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ACUTE MYOCARDIAL INFARCTION IN ESTONIA: CLINICAL CHARACTERISTICS, MANAGEMENT AND OUTCOME

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LIST OF ORIGINAL PUBLICATIONS

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III Ainla T, Baburin A, Eha J, Teesalu R. Vanuse mõju ägeda müokardiinfarkti haigete ravikäsitlusele ja -tulemusele. Eesti Arst 2005; 84: 13–17.

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ABBREVIATIONS

AMI	acute myocardial infarction
ACE	angiotensin converting enzyme
ACS	acute coronary syndromes
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CI	confidence interval
CK	creatinine kinase
CVD	cardiovascular disease
DIGAMI	Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction
ECG	electrocardiogram
EMIR	Estonian Myocardial Infarction Registry; Eesti müokardiinfarktiregister
GIK	glucose-insulin-potassium
Glc	glucose
GRACE	Global Registry of Acute Coronary Events
ICD-10	International Classification of Diseases 10th Revision
LVEF	left ventricular ejection fraction
MI	myocardial infarction; müokardiinfarkt
MONICA	Multinational monitoring of trends and determinants in cardiovascular disease
NA	not applicable
NRMI	National Registry of Myocardial Infarction
OR	odds ratio
PCI	percutaneous coronary intervention
RIKS-HIA	The Register of Information and Knowledge about Swedish Heart Intensive Care Admissions
RR	rate ratio
STEMI	ST-elevation myocardial infarction
SVH	südame-veresoonkonna haigused
VF	ventricular fibrillation
WHO	World Health Organization
ÄMI	äge müokardiinfarkt

1. INTRODUCTION

Cardiovascular disease (CVD), including acute myocardial infarction (AMI), is the main cause of death in the world. Developed countries have shown a marked decline in coronary artery disease (CAD) mortality during the past three decades, whereas several countries in Eastern Europe have seen a substantial increase (Sans *et al.* 1997). In Estonia, CVD accounts for more than 50% of all causes of death (Ministry of Social Affairs of Estonia 2004). Death rates from CVD, and CAD mortality have both remained high during the last decades (Leinsalu 1995; Baburin *et al*. 1997).

Epidemiologists and health service planners use a number of different data sources to get a picture of the current burden and likely trends in CVD in a population. There is a long history of standardisation of cardiovascular survey methods, with international collaboration for comparing trends within countries and between countries. The World Health Organization (WHO) published the first edition of cardiovascular survey methods in 1968 (Rose *et al.* 1982). Standardised survey and registration methods were also utilised in the WHO MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) Project with the overall objective of monitoring trends in CVD mortality and morbidity, and its determinants (Tunstall-Pedoe *et al.* 1994). The project monitored coronary events from the mid-1980s to the mid-1990s. In the recent years, the European Society of Cardiology has initiated several Euro Heart Surveys concerning CAD.

In Estonia, different epidemiological aspects of AMI have been investigated episodically in 1960–1970 in Tallinn and Tartu (Randvere 1970; Riiv 1979). It was found that indicators of morbidity and mortality of AMI were comparable with the others cities from the Former Soviet Union, but they remained stable during this period. The Tallinn Registry of AMI, although not part of the WHO MONICA project, followed the protocol of this project in data collection. This registry collected data during 1991–1997 and covered the 25–64 year-old population officially residing in Tallinn. Based on the data of this registry, acute CAD events had alarmingly high occurrence and case fatality during this period (Laks 2002).

As several studies have reported, the decline in CAD mortality is due to the combined effects of a decline in incidence, recurrence and case fatality of AMI (Rosamond *et al*. 1998; Tunstall-Pedoe *et al.* 1999; McGovern *et al*. 2001; Salomaa *et al.* 2003). One explanation for these changes is the growing effectiveness of the treatment of AMI and secondary prevention methods (Rosamond *et al*. 1998; Capewell *et al*. 1999; Tunstall-Pedoe *et al.* 2000; Heidenreich and McClellan 2001). Scientific studies have shown that improved emergency and hospital care, with new, rapid diagnostics and monitoring, new drugs and access to early invasive coronary procedures, improves both survival and quality of life, shortens hospitalisation, and accelerates rehabilitation to work.

However, gaps between medical care as actually practiced and the recommendations derived from evidence-based research are widespread and vary between hospitals and countries (Gottwik *et al*. 2001; Fox *et al*. 2002; Luthi *et al*. 2005). In order to improve quality of care given to AMI-patients and to contribute to decrease in morbidity and mortality, a comprehensive knowledge about every-day clinical diagnostic and management strategies, as well as outcome, is essential. International practice shows that prospective clinical registries, where all cases are registered, reflect the "real-world" situation of every-day practice most accurately (Zeymer and Senges 2003). In Estonia, regular evaluation of treatment modalities and outcomes, and subsequent use of this as a basis for systematic improvement efforts, has not previously been a standard procedure. Data from the Tallinn Registry of AMI enable data analysis in selected population group — aged 25–64 years. Based on literature sources, two-thirds of hospitalised AMI patients are older than 65 years (Tran *et al.* 2004). In addition, little data (thrombolysis, percutaneous coronary intervention, coronary artery bypass grafting) about in-hospital treatment has been collected. Therefore, there is a lack of information about different aspects of hospitalised AMI patients in Estonia. At the same time, the European Society of Cardiology has started the surveys to assess clinical practice in relation to existing guidelines and to assess the outcome of different management strategies.

Special attention has been paid in recent years to women with AMI, and to diabetic and elderly AMI patients. Numerous studies have shown that female (Malacrida *et al*. 1998; Hanratty *et al*. 2000), diabetic (Wahab *et al.* 2002; Otter *et al*. 2004), and elderly patients (Mehta *et al.* 2001; Ruiz-Bailén *et al*. 2002) have worse outcome after AMI. One possible reason for this is underutilisation of evidence-based medicine in these groups compared to the other AMI groups. Diabetes is a rapidly expanding disease worldwide, leading to the increased prevalence of CAD, including AMI (Haffner *et al.* 1998; King *et al*. 1998). Much research has been devoted during the last few years to the clarification of the impact of hyperglycaemia on patient outcome. Hyperglycaemia on admission in AMI patients enhances the risk of morbidity and mortality independent of a history of diabetes (Capes *et al*. 2000; Wahab *et al*. 2002; Stranders *et al*. 2004). Acute hyperglycaemia might be a new and modifiable risk factor during AMI (Ceriello 2005). The number of elderly patients with AMI is growing continuously due to the ageing of the population and their mortality has remained high (Goldberg *et al.* 1998).

The aim of this study was to evaluate the adherence to AMI management guidelines in two types of hospitals in Estonia, to assess the impact of gender and age on management and outcome of AMI patients and to evaluate the associations of diabetes and hyperglycaemia with respect to outcome for AMI patients.

2. REVIEW OF THE LITERATURE

2.1. Definition of acute myocardial infarction

The European Society of Cardiology consensus document regarding the redefinition of myocardial infarction was published in September 2000 (Joint European Society of Cardiology/American College of Cardiology Committee 2000). The recent introduction of cardiac troponins into routine daily clinical practice allows for highly accurate, sensitive and specific determination of myocardial injury. Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI: 1) typical rise and fall of biochemical markers (troponin T/I, CK-MB/CK-MB mass, CK) and one of the following: a) ischaemic symptoms; b) development of pathologic Q waves; c) ECG changes indicative of ischaemia; d) coronary artery interventions; 2) pathologic findings of an AMI by autopsy. Previous WHO diagnosis for AMI required the presence of two of the following three features: symptoms of myocardial ischemia, enzyme rise, and a typical ECG pattern involving the development of Q waves or persistent T wave changes (Report of the Joint International Society and Federation of Cardiology 1979). With the use of new sensitive biomarkers of myocardial necrosis, it has to be considered that the epidemiological incidence and prevalence of AMI have been altered. The committee for redefinition of MI suggested that their recommendations would increase the incidence of AMIs and reduce case fatality. In contrast, more precise diagnosis would lessen the number of false positive AMIs. Studies have already demonstrated that the new definition of AMI increased the number of patients with non-ST elevation acute coronary syndromes (ACS) receiving a diagnosis of AMI (Ferguson *et al*. 2002; Trevelyan *et al*. 2004). Therefore, such changes in definition might have a profound effect on the traditional monitoring of disease rates and outcomes and it might be difficult to compare current and future public health statistics dealing with AMI data from earlier eras. However, this is not a valid reason to hold onto old definitions of AMI, which no longer reflect current scientific thinking. Established definitions of AMI (e.g., Minnesota code, WHO MONICA) should be retained by specific epidemiologic centres for comparison with previously collected data. The redefinition of AMI will continue to have broad implications, not just for epidemiological research, but also for individual patients, patient` care and government policies.

2.2. Acute myocardial infarction mortality

General aspects

Approximately 16.7 million deaths from CVD occur every year globally, 7.2 million due to CAD (World Health Organization 2004). Acute coronary syndromes, which encompass Q-wave AMI, non-Q-wave AMI and unstable angina, are a common cause of emergency hospital admission and a major cause of mortality worldwide. The true number of AMIs is difficult to establish for different reasons: the common occurrence of silent infarction, the frequency of acute coronary death outside hospital and the varying methods used in the diagnosis of the condition.

Developed countries have shown a marked decline in CAD mortality during the past three decades (Sans *et al.* 1997; Capewell *et al*. 1999; Tunstall-Pedoe *et al*. 2000; Heidenreich and McClellan *et al*. 2001). Many studies have demonstrated that the decline in CAD mortality is due to the combined effects of a decline in incidence, recurrence and case fatality of AMI (Rosamond *et al.* 1998; Tunstall-Pedoe *et al*. 1999; McGovern *et al*. 2001; Salomaa *et al.* 2003).

AMI mortality trends

Community studies have consistently shown that the overall fatality of acute heart attacks in the first months is between 30% and 50%, and of these deaths about one-half occur within the first 2 h (Armstrong *et al.* 1972; Tunstall-Pedoe *et al.* 1999). This high initial mortality has altered little over the last 30 years (Norris 1998). By contrast, there has been a significant fall in the fatality of those patients treated in hospital. In the 1950s, patients with AMI were admitted for a protracted period to a general medicine ward without ECG or physiological monitoring (Theroux *et al*. 2000). Prior to the introduction of coronary care units in the 1960s, the in-hospital mortality was 25–30% (Norris *et al*. 1974). A systematic review of mortality studies in the pre-thrombolytic era of the mid 1980s showed an average fatality of 16% (de Vreede *et al*. 1991). The results of recent randomised clinical trials performed in patients with acute ST-elevation MI (STEMI) have shown that the short-term mortality is around 5–6% or even less (Topol *et al*. 2001; Antman *et al*. 2002). In the recent European Heart Survey, mortality in patients presenting with ST-segment elevation ACS was 8.4% at 1 month (Hasdai *et al*. 2002). That would imply that there is little room for improvement in efforts to reduce mortality in hospitalised patients with AMI. Unfortunately, this is not the “real world” situation. It has been well recognised that patients enrolled in randomised clinical trials are highly selected and represent in most cases a low risk subgroup of patients with AMI. A more realistic view of mortality and morbidity from AMI arises from prospective clinical registries. Based on the data of these registries the “real” in-hospital mortality ranges today from 9–15% (Buiatti *et al*. 2003; Stenestrand and Wallentin 2004; Terkelsen *et al*. 2005).

Reasons for AMI mortality decline

Decline of AMI mortality during the last decades is partially due to increased use of effective treatments and secondary prevention methods (Rosamond *et al.* 1998; Capewell *et al*. 2000; Heidenreich and McClellan 2001; McGovern *et al*. 2001). There is overwhelming evidence that reperfusion therapy (thrombolysis, primary percutaneous angioplasty) reduces morbidity and mortality in AMI patients (Second International Study of Infarct Survival Collaborative Group 1988; Fibrinolytic Therapy Trialists' Collaborative Group 1994; Zijlstra *et al*. 1999). Numerous clinical trials have demonstrated the benefits of adjunctive therapies (aspirin, beta-blockers, heparins, ACE inhibitors) for AMI patients with no contraindications (First International Study of Infarct Survival Collaborative Group 1986; Latini *et al.* 1995; Freemantle *et al*. 1999, Flather *et al.* 2000). Heidenereich and McClellan (2001) have shown that 71% of the decrease in 30-day mortality in Medicare AMI patients during 20 years (1975–1995) can be explained by the increase in the usage of aspirin, beta-blockers, ACE inhibitors and reperfusion therapy. Of the given therapies, aspirin had the greatest effect, followed by thrombolysis, primary angioplasty, beta-blockers, and ACE inhibitors. Therefore, one possibility to decrease CAD morbidity and mortality is to improve the treatment quality of AMI patients.

