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Assessing Cardiovascular Risk Prediction: From Conventional Scores to Biomarker-Guided Machine Learning

DOCTORAL DISSERTATION

Medical and Health Sciences,
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The dissertation was prepared between 2021 and 2025 at the Clinic of Heart and Vascular Diseases of Vilnius University, Lithuania.

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Petras Navickas

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ABBREVIATIONS

ACC/AHA — American College of Cardiology/American Heart Association;
ADMA — Asymmetric dimethylarginine;
AHA — American Heart Association;
AI — Artificial intelligence;
AIx — Augmentation index;
ARIC — Atherosclerosis Risk in Communities (study);
ASCVD — Atherosclerotic cardiovascular disease;
ASSIGN — Assessing Cardiovascular Risk using SIGN (Scottish Intercollegiate Guidelines Network);
AUC — Area under the curve;
AUC-ROC — Area under the receiver operating characteristic curve;
AusCVDRisk — Australian cardiovascular disease risk score;
BNP — B-type natriuretic peptide;
BMI — Body mass index;
cIMT — Carotid intima–media thickness;
cfDNA — Cell-free DNA;
cfPWV — Carotid–femoral pulse wave velocity;
CHD — Coronary heart disease;
CRP — C-reactive protein;
CV — Cardiovascular;
CVD — Cardiovascular disease;
DBP — Diastolic blood pressure;
DCA — Decision curve analysis;
DDAH — Dimethylarginine dimethylaminohydrolase;
EBM — Explainable Boosting Machine;
ECM — Extracellular matrix;
ED — Endothelial dysfunction;
EHR — Electronic health record(s);
ESC — European Society of Cardiology;
ET-1 — Endothelin-1;
EVA — Early vascular ageing;
eGFR — Estimated glomerular filtration rate;
eNOS — Endothelial nitric oxide synthase;
ePWV — Estimated pulse wave velocity;
FRS-HCHD — Framingham Risk Score for hard coronary heart disease;
GBD — Global Burden of Disease;
GBM — Gradient boosting machine;
GDF-15 — Growth differentiation factor-15;

HDL — High-density lipoprotein cholesterol;
ICAM-1 — Intercellular adhesion molecule-1;
IHD — Ischaemic heart disease;
IL-1 — Interleukin-1;
IL-6 — Interleukin-6;
JUPITER — Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin;
L1/L2 — L1/L2 (lasso/ridge) regularization;
LDL — Low-density lipoprotein cholesterol;
Lp(a) — Lipoprotein(a);
MESA — Multi-Ethnic Study of Atherosclerosis;
MI — Myocardial infarction;
ML — Machine learning;
MMPs — Matrix metalloproteinases;
NB — Net benefit;
NCEP — National Cholesterol Education Program;
NICE — National Institute for Health and Care Excellence;
NO — Nitric oxide;
NPV — Negative predictive value;
NT-proBNP — N-terminal pro–B-type natriuretic peptide;
PCE — Pooled Cohort Equations;
PPV — Positive predictive value;
PREVENT — Predicting Risk of cardiovascular disease EVENTs (equations);
PWV — Pulse wave velocity;
QRISK3 — QRISK3 cardiovascular risk algorithm (United Kingdom);
RF — Random forest;
ROC — Receiver operating characteristic;
ROS — Reactive oxygen species;
RPM — Risk prediction model;
RRS — Reynolds Risk Score;
SASP — Senescence-associated secretory phenotype;
SBP — Systolic blood pressure;
SCORE — Systematic Coronary Risk Evaluation;
SCORE2 — Systematic Coronary Risk Evaluation 2;
SD — Standard deviation;
SIGN — Scottish Intercollegiate Guidelines Network;
SVM — Support vector machine;
TC — Total cholesterol;
TG — Triglycerides;
UK — United Kingdom;

VCAM-1 — Vascular cell adhesion molecule-1;
hsCRP — High-sensitivity C-reactive protein.

1. INTRODUCTION

1.1 Relevance of the Research Issue

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, imposing a tremendous health burden [1]. Despite advances in prevention and treatment, global CVD deaths have risen from about 12 million in 1990 to 18.6 million in 2019, driven mainly by ischaemic heart disease and stroke [1]. This burden is especially high in Eastern Europe; in Lithuania, CVD accounts for more than half of all deaths – the highest proportion in the European Union [2]. These statistics underscore the urgent need for effective cardiovascular risk assessment and prevention strategies.

