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From registry to reality: insights into myocardial infarction care and prevention across Estonia and Europe

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From registry to reality: insights into myocardial infarction care and prevention across Estonia and Europe

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Press

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following four papers:

I. Blöndal M, Ainla T, Eha J, Lõiveke P, Marandi T, Saar A *et al.* Comparison of management and outcomes of ST-segment elevation myocardial infarction patients in Estonia, Hungary, Norway and Sweden according to national ongoing registries. *Qual Care Clin Outcomes. 2022 May 5;8(3):307–314.* https://doi.org/10.1093/ehjqcco/qcaa098.

II. Edfors R, Jernberg T, Lewinter C, Blöndal M, Eha J, Lõiveke P *et al.* Differences in characteristics, treatments and outcomes in patients with non-ST-elevation myocardial infarction: novel insights from four national European continuous real-world registries. *Qual Care Clin Outcomes. 2022 Jun 6;8(4):429–436.* https://doi.org/10.1093/ehjqcco/qcab013.

III. Lõiveke P, Marandi T, Ainla T, Fischer K, Eha J. Adherence to recommendations for secondary prevention medications after myocardial infarction in Estonia: comparison of real world data from 2004 to 2005 and 2017 to 2018. *BMC Cardiovasc Disord (2021) 21:505.* https://doi.org/10.1186/s12872-021-02321-x

IV. Asser P, Fischer K, Ainla T, Marandi T, Blöndal M, Saar A, Eha J. Examining the Impact of Renal Dysfunction and Diabetes on Post-Myocardial Infarction Mortality: Insights from a Comprehensive Retrospective Cohort Study Across Different Age Groups. *Scandinavian Cardiovascular Journal*, *58*(1). https://doi.org/10.1080/14017431.2024.2395875

The papers are referred to in the text by their Roman numerals (I–IV).

Author's contribution

Paper I and II: participation in the study design, interpretation of the results, and drafting the manuscripts.

Paper III and IV: participation in the study design, statistical analysis, interpretation of the result, preparation of tables and figures, and drafting the manuscripts.

Author's note on name change

During my doctoral studies, I changed my surname from Lõiveke to Asser. Three articles included in this thesis were published under Piret Lõiveke, and the most recent article under Piret Asser. Both names refer to the same author (the thesis author).

ABBREVIATIONS

ACC	American College of Cardiology
ACEi	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AHA	American Heart Association
AI	artificial intelligence
AMI	acute myocardial infarction
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor–neprilysin inhibitor
ASA	acetylsalicylic acid
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass graft
CKD	chronic kidney disease
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
DDD	defined daily dose
DM	diabetes mellitus
EAPCI	European Association of Percutaneous Cardiovascular Interventions
EAS	European Atherosclerosis Society
ECG	electrocardiogram
EHIF	Estonian Health Insurance Fund
EMIR	Estonian Myocardial Infarction Registry
EU	European Union
GDMT	guideline-directed medical therapy
GLP-1	glucagon-like peptide-1
HbA1c	glycated haemoglobin
HDL	high-density lipoprotein
HF	heart failure
HRQoL	health-related quality of life
HUMIR	Hungarian Myocardial Infarction Registry
IHD	ischaemic heart disease
IQR	interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MI	myocardial infarction
MRA	mineralocorticoid receptor antagonist
NORMI	Norwegian Myocardial Infarction Registry
NSTEMI	non–ST-segment elevation myocardial infarction
NYHA	New York Heart Association
OECD	Organisation for Economic Co-operation and Development

OHCA	out-of-hospital cardiac arrest
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
QoL	quality of life
RAAS	renin–angiotensin–aldosterone system
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SCORE	Systematic Coronary Risk Evaluation
SCORE2	Systematic Coronary Risk Evaluation 2
SEPHIA	secondary prevention after heart intensive care admission
SGLT2	sodium–glucose co-transporter 2
SPSS	Statistical Package for the Social Sciences
STEMI	ST-segment elevation myocardial infarction
SWEDEHEART	Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies
WHF	World Heart Federation
WHO	World Health Organization

1. INTRODUCTION

Cardiovascular diseases (CVD) remain the leading cause of death in Europe, despite significant advances in prevention and treatment over recent decades. While many Western European countries have experienced a pronounced decline in CVD mortality, variations persist across the continent, reflecting differences in risk profiles, healthcare resources, and lifestyle factors. Estonia has shown steady improvements in cardiovascular (CV) outcomes but continues to report higher age-standardized mortality rates compared with most Western Europe, underscoring the need for further targeted interventions (World Health Organization [WHO], n.d.)

To date, efforts in Estonia have largely focused on primary prevention and the monitoring and improvement of treatment for ischemic heart disease (IHD), specifically its most serious complication – myocardial infarction (MI). Doctoral theses by Tiia Ainla (2005) and Mai Blöndal (2012) systematically examined the management and outcomes of MI within Estonia. Findings from these studies prompted a series of nationwide educational initiatives in the following years, coordinated by the Estonian Society of Cardiology. During this period, expanded access to cardiac catheterization facilities and enhanced affordability of secondary prevention drugs further centralized MI care, with clear recommendations to transfer most MI patients to tertiary care centres without delay for invasive diagnostics and treatment.

In 2019, Aet Saar continued to evaluate trends in MI management and outcomes. By analysing data from the newly established Estonian Myocardial Infarction Registry (EMIR) in 2012 and comparing them with earlier 'snapshot' data from 2001, 2007, and 2011, her work demonstrated significant advances in acute MI management in both secondary- and tertiary-care hospitals. Meanwhile, the prevalence of comorbidities remained largely unchanged, and the average age of MI patients increased. Results also indicated that Estonian hospitals were functioning as an efficient network, providing equitable care to MI patients. However, a risk–treatment paradox was identified among intermediate- (GRACE 109–140) and high-risk (GRACE >140) MI populations.

Saar's thesis also addressed primary prevention by validating the prediction accuracy of the Systematic Coronary Risk Estimation (SCORE) chart in Estonia, designated a high-risk country. These results demonstrated that risk scores developed using low-risk populations function acceptably in high-risk settings, supporting their use in guiding primary prevention strategies.

Despite major advances in CVD care, the decline in CVD mortality in Estonia has slowed in recent years, likely reflecting rising diabetes (DM) and obesity alongside population ageing. Historically, roughly half of the mortality reduction has been attributed to evidence-based treatments and half to risk-factor modification (Mensah et al., 2018). Yet guideline-recommended therapies remain underused; strengthening adherence to secondary prevention therefore represents a key opportunity for further gains, while acknowledging that frailty assessments

increasingly influence decisions in older or clinically complex patients (Byrne et al., 2023). Pharmacotherapy for secondary prevention is a cornerstone of contemporary care, reducing recurrent ischaemic events and improving survival after MI.

The MI case-mix is also changing, with greater representation of both younger and older patients. This shift is driven by increasing obesity and sedentary behaviour – particularly among younger cohorts – and by longer life expectancy. In parallel, the cardiovascular–kidney–metabolic (CKM) framework underscores the clustering of cardiometabolic and renal disease, further diversifying patient profiles (Ndumele et al., 2023).

Because implementation of guideline-based therapies varies across European health systems, cross-country comparative analyses are essential to identify gaps and benchmark care. Accordingly, this thesis (i) examines temporal trends in MI management and outcomes in Estonia, with particular attention to adherence to guideline-directed pharmacotherapy; (ii) compares STEMI and NSTEMI patient characteristics and treatment patterns across four national MI registries to place Estonian practice in an international context; and (iii) quantifies the impact of DM and chronic kidney disease (CKD) on post–MI mortality to inform more individualized, intensive secondary prevention. The principal data source is the EMIR, a real-time, nationwide registry providing contemporary, population-based evidence for the analyses that follow.

2. REVIEW OF THE LITERATURE

2.1. Epidemiology of IHD and MI in Europe: mortality burden, temporal trends, and regional variation

2.1.1. Mortality burden and economic impact of CVD in Europe

Historically, CVD has been the leading cause of mortality in Europe, accounting for over 4 million deaths annually, which represents more than half of all deaths among women and approximately 42% among men. Over the past two decades, the epidemiology of IHD and MI in Europe has exhibited notable trends (Nicholas et al., 2015). Age-standardized incidence and mortality rates have generally declined (Figure 1), attributed to improved awareness of lifestyle risk factors, public health initiatives, and advancements in medical treatments. However, CVD remain the leading cause of mortality in most European Union (EU) countries, accounting for over 1.7 million deaths (or 32% of all deaths) in the EU in 2021 (OECD & European Commission, 2024). A population-based cost study estimated that in 2021 CVD cost the EU approximately €282 billion annually. IHD and cerebrovascular diseases each account for approximately 27% of the total CVD costs, followed by heart failure, peripheral artery disease, and atrial fibrillation, highlighting their significant impact on healthcare systems and economies across Europe (Luengo-Fernandez et al., 2023).

Significant geographic disparities exist within the EU, with substantial variations in the burden and scale of CV mortality (Bugiardini, 2023). While Southern European countries report the lowest mortality rates, Central-Eastern and Baltic nations experience the highest. The underlying causes of these differences remain largely unclear (Khan et al., 2020).

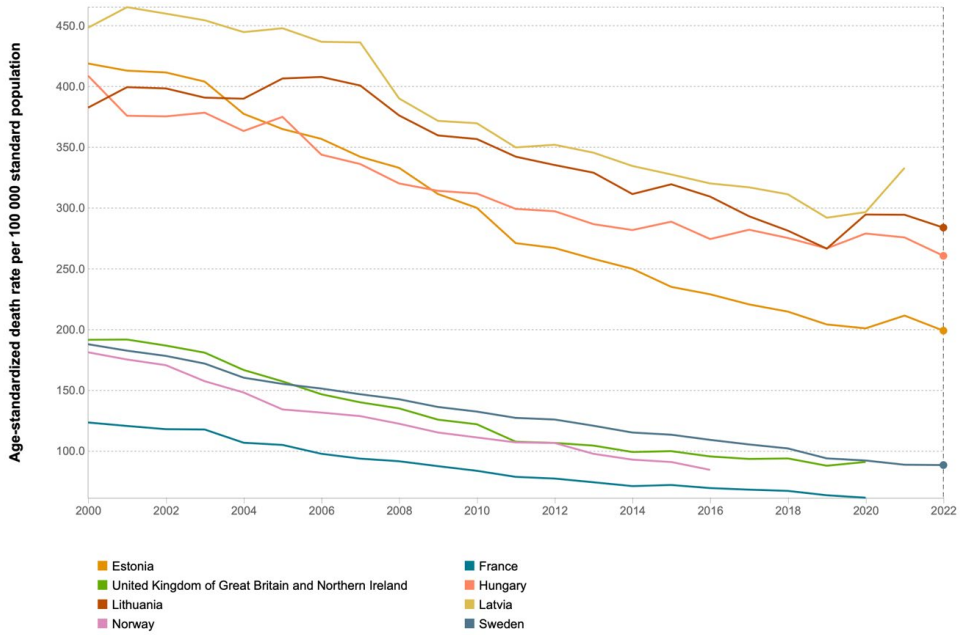

Figure 1. Age-standardized death rate of CVD per 100 000 standard population in European countries. Author-generated line graph using data from World Health Organization (n.d.), *Cardiovascular diseases – WHO Mortality Database (MDB)* (retrieved September 6, 2025, from https://platform.who.int/mortality/themes/theme-details/topics/topic-details/MDB/cardiovascular-diseases (World Health Organization [WHO], n.d).

2.1.2. Temporal trends and demographic differentials in IHD and MI

While age-adjusted MI mortality has continued to decline across the EU-27 (27 European Union countries after United Kingdom left the Union in 2020), the reduction has been more pronounced in individuals aged ≥65 years. In contrast, among patients younger than 65 years, the rate of improvement has slowed in recent years, suggesting a potential plateau in mortality reduction within this age group. Additionally, sex differences persist, with the decline in mortality being more pronounced in males, whereas among females, particularly in some Eastern European countries, progress has been less substantial (Zuin et al., 2023a).

2.1.3. Regional variation in mortality and CV care (Western, Southern, and Northern Europe)

Timmis et al. (Timmis et al., 2023) compare CVD trends between Western Europe and Southern Europe (Table 1). From 1990 to 2019, age-standardized mortality rates (ASMRs) declined markedly in both regions; however, in 2019 Southern Europe still recorded higher rates – 337.2 per 100,000 (95% CI 323.7–

367.2) for males versus 279.7 (95% CI 264.1–335.9) in Western Europe, and 247.3 (95% CI 232.2–268.3) versus 196.2 (183.3–228.8) for females. These reductions have been linked to declines in hypertension, dyslipidaemia, and smoking, combined with advances in acute and chronic CVD care. However, the rising prevalence of obesity and type 2 DM, as noted by Goodall et al. (Goodall et al., 2021), together with regional differences in healthcare provision, may be slowing further gains.

Table 1. Regional definitions of Europe used in this chapter.

European region	***Countries included***	***Reference used for this thesis***
Western Europe	Austria, Belgium, France, Germany, Ireland, Luxembourg, the Netherlands, Switzerland, United Kingdom	(Timmis et al., 2023)
Southern Europe	Cyprus, Greece, Italy, Portugal, Spain, Malta.	(Timmis et al., 2023)
Northern Europe (Northern region)	Denmark, Finland, Iceland, Norway, Sweden	(Højstrup et al., 2023)
North-Eastern Europe	Estonia, Latvia, Lithuania, Belarus, Ukraine	(Cenko et al., 2023)
Central-Eastern Europe	Poland, Czech Republic, Slovakia	(Cenko et al., 2023)
South-Eastern Europe	Romania, Bulgaria, Serbia, North Macedonia, Bosnia and Herzegovina, Albania.	(Cenko et al., 2023)

The study also highlights large disparities in CV procedure rates, with Western Europe performing substantially more diagnostic and therapeutic interventions. In 2019, diagnostic coronary arteriograms were 27% more frequent in Western Europe, while percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) rates were 61% and 51% higher, respectively, compared with Southern Europe (Timmis et al., 2023). Despite similar ST-elevation myocardial infarction (STEMI) incidence, these differences suggest that variations in primary PCI rates are driven more by healthcare access and infrastructure than by disease prevalence.

Højstrup et al. (Højstrup et al., 2023) examined the Nordic region of Europe, assessing trends in CVD mortality, healthcare access, and disparities across Denmark, Finland, Iceland, Norway, and Sweden. Their findings indicate that while the region has achieved significant reductions in CVD mortality over recent decades, disparities persist both between and within countries.

Compared with Western and Southern Europe, IHD mortality remains notably higher in Northern Europe, where median age-standardized rates per 100,000 are approximately 171.4 for males and 90.8 for females – more than twice the overall CVD rates in some regions. In contrast, stroke mortality is more pronounced in

Southern Europe, with median ASMRs of 172.0 for males and 131.4 for females, compared with 65.6 and 53.8, respectively, in high-income (mainly Western) countries. (Timmis et al., 2023). These disparities likely reflect a combination of differences in healthcare infrastructure, availability and timeliness of acute interventions, population-level risk factor profiles, and broader socioeconomic determinants of health, which together influence prevention, treatment, and long-term outcomes.

Although Northern Europe generally offers excellent healthcare access, marginalized populations remain at elevated risk of CVD-related mortality. Migrants, ethnic minorities, and socioeconomically disadvantaged groups face barriers such as limited health literacy, language difficulties, financial constraints, and delayed medical attention, which hinder prevention and treatment. Despite well-developed welfare systems, socioeconomic health inequalities persist, highlighting the need for policies that improve access for vulnerable groups through measures such as culturally adapted health education, community-based screening, interpreter services, and subsidized healthy food programmes, alongside targeted CVD prevention strategies (Højstrup et al., 2023).

2.1.4. Eastern Europe: life-expectancy differentials, subregional patterns, and determinants

Eastern European nations exhibit markedly reduced life expectancy compared to their Western counterparts, predominantly attributable to heightened mortality rates from IHD (Eurostat, 2025). The geographic disparities in IHD fatalities closely correlate with variations in life expectancy, highlighting the crucial influence of CV health on public health metrics. Within this framework, North-Eastern Europe – which encompasses the Baltic states, alongside Belarus and Ukraine – demonstrates consistently elevated IHD mortality rates relative to Central-Eastern Europe (Table 1) and South-Eastern Europe (Cenko et al., 2023). ASMRs exhibit significant variation, ranging from 399.2 per 100,000 in Ukraine to 71.3 in Poland, with IHD-related fatalities in North-Eastern Europe frequently occurring at younger ages, thereby exacerbating the strain on healthcare systems, economic productivity, and overall societal health (Zuin et al., 2023).

The high incidence of principal risk factors – including tobacco use, DM, dyslipidaemia, and hypertension – continues to be a fundamental contributor to elevated mortality rates, with prevalence levels in North-Eastern Europe surpassing those found in numerous other European regions. Despite enhancements in healthcare infrastructure that have augmented coronary revascularization rates in certain high-burden Eastern European nations, these interventions have not sufficiently equalized IHD mortality figures. While economic advancement is associated with improved CV health outcomes, income alone fails to account for the observed discrepancies; affluent nations within the region may still report persistently elevated mortality rates, indicative of deficiencies in healthcare accessibility, the quality of preventative care, and national public health strategies (World Health Organization [WHO], n.d.).

Variations among countries further elucidate the intricate nature of these disparities. From 2001 to 2019, Estonia realised a substantial reduction in IHD mortality (average annual percent change, AAPC –6.61%) in contrast to Lithuania (AAPC –2.23%) (Tran et al., 2022), potentially indicative of more effective public health initiatives, reforms within the healthcare sector, and strategies aimed at risk factor mitigation. Additionally, psychosocial and socioeconomic factors – including unemployment, limited material resources, depressive disorders, social isolation, and singlehood – have been independently linked to elevated CVD mortality rates in Eastern Europe (Tillmann et al., 2017).

2.1.5. Policy and surveillance implications for MI prevention

Marked geographical variations in CV mortality across Europe likely reflect a multifactorial interplay between socioeconomic, environmental, and lifestyle factors. Regions with higher income inequality, lower education levels, and limited access to high-quality healthcare generally show less favourable outcomes. Differences in diet, physical activity, and prevalence of risk factors such as smoking, obesity, and DM contribute further to this gradient. Climatic influences – including seasonal temperature extremes – may also affect event rates and survival. In addition, cultural attitudes toward health, prevention, and healthcare-seeking behaviour can shape both the incidence and outcomes of CVD. Together, these determinants underline that observed disparities in CVD mortality across Europe arise not solely from healthcare system performance, but from a complex web of social, environmental, and behavioural factors.

The multifaceted character of these disparities implies that a generalized approach is unlikely to yield significant success. Therefore, policies ought to be customized according to each nation's epidemiological profile and socioeconomic environment. Enhancing CV surveillance – via standardized data collection, systematic reporting, and comprehensive national registries – will be essential for tracking trends, facilitating accurate international comparisons, and formulating targeted interventions that can effectively mitigate IHD mortality across Europe (Batra et al., 2022; Movsisyan et al., 2020).

2.2. Registries

"Science tells us what we can do; guidelines what we should do; and registries what we are actually doing."
Dr. Lukas Kappenberger (2005)

2.2.1. Role of registries in CV care

Medical registries are organized systems that collect uniform data on defined populations (by disease, condition, or exposure) to evaluate processes and outcomes over time. In the context of MI, registries quantify case mix, treatment patterns, and outcomes in routine practice, thereby closing the evidence–practice

gap – monitoring uptake of guideline-directed therapies, identifying unwarranted variation, and informing service planning and policy (Gliklich et al., 2014).

Despite their benefits, medical registries face challenges related to data variability. Differences in data collection methods, definitions, and categorizations across institutions and countries can hinder data comparability. This lack of standardization complicates efforts to benchmark performance or conduct multicentre studies. Ensuring data quality and completeness is another persistent challenge, as incomplete data entry and varying levels of detail can compromise the integrity of the registry. Maintaining patient privacy and data security, especially in the era of digital health records, requires robust protocols and continuous monitoring (Pop et al., 2019).

Beyond clinical endpoints, patient-reported outcomes (PROs) – quality of life (QoL), symptom burden, functional status, and mental health – enhance secondary prevention by guiding rehabilitation and long-term management (Moons et al., 2023). Recent work (e.g., the RQoL substudy of post-MI β-blocker therapy; (Humphries et al., 2023)) and the Augsburg MI Registry (Meisinger et al., 2023) illustrate how PROs can be embedded at scale. Also, the Swedish SEPHIA module (the secondary-prevention module within SWEDEHEART) is a prominent example of structured secondary-prevention follow-up (Bäck et al., 2021).

