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LIST OF ORIGINAL PUBLICATIONS

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I. Saar A, Läll K, Alver M, Marandi T, Ainla T, Eha J, Metspalu A, Fischer K. Estimating the performance of three cardiovascular disease risk scores: the Estonian Biobank cohort study. *J Epidemiol Community Health.* 2019; 73:272–277.
II. Saar A, Marandi T, Ainla T, Fischer K, Blöndal M, Eha J. Improved treatment and prognosis after acute myocardial infarction in Estonia: cross-sectional study from a high risk country. *BMC Cardiovascular Disorders.* 2015;15:136.
III. Saar A, Marandi T, Ainla T, Fischer K, Blöndal M, Eha J. The risk-treatment paradox in non-ST-elevation myocardial infarction patients according to their estimated GRACE risk. *Int J Cardiol*. 2018;272:26–32.

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Papers II and III: Proposing the research questions, participation in the study design, statistical analysis, interpretation of the results, preparation of tables and figures, and drafting the manuscripts.

ABBREVIATIONS

4S	Scandinavian Simvastatin Survival Study
ACC/AHA	American College of Cardiology/American Heart Association
ACEi	angiotensin-converting enzyme inhibitor
ARB	angiotensin II receptor blocker
ATT	Antithrombotic Trialists' Collaboration
BMI	body mass index
CABG	coronary artery bypass grafting
CANTOS	Canakinumab Anti-Inflammatory Thrombosis Outcomes Study
CARDS	cardiology audit and registration data standards
CI	confidence interval
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
DM	diabetes mellitus
ECG	electrocardiogram
EF	ejection fraction
EHIF	Estonian Health Insurance Fund
EMIR	Estonian Myocardial Infarction Registry
EPICOR	Long-term Follow-up of Anti-thrombotic Management Patterns in Acute Coronary Syndrome Patients
EPR	Estonian Population Registry
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
GRACE	Global Registry of Acute Coronary Events
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
LDL	low-density lipoprotein
MI	myocardial infarction
MONICA	Monitoring Trends and Determinants in Cardiovascular Disease
NICE	National Institute for Health and Care Excellence
NSTEMI	non-ST-segment elevation myocardial infarction
OECD	Organization for Economic Co-operation and Development
PCE	Pooled Cohort Equations
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PURE	Prospective Urban Rural Epidemiology study
RCT	randomized controlled trial
SCORE	Systematic COronary Risk Estimation
SIR	standardized incidence ratio
STEMI	ST-segment elevation myocardial infarction

1. INTRODUCTION

The decreased incidence rate of ischaemic heart disease and increased survival after myocardial infarction (MI) are considered to be the main causes for the reduction of mortality from cardiovascular disease (CVD) seen in most European countries over the last decades. Decreased incidence has been attributed to the reduced influence of classical CVD risk factors and increased survival to advances in treatment of MI. However, similarly to other developed countries, ischaemic heart disease remains the major cause of death in Estonia, with the mortality rates still significantly higher than the European average.

To date, the focus in Estonia has been on monitoring the trends and improving treatment of ischaemic heart disease and, more specifically, its most serious complication – MI. A thesis published by Tiia Ainla in 2005 combined studies that systematically describe the management and outcomes of MI in Estonia. The results demonstrated shortcomings in MI management in the year 2001 – the use of evidence-based pharmacotherapy and reperfusion rates for ST-segment elevation myocardial infarction (STEMI) were both suboptimal. Furthermore, important discrepancies in care between hospital types and patient subgroups were found – elderly patients, women and patients with hyperglycaemia at presentation, but also patients who were managed in secondary care hospitals, received less guideline-recommended care, leading to a negative impact on their prognosis. The conclusions of the study prompted several educational events throughout Estonia in the following years, while at the same time the availability of cardiac catheterization facilities and affordability of many secondary prevention drugs improved.

The effect of these efforts was evaluated in a series of follow-up studies which were jointly published as a dissertation by Mai Blöndal in 2012. The results showed that while management of MI improved significantly over the period from 2001 to 2007, the changes were more pronounced in a tertiary care setting, indicating augmentation of disparities between hospital types if compared to 2001. Unexpectedly, improved management did not result in a significant decrease in mortality rates. This was attributed to increased age and higher rate of comorbidities of MI patients. Based on recommendations from the thesis, systematic educational work continued, and the management of MI became more centralized with clear recommendations that most MI patients should be transferred to tertiary care hospitals during their course of hospitalization without unnecessary delay to enable invasive diagnostics and treatment.

The current thesis continues monitoring trends in the management and outcomes of MI. The three snapshots carried out in 2001, 2007 and 2011 cover the period from 2001 to 2011; the thesis by Blöndal (2012) presents combined results from 2001 and 2007, and the current thesis combines results from all three studied years. The establishment of the national MI registry – the Estonian Myocardial Infarction Registry (EMIR) – in 2012 enables continuous monitoring

of management and outcomes of patients who suffer from MI. The first results from this country-wide registry will be presented in this thesis.

In order to comprehensively tackle high mortality from ischaemic heart disease in Estonia, additional attention must also be paid to primary prevention. An insufficient level of primary prevention in Estonia is illustrated by the fact that, according to data from the Organization for Economic Co-operation and Development (OECD, 2017), Estonia is among the three countries with the lowest statin use. The consumption of cholesterol-lowering drugs in Estonia in 2015 was approximately two times lower than the average in 28 countries monitored by the OECD. Moreover, the prevalence of lifestyle-associated risk factors, e.g. smoking and obesity, in Estonia is higher than the European average (Timmis et al, 2018). The European Society of Cardiology recommends using a validated risk estimation tool, for example Systematic COronary Risk Estimation (SCORE) charts, to guide treatment decisions in primary prevention. SCORE charts have been translated into Estonian, and their usage has been encouraged among physicians, but their prediction accuracy has never been validated in a high-risk country like Estonia.

Only comprehensive strategies that include all domains of ischaemic heart disease management – primary prevention, timely diagnosis of acute MI, acute phase treatment and secondary prevention – are capable of further reducing mortality from ischaemic heart disease in Estonia. For that reason, this thesis extends the scope of previous work, and, in addition to MI management and outcomes, it focuses on the primary prevention of ischaemic heart disease and MI in Estonia.

2. REVIEW OF THE LITERATURE

2.1 General overview of the epidemiology of ischaemic heart disease

Estonia, located in North Eastern Europe, has reported one of the fastest decreases in mortality rates from CVD, and more specifically from ischaemic heart disease, in Europe. Age-standardized mortality rates per 100,000 individuals from ischaemic heart disease fell from 1285 to 388 in men and from 837 to 211 in women from 1985 to 2014 (Timmis et al, 2018). Despite this huge improvement, in 2015 Estonia ranked 8th in the European Union in mortality from ischaemic heart disease, remaining among the highest-risk countries (Eurostat, 2015).

The mortality rate from a disease relies on two factors: how many individuals develop the disease and how large a proportion of these patients die from it. The incidence of ischaemic heart disease depends mostly on the prevalence of modifiable and non-modifiable risk factors. Access to modern medical therapies, including pharmacological, instrumental and lifestyle interventions, together with patient-specific factors, determines the prognosis after diagnosis of ischaemic heart disease. Modelling studies have tried to examine how much of the decrease in ischaemic heart disease mortality could be explained by changes in risk factors and how much can be attributed to improved treatments. Results indicate that more than half of the mortality decrease can be attributed to an improved risk factor profile and less than half to medical therapies (Björck et al, 2009).

The widespread presence of major modifiable ischaemic heart disease risk factors – raised blood pressure, dyslipidaemia, smoking, obesity and physical inactivity (Libby et al, 2007) – remains the leading cause of the disease, and their high prevalence in Estonia explains why mortality rates are still alarmingly high when compared to the rest of Europe. For example, the prevalence of hypertension in Estonia is estimated to be 26% in women and 38% in men – the highest in Europe (Timmis et al, 2018). The proportion of individuals with dyslipidaemia (blood cholesterol >6.2mmol/L) and who are insufficiently physically active is also among the top third when compared to other European countries. The prevalence of obesity (approximately 24% of population) and of smoking (31% in men and 15% women) are roughly comparable with respective European average parameters.

The treatment of ischaemic heart disease, and more specifically its most feared complication, acute MI, has improved significantly over the past years. One of the first studies describing outcomes for patients who experienced acute MI in Estonia was published as a thesis by Toivo Laks in 2001. The author described a high mortality rate after acute MI among the residents of Tallinn, Estonia, aged 35–64, in the period from 1991 to 1997, which was comparable with countries with the highest CVD rates in Europe (Dégano et al, 2015). High mortality from ischaemic heart disease was attributed mostly to high disease

incidence; however, suboptimal treatment probably also played a role. The first study that systematically investigated the treatment and outcomes of patients with MI in Estonia overall described the situation in 2001 and found low prevalence of use of guideline-recommended therapies; for example, 43% of STEMI patients received reperfusion therapy and only around 50% of MI patients received in-hospital ACEi and 15% statins (Ainla et al, 2006). A follow-up study in 2007 described significantly improved treatment – the overall rate of reperfusion therapy for STEMI increased to 48%, in-hospital prescription rates of ACEi increased to around 70%, and statins increased to 50% from 2001 to 2007 (Blöndal et al, 2012). Unfortunately, the latter study failed to show improved prognosis after MI, and this finding was associated with increasing mean age and higher burden of comorbidities. Additionally, the study highlighted important inequalities in MI management between different hospital types in Estonia.

In addition to quality of acute care, long-term secondary prevention determines the prognosis of MI, including smoking cessation, cardiac rehabilitation and longterm drug treatment. An analysis by the World Bank Group (2015) underscores shortcomings in the coordination of care after hospitalization – only approximately 50% of MI patients had a follow-up visit during first 90 days after hospital discharge. A study conducted in 2004–2005 described that only 40% of Estonian MI patients purchased a triple combination of a beta-blocker, an ACEi/ARB and a statin, which also implicates insufficient outpatient care (Marandi et al, 2010). Unfortunately, more data on treatment adherence after MI are currently not available in Estonia.

2.2 Primary prevention of ischaemic heart disease

The importance of primary prevention is highlighted by the fact that in approximately one third of the cases the first presentation of ischaemic heart disease may be a sudden cardiac death, making the application of secondary prevention impossible (Dudas et al, 2011). The only way to reduce these out-of-hospital deaths is through primary prevention at both levels – the general population level (e.g. smoking restrictions, food labelling, public sporting facilities, etc.) and the individual level (i.e. treating apparently healthy individuals who are at the highest risk for developing ischaemic heart disease) (Piepoli et al, 2016).

All major international CVD primary prevention guidelines share the principle of identifying the highest risk individuals and matching the intensity of preventive therapies according to an individual's absolute risk of developing the disease (Piepoli et al, 2016; Stone et al, 2013; NICE, 2014). However, there are some differences between these guidelines, e.g. the models that are used for risk prediction and decision thresholds for the initiation of drug treatment for dyslipidaemia and hypertension.

2.2.1 Risk scores used to estimate cardiovascular disease risk

The guidelines of the European Society of Cardiology recommend estimating total CVD risk with SCORE by using risk charts (Piepoli et al, 2016) or a web calculator (http://www.heartscore.org/). It is the most widely used risk score in Europe and targets individuals aged over 40 without chronic kidney disease or diabetes. SCORE, developed using a pooled dataset from 12 European countries (Estonia not included), evaluates a 10-year risk of CVD mortality (fatal ischaemic heart disease, stroke, hypertension, heart failure, peripheral artery disease or aortic disease) separately for low- and high-risk countries (Conroy et al, 2003).

QRISK2, which is recommended for risk prediction in the UK, was developed on cohorts in England and Wales recruited from 1993 to 2008, and it predicts a 10-year risk of developing atherosclerotic CVD (first diagnosis of coronary heart disease, stroke or transient ischaemic attack) on individuals aged 25–84 years without diabetes mellitus type I (Hippisley-Cox et al, 2008).

Pooled Cohort Equations (PCE), developed based on the US cohorts recruited in the 1990s, is recommended by American Heart Association/ American College of Cardiology (AHA/ACC) guidelines to estimate a 10-year risk of developing hard atherosclerotic CVD (first diagnosis of nonfatal MI, coronary heart disease death, fatal or nonfatal stroke) on persons aged 40–79 (Goff et al, 2014).

All three risk scores encompass information about age, sex, systolic blood pressure, smoking status and total cholesterol in risk estimation. PCE additionally includes high density lipoprotein, diabetes status, ethnicity and antihypertensive medication use. QRISK2 utilizes the widest set of risk factors and additionally contains body mass index, atrial fibrillation, rheumatoid arthritis, chronic kidney disease and family history on atherosclerotic CVD. Moreover, QRISK2 also incorporates information about social deprivation (using UK postcode as a proxy).

Accuracy of risk scores

The most frequently used parameters for assessing the clinical utility of risk scores are discrimination and calibration. Discrimination describes a risk score's ability to correctly differentiate between individuals who develop the disease ("cases") and those who do not ("non-cases"). Discrimination is usually expressed as a C-statistic, which is a measure of both the sensitivity and specificity (Pencina et al, 2012). In other words, the C-statistic expresses the probability that a randomly selected case will have higher absolute risk estimates than the randomly selected non-case. C-statistic values range from 0.50 (random chance) to 1.0 (perfect discrimination), while values <0.70 are considered inadequate; values between 0.70–0.80 are acceptable and >0.90 are excellent (Lloyd-Jones, 2010). As a C-statistic only evaluates a score's ability to correctly rank order individuals according to their absolute risk estimates and

does not take into account the absolute values of risk levels, another parameter is needed to estimate a risk score's ability to correctly estimate the level of absolute risk.

Calibration assesses the ability of a risk score to correctly predict the absolute level of risk that is subsequently observed (Crowson et al, 2016). There are several ways to express calibration. For example, it can be represented using expected and observed columns or ratios, where columns of the expected number of events and observed number of events are simply depicted side by side on the chart. For ratios, the number of expected cases is divided by the number of observed cases. Another easily interpretable option to describe calibration is to divide a population at risk into quintiles of predicted risk and to plot it against the observed risk.

Limitations of risk scores

In order to be clinically useful, a risk score has to have acceptable discrimination as well as calibration. As associations between major CVD risk factors and the development of the disease are relatively consistent across different populations, with age being by far the strongest predictor of risk (Wald et al, 2011), a score's discrimination is usually fairly constant when assessed in a new population setting. Calibration, on the other hand, varies greatly, mainly because of significant differences in incidence rates of the disease. For example, if a risk score that has been developed on a population with low CVD incidence rates was applied to a population with high incidence rates, it would lead to significant underestimation of the risk; i.e. expected rates would be significantly lower than observed rates. The risk scores' tendency to overestimate the actual risk in contemporary populations is confirmed by several studies from Western high-income countries with falling CVD mortality rates (Ulmer et al, 2005; Rana et al, 2016; deFilippis et al, 2017; Emdin et al, 2017), indicating the need for recalibration. However, recalibration is only possible after detecting the incorrect calibration, highlighting the importance of validation studies before applying a risk score to new populations where its performance accuracy has not been evaluated. The importance of using a locally validated risk score for CVD risk assessment is emphasized by the European CVD prevention guidelines (Piepoli et al, 2016).

Advantages of risk scores

In addition to providing direct guidance on when to start treatment and on whom, for example with statins or antihypertensive drugs, CVD risk scores can be used to improve public awareness of risk factors that cause a majority of CVD events. Furthermore, scores can be useful in communicating the need for lifestyle modifications in order to reduce one's risk. They can also improve patients' compliance with prescribed preventive therapy.

Possibilities for improvement of risk scores

Several studies have investigated possibilities to improve risk prediction through the addition of new biomarkers to existing risk scores. Graversen with co-authors (2016) evaluated potential improvement in SCORE's discrimination by adding 19 easily available risk markers (e.g. body mass index, waist-to-hip ratio, household income per year, etc.). Despite being significant independent predictors of SCORE's outcome (CVD mortality), none of the risk markers had a major effect on risk stratification. Furthermore, adding a marker with protecting effect – high density lipoprotein – has even caused deterioration of risk classification by placing more individuals into a low-risk category (Mortensen et al, 2015).

Rapid scientific developments in clinical genetics have opened up an entirely new chapter in risk prediction. After a parallel discovery of MI and ischaemic heart disease risk-increasing variant in chromosome 9p21.3 by three scientific groups (Samani et al, 2007; McPherson et al, 2007; Helgadottir et al, 2007), there has been a growing amount of literature investigating the potential utilization of genetic markers in risk prediction refinement. The combination of approximately 50,000 genetic markers into a polygenic risk score has demonstrated the potential clinical utility of complementing an existing clinical risk score by identifying individuals with increased risk for developing ischaemic heart disease (Abraham et al, 2016). However, further validation and cost-benefit analyses are needed before genetic risk scores could be implemented in routine clinical use.

Potential calibration errors, e.g. under- or overestimation of the actual risk by a risk score, could be addressed in several ways. The most straightforward way would be to simply recalibrate a score by adjusting the risk estimates according to the baseline hazard in a local population. The results of a recent study by Pennells and coauthors (2018) support this approach and indicate the need for regular recalibration of the risk-prediction algorithms. However, original web-tools or published risk charts could not be used after recalibration, which would limit the clinical applicability of a score. Another more feasible approach would be incorporating knowledge about potential calibration errors into clinician-patient discussions and decision-making regarding primary prevention (Martin et al, 2015). A promising approach to personalized decision-making includes the terms "up-risking" and "de-risking" by the use of positive or negative risk markers, respectively (Mortensen & Falk, 2018). For example, a 40-year old man whose 10-year risk of developing fatal CVD event is 4%, as estimated by SCORE, should not receive a statin according to the guideline (Piepoli et al, 2016). However, if he has certain additional high-risk features (i.e. positive family history or a plaque in a carotid artery) he should be "up-risked" and receive a statin despite a low SCORE risk estimate. In contrast, an elderly woman with an estimated SCORE risk of >10%, which, according to the guideline, would indicate the initiation of statin therapy, could be "de-risked" by demonstrating coronary artery calcium score of 0, and pharmacological therapy could be withheld (Mortensen & Falk, 2018).

2.2.2 Risk factor management

The development of CVD results from the complex interplay between protective and harmful effects of different risk factors. As these factors are closely entwined, their exact individual effect is difficult to evaluate and classify. Furthermore, influencing one risk factor (e.g. overweight) might affect several others (e.g. dyslipidaemia, high blood pressure). Nevertheless, risk factor management strategies could be divided into two broad categories – non-pharmacological and pharmacological interventions.

2.2.2.1 Non-pharmacological risk reduction

Physical activity

In addition to promoting general well-being and mental health, regular physical activity is a mainstay in prevention of ischaemic heart disease. A cohort study that was carried out in more than 300,000 European men and women demonstrated that moderate exercise compared to inactivity reduced the hazard of all-cause mortality by 16–30% over the follow-up period of 12.4 years (Ekelund et al, 2015). Positive effects from physical activity are confirmed by findings from the PURE study, in which higher recreational and non-recreational physical activity was associated with a lower risk of ischaemic heart disease and all-cause mortality (Lear et al, 2017). Current guidelines recommend at least moderate intensity aerobic exercise without further assessment to all healthy individuals whose CVD risk is estimated to be low (Piepoli et al, 2016).

Body weight management

The association between body mass index (BMI, the weight in kilograms divided by the square of height in meters) and mortality is probably J-shaped, which means that not only overweight and obesity are strongly and independently associated with all-cause and ischaemic heart disease mortality, but underweight may also be (Berrington de Gonzales et al, 2010). An analysis conducted in almost 1.5 million white adults from 19 prospective cohort studies estimated that all-cause mortality was generally lowest within the BMI range of 20.0–24.9 (Berrington de Gonzales et al, 2010). As overweight is associated with high blood pressure, lipid values and risk of developing type 2 diabetes mellitus – all established independent risk factors of ischaemic heart disease – aiming towards normal BMI would thus definitely improve the risk. However, the authors of the EPIC study have estimated inactivity to be a stronger determinant of death than high BMI; consequently, avoiding inactivity could reduce the number of deaths more than avoiding obesity (BMI >30) (Ekelund et al, 2015).

Nutrition

There is no doubt that poor dietary habits increase CVD risk, either directly or through an effect of other risk factors such as dyslipidaemia, high blood pressure and overweight. However, evidence-based recommendations on what constitutes a healthy diet are in conflict. Current dietary recommendations have been strongly opposed by the results of the PURE study, which has demonstrated that fat intake, including unsaturated and saturated fatty acids, was not associated with mortality risk, while high carbohydrate intake increased all-cause mortality (Dehghan et al, 2017). Moreover, it has been proposed that gut microbiota may play a role in the development of CVD (Kelly et al, 2016).

Smoking cessation

Smoking is a strong independent risk factor for developing MI and other CVDs, and interestingly its negative effect is more pronounced in women than in men (Prescott et al, 1988). Thus, current guidelines strongly recommend avoiding tobacco in any form in order to decrease the risk of developing CVD (Piepoli et al, 2015). Smoking cessation, including behavioural interventions and pharmacological treatment using nicotine replacement therapy, has been proven safe and effective (Stead et al, 2008; Benowitz et al, 2018) in assisting smokers to quit.

2.2.2.2 Pharmacological risk reduction

Treatment of dyslipidaemia

Currently there is no international consensus between different guidelines on how to approach the treatment of dyslipidaemia in primary prevention of MI and CVD (Goff et al, 2013; NICE 2014; Piepoli et al, 2016). The most remarkable differences include varying absolute risk thresholds, which are considered to be sufficient to warrant pharmacological treatment with statins, and a dilemma between LDL-cholesterol target values and fixed-dose statin recommendations.

