UIT THE ARCTIC UNIVERSITY OF NORWAY

Faculty of Health Sciences, Department of Community Medicine

The epidemiology of myocardial infarction

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

Jan Mannsverk

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Acknowledgements

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Contents

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, Bønaa 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, Bønaa, 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 it 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).

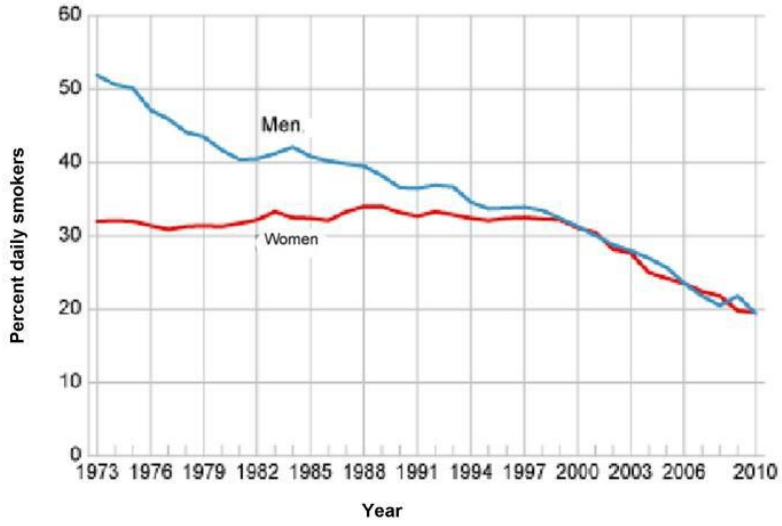
Approximately 20% of CHD patients have sudden cardiac death as the first clinical manifestation (14, 21).

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).

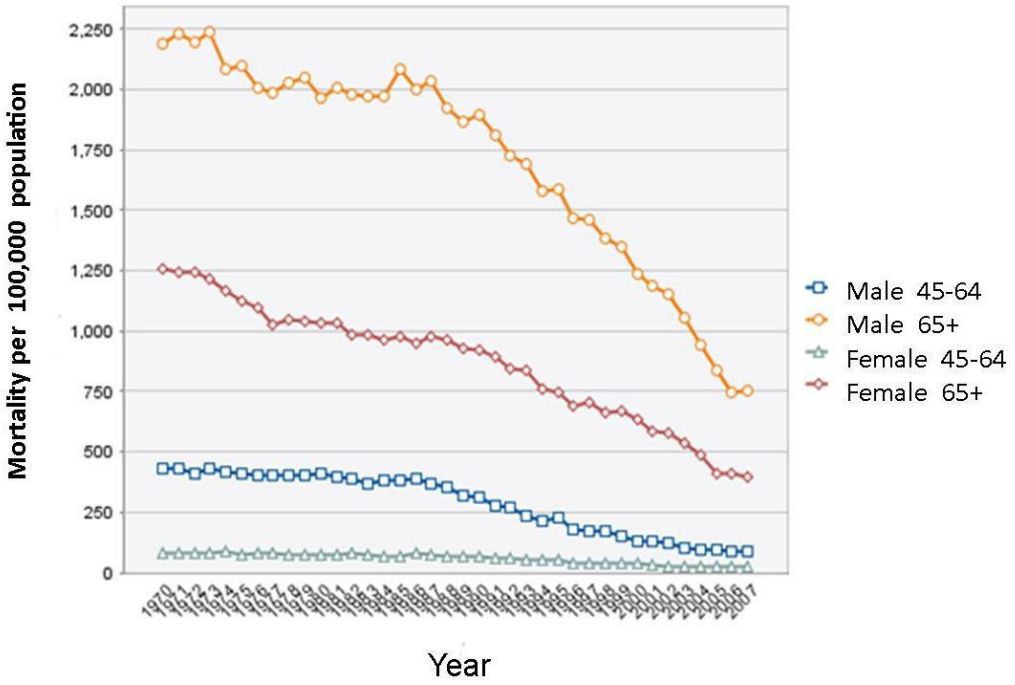
1.3 Time trends and burden of coronary heart disease mortality

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 (≈7%) of ACS presentations. Thus, the hospitalized ACS spectrum is now dominated by MI, composed of STEMI (≈1/3 of MIs) and NSTEMI (≈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 ≥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 31th 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 km^2) 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 βs 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 25^{th}-75^{th} 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 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/m²	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 where 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 selfreported 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.

8. References

1. U.S. National library of medicine and the National Institutes of Health. Medical subject headings. https://meshb.nlm.nih.gov/search

2. Glossary of epidemiology terms. Columbia University. http://www.cs.columbia.edu/digigov/LEXING/CDCEPI/gloss.html

3. Bhopal R. Concepts of Epidemiology. New York: Oxford University Press, 2002.

4. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119-177.

5. Crea F, Libby P. Acute coronary syndromes: the way forward from mechanisms to precision treatment. Circulation. 2017; 136: 1155–1166.

6. McManus DD, Gore J, Yarzebski J et al. Recent trends in the incidence, treatment, and outccomes of patients with STEMI and NSTEMI. Am J Med 2011; 124: 40-47.

7. Moon JC, De Arenaza DP, Elkington AG et al. The pathologic basis of Q-wave and non-Q-wave myocardial infarction: a cardiovascular magnetic resonance study. J Am Coll Cardiol. 2004; 44: 554–560.

8. Steg PG, James SK, Atar D et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33: 2569–2619.

9. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37: 267-315.

10. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019; 40: 87-165.

11. Dudas K, Lappas G, Stewart S et al. Trends in out-of-hospital deaths due to coronary heart disease in Sweden (1991 to 2006). Circulation 2011; 123: 46–52.

12. Chambless L, Keil U, Dobson A et al. Population versus clinical view of case fatality from acute coronary heart disease: results from the WHO MONICA Project 1985-1990. Circulation 1997; 96: 3849–59.

13. Gillum RF. Sudden coronary death in the United States: 1980-1985. Circulation 1989; 79: 756-65.

14. Monatagnana M, Lippi G, Franchini M et al. Sudden cardiac death: prevalence, pathogenesis, and prevention. Ann Med 2008; 40: 360-75.

15. Zheng ZJ, Croft JB, Giles WH et al. Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001; 104: 2158-63.

16. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies. Circulation 2003; 108: 2543–9.

17. Virmani R, Roberts WC. Sudden cardiac death. Hum Pathol 1987; 18(5): 485–92.

18. Myerburg R, Castellanos A. Cardiac arrest and sudden cardiac death. In: Braunwald E, editor. A Textbook of Cardiovascular Medicine. Philadelphia, PA: Saunders, 1996:742–79.

19. Kannel WB, Thomas HE Jr. Sudden coronary death: the Framingham Study. Ann N Y Acad Sci 1982; 382: 3-21.

20. Adabag AS, Peterson G, Apple FS et al. Etiology of sudden death in the community: results of anatomical, metabolic, and genetic evaluation. Am Heart J. 2010; 159: 33–39.

21. Priori SG, Aliot E, Blomstrom-Lundqvist C et al. Update of the guidelines on sudden cardiac death of the European Society of Cardiology. Eur Heart J. 2003; 24: 13-5.

22. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288: 2981–2997.

23. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 1999; 282:2340–2346.

24. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. N Engl J Med 2012; 366: 321-9.

25. Yusuf S, Hawken S, Ounpuu S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case– control study. Lancet 2004; 364: 937–52.

26. Gregg EW, Cheng YJ, Cadwell BL, et al. Secular trends in cardiovascular disease risk factors according to body mass index in US adults. JAMA. 2005; 293: 1868-1874.

27. Cowie CC, Rust KF, Ford ES et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. Diabetes Care. 2009; 32: 287–294.

28. Women and smoking: a report of the surgeon general. Executive summary. MMRW Recomm Rep 2002; 51: 1–30.

29. Stramba-Badiale M, Fox KM, Priori SG et al. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. Eur Heart J 2006; 27: 994–1005.

30. Anand SS, Islam S, Rosengren A et al. on behalf of the INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. European Heart Journal. 2008; 29: 932–940.

31. Albrektsen, G., Heuch, I., Lochen, M.L. et al. Lifelong gender gap in risk of incident myocardial infarction: the Tromso study. JAMA Intern. Med. 2016; 176: 1673–1679.

32. Jousilahti P, Vartiainen E, Tuomilehto J et al. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. Circulation 1999; 99: 1165–1172.

33. Roger VL. Epidemiology of myocardial infarction. Med Clin North Am 2007; 91: 537-552.

34. Nichols M, Townsend N, Scarborough P et al. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J. 2014; 35: 2950-2959.

35. Benjamin EJ, Blaha MJ, Chiuve SE et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017; 135: 146-603.

36. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 385: 117-171.

37. Roth GA, Forouzanfar MH, Moran AE et al. Demographic and Epidemiologic Drivers of Global Cardiovascular Mortality. N Engl J Med 2015; 372: 1333-1341.

38. Murray CJ, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. Lancet 2015; 386: 2145-91.

39. Mendis S, Thygesen K, Kuulasmaa K et al and Writing group on behalf of the participating experts of the WHO consultation for revision of WHO definition of myocardial infarction. World Health Organization definition of myocardial infarction: 2008–09 revision. Int J Epidemiol 2011; 40: 139–146.

40. World Health Organization. Hypertension and coronary heart disease: Classification and criteria for epidemiological studies. First report of the expert committee on cardiovascular diseases and hypertension. World Health Organization technical report series, No. 168. Geneva, 1959. 1959.

41. Weinstein BJ, Epstein FH; Working Subcommittee on Criteria and Methods, Committee on Epidemiological Studies, American Heart Association. Comparability of criteria and methods in the epidemiology of cardiovascular disease: report of a survey. Circulation. 1964; 30: 643–653.

42. World Health Organization Regional Office for Europe, Working Group on the Establishment of Ischaemic Heart Disease Registers. Report of the Fifth Working Group, Copenhagen, 26-29 April 1971. Copenhagen, Denmark: Regional Office for Europe, World Health Organization; 1971. Report No. Eur 8201(5). 1971

43. Section 8: Two-year incidence by exam interval by age and sex at exam 1. In: Kannel WB, Gordon T, eds. The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease. Bethesda, Md: US National Heart Institute; 1968. 1968.

44. Rapaport E. Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. Circulation 1979; 59: 607–9.

45. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P et al for WHO MONICA Project. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates and case fatality in 38 populations from 21 countries in 4 continents. Circulation 1994; 90: 583-612.

46. Tunstall-Pedoe H, Kuulasmaa K, Mähönen M et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet 1999; 353: 1547–1557.

47. Alpert JS, Thygesen K, Antman E et al. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol. 2000; 36(3): 959.

48. Richards AM, Lainchbury JG, Nicholls MG. Unsatisfactory redefinition of myocardial infarction. Lancet 2001; 357: 1635–6.

49. Tunstall-Pedoe H. Redefinition of myocardial infarction by a consensus dissenter. J Am Coll Cardiol 2001; 37: 1472-4.

50. French JK, White HD. Clinical implications of the new definition of myocardial infarction. Heart 2004; 90: 99–106.

51. Wong CK, White HD. Myocardial infarction: why can't we get the diagnosis right? Eur Heart J 2003; 24: 1177–9.

52. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. J Am Coll Cardiol 2007; 50: 2173–95.

53. Thygesen K, Alpert JS, Jaffe AS et al Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, ESC Committee for Practice Guidelines. Third universal definition of myocardial infarction. Eur Heart J 2012; 33: 2551–2567.

54. Yeh RW, Go AS, MD Rethinking the Epidemiology of Acute Myocardial Infarction Challenges and Opportunities. Arch Intern Med. 2010; 170(9): 759-764

55. Parikh NI, Gona P, Larson MG, et al. Long-term trends in myocardial infarction incidence and case fatality in the National Heart, Lung, and Blood Institute's Framingham Heart Study. Circulation. 2009; 119: 1203-1210.

56. White HD. Evolution of the definition of myocardial infarction: what are the implications of a new universal definition? Heart 2008; 94: 679-684.

57. Roger VL, Killian JM, Weston SA, et al. Redefinition of myocardial infarction: prospective evaluation in the community. Circulation 2006; 114: 790–7.

58. Anderson JL, Morrow DA. Acute myocardial infarction. N Engl J Med 2017; 376: 2053-64.

59. Roger VL, Weston SA, Gerber Y et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. Circulation. 2010; 121: 863–869.

60. Salomaa V, Ketonen M, Koukkunen H, et al. The effect of correcting for troponins on trends in coronary heart disease events in Finland during 1993–2002: the FINAMI study. Eur Heart J 2006; 27: 2394–9.

61. Pell JP, Simpson E, Rodger JC, et al. Impact of changing diagnostic criteria on incidence, management, and outcome of acute myocardial infarction: retrospective cohort study. BMJ 2003; 326: 134–5.

62. Meier MA, Al-Badr WH, Cooper JV et al. The new definition of myocardial infarction: diagnostic and prognostic implications in patients with acute coronary syndromes. Arch Intern Med 2002; 162: 1585–1589.

63. Salomaa V, Koukkunen H, Ketonen M, et al. A new definition for myocardial infarction: what difference does it make? Eur Heart J 2005; 26: 1719–1725.

64. Pell ACH, Pell JP. Was it a heart attack? Variations in access to and interpretation of troponin assays are wide [letter]. BMJ 2002; 324: 1216.

65. Willingham SAM, Kilpatrick ES. Evidence of gender bias when applying the new diagnostic criteria for myocardial infarction. Heart 2005; 91: 237–238.

66. Salomaa V, Rosamond W and Mähönen M. Decreasing mortality from acute myocardial infarction: effect of incidence and prognosis. J Cardiovasc Risk 1999; 6: 69–75.

67. Myerson M, Coady S, Taylor H et al, for the ARIC Investigators. Declining severity of myocardial infarction 1987 to 2002: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2009; 119: 503–514.

68. Goldberg RJ. Monitoring trends in severity of acute myocardial infarction: challenges for the next millennium. Am Heart J 2000; 139: 767–770.

69. Giannitsis E, Steen H, Kurz K et al. Cardiac magnetic resonance imaging study for quantification of infarct size comparing directly serial versus single time-point measurements of cardiac troponin T, J Am Coll Cardiol 2008; 51: 307-314.

70. Katus HA, Remppis A, Scheffold TH, et al. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. Am J Cardiol 1991; 67: 1360–7.

71. Critchley JA, Capewell S. Why model coronary heart disease? Eur Heart J 2002; 23: 110–116.

72. Capewell S, Morrison CE, McMurray JJ. Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. Heart 1999; 81: 380–386.

73. O'Flaherty M, Buchan I, Capewell S. Contributions of treatment and lifestyle to declining CVD mortality: why have CVD mortality rates declined so much since the 1960s? Heart. 2013; 99: 159–162.

74. Laatikainen T, Critchley J, Vartiainen E et al. Explaining the decline in coronary heart disease mortality in Finland between 1982 and 1997. Am J Epidemiol 2005; 162: 764–773.

75. Hotchkiss JW, Davies CA, Dundas R et al. Explaining trends in Scottish coronary heart disease mortality between 2000 and 2010 using IMPACTSEC model: retrospective analysis using routine data. BMJ. 2014; 348: g1088.

76. Capewell S, Beaglehole R, Seddon M et al. Explanation for the decline in coronary heart disease mortality rates in Auckland, New Zealand, between 1982 and 1993. Circulation 2000; 102: 1511–1516.

77. Aspelund T, Gudnason V, Magnusdottir BT, et al. Analyzing the large decline in coronary heart disease mortality in the Icelandic population aged 25–74 between the years 1981 and 2006. PLoS ONE 2010;5:e13957.

78. Ford ES, Ajani UA, Croft JB et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med 2007; 356: 2388–2398.

79. Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. Circulation 2004; 109: 1101–1107.

80. Bennett K, Kabir Z, Unal B et al. Explaining the recent decrease in coronary heart disease mortality rates in Ireland, 1985–2000. J Epidemiol Commun Health 2006; 60: 322–327.

81. Björck L, Rosengren A, Bennett K et al. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. Eur Heart J. 2009; 30: 1046-56.

82. Hu FB, Stampfer MJ, Manson JE et al. Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women. N Engl J Med. 2000; 343: 530–537.

83. Hardoon SL, Whincup PH, Lennon LT, et al. How much of the recent decline in the incidence of myocardial infarction in British men can be explained by changes in cardiovascular risk factors? Evidence from a prospective population-based study. Circulation 2008; 117: 598-604.

84. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart. 2010; 96: 1617-1621.

85. Peterson ED, Shah BR, Parsons L, et al. Trends in quality of care for patients with acute myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J. 2008; 156: 1045-1055.

86. Fox KA, Steg PG, Eagle KA et al; GRACE Investigators. Decline in rates of death and heart failure in acute coronary syndromes, 1999–2006. JAMA. 2007; 297: 1892–1900.

87. Mehta RH, RoeMT, Chen AY, et al. Recent trends in the care of patients with non-ST–segment elevation acute coronary syndromes: insights from the CRUSADE initiative. Arch Intern Med. 2006; 166(18): 2027-2034.

88. Ford ES, Roger VL, Dunlay SM et al. Challenges of ascertaining national trends in the incidence of coronary heart disease in the United States. J Am Heart Assoc. 2014; 3(6): e001097.

89. Rosamond WD, Chambless LE, Folsom AR et al Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. N Engl J Med. 1998; 339: 861– 867.

90. McGovern PG, Pankow JS, Shahar E et al. Recent trends in acute coronary heart disease: mortality, morbidity, medical care, and risk factors. N Engl J Med. 1996; 334: 884–890.

91. Chen J, Normand SL, Wang Y, et al. Recent declines in hospitalizations for acute myocardial infarction for Medicare fee-for-service beneficiaries: progress and continuing challenges. Circulation 2010; 121: 1322–1328.