Over the past decades, numerous risk prediction models have been developed to identify high-risk individuals for timely preventive interventions. One of the earliest and best-known tools, the Framingham Risk Score, was derived from the long-term Framingham Heart Study to estimate 10-year risk of coronary heart disease based on age, sex, blood pressure, cholesterol, and smoking. Subsequent models built on larger and more diverse cohorts and incorporated additional factors. For example, the Pooled Cohort Equations (PCE) introduced in 2013 broadened the U.S. risk paradigm by including race-specific equations and factors like diabetes [3]. The Reynolds Risk Score (RRS) pioneered the inclusion of biomarkers by adding high-sensitivity C-reactive protein (hsCRP) and family history to traditional risk factors [4], improving risk prediction in women compared to Framingham [5]. Another United States model, from the Multi-Ethnic Study of Atherosclerosis (MESA), includes optional subclinical atherosclerosis measures (e.g., coronary calcium) to enhance discrimination across diverse populations [6]. Most recently, the Predicting Risk of cardiovascular disease EVENTs (equations) (PREVENT) equations (2023) were derived from contemporary cohorts to update 10-year CVD risk estimates, representing the latest generation of risk scores based on modern epidemiology [7].

In parallel, risk scores tailored to other populations have emerged. In Europe, the Systematic Coronary Risk Evaluation (SCORE) system introduced in 2003 focused on 10-year fatal CVD risk, and it was updated as Systematic Coronary Risk Evaluation 2 (SCORE2) in 2021 to include non-fatal events. SCORE2 is now recommended in European guidelines (and used in Lithuania) for primary prevention [8]. Similarly, the United Kingdom's QRISK3 (2017) was developed using nationwide primary care data and incorporates numerous comorbidities and social determinants [9]. Scotland's Assessing Cardiovascular Risk using SIGN (Scottish Intercollegiate

Guidelines Network) (ASSIGN) score added a deprivation index to improve calibration for its population [10], while the Australian CVD Risk Calculator (AusCVDRisk) recalibrated a New Zealand–derived equation to Australian data [11]. Despite differences in design, these tools share a reliance on core risk factors and serve as foundational aids in preventive cardiology.

However, conventional risk scores have important limitations, especially when applied outside their original cohorts. Multiple studies have documented miscalibration – systematic over- or underestimation of risk – and reduced accuracy of these models in external populations [12]. For example, Framingham-based scores tend to overestimate risk by 30–50 % in European cohorts, whereas the original SCORE underestimated risk in certain high-incidence countries, prompting regional recalibrations. The U.S. PCE also shows variable performance across ethnic groups [13,14]. Consequently, an individual's risk category can vary widely between models. In a Lithuanian cohort, using SCORE2 (calibrated for very-high-risk Europe) labelled a majority of middle-aged adults as high-risk – far more than other models – indicating likely overestimation. One analysis found that only ~4 % of people would qualify for statin therapy under European Society of Cardiology (ESC)/SCORE2 criteria versus roughly 20–30 % under American or United Kingdom guidelines [15]. Such variability in risk estimates – and in resulting treatment decisions – underscores the need to improve risk stratification, as current scores may miss truly high-risk individuals while falsely flagging others.

These shortcomings have spurred interest in enhancing risk prediction with emerging biomarkers that reflect key disease pathways. Biomarkers of inflammation, endothelial dysfunction, and cardiac injury can capture "hidden" risk not captured by traditional risk factors. For instance, prospective cohorts have shown that people with elevated inflammatory markers (e.g., hsCRP or interleukin-6) are at higher risk of CVD events even when low-density lipoprotein (LDL) cholesterol is normal [16]. Accordingly, adding hsCRP to risk assessment – as done in the RRS – improved identification of at-risk patients (notably reclassifying many women who appeared low-risk on conventional scoring) [5]. Clinically, this residual risk was illustrated by the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial: statin therapy in apparently healthy individuals with high hsCRP reduced major CVD events by 44 % [17]. Beyond inflammation, markers of cardiac strain or injury (e.g., N-terminal pro–BNP and high-sensitivity troponin T (NT-proBNP)) provide independent prognostic value: even in asymptomatic adults, elevated NT-proBNP or troponin levels predict higher rates of heart failure and cardiovascular death

over time [18]. Furthermore, using multiple biomarkers together can improve risk stratification – a panel of hsCRP, troponin, NT-proBNP, and cystatin C significantly boosted risk discrimination and reclassification beyond traditional factors [19].

