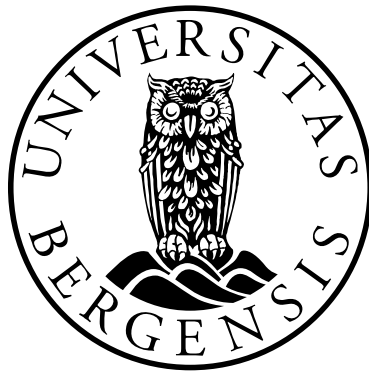


Hospitalization for acute myocardial infarction -

trends in case fatality, and the impact of changing definition on number of events, subtypes and mortality

Jørund Langørgen



Dissertation for the degree philosophiae doctor (PhD)
at the University of Bergen

2014

Dissertation date: 24/09/2014

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Year: 2014

Title: **Hospitalization for acute myocardial infarction – trends in case fatality, and the impact of changing definitions on number of events, subtypes and mortality**

Author: Jørund Langørgen

Print: AIT OSLO AS / University of Bergen



Scientific environment

The present thesis is based on studies carried out in collaboration between Department of Clinical Science and Department of Global Public Health and Primary Care, University of Bergen and Department of Heart Disease, Haukeland University Hospital.

Main supervisor: Professor Ottar Nygård
University of Bergen, Faculty of Medicine and Dentistry
Department of Clinical Science and
Department of Heart Disease, Haukeland University Hospital

Co-supervisors: Professor Jan Erik Nordrehaug
University of Bergen, Faculty of Medicine and Dentistry
Department of Clinical Science

Professor Stein Emil Vollset
University of Bergen, Faculty of Medicine and Dentistry
Department of Global Public Health and Primary Care

Acknowledgements

The present dissertation is based on data from the Western Norway Cardiovascular Registry 1972-2001, now included in the Norwegian Cardiovascular Registry, and patient data from Haukeland University Hospital 2002-2003. A research grant from the Western Norway Regional Health Authority and additional funding from the Department of Heart Disease, Haukeland University Hospital has given me the opportunity for 40% research time in addition to almost a full post as consultant since September 2005.

I would like to express my deep gratitude to my principal supervisor, Professor Ottar Nygård, who introduced me to scientific work. He has generously given me great challenges; he is always welcoming and ready to give support. My co-supervisor, Professor Jan Erik Nordrehaug, has inspired and supported me with his scientific knowledge and working capacity, and has never been hard to ask. I am indebted to my second co-supervisor, Professor Stein Emil Vollset for his statistical advice and instructions for improvements.

I warmly thank my co-authors Jannicke Igland, Marta Ebbing, Grethe S. Tell, Lorentz M. Irgens, Anne Kask and Maria Averina for their contributions in the study conception, data collection and interpretation, and for sharing their expertise in the publication process.

Ottar Nygård and Jan Erik Nordrehaug have encouraged me to supervise medical students in final writing projects during their studies. The students many questions and enthusiasm has been an inspiration in my work with the dissertation. Furthermore my supervisors have facilitated research activity at the Medical Intensive Care unit (MIO) where I have my daily work. We have participated in local and multicentre studies, and this has given us increased knowledge and understanding in the work with the sickest patients. The insight into other types of research such as randomized, controlled trials has given me valuable experience.

Participation in the advisory groups in the process of establishing the Norwegian Myocardial Infarction Register and the Norwegian Cardiac Arrest Register has been a long learning process. I wish to thank my fellow colleagues for interesting discussions including the definitions of acute myocardial infarction, which are relevant for my research.

Professor Jan Erik Nordrehaug, later Nils Walde and Kjell Vikenes as head of the department have provided invaluable backing and excellent working conditions at the Department of Heart Disease.

I am particularly thankful to Rune Fanebust, my good colleague and immediate boss, who has held the department together when I have been busy with research, he has encouraged me in the research, and we have discussed many aspects of medicine and life. I am very grateful to all my colleagues who are so dedicated to patients and research at MIO, the Department of Heart Disease, other departments at Haukeland University Hospital and the Department of Clinical Science at the University of Bergen, it's a great pleasure to work with you. Reinhardt Seifert, Kari Juul and Alf Aksland gave technical assistance. Thank you all.

A big thank you to all my friends for their friendship, hospitality, conversations, songs and music which enrich life. A special thanks to my parents Aase-Turid and Tore who have always supported and believed in me, as well to my extended families on both sides that are family, friends and a great support. I am endlessly fortunate to have Aina, Erlend and Gaute in my life. To them I owe the most.

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Abstract

Background Few studies of acute myocardial infarction (AMI) among hospitalized patients have had direct estimates of long-term case fatality after AMI, and the literature is conflicting regarding gender-related prognosis following AMI. Several revisions of the definition of AMI have complicated the analyses of trends in the number of AMI events and mortality.

Aims To provide age and gender specific estimates of trends in short- and long-term case fatality for a first AMI of patients hospitalized, and to analyse the impact of applying five different definitions of AMI on number of AMI events, types and long-term mortality.

Methods Paper I included patients hospitalized with a first AMI at Haukeland University Hospital during 1979-2001. Data were retrieved from The Western Norway Cardiovascular Registry and included additional data on long-term and all-cause death. The study period was divided into three periods and these were compared (p-trend). The clinicians used the WHO definition of AMI in the study period.

Paper II and Paper III examined a different patient cohort, which was hospitalized for AMI (815 patients) during 1 March 2002 and 28 February 2003. The cohort also included 679 patients hospitalized in the same period with at least one measurement of elevated cardiac troponin I (cTnI) during the hospital stay, but not diagnosed with AMI.

Results Paper I: The short- and long-term case fatality declined substantially during 1979-2001 in 11878 patients hospitalized with a first AMI. The unadjusted 28-day case fatality declined from 31.1% to 19.8% in men and from 37.3% to 26.8% in women from the first period (1979-1985) compared with last period (1994-2001) (p-trend <0.0001). Landmark analysis showed continued decline in 1-10 year case fatality. Case fatality rates were significantly lower in women than men in patients ≥ 60 years.

Paper II: The WHO 1979 definition of AMI with CK-MB mass as biomarker was used as reference and resulted in 566 definite AMIs among the 1494 total cohort of patients. When applying the ESC/ACC 2000, the AHA 2003, the Universal 2007 and the Universal 2012 definition of AMI with troponin I as biomarker we observed approximately 30%

more AMI events. The short- and long-term mortality were moderately higher applying the newer definitions.

Paper III: Applying the Universal 2012 definition compared with the Universal 2007 definition of AMI resulted in a minimal decrease in number of AMI events from 769 to 760, with numbers of patients classified with Type 1, 2, 3, 4a, 4b and 5 AMI according to the Universal 2012 definition being 685, 27, 28, 13, 3 and 4 patients respectively.

Conclusions There has been a substantial decline in short-term and long-term case fatality in patients hospitalized for a first AMI during 1979-2001. Women ≥ 60 years fare better than men do when we compare age-adjusted case-fatality rates. The number of AMI events depends on the definition of AMI and biomarker. When the WHO 1979 definition of AMI was used as reference, we found that applying three newer definitions of AMI resulted in approximately 30% more patients diagnosed with definite AMI. Few patients classified as Type 2 AMI is specifically noticed.

List of publications

- I. Langørgen J, Igland J, Vollset SE, Averina M, Nordrehaug JE, Tell GS, Irgens LM, Nygård O. 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 Oct; 16(5):621-7.
- II. Langørgen J, Ebbing M, Igland J, Vollset SE, Nordrehaug JE, Tell GS, Nygård O. Implications of changing definitions of myocardial infarction on number of events and all-cause mortality: the WHO 1979, ESC/ACC 2000, AHA 2003, and Universal 2007 definitions revisited. *Eur J Prev Cardiol.* 2013 Jun 3. [Epub ahead of print]
- III. Langørgen J, Ebbing M, Igland J, Vollset SE, Kask A, Nordrehaug JE, Tell GS, Nygård O. Impact of the third Universal 2012 definition of acute myocardial infarction compared to the Universal 2007 definition: Number and types of events, and long-term mortality. Submitted.

Abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AHA	American Heart Association
AMI	Acute myocardial infarction
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CDC	Centers for Disease Control and Prevention
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase myocardial band isoenzyme
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cTnI	Cardiac troponin I (inhibitory)
CV	Coefficient of variation
ECG	Electrocardiogram
ESC	European Society of Cardiology
HR	Hazard ratio
ICD-10	International Statistical Classification of Diseases version 10
IQR	Interquartile range
LBBS	Left bundle branch block
MI	Myocardial infarction
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease
NHLBI	National Heart, Lung and Blood institute
NSTEMI	Non-ST-segment elevation myocardial infarction
OR	Odds ratio
PCI	Percutaneous coronary intervention
SD	Standard deviation
SPSS	Statistical Product and Service Solutions
STEMI	ST-segment elevation myocardial infarction
WHF	World Heart Federation
WHO	World Health Organization

List of definitions

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 (1).

Coronary artery disease

Pathological processes of coronary arteries that may derive from a congenital abnormality, atherosclerotic, or non-atherosclerotic cause (2). In this dissertation, the term is used for atherosclerotic disease.