The latest guideline by the American College of Cardiology and American Heart Association (Stone et al, 2014) recommends statins for all individuals with LDL-cholesterol ≥4.9mmol/L or patients with LDL 1.8–4.9mmol/L who have diabetes mellitus or whose risk for developing hard atherosclerotic CVD over 10 years, estimated by the Pooled Cohort Equations, is ≥7.5%. Instead of stating LDL-target values, the guideline recommends initiating moderate to high intensity statin therapy depending on an absolute risk value and intended LDL-cholesterol reduction.

British National Institute for Health and Care Excellence (NICE) guidelines from 2014 endorse a similar approach, and LDL-target levels are not stated. However, treatment initiation thresholds differ, as the risk for developing atherosclerotic CVD over 10 years should be ≥10% to justify treatment.

The latest guideline by the European Society of Cardiology (Piepoli et al, 2016) has adopted a relatively different approach to risk estimation and treatment allocation. The guideline divides all individuals into four risk categories, and each category has a different LDL-cholesterol target level. The decision of when to start pharmacological treatment and on whom depends on both a patient's risk category and an initial LDL-cholesterol value (Table 1).

Table 1. Initiation of statin therapy for primary prevention depending on estimated risk and LDL-cholesterol value (modified from Piepoli et al, 2016)

Total risk of fatal CVD event over 10 years, (SCORE)	**LDL-cholesterol level**				
	<1.8mmol/L	**≥1.8… <2.6mmol/L**	**≥2.6… <4.0mmol/L**	**≥4.0… <4.9mmol/L**	**≥4.9mmol/L**
<1%	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled
≥1…<5%	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled
≥5…<10% or high-risk criteria*	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice and drug treatment	Lifestyle advice and drug treatment	Lifestyle advice and drug treatment
≥10% or very high-risk criteria*	Lifestyle advice, consider drug	Lifestyle advice and drug treatment	Lifestyle advice and drug treatment	Lifestyle advice and drug treatment	Lifestyle advice and drug treatment

CVD – cardiovascular disease, SCORE – Systematic COronary Risk Estimation, LDL – low density lipoprotein

* High-risk criteria – markedly elevated single risk factor (e.g. familial hypercholesterolaemia), diabetes mellitus, moderate chronic kidney disease; very high-risk criteria – documented cardiovascular disease in an imaging study, diabetes mellitus with target organ damage or a major risk factor

The mainstay of pharmacological risk reduction through the management of dyslipidaemia in CVD primary prevention is lipid-lowering drugs, mostly statins. Although they are not as effective as in secondary prevention, statins have been proved beneficial and safe in primary prevention. A meta-analysis consisting of 18 randomized controlled trials (RCT) concluded that the relative risk of all-cause mortality was reduced by 14% (odds ratio 0.86 95% confidence interval

0.79–0.94) without evidence of any serious harm (Taylor et al, 2013). However, more recent meta-analysis by Li et al (2019) described a benefit from statins in preventing ischaemic heart disease events but failed to show a mortality benefit (risk ratio 0.88 95% confidence interval 0.76 –1.01).

Due to a lack of evidence on the efficacy of other lipid-lowering drugs in primary prevention, they are used significantly less frequently and usually not as monotherapy, unless a patient is intolerant to statins.

Treatment of hypertension

A strong direct relationship between blood pressure and the risk of cardiovascular complications, including MI and stroke, has been described without any threshold down to as low as 115/75mmHg (Lewington et al, 2002). As blood pressure related risk is continuous, the level of abnormality is always arbitrary, which is strikingly illustrated by the differences in the thresholds from which hypertension is diagnosed in the USA and Europe. Recently updated guidelines by the ACC/AHA allow physicians to diagnose hypertension from 130/80mmHg (Whelton PK et al, 2018), while the European Society of Cardiology continues to follow a more lenient approach and defines hypertension from 140/90mmHg (Williams et al, 2018).

Lowering high blood pressure, either by lifestyle modifications alone or in combination with pharmacological treatment, improves cardiovascular outcomes including mortality reduction, with a relative risk reduction proportional to the magnitude of blood pressure lowering achieved (Ettehad et al, 2016). As relative reductions in risk of CVD seem to be similar across patients with different initial risk and blood pressure levels, the absolute benefits would be greatest among the individuals at highest baseline CVD risk. Thus, both US and European guidelines agree that high blood pressure should be managed in an integrated fashion with other risk factors, and the intensity of blood pressure management should depend on the risk of future CVD events. Patients with an overall low risk of vascular complications and with mild elevations in blood pressure could be initially counselled on necessary lifestyle modifications, and, if the risk of future events increases, blood pressure management should be intensified using pharmacological strategies (Whelton et al, 2018; Williams et al, 2018).

Treatment of inflammation

A growing body of literature supports the theory implicating that immune and inflammatory responses play a causal role in atherosclerosis and the development of CVD events, including MI (Libby et al, 2009). This hypothesis is supported by the successful use of inflammatory biomarkers, for example high sensitivity C-reactive protein (hs-CRP), to predict CVD risk, even after complete adjustment to traditional risk factors used in risk scores (Wilson et al, 2008). Evidence supports the use of statins, which are mainly considered to

decrease a CVD risk through lipid level reduction, also as anti-inflammatory drugs due to their suggested pleiotropic effects (Ridker et al, 2009). However, as statins inevitably affect lipid levels, the theory connecting an anti-inflammatory intervention with improved clinical outcomes still needed confirmation. The breakthrough came with a proof-of-concept CANTOS study that proved the inflammatory hypothesis of atherothrombosis (Ridker et al, 2017). Although not in clinical practice yet, especially not in the context of primary prevention, anti-inflammatory treatment seems to be a promising new option for preventing CVD events.

Treatment of diabetes mellitus

As diabetes mellitus (DM) confers approximately a two-fold excess risk of developing CVD (Sarwar et al, 2010), the targets, especially lipid and blood pressure, but also body mass index, waist circumference and smoking restriction, should be followed more stringently in these patients. Furthermore, as the excess risk is more pronounced for ischaemic heart disease, and DM is about a third more strongly related to fatal than to non-fatal MI (Sarwar et al, 2010), primary prevention is of paramount importance in people with DM. Taking into account significantly increased CVD risk, both US and European guidelines recommend initiating lipid-lowering therapy with statins for most individuals with DM over 40 years of age (Piepoli et al, 2016; Stone et al, 2013).

Antiplatelet therapy

Although long-term antiplatelet therapy with low-dose aspirin yielded a 12% relative risk reduction in vascular events (mainly non-fatal MI), it also increased major extracranial and intracranial bleeds (Antithrombotic Trialists' (ATT) Collaboration, 2009). As the expected benefits of aspirin might not exceed the risk of serious bleeding, the current consensus does not support using aspirin for primary prevention of vascular events in healthy individuals with a high risk of developing CVD (ATT Collaboration, 2009) nor in the individuals with DM (De Berardis et al, 2009).

2.3 Overview of temporal changes in acute myocardial infarction incidence

In the majority of developed European countries, including Estonia, the total number of deaths from CVD decreased between 1990 and 2013, with ischaemic heart disease, and more specifically MI, dominating among the causes of death (Timmis et al, 2018). This improvement was driven by a steep decline in age-standardized mortality rates from CVD and was observed despite aging of the population (Roth et al, 2015). Although improved treatment of MI and the related decrease in case death have contributed to the declining age-

standardized mortality rates from ischaemic heart disease, the majority of the observed fall could be attributed to a decline in event rates, i.e. decreasing MI incidence (O'Flaherty et al, 2013; Smolina et al, 2012).

Reports on the incidence of MI over the last decades from many high-income countries, for example Sweden (Yang et al, 2012), Denmark (Alzuhairi et al, 2015), and the US (Rosamond et al, 2012), have described declining incidence of first MI. However, this improvement has not been universal, as it is mainly driven by a steep decrease in incidence among middle-aged individuals, while in older (>90 years) and younger age groups (men <50 and women <60 years) MI incidence remained stable or even slightly increased (Alzuhairi et al, 2015).

Unfortunately, data on MI incidence from Estonia are scarce. Dégano with coauthors (2015) described the trends between 1985 and 2010 in six European populations based on registry data collected according to the World Health Organization (WHO) MONICA project methodology and found a significant decline in MI incidence in all populations with an exception of Tallinn, Estonia. However, the results should be interpreted cautiously, as the data from the period 2006–2010, in which most of the decline happened in other populations, were missing for Tallinn, Estonia. Moreover, this study included only patients <65 years, and the data from the capital city, Tallinn, cannot be extrapolated to the entire country of Estonia. Based on the same data, Laks with coauthors (2013) has described increasing incidence and mortality after MI over the period from 1991 to 1993. However, they found an important change in direction after 1993, when incidence and mortality after MI started to decrease. More recent data on the incidence of MI from Estonia are currently not available.

2.4 Subtypes and treatment of acute myocardial infarction

The definition of myocardial infarction

From the period of the first reports in the 1950s on diagnostic biomarkers of myocardial injury, cardiac high-sensitivity troponins (Garg et al, 2017), the diagnostic accuracy of acute MI has evolved significantly. Before the application of specific biomarkers of myocardial injury – troponins – the WHO defined MI according to symptoms and ECG abnormalities and not through cardiospecific enzymes. The first international definition of MI, published in 2000, specified that any necrosis (demonstrated by the appearance of troponins in blood samples) in the context of ischaemia should be diagnosed as MI (Alpert et Thygesen et al, 2000). The second (Thygesen et al, 2007), third (Thygesen et al, 2012) and fourth (Thygesen et al, 2019) universal definitions of MI have refined those principles to enable more sensitive and specific diagnosis of MI. The increasing sensitivity of troponin assays over the past decades has improved the diagnostic sensitivity of detecting small MIs and has also led to a changing balance between MI subtypes – the relative incidence of STEMI is decreasing, and non-ST-segment elevation myocardial infarction (NSTEMI) is increasing (Sugiyama et al, 2015).

ST-segment elevation and non-ST-segment elevation myocardial infarction

The main objective to distinguish between STEMI and NSTEMI includes immediate treatment strategy, whereas long-term management is similar after both MI subtypes (Ibanez et al, 2018; Roffi et al, 2016). Patients who present with ischaemic symptoms and fulfil the criteria of STEMI in ECG (ST-segment elevation in at least two contiguous leads) should undergo immediate reperfusion treatment using either fibrinolysis or primary percutaneous intervention (PCI). In contrast, MI patients presenting without ST-segment elevation should first receive pharmacological treatment, which is subsequently followed by coronary angiography to evaluate possibilities for revascularization (PCI or coronary artery bypass grafting, CABG). Secondary prevention drugs aimed at preventing repeated coronary events and heart failure and halting the progression of atherosclerosis should be used in a similar manner regardless of MI subtype.

Myocardial infarction classification according to underlying mechanism

In addition to classification into STEMI or NSTEMI, the consensus document divides MI into 5 subtypes based on pathophysiological and clinical characteristics (Thygesen et al, 2019). By far the most frequent is spontaneous MI related to atherosclerotic plaque rupture with resulting intracoronary thrombus formation, which leads to decreased myocardial blood flow and myocyte necrosis (MI type 1). MI type 2 is characterized by an ischaemic imbalance in which a condition other than coronary artery atherosclerosis contributes to an increased oxygen demand and/or decreased supply leading to myocardial injury with necrosis. MI Type 3 is diagnosed in the context of sudden cardiac death, with symptoms suggestive of myocardial ischaemia combined with ECG abnormalities when biomarkers of myocardial necrosis are not available. MI types 4 and 5 are associated with myocardial revascularization procedures, PCI and CABG, respectively. For obvious reasons, the majority of prevention strategies (primary or secondary) presented in the guidelines that are targeted against atherosclerosis, apply only to type 1 MI. Thus, the review of literature in this thesis covers mainly the treatment and outcomes of type 1 MI. According to the Swedish MI registry, the vast majority (85–95%) of registered MIs are type 1 MIs, while about 5–15% are type 2 MIs; the proportion of other types is negligible (Jernberg, 2018).

Invasive treatment of ST-segment myocardial infarction

After establishment of a working diagnosis of STEMI, which is usually based on symptoms consistent with ongoing myocardial ischaemia and ECG changes, reperfusion therapy should be commenced as soon as possible if no contraindications are present. The choice between primary PCI and fibrinolytic strategy depends on expected PCI-associated time delays: according to the latest European guideline, primary PCI is the preferable management strategy within 12 hours from symptom onset, provided it can be performed in a recommended

time frame by an experienced team (Ibanez et al, 2018). If timely (<120 minutes from a diagnosis) PCI cannot be performed, fibrinolytic therapy should be administered as soon as possible in patients without contraindications. This should be followed by emergent PCI as soon as possible in case of unsuccessful fibrinolysis (rescue PCI); in case of successful fibrinolysis, early coronary angiography and PCI of infarct-related artery should performed between 2 and 24 hours from a diagnosis (routine early PCI).

Based on principles presented in the position paper by the Acute Cardiovascular Care Organization (Bonnefoy-Cudraz et al, 2018), the Estonian Society of Cardiology has updated recommendations for the establishment of a formalized regional hospital network of acute coronary syndrome care to allow a vast majority of STEMI patients to benefit from primary PCI. According to the recommendations, STEMI patients should preferably be hospitalized into tertiary care hospitals with primary PCI availability 24 hours a day, 7 days a week (North-Estonia Medical Centre or Tartu University Hospital, first choice hospitals). If an expected delay from a STEMI diagnosis to reperfusion by PCI exceeds 120 minutes, the patient should be hospitalized into a secondary care hospital for fibrinolysis (second choice) with subsequent immediate transfer to the nearest first choice hospital. Hospitalization of STEMI patients into smaller community hospitals is not recommended (Figure 1).

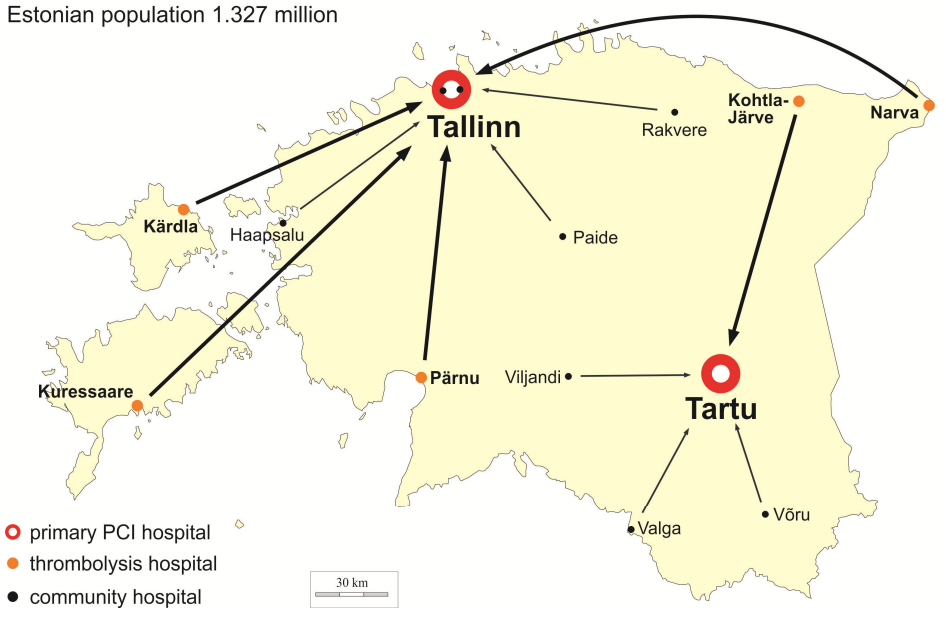


Figure 1. Recommendations for hospitalization of STEMI patients in Estonia in 2017. First choice hospitals are primary PCI hospitals (North Estonia Medical Centre in Tallinn and Tartu University Hospital in Tartu, red dots). Alternatively, patients could be hospitalized into second choice hospitals (Hiiumaa Hospital in Kärdla, Kuressaare Hospital in Kuressaare, Pärnu Hospital in Pärnu, Narva Hospital in Narva or Ida-Viru Central Hospital in Kohtla-Järve, orange dots) and transferred after fibrinolysis. Hospitalization into community hospitals (black dots) is not recommended.

Invasive treatment of NSTEMI

A majority of hospitalized NSTEMI patients should undergo invasive coronary angiography to a) confirm the diagnosis and clarify aetiology; b) identify the culprit lesion; c) establish possibility for coronary revascularization either via PCI or CABG; and d) ascertain their short- and long-term prognosis (Roffi et al, 2016). However, the decision for an invasive approach and the timing (angiography <2, 12 or 72 hours from a diagnosis of NSTEMI) depends on numerous factors, including patient characteristics like severity of condition at presentation, comorbidities, frailty, personal preferences or the presence of high-risk features like ongoing symptoms of ischaemia after initial treatment.

A recent meta-analysis of 8 RCTs indicated that although an invasive strategy improves the prognosis of all NSTEMI patients, most of the benefit comes from treating high-risk patients, for example, individuals with diabetes or the elderly (Fanning et al, 2016). This is in line with the principle that if the relative benefit from a treatment is similar, higher-risk patients have more to gain. The results highlight the importance of risk stratification in the management of NSTEMI in order to identify patients who are at increased risk for complications or death and to give these patients the benefits of treatment. The importance of formal risk stratification by means of validated risk scores is highlighted by guideline recommendations; ischaemic risk should be evaluated by the Global Registry of Acute Coronary Events (GRACE) risk score (Fox et al, 2006, 2014) and bleeding risk by the CRUSADE risk score (Subherwal et al, 2009).

The risk-treatment paradox

Previous research from developed countries with low CVD mortality has revealed that NSTEMI patients with the highest mortality risk are significantly less likely to receive evidence-based treatment (Fox et al, 2007a; Negers et al, 2017; Roe et al, 2006), a phenomenon called the risk-treatment paradox. Patients with diabetes mellitus (Gustafsson et al, 2015) or chronic kidney disease (Shaw et al, 2014), women (Amann et al, 2016) and the elderly (Devlin et al, 2008; Komócsi et al, 2016; Negers et al, 2017; Schoenenberger et al, 2008) are vulnerable groups whose treatment seems to be more influenced by this potentially harmful paradox. Possibly, clinicians are uncertain whether to opt for an invasive strategy in these high-risk patients, as the above-mentioned patients are frequently under-represented in clinical trials. Nevertheless, cohort studies have associated overall improved survival rates after NSTEMI mostly with the use of an invasive coronary strategy in intermediate- to high-risk patients (Hall et al, 2016).

Antithrombotic therapy

The main purposes of antithrombotic therapy for MI treatment include a) reducing the rate of acute ischaemic complications; b) preventing stent thrombosis if one is inserted; and c) preventing future ischaemic non-stent-related events (Roffi et al, 2016). Consequently, the recommendations for antithrombotic therapy are similar after STEMI and NSTEMI. Also, MI patients who are managed conservatively (i.e. PCI not performed) should receive dual antiplatelet therapy.

According to the European STEMI guideline, all patients undergoing primary PCI should receive dual antiplatelet therapy (DAPT), a combination of aspirin, a $P2Y_{12}$-receptor inhibitor (clopidogrel or ticagrelor) and a parenteral anticoagulant (preferentially unfractionated heparin) (Ibanez et al, 2016). Anticoagulation should be maintained until revascularization, if performed, or until hospital discharge. DAPT is indicated for 12 months, unless there are contraindications such as excessive bleeding risk. Aspirin is recommended indefinitely after a STEMI. STEMI patients who fail to receive reperfusion (e.g. delayed presentation, patient refusal) should nevertheless receive DAPT (aspirin and clopidogrel/ticagrelor) over 12 months and a parenteral anticoagulant until hospital discharge.

Similarly to STEMI, a combination of aspirin and a $P2Y_{12}$-receptor inhibitor for up to 12 months is recommended for all NSTEMI patients, irrespective of revascularization status (PCI, CABG or no revascularization) unless there are contraindications, like increased risk of bleeding. A parenteral anticoagulant is recommended until revascularization or until hospital discharge if PCI is not performed (Roffi et al, 2016).

Data from a large international registry suggest that NSTEMI patients undergoing revascularization more often received DAPT, whereas single antiplatelet therapy, either with aspirin or clopidogrel, was used more in conservatively managed patients (Bueno et al, 2016). One possible explanation for this finding includes the extension of the risk-treatment paradox to drug treatment – higher-risk patients, who often are denied coronary angiography, also tend to receive less guideline-recommended drugs, including DAPT (Motivala et al, 2011).

Currently there is an intense, ongoing debate about whether DAPT should be continued beyond the first 12 months after MI in order to prevent late and very late stent thrombosis as well as spontaneous MIs. However, as continued antiplatelet therapy comes with an increased bleeding risk (Bonaca et al, 2015), the current consensus does not support routine use of DAPT in all patients beyond the first year after MI, although according to the class IIb recommendation in the European guideline it may be considered (Roffi et al, 2016).

2.5 Secondary prevention after myocardial infarction

Despite significantly improved treatment during the acute phase of MI, the residual risk remains high, and recurrent ischaemic events happen in a substantial proportion of cases. For example, Stone with coauthors (2011) describes that 20% of acute coronary syndrome patients who were successfully treated with PCI experienced a major adverse CVD event during follow-up over three years. Approximately half of these events were related to initially treated coronary lesions and the other half with other previously untreated lesions, illustrating the systemic nature of atherosclerotic CVD. Consequently, all patients who have experienced MI are considered to be at a very high risk, and secondary prevention, including pharmacological treatment and risk factor management through lifestyle changes, is of paramount importance. The efficacy of secondary prevention in improving prognosis after MI has a strong evidence base, and both lifestyle changes and long-term pharmacological treatment have been shown to effectively reduce mortality (Chow et al, 2010; Ventura et al, 2019).

