paper 2 includes participants from the surveys undertaken in 1994-95 (Tromsø 4), 2001-02 (Tromsø 5), and 2007-08 (Tromsø 6), a total of 29,582 individuals ≥ 25 years who participated in 1, 2, or all 3 surveys. Follow-up extended from the date of first attendance in the population health screening to the date of incident event, date of emigration, death, or end of follow-up (31 December 2010), whichever came first. We studied the rates of out-of-hospital SCDs, the incidence, treatment, and outcome of hospitalized STEMI and NSTEMI, and the impact of changes in coronary risk factor levels on incidence trends. Participants who were still free of MI and attended the later surveys in 2001 to 2002 or in 2007 to 2008 had their CHD risk factor values updated at the date of their examination.

3.2 Study population, inclusion and exclusion criteria, and follow-up used in paper 3

The study population was recruited from UNN Tromsø's local catchment area (23100 km²) with about 125 000 inhabitants. The annual number of STEMI in this population is about 80-100. We included patients with presumed STEMI where primary PCI could not be performed within 90-120 min of FMC, and with PHT-decisions based on 12-leads ECG transmitted to UNN Tromsø. Criteria for STEMI required to start PHT treatment were central chest pain

with or without radiation, pain duration between 20 min and 6 hours, and ECG indicative of an acute STEMI: ≥ 2 mV ST-segment elevation in at least 2 contiguous leads or presumed new left bundle branch block. Exclusion criteria was age >80 years or standard contraindications to thrombolysis (table 2).

Table 2. Contra-indications to fibrinolytic therapy (4)

Absolute
Previous intracranial hemorrhage or stroke of unknown origin at anytime
Ischemic stroke in the preceding 6 months
Central nervous system damage or neoplasms or arteriovenous malformation
Recent major trauma/surgery/head injury (within the preceding month)
Gastrointestinal bleeding within the past month
Known bleeding disorder (excluding menses)
Aortic dissection
Non-compressible punctures in the past 24 hours (e.g. liver biopsy, lumbar puncture)
Relative
Transient ischaemic attack in the preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week postpartum
Refractory hypertension (SBP >180 mmHg and/or DBP >110 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer
Prolonged or traumatic resuscitation

DBP=diastolic blood pressure; SBP=systolic blood pressure

We examined 385 consecutively patients with presumed STEMI who had been given PHT, and then admitted directly to UNN Tromsø between March 2000 and December 2011. They were followed one year after index event with regard to mortality.

3.3 Myocardial infarction case identification and definition used in paper 1 and 2

Adjudication of hospitalized and out-of hospital events was performed by an end-point committee using information in medical records and medical notes, autopsy records, and death certificates. The national unique 11-digit identification number allowed linkage to national and local diagnosis registries. Cases of hospitalized MI were identified by searching the discharge diagnosis registry at UNN Tromsø, the only hospital in the area. In the period 1969-1979, the International Classification of Diseases (ICD) version 8 codes 410-414, 427, 795-796, from 1980 to 1998, ICD version 9 codes 410-414, 798, 427.5 and thereafter ICD version 10 codes I20-I25, R96, R98, R99, I46 were used. The National Causes of Death Registry allowed identification of fatal cases of MI that occurred as out-of-hospital deaths. For event ascertainment the endpoint committee followed a detailed protocol and examined all available medical records, including medical records from other hospitals and prehospital records from ambulance service, general practitioners, nursing homes and death certificates. Modified WHO MONICA/MORGAM (MONica Risk, Genetics, Archiving and Monograph) criteria were used and included clinical symptoms and signs, findings in ECGs, values of cardiac biomarkers, and autopsy reports when applicable (158). Biomarkers considered were CK, its myocardial fraction (CK-MB) (from 1990), and cTnT beginning in 1999. Biomarker levels were generally recorded three times during the first 3 days following admission or MI

onset. Biomarker increases associated with revascularization procedures were not included as MI. Silent MIs as defined by ECG only were not included as cases because of difficulties in determining the exact date of the event. We classified hospitalized STEMI and NSTEMI by using standard criteria (52, 53). Out-of-hospital SCD was defined as death caused by a probable MI (based on symptoms or autopsy) within 24 hours of symptom onset in non-hospitalized individuals, or deaths in individuals brought to hospital with a cardiac arrest and unsuccessful resuscitation with no evidence of a non-coronary cause of death. Case fatality was defined as the proportion of incident CHDs that were fatal within 28 days or 1 year. Trends in MI severity (1995–2010) were evaluated by calculating the proportion of events with new Q-waves or ST-segment elevation in ECG, and the peak CK values.

3.4 Coronary risk factors measurements used in paper 2

Each survey used a standardized and almost identical protocol including physical examination, blood sampling, and questionnaires. Blood pressure and heart rate were measured with an automatic device (159). The average of the last two measurements was used. Height and weight were measured with subjects wearing light clothes and no shoes. Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Nonfasting blood samples were analyzed (for total cholesterol, HDL cholesterol) by standard methods at the UNN Tromsø (159). Smoking status and diabetes mellitus was self-reported in a questionnaire. Participants were defined as physically active if they performed strenuous physical activity (i.e., became sweaty and breathless) at least 1 h/wk.

3.5 Data registrations used in paper 3

Data were obtained from a prospectively collected registry at UNN Tromsø organized by an experienced cardiologist. The registry included data from prehospital PHT forms, written records from ambulances and the UNN Tromsø Emergency Department and cardiac care unit, and reports from coronary angiography and PCI. We collected demographic data, times for symptom onset, ambulance arrival, pre-hospital ECG, start of “MONA” (morphine, oxygen, nitroglycerine, acetylsalicylic acid) and PHT, out-of-hospital cardiac arrest (OHCA), arrival at emergency department and cardiac care unit and time of coronary angiography and PCI at UNN Tromsø. Appropriateness of PHT, adverse PHT-events, in-hospital echocardiography, ECG, biomarkers, and patient discharge diagnosis were recorded. We defined “systolic heart failure” as LVEF < 40 %. Major bleeding was defined according to Bleeding Academic Research Consortium (BARC) type 2-5 bleeding (160). The date of death was obtained from the national Central Norwegian Population Register for calculation of 1-year case fatality. To investigate possible time trends, the study was divided into three time periods; 2000-03, 2004-07, and 2008-11. We have incomplete data on STEMI patients not treated with PHT (i.e. primary PCI), because a local registry of invasive cardiology was not established before mid-2000 with initially insufficient data.