The integration of digital solutions into medical registries offers promising avenues for enhancing data collection, analysis, and application. Mobile applications, wearable devices, and telemedicine platforms can facilitate real-time data capture, improve patient engagement, and enable remote monitoring. For example, the "afterAMI" mobile application provides educational resources, medication reminders, and vital sign diaries for patients' post-MI, demonstrating the potential of digital tools to support patient management and data collection (Krzowski et al., 2022).

Advancements in data analytics, including artificial intelligence and machine learning, can enhance the ability to identify patterns, predict outcomes, and personalize treatment strategies based on registry data. However, these developments also necessitate addressing challenges related to data interoperability, standardization, and security to fully realize their potential (Marra et al., 2024).

2.2.2. European MI registries: scope and benchmarking comparators

The European Unified Registries On Heart Care Evaluation and Randomized Trials (EuroHeart) is an initiative by the European Society of Cardiology (ESC) aimed at overcoming challenges within CV care. EuroHeart seeks to establish a standardized information technology (IT) platform for the collection and analysis of data related to acute coronary syndromes (ACS) and percutaneous coronary interventions (PCI) at a national level. By standardizing variable definitions, outcomes, and case-mix descriptors, EuroHeart improves interoperability and the validity of cross-country comparisons (Bhatty et al., 2024).

Cross-national benchmarking is currently limited by heterogeneity in data elements and coding. EuroHeart addresses these gaps by providing consensus data standards and tooling, enabling routine quality dashboards, equitable comparisons of processes/outcomes, and scalable observational and pragmatic trial designs across health systems.

Estonia has actively participated in the EuroHeart project as a pilot country, contributing to the development and implementation of the registry's IT platform. Led by the Estonian Society of Cardiology, the country has integrated the EuroHeart system into clinical practice, with Tartu University Hospital and North Estonia Medical Centre utilizing the platform to collect and analyse cardiovascular data (Timmis, 2025).

A primary data source for this thesis is the Estonian Myocardial Infarction Register (EMIR) – a national, government-funded, ongoing registry established in 2012. It collects data on all patients hospitalized with a diagnosis of acute MI, classified under the International Classification of Diseases 10th version (ICD-10) codes I21-I22. The primary purpose of EMIR is to facilitate national statistics and research related to CV health in Estonia.

Data reporting to EMIR is mandatory by law, ensuring that approximately 2,700 cases are reported annually from all Estonian hospitals. An electronic reporting system is utilized, comprising nearly 100 characteristics that detail patients' cardiovascular risk factors, concomitant diseases, in-hospital treatment (including procedures and medications), and recommended drug therapy at discharge. The dataset and definitions align with the Cardiology Audit and Registration Data Standards, and the validity of the data is maintained through routine error checking.

Notably, Estonian law permits the use of anonymized data from EMIR without the need for informed consent from participants for research purposes and for linking with other national databases. EMIR is linked annually with the Estonian Causes of Death Registry and the Estonian Health Insurance Fund (EHIF) database using personal identification numbers. According to routine annual internal audits the case coverage rate exceeds 95%.

In this thesis, two multicountry analyses used harmonised datasets from SWEDEHEART (Sweden), NORMI (Norway), and HUMIR (Hungary), with EMIR participating as an equal collaborating registry.

SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) is one of Europe's most comprehensive cardiac registry platforms. A national registry that includes all consecutive patients over 18 years of age admitted to a coronary care unit or other specialized facility with symptoms suggestive of acute MI. SWEDEHEART was consolidated in 2009 from earlier national registries, notably RIKS-HIA (acute cardiac care, launched 1995). Approximately 18,000 patients are enrolled annually and data on more than 100 variables is collected, including baseline characteristics, medication upon admission, in-hospital therapies, complications, and medications at discharge.

SWEDEHEART is widely regarded as a model CV registry because of its long continuity, national reach with high case coverage, and rigorous validation (approximately 96% agreement with source records). Its modular structure – acute care (RIKS-HIA/ACS) (Leosdottir et al., 2023), catheterization/PCI (SCAAR), cardiac surgery, and the SEPHIA secondary-prevention/rehabilitation module – provides end-to-end visibility from presentation to long-term follow-up (Bäck et al., 2021a). Near–real-time feedback and public reporting of quality indicators have driven measurable national improvements (e.g., uptake of guideline-directed therapy and time-to-reperfusion). Robust linkage to national mortality and prescription databases enables reliable outcome and treatment-adherence tracking. Finally, SWEDEHEART has underpinned influential observational studies and registry-based randomized trials, making it a benchmark for data quality, quality-improvement utility, and research productivity in CV care (SWEDEHEART, n.d.).

NORMI (Norwegian Myocardial Infarction Registry) was established in 2013 and enrols approximately 11,000–12,000 MI cases annually, with case coverage exceeding 90%. HUMIR (Hungarian Myocardial Infarction Registry) was launched in 2010 and enrols roughly 16,000 MI cases per year, with case coverage around 92%.

HUMIR (Hungarian Myocardial Infarction Registry) is a national, consecutive-case registry, HUMIR was launched in 2010 with web-based reporting that records 178 structured variables across the care pathway (prehospital, in-hospital, and coronary interventions). In 2017, HUMIR captured ~92% of all MI cases

2.3. Overview of CV risk factors and emerging modifiers

As new scientific evidence emerges, our understanding of CV risk factors continues to evolve, leading to regular updates in prevention guidelines and clinical recommendations. While classic risk factors remain the cornerstone of CVD prevention, new potential risk factors and modifying conditions are increasingly recognized as contributing to individual risk. The 2021 European Society of Cardiology (ESC) Guidelines on CV prevention (Visseren et al., 2021) highlight both established and emerging risk determinants, emphasizing the need for a dynamic approach to risk stratification and personalized prevention strategies.

2.3.1. Traditional CV risk factors

The ESC guidelines reaffirm the role of traditional risk factors, which continue to be the strongest predictors of CVD morbidity and mortality.

Age and sex

Age and sex are key non-modifiable IHD determinants: risk rises steeply with age, and men typically have higher risk than premenopausal women, with the gap narrowing thereafter (Visseren et al., 2021).

At the same time, MI is increasingly observed in younger adults, largely driven by type 2 DM, obesity, and physical inactivity (Gulati et al., 2020).

CVD remains the leading cause of death among women worldwide, yet it is frequently underdiagnosed and undertreated (Keteepe-Arachi et al., 2017). Beyond shared risk factors (hypertension, dyslipidaemia, DM, smoking), female-specific modifiers – pregnancy complications (e.g., gestational hypertension, preeclampsia, gestational diabetes (GDM), parity and pregnancy loss, infertility and artificial reproductivity treatment (ART) like *in vitro* fertilization (IVF), early or late menarche, and premature menopause (<40 years), as well as polycystic ovary syndrome (PCOS) and certain autoimmune diseases – confer substantial long-term risk; pregnancy-related disorders can double subsequent risk of hypertension, MetS, and MI, and premature menopause is associated with ~50% higher CVD risk (Rajendran et al., 2023). Women report more often atypical MI symptoms (fatigue, dyspnoea, nausea), contributing to diagnostic delay, and are less likely to receive statins, dual antiplatelet treatment (DAPT), or revascularisation despite similar treatment benefit (Hellgren et al., 2022).

Recent guidelines emphasize earlier screening for women with pregnancy-related complications, metabolic disorders, and early menopause to enable proactive prevention. Strategies such as lifestyle modifications, personalized pharmacotherapy, and structured follow-up programs tailored to female patients are crucial in closing the CV gender gap (Bugiardini & Gulati, 2024).

Smoking

Tobacco use remains a leading modifiable risk factor for IHD; both active smoking and second-hand exposure contribute substantially to disease burden.

In the EU, daily smoking among 15–24-year-olds was 15% in 2019 (men 18%, women 12%), ranging from 26% in Hungary to 5% in Sweden. Among adults, roughly 1 in 4 are current smokers, with higher prevalence in men (33%) than women (20%), and marked regional variation (Eastern Europe 28% vs Northern Europe 20%) (Kim et al., 2022).

E-cigarette use ("vaping") has risen, especially in youth. In 2023, 23.3% of Bulgarian adolescents aged 13–15 reported e-cigarette use (WHO, 2024). Among EU adults, 3.6% report current use, with highest prevalence in France 6.6%, Poland 6.0%, Netherlands 5.9%, and Spain 1.0% (Eurostat, 2019). Although often promoted as less harmful than combusted tobacco, long-term health effects of vaping remain uncertain; emerging evidence links vaping with respiratory problems, CV complications, and nicotine dependence (Centers for Disease Control and Prevention., 2024).

Smoking cessation following a MI is crucial for improving patient outcomes (Wu et al., 2022). However, maintaining long-term abstinence can be challenging. Studies indicate that while approximately 50% of patients quit smoking within six weeks after hospital discharge, a significant proportion relapse within the first year. For instance, a study reported that only about 52% of MI patients remained abstinent 6 to 12 months post-hospitalization (Hayrumyan et al., 2023).

Hypertension

Chronic high blood pressure is a major driver of atherosclerosis, heart failure, and stroke; its control is therefore a primary target in CVD prevention. The absolute benefit of lowering systolic blood pressure (BP) depends on baseline CV risk and the magnitude of BP reduction, with lower limits constrained by tolerability and safety (Visseren et al., 2021).

The 2024 ESC guideline updates the classification of BP and emphasizes out-of-office measurements (home and ambulatory) to confirm diagnosis and guide management, alongside risk-based treatment intensity and individualized targets – particularly in high-risk groups such as post-MI patients (McEvoy et al., 2024).

Following a MI, effective BP management is crucial for secondary prevention. Studies indicate that BP control post-MI is suboptimal. For instance, research has shown that only about 59.6% of patients achieve BP levels below 130/80 mmHg. Meanwhile, 24.1% maintain BP levels in the 130–139/80–89 mmHg range, which, although better than uncontrolled hypertension, still carries an elevated cardiovascular risk. Alarmingly, 16.3% of post-MI patients continue to have BP ≥140/90 mmHg, significantly increasing their risk of recurrent cardiovascular events. (Shan et al., 2020).

Dyslipidaemia

Dyslipidaemia play a pivotal role in both primary and secondary prevention of CVD. For primary prevention, the updated SCORE2 and SCORE-OP models refine risk assessment by incorporating age, sex, smoking status, BP, and lipid profiles to identify individuals at moderate, high, or very high risk, guiding the intensity of lipid-lowering therapy (SCORE2 working group and ESC Cardiovascular risk collaboration et al., 2021; SCORE2-OP working group and ESC Cardiovascular risk collaboration et al., 2021). In secondary prevention, patients with a prior MI are automatically deemed very high risk, necessitating at least a 50% LDL-C reduction and an LDL target below 1.4 mmol/L (Mach et al., 2020). Real-world European data (EUROASPIRE V and DA VINCI studies) reveal that between 40% and 60% of post-MI patients fail to meet these goals, underscoring the need for more intensive therapy and better adherence (Kotseva, 2019; Ray et al., 2021). Novel agents – such as PCSK9 monoclonal antibodies, a PCSK9 synthesis inhibitor (siRNA), and an ATP-citrate lyase inhibitors – provide additional LDL-lowering options, particularly for those not achieving recommended thresholds despite maximally tolerated statin and ezetimibe. Lipoprotein(a) measurement has also gained prominence, given its pro-atherogenic and pro-thrombotic properties. Elevated Lp(a) (>50 mg/dL) significantly amplifies residual cardiovascular risk, and although current treatments modestly reduce Lp(a), promising therapies like antisense oligonucleotides (e.g., pelacarsen) are under investigation (Alhomoud et al., 2023; Nissen et al., 2022).

Physical inactivity

Physical inactivity has been recognized as a major modifiable risk factor for CVD and overall mortality. The 2020 WHO guidelines recommend that adults

accumulate 150–300 minutes of moderate-intensity or 75–150 minutes of vigorous-intensity physical activity each week (or an equivalent combination) to achieve significant health benefits (Bull et al., 2020). However, recent estimates suggest that one in three adults worldwide fails to meet these recommendations, contributing to increased risks of hypertension, obesity, and type 2 DM (Guthold et al., 2018).

Beyond its direct role, physical inactivity acts as an independent predictor of adverse cardiovascular outcomes, particularly among individuals with metabolic syndrome (MetS) (Nichols et al., 2013). Recent evidence shows that an increasing proportion of young MI patients present with clustered metabolic abnormalities – such as obesity, insulin resistance, and dyslipidaemia – rather than isolated risk factors (Rizk & Blankstein, 2021). These trends support earlier screening and intervention for cardiometabolic risk in youth, combining targeted lifestyle change with timely pharmacotherapy (Sing et al., 2020).

DM and obesity

Over the past seventy years, Europe has witnessed a striking rise in the incidence of obesity (body mass index (BMI) ≥30 kg/m²) and DM, reflecting profound societal shifts in lifestyle, urbanization, and dietary patterns. In 1950, obesity affected approximately 5% of the population, a figure that surged to 23% by 2020 and is projected to reach 30% by 2045 according to International Diabetes Federation. Similarly, the prevalence of DM rose from around 2% in 1950 to 9.2% in 2020, with estimates suggesting an increase to 10.2% by 2045. (Magliano & Boyko, 2025; The European Health Report 2021.). These trends underscore the expanding burden of metabolic disorders, which are strongly implicated in the development of CVD.

The heightened risk of CVD in individuals with obesity and DM is driven by a network of interrelated pathophysiological mechanisms. Obesity serves as an independent CV risk factor by promoting insulin resistance, hyperinsulinemia, and dyslipidaemia – conditions that collectively accelerate atherosclerosis and cardiac dysfunction. Insulin resistance, a hallmark of obesity, precipitates a cascade of metabolic disturbances, including impaired glucose uptake, elevated hepatic glucose production, and dysregulated lipid metabolism. These changes contribute to dyslipidaemia, marked by increased triglycerides and reduced HDL cholesterol, and promote vascular inflammation and endothelial dysfunction. Hyperinsulinemia, in turn, exacerbates vascular abnormalities and accelerates atherogenesis, increasing the risk of MI and stroke (Ndumele et al.,). The chronicity of DM further amplifies this risk; prolonged exposure to hyperglycaemia and associated metabolic insults heightens the likelihood of CV events (Whaley-Connell & Sowers, 2014). Consequently, young adults with DM exhibit a 2–4-fold higher risk of MI compared with their non-diabetic peers (Hanssen et al., 2023), and obesity further amplifying IHD risk via chronic inflammation, dyslipidaemia, and hypertension (Hasebe & Hasebe, 2022).

This complex interplay of metabolic dysfunctions is encapsulated in the concept of cardiometabolic syndrome (CMS), a clinical entity that merges central

obesity (defined by waist circumference normative in each population), insulin resistance, hypertension, and dyslipidaemia. CMS significantly elevates the risk of adverse CV outcomes and is estimated to affect 20–30% of the global population, though prevalence varies by region and diagnostic criteria (Ndumele et al., 2023).

2.3.2 Emerging modifiers of CV risk

Cardiovascular-kidney-metabolic (CKM) syndrome

CKM syndrome (also termed cardio-renal-metabolic, CRM) recognises the interdependent, progressive interaction of CV, renal, and metabolic disease. The 2023 AHA statement frames CKM syndrome as a continuum driven by shared pathways – chronic inflammation and oxidative stress, neurohormonal renin-angiotensin-aldosterone system (RAAS) activation, endothelial and mitochondrial dysfunction, and lipid/energy dysregulation – rather than the mere coexistence of conditions (Marassi & Fadini, 2023; Ndumele et al. 2023). Figure 2 illustrates these core mechanisms of the CKM syndrome.

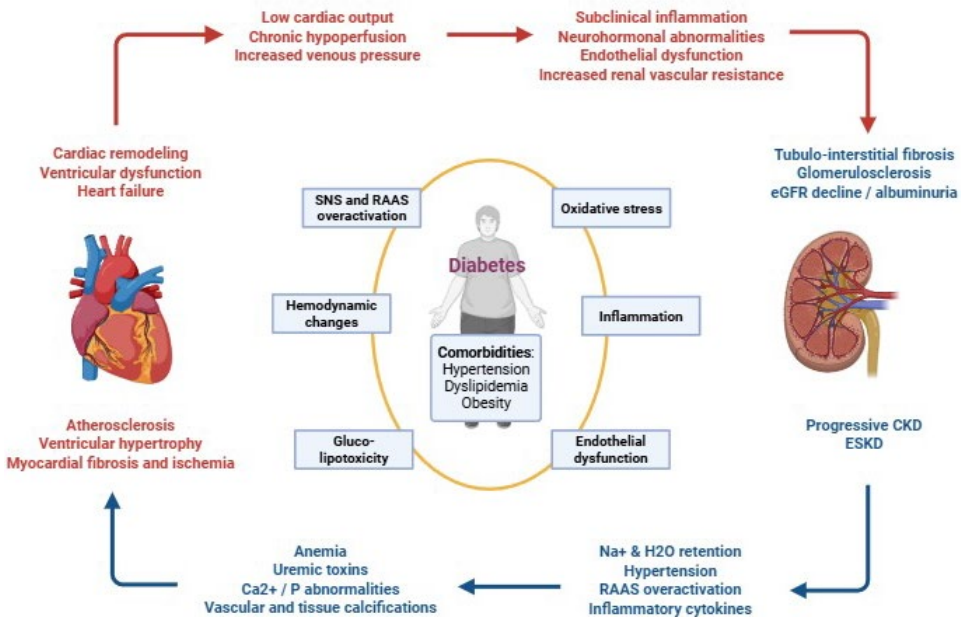

Figure 2. Pathophysiology of cardiovascular-kidney-metabolic syndrome**.** Adapted from (Marassi & Fadini, 2023).

eGFR estimated glomerular filtration rate; CKD chronic kidney disease; ESKD end stage kidney disease; RAAS renin-angiotensin-aldosterone system; SNS sympathetic nervous system

For clinical use, the AHA proposes a five-stage CKM syndrome classification spanning from excess adiposity (stage 1) through metabolic risk/CKD (stage 2) to subclinical and clinical CVD (stages 3–4) **(**Table 2) (Ndumele et al., 2023).

Table 2. Stages of CKM syndrome

Stage	*Definition*	*Key Features*
0	No CKM health risk factors	No obesity, metabolic risk factors, CKD, or CVD'
1	Excess and/or dysfunctional adiposity	Overweight, abdominal obesity, or impaired adipose tissue
2	Metabolic risk factors and/or CKD	Presence of hypertension, DM 2, dyslipidaemia, or CKD
3	Subclinical CVD in CKM	Evidence of subclinical atherosclerosis or early heart failure
4	Clinical CVD in CKM	Manifest CVD, such as IHD, stroke, or overt heart failure

CKM cardiovascular-kidney-metabolic; CKD chronic kidney disease; DM 2 type 2 diabetes mellitus; CVD cardiovascular disease; IHD ischemic heart disease

Decreased kidney function as a CV risk amplifier

Reduced estimated glomerular filtration rate (eGFR) independently increases CVD morbidity and mortality through both shared risk factors (hypertension, DM, dyslipidaemia) and CKD-specific processes, including uremic toxin accumulation, persistent inflammation/oxidative stress, endothelial dysfunction, vascular calcification, anaemia, and RAAS-mediated fibrosis (Jankowski et al., 2021; Vondenhoff et al., 2024; Whaley-Connell & Sowers, 2014; Zhu et al., 2025). Around 30–40% of people with type 2 DM have renal impairment, and CVD is the leading cause of death in CKD (Meng et al., 2025; Ndumele et al., 2023).

CV risk rises markedly once eGFR falls <60 mL/min/1.73 m², but a graded association is evident across the full range. Importantly, younger adults show risk increases even at higher eGFR thresholds (e.g., <80 in age groups 18–39 and 40–49), whereas relative risks attenuate in older adults amid higher baseline comorbidity – though absolute risk remains high (Hussain et al., 2023; Liu et al., 2024; O'Hare et al., 2006).

Reduced eGFR is a potent prognostic marker in acute MI, particularly in young patients. Chronically decreased kidney function confers a 3.6-fold increase in long-term mortality post-AMI, with eGFR at admission serving as a strong predictor of both short- and long-term outcomes (Gyurjian et al., 2022; Kula et al., 2022). Patients with severely impaired renal function (eGFR <30 mL/min/1.73 m²) experience the highest rates of adverse CV events and mortality (Chiang et al., 2021).

Despite the elevated risk, younger patients with impaired kidney function are often undertreated – receiving fewer guideline-recommended therapies such as

statins and P2Y12 inhibitors – further compounding their vulnerability. Additionally, the combination of renal impairment and left ventricular dysfunction amplifies the risk of major adverse CV events (MACE) in STEMI patients (Anjarwani et al., 2025; Savic et al., 2023). These associations persist over extended follow-up, reinforcing the necessity of vigilant renal and CV monitoring post-MI (Savic, 2018).