2.5.1 Pharmacological treatment

Beta-blockers

There is a strong consensus that beta-blockers are beneficial for MI patients with reduced left ventricular systolic function (Dargie et al, 2001). As no contemporary trial has properly evaluated the benefit of beta-blockers in patients with preserved ejection fraction, the evidence comes mostly from observational studies. Several recent studies, however, suggest no significant association between the use of beta-blockers among patients without heart failure or reduced left ventricular systolic function and clinical outcomes (Bangalore et al, 2012; Dondo et al, 2017). Consequently, European guidelines recommend long-term beta-blockers only for MI patients who have reduced left ventricular systolic function (ejection fraction [EF] <40%) or heart failure (Ibanez et al, 2018; Roffi et al, 2016). However, beta-blockers may be considered in all STEMI patients (Ibanez et al, 2018).

Angiotensin-converting enzyme inhibitors (ACEi)

Treatment with ACEi is recommended for STEMI patients with reduced left ventricular systolic function (EF <40%) or who have had symptoms of heart failure in the early phase; ACEi should be considered in all STEMI patients. In NSTEMI, ACEi are recommended for patients with reduced LV systolic function (EF <40%) and for patients with concomitant diabetes or hypertension. ARBs are an alternative if intolerance to ACEi appears (Ibanez et al, 2018; Roffi et al, 2016).

Lipid-lowering drugs

High intensity lipid-lowering therapy with statins is indicated for all patients early after acute MI, irrespective of lipid levels at presentation, as treatment reduces adverse events and improves survival after MI largely irrespective of initial lipid levels (Baigent et al, 2005). The net absolute benefit from statin therapy depends on absolute LDL-cholesterol reduction achieved, and therefore the LDL-cholesterol goal for high-risk post-MI patients is set to as low as <1.8mmol/L or at least a 50% reduction if the baseline is between 1.8–3.5mmol/L (Ibanez et al, 2018; Roffi et al, 2016).

Several other non-statin drugs (selective cholesterol uptake inhibitor ezetimibe [Cannon et al, 2015] and proprotein convertase subtilisin/kexin type 9 inhibitors evolocumab [Sabatine et al, 2017] and alirocumab [Schwartz et al, 2018]) have been investigated to decrease the residual risk after MI. However, based on this relatively limited body of evidence, a non-statin lipid-lowering therapy should currently be considered only in very high-risk patients who do not reach LDL-cholesterol treatment goals despite a maximally tolerated statin dose.

2.5.2 Non-pharmacological treatment

Although drug treatment has taken the forefront in secondary prevention of MI, non-pharmacological measures should not be overlooked as equally important targets for improving prognosis. Lifestyle modification, including following a Mediterranean-like diet, smoking cessation and exercise have proven to be effective preventive interventions in post-MI patients (Chow et al, 2010). The main components and goals of non-pharmacological secondary prevention do not differ significantly from the ones in primary prevention (Piepoli et al, 2015).

Based on a general principle that the potential benefits of an intervention are dependent on a patient's baseline risk multiplied by the relative risk reduction caused by an intervention, high-risk post-MI patients have larger absolute benefits when compared to healthy individuals to whom primary prevention is targeted. For example, a recent systematic review found that exercise-based cardiac rehabilitation leads to a 26% relative risk reduction in CVD mortality in a median follow-up of 1 year (Anderson et al, 2016). Given the 1-year mortality rate of <80 years old MI patients of around 15% (Jernberg, 2018), this relative risk reduction of 26% does give a meaningful survival benefit. Based on these data, the European guidelines state that all patients should be advised on necessary lifestyle modifications during hospitalization and should participate in a cardiac rehabilitation program to ensure implementation of these changes (Ibanez et al, 2018; Roffi et al, 2016).

2.6 Mortality after myocardial infarction

Sources of outcome data

Measuring and comparing MI outcomes between and within populations is complex, as data sources track different outcomes, use varying definitions and include patient cohorts with differing baseline risk levels. Generally, three main sources can be used to collect information on the outcomes of MI: RCTs, clinical registries, and administrative databases.

RCTs, which are the gold standard for studying treatment efficacy, are capable of providing information on outcomes. Despite uniformly defined outcomes and precise measuring of these outcomes, these results have limited usefulness, as trials include selected patient populations, and findings on mortality outcomes are not generalizable to the entire population. Thus, mortality rates recorded in RCTs are generally lower than those seen in registries or administrative databases. An example of how RCTs reflect temporal mortality changes could be drawn from two lipid-lowering secondary prevention trials – 4S on simvastatin, published in 1994, and FOURIER on evolocumab, published in 2017 (Pedersen et al, 1994; Sabatine et al, 2017). In the 4S placebo group, 68 out of 418 MIs (16.3%) were fatal during the follow-up period, while only 30 out of 639 (4.7%) were fatal in the placebo group of FOURIER, indicating a significant mortality reduction over the last decades.

The second source for MI outcomes research – administrative data – is primarily collected for other purposes than scientific. These data sets provide a cheap and easily available source of information reflecting everyday clinical practice over long periods of time. The wide scope of administrative data is often considered its main value for research purposes. The biggest limitation of administrative data is usually an insufficient amount of clinical information. Furthermore, administrative databases may not be accurate enough for research purposes due to the absence of control that the researchers have during data collection.

The scope of clinical registries lies somewhere between that of trial data and of administrative databases. Registries collect data systematically with broad inclusion and few exclusion criteria, aiming to be representative of routine clinical practice. While registries are highly effective in tracking temporal trends within a population, the comparison of raw data between registries remains challenging, as registries use different outcome definitions and slightly different inclusion criteria. Using risk standardization to eliminate selection bias, the comparison of different registries can be used to benchmark quality and explore a health system's performance.

Chung with coauthors (2014) compared the treatment and outcomes of MI in Sweden and the UK – two countries with national MI registries with nationwide coverage. They included all consecutive patients hospitalized for acute MI between 2004 and 2010 and found clinically significant differences: case-mix standardized 30-day mortality was lower in Sweden (7.6%, 95% CI 7.4–7.7%)

than in the UK (10.5%, 95% CI 10.4–10.6%), which they attributed to the delayed adoption of effective MI treatments in the UK.

Several studies have aimed to compare mortality rates between countries and health care systems based on registry data (Kristensen et al, 2014; Smith et al, 2014), but this approach may be misleading due to great variation in patient selection criteria (i.e. suspected or discharge diagnosis of acute coronary syndrome, unstable angina included or only MIs, only patients treated in PCI centres, etc.). In other words, referring to certain mortality numbers can cause confusion, while describing temporal trends within the same setting would produce more meaningful results.

Despite all of the described methodological problems, data from all three above-mentioned sources agree that there has been a fall in short- and long-term mortality after MI over the last decades (Jernberg et al, 2011; Fox et al, 2007b; Radovanovic et al, 2017; Sugiyama et al, 2015; Szummer et al, 2017, 2018). The decline in short-term mortality after MI has been associated with improved in-hospital treatment mostly due to greater use of an invasive coronary strategy but also to increased use of guideline-recommended pharmacotherapies (Hall et al, 2016).

Short- and long-term outcome data

Short-term, usually in-hospital and 30-day mortality rates are commonly used as indicators of quality of care after MI. Whether short-term mortality differences are translated into differences in the long-term is less certain, as long-term mortality is influenced by several other factors, such as secondary prevention and concomitant diseases. However, a study that used administrative data of 119,735 patients and followed them over 17 years demonstrated a significant survival advantage for patients treated in high-performing hospitals (defined as the lowest quintile of 30-day risk standardized mortality rate). Patients who were treated in high-performing hospitals lived on average between 0.74 and 1.14 years longer, compared to those treated in low-performing hospitals (Bucholz et al, 2016). A study that included only STEMI patients also found a decrease in in-hospital, 30-day and 1-year mortality, which was sustained over a mean follow-up of 12 years (Jernberg et al, 2011). Both of these studies indicate that a short-term survival advantage gained by competent in-hospital management persists over long-term follow-up and provides a meaningful survival gain, illustrating the importance of high-quality acute MI management.

2.7 Estonian Myocardial Infarction Registry

The Estonian Myocardial Infarction Registry (EMIR) is a national registry which was founded in 2012 by the Public Health Act and is funded by the Estonian Ministry of Social Affairs. It is maintained by Tartu University Hospital and has a scientific board consisting of 10 members. EMIR was founded to

enable continuous monitoring of MI diagnostics and treatment quality and to facilitate conducting epidemiological studies. Since 2012, it is mandatory to submit information on all hospitalized MI cases; consequently, EMIR includes an unselected nationwide cohort of MI patients.

Information is submitted to EMIR through an electronic form, and data entry is shared by physicians and specifically trained secretaries. Data are collected according to the Cardiology Audit and Registration Data Standards (CARDS) project (Flynn et al, 2014) and includes each patient's personal identification number, demographical data, medical history, data about MI and associated time points, diagnostic and treatment methods used, in-hospital mortality and adverse events, and medications recommended at discharge. Using the personal identification number, which is unique to each inhabitant of Estonia, enables data linkage with other national databases, for example the Population Register. EMIR provides annual feedback by producing general reports for public use and hospital-specific reports for all participating hospitals.

2.8 Summary of the literature

To comprehensively tackle high mortality from CVD, more attention should be paid to primary prevention of the disease. The need is greatest in countries with high CVD mortality rates, which usually coincide with high prevalence of risk factors, e.g. hypertension and dyslipidaemia. The main purpose of primary prevention is finding the individuals with the highest risk for developing a disease and treating them to prevent it. To do this, several risk estimation tools have been developed and validated using large cohort studies mostly from countries with low ischaemic heart disease incidence and mortality rates. These data are missing for countries with high CVD risk. The lack of data on risk scores' performance may be among the reasons why the level of primary prevention has remained suboptimal in these countries – clinicians may be reluctant to use these scores, as inaccurate risk estimates can lead to under- or overtreatment.

Improved treatment of MI reduces overall CVD mortality, which has been demonstrated by several previous cohort studies. Pharmacological treatment and invasive coronary strategies that have proven to be beneficial in RCTs are incorporated into practice through the creation and dissemination of clinical practice guidelines. Adherence to the guidelines and possible effects on outcomes in routine clinical practice could be investigated using registry data. Currently, most of the data on acute coronary syndromes comes from high-income developed countries, e.g. the UK and Sweden, which have a significantly different CVD morbidity and mortality profile than Estonia. To date, high-quality data on non-selected MI patient populations are missing for countries with high CVD mortality rates, where the need for such information is greatest.

3. AIMS OF THE THESIS

The general purpose of this thesis is to describe the current situation in the prevention, management and outcomes of ischaemic heart disease in Estonia and to explore reasons behind high mortality rates from this disease.

To achieve this, the three aims of the thesis are as follows:

First, to characterize the predictive ability of widely used risk scores – PCE, QRISK2 and SCORE – in Estonia and to estimate their direct clinical utility in primary prevention of MI and CVD in general (paper I).

Second, to describe trends in short- and long-term mortality rates after hospitalization for acute MI over the period 2001–2011 in Estonian secondary and tertiary care hospitals while considering changes in baseline characteristics and treatment (paper II).

Third, to describe the treatment of NSTEMI in Estonia according to patients' estimated mortality risk on admission as evaluated by the GRACE risk score and to investigate the impact of treatment on prognosis in different risk categories (paper III).

4. METHODS

4.1 Study design

This thesis is based on three nationwide cohort studies. The first paper is based on a population-based cohort of the Estonian Genome Centre – the Estonian Biobank; follow-up data were obtained via linkage to the Estonian Health Insurance Fund (EHIF) database and the Estonian Causes of Death Register (paper I). The second study uses hospital records as a primary data source; for follow-up information the patient-level data were linked to the Estonian Population Registry (EPR, paper II). The third paper is based on data from Estonian Myocardial Infarction Registry (EMIR), which was linked to the EHIF database and the EPR (paper III).

All studies were approved by the Research Ethics Committee of the University of Tartu and comply with the Declaration of Helsinki.

4.2 Databases

The Estonian Biobank (n=51603) is a population-based cohort recruited between 2002 and 2011, and it includes information about adult individuals (aged 18+) from all counties of Estonia across all age and gender categories, as described in detail previously (Leitsalu et al, 2014). Detailed data on demographics, lifestyle and health status are available for each individual at recruitment with prevalent diseases recorded according to the International Statistical Classification of Diseases 10th revision (ICD-10).

The Estonian Causes of Death Register collects data on all cases of death registered on the Estonian territory and in Estonian foreign missions. The data are gathered in the form of death certificates. These are filled in by all doctors and forensic pathologists who have ascertained death.

The Estonian Population Register (EPR) is a database which contains the main personal data on Estonian citizens. For papers II and III the data on death (the time of death) or emigration (the time of emigration) were retrieved from the population register.

The Estonian Health Insurance Fund (EHIF) database contains information on confirmed diagnoses (i.e. acute MI I21–I22, stroke I60–I63 according to ICD-10) and performed procedures (according to the Nordic Medico-Statistical Committee Classification of Surgical procedures version 1.6). As EHIF is the only organization in Estonia dealing with compulsory health insurance and covers approximately 95% of the 1.3 million inhabitants, the database contains information on virtually all contacts with health care services. The validity against international diagnostic criteria of MI and stroke diagnoses in the EHIF database has been established previously (Ainla et al, 2005; Kõrv et al, 2010).

Estonian Myocardial Infarction Registry (EMIR) is an ongoing nation-wide register established in 2012 with mandatory reporting of all hospitalized acute MI cases (I21−I22 according to the ICD-10) in Estonia. The completeness and accuracy of the data are subject to routine error checking. According to the internal audit conducted for paper III, case coverage was approximately 95% for the study period.

All data linkages were done using personal identification numbers unique to all inhabitants of Estonia; the linkages were deterministic and 100% successful.

4.3 Study populations

Paper I

The formation of the study sample is depicted in Figure 2.

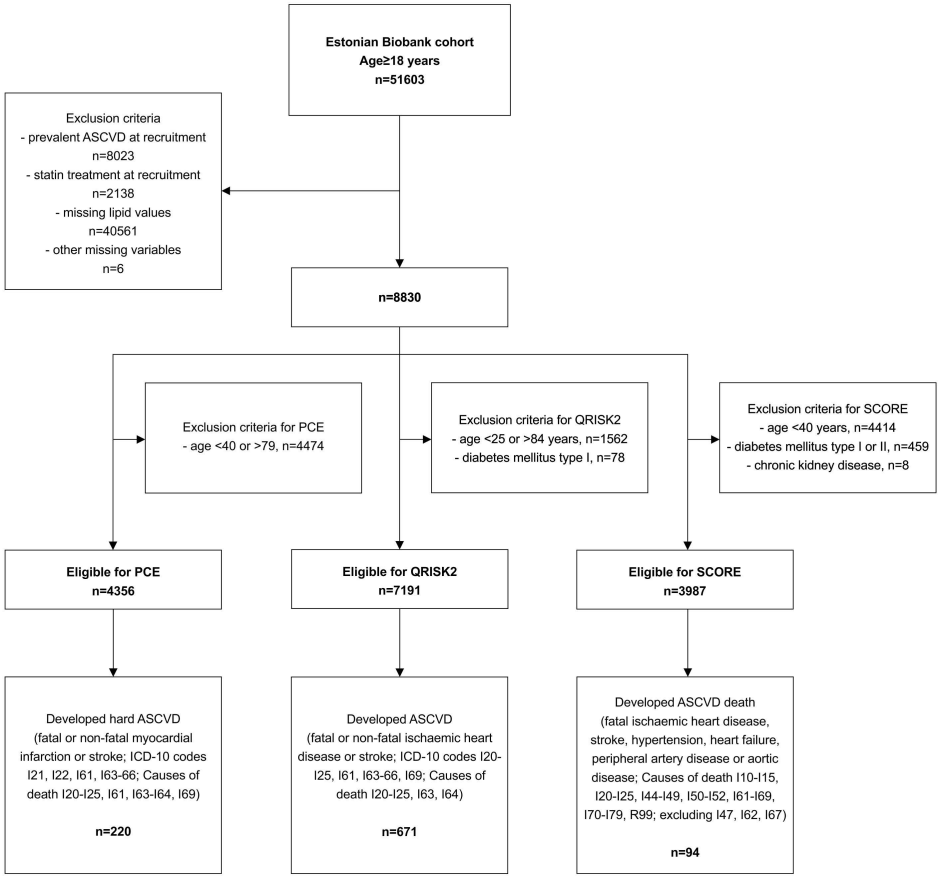


Figure 2. Formation of the study population in paper I.

PCE – Pooled Cohort Equations, SCORE – Systematic COronary Risk Estimation, ASCVD – atherosclerotic cardiovascular disease, ICD-10 – International Statistical Classification of Diseases and Related Health Problems 10th Revision

As the scope of the study was primary prevention of CVD, individuals with prevalent atherosclerotic CVD (ischaemic heart disease, ischaemic or haemorrhagic stroke, transient ischaemic attack, peripheral artery disease, coronary or other arterial revascularization procedure [ICD-10 codes I20-I25, I61, I63-I69, I70, G45, Z95.1, Z95.5, Z95.8, Z95.9]) or individuals on statin therapy were excluded. Only individuals who had their lipid values (total cholesterol and HDL-cholesterol) measured at recruitment were included in the study. After the exclusions, the final study sample consisted of 8830 individuals. For analyses investigating the performance of each risk score, exclusion criteria based on score-specific guideline recommendations (Goff et al, 2014; NICE, 2014; Piepoli et al, 2016), were applied. For a head-to-head comparison, an overlap of the three score-specific subsets was formed (n=4296), restricted to the age range 40–79 (n=4296, 67% women, 8% with diabetes).

Paper II

The study includes a representative sample of all hospitalized MI cases from the years 2001, 2007 and 2011 (Figure 3). The list of all MI cases for each year was obtained from the Estonian Health Insurance Fund (EHIF) database. According to the EHIF database, the total number of MI cases hospitalized (main diagnosis code I21-I22 according to the ICD-10) was 2365 in 2001, 3251 in 2007 and 3488 in 2011. As the intention was to evaluate the treatment of MI in the hospital where each patient was primarily hospitalized, the following exclusion criteria were applied: a) patients who were not primarily hospitalized into one of the study hospitals; b) patients who were re-admitted with MI diagnosis within 28 days after the first admission (only the second admission was excluded); c) patients whose length of hospital stay was less than 3 days if they were discharged alive and were not transferred, which made the diagnosis of MI very unlikely.

From the remaining cases a study sample was formed by the use of random selection. The sampling was performed separately in each participating hospital in order to get a cross-sectional overview of all cases admitted into different types of hospitals. To ensure data comparability across years, the formation of the study sample was similar in 2001, 2007 and 2011.

Medical records from the study hospitals were obtained, and data were collected retrospectively by experts according to the data standards for acute coronary syndromes later presented in the CARDS Project (Flynn et al, 2005). The experts were certified cardiologists or cardiologists in training and all had received additional instructions on data collection for the study. Every MI case was reviewed by one expert, which was followed by random re-abstraction by another expert for data quality monitoring purposes. If discrepancies were determined, the experts were additionally trained. Data on mortality were obtained from the Estonian Population Registry. The criteria applied for MI diagnosis on 2001 and 2007 study populations were based on the first universal definition of MI (Alpert et Thygesen et al, 2000). For the 2011 cohort, the

criteria were based on the second definition of MI published in 2007 (Thygesen et al, 2007). As the aim of the study was to evaluate the quality of care in the first hospital where the patient was admitted, data collection stopped after the patient was transferred from a secondary care to a tertiary care hospital. Data on discharge medications were available only for those secondary care patients who were not transferred to a tertiary care hospital.

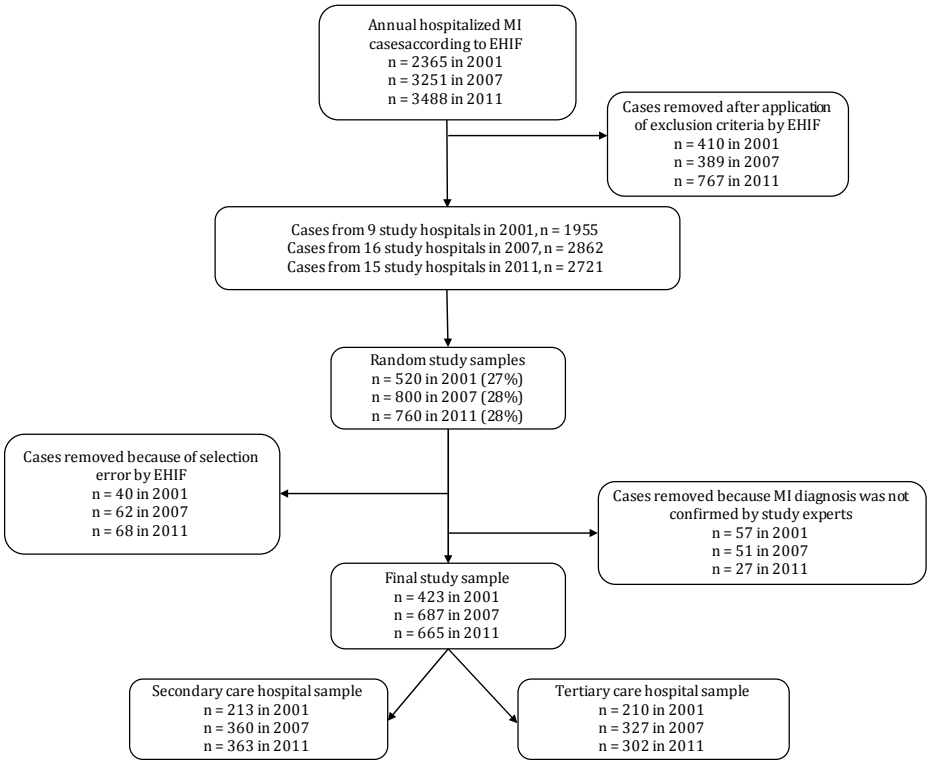


Figure 3. Formation of the study sample in paper II

MI – myocardial infarction, EHIF – Estonian Health Insurance Fund

Paper III

The study included all patients hospitalized in Estonia from 2012 to 2014 with a final diagnosis of NSTEMI according to the Estonian Myocardial Infarction Registry (EMIR) (Figure 4). The diagnosis was made by the treating physician based on symptoms, clinical signs and results of inpatient investigations using the third universal definition of MI (Thygesen et al, 2012). Patients with a missing personal identification number (n=3) or missing post-discharge mortality information (n=6) were excluded from the cohort. If a patient was re-hospitalized with NSTEMI during the study period (n=256), then the first hospi-

talization was considered as the start of follow-up and the subsequent hospitalization as an outcome event.