92. Yeh RW, Sidney S, Chandra M et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010; 362: 2155–2165.

93. Rosamond WD, Chambless LE, Heiss G, et al. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987-2008. Circulation. 2012; 125(15): 1848-1857.

94. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics — 2016 update: a report from the American Heart Association. Circulation 2016; 133: e38-e360.

95. Cobb LA, Fahrenbruch CE, Olsufka M et al. Changing incidence of out-of-hospital ventricular fibrillation, 1980–2000. JAMA. 2002; 288: 3008–3013.

96. McManus DD, Piacentine SM, Lessard D, et al. Thirty-year (1975 to 2005) trends in the incidence rates, clinical features, treatment practices, and short-term outcomes of patients <55 years of age hospitalized with an initial acute myocardial infarction. Am J Cardiol 2011; 108: 477-82.

97. Sulo G, Igland J, Nygard O et al. Favourable trends in incidence of AMI in Norway during 2001-2009 do not include younger adults: a CVDNOR project. Eur J Prev Cardiol 2014; 21: 1358-64.

98. Yang D, Dzayee DA, Beiki O, et al. Incidence and case fatality after day 28 of first time myocardial infarction in Sweden 1987–2008. Eur J Prev Cardiol 2012; 19: 1304–1315.

99. Pajunen P, Paakkonen R, Juolevi A, et al. Trends in fatal and non-fatal coronary heart disease events in Finland during 1991–2001. Scand Cardiovasc J 2004; 38: 340–344.

100. Fischer T, Lundbye-Christensen S, Johnsen SP, et al. Secular trends and seasonality in first-time hospitalization for acute myocardial infarction – a Danish population-based study. Int J Cardiol 2004; 97: 425–431.

101. Schmidt M, Jacobsen JB, Lash TL et al. 25 year trends in first time hospitalization for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. BMJ 2012; 344: e356.

102. Koopman C, Bots ML, van Oeffelen AA, et al. Population trends and inequalities in incidence and short-term outcome of acute myocardial infarction between 1998 and 2007. Int J Cardiol 2013; 168: 993-8.

103. Davies AR, Grundy E, Nitsch D et al. Constituent country inequalities in myocardial infarction incidence and case fatality in men and women in the United Kingdom, 1996-2005. J Public Health (Oxf) 2011; 33: 131-8.

104. Dudas K, Lappas G, Rosengren A. Long-term prognosis after hospital admission for acute myocardial infarction from 1987 to 2006. Int J Cardiol. 2012; 155: 400-5.

105. Fornari C, Cesana GC, Chambless LE, et al. Time trends of myocardial infarction 28-day case-fatality in the 1990s: is there a contribution from different changes among socioeconomic classes? J Epidemiol Community Health 2008; 62: 593-8.

106. Langorgen J, Igland J, Vollset SE et al. Short-term and long-term case fatality in 11 878 patients hospitalized with a first acute myocardial infarction, 1979-2001: the Western Norway cardiovascular registry. Eur J Cardiovasc Prev Rehabil 2009; 16: 621–7.

107. Oyen N, Nygard O, Igland J, et al. Hospital admission rates for cardiovascular diseases in Western Norway, 1992–2001. Tidsskr Nor Laegeforen 2008; 128: 17–23.

108. Roger VL, Weston SA, Killian JM, et al. Time trends in the prevalence of atherosclerosis: a population-based autopsy study. Am J Med 2001; 110: 267-73.

109. Webber BJ, Seguin PG, Burnett DG, et al. Prevalence of and risk factors for autopsy-determined atherosclerosis among US service members, 2001-2011. JAMA 2012;308:2577-83.

110. Jennings SM, Bennett K, Lonergan M et al. Trends in hospitalisation for acute myocardial infarction in Ireland, 1997-2008. Heart 2012; 98: 1285-1289.

111. Maier B, Thimme W, Schoeller R et al. Improved therapy and outcome for patients with acute myocardial infarction – Data from the Berlin myocardial infarction register from 1999 to 2004. Int J Cardiol 2008; 130: 211-219.

112. Khera S, Kolte D, Gupta T et al. Temporal trends and sex differences in revascularization and outcomes of st-segment elevation myocardial infarction in younger adults in the United States. J Am Coll Cardiol 2015; 66: 1961–1972.

113. Terkelsen CJ, Lassen JF, Norgaard BL et al. Mortality rates in patients with ST-elevation vs. non-ST-elevation acute myocardial infarction: observations from an unselected cohort. Eur Heart J 2005; 26: 18–26.

114. Towfighi A, Markovic D, Ovbiagele B. National gender-specific trends in myocardial infarction hospitalization rates among patients aged 35 to 64 years. Am J Cardiol 2011; 108: 1102-7.

115. Roger VL, Jacobsen SJ, Weston SA et al. Trends in the incidence and survival of patients with hospitalized myocardial infarction, Olmsted County, Minnesota, 1979 to 1994. Ann Intern Med 2002; 136: 341–348.

116. Lehto HR, Lehto S, Havulinna AS, et al. Are coronary event rates declining slower in women than in men — evidence from two population-based myocardial infarction registers in Finland? BMC Cardiovasc Disord 2007; 7: 35.

117. Lundblad D, Holmgren L, Jansson JH et al. Gender differences in trends of acute myocardial infarction events: the Northern Sweden MONICA study 1985–2004. BMC Cardiovasc Disord 2008; 8: 17.

118. Nedkoff LJ, Briffa TG, Preen DB, et al. Age- and sex-specific trends in the incidence of hospitalized acute coronary syndromes in Western Australia. Circ Cardiovasc Qual Outcomes 2011; 4: 557–564.

119. Towfighi A, Zheng L, Ovbiagele B. Sex-specific trends in midlife coronary heart disease risk and prevalence. Arch Intern Med 2009; 169: 1762-6.

120. Egred M, Viswanathan G, Davis GK. Myocardial infarction in young adults. Postgrad Med J 2005; 81: 741–745.

121. Widimsky P, Wijns W, Fajadet J, et al; European Association for Percutaneous Cardiovascular Interventions. Reperfusion therapy for ST elevation acute myocardial

infarction in Europe: description of the current situation in 30 countries. Eur Heart J. 2010; 31(8): 943-957.

122. The Reperfusion Therapy Consensus Group. Selection of reperfusion therapy for individual patients with evolving myocardial infarction. Eur Heart J 1997; 18: 1371–81.

123. Keeley EC, Boura JA, Grines C. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials. Lancet 2003; 361: 13–20.

124. Bonnefoy E, Steg PG, Boutitie F, et al. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. Eur Heart J. 2009; 30: 1598-606.

125. Morrison LJ, Verbeek PR, McDonald AC et al. Mortality and pre-hospital thrombolysis for acute myocardial infarction: A meta-analysis. JAMA 2000; 283: 2686–2692.

126. Bonnefoy E, Lapostolle F, Leizorovicz A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. Lancet. 2002; 360: 825-9.

127. Danchin N, Puymirat E, Steg PG, et al. Five-year survival in patients with ST-segment-elevation myocardial infarction according to modalities of reperfusion therapy: the French Registry on Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) 2005 Cohort. Circulation. 2014; 129: 1629-36.

128. Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2013; 368: 1379-87.

129. Boersma E, Maas ACP, Deckers JW et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996; 348: 771–775.

130. Steg PG, Bonnefoy E, Chabaud S et al. Impact of time to treatment on mortality after pre-hospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. Circulation 2003; 108: 2851–2856.

131. Pinto DS, Frederick PD, Chakrabarti AK et al. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. Circulation 2011; 124: 2512–2521.

132. Westerhout CM, Bonnefoy E, Welsh RC et al. The influence of time from symptom onset and reperfusion strategy on 1-year survival in ST-elevation myocardial infarction: a pooled analysis of an early fibrinolytic strategy versus primary percutaneous coronary intervention from CAPTIM and WEST. Am Heart J. 2011; 161(2): 283-90.

133. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. Lancet. 2004; 364: 1045-53.

134. Gershlick AH, Stephens-Lloyd A, Hughes S, et al. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med. 2005; 353: 2758-68.

135. Borgia F, Goodman SG, Halvorsen S et al. Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. Eur Heart J 2010; 31: 2156–2169.

136. D'Souza SP, Mamas MA, Fraser DG et al. Routine early coronary angioplasty versus ischaemia-guided angioplasty after thrombolysis in acute STelevation myocardial infarction: a meta-analysis. Eur Heart J 2011; 32: 972–982.

137. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2: 349–360.

138. Sabatine MS, Cannon CP, Gibson CM et al, CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005; 352(12): 1179–1189.

139. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001; 358: 605–613.

140. Jernberg T, Johanson P, Held C et al; SWEDEHEART/RIKS-HIA. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA. 2011; 305: 1677-84.

141. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994; 343(8893): 311–322.

142. Ng VG, Lansky AJ, Meller S et al. The prognostic importance of left ventricular function in patients with ST-segment elevation myocardial infarction: the HORIZONS-AMI trial. Eur Heart J Acute Cardiovasc Care 2014; 3: 67–77.

143. Sutton NR, Li S, Thomas L et al. The association of left ventricular ejection fraction with clinical outcomes after myocardial infarction: Findings from the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry-Get With the Guidelines (GWTG) Medicare-linked database. Am Heart J 2016; 178: 65–73.

144. Buxton AE. Should everyone with an ejection fraction less than or equal to 30% receive an implantable cardioverter-defibrillator? Not everyone with an ejection fraction ≤30% should receive an implantable cardioverter-defibrillator. Circulation. 2005; 111: 2537–2549.

145. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med. 1983; 309: 331–336.

146. Rouleau JL, Talajic M, Sussex B et al. Myocardial infarction patients in the 1990s—their risk factors, stratification and survival in Canada: the Canadian Assessment of Myocardial Infarction (CAMI) Study. J Am Coll Cardiol. 1996; 27: 1119 –1127.

147. Velagaleti RS, Pencina MJ, Murabito JM et al. Long-term trends in the incidence of heart failure after myocardial infarction. Circulation 2008; 118: 2057–2062.

148. Desta L, Jernberg T, Lofman I et al. Incidence, temporal trends, and prognostic impact of heart failure complicating acute myocardial infarction. The SWEDEHEART Registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies): a study of 199,851 patients admitted with index acute myocardial infarctions, 1996 to 2008. JACC Heart Fail 2015; 3: 234–242.

149. Goldberg RJ, Spencer FA, Gore JM et al. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction a population-based perspective. Circulation 2009; 119: 1211–1219.

150. Townsend N, Wilson L, Bhatnagar P et al. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J 2016; 37(42): 3232–3245.

151. Puymirat E, Simon T, Steg PG et al, USIK USIC 2000 Investigators, FAST MI Investigators. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. JAMA 2012; 308(10): 998–1006.

152. Gale CP, Allan V, Cattle BA et al. Trends in hospital treatments, including revascularisation, following acute myocardial infarction, 2003-2010: a multilevel and relative survival analysis for the National Institute for Cardiovascular Outcomes Research (NICOR). Heart 2014; 100(7): 582–589.

153. Pedersen F, Butrymovich V, Kelbaek H et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. J Am Coll Cardiol 2014; 64: 2101–2108.

154. Fokkema ML, James SK, Albertsson P et al. Population trends in percutaneous coronary intervention: 20-year results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). J Am Coll Cardiol 2013; 61: 1222–1230.

155. Mandelzweig L, Battler A, Boyko V et al. The Second Euro Heart Survey on Acute Coronary Syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean basin in 2004. Eur Heart J 2006; 27: 2285–2293.

156. Jacobsen BK, Eggen AE, Mathiesen EB et al. Cohort profile: the Tromso Study. Int J Epidemiol. 2012; 41: 961-967.

157. Njølstad I, Mathiesen EB, Schirmer H et al. The Tromsø study 1974–2016: 40 years of cardiovascular research. Scandinavian Cardiovascular Journal 2016; 50: 276-281.

158. WHO MONICA Project. MONICA Manual. https://thl.fi/publications/monica/index.html http://www.thl.fi/publications/morgam/manual/contents.htm Accessed 06 January, 2019

159. Eggen AE, Mathiesen EB, Wilsgaard T et al. The sixth survey of the Tromso Study (Tromso 6) in 2007-08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. Scand J Public Health. 2013; 41: 65–80.

160. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011; 123: 2736-47.

161. Lunn M, McNeil D. Applying Cox regression to competing risks. Biometrics. 1995; 51: 524–532.

162. Jortveit J, Govatsmark RE, Digre TA, et al. Myocardial infarction in Norway in 2013. Tidsskr Nor Laegeforen. 2014; 134: 1841-6.

163. Grimes DA, Schulz KF. Descriptive studies: what they can and cannot do. Lancet. 2002; 359: 145-9.

164. NCI Dictionary of Cancer Terms https://www.cancer.gov/publications/dictionaries/cancer-terms/def/consecutive-case-series?redirect=true

165. NCI Dictionary of Cancer Terms. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/nonconsecutive-case-series?redirect=true

166. Chan K, Bhandari M. Three-minute critical appraisal of a case series article. Indian J Orthop 2011; 45: 103-104.

167. Mathes T, Pieper D. Clarifying the distinction between case series and cohort studies in systematic reviews of comparative studies: potential impact on body of evidence and workload. BMJ Medical Research Methodology 2017; 17: 107.

168. Kooistra B, Dijkman B, Einhorn TA et al. How to design a good case series. J Bone Joint Surg Am. 2009; 91 Suppl 3: 21-6.

169. Armstrong BK, White E, Saracci R. Principles of exposure measurement in epidemiology. New York: Oxford University Press, 1992.

170. Schwarz, PE, Muylle F, Valensi P, et al. The European perspective of diabetes prevention. Horm Metab Res 2008; 40: 511-514.

171. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015; 16: 233-271.

172. Quinones MA, Douglas PS, Foster E et al. ACC/AHA clinical competence statement on echocardiography: a report of the American College of Cardiology/American Heart Association/American College of Physicians–American Society of Internal Medicine Task Force on clinical competence. J Am Soc Echocardiogr 2003; 16: 379–402.

173. Kleijn SA, Aly MFA, Terwee CB: Reliability of left ventricular volumes and function measurements using three-dimensional speckle tracking echocardiography. Eur Heart J Cardiovasc Imaging 2012; 13: 159–168.

174. Hoffmann R, von Bardeleben S, Kasprzak JD et al. Analysis of regional left ventricular function by cineventriculography, cardiac magnetic resonance imaging, and unenhanced and contrast-enhanced echocardiography: a multicenter comparison of methods. J Am Coll Cardiol 2006; 47: 121–8.

175. Blondheim DS, Beeri R, Feinberg MS et al. Reliability of visual assessment of segmental and global left ventricular function: a multicenter study by the Israeli Echocardiography Research Group. J Am Soc Echocardiogr 2010; 23: 258–64.

176. Kaufmann BA, Min SY, Goetschalckx K et al. How reliable are left ventricular ejection fraction cut offs assessed by echocardiography for clinical decision making in patients with heart failure? Int J Cardiovasc Imaging 2013; 29: 581–588.

177. Greenland S, Robins JM, Pearl J. "Confounding and Collapsibility in Causal Inference". Statistical Science 1999; 14: 29–46.

178. Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies, 2: Assessing potential for confounding. BMJ. 2005; 330: 960-962.

179. Zaccai JH. How to assess epidemiological studies. Postgrad Med J 2004; 80: 140-147.

180. Hill AB. The environment and disease: association or causation? J R Soc Med 1965; 58: 295-300.

181. Nemetz PN, Roger VL, Ransom JE et al. Recent trends in the prevalence of coronary disease. A population-based autopsy study of nonnatural deaths. Arch Intern Med 2008; 168: 264–270.

182. Evans A, Tolonen H, Hense H-W et al for the WHO MONICA Project. Trends in coronary risk factors in the WHO MONICA Project. International journal of epidemiology 2001; 30: S35-S40.

183. Molarius A, Parsons RW, Dobson AJ et al: Trends in cigarette smoking in 36 populations from the early 1980s to the mid-1990s: findings from the WHO MONICA Project. Am J Public Health 2001; 91(2): 206-212.

184. Grundtvig M, Hagen TP, German M et al. Sex-based differences in premature first myocardial infarction caused by smoking: twice as many years lost by women as by men. Eur J Cardiovasc Prev Rehabil 2009; 16: 174–179.

185. Norgeshelsa. http://norgeshelsa.no/norgeshelsa/?language=en (accessed March 2018).

186. The Tromsø Study. http://tromsoundersokelsen.uit.no/tromso/ (accessed March 2018).

187. Tunstall-Pedoe H, Woodward M, Tavendale R et al: Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study. BMJ (Clinical research ed) 1997; 315(7110): 722-729.

188. Prescott E, Hippe M, Schnor P et al. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ 1998; 316: 1043–1047.

189. Lee WL, Cheung AM, Cape D et al. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. Diabetes Care 2000; 23: 962-968.

190. Mosca L, Appel LJ, Benjamin EJ et al: Evidence-based guidelines for cardiovascular disease prevention in women. Circulation 2004, 109(5):672-693.

191. Brieger D, Eagle KA, Goodman SG et al. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. Chest 2004; 126: 461–469.

192. Mosca L, Ferris A, Fabunmi R et al. Tracking women's awareness of heart disease. An American Heart Assosiation National Study. Circulation 2004; 109: 573–579.

193. Mosca L, Mochari-Greenberger H, Dolor RJ et al. Twelve-year follow-up of American women's awareness of cardiovascular disease risk and barriers to heart health. Circ Cardiovasc Qual Outcomes. 2010; 3: 120–127.

194. Hochman JS, McCabe CH, Stone PH et al. Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIB. TIMI Investigators. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol 1997; 30: 141-8.

195. Rosengren A, Wallentin L, Gitt AK et al: Sex, age, and clinical presentation of acute coronary syndromes. Eur Heart J 2004, 25(8): 663-670.