2.3. Adherence to guidelines of acute myocardial infarction management in clinical practice

The past decade has witnessed a rapid evolution in therapeutic options for patients with AMI. These changes reflect improved understanding of pathogenic mechanisms and the impact of a complex array of clinical trials. Based on analyses of the published trial data, meta-analyses, and registries data, guideline groups from the American College of Cardiology, the American Heart Association and the European Society of Cardiology have reached largely consistent interpretations and recommendations. There is convincing evidence that treatment of AMI according to guidelines is associated with better outcome. Nevertheless, substantial gaps between every-day clinical practice and the recommendations derived from evidence-based research are common (Hasdai *et al*. 2002; Steg *et al.* 2002). Studies have shown large variations in practice patterns for management of AMI, not only between but also within countries (Gottwik *et al*. 2001; Matsui *et al*. 2001; Luthi *et al*. 2005). Many physicians do not have a sufficient number of patients with a particular condition to establish a typical practice pattern. Analysis of Australian national mortality data revealed an excess of deaths due to AMI in the population living outside the capital city, raising concerns that management of AMI may be less optimal in community than in tertiary care hospitals (Sexton and Sexton 2000). Numerous studies have shown that physicians who practice in tertiary care settings show better

adherence to guidelines than physicians in other settings (Jollis *et al*. 1996; Casale *et al.* 1998; Gottwik *et al*. 2001). The most reasonable explanation for this difference is that tertiary care physicians are more familiar with current recommendations and have more experience in the treatment of AMI.

Thus, a major need for the improvement of treatment quality exists, in order to offer effective cardiac care on equal terms to all patients.

2.4. Possibilities to improve treatment quality for acute myocardial infarction patients

Several regional quality assurance and improvement projects for AMI-subjects have been published (Marciniak *et al.* 1998; Mehta *et al*. 2004). In order to improve quality of care given to AMI-patients, a comprehensive knowledge about present-day diagnostic and treatment strategies, as well as hospital-associated outcomes, is essential. To accomplish this aim, national and international registries and surveys have been created, which help to evaluate time trends in the quality of care, the adherence to guidelines, and the implementation of new therapies. The multinational Global Registry of Acute Coronary Events (GRACE) project was established to provide robust, real-life, population-based treatment data for patients with an ACS. The GRACE study reveals substantial differences in the management of patients, based on hospital type and geographical location (Fox 2000; Fox *et al.* 2002; Steg *et al*. 2002). Also the Euro Heart Survey of ACS demonstrated the discordance between existing guidelines for ACS and current practice, across a broad region in Europe (Hasdai *et al*. 2002). The most well known national registries are — NRMI (National Registry of Myocardial Infarction) in the United States and RIKS-HIA (The Register of Information and Knowledge about Swedish Heart Intensive care Admissions) in Sweden (Gibson 2004; Stenestrand and Wallentin 2004). The NRMI is one of the oldest and largest registries of AMI. The NRMI has identified processes of care associated with worse outcomes in AMI patients, one of the most significant being time-to-treatment. The success and profound impact of the NRMI and RIKS-HIA studies are well recognised: they have improved our understanding of AMI and enabled us to assess treatment approaches, identify trends in risk factors and characteristics, evaluate performance, and drive quality improvement (French 2000; Gibson 2004).

2.5. Registry data versus randomized clinical trials data

Patients enrolled in clinical trials are generally younger and healthier than those who present to the same institutions and are not included. Clinical registries have systematically shown that routine clinical practice deals with sicker patients and faces higher morbidity and mortality than the artificial environment

of strictly defined randomized-controlled trials. Recently, there has been an increase in the number and proportion of women that have participated in clinical trials, although many early CVD trials did not include women and other important subpopulations (diabetics, elderly patients) (Lee *et al*. 2001). It is known that the level of care may be substantially affected by the patient`s enrolment in trials. Information received from clinical trial databases in selected centres and patients may reflect distinct differences in practice for patients with AMI, as compared with strategies used in every-day practice. Furthermore, because many patients seen in clinical practice may have characteristics that are not similar to those of clinical trial participants, it is necessary to draw inferences about the likelihood that data can be generalized from research to clinical settings. Clinical prospective registries are the link between randomized clinical trials, guidelines, and daily clinical practice (Zeymer and Senges 2003; Urban 2005).

Based on the data from clinical registries, it is possible to find the risk groups of AMI patients whose worse outcome may be related to less frequent use of evidence-based treatment modalities. During the last years much attention has been given to the following special patients groups with AMI — women, the elderly and diabetics.

2.6. Gender differences in acute myocardial infarction

General aspects

CVD is the leading cause of death in most countries, in men, as well in women. CVD is the largest single cause of mortality among women, accounting for one-third of all deaths in women worldwide (World Heart Federation Fact-Sheet, 2002). The incidence of CVD in women over 70 years of age is similar to that of men, and recent reports indicate that currently a larger number of women than men die from CVD in the United States and the gap continues to widen (American Heart Association 1999). Because of this, in 2004 the American Heart Association started the campaign “Go Red for Women”, designed to raise awareness in both women and healthcare professionals that heart disease is the greatest threat to women`s health (Jacobs and Eckel 2005). The European Society of Cardiology launched its new initiative “Women at Heart” in 2005. “Women at Heart” is aimed at medical professionals, to highlight the growing burden and under-appreciation of women’s heart disease and to promote the improved handling of women at risk of CVD in clinical practice (European Society of Cardiology 2005).

Gender differences in cardiovascular care and outcome have been studied in numerous epidemiological and clinical studies (Ayanian and Epstein 1991; Wenger *et al*. 1993; Hasdai *et al.* 2003). Gender differences in the clinical features, management, and outcome of AMI patients have been investigated, but results have been inconsistent (Becker *et al.* 1994; Kudenchuk *et al.* 1996;

Weaver *et al*. 1996; Vaccarino *et al*. 1999; Gan *et al* 2000; Mahon *et al*. 2000; Alter *et al*. 2002; Heer *et al*. 2002; Carrabba *et al*. 2004; Griffith *et al*. 2005). Generally women are considered to have a worse prognosis after AMI. Explanations have included gender-related differences in pathophysiology and response to treatment, prehospital delays in symptom recognition and action, in the usage of evidence-based treatment as well as management strategies.

Gender differences in clinical characteristics and management of AMI patients

There is conflicting information about gender differences in clinical characteristics and management of AMI patients. Most investigations have shown that women are older than men when they experience AMI and women have a higher prevalence of hypertension, diabetes and congestive heart failure (Kostis *et al*. 1994; Stone *et al*. 1995; Kober *et al*. 1996; Kudenchuck *et al*. 1996; Malacrida *et al*. 1998; Gottlieb *et al*. 2000; Mahon *et al*. 2000; Heer *et al*. 2002; Mehilli *et al*. 2002). However, the management for AMI should be the same for women as for men, because multiple studies have shown equal benefits for both sexes (Woodfield *et al*. 1997; Mehilli *et al*. 2002; Carrabba *et al*. 2004). Some studies have found that women are less likely to be treated with aspirin (Vaccarino *et al*. 1999; Gan *et al*. 2000) and beta-blockers (Goldberg *et al*. 1993; Chu *et al*. 1998; Vaccarino *et al*. 1999), but more likely to be treated with digitalis (Goldberg *et al*. 1993; Vaccarino *et al*. 1999). Researchers have reported that women are less likely to be given thrombolysis and to undergo invasive coronary interventions than men (Kostis *et al*. 1994; Kober *et al*. 1996; Kudenchuk *et al*. 1996; Maynard *et al*. 1997; Gan *et al*. 2000; Heer *et al*. 2002). Several studies have shown that women are less likely to receive thrombolysis even after adjustment for ineligibility due to older age, comorbid conditions, and late arrival (Gan *et al*. 2000; Heer *et al*. 2002). One consideration is that women experience more frequently atypical symptoms (Herlitz *et al*. 1999; Patel *et al*. 2004) associated with AMI, which has been suggested to account for misdiagnosis of AMI and consequent mistreatment in female patients, particularly in younger age group. It is noteworthy that not all studies were able to demonstrate that AMI symptoms in men and women differ.

Less aggressive diagnostic and management strategies for women than for men have been claimed to reflect a "gender bias" (Alter *et al*. 2002). However, not all studies have found important gender differences in the delivery of evidence-based treatment of AMI. Many studies have focused on gender as an isolated entity when determining its relationship to treatments, ignoring its interaction with other biological factors such as age. Researchers have found greater similarity in medical management for both gender groups after adjustment for age or other confounding covariates (Hanratty *et al*. 2000; Mahon *et al*. 2000; Alter *et al*. 2002). The age-dependent effects of gender may account for inconsistencies in findings across studies examining gender variations in treatments after AMI (Kostis *et al*. 1994; Vaccarino *et al*. 1995). Age seems to be a more important determinant of the process of care than gender.

Gender differences in mortality of AMI patients

During recent years the question of whether female gender is an independent predictor of mortality after AMI has been much debated. This question still remains unanswered. Numerous studies have found that women have poorer outcomes than men after AMI (Kober *et al*. 1996; Kudenchuk *et al*. 1996; Malacrida *et al*. 1998, Hanratty *et al.* 2000). It is frequently reported that women with AMI are older and have more comorbidities, and that these characteristics may be responsible for the higher mortality in women. A systematic review identified 17 studies published before 1995 that compared short-term mortality rates after AMI between women and men (Vaccarino *et al*. 1995). The review concluded that much, though perhaps not all, of the higher mortality rate among women was explained by their older age and the presence of more unfavourable prognostic factors. In addition, women have more complications after AMI than men, such as congestive heart failure, cardiogenic shock, infarct extension, and cardiac rupture (Goldberg *et al*. 1993; Maynard *et al*. 1997; Malacrida *et al*. 1998; Gan *et al*. 2000; Gottlieb *et al.* 2000; Mahon *et al*. 2000; Heer *et al.* 2002). Some studies have found a similar outcome (short- and long-term) in men and women after adjustment for age and other prognostic factors (Goldberg *et al*. 1993; Vaccarino *et al*. 1998; Gan *et al*. 2000), whereas others failed to show the impact of age and risk factors on the higher mortality rates in women (Stone *et al.* 1995; Kudenchuck *et al*. 1996; Malacrida *et al*. 1998; Mahon *et al*. 2000).

Reports have demonstrated an age-gender mortality interaction for AMI, so that younger women, not older ones, have higher mortality rates compared with men (Demirovic *et al*. 1995; Vaccarino *et al*. 1998; Mahon *et al*. 2000; Zubaid *et al*. 2001). It is supposed that the reason lies in a higher rate of comorbid conditions in younger women compared to men (Vaccarino *et al*. 1998; Rosengren *et al.* 2001). For example, diabetes has been found to negate the protective effect of female gender against CAD and death from CVD (Sowers 1998) and to be a stronger prognostic factor after AMI in women than in men (Donahue *et al*. 1993; Rosengren *et al*. 2001). One explanation is that AMI is less typical in women than in men, especially at younger ages, and it is possible that less severe cases of AMI are more often missed in women (Vaccarino *et al.* 1998; Mahon *et al.* 2000). A population-based study has suggested that the age-gender mortality interaction among patients with AMI may be attributable to selection bias or a survivor effect arising from gender differences in the rates of out-of-hospital deaths. The excess deaths occurring out of hospital in men offset the excess risk for death following admission to hospital in younger women (MacIntyre *et al*. 2001).

Explanations for inconsistencies of results

Considering inconsistent information in the area of in-hospital management, as well as early and long-term outcome of AMI, additional research is warranted to investigate further gender differences. Vaccarino *et al.* (1995) suspected that

conflicting information between results of studies may be explained by differences in patient selection, study design, and methods used. It is accepted that registries consisting of unselected consecutive cases of AMI provide more comprehensive and accurate data reflecting the real situation compared to data derived from clinical trials.

2.7. Age and acute myocardial infarction

General aspects

The elderly are the fastest-growing group within the population in most countries. CAD is highly prevalent and accounts for the majority of disabilities and deaths in elderly people. Based on the data of Goldberg *et al.* (1998), 25.4% of patients with AMI were aged ≥75 years during the 1975/78 period, whereas 38.4% were aged ≥75 years in the 1993/1995 period. A recently published study has shown that two thirds of hospitalised AMI patients were aged ≥ 65 years (Tran *et al.* 2004). Thus, the number of elderly patients experiencing AMI is growing, emphasizing the importance of examining trends in outcomes in elderly and very elderly patients (Gottlieb *et al.* 1997; Goldberg *et al.* 1998; Reikvam *et al*. 2002). Many of the randomized clinical trials evaluating the effects of therapeutic interventions in the setting of AMI have excluded patients aged ≥75 years, thereby providing only limited insight into the natural history and mortality patterns of these high-risk patients.

