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MAI BLÖNDAL

Changes in the baseline characteristics, management and outcomes of acute myocardial infarction in Estonia

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Department of Cardiology, University of Tartu, Tartu, Estonia

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To my family

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LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following papers referred to in the text by their Roman numerals (I–IV):

I Blöndal M, Ainla T, Marandi T, Baburin A, Eha J. Changes in treatment and mortality of acute myocardial infarction in Estonian tertiary and secondary care hospitals in 2001 and 2007. BMC Research Notes 2012; 5: 71.

II Blöndal M, Ainla T, Marandi T, Baburin A, Rahu M, Eha J. Better outcomes for acute myocardial infarction patients first admitted to PCI hospitals in Estonia. Acta Cardiologica 2010; 65: 541–548.

III Blöndal M, Ainla T, Marandi T, Eha J. ST-elevatsiooniga ja ST-elevatsioonita ägeda müokardiinfarkti haigete ravi hilistulemused pärast perkutaanset koronaarinterventsiooni: registriandmete linkimisuuring. Eesti Arst 2012; 91: 343–348.

IV Blöndal M, Ainla T, Marandi T, Baburin A, Eha J. Sex-specific outcomes of diabetic patients with acute myocardial infarction who have undergone percutaneous coronary intervention. Cardiovascular Diabetology 2012; 11: 96.

Author's contribution:
Mai Blöndal was involved in the study design, data collection, data linkage, statistical analysis as well as wrote the first draft of the manuscript for all the papers.

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitors
AMI	acute myocardial infarction
ARB	angiotensin II receptor blockers
ASA	acetyl salicylic acid
BMI	Body Mass Index
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CARDS	Cardiology Audit and Registration Data Standards for Coronary Care Unit/Acute Coronary Syndrome admissions
CI	confidence interval
DM	diabetes mellitus
ECG	electrocardiogram
EDMD	European Detailed Mortality Database
EHIF	Estonian Health Insurance Fund
EMIR	Estonian Myocardial Infarction Registry
ESC	Estonian Society of Cardiology
FHS	Framingham Heart Study
GRACE	Global Registry of Acute Coronary Events
HR	hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th revision
IQR	interquartil range
LBBB	left bundle branch block
LMWH	low-molecular-weight heparin
NA	not applicable
NSTEMI	non-ST-segment elevation myocardial infarction
NRMI	National Registry of Myocardial Infarction
OR	odds ratio
PCI	percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
SD	standard deviation
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
UFH	unfractionated heparin
WHO	World Health Organization

I. INTRODUCTION

Coronary artery diseases (CAD) are the leading cause of death in the world [World Health Organization (WHO) Mortality Database 2012]. They cause considerable costs in terms of medical expenditures, lost production, suffering and premature death (Wieser *et al.* 2012).

CAD mortality has continuously been decreasing in most of the Western high-income countries over the last few decades (WHO European Detailed Mortality Database 2012), in some regions even more than 50% (Bjorck *et al*. 2009). The decreasing mortality trends can partially be explained by changes in the major cardiovascular risk factors including total cholesterol, smoking, and blood pressure levels (Capewell *et al*. 1999; Tunstall-Pedoe *et al*. 2000; Unal *et al*. 2004; Ford *et al.* 2007; Bandosz *et al*. 2012). The other major factor contributing to the decline in the mortality is the rapid uptake of effective medical therapies and coronary revascularization methods. This has led to the lower case fatality of acute myocardial infarction (AMI), which has one of the highest risks among CAD. Community studies have shown that the overall case fatality rate of patients with AMI in the first month can be as high as 50%, and of these deaths about half occur within the first two hours (Tunstall-Pedoe *et al.* 1999). The prognosis of patients with AMI can considerably be improved with the timely use of efficient modern management strategies. This includes the use of coronary angiography and percutaneous coronary intervention (PCI), which have revolutionized management and outcomes in these high-risk patients.

In Eastern Europe mortality from CAD has steadily been decreasing over the last decade. Still, mortality rates remain higher than they are in the Western high-income countries (Eurostat 2012). Furthermore, Estonia has reported one of the highest rates of CAD mortality in Europe. The data from the Euro Heart mapping project in 2009 (www.eurekalert.org) revealed that Estonia has one of the highest rates of death from cardiovascular diseases among men and women under 65 years of age.

The health care system of Estonia has undergone considerable changes during the last decade. Much effort has been made to improve the quality of care for AMI patients through better application of recommendations in the management guidelines. A study conducted in 2001 (Ainla *et al.* 2006) showed important disparities in the management and outcomes of patients with AMI in tertiary and secondary care hospitals in Estonia. The use of PCI was low and only one fourth of the patients in specialized hospitals were treated with this management method. Therefore, one of the main priorities has been to increase access to PCI and to enable more ST-segment elevation AMI (STEMI) patients to receive timely reperfusion therapy, including primary PCI. Nevertheless, owing to the small population of 1.3 million, as well as to technical requirements and economical reasons, PCI facilities are available only in specialized hospitals. Although several studies have clearly demonstrated the association between the availability of on-site PCI facilities and their use in the management of patients with AMI, its impact on short- and long-term outcomes is

conflicting and prone to regional variations. There are currently little data in Estonia comparing the changes in the management, including selection for PCI, and outcomes of AMI patients first admitted to hospitals with different level of care and unequal availability of PCI. Furthermore, as access to personalized data has been restricted for legal reasons, research on the long-term fatal and non-fatal outcomes of AMI patients has been halted for several years. Yet, such information is crucial to both the public and to health care professionals when aiming to offer equitable healthcare services to all patients in Estonia in a setting of limited health care resources.

There is urgent need for data on the management and outcomes of AMI in the real life setting. The concept of modern evidence-based care is mostly based on the results derived from randomized controlled studies (Sackett *et al.* 1996; Chalmers 1998). Yet these include younger patients with less co-morbidities, more often of the male sex (Hannan 2008). However, in the clinical practice the management and outcomes of AMI are challenged by the aging of the population, the higher rates of female patients, and the increasing presence of co-morbidities such as diabetes mellitus (DM) (Alexander *et al.* 2005; Koek *et al*. 2007). Indeed, the prevalence of DM in the population is rapidly rising, especially among women (Wild *et al.* 2004; International Diabetes Federation, Diabetes Atlas 2011). At the same time, data about the effect of DM on the sex-specific outcomes of patients with AMI are conflicting (Hyvarinen *et al.* 2009).

The current study was undertaken to evaluate the changes in the baseline characteristics, management and outcomes of patients with AMI in Estonia during the last decade as well as to study the long-term outcomes after PCI in different AMI patient subgroups.

2. REVIEW OF THE LITERATURE

2.1. Pathogenesis of AMI

AMI represents a life-threatening manifestation of atherosclerosis. It is usually precipitated by acute thrombosis that is induced by a ruptured or eroded atherosclerotic plaque. This will lead to sudden and critical reduction in the blood flow in the coronary arteries resulting in the death of cardiomyocytes. In rare cases AMI may have a non-atherosclerotic etiology such as arteritis, trauma, dissection, thrombo-embolism, congenital anomalies, and complications of coronary angiography. The complete necrosis of all myocardial cells at risk requires at least 4 h to 6 h or longer, depending on the presence of collateral blood flow into the ischemic zone, persistent or intermittent coronary artery occlusion and the sensitivity of the myocytes (Libby *et al.* 2007).

2.2. Definition of AMI

In 1979 the WHO defined AMI by a combination of two of the three characteristics: typical symptoms, enzyme rise and a typical electrocardiogram (ECG) pattern involving development of Q waves. However, progress in the development of more sensitive and specific biomarkers and precise imaging techniques (echocardiogarphy, radionuclide imaging, magnetic resonance imaging, computed tomography) has enabled to detect smaller amounts of myocardial necrosis.

In 2000, the Joint European Society of Cardiology/ American College of Cardiology Committee published the consensus document regarding the redefinition of myocardial infarction (Alpert *et al.* 2000). This document implied that any necrosis in the setting of myocardial ischaemia should be labelled as AMI and the use of cardiac troponins (Troponin T or Troponin I) was introduced into the clinical practice.

The criteria for an AMI were the following:

1) Typical rise and gradual fall of troponin and/or creatine kinase MB with at least one of the following:
   a. ischaemic symptoms;
   b. changes on the ECG indicative of ischemia (ST-segment elevation or depression);
   c. development of pathologic Q-waves on the ECG; or
   d. coronary artery intervention.
2) Pathological findings of an AMI.

By 2007, the new generation of troponin assays enabled a more sensitive and more specific detection of the increase in the cardiac troponin levels. This resulted in the launch of the universal definition of myocardial infarction by the Joint European Society of Cardiology/ American College of Cardiology/ American Heart Association/ World Heart Federation Task Force (Thygesen *et al.* 2007). Additionally, the document recognized the importance of imaging techniques in

the diagnosis of AMI. The new diagnosis guidelines were adapted in Estonia in June 2010 (Eesti Kardioloogide Selts, Eesti Laborimeditsiini Ühing 2010).

The third universal definition of AMI (Thygesen *et al*.), released in august 2012, recognizes that very small amounts of myocardial injury or necrosis can be detected with the help of biochemical markers and/or imaging. The latest generation, high sensitivity troponin assays, enable the detection of myocardial damage already within the first hours of the onset of AMI (Hamm *et al.* 2011). These assays have high sensitivity with the cost of lower specificity, making recognition of ischemic symptoms in the diagnosis of AMI even more important (Keller *et al*. 2011).

Subtypes of AMI

The major subdivision of AMI is based on the findings in the ECG: (1) persistent ST-segment elevation/ new left bundle branch block (STEMI/LBBB AMI) or (2) non-ST-segment elevation (NSTEMI). The underlying pathogenesis in these two entities is different. The thrombus is fibrin rich and completely occlusive in STEMI, whereas it is platelet-rich and partially or intermittently occlusive in NSTEMI (Libby *et al.* 2007).

2.3. Epidemiology of AMI

Information on AMI incidence rates is used to estimate the burden of CAD within and across populations. It also gives useful data regarding the impact of developments in the AMI management in time, especially if data are collected in a manner distinguishing between new and recurrent events in a patient. Hospitalization for AMI is often used as a proxy to study the trends in AMI incidence. However, their interpretation is often challenging given the reliance on hospital administrative systems.

During the last few decades the Western high-income countries have observed detrimental trends in the cardiovascular risk factor profile among the populations, including less physical activity, more obesity and DM, and aging of the population (Danaei *et al.* 2011; Farzadfar *et al*. 2011; Finucane *et al.* 2011). At the same time a range of lifestyle, medical and interventional strategies for primary and secondary prevention of AMI have been adopted.

Starting from the 1950ies, several landmark studies in the USA and Europe have observed declines in the rates of hospitalization for AMI (Rosen *et al*. 2000; McGovern *et al.* 2001; Messner *et al*. 2003; Fox *et al*. 2004; Floyd *et al*. 2009; Myerson *et al*. 2009; Parikh *et al*. 2009; Yang et al. 2011). The rates decreased modestly or in some countries even increased until the end of the 1990 and thereafter started to decrease substantially (Yeh *et al*. 2010; Fang *et al*. 2010). Also the rates of out-of-hospital deaths from AMI have declined (McGovern *et al*. 2001; Abildstrom *et al*. 2003; Lundblad *et al*. 2008).

The interpretation of epidemiological trends is challenged by the introduction of cardiac biomarkers of varying sensitivity and specificity for detection of AMI over time. Indeed, the reported hospitalization rate of AMI increased

slightly after the diagnostic criteria for AMI were introduced in 2000 (Ferguson *et al*. 2002). Nevertheless, it should be noted that the rates of AMI diagnosed by ECG have declined by 50%, whereas the rates of AMI diagnosed by cardiac markers have doubled (Rogers *et al.* 2008).

Epidemiology of AMI subtypes

Since the middle of the 1990, the proportion of patients with NSTEMI has increased from approximately 60% to 75% (Yeh *et al*. 2010; Jernberg *et al*. 2010; Floyd *et al.* 2009). The changes have been more pronounced since 2000 (Ferguson *et al.* 2002; Yeh *et al*. 2010) when the new definition document of AMI was issued (Alpert *et al*. 2000). However, it is considered that the higher rates of NSTEMI are due to the aging of the population, greater prevalence of co-morbidities, and substantial improvements in primary prevention efforts such as management of dyslipidemia and hypertension, that might lessen ischemia and retard platelet aggregation (Myerson *et al.* 2009).

Epidemiology of AMI according to sex

The decrease in the age-standardized rate for hospitalizations for AMI has been less pronounced in women than in men (Rosen *et al*. 2000; Roger *et al*. 2002; Messner *et al*. 2003; Yang et al. 2011). Interestingly, among women the events are declining mainly for recurrent AMI, whereas both first and recurrent AMIs decline among men (Lundblad *et al.* 2008).

Epidemiology of AMI in Estonia

In Estonia, recent research data on the incidence of AMI is available from the Tallinn AMI Registry, that included residents aged 35–64 years during two time periods, 1991–1997 and 2003–2005 (Laks *et al*. 2012). When analyzed annually, the rates of AMI increased from 1991 to 1993 in both sexes. Thereafter the incidence of the first AMI started to decline, and this trend continued until 2005.

Hospitalization rates for AMI [main diagnosis code I21–I22 according to the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10)] for the whole of Estonia during 1998–2010 are available from the National Institute for Health and Development's Health Statistics and Health Research Database (2012). According to this administrative database the rate of hospitalization for AMI show an increase during the last decade. The validity of this database has not been established and the trends have not been studied further.