Coronary heart disease

An imbalance between myocardial functional requirements and the capacity of the coronary vessels to supply sufficient blood flow (2). It is a form of myocardial ischemia (insufficient blood supply to the heart muscle) caused by a decreased capacity of the coronary vessels.

Landmark analysis

An observational method used for comparing time-to-event outcome between groups determined during study follow-up. The goal of the landmark method is to estimate in an unbiased way the time-to-event probabilities in each group conditional on the group membership of patients at a specific time point, the landmark time (3).

Mortality rate

A measure of the frequency of occurrence of death in a defined population during a specified interval of time (1).

Myocardial infarction

Necrosis of the myocardium caused by an obstruction of the blood supply to the heart (coronary circulation) (2).

Risk factor

An aspect of personal behaviour or lifestyle, environmental exposure, or inborn or inherited characteristic, which, on the basis of epidemiologic evidence, is known to be associated with a health-related condition considered important to prevent (2).

1. Introduction of acute myocardial infarction

1.1 Historical perspectives

Initial description and treatment

“But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris.”

After William Heberden’s classic description of angina pectoris in 1772, it took more than a century before pathologist Ludvig Hektoen in 1879 concluded that myocardial infarction is caused by coronary thrombosis secondary to sclerotic changes in the coronaries (4-6).

In 1910, the Russian clinicians Obrastzov and Straschesko published the first description of a nonfatal myocardial infarction (7). Two years later James B. Herrick published a paper, informing the American physicians about the symptoms of heart infarction based on the Russian paper (8). He further stimulated clinical use of the electrocardiogram as a diagnostic tool, and he emphasized “total bed rest” as the treatment for acute myocardial infarction (AMI). These approaches were standard care of patients with AMI until the beginning of the 1950s. Hospital mortality was high, more than 30%, and only morphine, and later diuretics and anticoagulants were used (9;10).

Initial epidemiological observations

The previous century can be roughly divided into two concerning the overall incidence of disease in Western countries. Infections dominated before 1950, and in the second half cardiovascular disease and cancer became leading causes of illness and death (11). In the United States an increase of coronary mortality among middle aged men was observed already during the 1930-40s (12). This was the background of the Framingham Heart study, established by the National Heart Institute in 1947, with

close collaboration between clinical cardiology, biostatistics and epidemiology (13). Their first findings indicated that elevation in blood pressure and cholesterol levels were associated with an increased incidence of ischemic heart disease and AMI (14). The identification of coronary risk factors resulted in emphasis on prevention (15-19).

In Norway the Department of the Interior established a cause of death register already in 1853, with relatively reliable statistics from approximately year 1900 (11). Incidence and death rates among Norwegian patients with cardiovascular diseases increased moderately in the beginning of the 1900th century (20;21). Mortality due to coronary disease was relatively similar in men and women, with a decline in both genders during 1940-45 (21). However, from 1950 until today there has been a significant gender difference regarding mortality from AMI and ischemic heart disease (22-25). When comparing mortality rates in Figure 1 we observe an increase of 130% in men and 60% in women aged 45-64 years in the period 1966-70 compared with 1951-55. After the peak, there was a steady decline in mortality to a lower level than in 1951-55, and the mortality rates for men and women have again approached each other.

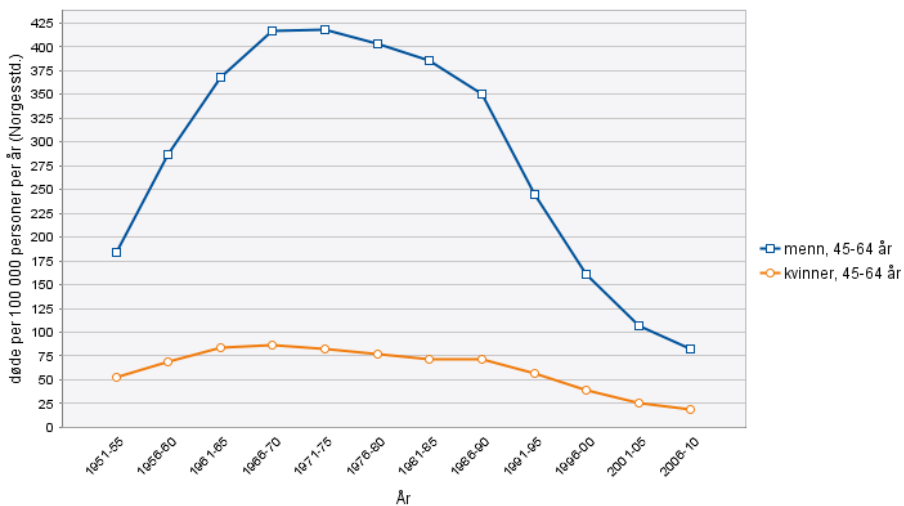


Figure 1: Mortality from myocardial infarction and other ischemic heart disease in men and women aged 45-64 years. Deaths per 100000 inhabitants, age standardized. Source: Cause of Death Register. Statistics Norway. (<http://www.fhi.no/eway/>)

Discovery of risk factors

Strøm and Jensen described a decrease of cardiovascular and coronary morbidity during World War II (21). Their hypothesis was that the cause of reduced mortality was a reduction of saturated fat in the diet and a decrease in smoking. They also assumed that the rapid change in mortality probably was due to change in the tendency of coronary thrombosis rather than atherosclerosis. In 1962 the combined results of the Framingham and Albany studies were published, documenting strong relationship between smoking and the incidence of myocardial infarction (17). Other major risk factors as hypertension, high serum cholesterol, diabetes mellitus and advancing age have been studied at Framingham and in other studies such as the Interheart study (26-30).

Establishment of coronary units and acute treatment

In the 1960s coronary care units were established in many hospitals to monitor AMI patients, and ventricular fibrillation could be treated with resuscitation and defibrillation which reduced hospital mortality significantly (31). By the 1970s, in-hospital mortality from AMI dropped to approximately 15% among patients treated in coronary care units. Beta-blockers and nitroglycerine were given during acute attacks and active rehabilitation was introduced (32). The reperfusion era evolved in the 1980s and the GISSI trial (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) demonstrated in 1986 that intravenous streptokinase reduced early mortality in patients with ST-segment elevation myocardial infarction (STEMI) (33). The ISIS-2 study (Second International Study of Infarct survival) showed that the combination of streptokinase and aspirin led to further reduction in mortality (34).

The field of invasive cardiology emerged after Andreas Grüntzig performed the first balloon angioplasty in 1977 (35). The initial technique was followed by the insertion of stents, and further drug-eluting stents to prevent coronary restenosis. The treatment with primary percutaneous coronary intervention (PCI) developed during the 1990s, and since year 2000 most Western countries have established PCI-centres with acute treatment of STEMI. Among selected patients who have undergone PCI within six hours after symptom onset, studies have shown in-hospital mortality as low as 3-5% (36;37).

The efficacy of acute reperfusion also depends on public and professional education programs, and the development of ambulance services with a short interval between onset of symptoms and the patient's arrival at the hospital (38;39). Although mortality among unselected patients with AMI also is decreasing significantly, the in-hospital mortality is still 7-15% (40-42).

Secondary prevention

The Survival and Ventricular Enlargement (SAVE) trial demonstrated that long-term treatment with angiotensin-converting-enzyme (ACE)-inhibitors reduced mortality among patients with left ventricular dysfunction after AMI (43). The LDL-cholesterol pathway was delineated in the 1970s, and the HMG-CoA reductase inhibitors (statins) appeared to selectively lower LDL-cholesterol in plasma (44;45). The 4S study and several other clinical studies demonstrated that statin treatment reduces the risk of AMI and prolong life (46;47).

Primary prevention

The epidemic wave of cardiovascular disease and AMI in the Western world during 1960-1970 combined with documentation of risk factors resulted in further research on the effect of reducing risk factors. The Oslo study showed a significant effect of diet and smoking intervention on the incidence of myocardial infarction (48). Different risk charts have been used in clinical practice, and studies have shown that primary prevention can explain approximately 50% of the decline in AMI seen in the recent decades (49;50).

Epidemiology in recent years

The reductions of risk factors and advances in treatment have contributed to the reduction of coronary deaths in the Norway over the past 40 years (23;24;51;52). We have changed status from a high-risk to a low-risk country at the same level as the Mediterranean countries (Figure 2). Figure 2 further illustrate some of the known north-east to south-west gradient in mortality from AMI among European countries (53;54). Studies have revealed lowest mortality rates due to AMI for both women and men in Spain, France, Italy and Switzerland and highest rates in Central and East Europe such as Bulgaria or the Russian Federation.