3.6 Statistical analyses in paper 1

For incidence analysis, we used the split function in STATA 10 (Stata Corp LP, College Station, TX) to produce a new record for each follow-up year for each person. Years were adjusted to a 365.25-day length and age was updated on the first of July in every year the participants were being followed up. The MI incidence rates were calculated by dividing the number of all events over a period of time by the corresponding person-years at risk. To account for non-linear time trends, calendar year was fitted using fractional polynomials and regressed on MI incidence and case fatality in Poisson and logistic regression models, respectively. All analyses of incidence rates and case fatality were age adjusted by including age as a continuous variable in the regression models, and stratified on sex and age (35–49 years, 50–64 years, 65–79 years and 80 years and older). Differences in hospitalized MI severity across time (2000–4 compared to 1995–99) were assessed by logistic regression for binary severity indicators (new Q-wave or ST-segment elevation in ECG) and linear regression for the natural log of peak CK, adjusted for age and sex. Trends across age and between sexes were compared by including two-way interaction terms between year and age and year and sex.

3.7 Statistical analyses in paper 2

Statistical analyses were performed with STATA 12 (Stata Corp LP, College Station, TX) and SAS 9.3 (SAS Institute, Cary, NC). Age- and sex-adjusted means or prevalence of risk factors over time was estimated from generalized estimating equations to account for dependencies between repeated observations. The identity and logit link functions were used for continuous and binary variables, respectively, and the estimates were calculated with the

use of the mean value for age and sex (57.9 years and 46% male) in the regression models. Hazard ratios of CHD for coronary risk factors were estimated with Cox proportional hazards regression adjusted for age and sex. Hazard ratios of subtypes of CHD were estimated with the augmented data approach (161). For incidence analysis, we used the split function as in paper 1. Time trends in event and mortality rates and case fatality proportions were age and sex standardized with the Tromsø population in 2007 used as the standard population for the first 2 end points and the CHD event cohort for the last end point. The CHD mortality decline explained by out-of-hospital SCDs was estimated as the difference in out-of-hospital SCD rate between 2010 and 1995 divided by the difference in total CHD mortality rate between 2010 and 1995. The proportion of the CHD mortality decline that was explained by the decline in incidence rates or case fatality was calculated as in the MONICA study: the average annual change in mortality rate is the sum of the average annual changes in event rate and case fatality proportion, expressed as percentages (46). Poisson regression models were used to estimate linear time trends in events. The proportion of the CHD incidence decline that was explained by change in each risk factor was estimated by the expression $(\beta_0 - \beta_1)/\beta_0$, where the β s are time-trend coefficients from Poisson regression models, the former adjusted for age and sex and the latter with additional adjustment for risk factors added to the model as time-dependent covariates. End of follow-up was defined as 2001 for those who did not attend the 2001–2002 survey and as 2007 for those who did not attend the 2007–2008 survey. Individuals who had a CHD event were censored from the analyses at the time of their event. One thousand bootstrapped samples were simulated (with replacement) to estimate the 95% confidence interval (CI) for the explained decline.

3.8 Statistical analyses in paper 3

Data were expressed as medians (with 25th-75th percentile) or percentages. The chi-squared test was used for comparisons of binary variables. We used logistic regression models for categorical variables to estimate linear time trends and either linear regression models or non-parametric tests (Jonckheere trend test) for continuous variables. All statistical analyses were done using STATA 14 (StataCorp LP[®], College Station, TX).

4. Summary of results

4.1 Paper 1

From 1974 to 2004, a total of 1669 incident MIs occurred among the 31,323 participants during a total follow-up time of 400,572 person-years. Seventy-one percent of incident MIs occurred in men. The mean age at the time of the MI event was 62 years for men and 73 years for women. Seventy-nine percent of all events were treated in hospital, whereas 15% of all events were out-of-hospital deaths. The overall 28-day case fatality was 32%.

Trends in the incidence of MI differed significantly by sex and age. From 1995 to 2004 the age-adjusted incidence of MI in participants of 35–79 years declined by 26% in men, but increased by 61% in women. In both genders, MI incidence among patients over 80 years did not change. Temporal trends in the incidence of MI did not change notably when troponin-only cases were excluded.

From 1995 to 2004 the age-adjusted odds of death within 28 days fell significantly by 52 % among men and by 59% among women aged 35–79 years. For patients older than 80 years, case fatality decreased significantly in men, but not in women. Among patients younger than 50 years of age, case fatality did not change in men whereas in women there were too few cases for analysis. Furthermore, there was a significant 52 % decline in the odds of 1-year case fatality over the same period, adjusted for age and sex and were similar regardless of troponin.

In all hospitalized patients with MIs between 1995 and 2004, the proportion with Q-wave pattern on ECG decreased significantly, as did the peak CK level, and a similar trend was observed for the frequency of ST-segment elevation in ECG. Furthermore, the 28-day case fatality declined significantly. The trends in case fatality, ECG findings and CK were similar in men and women and across all age groups, and also when cases meeting only troponin criteria were excluded. Among all hospitalized MIs between 1995 and 2004, the use of revascularization (PCI and/or CABG) within 28 days and the use of aspirin, β -blockers and statins at dismissal increased markedly over time.

4.2 Paper 2

We identified 1845 patients (39% women) with an incident CHD event between 1995 and 2010, representing a period of 375 064 person-years. Seventy-eight percent of the patients (n=1441) were hospitalized. Among those were 523 patients (36%) with STEMI, 869 (60%) with NSTEMI, and 49 with unclassifiable MI. A total of 236 hospitalized patients (16%) died within 28 days. Among the 404 nonhospitalized patients, there were 332 out-of-hospital SCDs and 341 deaths within 28 days after symptom onset. Thus, 58% of all fatal incident CHD events occurred as an out-of-hospital SCD.

The age- and sex-adjusted incidence of total CHD decreased by 3% each year. This decline was driven by decreases in out-of-hospital SCD (annual decline 7.6%) and hospitalized STEMI (annual decrease, 4.3%). In contrast, hospitalizations for NSTEMI increased in the first half of the study period.

Favorable changes in coronary risk factors during the study period accounted for 66% of the decline in the incidence of total CHD. Favorable changes in cholesterol contributed 32% to the decline, whereas blood pressure, smoking, and physical activity each contributed 14%, 13%, and 9%, respectively. Increases in BMI and the prevalence of diabetes mellitus were associated with 7% and 2% increase in the risk of CHD, respectively.