Given the CKM syndrome framework and the strong, age-sensitive gradient between eGFR and CV risk, the thesis specifically evaluates the joint impact of DM and eGFR on post-MI mortality, supporting earlier risk identification and targeted secondary prevention.

Polygenic risk scores (PRS)

PRS aggregate thousands–millions of common genetic variants into a single measure of inherited cardiovascular risk, complementing traditional factors (Vassy et al., 2023). In coronary disease, PRS can reclassify borderline-risk patients – especially younger adults without overt risk factors – by identifying those in the highest percentiles who carry ~2–5× greater risk and may merit earlier/intensified prevention (targeted lifestyle change, statins) and selective screening (e.g., coronary calcium) (Busby et al., 2023; Patel et al., 2023). PRS are increasingly piloted in electronic health record-integrated workflows and guideline discussions; one genotyping provides lifelong risk information (O'Sullivan et al., 2022). Because performance varies by ancestry, population-specific validation and clear communication/counselling are essential (Patel et al., 2023).

Estonia has been a European frontrunner via the Estonian Biobank and national e-health pilots, demonstrating the feasibility of population-scale PRS to inform prevention (Viigimaa et al., 2022). Work in Estonia is ongoing: a large randomized pragmatic primary-prevention trial – the EE-PRS statin study (Jürisson, 2025) – is currently enrolling by invitation, targeting ~2,500 adults in the top 20% of a IHD PRS to test rosuvastatin 20 mg versus usual care, with recruitment via the Estonian Biobank and sites including North Estonia Medical Centre.

In contemporary large-scale cohorts such as the UK Biobank, traditional clinical risk factors account for the majority of population coronary risk (≈82–84%). Incorporating genetic and novel biomarkers increases the explained population-attributable risk to ≈89%. Within this framework, PRS alone contribute ≈37–38%, a magnitude comparable to hypertension (≈32%) and exceeding lipid ratios such as apolipoprotein B/A1 (≈16–17%). These findings underscore that while traditional factors remain dominant, genetic and emerging biomarkers provide meaningful additional explanatory power (Bhattacharya et al., 2024; Marnell et al., 2021).

Beyond the previously discussed risk factors, the ESC recognises several additional and emerging CV risk modifiers, including inflammatory/autoimmune conditions, air pollution, psychosocial and sleep-related factors, ethnicity, frailty, and imaging-based reclassifiers (e.g., coronary artery calcium). Detailed discussion

of these domains lies outside the scope of the present thesis and is addressed in dedicated reviews (Visseren et al. 2023)

2.4. Secondary prevention of MI

Secondary prevention seeks to reduce the risk of recurrent CV events in patients with a history of MI through a comprehensive strategy that includes lifestyle changes, pharmacological therapy, and efforts to ensure consistent medication use. While these measures are highly effective in lowering CV mortality, their impact is frequently diminished by poor adherence, which remains a persistent challenge in post-MI care.

Medication adherence is a cornerstone of secondary prevention in post-MI patients. Guideline-directed medical therapy (GDMT) for secondary prevention of MI (Byrne et al., 2023; Virani et al., 2023; Visseren et al., 2023) is a dynamic, evidence-based framework that addresses the multifactorial nature of atherothrombotic disease. The core pharmacological components – antiplatelets, statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs), and in selected cases, sodium–glucose cotransporter 2 (SGLT2) inhibitors and proprotein convertase subtilisin/kexin type 9 **(**PCSK9) inhibitors – have been shown to significantly reduce recurrent events and improve survival. As new evidence emerges, particularly concerning inflammation and metabolic modulation, GDMT continues to evolve, necessitating frequent guideline updates and clinician awareness to ensure optimal patient outcomes.

2.4.1. Core components of GDMT

Antiplatelet therapy

Antiplatelet agents are the cornerstone of secondary prevention in post-MI patients. Dual antiplatelet therapy (DAPT) consists of aspirin (acetylsalicylic acid, ASA) and a P2Y12 inhibitor. Adherence to DAPT has been associated with a 21 % reduction in mortality; however, in a nationwide Austrian acute MI cohort in 2024, only 29.3% of patients consistently followed DAPT guideline recommendations (Hammer et al., 2024).

After acute MI (STEMI or NSTEMI), DAPT with aspirin plus a P2Y12 inhibitor for 12 months is recommended, irrespective of whether the patient undergoes PCI or is managed non-invasively. A potent P2Y12 inhibitor (ticagrelor – or prasugrel when PCI is performed) is preferred over clopidogrel when ischaemic risk is moderate–high and bleeding risk is not high. Shortened DAPT (≈3–6 months) may be considered in high bleeding-risk patients, whereas prolonged DAPT (>12 months) may be considered in selected very high ischaemic-risk patients. After completion of DAPT, long-term single antiplatelet therapy is indicated, usually low-dose aspirin (clopidogrel if aspirin-intolerant) (Byrne et al., 2023).

Lipid-lowering therapy

Statin therapy is central to secondary prevention after MI, with high adherence strongly associated with better outcomes. High statin adherence (≥ 80% of prescribed doses) has been consistently associated with lower all-cause and CV mortality in post-MI populations *(Brown et al., 2021; Giacobbe et al., 2024)*. In the FAST STEMI registry, optimal adherence corresponded to adjusted HR of ~0.03 for both all-cause and CV mortality at one year (Giacobbe et al., 2024), underscoring the magnitude of potential benefit. However, effect sizes vary across cohorts and follow-up durations (Brown et al., 2021), and observational designs remain susceptible to residual confounding, including the "healthy adherer" effect. Thus, while high adherence robustly predicts improved outcomes, reported risk reductions should be interpreted with caution. Conversely, early discontinuation carries substantial risk: stopping statins within six months of MI is associated with 2.23-fold higher CV and 2.32-fold higher all-cause mortality, and suboptimal adherence independently relates to higher ischaemic stroke incidence (Giacobbe et al., 2024; Morena et al., 2023).

Guideline-directed lipid lowering after MI recommends high-intensity statin therapy for all patients, targeting a ≥50% low density lipoprotein cholesterol (LDL-C) reduction. If LDL-C remains ≥1.4 mmol/L**,** ezetimibe is indicated; if the target is still unmet on maximally tolerated statin and ezetimibe, addition of a PCSK9 monoclonal antibody **(**evolocumab or alirocumab**)** is recommended**.** In selected very-high-risk patients with a recurrent event within two years, an even lower goal of <1.0 mmol/L may be considered (Mach et al., 2020).

Where monoclonal antibodies are unsuitable or unavailable, further intensification may include a PCSK9 synthesis inhibitor (siRNA) **(**inclisiran**,** ~50% LDL-C reduction with twice-yearly maintenance) and an ATP-citrate lyase inhibitor **(**bempedoic acid**,** ~18–25% LDL-C reduction with demonstrated MACE reduction in statin-intolerant patients) (Nissen et al., 2023; Ray et al., 2021).

Beta-blockers

Beta-blockers represent a critical component of pharmacologic therapy for patients recovering from MI, especially those with reduced left ventricular ejection fraction (LVEF ≤40%). Their role in reducing myocardial oxygen demand, preventing arrhythmias, and improving survival is well established. Recent studies have confirmed that optimal adherence to beta-blocker therapy significantly lowers both all-cause and cardiovascular mortality**,** with the greatest benefit observed in patients with impaired systolic function (Giannino et al., 2023, 2024).

However, emerging evidence suggests that the survival benefit of beta-blockers may be less pronounced in post-MI patients with preserved LVEF, where the pathophysiological mechanisms differ, and the need for long-term beta-blockade is less clearly defined (Gomes et al., 2025). This distinction highlights the importance of individualizing therapy based on cardiac function, rather than adopting a uniform approach for all patients following MI (Giannino et al., 2023, 2024).

Renin-angiotensin system inhibition

ACEi and ARBs are foundational components of GDMT in the secondary prevention of MI, particularly in patients with specific high-risk profiles. Adherence to these therapies has been consistently associated with significant clinical benefits. Recent studies demonstrate that adherence to ACEi or ARBs results in a substantial reduction in both CV and all-cause mortality, with optimal adherence linked to a 51% reduction in CV mortality (Giannino et al., 2023; Sotorra-Figuerola et al., 2021).

Clinical guidelines recommend ACEi for all post-MI patients with reduced left ventricular ejection fraction (LVEF ≤40%), as well as for those with comorbid conditions such as DM, hypertension, or CKD. The primary benefits of these agents lie in their ability to improve survival, prevent adverse ventricular remodelling, and mitigate neurohormonal activation that drives disease progression (McDonagh et al., 2023).

In patients who are unable to tolerate ACEi due to cough, angioedema, or other adverse effects, ARBs such as losartan or valsartan provide a clinically effective alternative. While the evidence base for ARBs is slightly less robust compared to ACEi, they offer comparable efficacy in reducing CV risk in this population (McDonagh et al., 2023).

Furthermore, the role of angiotensin receptor-neprilysin inhibitors (ARNIs) is expanding, particularly in patients with heart failure with reduced ejection fraction (HFrEF). Emerging data and updated heart failure guidelines support the use of ARNIs as a superior alternative to ACEi in selected patients, particularly those with persistent symptoms despite standard therapy. While their role in the post-MI setting is still evolving, ARNIs represent a promising therapeutic option in the broader landscape of neurohormonal modulation for cardiovascular protection (Fu et al., 2023; McDonagh et al., 2023; Reyaz et al., 2023).

2.4.2. Emerging drug classes in secondary prevention of MI

Recent scientific advances have led to the emergence of novel drug classes that target additional pathophysiological pathways involved in post-MI progression – specifically, metabolic dysfunction, inflammation, neurohormonal activation, and lipid imbalance. Among these, SGLT2 inhibitors, PCSK9 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, mineralocorticoid receptor antagonists (MRAs) including finerenone, and anti-inflammatory agents are showing increasing clinical utility in post-MI care.

SGLT2 inhibitors

SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin) were originally developed as glucose-lowering agents for type 2 DM, but have demonstrated compelling CV and renal benefits in patients with or without DM. By inhibiting the sodium–glucose cotransporter 2 in the renal proximal tubules, these agents promote glucosuria and natriuresis, leading to reduced preload, afterload, blood pressure, and

interstitial volume. These hemodynamic effects, alongside their modulation of myocardial fibrosis and inflammation, are thought to underlie their cardioprotective properties. The EMPA-REG OUTCOME (Zinman et al., 2015) and DAPA-HF (McMurray et al., 2019) trials confirmed significant reductions in CV death and hospitalization for heart failure in high-risk populations. SGLT2 inhibitors have been shown to significantly reduce MACE and hospitalization due to heart failure in patients with and without prior MI or IHD (He et al., 2023). SGLT2 inhibitors also demonstrate significant mortality benefits after MI, with a 21% reduction in all-cause mortality (HR 0.79, 95% CI 0.68-0.91). Benefits are consistent across early and delayed initiation, with empagliflozin and dapagliflozin showing comparable efficacy, though type 2 DM presence enhances mortality reduction (H. Ebaid et al., 2025; Maremmani et al., 2025). These results have led to SGLT2 inhibitors being incorporated into guidelines for patients with heart failure, CKD, and increasingly, for atherosclerotic CV disease.

GLP-1 receptor agonists

GLP-1 receptor agonists (e.g., liraglutide, semaglutide) are another class of incretin-based therapies that have demonstrated CV benefit in patients with type 2 DM and high CV risk. These agents improve glycaemic control, reduce body weight and blood pressure, and possess anti-inflammatory and anti-atherogenic properties. The LEADER (Marso, Daniels, et al., 2016) and SUSTAIN-6 (Marso, Bain, et al., 2016) trials showed a reduction in MACE, including MI and stroke, in patients receiving GLP-1 receptor agonists. While not currently a first-line therapy for secondary prevention in non-DM populations, their expanding indications make them relevant in multimorbid patients with ISH and DM (Spasovski et al., 2024).

Mineralocorticoid receptor antagonists

MRAs have long been established in post-MI care, particularly in patients with reduced ejection fraction or heart failure. Steroidal MRAs such as spironolactone and eplerenone have been shown to reduce mortality and heart failure hospitalization, primarily by blocking aldosterone-induced fibrosis and sodium retention. The EPHESUS trial (Pitt et al., 2003) specifically demonstrated the benefit of eplerenone in post-MI patients with heart failure or DM. Finerenone, a novel non-steroidal MRA, has emerged as a safer and more targeted alternative. It exerts strong anti-inflammatory and anti-fibrotic effects with a lower risk of hyperkalaemia. The FIDELIO-DKD (Bakris et al., 2020) and FIGARO-DKD (Pitt et al., 2021) trials demonstrated CV and renal protection in patients with type 2 DM and CKD, suggesting its potential for broader CV use, including in secondary prevention.

Anti-inflammatory therapy

A further emerging class of interest is anti-inflammatory therapy, with colchicine being the most prominent agent studied to date. Inflammation plays a central role in atherosclerosis and plaque destabilization. The COLCOT (Tardif et al., 2019) and LoDoCo2 (Nidorf et al., 2020) trials showed that low-dose colchicine

significantly reduces the incidence of ischemic cardiovascular events in patients with stable coronary disease and recent MI, likely by inhibiting the NLRP3 inflammasome and neutrophil activation. While not yet universally recommended, colchicine represents a promising adjunct in selected high-risk individuals with residual inflammatory risk. Current guidelines position colchicine as an add-on therapy to optimal medical management, including statins and antiplatelet agents (Arnold & Koenig, 2025; Moras et al., 2024).

An overview of established and emerging pharmacotherapies for secondary prevention after MI is presented in Table 3. However, optimal secondary prevention extends beyond pharmacological therapy. Evidence from meta-analyses demonstrates that comprehensive, exercise-based cardiac rehabilitation, when combined with lifestyle modification and medication optimisation, reduces post-MI CV and all-cause mortality by approximately 20% (Lawler et al., 2011). Integrating physiotherapy and structured rehabilitation into post-MI care is therefore essential to improve functional recovery, enhance adherence, and sustain long-term CV health.

In summary, effective secondary prevention after MI rests on three interdependent pillars: GDMT, lifestyle modification, and well-coordinated, exercise-based cardiac rehabilitation. Together, these strategies substantially improve long-term CV outcomes and survival.

The evolving armamentarium for secondary prevention of MI reflects a deeper understanding of the multifaceted nature of IHD. The incorporation of SGLT2 inhibitors, PCSK9 inhibitors, GLP-1 receptor agonists, MRAs, and anti-inflammatory agents allows clinicians to personalize therapy based on patient comorbidities and pathophysiologic risk profiles. These developments underscore the need for ongoing updates to clinical guidelines and a multidisciplinary approach to post-MI care.

Registry-driven quality systems (e.g., RIKS-HIA/SWEDEHEART) show how continuous feedback improves adherence to secondary prevention and national outcomes (Leosdottir et al., 2023). Emerging digital health tools can support goal attainment and follow-up at scale, with meta-analytic signals for improved risk-factor control and fewer rehospitalisations (Laranjo et al., 2024).

In Estonia, a post-MI secondary prevention pathway pilot is being implemented in larger hospitals to formalise this continuum – from a standardised discharge bundle and early post-discharge review to systematic referral to cardiac rehabilitation and structured lipid/BP target tracking.

A priority for this thesis is to enable comparative analyses using real-world national registries to benchmark Estonia's MI care against countries with contrasting CV mortality profiles. Risk-adjusted, harmonized comparisons – drawing on EMIR alongside mature registries such as SWEDEHEART, NORMI, and HUMIR – are essential to identify actionable gaps across the patient journey. Such cross-country benchmarking complements trial evidence by revealing how well evidence is implemented in routine practice and where system-level improvements may yield the greatest benefit.

Table 3. Pharmacological classes for secondary prevention after MI: core and emerging components of GDMT

Category	*Medication class*	*Representative agents*	*Mechanism / therapeutic target*
Core components of GDMT	Antiplatelet therapy	Aspirin (ASA); P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor)	Inhibition of platelet aggregation to prevent recurrent thrombosis
	Statins and adjunct lipid-lowering therapy	Atorvastatin, rosuvastatin; ezetimibe; PCSK9 mAbs (evolocumab, alirocumab); siRNA inclisiran; bempedoic acid	LDL-C lowering, plaque stabilization, anti-inflammatory effects
	β-blockers	Metoprolol, bisoprolol, carvedilol	↓ Myocardial oxygen demand, anti-arrhythmic, improve LV remodelling
	Renin–angiotensin system inhibition	ACEi (ramipril, perindopril), ARBs (valsartan, losartan), ARNIs (sacubitril/valsartan)	Neurohormonal blockade, ↓ afterload, prevent remodelling
Emerging / adjunctive drug classes	SGLT2 inhibitors	Empagliflozin, dapagliflozin	Inhibit renal glucose–sodium reabsorption → glucosuria, natriuresis, anti-fibrotic and anti-inflammatory effects
	GLP-1 receptor agonists	Liraglutide, semaglutide	Incretin-mediated glucose control, weight loss, anti-inflammatory and anti-atherogenic effects
	Mineralocorticoid receptor antagonists (MRAs)	Spironolactone, eplerenone, finerenone	Aldosterone blockade → ↓ fibrosis and Na^+ retention
	Anti-inflammatory therapy	Colchicine (low-dose)	NLRP3 inflammasome inhibition, reduced neutrophil activation

*MI myocardial infarction; GDMT guideline directed medical therapy; mAbs monoclonal antibodies**;** siRNA* small interfering RNA; *LDL-C low density lipoprotein cholesterol; LV left ventricle; ACEi angiotensin-converting enzyme inhibitor; ARB angiotensin II receptor blocker; ARNI angiotensin receptor–neprilysin inhibitor; SGLT2 sodium–glucose cotransporter 2; GLP-1 glucagon-like peptide-1; MRA mineralocorticoid receptor antagonist; NLRP3 NOD-like receptor family pyrin domain–containing protein*

2.5. Summary of the literature

Across Europe, IHD and MI remain leading contributors to mortality and cost, despite long-term declines in age-standardized rates. Marked regional heterogeneity persists: Western and Southern Europe have seen substantial reductions, yet Central-Eastern and Baltic countries continue to experience higher IHD mortality; improvements in younger adults have slowed, and sex differences remain. These patterns likely reflect differences in risk-factor profiles, access to timely reperfusion and evidence-based therapies, and broader socioeconomic determinants.

Real-world registries are critical for understanding how guideline recommendations translate into practice and for identifying system-level gaps. Estonia's national MI registry (EMIR) enables population-level surveillance and deterministic linkage to outcomes, while mature Nordic and Central-Eastern registries – SWEDEHEART (Sweden), NORMI (Norway), and HUMIR (Hungary) – provide complementary comparators for like-for-like benchmarking of case mix, processes, and outcomes. Harmonized, risk-adjusted comparisons across such registries are essential to prioritize improvements where the potential health gains are greatest.

The contemporary risk landscape is driven by classical factors – smoking, hypertension, dyslipidaemia, DM, obesity, and physical inactivity – with growing recognition of emerging modifiers. The CKM framework highlights CKD as a powerful amplifier of CV risk, with graded hazards apparent even at modest reductions in eGFR. Female-specific factors (e.g., adverse pregnancy outcomes, premature menopause) and lipoprotein(a) further refine risk, while early evidence suggests that polygenic risk scores can help identify high-risk individuals before clinical risk becomes apparent.

Secondary prevention after MI is proven to reduce recurrent events and mortality, yet its implementation remains inconsistent across Europe. Although high-intensity statins, antiplatelet therapy, and RAAS blockade form the cornerstone of GDMT, many patients fail to reach treatment targets or maintain adherence over time. Expanding use of novel agents such as PCSK9 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists offers further potential, but their uptake in real-world practice remains uneven.

Exercise-based cardiac rehabilitation is a key component of comprehensive secondary prevention. Structured rehabilitation programmes combining supervised physical activity, lifestyle counselling, and optimisation of pharmacotherapy have consistently demonstrated reductions of approximately 20% in CV and all-cause mortality (Lawler et al., 2011). Despite this robust evidence, participation and completion rates remain suboptimal, highlighting an important opportunity to improve long-term outcomes through better integration of physiotherapy and follow-up systems.

Despite extensive clinical trial evidence, substantial inter-country variation in MI outcomes persists, and the real-world implementation of secondary prevention remains inconsistent. Existing studies provide limited comparative

insight into how patient characteristics, healthcare system factors, and adherence to GDMT collectively influence long-term outcomes, particularly in Central-Eastern Europe. Furthermore, population-based evidence on age- and risk-specific mortality patterns after MI in Estonia is scarce. These gaps underline the need for comprehensive, registry-based analyses that integrate temporal trends, cross-country comparisons, and risk-group–specific outcomes. The present thesis was undertaken to address these gaps and to provide evidence that can inform more equitable, effective, and data-driven strategies to reduce post-MI mortality in Estonia and across Europe.