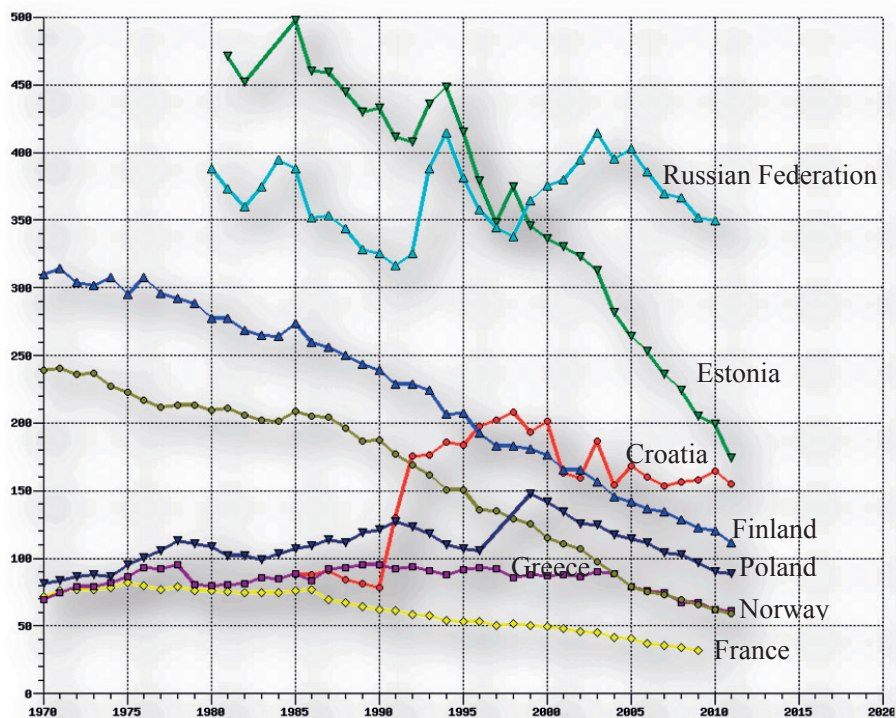


Figure 2: Deaths due to myocardial infarction in Croatia, Estonia, Finland, France, Greece, Norway, Poland and the Russian Federation 1970-2012, all age group. Per 100000 inhabitants. **Source:** WHO, European HFA Database, July 2013. (<http://data.euro.who.int/hfad/>)

Cardiovascular disease is still the leading cause of death worldwide, with AMI as the most important contributor (55). The global burden of coronary disease is expected to increase due to tobacco use, unhealthy food, decreased physical activity and a longer average life span in the middle- and low-income countries (56). Although the Western world has seen the epidemic wave of AMI decline in recent years, recent papers demonstrate a slight increasing hospitalizations rate of AMI in younger age groups (52;57;58).

1.2 Definitions

The first WHO 1959 definition and other early definitions

The definition of acute myocardial infarction (AMI) was introduced by the World Health Organization (WHO) in 1959 with emphasis on chest pain and changes in successive ECGs (Table 1) (59). It was followed by reports from *American Heart Association (AHA)* in 1964 and the *WHO* in 1971, and the *Framingham study* provided further specifications (60-62). The diagnosis of AMI was based on the presence of at least two of three criteria: typical symptoms, typical ECG abnormalities and increase in enzymes indicating myocardial injury. WHO revised the diagnosis of ischemic heart disease in 1979 (*WHO 1979 definition*) with introduction of definite and possible AMI (63). In epidemiological studies there had been variation and inconsistency in the populations and in definition of AMI used. This was the background for the *WHO MONICA project* (Multinational MONItoring of trends and determinants in Cardiovascular disease), with the objective to measure the trends in cardiovascular mortality and incident coronary heart disease (CHD), classifying the events into five categories, related to risk factors (64-67).

The ESC/ACC 2000 definition

The requirement for a more precise definition of AMI resulted in the redefinition of AMI from the European Society of Cardiology (ESC) and American College of Cardiology (ACC) published in year 2000 (ESC/ACC 2000 definition) (68). This definition includes only the definite category of AMI, which may lead to underestimation of the incidence of AMI in epidemiological studies. The ESC/ACC was criticised for changing the definition of AMI, first because of problems with comparisons with previous definitions and populations, secondly because of lack of a group of sudden cardiac death (69;70). A problem regarding the interpretation of troponin included in this definition was “a typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis”. In clinical practice a sufficient number of troponin values are often lacking, and many researchers and clinicians accepted troponin “rise or fall” as the diagnostic criterion (71;72).

The AHA 2003 definition

In 2003, epidemiological researchers from AHA, World Heart Federation (WHF), ESC, Centers for Disease Control and prevention (CDC) and the National Heart, Lung and Blood Institute (NHLBI) published an AHA scientific statement (AHA 2003 definition) to address the specific needs of population surveillance (73).

The Universal 2007 definition

Later, the ESC, ACC, AHA and WHF published the Universal 2007 definition which addressed several of the weaknesses of the 2000 definition (74). The Universal 2007 definition included five new categories of AMI. Minor changes in the ECG criteria for AMI were introduced.

The WHO 2009 revision

The WHO 2009 revision of the definition of AMI acknowledged that the new biomarkers and even ECG equipment are often not available in low-income countries (75). The "Universal" definition of AMI is not applicable in these countries. The WHO 2009 definition of AMI is divided in three categories; Category A is identical with the Universal 2007 definition, Category B is applied when the information of cardiac biomarkers is incomplete together with ischemic symptoms and development of pathological Q-waves. Category C (probable MI) is applied in persons with ischemic symptoms, when either ECG changes are suggestive of MI, or the information on cardiac biomarkers is incomplete.

The Universal 2012 definition

The Universal 2012 definition of myocardial infarction was developed as a result of the new generations of troponin which have become increasingly sensitive to myocardial injury (76). As compared with the Universal 2007 definition the Universal 2012 definition requires a higher troponin threshold for Type 4a (PCI) and Type 5 (CABG), and additional symptoms or signs for Type 4a AMI. The new definition seeks to further clarify the difference between AMI and myocardial injury.

Table 1 Main criteria and change in the definition of acute myocardial infarction

Definition	Fundamental criteria	Change	Subgroups
First WHO 1959 definition	History of myocardial infarction and changes in successive ECGs		
WHO 1979 definition	Definite AMI: Unequivocal ECG changes and/or unequivocal enzyme changes, history typical or atypical. Possible AMI: Serial equivocal ECG changes >24 hours, +/- unequivocal enzyme changes. History typical or atypical	Enzymes added. Division in definite and possible AMI	Definite Possible
WHO MONICA 1983 definition	WHO 1979 definition and the Minnesota codes for ECG from US studies	Comprehensive classification for epidemiology	Definite Possible Ischemic cardiac arrest No AMI or coronary death Unclassifiable
ESC/ACC 2000 definition "Rise and fall"	Typical rise <i>and</i> gradual fall of troponin or CK-MB with at least one of the following: Ischemic symptoms, new pathologic Q-wave, ST-elevation or ST-depression, PCI or AMI at autopsy	Biomarkers a new crucial role	Definite
ESC/ACC 2000 definition "Rise or fall"	Most clinicians and researchers interpreted the –ESC/ACC 2000 def. as: "Typical rise <i>or</i> gradual fall of troponin or CK-MB"	Alternative interpretation of the ESC/ACC 2000 definition	Definite
AHA 2003 definition (AHA, WHF, ESC, CDC, NHLBI)	The ESC/ACC 2000 def. with rise or fall of troponin or CK-MB. The classification of ECG and biomarkers defined as diagnostic, equivocal, missing or normal. Cardiac symptoms and signs present or absent	Implementing officially the "rise or fall" of Troponin or CK-MB. For epidemiological surveillance	Definite Probable Possible
Universal 2007 definition (ESC, ACC, AHA, WHF)	The ESC/ACC 2000 def. with a "rise or fall" of troponin/CK-MB.	Including sudden cardiac death Changes in ECG-def: V1-3 and T-inversion 5 subtypes of AMI	<ul style="list-style-type: none"> • Type 1 "Spontaneous" • Type 2 "Secondary" • Type 3 "Death" • Type 4a "PCI" • Type 4b "Stent-thrombus" • Type 5 "CABG"
WHO 2009 definition	The WHO MONICA 1981 definition and the Universal 2007 definition	Three categories, include settings with small resources, and the category of probable AMI	Category A: Identical with the Universal 2007 definition Category B: Biomarkers are incomplete, ischemic symptoms and pathological Q-waves Category C (probable MI): Ischemic symptoms, when either ECG changes are suggestive of MI or incomplete information on biomarkers
Universal 2012 definition (ESC, ACC, AHA, WHF)	The ESC/ACC 2007 definition with a "rise or fall" of troponin/CK-MB.	Higher troponin cut-off values for PCI and CABG related AMI, and demand of symptoms or clinical findings (Type 4a) Changes in ECG-def: V2-3 for men <40 year	<ul style="list-style-type: none"> • Type 1 "Spontaneous" • Type 2 "Secondary" • Type 3 "Death" • Type 4a "PCI" • Type 4b "Stent-thrombus" • Type 4c "Restenosis" • Type 5 "CABG"
ACC: American College of Cardiology; AHA: American Heart Association; AMI: Acute myocardial infarction; CABG: Coronary artery bypass graft; CDC: Centers for Disease Control and prevention; CK-MB: Creatine kinase myoglobin; cTnI: cardiac Troponin I; ECG: Electro cardiogram; ESC: European Society of Cardiology; NHLBI: National Heart, Lung and Blood Institute; MONICA: Multinational MONItoring of trends and determinants in Cardiovascular disease; PCI: Percutaneous coronary intervention; WHF: World Heart Federation; WHO: World Health Organisation.			