AMI mortality trends in elderly patients

Hospital mortality of elderly patients with AMI remains high (Ruiz-Bailén *et al.* 2002), although mortality after AMI declined in the 1990s with the introduction of new therapeutic modalities. Trends of improving long-term prognosis have been discovered in patients discharged in the mid-1990s compared with those discharged in the mid-to late 1970s, for patients aged <85 years (Goldberg *et al*. 1998). The results demonstrate the marked impact of advancing age on survival after AMI (Gurwitz *et al*. 1994; Goldberg *et al.* 1998; Mehta *et al*. 2001; Ruiz-Bailén *et al*. 2002). Despite the adverse impact of age on prognosis, encouraging trends in prognosis were observed in all age groups, although to a lesser extent in very elderly patients. Researchers suggest that changes in therapeutic management may have contributed to the improved outcome and suggest that these be used more in elderly patients too (Goldberg *et al.* 1998).

Elderly patients have an increased prevalence of poor prognostic factors, including diabetes, previous MI, congestive heart failure, hypertension, stroke and transient ischemic attack (Goldberg *et al*. 1998; Ruiz-Bailén *et al*. 2002; Rathore *et al*. 2003). As a consequence of this increasing risk profile, these patients may benefit from the application of evidence-based therapy aimed at reducing the burden of ACS to even a greater degree than younger patients.

However, rates of potentially life saving and life enhancing cardiological interventions have been reported to vary widely by age (Mehta *et al*. 2001).

Effects of age on AMI treatment

Previous quality of care studies, most of which were conducted in the United States, have documented the underuse of invasive cardiac procedures and evidence-based treatments for AMI in elderly patients (McLaughlin *et al*. 1996; Spencer *et al*. 2001; Rathore *et al*. 2003; Avezum *et al*. 2005; Collinson *et al*. 2005). Despite their adverse clinical profile, older patients are less likely to be treated with therapies shown be beneficial in elderly AMI patients. Suboptimal treatment of elderly patients with ACS has been reported, even when data from "ideal" candidates for these therapies were analysed (Krumholz *et al*. 1998; Tran *et al*. 2004; Avezum *et al*. 2005), indicating that the decision has been based primarily on age. It has been suggested that variations in care may reflect ageism or bias against the use of medical therapy or intensity of medical care in elderly patients (Bowling 1999).

Several factors may contribute to age-associated variations in treatment. Elderly patients are more likely to have an atypical presentation of AMI, delayed presentation and nondiagnostic electrocardiograms (Bayer *et al*. 1986; Devlin *et al*. 1995; Aronow *et al*. 1996; Then *et al*. 2001; Avezum *et al*. 2005), and the resulting uncertainty in the diagnosis may explain why age-associated variations in therapy use are greater on admission than at discharge (Rathore *et al*. 2003). Although advanced age is considered a high-risk feature in recently released international guidelines, the use of new antithrombotic medications and of an aggressive approach is still the subject of controversy. The uncertainty about treatment strategies is further increased by the fact that elderly patients are frequently excluded from randomised trials by enrolment criteria as well as by the limited information available about the outcome of such patients undergoing different treatment modalities. Clinicians may believe that benefits in younger patients may not generalize to elderly patients.

Therapy-specific considerations may also explain differences in treatment. Variations in the use of acute reperfusion therapy likely reflect uncertainty about the appropriate use of thrombolytic therapy in elderly patients. While a meta-analysis of randomised controlled trials of thrombolytic therapy suggests benefit in older patients (Fibrinolytic Therapy Trialists´ Collaborative Group 1994), observational assessment has suggested harm in patients over 75 years of age (Thiemann *et al*. 2000). Concerns about the risk of bleeding, particularly intracranial haemorrhage, are of paramount concern when clinicians decide on the use of thrombolytic therapy in elderly patients. At the same time, clinical studies have shown that compared with thrombolysis, primary angioplasty in elderly patients with AMI is associated with better clinical outcomes and a lower risk of bleeding complications (de Boer *et al*. 2002; Goldenberg *et al*. 2003).

However, elderly patients may not receive optimal treatment for AMI, despite the availability of proven, scientific evidence. On the basis of ethics and clinical knowledge, age should not be used as a determining factor in treatment decisions, yet this continues to be the case (Bowling 1999).

2.8. Diabetes and acute myocardial infarction

General aspects

Type 2 diabetes, a presently rapidly expanding disease, is a major risk factor for CVD morbidity and mortality (Haffner *et al*. 1998). The number of adults with diabetes in the world is predicted to rise from 135 million in 1995 to 300 million in the year 2025 (King *et al*. 1998). Diabetes is associated with a marked increase in the risk of CAD. Diabetic patients without previous MI have as high a risk of AMI as nondiabetic patients with previous MI (Haffner *et al.* 1998). The increased risk for CAD is apparent already at modestly elevated levels of blood glucose that are still below the present threshold for diabetes (Coutinho *et al*. 1999; DECODE Study Group 2003).

The Euro Heart Survey on diabetes and the heart demonstrated that normal glucose metabolism is less common than abnormal glucose regulation in CAD patients (Bartnik *et al.* 2004). Diabetic patients with CAD and ACS, including AMI, have worse outcomes than nondiabetic patients after these events (Haffner *et al*. 1998; Norhammar *et al*. 2003; McGuire *et al*. 2004; Otter *et al.* 2004). Diabetic patients have more extensive concomitant cardiovascular risk factors, poor cardiac reserve and diffuse CAD (Granger *et al*. 1993). It has been demonstrated that several evidence-based treatment strategies are less frequently utilized among patients with diabetes mellitus (Norhammar *et al*. 2003; Schnell *et al*. 2004), which could be the reason for higher mortality.

Hyperglycaemia and AMI outcome

– *Definitions and meaning of hyperglycaemia in AMI patients*

Hyperglycaemia is a common finding among AMI patients on admission in diabetic and non-diabetic patients. Different thresholds of glucose level are used to define stress hyperglycaemia in AMI patients, ranging from 5.6 mmol/l to 11.0 mmol/l (on admission), or from 6.1 to 8.0 mmol/l (fasting, the morning after admission) (Capes *et al*. 2000; Bolk *et al*. 2001). Because of this, studies have shown different prevalence of hyperglycaemia in AMI patients. Several studies have reported a relationship between elevated blood glucose in the early phase of AMI and a subsequent increase in adverse events, including congestive heart failure, cardiogenic shock, and death, in patients both with and without diabetes mellitus (Capes *et al*. 2000; Bolk *et al*. 2001; Wahab *et al*. 2002; Foo *et al*. 2003; Stranders *et al*. 2004). It has been shown that patients without diabetes who were hyperglycaemic at the time of their AMI admission had an almost 4-

fold higher risk of death than those who had normal glucose levels (Capes *et al*. 2000).

Among patients with no previous history of diabetes, acute phase hyperglycaemia may reflect undiagnosed diabetes, impaired glucose tolerance, a response to severe stress or a combination of these (Yudkin and Oswald 1987; Capes *et al*. 2000; Umpierrez *et al*. 2002). A recent report showed that among patients with unknown diabetes at the time of AMI and blood glucose less than 11.0 mmol/l on admission, impaired glucose tolerance was detected in 40% and new-onset diabetes in 25% three months after discharge (Norhammar *et al*. 2002). Tenerz *et al.* (2001) have shown that 50% of those with admission blood glucose >11.0 mmol/l turned out to have diabetes. Although the diagnosis of diabetes can not be made on the basis of a single blood glucose level measurement (Report of the Expert Committee on the Diagnosis and Classifications of Diabetes Mellitus 2002), casual blood glucose levels of 11.1 mmol/l or more may suggest the existence of diabetes, and as a consequence, the risk of mortality after AMI may be disproportionately high in this group and should be evaluated separately.

A relatively worse outcome has been shown in the hyperglycaemic AMI population without known diabetes compared to hyperglycaemic patients with known diabetes (Capes *et al*. 2000; Wahab *et al*. 2002), and this still warrants explanation.

– *Mechanisms of the association between hyperglycaemia and poor outcome from AMI*

At present, it is unclear whether stress hyperglycaemia is merely a marker for more severe disease or whether it has any direct deleterious effect on ischemic myocardium. However, the observation that use of insulin to lower glucose concentration at the time of the infarction improves the outcome makes the opinion that “stress hyperglycaemia” may simply be an epiphenomenon of the stress response unlikely (Davies and Lawrence 2002). The underlying mechanism of hyperglycaemia is considered to be related to the rise in stress hormones, leading to relative insulin deficiency, but it may also reflect the presence of pancreatic beta-cell dysfunction. Insulin deficiency is associated with increased lipolysis and excess circulating free fatty acids. Free fatty acids, although normally the substrate of choice for healthy myocardium, are toxic to ischaemic myocardium and may lead to damaged cardiac cell membranes and calcium overload. These changes may reduce myocardial contractility, lead to pump failure, and may promote arrhythmias (Vetter *et al.* 1974; Oliver and Opie 1994).

Acute hyperglycaemia is known to abolish the effect of ischemic preconditioning, probably through attenuation of mitochondrial adenosine triphosphate-regulated potassium channel activation (Kersten *et al*. 1998). It has been shown that prodromal angina pectoris within 24 hours before AMI was associated with enhanced improvement of left ventricular function and survival

after AMI, which was lost in patients with acute hyperglycaemia, regardless of the presence of diabetes (Ishihara *et al*. 2003). Hyperglycaemia may cause dehydration leading to volume depletion, decreased stroke volume, and output failure of the compromised left ventricle (Holubarsch *et al*. 1996). In addition, acute hyperglycaemia may induce oxidative stress, adversely affecting platelet function (Sakamoto *et al*. 2000), coagulation and fibrinolysis (Jain *et al*. 1993), as well as various endothelial functions (Giugliano *et al.* 1997; Williams *et al.* 1998).

Consequently, hyperglycaemia at the time of AMI in patients with and without diabetes may be an important and potentially modifiable risk factor for poor outcome (Ceriello 2005).

– *Treatment of hyperglycaemia in AMI patients*

Many studies have evaluated the importance of controlled glucose concentration in the early phase of AMI (Malmberg *et al*. 1997; Diaz *et al*. 1998). It has been shown that tight glycaemic control by insulin infusion significantly reduces morbidity and mortality in critically ill subjects admitted to a surgical intensive care unit (van den Berghe *et al*. 2001). Recent works have additionally also revealed several morbidity benefits of intensive insulin therapy, such as the protection of mitochondrial integrity and function (Vanhorebeek *et al*. 2005), and the prevention of sepsis, anaemia, and organ failure in intensive care patients (van den Berghe *et al.* 2003). The current evidence suggests that the patient`s glycometabolic status is important during the peri-infarct period, and that glucose-insulin-potassium (GIK) infusion is likely to have some role in the acute management of AMI. GIK solution was proposed for the first time by Sodi-Pallares in 1962 as a polarizing agent to promote electrical stability in AMI (Sodi-Pallares *et al.* 1962). Subsequent studies used GIK with the intention of providing metabolic support to the myocardium during AMI and glycaemic control. At the same time, clarification is required regarding the appropriate insulin/glucose doses, the need to include potassium as part of the infusion, and the type of patients who would derive most benefit, before this treatment gains widespread acceptance (Wong *et al*. 2003). Further studies are warranted to clarify uncertainties in glycose-insulin treatment of AMI patients.

3. OBJECTIVES OF THE STUDY

The general objective of this study was to provide information about clinical aspects of hospitalised AMI patients, their management and outcome in Estonia.

Accordingly, the present study had the specific objectives:

1. To compare treatment of AMI patients between tertiary and secondary care hospitals.
2. To compare the baseline characteristics, management and 30-day mortality of AMI in men and women.
3. To assess age-related differences in the risk factors, management and in-hospital mortality of patients with AMI.
4. To determine the relation between hyperglycaemia on admission, previously known diabetes and 180-day mortality in AMI patients.

4. SUBJECTS AND METHODS

4.1. Subjects

Subjects in Study I

Two tertiary and seven secondary care hospitals responsible for the treatment of most AMI patients in Estonia were included into the analysis. Hospitals were classified based on the availability of pecutaneous coronary intervention. A random sample of patients admitted to these hospitals due to an AMI in 2001 was taken from the Estonian Health Insurance Fund database. During the period 1 January to 31 December 2001, 2686 hospitalised cases with AMI diagnosis (2365 individuals) were found [diagnosis code I21–I22 according to International Classification of Diseases 10th Revision (ICD-10)] (World Health Organization 1992). For the purposes of our research the following exclusion criteria were applied: 1) cases in which patients were re-admitted with AMI within 28 days of the first admission, in order to identify initial hospitalisation; 2) a length of stay less than 3 days if the patient was discharged alive and not transferred to another hospital; 3) patients who were not admitted to the hospitals studied. A stratified (by type of hospitals) random sample (N=520) was derived from the remaining cases (N=1955). Forty of the cases were excluded due to selection errors by the Health Insurance Fund. 210 cases from tertiary and 213 cases from secondary care hospitals with confirmed AMI diagnoses were included in the subsequent analysis.