EMIR provided patient-level data on baseline characteristics, time of symptom onset, diagnostics and treatment during the hospitalization period, in-hospital complications and recommendations for outpatient drug treatment.

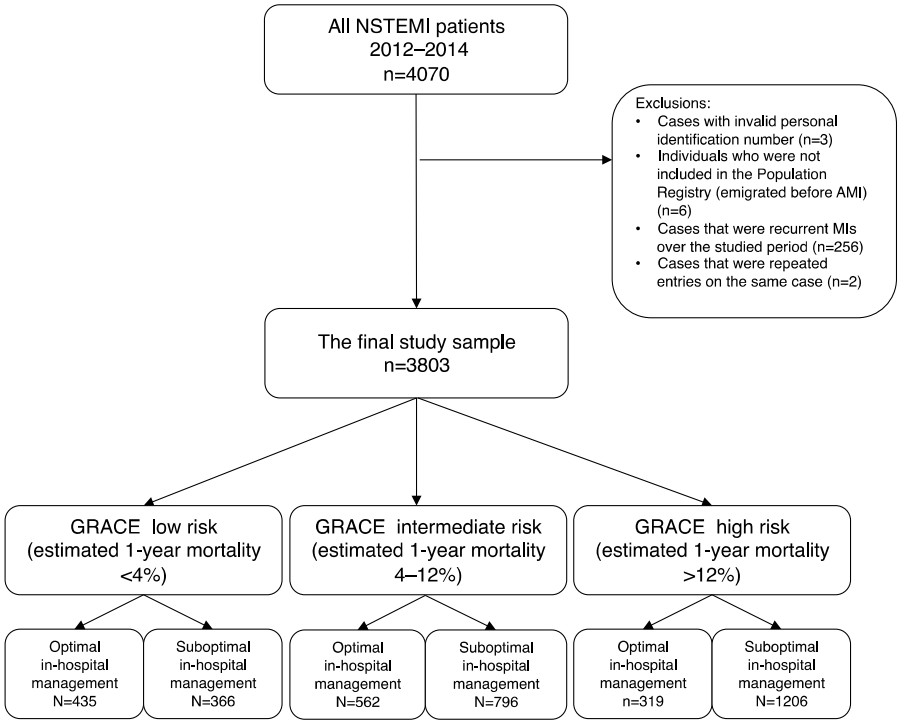


Figure 4. Formation of study sample in paper III. Patients were stratified according to their estimated 1-year mortality risk according to the GRACE risk score (http://www.gracescore.org/WebSite/WebVersion.aspx). Optimal in-hospital management defined as concomitant use of coronary angiography, aspirin, $P2Y_{12}$-receptor inhibitor, statin, beta-blocker, ACEi/ARB and parenteral anticoagulant. All patients who missed at least one above-mentioned treatment were classified into the suboptimal in-hospital management group.

GRACE – The Global Registry of Acute Coronary Events, NSTEMI – non-ST-segment elevation myocardial infarction, AMI – acute myocardial infarction, MI – myocardial infarction, GRACE – The Global Registry of Acute Coronary Events

4.4 Study outcomes

Paper I

The outcome of Pooled Cohort Equations – 10-year risk of developing hard atherosclerotic CVD (first diagnosis of nonfatal MI, ischaemic heart disease death, fatal or nonfatal stroke).

The outcome of QRISK2 – 10-year risk of developing atherosclerotic CVD (first diagnosis of ischaemic heart disease, stroke or transient ischaemic attack).

The outcome of SCORE – 10-year risk of cardiovascular mortality (fatal ischaemic heart disease, stroke, hypertension, heart failure, peripheral artery disease or aortic disease).

The median follow-up time of the study sample was 7.8 years. As more than 70% of the individuals were followed for at least 7 years, the score-specific events were censored at 7 years, and the original scores of 10-year risk were modified to obtain 7-year risk estimates using the methodology proposed by Viallon and coauthors in 2009 that takes into account individual's event status.

Paper II

30-day and 1-year all-cause mortality of acute MI patients from the years 2001, 2007 and 2011; analysed according to the hospital type (secondary or tertiary care) where the patient was initially hospitalized.

Paper III

Death or a non-fatal event (recurrent MI, stroke, unplanned revascularization by PCI or coronary artery bypass grafting) of NSTEMI patients from the period 2012 – 2014. The follow-up period started on the day of hospitalization for NSTEMI and ended on 31 December 2015, resulting in a mean follow-up of 2.4±1.3 years. The analysis was stratified according to patients' estimated mortality risk at admission.

4.5 Statistical analysis

Paper I

Cox proportional hazard models were fitted for each outcome with the 7-year risk score estimate as the only covariate. Subsequently, Harrell's C-statistic was extracted to assess the discriminative ability of the risk score (Pencina et al, 2014). Calibration of the risk scores was explored using standardized incidence ratios (SIRs, expected number divided by observed number of events) and calibration plots. The expected number of events was calculated as the sum of the modified 7-year risk scores in the eligible subset of individuals.

A head-to-head comparison of the scores was performed at the intersection of the three score-specific sub-cohorts. The level of education was used as a proxy for the Townsend deprivation index in calculating the QRISK2 score. The predictive ability of the risk scores was assessed by Harrell's C-statistic for all score-specific outcomes. The pairwise differences between the C-statistics corresponding to the scores were calculated, and 99% confidence intervals were obtained with bootstrapping to compensate for multiple testing.

To illustrate the implications of risk prediction, three categories of recommendations for statin treatment were formed based on the ACC/AHA, NICE, and ESC guidelines (NICE, 2014; Piepoli et al, 2016; Stone et al, 2014) on a common subset of individuals who were eligible for risk evaluation by all three risk scores (n=3729, aged 40–70 without type I or II diabetes and chronic kidney disease). According to the ACC/AHA guidelines, statins for primary prevention are recommended for individuals with a) LDL $\geq$ 4.9 mmol/L, b) aged 40–75 years with LDL 1.8–4.9 mmol/L and diabetes mellitus, c) aged 40–75 years with LDL 1.8–4.9 mmol/l and estimated 10-year risk for developing hard atherosclerotic CVD according to PCE $\geq$ 7.5%; statins for primary prevention should be considered for individuals with a) diabetes mellitus who are <40 or >75 years or with LDL <1.8mmol/L, b) aged 40–75 years with LDL 1.8–4.9 mmol/L and estimated 10-year risk for developing hard ASCVD according to PCE 5–7.5% (Stone et al, 2014). According to the NICE guidelines, statins are recommended for individuals with a) estimated risk of developing atherosclerotic CVD according to QRISK2 $\geq$10%, b) diabetes mellitus type I, c) chronic kidney disease (NICE, 2014). The European Society of Cardiology guidelines regarding using statins for primary prevention depend on the 10-year risk of developing fatal atherosclerotic CVD estimated by SCORE and on the baseline LDL-cholesterol level (Piepoli et al, 2016).

Paper II

For all patient characteristics and outcome variables of interest, comparisons between three years (2001, 2007 and 2011) and two types of hospital (tertiary and secondary care) of primary hospitalization were made. In addition to crude mortality rates, baseline-adjusted (age, sex, MI subtype, diabetes, hypertension, previous heart failure, previous MI) mortality rates were compared using the Cox proportional hazards model. Patients initially hospitalized into a secondary care hospital but transferred and treated in a tertiary care hospital were included in the mortality analysis as secondary care patients.

Paper III

The estimated probability of 1-year mortality according to the GRACE risk score using age, systolic blood pressure, heart rate, serum creatinine, Killip class, and presence of ST-segment deviation, positive initial cardiac markers and cardiac arrest at presentation was calculated for each patient (Fox et al,

2014). For patients with missing creatinine value (29%) or Killip class (18%), the components were substituted with a history of renal failure and the use of diuretics, respectively, as suggested in the original publication. The proportion of other missing GRACE variables varied from 0.5% (cardiac arrest at presentation) to 9% (ST-segment deviation, cardiac markers), and they were imputed by predictions based on other available covariates using the MICE package in R (van Buuren et al, 2011). Based on the estimated 1-year mortality risk, all patients were then assigned either to a low (<4%), intermediate (4–12%) or high (>12%) risk category.

To estimate the effect of in-hospital management on outcomes across the three risk categories, in-hospital management of each patient was classified as being either optimal or suboptimal. Optimal in-hospital management was defined as concomitant use of coronary angiography, aspirin, a $P2Y_{12}$-receptor inhibitor, a statin, a beta-blocker, an ACEi/ARB and a parenteral anticoagulant among patients with a class I guideline indication to the treatment; patients not having received at least one of the abovementioned treatments during the initial hospitalization for which they had a class I guideline recommendation were classified into suboptimal management group. Drug-specific contraindications, allergies and patients' refusals were not taken into account. Only in-hospital pharmacological treatment was considered while dividing patients into optimal and suboptimal treatment categories, as discharge recommendations were available only for patients who survived the hospital period and were discharged home.

Patients who died in hospital during the first 24 hours after admission (n=94) were removed from the analysis investigating the association between in-hospital treatment and long-term outcomes, as their serious condition at presentation might have prevented them from receiving guideline-indicated care.

The incidence of outcomes was compared between optimally and suboptimally managed patients, using the Cox regression.

To further investigate whether the effect of in-hospital treatment differs between GRACE risk groups, an interaction between in-hospital treatment and GRACE risk was tested. To provide sufficient statistical power, the in-hospital treatment status (optimal or suboptimal treatment) was transformed into a continuous variable (count of received in-hospital treatments divided by all the recommended treatments and GRACE risk category transformed back into the GRACE 1-year mortality probability).

Data in all papers are summarized using percentages for categorical data and means with standard deviations or medians with interquartile ranges for continuous variables. Two-sided P values <0.05 were considered statistically significant, unless specified otherwise. For all analyses, R software (version 3.3.2 in the paper I and version 3.1.1 in the papers II and III) was used (R Development Core Team, 2008).

5. RESULTS

5.1 The performance of PCE, QRISK2 and SCORE in Estonia (paper I)

Baseline characteristics

The mean age of the study sample (n=8830) was 40.8 years, and 64.1% were women. According to the guideline-specific exclusion criteria, 4356, 7191 and 3987 persons were eligible for the calculation of PCE, QRISK2 and SCORE risk estimates, respectively (Figure 2).

The average 7-year risk for hard atherosclerotic CVD estimated by PCE was 5.5% (8.7% in men and 3.9% in women), for atherosclerotic CVD based on QRISK2 was 5.1% (7.3% in men, 3.9% in women), and the average 7-year risk for atherosclerotic CVD mortality estimated by SCORE was 2.5% (4.4% in men and 1.5% in women).

Discrimination

During the follow-up of 7 years, 220, 671 and 94 score-specific events occurred according to PCE (hard atherosclerotic CVD), QRISK2 (atherosclerotic CVD) and SCORE (fatal atherosclerotic CVD), respectively. The Harell's C-statistics corresponding to the model with risk score as the only covariate were 0.778, 0.812 and 0.865 for the PCE-, QRISK2- and SCORE-specific outcomes, respectively.

As expected, individuals with incident atherosclerotic CVD events had on average higher risk estimates than those without (Figure 5). However, there was a great overlap in the risk estimates of events and non-events. For roughly a quarter of men and one third of women who developed a score-specific outcome during the follow-up, the estimated risk was lower than 5%, generally referred to as moderate or low risk. While SCORE discriminates cases from non-cases most accurately in women, the risk estimates by QRISK2 are more similar across sexes.

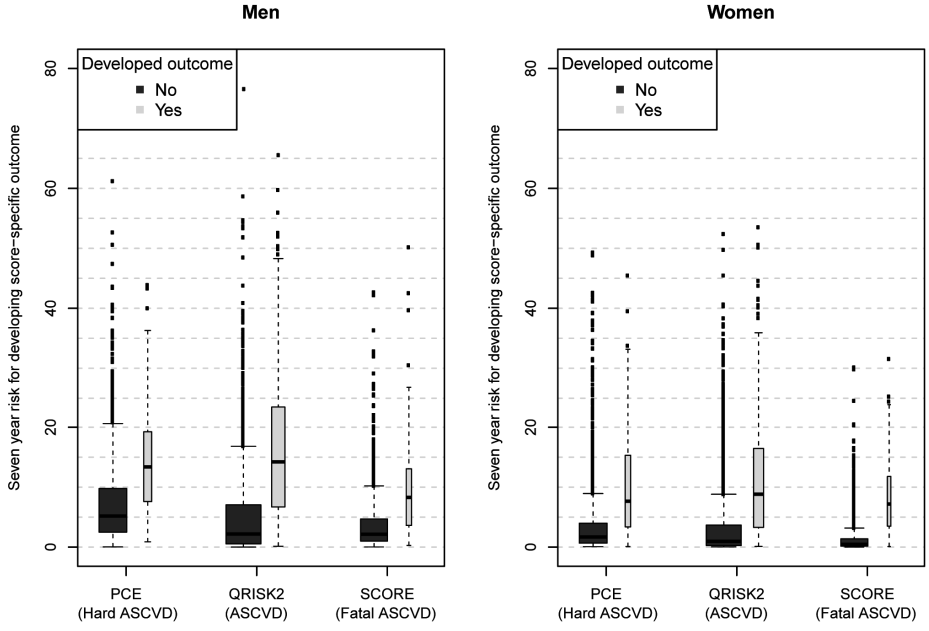


Figure 5. Risk estimation distributions in individuals who developed an outcome and in those who did not. N_{PCE}= 3374, N_{QRISK2}=7191, N_{SCORE}=3987.

PCE – Pooled Cohort Equations, SCORE – Systematic COronary Risk Estimation; ASCVD – atherosclerotic cardiovascular disease

Calibration

While 220 hard atherosclerotic CVD events occurred during the 7-year follow-up period, PCE predicted 227.1 events among the eligible individuals, which means there were 3.2% more expected cases than observed (Table 2). QRISK2 heavily underestimated the risk of atherosclerotic CVD, as 47.8% fewer cases were expected than observed, and SCORE predicted 1.1% fewer atherosclerotic CVD deaths than occurred. Calibration plots in Figure 6 illustrate prediction accuracy in different risk quintiles.

Table 2. Calibration accuracy evaluated by standardized incidence ratios

Risk score Outcome	**PCE** Hard ASCVD events	**QRISK2** ASCVD events	**SCORE** Fatal ASCVD events
Observed events	220	671	94
Men (n)	110	312	49
Women (n)	110	359	45
Expected events	227	350	92
Men (n)	118	169	54
Women (n)	108	180	38
SIR (all)	1.03 (95% CI 0.90–1.18)	0.52 (95% CI 0.48–0.56)	0.99 (95% CI 0.81–1.21)
SIR (men)	1.08 (95% CI 0.90–1.30)	0.54 (95% CI 0.49–0.61)	1.1 (95% CI 0.83–1.46)
SIR (women)	0.99 (95% CI 0.82–1.19)	0.5 (95% CI 0.45–0.56)	0.86 (95% CI 0.64–1.15)

ASCVD – atherosclerotic cardiovascular disease, PCE – Pooled Cohort Equations, SCORE – Systematic COronary Risk Estimation, SIR – standardized incidence ratio

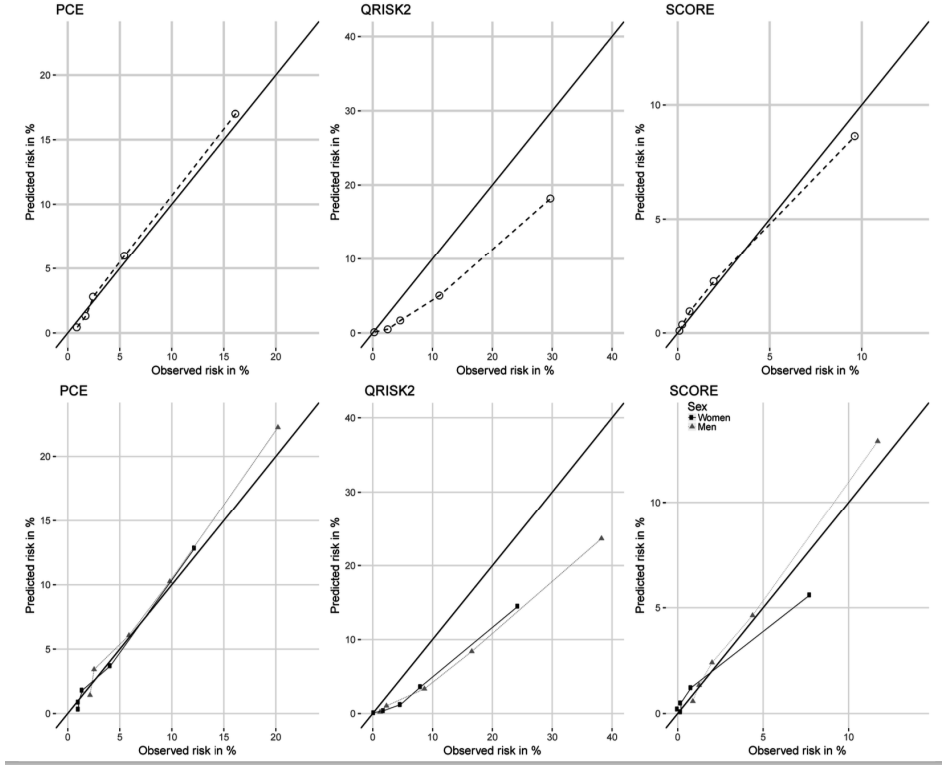


Figure 6. Calibration plots illustrating scores' performance in different risk quintiles over the follow-up period of 7 years.
A) Overall calibration in score specific subsets; B) Calibration estimated separately for men and women; PCE – Pooled Cohort Equations, SCORE – Systematic COronary Risk Estimation

Head-to-head comparison

In the common sample of 4296 individuals, there occurred 213 PCE outcome events (hard atherosclerotic CVD), 609 QRISK2 outcome events (fatal or non-fatal atherosclerotic CVD) and 98 SCORE outcome events (fatal atherosclerotic CVD) during the 7-year follow-up. While the QRISK2 displayed the highest Harell's C-statistics for hard atherosclerotic CVD, as well as fatal or non-fatal atherosclerotic CVD events, no statistically significant differences were found between the predictive ability of the three scores (Table 3).

Table 3. Head-to-head comparison of the risk scores for predicting hard atherosclerotic cardiovascular disease, fatal or non-fatal atherosclerotic cardiovascular disease, and fatal atherosclerotic cardiovascular disease according to Harrell's C-statistic.

	C_{PCE}	C_{QRISK2}	C_{SCORE}	$\Delta(C_{PCE}\text{-}C_{SCORE})$ (99% CI)	$\Delta(C_{QRISK2}\text{-}C_{SCORE})$ (99% CI)	$\Delta(C_{QRISK2}\text{-}C_{PCE})$ (99% CI)
Hard ASCVD n=213	0.778	0.781	0.767	0.0109 (–0.0044, 0.0248)	0.0139 (–0.0108, 0.0385)	0.0030 (–0.0115, 0.0201)
Fatal or non-fatal ASCVD n=609	0.724	0.731	0.718	0.0062 (–0.0070, 0.0166)	0.0117 (–0.0022, 0.0244)	0.0055 (–0.0018, 0.0150)
Fatal ASCVD n=98	0.843	0.839	0.835	0.0080 (–0.0145, 0.0287)	0.0047 (–0.0279, 0.0376)	–0.0033 (–0.0211, 0.0128)

PCE – Pooled Cohort Equations, SCORE – Systematic Coronary Risk Estimation, ASCVD – atherosclerotic cardiovascular disease, CI – confidence interval

5.2 Treatment and outcomes after acute myocardial infarction in Estonia in 2001, 2007 and 2011 (paper II)

Baseline characteristics

The final study sample included 423, 687, and 665 cases from the years 2001, 2007 and 2011, respectively. Although the mean age of the study sample increased in both hospital types during the period, there were no significant changes in the frequency of most comorbidities, with the exception of hypertension in secondary care hospitals (Table 4). The results show an increased proportion of patients with NSTEMI compared to that of patients with STEMI in both hospital types over time.