1.3 Symptoms

The WHO 1959 definition

The WHO 1959 definition of AMI described the symptoms of myocardial infarction as: “a gradual, or more often, a sudden onset of severe chest pain, similar to that of definite angina of effort. The pain may have been associated with symptoms of collapse and/or other symptoms, often serious enough to require prolonged bed-rest at home or in hospital” (59). The definite angina pectoris is described as: “A pain occurring centrally in the front of the chest at the mid- or upper- sternal level brought on by effort (e.g. exercise, emotional stress, ingestion of food, or exposure to cold).

The WHO 1979 definition

In the revised WHO 1979 definition of AMI history was briefly described as: “The history is typical if severe and prolonged chest pain is present: Sometimes the history is atypical and the pain may be mild or even absent, or other symptoms may predominate” (63).

The WHO MONICA definition

The WHO MONICA project developed a comprehensive definition of AMI for epidemiological studies (64;66). Typical symptoms were described as “When chest pain is present and characterized by duration of more than 20 minutes and without definite noncardiac or cardiac nonatherosclerotic cause”. Atypical symptoms were described as “If symptoms were not typical but there was one or more of atypical pain, acute left ventricular failure, shock and syncope, and the absence of cardiac disease other than ischemic heart disease, and no definite noncardiac or cardiac nonatherosclerotic cause”. The WHO MONICA project further classified; other symptoms, no symptoms, inadequately described symptoms and insufficient data.

The ESC/ACC 2000 definition

According to the ESC/ACC 2000 definition of AMI possible ischemic symptoms “include chest, epigastric, arm, wrist or jaw discomfort with exertion or at rest. The discomfort associated with AMI usually lasts at least 20 minutes, but may be shorter in duration. The discomfort may develop in the central or left chest and then radiate to the arm, jaw,

back or shoulder. The discomfort is usually not sharp or highly localized and may be associated with dyspnea, diaphoresis (excess sweating), nausea, vomiting or lightheadedness (68).” Further; “The discomfort is not affected by moving the muscles of the region where the discomfort is localized, nor is it worsened by deep inspiration.”

The AHA 2003 definition

The AHA 2003 definition of AMI described cardiac symptoms as: “Presence of acute chest, epigastric, neck, jaw, or arm pain or discomfort or pressure without apparent noncardiac source. More general, atypical symptoms, such as fatigue, nausea, vomiting, diaphoresis, faintness, and back pain, should not be used as a diagnostic criterion, although they are clinically useful in arriving at the correct diagnosis” (73). Cardiac signs: “Acute congestive heart failure or cardiogenic shock in the absence of non-CHD causes”.

The Universal 2007 definition

The Universal 2007 definition of AMI describes possible ischaemic symptoms as: “Various combinations of chest, upper extremity, jaw or epigastric discomfort with exertion or at rest. The discomfort associated with AMI usually last at least 20 minutes. Often, the discomfort is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnoea, diaphoresis, nausea, or syncope. These symptoms are not specific to myocardial ischaemia and can be misdiagnosed and thus attributed to gastrointestinal, neurological, pulmonary, or musculoskeletal disorders. Myocardial infarction may occur with atypical symptoms, or even without symptoms, being detected only by ECG, biomarker elevation, or cardiac imaging (74).”

The WHO 2009 and the Universal 2012 definitions

The WHO 2009 definition and the Universal 2012 definition of AMI adopted the symptoms criteria from the Universal 2007 definition (75;76).

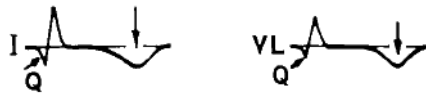
1.4 ECG

The WHO 1959 definition

The WHO 1959 definition of AMI divided the ECG changes in two; those considered to be diagnostic of “very probable” (Q-waves) and “possible” (transient ST-elevation or ST-depression) myocardial infarction (59). The ECG changes were illustrated to clarify the description, as seen in these two examples:

A. “Very probable” myocardial infarction

- (a) Association of **Q I** not less than 20% of **R I**, and negative **T I** (a sign of anterolateral infarction which has to be confirmed by precordial leads, as illustrated in (c) and (d) below). VL is much like lead I.



- (e) **Injury current**—evolution and disappearance in three stages. Probability of myocardial infarction in any stage is almost 100%.

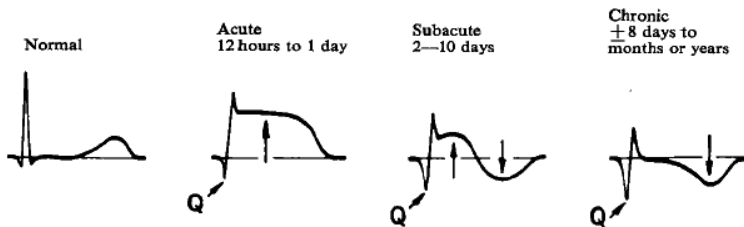


Figure 3 Classification and criteria for epidemiological studies. WHO 1959 (59).

The WHO 1979 definition

The WHO 1979 definition of AMI described ECG as:

1. Unequivocal changes

“Unequivocal changes in ECG are the development of abnormal, persistent Q or QS waves, and evolving injury current lasting longer than 1 day. When the ECG shows these unequivocal changes, the diagnosis may be made on the ECG alone” (63).

2. Equivocal changes

“In other cases, the ECG may show equivocal changes, consisting of

- a) Stationary injury current,

-
- b) Symmetrical inversion of the T wave,
 - c) Pathological Q wave in single ECG record, or
 - d) Conduction disturbances.”

The WHO MONICA definition

The WHO MONICA project classified ECGs according to the Minnesota code manual of ECG findings in a very accurate way (64). However, we have not used this classification in our studies.

Code 1: Definite ECG

(A) The development in serial records of a diagnostic Q-wave (with subsections 1.1-1.7)

And/or

(B) The evolution of an Injury current that lasts more than 1 day

Code 2: Probable ECG: Evolution of repolarization changes

Code 3: Ischemic ECG (in one or more records)

Code 4: Other ECG

Code 5: Uncodable ECG

Code 9: ECG absent

The ESC/ACC 2000 definition

The ESC/ACC 2000 definition of AMI states that ST-changes and T-inversion reflect myocardial ischemia and that the diagnosis of AMI additionally requires an increase in troponin (68).

ECG changes that may progress to myocardial infarction:

1. “Patients with ST segment elevation:
New or presumed new ST segment elevation at the J point in two or more contiguous leads with the cut-off points ≥ 0.2 mV in leads V_1 , V_2 or V_3 and ≥ 0.1 mV in other leads (contiguity in the frontal plane is defined by the lead sequence aVL, I, inverted aVR, II, aVF, III)
2. Patients without ST segment elevation:
 - a. ST segment depression
 - b. T wave abnormalities only

New or presumed new ST segment depression or T wave abnormalities, or both, should be observed in two or more contiguous leads. Also, new or presumed new symmetric inversion of T waves ≥ 1 mm should be present in at least two contiguous leads.”

Electrocardiographic changes in established myocardial infarction, in absence of QRS confounders (left bundle branch block, left ventricular hypertrophy, Wolff-Parkinson-White syndrome):

“Any QR wave in leads V_1 through V_3 ≥ 30 ms (0.03 s); abnormal Q wave in lead I, II, aVL, aVF or V_4 through V_6 in any two contiguous leads and at least 1 mm in depth. New Q waves in the presence of left bundle branch block should be considered as pathologic.”

The AHA 2003 definition

The AHA 2003 definition of AMI follows the WHO MONICA project when applying the Minnesota ECG coding (73). The ECGs is divided into four categories:

- A. Evolving diagnostic ECG
- B. Positive ECG
- C. Nonspecific ECG
- D. ECG negative for ischemia

The categories are supplied with exact description of every possible variation of ECG changes.

The Universal 2007 definition

The Universal 2007 definition of AMI is based on the ESC/ACC 2000 definition, but is more specific in its description of the ECG (74). There are two new amendments:

1. The limit for ST-elevation in V_{2-3} is now ≥ 0.15 mV among women (instead of ≥ 0.2 mV)
2. New horizontal or down-sloping ST-depression ≥ 0.05 mV (instead of ≥ 0.1 mV)

The WHO 2009 definition

The WHO 2009 definition follows the ECG interpretation according to the Minnesota code (75).

The Universal 2012 definition

The Universal 2012 definition of AMI is almost identical to the Universal 2007 definition regarding the ECG interpretation (76). However, the cut off for ST-elevation in V_{2-3} is now ≥ 0.25 mV in men <40 years (instead of ≥ 0.20 mV).

1.5 Biomarkers

When myocytes die in connection with AMI, protein inside the cell will be released. The blood flow in the area of infarction is occluded and most of the proteins reach the blood via the lymphatics, and appear in blood after some degradation (77). Diffusion rate is determined by molecular size and molecular weight; hence the biomarkers with smallest molecular weight diffuse out of the necrotic region most rapidly.

Aspartate transaminase

The first practical test introduced for myocardial necrosis was Aspartate transaminase (AST or ASAT), also called serum glutamin oxaloacetic transaminase (SGOT), which is an important enzyme in the amino acid metabolism. AST was defined as a biochemical marker for the diagnosis of AMI in 1954 (78).

Lactate dehydrogenase

Lactate dehydrogenase (LD or LDH) is found in many body tissues as blood cells and heart, a main function of LD is to catalyse the conversion of pyruvate to lactate and back. LD has five isoenzymes, LDH-1 is predominant in the heart and red blood cells and LDH-5 is the major isoenzyme of skeletal muscle and liver. LD is normally present in a small amount and can be measured as a surrogate marker for tissue breakdown as in AMI (79).