The age- and sex-standardized CHD mortality rate fell by 7.3 % annually, and case fatality by 4.0 % annually. Thus, changes in incidence and case fatality contributed 43 % and 57 %, respectively, to the decline in CHD mortality. Furthermore, 65 % of the decline in CHD mortality was attributable to a decrease in the rates of out-of-hospital SCDs.

Peak CK levels decreased significantly in patients with NSTEMI, and the proportion of patients who developed Q waves on ECG decreased significantly over time among patients with both STEMI and NSTEMI. Revascularization and the proportion of patients receiving β -blockers, acetylsalicylic acid, and statins at discharge increased over time. Age- and sex-adjusted 28-day case fatality decreased by 26% (not statistically significant) in STEMI patients and by 43% in NSTEMI patients in 2005 to 2010 compared with 1995 to 1999.

4.3 Paper 3

Successful ECG-transmission from ambulances to UNN Tromsø were completed in 99 %, and ECG criteria for STEMI were present in 93 % of the 385 consecutive patients. Anterior and

inferior wall MI accounted for 46 % and 43 %, respectively, UAP 3 %, while 8 % did not suffer from ACS and should not have been given PHT. Median age was 61 years and 77 % were male. The median time from onset of chest pain to ECG was 110 minutes and the median time from first prehospital ECG (a proxy for FMC) to start PHT was 36 minutes. The median time from symptom onset to PHT was 150 minutes, and 31 % of patients received PHT within 120 minutes. Median evacuation time to UNN Tromsø following PHT was 93 minutes, whilst the median time from hospital admission to primary PCI ('door-to-balloon') has been estimated to 38 minutes (162). Thus, the early prehospital diagnosis and thrombolytic therapy may have saved 2 hours 11 minutes to initiation of reperfusion therapy. The majority (82 %) of patients underwent coronary angiography within 24 hours, and a total of 69 % received PCI while 10% underwent CABG during hospital stay.

The proportion of patients who received PHT within two hours after symptom onset increased from 21 % in 2000-03 to 39 % in 2008-11, whilst the proportion of patients receiving inappropriate PHT fell from 14 % to 2 % in the same period. The proportion of patients receiving thrombolytic therapy who had coronary angiography or PCI within 24 hours of FMC increased from 56 % to 95 %. Based on our local registry of invasive cardiology, an increasing number of STEMI patients received primary PCI from 2006 to 2011, while the proportion treated with PHT declined from about 40% to 30% (data not shown). The one-year mortality rate among patients treated with PHT fell from 11 % in 2000-03 to 6 % in 2008-11 (not statistically significant), whilst the proportion who developed systolic heart failure (i.e. LVEF <40%) decreased significantly over time from 19 % in 2000-03 to 8 % in 2008-11. Maximum cTnT levels decreased significantly over time. Among the 355 patients with ACS, 56 % obtained successful ST-segment resolution (≥ 50 %), and 36 % obtained <50%

ST-segment resolution. One-year mortality was 4 % and 11 %, respectively. We lack information about ST-segment resolution in 30 patients (8 %). Based on our registry of invasive cardiology, 35 % of PHT-treated patients received rescue PCI during 2006-2011. Thirteen (3 %) of the 385 patients suffered acute OHCA with ventricular fibrillation. All of the 13 patients received successfully out-of-hospital resuscitation with a return of spontaneous circulation (ROSC) on hospital admission, and 12 of the 13 patients were discharged alive. Three of the patients given PHT (0.8 %) developed cardiogenic shock and died before reaching hospital. Ten patients (2.6 %) suffered a major bleeding: eight had gastrointestinal or groin bleedings after PCI, two required a transfusion of at least two units of blood. Two patients (0.5 %) suffered intracerebral hemorrhage.

5. Discussion – methodology

5.1 Study classifications in epidemiological and clinical research

Studies can be classified into descriptive and analytic studies. Descriptive studies are always observational studies and describe general disease characteristics related to person, place, and time. They include cross-sectional studies, and case series (3, 163). Analytic studies test a hypothesis about a causal relation between exposure and outcome. They can be observational, such as case-control and cohort studies, or controlled, such as the randomized controlled trial (RCT) (3). The results of RCTs are considered the highest level of evidence because randomization controls for prognostic factors between two comparison groups, thereby minimizing the role of confounding bias and optimizing the internal validity.

5.2 Study design in paper 1 and 2

The Tromsø Study is a prospective cohort study, as individuals are screened for risk factors prior to disease and followed up by repeated screenings. A cohort study tracks two or more groups forward from exposure to outcome. The temporal sequence between putative cause and outcome is usually clear: the exposed and unexposed can often be seen to be free of the outcome at the outset. All participants are followed up with regard to mortality and disease incidence. A cohort study is the best way to identify incidence and natural history of a disease. Research purposes are to study natural history of disease, measure incidence, and to link disease outcomes to possible disease causes, i.e. seek associations (3, 163).

5.3 Study design in paper 3

A (clinical) case-series is a study that follows a group of patients who have a known exposure, such as a similar diagnosis or who are undergoing the same procedure over a specific period of time. Case series may be consecutive (164) or non-consecutive (165), depending on whether all cases over a period were included, or only a selection. Research purposes in case-series are to study signs and symptoms, create disease definitions, surveillance of mortality/morbidity rates, and seek associations (3). Case series are often used to describe outcomes of novel treatments. The information gained can be used to generate hypotheses that lead to focused studies of a stronger design. They are also helpful in refining new techniques or treatment protocols before they are studied in more advanced trials (166). Distinguishing cohort studies from case series can be difficult. They share a main design feature of having a follow-up period examining the exposed individuals over time. The major difference between cohort studies and case series in many definitions is that cohort studies compare different groups (i.e., examine the association between exposure and outcome), while case series do not include a comparison group. (167).

5.4 Weaknesses of observational studies

Results of observational studies are susceptible to the effects of chance (random error), bias (systematic error) and confounding. They may produce spurious results, leading us to

conclude the existence of a valid statistical association when one does not exist (type 1 error) or alternatively the absence of an association when one is truly present (type 2 error) (3). Random errors give imprecise study results and can be minimized with large sample sizes. The relatively small number of study patients is therefore a weakness in paper 3. The role of chance can be assessed by performing appropriate statistical tests to produce a p-value and by calculation of confidence intervals. Statistical methods only assess the effect of sampling variation and cannot control for non-sampling errors such as confounding or bias in the design, conduct or analysis of a study. Systematic errors give inaccurate study results, a deviation of results from the truth, and increasing the sample size is not going to help. Types of bias can broadly be grouped into two categories: selection bias and information bias.