2.4. Baseline characteristics of patients with AMI

Several studies in the USA and Europe have demonstrated the changing baseline characteristics of hospitalized AMI patients over the last decades.

Collectively these studies show that patients with AMI have become significantly older – the proportion of patients over 75 years of age has risen to approximately 40% and those over 85 years to 20%. This is probably reflective

of the aging of the Western population, as well as of the increasing adoption of healthy lifestyle practices and other primary preventive modalities in the general population and in various at-risk groups.

The AMI patients are now more likely to be obese (Body Mass Index ≥ 30 kg/m^2, 20–36%), have dyslipidemia (42–49%), have a prior history of DM (23–40%), hypertension (60–75%), stroke (7–9%), chronic heart failure (20–30%), and peripheral vascular disease (7–21%). This likely mirrors the growing epidemics of obesity and glycometabolic disturbances. It is also possible that the redefinition of hypertension and hypercholesterolemia over time has resulted in an increase in the rates of these diseases. Particularly striking is the increase in the prevalence of prior AMI (18–34%), PCI (8–17%), and coronary artery bypass grafting (CABG; 4–13%). The rate for current smokers has decreased to about 22–33% (Goldberg *et al*. 2004; Kuch *et al*. 2008; Floyd *et al*. 2009; Rogers *et al*. 2008; Krumholz *et al*. 2009; Goodman *et al*. 2009; Nauta *et al*. 2011; Gierlotka *et al*. 2012).

Patients with either cardiac arrest before admission or with significant hemodynamic disorders (pulmonary edema and cardiogenic shock) on admission have become significantly less frequent (Isaksson *et al*. 2008). The duration of pre-hospital delay after the onset of AMI has remained essentially unchanged over the two last decades (Goldberg *et al*. 2004; Isaksson *et al.* 2008; Saczynski *et al.* 2008; Goldberg *et al.* 2009; Floyd *et al.* 2009; Fang *et al.* 2010; Nguyen *et al.* 2010a; Nguyen *et al*. 2010b).

Baseline characteristics of AMI subtypes

Compared to STEMI patients, those with NSTEMI are older, show higher rates of co-morbidities (Maier *et al*. 2008; Nauta *et al*. 2011; McManus *et al.* 2011), and have more extensive coronary artery disease (Abbott *et al*. 2007). Patients with NSTEMI are nearly twice more likely to present without chest pain than patients with STEMI (Canto *et al.* 2012). At the same time, patients with STEMI have more frequently pre-hospital cardiac arrest and acute heart failure at presentation (Xu *et al.* 2011).

Baseline characteristics of AMI according to sex

The proportion of women has increased and they comprise now over a third of the AMI population (Rogers *et al*. 2008; Krumholz *et al*. 2009; Goodman *et al*. 2009; Nauta *et al*. 2011). The reason for the increase in the proportion of females to males, especially among patients with NSTEMI, may be related to the increasing emphasis on the clinical recognition of acute coronary syndromes in women (Mosca *et al*. 1997). Alarmingly, recent data suggest that the proportion of younger women presenting with STEMI may be increasing (Puymirat *et al.* 2012).

When studying sex differences in baseline characterisics it can be seen that women are older with a higher prevalence of hypertension, chronic heart failure, and DM; but they are also less likely to have a history of prior AMI or to be

smokers (Bakler *et al.* 2004; Jneid *et al.* 2008; Tatu-Chitoiu *et al*. 2009; Dey *et al.* 2009).

Upon presentation to hospitals a lower proportion of women than men have typical chest pain symptoms (approximately 55% vs 70%; Isaksson *et al.* 2008; Coventry *et al*. 2011; Canto *et al*. 2012). There seems to be an interaction between age and sex with typical symptoms at presentation, with a larger sex difference in younger than older patients, which becomes attenuated with advancing age (Canto *et al.* 2012). A greater proportion of women than men present with congestive heart failure at the time of hospital admission (Tatu-Chitoiu *et al.* 2009).

2.5. Management of patients with AMI

The overall goal of the management of AMI is to reduce morbidity, to prevent complications, including death, and to enable the patients to return to their daily activities as soon as possible. Numerous randomized clinical trials conducted in recent decades have led to the development of effective management strategies for AMI. On the basis of these trials, detailed management guidelines for STEMI and NSTEMI have been compiled (Bertrand *et al*. 2002; Braunwald *et al*. 2002; Van de Werf *et al*. 2003; Antman *et al*. 2004; Bassand *et al.* 2007; Van de Werf *et al.* 2008; Wijns *et al*. 2010; Hamm *et al*. 2011; Steg *et al.* 2012).

2.5.1. Medical management

Anti-platelet therapy

Platelet activation and aggregation play a major role in the mechanism of thrombosis and therefore are the key therapeutic targets in the management of AMI. Platelets can be inhibited by three classes of drugs, each of which has a distinct mechanism of action.

Acetyl salicylic acid (ASA) is an established drug in the treatment of AMI since the Second International Study of Infarct Survival (ISIS-2 Collaborative Group 1988). It acts through irreversible inactivation of cyclooxygenase-1, thus inhibiting thromboxane A2 formation and, consequently inhibiting permanently the function of platelets. According to the current guidelines (Hamm *et al*. 2011; Steg *et al.* 2012), in suspicion of an AMI, ASA should be given as soon as possible in the absence of contraindications like active gastrointestinal bleeding, known clotting disorders, hypersensitivity, and severe hepatic disease. In the long-term secondary prevention of AMI, ASA reduces the risk of serious cardiovascular events by a quarter (Baigent *et al.* 2009).

In addition to the effects of ASA, other complementary platelet aggregation pathways must be inhibited to ensure effective treatment and prevention of coronary thrombosis. The antagonists of the $P2Y_{12}$ receptor, such as thienopyridines, have proven to be major therapeutic tools in the treatment of AMI. The thienopyridine prodrugs such as clopidogrel and prasugrel are actively

biotransformed into molecules that bind irreversibly to the $P2Y_{12}$ receptor. A newer class of drug on the market is the pyrimidine derivative ticagrelor, which without biotransformation binds reversibly to the $P2Y_{12}$ receptor. Over the years, as more research data has emerged, the use of $P2Y_{12}$ receptor inhibitors has become more prevalent. According to the current AMI guidelines (Hamm *et al*. 2011; Steg *et al.* 2012), a $P2Y_{12}$ receptor inhibitor should be added to ASA as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.

A third group of antiplatelet drugs that target the final common pathway of platelet aggregation by inhibiting fibrinogen binding to platelets are the glycoprotein receptor IIb/IIIa antagonists which are administered intravenously and only during hospitalization. The use of these drugs on top of ASA and a $P2Y_{12}$ receptor inhibitors is reserved for high-risk patients when the the risk of bleeding is low (Hamm *et al*. 2011; Steg *et al.* 2012).

Anticoagulants

Anticoagulation is recommended for all patients in addition to antiplatelet therapy (Hamm *et al*. 2011; Steg *et al.* 2012). The choice of combination of antiplatelet agents and anticoagulants should be made in relation to the risk of ischemic and bleeding events. Newer anticoagulat regimes aim at decreasing thromboembolic events without increasing the risk of bleeding complications.

Anticoagulants act through reducing thrombus-related events by inhibiting thrombin generation and activity. Currently the there are several indirect and direct inhibitors of coagulation available. Among the indirect inhibitors there are the older drugs, unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH) that bind to antithrombin III and enhance inactivation of factors Xa and thrombin. As compared to UFH, LMWH has a predictable pharmacokinetic profile, high bioavailability, and long plasma half-life, all of which result in effective levels of anticoagulant activity after subcutaneous administration without the need of constant laboratory monitoring. Fondaparinux, a relatively newer drug, is the only selective factor Xa inhibitor available for clinical use. Fondaparinux is easy to use, is not associated with the risk of heparin-associated thrombocytopenia and has currently one of the most favourable efficacy-safety profiles among the anticoagulants on the market.

Bivalirudin, belonging also to the newer drugs, is at the moment the only direct inhibitor of coagulation that has proven to be efficacious in the treatment of AMI. It binds directly to thrombin and thereby inhibits the thrombin-induced conversion of fibrinogen to fibrin.

Beta-blockers

Beta-blockers competitively inhibit the myocardial effects of circulating catecholamines and reduce myocardial oxygen consumption by lowering heart rate, blood pressure, and contractility. The evidence for the use of beta-blockers in AMI is mainly derived from older trials conducted before the reperfusion era (Freemantle *et al.* 1999). In the absence of contraindications, beta-blockers are

recommended in all AMI patients as secondary prevention, especially if the left ventricular function is reduced or if there have been signs of heart failure (Hamm *et al*. 2011; Steg *et al.* 2012). However, in the acute phase they increase the risk of cardiogenic shock (Chen *et al.* 2005) and should rather be used in patients in a stable hemodynamic condition (Killip class < III) with hypertension and/or tachycardia.

Angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers
Angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers (ACEIs/ARBs) reduce infarct size, limit ventricular remodeling, and improve survival after AMI (Dagenais *et al.* 2006; Danchin *et al.* 2006). Over the years their rutine use has increased (Marguils *et al.* 2011) and the current guidelines state that in the absence of contraindications, they should be started already within the first 24 hours of hospitalization, especially in patients with evidence of heart failure, left ventricular systolic dysfunction, diabetes, hypertension, or an anterior infarct (Hamm *et al*. 2011; Steg *et al.* 2012).

Statins
In the 1950s and 1960s, it became apparent that dyslipidemia was a major cardiovascular risk factor. This is targeted by statins by inhibiting the HMG-CoA reductase which acts as a central enzme in the biosynthetic pathway of cholesterol. Since the first studies, conducted at the end of the 1980s (Tobert 2003), the use of statins has increased for the secondary prevention of AMI (Marguils *et al.* 2011). They are currently recommended to be initiated in high dose early after admission in all AMI patients without contraindication or history of intolerance, regardless of initial cholesterol values (Hamm *et al*. 2011; Steg *et al.* 2012).

Nitrates
The therapeutic benefit of nitrates is related to their venodilator effects that lead to a decrease in the myocardial preload and left ventricular end-diastolic volume, resulting in a decrease in myocardial oxygen consumption. In addition, nitrates dilate normal as well as atherosclerotic coronary arteries and increase coronary collateral flow (Libby *et al.* 2008). The routine use of nitrates has not proven to reduce mortality (Fourth International Study of Infarct Survival Collaborative Group 1995).

2.5.2. Invasive management

Coronary angiography and revascularization
Coronary angiography defines coronary anatomy and provides valuable decision-facilitating information for further invasive or non-invasive management strategies and enables more precise risk stratification. The current guidelines recommend coronary angiography and, if applicable, revascularization

(PCI and/or CABG) for all AMI patients in the absence of contraindications (e.g. risk of bleeding, patient does not consent) (Wijns *et al*. 2010; Hamm *et al*. 2011; Steg *et al.* 2012).

Since Andreas Grüntzig performed the first intraoperative balloon angioplasty on the human heart in 1979 (Grüntzig *et* Kumpe 1979) the method of PCI has witnessed significant technological advances, in particular, the use of drug-eluting stents (DES) and it has become a vital component in the management of AMI patients. The possible complications of PCI for AMI include death (3.5%), non-fatal AMI (2.0%), major bleeding (1.5%), and non-fatal stroke (0.5%; Wang *et al*. 2011).

Revascularization for NSTEMI

In NSTEMI the timing of angiography (urgent <2 h, early <24 h, or late <72 h) depends on the clinical presentation and cardiovascular risk of the patient. The revascularization strategy (PCI and/or CABG) should be based on the clinical status as well as the disease severity, i.e. distribution and coronary lesions and their characteristics (Wijns *et al*. 2010; Hamm *et al*. 2011).

Reperfusion and revascularization for STEMI

In STEMI myocardial necrosis caused by complete coronary artery occlusion begins to develop after 15–30 min of severe ischemia (no forward or collateral flow) and progresses from the subendocardium to the subepicardium in a time-dependent fashion (Libby *et al.* 2007). So the patients should receive reperfusion as soon as possible to save the myocardium at risk from undergoing necrosis.

Reperfusion therapy for STEMI is indicated in all patients with a history of chest pain/discomfort of <12 h and with persistent ST-segment elevation or (presumed) new left bundle-branch block (Steg *et al.* 2012). In case of evidence of ongoing ischemia, even if symptoms may have started >12 h earlier, reperfusion may be beneficial.

As randomized controlled trials and meta-analyses have shown the superiority of primary PCI over in-hospital thrombolysis through more effective restoration of vessel patency, less re-occlusion, improved residual left ventricular function, and better clinical outcome, it has become the treatment of choice if it can be performed in a timely manner (Zijlstra *et al.* 1999; Keeley *et al.* 2003; Widimsky *et al.* 2003; Widimsky *et al.* 2007).

The current European STEMI guideline emphasizes the importance of a well existing national STEMI network between hospitals with various levels of technology, connected by an efficient ambulance (or helicopter) service (Figure 1) (Steg *et al.* 2012). It has been associated with diminished patient delay to reperfusion and could reduce mortality due to out-of-hospital cardiac arrest (Taglieri *et al*. 2011). Electronic transmission of a pre-hospital 12-lead ECG in chest pain patients has proven to reduce time to PCI (Sejersten *et al*. 2008) and is an established tool to accelerate correct and timely management (Bradley *et al*. 2007). Unfortunately, the possibility of pre-hospital electronic transmission of ECG has not been established in Estonia yet.