3. AIMS OF THE THESIS

The overall purpose of this thesis is to describe and analyse changes over time in the characteristics, management, and outcomes of patients with MI; to assess the implementation and uptake of GDMT for secondary prevention; and to identify and characterise high-risk patient subgroups to inform strategies for reducing post-MI mortality in Estonia.

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

I. To compare and evaluate the baseline characteristics, in-hospital management, and clinical outcomes of hospitalized MI patients across Estonia, Hungary, Norway, and Sweden to identify variations in care and outcomes between healthcare systems.

II. To evaluate adherence to guideline-recommended medications for secondary prevention of MI in 2017–2018, compare it with data from 2004–2005 in Estonia, and determine trends, progress, and persisting gaps in implementation over time.

III. To identify and characterize specific high-risk patient subgroups and evaluate their long-term mortality following MI across different age groups.

4. METHODS

4.1. Study design

This thesis is based on three retrospective cohort studies that utilize data from various national databases and registries. The primary source of data for all research conducted was the Estonian Myocardial Infarction Registry (EMIR).

In the first substudy (Papers I and II), EMIR served as the main data source for the Estonian component of a comparative study involving retrospective cross-country registry data. This study additionally engaged national MI registries from Norway, Hungary, and Sweden in an international collaboration aimed at facilitating data comparison. STEMI and NSTEMI patients were analysed separately to ensure clinically meaningful and methodologically consistent comparisons across countries, as these two entities differ in pathophysiology, acute management strategies, and prognosis. Separate analyses allowed for more accurate benchmarking of country-specific practices – such as reperfusion treatment in STEMI and invasive management or pharmacotherapy in NSTEMI – thereby highlighting system-level differences relevant to each MI subtype.

In the second substudy (Paper III), the Defined Daily Dose (DDD) methodology was employed to analyse drug utilization for the secondary prevention of MI. Developed by the World Health Organization (WHO), this methodology defines the DDD as the assumed average maintenance dose per day for a drug utilized for its primary indication in adults. Data from two distinct study periods were compared: Period I encompassed the years 2004 to 2005 (as undertaken by Dr. Toomas Marandi and colleagues in 2010 (Marandi et al., 2010)), while Period II covered the years 2017 to 2018. By linking personal identification numbers from EMIR, Estonian Health Insurance Fund (EHIF) and Estonian Medical Prescription Centre (EMPC) were used.

For the third substudy (Paper IV), EMIR again provided the foundation for the retrospective study cohort, with supplementary data acquired by linking personal identification numbers to information from the Estonian Population Register (EPR) and the databases of the six largest hospitals in Estonia.

All studies received ethical approval from the Research Ethics Committee of the University of Tartu and were conducted in accordance with the Declaration of Helsinki.

4.2. Databases

Several registries and databases were utilized in the development of the substudies. All data linkages between these databases were performed using unique personal identification numbers assigned to every resident of Estonia. The linkage process was deterministic and achieved 100% success.

The Estonian Myocardial Infarction Register (EMIR)
EMIR, previously detailed in Section 2.2.2 (p. 14), served as the primary data source for all four papers in this thesis.

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

Estonian Health Insurance Fund (EHIF)
The EHIF administrative claims database records reimbursed healthcare encounters and services in Estonia, including confirmed diagnoses (ICD-10; e.g., acute MI I21–I22) and procedures submitted on provider invoices. As the single payer for compulsory health insurance – covering ~95% of Estonia's 1.3-million population – the database captures nearly all interactions with the healthcare system. Data on reimbursed medication prescriptions were retrieved from EHIF for substudy II.

Estonian Medical Prescription Centre (EMPC)
The EMPC is the national e-prescription and medical-device card processing database, established to manage the issuance and processing of prescriptions and device cards. It records prescriptions and dispensing events and supports the reimbursement process under the Health Insurance Act. Its objectives include protecting prescription-medicine users, monitoring the accuracy and justification of dispensing, and enabling the state to compile medication statistics. EHIF is the responsible processor of the EMPC. Data on medication prescriptions were retrieved from the EMPC for substudy II.

The hospital databases
For substudy III, data were extracted from the EMIR list for patients hospitalized in the six largest Estonian hospitals: North Estonia Medical Centre, Tartu University Hospital, East Tallinn Central Hospital, West Tallinn Central Hospital, Pärnu Hospital, and East Viru Central Hospital. Creatinine levels, eGFR, and glycated haemoglobin (HbA1c) data were collected from the hospital databases. All laboratories follow standardized and validated methodologies, ensuring that measurements are comparable across hospitals.

Participating national MI registries.
The acute MI registries in Estonia **(**EMIR), Hungary (HUMIR), Norway (NORMI), and Sweden (SWEDEHEART) are among the few European national registries with continuous data collection and high case coverage. Substudy I used country-level aggregated data from these sources to enable like-for-like comparisons.

EMIR and SWEDEHEART are described in detail in Section 2.2.2 (pp. 14–15).

Norwegian Myocardial Infarction Registry (NORMI)
A government-funded, mandatory registry established in 2013, NORMI enrols ~11,000–12,000 hospitalized MI cases annually. It captures standardized information on presentation, management (including invasive procedures and pharmacotherapy), in-hospital complications, and discharge treatment. Case coverage exceeds 90%, with routine completeness and quality checks supporting high data validity.

Hungarian Myocardial Infarction Registry (HUMIR)
A national, consecutive-case registry, HUMIR was launched in 2010 with web-based reporting that records 178 structured variables across the care pathway (prehospital, in-hospital, and coronary interventions). In 2017, HUMIR captured ~92% of all MI cases relative to the national reimbursement dataset; data undergo continuous validation by dedicated staff, and outcomes (vital status, readmissions) are regularly obtained via linkage to the national health insurance database.

4.3. Study populations

Cohorts were derived from established registries, ensuring high data quality and case coverage, while methodologies adhered to ethical standards, protecting patient privacy and complying with data protection regulations.

Substudy I. Epidemiology, management, and outcomes of STEMI and NSTEMI in four European countries (Papers I and II)
Substudy I focus on consecutive MI patients from EMIR, HUMIR, NORMI, and SWEDEHEART. Variables extracted from these national registries included demographic variables, CV risk factors, previous CV diseases, various hospital presentation variables, features of in-hospital management, discharge medications and in-hospital complications. The comparativeness of the definitions across the registries was assessed during joint discussions and overall, the definitions were harmonious throughout the registries. Cross-matching with nationwide registries using unique personal identification numbers allowed for the analysis of follow-up data, including ICD codes, vital status, and causes of death.

- Paper I analyse STEMI cases diagnosed between January 1, 2014, and December 31, 2017.
- Paper II focuses on NSTEMI patients within the same period, with NORMI data extending from January 1, 2013, to December 31, 2016.

Diagnoses were confirmed using the European Society of Cardiology's (ESC) third universal definition of myocardial infarction (Thygesen et al., 2012).

In Paper I EMIR, HUMIR, and NORMI provided full follow-up data for vital status during the study period. In SWEDEHEART, follow-up data for vital status was available until June 30, 2018. While the 2014–2016 cohort had no loss of follow-up, the 2017 cohort exhibited substantial missingness in vital status data. Consequently, 30-day and 1-year mortality analyses for SWEDEHEART were

restricted to the 2014–2016 cohort, with no significant impact on anticipated mortality rates.

In Paper II all registries offered full 1-year follow-up for NSTEMI patients. However, SWEDEHEART data on vital status was available only until June 30, 2018. Mortality analyses for SWEDEHEART were thus restricted to the 2014–2017 cohort.

Substudy II. Secondary prevention of MI (Paper III)

Substudy II investigates drug utilization patterns for secondary prevention of MI, employing a methodology akin to that used by Dr. Toomas Marandi and colleagues in 2010 (Marandi et al., 2010) for the period 2004–2005 (Period I). Data for the current study (Figure 3) was sourced from EMIR and EHIF, encompassing inpatient MI cases (ICD-10 codes I21–I22) from January 1, 2017, to December 31, 2018 (Period II). The index episode was defined as the first MI hospitalization during this period.

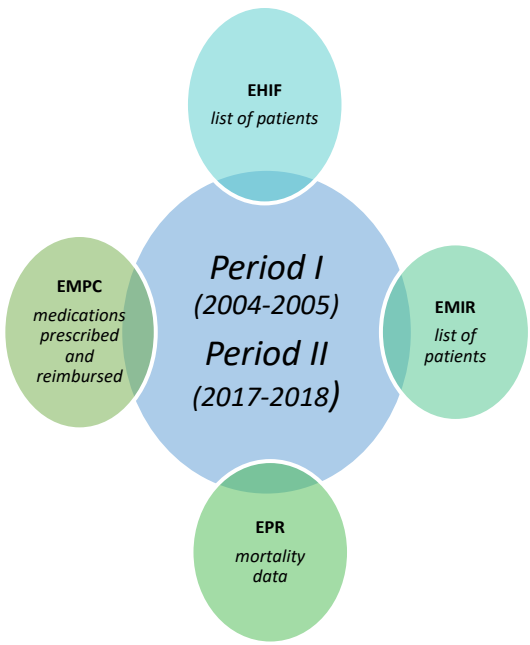

Figure 3. Formation of patient populations for Period I and II in Paper III.

EHIF Estonian Health Insurance Fund; EMIR Estonian Myocardial Infarction Register; EMPC Estonian Medical Prescription Centre; EPR Estonian Population Register

The analysis included patients who survived >30 days post-index episode, with a follow-up extending 365 days after the event. Mortality data were obtained from the EPR. Medications prescribed and reimbursed within 183 days prior to the index episode (indicating a valid prescription) and up to 365 days afterward were analysed. The list of medications, including statins, ACEi, ARBs, beta-blockers, and P2Y12 inhibitors, was issued by the EMPC and assessed using the DDD methodology (Table 4).

Table 4. Daily Defined Doses analysed in substudy II.

Defined Daily Dose (DDD) is the assumed average maintenance dose per day for a drug utilized for its primary indication in adults.	
Statins	Simvastatin 30 mg Atorvastatin 20 mg Rosuvastatin 10 mg Pravastatin 30 mg Fluvastatin 60 mg
ACEi	Ramipril 2.5 mg Enalapril 10 mg Perindopril 4 mg Fosinopril 15 mg Lisinopril 10 mg Trandolapril 2 mg
ARBs	Telmisartan 40 mg Losartan 50 mg Valsartan 80 mg Candesartan 8 mg Olmesartan 20 mg
Beta-blockers	Carvedilol 37.5 mg Metoprolol 150 mg Propranolol 160 mg Sotalol 160 mg Atenolol 75 mg Nebivolol 5 mg Bisoprolol 10 mg
P2Y12 inhibitors	Clopidogrel 75 mg Ticagrelor 180 mg

ACEi – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers

Data on P2Y12 inhibitors were limited to Period II, as ticagrelor was not available during Period I, and clopidogrel was not recommended as a first-line choice for MI patients in Estonia at that time. All reimbursed medications were considered as being used by patients.

Substudy III. DM, decreased renal function and outcome of MI (Paper IV)
Substudy III focuses on biomarker data for MI patients hospitalized in six major Estonian hospitals from 2012 to 2019: North Estonia Medical Centre, Tartu University Hospital, East Tallinn Central Hospital, West Tallinn Central Hospital, Pärnu Hospital, and East Viru Central Hospital.

Data on creatinine, eGFR, and HbA1c were extracted from hospital databases. HbA1c measurements had to be taken within one month before hospitalization, while eGFR values were required within 24 hours of admission. In cases where eGFR was unavailable but creatinine was measured, eGFR was calculated using the formula: eGFR = 175 × [creatinine × 0.011312] − 1.154 × [age] − 0.203 × [0.742 if female]

Patients without available renal function or HbA1c data were excluded from the analysis. Mortality data were obtained from the EPR, with follow-up concluding on December 31, 2021.

4.4. Study outcomes

Substudy I (Papers I and II)
Baseline demographic and clinical characteristics, in-hospital management and treatments of STEMI and NSTEMI patients across four European countries: Estonia, Hungary, Norway, and Sweden. 30-day and 1-year all-cause mortality after NSTEMI and STEMI in these countries.

Substudy II (Paper III)
Adherence to guideline-recommended medications for secondary prevention of MI during 2017–2018, with a comparative analysis to data from 2004–2005 in Estonia. Also 30-day and 1-year all-cause mortality were assessed for both study periods.

Substudy III (Paper IV)
The impact CKD and DM status on 30-day and 1-year all-cause mortality after MI, stratified by various age groups.

4.5. Statistical analysis

Substudy I (Papers I and II)
Data were aggregated and analysed at the country level. STEMI and NSTEMI cohorts were analysed separately to account for their distinct clinical profiles, treatment strategies, and outcome patterns, ensuring valid and comparable cross-country analyses. Categorical variables were expressed as percentages with 95% confidence intervals, and continuous variables as means ± standard deviations or medians with interquartile ranges.

For STEMI patients in Paper I, logistic regression models estimated country-level predictors of reperfusion, incorporating baseline characteristics: demographics (age, gender), risk factors (BMI, smoking, DM, dyslipidaemia, hypertension), and prior CV conditions (MI, heart failure, stroke, and peripheral artery disease). Missing covariate data, ranging from <0.1% to 34.8%, were handled using chained multiple imputation with 20 datasets, ensuring robust analysis. Age standardization was performed to compare 30-day and 1-year mortality rates using a reference population created from all study cohorts.

For NSTEMI patients in Paper II, crude and adjusted logistic regression models examined associations between selected clinical variables (e.g., DM, prior MI, or heart failure) and death rates across countries. Adjusted models included age (as a continuous variable), gender, BMI, smoking status, DM, hypertension, dyslipidaemia, and prior CV conditions as covariates. Missing covariate values were multiply imputed using a model including gender, BMI (continuous), current smoking, DM, hypertension, dyslipidaemia, prior MI, prior heart failure, prior stroke, and prior peripheral artery disease. Each imputed dataset was analysed with the same logistic models; estimates and standard errors were then pooled across imputations.

Statistical analyses were conducted using Stata (versions 11 and 16), R (version 3.6.0), and SPSS for Mac (version 26).

Substudy II (Paper III)

Categorical data were expressed as frequencies and analysed using Pearson's χ^2 test. Age was reported as mean ± standard deviation. DDDs, summarized by drug class, were calculated and expressed as medians per life days across age groups. Differences in DDDs between genders were assessed using the Mann–Whitney U test, with 95% confidence intervals and $\alpha < 0.01$ considered significant. Logistic regression models evaluated associations between age, gender, allocated drugs, and drug combinations, with results presented as odds ratios and 95% confidence intervals. Comparisons between study periods were performed using frequency tables. All analyses, including DDD calculations and associated statistical tests, were performed in R (version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria).

Substudy III (Paper IV)

The primary clinical outcome assessed in this study was post-MI all-cause mortality. Patients were stratified into distinct groups based on their renal function and age. Four age groups were formed: <50 years, 50–64 years, 65–79 years, and ≥80 years. Renal function was classified according to the Kidney Disease: Improving Global Outcome (KDIGO) criteria:

- eGFR ≥90 ml/min/1.73 m^2 (G1, normal);
- eGFR 60–89 ml/min/1.73 m^2 (G2, mildly decreased);
- eGFR 45–59 ml/min/1.73 m^2 (G3a, mildly to moderately decreased);
- eGFR 30–44 ml/min/1.73 m^2 (G3b, moderately to severely decreased);

- eGFR <30 ml/min/1.73 m^2 (including G4 + G5, severely decreased and kidney failure).

Baseline characteristics, in-hospital management, and recommendations for outpatient medications were summarized for each age group, using percentages for categorical data, and means with standard deviations for continuous variables. Patients were also stratified based on their DM status using data from the EMIR and HbA1c values:

- No DM: no prior DM diagnosis in EMIR, HbA1c < 5.7 %
- Pre-DM: no previous DM diagnosis in EMIR, HbA1c 5.7–6.5 %
- Newly diagnosed DM: no prior DM diagnosis in EMIR, HbA1c > 6.5 %
- Known DM: previous DM diagnosis in EMIR, HbA1c considered irrelevant.

All-cause short- and long-term mortality was compared among CKD status and age groups using the Cox proportional hazards regression model, adjusting for sex and DM status. Kaplan–Meier's curves were employed to illustrate the occurrence of the endpoint in distinct groups.

Two-sided *p* values <0.005 were deemed statistically significant. The analyses were conducted using R (version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria).

5. RESULTS

5.1. Substudy I. Epidemiology, management, and outcomes of STEMI and NSTEMI in four European countries (Papers I and II)

Baseline characteristics

A total of 64,025 STEMI patients (EMIR: 4,584; HUMIR: 23,685; NORMI: 12,414; SWEDEHEART: 23,342) and 119,191 NSTEMI patients (EMIR: 5,817; HUMIR: 30,787; NORMI: 33,054; SWEDEHEART: 49,533) were registered across the four national registries. Table 5 presents an overview of the basic patient characteristics in these registries, comparing NSTEMI and STEMI patients.

NSTEMI patients were generally older, more often women, and had more comorbidities and prior cardiovascular disease than STEMI patients across all registries. The overall trends were consistent, but some registry-specific differences stood out: HUMIR reported the highest prevalence of diabetes in both STEMI and NSTEMI, while SWEDEHEART had the largest proportion of patients with a history of prior MI, particularly in NSTEMI. EMIR patients showed relatively high rates of hypertension and heart failure. Presentation at admission also differed: STEMI patients were more likely to present with out-of-hospital cardiac arrest, especially in NORMI, whereas NSTEMI patients more often had higher Killip classes, suggesting more advanced heart failure.

In-hospital management

Results are summarized in Table 6. For STEMI patients, the use of reperfusion therapy varied considerably between countries. Primary PCI rates ranged from 63.4% in Estonia (EMIR) to 80.6% in Hungary (HUMIR) and 77.3% in Sweden (SWEDEHEART), while Norway showed intermediate use. Thrombolysis was used much less frequently in Hungary (0.5%) and Sweden (3.2%) compared with Estonia (12.4%) and Norway (13.2%), reflecting geographic characteristics, different reperfusion strategies and system capacities.

Among NSTEMI patients, the frequency of coronary angiography also differed substantially. Estonia had angiography in 66.4% of patients, while Hungary and Sweden showed higher rates (74.9% and 74.6%, respectively), and Norway the lowest at 58.0%.

The use of echocardiography for LVEF assessment was high in Estonia and Sweden for both NSTEMI and STEMI (generally ≥80%), whereas Hungary and Norway showed lower assessment rates. The distribution of LVEF values also varied, reflecting differences in patient severity and clinical practices across registries.

Discharge treatment

Results are summarized in Table 7. Across registries, STEMI patients were more often discharged on guideline-recommended medications (aspirin, DAPT, statins, ACEi/ARB, beta-blockers) than NSTEMI patients, while oral anticoagulants were consistently more frequent in NSTEMI. Between registries, SWEDEHEART and HUMIR showed the highest overall adherence to guideline therapy, with >90% use of aspirin and statins. EMIR reported comparatively lower rates, particularly for DAPT in NSTEMI. NORMI stood out with markedly lower ACEi/ARB prescriptions but higher use of oral anticoagulants in NSTEMI.