5.5 Selection bias

Selection bias occurs when there is a systematic difference in the characteristics between those who are selected for a study and those who are not (3). A selection bias comes from any error in selecting the study participants and/or from factors affecting the study participation. As a consequence, the relationship between exposure and disease differs between those included in the study and those potentially eligible for the study (including non-participants or non-responders).

Participation in the Tromsø Study is voluntarily, and although the general participation rate is high, there is a possibility for selection bias. Local restrictions given by the Norwegian Data Inspectorate preclude detailed analyses of mortality and morbidity according to attendance. Generally, the non-attendees in the Tromsø Study tended to be younger and had a higher

proportion of men and single (156). Furthermore, participants in cohort studies may be healthier than the general population (159). To explore this further, we will describe differences in risk factor values in the survey undertaken in 1994-95 between those who attend subsequent examinations (in 2000-01 and/or 2007-08) and those who did not attend (table 3).

Table 3 Risk factor levels in 1994-95 among subjects who were invited but did not attend later surveys and subjects who were invited and attended later surveys.

Survey conducted in 2000-01 or 2007-08	N	Age in years, mean	Male gender, %	Total cholesterol, mmol/l	HDL cholesterol, mmol/l	Systolic blood pressure, mmHg	BMI, kg/m ²	Daily smoking, %	Diabetes mellitus, %	Resting heart rate, beats/min	Physical active %
Invited, did not attend	2448	46.1	51	6.11	1.48	138	25.3	47	1,9	76	29
Invited, attended	12676	49.3	45	6.20	1.53	135	25.4	34	1,4	73	30

Non-attenders in later surveys were likely to be younger men with slightly higher risk profile than attenders in later surveys. Nevertheless, the main impression is that the difference is not substantial. We believe that participants in the Tromsø Study are representative of the source population and that our findings can be generalized to a Caucasian population.

Loss to follow-up (because of death, disability, relocation, or drop-out) can be a difficulty, particularly so with longitudinal studies that continue for decades. Differential losses to follow-up between those exposed and unexposed can bias results (163). However, loss to follow-up is not of a major concern in the Tromsø Study. The national 11-digit unique personal identification number facilitates complete follow-up by allowing linkage to disease registries, the cause of death register, and the Norwegian Patient Registry. The Population Register of Norway registers emigration from the municipality and date of death. The University Hospital of North Norway is the only hospital in Tromsø, admissions to other hospitals are unlikely because of long distances.

Case-series are susceptible to bias, particularly selection bias. Case-series draw their patients from a particular population (such as a hospital or clinic), which may not appropriately represent the wider population. However, a population case-series study, consisting of a complete set of cases in a defined population (or catchment area) and time, lays the foundation for description of disease by place, time, and characteristics of population (3). This is possible for rural areas with small populations and a single healthcare provider, as in our study. Furthermore, our study contains several key criteria that constitute a well-designed case series, which will help limit selection bias (166, 168). The study had clear objectives with a well-defined, a priori study protocol. The inclusion and exclusion criteria were explicitly stated, and there were no patients loss to follow-up. However, one weakness is that the list of cases may be incomplete, i.e. cases were not consecutively selected. We cannot preclude that some prehospital deaths are missing. Additionally, over time an increasing proportion of STEMI patients received primary PCI instead of PHT. The

PHT and primary PCI groups may differ in characteristics that affect the study outcome. The risk of selection bias is therefore present and requires caution in comparing between time periods.

5.6 Information bias

Information bias refers to bias arising from measurement error, i.e. when key study variables (exposure, health outcome, or confounders) are inaccurately measured or classified. This may mean that study participants are placed in the wrong exposure- or outcome category, leading to an incorrect estimate of the association between exposure and outcome (3, 169). Misclassification may be introduced by the observer (observer bias), by the study participant (responder bias) or by measurement tools such as questionnaires or instruments such as weighing scales or blood pressure cuffs (instrument bias). There are two types of misclassification – differential and non-differential.

Non-differential (random) misclassification occurs if there is equal misclassification of exposure between subjects that have or do not have the health outcome or if there is equal misclassification of the health outcome between exposed and unexposed subjects. Non-differential misclassification increases the similarity between the exposed and non-exposed groups, and may result in an underestimate (dilution) of the true strength of an association between exposure and disease, i.e. a “bias towards the null”. Differential (non-random) misclassification occurs when the variable misclassified is dependent on the outcome or the

exposure. This type of error is considered a more serious problem, as one of the groups is more often misclassified than the comparison group and this may introduce bias.

Differential misclassification may be introduced in a case control study as a result of recall bias or observer/interviewer bias. In cohort studies like the Tromsø Study there is little room for differential misclassification, as the relevant data on exposure(s) are collected at baseline (without knowledge on outcomes) using standardized methods.

Non-differential misclassification is more common in cohorts and may occur in this thesis due to incomplete medical records or questionnaires. Study participants may have difficulties to remember past exposure when completing questionnaires, or questions could be misunderstood or skipped. In addition, some of the participants will not know that they have the condition that is being requested. An example is diabetes mellitus, which is defined based on self reporting in the Tromsø Study. This may explain why the prevalence of diabetes mellitus type 2 is markedly reduced in the Tromsø Study compared with the general population (170). Another example of self-reporting bias is social desirability bias when participants answer in a way to portray themselves in a good light. It is important to use questionnaires that are constructed to maximize accuracy and completeness. The most precise and accurate measures of exposure and outcome will protect against random misclassification producing a type 2 error.

Classification of individuals (exposure or outcome status) can be affected by changes in diagnostic procedures. To control for information bias, it is important to implement standardized protocols for collecting data across groups. A limitation of the present studies

in paper 1 and 2 is the introduction of troponin as markers of myocardial injury, a marker not included in the MONICA criteria for validation and classification of MI events. This means that MI definition before and after the year 2000 differs somewhat. The true effect of changes in diagnostic sensitivity of biomarkers could not be fully quantified. However, the potential bias from this would be an overestimation of the incidence of NSTEMI in later years. The use of three different ICD classification systems during the 36-year period should not be a bias since the codes only have been used to collect possible cases. Accurate coding of cause of death may represent a challenge in individuals dying outside of hospitals. In our material, only 9 % of individuals with out-of-hospital SCDs underwent medical autopsy. As there have been no changes in registering causes of deaths during the study period it is likely that misclassification did not change over time, and therefore did not affect our trend analyses.