While the patient-related pre-hospital delays have changed little over the years, the door-to-needle times for thrombolysis and door-to-balloon times for primary PCI have been reduced considerably (Gibson *et al.* 2008; Schiele *et al.* 2010; Flynn *et al.* 2010; Towae *et al.* 2011).

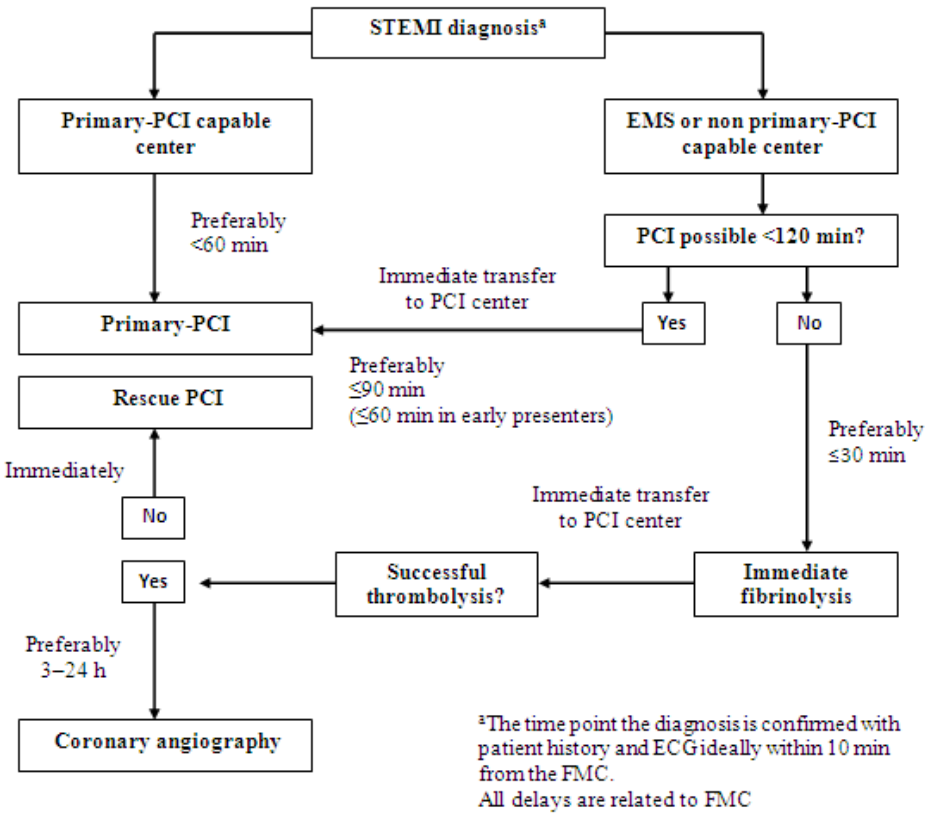

Figure 1. Prehospital and in-hospital management, and reperfusion strategies within 24 h of FMC (modified from Steg *et al*. 2012)
FMC – first medical contact; STEMI – ST-segment elevation myocardial infarction; PCI – percutaneous coronary intervention

2.5.3. Treatment quality indicators

With reference to the performance measures presented in the AMI guidelines, several countries have developed quality indicators for measuring the management and outcomes of AMI (Spertus *et al.* 2005; Tu *et al*. 2008). An illustrative list of the most commonly used quality indicators for in-hospital management is presented in Table 1.

Table 1. In-hospital process-of-care, outcome and system indicators* for acute myocardial infarction

Pharmacologic process-of-care indicators
− Acetyl salicylic acid prescribed during hospitalization and at discharge
− $P2Y_{12}$ blockers prescribed during hospitalization and at discharge
− Beta-blockers prescribed during hospitalization and at discharge
− Angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers prescribed during hospitalization and at discharge
− Statin prescribed during hospitalization and at discharge
− Use of low-molecular-weight heparin /heparin/fondaparinux during hospitalization
− Thrombolysis within 30 minutes after hospital arrival
Non-pharmacologic process-of-care indicators
− Electrocardiogram within 10 minutes after hospital arrival
− Primary percutaneous coronary intervention within 90 minutes after hospital arrival
− Reperfusion therapy in eligible patients with ST-segment elevation myocardial infarction
− Coronary angiography and percutaneous coronary intervention done or planned for non-ST-segment elevation myocardial infarction
− Risk stratification (i.e., coronary angiography, exercise stress testing, perfusion imaging or stress echocardiography)
− Assessment of left ventricular function
− Smoking cessation advice, counseling or therapy during hospital stay
− Referral to cardiac rehabilitation
Outcome indicator
− In-hospital mortality

*These indicators are measurable from chart review

The idea of these indicators is to enhance the application of evidence-based care in real clinical practice and by doing so to improve the prognosis of patients with AMI. When most registries and quality of care improvement programs only focus on in-hospital management then there are some exceptions like the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies; Jernberg *et al.* 2010), which allow also to gather data during follow-up. A corresponding illustrative list can be found in Table 2.

The above quality indicators are used nationally and internationally for benchmarking hospitals and for suggesting further improvements in AMI management. The concept and composition of the quality indicators have been a matter of considerable debate over the years. Furthermore, a fair inter-hospital comparison requires high-quality data and sophisticated data analysis, including proper adjustment for confounding factors. This is often hard to achieve as administrative databases are usually not fit to meet such high demands. It has been argued whether inter-hospital comparisons of in-hospital AMI mortality can really serve the purpose of fostering quality improvement (Aelvoet *et al.*

2010). Nevertheless, as the Get With the Guidelines-Coronary Artery Disease quality improvement program in the USA showed, participation in such a program significantly improves the management and outcomes of AMI patients (Xian *et al*. 2010; Peterson *et al.* 2006).

Table 2. Out-of-hospital process-of-care and outcome indicators* for acute myocardial infarction

Pharmacologic process-of-care indicators
− Prescription for beta-blocker filled within 30 days after discharge
− Adherence to beta-blocker therapy 1 year after discharge
− Prescription for angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker filled within 30 days after discharge
− Adherence to angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker therapy 1 year after discharge
− Prescription for statin filled within 30 days after discharge
− Adherence to statin therapy 1 year after discharge
Non-pharmacologic process-of-care indicators
− Physician visit within 4 weeks of discharge
− Median waiting time (in days) for coronary angiography after myocardial
− infarction
− Median waiting time (in days) for percutaneous coronary intervention after myocardial infarction
− Median waiting time (in days) for coronary artery bypass graft surgery after myocardial infarction
Outcome indicators
− 30-day mortality
− 1-year mortality
− 30-day readmission rate because of acute myocardial infarction
− 1-year readmission rate because of acute myocardial infarction
− 30-day readmission rate because of congestive heart failure
− 1-year readmission rate because of congestive heart failure
− 30-day readmission rate because of unstable angina
− 1-year readmission rate because of unstable angina
− 30-day need for revascularization
− 1-year need for revascularization

*These indicators are measurable using administrative data

Application of guideline recommendations

Implementation of evidence-based management strategies into clinical practice for treatment of AMI has increased considerably over time (McGovern *et al.* 2001; Goldberg *et al.* 2004; Gislason *et al.* 2005; Kuch *et al.* 2008; Maier *et al.* 2008; Floyd *et al*. 2009; Janion *et al.* 2009; Tatu-Chitoiu *et al.* 2009; Goodman *et al.* 2009; Jernberg *et al.* 2011; Nauta *et al.* 2011; Aliprandi-Costa *et al.* 2011; Gierlotka *et al.* 2012).

Such progress has been evident in all age groups, including the elderly (Schiele *et al.* 2009; Nauta *et al.* 2012). Still, although adherence to guidelines has been shown to be associated with improved outcomes, their implementation remains sub-optimal. As demonstrated by the Get With the Guidelines-Coronary Artery Disease quality improvement program (Medina *et al.* 2011) important age-related gaps remain in management and outcomes, suggesting opportunities to improve prognosis in high-risk populations. There appears to be a "risk-management paradox" wherein higher-risk patients are less likely to receive guideline recommended therapies (Motivala *et al.* 2011). Previous studies have also demonstrated that women are treated less aggressively and less invasively than men (Hvelplund *et al.* 2010).

As not all hospitals have access to coronary angiography and revascularization facilities, the rate of patients undergoing these management options varies across hospitals and is the underlying reason for inequalities in application of management strategies (Luthi *et al.* 2005; Ainla *et al.* 2006; Radovanovic *et al.* 2010; Widimsky *et al.* 2010). In addition, adherence to recommendations in the AMI guidelines has been shown to be higher in academic hospitals compared to their non-academic counterparts (Belle *et al.* 2012).

Adherence to secondary prevention of AMI

When the in-hospital mortality of AMI has decreased significantly during the last decades, then the decrease in long-term mortality is less pronounced (Grau *et al.* 2012). This indicates the importance of lifelong adherence to the secondary prevention strategies of AMI. Optimal medical therapy for the secondary prevention of AMI over one year has been associated with a significantly lower mortality of patients with AMI in clinical practice (Bramlage *et al.* 2010). Total mortality is reduced by 74% in patients receiving optimal medical therapy versus patients receiving one or no drug.

However, optimal medical therapy is provided to less than half of eligible patients. Eagle *et al.* (2004) found that among the patients for whom key evidence-based medications at discharge was prescribed, 8% to 20% were no longer taking their medication after 6 months. A recent study concerning drug utilization in different age and gender groups following AMI in Estonia found that only 40% were treated by combinations of beta-blockers, ACEIs/ ARBs and statins at 1-year follow-up (Marandi *et al.* 2010).

The reasons for noncompliance are complex and depend on the characteristics of patients, physicians, hospitals and communities. Clearly the first key to adherence to the secondary prevention methods is initiation of medications already during hospitalization for AMI. Interestingly, patients who receive care from non-cardiologists and physicians with many years of experience tend to receive substantially less evidence-based drug therapies after discharge (Austin *et al.* 2008). There is a wide inter-hospital and inter-physician variation in initiating drugs, the most pronounced being for newer drugs like statins (Margulis *et al.* 2011). Furthermore, there seems to be inter-drug variation in patient adherence as well (Sorensen *et al*. 2008).

2.5.4. Overview of the types of hospitals treating patients with AMI in Estonia

In 2001, the management of AMI patients was shared among 27 Estonian hospitals with a different number of beds. There were 2 tertiary care hospitals, which had the availability of PCI, but only during working hours (Fig. 2). In the secondary care hospitals the number of annual AMI cases ranged from 7 to 165 and the attending physicians were mainly anesthesiologists or internists and in some hospitals also cardiologists. None of the secondary care hospitals had angiography or PCI facilities.

By 2007, as a result of changes in the hospital network, only 20 hospitals admitted AMI patients. The 2 tertiary hospitals had PCI availability 24 hours 7 days a week. In the secondary care hospitals the number of annual AMI cases ranged from 16 to 267 and one hospital had on-site PCI facilities but only during working hours. In 2012, there are 2 tertiary care PCI-capable hospitals operating 24 hours 7 days a week and 3 secondary care hospitals with onsite PCI (one of them operating 24/7).

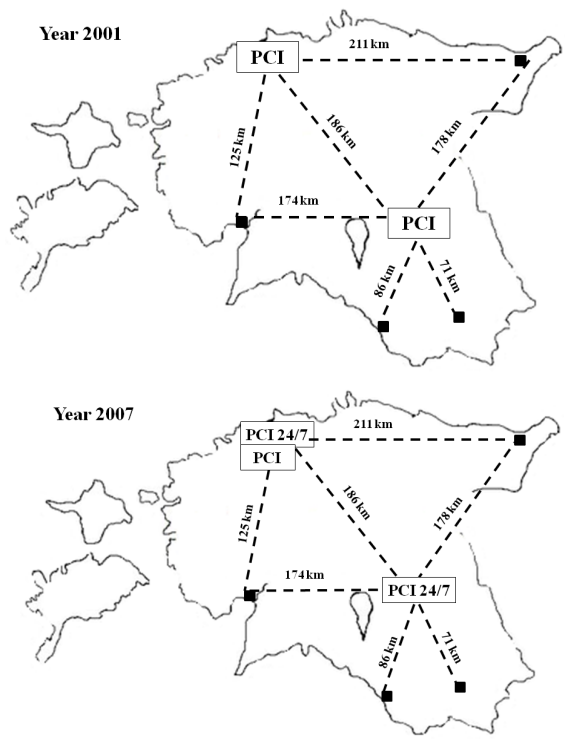

Figure 2. Location of hospitals with on-site PCI facilities and longest transfer distances between hospitals in Estonia in 2001 and 2007
PCI – percutaneous coronary intervention available during working hours
PCI 24/7 – percutaneous coronary intervention available 24 hours a day 7 days a week

2.6. Outcomes of patients with AMI

Community studies have shown that the overall case fatality rate for patients with presumed AMI or acute coronary syndrome in the first month can be as high as 50%, and out of these deaths about half occur within the first two hours (Tunstall-Pedoe *et al.* 1999).