196. Mahon NG, McKenna CJ, Codd MG et al. Gender differences in the management and outcome of acute myocardial infarction in unselected patients in the thrombolytic era. Am J Cardiol 2000; 85(8): 921–926.

197. Burke AP, Farb A, Malcom GT et al. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med. 1997; 336: 1276–1282.

198. Albert CM, Ruskin JN. Risk stratifiers for sudden cardiac death (SCD) in the community: primary prevention of SCD. Cardiovascular Research 2001; 50: 186-196.

199. Johansen CD, Olsen RH, Pedersen LR et al. Resting, night-time, and 24 h heart rate as markers of cardiovascular risk in middle-aged and elderly men and women with no apparent heart disease. Eur Heart J. 2013; 34: 1732–1739.

200. Jouven X, Empana JP, Schwartz PJ et al. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med. 2005; 352: 1951–1958.

201. Fox K, Borer JS, Camm AJ et al; Heart Rate Working Group. Resting heart rate in cardiovascular disease. J Am Coll Cardiol. 2007; 50: 823–830.

202. Rosengren A, Wallentin L, Simoons M et al. Cardiovascular risk factors and clinical presentation in acute coronary syndromes, Heart , 2005; 91: 1141-1147.

203. Levantesi G, Scarano M, Marfisi R, et al: Metaanalysis of effect of statin treatment on risk of sudden death. Am J Cardiol 2007; 100: 1644-1650.

204. Spencer FA, Santopinto JJ, Gore JM et al. Impact of aspirin on presentation and hospital outcomes in patients with acute coronary syndromes (The Global Registry of Acute Coronary Events [GRACE]). Am J Cardiol. 2002; 90: 1056-61.

205. Go AS, Iribarren C, Chandra M, et al. Statin and beta-blocker therapy and the initial presentation of coronary heart disease. Ann Intern Med 2006; 144: 229-38.

206. Capewell S, O'Flaherty M. Can dietary changes rapidly decrease cardiovascular mortality rates? Eur Heart J 2011; 32: 1187-9.

207. Meyers DG, Neuberger JS, He J. Cardiovascular effect of bans on smoking in public places: a systematic review and meta-analysis. J Am Coll Cardiol 2009; 54: 1249–55.

208. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2010; 7: e1000252.

209. Ström A, Jensen RA. Mortality from circulatory diseases in Norway 1940–1945. Lancet 1951; 1: 126–29.

210. Salomaa V, Ketonen M, Koukkunen H et al. Decline in out-of hospital coronary heart disease deaths has contributed the main part to the overall decline in coronary heart disease mortality rates among persons 35 to 64 years of age in Finland: the FINAMI study. Circulation. 2003; 108: 691–696.

211. Engdahl J, Holmberg M, Karlson BW et al. The epidemiology of out-of-hospital "sudden" cardiac arrest. Resuscitation. 2002; 52: 235–245.

212. Saczynski JS, Yarzebski J, Lessard D et al. Trends in prehospital delay in patients with acute myocardial infarction (from the Worcester Heart Attack Study). Am J Cardiol. 2008; 102: 1589–1594.

213. Gerber Y, Weston SA, Jiang R et al. The changing epidemiology of myocardial infarction in Olmsted County, Minnesota, 1995-2012. Am J Med. 2015; 128: 144–151.

214. Sulo E, Vollset SE, Nygard O. Trends in 28-day and 1-year mortality rates in patients hospitalized for a first acute myocardial infarction in Norway during 2001–2009: a "Cardiovascular disease in Norway" (CVDNOR) project. J Intern Med 2015; 277(3): 353–361.

215. Fothergill RT, Watson LR, Virdi GK et al. Survival of resuscitated cardiac arrest patients with ST-elevation myocardial infarction (STEMI) conveyed directly to a Heart Attack Centre by ambulance clinicians. Resuscitation. 2014; 85(1): 96-8.

216. Terkelsen CJ, Sorensen JT, Maeng M et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA 2010; 304: 763–771.

217. Roule V, Ardouin P, Blanchart K, et al. Prehospital fibrinolysis versus primary percutaneous coronary intervention in ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Crit Care. 2016; 20(1): 359.

218. Bohmer E, Hoffmann P, Abdelnoor M et al. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). J Am Coll Cardiol. 2010; 55: 102-10.

219. Bhatnagar P, Wickramasinghe K, Williams J et al. The epidemiology of cardiovascular disease in the UK 2014. Heart 2015; 0: 1-8.

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Age and gender differences in incidence and case fatality trends for myocardial infarction: a 30-year follow-up. The Tromsø Study

Jan Mannsverk[1,2], Tom Wilsgaard[2], Inger Njølstad[2], Laila Arnesdatter Hopstock[2], Maja-Lisa Løchen[1,2], Ellisiv B Mathiesen[3,4], Dag S Thelle[5], Knut Rasmussen[4] and Kaare Harald Bønaa[2,6,7]

Abstract

Background: Although the mortality of coronary heart disease (CHD) has declined in Western countries during the last decades, studies have suggested that the prevention and treatment of CHD may not have been as effective in women as in men. We examined gender- and age-specific trends in incidence, case fatality and the severity of first myocardial infarction (MI) in a large Norwegian population-based study.

Design: Prospective population-based cohort study.

Methods: A total of 31,323 participants enrolled between 1974 and 2001 were followed throughout 2004 for a total of 400,572 person-years. Suspected coronary events were adjudicated by a review of hospital records and death certificates. A total of 1669 events fulfilled standardized criteria of first-ever fatal or non-fatal MI.

Results: In the age group 35–79 years, the age-adjusted incidence of MI declined significantly in men, whereas an increase was observed in women. For men and women $\geq$80 years the incidence rates remained unchanged. The severity of MI and the 28-day and 1-year case fatality rates declined significantly and similarly in men and women.

Conclusion: Trends in MI incidence differed by sex and age; in the age group 35–79 years a marked decrease was observed among men but an increase was observed among women, while no change was observed among older patients. MI severity and case fatality were clearly reduced for both sexes. These data suggest that the burden of CHD is shifting from middle-aged men toward middle-aged women and elderly patients.

Keywords

Myocardial infarction, incidence, case fatality, epidemiology, gender

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Introduction

Age-standardized coronary heart disease (CHD) mortality has declined substantially in most industrialized countries during the last several decades.[1,2] The decline is thought to represent effects of changes in

[1]Department of Heart Disease, Division of Cardiothoracic and Respiratory Medicine, University Hospital of North Norway, Tromsø, Norway.
[2]Department of Community Medicine, University of Tromsø, Tromsø, Norway.
[3]Department of Neurology, Division of Neurosciences and Orthopedics, University Hospital of North Norway, Tromsø, Norway.
[4]Department of Clinical Medicine, University of Tromsø, Tromsø, Norway.
[5]Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway.
[6]Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.
[7]Clinic for Heart Disease, St Olav's University Hospital, Trondheim, Norway.

Corresponding author:
Jan Mannsverk, Department of Heart Disease, Division of Cardiothoracic and Respiratory Medicine, University Hospital of North Norway, N-9038, Tromsø, Norway
Email: jan.mannsverk@unn.no

lifestyle factors and treatment approaches, which in turn affect incidence of coronary events and survival of those affected.[3,4] However, evaluating temporal trends in the incidence and outcome of myocardial infarction (MI) is challenging since there have been changes over time in the criteria utilized for the diagnostic confirmation of MI.[5] Increased use of the highly sensitive biomarker troponin, enabling the detection of smaller amounts of necrosis, might increase the incidence of MI and decrease the severity of diagnosed cases.[6]

Concern has been raised that the favourable trends in CHD mortality and MI incidence may be less impressive in women than in men.[7–11] Emerging trends in coronary risk factors support these observations.[7,12] The increasing prevalence of obesity in Western populations is associated with diabetes mellitus, hypertriglyceridaemia, and the metabolic syndrome, which are stronger CHD risk factors in women than in men.[13–15] Furthermore, in some populations there has been only a modest or no decrease in smoking in women.[16] In addition, cardiovascular risk in women may traditionally have been underestimated, which may have led to deficient prevention and treatment efforts.[12]

The changes in diagnostics and inconsistent findings regarding the MI incidence in the two genders indicate a need for population-based long-term data on sex-and age-specific incidence and case fatality of first coronary event, taking into account more sensitive diagnostics. The main purpose of this study was to describe sex- and age-specific trends in incidence and case fatality rates of MI and the severity of the disorder in a Norwegian population from 1974 to 2004. We used a cardiovascular research registry set up as part of the population-based Tromsø Study, where each MI event has been validated according to standardized diagnostic criteria.

Methods

Study population and follow-up

The Tromsø Study is an ongoing, open, population-based cohort study in the municipality of Tromsø, Norway. Tromsø is the largest town in Northern Norway with a current population of 68,000 inhabitants. The Tromsø Study started in 1974 as a cardiovascular survey among 20–49-year-old men, with additional surveys being conducted in 1979–80, 1986–87, 1994–95, 2001 and 2007–8. A detailed description of the study population and study design has been published.[17] The surveys differed by size as well as age- and birth-cohort composition (Table 1). Women were included in the 1979 survey and onwards. Information on cardiovascular diseases and risk factors was obtained through standardized questionnaires, physical examinations and laboratory tests.[18] The surveys were performed by the University of Tromsø in cooperation with the National Health Screening Service. Approvals were obtained from the Regional Board of Research Ethics, the Data Inspectorate and the Directorate of Health and Social Affairs. The 38,164 who participated in at least one of the surveys up to 2001 form the basis of this longitudinal analysis. We excluded 5469 participants who were younger than 35 years, 390 participants with a history of prior MI, 160 participants not officially registered as inhabitants of Tromsø at the date of enrolment and 222 participants who did not give written consent to research. Follow-up time was assigned from the date of first attendance until date of first-ever fatal or non-fatal

Table 1. Year of screening, birth year and number of participants and percentage of eligible population examined (The Tromsø Study)

Year of screening	Gender	Birth year	Participants[a] *N*%
1974–75 (Tromsø 1)	Men	1925–1954	6595 83
1979–80 (Tromsø 2)	Men	1925–1959	8477 82
	Women	1929–1959	8143 88
1986–87 (Tromsø 3)	Men	1922–1974	10,963 78
	Women	1920–1974	10,863 85
1994–95 (Tromsø 4)	Men	1897–1969	12,865 74
	Women	1897–1969	14,293 79
2001 (Tromsø 5)	Men	1912–1971	3511 76
	Women	1912–1971	4619 81

[a]*N* denotes the total number of persons attending the screening, and % denotes *N* as a percentage of the eligible population.

MI, emigration from Tromsø, death from other causes or 31December 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).[17] 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. Due to these age-limitations set for the trend analyses, we excluded an additional 600 subjects. Thus, a total of 31,323 participants were included in the present analysis, 15,566 men and 15,757 women.

Identification and validation of first MI

Hospitalized cases of incident MI were identified by linking the Tromsø Study participant list to the discharge diagnosis register at the University Hospital of North Norway, the only local hospital serving the Tromsø population. To identify all possible first-ever MI cases, we used a wide search strategy that included the following diagnostic codes of cardiovascular diseases (CVD): from 1974–79 International Classification of Diseases (ICD) 8 codes 410-414, 430-438; from 1980–98 ICD 9 codes 410-414, 430-438; and thereafter ICD 10 codes I20-I25, I60-I69 were used. The hospital medical record was then retrieved for case validation. Discharge letters from hospitalizations in other hospitals were also collected when appropriate. Further, the Tromsø Study participant list was linked with the National Causes of Death Registry at Statistics Norway and the death certificates were retrieved for those with an underlying or contributing diagnosis of CVD or sudden unexpected death. Relevant information was collected from additional sources such as autopsy reports and records from nursing homes, ambulance services and general practitioners. This procedure identified fatal incident cases of MI that occurred as out-of-hospital deaths, including deaths that occurred outside Tromsø. Dates of emigration were obtained from the Population Registry of Norway.

Medical records and death certificates were reviewed by trained physicians of the Tromsø Study Endpoint Committee. Cases meeting diagnostic criteria for definite or probable fatal or non-fatal first-ever MI were classified as MI. WHO MONICA/MORGAM criteria were used in the algorithms and included clinical symptoms and signs, findings in electrocardiograms (ECG), values of cardiac biomarkers and (when applicable) autopsy reports.[19] Autopsy was performed in 25% of those who died on the day of attack. At the University Hospital, biomarkers used included creatine kinase (CK) (throughout the study period), its MB fraction (CK-MB) (from 1990) and troponin (from 2000). Biomarker levels were generally recorded three times during the first 3 days following admission or MI onset. When circumstances that might invalidate biomarker values were present, the biomarker results were downgraded from abnormal to equivocal in our algorithm. Silent MIs as defined by ECG only were not included as cases because of difficulties in determining the exact date of the event. Case fatality was defined as the proportion of all incident MIs that were fatal within 28 days and 1 year. Trends in MI severity (1995–2004) were evaluated by calculating the proportion of events with new Q-waves and ST-segment elevation in ECG, and the peak CK values. All blood measurements were done at the Department of Clinical Chemistry, the University Hospital of North Norway. The methods of measurements, the upper limits of normal, and the number of assays performed during hospitalization for MI, did not change over time.

Statistical analysis

Statistical analyses were performed using STATA version 10 (Stata Corp LP Texas, USA). The split function in STATA was used 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. Calendar year-specific MI incidence rates were estimated per 1000 person-years of observation. 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. All significance

tests were two-sided with the significance level set at 5%.

Results

From 1974 to 2004, 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 (supplementary Table 1 and supplementary Table 2). At the time of the index event, the mean age was 62 years (SD 13) for men and 73 years (SD 12) for women. Seventy-nine percent of all events were treated in hospital, whereas 15% of all events were out-of-hospital deaths. Sixty-three percent of all fatal cases on the day of the event were out-of-hospital deaths. The overall 28-day case fatality was 32%. Of all incident events, troponins were measured in 458 cases. Among these, 23 (5%) did not meet MI criteria for CK/CK-MB and/or ECG and met only troponin-based criteria.

Incidence of MI

Trends in the incidence of MI differed significantly by sex and age over the time periods under study (Figures 1 and 2). MI incidence fell significantly among men below the age of 80 years: in men aged 35–49 years, incidence fell by 52% ($p = 0.001$) between 1974 and 2004; in men aged 50–64 years. incidence fell by 49% ($p < 0.001$) between 1988 and 2004; and in men aged 65–79 years, incidence fell by 34% ($p = 0.027$) between 1995 and 2004. Conversely, in women non-significant increases in MI incidence were found in the age groups 35–49, 50–64 and 65–79 years. In both genders, MI incidence among patients over 80 years did not change.

From 1995 to 2004 (the time period when we have follow-up data for all age groups) the age-adjusted incidence of MI in participants of 35–79 years declined by 26% (95%CI 6–42%) in men, but increased by 61% (95%CI 3–151%) in women (Figure 2) ($p = 0.012$ for the time × sex interaction term). Temporal trends in the incidence of MI did not change notably when troponin-only cases were excluded.

Case fatality of first MI

From 1995 to 2004 the age-adjusted odds of death within 28 days fell by 52% (95%CI 14–73%) among men and by 59% (95%CI 2–83%) among women aged 35–79 years (Table 2). Trends in 28-day case fatality were similar when cases meeting only troponin-based criteria were excluded. 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. Among all incident MIs, the age- and sex-adjusted odds ratio of death within 1 year for an MI occurring in 2004 as compared with 1994 was 0.48 (95%CI, 0.32–0.71; $p < 0.001$), indicating a 52% decline in the odds of 1-year case fatality over the last decade. The temporal trends did not differ by age or sex (year × age interaction, $P = 0.07$; year × sex interaction, $P = 0.22$) and were similar regardless of troponin.

Severity and treatment of hospitalized cases with first MI

When all hospitalized patients with MIs between 1995 and 2004 were analysed, the proportion with Q-wave pattern on ECG decreased significantly ($p < 0.001$), as did the peak CK level ($p < 0.001$), and a similar trend was observed for the frequency of ST-segment elevation in ECG ($p = 0.078$) (Table 3). Furthermore, the 28-day case fatality declined significantly ($p = 0.004$). 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 (percutaneous coronary intervention and/or coronary artery bypass grafting) within 28 days and the use of aspirin, β-blockers and statins at dismissal increased markedly over time (Table 3).

Discussion

Temporal trends in MI incidence 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. In contrast to these opposing incidence trends, we found similar reductions among men and women in case fatality and in the severity of first MI. Notably, these changes were not related to the introduction of troponin measurements.