The term reliability refers to the precision and reproducibility of the data collected. There are several ways to enhance reliability: using clearly defined diagnostic criteria, standardizing the measurement methods, training and supervision of observers, calibrated equipment, repeating the measurement and using the mean of two or more readings (169). LVEF is one of the most commonly reported measures of LV systolic function. Prognosis and therapeutic decisions are often based on LVEF, which means the LVEF needs to be accurately measured. Many imaging modalities can measure LVEF (echocardiography, cineventriculography, magnetic resonance imaging [MRI], computed tomography [CT], multiple-gated acquisition[MUGA], and gated myocardial perfusion imaging with either single-photon emission computed tomography [SPECT] or positron emission tomography [PET]), and each

of these modalities is subject to measurement errors that can lead to the inaccurate calculation of LVEF. Currently, there is no universally accepted “gold standard” for measuring LVEF. With any method, the endocardial border needs to be accurately detected to ensure accurate LV cavity detection and LVEF calculation.

Echocardiography, used in paper 3, is the most frequently used imaging modality for the evaluation of LV volumes and function. The biplane method of disks (modified Simpson method) is a 2-dimensional echocardiographic technique requiring tracing the LV endocardial border in the apical 4- and 2-chamber views in both end-diastole and end-systole. This is the method recommended by the American Society of Echocardiography for measuring LVEF (171). LVEF measurements at UNN Tromsø was done primarily by the Simpson’s volumetric method whenever possible, or by 2-dimensional visual estimation. Visual assessment of the LVEF and segmental wall motion requires extensive skill and expertise of the reader and ultimately remains subjective (172). Additionally, 2-dimensional assessment of global LV volumes and EF with the biplane method of discs relies on geometric assumptions and is subject to plane positioning errors. More important, all these methods of LV assessment are known to have limited inter-observer and test–retest reliability (173-176). For an instrument such as 2-dimensional echocardiography to be useful in clinical practice, it needs to yield similar results when applied by different users and at different times. In our study, all measurements and analyses were performed by experienced physician echocardiographers, but without a standardized protocol for examination techniques and measurement procedures, and the interobserver variability was not determined.

5.7 Confounding

Confounding bias occurs in the presence of confounders, that is, factors that distort the true relationship of the study variable of interest by also being related to the outcome of interest (177, 178). In order for a variable to be considered as a confounder the variable must be independently associated with the outcome (i.e. be a risk factor), and the variable must be associated with the exposure under study in the source population, and finally, it should not lie on the causal pathway between exposure and disease. Confounding involves the possibility that an observed association is due, totally or in part, to the effects of differences between the study groups (other than the exposure under investigation) that could affect their risk of developing the outcome being studied. The consequence of confounding is that the estimated association is not the same as the true effect. The potential for confounding should be considered in the design and implementation of the study. Factors which might be associated with the outcome other than the putative risk factor/exposure need to be measured. To some extent, confounding can be accounted during analysis with stratification or mathematical modeling such as multiple logistic regression, assuming that such factors have been measured as part of the study. In our studies, we used regression models to limit possible confounding. Confounding bias is not present in case series for the simple reason that there is no control group (168). However, when analyzing time trends in observational studies, there is always a possibility that other external factors change over time and thereby confound the results. In paper 3, a healthier population joining the registry late might have resulted in better outcomes over time.

5.8 Validity

Validity is used in epidemiology to assess the degree to which the information collected accurately answers the research question; i.e., the extent to which the results are accurate and the extent to which the conclusions derived can be generalized (Zaccai). Internal validity refers to whether the results are representative for the population under study. Selection bias, information bias, uncontrolled confounding, or an unduly small study sample may impair internal validity. External validity is to what degree the results of a study are generalizable to a broader population beyond the study population. Internally validity must be established before one can consider whether the results are externally valid.

As most RCTs have strict criteria for participants included in the trial, the external validation is often questioned. In a cohort study with a large number of participants from the general population and minimal loss to follow up, like the Tromsø Study, there will be a high degree of generalization, increasing the external validity of the study. Case-series, as in paper 3, have apparently high external validity with no interference in treatment decision process and a wide range of patients. However, internal validity of case series studies is usually low, due to the lack of a comparison (control) group exposed to the same array of intervening variables. Conducting a case series prospectively or retrospectively makes a difference as to the extent of selection and measurement bias in the observations. A retrospective design may decrease the completeness of inclusion, data collection, and patient follow-up. Additionally, if the data are not measured in a standardized way, the measurement bias may increase.

5.9 Causality

Statistical associations do not necessarily imply causal associations (3). Spurious associations are the result of selection bias, information bias, and chance. By contrast, indirect associations (which stem from confounding) are real but not causal. Criteria which ought to be fulfilled before assuming causality were drawn up by Hill in 1965 (180). Briefly, these criteria require a consistent body of evidence to have accumulated. The most robust criterion is temporality: the cause must antedate the effect. Strong associations (relative risks more than 3), and evidence of a biological gradient (dose-response relation) supports a causal association too. A single epidemiological study is never sufficient to determine a causal relationship.

Case series have a descriptive study design. Unlike studies that use an analytic design (e.g. cohort studies or RCT), case series do not usually involve hypothesis testing to look for evidence of cause and effect. Case series reports on data from a subject group without a comparison (control) group. A control group is a group of patients who share all of the characteristics of the patients of the treatment group except that they do not receive the treatment. When a study lacks a control group, no causal inferences should be made about the relationship between the treatment and the outcomes, since it is impossible to determine whether the outcomes are attributable to the treatment effect or to other patient characteristics (168). The effects seen may be wholly or partly due to intervening effects such as the placebo effect, time effects, practice effects or the natural history effect. As a result, hypotheses can only be made about apparent relationships. However, a well-

designed case series can provide information that allows hypotheses to develop, leading to further advanced studies. Treatment safety and diagnostic accuracy are the principal outcomes that can be assessed fairly and reliably in a case series.