Table 5. Baseline characteristics for Papers I and II

% (95% CI)	*EMIR*		*HUMIR*		*NORMI*		*SWEDEHEART*	
	NSTEMI (n = 5,817)	***STEMI (n = 4,584)***	***NSTEMI (n = 30,787)***	***STEMI (n = 23,685)***	***NSTEMI* (n = 33,054)***	***STEMI (n = 12,414)***	***NSTEMI (n = 49,533)***	***STEMI (n = 23,342)***
Demography								
<60 years	15.1 (14.2–16.0)	25.2 (24.0–26.5)	21.9 (21.4–22.3)	36.4 (35.8–37.0)	18.3 (17.8–18.7)	32.6 (31.8–33.5)	14.9 (14.6–15.2)	23.1 (22.6–23.7)
60–69 years	23.4 (22.3–24.5)	27.2 (25.9–28.5)	27.9 (27.4–28.4)	28.6 (26.2–27.7)	21.5 (21.1–22.0)	26.9 (26.2–27.7)	22.5 (22.1–22.9)	23.1 (22.6–23.7)
70–79 years	29.5 (28.3–30.7)	23.1 (21.9–24.3)	28.3 (27.8–28.8)	21.0 (20.4–21.5)	23.9 (23.4–24.3)	20.4 (19.7–21.1)	30.8 (30.4–31.2)	26.9 (26.3–27.4)
80+ years	32.0 (30.8–33.2)	24.4 (23.3–25.7)	21.9 (20.5–22.2)	14.0 (13.6–14.5)	36.4 (25.9–36.9)	20.0 (19.3–20.7)	31.8 (31.1–32.2)	27.6 (27.0–28.2)
Men	56.5 (55.2–57.8)	61.4 (60.0–62.8)	58.2 (57.6–58.3)	61.6 (60.9–62.2)	61.6 (61.0–62.1)	70.8 (70.0–71.6)	63.8 (63.4–64.2)	69.2 (68.6–69.8)
Risk factors								
BMI, median (IQR)	28.4 (25.2–32.5)	28 (25–31)	28 (25–31)	27 (24–31)	26.4 (23.8–29.5)	26 (24–29)	26.5 (23.9–29.7)	26 (24–29)
Current smoker	20.7 (19.6–21.7)	34.5 (33.1–35.9)	19.4 (17.8–21.2)	32.0 (30.3–33.2)	24.2 (23.7–24.7)	38.0 (37.1–38.8)	15.7 (15.3–16.0)	25.1 (24.6–25.7)
Hypertension	84.4 (83.8–85.7)	78.6 (77.4–79.8)	85.5 (85.1–85.9)	73.9 (73.3–74.5)	51.0 (50.4–51.5)	39.2 (38.3–40.0)	60.6 (60.2–61.0)	49.4 (48.7–50.0)
DM	26.6 (25.4–27.7)	20.6 (19.5–21.8)	37.4 (35.9–39.1)	28.3 (27.7–28.9)	20.8 (20.4–21.2)	13.9 (13.3–14.5)	27.9 (27.5–28.3)	18.9 (18.4–19.4)
Hyperlipidemia	61.0 (59.7–62.2)	66.1 (64.7–67.5)	32.4 (31.4–33.2)	28.7 (28.1–29.4)	40.1 (39.5–40.6)	22.5 (21.8–23.3)	40.0 (39.5–40.4)	23.2 (22.7–23.8)
CKD (eGFR<60)	*NC*	*NC*	26.8 (25–28.2)	16.3 (15.8–16.7)	34.6 (34.1–35.1)	21.7 (21.0–22.5)	33.5 (33.1–33.9)	24.0 (23.4–24.6)

% (95% CI)	EMIR		HUMIR		NORMI		SWEDEHEART	
	NSTEMI (n = 5,817)	STEMI (n = 4,584)	NSTEMI (n = 30,787)	STEMI (n = 23,685)	NSTEMI* (n = 33,054)	STEMI (n = 12,414)	NSTEMI (n = 49,533)	STEMI (n = 23,342)
Previous CVD								
MI	31.9 (30.7–33.1)	16.0 (15.0–17.1)	30.5 (28.8–31.1)	13.7 (13.3–14.2)	28.0 (27.5–28.4)	14.2 (13.6–14.9)	37.0 (36.6–37.4)	18.9 (18.3–19.3)
Heart failure	40.8 (39.5–42.1)	28.1 (26.8–29.4)	20.3 (18.9–21.5)	8.7 (8.4–9.1)	10.8 (10.4–11.1)	3.4 (3.1–3.8)	21.5 (21.2–21.9)	9.2 (8.8–9.5)
Stroke	13.0 (12.2–13.9)	9.7 (8.9–10.6)	11.5 (10.7–12.4)	7.7 (7.3–8.0)	10.2 (9.9–10.6)	5.6 (5.2–6.0)	11.0 (10.7–11.3)	6.8 (6.5–7.1)
PAD	11.0 (10.2–11.8)	8.6 (7.8–9.5)	17.0 (16.6–18.4)	10.2 (9.7–10.6)	11.4 (11.0–11.7)	6.0 (5.6–6.4)	8.3 (8.1–8.6)	4.1 (3.9–4.4)
Presentation								
OHCA	2.1 (1.8–2.5)	*NC*	2.3 (2.2–2.5)	5.3 (5.0–5.6)	1.8 (1.6–1.9)	7.2 (6.7–7.7)	1.0 (0.9–1.1)	4.8 (4.5–5.1)
Heart rate, median (IQR)	80 (69–98)	78 (66–91)	80 (70–94)	80 (70–94)	79 (66–95)	77 (65–90)	80 (69–96)	77 (65–91)
Systolic BP, median (IQR)	140 (123–160)	138 (119–155)	136 (120–151)	130 (120–152)	142 (124–161)	133 (115–151)	150 (130–170)	140 (120–160)
Killip class II–IV	25.4 (24.3–26.5)	28 (26.7–29.3)	18.3 (17.5–19.4)	10.5 (10.1–10.9)	*NC*	*NC*	11.6 (11.3–11.9)	9.5 (9.1–9.9)

** Data for 2013–2016; CI confidence interval; BMI body mass index; IQR interquartile range; DM diabetes mellitus; CKD chronic kidney disease; eGFR estimated glomerular filtration rate; NC data not collected; CVD cardiovascular disease; MI myocardial infarction; PAD peripheral artery disease; OHCA out of hospital cardiac arrest; BP blood pressure*

Table 6. Comparison of in-hospital management

% (95% CI)	EMIR		HUMIR		NORMI		SWEDEHEART	
	NSTEMI (n = 5,817)	STEMI (n = 4,584)	NSTEMI (n = 30,787)	STEMI (n = 23,685)	NSTEMI* (n = 33,054)	STEMI (n = 12,414)	NSTEMI (n = 49,533)	STEMI (n = 23,342)
Reperfusion	*NC*	75.7 (74.4–76.9)	*NC*	82.0 (81.3–82.3)	*NC*	79.4 (78.7–80.1)	*NC*	84.0 (83.5–84.4)
Thrombolysis	*NC*	12.4 (11.5–13.4)	*NC*	0.5 (0.4–0.5)	*NC*	13.2 (12.6–13.8)	*NC*	3.2 (3.0–3.4)
Primary PCI	*NC*	63.4 (62.0–64.8)	*NC*	80.6 (80.1–81.1)	*NC*	66.2 (65.4)	*NC*	77.3 (76.8–77.9)
Time to reperfusion, median (IQR)	*NC*	236 (165–375)	*NC*	295 (181–655)	*NC*	*NC*	*NC*	198 (124–475)
Coronary angiography	66.4 (65.1–67.6)	80.4 (79.2–81.5)	74.9 (73.9–75.2)	83.1 (82.6–83.5)	58.0 (57.4–58.5)	84.6 (83.9–85.2)	74.6 (74.2–75.0)	93.0 (92.7–93.4)
PCI	48.9 (47.6–50.2)	72.8 (71.5–74.1)	44.6 (42.9–45.4)	81.3 (80.8–81.8)	37.7 (37.2–38.3)	77.8 (77.1–78.6)	55.3 (54.9–55.8)	89.1 (88.7–89.5)
CABG	3.2 (2.8–3.7)	1.0 (0.8–1.3)	*NC*	*NC*	3.4 (3.2–3.6)	1.5 (1.3–1.7)	5.9 (5.7–6.1)	2.0 (1.8–2.2)
LVEF assessment performed by echocardiography	86.4 (8.5–87.2)	91.7 (90.9–92.5)	78.6 (76.9–79.0)	79.6 (79.1–80.1)	58.2 (57.7–58.5)	79.5 (78.8–80.2)	76.4 (76.0–76.7)	86.9 (86.2–87.1)
LVEF ≥ 50 %	54.1 (52.8–55.5)	42.3 (40.8–43.8)	54.5 (52.9–56.5)	39.5 (38.3–40.1)	-	39.3 (38.4–40.1)	64.3 (63.8–64.8)	47.6 (46.9–48.2)
LVEF 40–49 %	22.7 (21.6–23.9)	29.1 (27.7–30.5)	22.4 (21.9–23.6)	23.2 (22.6–23.7)	-	32.9 (32.1–33.7)	18.2 (17.8–18.6)	26.8 (26.2–27.4)
LVEF 30–39 %	14.8 (13.8–15.8)	20.7 (19.5–22.0)	14.2 (13.6–15.3)	12.3 (11.9–12.8)	-	-	10.8 (10.5–11.1)	17.0 (16.5–17.5)
LVEF < 30 %	7.1 (7.0–8.5)	7.2 (6.4–7.9)	7.6 (6.9–8.5)	4.6 (4.3–4.9)	-	7.3 (6.8–7.7)	5.7 (5.5+5.9)	7.7 (7.3–8.0)

** Data for 2013–2016; CI confidence interval; IQR interquartile range; NC data not collected; – error in dataset; PCI percutaneous coronary intervention; CABG coronary artery bypass graft; LVEF left ventricular ejection fraction*

Table 7. Recommendations of medications at discharge

% (95% CI)	***EMIR***		***HUMIR***		***NORMI***		***SWEDEHEART***	
	NSTEMI (n = 5,817)	***STEMI (n = 4,584)***	***NSTEMI (n = 30,787)***	***STEMI (n = 23,685)***	***NSTEMI* (n = 33,054)***	***STEMI (n = 12,414)***	***NSTEMI (n = 49,533)***	***STEMI (n = 23,342)***
Aspirin	87.0 (86.1–87.9)	92.0 (91.1–92.8)	90.0 (89.1–91.0)	95.7 (95.4–95.9)	88.4 (88.0–88.8)	96.3 (95.9–96.6)	87.3 (87.0–87.6)	92.3 (91.9–92.6)
DAPT	60.5 (59.1–61.8)	78.1 (76.8–79.2)	74.9 (74.5–75.2)	92.4 (92.1–92.8)	68.4 (67.9–69.0)	90.2 (89.6–90.7)	69.9 (69.2–70.0)	83.1 (82.6–83.6)
Oral anticoagulants	14.1 (13.2–15.1)	10.5 (9.5–11.5)	9.1 (8.8–9.3)	5.9 (5.6–6.3)	21.6 (21.2–22.1)	13.7 (13.0–14.3)	15.9 (15.6–16.2)	11.2 (10.8–11.6)
Beta-blockers	83.5 (82.5–84.5)	84.4 (83.3–85.5)	88.2 (86.9–90.0)	87.0 (86.5–87.5)	73.0 (77.8–78.7)	80.5 (79.7–81.1)	85.6 (85.3–85.9)	88.8 (88.4–89.2)
Statins	78.5 (77.4–79.6)	86.5 (85.4–87.5)	89.3 (88.7–90.4)	91.8 (91.5–92.2)	78.3 (77.8–78.7)	90.1 (89.5–90.6)	86.0 (85.7–86.3)	92.1 (91.8–92.5)
ACEi/ARB	76.5 (75.1–77.6)	78.0 (76.6–79.2)	86.4 (85.6–87)	83.9 (83.4–84.4)	49.8 (49.2–50.3)	61.5 (60.6–62.4)	76.3 (76.0–76.7)	84.6 (84.2–85.1)

** Data for 2013–2016; CI confidence interval; DAPT dual antiplatelet treatment; ACEi/ARB angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers*

Mortality

Figure 4 presents 1-month and 1-year mortality for NSTEMI and STEMI patients across the four registries. In every registry, STEMI exhibits higher short-term (1-month) mortality than NSTEMI, with the largest gap observed in SWEDEHEART (4.7 percentage points). Notably, SWEDEHEART also reports the lowest 1-month mortality rates overall.

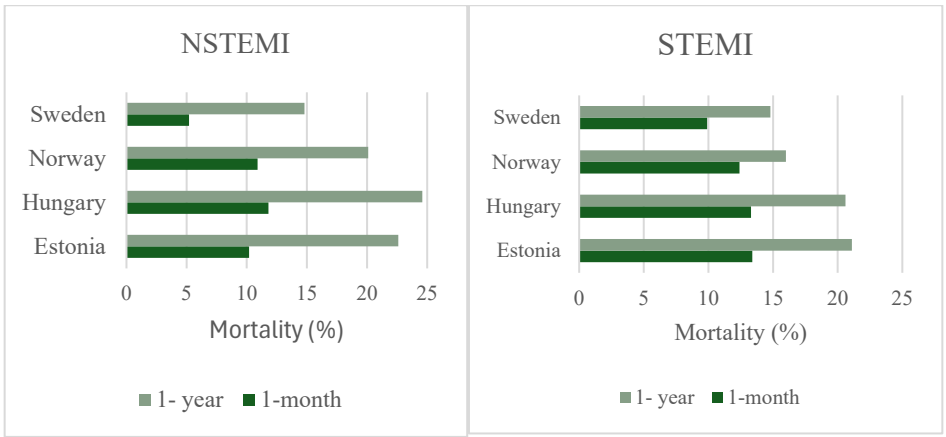

Figure 4. 1-month and 1-year mortality rates in Estonia, Hungary, Norway and Sweden after myocardial infarction.
STEMI ST elevation myocardial infarction; NSTEMI non-ST elevation myocardial infarction

Beyond the first month, NSTEMI patients generally face equal, or higher 1-year mortality compared to STEMI in each registry, except in SWEDEHEART, where both diagnoses share the same 1-year mortality rate (14.8%). HUMIR shows the highest 1-year mortality for NSTEMI (24.6%). Overall, these findings suggest a higher early (1-month) risk for STEMI patients, whereas longer-term (1-year) mortality is often greater in NSTEMI. Additionally, notable inter-registry differences exist, with SWEDEHEART consistently reporting the lowest mortality rates and HUMIR tending toward the highest.

5.2. Substudy II. Adherence to guideline recommended medications for secondary prevention of MI in Estonia (Paper III)

Baseline characteristics

A total of 6,694 and 6,060 MI cases were reported in Period I (2004–2005) and Period II (2017–2018), respectively, of which 4,900 and 5,067 were defined as index episodes. Between these two periods, one-year mortality declined in both men (from 25.6% to 19.1%) and women (from 35.0% to 30.0%). Over the same timeframe, the average age of the study population increased, with women consistently presenting at older ages than men in both periods (72.7 vs. 64.7 years in Period I and 76.4 vs. 66.5 years in Period II) (Table 8).

Table 8. Characteristics of study populations.

	Period I (2004–2005)		***Period II (2017–2018)***		***P value*****
	Men	***Women***	***Men***	***Women***	
Total number of index episodes, (%)	2,772 (56.6)	2,128 (43.4)*	3,039 (60.0)	2,028 (40.0)*	
One-year mortality, no. (%)	709 (25.6)	744 (35.0)*	581 (19.1)	602 (30.0)*	< 0.001
30-day mortality, no. (%)	407 (15.0)	468 (22.0)*	335 (11.0)	360 (17.8)*	< 0.001
Study population Number of patients who survived > 30 days, (%)	2,365 (85.3)	1,660 (78.0)*	2,704 (89.0)	1,668 (82.2)*	< 0.001
Age (years; mean, ± SD)	64.7 ±11.5	72.7 ±9.9*	66.5 ±12.1	76.4 ±10.9*	< 0.001
20–39 years, no. (%)	34 (1.4)	4 (0.2)	29 (1.1)	6 (0.4)	
40–59 years, no. (%)	740 (31.3)	166 (10.0)	779 (28.8)	126 (7.6)	
60–79 years, no. (%)	1,383 (58.5)	1,075 (64.8)	1,498 (55.4)	835 (50.0)	
> 80 years, no. (%)	208 (8.8)	415 (25.0)	398 (14.7)	701 (42.0)	
One-year mortality, no. (%)	302 (12.8)	276 (16.6)*	246 (9.1)	242 (14.5)*	< 0.001

**p < 0.01 for comparison between genders. Age was compared with the t test, otherwise Pearson's χ^2 test was used; SD standard deviation; ** p value for comparison between periods, men and women combined*

Drug utilisation

In Period I, 94.4% of patients surviving beyond 30 days received at least one of the recommended drug classes (statins, BB, ACEi/ARBs). In Period II, among 4,372 patients who survived >30 days, 91.7% (n = 4,009) were treated with at least one guideline-recommended agent (now including P2Y12 inhibitors) (Table 9).

Table 9. Proportion of patients with at least one prescription for guideline-recommended medications among patients who survived > 30 days.

	Period I 2004–2005 (n = 4025)			***Period II 2017–2018 (n = 4372)***			***P value (comparison between periods, total)***
	Men	**Women**	**Total**	**Men**	**Women**	**Total**	
BB, No. (%)	1,907 (80.6)	1,344 (81.0)	3,251 (81.0)	2,265 (84.0)	1,385 (83.0)	3,650 (83.5)	0.001
ACEi/ARB, No. (%)	1,780 (75.3)	1,317 (79.3)	3,097 (76.9)	1,817 (67.2)	1,070 (64.1)	2,887 (66.0)	<0.001
Statins, No. (%)	946 (40.0)	826* (50.0)	1,772 (44.0)	1,910 (70.6)	1,020* (61.2)	2,930 (67.0)	<0.001
P2Y12 inhibitors, No. (%)	*NA*	*NA*	*NA*	2,194 (81.1)	1,147* (69.0)	3,341 (76.4)	*NA*

*BB beta-blockers; ACEi/ARB angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NA not available; *P <0.01 for comparison between men and women with Pearson's χ^2 test. Pearson's χ^2 test used for comparison between periods.*

Figure 5 illustrates median daily dosages (DDDs per life day) for BBs, ACEi/ ARBs, and statins across age groups and gender in both periods; P2Y12 inhibitor dosages were only calculated for Period II. The latter were around 1.0 in most groups except those >80 years old, who received lower doses (men 0.84 [95% CI 0.69–0.92], women 0.61 [95% CI 0.46–0.77], p = 0.0009).

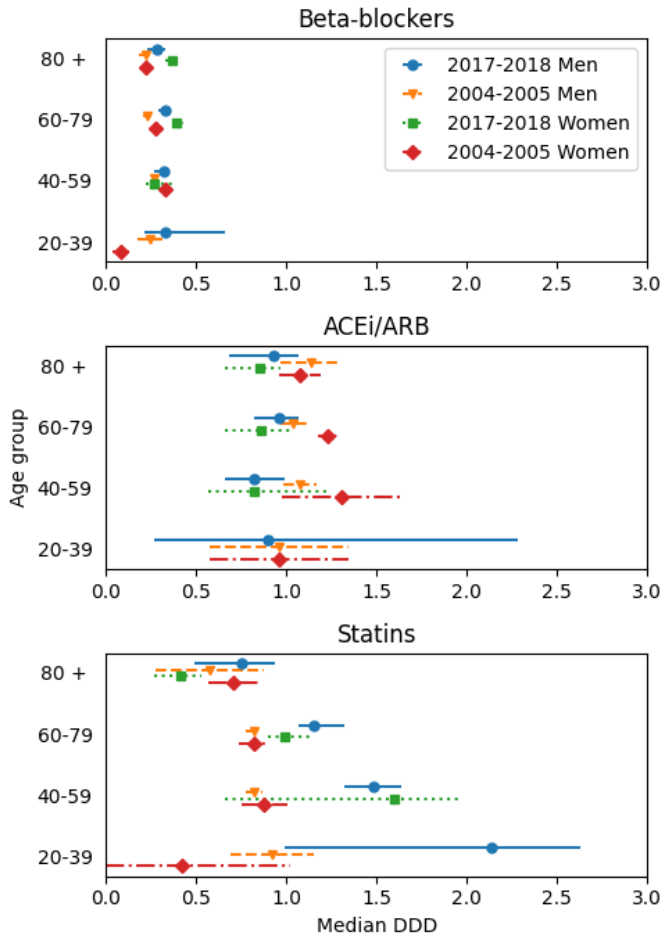

Figure 5. Median daily dosages of statins, angiotensin converting enzyme inhibitors/ angiotensin II receptor blockers (ACEi/ARB) and beta-blockers presented as defined daily dosages (DDD) per lifeday with 95% confidence interval for age groups and gender for patients who survived >30 days in comparison of periods I (2004–2005) and II (2017–2018).

Except for ACEi/ARBs, all guideline-recommended drug classes were prescribed more frequently in Period II (Table 10). The proportion of patients receiving the triple combination of BBs, ACEi/ARBs, and statins rose from 40.8% in Period I to 46.2% in Period II ($p < 0.01$), and a noticeable gender difference emerged.

Table 10. Combinations of prescribed treatments for patients who survived > 30 days.

	Period I 2004–2005 (n = 4,025)		***Period II 2017–2018 (n = 4,372)***		***P value*****
	Men	***Women***	***Men***	***Women***	
Only BB, No. (%)[1]	176 (7.4)	123 (7.4)	158 (5.8)	141* (8.5)	0.314
Only ACEi/ARB, No. (%)[1]	170 (7.2)	145 (8.3)	39 (1.4)	31 (1.9)	<0.001
Only Statin, No. (%)[1]	17 (0.7)	12 (0.7)	37 (1.3)	25 (1.5)	0.003
BB + ACEi/ARB, No. (%)[1]	602 (25.5)	525* (31.6)	338 (12.5)	301* (18.0)	<0.001
BB + statins, No. (%)[1]	130 (5.5)	49* (3.0)	433 (16.0)	257 (15.4)	<0.001
ACEi/ARB + statin, No. (%)[1]	141 (6.0)	63* (3.8)	104 (3.8)	52 (3.1)	0.001
BB + ACEi/ARB + statin, No. (%)[1]	999 (42.2)	647 (39.0)	1,336 (49.4)	686* (41.1)	<0.001
None of the above medications, No. (%)	130 (5.5)	96 (6.0)	214 (7.9)	148 (9.0)	<0.001

*[1] P2Y12 inhibitor use not accounted for; BB beta-blockers; ACEi/ARB angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NA not available; *P <0.01 for comparison between men and women with Pearson's χ^2 test; ** P value for comparison between periods, men and women combined with Pearson's χ^2 test*

Logistic regression (Figure 6) indicated that women were prescribed P2Y12 inhibitors significantly less often in Period II (OR 0.61, 95% CI 0.51–0.73, p <0.001).