Our results are in line with findings in other populations. In the Olmsted County Study the incidence of hospitalized MI in men decreased from 1979 to 1994, whereas an increase was observed in women and the elderly.[8] In Northern Sweden, MI incidence was reduced in middle-aged men, but not in middle-aged women during 1985–2004.[9] Similarly, two large Finnish population-based MI registers suggested smaller declines in incidence of MI events in women than in men.[10] A recent survey of the US population found that MI prevalence had increased among middle-aged women during the past two

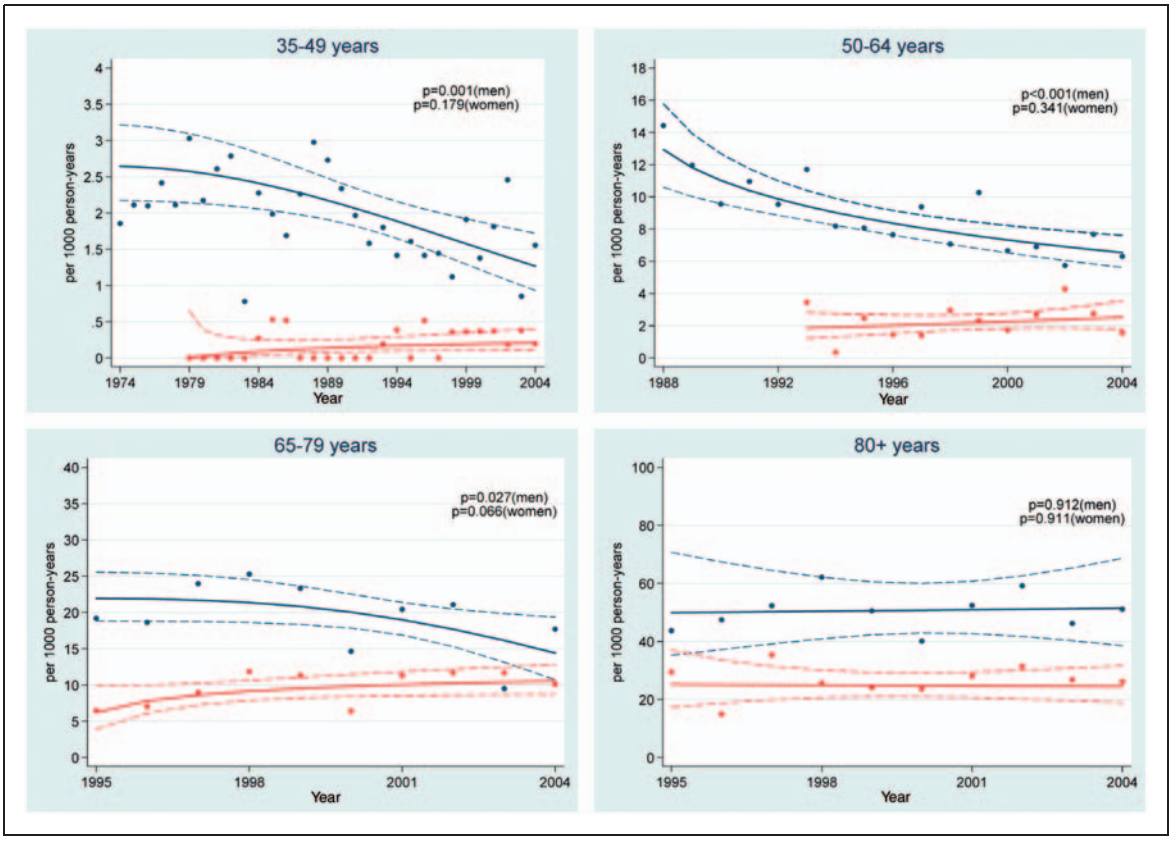

Figure 1. Age-adjusted time trends in incidence rates of myocardial infarction among men and women stratified by age. Note that start of follow-up differ according to sex and age-group. Blue dots and lines represent men, red dots and lines represent women. Each dot represent annual rate per 1000 person-years with best fitted regression lines (solid lines) and 95% confidence interval (dashed lines). *P* values are for time trends using fractional polynomials. (The Tromsø Study).

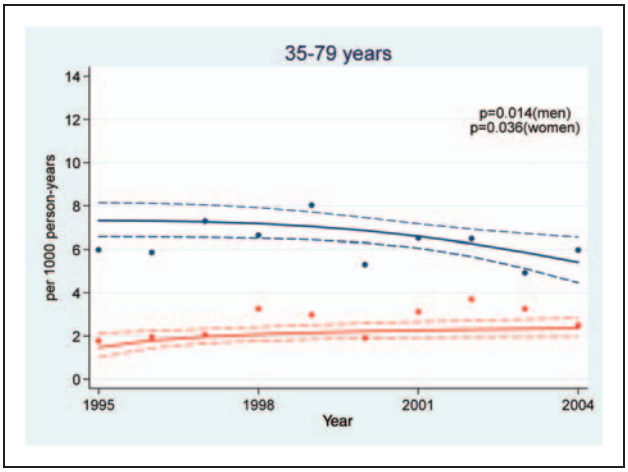

Figure 2. Age-adjusted time trends in incidence rates of myocardial infarction 1995–2004 among men and women aged 35–79 years. Blue dots and lines represent men, red dots and lines represent women. Each dot represent annual rate per 1000 person-years with best fitted regression lines (solid lines) and 95% confidence interval (dashed lines). *P* values are for time trends using fractional polynomials. (The Tromsø Study).

decades, while declining in men.[7] Similarly, cardiovascular risk factor levels showed decreasing trends in men, but increasing trends in women.[7] These findings are supported by autopsy studies of non-natural deaths showing greater temporal declines in high-grade coronary artery disease during 1981–2004 for males than for females, and greater for younger than for older individuals.[20]

The observed increase in MI incidence in middle-aged women is noteworthy. Does it reflect a true increase, or an increased detection of events that formerly went unrecognized? Recent surveys of the general public in the US indicate that the awareness of heart disease in women has increased in recent years.[21] 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. In 2000, the European Society of Cardiology and the American College of Cardiology recommended that any elevation of troponin in the context of symptoms and signs of an acute coronary syndrome (ACS) should be considered diagnostic of MI.[5] Compared with CK and its myocardial band

Table 2. Secular trends in 28-day case fatality of incident myocardial infarction according to gender, age, and time period (The Tromsø Study)

Gender	Age (years)	Time period	Fatal MI/all MI[b]	Case fatality[a]		OR(95%CI)[c]	*P*-value for trend
				First year of time period	Last year of time period		
Men	35–49	1974–2004	56/258	20.1	20.9	1.05 (0.35–3.14)	0.926
	50–64	1988–2004	118/490	30.6	15.3	0.41 (0.21–0.82)	0.011
	65–79	1995–2004	106/295	44.8	26.3	0.44 (0.20–0.98)	0.044
	80+	1995–2004	72/138	73.5	34.4	0.19 (0.06–0.62)	0.006
	35–79	1995–2004	188/664	28.5	16.2	0.48 (0.27–0.86)	0.014
Women	35–49	1979–2004	4/23	NA	NA	NA	NA
	50–64	1993–2004	17/103	27.2	8.1	0.24 (0.04–1.33)	0.102
	65–79	1995–2004	61/195	37.4	24.5	0.54 (0.20–1.49)	0.236
	80+	1995–2004	95/167	62.2	48.5	0.57 (0.20–1.63)	0.297
	35–79	1995–2004	78/303	24.1	11.5	0.41 (0.17–0.98)	0.044

MI, myocardial infarction; OR, odds-ratio; CI, confidence interval; NA, not applicable. [a]Percentage of all MIs that were fatal within 28 days. The figures are age-adjusted estimates from logistic regression analyses using fractional polynomials. [b]The figures are number of MIs (*N*). [c]Age-adjusted OR for case fatalities between the last year (2004) and first year of each time period.

Table 3. Clinical characteristics in 962 patients hospitalized with first myocardial infarction in 1995–1999 and 2000–2004 (The Tromsø Study)

Characteristics	1995–1999 estimate[a] ($n = 459$)	2000–2004 estimate[a] ($n = 503$)	OR[b] or ratio[c] (95%CI)	*P*-value for trend
MI severity indicators				
Q-waves (%)	52	24	0.30 (0.23, 0.40)	<0.001
ST-segment elevation (%)[d]	43	37	0.77 (0.57, 1.03)	0.078
Peak creatine kinase (U/l)[e]	935	615	0.66 (0.56, 0.77)	<0.001
28-day case fatality (%)	22	15	0.61 (0.44, 0.85)	0.004
Treatment				
Revascularization within 28 days (%)[f]	11	52	8.92 (6.29, 12.64)	<0.001
B-blockers at discharge (%)[g]	76	83	1.57 (1.02, 2.41)	0.039
Aspirin at discharge (%)[g]	80	89	2.12 (1.32, 3.40)	0.002
Statins at discharge (%)[g]	42	65	2.60 (1.77, 3.80)	<0.001

Percentage missing values for Q-waves, ST-segment elevation, creatine kinase, 28-day case fatality, revascularization within 28 days, and use of β-blockers, aspirin and statins were 6.9, 12.4, 11.7, 0.0, 0.0 and 12.1 respectively. [a]The values are age-and sex-adjusted estimates from logistic regression models, or, for peak creatine kinase, a linear regression model, with year modelled as a two-level categorical variable. [b]Age-and sex-adjusted odds ratio (95%CI) for 2000–04 compared to 1995–99 as estimated from a logistic model. [c]For peak creatine kinase, the ratio estimates are age-and sex-adjusted ratio (95%CI) of the level in 2000–04 to the level in 1995–99 as estimated from a linear model. Analyses were done on log transformed data. [d]ST-segment elevation in hospitalized incident myocardial infarctions from 1996 to 2004. [e]Geometric mean. [f]Revascularization means percutaneous coronary intervention and/or coronary artery bypass grafting. [g]Based on 763 patients discharged from hospital alive.

fraction (CK-MB), troponins are more sensitive, enabling the detection of smaller amounts of necrosis. This may increase the number of MIs, shift the clinical spectrum of the disease toward smaller MIs and change case fatality estimates.[6,22] Women with ACS have a higher prevalence of unstable angina rather than MI, and a higher likelihood of having clinically insignificant disease on coronary angiography.[23] In the FINAMI study, correction for the effect of troponins reduced the incidence of MI especially in women and elderly subjects.[24] However, the use of troponins is not likely to explain temporal trends in the Tromsø population, because 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 our study, 5% of the cases with troponin measurements met only troponin-based criteria. This figure is smaller than in comparable studies,[25] probably due to incomplete implementation of the new criteria in clinical practice.[26]

Previous studies have shown favourable trends in CHD risk factor levels in both genders, but less pronounced in women.[12] 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).[27,28] Data from the Tromsø Study surveys show similar trends.[29] Body mass index and prevalence of diabetes mellitus also increased in both genders.[29,30] Smoking and diabetes mellitus appear to be stronger MI risk factors in women than in men[13,28,31] and could thus partly account for the opposing incidence trends among men and women. 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.[28]

In line with results from other studies,[25,32] we found a substantial decline in the severity of first MI as evaluated by biomarkers and ECG. 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 and advances in evidence-based treatments (increased use of aspirin, statins, β-blockers and revascularization). 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.[25,32] It is likely that the decline in MI severity is a major determinant of the decline in case fatality in the Tromsø population. Case fatality has been reported to be higher among women compared with men, possibly due to differences in the level of acute coronary care.[33] 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.

The strengths of the present study are its population-based design, the standardized diagnostic criteria, simultaneous measurement of both sets of biomarkers (since 2000 or later), the inclusion of both hospitalized and out-of-hospital cases of first-ever MIs, and the high participation proportion. Whereas these features support the internal validity of the study, our findings may not necessarily be generalizable to other populations because of regional differences in risk factor levels, treatments and CHD rates.[4]

The present study indicates that the burden of CHD is shifting towards women and elderly patients, suggesting that preventive gains have not penetrated equally throughout the population. The severity of the disease, however, is declining in all groups. A substantial fraction of this fall may be due to therapeutic efforts. However, the disease is not disappearing and a maintained therapeutic alertness is therefore warranted.

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Conflicts of interest

None declared.

References

1. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics-2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008; 117: e25–e146.
2. Kesteloot H, Sans S and Kromhout D. Dynamics of cardiovascular and all-cause mortality in Western and Eastern Europe between 1970 and 2000. *Eur Heart J* 2006; 27: 107–113.
3. Salomaa V, Rosamond W and Mähönen M. Decreasing mortality from acute myocardial infarction: effect of incidence and prognosis. *J Cardiovasc Risk* 1999; 6: 69–75.
4. Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, Tolonen H, Ruokokoski E and Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999; 353: 1547–1557.
5. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000; 21: 1502–1513.

6. Roger VL, Killian JM, Weston SA, Jaffe AS, Kors J, Santrach PJ, et al. Redefinition of myocardial infarction: prospective evaluation in the community. *Circulation* 2006; 114: 790–797.
7. Towfighi A, Zheng L and Ovbiagele B. Sex-specific trends in midlife coronary heart disease risk and prevalence. *Arch Intern Med* 2009; 169: 1762–1766.
8. Roger VL, Jacobsen SJ, Weston SA, Goraya TY, Killian J, Reeder GS, et al. Trends in the incidence and survival of patients with hospitalized myocardial infarction, Olmsted County, Minnesota, 1979 to 1994. *Ann Intern Med* 2002; 136: 341–348.
9. Lundblad D, Holmgren L, Jansson JH, Näslund U and Eliasson M. Gender differences in trends of acute myocardial infarction events: the Northern Sweden MONICA study 1985–2004. *BMC Cardiovasc Disord* 2008; 8: 17.
10. Lehto HR, Lehto S, Havulinna AS, Ketonen M, Lehtonen Aa, Kesäniemi YA, et al. for the FINAMI Study Group. Are coronary event rates declining slower in women than in men – evidence from two population-based myocardial infarction registers in Finland? *BMC Cardiovasc Disord* 2007; 7: 35.
11. Kattainen A, Salomaa V, Härkänen T, Jula A, Kaaja R, Kesäniemi YA, et al. Coronary heart disease: from a disease of middle-aged men in the late 1970s to a disease of elderly women in the 2000s. *Eur Heart J* 2006; 27: 296–301.
12. Stramba-Badiale M, Fox KM, Priori SG, Collins P, Daly C, Graham I, et al. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. *Eur Heart J* 2006; 27: 994–1005.
13. Lee WL, Cheung AM, Cape D and Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care* 2000; 23: 962–968.
14. Hokanson JE and Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein level: a meta- analysis of population-based prospective studies. *J Cardiovasc Risk* 1996; 3: 213–219.
15. Lin J-W, Caffrey J, Chang M-H and Lin Y-S. Sex, menopause, metabolic syndrome, and all-cause and cause-specific mortality-cohort analysis from the Third National Health and Nutrition Examination Survey. *J Clin Endocrinol Metab* 2010; 95: 4258–4267.
16. Molarius A, Parsons RW, Dobson AJ, Evans A, Fortmann SP, Jamrozik K, et al. Trends in cigarette smoking in 36 populations from the early 1980s to the mid-1990s: findings from the WHO MONICA Project. *Am J Public Health* 2001; 91: 206–212.
17. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T and Njølstad I. Cohort profile: the Tromsø study. *Int J Epidemiol* 2011; 00: 00–00.
18. Thelle DS, Førde OH, Try K and Lehmann EH. The Tromsø Heart Study: Methods and main results of the cross-sectional study. *Acta Med Scand* 1976; 200: 107–118.
19. MORGAM Manual. http://www.ktl.fi/publications/morgam/manual/followup/form22.htm (accessed July 2011).
20. Nemetz PN, Roger VL, Ransom JE, Bailey KR, Edwards WD and Leibson CL. Recent trends in the prevalence of coronary disease. A population-based autopsy study of nonnatural deaths. *Arch Intern Med* 2008; 168: 264–270.
21. Mosca L, Ferris A, Fabunmi R and Robertson RM. Tracking women's awareness of heart disease. An American Heart Assosiation National Study. *Circulation* 2004; 109: 573–579.
22. Parikh NI, Gona P, Larson MG, Fox CS, Benjamin EJ, Murabito JM, et al. Long-term trends in myocardial infarction incidence and case fatality in the National Heart, Lung, and Blood Institute's Framingham Heart Study. *Circulation* 2009; 119: 1203–1210.
23. Hochman J, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. *N Engl J Med* 1999; 341: 226–232.
24. Salomaa V, Ketonen M, Koukkunen H, Immonen-Räihä I, Lehtonen A, Torppa J, et al, for the FINAMI Study Group. The effect of correcting for troponins on trends in coronary heart disease events in Finland during 1993–2002: the FINAMI study. *Eur Heart J* 2006; 27: 2394–2399.
25. Roger VL, Weston SA, Gerber Y, Killian JM, Dunlay SM, Jaffe AS, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. *Circulation* 2010; 121: 863–869.
26. Pell ACH and Pell JP. Variations in access to and interpretation of troponin assays are wide [letter to the editor]. *BMJ* 2002; 324: 1216.
27. Norgeshelsa. http://norgeshelsa.no/norgeshelsa/?language=en (accessed March 2010).
28. Grundtvig M, Hagen TP, German M and Reikvam Å. Sex-based differences in premature first myocardial infarction caused by smoking: twice as many years lost by women as by men. *Eur J Cardiovasc Prev Rehabil* 2009; 16: 174–179.
29. The Tromsø Study. http://tromsoundersokelsen.uit.no/tromso/ (accessed July 2011).
30. Jacobsen BK, Njølstad I, Thune I, Wilsgaard T, Løchen ML and Schirmer H. Increase in weight in all birth cohorts in a general population: the Tromsø Study, 1974–1994. *Arch Intern Med* 2001; 161: 466–472.
31. Prescott E, Hippe M, Schnor P, Hein HO and Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ* 1998; 316: 1043–1047.
32. Myerson M, Coady S, Taylor H, Rosamond W and Goff D, for the ARIC Investigators. Declining severity of myocardial infarction 1987 to 2002: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2009; 119: 503–514.
33. Mahon NG, McKenna CJ, Codd MG, O'Rorke C, McCann HA and Sugrue DD. Gender differences in the management and outcome of acute myocardial infarction in unselected patients in the thrombolytic era. *Am J Cardiol* 2000; 85(8): 921–926.

Paper 2

Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population

Jan Mannsverk, MD; Tom Wilsgaard, MSc, PhD; Ellisiv B. Mathiesen, MD, PhD; Maja-Lisa Løchen, MD, PhD; Knut Rasmussen, MD, PhD; Dag S. Thelle, MD, PhD; Inger Njølstad, MD, PhD; Laila Arnesdatter Hopstock, MSc, PhD; Kaare Harald Bønaa, MD, PhD

Background—Few studies have used individual person data to study whether contemporary trends in the incidence of coronary heart disease are associated with changes in modifiable coronary risk factors.