6. Discussion – results

6.1 Declining incidence trends in men, not in women in the time period 1974 -2004

Temporal trends in MI incidence between 1974 and 2004 differed markedly by sex and age. Among persons below 80 years of age, MI incidence decreased in men and increased in women, whereas in persons aged ≥ 80 years the trends remained stable in both genders. Comparisons with results from other studies should be done with caution due to possible methodological differences. However, our results are in line with findings in some other populations, both incidence studies (114-118) and prevalence reports (119, 181). A decrease in the incidence of CHD events is mainly considered to be due to favourable risk factor development in the population. The WHO MONICA Project has monitored coronary risk factors in 38 populations from 21 countries in four continents over a 10-year period (182). The study found that cholesterol levels, and the blood pressure levels and the treatment of elevated blood pressure improved in both genders (182). The prevalence of smoking declined among men, whereas no decline or even an increasing trend was observed in women (182, 183). The proportion of daily smokers among Norwegian men fell from 51% in 1974 to 27% in 2004, but fell less in women (from 32 to 25%) and even increased slightly in some age groups (from 22 to 25% in the age group 55–64 years and from 10 to 15% in age group 65–74 years) (figure 1) (184, 185). Data from the Tromsø Study surveys show similar trends (186). Exposure to tobacco smoke has been found to be a stronger risk factor for MI in women than in men (184, 187, 188). In one study, first MI occurred significantly earlier in female smokers compared to male smokers, implying that twice as many years were lost by female as by male smokers (184). Accordingly, we can hypothesize that the increased

smoking among young and middle-aged women may be a partial explanation for the present findings. Other possibilities include obesity and diabetes, which have increased in both genders, but diabetes is known to be a stronger risk factor for CHD in women than in men (189). The AHA and the ESC have focused special attention on women's cardiovascular disease (29, 190). The rationale is that the cardiovascular risk may have been underestimated in women, which in turn may have led to insufficient prevention and treatment efforts in women.

An obvious question is whether the differences in MI event trends between men and women reflect real occurrence of the disease or whether they reflect increased detection of events that formerly went unrecognized. ACS patients presenting without chest pain are frequently older and more likely to be women (191). However, recent surveys of the general public in the US indicate that the awareness of heart disease in women has increased in recent years (192, 193). It may be that women with chest discomfort during the follow-up period in our study have been more inclined to seek health advice, and that some of the increasing incidence is due to detection bias. Furthermore, the greater sensitivity of troponins may help in finding those acute MIs where the patient presents to the clinician with less obvious acute coronary symptoms. Women with ACS have a higher prevalence of unstable angina rather than MI, more frequent NSTEMI than STEMI, and a higher likelihood of having clinically insignificant disease on coronary angiography (194, 195). Previously studies have shown that the adoption of troponins has caused a greater increase in MI diagnoses among women than among men (60). It is, however, unlikely that the adoption of troponins could explain the gender by age group interaction observed in the present study. The trends did not differ whether or not cases meeting only troponin-based MI criteria were included in the analyses.

Furthermore, the trends were emerging before the introduction of troponin in 2000 (Figures 1 and 2 in paper 1). In our study, 5% of the cases with troponin measurements met only troponin-based criteria. This figure is smaller than in comparable studies (59), probably due to incomplete implementation of the new criteria in clinical practice (57, 64).

6.2 Outcome and treatment similar in men and women

In contrast to these opposing incidence trends, we found similar reductions among men and women in 28-day and 1-year case fatality and in the severity of first MI as evaluated by biomarkers and ECG. This is in line with results from other studies (59, 67, 117). Among all incident MIs, we found a 52 % decline in the age- and sex-adjusted odds of 1-year case fatality between 1994 and 2004. Furthermore, we found a substantial decline in the severity of hospitalized first MIs as evaluated by both biomarkers, ECG (Q-waves and ST-segment elevation), and 28-day case fatality. Notably, these changes were not related to the introduction of troponin measurements.

The consistency across MI severity indicators supports the robustness of the trends, and the hypothesis of declining MI severity over time. Possible explanations may be improved risk factors levels, more sensitive biomarker diagnostics, and advances in evidence-based treatments (increased use of aspirin, statins, b-blockers and revascularization). It is likely that the decline in MI severity is a major determinant of the decline in case fatality in the Tromsø population. A weakness in our study is that we did not assess time trends in the

delay between the onset of symptoms and hospitalization, which may confound any association between calendar year and MI severity. However, time to admission did not change over time in two comparable studies (59, 67). Case fatality has been reported to be higher among women compared with men, possibly due to differences in the level of acute coronary care (196). However, we found no significant gender differences in MI severity or case fatality and no gender differences in the use of invasive revascularization or medications.

6.3 Declines in out-of-hospital sudden death and STEMI

We found that that age- and sex-adjusted incidence of total MI decreased by 3% annually over a 15 years of follow-up between 1995 and 2010). The decrease was driven by a 50% reduction in severe MIs, i.e. SCDs outside hospitals and hospitalized STEMI infarction. Substantial reductions in serum cholesterol accounted for approximately one-third of the event decline, but decreases in smoking, blood pressure, and heart rate and increased physical activity all contributed. Overall, risk factors accounted for 66% of the decline in incidence of hospitalized and nonhospitalized fatal and nonfatal MI. Interestingly, increases in body mass index and diabetes mellitus were associated with modest increases in disease outcomes. This study extends results of previous studies that found modifiable risk factors to account for most cases of hospitalized, nonfatal MI (25).

The study demonstrates that primary prevention by modification of risk factors by means of a healthy lifestyle or medication will influence both incident CHD and case fatality in populations, shown by the association between coronary risk factors and out-of-hospital sudden deaths. Thus, sudden death is a preventable condition (20, 197, 198). Studies have shown that the majority of the SCD victims in the community had severe subclinical CHD, and that traditional coronary risk factors were prevalent and under-treated (20). In our study, higher resting heart rate was more strongly associated with out-of-hospital sudden death than with STEMI or non-STEMI (Table 2 in paper 2). Higher heart rates are associated with myocardial ischemia, ventricular arrhythmias, and coronary atherosclerosis (199-201). Correspondingly, we found that physical activity, which lowers resting heart rate, was associated with a lower risk of out-of-hospital sudden death and accounted for 9% of the decline in total CHD.

We found that cardiovascular risk factors had different impacts on subtypes of CHD, suggesting that the spectrum of CHD manifestations among populations and over time may differ, depending on the relative prevalence of the risk factors. Our findings suggest that reduced prevalences of hypercholesterolemia and smoking are major driving forces for the decline in the incidence of STEMI, indicating that primary prevention efforts result in fewer severe events (59, 67). In line with this, others have found that cholesterol is associated with rupture of vulnerable plaques and that smoking is associated with coronary thrombosis (197). In a large survey of patients with ACS from 25 countries in Europe and the Mediterranean basin, it was found that smoking was related to patients presenting with STEMI (202). The use of certain cardioprotective medications (e.g., statins, β -blockers, and

acetylsalicylic acid) has increased over time, and these agents may have beneficial effects beyond their effect on risk factors and may contribute to a lower severity of subsequent cardiac events (203-205). The prevalence of self-reported angina pectoris fell by 29% (Table 3 in paper 2), suggesting that risk factor changes led to the less coronary atherosclerosis.