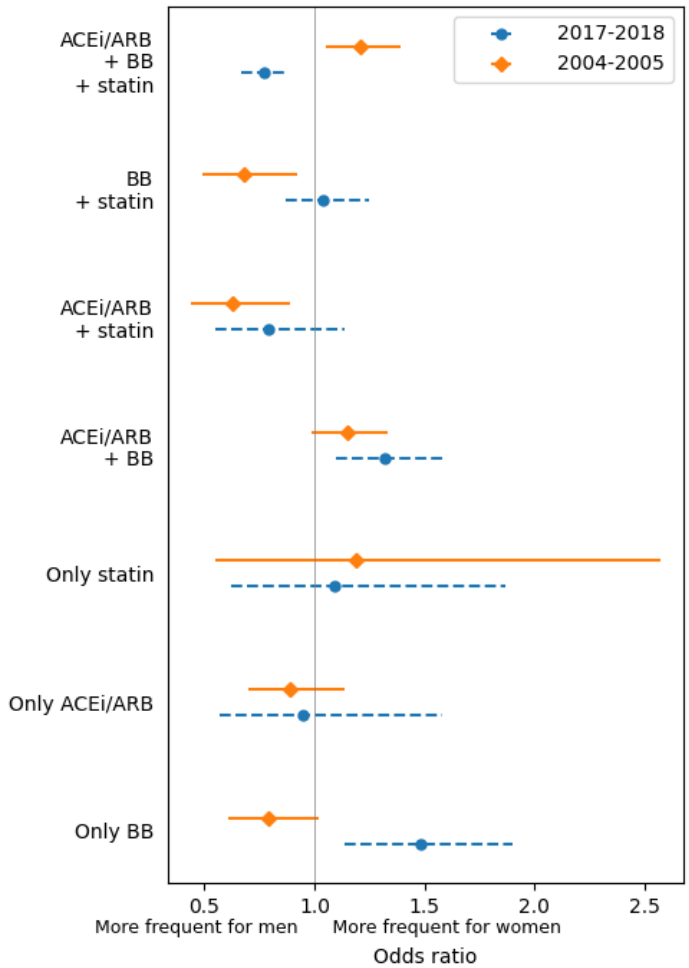

Figure 6. Relationship of drug allocation and gender in patients who survived >30 days.

BB beta-blockers, ACEi/ARB angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, OR odds ratio. Men were used as reference groups for logistic regression model

By age, older patients were less likely to receive the triple combination; in Period II, those aged 60–79 (OR 0.48, 95% CI 0.35–0.65, p<0.001) and those >80 (OR 0.18, 95% CI 0.13–0.24, p<0.001) were significantly less likely to be prescribed P2Y12 inhibitors compared to younger groups (Table 11).

Table 11. Relationship of drug allocation and age in patients who survived >30 days in 2004–2005 (period I) and 2017–2018 (period II).

	20–59 years OR (95 % CI)	*60 – 79 years OR (95 % CI)*		*> 80 years OR (95 % CI)*	
		2004–2005	*2017–2018*	*2004–2005*	*2017–2018*
BB	1.00	0.97 (0.29–3.19)	1.00 (0.73 – 1.39)	1.93 (0.58–6.47)	1.08 (0.75–1.58)
ACEi/ARB	1.00	2.49* (1.67–3.70)	1.38 (0.67–3.12)	5.69* (3.66–8.82)	3.16** (1.49–7.35)
Statins	1.00	0.88 (0.38–2.06)	1.32 (0.68–2.75)	0.17 (0.02–1.37)	1.45 (0.50–2.69)
ACEi/ARB + BB	1.00	1.21 (0.57–2.57)	1.06 (0.84–1.36)	1.92 (0.89–4.14)	1.85** (1.42–2.42)
ACEi/ARB + statin	1.00	0.32* (0.12–0.84)	1.06 (0.7 –1.72)	0.19* (0.06–0.58)	1.09 (0.66–1.81)
Statin + BB	1.00	0.81 (0.24–2.66)	1.01 (0.82–1.25)	0.28 (0.08–1.06)	0.75* (0.57–0.97)
BB + ACEi/ARB + statin	1.00	1.02 (0.53–1.96)	0.93 (0.79–1.09)	0.28* (0.14–0.55)	0.72** (0.59–0.87)
None of the above	1.00	NA	1.31 (1.00–1.73)	NA	1.66** (1.20–1.30)
BB + ACEi/ARB + statin + P2Y12 inhibitor	1.00	NA	0.82* (0.70–0.94)	NA	0.52** (0.42–0.63)
P2Y12 inhibitor	1.00	NA	1.31 (1.00–1.73)	NA	1.66** (1.20–1.30)

*BB beta-blockers; ACEi/ARB angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; OR odds ratio; CI confidence interval. Due to small number of patients in 20–39 years and 40–59 years age groups they were merged and used as reference groups for logistic regression model. *p <0.05; **p <0.001 for comparison between age groups within one time period.*

5.3. Substudy III. Impact of renal dysfunction and DM on post MI mortality in various age groups in Estonian cohort (Paper IV)

Baseline characteristics

The EMIR-based cohort initially comprised 19,575 patients, of whom 17,085 had valid renal function data and were thus included in the final survival analysis. The mean age was 70.1 years (SD 12.4), ranging from 22 to 102.

Table 12 contrasts demographic and risk factor profiles between younger and older patients. The younger subgroup included more men, with smoking and hyperlipidaemia emerging as key cardiovascular risk factors. In contrast, the older subgroup exhibited higher rates of DM, hypertension, and chronic heart failure. The eGFR distribution showed a clear trend of declining renal function with advancing age. Notably, over 10% of data points were missing for hyper-cholesterolemia, smoking, and heart failure, and 12.7% of eGFR values were unavailable.

Table 12. Baseline characteristics of the cohort of 19,575 MI patients in age groups.

Age group	*All*	*22–49*	*50–64*	*65–79*	*80–102*
	19,575 (100)	*1,117 (5.7)*	*5,083 (26.0)*	*7,850 (40.1)*	*5,525 (28.2)*
Male sex	11,447 (58.5)	991 (88.7)	3,248 (79.5)	3,441 (57.4)	1,187 (33.5)
Prior MI	3,331 (17.0)	77 (6.9)	691 (13.6)	1,500 (19.1)	1,063 (19.2)
Previous PCI	2,087 (10.7)	60 (5.4)	551 (10.8)	1,055 (13.4)	421 (7.6)
Previous CABG	898 (4.6)	4 (0.4)	166 (3.3)	475 (6.1)	253 (4.6)
Hypertension	15,174 (77,5)	620 (55.5)	3,619 (71.2)	6,303 (80.3)	4,632 (83.8)
Dyslipidaemia	11,083 (56.6)	757 (67.8)	3,399 (66.9)	4,668 (59.5)	2,259 (40.9)
Diabetes					
Known DM	4,492 (22.9)	133 (11.9)	975 (19.2)	2,112 (26.9)	1,272 (23.0)
New DM	326 (1.7)	10 (0.9)	90 (1.8)	122 (1.6)	104 (1.9)
Prediabetes	3,863 (19.7)	163 (14.6)	1,079 (21.2)	1,659 (21.1)	962 (17.4)
Previous or active smoker	7,827 (40.0)	856 (76.6)	3,440 (67.7)	2,888 (36.8)	643 (11.6)
Chronic heart failure					
NYHA II–IV	3,654 (18.7)	40 (3.6)	408 (8.0)	1,440 (18.3)	1,766 (32.0)
Renal function (eGFR)					
≥ 90 ml/min/1.73 m²	4,296 (21.9)	708 (63.4)	2,353 (46.3)	1,143 (14.6)	92 (1.7)
60–89 ml/min/1.73 m²	6,976 (35.6)	274 (24.5)	1,778 (35.0)	3,411 (43.5)	1,513 (27.4)
45–59 ml/min/1.73 m²	2,852 (14.6)	20 (1.8)	346 (6.8)	1,314 (16.7)	1,172 (21.2)
30–44 ml/min/1.73 m²	1,853 (9.5)	17 (1.5)	146 (2.9)	659 (8.4)	1,031 (18.7)
< 30 ml/min/1.73 m²	1,108 (5.7)	15 (1.3)	83 (1.6)	396 (5.0)	614 (11.1)

DM diabetes mellitus; MI myocardial infarction; PCI percutaneous coronary intervention; CABG coronary artery bypass grafting; NYHA New York Heart Association; eGFR estimated glomerular filtration rate. All data are presented as numbers (%) of patients in the category.

Younger patients (22–49 years) were more often diagnosed with STEMI (59.4%) and underwent PCI at a higher rate (74.0%). In contrast, older groups increasingly presented with NSTEMI (up to 54.7% in the ≥80 group), and PCI rates decreased with advancing age. CABG was most frequent among those aged 65–79 (8.4%). DAPT usage was highest (80.6%) among those under 50, then progressively declined with age (44.7% in ≥80). BB, ACEi/ARBs, and statins were prescribed at generally high levels across all groups but tended to be slightly lower in the oldest subgroup (Table 13).

Table 13. Characteristics of the index hospitalization by age groups

Age group	*All*	*22–49*	*50–64*	*65–79*	*80–102*
	19,575 (100)	*1,117 (5.7)*	*5,083 (26.0)*	*7,850 (40.1)*	*5,525 (28.2)*
STEMI/LBBB	8,793 (44.9)	664 (59.4)	2,688 (52.9)	3,315 (42.2)	2,126 (38.5)
NSTEMI	9,744 (49.8)	408 (36.5)	2,199 (43.3)	4,115 (52.4)	3,022 (54.7)
Underwent PCI	10,437 (53.3)	827 (74.0)	3,514 (69.1)	4,333 (55.2)	1,763 (31.9)
Underwent CABG	1,165 (6.0)	36 (3.2)	323 (6.4)	657 (8.4)	149 (2.7)
Patients discharged alive	***17,301 (88.4)***	***1,078 (96.5)***	***4,854 (95.5)***	***7,010 (89.3)***	***4,359 (78.9)***
Medication at discharge					
DAPT	10,967 (63.4)	869 (80.6)	3,672 (75.6)	4,478 (63.9)	1,948 (44.7)
BB	13,382 (77.3)	826 (76.6)	3,703 (76.3)	5,400 (77.0)	3,453 (79.2)
ACEi or ARB	12,318 (71.2)	731 (67.8)	3,516 (72.4)	5,048 (72.0)	3,023 (69.4)
Statin	13,120 (75.8)	896 (83.1)	4,010 (82.6)	5,408 (77.1)	2,806 (64.4)
Any medication for DM	3,866 (22.3)	*125 (11.6)*	903 (18.6)	1,829 (26.1)	1,009 (23.1)

No. number; STEMI ST segment elevation myocardial infarction; LBBB left bundle branch block; NSTEMI non-ST segment elevation myocardial infarction; PCI percutaneous coronary intervention; CABG coronary artery bypass grafting; DAPT dual antiplatelet therapy; BB beta blocker; ACEi angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; DM diabetes mellitus. All data are presented as numbers (%) of patients in the category.

Clinical outcomes

Figures 5 and 6 and Table 12 illustrate the clinical outcomes. Figure 7 shows short-term (first 30 days) and long-term (beyond 30 days) mortality, stratified by renal function and age group. The median follow-up for long-term mortality was 5.5 years, with all models adjusted for DM status and sex. A clear negative correlation emerged between declining renal function and post-MI mortality.

Among patients under 65 years old, even a mild reduction in renal function (eGFR 60–89 mL/min/1.73 m^2) significantly increased both short-term (HR 2.79, 95% CI 1.71–4.55) and long-term (HR 1.24, 95% CI 1.05–1.47) mortality, particularly within the first 30 days. An additional analysis focusing on those under 50 years revealed an even stronger effect of mild renal dysfunction on short-term (HR 3.46, 95% CI 1.06–11.4) and long-term (HR 2.10, 95% CI 1.28–3.42) mortality, though the sample size was limited to 37 patients.

In the 65–79 years group, post-MI mortality rose when eGFR fell below 60 mL/min/1.73 m^2, whereas in patients over 80, mortality increased only when eGFR dropped below 44 mL/min/1.73 m^2.

With respect to DM, newly diagnosed DM patients had a significantly higher post-MI mortality rate (mean HR 1.53, 95% CI 1.45–1.62), similar to that of known DM patients, when compared to those with normal glucose metabolism. No significant difference was detected for the pre-DM group (HR 0.98, 95% CI 0.91–1.05). In the Cox regression model evaluating the effect of CKD by age group, non-DM and pre-DM individuals were combined, as were newly diagnosed and known DM patients (Table 14).

Across all DM statuses, a strong negative association persisted between diminished renal function and long-term post-MI mortality. The interaction term for DM status and renal impairment was not statistically significant, indicating that renal failure independently predicts post-MI mortality regardless of DM status.

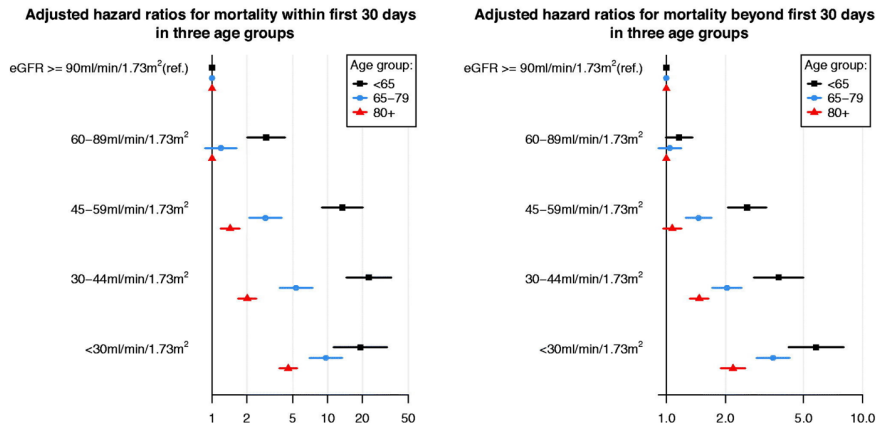

Figure 7. Short- and long-term mortality in age groups by renal function adjusted for DM status and sex.
eGFR estimated glomerular function; DM diabetes mellitus

Kaplan–Meier survival curves in Figure 8 reinforce the detrimental impact of renal dysfunction on long-term survival, showing notably poorer outcomes in younger patients who exhibit even a mild decline in renal function.

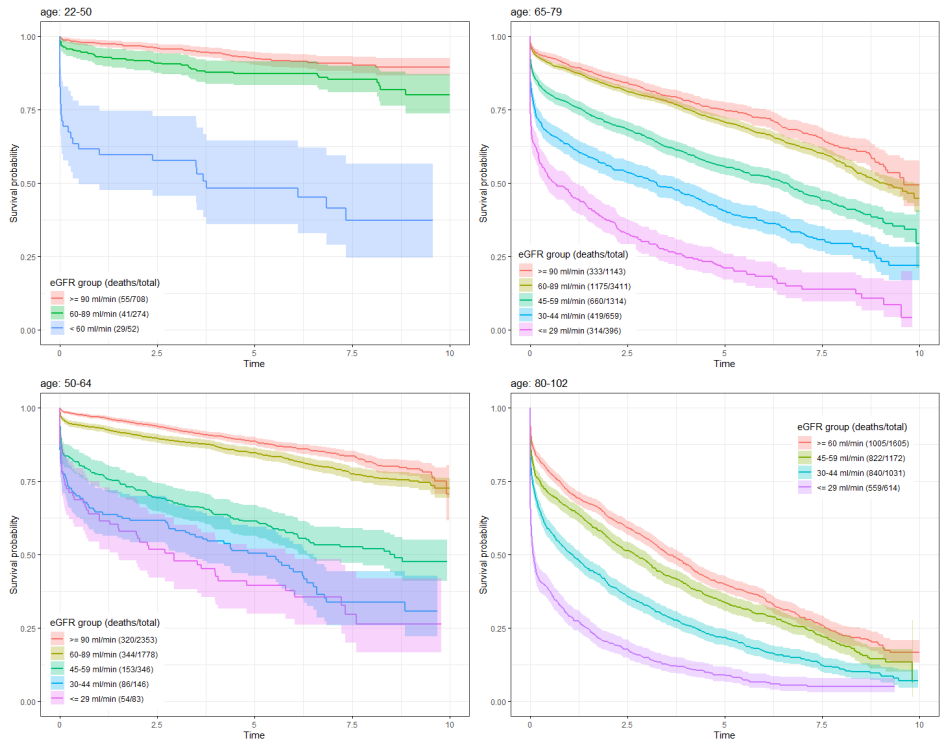

Figure 8. Kaplan-Meier's survival curves for age groups and renal function.
eGFR estimated glomerular filtration rate

Table 14. Mortality in age groups presented as hazards ratios with 95% confidence intervals.

	22–64 years		***65–79 years***		***≥ 80 years***	
	30-day mortality	***1-year mortality***	***30-day mortality***	***1-year mortality***	***30-day mortality***	***1-year mortality***
Deaths/total	***146/4816***	***699/4670***	***438/5667***	***1803/5229***	***580/3235***	***1675/2655***
eGFR (ref. ≥90 ml/min/1.73 m²)						
60–89 ml/min/1.73 m²	2.79 (1.71–4.55) ***	1.24 (1.05–1.47) *	1.28 (0.87–1.89)	1.09 (0.94–1.27)	1 *(incl. in reference)*	1 *(incl. in reference)*
45–59 ml/min/1.73 m²	14.4 (8.57–24.3) ***	2.40 (1.84–3.12) ***	2.88 (1.93–4.30) ***	1.55 (1.31–1.83) ***	1.42 (1.12–1.81) **	1.09 (0.96–1.23)
30–44 ml/min/1.73 m²	20.0 (11.3–35.4) ***	4.29 (3.16–5.82) ***	5.17 (3.42–7.80) ***	2.05 (1.70–2.49) ***	1.93 (1.53–2.44) ***	1.46 (1.29–1.66) ***
<30 ml/min/1.73 m²	19.8 (10.2–38.6) ***	6.09 (4.26–8.69) ***	9.01 (5.95–13.6) ***	4.01 (3.23–4.96) ***	4.01 (3.15–5.10) ***	2.19 (1.84–2.60) ***
DM (new or known)	1.62 (1.38–2.04) **	1.54 (1.31–1.81) ***	1.68 (1.38–2.04) ***	1.59 (1.44–1.75) ***	1.29 (1.09–1.53) **	1.45 (1.31–1.60) ***

*eGFR estimated glomerular filtration rate; DM diabetes mellitus; *** p<0.0001, ** p<0.001, * p<0.05*

6. DISCUSSION

6.1. Cross-national comparison of MI patient characteristics and treatments in Estonia, Hungary, Norway, and Sweden (Papers I and II).

We conducted two cross-country registry studies in Estonia, Hungary, Norway, and Sweden – countries that differ in post-MI outcomes and represent diverse socioeconomic contexts within Europe. Drawing on national MI registries that reflect real-world clinical practice, we analysed patient baseline characteristics, in-hospital management, and secondary prevention strategies in both NSTEMI and STEMI populations.

6.1.1. Coverage, definitions, and cross-country comparability

The robustness of our comparative analysis is supported by the high case coverage and methodological consistency of the national MI registries, which collect extensive real-world data on hospitalised MI patients. Estonia, Hungary, and Norway reported over 90% annual case coverage, ensuring high representativeness. SWEDEHEART, while comprehensive overall, demonstrated a slightly lower case coverage at approximately 88% during the study period. Notably, SWEDEHEART showed underrepresentation of patients aged 80 and above, with coverage around 80% in this subgroup. Nevertheless, Sweden had the highest overall proportion of patients over 80 across the registries, which supports the general comparability of the data. This aligns with Sweden's higher average life expectancy (≈83.6 years) compared with Norway (≈83.1), Estonia (≈78.8), and Hungary (≈76.4), which may partly explain the larger proportion of elderly patients in SWEDEHEART (Eurostat. Life Expectancy at Birth by Sex. Luxembourg: European Commission., n.d.).