Markers of vascular ageing and subclinical atherosclerosis are likewise promising. Arterial stiffness, often measured by carotid-femoral pulse wave velocity (PWV), reflects cumulative arterial damage. A higher-than-expected PWV indicates advanced vascular ageing and correlates with elevated CVD risk, even if the standard risk factor profile appears favourable [20]. Incorporating PWV into risk models has shown improvement: adding PWV to traditional risk factors reclassified roughly 15–20 % of intermediate-risk patients to higher risk categories [20]. Another emerging marker is lipoprotein(a) (Lp(a)), a genetically determined LDL-like particle that independently elevates atherosclerotic risk. Lp(a) levels above ~105 nmol/L or 50 mg/dL are now considered a risk-enhancing factor in prevention guidelines [21]. By integrating biomarkers reflecting inflammation, vascular health, and genetic predisposition, there is potential to more precisely stratify individuals who might otherwise be under- or over-treated by conventional algorithms.

Another avenue for improvement is the application of artificial intelligence (AI) and machine learning (ML) techniques. Modern ML algorithms can analyse far more predictors than traditional risk equations and can model complex, non-linear interactions among variables [22]. This capability is especially useful for integrating multiple biomarkers and clinical parameters to produce individualised risk estimates. ML models can also be retrained on local data, potentially improving calibration for specific populations. Early studies suggest that ML-based models achieve comparable – and sometimes better – predictive performance than conventional scores. An artificial neural network, for example, slightly outperformed the American College of Cardiology/American Heart Association (ACC/AHA) PCE in an external validation (C-statistic ~0.75 vs ~0.74) [23]; similarly, a meta-analysis found that ML algorithms attained a marginally higher average C-index (~0.77) than standard risk scores (~0.75) [24]. Notably, machine learning excels at leveraging high-dimensional data: in one study, integrating an extensive lipidomic profile (153 lipid species) into an ML model improved the AUC from ~0.55 (Framingham-based model) to ~0.66 [25]. These examples illustrate the potential of data-driven approaches to uncover subtle risk predictors and improve individual risk stratification beyond what traditional models can offer.

In summary, the heavy CVD burden and the limitations of current risk scoring methods underscore the need for more accurate and personalised risk prediction. Enhancing traditional risk models with biomarker data and leveraging machine learning for multiparametric analysis are promising strategies to meet this need. This thesis is premised on the idea that integrating vascular biomarkers with a machine learning (ML)-based model will improve cardiovascular risk assessment and better capture individual vascular ageing compared to conventional risk tools.

1.2 The Hypothesis of the Research

It is hypothesised that integrating vascular ageing biomarkers with advanced machine-learning algorithms will yield more accurate cardiovascular risk prediction than conventional risk assessment models.

1.3 The Objectives of the Research

1. To perform a head-to-head comparative analysis of widely used cardiovascular risk prediction models, examining their risk stratification of patients, statin therapy eligibility implications, and overall prognostic performance in the study cohort.
2. To investigate key vascular biomarkers associated with vascular ageing and cardiometabolic risk – evaluating the feasibility and potential benefit of integrating these biomarkers into risk prediction algorithms.
3. To develop and evaluate a personalised, multiparametric cardiovascular risk prediction model using machine-learning techniques, integrating conventional risk factors with selected biomarkers, and to compare its performance against that of traditional risk scores.

1.4 The Scientific Novelty of the Research

- This dissertation presents the first direct evaluation of nine widely used risk scoring tools (including the U.S. Pooled Cohort Equations, European SCORE2, UK QRISK3, the new AHA PREVENT model, the Reynolds Risk Score, etc.) on the same population. Assessing all these models side by side in a local cohort provides unique insights into their relative performance and applicability in Lithuania.
- The study is among the first to externally evaluate recently introduced risk prediction models—most notably the PREVENT equations (released in 2023)—alongside established scores. Incorporating such new calculators (which had not yet been widely validated outside their original

development datasets) adds a cutting-edge aspect to the analysis and addresses a gap in understanding how these emerging tools perform in practice.