How quickly might population health benefits follow improvements in population risk factor levels? The analysis was based on the assumption that the effects of changes in risk factors on CHD outcomes occurred within the time between consecutive surveys (≈ 6 years) or between the last survey and 2010 (≈ 3 years). This might underestimate the effects of a risk factor change if a lag time of >3 to 5 years is present before the benefits of a risk factor change are realized. However, extensive empirical and trial evidence shows that substantial reductions in mortality can occur within months of decreases in smoking, and within 1–3 years of dietary changes (206-209). This reduction applies to both individuals and to entire populations.

The substantial decline in CHD mortality was driven by significant reductions in the incidence of out-of-hospital SCD and hospitalized STEMI and by a significant reduction in case fatality among hospitalized patients. The decline in event rates and the decline in case fatality each explained 50% of the decline in CHD mortality. We observed that three out of five fatalities represented out-of-hospital deaths. In line with others, we found that changes in the rates of out-of-hospital SCD had a stronger impact on CHD mortality trends than changes in mortality of hospitalized patients (105, 210). In contrast, a study from Sweden based on administrative registers reported a faster decline in in-hospital than in out-of-hospital mortality rates (11).

Many fatal events still occur out of the hospital in spite of the improvement in CHD mortality and advances in CHD medical treatment, prevention, and emergency transport systems (15, 210, 211). It is therefore of concern that the time from onset of chest pain to arrival at the hospital has not improved despite community education efforts (212). To achieve further reduction in CHD-related case fatality, primary prevention is increasingly more important, as are efforts to convince individuals to seek hospital treatment as soon as symptoms of a major coronary event occur.

The decline in out-of-hospital and hospitalized MI incidence rates is consistent with data from recent international studies (11, 92, 102, 213). In Olmsted County, MN, between 1995 and 2012, the population rate of MI declined 3.3% per year, with the greatest declines occurring for prehospital fatal MI (213). Both hospitalized case-fatality and out-of-hospital mortality decreased over time, as reported in other studies (11, 102, 104, 105). Sulo et al published in 2013 the first study to report trends in MI incidence for the whole Norwegian population, using data from all somatic hospitals in the country, as well as from the Norwegian Cause of Death Registry. They found that MI incidence rates declined during 2001–2009, a decline that was due to reductions in rates of out-of-hospital deaths and hospitalizations in individuals 45 years or older (97). The patient administrative systems in Norway do not include information on MI subtype, so they were not able to examine whether the trends observed apply to both STEMI and NSTEMI. In line with other studies we found a declining percentage of MI cases with ST-segment elevation (59, 92, 96). In an analysis in the northern California, the percentage of MI cases with ST-segment elevation decreased from 47 % to 23 % between 1999 and 2008 (92). The corresponding figure from

Sweden is a decline from 45% in 1995 to 27% in 2008 (84). As observed by others, we found an increasing incidence of NSTEMI in the first part of the study period (52, 92, 96), likely reflecting the use of more sensitive biomarkers that detect smaller myocardial necrosis. This is supported by declining peak CK levels among NSTEMI patients, whereas the levels were stable in STEMI patients. We believe that the decline in STEMI is real and that the initial changes in NSTEMI reflect increased diagnostic sensitivity. Reductions in case fatality rates for hospitalized MI are due, at least partly, to a decrease in the incidence of STEMI, a lower rate of death after NSTEMI, but also to the increasing detection of less severe MIs with troponin testing. Mortality at 28 days and 1 year after hospitalization for a first AMI declined in Norway between 2001 and 2009 in both men and women and in all age groups (214).

6.4 Implementation and results following prehospital thrombolytic therapy

An important finding of this study is that ambulance clinicians with the support of GPs and hospital cardiologists can safely and effectively perform PHT. Next, the study shows that the implementation of a decentralized PHT-system, combined with improved availability of 7/24 invasive diagnosis and treatment-services, was gradual. The third important finding is that the adoption of evidence-based and guideline-recommended treatments was associated with significant reductions in time delays and earlier reperfusion therapy, and this was associated with a decline in left ventricular systolic heart failure visualized by echocardiography. This observation was supported by a significant decrease in peak cTnT levels over time. It has been found that cTnT-levels at a single point on any of the first 4 days or using the peak value correlates with infarct size determined by contrast-enhanced

magnetic resonance imaging (69). We routinely applied AED-defibrillation pads to the chest pain patients while administering MONA to enable the earliest possible defibrillation of any VF or pulseless ventricular tachycardia during diagnostics and thrombolytic treatment. Like others, we report an excellent outcome in STEMI patients suffering OHCA (215).

The percentage who received PHT within 2 hours increased by 85 % ($p=0.003$) between 2000-2003 and 2008-2011, to a total of 40 % in 2008-2011. Thrombolytic therapy has best effect if given as soon as possible and within 2 hours after pain onset (124, 129, 130). Early administration of PHT has been reported to be associated with improved 1-year survival compared with primary PCI (2.8 % versus 6.9 %, respectively; $p=0.021$) (132). In our study, one-year mortality for patients with ACS was 2.7 % if PHT was given within 2 hours, but increased significantly to 10.4 % if given later ($p = 0.04$). The “system delay” is the delay between FMC and reperfusion therapy, and it is more readily modifiable by organizational measures than patient delay. It is an indicator of quality of care and a predictor of outcomes (216). If the reperfusion therapy is thrombolysis, the goal is to reduce this delay (FMC to needle) to ≤ 30 min (8). In our study, the median time from first prehospital ECG (i.e. FMC) to start PHT was 36 minutes, and did not improve over time. It is important continuously to trim and maintain the system and to detect and remove the “time thieves”. The ECG transmission requires flawless technology and immediately available hospital physicians to confirm the STEMI diagnosis and decide on PHT without avoidable delays.