Subjects in Study II, III and IV

These studies included patients from the Estonian Myocardial Infarction Registry (EMIR), who were admitted to the Tartu University Clinics between January 2001 and December 2003. Study II included patients who were admitted between January 2001 and February 2002. Exclusion criteria for this study were transfer from another hospital and development of AMI after coronary artery bypass grafting or invasive cardiac procedures. Study III included patients who were admitted between January 2001 and December 2003. Exclusion criterion was transfer from another hospital. Study IV included all patients with available admission plasma glucose between January 2001 and December 2002. Table 1 shows data about the number of eligible patients, mean age and proportions of women in each study.

Table 1. Baseline characteristics of the four studies constituting the thesis

Study number	Number of patients	Mean age±SD, years	Percentage of women
Study I	423	68.3±12.5	40.7
Study II	395	68.9±12.5	42.3
Study III	1201	69.1±12.2	41.4
Study IV	779	67.7±12.7	41.5

SD – standard deviation.

4.2. Methods

Diagnostic criteria for AMI

The criteria for the AMI diagnosis were based on the consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction (Joint European Society of Cardiology/American College of Cardiology Committee 2000). AMI criteria consisted of the typical rise and fall of biochemical markers (troponin T, CK-MB mass) and one of the following: a) ischemic symptoms; b) development of pathologic Q waves; c) ECG changes indicative of ischemia. In addition, for patients who died and for whom no cardiac markers were obtained, or cardiac marker(s) were negative because of the short time of attack onset, the presence of new ST-segment elevation and new chest pain were considered to meet the criteria for AMI.

Data collection

The EMIR is an Internet-based secure database for the collection of data on unselected patients with AMI who have been treated in hospitals joined to the registry. The registry was initiated in January 2001 in the Tartu University Clinics. Information on a pre-specified form that comprises 78 variables with definitions was completed by physicians at discharge or, if the patient died, on the day of death. The form includes personal identification data, risk factors, symptoms, ECG description, complications during hospital stay, pharmacological treatment, interventional procedures, peak of biochemical markers, cholesterol values, discharge diagnosis according to ICD-10, mortality, date of admission and discharge. This form has been approved by the Scientific Council of EMIR. The data completeness in registry was ascertained by regular review of the discharge lists of the hospital. Records of patients with ICD-10 codes of I21–I22, present on the list of discharge but not in the registry, were checked and evaluated for registration.

Standardized data collection form in Study I included additional data to the EMIR form — medication recommendations at discharge. Medical records were reviewed by trained experts using this collection form. Data quality was monitored by random reabstractions for determining the causes of discrepancies and was followed by retraining of experts.

A retrospective medical record review was conducted for Study IV. More detailed information was obtained from patient records in addition to the data collected in the registry. This included laboratory data (glucose, creatinine), and clinical data on admission.

Mortality follow-up

Mortality rate at 30 days and 180 days was assessed by matching the personal identification number of patients with the data of the Estonian Population Registry, which includes the vital status of the population of Estonia.

Definitions and data analysis

STEMI was defined if on admission electrocardiogram presented ST-segment elevation of ≥1 mm in 2 or more contiguous leads, or a new left bundle branch block (Study I, II, III, IV).

Out-of-hospital resuscitation was defined as cardiopulmonary resuscitation due to cardiac arrest before reaching hospital (Study II, IV).

Typical symptoms of AMI were defined as chest pain or pressure.

To examine effect of age, the patients were stratified into five age groups: <55 years, 55–64 years, 65–74 years, 75–84 years, ≥85 years (Study III).

Hyperglycaemia was defined as a blood glucose level >11.0 mmol/l on admission (Study IV).

Diabetes mellitus was considered to be present if a patient had been informed of this diagnosis and was on prescribed antidiabetic treatment (Study IV).

To assess an association between hyperglycaemia on admission, known diabetes mellitus and 180-day mortality, patients were stratified into four groups, based on their history of diabetes mellitus and glycaemic status on admission (Study IV).

Statistical methods

All analyses were performed with the STATA program version 6.0 or 8.1 (Stata user`s guide 1997). The continuous variables are presented in tables as mean ± SD or as median. Differences between categorical variables were tested by Pearson chi-square statistic; continuous variables were compared by t test or Mann-Whitney U test. Analysis of variance was used to compare continuous variables between study groups (Study III, IV). Logistic regression analysis was used to estimate crude and adjusted odds ratio (OR) with 95 percent confidence interval (95% CI) (Study I, II, IV). Age trends were assessed by using the nonparametric test for categorical variables and quantile regression of medians for continuous variables (Study III).

Survival proportions were calculated with the Kaplan-Meier method and differences between survival curves were assessed by the log-rank test (Study IV).

The rate ratio (RR) with 95% confidence intervals was displayed as a ratio of the rate in tertiary care hospitals to the rate in secondary care hospitals, and it was calculated with software Compare2, version 1.31 (Abramson 2001) (Study I). $P<0.05$ was considered statistically significant.

5. RESULTS

5.1. Impact of hospital type on treatment of acute myocardial infarction patients

Baseline characteristics

Baseline characteristics are summarized in Table 2. Mean age of patients was similar in two types of hospitals. Proportion of female patients was higher in secondary care hospitals. Hypertension was more prevalent among the patients of tertiary care hospitals. Smoking status of patients was not documented in the medical records in 40% of cases in tertiary care hospitals and in 46% of cases in secondary care hospitals. After exclusion of cases with unknown smoking status, current smokers constituted 21.4% of patients admitted to tertiary and 18.3% of those admitted to secondary care hospitals. Lipid profiles (previous known cholesterol values or cholesterol measurements during 24 hours of index hospital admission) were found in medical records in 39.5% of cases in tertiary compared to 33.8% of cases in secondary care hospitals.

Table 2. Baseline characteristics of AMI patients in tertiary and secondary care hospitals in Estonia, 2001

	Tertiary care hospitals N=210	Secondary care hospitals N=213	RR (95% CI)	p
Age, years (mean)	68.3±12.7	68.3±12.4		0.942
<75 years, %	69.1	65.7	1.05 (0.92–1.20)	0.467
Men, %	66.7	52.1	1.28 (1.09–1.50)	0.002
Hypertension, %	70.0	57.3	1.22 (1.06–1.41)	0.007
Diabetes, %	19.1	16.4	1.16 (0.77–1.75)	0.481
Previous MI, %	29.5	23.9	1.23 (0.90–1.69)	0.195
Previous chronic heart failure, %	27.1	26.8	1.01 (0.74–1.39)	0.929
STEMI, %	61.4	56.3	1.09 (0.93–1.28)	0.287
Anterior MI, %	36.7	34.7	1.06 (0.82–1.36)	0.680
Length of stay, days (median)	10.0	12.0		0.031

MI — myocardial infarction; STEMI — ST-elevation myocardial infarction.

In-hospital management

The use of pharmacological and reperfusion therapy is shown in Table 3. ACE inhibitors and statins were used more frequently in tertiary care hospitals. Usage of reperfusion therapy was equal in secondary and tertiary care hospitals. The median time from admission to the start of thrombolytic therapy was 0.67 hours and did not differ substantially among patients admitted to different types of hospitals (0.58 hours in tertiary and 0.70 hours in secondary care hospitals, p=0.627).

Table 3. In-hospital treatment of AMI patients in tertiary and secondary care hospitals in Estonia, 2001

	Tertiary care hospitals, % N=210	Secondary care hospitals, % N=213	RR (95% CI)	p
Aspirin	87.1	88.3	0.99 (0.92–1.06)	0.726
Beta-blockers	79.5	76.1	1.05 (0.94–1.16)	0.391
ACE inhibitors	70.5	37.1	1.90 (1.56–2.31)	<0.001
Statins	26.7	5.6	4.73 (2.61–8.57)	<0.001
Any reperfusion therapy in STEMI patients	42.6	43.3	0.98 (0.74–1.31)	0.912
Thrombolysis in STEMI patients	34.9	43.3	0.81 (0.59–1.10)	0.172
Primary PCI in STEMI patients	7.7	NA		–

ACE inhibitors — angiotensin converting enzyme inhibitors; STEMI — ST-elevation myocardial infarction; PCI — percutaneous coronary intervention; NA — PCI facilities not available in secondary care hospitals.

In-hospital mortality and complications

In-hospital mortality and complications are presented in Table 4.

Table 4. In-hospital mortality and complications of AMI patients in tertiary and secondary care hospitals in Estonia, 2001

	Tertiary care hospitals, % N=210	Secondary care hospitals, % N=213	Unadjusted OR (95% CI)	[1]Adjusted OR (95% CI)
VF/asystole	14.3	14.6	0.98 (0.59–1.76)	1.02 (0.59–1.79)
Cardiogenic shock	13.3	17.4	0.73 (0.43–1.24)	0.81 (0.47–1.39)
Pulmonary oedema	12.4	16.0	0.74 (0.43–1.25)	0.86 (0.48–1.51)
Reinfarction	4.3	0.9	4.72 (1.01–22.12)	4.31 (0.90–20.65)
Death	13.8	16.9	0.79 (0.46–1.34)	0.86 (0.50–1.49)

VF — ventricular fibrillation.

[1] — by multivariate logistic regression analysis adjusting for gender and hypertension.

Medications at discharge

ACE inhibitors and statins were recommended at discharge more frequently in tertiary, and nitrates in secondary care hospitals (Table 5).

Table 5. Treatment recommendations for AMI patients at discharge in tertiary and secondary care hospitals in Estonia, 2001

	Tertiary care hospitals, % N=181[1]	Secondary care hospitals, % N=163[1]	RR (95% CI)	p
Aspirin	85.1	79.8	1.07 (0.97–1.18)	0.193
Nitrates	61.9	85.3	0.73 (0.64–0.83)	<0.001
Beta-blockers	71.3	68.7	1.04 (0.90–1.19)	0.605
Calcium antagonists	21.6	14.1	1.53 (0.95–2.44)	0.073
ACE inhibitors	66.3	37.4	1.77 (1.42–2.22)	<0.001
Statins	31.5	14.5	2.14 (1.39–3.28)	<0.001

ACE inhibitors — angiotensin converting enzyme inhibitors.

[1] Proportions of medication recommendation were calculated per patient discharged alive and not transferred.

5.2. Gender differences in acute myocardial infarction patients

Baseline characteristics

Baseline characteristics are shown in Table 6. Women were significantly older than men and had more comorbidity. The prevalence of diabetes, hypertension and history of chronic heart failure remained significant after adjustment for age. The initial cholesterol values were higher in women. Women had a longer delay from pain to admission. Also the mean time from pain onset to thrombolysis was slightly longer for women than for men.

Table 6. Gender differences in baseline characteristics of acute myocardial infarction in the Tartu University Clinics, January 2001–February 2002

	Women N=167	Men N=228	p	Women vs men	
				Unadjusted OR (95% CI)	Age-adjusted OR (95% CI)
Age, years (mean)	73.49±10.95	65.63±12.60	0.000		
≥ 75 years, %	52.1	25.0	0.000		
Current smoking, %	8.4	26.3	0.000	0.25 (0.13–0.47)	0.51 (0.25–1.04)
Diabetes, %	28.7	13.2	0.000	2.65 (1.59–4.42)	2.48 (1.45–4.24)
Hypertension, %	59.9	40.8	0.001	2.02 (1.34–3.05)	1.78 (1.15–2.76)
Previous MI, %	31.1	32.0	0.976	0.99 (0.64–1.53)	0.80 (0.50–1.27)
Previous chronic heart failure, %	51.5	25.4	0.000	3.22 (2.08–4.97)	2.14 (1.32–3.46)
Current attack					
Cardiac arrest outside hospital, %	3.0	6.6	0.108	0.44 (0.16–1.23)	0.52 (0.18–1.52)
ST-elevation on initial ECG, %	52.2	47.9	0.355	0.81 (0.54–1.22)	0.91 (0.59–1.40)
Q-wave MI, %	50.3	56.6	0.307	0.81 (0.54–1.21)	0.86 (0.56–1.32)
Anterior MI, %	43.7	37.3	0.197	1.31 (0.87–1.96)	1.31 (0.85–2.01)
Within 4 hours hospitalisation, %	36.5	48.7	0.024	0.62 (0.41–0.94)	0.56 (0.36–0.87)
Mean time from pain onset to thrombolysis (h)	4.32±2.56	3.46±1.93	0.091		
Length of stay, days (mean)	9.56±4.84	9.44±4.09	0.793		
S-chol (mmol/l)	5.69±1.43	5.28±1.33	0.006		

ECG — electrocardiogram; MI — myocardial infarction.

In-hospital management

In-hospital management is presented in Table 7. Women were less often treated with glycoproteins IIb/IIIa inhibitors and statins but more often treated with digitalis and diuretics. After age-adjustment, the difference that remained was that women were treated more often with diuretics and less often with statins. The other medication used was similar for both sexes. Further adjustment for age and other covariates did not significantly change these ORs. Thrombolytic therapy was less frequently used in women than in men, a difference that already disappeared after age-adjustment. Coronary angiography and PCI were performed less frequently in women than in men, these differences were lost after adjustment for age alone.