Methods and Results—We identified 29 582 healthy men and women ≥25 years of age who participated in 3 population surveys conducted between 1994 and 2008 in Tromsø, Norway. Age- and sex-adjusted incidence rates were calculated for coronary heart disease overall, out-of-hospital sudden death, and hospitalized ST-segment–elevation and non–ST-segment–elevation myocardial infarction. We measured coronary risk factors at each survey and estimated the relationship between changes in risk factors and changes in incidence trends. A total of 1845 participants had an incident acute coronary heart disease event during 375 064 person-years of follow-up from 1994 to 2010. The age- and sex-adjusted incidence of total coronary heart disease decreased by 3% (95% confidence interval, 2.0–4.0; $P<0.001$) each year. This decline was driven by decreases in out-of-hospital sudden death and hospitalized ST-segment–elevation myocardial infarction. Changes in coronary risk factors accounted for 66% (95% confidence interval, 48–97; $P<0.001$) of the decline in total coronary heart disease. Favorable changes in cholesterol contributed 32% to the decline, whereas blood pressure, smoking, and physical activity each contributed 14%, 13%, and 9%, respectively.

Conclusions—We observed a substantial decline in the incidence of coronary heart disease that was driven by reductions in out-of-hospital sudden death and hospitalized ST-segment–elevation myocardial infarction. Changes in modifiable coronary risk factors accounted for 66% of the decline in coronary heart disease events. **(*Circulation*. 2016;133:74-81. DOI: 10.1161/CIRCULATIONAHA.115.016960.)**

Key Words: coronary disease ■ epidemiology ■ incidence ■ mortality ■ myocardial infarction ■ risk factors

Coronary heart disease (CHD) mortality rates have decreased in many countries during the last decades.[1,2] Both changes in the rates of out-of-hospital CHD deaths and hospitalization rates and the outcome of myocardial infarction (MI) with ST-segment elevation (STEMI) and non–ST-segment elevation (non-STEMI) will affect mortality.[3]

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Clinical Perspective on p 81

It has been suggested that 45% to 75% of the decrease in deaths from CHD can be attributed to decreases in smoking, blood pressure, and cholesterol.[4–8] These studies based their estimates on ecological data or mathematical modeling of aggregate data. Few studies used individual person data,[9,10] and the studies were limited to population subgroups and did not study out-of-hospital CHD or subtypes of MI.

We used individual person data from repeated surveys of a general population to study the rates of out-of-hospital CHD; the incidence, treatment, and outcome of hospitalized STEMI and non-STEMI; and the impact of changes in coronary risk factor levels during the years 1995 to 2010.

Methods

Study Population

The Tromsø Study is a population-based, prospective study of various health issues and chronic diseases. It consists of 6 surveys of both sexes conducted in the municipality of Tromsø, Norway, from

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From Department of Heart Disease, Division of Cardiothoracic and Respiratory Medicine (J.M., K.R.) and Department of Neurology, Division of Neurosciences and Orthopedics (E.B.M.), University Hospital of North Norway, Tromsø; Departments of Community Medicine (J.M., T.W., M.-L.L., I.N., L.A.H., K.H.B.) and Clinical Medicine (E.B.M., K.R.), UiT, Arctic University of Norway, Tromsø; Department of Biostatistics, Institute of Basic Medical Science, University of Oslo, Norway (D.S.T.); Clinic for Heart Disease, St. Olavs University Hospital, Trondheim, Norway (K.H.B.); and Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim (K.H.B.).

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Correspondence to Jan Mannsverk, MD, Department of Heart Disease, Division of Cardiothoracic and Respiratory Medicine University Hospital of North Norway, 9038 Tromsø, Norway. E-mail jan.mannsverk@unn.no

1974 to 2008.[11] The present study includes participants from the surveys undertaken in 1994 to 1995, 2001 to 2002, and 2007 to 2008, including a total of 29 582 individuals ≥25 years and older who participated in 1, 2, or all 3 surveys. The attendance rates of the 1994–1995, 2001–2002, and 2007–2008 surveys were 72%, 79% and 66%, respectively. Table I in the online-only Data Supplement shows a summary of the surveys. Participants who had previous MI (n=734) or had emigrated before the date of examination (n=45) were excluded from the analyses. 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. The study was approved by the Regional Committee for Medical and Health Research Ethics and the Data Inspectorate of Norway. Each subject gave written informed consent.

Coronary Risk Factors

Each survey used a standardized almost-identical protocol including physical examination, blood sampling, and questionnaires.[11,12] Blood pressure was measured with an automatic device.[12] Nonfasting blood samples were analyzed by standard methods at the University Hospital of Northern Norway.[12] Smoking status was self-reported in a questionnaire. Participants were defined as physically active if they performed strenuous physical activity (ie, became sweaty and breathless) at least 1 h/wk.

Identification and Validation of Incident CHD

Incident cases of CHD were recorded from each participant's study entry in 1994 to 1995, 2001 to 2002, or 2007 to 2008 until December 31, 2010. Adjudication of hospitalized and out-of hospital events was performed by an independent end-point committee using 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 CHD were identified by linkage to the discharge diagnosis registry at the University Hospital of Northern Norway, the only hospital in the area, with search for *International Classification of Diseases, 10th Revision* codes I20 to I25, I46, R96, R98, and R99. Modified World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (MONICA)/MONICA Risk, Genetics, Archiving and Monograph (MORGAM) criteria were used and included clinical symptoms and signs, findings in electrocardiograms, values of cardiac biomarkers, and autopsy reports when applicable (http://www.thl.fi/publications/morgam/manual/contents.htm). Biomarkers considered were creatine kinase, its myocardial fraction (creatine kinase-MB), and troponin T beginning in 1999. Biomarker increases associated with revascularization procedures were not included as MI. The National Causes of Death Registry allowed identification of fatal cases of MI that occurred as out-of-hospital deaths and provided information on all-cause mortality. Death certificate information was used to collect relevant information from additional sources such as autopsy reports and records from nursing homes, ambulance services, and general practitioners. We classified hospitalized STEMI and non-STEMI by using standard criteria.[13] Out-of-hospital sudden death was defined as death caused by a probable MI (based on symptoms or autopsy) within 24 hours of symptom onset in nonhospitalized individuals or deaths in individuals brought to hospital with a cardiac arrest and unsuccessful resuscitation with no evidence of a noncoronary cause of death. Case fatality was defined as the proportion of incident CHDs that were fatal within 28 days. Dates of emigration were obtained from the Population Registry of Norway.

Statistical Analysis

Statistical analyses were performed with STATA 12 (StataCorp 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. Follow-up extended from study entry to the date of incident event, date of emigration, death, or end of follow-up, whichever came first. 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.[14] The proportional hazard assumption was verified by Schoenfeld residuals.

For incidence analysis, we used the split function to produce a new record for each follow-up year for each person, and age was updated every year that the participants were under follow-up. Crude event rates were estimated as the number of events per 100 000 person-years. 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. We used a symmetrical moving average with a span of 5. This means that we calculated the average of the first 2 lagged values, the current value, and the first 2 forward terms of the series, with each term in the average receiving a weight of 1. The CHD mortality decline explained by out-of-hospital sudden deaths was estimated as the difference in out-of-hospital sudden death 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.[15] 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 could be determined in those who participated in the 1994–1995 survey and was estimated by the expression $(\beta 0-\beta 1)/\beta 0$. We used the same long data set as for the incidence analyses described previously. The βs 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. A 2-sided significance level was used.

Results

We identified 1845 patients (39% women) with an incident CHD event between 1995 and 2010, representing a period of 375 064 person-years (Table 1). Seventy-eight percent of the patients (n=1441) were hospitalized. Among those were 523 patients (36%) with STEMI, 869 (60%) with non-STEMI, 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 sudden deaths and 341 deaths within 28 days after symptom onset. Thus, 58% of all fatal incident CHD events occurred as an out-of-hospital sudden death.

CHD Mortality

CHD mortality declined from 137 cases per 100 000 person-years in 1995 to 65 cases per 100 000 person-years in 2010 ($P<0.001$); out-of-hospital sudden death declined from 89 cases per 100 000 person-years in 1995 to 42 cases per 100 000 person-years in 2010 ($P<0.001$); and mortality rates among hospitalized MI patients declined from 50 cases per 100 000 person-years in 1995 to 28 cases per 100 000 person-years in 2010 ($P<0.001$; Figure, A). Thus, 65% of the decline in CHD mortality was attributable to a decrease in the rates of out-of-hospital sudden deaths.

Using Poisson regression models, we found that the age- and sex-standardized CHD mortality rate fell by 7.3% annually (95% CI, 5.6–8.9; $P<0.001$ for linear trend), the incidence of total CHD by 3.0% annually (95% CI, 2.0–4.0; $P<0.001$

Table 1. Baseline Distribution of Risk Factors According to Occurrence of CHD During Follow-Up: The Tromsø Study

Characteristic	No CHD (n=27 737), % (n)	Any CHD* (n=1845), % (n)	Out-of-Hospital Sudden Death†(n=332), % (n)	Hospitalized STEMI‡ (n=523), % (n)	Hospitalized Non-STEMI‡ (n=869), % (n)	*P* Value§
Male sex	46 (12 735)	61 (1130)	56 (186)	67 (351)	59 (515)	0.002
Age ≥60 y	17 (4750)	60 (1111)	73 (242)	49 (258)	61 (532)	<0.001
Hyperlipidemia‖	25 (6821)	51 (935)	47 (154)	55 (286)	50 (431)	0.05
Hypertension¶	31 (8725)	71 (1306)	76 (252)	65 (340)	72 (623)	0.002
Daily smoking	36 (9850)	41 (756)	39 (128)	49 (255)	37 (323)	<0.001
Overweight#	47 (12 942)	65 (1205)	60 (199)	67 (349)	67 (584)	0.04
Diabetes mellitus	2 (402)	7 (121)	7 (24)	5 (25)	8 (66)	0.11
Angina pectoris	2 (544)	14 (256)	15 (49)	10 (51)	16 (141)	0.003
High heart rate**	27 (7419)	33 (611)	40 (133)	32 (168)	32 (278)	0.02
Physical activity††	33 (9018)	20 (370)	15 (50)	23 (120)	21 (177)	0.02

CHD indicates coronary heart disease; and STEMI, ST-segment–elevation myocardial infarction.
*All baseline characteristics were significantly different among persons who did and did not develop CHD (all $P<0.001$).
†Nonhospitalized patients who survived 24 hours (n=72) were not included.
‡Patients hospitalized with unknown myocardial infarction subtype (n=49) were not included.
§*P* value for overall difference between out-of-hospital sudden death, hospitalized STEMI, and hospitalized non-STEMI.
‖Ratio of total cholesterol to HDL cholesterol >5.
¶Systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or using blood pressure lowering drugs.
#Body mass index >25 kg/m^2.
**Resting heart rate >80 bpm
††Strenuous physical activity ≥1 h/wk.

for linear trend), and case fatality by 4.0% annually (95% CI, 2.2–5.7; $P<0.001$ for linear trend; Figure, A–C). Thus, changes in incidence and case fatality contributed 43% and 57%, respectively, to the decline in CHD mortality.

Incidence of CHD

The age- and sex-adjusted incidence of hospitalized STEMI decreased from 132 cases per 100 000 person-years in 1995 to 80 cases per 100 000 person-years in 2010 (average annual decrease, 4.3%; 95% CI, 2.5–6.1; *P* value for linear trend <0.001; Figure, B). Similarly, there was a 7.6% (95% CI, 5.5–9.8; *P* value for linear trend <0.001) annual decline in out-of-hospital sudden death. In contrast, hospitalizations for non-STEMI increased from 120 cases per 100 000 person-years in 1995 to a peak of 203 cases per 100 000 person-years in 2003, followed by yearly decreases to 144 cases per 100 000 person-years in 2010. The increase in hospitalization for non-STEMI in the first half of the study period led to increased incidence rates for total CHD from 367 cases per 100 000 person-years in 1995

Table 2. Age-and Sex-Adjusted Hazard Ratios (95% CIs) for CHD by Baseline Risk Factors: The Tromsø Study

Characteristic	Any CHD (n=1845)	Out-of-Hospital Sudden Death* (n=332)	Hospitalized STEMI† (n=523)	Hospitalized Non-STEMI† (n=869)	*P* Value‡
Male sex	1.86 (1.70–2.05)	1.50 (1.21–1.86)	2.40 (2.00–2.88)	1.72 (1.50–1.97)	0.002
Age ≥60 y	7.60 (6.92–8.34)	12.95 (10.21–16.55)	4.75 (4.01–5.65)	8.11 (7.07–9.29)	<0.001
Hyperlipidemia§	2.01 (1.84–2.21)	1.66 (1.33–2.06)	2.41 (2.02–2.86)	1.94 (1.70–2.22)	0.02
Hypertension‖	1.82 (1.63–2.03)	1.75 (1.33–2.29)	1.70 (1.39–2.07)	1.92 (1.63–2.25)	0.63
Daily smoking	1.80 (1.64–2.00)	1.87 (1.49–2.35)	2.23 (1.87–2.65)	1.54 (1.34–1.77)	0.005
Overweight¶	1.43 (1.30–1.58)	1.10 (0.88–1.37)	1.58 (1.32–1.90)	1.55 (1.34–1.78)	0.02
Diabetes mellitus	2.44 (2.02–2.94)	2.18 (1.43–3.32)	1.88 (1.25–2.81)	2.86 (2.21–3.68)	0.19
Angina pectoris	2.19 (1.90–2.51)	1.78 (1.30–2.44)	1.73 (1.28–2.33)	2.74 (2.27–3.31)	0.01
High heart rate#	1.30 (1.18–1.43)	1.73 (1.39–2.16)	1.26 (1.05–1.52)	1.25 (1.08–1.44)	0.03
Physical activity**	0.84 (0.74–0.94)	0.73 (0.53–0.99)	0.88 (0.71–1.08)	0.85 (0.72–1.01)	0.60

CHD, coronary heart disease; CI, confidence interval; and STEMI, ST-segment–elevation myocardial infarction.
*Nonhospitalized patients who survived 24 hours (n=72) were not included.
†Patients hospitalized with unknown myocardial infarction subtype (n=49) were not included.
‡*P* value for overall difference between out-of-hospital sudden death, hospitalized STEMI, and hospitalized non-STEMI. All hazard ratios were adjusted for sex and age, except for male sex and age >60 years, which were not adjusted.
§Ratio of total cholesterol to high-density lipoprotein cholesterol >5.
‖Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or use of blood pressure–lowering drugs.
¶Body mass index >25 kg/m^2.
Resting heart rate >80 bpm.
**Strenuous physical activity ≥ 1 h/wk.

to a peak of 431 cases per 100 000 in 2000, then decreasing each year to 280 cases per 100 000 in 2010 (Figure, B).

Pre-Event Coronary Risk Factor Levels and Manifestations of CHD

Coronary risk factors were associated differently with out-of-hospital sudden death, hospitalized STEMI, and hospitalized non-STEMI (Table 2). Participants with sudden death were older, had higher resting heart rates, and were less likely to be physically active than those with STEMI or non-STEMI. Male sex, hyperlipidemia, and smoking were more strongly associated with STEMI than with non-STEMI and sudden death. Overweight was associated with increased risk of STEMI and non-STEMI but not with sudden death. Angina pectoris was a stronger risk factor for non-STEMI than for STEMI.

Changes in Coronary Risk Factors and the Decline in CHD

Major coronary risk factors changed favorably during the study period (Table 3). Mean levels of cholesterol, blood pressure, resting heart rate, and smoking were reduced, and physical activity was increased. In contrast, overweight and diabetes mellitus increased.

The proportion of the decline in the incidence of CHD that was attributable to changes in risk factors is presented in Table 4. The largest single contribution was declining cholesterol, which accounted for 32% of the observed 51% decline in incident CHD between 1995 and 2010. Changes in systolic blood pressure, smoking, resting heart rate, and physical activity each accounted for 9% to 14% of the decline in risk of CHD. Increases in body mass index and the prevalence of diabetes mellitus were associated with 7% and 2% increase in the risk of CHD, respectively. All risk factors together accounted for 66% of the decline in the incidence of CHD (Table 4): 64% in women and 61% in men (Tables II and III in the online-only Data Supplement).

Characteristics and Treatments of Hospitalized Patients

Peak creatine kinase levels was stable over time in patients with STEMI but decreased significantly in patients with non-STEMI, indicating that non-STEMIs became smaller in the latter part of the period (Table 5). The proportion of patients who developed Q waves on ECG decreased significantly over time among patients with both STEMI and non-STEMI. 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% (P=0.38) in STEMI patients and by 43% (P=0.01) in non-STEMI patients in 2005 to 2010 compared with 1995 to 1999.