Table 4. Baseline characteristics of myocardial infarction patients hospitalized primarily into tertiary and secondary care hospitals in the years 2001, 2007 and 2011

	Tertiary care hospitals				**Secondary care hospitals**			
	2001	2007	2011	P for trend	2001	2007	2011	P for trend
Hospital days, mean, (SD)	11.4(9.1)	10.0(8.4)	9.2(6.5)	0.002	11.4(6.8)	9.4(7.6)	6.5(6.3)	<0.001
Mean age (SD), years	68.3 (12.7)	69.7 (12.0)	71.0(12.0)	0.015	68.4 (12.4)	71.8(11.4)	72.8(12.2)	<0.001
≥75 years, %	31.0	37.0	41.4	0.017	34.3	44.7	47.4	0.002
Men, %	66.7	58.1	62.3	0.3	52.1	51.9	48.5	0.4
STEMI, %	61.9	49.5	53.0	0.043	59.6	51.4	44.4	<0.001
Diabetes mellitus,%	19.0	27.2	26.2	0.065	16.4	31.1	21.5	0.225
Hypertension,%	70.0	70.0	75.2	0.206	57.3	75.8	74.7	<0.001
Previous MI, %	29.5	29.4	29.1	0.925	23.9	27.2	30.9	0.073
Previous heart failure, %	27.1	28.1	25.2	0.626	26.8	31.7	32.2	0.176
Time to presentation (hrs),	%	%	%		%	%	%	0.993
≤3	47.6	41.9	44.7		31.0	30.6	30.0	
3–12	23.8	24.8	23.2		25.8	25.0	26.4	
>12	28.6	33.3	32.1		43.2	44.4	43.5	

SD – standard deviation, STEMI – ST-segment elevation myocardial infarction, MI – myocardial infarction

Treatment

Guideline-recommended treatments were more likely to be used for patients hospitalized in 2011 than in the earlier years in both hospital types (Table 5). Cardiac catheterization and percutaneous revascularization if possible had become a dominant strategy in the tertiary care setting by the year 2011.

Table 5. In-hospital management of MI patients hospitalized primarily into tertiary and secondary care hospitals

	Tertiary care				**Secondary care**			
	2001 n=210	2007 n=327	2011 n=302	P for trend	2001 n=213	2007 n=360	2011 n=363	P for trend
	%	%	%		%	%	%	
Medications								
Aspirin	87.1	94.2	94.4	0.003	88.3	86.4	85.7	0.383
$P2Y_{12}$-inhibitors	17.1	61.5	70.5	<0.001	0	10.6	26.4	<0.001
Anticoagulants	89.0	93.0	92.7	0.133	85.4	92.8	95.0	<0.001
GP IIb/IIIa-b	12.4	38.8	29.1	<0.001	0.5	3.1	5.2	0.003
Beta-blockers	79.5	82.6	82.1	0.452	76.1	77.8	73.0	0.384
Nitrates	92.4	78.9	76.2	<0.001	96.7	85.6	78.8	<0.001
ACEi/ARB	70.5	74.9	81.1	0.006	37.1	62.2	55.9	<0.001
Statins	26.7	67.9	77.2	<0.001	5.6	30.8	49.0	<0.001
Cardiac catheterization	35.7	78.6	80.8	<0.001	0	6.7	18.5	<0.001
Revascularisation	27.6	64.2	73.5	<0.001	0	4.2	14.3	<0.001
PCI	22.4	61.5	67.9	<0.001	0	4.2	14.3	<0.001
CABG	5.2	3.7	6.0	0.722	0	0	0	–
Reperfusion for STEMI	42.3	64.2	63.1	<0.001	44.1	34.1	37.9	0.251
Thrombolysis	35.4	7.4	0.6	<0.001	44.1	34.1	29.2	0.008
Primary PCI	6.9	56.8	62.5	<0.001	0	0	8.7	–
Echocardiography	81.9	85.3	88.4	0.044	52.1	51.9	50.7	0.735
Stress testing	19.0	1.8	1.3	<0.001	8.0	3.6	0.6	<0.001
Transferred to a tertiary care hospital	–	–	–		5.8	24.8	40.1	<0.001

GP IIb/IIIa-b – glycoprotein IIb/IIIa receptor blockers, ACEi/ARB – angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, PCI – percutanous coronary intervention, CABG – coronary artery bypass grafting, STEMI – ST-segment elevation myocardial infarction

The reperfusion rates for STEMI increased from 42.3% to 63.1% (p<0.001) in the tertiary care hospitals, while there was no statistically significant change in the secondary care hospitals. Meanwhile, there was an important increase in the proportion of patients who were referred from a secondary to a tertiary care hospital for further diagnostics and treatment (from 5.8% in 2001 to 40.1% in 2011, p<0.001). The prescription rates of guideline-recommended cardio-vascular drugs at discharge increased in all five drug-groups in both hospital types with the exception of aspirin in secondary care and beta-blockers in both hospital types.

Mortality

There was a statistically significant decrease from 20.2% to 12.4% (adjusted p=0.003) in 30-day mortality rate in the secondary care setting during the period studied (Table 6). The 30-day mortality reduction was not statistically significant in the tertiary care hospitals. Results from long-term mortality analysis show a decrease from 29.5% to 20.2% (adjusted p=0.004) in the tertiary care hospitals and from 32.4% to 23.1% (adjusted p=0.006) in the secondary care hospitals in 1-year mortality rates.

Table 6. Mortality of acute myocardial infarction patients primarily hospitalized into tertiary and secondary care hospitals

Mortality	2001 %	2007 %	2011 %	P value for trend, unadjusted	HR (95% CI) change per year, unadjusted	P value for trend, adjusted*	HR (95% CI) change per year, adjusted*
30-day							
Tertiary care hospitals	17.6	13.1	13.2	0.181	0.97 (0.926–1.015)	0.061	0.96 (0.913–1.002)
Secondary care hospitals	20.2	22.5	12.4	0.022	0.96 (0.920–0.994)	0.003	0.94 (0.904–0.980)
1-year							
Tertiary care hospitals	29.5	24.5	20.2	0.026	0.96 (0.928–0.995)	0.004	0.95 (0.917–0.984)
Secondary care hospitals	32.4	35.0	23.1	0.026	0.97 (0.938–0.996)	0.006	0.95 (0.918–0.977)

* – adjusted for age, sex, myocardial infarction subtype (STEMI vs NSTEMI), previous myocardial infarction, previous heart failure, diabetes, hypertension
STEMI – ST-segment elevation myocardial infarction, NSTEMI – Non-ST-segment elevation myocardial infarction, HR – hazard ratio, CI – confidence interval

From the results of mortality analysis comparing different years and hospital types, we found a marked decline in mortality rates in both types of hospitals, which took place first in the tertiary and then in the secondary care. Mortality rates were similarly high in 2001. 30-day and 1-year mortality had decreased by the year 2007 only in the tertiary care. By 2011, mortality rates had declined in both hospital types; the mortality gap between the secondary and the tertiary care hospitals disappeared (Figure 6).

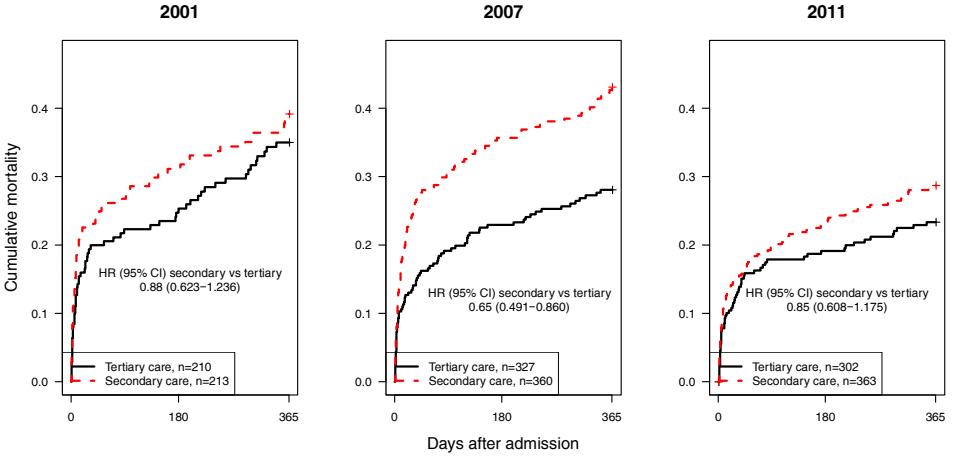


Figure 6. Cumulative mortality hazards of patients hospitalized primarily into tertiary and secondary care hospitals

HR – hazard ratio, CI – confidence interval

5.3 Treatment and outcomes after non-ST-segment elevation myocardial infarction over the period 2012–2014 in Estonia according to patients' estimated mortality risk (paper III)

Baseline characteristics

The final study sample consisted of 3803 NSTEMI patients. The median (inter-quartile range) age of the subjects was 73 (63–81) years, and 44% were women. Based on GRACE risk scoring at admission, 20% of patients were classified into low-, 35% into intermediate- and 45% into high-risk categories (Table 7). With the exception of dyslipidaemia, comorbidities were more prevalent in the high compared to the low and intermediate risk groups. In addition, high-risk patients were more often primarily hospitalized into hospitals without cardiac catheterization facilities.

Table 7. Baseline characteristics of NSTEMI patients, according to estimated mortality risk by GRACE

	All NSTEMI n=3803	Low risk n=753	Intermediate risk n=1328	High risk n=1722
Female Sex, % (n)	43.6 (1660)	22.2	39.8	56.0
Median age, years (IQR)	73 (63–81)	57 (52–63)	71 (64–75)	81 (75–85)
<55 years, %		37.6	4.4	1.2
55 – 65 years, %		46.1	21.8	4.3
65 – 75 years, %		15.4	43.4	16.0
>75 years, %		0.9	30.4	78.5
Mean BMI, SD, kg/m^2 (n)	28.4, 5.2 (3311)	29.3, 5.2	28.6, 5.2	27.7, 5.1
Current smoking, % (n)	23.7 (801)	51.5	23.9	9.5
Ever smoking, % (n)	41.4 (1396)	68.2	45.6	24.1
Previous diagnoses, % (n)				
Hypertension	84.2 (3072)	75.2	84.4	88.1
Heart failure	45.1 (1500)	16.7	35.8	66.5
Diabetes	26.4 (972)	17.4	26.5	30.4
Dyslipidaemia	68.8 (2166)	81.3	72.5	58.6
Stenocardia	56.9 (1907)	57.9	57.4	55.9
PAD	12.3 (404)	6.1	12.6	15.1
Previous myocardial infarction	28.6 (1028)	18.3	27.3	34.4
Stroke	13.6 (485)	5.6	12.5	19.1
Previous PCI	16.6 (595)	14.6	19.1	15.5
Previous CABG	7.8 (278)	4.8	8.8	8.3
Creatinine, median , IQR, (μmol/L)	86, 72–108 (2680)	75, 66–85	83, 70–97	108, 85–137
Characteristics at presentation,%				
Presentation delay				
<3h	24.7	20.7	26.1	25.4
3 – 12h	23.9	30.4	22.9	21.8
>12h	38.7	41.4	39.9	36.5
Presentation delay unspecified	12.8	7.4	11.1	16.3
Primary hospitalization into PCI hospital (n)	82.1 (3121)	86.8	85.3	77.6
Killip class III–IV (n)	13.0 (418)	0.3	2.6	28.7
Cardiac arrest (n)	1.9 (73)	0	0.4	4.0
Echocardiography, % (n)	85.4 (3245)	92.2	90.6	78.5
among those EF ≤ 40% (n)	44.7 (1424)	27.1	40.2	57.9

NSTEMI – non-ST-segment elevation myocardial infarction, GRACE – Global Registry of Acute Coronary Events, IQR – interquartile range, BMI – body mass index, SD – standard deviation, PAD – peripheral artery disease, PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting, EF – ejection fraction

Low risk – estimated GRACE 1-year mortality risk <4%, intermediate risk 4–12%, high risk >12%

In-hospital management

Overall, 62% of the low-, 46% of the intermediate- and 23% of the high-risk patients received optimal in-hospital management, defined as concomitant use of drugs from all six guideline-recommended classes and coronary angiography (Table 8).

Lack of in-hospital $P2Y_{12}$-receptor inhibitor use was the most frequent reason for being classified into suboptimal management group – a finding present in all three risk categories. Additionally, patients in the high-risk group were frequently classified into suboptimal management because coronary angiography was not performed and statins were not used during hospital stay.

Table 8. In-hospital management of NSTEMI patients according to estimated mortality risk by GRACE

	All NSTEMI n=3803	Low risk n=753	Intermediate risk n=1328	High risk n=1722	P value*
Medical therapy, % (n)					
Dual antiplatelet	63.2 (3548)	84.6	70.2	47.1	<0.001
ASA	98.3 (3548)	99.3	98.2	97.9	0.04
$P2Y_{12}$-inhibitors	64.9 (3563)	85.1	72.0	49.4	<0.001
Anticoagulants (*parenteral*)	98.8 (3419)	99.7	98.8	98.2	<0.001
GP IIb/IIa-b	8.1 (3793)	15.2	8.7	4.5	<0.001
Beta-blockers	86.1 (3802)	87.5	87.5	84.3	0.02
ACEi/ARBs	77.5 (3801)	83.9	79.6	73.1	<0.001
Statins	73.4 (3800)	89.9	82.2	59.5	<0.001
Calcium-channel blockers	29.0 (3795)	27.2	32.6	26.9	0.001
Nitrates	77.0 (3800)	85.0	79.2	71.9	<0.001
Digoxin	8.6 (3798)	1.6	4.7	14.6	<0.001
Coronary angiography	70.2 (3742)	93.2	83.6	49.4	<0.001
PCI	49.2 (3797)	72.9	59.0	31.2	<0.001
CABG	4.4 (3792)	4.4	5.3	3.6	0.08
Optimal hospital management **	35.7	61.8	46.2	22.5	<0.001

NSTEMI – non-ST-segment elevation myocardial infarction, GRACE – Global Registry of Acute Coronary Events, GP IIb/IIa-b – glycoprotein IIb/IIIa receptor blockers, ACEi/ARB – angiotensin-converting enzyme inhibitor / angiotensin II receptor blocker, PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting.

* The three GRACE risk classes were compared using Chi^2 –test

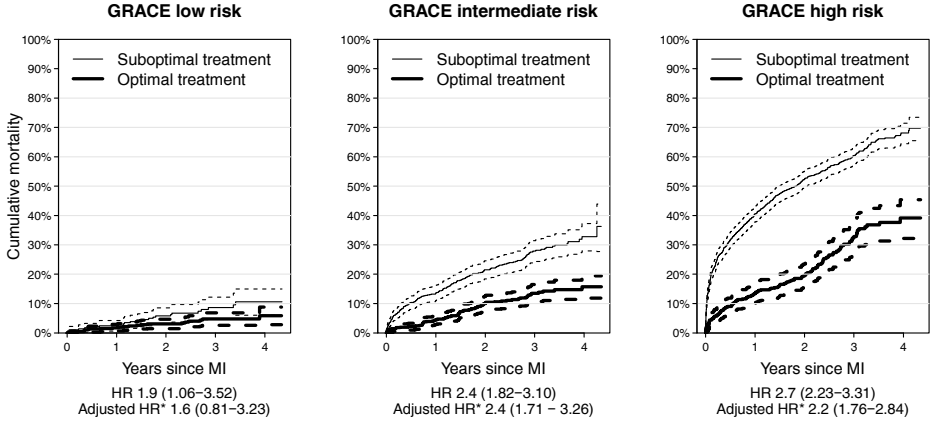
** Optimal hospital management defined as concomitant use of coronary angiography, aspirin, $P2Y_{12}$-receptor inhibitor, statin, beta-blocker, ACEi/ARB and parenteral anticoagulant among patients with class I guideline indication for respective drugs

Impact of optimal in-hospital management on long-term outcomes

After exclusion of patients who died during the first 24 hours after hospitalization, 752 from the low-, 1318 from the intermediate- and 1639 from the high-risk group were included in the analysis investigating long-term outcomes. Long-term unfavourable outcomes following NSTEMI were common – approximately one third of patients (29%) experienced the composite endpoint of all-cause death (21%), including recurrent MI (6%), stroke (3.5%) or unplanned revascularization by PCI (5%) or CABG (0.2%) during the first year.

Regardless of the risk group, patients receiving suboptimal in-hospital care experienced significantly higher rates of all-cause death and the composite endpoint in comparison to optimally managed patients from the same risk category (Figure 7). When all three GRACE categories were analysed together and the potential interaction between in-hospital management and GRACE category was accounted for, it was found that suboptimal in-hospital management remained a significant predictor of all-cause mortality and the composite endpoint with a significant interaction between the suboptimal in-hospital treatment score and the GRACE 1-year mortality estimation.

A)



B)

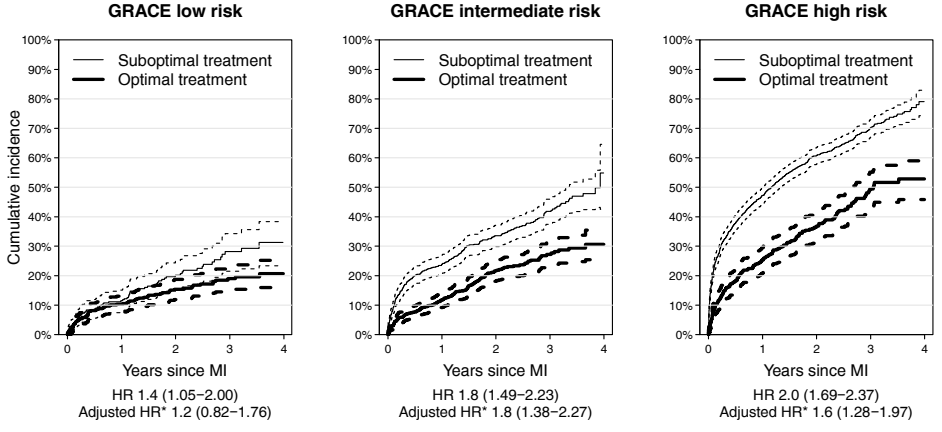


Figure 7. Cumulative all-cause mortality (A) and development of composite endpoint (B) in NSTEMI patients according to treatment status (optimal or suboptimal in-hospital management) separately for the low, intermediate and high mortality risk group estimated by GRACE

NSTEMI – non-ST-segment elevation myocardial infarction, GRACE – Global Registry of Acute Coronary Events, MI – myocardial infarction, HR – hazard ratio

* Adjusted for all the baseline characteristics that that were significant predictors of outcome in univariate analysis (all-cause mortality, panel A: heart failure, diabetes mellitus, peripheral artery disease, previous myocardial infarction, previous stroke, previous coronary artery bypass grafting, presentation delay >12 hours, ejection fraction; composite endpoint, panel B: current smoking, hypertension, heart failure, diabetes mellitus, peripheral artery disease, previous myocardial infarction, previous stroke, previous coronary artery bypass grafting, presentation delay >12 hours, primary hospitalization into percutaneous coronary intervention hospital, ejection fraction)

6. DISCUSSION

6.1 The performance of atherosclerotic cardiovascular disease risk scores

We investigated the performance of three widely used risk scores in a representative population-based cohort – the Estonian Biobank cohort – and found that two out of the three evaluated scores – PCE and SCORE – performed overall at an acceptable level, while QRISK2 heavily underestimated the atherosclerotic CVD risk.

In terms of discrimination, SCORE and QRISK2 had an excellent discriminative ability, Harell's C-statistics 0.865 and 0.812, respectively, which indicates that over 80% of individuals with a higher estimated risk had a shorter time to an event than individuals with a lower estimated risk. PCE's C-statistic of 0.778 could be considered as acceptable discrimination. As the CVD risk level and also the intensity of preventive actions are continuums rather than simple binary decisions, and the general principle in prevention guidelines states that the intensity of intervention should depend on the level of absolute risk, it is evident that in addition to acceptable discrimination, scores have to be accurately calibrated.

Calibration depends heavily on the baseline risk, and thus it is mandatory to evaluate the performance of a score before applying it to a cohort that may differ from the derivation cohorts. For example, in the QRISK2 original cohort, the crude incidence rate of atherosclerotic CVD per 1000 person-years was 7.3 for women and 10.5 for men (Hippisley-Cox et al, 2008), which are approximately two times lower than those seen in the Estonian Biobank cohort. Miscalibration has direct consequences on treatment decisions, as depicted in Figure 8. Using QRISK2 together with NICE guidelines would lead to significantly lower treatment recommendations, when compared to the recommendations based on risk estimation by PCE or SCORE. Consequently, recalibration using the local baseline risk is a prerequisite for utilization of QRISK2 in the Estonian population.

Besides differences in the baseline risk, temporal changes in disease incidence can be an additional source of calibration errors. Given that atherosclerotic CVD incidence has significantly decreased over the last decades (Levi et al, 2008), using risk scores that were developed on historical cohorts would lead to an overestimation of the actual risk, which has been demonstrated repeatedly in countries with low CVD incidence (DeFilippis et al, 2017; Emdin et al, 2017; Rana et al, 2016; Ulmer et al, 2005).

Both abovementioned sources of calibration error (different disease incidence and temporal changes in it) may explain why PCE and the high-risk version of SCORE exhibit good calibration accuracy in the Estonian Biobank cohort. The decrease in mortality rates in Estonia and other high-risk countries lags behind the decline seen in European low-risk countries. In other words, the incidence

rates in Estonia are currently similar to those seen in the low-risk countries a few decades ago, when SCORE and PCE were developed.

Statin recommendations according to different guidelines

To illustrate differences associated with using American, British or European prevention guidelines in treatment allocation, the hypothetical proportions of patients who would be eligible for statin use in a common subset of healthy individuals from the Estonian Biobank cohort were calculated. The recommendations regarding statin use in primary prevention were rather similar between the different guidelines, advocating treatment in an atherosclerotic CVD-free population for roughly one fifth of women and half of men (Figure 8). An additional 14% of men and 7% of women, according to ACC/AHA, and 49% of men and 35% of women, according to ESC, should be considered for statin treatment.