Table 7. Gender differences in the management of acute myocardial infarction in the Tartu University Clinics, January 2001–February 2002

	Women, % N=167	Men, % N=228	p	Women vs men		
				Unadjusted OR (95% CI)	Age-adjusted OR (95% CI)	Age- and other covariates adjusted[1] OR (95% CI)
Aspirin	92.2	93.0	0.538	0.78 (0.36–1.71)	0.79 (0.34–1.83)	0.76 (0.26–2.24)
Anticoagulants	90.4	90.8	0.716	0.88 (0.43–1.79)	1.06 (0.50–2.24)	1.23 (0.52–2.89)
ACE inhibitors	71.9	63.6	0.136	1.39 (0.90–2.15)	1.36 (0.86–2.16)	1.33 (0.77–2.31)
Beta-blockers	68.3	74.6	0.110	0.70 (0.45–1.09)	0.91 (0.57–1.47)	0.83 (0.49–1.42)
Calcium antagonists	26.3	20.2	0.159	1.40 (0.87–2.25)	1.43 (0.87–2.37)	1.42 (0.80–2.52)
Digitalis	19.2	10.5	0.017	1.99 (1.12–3.52)	1.61 (0.88–2.93)	1.18 (0.58–2.38)
Diuretics	74.9	44.7	0.000	3.56 (2.30–5.51)	2.68 (1.69–4.25)	2.55 (1.52–4.28)
Glycoproteins IIb/IIIa inhibitors	5.4	12.3	0.022	0.41 (0.19–0.90)	0.75 (0.32–1.75)	0.71 (0.29–1.76)
Inotropic agents	27.5	22.8	0.300	1.28 (0.81–2.02)	1.15 (0.71–1.87)	1.42 (0.80–2.50)
Statins	33.5	53.1	0.000	0.45 (0.30–0.68)	0.61 (0.39–0.96)	0.64 (0.39–1.05)
Nitrates	91.0	91.2	0.719	0.88 (0.43–1.80)	0.99 (0.46–2.12)	1.00 (0.40–2.49)
Thrombolysis	15.6	25.4	0.016	0.53 (0.32–0.89)	0.62 (0.36–1.06)	0.76 (0.39–1.51)[2]
Coronary angiography	19.8	39.0	0.000	0.38 (0.24–0.60)	0.68 (0.39–1.17)	0.74 (0.40–1.36)
PCI	15.6	26.3	0.011	0.52 (0.31–0.87)	0.96 (0.54–1.72)	1.00 (0.53–1.89)
CABG	1.2	1.3	0.916	0.91 (0.15–5.50)	1.70 (0.27–10.84)	1.48 (0.20–10.91)

ACE inhibitors — angiotensin converting enzyme inhibitors; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention.

[1] By multivariate logistic regression analysis adjusting for age, diabetes, hypertension, previous myocardial infarction, previous chronic heart failure, anterior infarction, thrombolysis; [2] By multivariate logistic regression analysis adjusting for age, diabetes, hypertension, previous myocardial infarction, previous heart failure, ST-elevation on initial electrocardiogram, anterior infarction.

In-hospital complications and 30-day mortality

The rate of in-hospital complications (Table 8) was similar in both genders, except for pulmonary oedema. After adjustment for age the difference disappeared; only reinfarction tended to be more frequent in men than in women. 30-day mortality was 13.2% of men and 17.4% of women (p=NS), unadjusted odds ratio for women compared with men was 1.39 (95% CI 0.80-2.41). Adjustment for age reduced the odds ratio to 1.03 (95% CI 0.57-1.85) (Table 6). Further adjustments for age, diabetes, hypertension, previous infarction, previous heart failure, cardiac arrest outside hospital, Q-wave infarction, and anterior infarction also reduced the odds ratio (OR 0.98, 95% CI 0.44-2.20). Additional adjustment for other covariates of treatment (thrombolysis, PCI, beta-blockers, aspirin and ACE inhibitors) revealed similar results. When patients were examined by age group, women younger than 65 years of age tended to have a higher mortality than men (Figure 1).

Table 8. Gender differences in in-hospital complications of acute myocardial infarction in the Tartu University Clinics, January 2001–February 2002

	Women, % N=167	Men, % N=228	p	Women vs men		
				Unadjusted OR (95% CI)	Age-adjusted OR (95% CI)	p
VF/asystole	18.0	13.6	0.250	1.38 (0.79–2.38)	1.16 (0.65–2.05)	0.623
Cardiogenic shock	15.0	11.4	0.312	1.35 (0.75–2.44)	1.19 (0.64–2.23)	0.585
Pulmonary oedema	17.4	9.2	0.017	2.06 (1.13–3.76)	1.63 (0.86–3.07)	0.131
Reinfarctus	1.8	4.4	0.159	0.40 (0.11–1.49)	0.30 (0.08–1.15)	0.079
Stroke	6.0	3.1	0.155	2.02 (0.75–5.43)	2.38 (0.83–6.84)	0.107

VF — ventricular fibrillation.

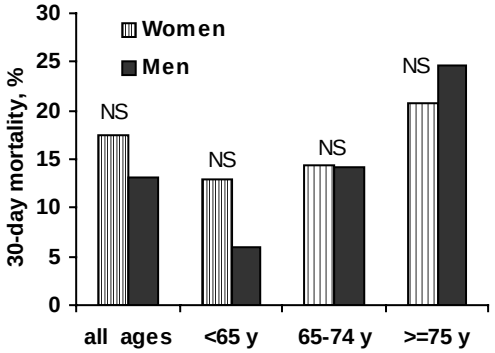

Figure 1. The 30-day mortality of women and men with acute myocardial infarction by age groups in the Tartu University Clinics, January 2001–February 2002.
NS — nonsignificant ($p<0.05$).

5.3. Age-related differences in acute myocardial infarction patients

Baseline characteristics

The baseline characteristics of the patients according to age are shown in Table 9. Two thirds of patients were older than 65 years. The proportion of women increased with advancing age. Elderly patients had more hypertension, previous MI, and history of chronic heart failure. Current smoking was more prevalent in the younger groups. The prevalence of diabetes was higher in patients aged 65–74 years. Typical AMI symptoms were less manifested in very elderly patients. STEMI was more frequent in younger patients. Pre-hospital delay was longer in the elderly groups.

Table 9. Baseline characteristics of acute myocardial infarction patients stratified by age in the Tartu University Clinics, 2001–2003

	<55 years N=186	55–64 years N=210	65–74 years N=383	75–84 years N=336	≥85 years N=86	p	Age trend, p
Mean age, years	48.26±5.81	60.64±3.00	70.39±2.87	79.47±2.63	88.55±2.65		
Male, %	86.6	74.3	60.1	37.8	34.9	0.00	0.00
Current smoking, %	60.2	37.1	11.9	3.0	2.3	0.00	0.00
Diabetes, %	9.1	20.0	24.1	22.2	16.3	0.00	0.01
Hypertension, %	36.0	53.8	57.5	61.0	52.3	0.00	0.00
Previous MI, %	24.7	28.1	32.9	46.1	44.2	0.00	0.00
Previous chronic heart failure, %	9.1	20.9	41.4	57.4	70.9	0.00	0.00
Hyperlipidemia, %	57.0	63.8	59.3	50.9	33.7	0.03	0.12
Typical symptoms, %	87.1	85.2	79.6	82.1	68.6	0.01	0.00
STEMI	67.7	57.6	49.1	53.3	47.7	0.00	0.00
Anterior MI, %	46.8	43.8	36.0	42.9	38.4	0.11	0.24
Q-wave MI, %	59.1	49.5	45.1	44.0	32.6	0.00	0.00
Pre-hospital delay, h (median)	3.66	3.08	4.57	5.05	5.96	0.05	0.01
Length of stay, days (median)	8.00	9.00	9.00	9.00	7.00	0.02	1.00

MI — myocardial infarction; STEMI — ST-elevation myocardial infarction; PCI — percutaneous coronary intervention.

In-hospital management

In-hospital management in different age groups is presented in Table 10. Only usage of aspirin was similar in all age groups. There were no large differences in the usage of anticoagulants, beta-blockers and ACE inhibitors between age groups, except in very elderly patients (≥85 years). Usage of statins, glycoprotein IIb/IIIa inhibitors and clopidogrel showed clear age trends.

Age trends were also clearly revealed in receiving of reperfusion therapy and performing invasive procedures — they were used less frequently in elderly patients.

In-hospital mortality

In-hospital mortality increased with age (Figure 2). In the youngest groups, mortality rates were 7.6% and 7.8%, compared with 36.1% among those aged ≥85years.

Table 10. In-hospital management of acute myocardial infarction patients stratified by age in the Tartu University Clinics, 2001–2003

	<55 years, % N=186	55–64 years, % N=210	65–74 years, % N=383	75–84 years, % N=336	≥85 years, % N=86	p	Age trend, p
Aspirin	91.9	94.8	91.4	91.7	87.2	0.29	0.17
Anticoagulants	93.0	93.3	90.4	91.4	82.6	0.03	0.02
ACE inhibitors	67.7	67.6	70.5	73.5	51.2	0.00	0.63
Beta-blockers	76.9	76.2	70.6	69.9	51.2	0.00	0.00
Clopidogrel	38.7	38.1	16.7	9.2	–	0.00	0.00
Ticlopidine	2.7	3.8	1.0	0.3	–	0.01	0.00
Glycoprotein IIb/IIIa inhibitors	24.2	17.6	8.5	4.5	–	0.00	0.00
Calcium antagonists	22.0	24.3	30.6	26.5	15.1	0.02	0.92
Diuretics	30.1	43.3	57.2	70.8	79.1	0.00	0.00
Inotropic agents	19.9	24.8	26.4	26.2	40.7	0.01	0.00
Digitalis	7.5	6.7	13.7	17.9	17.4	0.00	0.00
Nitrates	81.7	88.1	88.9	91.1	79.1	0.00	0.19
Statins	63.4	58.1	44.6	26.5	11.6	0.00	0.00
Any reperfusion therapy in STEMI patients	60.3	52.0	42.5	23.5	12.2	0.00	0.00
Thrombolysis in STEMI patients	38.1	41.3	32.4	22.9	12.2	0.00	0.00
Primary PCI in STEMI patients	22.2	10.7	10.1	0.6	–	0.00	0.00
Coronary angiography	71.0	64.8	45.1	16.7	1.2	0.00	0.00
PCI	47.2	45.7	22.3	9.8	–	0.00	0.00
CABG	2.7	3.8	3.1	1.2	–	0.15	0.05

ACE inhibitors — angiotensin converting enzyme inhibitors; STEMI — ST-elevation myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting.

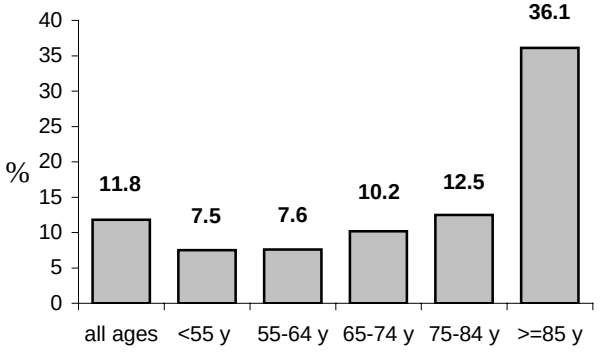

Figure 2. In-hospital mortality of acute myocardial infarction patients stratified by age in the Tartu University Clinics, 2001–2003.

5.4. The associations between hyperglycaemia on admission, previously known diabetes, and acute myocardial infarction mortality

Baseline characteristics, laboratory and clinical findings on admission

Patient baseline characteristics in the four study subgroups are shown in Table 11. Patients who were not previously known to have diabetes but who had hyperglycaemia in the diabetic range on admission made up 14% of the total. There were no differences in the mean age between groups. In diabetic groups, the proportion of women and of hypertension was higher than in groups without a history of diabetes. AMI characteristics were similar for all groups. Left ventricular ejection fraction was lower in the diabetics groups and in the non-diabetic hyperglycaemic group compared to the "normal" group. Laboratory data and clinical findings on admission are presented in Table 12. The non-diabetic hyperglycaemic patients had undergone significantly more cardio-pulmonary resuscitation outside hospital and they had the highest creatinine value on admission. Hyperglycaemic patients, independent of their history of diabetes, had more cardiogenic shock and pulmonary oedema on admission.