This high initial mortality has altered little over the last years in contrast to in-hospital mortality (Goldberg *et al.* 2006). Prior to the introduction of coronary care units in the 1960s, the in-hospital mortality seems to have averaged between 25 and 30%. In the pre-reperfusion era, in the mid-1980s, the in-hospital mortality was approximately 16% (Sarmento-Leite *et al.* 2001; Mukau 2011). With the widespread use of coronary interventions, thrombolytic agents, antithrombotic therapy, and secondary prevention, the overall 1-month mortality has since been reduced to 4–6%, at least in patients who have participated in the latest randomized large-scale trials and qualified for thrombolysis and/or coronary interventions (De Boer *et al.* 2010). However, mortality rates in registry studies are much higher, suggesting that the patients included in randomized controlled trials are at a lower risk when compared with those in observational studies (Fox *et al.* 2006).

The decline in the short- and long-term mortality of patients with AMI has been demonstrated by several large registry studies in the USA and Europe since the 1950 (Parikh *et al.* 2009; Floyd *et al.* 2009; Movahed *et al.* 2011; Hardoon *et al.* 2011; Smolina *et al.* 2012), including the National Registry of Myocardial Infarction (NRMI; Rogers *et al.* 2008). The improved prognosis can be assigned to all AMI patient subgroups independently of sex, age, and comorbidity (Schmidt *et al.* 2012). The age- and sex-adjusted 30-day, 1-year, and 5-year AMI mortality has declined by approximately 60%. The Register of Information and Knowledge about Swedish Heart Intensive Care Admission showed that for STEMI the estimated in-hospital, 30-day and 1-year mortality decreased during 1996–2007 from 12.5% to 7.2%; from 15.0% to 8.6%; and from 21.0% to 13.3%, respectively (Jernberg *et al.* 2011). The improvements in survival tended to be greater in the latter part of this 12-year period. This probably reflects the advances in the coronary reperfusion techniques, development of more effective adjunctive cardiac therapies, and increased utilization of these management modalities.

As increasingly more AMI patients survive during hospitalization, more attention is paid to non-fatal outcomes during hospitalization and follow-up. The Global Registry of Acute Coronary Events (GRACE) showed that during hospitalization for AMI the rates of cardiogenic shock, congestive heart failure and pulmonary edema have declined both in STEMI and NSTEMI populations (Fox *et al.* 2007). Still, recurrent ischemic symptoms occured approximately in 20%, heart failure in 13%, re-infarction in 11%, and major bleeding and stroke in less than 2% of the patients (Goodman *et al*. 2009). At 6-months follow-up after hospitalization for AMI, 18% were re-admitted for chronic heart failure, 9% underwent PCI and 6% CABG (Goldberg *et al*. 2004).

AMI subtype specific outcomes

The proportion of patients presenting with NSTEMI is increasing. Compared to STEMI, patients who experience a NSTEMI have lower 30-day mortality (Armstrong *et al.* 1998). However, the 6-month mortality rates are similar for STEMI and NSTEMI patients (Volmink *et al.* 1998). There are thought to be several reasons for this. Patients with STEMI have more frequently pre-hospital cardiac arrest and acute heart failure at presentation, which has a negative impact on the outcomes. Additionally, lower ischemic preconditioning and larger infarct sizes in patients with STEMI have been described (Xu *et al.* 2011). In contrast, higher age and higher prevalence of co-morbidities increase the rate of mortality for NSTEMI during long-term follow-up. In addition, NSTEMI patients often seem to be undertreated compared to STEMI patients (Roe *et al.* 2005).

The shift in the proportion of AMI subtypes also implies that hospitalized AMI cases have smaller infarct sizes (Xu *et al.* 2011). Furthermore, as less patients die during hospitalization, more patients develop chronic heart failure afterwards (Ezekowitz *et al.* 2009). This increases the mortality risk during the long-term follow-up and highlights the importance of life-long secondary prevention for AMI.

Sex-specific outcomes of AMI

Despite the overall reduction in the death rate due to CAD over the several recent decades, the rate of the decline is less pronounced for women than for men (Heart Disease and Stroke Statistics update 2011). Also the mortality rates after AMI have decreased less for women than for men (Grau *et al.* 2012).

Women suffer acute coronary syndromes approximately ten years later than men and have a higher cardiovascular risk factor burden at the time of presentation (Coppieters, *et al.* 2011). However, the increased risk of mortality among women with AMI compared to men is not consistently eliminated after adjustments for co-morbidities (Chandra *et al.* 1998; Vaccarino *et al.* 1999; Jneid *et al.* 2008; Dey *et al.* 2009). Many studies have attributed this finding to difficulties in recognizing symptoms, delay in presentation to the hospital and diagnosis, or under-use of recommended diagnostic tests and therapies in women (Jneid *et al.* 2008; Dey *et al.* 2009; Bugiardini *et al.* 2011; Canto *et al.* 2012; Ravn-Fischer *et al*. 2012). For instance, women with AMI are referred less often for invasive diagnostic procedures and thus they undergo percutaneous or surgical revascularization less frequently than men (Harrold *et al.* 2003; Haglund *et al.* 2004; Vikman *et al.* 2007; Lee *et al.* 2008; Peterson *et al.* 2008; Nguyen *et al.* 2010a; Tavris *et al.* 2010). Furthermore, in women higher rates of procedural complexity, peripheral complications, and bleeding after PCI have been reported in contemporary large real-world studies (Tillmanns *et al.* 2005; Marso *et al.* 2007; Alfredsson *et al.* 2011; Al-Fiadh *et al.* 2011; Pu *et al.* 2011; Ortolani *et al*. 2012).

The effect of DM on the outcomes of AMI

It is estimated that by 2030 the prevalence of DM will have risen to 7.7% among adult population, which is three times higher than in 2000. DM is one of the most frequent co-morbidity to complicate the management of patients with AMI. It increases the risk of mortality 2- to 5-fold compared with the non-diabetic subjects of similar age (Koek *et al*. 2007; Kahn *et al*. 2012; Brener *et al*. 2012). AMI patients with DM also have higher rates of recurrent AMI, and a need for repeated coronary artery revascularization (Lee *et al.* 2012). The underlying reason for this is that diabetic patients with CAD have more often plaques with characteristics of plaque vulnerability, multi-vessel disease, and increased inflammatory status compared with non-diabetic patients (Hong *et al.* 2009).

The effect of DM on the sex-specific outcomes of AMI

The prevalence of DM is higher in men than in women but there are more women with DM than men (Wild *et al.* 2004). The prevalence of DM is expected to rise more rapidly in women than in men (International Diabetes Federation, Diabetes Atlas 2011). This will inevitably result in increasing proportions of female AMI patients with DM.

Women and diabetics are more prone to develop diffuse small-vessel disease and therefore diabetic women have more frequently diabetic cardiomyopathy than diabetic men. DM is also associated with a significantly higher prevalence of left ventricular hypertrophy and left atrial enlargement in hypertensive women but not in men (Tenenbaum *et al.* 2003). There are some fundamental biological differences in the composition of the atherosclerotic plaque between men and women (Boccuzzi *et al.* 2005; Kamran *et al.* 2008; Mortensen *et al.* 2009; Reynolds *et al.* 2011). Also the role of the lack of ovarian hormones with cardiovascular protective effects in postmenopausal women is widely discussed (Vaccarino *et al.* 2011). The mechanisms associated with the onset of AMI may be compromised to a greater extent in women than in men with DM as there are sex differences in endothelial dysfunction, myocardial contractile function, neuroendocrinal regulatory mechanisms, sensitivity to aggregating stimuli of platelets, and tolerance to stress (Graham *et al.* 2003; Ren *et* Ceylan-Isik 2004; Jacobs 2009). Women have a more pronounced inflammatory reaction to hyperglycemia than men, making women with DM a high risk group for cardiovascular adverse events (Sheikh *et al.* 2012; Kawamoto *et al.* 2011).

Studies on the effect of DM on the sex-specific outcomes of AMI are scarce and demonstrate conflicting results. These have included mixed cohorts of patients with stable and unstable coronary artery disease where variable proportions of patients undergo PCI (Rosengren *et al.* 2001; Crowley *et al.* 2003; Maier *et al.* 2006; Champney *et al.* 2007; Ouhoummane *et al.* 2009; Meisinger *et al.* 2010; Winell *et al.* 2010; Ogita *et al.* 2011; Eliasson *et al.* 2011). Furthermore, these studies have mostly concentrated on all-cause mortality only. It is possible that women with DM may need more specifically targeted management strategies when undergoing PCI for AMI.

3. AIMS OF THE RESEARCH

The overall purpose of the work was to evaluate the changes in the baseline characteristics, management and outcomes of patients with AMI in Estonia during the last decade as well as to study the long-term outcomes after PCI in different AMI patient subgroups.

The present study consisted of the following aims:

1. To determine the changes in in-hospital management as well as in 30-day and 3-year mortality of AMI patients hospitalized into tertiary vs secondary care hospitals in Estonia in 2001 and 2007.
2. To compare the management, in-hospital outcomes, and 1-year mortality of AMI patients first admitted to tertiary and secondary care hospitals in Estonia in 2007.
3. To compare the long-term outcomes of patients with STEMI and NSTEMI who have undergone PCI in terms of non-fatal AMI, revascularization, and all-cause mortality.
4. To evaluate the sex-specific outcomes of diabetic and non-diabetic patients with AMI who have undergone PCI in terms of non-fatal AMI, revascularization, and all-cause mortality.

4. METHODS

4.1. Study design

Paper I and Paper II
Cross-sectional studies based on patient records.

Paper III and Paper IV
Registry linkage studies conducted by linking data from the following registries: the Estonian Myocardial Infarction Registry (EMIR), the Estonian Health Insurance Fund (EHIF) database, and the Estonian Population Registry (EPR). Data linkage was done with the help of a unique personal identification number assigned to all persons at birth or at immigration to Estonia.

The EMIR was founded in 2001 with the purpose to perform continuous surveillance of AMI management and outcomes across Estonian hospitals. Due to legal and economic reasons the current database includes AMI cases since 2006 and hospitals have been reporting cases on a voluntary basis. In January 2012 the EMIR became a national registry and reporting to the registry is mandatory. The EMIR has a scientific board which consists of representatives from Estonian hospitals.

Data are reported to the database through an electronic web-based form which includes the following information: personal data (including unique personal identification number); cardiovascular risk factors; management, investigations, and outcomes during hospitalization; recommendations for outpatient management. The dataset complies with the Cardiology Audit and Registration Data Standards in Europe (CARDS 2004).

4.2. Study populations

Paper I and Paper II
The formation of the study samples is presented in Fig 3. The list of all AMI cases (main diagnosis code I21–I22 according to ICD-10) hospitalized from January 1 to December 31, 2001 and 2007, was obtained from the database of the EHIF. The Estonian health insurance system is a social insurance relying on the principle of solidarity and of the 1.3 million inhabitants about 95% are insured.

The EHIF applied the following exclusion criteria for case selection: (1) patients who were treated as transferred cases in one of the study hospitals; (2) patients who were re-admitted with AMI within 28 days of the first admission; and (3) patients whose length of hospital stay was less than 3 days if they were discharged alive and were not transferred to another hospital, which made the diagnosis of AMI unlikely.

In 2001, according to the EHIF database, 2365 AMI cases were hospitalized during the study period. The management of AMI patients was shared among 27 Estonian hospitals with a different number of beds. As we aimed to evaluate the management of AMI patients in hospitals that treat the major proportion of annual AMI cases, the study included 9 hospitals: 2 tertiary PCI-capable and 7 secondary care hospitals (Table 3). After the application of the exclusion criteria by the EHIF, there remained 1955 cases, out of which a random sample of 520 cases (27%) was formed. Sampling was performed by clusters according to the hospitals involved.

The study cohort of Paper I in year 2007 and the study cohort of Paper II were the same. Altogether 3251 AMI cases were hospitalized in Estonia. Due to changes in the hospital network only 20 hospitals admitted AMI patients in 2007. The study included 16 hospitals that treated the major proportion of annual AMI cases: 2 tertiary 24/7 PCI-capable and 14 secondary care hospitals. The tertiary care hospitals were the same in both time periods. After the application of the exclusion criteria by the EHIF, there remained 2862 cases, out of which a random sample of 800 cases (28%) was formed. Sampling was performed in clusters according to the hospitals involved.