Discussion

We found a substantial decline in CHD mortality between 1995 and 2010 that was driven by significant reductions in the incidence of out-of-hospital sudden death and STEMI. Changes in cardiovascular risk factors accounted for 66% of the change in hospitalized and nonhospitalized fatal and nonfatal CHD, with an upper CI close to 100%. This study thus extends results of previous studies that found modifiable risk factors to account for most cases of hospitalized, nonfatal MI.[16]

Table 3. Cardiovascular Risk Factor Levels in 1994 to 1995, 2001 to 2002, and 2007 to 2008: The Tromsø Study

Risk Factor	1994–1995 (n=15 718)	2001–2002 (n=6436)	2007–2008 (n=9569)	Relative Change From 1994–2008, %	*P* Value*
Age, mean (SD), y	54.8 (10.7)	62.9 (10.3)	59.7 (10.6)		<0.001
Male sex, % (n)	47 (7452)	42 (2686)	46 (4414)		0.81
Hyperlipidemia†	31 (30–32)	30 (29–31)	18 (17–19)	-42	<0.001
Total cholesterol, mmol/L	6.51 (6.49–6.53)	6.11 (6.09–6.14)	5.61 (5.59–5.63)	-14	<0.001
HDL cholesterol, mmol/L	1.55 (1.54–1.55)	1.45 (1.44–1.46)	1.52 (1.51–1.53)	-2	<0.001
Hypertension‡	52 (51–53)	47 (46–48)	48 (47–50)	-8	<0.001
Systolic blood pressure, mm Hg	141.9 (141.6–142.3)	136.6 (136.2–137.0)	135.5 (135.1–135.9)	-5	<0.001
Diastolic blood pressure, mm Hg	82.1 (81.9–82.3)	80.2 (79.9–80.4)	77.7 (77.5–78.0)	-5	<0.001
Drug-treated hypertension	8 (7–8)	14 (13–14)	19 (18–20)	138	<0.001
Daily smoking	34 (33–35)	31 (30–32)	22 (21–23)	-35	<0.001
Overweight§	55 (54–56)	63 (62–64)	63 (62–64)	15	<0.001
Diabetes mellitus	2.2 (1.9–2.4)	2.8 (2.5–3.1)	4.0 (3.7–4.4)	82	<0.001
Angina pectoris	3.1 (2.9–3.4)	2.9 (2.6–3.2)	2.2 (1.9–2.5)	-29	<0.001
High heart rate ‖	30 (29–31)	23 (22–24)	11 (10–11)	-63	<0.001
Physical activity¶	22 (21–23)	36 (34–37)	38 (37–39)	73	<0.001

Values (except for age and sex) are age- and sex-adjusted mean or prevalence (%) with 95% confidence interval for the age group of 40 to 79 years. HDL indicates high-density lipoprotein.

*Test for linear trend.

†Total cholesterol/HDL cholesterol ratio >5.

‡Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or the use of blood pressure–lowering drugs.

§Body mass index ≥25 kg/m^2.

‖Resting heart rate >80 bpm.

¶Strenuous physical activity ≥1 h/wk.

Table 4. Decline in the Risk of a First CHD Event and Percentage of Risk Declines Accounted for by Risk Factors: The Tromsø Study

Models	Calendar Time β Coefficient per Year	Decline in Risk per Year, % (95% CI)	Decline in Risk per 15 Years, %*	Explained Decline by Risk Factors†, % (95% CI)‡
Model 1, age+sex adjusted	−0.0475	4.6 (3.3 to 5.9)	50.9	Referent
Model 1+total cholesterol	−0.0323	3.2 (1.8 to 4.5)	38.4	31.9 (22.7 to 48.9)
Model 1+HDL cholesterol	−0.0473	4.6 (3.3 to 5.9)	50.8	0.4 (−1.2 to 2.7)
Model 1+SBP	−0.0408	4.0 (2.7 to 5.3)	45.7	14.2 (9.5 to 20.4)
Model 1+daily smoking	−0.0411	4.0 (2.7 to 5.3)	46.1	13.4 (8.8 to 20.3)
Model 1+BMI	−0.0508	5.0 (3.6 to 6.3)	53.3	−7.0 (−11.4 to −3.6)
Model 1+diabetes mellitus	−0.0486	4.7 (3.4 to 6.0)	51.7	−2.3 (−4.7 to −0.5)
Model 1+resting HR	−0.0406	4.0 (2.6 to 5.3)	45.6	14.5 (6.9 to 24.0)
Model 1 + physical activity	−0.0431	4.2 (2.9 to 5.5)	47.6	9.2 (5.0 to 14.5)
Model 1 + all risk factors	−0.0162	1.6 (0.1 to 3.0)	21.6	66.1 (47.6 to 96.8)

Physical activity refers to strenuous physical activity ≥1 h/wk. BMI indicates body mass index; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, resting heart rate; and SBP, systolic blood pressure

*Decline in risk over 15 years=100%×[1−exp(β×15)].

†Percentage of the observed decline in risk explained by the risk factors=100%×(β0−β1)/β0, where β0 is the coefficient for calendar time in the model with adjustment for age and sex only (model 1) and β1 is the coefficient for calendar time in the model with additional adjustment for the risk factor(s).

‡The 95% CI are estimated with 1000 bootstrapped samples.

In line with others, we found that changes in the rates of out-of-hospital sudden death had a stronger impact on CHD mortality trends than changes in mortality of hospitalized patients.[17] 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

Table 5. Characteristics, Treatments, and Case Fatality for Patients Hospitalized With MI in 1995 to 1999, 2000 to 2004, and 2005 to 2010: The Tromsø Study

	1995–1999	2000–2004	2005–2010	*P* Value*
Patients hospitalized with STEMI				
Patients, n	190	162	171	
Age, mean (SD), y	67.5 (12.2)	66.1 (12.8)	66.5 (11.9)	0.46
Male sex, % (n)	68 (130)	62 (101)	70 (120)	0.93
Q-wave in ECG at discharge, % (n)	81 (103)	65 (104)	58 (95)	<0.001
Peak creatine kinase, median (IQR), U/L	1489 (661–3327)	1403 (601–2896)	1411 (551–2540)	0.09
Revascularization within 28 days, % (n)	14 (26)	64 (103)	87 (149)	<0.001
β-Blockers at discharge, % (n)	79 (90)	94 (129)	89 (116)	0.038
Acetylsalicylic acid at discharge, % (n)	79 (90)	97 (134)	97 (127)	<0.001
Statins at discharge, % (n)	57 (64)	83 (114)	95 (124)	<0.001
Case fatality within 28 d, % (n)	15 (29)	16 (26)	11 (18)	
Relative risk	1 (Referent)	1.11 (0.66–1.90)	0.74 (0.42–1.35)	0.38
Patients hospitalized with non-STEMI				
Patients, n	216	300	353	
Age, mean (SD), y	69.3 (12.5)	71.2 (13.0)	72.7 (13.1)	0.006
Male sex, % (n)	64 (139)	56 (169)	59 (207)	0.86
Q-wave in ECG at discharge, % (n)	37 (61)	14 (40)	13 (45)	<0.001
Peak creatine kinase, median (IQR), U/L	762 (432–1431)	404 (187–961)	326 (130–876)	<0.001
Revascularization within 28 days, % (n)	15 (32)	48 (145)	55 (195)	<0.001
β-Blockers at discharge, % (n)	80 (117)	78 (198)	84 (223)	0.02
Acetylsalicylic acid at discharge, % (n)	81 (120)	86 (217)	86 (227)	0.035
Statins at discharge, % (n)	48 (69)	58 (114)	73 (192)	<0.001
Case fatality within 28 d, % (n)	19 (42)	12 (37)	14 (50)	
Relative risk	1 (Referent)	0.55 (0.36–0.86)	0.57 (0.38–0.86)	0.01

IOR indicates interquartile range; MI, myocardial infarction; and STEMI, ST-segment elevation myocardial infarction.

*Age- and sex-adjusted *P* values for linear trend.

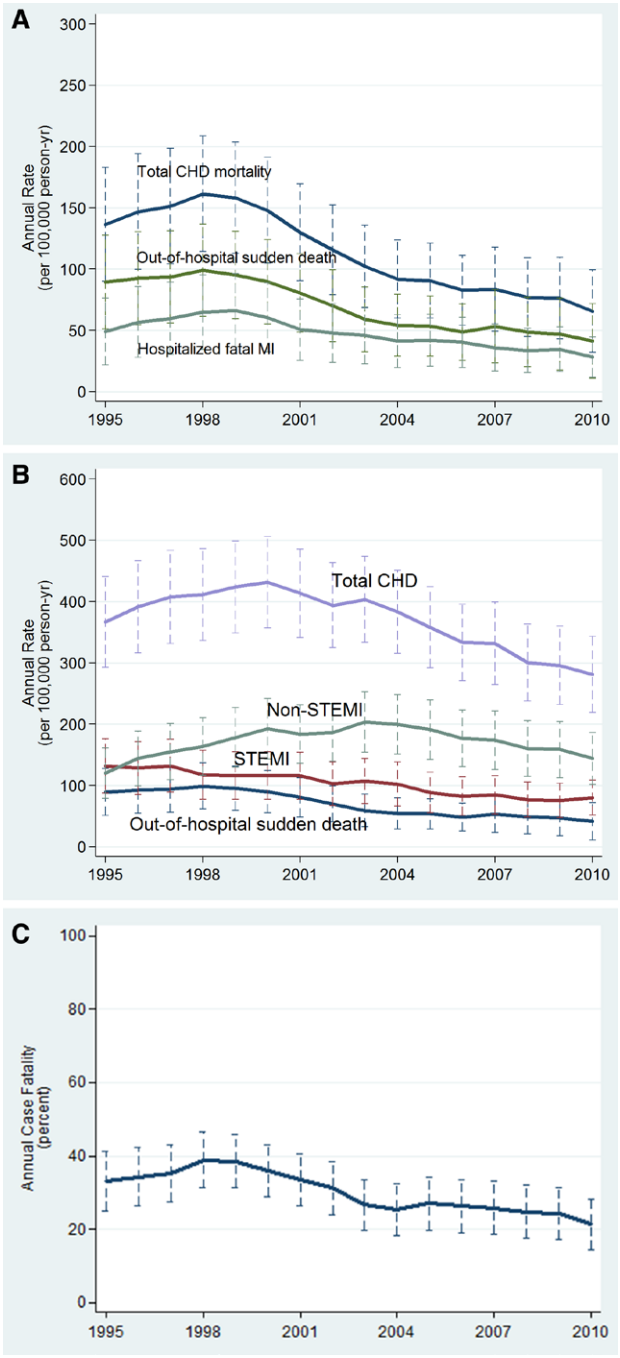

Figure 1. A, Trends in annual incidence rates of total coronary heart disease (CHD) mortality, out-of-hospital sudden death, and hospitalized fatal myocardial infarctions (MIs), 1995 to 2010, the Tromsø Study. The incidence rates are fitted as 5 years–moving mean. Each bar represents 95% confidence intervals. Rates are directly age- and sex-standardized to the Tromsø population. **B**, Trends in annual incidence rates of coronary heart disease, 1995 to 2010, the Tromsø Study. The incidence rates are fitted as 5 years–moving mean. Each bar represents 95% confidence intervals. Rates are directly age- and sex-standardized to the Tromsø population. STEMI indicates ST-segment–elevation myocardial infarction. **C**, Trends in annual case fatality proportion, 1995 to 2010, the Tromsø Study. The case fatality proportions are fitted as 5 years–moving mean and directly age- and sex-standardized with the event cohort as the standard population. Each bar represents 95% confidence intervals.

in populations, shown by the association between coronary risk factors and out-of-hospital sudden deaths. Thus, sudden death is a preventable condition.[18,19]

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.[20,21] In line with this, others have found that cholesterol is associated with rupture of vulnerable plaques and that smoking is associated with coronary thrombosis.[19]

Higher resting heart rate was more strongly associated with out-of-hospital sudden death than with STEMI or non-STEMI (Table 2). Higher heart rates are associated with myocardial ischemia, ventricular arrhythmias, and coronary atherosclerosis.[22–24] 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. The prevalence of self-reported angina pectoris fell by 29% (Table 3), suggesting that risk factor changes led to the less coronary atherosclerosis.

As observed earlier, we found an increasing incidence of non-STEMI in the first part of the study period,[21,25,26] likely reflecting the use of more sensitive biomarkers that detect smaller myocardial necrosis. This is supported by declining peak creatine kinase levels among non-STEMI patients, whereas the levels were stable in STEMI patients. We believe that the decline in STEMI is real and that the initial changes in non-STEMI reflect increased diagnostic sensitivity.

A strength of our study is that we used data on an individual level from a population-based study with a high attendance rate and standardized survey methods. In addition, case finding followed a standardized protocol for ascertainment of out-of-hospital and hospitalized events. The inclusion of incident cases only reduces the possibility that previous cardiovascular disease might have affected the risk factor levels. Finally, loss to follow-up is negligible because hospital treatment in Norway is free of charge and because of the use of the unique personal identity number to search official health registries.

Our study has limitations. We have included a largely homogeneous population from Norway that is distinct from the US population in which the rate of physical activity is lower, the rate of obesity is greater, and the smoking rate is lower. The autopsy rate for individuals with out-of-hospital deaths in our study was low (9%). This can lead to misclassifications even if the predominant cause of sudden death is CHD.[18,27,28] In addition, the true effect of changes in diagnostic sensitivity of biomarkers could not be fully quantified. The potential bias from this would be an overestimation of the incidence of MI in later years. The associations between trends in CHD and risk factors were necessarily based on attendees in subsequent surveys and not the entire source population, which could have introduced response and survival biases. 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, substantial benefits from smoking cessation, changes in blood lipids, and changes in blood pressure have been observed within 1 to 3 years.[29,30]

Conclusions

The substantial decline in CHD mortality was driven by significant reductions in the incidence of out-of-hospital sudden death 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. Favorable changes in modifiable risk factors accounted for 66% of the decline in fatal and nonfatal CHD events in this population.

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Disclosures

None.

References

1. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe: epidemiological update. *Eur Heart J*. 2013;34:3028–3034. doi: 10.1093/eurheartj/eht356.
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129:399–410. doi: 10.1161/01.cir.0000442015.53336.12.
3. Yeh RW, Go AS. Rethinking the epidemiology of acute myocardial infarction: challenges and opportunities. *Arch Intern Med*. 2010;170:759–764. doi: 10.1001/archinternmed.2010.88.
4. Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation*. 2004;109:1101–1107. doi: 10.1161/01.CIR.0000118498.35499.B2.
5. Laatikainen T, Critchley J, Vartiainen E, Salomaa V, Ketonen M, Capewell S. Explaining the decline in coronary heart disease mortality in Finland between 1982 and 1997. *Am J Epidemiol*. 2005;162:764–773. doi: 10.1093/aje/kwi274.
6. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med*. 2007;356:2388–2398. doi: 10.1056/NEJMsa053935.
7. O'Flaherty M, Buchan I, Capewell S. Contributions of treatment and lifestyle to declining CVD mortality: why have CVD mortality rates declined so much since the 1960s? *Heart*. 2013;99:159–162. doi: 10.1136/heartjnl-2012-302300.
8. Hotchkiss JW, Davies CA, Dundas R, Hawkins N, Jhund PS, Scholes S, Bajekal M, O'Flaherty M, Critchley J, Leyland AH, Capewell S. Explaining trends in Scottish coronary heart disease mortality between 2000 and 2010 using IMPACTSEC model: retrospective analysis using routine data. *BMJ*. 2014;348:g1088.
9. Hu FB, Stampfer MJ, Manson JE, Grodstein F, Colditz GA, Speizer FE, Willett WC. Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women. *N Engl J Med*. 2000;343:530–537. doi: 10.1056/NEJM200008243430802.
10. Hardoon SL, Whincup PH, Lennon LT, Wannamethee SG, Capewell S, Morris RW. How much of the recent decline in the incidence of myocardial infarction in British men can be explained by changes in cardiovascular risk factors? Evidence from a prospective population-based study. *Circulation*. 2008;117:598–604. doi: 10.1161/CIRCULATIONAHA.107.705947.
11. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njølstad I. Cohort profile: the Tromso Study. *Int J Epidemiol*. 2012;41:961–967. doi: 10.1093/ije/dyr049.
12. Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njølstad I. The sixth survey of the Tromso Study (Tromso 6) in 2007-08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. *Scand J Public Health*. 2013;41:65–80. doi: 10.1177/1403494812469851.
13. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction; ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33:2551–2567. doi: 10.1093/eurheartj/ehs184.
14. Lunn M, McNeil D. Applying Cox regression to competing risks. *Biometrics*. 1995;51:524–532.
15. Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations: Monitoring Trends and Determinants in Cardiovascular Disease. *Lancet*. 1999;353:1547–1557.
16. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952. doi: 10.1016/S0140-6736(04)17018-9.
17. Salomaa V, Ketonen M, Koukkunen H, Immonen-Räihä P, Jerkkola T, Kärjä-Koskenkari P, Mähönen M, Niemelä M, Kuulasmaa K, Palomäki P, Mustonen J, Arstila M, Vuorenmaa T, Lehtonen A, Lehto S, Miettinen H, Torppa J, Tuomilehto J, Kesäniemi YA, Pyörälä K. Decline in out-of-hospital coronary heart disease deaths has contributed the main part to the overall decline in coronary heart disease mortality rates among persons 35 to 64 years of age in Finland: the FINAMI study. *Circulation*. 2003;108:691–696. doi: 10.1161/01.CIR.0000083720.35869.CA.
18. Adabag AS, Peterson G, Apple FS, Titus J, King R, Luepker RV. Etiology of sudden death in the community: results of anatomical, metabolic, and genetic evaluation. *Am Heart J*. 2010;159:33–39. doi: 10.1016/j.ahj.2009.10.019.
19. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997;336:1276–1282. doi: 10.1056/NEJM199705013361802.
20. Myerson M, Coady S, Taylor H, Rosamond WD, Goff DC Jr; ARIC Investigators. Declining severity of myocardial infarction from 1987 to 2002: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2009;119:503–514. doi: 10.1161/CIRCULATIONAHA.107.693879.
21. Roger VL, Weston SA, Gerber Y, Killian JM, Dunlay SM, Jaffe AS, Bell MR, Kors J, Yawn BP, Jacobsen SJ. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. *Circulation*. 2010;121:863–869. doi: 10.1161/CIRCULATIONAHA.109.897249.
22. Johansen CD, Olsen RH, Pedersen LR, Kumarathurai P, Mouridsen MR, Binici Z, Intzilakis T, Køber L, Sajadieh A. Resting, night-time, and 24 h heart rate as markers of cardiovascular risk in middle-aged and elderly men and women with no apparent heart disease. *Eur Heart J*. 2013;34:1732–1739. doi: 10.1093/eurheartj/ehs449.
23. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med*. 2005;352:1951–1958. doi: 10.1056/NEJMoa043012.
24. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, Steg PG, Tardif JC, Tavazzi L, Tendera M; Heart Rate Working Group. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol*. 2007;50:823–830. doi: 10.1016/j.jacc.2007.04.079.

25. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155–2165. doi: 10.1056/NEJMoa0908610.
26. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med*. 2011;124:40–47. doi: 10.1016/j.amjmed.2010.07.023.
27. Engdahl J, Holmberg M, Karlson BW, Luepker R, Herlitz J. The epidemiology of out-of-hospital "sudden" cardiac arrest. *Resuscitation*. 2002;52:235–245.
28. Chugh SS, Reinier K, Teodorescu C, Evanado A, Kehr E, Al Samara M, Mariani R, Gunson K, Jui J. Epidemiology of sudden cardiac death: clinical and research implications. *Prog Cardiovasc Dis*. 2008;51:213–228. doi: 10.1016/j.pcad.2008.06.003.
29. Capewell S, O'Flaherty M. Rapid mortality falls after risk-factor changes in populations. *Lancet*. 2011;378:752–753. doi: 10.1016/S0140-6736(10)62302-1.
30. Capewell S, O'Flaherty M. Can dietary changes rapidly decrease cardiovascular mortality rates? *Eur Heart J*. 2011;32:1187–1189. doi: 10.1093/eurheartj/ehr049.

CLINICAL PERSPECTIVE

We used individual person data from repeated surveys of a general population to study the incidence and outcome of myocardial infarction (MI). From 1995 to 2010, the age- and sex-adjusted incidence of MI decreased by 3%/y. The decline was driven by decreases in both out-of-hospital sudden death probably caused by MI and hospitalized ST-segment–elevation MI. In contrast, the incidence of hospitalized non–ST-segment–elevation MI increased in the first part of the study period, probably reflecting the use of more sensitive biomarkers for myocardial damage. We found a reduction in case fatality among hospitalized patients. The decline in event rates and case fatality each explained 50% of the decline in MI mortality. Sixty-six percent of the decline in MI incidence could be explained by favorable time trends in coronary risk factors. The population mean cholesterol level fell 14% between 1995 and 2008. This accounted for 32% of the decline in MI incidence. These results indicate that population-wide changes in risk factor levels have a large potential for reducing the MI incidence in a population. This study also found that risk factors had different impacts on subtypes of MI, suggesting that the spectrum of MI manifestations among populations and over time may differ, depending on the prevalence of risk factors. The association between risk factors and out-of-hospital sudden death indicates that primary prevention by modification of risk factors will influence both incident MI and case fatality in populations.

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Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population

Jan Mannsverk, Tom Wilsgaard, Ellisiv B. Mathiesen, Maja-Lisa Løchen, Knut Rasmussen, Dag S. Thelle, Inger Njølstad, Laila Arnesdatter Hopstock and Kaare Harald Bønaa

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SUPPLEMENTAL MATERIAL

Supplemental table 1. Study population. The Tromsø Study

Examination year	Age groups (years)	Invited	Attended (%)*
1994-95	25-97	37558	27158 (77)
2001-02	30-89	10353	8130 (79)
2007-08	30-87	19762	12984 (66)

*Adjusted for deaths, emigration from Tromsø during the survey period etc.

Supplemental table 2. Fall in the risk of a first coronary heart disease event and percentage of this fall explained by risk factors from Poisson regression analyses with time-dependent covariates in men. The Tromsø Study.

Models	Calendar time β–coefficient, per year	Fall in risk per year, % (95% CI)	Fall in risk per 15 years, %*	Explained decline by risk factors†, % (95% CI)‡
Model 1, age+ sex adjusted	-0.0500	4.9 (3.2, 6.5)	52.7	Ref
Model 1 + total cholesterol, mmol/l	-0.0330	3.2 (1.5, 4.9)	39.0	34.0 (22.1, 54.5)
Model 1 + HDL cholesterol, mmol/l	-0.0501	4.9 (3.2, 6.5)	52.8	-0.3 (-2.8, 2.1)
Model 1+ SBP, mmHg	-0.0450	4.4 (2.7, 6.0)	49.1	10.0 (5.7, 17.1)
Model 1 + daily smoking	-0.0435	4.3 (2.6, 5.9)	48.0	12.8 (7.3, 21.4)
Model 1 + BMI, kg/m^2	-0.0560	5.4 (3.8, 7.1)	56.9	-12.2 (-20.8, -6.7)
Model 1 + diabetes mellitus	-0.0510	5.0 (3.3, 6.6)	53.5	-2.1 (-5.1, -0.2)
Model 1 + resting HR beats/min	-0.0432	4.2 (2.5, 5.9)	47.7	13.6 (6.3, 24.1)
Model 1 + physical activity	-0.0455	4.4 (2.8, 6.1)	49.5	8.9 (4.5, 15.0)
Model 1 + all risk factors	-0.0194	1.9 (0.1, 3.7)	25.2	61.4 (41.4, 95.0)

* Fall in risk over 15 years=100% x [1-exp (β x 15)]. † Percentage of the observed decline in risk explained by the risk factors = 100% x (β0-β1)/β0 where β0 is the coefficient for calendar time in the model with adjustment for age and sex only (model 1), and β1 is the coefficient for

calendar time in the model with additional adjustment for the risk factor(s). ‡ 95% CI are estimated using 1000 bootstrapped samples. SBP denotes systolic blood pressure, BMI body mass index, HR resting heart rate, and physical activity strenuous physical activity ≥ 1 hour per week..

Supplemental table 3. Fall in the risk of a first coronary heart disease event and percentage of this fall explained by risk factors from Poisson regression analyses with time-dependent covariates in women. The Tromsø Study.

Models	Calendar time β–coefficient, per year	Fall in risk per year, % (95% CI)	Fall in risk per 15 years, %*	Explained decline by risk factors†, % (95% CI)‡
Model 1, age+ sex adjusted	-0.0382	3.7 (1.5, 5.9)	43.6	Ref
Model 1 + total cholesterol, mmol/l	-0.0295	2.9 (0.6, 5.2)	35.8	22.7 (6.5, 66.0)
Model 1 + HDL cholesterol, mmol/l	-0.0378	3.7 (1.5, 5.9)	43.3	1.0 (-1.8, 7.0)
Model 1+ SBP, mmHg	-0.0300	2.9 (0.7, 5.2)	36.3	21.4 (11.6, 48.3)
Model 1 + daily smoking	-0.0343	3.4 (1.1, 5.6)	40.2	10.1 (3.1, 27.1)
Model 1 + BMI, kg/m^2	-0.0391	3.8 (1.6, 6.0)	44.3	-2.2 (-6.8, 1.0)
Model 1 + diabetes mellitus	-0.0394	3.9 (1.6, 6.0)	44.6	-3.0 (-10.1, 1.0)
Model 1 + resting HR beats/min	-0.0315	3.1 (0.8, 5.4)	37.7	17.6 (1.5, 45.2)
Model 1 + physical activity	-0.0347	3.4 (1.1, 5.6)	40.5	9.3 (-2.4, 26.1)
Model 1 + all risk factors	-0.0136	1.4 (-1.1, 3.8)	18.5	64.3 (33.2, 152.0)

* Fall in risk over 15 years=100% x [1-exp (β x 15)]. † Percentage of the observed decline in risk explained by the risk factors = 100% x (β0-β1)/β0 where β0 is the coefficient for calendar time in the model with adjustment for age and sex only (model 1), and β1 is the coefficient for

calendar time in the model with additional adjustment for the risk factor(s). ‡ 95% CI are estimated using 1000 bootstrapped samples. SBP denotes systolic blood pressure, BMI body mass index, HR resting heart rate, and physical activity strenuous physical activity ≥ 1 hour per week..

Paper 3

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Trends in clinical outcomes and survival following prehospital thrombolytic therapy given by ambulance clinicians for ST-elevation myocardial infarction in rural sub-arctic Norway

Jan Mannsverk[1], Terje Steigen[1,2], Harald Wang[1], Pål Morten Tande[1], Birgitte Mannsverk Dahle[1], Maret Lajla Nedrejord[1], Ida Olsen Hokland[1] and Mads Gilbert[2,3,4]

Abstract

Background: Prehospital thrombolytic therapy given by ambulance emergency medical services to patients with acute ST-segment elevation myocardial infarction (STEMI) may produce earlier reperfusion than percutaneous coronary intervention. Clinical results from prehospital thrombolytic therapy in rural areas are scarce.

Methods: We studied outcomes during 11 years of a prehospital thrombolytic therapy system in rural sub-arctic Norway. Ambulance personnel gave protocol basic treatment and transmitted electrocardiograms to hospital physicians who made the decision for prehospital thrombolytic therapy. The study was divided into three time periods; 2000–2003, 2004–2007 and 2008–2011.

Results: A total of 385 STEMI patients received prehospital thrombolytic therapy, median patient age was 61.2 years, and 77% were men. Time saved by prehospital reperfusion therapy was 131 minutes. The proportion who got prehospital thrombolytic therapy within 2 hours of symptom onset increased from 21% in 2000–2003 to 39% in 2008–2011 (P=0.003). The proportion who underwent coronary angiography or percutaneous coronary intervention within 24 hours of first medical contact increased from 56.4% to 95.4% (P<0.001). Post-STEMI systolic heart failure decreased from 19.4% to 8.1% (P=0.02), while 1-year mortality fell, non-significantly, by 50% over time to reach 5.6%. Thirteen patients suffered acute out-of-hospital cardiac arrest; all were successfully defibrillated. Ten patients had major bleeding events (2.6%).

Conclusion: A decentralised prehospital thrombolytic therapy system based on ambulance personnel, telemetry and centralised 7/24 invasive diagnosis and treatment service, combined with system maturation over time, was associated with earlier reperfusion, improved clinical outcomes and better survival. Prehospital thrombolytic therapy is a feasible and safe intervention used in rural settings with long evacuation lines to percutaneous coronary intervention facilities.

Keywords

Thrombolytic therapy, emergency medical services, prehospital, myocardial infarction, STEMI, rural

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[1]Department of Cardiology, University Hospital of North Norway, Norway
[2]Cardiovascular Diseases Research Group, UiT The Arctic University of Norway, Norway
[3]Clinic of Emergency Medical Services, University Hospital of North Norway, Norway
[4]Anesthesia and Critical Care Research Group, UiT The Arctic University of Norway, Norway

Corresponding author:
Jan Mannsverk, Department of Cardiology, University Hospital of North Norway, Tromsø 9038, Norway.
Email: jan.mannsverk@unn.no

Introduction

Percutaneous coronary intervention (PCI) is preferred over thrombolytic therapy in acute ST-segment elevation myocardial infarction (STEMI), but only if PCI is performed in a timely fashion.[1,2] Patients suffering acute STEMI far away from PCI centres may have significant delays in reaching primary PCI. These patients benefit from earliest possible STEMI diagnosis and prehospital thrombolytic therapy (PHT) given by 'ambulance clinicians' (ambulance paramedics with extended training).[3–6] Twenty years ago, Rawles et al. concluded that the magnitude of the benefit from earlier thrombolytic therapy is such that giving thrombolytic therapy to patients with acute myocardial infarction 'should be accorded the same degree of urgency as treatment of cardiac arrest'. It was recommended to give thrombolytic therapy on-site by the first qualified medical person to see the patient.[7,8] Combination of early PHT before immediate transport to a PCI centre is the preferred strategy (the pharmaco-invasive strategy) for rural STEMI patients far away from hospital.[1,2]

We studied the implementation and clinical results of the pharmaco-invasive strategy for STEMI patients in rural sub-arctic north Norway during 11 years following the introduction of community-based PHT.

Methods

Programme implementation

The north-Norwegian region covers an area of 112,975 km^2 and has a population of 483,000 inhabitants. A well-developed public emergency medical service with 150 ground, sea and air ambulances with professional ambulance clinicians works closely with primary healthcare general practitioners (GPs) and decentralised primary healthcare centres.

The University Hospital of North Norway (UNN Tromsø) in the regional capital Tromsø (72,000 inhabitants), serves as PCI and open-heart surgery centre for 12 local emergency hospitals, performing around 800 emergency angioplasties annually.

In 1999 we expanded diagnosing and early treatment of acute coronary syndrome (ACS) to the municipality level and trained the ambulance clinicians (mainly ambulance paramedics) and GPs in early diagnosis, stabilisation and administration of PHT to STEMI patients.

We trained about 300 ambulance clinicians at 48 prehospital ground and three boat ambulance stations, all air ambulance crews, dispatch and emergency nurses and GPs in UNN Tromsø's 25 local hospital catchment area municipalities and relevant hospital staff in early diagnosis and management of ACS/STEMI, use of 12-lead telemedicine ECG, morphine, oxygen, nitroglycerine, acetylsalicylic acid (MONA) – and PHT treatment. We used a dedicated written form with checklist to document the indication and treatment of each patient.

All prehospital units were equipped with PHT kits (ECG machine with telemetry, thrombolytic agent, anticoagulants, standard checklist and documentation form). Following the pilot project (2000–2004), we introduced new multimonitors/defibrillators with telemetric, 12-lead ECG (ZOLL-M; ZOLL Medical Corporation, Chelmsford, MA, USA), and changed the fibrinolytic drug from reteplase (Rapilysin) to tenecteplase (Metalyse). All costs were covered by the regional hospital trust. The public was informed by media campaigns.

Clinical procedures

Patients with presumed STEMI calling the public emergency medical number (113) or local Doctor's Watch were triaged according to the national criteria-based dispatch protocol (Norwegian Index for Emergency Medical Dispatch) and allocated the highest urgency category eliciting the fastest ambulance response.[9] Upon arrival, the chest pain patient was given MONA, connected to the automated external defibrillator by defibrillation pads prior to the acquisition of a diagnostic 12-lead ECG that was telemetrically transferred to the hospital's emergency medical dispatch centre.

Decision-makers for PHT were GPs or hospital physicians on call following evaluation of ECG and patient history. PHT-eligible patients received a weight-based dose of intravenous tenecteplase followed by intravenous enoxaparin 30 mg in patients under 75 years of age. Ground or air ambulance transfer to the cardiac care unit or catheter laboratory at UNN Tromsø followed regional guidelines for PHT or primary PCI.

Study population and inclusion criteria

The study population came from UNN Tromsø's local catchment area (23,100 km^2) with about 125,000 inhabitants and 80–100 STEMI patients annually. Average ground ambulance mission distance and duration to UNN Tromsø is 190 km or 137 minutes. We included patients with PHT decisions based on 12-lead ECG transmitted to the dispatch centre in UNN Tromsø. Criteria for STEMI required to start PHT treatment were central chest pain with or without radiation, pain duration between 20 minutes and 6 hours, and ECG indicative of an acute STEMI: 2 mV or greater ST-segment elevation in at least two contiguous leads or presumed new left bundle branch block. Exclusion criteria were age greater than 80 years or standard contraindications to thrombolysis.

Data registration

Data were obtained from a prospectively collected registry at UNN Tromsø organised 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 searched the discharge diagnosis registry at UNN Tromsø for International Classification of Diseases 10th Revision codes I21 and I46 to identify eligible patients.

We collected demographic data, times of symptom onset, ambulance arrival, prehospital ECG, start of MONA and PHT treatment, out-of-hospital cardiac arrest (OHCA),[10] arrival at the emergency department and cardiac care unit and time of coronary angiography and PCI at UNN Tromsø. Appropriateness of PHT, adverse PHT events, inhospital echocardiography, ECG, biomarkers, and patient discharge diagnosis were recorded.

Coronary angiography and PCI were performed according to standard procedures, and subsequent treatment strategy was at the discretion of the interventional cardiologist. Left ventricular ejection fraction (LVEF) at discharge was available in 82% of the patients, 79% determined by echocardiography, the rest by cardiac ventriculography or multigated acquisition scan. We defined systolic heart failure as LVEF less than 40%. Major bleeding was defined according to Bleeding Academic Research Consortium (BARC) type 2–5 bleeding.[11] The date of death was obtained from the national Central Norwegian Population Register for the calculation of 1-year case fatality. To investigate possible time trends, the study was divided into three time periods: 2000–2003, 2004–2007 and 2008–2011.

We have incomplete data on STEMI patients not treated with PHT (i.e. primary PCI). A local registry of invasive cardiology was not established before mid-2000. We have data for the period 2006–2011, while some data are missing or not quality assured.

Statistical methods

Data were expressed as medians (with 25th–75th percentile) or percentages. The chi-squared test was used for comparison 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. A *P* value of less than 0.05 (two-sided test) was considered significant. All statistical analyses were done using STATA 14 (StataCorp LP, College Station, TX, USA).

The data protection officer at UNN Tromsø approved the project as a quality control study.

Results

During March 2000 to December 2011 we included 385 patients with presumed acute STEMI, which accounted for 40% of all STEMIs in the recording area during this time period. Successful ECG transmission from ambulances to UNN Tromsø was completed in 98.7% of cases. ECG criteria for STEMI were present in 357 (92.7%) patients, but not in 24 patients (6.2%), six of whom did not have an ACS. Prehospital ECG was missing in four patients. About a quarter of the PHT treatments were given by ambulance clinicians alone, without a medical doctor present. The decision to start PHT was always made by medical doctor(s), typically the on-call hospital cardiologist. Anterior and inferior wall myocardial infarction accounted for 46% (*n*=177) and 43% (*n*=167), respectively, unstable angina 3% (*n*=11), while 7.8% (*n*=30) did not suffer from ACS and should not have been given PHT.

Patient characteristics and time delays

Patient characteristics, time delays and invasive procedures for the whole population of STEMI patients during the study period are summarised in Table 1. Median age was 61.2 years and 77% were men. The median time from onset of chest pain to ECG was 110 minutes and the median time from first prehospital ECG (first medical contact (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 hospital following PHT was 93 minutes. Median time from FMC to angiography was 7.4 hours. The majority (82%) of patients underwent coronary angiography within 24 hours. A total of 69% received PCI while 10% underwent coronary artery bypass grafting during hospital stay. Median time from hospital admission to primary PCI (door-to-balloon) is estimated at 38 (20–97) minutes in our hospital.[12] Thus, early prehospital diagnosis and thrombolytic therapy saved 2 hours 11 minutes to initiation of reperfusion therapy.