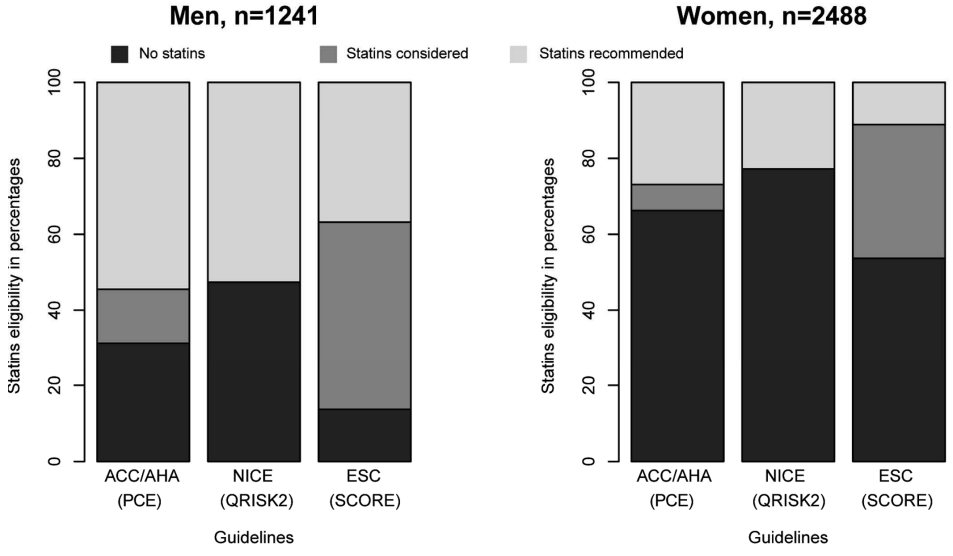


Figure 8. Theoretical statin recommendations according to three cardiovascular disease prevention guidelines – the American College of Cardiology/American Heart Organization (ACC/AHA), the National Institute for Health and Care Excellence (NICE) and the European Society of Cardiology (ESC) guidelines, when applied to common subset of atherosclerotic cardiovascular disease-free individuals, aged 40–79, without diabetes mellitus or chronic kidney disease (n=3729). The respective risk scores used by the guidelines are Pooled Cohort Equations (PCE), QRISK2 and Systematic COronary Risk Estimation (SCORE).

Considering all abovementioned, we can conclude that both PCE and SCORE are suitable for guiding management decisions (e.g. initiation of dyslipidaemia or hypertension treatment as well as lifestyle counselling) in primary prevention of ischaemic heart disease, and their use among Estonian physicians should be

encouraged. As Figure 8 depicts, according to the current European guidelines, statins should be considered for more than 80% of men and 50% of women in a population of middle-aged healthy individuals in the Estonian Biobank cohort. Interestingly, actual statin use in this cohort registered at recruitment was only 4.2%, indicating a significant gap between guidelines and clinical practice. Therefore more assertive but still risk-guided treatment decisions in primary prevention should be promoted in order to decrease ischaemic heart disease incidence in Estonia.

6.2 General trends in mortality after myocardial infarction

Another important driver of decreasing CVD mortality – mortality after MI – was investigated in papers II and III. The results in paper II demonstrate a decrease in short- and long-term mortality of both NSTEMI and STEMI patients between 2001 and 2011, which was associated with increased adoption of guideline-recommended therapies as well as more frequent transfer of secondary care patients to tertiary care hospitals. Paper III continued monitoring the treatment and outcomes of NSTEMI using complete nationwide data from the Estonian Myocardial Infarction Registry. Investigating the period from 2012 to 2014, we found that patients with a low estimated 1-year mortality risk according to the GRACE score received significantly more guideline-recommended in-hospital drugs and underwent coronary angiography more often than patients with an intermediate or high risk. Optimal in-hospital management was associated with better long-term outcomes, a finding more pronounced in the intermediate- and high-risk groups than in the low-risk group.

The described improvements in treatment and associated decrease in mortality have not happened without external causes and stimuli. During the last decades, led by the Estonian Society of Cardiology and executed by the hospitals of the STEMI network, much effort has been offered to improve diagnostics and treatment of MI. Quality improvement measures have targeted different aspects of disease management, including prehospital triage and establishing an acute coronary syndrome network, therapies during hospitalization and at discharge, and outpatient care. For example, the local STEMI guideline was published (Soopõld et al, 2004), European MI definitions and guidelines were translated into Estonian and published in local medical journal Eesti Arst, and several educational events throughout Estonia were continuously organized. At the same time, the availability of cardiac catheterization facilities and contemporary cardiovascular drugs has improved.

6.3 The prevalence of myocardial infarction subtypes

Similarly to other countries, the proportion of STEMI has decreased in Estonia, which is counter-balanced by higher proportion of NSTEMI. Improved coronary risk factor management and treatment after the first coronary event may have contributed to the observed trend (Rogers et al, 2008). Another plausible explanation is the rising mean age, which is consistent with earlier studies describing higher prevalence of NSTEMI among the elderly (Avezum et al, 2005). Third and probably the most important explanation for the growing ratio of NSTEMI to STEMI is the more widespread use of high-sensitivity troponin assays, which has resulted in more sensitive diagnostics of MI (McManus et al, 2011).

6.4 ST-segment elevation myocardial infarction management

Reperfusion treatment

Reperfusion rates for STEMI are used as performance measures of MI treatment. Findings in paper II indicate that reperfusion rates in the tertiary care hospitals were by the year 2011 comparable with respective rates from North, West, and Central Europe (Kristensen et al, 2014; Puymirat et al, 2013). Results were different for the secondary care hospitals – only approximately 40% of Estonian STEMI patients were offered reperfusion, with no increase between 2001 and 2011. However, low reperfusion rates in our study should be interpreted with caution – in 2011, more than 40% of secondary care patients were referred to a tertiary care centre for further management. Consequently, some of the secondary care patients might have received reperfusion which was not captured by the study. Nevertheless, transfer increases the delays and reduces the probability of timely PCI. This is confirmed by data from an international EPICOR registry, indicating that recommended times are often not met when STEMI patients are transferred for primary PCI (Sinnaeve et al, 2014). Primary PCI is recommended as a first-line therapy for STEMI, but it should be emphasized that fibrinolysis is also an appropriate and proven reperfusion strategy (Huber et al, 2014). However, more frequent referral to tertiary care hospitals agrees with guidelines that recommend invasive management for STEMI or high-risk NSTEMI patients (Ibanez et al, 2018; Roffi et al, 2016).

Drug treatment

In addition to reperfusion, concomitant drug therapy and discharge medications play a major role in determining prognosis after STEMI. Similarly to invasive treatment, there was a dramatic increase in the adoption of dual antiplatelet therapy, statins and ACEi/ARBs, while the use of older guideline-recommended

drugs like beta-blockers and aspirin remained relatively stable over the period from 2001 to 2011.

However, not all patient groups have gained equally from these improvements. As paper II shows, prescription rates of secondary prevention drugs were still significantly lower in secondary care hospitals when compared to tertiary care hospitals. These inconsistencies can partly be explained by differences in the baseline characteristics. Patients in the secondary care hospitals were older, and it has been shown that elderly patients are less likely to receive medications recommended by guidelines (Lee HY et al, 2008; Komócsi et al, 2016). Previously described lower adherence to guidelines in smaller non-academic hospitals, staffed less frequently with certified cardiologists, is another plausible explanation (Dorsch et al, 2003; O'Brien et al, 2014).

6.5 Non-ST-segment elevation myocardial infarction management

Similarly to STEMI, the management of NSTEMI has improved significantly over the period of 14 years in Estonia. This finding is in concordance with data from several other countries that have countrywide registries aiming to capture all hospitalized MIs, for example Sweden (Szummer et al, 2018) and the UK (Hall et al, 2016). Both reports have described gradual adoption of new evidence-based therapies and have associated it with improved short- and long-term survival after NSTEMI. A recent report from Hungary, another country with a nationwide MI registry, also describes important progress in the adoption of an invasive strategy – the proportion of elderly NSTEMI patients who underwent PCI increased from 20% to 60% between 2008 and 2013 (Komócsi et al, 2016).

There are several important differences between the treatment strategies of the two MI subtypes. STEMI management guidelines state explicitly that all patients without contraindications should receive immediate reperfusion. NSTEMI guidelines, on the other hand, leave more room for interpretation and place great emphasis on formal risk assessment, stressing the importance of risk-guided treatment decisions. Thus, one purpose of risk stratification is to identify individuals at the highest risk for poor outcomes and target them with evidence-based treatments in order to improve their prognosis while withholding treatment for the lowest-risk individuals to prevent possible procedure-related complications, which would not weigh out the potential benefit from the treatment. However, as the results in the paper III and several other studies in the literature prove, coronary angiography and guideline-recommended pharmacotherapy still seem to be underused in high-risk patients, i.e. subjects with the greatest potential absolute treatment benefit (Damman et al, 2015; Negers et al, 2017).

Possible causes of risk-treatment paradox

The causes of risk-treatment paradox have not been sufficiently studied. According to previous studies, it could partly be explained by clinicians' reluctance to perform invasive procedures in patients perceived to be at high risk for developing procedure-related complications, e.g. bleeding, contrast-induced kidney injury, or stroke. Indeed, our study demonstrates a trend towards more bleeding complications in higher-risk patients, but overall bleeding rates remained low. This is supported by a recent meta-analysis describing declining PCI-related bleeding events in elderly high-risk NSTEMI patients, with more recent studies showing no excess in bleeding complications – a finding attributed to increased use of radial access and lower use of glycoprotein IIa/IIIb receptor blockers (Gnanenthiran et al, 2017). Our data in paper III confirm these findings. Additionally, in-hospital stroke rates were similarly low, around 1%, across all three risk categories, indicating no excess stroke risk in the high-risk group.

Contrast-induced kidney injury, a feared complication of PCI, occurs in approximately 7% of patients undergoing the procedure (Tsai et al, 2014). Baseline chronic kidney disease remains its strongest predictor. As the GRACE score includes serum creatinine, the proportion of patients with chronic kidney disease was higher in the high- compared to lower-risk groups among the NSTEMI patient cohort in paper III. Fear of contrast-induced kidney injury potentially affected the decision towards non-invasive management of patients in the high-risk group. Similarly to other high-risk populations, data from RCTs of patients with chronic kidney disease are limited (Coca et al, 2006). However, cohort studies have described lower mortality in invasively managed NSTEMI patients with mild to moderate renal dysfunction, indicating that opting for non-invasive treatment just because of chronic kidney disease may not always be reasonable (Degano et al, 2017; Szummer et al, 2009).

The issue of subjective decision-making by clinicians while choosing between an invasive or non-invasive strategy has been addressed only in a few studies. Lee CH with coauthors (2008) describes that 68% of NSTEMI patients not referred to coronary angiography were perceived to not be at a high enough risk to justify procedure-related risks. This implies a tendency to overestimate procedure-related risk and underestimate disease-related risk if formal risk assessment is not performed. However, despite strong guideline recommendations, the use of cardiac risk scores, including ischaemic and bleeding risk scores, has still not been fully implemented in routine clinical practice (Engel et al, 2015).

An additional important factor besides coronary angiography in determining the prognosis after NSTEMI is the use of secondary prevention pharmacotherapy. Overall, the use of in-hospital pharmacotherapy in the period 2012–2014 in Estonia was lower than that described previously in developed countries. A majority of low-risk patients did receive a $P2Y_{12}$-inhibitor, indicating that insufficient overall in-hospital dual antiplatelet therapy was mainly caused by lower treatment rates in the intermediate- and high-risk groups. A similar

pattern was present in statin use. These results illustrate the extension of the risk-treatment paradox to decisions in pharmacotherapy. Previous research has shown that MI patients who are under the care of internists, general practitioners and other non-cardiologist specialists tend to receive fewer guideline-recommended drugs – another possible reason for the risk-treatment paradox in pharmacotherapy, especially in secondary care hospitals staffed less frequently with cardiologists (Austin et al, 2008).

6.6 Strengths and limitations of the thesis

This thesis includes information from several nationwide databases (e.g. EMIR, EHIF database) and also information from a database that is a representative sample of the entire Estonian adult population – the Estonian Biobank database. By describing the treatment and outcomes of MI using three consecutive surveys from the years 2001, 2007 and 2011, which were based on a representative sample of all hospitalized Estonian MI cases, we are able to provide information about temporal changes in MI management over the period from 2001 to 2014. Taken together, these data give a thorough overview of the situation in a country with high CVD mortality with a high degree of generalizability and external validity. It is noteworthy that, to date, most of the data describing nationwide trends in primary and secondary prevention of CVD have been collected and analysed in high-income western countries with significantly lower CVD mortality.

Clinical registries with mandatory reporting of all hospitalized MI cases offer the advantage of providing data on patient groups that are often underrepresented in trials or in registries that have specific inclusion criteria, e.g. informed consent or hospitalization into a coronary care unit. Furthermore, linkage with EHIF and EPR by using personal identification numbers enables the collection of personal-level data on long-term outcomes including death, recurrent MIs, strokes and unplanned revascularizations.

Nevertheless, the current research has a number of limitations which all arise from the type of data used. First, using an administrative database (EHIF) might have caused some imprecisions in data quality. As EHIF's main purpose is to collect billing data, hospitals are financially motivated to report. However, as EHIF is the only organization in Estonia dealing with compulsory health insurance, covering 95.5% of the Estonian population, and as the accuracy of some diagnoses (i.e. MI and stroke) has been validated against international diagnostic criteria, we believe that the database of EHIF has sufficient quality for use in research. Imprecisions in data quality may partly explain the underestimation of risk by QRISK2, which is the only risk score that includes soft outcomes. However, in the QRISK2 derivation cohort, the outcome measures were also obtained from general practice records (Hippisley-Cox et al, 2008), which may suffer from similar limitations because soft outcomes generally lack strict diagnostic criteria and are therefore difficult or even

impossible to validate. The second, more general limitation arises from using observational data, which can never prove causality between observed treatment changes and outcomes. Through adjusting for major demographic variables and more important comorbidities, we can reduce the possibility that differences in the patient population accounted for the change, but there always remains some unmeasured residual confounding which cannot be accounted for. However, as prospective RCTs preferentially recruit patients with low-risk features (Kandzari et al, 2005), evidence from observational studies with unselected patient cohorts continues to be important. Third, in papers II and III describing the treatment of MI, we were not able to take into account drug-specific contraindications and patient refusals, as these data were not collected. Fourth, we did not collect data about drug compliance and utilization of other secondary prevention methods, including smoking cessation, etc., which do have a great impact in determining the prognosis after MI. Thus, we were unable to account for the effect of these or any other unmeasured confounders which might have an influence on long-term outcomes.

7. CONCLUSIONS

I. Risk scores SCORE and PCE perform at an acceptable level in Estonia and can be used for atherosclerotic CVD risk prediction without further modifications. Despite serious underestimation of atherosclerotic CVD risk, QRISK2 presents excellent discrimination, indicating the need for recalibration before utilization. The results demonstrate that widely used risk scores that are developed on low-risk populations perform at an acceptable level in high-risk countries, and their use should be encouraged for treatment allocation in primary prevention of atherosclerotic CVD.

II. Treatment of acute MI advanced remarkably over the period from 2001 to 2011 in Estonia in both secondary and tertiary care hospitals, while the prevalence of most comorbidities remained unchanged and the mean age of STEMI and NSTEMI patients increased. Inconsistency in the speed of implementation of new treatment strategies was reflected as a marked mortality gap in 2007 between the secondary and the tertiary care hospitals. By the 2011, the differences in treatment persisted, but a significant proportion of secondary care patients were transferred for further management to tertiary care hospitals. Consequently, the noticeable mortality gap between the secondary and tertiary care hospitals was no longer present in 2011. This indicates that by the end of the study period, Estonian hospitals were functioning as an efficient network, delivering equal care to MI patients.

III. NSTEMI patients at the highest risk for unfavourable long-term outcomes according to the GRACE risk score remain undertreated with guideline-recommended drugs during their hospital stay. Moreover, these high-risk patients are less frequently referred to coronary angiography compared to patients with a lower estimated GRACE risk. Inequalities in treatment seem to translate into higher mortality and unfavourable outcome rates, which is especially pronounced in intermediate- and high-risk patients.

8. FUTURE RESEARCH

Future research should be aimed at developing and validating a new atherosclerotic CVD risk-estimation algorithm that combines information from an already-existing risk score and a polygenic risk score in order to refine treatment allocation in primary prevention. According to the head-to-head comparison of the scores, all three scores are suitable for this purpose, as none was significantly superior to the others in predicting adverse outcomes.

A direct comparison of quality of care and clinical outcomes of MI with countries with different CVD profiles (e.g. the UK, Sweden, Hungary) could provide insight on how to further improve outcomes after MI in Estonia. International comparisons that use data from nationwide registries are informative about the relative performance of a health care system and could facilitate quality improvement in countries with higher mortality rates.

Furthermore, future studies should determine the reasons why many high-risk patients currently remain undertreated when compared to lower-risk patients. Increasing mean age and prevalence of comorbidities (e.g. cancer, dementia) demands personalised management decisions, as not all high-risk patients have the potential to gain from a more intensive treatment strategy. On the other hand, unjustified withholding of treatment leads inevitably to poor prognosis. Future research should be aimed at identifying specific patient subgroups among high-risk patients who would benefit most from more intensive management of MI.

Patient adherence to pharmacological and non-pharmacological secondary prevention, including exercise-based cardiac rehabilitation and smoking cessation, which determines significant part of the prognosis after MI, should be investigated in Estonia. A general overview of the current situation should be followed by an identification of subgroups with suboptimal adherence and then subsequently targeting them with an intervention programme.

9. SUMMARY IN ESTONIAN

Äge müokardiinfarkt Eestis 2001–2014: suund riskipõhisele ennetusele ja ravile

Kardiovaskulaarhaigustest, eelkõige südame isheemiatõvest ja müokardiinfarktist (MI) põhjustatud suremus Eestis on sarnaselt ülejäänud arenenud riikidega viimastel kümnenditel oluliselt vähenenud. Võrreldes teiste Euroopa riikidega on muutused Eestis rohkem väljendunud – aastatel 1985–2014 langes vanusele kohandatud südame isheemiatõve suremus 100 000 elaniku kohta meestel 1285-lt 388-ni ja naistel 837-lt 211-ni (Timmis et al, 2018). Kiirele arengule vaatamata kuulub Eesti jätkuvalt kõrgeima kardiovaskulaarhaiguse riskiga riikide hulka Euroopas.

Suremust südame isheemiatõve tagajärjel nii Eestis kui ka mujal mõjutavad peamiselt kaks tegurit: kui palju inimesi haigestub ja kui suur osa nendest sureb. Haigestumise langetamiseks tuleb vähendada riskifaktorite – näiteks suitsetamine, kõrge vererõhk ja düslipideemia – esinemist rahvastikus. Suremuse langetamine nõuab paremat MI ravi ja efektiivsemat sekundaarset preventsiooni korduvate atakkide vältimiseks. Järelikult on südame isheemiatõve suremuse edasiseks langetamiseks vajalik kompleksne lähenemine: tähelepanu tuleb pöörata ennetamisele ehk primaarsele preventioonile, MI ägeda faasi ravile ja kordumise ennetamisele ehk sekundaarsele preventsioonile.

Senine südame isheemiatõve kohta publitseeritud teadustöö Eestis keskendus peamiselt ägeda MI ravile. Dr. Tiia Ainla kirjeldas 2005. aastal avaldatud doktoritöös olulisi puudujääke nii MI invasiivse kui ka medikamentoosse ravi osas. Reperfusiooni ehk verevoolu taastamist sulgunud koronaararteris trombolüüsi või primaarse perkutaanse koronaarinterventsiooni abil rakendati kõigest 43%-l 2001. aastal Eestis hospitaliseeritud ST-segmendi elevatsiooniga müokardiinfarkti (STEMI) patsientidel; AKE-inhibiitoreid kasutati haiglaravi jooksul 50%-l ja statiine ainult 15%-l STEMI patsientidest. Eraldi probleemidena toodi välja ravikvaliteedi suur kõikumine haiglatüüpide lõikes ja teatud patsiendigruppide (näiteks eakad, naised, diabeetikud) vähem intensiivne ravi. Uuringu tulemustele toetudes tehti mitmeid jõupingutusi MI käsitluse ühtlustamiseks ja parandamiseks; samaaegselt kasvas ravijuhistes soovitatud ravimite ning koronaarinterventsioonideks vajaliku infrastruktuuri kättesaadavus Eestis.

Nende muudatuste tulemuste hindamiseks viidi 2007. aastal läbi jätku-uuring, mille andmete analüüsi alusel kirjeldati oluliselt paranenud MI ravikvaliteeti. Näiteks suurenes AKE-inhibiitorite haiglasisesne kasutamine STEMI patsientidel 70% ja statiinide kasutamine 50%-ni; reperfusioonravi osakaal jõudis 48%-ni. (Blöndal et al, 2012). Paraku ei toonud paranenud ravi kaasa MI järgse suremuse olulist langust, seda seostati haigete keskmise vanuse tõusu ja kaasuvate haiguste sagenemisega. Jätkuvalt oli probleemiks ebaühtlane ravikvaliteet haiglatüüpide lõikes. Neid teadmisi arvesse võttes jätkus Eesti Kardioloogide Seltsi eestvedamisel süstemaatiline töö MI patsientide käsitluse parandamiseks ja ühtlustamiseks Eestis.