Table 3. Hospitals involved in Paper I and Paper II

Type of hospital	Paper I, year 2001	Paper I, year 2007 Paper II
Tertiary care	North Estonia Medical Centre Tartu University Hospital	North Estonia Medical Centre Tartu University Hospital
Secondary care	East-Tallinn Central Hospital East-Viru Central Hospital Narva Hospital Pärnu Hospital South-Estonia Hospital Viljandi Hospital West-Tallinn Central Hospital	East-Tallinn Central Hospital East-Viru Central Hospital Narva Hospital Pärnu Hospital South-Estonia Hospital Viljandi Hospital West-Tallinn Central Hospital Hiiumaa Hospital Järvamaa Hospital Kuressaare Hospital Läänemaa Hospital Rakvere Hospital Rapla Hospital Valga Hospital

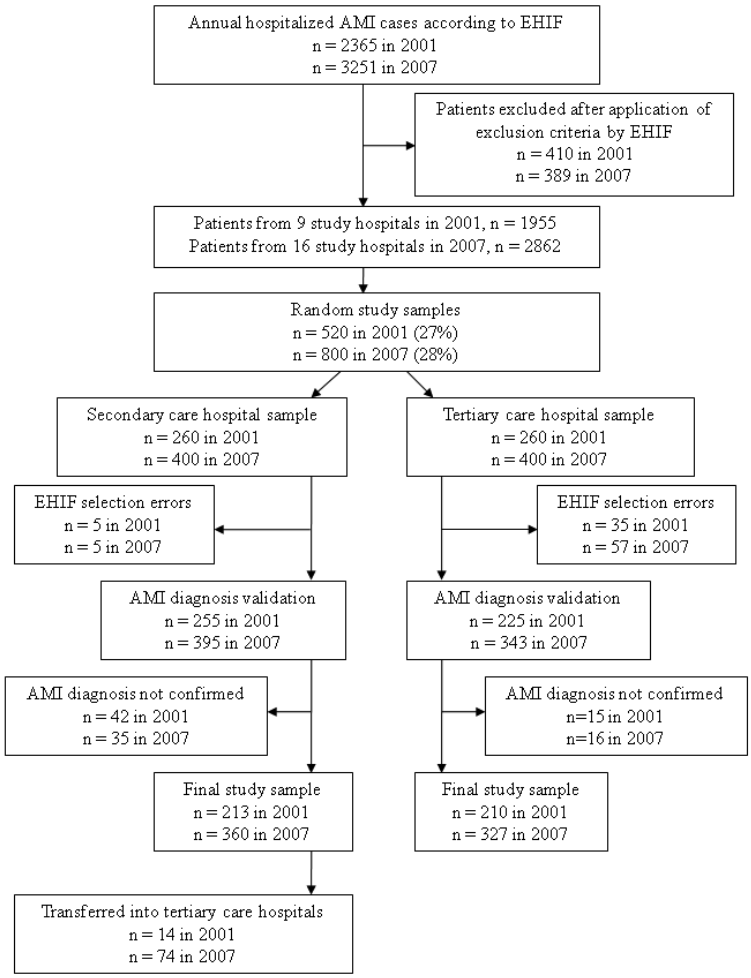

Figure 3. Formation of the study samples for Paper I and Paper II. For Paper II only the cases hospitalized in 2007 were included.
AMI, acute myocardial infarction; EHIF, Estonian Health Insurance Fund

Paper III and Paper IV

The studies included consecutive AMI cases hospitalized into a tertiary care PCI centre, Tartu University Hospital, from 1 January 2006 until 31 December 2009. We included only cases which had undergone PCI during the index hospitalization. If a patient was admitted several times with AMI during the study period, we included only the first case of hospitalization into the study. According to the internal audit conducted for the purpose of this study, the case coverage for the study period was 99.8%. EMIR provided the following data:

(1) patient baseline characteristics (including the diagnosis of DM and the subtype of AMI); (2) prescription of medications during hospitalization and for outpatient use; (3) use of coronary angiography, revascularization, and echocardiography during the index hospitalization; and (4) in-hospital outcomes.

Data on mortality during the follow-up was obtained from the EPR.

Data on the non-fatal AMI and repeated revascularization during follow-up was provided by the EHIF. Consistency in reporting to the EHIF database and the validity of the data has been established (Ministry of Social Affairs of Estonia and WHO Regional Office for Europe 2004). Data on non-fatal AMI included the date of hospitalization and the diagnosis code according to the ICD-10 classification (I21–I22, main diagnosis). The EHIF provided the data on the method and date of revascularization according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures, version 1.6: percutaneous coronary intervention (procedure code FNG with numeric characters of the code) and coronary artery bypass graft (procedure codes FNA, FNC, and FNE with numeric characters of the codes) (Nordic Medico-Statistical Committee 2001).

4.3. Data collection

Paper I and Paper II

Data from medical records were retrospectively abstracted by the study experts according to a standardized data collection form. Most of the experts were certified cardiologists and all had received additional training in data collection for this study. Data quality was monitored by random re-abstractions for determining the causes of discrepancies and followed by retraining of the experts. The abstracted data included: (1) patient baseline characteristics; (2) coronary angiography, revascularization, and non-invasive cardiac testing during hospitalization; (3) in-hospital and discharge medications; and (4) in-hospital mortality. The date of death during 3-year follow-up was obtained from the Estonian Population Register by the EHIF.

In Paper I we aimed to assess the quality of care of the first hospital where a patient was hospitalized, so data collection stopped when patients were transferred from a secondary care to a tertiary care hospital.

In Paper II all procedures performed on a patient, as well as in-hospital and discharge medications, in-hospital outcomes, and 1-year mortality were attributed to the hospital where the patient was admitted first, even if he/she from a secondary care hospital had been referred to a tertiary care hospital.

Paper III and Paper IV

Data collection into the EMIR in Tartu University Hospital is organized at the hospital level. The data is collected in a prospective manner by trained personnel. Data on follow-up was obtained from the databases of the EHIF and EPR.

4.4. Definitions

Definition of AMI

In all four studies, the diagnosis of AMI was based on the redefinition document of AMI published in 2000 (Alpert *et al.* 2000). Troponin T was used as the primary biochemical marker, and the cut-off value for the diagnosis of AMI was set at ≥0.10 ng/ml. Additionally, patients who died before cardiac markers were obtained, or patients whose cardiac markers did not exceed the cut-off value because of a too short time interval from attack onset, the presence of a new ST-segment elevation with symptoms suggestive of myocardial ischemia was considered to meet the AMI criteria.

AMI was classified as STEMI if there was a 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 V1, V2, or V3 and ≥0.1 mV in other leads; or if there was evidence of a new or presumed new left bundle branch block.

Definition of DM

Patients are classified as diabetic if they have a history of DM documented by a physician, or patients are diagnosed with DM during the current episode.

4.5. Study outcomes

Paper I

30-day and 3-year all-cause mortality

Paper II

Outcomes during hospitalization (ventricular fibrillation/cardiac arrest, cardiogenic shock, cardiogenic pulmonary edema, re-infarction, stroke, bleeding complications, mechanic complications, and mortality) and 1-year all-cause mortality

Paper III and Paper IV

The primary composite outcome was defined as the following: non-fatal AMI, repeated revascularization (coronary artery bypass-grafting; target or new lesion PCI), or all-cause mortality whichever occurred first. Follow-up started on the date of PCI during index hospitalization and ended if a case reached the primary outcome, or the follow-up period ended (31 December 2010). We also studied all-cause mortality separately as a secondary outcome. For all-cause mortality, follow-up ended when the patient died or reached the date for the end of follow-up.

4.6. Statistical analysis

In all four studies categorical variables were expressed as frequencies and percentages, and continuous variables as means and standard deviations (SD), or as medians and interquartile ranges (IQR). To compare study the groups in respect to baseline characteristics, in-hospital management and discharge prescription rates of medications, the Chi-Square or the Fisher's exact test for categorical variables and the t-test for two independent samples or the Wilcoxon-Mann-Whitney test for continuous variables were used.

Two-sided p values ≤ 0.05 were considered statistically significant. Analyses were performed using the statistical softwares of Stata, version 11 (StataCorp 2009) and the R, version 2.10.1 (Crawley 2010).

The outcome analysis in separate studies

Paper I

The outcome was expressed as 30-day and 3-year mortality. The crude and baseline-adjusted (age, sex, AMI subtype, DM, arterial hypertension, previous AMI, chronic heart failure) hazard ratios (HRs) of mortality for patients admitted into the tertiary and secondary care hospitals in 2001 vs 2007 were estimated with Cox's proportional hazards regression. The ratio with the 95% confidence interval (CI) was presented as the ratio of the rate in 2007 to the rate in 2001 in the tertiary or secondary care hospitals.

The experts found that the documentation of smoking status and lipid profiles in medical records was incomplete in 2001 and 2007 (percentage of missing values ranged from 14.5–48.8) and those variables were not further analyzed in the patient characteristics of the results section.

Paper II

The crude odds ratios (ORs) for differences in in-hospital outcomes for patients first admitted to tertiary vs secondary care hospitals was estimated using logistic regression. The crude HR for 1-year mortality was estimated with Cox's proportional hazards regression. The ratio with the 95% CI was displayed as the ratio of the rate in tertiary care hospitals to the rate in secondary care hospitals.

Owing to the study design, the dataset included missing values for variables concerning cardiovascular history and risk factors. Values were missing at random. The percentage of missing values ranged from 3.5 to 28.7. In our analysis, we excluded variables with missing values for more than 15% of the cases. Hence data on smoking and Body Mass Index were not included in the analysis. When comparing the differences in in-hospital outcomes and 1-year mortality between the two study groups, we adjusted for baseline characteristics (age, sex, AMI subtype, DM, arterial hypertension, dyslipidemia, previous AMI, chronic heart failure, previous stroke, peripheral vascular disease, previous PCI, previous CABG, out-of-hospital cardiac arrest, Killip class III/IV on admission). We used case deletion and multiple imputation as comparative approaches to handling patients with missing observations. Performing full-case

analysis would have led to biased analysis and would have excluded 22.9% of the cases. We performed multiple imputation for all baseline characteristics with missing values (van Buuren *et al*. 1999): DM, arterial hypertension, dyslipidemia, previous AMI, previous chronic heart failure, previous stroke, previous peripheral vascular disease, and previous PCI. We used 10 imputed datasets for this study to ensure that our effect estimates were not overly inaccurate due to Monte Carlo variability.

Paper III

Cox's proportional hazards regression was used to calculate HRs of primary and secondary outcome with the 95% CIs to compare the outcomes of STEMI patients to NSTEMI patients. The multivariate model included baseline characteristics (age, DM, arterial hypertension, dyslipidemia, current smoking, previous AMI, chronic heart failure, previous stroke, peripheral vascular disease, previous PCI, previous CABG, Killip class III/IV on admission, LVEF <40%) and the number of diseased vessels (1–2 or 3–4 vessel disease).

Paper IV

Cox's proportional hazards regression was used to calculate HRs of primary and secondary outcome with the 95% CIs to compare the outcomes of diabetic and non-diabetic patients by sex. The multivariate model included baseline characteristics (age, AMI subtype, arterial hypertension, dyslipidemia, current smoking, previous AMI, chronic heart failure, previous stroke, peripheral vascular disease, previous PCI, previous CABG, Killip class III/IV on admission, LVEF <40%, the number of diseased vessels (1–2 or 3–4 vessel disease), and the delay to first medical contact.

5. RESULTS

5.1. Changes in the baseline characteristics, management and outcomes of AMI in the tertiary and secondary care hospitals in Estonia (Paper I and Paper II)

Baseline characteristics

Compared to 2001 in 2007 the patients hospitalized for AMI had become older – approximately 40% of patients were over 75 years old. The increase in the mean age was especially pronounced in the secondary care hospitals: when in 2001 the mean age of AMI patients in both types of hospitals was about 68 years, then in 2007, the patients in the secondary care hospitals were about two years older than the patients in the tertiary care hospitals (Table 1, Paper I; Table 1, Paper II).

An important finding was that the rate of patients with DM had doubled by 2007 in both types of hospitals (Table 1, Paper I). In the secondary care hospitals a higher proportion of patients were hypertensive in 2007 than in 2001. Furthermore, in 2007 the rate of hypertensive patients was higher in the secondary care hospitals than in the tertiary care hospitals (Table 1, Paper II).

The further comparison between the two hospital types in 2007 revealed that the patients admitted to the tertiary care hospitals were more likely to have a history of prior PCI and out-of-hospital cardiac arrest. In contrast, the patients first admitted to the secondary care hospitals were more likely to present later at the hospital after symptom onset (Table 1, Paper II).

Recommendation of medications

The use of evidence-based medications was higher in 2007 compared to 2001 in both types of hospitals. In the tertiary care hospitals the rates for ASA reached 94%, however the rates for beta-blockers, ACEIs and/or ARBs, and statins remained below 83%. In 2007 in the secondary care hospitals the respective rates were even lower, especially for statins that were recommended for less than 38% of patients (Table 2 and 3, Paper I). When making comparisons between the two hospital types we observed that the recommendation of nitrates for out-patient use was considerably higher in the secondary care hospitals, respectively 46% vs 22% (Table 3, Paper II).

Reperfusion for STEMI

The patients of the tertiary care hospitals underwent reperfusion for STEMI almost twice as often in 2007 as in 2001 (42% vs 64%) and primary PCI became the reperfusion method of choice. Still, the door-to-needle and door-to-balloon delay times were long.

Meanwhile, the reperfusion rates did not change significantly in the secondary care hospitals (Table 2, Paper I). In fact, the STEMI patients first

admitted to secondary care hospitals were almost twice as unlikely to receive reperfusion as those first admitted to tertiary care hospitals (38% vs 64%; Table 2, Paper II).

In 2007 a major reason for not receiving reperfusion for patients from both types of hospitals was a long prehospital delaly (Paper II). Nevertheless for 13% in the tertiary care hospitals and for 29% in the secondary care hospitals the reason for not performing reperfusion was not clear.

Coronary angiography and revascularization

The patients of the tertiary care hospitals underwent coronary angiography and revascularisation up to two times more often in 2007 as in 2001 and about 80% were referred for coronary angiography (Table 2, Paper I).

In the secondary care hospitals a higher rate of patients was referred into a tertiary care hospital for further management in 2007 than in 2001 (21% vs 7%, respectively). Those selected for coronary angiography were more likely to be younger, have STEMI and a history of prior PCI. In contrast, the non-selected patients had higher rates of prior AMI, chronic heart failure, prior stroke and Killip class III/IV at presentation. Nevertheless, in 2007 the rates of coronary angiography were three times higher for patients first admitted to the tertiary care hospitals compared to those admitted to the secondary care hospitals, 80% vs 25% respectively (Table 2, Paper II).