Time trends for PHT and invasive procedures

The age and sex distribution of the patients did not differ among the time periods (Table 1). The median time from symptom onset to start of PHT decreased non-significantly from 155 minutes in 2000–2003 to 146 minutes in 2008–2011 (*P*=0.07). The proportion of patients who received PHT within 2 hours after symptom onset increased significantly from 21% in 2000–2003 to 39% in 2008–2011 (*P*=0.003). We found a non-significant trend of decreasing time from symptom onset to first ECG from 113 minutes in 2000–2003 to 108 minutes in 2008–2011.Time from first ECG to the start of PHT remained relatively constant over the years. Median time from PHT to hospital admission increased significantly over time. The proportion of patients receiving inappropriate PHT fell from 13.6% in 2000–2003 to 2.2% in 2008–2011 (*P*=0.002).

The use of coronary angiography, PCI and coronary artery bypass grafting increased over time (Table 1).Time from FMC to coronary angiography or PCI decreased

Table 1. Characteristics of patients treated with PHT for assumed STEMI during 2000 to 2011.

Variable[a]	2000–2011 (*N*=385)	2000–2003 (*N*=140)	2004–2007 (*N*=155)	2008–2011 (*N*=90)	*P* value[b]
Patient characteristic					
Male sex,% (n)	77 (295)	76 (106)	75 (116)	81 (73)	0.40
Age, median (IQR), years	61.2 (53.2–69.8)	61.9 (53.1–71.3)	60.7 (53.4–69.8)	61.4 (53.4–67.7)	0.61
Time delays					
Symptom onset to ECG, median (IQR), minutes	110 (65–170)	113 (84–175)	103 (57–161)	108 (62–165)	0.12
Prehospital ECG to PHT, median (IQR), minutes	36 (25–53)	34 (26–50)	37 (25–55)	36 (23–53)	0.72
Symptom onset to PHT, median (IQR), minutes	150 (108–211)	155 (124–210)	143 (105–207)	146 (93–218)	0.07
Symptom onset to PHT <2 hours, % (*n*)	30.7 (116)	21.3 (29)	34.0 (52)	39.3 (35)	0.003
PHT to hospital arrival, median (IQR), minutes	93 (67–132)	83 (63–111)	90 (65–130)	122 (85–148)	<0.001
FMC to angiography, median (IQR), hours	7.4 (3.3–21.1)	23.7 (4.1–53.2)	5.7 (3.1–14.2)	4.3 (2.9–14.3)	<0.001
FMC to angiography <24 hours, % (*n*)	81.8 (270)	56.4 (57)	91.5 (130)	95.4 (83)	<0.001
Inappropriate PHT, % (*n*)					
	7.8 (30)	13.6 (19)	5.8 (9)	2.2 (2)	0.002
Invasive procedures					
Coronary angiography, % (*n*)	87.8 (338)	73.6 (103)	94.2 (146)	98.9 (89)	<0.001
Percutaneous coronary intervention, % (*n*)	69.1 (266)	60.0 (84)	72.3 (112)	77.8 (70)	0.003
Coronary artery bypass grafting, % (*n*)	9.9 (38)	4.3 (6)	12.3 (19)	14.4 (13)	0.01

PHT: prehospital thrombolytic therapy; STEMI: ST-segment elevation myocardial infarction; IQR: interquartile range; FMC: first medical contact.
[a]Continuous variables are summarised as medians (with 25th–75th percentile/IQR) and categorical variables as proportions (with number).
[b]Test for linear trend, logistic regression for binary variables, and Jonckheere's trend test for continuous variables.

sharply from 23.7 hours in 2000–0303 to 4.3 hours in 2008–2011 (P<0.001). The proportion of patients receiving thrombolytic therapy who had coronary angiography or PCI within 24 hours of FMC increased from 56.4% to 95.4% (P<0.001). Inhospital use of evidence-based medical treatments during the hospital stay increased gradually over the same 11-year period, according to guidelines shift.[2]

Based on our local registry of invasive cardiology (containing data from 2006 onwards), an increasing number of STEMI patients received primary PCI from 2006 to 2011, while the proportion treated with PHT was reduced from about 40% to 30% (data not shown). Patients with shorter evacuation time to the PCI centre received primary PCI while patients from more remote areas were still triaged to PHT treatment. This might explain why fewer patients received PHT from 2008 to 2011 (Table 1) and why time from PHT to hospital arrival increased in the same period.

Time trends in outcomes in relation to time period

Inhospital mortality was 4.4% and 1-year mortality was 8.1% for the whole study period (Table 2). The 1-year mortality fell from 11.4% in 2000–2003 to 5.6% in 2008–2011 (P=0.09). The proportion who developed systolic heart failure decreased significantly over time from 19.4% in 2000–2003 to 8.1% in 2008–2011 (P=0.02). Maximum troponin levels decreased significantly over time (P=0.03).

Trends in outcomes in relation to time delay between symptom onset and prehospital thrombolysis

Mortality and systolic heart failure were related to age, but not gender. When stratified according to time to start of PHT, we found a stepwise increase in subsequent systolic heart failure and 1-year mortality (Table 3). In regression analysis adjusting for age and gender, these associations were significant (P=0.002 and P=0.01, respectively). The results were similar when time period was included as a covariate in the analyses. When adjusted for age and gender, we found that the risk of dying within 1 year increased by 14% for each 30 minutes delays to PHT treatment (odds ratio (OR) 1.14, 95% confidence interval (CI) 1.04–1.25, P=0.004). We also found a stepwise increase in 1-year mortality with decreasing LVEF (1.0%, 9.6%, 15.4% and 35.7%, with LVEF >50%, 41–50%, 31–40% and <30%, respectively).

Rescue PCI

Among the 355 patients with ACS, 198 patients (56%) obtained successful ST-segment resolution (≥50%), and 127 patients (36%) obtained less than 50% ST-segment resolution. One-year mortality was 4% and 11%, respectively (P=0.01). We lack information about ST-segment resolution in 30 patients (8%). Based on our registry of

Table 2. Left ventricular function, maximum troponin levels, and mortality among patients treated with PHT during 2000 to 2011.

Variable[a]	2000–2011 (N=385)	2000–2003 (N=140)	2004–2007 (N=155)	2008–2011 (N=90)	*P* value[b]
Outcomes					
Left ventricular EF <40%, % (*n*)[c]	12.7 (40)	19.4 (21)	9.8 (13)	8.1 (6)	0.02
1-year mortality, % (*n*)	8.1 (31)	11.4 (16)	6.5 (10)	5.6 (5)	0.09
Q-wave myocardial infarction, % (*n*)[c]	69.7 (239)	73.4 (83)	70.6 (101)	63.2 (55)	0.13
Peak troponin T, median (IQR), µg/L[c,d]	6.1 (2.8–10.85)	7.3 (3.7–12.9)	5.8 (2.7–10.3)	5.0 (2.1–9.2)	0.03

PHT: prehospital thrombolytic therapy; EF: ejection fraction; IQR: interquartile range.
[a]Continuous variables are summarised as medians (with 25th–75th percentile/IQR) and categorical variables as proportions (with number).
[b]Test for linear trend, logistic regression for binary variables, and Jonckheere's trend test for continuous variables.
[c]Patients with no acute coronary syndrome were not included.
[d]Highly sensitive troponin with measuring unit ng/L was implemented from July 2009. These values are divided by 1000 to get µg/L.

Table 3. Characteristics and outcomes in patients with STEMI in relation to time from symptom onset to the start of prehospital thrombolytic therapy.

	Time from symptom onset to start of PHT (minutes)			*P* value[a]
	<120	120–239	≥240	
Patient characteristics				
Male sex, % (*n*)	75.4 (83)	78.7 (133)	72.2 (52)	
Age, median (IQR), years	59.0 (50.9–67.7)	61.6 (53.4–70.3)	63.3 (56.0–72.0)	
Time period studied				
2000–2003, % (*n*)	21.7 (26)	57.5 (69)	20.8 (25)	
2004–2007, % (*n*)	34.0 (49)	43.8 (63)	22.2 (32)	
2008–2011, % (*n*)	40.2 (35)	42.5 (37)	17.2 (15)	
Outcomes				
Systolic heart failure,[b] % (*n*)	5.2 (5)	12.3 (19)	23.3 (14)	0.002
1-year mortality, % (*n*)	2.7 (3)	8.3 (14)	15.3 (11)	0.01

Patients without acute coronary syndromes were excluded.
IQR: interquartile range; STEMI: ST-segment elevation myocardial infarction.
[a]*P* values were calculated with the use of logistic regression adjusted for age and sex.
[b]Defined as left ventricular ejection fraction less than 40%.

invasive cardiology, 59 of a total 170 patients (35%) were treated with rescue PCI during 2006–2011.

Complications

Thirteen (3%) of the 385 patients suffered acute OHCA with ventricular fibrillation (VF). All were successfully resuscitated prehospital with return of spontaneous circulation on hospital admission; 12 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 haemorrhage. Inappropriate PHT was given to 30 (8%) patients due to wrong diagnosis. Errors were ECG misinterpretation of pericarditis, old STEMI with persistent ST-segment elevation, early repolarisation, pulmonary embolism, nephrolithiasis, pneumonia, cholelithiasis, dyspepsia, uncharacteristic chest pain, epilepsy and VF. Two patients died: one with aortic dissection and one with acute subarachnoid haemorrhage.

Discussion

Following the implementation of a decentralised, early prehospital, thrombolytic treatment programme for ACS and STEMI patients in a mixed rural–urban sub-arctic region, we found a substantial, 50% reduction in 1-year mortality and post-infarct systolic heart failure during the study period. Systolic heart failure was reduced by 58% (P=0.02) and mortality by 50% (P=0.09), respectively, in 2008–2011 compared with 2000–2003.

We found that over time, earlier diagnosis and PHT treatment was given to an increasing number of acute STEMI patients. PHT was given 10 minutes earlier after symptom onset in 2008–2011 compared with 2000–2003, and the percentage who received PHT within 2 hours increased by 85% (P=0.003) to a total of 40% receiving early treatment.

Thrombolytic therapy has the best effect if given as soon as possible but within 2 hours after pain onset,[13–15] as has been reported to be associated with improved 1-year survival compared with primary PCI (2.8% vs. 6.9%, respectively; P=0.021).[16] In our study, 1-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).

We routinely applied automated external 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 with OHCA.[17] We have shown that changing focus from the onset of 'collapse' in OHCA to the onset of chest pain in patients with ACS, more OHCA patients survive by saving time to alarm, dispatch, diagnosis and first defibrillation.[18]

Ramping up capacity and preparedness for coronary angiography and PCI, combined with implementation and strict adherence to evidence-based medical guidelines, resulted in a 25% increase in invasive investigations (P<0.001) and a 28% increase in revascularisations in this group of acute STEMI patients (P<0.001).

Regional application of the pharmacoinvasive strategy for STEMI patients and a strong prehospital chain of survival yielded earlier access to timely invasive diagnosis and treatment, in sum increasing reperfusion treatment rates. Our good results from a strategic development of a joint ambulance clinician/GP strategy for earliest possible PHT in STEMI patients are likely to be augmented by an aggressive invasive approach following the thrombolytic therapy.

The pharmacoinvasive strategy combining PHT and rapid transfer to planned PCI within 3–24 hours after ictus in haemodynamically stable patients and rescue angioplasty for failed fibrinolysis is an efficient reperfusion strategy for STEMI patients.[19,20] Randomised trials comparing PHT with primary PCI in patients who present early show no statistical difference in 30-day mortality or re-infarction.[5,14] The STREAM study recently 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 favourably with those of primary PCI performed beyond 60 minutes of diagnosis.[6] The study supported the need for immediate transfer of all STEMI patients so that urgent rescue PCI could be delivered in the minority of those who failed to reperfuse.[21]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.[22] A French registry (FAST-MI) demonstrated high 5-year survival rates for STEMI patients whether treated with primary PCI or a pharmacoinvasive strategy. The pharmacoinvasive strategy produced results at least as good as those of primary PCI.[4]

Our treatment strategy with early PHT caused few complications. Three patients died in cardiogenic shock before reaching hospital. One patient with aortic dissection and one patient with subarachnoid haemorrhage also died. The thrombolytic therapy could have been a factor in these two patients.

The percentage of inappropriate PHT treatment dropped significantly during the study period from 13.6% to 2.2% (P=0.002), reflecting system maturation, although the shift of strategy from PHT to primary PCI could also have played a role.

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.

Limitations

Our study has the limitations of observational studies. Confounding factors could possibly have contributed to the results. We have incomplete data for patients who received primary PCI, and cannot compare patients who received primary PCI and PHT. In the last period, an increasing proportion of STEMI patients received primary PCI instead of PHT. This is most likely linked to the implementation of evidence-based medical guidelines and an increase in the capacity of coronary angiography and PCI, and as such is a wanted progress. However, the risk of selection bias is present and requires caution in comparing between time periods. Primary PCI may be applicable to those STEMI patients with heart failure, long duration of pain or uncertain diagnosis. This will affect the composition of the PHT population. Thus, trends in clinical outcomes and survival may be a combination of the fact that PHT really was given faster, that the proportion of primary PCI increased and that PHT treated patients received more invasive investigation and treatment (pharmacoinvasive strategy).

Our data are derived from a single centre with a limited number of patients and a risk of type 1 error.

Conclusion

We have demonstrated significant time gains and earlier reperfusion therapy following the implementation of a decentralised PHT system, upgraded and matured over 11 years, combined with improved availability of 7/24 invasive diagnosis and treatment services. Early, prehospital diagnosis and thrombolytic treatment of STEMI patients provided by ambulance clinicians and GPs was associated with a significant reduction in post-infarct systolic heart failure and high survival rates in STEMI patients with OHCA.

We conclude that ambulance clinicians with the support of GPs and hospital cardiologists can safely perform PHT.

Early prehospital diagnosis and immediate PHT should be available as national programmes, readily available for all eligible patients with ACS/STEMI in mixed rural–urban areas with sparse populations and long evacuation lines to PCI centres irrespective of patients' habitat and the trust the patients belong to.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

1. Beygui F, Castren M, Brunetti ND, et al. Pre-hospital management of patients with chest pain and/or dyspnoea of cardiac origin: a position paper of the Acute Cardiovascular Care Association (ACCA) of the ESC. *Eur Heart J Acute Cardiovasc Care* 2015. Epub ahead of print 27 August 2015. DOI: 10.1177/2048872615604119.
2. Steg PG, James SK, Atar D, et al.; Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33: 2569–2619.
3. Bonnefoy E, Lapostolle F, Leizorovicz A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet* 2002; 360: 825–829.
4. Danchin N, Puymirat E, Steg PG, et al. Five-year survival in patients with ST-segment-elevation myocardial infarction according to modalities of reperfusion therapy: the French Registry on Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) 2005 Cohort. *Circulation* 2014; 129: 1629–1636.
5. Roule V, Ardouin P, Blanchart K, et al. Prehospital fibrinolysis versus primary percutaneous coronary intervention in ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Crit Care* 2016; 20: 359.
6. Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013; 368: 1379–1387.
7. Rawles J. Halving of mortality at 1 year by domiciliary thrombolysis in the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol* 1994; 23: 1–5.
8. Rawles JM. Quantification of the benefit of earlier thrombolytic therapy: five-year results of the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol* 1997; 30: 1181–1186.
9. Norsk indeks for medisinsk nødhjelp [The Norwegian Emergency Medical Index]. 3. utg, 2009. Norwegian: The Norwegian Medical Association.
10. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation* 1991; 84: 960–975.
11. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; 123: 2736–2747.
12. Jortveit J, Govatsmark RE, Digre TA, et al. Myocardial infarction in Norway in 2013. *Tidsskr Nor Laegeforen* 2014; 134: 1841–1846.
13. Boersma E, Maas AC, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; 348: 771–775.
14. Bonnefoy E, Steg PG, Boutitie F, et al. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. *Eur Heart J* 2009; 30: 1598–1606.
15. Steg PG, Bonnefoy E, Chabaud S, et al. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation* 2003; 108: 2851–2856.
16. Westerhout CM, Bonnefoy E, Welsh RC, et al. The influence of time from symptom onset and reperfusion strategy on 1-year survival in ST-elevation myocardial infarction: a pooled analysis of an early fibrinolytic strategy versus primary percutaneous coronary intervention from CAPTIM and WEST. *Am Heart J* 2011; 161: 283–290.
17. Fothergill RT, Watson LR, Virdi GK, et al. Survival of resuscitated cardiac arrest patients with ST-elevation myocardial infarction (STEMI) conveyed directly to a Heart Attack Centre by ambulance clinicians. *Resuscitation* 2014; 85: 96–98.
18. Lien Nilsen JM, Bo I, Rasmussen JR, et al. Doubled survival from out-of-hospital cardiac arrest in a rural community in North-Norway following implementation of an aggressive chest pain protocol with early prehospital thrombolysois for STEMI. *Circulation* 2011; 124 (Suppl 21): A17087.
19. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 2004; 364: 1045–1053.
20. Gershlick AH, Stephens-Lloyd A, Hughes S, et al. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 2005; 353: 2758–2768.
21. Welsh RC, Goldstein P, Sinnaeve P, et al. Relationship between community hospital versus pre-hospital location of randomisation and clinical outcomes in ST-elevation myocardial infarction patients: insights from the Stream study. *Eur Heart J Acute Cardiovasc Care* 2017. Epub ahead of print 1 June 2017. DOI: 10.1177/2048872617700872.
22. Bohmer E, Hoffmann P, Abdelnoor M, et al. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). *J Am Coll Cardiol* 2010; 55: 102–110.