- Beyond comparing overall outputs, this research introduces new methods to quantify how closely different risk models agree on patient risk categorisation. Pairwise agreement between models was measured using Cohen's kappa statistic, and a hierarchical clustering analysis was applied to group models with similar classification patterns. This multifaceted approach to agreement is novel in the context of cardiovascular risk scores, offering deeper insight into which calculators tend to classify patients similarly or divergently.
- The dissertation evaluates each risk model's prognostic performance separately for distinct cardiovascular endpoints (e.g., composite cardiovascular events, myocardial infarction, stroke, etc.), rather than taking all outcomes together. By conducting discrimination and calibration analyses for specific outcomes, the study identifies that no single model is uniformly superior across all endpoints – a novel finding that underscores the importance of matching risk tools to the outcome of interest. This granular benchmarking provides a more nuanced understanding of each model's strengths and limitations for different types of events.
- A key original contribution is the creation and evaluation of a personalised cardiovascular risk prediction model using machine-learning techniques. This novel model combines traditional risk factors with markers of vascular ageing (such as carotid-femoral pulse wave velocity and other relevant biomarkers) to improve risk stratification. The thesis demonstrates that incorporating these vascular biomarkers into an ML-based algorithm can enhance risk prediction, better capturing individual vascular health status, and it compares this model's performance against conventional risk scores to highlight its potential benefits.
- The research thoroughly examines how well-established risk scores are calibrated in the Lithuanian population. It reveals that many widely used models (for example, SCORE2) are miscalibrated when applied to this cohort – typically overestimating absolute risk levels. This is a novel, region-specific insight indicating the need for local recalibration or adjustment of these tools. By evaluating calibration and accuracy in a previously unstudied population, the study adds methodological value and ensures the findings are directly relevant to local clinical practice.
- The comparative findings carry important public health and clinical implications. The thesis shows that the choice of risk model can lead to

materially different treatment decisions – for instance, the proportion of individuals deemed eligible for statin therapy varies greatly between algorithms due to differing risk thresholds and estimations. By quantifying these discrepancies, the research highlights potential inconsistencies in guideline-driven care and provides evidence to inform future guideline adaptations.

1.5 Defence Statements of the Doctoral Thesis

1. There is significant heterogeneity among cardiovascular risk prediction models in classifying patients' risk and determining statin eligibility, leading to materially divergent treatment recommendations.
2. The predictive performance (discrimination and clinical utility) of conventional cardiovascular risk scores differs across endpoints, with no single model uniformly superior for all outcomes.
3. When applied to a Lithuanian primary-prevention cohort, conventional risk models are miscalibrated—typically overestimating absolute risk—indicating the need for local recalibration or context-specific adaptation.
4. Integrating vascular ageing biomarkers—particularly carotid-femoral pulse wave velocity—into risk assessment provides incremental prognostic value beyond traditional risk factors.
5. Machine-learning prediction models that combine conventional risk factors with selected biomarkers achieve performance comparable to established scores.

2. LITERATURE REVIEW

2.1 Global Burden of Cardiovascular Disease

Although multifaceted prevention strategies and advancements in treatment have been implemented, adverse health behaviours and environmental influences have continued to offset these benefits, leading to a sustained increase in overall cardiovascular disease mortality over the past three decades [1]. The global surge in metabolic disorders [26-28], alongside upstream social determinants of health, shares common pathogenic mechanisms that accelerate CVD progression, yielding substantial social and economic consequences worldwide [29,30]. Furthermore, the heterogeneity and complexity of CVDs—shaped by cultural, genetic [31], socioeconomic [32], and region-specific determinants—complicate the formulation of a universal strategy for mitigating the global CVD burden.

Historical analyses from previous Global Burden of Disease (GBD) studies indicate that global CVD mortality has escalated from 12.1 million in 1990 to 18.6 million in 2019, predominantly driven by ischaemic heart disease (IHD) and stroke [1]. The predominance of atherosclerotic diseases in today's CVD landscape is likely related to the rapidly ageing global population, with projections suggesting that the number of individuals aged over 60 will double, and those over 80 will triple between 2020 and 2050 [33].

The broader societal and economic repercussions of atherosclerotic CVD include escalating healthcare costs, reduced accessibility to care, diminished quality of life, and increasing non-medical needs. In the United States alone, it is projected that this burden will reach approximately US$509 billion by 2035 [34].

Despite sustained global prevention efforts, the age-standardised prevalence of CVD is expected to remain relatively stable in the upcoming decades, implying limited net improvement. Between 2025 and 2050, age-standardised CVD mortality is projected to decrease by 30.5 %, driven by improved post-diagnosis care. Nevertheless, absolute CVD mortality is forecasted to surge by 73.4 %, highlighting population ageing as a pivotal contributor to the rising cardiovascular burden. IHD and stroke will continue to be the primary drivers of the CVD epidemic, a trend compounded by the deteriorating global patterns of hypertension [35].