Non-invasive risk stratification

In 2007, echocardiography was performed more frequently in patients first admitted to tertiary care hospitals than in those admitted to secondary care hospitals, respectively 85% vs 65% (Paper II).

Outcomes

In crude and baseline-adjusted analysis there were no significant differences in the 30-day mortality and 3-year mortality within the two hospital types in 2007 compared to 2001 (Table 4, Figure 4).

However, in 2007, the short-term mortality was significantly lower in the tertiary care hospitals than in the secondary care hospitals in crude and baseline-adjusted analysis (Table 4, Paper II). The differences in the mortality persisted also after one year (Table 4 and Figure 1, Paper II) and three years (Paper I) of follow-up.

Table 4. Mortality of patients hospitalized into tertiary and secondary hospitals in Estonia in 2001 and 2007

Mortality	Year 2001 %	Year 2007 %	p	Adjusted HR (95% CI)
30-day				
Tertiary care hospitals	17.6	13.2	0.156	0.69 (0.42–1.13)
Secondary care hospitals	20.2	22.5	0.516	1.01 (0.66–1.55)
3-year				
Tertiary care hospitals	35.7	32.7	0.475	0.90 (0.65–1.23)
Secondary care hospitals	38.5	45.3	0.113	1.03 (0.77–1.37)

CI – confidence interval; HR – hazard ratio

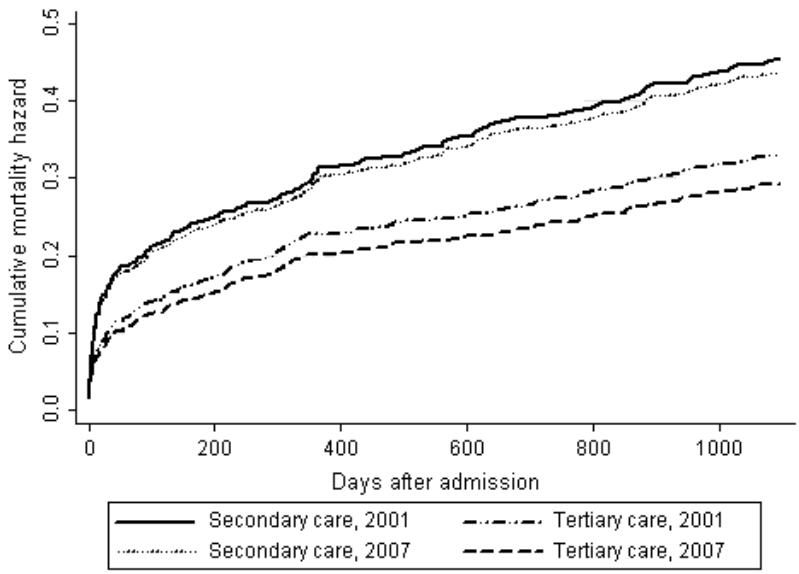

Figure 4. Baseline-adjusted 3-year cumulative mortality hazards of patients hospitalized into tertiary and secondary care hospitals in Estonia in 2001 and 2007

5.2. Long-term outcomes in different AMI patient subgroups after PCI

Long-term outcomes according to the AMI subtype (Paper III)

From the 2330 AMI cases hospitalized during the study period, 83% of STEMI and 55% of NSTEMI patients underwent PCI ($p<0.001$) and were included into the final study sample.

Compared to those not selected for PCI the STEMI and NSTEMI patients from the PCI group were about five years younger and they had less frequently chronic heart failure, previous stroke, peripheral artery disease and acute heart failure at presentation.

STEMI patients, compared to those with NSTEMI, were more often current smokers and they had acute heart failure on presentation (Table 1, Paper III). Meanwhile the NSTEMI patients had more often hypertension, previous AMI, chronic heart failure and they had undergone revascularization previously. There were no major differences in the extent of coronary artery disease between the two study groups (Table 2, Paper III). There were also no major differences in the use of guidelines-recommended medications, except for heparins and glycoprotein IIb/IIIa receptor inhibitors during hospitalization that were more often used in STEMI patients (Table 3, Paper III).

Among the patients with STEMI 72% received reperfusion within 12 h after symptom onset. The method of reperfusion was primary PCI in 86% of patients and thrombolysis in 14% of patients, which was done for patients referred from secondary care hospitals. Among the patients with NSTEMI 16% and 69% of patients received PCI respectively within 2 hours and 12 hours for after arrival to the hospital.

In crude analysis, patients with STEMI had higher rates of primary and secondary outcome than patients with NSTEMI (Table 5). The patients with STEMI had worse long-term outcomes also after adjustment for baseline characteristics: HR for primary outcome 1.30 (95% CI 1.09–1.56) and for secondary outcome 1.57 (95% CI 1.19–2.08).

Table 5. Outcomes during follow-up among patients with STEMI and NSTEMI who have undergone percutaneous coronary intervention, Tartu University Hospital, 2006–2009

Outcomes	STEMI (n=1107) %	NSTEMI (n=545) %	p
Primary outcome	41.8	34.8	0.007
Non-fatal AMI	9.6	9.7	
Revascularization	12.0	12.5	
Death	20.2	12.7	
Secondary outcome	22.0	15.4	0.001
In-hospital death	6.9	3.8	0.014

AMI – acute myocardial infarction; NSTEMI – non-ST-segment elevation myocardial infarction; STEMI – ST-segment elevation myocardial infarction

Sex-specific long-term outcomes of diabetic patients (Paper IV)

Of the 2330 patients with AMI hospitalized during the study period, 75% men and 65% women underwent PCI during the index episode ($p<0.001$) and were included into the study. In the final study population 15% of men and 24% of women had DM ($p<0.001$).

Overall, the patients with DM had higher rates of cardiovascular risk factors, co-morbidities, and 3–4 vessel disease among both men and women. Women with DM were younger, had longer delay times to first medical contact, and presented less frequently with typical symptoms of chest pain than those without DM (Table 1, Paper IV).

During the index hospitalization among women with STEMI a significantly lower proportion of patients with DM than those without received reperfusion within 12 hours after symptom onset (Table 2, Paper IV). When assessing the utilization of medications during the index hospitalization, women with DM were found to receive ASA less often than those without DM (Table 3, Paper IV). Men with DM received more often management with ACEIs and/or ARBs than men without DM. The rates of recommendation of the studied drugs for out-patient management were similar to the rates of drug utilization during the index hospitalization, though no differences within sex-groups were observed.

In univariate analysis, patients with DM both among men and women had a higher risk of primary and secondary outcome (Table 6). In multivariate analysis, however, DM was associated with a higher risk of primary and secondary outcome only in women (Table 6; Fig 1 and 2, Paper IV).

Table 6. Crude and adjusted hazard ratios for outcomes during follow-up after percutaneous coronary intervention among men and women with diabetes compared to those without diabetes, Tartu University Hospital, 2006–2009

	Men		Women	
Outcome	HR (95% CI)	AHR (95% CI)	HR (95% CI)	AHR (95% CI)
Primary[¥]	1.54 (1.20–1.98)*	1.29 (0.98–1.68)	1.60 (1.21–2.13)*	1.44 (1.05–1.96)*
Secondary[€]	1.53 (1.06–2.20)*	1.19 (0.80–1.76)	1.65 (1.11–2.44)*	1.83 (1.17–2.89)*

AHR – adjusted hazard ratio
HR – hazard ratio
[¥]Primary outcome – non-fatal AMI, revascularization, or all-cause mortality
[€]Secondary outcome – all-cause mortality
*$p < 0.05$

6. GENERAL DISCUSSION

6.1. Changes in the baseline characteristics, management and outcomes of AMI in the tertiary and secondary care hospitals in Estonia

6.1.1. Changes in the baseline characteristics

The higher age of the AMI patients in 2007 compared to 2001 is probably caused by the fact that the uptake of effective primary prevention methods has shifted the age for the onset of AMI. In any case, higher age increases the risk for worse outcomes and poses a challenge for the treatment of AMI patients.

An important finding that has also been noted previously (Fang *et al.* 2010) was that the proportion of patients with DM had doubled by 2007. This probably mirrors the rising prevalence of glycometabolic disturbances in the population (Wild *et al.* 2004; International Diabetes Federation, Diabetes Atlas 2011). The reason for the higher rate of patients with hypertension in the secondary care hospitals could first be that in 2007 the patients were older and, secondly, that the clinicians increasingly recognize hypertension as an important cardiovascular risk factor.

Our study did not include information about non-cardiovascular co-morbidities such as chronic kidney disease and cancer which could be more prevalent among older patients and could influence management decisions and prognosis. Still, overall it seems that the trends in the patterns of differences in the baseline characteristics of AMI patients in different types of hospitals were similar to those reported in previous studies (Labarere *et al.* 2007; Radovanovic *et al.* 2010): patients admitted into secondary care hospitals were older, more frequently female, hypertensive, and had more severe co-morbidities. There could be two explanations for this: first, emergency medical services tend to transport younger (who are more often male) and healthier AMI patients into tertiary care facilities, and second, patients living in the rural area tend to be older, have more co-morbidities and be more often of female sex.

6.1.2. Changes in the management

Our country-wide study showed that in Estonia the management of patients with AMI improved both in the tertiary and secondary care hospitals between 2001 and 2007; however, the progress was not uniform.

Evidently the observed improvements of management were partly due to the release of the new European and Estonian guidelines for the management of AMI (Bertrand *et al.* 2002; Braunwald *et al.* 2002; Van de Werf *et al.* 2003; Antman *et al.* 2004; Soopõld *et al.* 2004) as well as the launching of several training programs at the ESC and hospital level. Thus much effort has been put into improving the implementation of the recommendations of the diagnosis and management guidelines for AMI. The process of improvement in management

quality has also involved the awareness of the importance of risk factor modification among AMI patients. The progress done is mirrored by the decline in the rate of missing data in the patient files for such cardiovascular risk factors as dyslipidemia, smoking and BMI.

Changes in the recommendation of medications

An encouraging finding was the increased use of ASA in 2007 compared to 2001 in the tertiary care hospitals. However, in the secondary care hospitals only about 85% of the patients were recommended ASA during hospitalization and for out-patient use. As ASA is a well established drug in the secondary prevention of AMI (Antithrombotic Trialists' Collaboration 2009), we believe that the low rates of recommendation are at least to some extent related to the deficiencies in the documentation in the patient files.

The recommendation of beta-blockers and ACEIs/ARBs increased in both types of hospitals. Still, in 2007, the mean rate of recommendation of these drugs during hospitalization and for outpatient use remained below 83%. In fact, similar rates were also found in the GRACE (Goodman *et al.* 2009) and in the second Euro Heart Survey on acute coronary syndromes (Mandelzweig *et al.* 2006). An interesting finding was that in the secondary care hospitals the rate of recommendation of such older drugs as beta-blockers was quite similar to the rate in the tertiary care hospitals. At the same time, although the recommendation of ACEIs/ARBs had increased considerably during the study period in the secondary care hospitals, the rates remained still lower than in the tertiary care hospitals. The use of statins in the secondary care hospitals causes concern as although the rates increased markedly during the study period, their use was still below 38%. The fact that the quality of care of AMI patients in the secondary care hospitals lags behind that in their tertiary care counterparts may be due to the known slower implementation of guideline-recommended medications in the secondary care hospitals in general (Dorsch *et al.* 2004). As our study demonstrated, patients in the secondary care hospitals tend to be older and have more co-morbidities, which may influence management decisions.

The results of our study demonstrated that although the recommendation of medications improved in both types of hospitals between 2001 and 2007 the developments are still suboptimal. We suspect that one of the major reasons for this is the "risk-management paradox" wherein higher-risk patients are less likely to receive guideline recommended therapies (Sabouret *et al.* 2010; Abtahian *et al.* 2011; Motivala *et al.* 2011). This phenomenon is probably more pronounced in secondary care hospitals, where the patients are older and have more co-morbidities and possibly also poorer functional capacity. Clinicians perhaps preferentially avoid preventive therapies out of the fear of non-compliance to prescribed medications. It should be admitted that this pre-judgment by clinicians is justifiable. However, a recent study found that even in the absence of co-morbidity, elderly patients were denied indicated medical managements probably because of their age alone (Moubarak *et al.* 2012). Another reason for this "risk-management paradox" is probably the fact that

clinicians are concerned about applying evidence from clinical trials to their everyday practice because trials tend to exclude older higher-risk patients.

The existence of the "risk-management paradox" must be kept in mind when clinicians feel reluctance to initiate or continue therapies to patients presenting with an AMI. Whenever possible, objective data should be used to carefully weigh the risks and the benefits before withholding evidence-based therapies in these patients as there may be misperceptions regarding contraindications and lack of tolerability to medications in older patients. Management approaches that have proven to be associated with lower risk of complications should be preferred. For instance, temporal changes in the antithrombotic strategies have led to a nearly 20% reduced risk of post-PCI bleeding (Subherwal *et al.* 2012). Additionally, patients in secondary care hospitals may benefit from the routine onsite rotations of cardiologists from tertiary care hospitals (Joynt *et al.* 2011; Bradley *et al.* 2005; Bradley *et al.* 2012).

Changes in the reperfusion therapy for STEMI

While between 2001 and 2007 in the tertiary care hospitals reperfusion rates increased and primary PCI became the preferred method of reperfusion for STEMI, then in the secondary care hospitals the reperfusion rates showed little change.