Käesolev doktoritöö jätkab MI patsientide ravikvaliteedi ja tulemuste jälgimist Eestis, kasutades selleks andmeid kahest peamisest allikast. Järjestikused läbilõikeuuringud aastatest 2001, 2007 ja 2011 võimaldavad ülevaatlikult hinnata MI käsitluse muutusi Eestis kümnendi jooksul. Alates 2012. aastast tegutseb Eestis riiklik müokardiinfarktiregister, kuhu kogutakse andmeid kõikide hospitaliseeritud ägeda MI juhtude kohta, võimaldades jooksvalt jälgida ja analüüsida ägeda MI ravi ning selle tulemusi.

Lisaks MI ravile keskendub käesolev doktoritöö kardiovaskulaarhaiguste, kitsamalt südame isheemiatõve ja MI ennetamisele ehk primaarsele preventsioonile. Vaatamata riskifaktorite kõrgele levimusele ei ole Eestis seni MI primaarsele preventsioonile piisavalt tähelepanu pööratud. Näiteks võib tuua vere kolesteroolisisaldust langetavate ravimite kasutamise Eestis, mis on OECD 28 riigi hulgas üks madalamaid (OECD, 2017). Raviotsuste juhtimiseks primaarses preventsioonis soovitab Euroopa ravijuhis kasutada kardiovaskulaarhaiguse riski hindamise algoritme ehk riskiskoore, nt SCORE riskitabeleid (Piepoli et al, 2016). Seni ei ole riskiskooride ennustusvõimet ja täpsust Eestis hinnatud, mis võib olla üheks takistuseks nende kasutamisel kliinilises praktikas.

Südame isheemiatõvest põhjustatud suremuse edasine vähendamine eeldab terviklikku lähenemist kõigile haigusega seotud aspektidele: ennetamisele, varasele diagnoosimisele ja ravile ning kordumise vältimisele. Järelikult tuleb hinnata kardiovaskulaarset riski, selle alusel tõhustada riskifaktorite ohjamist, jätkata MI ravikvaliteedi jälgimise ja parandamisega ning tõhustada sekundaarset preventsiooni. Käesolev doktoritöö jätkab ja laiendab varasemalt tehtud uurimistööd, keskendudes lisaks MI ravikvaliteedile ka primaarsele preventsioonile Eestis.

UURIMUSE EESMÄRGID

Doktoritöö üldiseks eesmärgiks on kirjeldada kardiovaskulaarhaiguste, eelkõige südame isheemiatõve ennetust ja ravi Eestis ning selgitada kõrge suremuse põhjuseid. Sellest lähtuvalt on tööl kolm alameesmärki:

Esiteks, hinnata kolme kardiovaskulaarhaiguse riski hindamise skoori (*Pooled Cohort Equations* ehk PCE, QRISK2 ja *Systematic COronary Risk Estimation ehk* SCORE) ennustusvõimet ja täpsust Eesti rahvastikul.

Teiseks, kirjeldada muutusi MI haigete suremuses 2001–2011, võttes arvesse muutunud põhinäitajaid ja ravikäsitlust ning uurida, kas prognoos sõltub haiglatüübist, kuhu patsient esmaselt hospitaliseeriti.

Kolmandaks, kirjeldada ST-segmendi elevatsioonita MI (NSTEMI) patsientide ravikäsitlust ja selle tulemusi sõltuvalt GRACE (*Global Registry of Acute Coronary Events*) skoori abil hinnatud riskist ning uurida, kas ravikäsitluse mõju prognoosile erineb madala, keskmise ja kõrge riskiga patsientidel.

METOODIKA

Doktoritöö põhineb kolmel rahvastikupõhisel kohortuuringul. I artikli valimi moodustasid Tartu Ülikooli Eesti Geenivaramu andmebaasi kuuluvad ilma kardiovaskulaarhaiguse diagnoosita inimesed (n=8830); jälgimisperioodil toimunud sündmuste kohta lisati andmed Eesti Haigekassa andmebaasist ja surmapõhjuste registrist. II artikli aluseks oli juhuvalim kõikidest 2001, 2007 ja 2011. aastal Eesti Haigekassa andmebaasi alusel MI-ga hospitaliseeritud patsientidest (n_{2001}=520, n_{2007}=800, n_{2011}=760); andmed koguti retrospektiivselt haiguslugudest ja jälgimisperioodil surnud patsientide kohta saadi andmed rahvastikuregistrist. III artikli valimisse kuulusid kõik Eesti müokardiinfarkti-registri andmetel 2012–2014 NSTEMI-ga hospitaliseeritud patsiendid; jälgimis-perioodil toimunud sündmused lisati Eesti Haigekassa andmebaasist ja rahvastikuregistrist.

Andmete töötlemiseks kasutati andmetöötlustarkvara R (versiooni 3.3.2 I artiklis ja versiooni 3.11 artiklites II ja III).

UURIMUSE TULEMUSED JA JÄRELDUSED

Kolmest uuritud riskiskoorist kaks, PCE ja SCORE, ennustasid piisava täpsu-sega ateroskleroötilise kardiovaskulaarhaiguse ja MI teket Eesti rahvastikul. Nii PCE kui ka SCORE sobivad hästi ennetava ravi alustamise juhtimiseks kardiovaskulaarhaiguste, täpsemalt südame isheemiatõve ja MI preventsioonis. QRISK2 alahindas oluliselt ateroskleroötilise KVH avaldumise riski, järelikult vajab skoor ümberkalibreerimist enne Eesti rahvastikul kasutamist.

MI-ga patsientide suremus langes oluliselt perioodil 2001–2011, saavutades uuringuperioodi lõpuks sarnase taseme esmaselt piirkondlikku ja madalama etapi haiglatesse hospitaliseeritud patsientidel. MI patsientide keskmine vanus kasvas, kuid peamiste kaasuvate haiguste esinemissagedus ei muutunud. Prog-noosi paranemist võib seostada paranenud ravikäsitlusega: uuringuperioodil suurenes patsientide osakaal, kellel teostati invasiivne angiograafia ja revasku-lariseerimine, samuti kasvas ravijuhistes soovitatud medikamentoosse ravi määramine nii haiglaravi ajal kui ka ambulatoorseks kasutamiseks. Märgatavalt suurenes patsientide suunamine madalama etapi haiglatest piirkondlikesse haiglatesse, mis on kooskõlas ravijuhistes soovitatuga.

Kõrge GRACE riskiga NSTEMI patsientidele määratakse haiglaperioodil vähem ravijuhistes soovitatud ravimeid võrreldes keskmise ja madala riskigrupi patsientidega. Lisaks suunatakse kõrgesse riskigruppi kuuluvaid patsiente harvem koronarograafiale ning neil teostatakse vähem revaskulariseerivat ravi. Erinevused haiglasiseses ravis mõjutavad NSTEMI patsientide prognoosi – sõltumata riskigrupist oli haiglaperioodil intensiivsemalt ravitud patsientide suremus madalam võrreldes nende patsientidega, kellel vähemalt ühte ravi-juhistes soovitatud ravimeetodit ei rakendatud. Ravikäsitluse mõju suremusele oli enam väljendunud keskmise ja kõrge GRACE riskiga patsientidel, madala riskiga patsientidel mõjutas ravikäsitlus suremust vähem.

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11. REFERENCES

Abraham G, Havulinna AS, Bhalala OG et al. Genomic prediction of coronary heart disease. *Eur Heart J*. 2016;37:3267–3278.

Ainla T. *Acute myocardial infarction in Estonia: clinical characteristics, management and outcome.* Tartu: Tartu Ülikooli Kirjastuse trükikoda, 2005. https://dspace.ut.ee/handle/10062/1296 (accessed 11.04.2019)

Ainla T, Marandi T, Teesalu R, et al. Diagnosis and treatment of acute myocardial infarction in tertiary and secondary care hospitals in Estonia. *Scand J Public Health.* 2006;34:327–331.

Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined – a consensus document of the joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol.* 2000;36:959–969.

Alzuhairi KS, Søgaard P, Ravkilde J et al. Incidence and outcome of first myocardial infarction according to gender and age in Denmark over a 35-year period (1978–2012). *Eur Heart J Qual Care Clin Outcomes*. 2015;1:72–78.

Amann U, Kirchberger I, Heier M et al. Predictors of non-invasive therapy and 28-day-case fatality in elderly compared to younger patients with acute myocardial infarction: an observational study from the MONICA/KORA Myocardial Infarction Registry. *BMC Cardiovasc Disord*. 2016;16:151.

Anderson L, Oldridge N, Thompson DR et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. *J Am Coll Cardiol*. 2016;67:1–12.

Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet.* 2009;373:1849–1860.

Austin PC, Tu JV, Ko DT, Alter DA. Factors associated with the use of evidence-based therapies after discharge among elderly patients with myocardial infarction. *CMAJ.* 2008;179:901–908.

Avezum A, Makdisse M, Spencer F et al. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J.* 2005;149:67–73.

Baigent C, Keech A, Kearney PM et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.

Bangalore S, Steg G, Deedwania P et al. β-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA*. 2012;308:1340–1349.

Benowitz NL, Pipe A, West R et al. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. *JAMA Intern Med*. 2018;178:622–631.

Berrington de Gonzalez A, Hartge P, Cerhan JR et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363:2211–2219.

Björck L, Rosengren A, Bennett K, Lappas G, Capewell, S. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. *Eur Heart J*. 2009;30:1046–1056.

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

Blöndal M. *Changes in the baseline characteristics, management and outcomes of acute myocardial infarction in Estonia.* Tartu: Tartu Ülikooli Kirjastuse trükikoda, 2012. http://dspace.ut.ee/handle/10062/28550 (accessed 11.04.2019)

Bonaca MP, Bhatt DL, Cohen M et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800.

Bonnefoy-Cudraz E, Bueno H, Casella G et al. Acute Cardiovascular Care Association position paper on intensive cardiovascular care units: an update on their definition, structure, organisation and function. *Eur Heart J Acute Cardiovasc Care*. 2018; 7:80–95.

Bucholz EM, Butala NM, Ma S, Normand ST, Krumholz HM. Life expectancy after myocardial infarction, according to hospital performance. *N Engl J Med*. 2016; 375:1332–1342.

Bueno H, Sinnaeve P, Annemans L et al. Opportunities for improvement in anti-thrombotic therapy and other strategies for the management of acute coronary syndromes: Insights from EPICOR, an international study of current practice patterns. *Eur Heart J Acute Cardiovasc Care*. 2016;5:3–12.

Cannon CP, Blazing MA, Giugliano RP et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.

Chow CK, Jolly S, Rao-Melacini P et al. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. *Circulation*. 2010;121:750–758.

Chung SC, Gedeborg R, Nicholas O et al. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *Lancet*. 2014;383:1305–1312.

Coca SG, Krumholz HM, Garg AX, Parikh CR. Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *JAMA*. 2006;296:1377–1384.

Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003.

Crowson CS, Atkinson EJ, Therneau TM. Assessing calibration of prognostic risk scores. *Stat Methods Med Res*. 2016; 25:1692–1706.

Damman P, Jernberg T, Lindahl B et al. Invasive strategies and outcomes for non-ST-segment elevation acute coronary syndromes: a twelve-year experience from SWEDEHEART, *EuroIntervention.* 2016;12:1108–1116.

Dargie HJ et al. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001; 357:1385–1390.

De Berardis G, Sacco M, Strippoli GF. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ*. 2009;339:b4531.

DeFilippis AP, Young R, McEvoy JW et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. *Eur Heart J.* 2017;38:598–608.

Dégano IR, Salomaa V, Veronesi G et al. Twenty-five-year trends in myocardial infarction attack and mortality rates, and case-fatality, in six European populations. *Heart*. 2015;101:1413–1421.

Dégano IR, Subirana I, Fusco D et al. Percutaneous coronary intervention reduces mortality in myocardial infarction patients with comorbidities: Implications for elderly patients with diabetes or kidney disease, *Int J Cardiol*. 2017;249:83–89.

Dehghan M, Mente A, Zhang X et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet*. 2017;390:2050–2062.

Devlin G, Gore JM, Elliott J et al. Management and 6-month outcomes in elderly and very elderly patients with high-risk non-ST-elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. *Eur Heart J*. 2008;29:1275–1282.

Dondo TB, Hall M, West RM et al. *β*-Blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. *J Am Coll Cardiol*. 2017;69:2710–2720.

Dorsch MF, Lawrance RA, Sapsford RJ et al. An evaluation of the relationship between specialist training in cardiology and implementation of evidence-based care of patients following acute myocardial infarction. *Int J Cardiol.* 2004;96:335–340.

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

Ekelund U, Ward HA, Norat T et al. Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: the European Prospective Investigation into Cancer and Nutrition Study (EPIC). *Am J Clin Nutr.* 2015;101:613–621.

Emdin CA, Khera AV, Natarajan P, et al. Evaluation of the pooled cohort equations for prediction of cardiovascular risk in a contemporary prospective cohort. *Am J Cardiol.* 2017;119:881–885.

Engel J, van der Wulp I, de Bruijne M, Wagner C. A cross-sectional multicentre study of cardiac risk score use in the management of unstable angina and non-St-segment elevation myocardial infarction. *BMJ Open.* 2015;5:e008523.

Ettehad D, Emdin CA, Kiran A et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016; 387:957–967.

Eurostat. *Causes of death statistics,* 2015 https://ec.europa.eu/eurostat/statistics-explained/index.php/Causes_of_death_statistics (Accessed 16.01.2019).

Fanning JP, Nyong J, Scott IA et al. Routine invasive strategies versus selective invasive strategies for unstable angina and non-ST elevation myocardial infarction in the stent era. *Cochrane Database of Systematic Reviews*, 2016.

Flynn MR, Barrett C, Cosío FG et al. The Cardiology Audit and Registration Data Standards (CARDS), European data standards for clinical cardiology practice. *Eur Heart J*. 2005;26:308–313.

Fox KA, Dabbous OH, Goldberg RJ et al. Prediction of risk of death and myocardial infarction in the six months after presentation with ACS: a prospective, multinational, observational study (GRACE). *BMJ.* 2006;333:1091–1094.

Fox KA, Anderson FA Jr, Dabbous OH et al. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). *Heart*. 2007a;93:177–182.

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

Fox KA, Fitzgerald G, Puymirat E et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open*. 2014;4:e004425.

Garg P, Morris P, Fazlanie AL et al. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. *Intern Emerg Med*. 2017;12:147–155.

Gnanenthiran SR, Kritharides L, D'Souza M, Lowe HC, Brieger DB. Revascularisation compared with initial medical therapy for non-ST-elevation acute coronary syndromes in the elderly: a meta-analysis. *Heart*. 2017;103:1962–1969.

Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129:S49–73.

Graversen P, Abildstrøm SZ, Jespersen L, Borglykke A, Prescott E. Cardiovascular risk prediction: Can Systematic Coronary Risk Evaluation (SCORE) be improved by adding simple risk markers? Results from the Copenhagen City Heart Study. *Eur J Prev Cardiol*. 2016;23:1546–1556.

Gustafsson I, Hvelplund A, Hansen KW et al. Underuse of an invasive strategy for patients with diabetes with acute coronary syndrome: a nationwide study. *Open Heart*. 2015;2:e000165.

Hall M, Dondo TB, Yan AT et al. Association of clinical factors and therapeutic strategies with improvements in survival following non-ST-segment elevation myocardial infarction, 2003–2013. *JAMA*. 2016;316:1073–1082.

Helgadottir A, Thorleifsson G, Manolescu A et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science*. 2007;316:1491–1493.

Hippisley-Cox J, Coupland C, Vinogradova Y et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ.* 2008;336:1475–1482.

Huber K, Gersh BJ, Goldstein P, Granger CB, Armstrong PW. The organization, function, and outcomes of ST-segment elevation myocardial infarction networks worldwide: current state, unmet needs and future directions. *Eur Heart J.* 2014;35:1526–1532.

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

Jernberg T, Johanson P, Held C. Association between adoption of evidence-based treatment and survival for patients with ST-segment elevation myocardial infarction. *JAMA*. 2011;305:1677–1684.

Jernberg T. *SWEDEHEART Annual report 2017*. Stockholm: Danderyd Hospital, 2018 http://www.ucr.uu.se/swedeheart/arsrapport-2017/swedeheart-annual-report-2017 (Accessed 17.01.2019).

Kandzari DE, Roe MT, Chen AY et al. Influence of clinical trial enrollment on the quality of care and outcomes for patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J*. 2005;149:474–481.

Kelly TN, Bazzano LA, Ajami NJ et al. Gut Microbiome Associates With Lifetime Cardiovascular Disease Risk Profile Among Bogalusa Heart Study Participants. *Circ Res*. 2016;119:956–64.

Komócsi A, Simon M, Merkely B et al. Underuse of coronary intervention and its impact on mortality in the elderly with myocardial infarction. A propensity-matched

analysis from the Hungarian Myocardial Infarction Registry. *Int J Cardiol*. 2016;214:485–490.
Kõrv J, Gross-Paju K, Haldre S, et al. Insuldi käsitlus Eestis: hetkeseis ja suundumused. *Eesti Arst.* 2010;89:409–415. [in Estonian].
Kristensen SD, Laut KG, Fajadet J et al. Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. *Eur Heart J*. 2014;35:1957–1970.
Laks T. *Äge müokardiinfarkt: haigestumus, suremus, letaalsus, riskifaktorid ja rekanaliseeriv ravi : kliinilis-epidemioloogiline uurimus: Tallinna Ägeda Müokardiinfarkti Register 1991–1997*. Tallinn: Tallinna Raamatutrükikoda, 2002. [in Estonian]
Laks T, Jõeste E, Pullisaar O et al. Trends in incidence, attack rate, and mortality of acute myocardial infarction in Estonia: The Tallinn AMI Registry 1991–2005. *Ann Med.* 2013;45:107–11.
Lear SA, Hu W, Rangarajan S et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet*. 2017;390:2643–2654.
Lee CH, Tan M, Yan AT et al. Use of cardiac catheterization for non-ST-segment elevation acute coronary syndromes according to initial risk: reasons why physicians choose not to refer their patients. *Arch Intern Med*. 2008;168:291–296.
Lee HY, Cooke CE, Robertson TA. Use of secondary prevention drug therapy in patients with acute coronary syndrome after hospital discharge. *J Manag Care Pharm*. 2008;14:271–280.
Leitsalu L, Haller T, Esko T, et al. Cohort profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. *Int J Epidemiol.* 2015;44:1137–1147.
Levi F, Chatenoud L, Bertuccio P et al. Mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world: an update. *Eur J Cardiovasc Prev Rehabil.* 2009;16:333–335.
Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360:1903–1913.
Li M, Wang X, Li X et al. Statins for the primary prevention of coronary heart disease. *Biomed Res Int*. 2019;2019:4870350.
Libby P, Bonow RO, Zipes DP, Mann DL. *Braunwald's Heart Disease: a Textbook of Cardiovascular Medicine, 8th Ed*. Philadelphia: Elsevier Health Sciences, 2007.
Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol*. 2009;54:2129–2138.
Lloyd-Jones DM. Cardiovascular risk prediction: basic concepts, current status, and future directions. *Circulation*. 2010;121:1768–1777.
Marandi T, Baburin A, Ainla T. Use of evidence-based pharmacotherapy after myocardial infarction in Estonia. *BMC Public Health*. 2010;10:358
Martin SS, Sperling LS, Blaha MJ et al. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA Guidelines. *J Am Coll Cardiol*. 2015;65:1361–1368.
McManus DD, Gore J, Yarzebski J et al. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med*. 2011;124:40–47.
McPherson R, Pertsemlidis A, Kavaslar N et al. A common allele on chromosome 9 associated with coronary heart disease. *Science*. 2007;316:1488–1491.
Mortensen MB, Afzal S, Nordestgaard BG, Falk E. The high-density lipoprotein-adjusted SCORE model worsens SCORE-based risk classification in a contemporary

population of 30,824 Europeans: the Copenhagen General Population Study. *Eur Heart J*. 2015;36:2446–2453.
Mortensen MB, Falk E. Primary prevention with statins in the elderly. *JACC*. 2018; 71:85–94.
Motivala AA, Cannon CP, Srinivas VS et al. Changes in myocardial infarction guideline adherence as a function of patient risk: an end to paradoxical care? *J Am Coll Cardiol*. 2011;58:1760–1765.
National Institute for Health and Care Excellence (NICE). *Cardiovascular disease: risk assessment and reduction, including lipid modification*. London: NICE, 2014.
Negers A, Boddaert J, Mora L et al. Determinants of invasive strategy in elderly patients with non-ST elevation myocardial infarction. *J Geriatr Cardiol*. 2017; 14:465–472.
O'Brien E, Subherwal S, Roe MT et al. Do patients treated at academic hospitals have better longitudinal outcomes after admission for non-ST-segment elevation myocardial infarction? *Am Heart J*. 2014;167:762–769.
O'Flaherty M, Buchan I, Capewell S. Contributions of treatment and lifestyle to declining CVD mortality: why have CVD mortality rates declined so much since the 1960s? *Heart*. 2013;99:159–162.
Organization for Economic Co-operation and Development (OECD), *Health at a Glance 2017*. Paris: OECD Publishing, 2017.
Pedersen et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994; 344:1383–1389.
Pencina MJ, D'Agostino RB Sr, Song L. Quantifying discrimination of Framingham risk functions with different survival C statistics. *Stat Med*. 2012;31:1543–1553.
Pennells L, Kaptoge S, Wood A et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. *Eur Heart J*. 2019;40:621–631.
Piepoli MF, Hoes AW, Agewall S et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J*. 2016;37:2315–2381.
Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ*. 1998;316:1043–1047.
Puymirat E, Battler A, Birkhead J et al. Euro Heart Survey 2009 Snapshot: regional variations in presentation and management of patients with AMI in 47 countries. *Eur Heart J Acute Cardiovasc Care*. 2013;2:359–370.
R Development Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2008. ISBN 3-900051-07-0.
Radovanovic D, Seifert B, Roffi M et al. Gender differences in the decrease of in-hospital mortality in patients with acute myocardial infarction during the last 20 years in Switzerland. *Open Heart*. 2017;4:e000689.
Rana JS, Tabada GH, Solomon MD et al. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. *J Am Coll Cardiol*. 2016;67:2118–2130.
Ridker PM, Danielson E, Fonseca FA et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet*. 2009;373:1175–1182.