Table 2 Types of cardiac biomarkers

Biomarker	Molecular Weight (kDa)	Elevated after AMI (hours)	Peak after AMI	Normal after (days)	Description
Aspartate transaminase (AST)	90	12 h	1-2 days	3-5 d	Defined as a marker of cardiac damage in 1954. Not specific for heart, also a marker of liver damage
Lactate dehydrogenase (LD or LDH)	140	18 h	2-3 days	7 d	In many body tissues as heart, blood cells, skeletal muscle and liver
Creatine kinase (CK)	86	4-6 h	24 h	2-3 d	Found in heart, brain and skeletal muscle
Creatine kinase isoenzyme MB (CK-MB)	86	4-9 h	10-24 h	1-3 d	Relatively specific for heart damage when damage of skeletal muscle is not present
Myoglobin	18	1-3 h	4-12 h	1 d	Low specificity (60-90%). Rarely used in clinical practice
Troponin I	24	3-6 h	12-24 h	7-14 d	Only in cardiac tissue.
Troponin T	35	3-6 h	12-24 h	7-14 d	Troponin I and troponin T are more specific markers for myocardial damage and hence superior to CK-MB. Elevated cTnT may in some cases be due to foetal cTnT in diseased and regenerating skeletal muscle.

kDa: kilo Dalton, h: hour, d: day

Creatine kinase

Creatine kinase (CK) is an enzyme which catalyses creatinine and consumes adenosine triphosphate (ATP) to create phosphocreatine and adenosine diphosphate (ADP). This enzyme reaction is reversible and ATP can be generated from phosphocreatine and ADP. In cells that consume ATP rapidly as skeletal muscle, but also heart and brain, phosphocreatine serves as an energy reservoir for rapid buffering and regeneration of ATP on the spot (80). CK is an important enzyme in such tissues, and was introduced in the diagnostic of AMI in the middle of the 1960s (81;82).

Myoglobin

Myoglobin is an oxygen-binding protein, with high concentration in both skeletal and heart muscle (83). Myoglobin has been rarely used in clinical practice due to its low

specificity (60-90%), and has not been used in our studies. However, myoglobin is potentially useful for ruling out but not for confirming the AMI diagnosis.

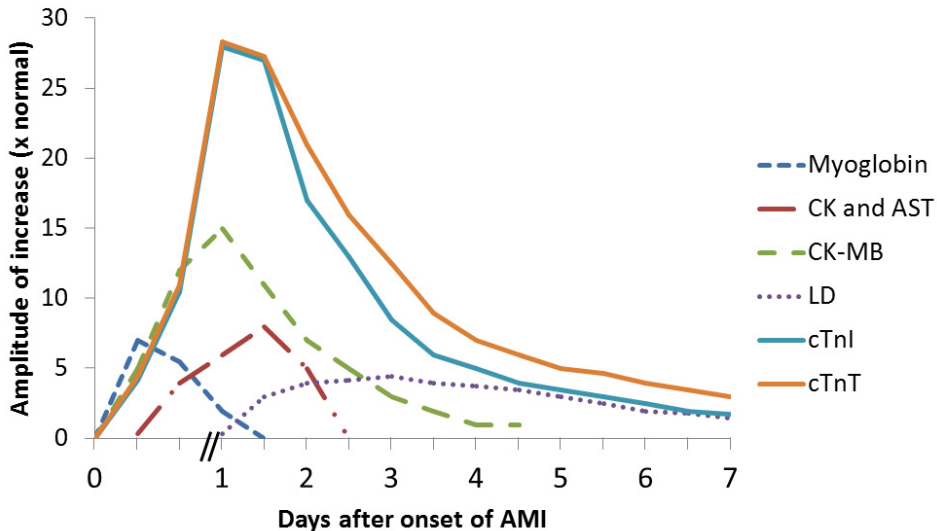


Figure 4 Typical rise and fall of cardiac biomarkers following myocardial infarction. Modified from Lewandrowski, K. et al. (84)

Creatine kinase isoenzyme (CK-MB)

CK enzymes consist of B (brain type) or M (muscle type), and there are three different isoenzymes: CK-MM, CK-BB and CK-MB. The heart expresses CK-MB at 25-30% and CK-MM at 70%. However, the skeletal muscle expresses CK-MB at 1% and CK-MM at 98%. Normal activity in serum is almost entirely from the CK-MM, and the CK-MB in normal serum is usually undetectable. Serum CK-MB activity >5% of total is considered diagnostic for AMI. The determination of CK isoenzymes as a marker for AMI was introduced in the early 1970s (85). CK-MB were measured by labour-intensive electrophoretic techniques, and was replaced by automated CK-MB mass assays during the mid-1990s, which performed testing faster, more frequently and at a lower cost.

Troponin

Troponin is a complex of three regulatory proteins in both cardiac and skeletal muscles:

- Troponin C – the calcium binding component
- Troponin I (24 kDa) – the inhibitory component – binding of actin
- Troponin T (35 kDa) - the tropomyosin binding component

Together with myosin and actin the troponin complex forms the contractile part of the musculature (86). Cardiac troponin I (cTnI) is exclusively found in cardiac tissue. However, cardiac troponin T (cTnT) is found in a foetal form in diseased and regenerating skeletal muscle, and there is an ongoing discussion if new generations of cTnT assays avoid detection of foetal cTnT or not (87;88). The cTnI and cTnT can be detected by assays of monoclonal antibodies directed against heart specific antigen (89). Troponin is released during AMI from the cytosolic pool of the myocytes. Its subsequent release is prolonged with degradation of actin and myosin filaments. Differential diagnosis of troponin elevation includes acute infarction, severe pulmonary embolism, heart failure, myocarditis and several other medical conditions. Analysis of troponins can also be used to calculate infarct size, but the peak level must be measured day 3-4 after the onset of AMI (90).

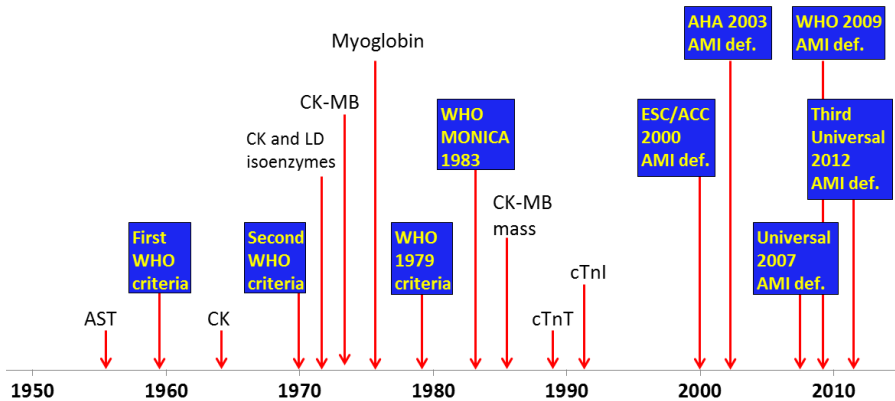


Figure 5: Evolving methods of cardiac biomarkers and changing definitions of acute myocardial infarction. Modified from Alpert, JS et al. (91).

1.6 Imaging techniques

Cardiac imaging techniques were introduced with the Universal 2007 definition and continued with the Universal 2012 definition of AMI as a diagnostic criteria in line with symptoms and ECG changes; “Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality” (74;76). Echocardiography, computed tomography (CT) and magnetic resonance imaging (MRI) have been increasingly used in the setting of acute coronary syndrome (ACS) in recent years (92;93). Since our patient’s cohorts were included until 2003, imaging techniques were not included in the AMI definitions at that time and we have not used this criterion in our studies.

1.7 Elevation of cardiac troponin without AMI

The Universal 2007 definition of AMI and the Universal 2012 definition emphasize that *troponin elevation alone is never sufficient to diagnose AMI*. This is specified in the criteria for AMI; “the term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia” (74;76). Rise and/or fall of cardiac biomarkers (preferably troponin) together with at least one of the following are required; symptoms of ischemia, ECG changes indicative of new ischemia, imaging evidence of a new AMI or identification of an intracoronary thrombus by angiography or autopsy. The Universal 2012 definition of AMI introduces the term “myocardial injury”, defined as cell death marked by cardiac troponin elevation. Table 3, modified from the consensus document of the Universal 2012 definition of AMI, include conditions related to AMI and conditions not related to AMI:

Table 3 Causes of elevation of cardiac troponin values due to myocardial injury

Injury related to primary myocardial ischaemia
Plaque rupture
Intraluminal coronary artery thrombus formation
Injury related to supply/demand imbalance of myocardial ischaemia
Tachy-/brady-arrhythmias
Aortic dissection or severe aortic valve disease
Hypertrophic cardiomyopathy
Cardiogenic, hypovolemic, or septic shock
Severe respiratory failure
Severe anaemia
Hypertension with or without left ventricular hypertrophy
Coronary spasm
Coronary embolism or vasculitis
Coronary endothelial dysfunction without significant coronary artery disease
Injury not related to myocardial ischaemia
Cardiac contusion, surgery, ablation, pacing, or defibrillator shocks
Rhabdomyolysis with cardiac involvement
Myocarditis
Cardiotoxic agents, e.g. anthracyclines, trastuzumab
Multifactorial or indeterminate myocardial injury
Heart failure
Stress (Takotsubo) cardiomyopathy
Severe pulmonary embolism or pulmonary hypertension
Sepsis or critical ill patients
Renal failure
Severe acute neurological diseases, e.g. stroke, subarachnoid haemorrhage
Infiltrative diseases, e.g. amyloidosis, sarcoidosis
Strenuous exercise

Modified from Thygesen, K. et al (76)

2. Aims of the present study

Main Aims

To provide age and gender specific estimates of trends in short- and long-term case fatality for a first AMI of hospitalized patients, and to analyse the impact of applying five different definitions of AMI on number of AMI events, types and long-term mortality.