Nevertheless, only 64% of the patients in 2007 in the tertiary care hospitals, received reperfusion (primary PCI 57%), 33% within the recommended time windows after hospital admission. Although further studies are needed, the reperfusion rates and the in-hospital delays remained slightly lower than the 70%, recommended by the Stent for Life initiative (stentforlife.com), as well as lower than the rates reported in the third Euro Heart Survey (Schiele *et al.* 2010), in the NRMI (Gibson *et al.* 2008), and in the GRACE (Eagle *et al.* 2008). A major reason for not receiving reperfusion was a long pre-hospital delay. In fact, the EMIR report for 2010 for tertiary care hospitals (available at www.infarkt.ee) demonstrated that among the STEMI patients who presented within 12 hours of symptom onset and who were not transferred from a secondary care hospital, the rate of reperfusion was as high as 83% (75% for primary PCI).

In 2007, STEMI patients admitted to secondary care hospitals were twice as unlikely to receive reperfusion compared to patients first admitted to tertiary care hospitals. The reasons for such a difference are not clear. It is possible that some STEMI patients were transferred into a tertiary care hospital for primary PCI before they received thrombolysis at the secondary care hospital. Still, in 29% of the cases the reason for not performing reperfusion was not clear for the study experts. There might be deficient documentation of contraindications for thrombolysis in patient files, such as the risk of bleeding and a recent stroke. Additionally, clinicians probably tend to be quite conservative in treating elderly persons with thrombolysis as they have a higher risk of stroke (the GUSTO investigators 1993). The reasons for the low rates of reperfusion in the secondary care hospitals are probably a combination of high age of the patients

and late presentation at hospital, little experience of clinicians in performing thrombolysis, and insufficient implementation of the recommendations in the guidelines.

A possible solution that might help increase the proportion of STEMI patients who receive reperfusion within 12 hours of symptom onset is the electronic transmission of ECG from ambulance to hospital (Sorensen *et al.* 2011). In the ideal case, the contraindications for thrombolysis should be assessed already in the ambulance so that patients could be transported appropriately. In selected cases the patients could benefit more from primary PCI than from thrombolysis, even at the expense of a longer delay (Tarantini *et al.* 2010; The GUSTO investigators 1993; De Luca *et al*. 2008).

Changes in the use of coronary angiography and revascularization

In 2007, patients with AMI in the tertiary care hospitals underwent two times as frequently coronary angiography and revascularization than in 2001. At the same time, in the secondary care hospitals, the transfer of patients for further cardiac testing and revascularisation into tertiary care hospitals increased. Still, the transfer rates remained low compared to previous studies (Radovanovic *et al.* 2010; Labarere *et al.* 2007).

Our study suggests uneven access to PCI facilities across Estonian hospitals. In 2007, the patients primarily admitted to secondary care hospitals were three times less likely to undergo coronary angiography compared to the patients primarily admitted to tertiary care hospitals. Similarly to the study of Muus *et al*. (2011), an important finding of this study was that in the secondary care hospitals the patients selected for transfer into a higher care facility for further management, including PCI, were younger and healthier; they had more frequently STEMI and a better clinical status on presentation compared to those who were not selected for PCI. As previous studies (Stukel *et al.* 2005; Cohen *et al.* 2009) have shown in both hospital types the use of coronary angiography appears to target younger, lower risk patients who would derive less benefit from revascularization. Yet in secondary care hospitals, age seems to be a much stronger selection determinant and referral for coronary angiography and consequent revascularization is even more biased than in tertiary care hospitals.

The results of our paper III characterize trends in the selection of patients for PCI in a tertiary care hospital in more detail. Much higher rates of patients with STEMI than with NSTEMI are selected for PCI (83% vs 55%). This is wholly understandable as according to the guidelines, in the absence of contra-indications all STEMI patients should receive reperfusion, and in tertiary care hospitals the preferred method is primary PCI. Regarding patients with NSTEMI, indications for coronary angiography and PCI and the timing of it depend more on the symptoms, clinical presentation, and risk stratification. Like in previous studies (Sabouret *et al.* 2010; Motivala *et al.* 2011), NSTEMI patients who underwent PCI were younger and had lower rates of cardiac co-morbidities than those who were not selected for this procedure.

It can be speculated that certain invasive in-hospital therapies were withheld from higher-risk patients out of a genuine concern for the risk of adverse effects in these patients. The patients themselves may also have been less ready to take the risk associated with an invasive procedure. Still, the "risk-management paradox" must be kept in mind and objective data should be used to make risk adjusted decisions for invasive management. Additionally, the use of transradial access is one possibility to improve outcomes as it is associated with a significant reduction in mortality, major adverse cardiovascular events, and major access site complications compared with a transfemoral approach (Mamas *et al.* 2012).

It is evident that universal triage/transfer of all AMI patients to tertiary care hospitals would on exceed their capability (Wharton *et al.* 2001; Bosk *et al.* 2011). The key factor in this case is to promote partnerships between hospitals with and without the availability of PCI.

Changes in the non-invasive risk stratification

It could be expected that in hospitals where PCI is not available, non-invasive risk stratification (incl. stress-testing) is more often used to select patients for referral to coronary angiography and revascularisation into a higher care hospital. Like a study of Halabi *et al.* (2006), our study found a low use of stress-testing in secondary care hospitals. Furthermore, the use of echocardiography was significantly lower than in tertiary care hospitals. To some extent, this could be explained by the lower on-site availability of these investigation methods. However, when considering the low rates of patients selected for referral, it can be hypothesized that the cardiovascular risk stratification of AMI patients in secondary care hospitals is suboptimal, which could also explain the higher need to prescribe nitrates during hospitalization and at discharge.

6.1.3. Changes in the short- and long-term mortality of AMI in the tertiary and secondary care hospitals

Several studies have demonstrated that closer adherence to published guidelines for AMI management have resulted in improved short- and long-term outcomes and this even despite the growing prevalence of risk factors (older age, history of dyslipidemia and DM) at presentation (Mandelzweig *et al.* 2006; Fox *et al.* 2007; Gibson *et al.* 2008; Peterson *et al.* 2008; Rogers *et al.* 2008; Janion *et al.* 2009; Stolt Steiger *et al.* 2009; Tatu-Chitoiu *et al.* 2009; Krumholz *et al.* 2009; Monhart *et al.* 2010; Fang *et al.* 2010). Although our study demonstrated a marked improvement in the management of AMI patients in 2007 compared to 2001, especially in the tertiary care hospitals, it failed to establish a significant decrease in short- and long-term mortality.

It is possible that our study was underpowered to detect a mortality difference within a hospital type. Nevertheless, these findings may largely be due to the higher age and higher prevalence of co-morbidities among the study

samples in 2007. For instance, the rates of DM had almost doubled in both types of hospitals. To further clarify this issue, we performed a sub-analysis comparing the baseline characteristics, management, and mortality separately among patients aged <75 and ≥75 years in 2001 and 2007 in the tertiary care hospitals. It suggested that in the tertiary care hospitals the reasons why better management had not resulted in better outcomes was that, firstly, the rate of patients over 75 years of age with more co-morbidities had increased and, secondly, improvement targeted those who were younger and healthier with a lower risk of mortality. This finding is supported by a previous age-group stratified study conducted in an Estonian tertiary care hospital during 2001–2003. It demonstrated that patients aged <75 years had shorter pre-hospital delay times; they also received more often reperfusion, coronary angiography and PCI as well as beta-blockers and statins than those aged ≥75 years (Ainla *et al.* 2005a).

6.1.4. Differences in the short- and long-term outcomes of AMI between the tertiary and secondary care hospitals in 2007

The observed finding of lower short and long-term mortality in the tertiary care hospitals compared to the secondary care hospitals in 2007 is intriguing. It can probably be explained by a combined effect of improved management possibilities in the tertiary care hospitals and different patient baseline characteristics in the two hospital types. The patients admitted to the secondary care hospitals were more likely to be older and have a higher cardiovascular risk. Moreover, as the elderly often present with atypical symptoms and have a greater burden of cardiac and non-cardiac co-morbidities, clinicians could be more reluctant to treat them aggressively, the more so when the outcomes of interventions and surgery may be poorer (Bridges *et al.* 2003; Alexander *et al.* 2005).

These findings are consistent with the results of recent retrospective and prospective observational studies (Khadour *et al.* 2003; Tang *et al.* 2006; Labarere *et al.* 2007; Radovanovic *et al.* 2010; Belle *et al.* 2012) showing that hospitalization to a tertiary care hospital is associated with lower in-hospital and long-term mortality. At the same time, with follow-up extending to three years, some studies have revealed no favorable impact of management in hospitals equipped with coronary angiography facilities on patient mortality. This controversy may be explained by the comparable rates of reperfusion, coronary angiography and revascularization, as well as by the recommendation of evidence-based drugs in both hospital types (Krumholz *et al.* 1998; Rogers *et al.* 2000; Ambardekar *et al.* 2010). Nor did the GRACE (Van de Werf *et al.* 2005) show survival benefit by 6 months for patients admitted to hospitals with coronary angiography facilities. However, many of the patients from this retrospective analysis were enrolled before the routine use of clopidogrel, glycoprotein IIb/IIIa inhibitors and drug-eluting stents, which have contributed to the improved outcomes observed with an invasive strategy.

Although our study demonstrated an outcome difference between the patients first hospitalized into tertiary and secondary care hospitals, it is clear that whether a hospital type improves outcomes depends on the magnitude of existing differences, not on the type of hospital alone (Chen *et al.* 2010).

6.2. Long-term outcomes in different AMI patient subgroups after PCI

Our register linkage studies among patients in a tertiary care hospital were the first in Estonia to assess the long-term outcomes of AMI patients who have undergone PCI and this not only in terms of all-cause mortality but also in terms of non-fatal AMI and revascularization.

It should be recognized that AMI patients who have undergone PCI have a serious prognosis in terms of non-fatal AMI, revascularization and all-cause mortality. With a median follow-up time of almost three years, about 40% of the study population experienced a primary outcome event and by the end of follow-up 20% of the patients were dead. These findings are in accordance with previous studies (Abbott *et al.* 2007; Chan *et al.* 2009; McManus *et al.* 2011), although our study had a longer follow-up period. This demonstrates the fact that patients with AMI have a high cardiovascular risk also after hospitalization and proper use of guideline-recommended secondary prevention methods of AMI is warranted.

Long-term outcomes according to the AMI subtype

Our Paper III showed that among patients who have undergone PCI, those with STEMI have significantly worse long-term outcomes than those with NSTEMI. Furthermore, the differences are mostly driven by a higher mortality of STEMI patients during follow-up.

Indeed, patients with STEMI are known to have a higher short-term risk (Terkelsen *et al.* 2005; Roe *et al.* 2005; Chan *et al.* 2009). However, as our findings regarding the long-term outcomes for the two AMI subtypes were contradictory to those obtained in previous studies including unselected cohorts, we concluded that NSTEMI patients selected for PCI had a lower cardiovascular risk than NSTEMI patients generally have. In a recent study also Abbot *et al.* (2007) found that patients with STEMI showed a trend towards worse outcomes during 1-year follow-up. Unfortunately, the study was underpowered to detect a statistically significant difference.

Sex-specific long-term outcomes of diabetic patients

We found that among patients with AMI who have undergone PCI, DM is associated with significantly worse outcomes in women than in men. This excess risk seemed to be largely driven by a high in-hospital mortality of diabetic women. The results extend the findings of previous studies by demonstrating the sex-specific outcomes of diabetic patients in a cohort of AMI patients where all

patients have undergone PCI (Rosengren *et al.* 2001; Crowley *et al.* 2003; Maier *et al.* 2006; Champney *et al.* 2007; Ouhoummane *et al.* 2009; Meisinger *et al.* 2010; Winell *et al.* 2010; Eliasson *et al.* 2011; Ogita *et al.* 2011).

The prerequisite for similar outcomes in diabetic and non-diabetic women is similar management of AMI (Kramer *et al.* 2012). Firstly, in our study ASA was recommended less frequently for women with DM than for those without DM. The analysis also showed that in women with STEMI, those with DM received less often reperfusion within 12 hours of symptom onset compared to those without DM. Secondly, female diabetic patients presented later and less often with typical symptoms of chest pain compared to non-diabetics. Medical professionals as well as patients with CAD should be more aware of the higher prevalence of atypical symptoms among women and strive towards shorter pre-hospital delay times.

Although in our study women with DM were younger, the rates of previous AMI and chronic heart failure were higher than in those without DM. Besides, older women with DM could have more pronounced risk factor clustering and worse self-rated health than older men (Leosdottir *et al.* 2011). This adds to the excess cardiovascular risk of women with DM, which in combination with higher age, contributes to sex-specific outcomes of AMI patients with DM (Norhammar *et al.* 2008). Therefore, in order to alleviate this unfavorable situation for women, improvements should target already the primary prevention strategies of AMI (Kautzky-Willer *et al.* 2010; Franzini *et al.* 2012).

As presented above, several studies have suggested possible pathophysiological reasons for such sex-specific outcomes (Tenenbaum *et al.* 2003; Graham *et al.* 2003; Ren *et* Ceylan-Isik 2004; Boccuzzi *et al.* 2005; Kamran *et al.* 2008; Mortensen *et al.* 2009; Jacobs 2009; Reynolds *et al.* 2011, Vaccarino *et al.* 2011; Sheikh *et al.* 2012). However, it is not clear which management strategies should be applied in order to improve the outcomes of women with AMI. The study of Champney *et al.* (2007) demonstrated that the overall stronger effect of DM among women was more pronounced in the 1990s than in more recent years. Eliasson *et al.* (2008) observed that the survival rates have improved in subjects with DM since the early 1980s, more so in women than in men, thereby decreasing the gap to non-diabetic women. These findings could be associated to the developments in the management strategies of high risk AMI patients undergoing PCI.