2.2 Conventional Cardiovascular Risk Assessment Models

The Framingham Risk Score for Hard Coronary Heart Disease (FRS-HCHD) is one of the earliest risk calculators, derived from the long-term Framingham cohort to estimate 10-year risk of myocardial infarction or coronary death based on age, sex, blood pressure, cholesterol levels, and smoking status [36].

Subsequent American models built on larger and more diverse datasets: for example, the Pooled Cohort Equations (PCE) were introduced in 2013 to predict 10-year risk of atherosclerotic CVD in U.S. adults (age 40–79) by integrating traditional factors (age, sex, systolic blood pressure (SBP), total and high-density lipoprotein cholesterol (HDL) cholesterol, hypertension treatment) along with diabetes status, smoking, and race (with separate equations for White and Black populations) [3].

The Reynolds Risk Score (RRS) pioneered the inclusion of novel biomarkers by incorporating high-sensitivity C-reactive protein and family history of premature heart disease into a 10-year risk model (initially in women, later in men), alongside the conventional risk factors [4].

The Multi-Ethnic Study of Atherosclerosis (MESA) risk score, derived from the multi-ethnic MESA cohort in the U.S., estimates 10-year CVD risk in adults aged 45–85 and can optionally include a measure of subclinical atherosclerosis (coronary artery calcium score) to improve risk discrimination across diverse racial groups [6].

Most recently, the AHA's Predicting Risk of cardiovascular disease EVENTs (PREVENT) equations (2023) were developed using data from over 6 million U.S. patients to provide updated 10-year (and 30-year) risk estimates, representing the latest generation model based on contemporary cohorts and incorporating geographic and metabolic health factors [7,37].

Several risk scores have been developed to cater to non-U.S. populations and healthcare contexts. Systematic Coronary Risk Evaluation 2 (SCORE2), introduced in 2021 as an update to the European SCORE system, estimates 10-year combined fatal and non-fatal CVD risk in adults 40–69 years old with no prior CVD, using core predictors (age, sex, SBP, non-HDL cholesterol, and smoking status) and calibrated to different regional risk profiles across Europe [8].

In the United Kingdom, the QRISK3 algorithm (2017) builds upon earlier QRISK versions to estimate 10-year CVD risk in adults aged 25–84, incorporating not only traditional risk factors but also additional variables (e.g., chronic inflammatory diseases, severe mental illness, corticosteroid use, and other comorbidities) to better reflect risk in contemporary UK primary care populations [9].

Scotland's Assessing cardiovascular risk using Scottish Intercollegiate Guidelines Network (SIGN) (ASSIGN) score similarly extends the traditional risk factor paradigm by including a measure of social deprivation (Scottish Index of Multiple Deprivation) and family history, which improved its calibration for the Scottish population and led to its adoption in national guidelines [10].

The Australian CVD Risk calculator (AusCVDRisk) provides a 5-year risk estimate for Australians aged 30–79 without established CVD, adapting a New Zealand–derived equation (the PREDICT model) that has been recalibrated to Australian epidemiological data and guidelines [11]. Each of these models emerged as an important regional tool for guiding preventive interventions in its respective population.

Despite their varied origins, these risk models share a reliance on a core set of predictors. Age and sex are universal inputs, and nearly all include blood pressure (typically SBP), blood lipid measurements (either total cholesterol with HDL or non-HDL cholesterol), and smoking status. Many also account for the presence of diabetes or hypertension treatment, and some incorporate family history or other risk modifiers (such as high-sensitivity C-reactive protein (CRP) in RRS, rheumatoid arthritis or chronic kidney disease in QRISK3, or socio-economic deprivation in ASSIGN) to refine risk estimates.

A more detailed descriptions of each risk model, including their equations and risk category definitions, are provided in the Methods section of this thesis.

2.3 Emerging Role of Vascular Biomarkers

2.3.1 Pathophysiological Basis of Vascular Ageing

Vascular ageing is characterised by structural and functional changes in the arterial wall, driven by intertwined mechanisms of oxidative stress, chronic inflammation, and extracellular matrix (ECM) remodelling. With age, large arteries develop endothelial dysfunction and reduced compliance alongside increased stiffness [38]. These changes reflect a shift in ECM composition: collagen fibres accumulate (being far stiffer than elastin) while elastin fibres are lost or fragmented [38]. Remaining elastin may become calcified [39] and collagen is increasingly cross-linked (e.g., by advanced glycation end-products), compounding arterial rigidity [40]. Aged arteries also show upregulation of matrix metalloproteinases (MMPs) that degrade structural proteins, and indeed enhanced MMP-2/7/9/14 activity is demonstrable in aged vessels [41]. Correspondingly, vascular smooth muscle cells exhibit a

senescent phenotype with reduced proliferation and a secretory profile that includes pro-inflammatory cytokines and MMPs, further promoting ECM remodelling and stiffness [42].