Table 11. Patient baseline characteristics according to diagnosis of diabetes and glycaemic status in the Tartu University Clinics, 2001–2002

	Non-diabetic Glc ≤11.0mmol/l N=556	Non-diabetic Glc >11.0mmol/l N=109	Diabetic Glc ≤11.0mmol/l N=30	Diabetic Glc >11.0mmol/l N=84	p
Age, years (mean)	67.2±13.1	68.7±13.3	70.1±10.4	68.8±9.8	0.379
Male, %	63.2	59.6	43.3	36.9	<0.0001
Current smoking, %	25.1	19.2	10.0	10.7	0.015
Hypertension, %	48.7	44.0	86.7	77.4	<0.0001
Previous MI, %	23.7	33.9	36.7	32.1	0.047
Previous chronic heart failure, %	26.4	46.8	63.3	51.2	<0.0001
STEMI, %	57.9	61.5	50.0	64.3	0.276
Anterior MI, %	37.8	46.8	30.0	42.9	0.204
Q-wave MI, %	51.4	47.7	43.3	53.6	0.536
LVEF, %	50.9±12.3	46.7±13.8	44.2±14.6	47.2±13.3	0.204

Glc — glucose; MI — myocardial infarction; STEMI — ST-elevation myocardial infarction; LVEF — left ventricular ejection fraction.

Table 12. Patient laboratory data and clinical findings on admission according to diagnosis of diabetes and glycaemic status in the Tartu University Clinics, 2001–2002

	Non-diabetic Glc ≤11.0mmol/l N=556	Non-diabetic Glc >11.0mmol/l N=109	Diabetic Glc ≤11.0mmol/l N=30	Diabetic Glc >11.0mmol/l N=84	p
Glucose (mmol/l)	7.3±1.6	15.8±4.7	8.5±2.2	19.0±7.4	<0.0001
Creatinine (micromol/l)	111.9±37.1	137.6±57.5	136.3±65.0	120.5±32.1	<0.0001
Out-of-hospital resuscitation, %	2.0	31.2	6.7	6.0	<0.0001
Cardiogenic shock, %	0.5	8.3	0.0	6.0	<0.0001
Pulmonary oedema, %	4.0	22.9	10.0	15.5	<0.0001

Glc — glucose.

In-hospital management

In-hospital management is shown in Table 13. Aspirin, ACE inhibitor and statins were used less in patients with hyperglycaemia without previously known diabetes.

There was a tendency to use thrombolysis less frequently in non-diabetic hyperglycaemic and diabetic normoglycaemic patients.

180-day mortality

180-day mortality was significantly higher in the non-diabetic hyperglycaemic group than in the others (47.7% vs. non-diabetic non-hyperglycaemic 14.1% vs. diabetic non-hyperglycaemic 26.7% vs. diabetic hyperglycaemic 29.8%, $p<0.0001$). Figure 3 shows the comparable effects of “hyperglycaemia on admission” and “history of diabetes” on 180-day survival. Hyperglycaemic status on admission, independent of history of diabetes, was the predictor of 180-day mortality before adjustment (hyperglycaemic non-diabetic OR 5.58, 95% CI 3.57–8.71; hyperglycaemic diabetic OR 2.59, 95% CI 1.53–4.38). After adjustment for the potentially confounding factors (age, gender, hypertension, previous myocardial infarction, previous chronic heart failure, Q-wave infarction, anterior infarction, resuscitation outside hospital, creatinine, left ventricular ejection fraction, thrombolysis, aspirin, beta-blockers, ACE inhibitors, statins), hyperglycaemic non-diabetic (OR 4.35, 95% CI 1.79–10.59, $p=0.001$), but not diabetic (OR 1.79, 95% CI 0.62–5.15, $p=0.258$) status, remained an independent predictor. Further adjustment with insulin reduced the odds ratio (non-diabetic hyperglycaemic OR 3.64, 95% CI 1.41–9.37; diabetic hyperglycaemic OR 0.90, 95% CI 0.24–3.40).

Table 13. Patient in-hospital management according to diagnosis of diabetes and glycaemic status in the Tartu University Clinics, 2001–2002

	Non-diabetic Glc ≤11.0mmol/l, % N=556	Non-diabetic Glc >11.0mmol/l, % N=109	Diabetic Glc ≤11.0mmol/l, % N=30	Diabetic Glc >11.0mmol/l, % N=84	p
Aspirin	95.5	80.7	90.0	94.1	<0.0001
ACE inhibitors	64.2	58.3	73.3	77.1	0.036
Beta-blockers	75.3	75.9	76.7	69.1	0.642
Statins	53.9	30.6	46.7	47.0	<0.0001
Oral hypoglycemic agents	0.0	9.4	66.7	79.5	<0.0001
Insulin	1.8	25.2	40.0	69.1	<0.0001
Thrombolysis	25.1	16.7	10.0	22.6	0.082
Primary PCI	7.4	6.4	3.3	3.6	0.516

Glc — glucose; ACE inhibitors — angiotensin converting enzyme inhibitors; PCI — percutaneous coronary intervention.

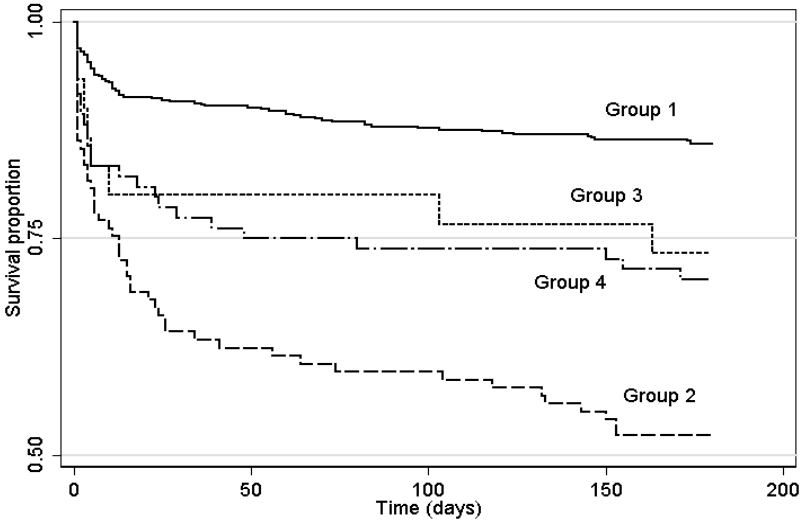

Figure 3. Kaplan-Meier estimates of survival after AMI according to study groups (log rank test for all comparisons, p<0.0001). Group 1 — no previous diagnosis of diabetes and glucose on admission ≤11.0mmol/l; Group 2 — no previous diagnosis of diabetes and glucose on admission >11.0 mmol/l; Group 3 — known diabetes and glucose on admission ≤11.0mmol/l; Group 4 — known diabetes and glucose on admission >11mmol/l.

6. DISCUSSION

6.1. Patients and methods

During the past decade, there has been increased interest in measuring and improving the quality of health care. Health information systems are essential for monitoring the extent to which the aims of the health services are being achieved. Increasing attention has been paid in recent years to the substantial scientific potential of routine medical information systems. Administrative data are readily available, are inexpensive to acquire, are computer readable, and typically encompass large populations. However, gaps in clinical information and the billing context compromise the ability to derive valid quality assessment from administrative data. In addition, questions about the accuracy, completeness and clinical details of administrative data arise (Iezzoni 1997).

In 2001, local guidelines for management of AMI were not implemented in Estonia. However, the use of European and American guidelines (Task Force of the European Society of Cardiology 1996; Committee on Management of Acute Myocardial Infarction 1999) was recommended by the Estonian Society of Cardiology. As a first step in harmonization process of AMI treatment activities in Estonia with Western experience, the guidelines for the management of patients with ACS (AMI, unstable angina) were elaborated and issued in 2002 by Acute Coronary Syndromes Working Group of Estonian Society of Cardiology (Acute Coronary Syndromes Working Group of Estonian Society of Cardiology 2002).

The Estonian health insurance system is a social insurance and it relies on the principle of solidarity. On December 31, 2001, 93.9% of the population of Estonia (1 278 086 of 1 361 200 inhabitants) was insured. Estonian Health Insurance Fund database has information about the health care provided, including medical claims for all hospital stays and outpatient visits, and prescription claims for reimbursable medicines. Related to the above-mentioned limitations of an administrative database, we used the Health Insurance Fund database to obtain a random sample of AMI patients from different Estonian hospitals. Retrospective medical records review by trained experts using a standardized data collection form was performed for the purpose of the study. The limitation of our study is that a high proportion of patients were not included in the study, which can cause selection bias. Although medical records were selected at random, it is possible that the findings are not generalizable to the larger population.

Data about the “real world” situation of AMI patients comes from well-designed prospective national and international registries. In order to develop high-quality services and to ensure efficiency, it is necessary to get comprehensive data about unselected real-life patients, their risk profile, every-day diagnostic and management strategies as well as hospital-associated outcomes.

Myocardial infarction registries, including indicators of treatment quality, are helpful for evaluating the adherence to guidelines, for adapting national guidelines according to local possibilities and for working out treatment quality improvement projects in order to decrease morbidity and mortality among AMI patients and to increasing cost effectiveness. In our study, we used data from the EMIR on patients, who were admitted to the Tartu University Clinics during three years. The registry includes all patients who have a discharge diagnosis of AMI, independent of the department where patients were admitted (not only coronary care unit patients, but also cardiology and internal medicine patients with this diagnosis) and independent of pre-hospital delay time. These data reflect every-day clinical practice patients, their management and outcome in one hospital. Of course, using single-centre data it is possible that the findings are not generalizable to the larger population, especially as concerns treatment and outcome.

6.2. Impact of hospital type on treatment of acute myocardial infarction patients

The current study shows that in 2001, tertiary care physicians adhered more strongly to the guidelines on the treatment of AMI than secondary care physicians. This study is further observational evidence of the fact that management of AMI patients differs depending on the type of hospital (Casale *et al.* 1998; Gottwik *et al.* 2001; Fox *et al.* 2002). However, treatment strategies for AMI need more attention and standardising according to international guidelines in both tertiary care and secondary care hospitals.

Baseline characteristics

In the present study, the patient´ groups of the different types of hospitals were similar in most characteristics, except for the proportion of women and the prevalence of hypertension. This may be the result of chance or a consequence of simple randomisation procedure. Previous studies have found similar findings no great difference in patient characteristics and prevalence of concomitant disease between the two types of hospital (Gottwik *et al.* 2001; Scott *et al*. 2003). This study clearly demonstrated insufficient reporting of smoking status in medical records in both types of hospitals in Estonia. Similar findings have also been reported by others (van Berkel *et al*. 1999). In addition, the lipid profiles of patient were often not known or were not measured according to recommendations.

In-hospital management and complications

Reperfusion therapy and adjunctive medical therapy with aspirin, beta-blockers, and ACE inhibitors have been proven to reduce mortality in AMI patients (First

International Study of Infarct Survival Collaborative Group 1986; Freemantle *et al.* 1999; Flather *et al.* 2000). In the present study, the use of reperfusion treatment is fairly similar in different types of hospitals. At the same time, more than 50% of ST-elevation AMI patients did not receive reperfusion therapy. The proportion of nonreperfused patients is larger compared to the findings of other studies (Hasdai *et al*. 2002; Steg *et al.* 2002). This finding sets a clear target for improvement and challenges each hospital to carefully review this aspect. The median door-to-drug (thrombolysis) time was 40 min and did not differ between tertiary and secondary care hospitals. The results from large registries confirm that educational programmes and local in-hospital guidelines are urgently needed in order to shorten this time-delay (Zeymer and Senges 2003). Delays in reperfusion therapy of AMI patients directly correlate to mortality (Gibson 2004). The rate of primary PCI was so low because, at this time Estonia had only two hospitals with catheterization laboratories, which operated 5 days/week during working hours.

We found similar utilisation of beta-blockers and aspirin in both hospital settings. However, these medications are underused in Estonian hospitals and further improvement is required. Wide variation between hospitals existed in the usage of ACE inhibitors and statins. The most reasonable explanation for this difference is that tertiary care physicians are more familiar with current recommendations. The variation in use of statins may be related to current uncertainty about the early use of statins following a cardiac event. The use of glycoprotein IIb/IIIa inhibitors observed in the present study was very low compared to recommendations. The efficacy of this therapy in AMI patients has been established in cases of PCI; the benefit in other settings has to be confirmed and discussed on the basis of local health-care resources and knowledge in smaller hospitals in Estonia.

The results of our study are in accordance with previous studies (Fox *et al*. 2002; Scott *et al*. 2003), where large differences between hospital types regarding complications and in-hospital death rate were not detected. Some studies have reported lower in-hospital mortality in AMI patients treated at cardiology departments. They explain these differences with more frequent use of aspirin, beta-blockers and ACE inhibitors, as well as the higher rate of reperfusion therapy at these departments (Jollis *et al.* 1996; Gottwik *et al*. 2001).

Treatment recommendations at discharge

ACE inhibitors and statins were less frequently recommended at discharge by physicians at secondary care hospitals, compared to tertiary care hospitals. The overall rate of statins recommendation at discharge was 23.1%, despite their established efficacy in long-term secondary prevention. In 2001, it might partly have been related to the quite high cost of statins and other unknown subjective factors. In addition, there were more frequently recommendations for the use of nitrates in the discharge summaries of secondary care hospitals although there is no evidence that nitrates improve prognosis after AMI.