The analysis of Kornowski *et al.* (2012) indicated a profound prognostic advantage for drug eluting stents versus bare metal stents among both sexes, though women appeared to derive the greatest benefit. This is a possible opportunity to improve the outcomes in female AMI patients with DM. It may be hypothized that medications such as antiplatelet agents, anticoagulants, and beta-blockers may have different effects in women and men with DM (Szerlip *et* Grines 2009). However, there is currently no clear scientific evidence to support this hypothesis. It is essential to include more women in future randomized controlled studies and find more potent management strategies better suited for women with DM.

7. CONCLUSIONS

1. In Estonia, tertiary and secondary care hospitals underwent considerable improvement in AMI management between 2001 and 2007. However, changes were more pronounced in the tertiary care setting, especially with respect to the use of reperfusion and revascularisation. Low rates of reperfusion and transfer to PCI clearly need to be addressed in secondary care hospitals.

   The improvement in the management of AMI between 2001 and 2007 in Estonia did not result in a significant decrease in mortality in tertiary or secondary care hospitals. Higher age and higher rate of co-morbidities of the patients pose a challenge for AMI management.
2. There were disparities in the process of care and in in-hospital and 1-year mortality between the patients first admitted to tertiary care and secondary care hospitals in Estonia in 2007. Patients first admitted to secondary care hospitals should undergo more vigorous risk stratification with invasive and non-invasive methods and the use of evidence-based medicine should be encouraged even if cardiac revascularization is not provided.
3. The risk of fatal and non-fatal outcomes is high among patients who have undergone PCI. Those with STEMI have worse long-term outcomes than those with NSTEMI. This may be explained by the selection of low risk NSTEMI patients to undergo PCI.
4. Diabetic women with AMI who have undergone PCI represent a high-risk group warranting special attention in management strategies, especially during hospitalization. There is a need to improve the expertise to detect AMI earlier, to reduce disparities in management, and to find targeted PCI strategies with adjunctive antithrombotic regimes in women with DM.

8. FUTURE RESEARCH

1. Further studies are needed to assess the changes in the management and outcomes of AMI patients in hospitals of diferrent levels of care in Estonia. This includes the management and outcomes of AMI according to sex, age group, and subtype.
2. Further studies are needed to assess the non-fatal long-term outcomes of AMI patients hospitalized into hospitals of different levels of care.
3. It remains to be evaluated how different patient subgroups adhere to the secondary prevention methods of AMI and how it affects their long-term fatal and non-fatal outcomes.

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SUMMARY IN ESTONIAN

Äge müokardiinfarkt Eestis: muutused kliinilistes tunnustes, ravikäsitluses ja -tulemustes

Südame isheemiatõbi (SIT) on üks sagedaseimaid surmapõhjusi maailmas. Kõrge elatustasemega lääneriikides on SIT suremus viimase kümnendi jooksul oluliselt langenud, mõnedes riikides isegi kuni poole võrra. SIT suremus on langenud ka Eestis, kuid sellele vaatamata oleme Euroopas endiselt edetabeli esikolmikus. Eestis tuleb lisaks esile tuua just kõrget suremust alla 65 aastaste seas.

Uuringud näitavad, et SIT suremuse vähenemine on 50% ulatuses seletatav muutustega peamistes kardiovaskulaarsetes riskitegurites nagu düslipideemia, suitsetamine ja kõrge vererõhk. Lisaks mängib olulist rolli uute tõenduspõhiste ravimite kasutamine ja revaskulariseerimismeetodite areng ning üha parem kättesaadavus. See on toonud kaasa ka ägedasse müokardiinfarkti (ÄMI) haigestumuse ja suremuse vähenemise. On teada, et letaalsus ÄMI tõttu esimese kuu jooksul võib olla kuni 50% ning ligi pooled surmadest leiavad aset esimese paari tunni jooksul alates ataki algusest. Siiski saab patsientide prognoosi oluliselt parandada kaasaegsete ravivõtete viivitamatul rakendamisel.

Sarnaselt teiste Ida-Euroopa riikidega on Eesti meditsiinisüsteemis toimunud olulised muutused. Viimase kümnendi jooksul on tehtud suuri jõupingutusi ÄMI ravikäsitluse parandamiseks ja ühtlustamiseks. 2001. a. hospitaliseeritud ÄMI haigete kohordi põhjal tehtud uuring näitas, et teise ja kolmanda etapi haiglates erineb ravikäsitlus olulisel määral. Selgus, et ÄMI patsiente suunatakse koronarograafiale harva ja ka perkutaanset koronaarinterventsiooni (PKI) rakendatakse vähe – nt ainult neljandikul kolmanda etapi haigla ÄMI patsientidest teostati PKI. Seetõttu on Eestis viimastel aastatel lisaks tõenduspõhiste raviskeemide rutiinse kasutamise vajalikkuse rõhutamisele olnud üheks prioriteediks suurendada invasiivse reperfusioonravi (PKI) kättesaadavust. Täna on tehnilistele nõuetele vastavad ööpäevaringse erakorralise PKI võimalused tagatud ainult kolmanda etapi haiglates, tööpäevadel aga plaanilisteks protseduurideks ka juba mitmetes teise etapi haiglates. Arvestades viimasel kümnendil tehtud jõupingutusi ÄMI ravikorralduse muutusteks, on oluline hinnata selle rakendumist reaalses igapäevases kliinilises praktikas haiglatüübiti ja dünaamikas. Lisaks on tähtis hinnata tervishoiukorralduse muutuste mõju ravitulemustele. Varasemalt on Eestis piiratud ligipääsu isikustatud andmetele, mistõttu pole olnud võimalik analüüsida erinevate tegurite mõju ÄMI patsientide ravikäsitluse hilistulemustele. Vastavad teadmised on aga üliolulised, kui eesmärgiks on pakkuda võrdset tervishoiuteenuse kvaliteeti kogu Eestis.

Tänapäeval rõhutatakse järjest enam suurt vajadust kasutada uuringutes registriandmeid, mis pärinevad reaalsest kliinilisest igapäevaelust. Ühest küljest baseerume küll palju tõenduspõhise meditsiini kontseptsioonile, kuid tuleb arvestada, et see põhineb eelkõige randomiseeritud kontrollitud uuringutel, kuhu reeglina kaasatakse nooremad, vähemate kaasuvate haigustega, sageda-

mini meessoost patsiendid. Teisalt, kliinilises igapäevaelus on probleemiks just eakate ja naissoost patsientide osakaalu suurenemine, samuti kaasuvate krooniliste haiguste, nagu diabeet, üha suurem esinemissagedus. Näiteks varasemates uuringutes on viiteid, et naistel võib diabeet olla seotud kõrgema kardiovaskulaarse riskiga kui meestel. Samas, uuringuid diabeetikute soospetsiifiliste ravikäsitluse tulemuste kohta peale ÄMI on siiski vähe ning nende tulemused on vastukäivad. Need on sageli läbi viidud patsiendikohortidel, kus ainult väikesel osal patsientidest on tehtud PKI, mis võib omakorda olla aluseks erinevustele ravitulemustes ja olla raskesti interpreteeritavad tänast üha invasiivsemat ravikäsitlust arvestades.

Uurimuse eesmärgid

1. Hinnata muutusi teise ja kolmanda etapi haiglatesse hospitaliseeritud ÄMI patsientide ravikäsitluses ning 30-päeva ja 3-aasta suremuses Eestis aastatel 2001 vs 2007.
2. Võrrelda ravikäsitlust, haiglasiseseid ravitulemusi ja 1-aasta suremust teise ja kolmanda etapi haiglatesse esmashospitaliseeritud ÄMI patsientide seas Eestis 2007. aastal.
3. Võrrelda STEMI ja NSTEMI patsientide ravi hilistulemusi peale PKI-d, seejuures hinnata lisaks suremusele ka korduva mittefataalse ÄMI esinemist ja korduva revaskulariseerimise teostamist.
4. Hinnata ÄMI patsientide soospetsiifilisi ravitulemusi diabeetikutel ja mittediabeetikutel, seejuures hinnates lisaks suremusele ka korduva mittefataalse ÄMI esinemist ja korduva revaskulariseerimise teostamist.

Patsiendid ja metoodika

Publikatsioonide I ja II andmed pärinesid läbilõikeuuringutest, kus analüüsiti 2001. ja 2007. aastal Eesti haiglatesse hospitaliseeritud ÄMI haigete ravikäsitlust (põhidiagnoosi kood I21–I22 rahvusvahelise haiguste ja nendega seotud terviseprobleemide statistilise klassifikatsiooni 10. versiooni (RHK-10) järgi). Juhuvalimisse (28% aastate ravijuhtudest) sattunud haigusjuhtude loetelu saadi Haigekassa andmebaasist. Uuringu eksperdid analüüsisid haigusjuhtusid standardiseeritud uuringuvormi alusel, mis sisaldas andmeid patsientide demograafiliste andmete, kliiniliste tunnuste ning haiglasisese ravikäsitluse ja -tulemuste kohta. Surma fakti ja kuupäeva andmed haiglajärgselt saadi rahvastikuregistrist.

Publikatsioonides III ja IV kajastatud uuringud põhinesid Müokardiinfarktiregistri (MIR) ning Haigekassa ja rahvastikuregistri andmebaaside linkimisel saadud andmetel. MIR on alates 01. jaanuarist 2012 riiklik register, millesse kogutakse jooksvalt andmeid hospitaliseeritud ÄMI patsientide kohta (RHK-10 koodid I21–I22). MIRi andmekoosseis on kooskõlas projektiga „*Cardiology Audit and Registration Data Standards in Europe*“, mille eesmärk on ühtlustada Euroopas ägedate koronaarsündroomide registrite ja auditite

raames kogutavate andmete koosseis ning definitsioonid. Analüüsitava lõppvalimi moodustasid Tartu Ülikooli Kliinikumi kõik ÄMI patsiendid, kes olid hospitaliseeritud ajaperioodil 2006–2009 ning kellel oli tehtud PKI. Patsientide isikuandmed ja andmed kliiniliste tunnuste (sh ÄMI alatüüp ja diabeedi olemasolu) ning haiglasisese ravikäsitluse ja -tulemuste kohta pärinesid MIRist; surma fakti ja kuupäeva andmed haiglajärgselt pärinesid rahvastikuregistrist; andmed korduva ÄMI esinemise ning korduvate revaskulariseerimiste teostamise ja meetodi kohta pärinesid Haigekassa andmebaasist.

Andmete statistiliselt töötlusel kasutati andmetöötlusprogrammi Stata (versioon 11) ja R (versioon 2.10.1).

Uurimuse peamised tulemused ja järeldused

1. Aastatel 2001 vs 2007 paranes ÄMI patsientide ravikäsitlus nii teise kui kolmanda etapi haiglates. Siiski olid soodsad muutused rohkem väljendunud kolmanda etapi haiglates, eriti reperfusioonravi ja revaskulariseerimise kasutamise osas. Teise etapi haiglates tuleb rohkem tähelepanu pöörata reperfusioonravi rakendamisele ja haigete õigeaegsele suunamisele koronarograafiale.

   Ravikäsitluse paranemine Eestis aastatel 2001 vs 2007 ei toonud kaasa suremuse vähenemist haiglates. Patsientide kõrgem iga ja suurenev kardiovaskulaarne risk on väljakutseks ÄMI ravikäsitluse edasisel parandamisel.
2. 2007. aastal esines oluline erinevus teise ja kolmanda etapi haiglatesse esmashospitaliseeritud ÄMI patsientide ravikäsitluses ning haiglasiseses- ja hilissuremuses. Esmalt teise etapi haiglatesse hospitaliseeritud patsientidel tuleks pöörata suuremat rõhku õigeaegsele riski hindamisele mitte-invasiivsete ja invasiivsete meetoditega ning julgustada ravijuhistes soovitatud ravimite kasutamist, isegi siis kui haiget invasiivsele ravikäsitlusele ei suunata.
3. Peale PKI-d on ÄMI patsientide prognoos tõsine nii fataalsete kui ka mittefataalsete kardiovaskulaarsete tulemusnäitajate esinemise osas. Võrreldes NSTEMI patsientidega on STEMI patsientide ravi hilistulemused oluliselt halvemad. Erinevused võivad olla tingitud asjaolust, et PKI-le suunatud NSTEMI patsientidel on väiksem kardiovaskulaarne risk kui keskmisel NSTEMI patsiendil üldiselt.
4. Koronaarinterventsiooniga ravitud haigetest on just naissoost ÄMI ja diabeediga patsiendid kõrgema riskiga grupp, kelle puhul peab pöörama erilist tähelepanu kasutatavatele ravistrateegiatele, iseäranis haiglaperioodil. Selle kõrge riskiga grupi puhul on oluline parandada oskusi ÄMI varasemaks diagnoosimiseks, järgida hoolikamalt ravijuhiste soovitusi ning leida suunitletud PKI strateegiaid, mille toeks on soodsa ohutusprofiiliga tõhus antitrombootiline raviskeem.

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PUBLICATIONS

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