Ridker PM, Everett BM, Thuren T et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131.
Roe MT, Peterson ED, Newby LK et al. The influence of risk status on guideline adherence for patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J.* 2006;151:1205–1213.
Roffi M, Patrono C, Collet JP et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315.
Rogers WJ, Frederick PD, Stoehr E et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J*. 2008;156:1026–1034.
Rosamond WD, Chambless LE, Heiss G et al. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987–2008. *Circulation*. 2012;125:1848–1857.
Roth GA, Forouzanfar MH, Moran AE et al. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med*. 2015;372:1333–1341.
Sabatine MS, Giugliano RP, Keech AC et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.
Samani NJ, Erdmann J, Hall AS et al. Genomewide association analysis of coronary artery disease. *N Engl J Med.* 2007;357:443–453.
Sarwar N, Gao P, Kondapally Seshasai SR et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet.* 2010;375:2215–2222.
Schoenenberger AW, Radovanovic D, Stauffer JC et al. Age-related differences in the use of guideline-recommended medical and interventional therapies for acute coronary syndromes: a cohort study. *J Am Geriatr Soc*. 2008;56:510–516.
Schwartz GG, Steg PG, Szarek M et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. 2018;379:2097–2107
Shaw C, Nitsch D, Steenkamp R et al. Inpatient coronary angiography and revascularisation following non-ST-elevation acute coronary syndrome in patients with renal impairment: a cohort study using the Myocardial Ischaemia National Audit Project. *PLoS One*. 2014;9:e99925.
Sinnaeve PR, Zeymer U, Bueno H et al. Contemporary inter-hospital transfer patterns for the management of acute coronary syndrome patients: Findings from the EPICOR study. *Eur Heart J Acute Cardiovasc Care*. 2015;4:254–262.
Smith FG, Brogan RA, Alabas O et al. Comparative care and outcomes for acute coronary syndromes in Central and Eastern European Transitional countries: A review of the literature. *Eur Heart J Acute Cardiovasc Care*. 2015;4:537–554.
Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. *BMJ*. 2012;344:d8059.
Soopõld Ü, Marandi T, Ainla T et al. Estonian guidelines for the management of patients with ST-segment elevation myocardial infarction. *Eesti Arst.* 2004;12 Suppl 1:2–48. [in Estonian]
Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews,* 2008.

Stone GW, Maehara A, Lansky AJ et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226–235.

Stone NJ, Robinson JG, Lichtenstein AH et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129:S1–45.

Subherwal S, Bach RG, Chen AY et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation*. 2009;119:1873–1882.

Sugiyama T, Hasegawa K, Kobayashi Y et al. Differential time trends of outcomes and costs of care for acute myocardial infarction hospitalizations by ST elevation and type of intervention in the United States, 2001–2011. *J Am Heart Assoc*. 2015; 4:e001445.

Szummer K, Lundman P, Jacobson et al. Influence of renal function on the effects of early revascularization in non-St-segment elevation myocardial infarction: data from the Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Circulation.* 2009;120:851–858.

Szummer K, Wallentin L, Lindhagen L et al. Improved outcomes in patients with ST-segment elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDE-HEART registry 1995–2014. *Eur Heart J.* 2017;38:3056–3065.

Szummer K, Wallentin L, Lindhagen L et al. Relations between implementation of new treatments and improved outcomes in patients with non-ST-segment elevation myocardial infarction during the last 20 years: experiences from SWEDEHEART registry 1995 to 2014. *Eur Heart J*. 2018;39:3766–3776.

Taylor F, Huffman MD, Macedo AF et al. Statins for the primary prevention of cardiovascular disease*. Cochrane Database of Systematic Reviews,* 2013.

The World Bank Group, *The State of Health Care Integration in Estonia,* 2015 https://www.haigekassa.ee/sites/default/files/Maailmapanga-uuring/summary_report_hk_2015.pdf (Accessed 16.01.2019).

Thygesen K, Alpert JS, White HD et al. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28:2525–2538.

Thygesen K, Alpert JS, Jaffe AS et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33:2551–2567.

Thygesen K, Alpert JS, Jaffe AS et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40:237–269.

Timmis A, Townsend N, Gale C et al. European Society of Cardiology: Cardiovascular Disease Statistics 2017. *Eur Heart J*. 2018;39:508–579.

Tsai TT, Patel UD, Chang TI et al. Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the national cardiovascular data registry Cath-PCI registry. *J Am Heart Assoc*. 2014;3:1–13.

Ulmer H, Kollerits B, Kelleher C, et al. Predictive accuracy of the SCORE risk function for cardiovascular disease in clinical practice: a prospective evaluation of 44 649 Austrian men and women. *Eur J Cardiovasc Prev Rehabil*. 2005;12:433–441.

Van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R, *J Stat Softw*. 2011;45:1–67.

Ventura M, Belleudi V, Sciattella P et al. High quality process of care increases one-year survival after acute myocardial infarction (AMI): A cohort study in Italy. *PLoS One*. 2019;14:e0212398.

Viallon V, Ragusa S, Clavel-Chapelon F et al. How to evaluate the calibration of a disease risk prediction tool. *Stat Med*. 2009;28:901–916.

Wald NJ, Simmonds M, Morris JK. Screening for future cardiovascular disease using age alone compared with multiple risk factors and age. *PLoS One*. 2011;6(5).

Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248.

Williams B, Mancia G, Spiering W et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–3104.

Wilson PW, Pencina M, Jacques P et al. C-reactive protein and reclassification of cardiovascular risk in the Framingham Heart Study. *Circ Cardiovasc Qual Outcomes*. 2008;1:92–97.

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

PUBLICATIONS

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Education

2014–	University of Tartu, Faculty of Medicine, Department of Cardiology, PhD programme
2013–	University of Tartu, Institute of Clinical Medicine, Department of Cardiology, Residency in General Cardiology
2007–2013	University of Tartu, Faculty of Medicine, Medical Doctor degree

Work experience

2014–	North-Estonia Medical Centre, physician
2013–2014	Läänemaa Hospital, physician
2012–2013	Läänemaa Hospital, physician assistant

Professional associations

2014–	Estonian Society of Cardiology, member of Working Group of Young Cardiologists; member of Working Group of Acute Coronary Syndromes
2014–	European Society of Cardiology
2013–	Estonian Junior Doctors Association

Publications

Saar, Aet; Läll, Kristi; Alver, Maris; Marandi, Toomas; Ainla Tiia; Eha Jaan; Metspalu Andres; Fischer Krista. Estimating the performance of three cardiovascular disease risk scores: the Estonian Biobank cohort study. *J Epidemiol Community Health*. 2019;73:272–277.

Alver, Maris; Palover, Marili; Saar, Aet; Läll, Kristi; Zekavat, Seyedeh Maryam; Tõnisson, Neeme; Leitsalu, Liis; Reigo, Anu; Nikopensius, Tiit; Ainla, Tiia; Kals, Mart; Mägi, Reedik; Gabriel, Stacey B; Eha, Jaan; Lander, Eric S; Irs, Alar; Philippakis, Anthony; Marandi, Toomas; Natarajan, Pradeep; Metspalu, Andres; Kathiresan, Sekar; Esko, Tõnu. Recall by genotype and cascade screening for familial hypercholesterolemia in a population-based biobank from Estonia. *Genet Med*. 2018 doi: 10.1038/s41436-018-0311-2.

Saar, Aet; Marandi, Toomas; Ainla, Tiia; Fischer, Krista; Blöndal, Mai; Eha, Jaan. The risk-treatment paradox in non-ST-elevation myocardial infarction

patients according to their estimated GRACE risk. *Int J Cardiol*. 2018;272:26–32.

Saar, Aet; Marandi, Toomas; Alver, Maris; Ainla, Tiia; Fischer, Krista; Eha, Jaan Coronary artery disease risk prediction using genetic markers. *Eesti Arst*, 2015;94:522–529 /in Estonian/.

Saar, Aet; Marandi, Toomas; Ainla, Tiia; Fischer, Krista; Blöndal, Mai; Eha, Jaan. Improved treatment and prognosis after acute myocardial infarction in Estonia: cross-sectional study from a high risk country. *BMC Cardiovascular Disorders*, 2015;15:136.

Presentations

2019 Poster presentation at Acute Cardiovascular Care Congress in Malaga. Aet Saar, Toomas Marandi, Tiia Ainla, Mai Blöndal, Krista Fischer, Jaan Eha. The plateauing in the management and outcomes of ST-segment elevation myocardial infarction – long term data from Estonia.

2018 Moderated poster presentation at Acute Cardiovascular Care Congress in Milan. Aet Saar, Toomas Marandi, Tiia Ainla, Mai Blöndal, Krista Fischer, Jaan Eha. "The treatment and mortality of patients with non-ST-elevation myocardial infarction according to estimated risk – real-world data from Estonian Myocardial Infarction Registry".

2016 Moderated poster presentation at Acute Cardiovascular Care Congress in Lisbon Aet Saar, Toomas Marandi, Tiia Ainla, Mai Blöndal, Krista Fischer, Jaan Eha. "The risk-treatment paradox in patients with diabetes mellitus hospitalized with acute myocardial infarction in Estonia".

2016 Moderated poster presentation at European Society of Cardiology Congress in Rome. Saar, Aet; Läll, Kristi; Alver, Maris; Marandi, Toomas; Ainla Tiia; Eha Jaan; Metspalu Andres; Fischer Krista. "Accuracy of PCE, SCORE and QRISK2 scores in predicting cardiovascular disease in Estonia, a high risk European Country".

2015 Poster presentations at "XXV Nordic-Baltic Congress of Cardiology 2015" in Tallinn. Aet Saar, Toomas Marandi, Mai Blöndal, Tiia Ainla, Krista Fischer, Jaan Eha "Improved Treatment and Prognosis after Myocardial Infarction in Estonia between 2001 and 2011".

2015 Oral presentation at European Society of Cardiology Congress in London. Aet Saar, Toomas Marandi, Tiia Ainla, Mai Blöndal, Krista Fischer, Jaan Eha.*"Impact of national PCI network on prognosis after acute myocardial infarction in Estonia"*

2014 Two poster presentations at Acute Cardiovascular Care in Geneva. Aet Saar, Tiia Ainla, Mai Blöndal, Jaan Eha, Toomas Marandi "Medical contacts during 30 days before admission due to acute myocardial infarction–should we change our routine?"

Aet Saar, Tiia Ainla, Mai Blöndal, Toomas Marandi, Jaan Eha. "The changes in in-hospital treatment and mortality of STEMI patients in Estonian tertiary care hospitals in 2001 vs 2007 vs 2011".

2011 Poster presentation at The 9th International Congress on Coronary Artery Disease in Venice. Aet Saar, Natalia Kapitan, Henery Kroon, Laura Lipping, Ksenia Lodeikina, Taavi Põdramägi, Susan Sündema, Mary Vaarpu, Alla Vishnevskaya, Mai Blöndal, Jaan Eha. "Differences in mortality of patients with stabile angina and acute coronary syndromes who have undergone percutaneous coronary intervention".

2011 Oral presentation at Annual Anniversary Conference, University of Tartu, Faculty of Medicine. Aet Saar, Natalia Kapitan, Henery Kroon, Laura Lipping, Ksenia Lodeikina, Taavi Põdramägi, Susan Sündema, Mary Vaarpu, Alla Vishnevskaya, Mai Blöndal, Jaan Ehe. "Differences in mortality between stable coronary arterty disease and acute coronary syndrome patients after percutaneous coronary intervention (REPRO study)" /in Estonian/

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2013–	Tartu Ülikool, Kliinilise Meditsiini Instituut, Südamekliinik. Residentuur
2007–2013	Tartu Ülikool, Kliinilise Meditsiini Instituut, Arstiteaduse bakalaureuse- ja magistriõppe integreeritud õpe

Teenistuskäik

2014–	SA Põhja-Eesti Regionaalhaigla, arst
2013–2014	SA Läänemaa Haigla, arst
2012–2013	SA Läänemaa Haigla, abiarst

Kuulumine ühendustesse

2014–	Eesti Kardioloogide Selts, noorkardioloogide ja ägedate koronaarsündroomide töögruppide liige
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2013–	Eesti Nooremarstide Ühendus

Publikatsioonid

Saar, Aet; Läll, Kristi; Alver, Maris; Marandi, Toomas; Ainla Tiia; Eha Jaan; Metspalu Andres; Fischer Krista. Estimating the performance of three cardiovascular disease risk scores: the Estonian Biobank cohort study. *J Epidemiol Community Health*. 2019;73:272–277.

Alver, Maris; Palover, Marili; Saar, Aet; Läll, Kristi; Zekavat, Seyedeh Maryam; Tõnisson, Neeme; Leitsalu, Liis; Reigo, Anu; Nikopensius, Tiit; Ainla, Tiia; Kals, Mart; Mägi, Reedik; Gabriel, Stacey B; Eha, Jaan; Lander, Eric S; Irs, Alar; Philippakis, Anthony; Marandi, Toomas; Natarajan, Pradeep; Metspalu, Andres; Kathiresan, Sekar; Esko, Tõnu. Recall by genotype and cascade screening for familial hypercholesterolemia in a population-based biobank from Estonia. *Genet Med*. 2018 doi: 10.1038/s41436-018-0311-2.

Saar, Aet; Marandi, Toomas; Ainla, Tiia; Fischer, Krista; Blöndal, Mai; Eha, Jaan. The risk-treatment paradox in non-ST-elevation myocardial infarction patients according to their estimated GRACE risk. *Int J Cardiol*. 2018; 272:26–32.

Saar, Aet; Marandi, Toomas; Alver, Maris; Ainla, Tiia; Fischer, Krista; Eha, Jaan Südame isheemiatõve riski ennustamine geneetiliste markerite abil. *Eesti Arst*, 2015;94:522–529.

Saar, Aet; Marandi, Toomas; Ainla, Tiia; Fischer, Krista; Blöndal, Mai; Eha, Jaan. Improved treatment and prognosis after acute myocardial infarction in Estonia: cross-sectional study from a high risk country. *BMC Cardiovascular Disorders*, 2015;15:136.

Ettekanded rahvusvahelistel konverentsidel

2019 Posterettekanne *Acute Cardiovascular Care* kongressil Malagas. Aet Saar, Toomas Marandi, Tiia Ainla, Mai Blöndal, Krista Fischer, Jaan Eha. *The plateauing in the management and outcomes of ST-segment elevation myocardial infarction – long term data from Estonia.*

2018 Modereeritud posterettekanne *Acute Cardiovascular Care* kongressil Milanos. Aet Saar, Toomas Marandi, Tiia Ainla, Mai Blöndal, Krista Fischer, Jaan Eha. *The treatment and mortality of patients with non-ST-elevation myocardial infarction according to estimated risk – real-world data from Estonian Myocardial Infarction Registry.*

2016 Modereeritud posterettekanne *Acute Cardiovascular Care* kongressil Lissabonis. Aet Saar, Toomas Marandi, Tiia Ainla, Mai Blöndal, Krista Fischer, Jaan Eha. *The risk-treatment paradox in patients with diabetes mellitus hospitalized with acute myocardial infarction in Estonia.*

2016 Modereeritud posterettekanne Euroopa Kardioloogide Seltsi kongressil Roomas. Saar, Aet; Läll, Kristi; Alver, Maris; Marandi, Toomas; Ainla Tiia; Eha Jaan; Metspalu Andres; Fischer Krista. *Accuracy of PCE, SCORE and QRISK2 scores in predicting cardiovascular disease in Estonia, a high risk European Country*.

2015 Posterettekanne XXV Põhja- ja Baltimaade kardioloogiakongressil Tallinnas. Aet Saar, Toomas Marandi, Mai Blöndal, Tiia Ainla, Krista Fischer, Jaan Eha *Improved Treatment and Prognosis after Myocardial Infarction in Estonia between 2001 and 2011*.

2015 Suuline ettekanne Euroopa Kardioloogide Seltsi kongressil Londonis. Aet Saar, Toomas Marandi, Tiia Ainla, Mai Blöndal, Krista Fischer, Jaan Eha. *Impact of national PCI network on prognosis after acute myocardial infarction in Estonia.*

2014 Kaks posterettekannet Acute Cardiovascular Care kongressil Genfis. Aet Saar, Tiia Ainla, Mai Blöndal, Jaan Eha, Toomas Marandi. *Medical contacts during 30 days before admission due to acute myocardial infarction–should we change our routine?*

Aet Saar, Tiia Ainla, Mai Blöndal, Toomas Marandi, Jaan Eha. *The changes in in-hospital treatment and mortality of STEMI patients in Estonian tertiary care hospitals in 2001 vs 2007 vs 2011.*

2011 Posterettekanne konverentsil: "*The 9th International Congress on Coronary Artery Disease*" Veneetsias. Aet Saar, Natalia Kapitan, Henery Kroon, Laura Lipping, Ksenia Lodeikina, Taavi Põdramägi, Susan Sündema,

Mary Vaarpu, Alla Vishnevskaya, Mai Blöndal, Jaan Eha. *Differences in mortality of patients with stabile angina and acute coronary syndromes who have undergone percutaneous coronary intervention.*

2011 Suuline ettekanne arstiteaduskonna aastapäeva konverentsil. Aet Saar, Natalia Kapitan, Henery Kroon, Laura Lipping, Ksenia Lodeikina, Taavi Põdramägi, Susan Sündema, Mary Vaarpu, Alla Vishnevskaya, Mai Blöndal, Jaan Eha. Erinevused perkutaanse koronaarinterventsiooni läbi teinud ägeda koronaarsündroomi ja stabiilse stenokardiaga patsientide suremuses (REPRO uuring).

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

1. **Heidi-Ingrid Maaroos**. The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
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36. **Oleg Milenin**. Reconstruction of cervical part of esophagus by revascularised ileal autografts in dogs. A new complex multistage method. Tartu, 1998.
37. **Sergei Pakriev**. Prevalence of depression, harmful use of alcohol and alcohol dependence among rural population in Udmurtia. Tartu, 1998.
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42. **Heli Grünberg**. The cardiovascular risk of Estonian schoolchildren. A cross-sectional study of 9-, 12- and 15-year-old children. Tartu, 1998.
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45. **Tiina Ristimäe**. Heart rate variability in patients with coronary artery disease. Tartu, 1998.
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47. **Bela Adojaan**. Immune and genetic factors of childhood onset IDDM in Estonia. An epidemiological study. Tartu, 1999.
48. **Jakov Shlik**. Psychophysiological effects of cholecystokinin in humans. Tartu, 1999.
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54. **Eve Pihl**. Cardiovascular risk factors in middle-aged former athletes. Tartu, 1999.
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59. **Anneli Beilmann**. Epidemiology of epilepsy in children and adolescents in Estonia. Prevalence, incidence, and clinical characteristics. Tartu, 1999.
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64. **Jana Kivastik**. Lung function in Estonian schoolchildren: relationship with anthropometric indices and respiratory symptomas, reference values for dynamic spirometry. Tartu, 2000.
65. **Karin Kull**. Inflammatory bowel disease: an immunogenetic study. Tartu, 2000.
66. **Kaire Innos**. Epidemiological resources in Estonia: data sources, their quality and feasibility of cohort studies. Tartu, 2000.
67. **Tamara Vorobjova**. Immune response to *Helicobacter pylori* and its association with dynamics of chronic gastritis and epithelial cell turnover in antrum and corpus. Tartu, 2001.
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69. **Annika Krüüner**. *Mycobacterium tuberculosis* – spread and drug resistance in Estonia. Tartu, 2001.
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77. **Tõnu Rätsep**. Aneurysmal subarachnoid haemorrhage: Noninvasive monitoring of cerebral haemodynamics. Tartu, 2002.
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79. **Katre Maasalu**. Changes in bone quality due to age and genetic disorders and their clinical expressions in Estonia. Tartu, 2003.
80. **Toomas Sillakivi**. Perforated peptic ulcer in Estonia: epidemiology, risk factors and relations with *Helicobacter pylori*. Tartu, 2003.
81. **Leena Puksa**. Late responses in motor nerve conduction studies. F and A waves in normal subjects and patients with neuropathies. Tartu, 2003.
82. **Krista Lõivukene**. *Helicobacter pylori* in gastric microbial ecology and its antimicrobial susceptibility pattern. Tartu, 2003.

83. **Helgi Kolk**. Dyspepsia and *Helicobacter pylori* infection: the diagnostic value of symptoms, treatment and follow-up of patients referred for upper gastrointestinal endoscopy by family physicians. Tartu, 2003.
84. **Helena Soomer**. Validation of identification and age estimation methods in forensic odontology. Tartu, 2003.
85. **Kersti Oselin**. Studies on the human MDR1, MRP1, and MRP2 ABC transporters: functional relevance of the genetic polymorphisms in the *MDR1* and *MRP1* gene. Tartu, 2003.
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