Specific Aims

1. To investigate age and gender specific time trends in short- and long-term case fatality up to 10 years among patients hospitalized with a first AMI at Haukeland University Hospital during 1979-2001.
2. Study the impact of applying four different definitions of AMI on the number and types of AMI events and long-term mortality.
3. To compare the most recent Universal 2012 definition of AMI to the previous definition with respect to number and types of AMI events. Further to study the short- and long-term all-cause mortality.

3. Methods

3.1 Study populations

Paper I

We examined patients with a first AMI (I21) admitted to Haukeland University Hospital between 1 January 1979 and 31 December 2001. The patient data were obtained from the Western Norway Cardiovascular Registry (WENOCARD), a regional registry of all patients with cardiovascular diagnoses and procedures recorded in the hospital discharge and administrative system in Western Norway. WENOCARD was later included in the Norwegian Cardiovascular Disease Registry (NorCVD), and contains data from Haukeland University Hospital from 1 January 1972.

Paper II and Paper III

We retrospectively studied patients hospitalised at Haukeland University Hospital during the period 1 March 2002 through 28 February 2003. Eligible patients were men and women of all ages, with either a discharge diagnosis of a first (I 21) or recurrent (I 22) AMI, or without any discharge diagnosis of AMI but with at least one measurement of elevated cardiac troponin I (cTnI) during the hospital stay.

3.2 Clinical data

Symptoms

Paper I

The clinicians applied the WHO definition of AMI with presence of at least two of three criteria: Typical symptoms, typical ECG abnormalities and increase in enzymes indicating myocardial injury (63). Enzyme changes included serum alanin aminotransferase, aspartate aminotransferase, creatine kinase and CK-MB. Troponin I was not officially implemented in the diagnostic criteria at the hospital until after the study period. The ECGs were interpreted by clinicians at the hospital without subsequent validation. For coding, the International Classification of Diseases ICD-8 and ICD-9 (410) were used through 1998, and ICD-10 (I21 or I22) from 1999.

Paper II and Paper III

The patients' medical records were examined for information on symptoms, ECG, cardiac biomarkers, comorbidity, coronary risk factors and treatment during the hospital stay. Discomfort or pain in the chest, upper extremity, jaw or epigastriae lasting for >20 minutes were interpreted as ischemic symptoms.

Cardiac biomarkers**Paper II and Paper III**

Patients with suspected acute coronary syndrome at admission or during the hospitalization had a blood sample drawn for measurements of CK-MB mass and cTnI levels as soon as possible and 6-9 hours later. If at least one of the biomarkers was elevated, a third sample was collected at least 12 hours after the second sample. In addition blood samples were routinely drawn from patients treated with PCI or CABG. CK-MB mass level values were classified according to the WHO-1979 definition, which describes unequivocal enzymes change as serial change, or initial rise and subsequent fall. CK-MB mass was not used in Paper III.

The level of cTnI was measured using the Bayer Technicon Immuno assay, with a decision limit at cTnI >0.10 µg/L according to the 99th percentile of a healthy population (94). However, acceptable imprecision of troponin assays is a CV <10% at the 99th percentile reference limit, with the decision limit at cTnI >0.34 µg/L for our assay, which we applied in our analyses. The patients' cTnI levels were classified as typical rise, gradual fall, both, or none of these. A cTnI change of >20% from the index level was classified as typical rise or fall (95). For lower cTnI index levels, we chose an absolute concentration change (delta) between two cTnI measurements of 0.20 µg/L in a setting of typical rise or gradual fall (96).

ECG**Paper II and Paper III**

ECGs were evaluated in all patients with a clinical presentation consistent with myocardial ischemia. The ECGs were analysed retrospectively by the first author

blinded to clinical outcome and in accordance with the ECG criteria from the four different AMI definitions studied. Patients with ECG changes indicative of AMI but with normal or missing troponin measurement were not included in the current investigation with one exception, patients with sudden cardiac death. For validation purposes a second cardiologist validated randomly extracted ECGs from 100 patients. The interpretation of ST-elevation between the two cardiologists differed in <3%.

3.3 Diagnosis

Paper I

We defined the first AMI as the first hospitalization with AMI as the main or secondary diagnosis, recorded in WENOCARD on condition that no previous AMI had been recorded in the registry. To identify and include only incident (first) and not recurrent AMI, a period prior to the AMI of seven years (1972-1978) or more without a registration of an AMI was required.

Paper II

Attending physicians set the discharge diagnoses recorded in the hospital's Patient Administrative System. The medical records for all patients with the selected discharge diagnoses were reviewed by trained medical students, and data entered into a database. The first author reviewed all registered data and classified the AMI diagnoses according to the different AMI definitions and subtypes according to the Universal-2007 definition (74).

Paper III

In Paper III two cardiologists independently reviewed all registered data and classified the AMI diagnoses and AMI types according to the two Universal AMI definitions. The classification initially differed in 67 events (4.5%). In all these cases the cardiologists agreed after in-depth discussion.

3.4 Subtypes of AMI

Paper II and Paper III

The Universal 2007 definition and Universal 2012 definition of AMI do not specify whether coronary angiography is required to distinguish Type 2 from Type 1 AMI. Coronary artery spasm with resulting ischemia and rise in troponin levels is mentioned as a mechanism of Type 2 AMIs. However, patients with coronary artery spasm may in addition have coronary plaque erosion with resulting intraluminal thrombus. We have therefore chosen to interpret Type 2 AMI as an exclusion diagnosis after performed coronary angiography, as have others (97).

3.5 Follow up and mortality

Paper I

Data on all-cause and diagnosis-specific death were obtained from the Cause of Death Registry, Statistics Norway. All surviving patients were followed until 31 December 2006.

Paper II and Paper III

Information on all-cause mortality was obtained from the National Population Registry, and all patients were followed from admission until death, and 31 December 2011 or 1 March 2013 respectively.

3.6 Statistical analysis

Results are shown as numbers and percentages (%), means with standard deviation (SD) or median with interquartile range (IQR) for variables not normally distributed. We assessed differences in baseline characteristics between groups using χ^2 -test for categorical and t-test for continuous variables. A two-sided p-value <0.05 was considered statistically significant throughout.

Paper I

In Paper I the patients were separated into three groups representing the study periods: 1979–1985, 1986–1993 and 1994–2001, based on data on admission. Survival was studied using all-cause death as main endpoint. Survival time was calculated as the number of days between the admission date and the date of death, or 31 December 2006. Kaplan–Meier survival curves were estimated for both sex groups and age groups (<60, ≥60 years). For each sex-age group, the Kaplan–Meier curves were stratified by study period, and difference in survival across time periods were tested using the log rank test. To provide separate descriptions of the short-term and long-term survival we also performed a landmark analysis with prespecified landmarks at day 28 and day 365 (98). When plotting the survival curves, the analyses were reset at each of the two landmark time points. Each analysis included only patients alive at the landmark time point. Trends in 28-day, 1-year and 10-year case-fatality rates across the three study periods were assessed using logistic regression with period included as a three-level covariate with the first period (1979–1985) as the reference level. Cases from 1997–2001 with less than 10 years of follow-up were excluded in the 10-year case-fatality calculations.

Paper II

In Paper II we chose the first event for the study period as the reference for mortality in accordance with other studies (99;100). Difference in short- and long-term mortality after AMI between groups was assessed using logistic regression and Cox regression. As there was no loss to follow-up and both methods led to the same conclusions, we presented the results from logistic regression in order to be able to compare mortality at exactly 28 days, 1 year, 5 years and 8 years. We have used McNemar’s test to test the differences in number of AMI events explained by the use of the Universal 2007 definition compared to the WHO 1979 definition, with the WHO 1979 definition as the reference definition.

Paper III

In Paper III differences in baseline characteristics between Type 1 and Type 2 AMI were assessed using Chi-square or Fisher’s exact tests for categorical and t-tests for

continuous variables. Unadjusted 28 days, 1, 5 and 10 years all-cause mortality rates were calculated separately for types of AMI within each of the two definitions.

We used SPSS version 18 and 21 (IBM SPSS Statistics), Stata IC version 12 (StataCorp LP), SAS Version 9.1.3 (SAS Institute Inc., Cary, North Carolina, USA) and S-PLUS 7.0 for Windows (Insightful Corporation, Seattle, Washington, USA) for statistical analyses.

3.7 Ethics

The studies were approved by the Regional Committee for Medical and Health Research Ethics and conducted in accordance with the Declaration of Helsinki. The Data Inspectorate and the Norwegian Directorate of Health gave the necessary permissions, including an exemption from the requirement of obtaining patient's consent.