The use of coronary angiography, PCI and CABG increased over time. The proportion of patients who had coronary angiography or PCI within 24 hours of FMC increased from 56%

to 95% ($p < 0.001$). The pharmacoinvasive strategy combining PHT and rapid transfer to planned PCI within 3-24 hours after ictus in hemodynamically stable patients and rescue PCI for failed thrombolysis, is an efficient reperfusion strategy for STEMI patients (133, 134). Randomized trials comparing PHT with primary PCI in patients who present early show no statistical difference in 30-day mortality or re-infarction (124, 217). Recently, the STREAM study also showed that the major cardiac events at 30 days following a pharmacoinvasive strategy in patients with FMC within 3 hours of symptom onset compared favorably with those of primary PCI performed beyond 60 minutes of diagnosis (128). The Norwegian NORDISTEMI-study suggests that an early invasive strategy may be the preferred option in patients receiving thrombolytic therapy, also in areas with long transfer distances (218).

Ten patients (2.6 %) suffered a major bleeding, two patients (0.5 %) had intracerebral hemorrhage). In the latest trials, intracranial bleeding occurred in 0.9–1.0% of the total population studied (128). The percentage of inappropriate PHT-treatment dropped significantly during the study period from 13.6 % to 2.2 % ($p = 0.002$), probably reflecting system maturation. The improved heart function and 1-year mortality may reflect the more widespread use of therapies proven in trials to lower the risk of complications and mortality. Analysis of data from the GRACE multinational observational cohort study of patients with ACS found evidence of an increased use of pharmacological (including β -blockers, statins, ACE inhibitors, and P2Y12 inhibitors) and interventional treatments over time. These practice changes were accompanied by significant decreases in the rates of in-hospital death, cardiogenic shock, recurrent MI, and heart failure among patients presenting with STEMI (86). In paper 2 we showed that revascularization and the proportion of STEMI-

patients receiving β -blockers, acetylsalicylic acid, and statins at discharge increased over time.

From 2000 to 2011, the post-MI systolic heart failure and 1-year mortality have been halved with an absolute reduction in systolic heart failure of almost 11 %. It should be noted, however, that this is an observational study and despite adjustments in the statistical models, no causality can be proven concerning the effect of changes of the treatment strategies. When analyzing time trends in observational studies, there is always a possibility that other external factors change over time and thereby confound the results. The study population might have included fewer high-risk patients at the end of the study. A similar trend has been seen in other studies and may be explained by improved primary and secondary prevention strategies (59, 205). Another explanation may be that an increasing proportion of STEMI patients over time received primary PCI instead of PHT. This is most likely linked to the implementation of evidence-based medical guidelines and an increase in the availability of coronary angiography and PCI. However, this treatment shift could affect the composition of the PHT population. Primary PCI may be a preferred reperfusion strategy for STEMI patients with heart failure, long duration of pain, and uncertain STEMI diagnosis. Thus, there is a risk of selection bias when comparing time periods. The observed trends in clinical outcomes and survival may be a combination of the fact that PHT really was given faster, that PHT treated patients received more and timely invasive investigation and treatment (pharmacoinvasive strategy), and that the proportion of primary PCI increased. Furthermore, time savings were estimated without a PCI comparison group for determining actual time savings. Finally, this registry include only patients entering the hospital, patients

not admitted were not included. Patients' dying before reaching the hospital might accordingly have influenced the outcome in the hospitalized patients.

7. Conclusions and future perspectives

In paper 1, we showed for the first time in Norway (157) that a substantial part of the decline in CHD mortality in the young and middle-aged population was due to a decreased incidence of the disease. The study indicates that the population burden of CHD may be shifting towards women and elderly patients, suggesting that preventive gains have not penetrated equally throughout the population. The severity and case fatality of the disease, however, was declining in all groups.

In paper 2, we found that age- and sex-adjusted incidence of total CHD decreased by 3% annually over 15 years of follow-up. The decrease was found primarily in reductions in out-of-hospital SCD and hospitalized severe myocardial infarctions (STEMI). Reductions in serum cholesterol accounted for approximately one-third of the event decline, and decreases in smoking, blood pressure, and heart rate and increased physical activity also contributed. Increases in body mass index and diabetes mellitus were associated with modest increases in disease outcomes. Overall, risk factors accounted for 66% of the decline in incidence. Furthermore, the decline in event rates and the decline in case fatality each explained roughly 50% of the decline in CHD mortality. This was partly explained by less severe disease in those afflicted, but also by a major improvement in treatment.

In paper 3, we showed that ambulance clinicians with the support of GPs and hospital cardiologists could safely and effectively perform PHT. The implementation of a decentralized PHT-system was associated with significant reduction in time delays of

reperfusion therapy, and reduction in post-infarct systolic heart failure, and high survival rates among STEMI-patients suffering OHCA.

The Tromsø Study showed declining trends in CHD incidence and case fatality over 35 years.

To our knowledge, this is the longest population-based study published relying on individual person data and standardized data collection procedures. The combination of lower incidence and higher survival rate translates into a substantial improvement in mortality.

Our study of MI incidence highlights the role of widespread prevention in contributing to this decline, because improvements in risk factors play a crucial role in the trends. This finding does not negate the effect of acute care and secondary prevention, both of which play important roles. The observed reduction in case fatality, is assumed to be attributed to closer adherence to guideline-based therapy. Continued efforts aimed at improving the translation of evidence-based interventions into routine practice are essential.

We report changing secular trends in the relative proportion of STEMI and NSTEMI. If confirmed, this may have important implications for the ways that community and health care system resources are organized in the future, because current guidelines have extremely different recommendations for the short-term management of these two entities. It would be of interest to follow trends in incidence and case fatality further on, especially for STEMI. Recent National statistics have shown a continuing decline in CHD mortality. Can this partly be explained by ongoing declines in incidence and case fatality for STEMI?

The substantial decline in out-of-hospital SCD rates has had a major impact on the favorable changes observed for CHD mortality. However, most CHD deaths still occur outside the

hospital. More effective prevention strategies and greater focus on information about the importance of seeking medical assistance once coronary symptoms develop will help to reduce the burden of out-of-hospital SCD.

Despite progress in the last few decades in the form of falling CHD incidence and mortality rates, MI will likely continue to be a major public health problem both in terms of health and economic costs (219). This is due to an ageing population, and increasing prevalence due, in part, to decreased mortality, and consequently high numbers of prescriptions for secondary prevention. In addition, there is reason to worry about the steady increase in the proportion with overweight and diabetes. Measures that can counteract the increase in weight and evolution of diabetes will be important in the further preventive work. At the same time, the disease panorama is changing: we must expect an increase in the morbidity of degenerative heart disease such as heart failure and atrial fibrillation. These conditions show a clear relationship with age, and with undergone MI. We must therefore continue to focus on both prevention and treatment of MI.

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