6.3. Gender differences in acute myocardial infarction patients

Results of our study contribute to the opinion that management and outcome difference in men and women with AMI largely reflect an issue of "age bias" rather than "gender bias".

Baseline characteristics

Our findings are in accordance with previous studies (Kostis *et al*. 1994; Kober *et al*. 1996; Kudenchuck *et al*. 1996; Malacrida *et al*. 1998; Gottlieb *et al*. 2000; Mahon *et al*. 2000; Heer *et al*. 2002; Mehilli *et al*. 2002), which have shown that women and men were different in their risk profiles: women are older and have a higher prevalence of hypertension, diabetes mellitus, history of congestive heart failure, and higher cholesterol values, but the prevalence of cigarette smoking is more common in men.

In-hospital management

As there is no evidence that women obtain less benefit from the usage of evidence-based management strategies than men with AMI, these should be applied equally in men and women. However, some studies have found management bias (Chu *et al*. 1998; Vaccarino *et al*. 1999; Gan *et al*. 2000). Many studies have reported treatment similarity for both sexes after adjustment for age and covariates (Hanratty *et al*. 2000; Mahon *et al*. 2000; Alter *et al*. 2002). In the present study, after adjustment for age we found no evidence of differences in the use of treatments for AMI, except diuretics and statins. Diuretics were used significantly more frequently in women than in men, probably due to a greater prevalence of hypertension, congestive heart failure and pulmonary oedema in women. The reason why the women were treated less with statins is unclear. At the same time, initial cholesterol values were higher in women. It may be that we have a real gender bias in the usage of statins.

With regard to thrombolysis treatment, our findings matched those of previous studies (Gottlieb *et al*. 2000; Mahon *et al*. 2000). Any differences disappeared after adjustment for age and clinical variables. Although, some reports have shown that women were less likely to receive thrombolysis even after adjustment for confounding factors (Gan *et al.* 2000, Heer *et al.* 2002). In this study, the time from pain onset to arrival was longer in women, but there were no differences in the presence of typical symptoms (83.3% in men vs 78.4% in women, p=0.19).

Women had undergone less coronary angiography and revascularization than men. These differences disappeared after age adjustment. Our findings are in accordance with studies reporting similar rates of these procedures in men and women (Gottlieb *et al*. 2000; Mahon *et al*. 2000), but differ in this regard from others (Kostis *et al*. 1994; Vaccarino *et al*. 1999; Heer *et al*. 2002).

In-hospital complications and 30-day mortality

Many studies have reported higher complication rates in women with AMI compared with men (Maynard *et al*. 1997; Malacrida *et al.* 1998; Gan *et al*. 2000; Heer *et al*. 2002), also after adjustment for age (Mahon *et al*. 2000). In our study, both sexes had the same rate of in-hospital complications. It might be that the relative small sample used in our study has insufficient power to detect small differences. After age-adjustment, men tended to have more reinfarction; this may be due to more frequent intra-arterial manipulations. 8 cases of 10 reinfarctions in men were connected with angiography or PCI. It should be noted that the occurrence of cardiogenic shock in our population was more frequent than that shown in the other studies (Malacrida *et al*. 1998; Gottlieb *et al.* 2000). The reasons for these differences are not clear. One explanation might be the high percentage of previous heart failure in this unselected study group. Another consideration could be that an emergency medical aid system in this area is well organized, so that the patients who usually die outside hospital room reach the hospital. However, there is lack of data to support this idea.

There is conflicting data about gender differences in the early mortality of AMI patients after adjustment for age and other prognostic factors. Some researchers have shown a similar outcome in men and women after such adjustment (Goldberg *et al*. 1993; Gan *et al*. 2000), whereas others have not (Kober *et al*. 1996; Maynard *et al*. 1997; Malacrida *et al.* 1998; Mahon *et al*. 2000). Based on the Tallinn Acute Myocardial Infarction Registry data collected according to the MONICA protocol, there was no in-hospital mortality difference between men and women aged 25–64 years for the period 1991–1994 (11.9 % in men vs 12.6% in women) (Laks *et al*. 1999). Among unselected consecutive patients with AMI, our study showed similar 30-day mortality rates in men and women before adjustment. There was a slightly higher crude mortality for women, but this was insignificant. Female gender was not an independent predictor of mortality after age and covariates adjustment.

In addition, many reports have demonstrated an age-gender mortality interaction for AMI — only younger women have higher mortality rates than their male counterparts (Vaccarino *et al*. 1998; Mahon *et al*. 2000; Rosengren *et al.* 2001). In the present study, women aged under 65 years had a mortality rate that was almost twice as high as that of men (12.9% vs 6.0%, respectively). This result did not reach statistical significance, probably due to the small sample size. Studies from the Scottish and Glasgow MONICA projects have found that higher in-hospital mortality among younger women may be due to a difference in pre-hospital mortality between younger men and women, with more men dying before hospital (Sonke *et al.* 1996; Tunstall-Pedoe *et al*. 1996). One limitation of our study is that we analysed only hospitalised AMI cases.

6.4. Age-related differences in acute myocardial infarction patients

Our study demonstrated that elderly patients with AMI had an increased prevalence of poor prognostic factors, they less often received evidence-based therapies for AMI and had a higher in-hospital mortality.

Baseline characteristics

The results of the present study are in agreement with previous findings (Goldberg *et al.* 1998; Ruiz-Bailén *et al*. 2002; Rathore *et al*. 2003): compared to younger patients, the elderly patients are more likely to include a greater proportion of women, those with comorbidities, and persons who were more likely to have had a previous MI. Among traditional risk factors, smoking was the only factor inversely related to age, as others too have shown. This finding has been reported and suggests that either smoking may not be an important risk factor for AMI in elderly patients, or that smokers may have a shorter survival post CAD and therefore rarely reach an advanced age (Mehta *et al.* 2001). Pre-hospital delay is common among elderly patients, also in our study. This may be explained by the increasing frequency of atypical clinical presentations, cognitive impairment, and the presence of comorbidities that can mask a diagnosis of AMI (Aronow *et al*. 1996; Then *et al*. 2001). Therefore, such a high-risk population should be more cautiously evaluated to avoid significant delays after arrival in hospital and to reduce the likelihood of missing the diagnosis of AMI.

In-hospital management

Our study confirmed the results of others investigations (Goldberg *et al*. 1998; Ruiz-Bailén *et al*. 2002; Rathore *et al*. 2003) that, despite the adverse clinical profile of elderly patients, they were less likely to be treated with therapies shown to be beneficial in the management of AMI. Evidence-based medications were used significantly less frequently in very elderly patients compared to the other study groups, what has also been reported earlier (Goldberg *et al*. 1998). Because elderly patients may be more likely to have contraindications to therapy, one limitation of our study is that we did not identify patients who were eligible for specific therapies, which may have contributed to age-based variations in the use of these therapies. Nevertheless, many studies have shown that treatment differences remain also after such adjustment (Tran *et al*. 2004; Avezum *et al.* 2005). There was no age-related difference in the usage of aspirin. The smallest effect of age on aspirin use has been shown by Rathore *et al.* (2003). Our study demonstrated clear age-related trends in the usage of the medications that have recently been added to AMI treatment (glycoprotein IIb/IIIa inhibitors, statins, clopidogrel). Large differences were revealed in the usage of reperfusion therapy between age groups, which has also been found in other studies (Mehta *et al*. 2001; Ruiz-Bailén *et al*. 2002; Rathore *et al*. 2003). It might be that physicians overestimate treatment-associated adverse events

and withhold treatment in elderly patients because they are uncertain about the balance of benefit and risk in elderly patients. This explanation is consistent with our observation that age has no impact on the usage of aspirin, which has few contraindications and few treatment-related adverse effects, and the large impact on acute reperfusion therapy, which has restricted eligibility, severe adverse effects, and uncertain effectiveness in elderly patients.

Elderly patients with AMI have more comorbid conditions and use more medications than younger patients. Physicians may be influenced by the presentation of conditions other than those usually evaluated as contraindications for specific-therapies, as a result of considering possible medication interactions and side effects.

In-hospital mortality

We did not find statistically significant differences in in-hospital mortality between the first 4 age groups. Previous investigations have shown that increasing age is directly related to in-hospital mortality (Goldberg *et al*. 1998; Mehta *et al*. 2001; Ruiz-Bailén *et al*. 2002). Drastically high in-hospital mortality occurred in very elderly patients. Without any precise data, we can only speculate that the younger age groups included more patients who were resuscitated before reaching hospital. It might be that relatively small size of our study population reduced statistical power. At the same time, our study included unselected consecutive patients independent of the department where they were admitted. Studies often comprise only patients from coronary care units, which can cause systematic bias. However, it has to be emphasized that we evaluated only short-term outcome and we cannot assess the effect of treatments that influence the long-term prognosis of AMI patients. Despite very poor prognosis in the very elderly patients (≥ 85 years), it may be possible to improve prognosis by optimizing their management, probably with a greater use of primary angioplasty.

A large proportion of age-associated variation in mortality is attributable to age-related variation in patients` clinical characteristics and AMI care, since adjustment for these factors resulted in the greatest reduction in the age-adjusted odds of mortality (Mehta *et al*. 2001). These mortality patterns emphasize the need for heightened physician awareness and for the careful development and monitoring of therapeutic regimens. Physicians should reassess current patterns of management in elderly patients who have had a recent AMI and should be more aggressive in the treatment of those who are ideally suited for treatment with selected agents. The more aggressive management of elderly patients with AMI raises a number of clinical, quality-of-life, as well as ethical issues that need to be addressed by health care providers, patients, and their families. These discussions, however, appear justified given the markedly poorer in-hospital, as well as long-term, survival of elderly versus younger patients.

6.5. The association between hyperglycaemia on admission, diabetes and mortality in acute myocardial infarction patients

We found that hyperglycaemia on admission is common (it was present in 25% of patients admitted to the hospital) and that 56% of these patients had no history of diabetes before the admission. Our results in an unselected study population confirm the results of previous studies (Norhammar *et al*. 1999; Capes *et al*. 2000; Wahab *et al*. 2002; Foo *et al*. 2003) that patients presenting with an AMI who are hyperglycaemic on admission represent a high-risk population.

The worst outcome occurred in hyperglycaemic patients without a history of diabetes, as also reported by other researchers (Wahab *et al*. 2002). Hyperglycaemic status in non-diabetic, but not in diabetic patients, remained an independent predictor of 180-day mortality after adjustment for potentially confounding factors. The reasons for this difference are not fully clear. The definition of stress hyperglycaemia is intrinsically difficult in diabetic patients, as the unstressed baseline concentration of glucose is not known. It might be that for diabetic patients, the value for hyperglycaemia by our definition (>11mmol/l) was too low to allow differentiation between patients who did and did not have stress hyperglycaemia. For example, in the DIGAMI study, a striking increase was seen in long-term mortality in diabetic patients who had very high glucose concentrations; patients in the upper tertile of wholeblood glucose concentrations (>16.5 mmol/l) had about a 50% higher risk of death than those in the lowest and middle tertiles (Malmberg *et al.* 1999).

In the present study, the higher mortality in patients with newly detected acute hyperglycaemia may also be related to more frequent cardiopulmonary resuscitation outside of hospital and a higher creatinine level. In addition, efficacious therapy (aspirin, ACE inhibitors, statins) was less frequently used in this group which could be the reason for a higher mortality. Our results encourage further exploration of the causes why these patients receive less evidence-based therapy.

Patients with known diabetes are more likely to receive insulin during and after myocardial infarction (Capes *et al*. 2000). Our findings also confirmed this fact. Insulin may reduce the rise in free fatty acids during AMI and therefore may decrease adverse outcomes (Capes *et al*. 2000).

Some researchers suspect that such individuals are many years undiagnosed and untreated diabetic patients, who for that reason have a greater risk for macro- and microvascular morbidity (Wahab *et al.* 2002). However, acute phase hyperglycaemia may not only reflect undiagnosed diabetes. According to Umpierrez *et al.* (2002), so called stress hyperglycaemia, defined as a transient increase in blood glucose concentration during acute illness, represents two distinct populations: those with undiagnosed diabetes or impaired glucose tolerance, and those who develop hyperglycaemia as a result of severe stress and increased stress-hormones (cortisol, adrenaline, noradrenaline). We found

that the patient group with hyperglycaemia and without known diabetes was different from other groups. This group had more severe clinical manifestations on admission — more patients were resuscitated and had left ventricular failure. Therefore, it might be that newly diagnosed hyperglycaemia in some of our patients reflects a response to acute illness and severe stress. This idea is supported by the fact that only one third of these patients received some antidiabetic treatment (insulin or oral antidiabetic agents) during the in-hospital period. Because of the lack of HbA1c testing and the lack of follow-up after discharge we are unable to identify patients with impaired glucose tolerance or unrecognised diabetes. Several studies (Oswald *et al*. 1984; Tenerz *et al*. 2001; Norhammar *et al*. 2002; Tenerz *et al*. 2003) have shown that in patients with AMI, hyperglycaemia on admission, per se, is not reliable for the diagnosis of diabetes mellitus, and a follow-up is necessary to establish diagnosis. Norhammar *et al*. (2002) suggested that the only independent predictors of abnormal glucose tolerance at 3 months were HbA1c on admission and fasting blood glucose at discharge.