Oxidative stress and inflammation create a vicious cycle in vascular ageing. Excess reactive oxygen species (ROS) from mitochondria, NADPH oxidases, and eNOS uncoupling cause direct cellular damage (e.g., oxidative DNA lesions) and activate redox-sensitive pathways (like NF-κB), inducing inflammatory cytokines [42,43]. In parallel, low-grade chronic inflammation is present even in healthy older adults [44]. Inflammatory mediators (IL-1, IL-6, TNF-α, etc.) promote endothelial activation and recruit immune cells into the vessel wall, sustaining a state of ongoing vascular injury. Indeed, chronic inflammation coupled with increased oxidative stress negatively impacts arterial proteins (e.g., oxidising elastin, cross-linking collagen) and impairs endothelial vasodilatory function [45,46]. Endothelial cells in aged vessels produce less nitric oxide (NO) due to both reduced NOS activity and asymmetric dimethylarginine (ADMA)-mediated inhibition, resulting in blunted vasodilation [47]. The cumulative effect of these processes is arterial stiffening, higher pulse pressures, and heightened susceptibility to hypertension and atherosclerosis in the elderly. Notably, senescent endothelial cells and smooth muscle cells develop a pro-inflammatory secretory phenotype (SASP) that amplifies tissue inflammation, while DNA repair mechanisms (e.g., OGG1-dependent repair of 8-oxoguanine lesions) become less effective, linking genomic damage to ECM changes and vascular ageing [48]. In sum, oxidative stress, inflammation, and matrix remodelling act in concert to drive vascular ageing, creating an environment of endothelial dysfunction and arterial stiffness that predisposes to cardiovascular pathology.

2.3.2 Key Circulating Biomarkers

Circulating biomarkers reflecting these pathological processes have emerged as valuable indicators of vascular health and disease risk. C-reactive protein (CRP) and Interleukin-6 (IL-6) are prototypical inflammatory markers. IL-6 is a pro-inflammatory cytokine released by leukocytes and senescent cells, which stimulates hepatic CRP production. Both IL-6 and CRP circulate at low levels in healthy individuals but rise during systemic inflammation; they are considered markers of systemic vascular inflammation that herald atherothrombosis [49]. Mechanistically, IL-6 contributes to atherosclerosis by promoting leukocyte recruitment, and CRP is not merely a bystander; CRP can bind endothelial cells and oxidised LDL, activating complement and endothelial cells (though its direct causative role remains

debated). Clinically, high-sensitivity CRP is widely used to gauge inflammation, and IL-6 has similarly been linked to endothelial activation and plaque destabilisation [50]. Elevated levels of these markers signify an active inflammatory setting in the vasculature, and they often correlate with worse endothelial function and incipient plaque formation [51].

Another key biomarker is N-terminal pro–B-type natriuretic peptide (NT-proBNP), which reflects myocardial stress. NT-proBNP is the inert fragment cleaved from proBNP upon release of active BNP hormone from cardiomyocytes under stretch. The primary stimulus for BNP/NT-proBNP secretion is increased wall tension (e.g., pressure or volume overload of the ventricles) [52]. Thus, NT-proBNP rises in conditions of ventricular strain such as heart failure, but even modest elevations can indicate subclinical myocardial dysfunction or high cardiac preload. Mechanistically, BNP acts as a vasodilator and diuretic hormone counter-regulating volume load, whereas NT-proBNP serves as a stable marker of its release. Source-specific production occurs mainly in ventricles when myocardial fibres are stretched or hypoxic [52]. An elevated NT-proBNP in an asymptomatic individual may signal occult ventricular impairment or high filling pressures; accordingly, it has strong prognostic significance for incident heart failure, atrial fibrillation, and ischemic events in population studies.