Discrepancies in the definitions of baseline characteristics – such as hypertension, hyperlipidaemia, and chronic heart failure – were observed across the registries. These variations may stem from differences in national diagnostic criteria, healthcare policies, and reimbursement systems. For instance, Estonia and Hungary demonstrated a higher propensity to detect and report underlying CV risk factors, potentially influenced by specific healthcare incentives. Such heterogeneity necessitates caution when interpreting cross-country comparisons of management practices and outcomes.

While the registries offered robust clinical outcome data, they lacked patient-reported outcomes, particularly health-related quality of life (HRQoL). Recent evidence highlights HRQoL as an independent predictor of mortality and MACE in IHD. Conradie et al. (Conradie et al., 2022) found that lower baseline HRQoL, measured via EQ-5D-5L instrument (Herdman et al., 2011), was linked to higher one-year mortality and MACE in PCI patients. Integrating HRQoL into MI

registries could improve risk stratification and support more patient-centered care.

Our comparison of national MI registries underscores the importance of harmonised data collection and supports the case for a unified European registry. The EuroHeart initiative (ESC Euroheart Report 2023), led by the ESC, is a key step in this direction, promoting standardised data and improving cross-country comparability. Including patient-reported outcomes such as HRQoL would enhance understanding of patient health, support benchmarking, and inform strategies to improve long-term outcomes across Europe.

6.1.2. Patient characteristics

Comparison of MI patients across Estonia, Hungary, Norway, and Sweden revealed notable differences in patient characteristics, particularly in modifiable CV risk factors.

In the STEMI cohort, around one-third of patients were current smokers, peaking at 38% in Norway – substantially higher than general population averages – highlighting the need for focused prevention.

Hypertension and dyslipidaemia were recorded more frequently in Estonia and Hungary, a pattern that may reflect differences in case ascertainment, coding practices, and operational definitions across registries. However, population-level data support a genuinely higher burden: hypertension affects approximately 36% of Estonian adults (Kaldmäe et al., 2014) and 46.5% of Hungarians (Sonkodi et al., 2012), while DM prevalence is estimated at 8.7% in Estonia and 9.1% in Hungary (IDF: International Diabetes Federation, n.d.). These figures suggest that registry findings reflect real differences in underlying population risk. These differences may, in part, be influenced by broader contextual factors, including variations in public health infrastructure, access to preventive care, and socioeconomic conditions, which are known to shape CV risk profiles across Europe. These observations highlight the necessity for robust primary prevention programs and proactive identification of high-risk individuals, strategies that have been shown to effectively reduce CV morbidity and mortality (Stewart et al., 2020).

In the NSTEMI group, Hungary had the lowest median age (70 years), and both Hungary and Estonia showed higher comorbidity burdens, including a strikingly high rate of prior heart failure in Estonia (47%). This may be partly attributable to diagnostic incentives and highlights the challenge of comparing registry data across systems. Dyslipidaemia definitions also varied; although Estonia reported the highest prevalence (up to 60%), its use of lipid-lowering therapy at discharge was lowest (79%), suggesting a gap in secondary prevention.

While differences in out of hospital cardiac arrest rates may reflect registry inclusion criteria, their impact on long-term outcomes is likely limited. These findings again underline the need for harmonised data standards to ensure valid cross-country comparisons and inform better-targeted CV care strategies.

6.1.3. Reperfusion and revascularisation

STEMI

Management of STEMI was largely aligned with guideline recommendations across Estonia, Hungary, Norway, and Sweden, with reperfusion therapy rates ranging from 75.7% in Estonia to 84.0% in Sweden. PCI was the dominant reperfusion strategy, consistent with ESC guidelines advocating for PCI within 120 minutes of first medical contact (Byrne et al., 2023). Differences in infrastructure and geography shaped national approaches: Hungary's higher density of PCI centres facilitated broad access, while Norway's centralized model – adapted to geographic constraints – relied more heavily on thrombolysis. Estonia demonstrated a hybrid pattern.

An important determinant of STEMI outcomes is whether patients are transported directly to PCI-capable centres or initially routed to hospitals providing thrombolysis. In Estonia, the balance between thrombolysis and PCI has shifted markedly over the past decade. In 2011, thrombolysis was still used in about 29% of STEMI patients admitted to secondary hospitals, compared with only 0.6% in tertiary centres (Saar et al., 2015). By 2022, national EMIR data showed that thrombolysis had declined to 10.6% of STEMI patients overall, reflecting substantial progress toward wider use of primary PCI (EMIR Annual Report 2022). This development indicates a clear move away from non-invasive reperfusion and highlights the ongoing efforts to strengthen direct access to PCI-capable centres. While thrombolysis remains acceptable when timely PCI is not feasible, direct transfer to PCI centres is associated with better outcomes and is recommended as the preferred strategy by ESC guidelines (Byrne et al., 2023).

The experience from Norway further supports this shift. Despite having a relatively younger STEMI cohort with a favourable risk profile, short-term mortality in Norway was not lower than in Sweden. This may partly reflect a lower rate of reperfusion overall and a higher reliance on thrombolysis. Notably, the rate of prehospital cardiac arrest in Norway was also higher than in Sweden (7.2% vs. 4.8%), possibly linked to longer prehospital delays or system-level differences in care delivery. These findings highlight the clinical consequences of delayed definitive reperfusion and reinforce the need to minimize thrombolysis use in favour of primary PCI.

To reduce treatment delays and improve outcomes, broader implementation of pre-hospital triage supported by telemedicine is essential. Systems enabling ambulance-based ECG transmission and early cardiology consultation have been shown to expedite PCI and reduce mortality (Moxham et al., 2024). While some regional deployment exists, national coverage in Estonia remains limited. Strengthening these pathways would support a shift away from thrombolysis and toward consistent delivery of primary PCI.

NSTEMI

In Estonia, 66.4% of NSTEMI patients underwent coronary angiography, 48.9% received PCI, and 3.2% underwent CABG, leaving about 14% managed with

diagnostic angiography alone. Compared with the other registries, Estonia's invasive management is broadly similar to Sweden, higher than Norway, and slightly above Hungary for PCI use. Taken together, these figures suggest that Estonia has reached a relatively high uptake of invasive strategies for NSTEMI, yet the proportion receiving angiography without revascularisation points to scope for optimising patient selection for PCI or CABG. Importantly, registry analyses from Estonia have shown a risk–treatment paradox, with high-risk NSTEMI patients less likely to receive invasive or evidence-based pharmacological therapy despite their greater potential benefit (Saar et al., 2018). This pattern mirrors findings across Europe . (Chan Pin Yin et al., 2020; Saar et al., 2018) and underscores the continuing need to align NSTEMI management with ESC guideline recommendations advocating an early invasive approach in high-risk patients.

6.2. Cross-national comparison of MI patients' medication at discharge and secondary prevention (Papers I, II and III)

Adherence to guideline-directed medical therapy (GDMT) at discharge is pivotal for secondary prevention post-MI. Classical GDMT for secondary prevention following MI includes DAPT, statins, beta-blockers, and ACEi or ARBs, forming the cornerstone of post-MI care (Byrne et al., 2023).

6.2.1. Cross-national registry comparisons of medication at discharge

Comparative analyses across Estonia, Hungary, Norway, and Sweden reveal variations in adherence patterns, influenced by healthcare systems, demographic factors, and clinical practices.

In our registry comparison, a consistent pattern emerged: patients hospitalized with STEMI were more likely to receive GDMT at discharge than those with NSTEMI. This trend was evident across all four national MI registries – Estonia, Hungary, Norway, and Sweden. Several factors likely contribute to this discrepancy. First, STEMI patients benefit from the structured, time-sensitive "code STEMI" protocols that trigger rapid diagnosis, intervention, and standardized treatment pathways, often led by specialized cardiology teams. In contrast, NSTEMI patients present with a broader spectrum of clinical severity and comorbid conditions, which may lead to more individualized, and occasionally conservative, treatment decisions (Lange et al., 2024).

Multimorbidity is notably more prevalent among NSTEMI patients, especially older adults, which can lead to therapeutic hesitation due to concerns about polypharmacy, adverse effects, and interactions (Chung & Green, 2017). In Estonia, such patients are often hospitalised not in central PCI-capable centres but in smaller regional hospitals. This setting may exacerbate the treatment gap, as limited specialist access, combined with diagnostic complexity, may delay or

dilute guideline implementation, particularly in patients admitted to non-specialist units. Clinical inertia, under-recognition of risk, and uncertainty about benefit–risk ratios in frail patients may further contribute to suboptimal discharge prescriptions (Schoenenberger et al., 2008).

A closer examination of the individual registries reveals notable inter-country differences in discharge medication practices. Estonia consistently showed the lowest prescription rates across most drug classes, particularly for statins and DAPT. For example, only 78.5% of NSTEMI patients in Estonia were prescribed statins at discharge compared to 86.0% in Sweden. Similarly, DAPT was prescribed in just 60.5% of cases in Estonia versus 69.9% in Sweden.

Sweden consistently demonstrated the highest adherence to GDMT, reflecting a mature infrastructure for secondary prevention. Hungary showed moderately high adherence across most medication classes, though slightly lower than Sweden. This suggests the presence of systematic care structures, though potentially more variable in consistency and coverage. Norway, on the other hand, exhibited somewhat lower adherence in certain categories – for instance, only 49.8% of NSTEMI patients were discharged with ACEi or ARBs – despite otherwise high-quality CV services. These discrepancies may reflect regional variations in prescribing culture or differences in patient profiles, particularly the older population in Norway (Jortveit & Halvorsen, 2017).

6.2.2. Medication adherence in Estonia (Paper III)

Progress and evolving evidence in secondary prevention

When looking specifically at Estonia's practices in MI secondary prevention, our findings in Paper III show that while there has been meaningful progress between the two study periods – 2004–2005 (Period I) and 2016–2017 (Period II) – important gaps persist.

Between Period I and Period II, the prescription rates of key secondary prevention medications improved in Estonia, with statin use increasing from 44.0% to 67.0% and beta-blocker use rising from 81.1% to 83.5%. However, beta-blocker dosing remained suboptimal throughout. Our study showed that in Estonia, the majority of patients were discharged with beta-blocker doses well below guideline-recommended targets – a pattern comparable to findings by Pedersen et al, where only 8% of patients received more than 50% of the target dose at discharge, and just 31.5% reached that level within one year (Pedersen et al., 2016).

This persistent under-dosing reflects broader systemic barriers, including shortened hospital stays, limited follow-up capacity, and clinician concerns about tolerability in older, comorbid patients. Recent evidence has also prompted a reappraisal of the traditional use of beta-blockers in post-MI care. The 2023 ESC guidelines emphasize heterogeneity in outcomes among patients without heart failure or reduced ejection fraction, suggesting that a uniform approach to beta-blocker therapy may no longer be justified (Chi et al., 2025). Similarly, the

ACC/AHA guidelines recommend early post-MI use, but indefinite continuation is now more selectively advised (Kezerashvili et al., 2012). Notably, Estonia participated in the REDUCE-AMI trial, a large Scandinavian study investigating the necessity of long-term beta-blockers in MI patients with preserved ejection fraction (Yndigegn et al., 2024). Estonia's contribution underscores both its integration into contemporary European CV research and the importance of tailoring therapy to evolving evidence.

Persistent disparities by age and sex

Despite these advances, treatment disparities by age and gender remained prominent. In our analysis, elderly patients – particularly those over 80 years of age – and women were significantly less likely to receive triple therapy with beta-blockers, ACEi or ARBs, and statins, or DAPT. Our data further showed that in Estonia, women constituted the majority of the oldest age group, while younger females represented only a small fraction of the MI population. Importantly, global data indicate that women – including younger women (Thakkar et al., 2021) – are at particular disadvantage regarding timely diagnosis and the use of GDMT following MI (Zullo et al., 2019). The reasons are multifactorial, involving clinical hesitancy about treatment benefits in frail patients, as well as persistent perceptions that women, particularly those with non-obstructive coronary disease, may derive less benefit from standard secondary prevention – despite growing evidence to the contrary (Berther et al., 2024; Pana et al., 2024; Sári et al., 2025)

System-level gaps and future opportunities

Estonia's overall lag may reflect the absence of a structured, nationwide secondary prevention strategy. While awareness of the need for coordinated follow-up care is increasing, implementation remains fragmented and insufficiently supported at the policy level. To improve adherence and long-term outcomes, a state-enforced secondary prevention program – including systematic follow-up, patient counselling, and medication surveillance – is urgently needed in Estonia (Marandi, Toomas & et al, 2025). Sweden's experience highlights the potential benefits of such a model when embedded as a national health priority. National programs in Sweden, such as the SWEDEHEART registry's integration with structured follow-up and cardiac rehabilitation, enable medication optimization and long-term adherence monitoring (Bäck et al., 2021). These practices are further supported by national policy and funding mechanisms.

In addition to adopting structured, nationwide secondary prevention programs, Estonia could also benefit from the integration of artificial intelligence (AI)–supported solutions to improve long-term adherence and care continuity. AI-enabled digital tools, including mobile health applications and predictive adherence algorithms, have demonstrated potential in enhancing post-MI treatment engagement and early risk detection (Sridhar Rao Muthineni, 2025). For example, AI-enhanced platforms can deliver personalized reminders, monitor patient behaviour, and alert providers to non-adherence, particularly among

vulnerable groups such as elderly patients and those with multimorbidity (Koç, 2023; P et al., 2024; Vipin Gupta, 2024). Pilot programs in other European countries have already shown promising results in using AI for remote follow-up and medication management (Olivella et al., 2024). As Estonia advances its digital health infrastructure, the integration of AI-powered secondary prevention models could provide a scalable, cost-effective complement to traditional care – provided such initiatives are supported and coordinated at the national level.

6.3. Mortality outcomes of MI (Paper I, II and III)

Cross-country comparisons

In the comparative analyses of MI outcomes across four national registries – Estonia, Hungary, Norway, and Sweden – Estonia consistently exhibited some of the highest post-MI mortality rates for both STEMI and NSTEMI patients. One-year all-cause mortality in Estonia approached 21%, a rate comparable to Hungary and markedly higher than that observed in Sweden (15%) and Norway (15–20%).

While registry-based mortality data must always be interpreted with caution, Estonia's high case coverage (>90%) lends confidence to the representativeness of these findings. Importantly, EMIR coverage also includes elderly age groups (>80 years), who are sometimes underrepresented in other registries (e.g., SWEDEHEART ~80% coverage in this subgroup). This broader inclusion likely contributes to Estonia's higher observed mortality rates.

These outcomes are consistent with results from the national Estonian study (Paper III), which documented a significant reduction in short- and long-term mortality over a 13-year period – reflecting important progress. Specifically, 30-day mortality in Estonia decreased from 18.3% in 2004–2005 (Period I) to 11.0% in 2016–2017 (Period II), and 1-year mortality declined from 30.6% to 21.0% over the same period. These improvements likely reflect advances in in-hospital care and increased prescription rates of GDMT for secondary prevention. However, even in the more recent period, Estonia's mortality remained high in international comparison, indicating persistent challenges.

Determinants of poor outcomes

The Estonian MI population carries a greater burden of CV risk factors and comorbidities. Notably, the prevalence of prior heart failure is markedly higher in Estonia compared to the other countries in the comparison. This is significant, as prior heart failure is one of the strongest independent predictors of adverse outcomes following MI. Across all four national registries, logistic regression analyses confirmed that a history of heart failure was robustly associated with higher 1-year mortality, reinforcing prior findings from European cohort studies (Gill et al., 2022).

Several other factors may help explain Estonia's lagging outcomes. First, invasive management strategies remain underutilized, especially for NSTEMI

patients, among whom only 48.9% underwent PCI, compared to 55% in Sweden. Second, Estonia shows lower adherence to GDMT at discharge, particularly with regard to DAPT and statins. Paper III indicates that despite improvements, statin use reached only 67% in 2017–2018 and beta-blockers 83.5%, with notable underdosing.

Lessons from other countries

Sweden's more favourable outcomes likely reflect the country's strong tradition of structured post-MI care. Comprehensive secondary prevention programs, high prescription adherence, and the integration of follow-up into the national SWEDEHEART registry – particularly through SEPHIA (Secondary Prevention after Heart Intensive care Admission), its dedicated secondary prevention module launched in 2005 – support sustained improvements in outcomes. SEPHIA systematically tracks medication adherence, lifestyle modification, and participation in cardiac rehabilitation during the first year after MI, creating a structured feedback loop that links discharge management with long-term outcomes (Bäck et al., 2021).

Norway, despite showing lower rates of discharge medications, benefits from broader population health advantages and effective primary prevention, helping to offset gaps in acute MI management. Hungary, meanwhile, shares Estonia's elevated mortality despite comparable access to invasive treatment and medication, suggesting that broader factors – such as public health capacity, continuity of care, and adherence – may be critical determinants of long-term outcomes.

In conclusion, while Estonia has made measurable progress in reducing post-MI mortality, its outcomes remain significantly worse than those observed in Sweden and Norway. This disparity appears to stem from a combination of clinical, systemic, and population-level factors. Enhanced acute management, greater uptake of evidence-based medications, and, critically, the development of nationally coordinated secondary prevention programs – similar to those in place in Sweden – are likely essential to closing this mortality gap.

6.4. Identifying high-risk MI patients for personalised secondary prevention (Paper IV)

Given Estonia's high burden of CV risk factors and comorbidities – such as DM, hypertension, and CKD – it is essential to adopt a more proactive strategy for identifying and managing high-risk patients. This need is not unique to Estonia. Worldwide, the prevalence of obesity and metabolic disorders has surged, with approximately 40–46% of adults globally exhibiting metabolic syndrome, a cluster of risk factors that dramatically increases the risk of CV events and mortality (Laranjo et al., 2024). The rising prevalence of metabolic syndrome and obesity, especially among younger individuals, underscores the urgent requirement for targeted secondary prevention and intensified follow-up strategies.

Renal function and post-MI risk

Our analysis in Paper IV contributes to the growing evidence that individuals with even mild renal impairment face a significantly elevated risk of CV events and mortality (Ataklte et al., 2021). While the association between CKD and adverse outcomes is well established, limited data have explored the prognostic implications of mildly reduced renal function post-MI. In our cohort, young patients with an eGFR between 60–89 ml/min/1.73 m² exhibited significantly higher short- and long-term mortality compared to those with normal renal function (eGFR >90 ml/min/1.73 m²).

These findings support recent discussions on age-adapted thresholds for defining CKD, as proposed by Delanaye et al. (Delanaye et al., 2019), suggesting lower eGFR cutoffs for elderly patients due to age-related physiological changes in renal function. Indeed, our results indicate that in older adults, post-MI mortality increases notably only when eGFR falls below 44 ml/min/1.73 m². Conversely, even modest declines in eGFR among younger patients may signal a pathophysiologically relevant condition warranting aggressive secondary prevention.

Younger MI patients and metabolic risk

The rise in MI incidence among younger individuals has been well documented (Ando et al., 2022; Lv et al., 2021), with lifestyle-related factors such as smoking, dyslipidaemia, and obesity playing a central role. The increasing burden of early-onset type 2 DM, which carries a more aggressive CV risk profile than type 1 DM (Perng et al., 2023), further exacerbates this trend. Our findings align with prior studies showing that newly diagnosed DM patients have post-MI mortality risks comparable to those with long-standing DM, emphasizing the need for prompt intervention at first diagnosis (Bjarnason et al., 2020; Hermanides et al., 2020).

Elderly patients and multiple long-term conditions (MLTCs)

As Estonia's population ages and the proportion of patients with MLTCs continues to grow, treatment strategies must account for complexity, frailty, and the risk of polypharmacy (Birtcher et al., 2023). In our study, elderly patients demonstrated rising post-MI mortality only when eGFR fell below 44 ml/min/1.73 m², supporting a more individualized approach to CKD interpretation in seniors. The pragmatic management of MLTCs, including medication simplification and risk–benefit tailoring, is increasingly recognized as appropriate in this demographic (Khunti et al., 2023; Kurczewska-Michalak et al., 2021).

Implications for secondary prevention therapies

While GDMT was more frequently prescribed to younger patients in our cohort, overall adherence remained suboptimal compared to other European settings (Bjarnason et al., 2020; Hermanides et al., 2020). During the study period, newer cardioprotective agents such as SGLT2 inhibitors, GLP-1 receptor agonists, and

finerenone were not yet standard of care. However, trials like DAPA-CKD (Heerspink et al., 2020), EMPA-KIDNEY (The EMPA-KIDNEY Collaborative Group, 2023), and FIDELITY (Agarwal et al., 2022) have since demonstrated that these agents significantly reduce cardiorenal events and may play a pivotal role in reshaping secondary prevention strategies in CKD and DM populations. Their integration into post-MI care represents a promising avenue for patients, particularly for younger high-risk patients with overlapping metabolic and renal impairments.