4. Summary of results

4.1 Paper I

A total of 15873 patient's admissions with a first or recurrent AMI to Haukeland University hospital during 1972-2001 were studied. After censoring 3995 patients admissions during the first seven years (1972-1978), the study population consisted of 11878 patients (4243 women and 7635 men), with a first AMI hospitalized during 1979-2001 (Figure 6). During the three periods (1979-1985, 1986-1993 and 1994-2001), mean age at the onset of the AMI in women increased significantly from 73.5 to 75.2 years ($P < 0.0001$), whereas it was unchanged in men at 66 years. The proportion of women was stable at 36% throughout the entire study period. Among the patients under the age of 60 years, the proportion of women was approximately 16% throughout the study.

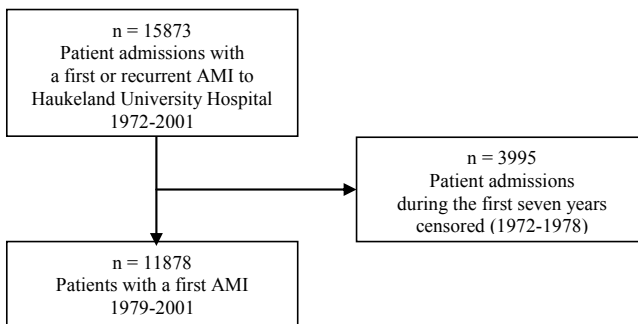


Figure 6: Flow chart illustrating selection of patients in paper I.

From 1979-1985 to 1994-2001, unadjusted 28-day case fatality declined from 31.1% to 19.8% in men and from 37.3% to 26.8% in women (both, P -trend < 0.0001). Unadjusted 10-year case fatality declined from 69.5% to 55.5% in men and from 80.8% to 66.1% in women (both, P -trend < 0.0001). Landmark analysis demonstrated a decline in 1-10 year case fatality, among patients < 60 years from 26.1% to 13.8% in men, and from 33.3% to 6.4% in women. In patients ≥ 60 years, the 28-day, 1-year and 10-year age-adjusted case fatality rates were significantly lower in women than men.

4.2 Paper II

The source population consisted of 1997 patient admissions with a diagnosis of AMI (815 patient admissions), and additionally 679 patients admissions with at least one measurement of elevated cardiac troponin I (cTnI) >0.10 mg/l during the hospital stay, but not diagnosed with AMI. After exclusion of 379 patient admissions with measured cTnI levels <0.34 mg/l and 124 recurrent admissions during the inclusion period, the study population consisted of 1494 patients. Men ($n = 974$) were younger (mean age 65.6 years) than women ($n = 520$, mean age 73.6 years) at admission ($p < 0.001$). Mean age, risk factors, clinical status, and treatment varied only slightly according to the different AMI definitions.

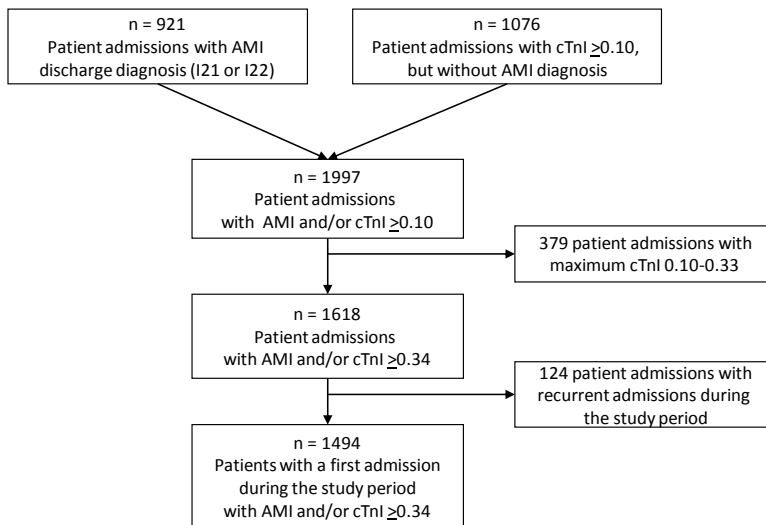


Figure 7: Flow chart illustrating selection of patients in paper II and paper III.

Applying the WHO 1979 definition resulted in 566 patients with definite AMI among the 1494 patients, and this number was used as reference. Excluding possible and probable AMIs according to the WHO 1979- and AHA 2003 definitions, the numbers (% compared with reference) of AMI were: 455 (-20%) by the original troponin “rise and fall” version of the ESC/ACC 2000 definition, 729 (+29%) by the troponin “rise or fall” interpretation of the ESC/ACC 2000 definition, 761 (+34%) by the AHA 2003 definition, and 743 (+31%) by the Universal 2007 definition (all p values < 0.001). Of the 743

patients with AMIs according to the Universal 2007 definition, a total of 659, 28, 30, 20, 2, and 4 patients had a type 1, type 2, type 3, type 4a, type 4b, and type 5 AMI, respectively. The 30 patients with type 3 AMI died shortly after admission and before possible detection of cTnI elevation.

Of the 1494 patients, 777 were classified with a definite AMI according to one or more different AMI definitions; 358 according to all four definitions, 375 according to ≥ 2 definitions, and 44 according to one single definition. The remaining 717 patients were classified with non-ischemic causes of elevated cTnI levels, such as infections, kidney failure, myocarditis and elective cardiac surgery.

4.3 Paper III

The study population of 1494 patients was identical with the population in paper II (Figure 7). After an additional validation by an additional physician 769 patients (51.5%) were classified with an AMI event according to the Universal 2007 definition, and 760 patients (50.9%) according to the Universal 2012 definition.

Among the 760 patients 685, 27, 28, 13, 3, 0 and 4 patients were classified with Types 1, 2, 3, 4a, 4b, 4c and 5 AMIs, respectively. Although we observed a trend towards younger patients with lower comorbidity classified with Type 2 compared to the Type 1 AMI, only the proportion of angiography and initiated treatment differed significantly between this two types.

The application of the Universal 2012 definition of AMI as compared with the Universal 2007 definition had no impact on all-cause mortality among the patients with AMI. The unadjusted 28 days, 1-year, 5-years and 10-years all-cause mortality according to both AMI definitions was 14%, 21%, 35% and 49%.

5. Discussion

This thesis demonstrates a substantial decline in short-term and long-term case fatality in patients hospitalized for a first AMI during 1979-2001. The number of AMI events however depends on which definition of AMI and biomarker is applied. When the WHO 1979 definition of AMI with CK-MB mass as biomarker was used as reference, we found that applying the ESC/ACC 2000, AHA 2003 and Universal 2007 definitions of AMI with cTnI as biomarker resulted in approximately 30% more patients diagnosed with definite AMI in the same cohort. The change of AMI definitions had a moderate impact on the AMI mortality among hospitalized patients. We observed a minor decrease in number of events of AMI and no change in mortality when applying the Universal 2012 definition of AMI as compared with the Universal 2007 definition.

5.1 Trends in long-term case fatality after a first AMI

The observed decline in short- and long-term case fatality in patients hospitalized for a first AMI during the study period 1979-2001, is in line with other studies (23;52;101). However, the observed 28-day case fatality during 1994-2001 of 22% may be unexpectedly high compared to randomized trials which report a 28-day case fatality of 5-6% (37;38). The significant difference is explained by our unselected cohort including patients from all departments of the hospital, including those who died soon after hospitalization, whereas randomized studies usually recruits patients from cardiac units with exclusions due to comorbidity and age ending up with highly selected study populations.

5.2 Age, gender and case fatality

In Paper I we observed that among patients >60 years the survival curves for the three time periods may seem paralleled after one year. However, Landmark analysis revealed a significant improvement in case fatality in both genders during days 29-365 and during 1-10 years after the first AMI, as observed previously in a Nordic study (101).

Further, we observed in Paper I a substantial decline in age-standardized case fatality rates both among men and women. However, the literature has been conflicting regarding short-term prognosis for women compared with men following an AMI. Large studies have found no gender differences after adjustment for age and comorbidity (102-104), whereas others have reported higher short-term case fatality in women (105). However, when we adjusted for age we observed a more favourable outcome in case fatality for women ≥ 60 years compared with men ≥ 60 years already after 28 days. In patients < 60 years we did not find a significant difference in case fatality between women and men. Some studies have found a higher short-term case fatality in young women with AMI (106-108), the difference may be explained by a higher prehospital death rate among younger men compared with younger women (57;107).

5.3 Changing definitions of AMI

We observed approximately 30% more AMI events among our study population according to the ESC/ACC 2000, AHA 2003, Universal 2007 and Universal 2012 definitions of AMI as compared with the WHO 1979 definition of AMI. Other studies have reported higher number of AMI events with the introduction of the ESC/ACC 2000 definition, ranging from 4% to 195% relative increase (99;109-114). The newer AMI definitions had a moderate impact on the AMI mortality among hospitalized AMI patients in our study, which is in line with a recent published study (115).

5.4 Subtypes of AMI

The introduction of Type 1-5 AMI is important for clinical and epidemiological research, especially regarding Type 3 (sudden cardiac death) and Type 4 and 5 (PCI and CABG) AMI.