The matrix metalloproteinases (MMPs) are another class of biomarkers relevant to vascular integrity. MMP-2 and MMP-9, in particular, are secreted by activated macrophages, neutrophils, and vascular cells and are responsible for degrading collagen, elastin, and other matrix components. In the context of atherosclerosis and vascular remodelling, excessive MMP activity can thin fibrous caps of plaques and weaken arterial walls [53]. High circulating MMP-9 has been linked to plaque instability and post-myocardial infarction (MI) remodelling; for example, MMP-9 levels correlate with myocardial infarct size and adverse left ventricular remodelling [53]. Moreover, MMP-9 has been associated with both cardiovascular and cerebrovascular death, as well as heart failure in cohort studies [53]. This suggests that elevated MMP-9 in the bloodstream reflects ongoing inflammatory tissue destruction in vessels or the heart, signifying worse outcomes. MMPs are thus mechanistically involved in ECM turnover and can serve as blood-accessible indicators of vascular wall remodelling and inflammation.

Emerging biomarkers of cellular injury, such as circulating cell-free DNA (cfDNA), have also garnered attention. cfDNA consists of fragments of DNA released into the plasma from dying cells (via apoptosis or necrosis) or actively secreted by immune cells (e.g., neutrophil extracellular traps). In cardiovascular contexts, elevated cfDNA levels are observed in acute events

like myocardial infarction and in chronic conditions like hypertension [54-56]. Mechanistically, cfDNA (especially if rich in unmethylated CpG motifs or mitochondrial DNA) acts as a danger-associated molecular pattern, activating toll-like receptors and inflammasomes – thereby directly driving inflammation [57]. Studies indicate that elevated cfDNA may be a marker of ongoing vascular endothelial injury and inflammation [54]. For instance, higher cfDNA levels have been associated with worse arterial elasticity and with increased CRP, IL-6, and TNF-α in patients, linking it to both stiffness and systemic inflammation [56]. In acute coronary syndromes, cfDNA correlates with troponin and CK release, underscoring that it reflects the magnitude of cellular necrosis [58-60]. Thus, cfDNA serves as a novel biomarker integrating information about cellular damage and pro-inflammatory signalling in the vasculature.

In summary, a spectrum of circulating biomarkers can inform on different aspects of vascular pathology: CRP and IL-6 quantify systemic and vascular inflammation, NT-proBNP signals hemodynamic myocardial stress, matrix metalloproteinases (MMPs) reflect active matrix degradation and vascular remodelling, and cfDNA denotes cellular injury and immunogenic debris. Each has distinct sources and mechanistic relevance – the liver for CRP (driven by IL-6), the heart for NT-proBNP (ventricular myocytes under strain), activated leukocytes or vascular cells for IL-6 and MMPs (in response to inflammatory stimuli), and dying cells throughout the cardiovascular system for cfDNA. These biomarkers complement one another in painting a picture of vascular health and are increasingly being studied for their utility in risk assessment and management.

2.3.3 Biomarkers of Endothelial Dysfunction and Arterial Stiffness

Because endothelial dysfunction (ED) and arterial stiffness are hallmarks of vascular ageing and atherosclerosis, researchers have identified specific biomarkers and measurements to quantify these processes. One important biomarker of ED is Endothelin-1 (ET-1). ET-1 is a potent vasoconstrictive peptide produced by endothelial cells, which also promotes smooth muscle proliferation and fibrosis [61]. In healthy endothelium, ET-1 is balanced by nitric oxide; however, dysfunctional endothelium often overproduces ET-1, tipping the scale toward vasoconstriction and hypertrophy of the vascular wall. Circulating ET-1 (or its precursor “big ET-1”) levels tend to rise with ageing, hypertension, and endothelial dysfunction [61]. Elevated ET-1 has been associated with signs of cardiac remodelling (e.g., higher left ventricular mass) and is being investigated as a risk marker: studies have shown ET-1 to

be a prognostic indicator in coronary artery disease, myocardial infarction, and heart failure, and even linked higher ET-1 levels to mortality in general populations [61]. These findings reinforce the mechanistic role of ET-1 in endothelial dysfunction – higher ET-1 denotes an endothelium that is contributing to vasospasm and vascular hypertrophy, often portending worse cardiovascular outcomes.