Building on these findings, the present results emphasise the importance of reinforcing the organisation of post–MI care in Estonia. While substantial progress has been achieved in acute management, long-term follow-up and adherence to secondary prevention remain insufficiently structured. A nationally coordinated, registry-based secondary prevention pathway – integrated with the EMIR and primary care – could help to ensure consistent follow-up, treatment optimisation, and equitable access to rehabilitation. The SWEDEHEART-SEPHIA model demonstrates how continuous quality feedback and structured follow-up can improve national outcomes, offering a framework adaptable to the Estonian context. Given the country's well-developed e-health infrastructure, digital and AI-assisted adherence tools could further enhance personalised care and monitoring.

6.5. Strengths and limitations

This thesis is based on three observational studies using national registry data, one of which involve cross-national comparisons (Substudy I) and two focused on the Estonian population (Substudy II and III). A key strength of the work lies in the use of large, unselected real-world cohorts with full national coverage, reducing selection bias and allowing for comprehensive characterisation of MI patients in various clinical contexts. The use of routinely collected administrative and clinical data limits interviewer and recall bias and supports strong external validity.

Substudy I applied harmonised methodologies to compare STEMI and NSTEMI patient management and outcomes across Estonia, Hungary, Norway, and Sweden. A consistent analytical approach – including standardised definitions, country-level multiple imputation for missing data, and sensitivity analyses – strengthened the comparability and robustness of these cross-national studies. Importantly, both papers adopted a descriptive framework to highlight real-world practice variation rather than benchmark against clinical guideline adherence, offering insights into systemic differences in care delivery.

Substudy II focused on medication adherence for secondary prevention in Estonia. A major strength of this study was the use of comprehensive national prescription and reimbursement data, which allowed population-level estimation of medication use without selection or recall bias. By applying the DDD

methodology – consistent with a prior national study – comparisons over time were possible.

Substudy III examined CKD and DM among MI patients in Estonia, using linked registry data. Its strength lies in the ability to describe the overlap of comorbidities and treatment patterns in a national cohort, providing novel insight into high-risk subgroups within the MI population.

Nonetheless, several limitations must be acknowledged. As with all observational research, the findings are susceptible to confounding, and causal inference is limited. In Papers I and II, the use of aggregated and retrospective data restricted individual-level statistical comparisons and adjustment for all relevant covariates. Clinical variables such as renal function, Killip class, and out-of-hospital cardiac arrest were inconsistently reported across registries, limiting detailed risk adjustment. The 2017 Swedish cohort lacked vital status data due to registry linkage delays and was excluded from mortality analyses. Variable definitions (e.g. hypertension, dyslipidaemia, delay to reperfusion) also differed between countries, potentially affecting comparability.

Missing data were another challenge. For example, smoking status was more frequently absent in Estonia and Hungary compared to Norway and Sweden, which may reflect differences in documentation or disease awareness and introduce bias. Although multiple imputation was applied in multivariate models, baseline characteristics were reported as originally recorded to preserve transparency.

In substudy II, the DDD methodology likely overestimated medication adherence and could not distinguish short-term from long-term users. Additionally, while dispensed medications serve as a validated proxy for use, actual intake could not be confirmed. The study also lacked data on contraindications, patient intolerance, or reasons for nonadherence, limiting interpretation. Furthermore, no comorbidity or socioeconomic data were available for the 2004–2005 cohort, and this limitation was carried forward to the 2017–2018 cohort to maintain methodological consistency.

Substudy III faced limitations due to registry structure: the EMIR database did not distinguish between type 1 and type 2 DM, and CKD aetiology could not be assessed. The absence of albuminuria data restricted CKD staging and its prognostic evaluation. Moreover, only age and sex were available as background characteristics, precluding analysis of other important social or clinical determinants.

In summary, while the studies in this thesis are subject to the typical constraints of observational and registry-based research – including issues of missingness, variable definitions, and confounding – they nonetheless offer valuable real-world insights into MI care, secondary prevention, and comorbidities. The strengths of national representativeness, methodological consistency, and inclusion of both cross-national and focused national analyses position this work as a meaningful contribution to CV epidemiology and health services research.

7. CONCLUSIONS

I. The cross-country comparison of four European MI registries showed that NSTEMI patients were older, more often female, and carried more comorbidities than STEMI patients, with these differences reflected in lower use of invasive management and secondary prevention. Estonia and Hungary had higher post-MI mortality than Sweden and Norway, explained in part by lower reperfusion rates in STEMI, undertreatment of high-risk NSTEMI patients, and lower adherence to GDMT at discharge. The Swedish experience illustrates how structured follow-up, and secondary prevention can translate into better long-term outcomes.

II. In Estonia, adherence to GDMT for secondary prevention of MI improved between 2004–2005 and 2017–2018, spanning a 13-year interval. Despite this progress, adherence remained suboptimal, particularly among women and older patients. To further reduce CV mortality, a more systematic and targeted approach to the implementation of secondary prevention guidelines is warranted.

III. There is an age-dependent association between eGFR and post-MI outcomes, with younger patients showing increased risk even with mild renal function decline, whereas in older individuals, adverse outcomes emerge primarily at lower eGFR levels. These findings underscore the importance of age-specific, individualised treatment strategies that consider both renal function and comorbidities.

8. FUTURE RESEARCH

Future research should prioritise strengthening registry infrastructure and improving the interoperability of national MI registries. Harmonised definitions and core datasets, as envisioned within the EuroHeart initiative, would enable reliable cross-national benchmarking and support the translation of best practices into national healthcare organisation and quality monitoring.

Further investigation is warranted to advance personalised prevention strategies. Earlier identification of high-risk individuals – particularly younger patients with unfavourable metabolic or renal profiles – could allow more targeted primary prevention and intensified secondary prevention after MI. The integration of PRSs into electronic health records may further refine early risk stratification and guide efficient resource allocation.

Finally, future studies should evaluate the feasibility, clinical effectiveness, and cost-efficiency of digitally supported and AI-assisted secondary prevention pathways within Estonia's e-health environment. Such evidence will be essential for implementing structured, data-driven CV care models and informing future national policy decisions.

9. SUMMARY IN ESTONIAN

Registriandmetest kliinilisse praktikasse: müokardiinfarkti käsitlus ja ennetus Eestis ja Euroopas

Südame-veresoonkonna haigused (SVH) on jätkuvalt peamine surmapõhjus Euroopas, põhjustades igal aastal üle nelja miljoni surma. Euroopa Liidus registreeriti 2021. aastal ligi 1,7 miljonit SVH-ga seotud surmajuhtu, mis moodustas umbes kolmandiku kogu suremusest. Ligikaudu veerandi kogu SVH koormusest moodustavad südame isheemiatõbi ja selle tõsiseim väljendus – müokardiinfarkt (MI). Lisaks inimelude kaotusele kaasneb suure SVH esinemissagedusega märkimisväärne majanduslik kulu, mis ulatub sadadesse miljarditesse eurodesse aastas. Eestis on SVH suremus jõudsalt vähenenud, kuid on endiselt suurem võrreldes Põhjamaadega.

Viimase kolme aastakümne jooksul on Lääne- ja Põhja-Euroopas täheldatud suremuse järsku vähenemist. Südame isheemiatõve standardiseeritud suremusmäär on langenud enam kui 50%. Rootsis ja Norras on MI järgne 30-päeva suremus langenud alla 6% ning 1-aasta suremus alla 12%. Kesk- ja Ida-Euroopa riikides, sealhulgas Eestis, on langus olnud aeglasem. Eestis oli 2001. aastal südame isheemiatõve standardiseeritud suremusmäär meestel 543 ja naistel 272 juhtu 100 000 elaniku kohta, kuid 2019. aastaks olid need langenud vastavalt 228 ja 113 juhuni. Võrdluseks oli Rootsis sama näitaja 2019. aastal meestel 94 ja naistel 52 juhtu 100 000 elaniku kohta.

Üldise MI esinemissageduse ja suremuse vähenemise foonil on nooremates vanuserühmades languse tempo selgelt aeglustunud. Samuti on märgata soolisi erinevusi: naiste puhul, eriti Ida-Euroopas, on langustrend olnud aeglasem. Eesti varasemad uuringud (Ainla, Blöndal, Saar) on näidanud olulisi positiivseid muutuseid MI invasiivses ravis ja haiglavõrgustiku arengus, kuid ka nn risk–ravi paradoksi esinemist, kus suurema riskiga patsiendid ei pruugi saada ravijuhistes soovitatud intensiivsemat ravi.

SVH kaasaegne käsitlus rõhutab klassikaliste riskitegurite kõrval ka uusi riski mõjutavaid faktoreid – näiteks kardiometaboolne sündroom ja krooniline neeruhaigus suurendavad oluliselt surma riski. Nende mõju on eriti väljendunud nooremate patsientidel. Samuti on üha enam tähelepanu pööratud naistel esinevatele spetsiifilistele riskifaktoritele (näiteks rasedustüsistused, varajane menopaus) ja polügeense riskiskoori abil hinnatavale geneetilisele eelsoodumusele, mis võimaldavad varasemat ja sihipärasemat ennetust.

Eestis on suitsetamise levimus vähenenud, kuid endiselt suitsetab ligi veerand täiskasvanud meestest ja umbes 15% naistest. Rasvumise esinemissagedus on viimase 20 aasta jooksul kahekordistunud ning ulatub 20%-ni täiskasvanutest. 2. tüüpi diabeedi levimus on tõusnud 4%-lt umbes 8%-ni. Sama trendi täheldatakse kogu maailmas, kus üha rohkem noori täiskasvanuid põeb diabeeti ja on ülekaalulised. Need patsiendid kuuluvad suure kardiovaskulaarse riski rühma ning võivad haigestuda esimesse infarkti juba tööeas. Samal ajal Euroopa ja Eesti

rahvastik vananeb ning eakate ja paljude kaasuvate haigustega patsientide osakaal suureneb. Eesti keskmine eluiga on viimase 30 aasta jooksul pikenenud ligi 8 aasta võrra. Vanemaealised patsiendid põevad sageli samaaegselt südame isheemiatõvega ka südamepuudulikkust, kroonilist neeruhaigust, diabeeti ja muid haiguseid. Seetõttu on MI patsientide kohort muutumises: üha rohkem satub haiglaravile nii noori suure riskiga patsiente kui ka väga eakaid hapraid patsiente.

Euroopa Kardioloogide Seltsi (ESC) juhised rõhutavad, et sekundaarne preventsioon pärast MI-d peab olema süsteemne ja mitmetahuline, hõlmates elustiili korrigeerimist ning tõenduspõhist farmakoteraapiat. Antiagregandid, statiinid, beeta-blokaatorid, ACEi/ARB-id ja vajadusel uuemad ravimid, näiteks SGLT2-inhibiitorid ja PCSK9-inhibiitorid, vähendavad korduvate sündmuste riski märkimisväärselt. Nende ravimite kasutamine vähendab korduva MI ja kardiovaskulaarse surma riski ligi kolmandiku võrra. Samas näitavad uuringud, et ligikaudu pooled Euroopa patsiendid ei saavuta eesmärkväärtusi, näiteks LDL-kolesterooli taset alla 1,4 mmol/l. Samuti on vähene osalus kardiaalses taastusravis, mis võiks vähendada suremust ligi viiendiku võrra.

Uurimuse eesmärgid

Käesoleva doktoritöö üldine eesmärk oli analüüsida Eesti MI patsientide ravi ja ravitulemusi, andes terviklik ülevaade patsientide kliinilistest tunnustest, ravipraktikatest ja ravitulemustest ning asetades need rahvusvahelisse konteksti. Sellest lähtuvalt olid töö alameesmärgid järgmised:

- Esiteks, võrrelda Eesti, Ungari, Norra ja Rootsi MI patsientide kliinilisi tunnuseid, ravi ja lühiajalist ning pikaajalist suremust.
- Teiseks, analüüsida MI järgse sekundaarse preventsiooni medikamentoosse ravi rakendamist Eestis kahel ajaperioodil, 2004–2005 ja 2017–2018, et hinnata muutusi ravimikasutuses ja tuvastada kitsaskohti.
- Kolmandaks, tuvastada ja kirjeldada spetsiifilised kõrge riskiga patsientide alarühmad ning hinnata nende MI-järgset pikaajalist suremust erinevates vanuserühmades.

Metoodika

Doktoritöö põhineb neljal retrospektiivsel kohortuuringul, mis kasutasid Eesti Müokardiinfarkti Registri (EMIR) ja teiste riiklike andmebaaside andmeid.

EMIR loodi 2012. aastal ning hõlmab kõiki Eestis hospitaliseeritud ägeda MI-ga patsiente, kokku ligikaudu 2700 juhtu aastas. Andmeid täiendati surmaregistri, haigekassa ja retseptikeskuse infoga, mis võimaldas lisada informatsiooni korduvate hospitaliseerimiste, ravimikasutuse ja suremuse kohta.

Esimese ja teise artikli raames viidi läbi rahvusvaheline koostööuuring, kus võrreldi STEMI ja NSTEMI patsiente Eestis, Ungaris, Norras ja Rootsis. Kaasati aastatel 2013–2017 hospitaliseeritud patsiendid. Analüüsiti demograafilisi tunnuseid, riskifaktoreid, teostatud reperfusioonravi ja revaskulariseerimist, tüsistusi ning ravimeid haiglast väljakirjutamisel. Tulemustena hinnati 30-päeva ja 1-aasta

suremust. Analüüsimisel kasutati logistilist regressiooni ja Coxi proportsionaalsete riskide mudeleid.

Kolmanda artikli fookuses oli Eesti patsientide ravimikasutuse muutus ajas. Kaasati patisendid perioodidest 2004–2005 ja 2017–2018. Ravimikasutust analüüsiti WHO defineeritud päevadoosi (DDD – defined daily dosage) metoodika alusel. Uuritavateks ravimiklassideks olid statiinid, beeta-blokaatorid, ACEi/ARB-id ja P2Y12-inhibiitorid. Lisaks hinnati ravimite kasutuse kestust ja ravijärgimust 12 kuu jooksul.

Neljanda artikli aluseks olid kuue Eesti suurhaigla patsiendiandmed aastates 2012-2019. Analüüsiti eGFR-i ja HbA1c väärtuste põhjal neerufunktsiooni ja diabeedi mõju. Patsiendid jaotati KDIGO kriteeriumide alusel viide kategooriasse (G1–G5). Analüüsiti eri vanuserühmi: alla 50, 50–64, 65–79 ja vähemalt 80-aastased. Jälgimisperiood kestis kuni 31. detsembrini 2021. Tulemusnäitajaks oli 30- ja 1-aasta suremus.

Kõik uuringud said Tartu Ülikooli inimuuringute eetika komitee heakskiidu ja viidi läbi vastavalt Helsingi deklaratsiooni põhimõtetele.

Uurimuse tulemused ja järeldused

Rahvusvaheline võrdlus näitas, et Eesti MI patsiendid olid keskmiselt nooremad, mediaanvanus 66 aastat, võrreldes Rootsi 71 aasta ja Norra 72 aastaga. Eestis oli diabeedi levimus 27%, Rootsis 22% ja Norras 20%. Düslipideemia ja hüpertensioon esinesid samuti sagedamini Eesti patsientidel. Reperfusioonravi said Eestis 65% STEMI patsientidest, Ungaris 60%, Rootsis 87% ja Norras 84%. Need erinevused kajastusid tulemustes: Eesti 30-päeva suremus STEMI korral oli 9,5% ja 1-aasta suremus 18%, Rootsis vastavalt 6% ja 12%. NSTEMI patsientidest teostati angioplastika Eestis vaid 48,9%, samal ajal kui Rootsis oli vastav näitaja 55%.

MI järgse sekundaarse preventsiooni ravimikasutuse analüüs näitas olukorra olulist paranemist. Statiinravi määramine suurenes 45%-lt 2004–2005 perioodil 83%-ni 2017–2018 perioodil. Beeta-blokaatorite kasutus tõusis 52%-lt 85%-ni, ACEi/ARB-ide kasutus 48%-lt 80%-ni ning P2Y12-inhibiitorite kasutus 15%-lt 78%-ni. Optimaalne ravijärgimus, st vähemalt 80% raviskeemist kinni pidamine, jäi siiski 63% tasemele. Eraldi analüüs näitas, et eakad ja naised kasutasid ravimeid järjepidevamalt vähem.

Neerufunktsiooni ja diabeedi mõju analüüs näitas olulisi vanuserühmade vahelisi erinevusi. Alla 50-aastastel patsientidel, kelle eGFR oli langenud vahemikku 60–89 ml/min/1,73 m², oli 1-aasta suremuse riskisuhe 2,1 võrreldes normaalsete väärtustega. 65–79-aastaste seas suurenes risk järsult alles siis, kui eGFR langes alla 45 ml/min/1,73 m². Vähemalt 80-aastaste seas oli absoluutne 1-aasta suremus kõrge, 34%, sõltumata täpsest eGFR väärtusest. See peegeldab multimorbiidsuse ja hapruse mõju MI järgsele suremusele.

Uuring tõi välja MI patsientide kohordi muutumist ajas: üha enam hospitaliseeritakse noori metaboolse sündroomiga patsiente, kellel esineb rasvumine ja varajane diabeet. Samal ajal suureneb väga eakate ja multimorbiidsete patsientide

osakaal, kelle ravi on keerulisem ja prognoos sageli halvem. See kahe äärmuse kasv nõuab tervishoiusüsteemilt suuremat paindlikkust ja personaalsemat käsitlust. ESC juhised rõhutavad vajadust vanuse- ja riskipõhiste strateegiate järele, et parandada tulemusi ja vähendada suremust.

Uuringutulemuste järeldused olid järgmised:

I. Nelja Euroopa MI registri võrdlus näitas, et NSTEMI patsiendid olid vanemad, sagedamini naised ning neil esines rohkem kaasuvaid haiguseid kui STEMI patsientidel. Need erinevused peegeldusid invasiivse ravi ja sekundaarse preventsiooni kasutamises väiksemas ulatuses. Eestis ja Ungaris oli MI järgne suremus kõrgem kui Rootsis ja Norras, mida selgitab osaliselt madalam reperfusioonravi osakaal STEMI patsientidel, kõrge riskiga NSTEMI patsientide alaravi ning väiksem juhistekohase medikamentoosse ravi rakendamine haiglast väljakirjutamisel. Rootsi kogemus näitab, et struktureeritud järelravi ja sekundaarne preventsioon võivad viia paremate pikaajaliste tulemusteni.
II. 13-aastasel ajavahemikul (aastatel 2004–2005 ja 2017–2018), paranes Eestis MI sekundaarse preventsiooni juhistekohase medikamentoosse ravi järgimus. Hoolimata sellest edust on ravijärgimus endiselt suboptimaalne, eriti naiste ja eakate patsientide seas. Kardiovaskulaarse suremuse edasiseks langetamiseks on vajalik süsteemsem ja sihipärasem lähenemine juhiste rakendamisel.
III. MI järgsete ravitulemuste ja neerufunktsiooni vahel esineb vanusest sõltuv seos: noorematel patsientidel suureneb risk juba kerge neerufunktsiooni languse korral, samas kui eakamatel avalduvad ebasoodsad tulemused märgatavalt madalama eGFR-i taseme korral. Need tulemused rõhutavad vanusespetsiifiliste ja individualiseeritud ravistrateegiate tähtsust, arvestades nii neerufunktsiooni kui ka kaasuvate haigustega.

Tuleviku uuringud

Tulevane teadustöö peaks keskenduma registripõhise andmebaasi tugevdamisele ja riiklike MI registrite paremale võrreldavusele, et toetada EuroHearti-sarnaste algatuste kaudu ühtseid kvaliteedistandardeid ja parimate ravimeetodite levikut. Tähtis on edendada personaliseeritud preventsiooni, tuvastades varakult kõrge riskiga patsiendid – eriti nooremad, diabeedi või neerukahjustusega inimesed – ning pakkuda neile intensiivsemat jälgimist ja ravi.

Eestis võiks rakendada SWEDEHEART-SEPHIA eeskujul registripõhist ja esmatasandiga integreeritud järelravi ja sekundaarse preventsiooni süsteemi, mis tagaks järjepideva järelkontrolli, parema ravijärgimuse ja taastusravi kättesaadavuse. Tulevased uuringud peaksid hindama selliste digitaalsete ja tehisintellektil põhinevate lahenduste rakendatavust, kliinilist tõhusust ja kulutõhusust, et toetada tõenduspõhist tervishoiukorraldust ja tugevdada riiklikul tasandil südame-veresoonkonna haiguste ennetamist.

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11. ACKNOWLEDGEMENTS

"Our doubts are traitors, and make us lose the good we oft might win, by fearing to attempt." – William Shakespeare, Measure for Measure.

The line reminds us that self-doubt can be a kind of treachery: it steals outcomes that might have been ours had we simply tried. In research – and in medicine – progress rarely arrives fully formed; it comes from beginning, learning, and beginning again. This thesis was sustained by those I thank below, who helped turn hesitation into deliberate action.

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