Our study did not address the question of whether treatment of hyperglycaemia may reduce high morbidity and mortality. However, many studies have evaluated the importance of controlled glucose concentration in the early phase of AMI (Malmberg *et al*. 1997; Diaz *et al*. 1998). In the DIGAMI study, 1240 patients were potentially eligible for the study, but 50% were immediately excluded. One exclusion criterion was inability to participate for reasons of health (Malmberg *et al*. 1997 and 1999). In our study, the patients who were resuscitated outside hospital accounted for 42% of the 180-day mortality figure among non-diabetic hyperglycaemic patients. Clarification is required to discover whether such patients derive benefit from insulin therapy.

Thus, plasma glucose level on admission could be a useful marker for the identification of patients with poor prognosis after AMI. It may characterize a group of patients who require intensive care focused on their glycometabolic status as well as more strict control of other modifiable risk factors of cardiovascular death.

7. CONCLUSIONS

1. Tertiary care physicians adhere more strictly than secondary care physicians to the current guidelines for the management of AMI. However, the present study demonstrates the discrepancies between guidelines and real clinical practice for treatment of AMI patients in Estonia. Further efforts are needed in both hospital settings to improve the management of AMI in accordance with international guidelines.

2. Age is a more important determinant of the management and outcomes in patients with AMI than gender. There are gender differences in risk profiles among AMI-patients. Women are older than men and have more comorbidities. After age-adjustment, the gender difference in management that remains, is that women are treated more frequently with diuretics and less frequently with statins. The female gender is not an independent predictor of 30-day mortality after AMI.

3. Age influences occurrence of the risk factors and comorbidities, as well as the management and in-hospital mortality of AMI patients. Elderly patients are less likely to receive guideline-indicated therapies when hospitalised with AMI, but this varies among medications. The very elderly patients receive the least of these therapies and have drastically high in-hospital mortality.

4. Hyperglycaemia (glucose >11.0 mmol/l) on admission in patients with AMI is associated with high risk for 180-day mortality. Hyperglycaemia in previously unknown diabetic (but not known diabetic) patients remains an independent predictor of mortality after adjustment for covariates and could therefore be a useful marker for the identification of patients with poor prognosis after AMI.

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9. SUMMARY IN ESTONIAN

Äge müokardiinfarkt Eestis: kliinilised tunnused, ravikäsitlus ja -tulemused

Südame-veresoonkonna haigused (SVH), kaasa arvatud äge müokardiinfarkt (ÄMI), on peamine surmapõhjus maailmas. Arenenud maades ilmneb oluline südame isheemiatõve suremuse langus viimase kolme kümnendi vältel. Ida-Euroopa maades, sealhulgas Eestis, niisugust südame isheemiatõve suremuse vähenemist ei esine. SVH Eestis on surmapõhjustest esikohal, moodustades rohkem kui 50% kõigist surmapõhjustest.

Suremuse vähenemist südame isheemiatõvesse seletatakse eelkõige fataalsete ja korduvate ÄMIde, vähem ÄMI esmashaigestumuse vähenemisega. Selle üheks põhjuseks peetakse ÄMI haigete ravikvaliteedi paranemist (õigeaegne ja laialdasem reperfusioonravi kasutamine, sekundaarsete preventsioonimeetmete tõhususe tõus). Seega üheks võimaluseks vähendada südame isheemiatõve suremust ja korduvhaigestumust on parandada ÄMI haigete ravikvaliteeti. Paraku rakendatakse tõenduspõhise meditsiini formaliseeritud ravijuhendeid igapäevases kliinilises praktikas veel puudulikult. Uuringute andmetel on leitud ÄMI ravis suuri varieeruvusi nii riigiti kui riigi piires. Parandamaks ÄMI haigete ravikvaliteeti on vajalik nende haigete diagnoosimise ja ravi eriaspektide kohta võimalikult täielike andmete saamine, mida võimaldavad kliinilised registrid. Eestis ei ole siiani ÄMI haigetel regulaarselt hinnatud rakendatavaid ravimeetodeid ega ravitulemusi. Tallinna Ägeda Müokardiinfarktiregister, mis kogus andmeid MONICA protokolli järgi aastatel 1991–1997, võimaldab analüüsida üksnes selekteeritud rühma väheseid raviandmeid.

Viimastel aastatel on palju tähelepanu pööratud järgnevatele ÄMI alarühmadele — naistele, diabeetikutele ja eakatele. Uuringud on näidanud, et naissoost, diabeetikutest ja eakatel ÄMI haigetel on prognoos elulemuse suhtes halvem. Üheks põhjuseks peetakse nendel haigetel tõenduspõhiste ravimite ja ravistrateegiate harvemat kasutamist võrreldes teiste ÄMI haigetega. Diabeet on üleilmselt väga kiiresti sagenev haigus, mis toob endaga kaasa südame isheemiatõve (sealhulgas ÄMI) esinemise tõusu. Ägedat hüperglükeemiat ÄMI haigetel on uuritud kui võimalikku uut modifitseeritavat riskitegurit. Eakate patsientide osakaal järjest suureneb ÄMI haigete hulgas rahvastiku vananemise tõttu, kuid nende letaalsus on jäänud kõrgeks.

Et Eestis puudub info hospitaliseeritud ÄMI haigete eespool nimetatud aspektide kohta, oli antud uurimustöö eesmärk hinnata haiglatüübi, soo ja vanuse efekti ÄMI haigete ravikäsitlusele ja -tulemusele ning diabeedi ja hüperglükeemia seost ÄMI haigete ravitulemusega.

Uurimistöö eesmärgid:

1. Võrrelda ÄMI haigete ravi kolmanda ja teise etapi haiglates.
2. Analüüsida ÄMI haigete põhinäitajaid, ravikäsitlust ja 30-päeva letaalsust meestel ja naistel.
3. Hinnata ÄMI haigete vanusega seotud riskitegurite, ravikäsitluse ja haiglasisese letaalsuse erinevusi.
4. Hinnata ÄMI haigete 180-päeva letaalsuse seost hospitaliseerimisel (*on admission*) sedastatud hüperglükeemia ja varem diagnoositud diabeediga.

Patsiendid ja meetodid

Hindamaks haiglatüübi efekti ÄMI haigete ravikäsitlusele, kaasati uuringusse kaks kolmanda ja seitse teise etapi haiglat, mis vastutavad enamike ÄMI haigete ravi eest Eestis. Haiglad klassifitseeriti perkutaanse koronaarinterventsioonide tegemise võimaluse alusel. Eesti Haigekassa andmebaasist saadi juhuvalim (N=520) patsientide kohta, kes hospitaliseeriti nendesse haiglatesse 2001. a jooksul ÄMI tõttu (diagnoosikoodid I21–I22 ICD-10 alusel). Valitud haigusjuhtudele vastavad haiguslood telliti haiglatest. 40 haigusjuhtu jäeti välja Haigekassa poolt tehtud valiku vigade tõttu. 210 juhtu kolmanda etapi haiglast ja 213 juhtu teise etapi haiglast, mis vastasid ÄMI diagnostilistele kriteeriumitele, võeti edasisse analüüsi. Eksperdid analüüsisid haigusjuhte, kasutades standarditud vormi, mis oli sarnane Eesti müokardiinfarktiregistri (EMIR) vormile. Lisaks registrisse kogutavatele tunnustele koguti andmeid ambulatoorsete ravisoovituste kohta.

Uurimistöö teiste eesmärkide täitmiseks kasutati EMIRi andmeid patsientide kohta, kes olid hospitaliseeritud Sihtasutus Tartu Ülikooli Kliinikumi ajavahemikus jaanuar 2001 kuni detsember 2003. Uuring, mille alusel hinnati ÄMI haigete soolisi erinevusi ravikäsitluses ja -tulemuses hõlmas patsiente (N=395), kes hospitaliseeriti 14 kuu jooksul (jaanuar 2001 kuni veebruar 2002). Vanuse efekti hindamiseks ÄMI haigete ravikäsitlusele ja haiglasisesele letaalsusele analüüsiti kolme aasta jooksul (2001–2003) hospitaliseeritud ÄMI juhte (N=1201). ÄMI haigete 180-päeva letaalsuse seost hospitaliseerimise hüperglükeemia (veresuhkur >11mmol/l) ja varem diagnoositud diabeediga analüüsiti kahe aasta jooksul (2001–2002) hospitaliseeritud juhtude alusel. Uuringusse võeti patsiendid (N=779), kellel oli kättesaadav haigusloost veresuhkur hospitaliseerimisel.

Ägeda MI diagnostilised kriteeriumid kõigis uuringutes vastasid Euroopa Kardioloogide Seltsi ja Ameerika Kardioloogide Kolledži MI redefinitsiooni konsensusdokumendile.

EMIR on internetipõhine register, kuhu kogutakse andmeid selekteerimata hospitaliseeritud ägeda MI juhtude kohta haiglatest, mis on sellega liitunud. Andmeid kogutakse standarditud elektroonilise vormi alusel, mis sisaldab 78

tunnust definitsioonidega, ja mis on kinnitatud Eesti Kardioloogide Seltsi juurde kuuluva EMIR teadusnõukogu poolt. Tunnused hõlmavad järgnevaid valdkondi: isikuandmed, riskitegurid ja eelnev kardiovaskulaarne anamnees, sümptomid, EKG kirjeldus, haiglaperioodil esinevad tüsistused, ravi ja protseduurid, laboritulemused, kliinilised diagnoosid vastavalt ICD-10-le, ravitulemus, hospitaliseerimise ja väljakirjutamise kuupäev ja kellaaeg. Uuring, kus hinnati hüperglükeemia ja diabeedi efekti ravitulemusele, tehti tagasivaatav haiguslugude läbivaatamine. Lisaks EMIR vormi tunnustele koguti haige hospitaliseerimise (*on admission*) laboratoorsed (veresuhkur, kreatiniin) ja kliinilised andmed.

Patsientide jälgimiseks saadi Eesti rahvastikuregistrist andmeid surmafakti ja -kuupäeva kohta.

Andmetöötlusel kasutati programmi STATA 6.0/8.1.

Uurimistööst tulenevad järeldused:

1. Kolmanda etapi haiglate arstid järgivad tänapäevaseid ÄMI ravijuhendeid täpsemalt kui teise etapi haiglate arstid. Siiski ilmnevad ÄMI haigete ravis lahknevused ravijuhendites olevate soovituste ja reaalse kliinilise praktika vahel. Edasised jõupingutused on vajalikud mõlema etapi haiglates, et parandada ÄMI haigete ravikäsitlust vastavalt rahvusvahelistele ravijuhenditele.
2. Vanus on soost olulisem tegur ravimite kasutamisel, ravistrateegiate valikul ja ravitulemuste puhul. ÄMI haigete hulgas esineb soolisi erinevusi riskitegurites. Naised on vanemad ja neil esineb rohkem kaasuvaid haigusi. Pärast vanuse järgi kohandamist jäävad püsima järgnevad soolised erinevused ravikäsitluses — naistel kasutatakse diureetikume rohkem ja statiine vähem. Sugu ei ole oluline prognostiline tegur 30-päeva letaalsuse korral.
3. Vanus mõjutab ÄMI haigete riskitegurite ja kaasuvate haiguste esinemist, ravikäsitlust ning haiglasisest letaalsust. Kõrgem vanus vähendab tõenäosust saada ravijuhendites soovitatud ravi, kuigi see ei kehti kõigi ravimite puhul. Väga eakatel patsientidel kasutatakse kõige harvemini soovituslikku ravi ja nende haiglasisene letaalsus on kõrgeim.
4. Hüperglükeemia (veresuhkur >11mmol/l) esinemine ÄMI haigetel hospitaliseerimisel seostub 180-päeva letaalsuse kõrge riskiga. Hüperglükeemia patsientidel, kellel diabeet oli varasemalt diagnoosimata (mitte aga varasemalt diagnoositud diabeediga), on 180-päeva letaalsuse sõltumatu prognostiline tegur ja seetõttu võib olla kasutatav marker ÄMI-järgse halva prognoosiga haigete väljaselgitamiseks.

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Teadustegevus

Peamiseks uurimisvaldkonnaks on ägeda müokardiinfarkti erinevad kliinilised aspektid — ravikäsitlus, ravitulemus, prognostilised tegurid.

18 teaduslikku publikatsiooni ja 4 ettekannet rahvusvahelistel konverentsidel.

Eesti Kardioloogide Seltsi, Eesti Hüpertensiooni Ühingu ja Eesti Müokardiinfarktiregistri teadusnõukogu liige.