However, the distinction between Type 1 and Type 2 AMI in the Universal 2012 definition of AMI is poorly defined and different studies have made different interpretation of Type 2 AMI resulting in a proportion of this subtype varying from 1.6% to 26% (97;116-119).

In Paper III we compared our study with a Danish study. They focused on Type 1 and Type 2 AMI and established their own criteria for classifying Type 2 AMI due to anaemia, shock, bradyarrhythmia, coronary embolus, respiratory failure, ventricular tachycardia, hypertensive pulmonary edema and hypertension with left ventricular hypertrophy (119). Coronary artery spasm was not defined in this study, which included patients with elevated troponin levels, and accordingly excluded Type 3 AMI. They found 553 patients with an AMI according to the Universal 2007 definition of AMI, 397 (72%) patients were classified with a Type 1 AMI and 144 (26%) patients with Type 2 AMI. Coronary angiography was performed in 281 patients with Type 1 AMI and 31 patients with Type 2 AMI, with significant coronary artery disease in 248 and 17 patients, respectively.

In our study the total of Type 1 and Type 2 AMI was 93% according to the Universal 2007 definition of AMI compared to 98% in the Danish study. However, the proportion of Type 2 AMI was highly different with an occurrence of 4% and 26%, respectively. Two main factors are probably responsible for the rather large difference. First, there is a difference in patient populations. Our study included patients with Type 3 AMI, whereas the other study excluded patients without troponin elevation. Secondly, our study had a conservative approach where plaque rupture with intraluminal thrombus should be ruled out before classifying an AMI as Type 2. In contrast, the Danish study emphasized predefined conditions where there may be an imbalance between oxygen demand and supply to the heart, without a requirement for coronary angiography.

Studies of coronary angiography have found no evidence of obstructive coronary artery disease among 7-10% patients with STEMI, and among 4-15% patients with NSTEMI (120-122). An angiography study demonstrated correlations between obstructive coronary disease and Type 1 AMI, and between non-obstructive coronary disease and Type 2 AMI (123). However, other recent studies have further examined AMI patients with non-stenotic coronary arteries. They found a significant number of plaque rupture or coronary ulcerations with computed tomography coronary angiography (CTCA) or intravascular ultrasound (IVUS) not detected by angiography (124;125). Thus, AMI classified as Type 2 AMI after a normal angiography may still have been due to a coronary thromboembolic event.

A clear definition of AMI is essential with minimal need for clinical judgement (126;127). One solution of this problem is to develop extensive criteria for Type 2 AMI (119;128). However, a distinction between Type 1 and Type 2 AMI does not seem to affect the acute treatment of AMI, which relates to the presentation of ST-elevation or non-ST-elevation in the ECG (129;130). Secondary prevention of AMI should be considered in both types of AMI, because many patients with a Type 2 AMI without stenotic coronary arteries at conventional coronary angiography may have plaque rupture demonstrated by IVUS and CTCA (124;125). Furthermore, the use of such criteria will be time consuming. An alternative may be to merge the AMI Type 1 and Type 2 into one type of AMI, since it will simplify the classification without influencing the total number of AMIs.

5.5 Non-ischemic causes of elevated troponin levels

The Universal 2012 definition of AMI states that cases of non-ischemic causes of elevated troponin levels should be labelled as myocardial injury, and not as AMI (76). In differentiating between AMI and non-ischemic myocardial injury it is important to adhere to the main criteria that AMI should be used in a clinical setting of acute myocardial ischemia, and the rise and/or fall of cardiac biomarker with at least of; ischemic symptoms, new ECG changes, imaging evidence, intracoronary thrombus by angiography or autopsy (76). It may be challenging to differentiate non-ischemic myocardial injury from Type 2 AMI with poorly defined criteria for Type 2 AMI (128). Our conservative approach where plaque rupture with intraluminal thrombus should be ruled out before classifying an AMI as Type 2 might simplify this differentiation.

In our hospital based study population, 48% of the patients were classified with non-ischemic causes of elevated cTnI levels, such as infections, kidney failure, myocarditis and elective cardiac surgery, consistent with a similar study (131). Regardless of the diagnosis of AMI or non-ischemic myocardial injury, patients with elevated cardiac biomarkers have increased short- and long-term mortality compared with patients without elevated troponin (128;132).

5.6 Strength and limitations

Paper I

A major strength is the large number of patients studied at a single university hospital over a long period of 23 years with a follow up for up to 10 years case fatality, which is longer than most other studies. In addition, nation-wide follow-up of all patients by linkage to the Cause of Death Registry contributes to that very few patients were lost during follow-up.

The WHO definition of AMI was used in the entire study period. However, there was no strict validation of the clinical basis for the AMI diagnosis, and the discharge diagnosis of the attending physician was accepted. Troponin was officially implemented in the diagnostic setting in 2002, and therefore troponin would not have any influence on the incidence of AMI in the study period 1979-2001. The potential bias from improvements in emergency care outside hospital, or change in diagnostic criteria, is unknown.

Paper II and Paper III

Paper II is one of few that compare number of AMI events and long-term mortality applying four different definitions of AMI. This was further explored in Paper III in the same patient cohort where we compared the Universal 2007 and the Universal 2012 definition of AMI. A major strength in these two papers is the registration of every measured troponin value and the precise categorisation of rise or fall of cTnI, as well as complete mortality follow up.

Paper II and Paper III have several limitations. First, using clinical judgement in the retrospective classification of AMIs according to five different definitions of AMI induces some risk of misclassifications. Second, the 4.5% inter-observer variation between primary classification by the first cardiologist and additional validation of a second cardiologist in Paper III was small, and after in-depth discussion, there was no variation left. The additional validation of AMI events resulted in 769 AMI events applying the Universal 2007 definition of AMI in relation to Paper III, compared with 743 AMI events in the same cohort in relation to Paper II. Third, Type 2 AMI is not well

defined in any of the Universal definitions. We applied our own interpretation of Type 2 AMI, and our results may not apply to other hospital populations. Forth, 137 patients had a single elevated cTnI. However, only 16 of these patients were lost as a potential Universal 2007 or Universal 2012 definition AMI, due to missing information on troponin values from the local hospital. Fifth, we did not examine the patient records of all patients who had undergone PCI or CABG during the inclusion period; only patients with elevated cTnI levels were included. We may therefore have underestimated the number of patients with Type 4 and Type 5 AMI. Sixth, we do not have data on Type 4c AMI (restenosis) according to the Universal 2012 definition, these are therefore included in the other subtypes of AMI as in the Universal 2007 definition.

5.7 Perspectives

The definition of AMI has been revised several times since the introduction of the first definition by the WHO in 1959, due to the advances in biomarkers and cardiac imaging (61;63;66;68;73-76). However, the changing AMI definitions have complicated the analyses of trends in the number of AMI events and mortality. It is therefore important to study the different AMI definitions with respect to number of AMI events and mortality. The definition of AMI should be as simple and clear as possible to facilitate clinical practice and research (126;127). It should probably not be changed more frequently than necessary, because it takes time before clinicians and researchers are familiar with a new definition.

The poorly defined distinction between Type 1 and Type 2 AMI in the Universal 2012 definition of AMI should be merged or better defined.

We have not known the exact incidence of AMI in Norway, due to lack of a register with personal identification numbers. This will be facilitated by the Norwegian Cardiovascular Disease Registry and the Norwegian Myocardial Infarction Register, established 2012 and 2013 respectively. These registries will provide us with further data for prevention, quality improvement and health research (57;133). Myocardial infarction is still an important cause of death in Norway and worldwide (55;134;135). Although we have seen a decline in incidence and mortality in our country during the last decades, recent studies demonstrate a trend towards increasing hospitalization rate of AMI in younger persons (52;57;58). Notably, the obesity epidemic is primarily influencing young and middle aged subjects, and is expected to promote increase in diabetes and a possible increase in AMI (56). This will pose a particular challenge for clinical and epidemiological surveillance (136).

6. Conclusions

1. **Impact on short- and long-term case fatality among patients hospitalized with a first acute myocardial infarction during 1979-2001**

There has been a substantial decline in short-term and long-term case fatality in patients hospitalized for a first AMI over a study period of 23 years in our university hospital. The improvement is observed in both sexes and in young and old patients. Women ≥ 60 years fare better than men do when we compare age-adjusted case fatality rates.

2. **Impact of applying four different definitions of AMI on the number of AMI events and mortality**

The number of AMI events depends on the definition of AMI and biomarkers. When the WHO 1979 definition of AMI with CK-MB mass as biomarker is used as reference, applying three newer definitions of AMI with cTnI as biomarker result in approximately 30% more patients diagnosed with definite AMI. The change of AMI definitions has a moderate impact on the AMI mortality among hospitalized patients.

3. **Impact of applying the Universal 2012 definition of AMI compared to the Universal 2007 definition with respect to number of events, subtypes and mortality**

The change from the Universal 2007 definition to the third Universal 2012 definition of AMI primarily involve the PCI- (Type 4a) and CABG-related (Type 5) AMIs, with a minor decrease in number of AMI events and unchanged mortality. Because distinction between Type 1 and Type 2 AMI is poorly defined in the Universal definition and few patients are diagnosed with Type 2 AMI, one may question whether the two definitions should be merged or better defined.

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