Conversely, a reduction in endothelial vasodilator function is captured by biomarkers like asymmetric dimethylarginine (ADMA). ADMA is an endogenous inhibitor of endothelial nitric oxide synthase (eNOS). When ADMA accumulates, it competitively blocks L-arginine binding to eNOS, thereby lowering NO production and impairing endothelium-dependent relaxation [47]. Elevated ADMA levels are in fact a biochemical signature of endothelial dysfunction; they have been observed in individuals with risk factors such as hypercholesterolemia, hypertension, diabetes, and chronic kidney disease, which may be due to reduced ADMA metabolism by dimethylarginine dimethylaminohydrolase (DDAH) or decreased renal clearance [62-65]. Clinically, high plasma ADMA has strong prognostic significance. For example, in prospective studies of patients with coronary artery disease or risk factors, those with high ADMA levels had a significantly greater risk of adverse cardiovascular events and mortality – even after adjusting for traditional risk factors and other biomarkers [66]. One cohort of men with acute coronary syndromes showed that the top tertile of ADMA was associated with ~2-fold higher risk of death or MI at 2 years compared to lower tertiles [66]. These data underscore ADMA's dual role as a mediator of endothelial dysfunction and a predictor of its clinical consequences.

Endothelial activation in inflammation is marked by increased expression of cell adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) on the endothelial surface. These adhesion molecules mediate the tethering and transmigration of leukocytes into the intima, a key early step in atherogenesis. Soluble forms of VCAM-1 and ICAM-1 shed into the circulation can be measured as indices of endothelial activation. Epidemiological studies have demonstrated that soluble ICAM-1 in particular correlates with incident cardiovascular events. In the PRIME study (a prospective cohort of ~10,000 healthy middle-aged men), those in the highest third of baseline sICAM-1 had about twice the risk of future coronary events (myocardial infarction or coronary death) compared to those in the lowest third, even after adjusting for lipids, blood pressure, and other risk factors [67]. This association remained significant when controlling for CRP, suggesting ICAM-1 adds independent prognostic information. Interestingly, the same study found soluble VCAM-1 was not significantly

associated with coronary outcomes, indicating that not all adhesion molecules have equal predictive value [67]. Nonetheless, elevated ICAM-1 (and to some extent E-selectin, another adhesion molecule) is viewed as a marker of endothelial inflammation and has been linked to the presence of atherosclerosis on imaging [68]. High levels of these molecules reflect an "activated" endothelium that is interacting with immune cells, consistent with active vascular inflammation and dysfunction.

Beyond blood biomarkers, arterial stiffness is often assessed by physiological measurements, the gold standard being carotid-femoral pulse wave velocity (PWV). PWV directly gauges the speed of the pressure wave travelling along arteries – stiffer arteries transmit waves faster. PWV increases with age and with processes like elastin fragmentation and collagen accumulation. It is thus considered a functional biomarker of vascular ageing [69]. Crucially, PWV has been shown to predict cardiovascular outcomes: numerous longitudinal studies and meta-analyses have documented that individuals with higher aortic PWV suffer higher rates of future cardiovascular events and mortality compared to those with more compliant arteries [70-72]. Furthermore, estimated PWV (ePWV), derived from age and blood pressure, has been shown to predict all-cause and cardiovascular mortality independently of traditional risk factors. In a large-scale study, each 1 m/s increase in ePWV was associated with a 44 % to 67 % increase in all-cause mortality and a 51 % to 73 % increase in cardiovascular mortality [73]. Other techniques, such as augmentation index or brachial flow-mediated dilation, are also used in research to evaluate endothelial function and arterial stiffness. Broadly, a higher PWV or impaired flow-mediated dilation indicates poor endothelial health and stiff arteries, which have been tied to adverse clinical endpoints [70].

In summary, multiple biomarkers can gauge endothelial health: ET-1 and ADMA capture the balance of vasoconstrictors vs. vasodilators (and hence ED), ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) reflect endothelial inflammatory activation, and PWV quantifies the macroscopic result of chronic endothelial and matrix changes (arterial stiffening). These markers not only elucidate mechanistic derangements – excessive vasoconstriction, insufficient NO, leukocyte adhesion, and loss of elasticity – but also have demonstrated associations with clinical cardiovascular outcomes.

2.3.4 Diagnostic and Prognostic Value in CVD Risk Stratification

Clinically, vascular biomarkers are being investigated and utilised to improve cardiovascular risk stratification beyond traditional risk factor models. In primary prevention, current risk scores (e.g., PREVENT or SCORE2) rely on demographics and classic factors (blood pressure, cholesterol, smoking, etc.), but the addition of certain biomarkers can refine risk estimates and identify high-risk individuals who would otherwise be missed. Inflammatory biomarkers have shown particular promise in this regard. For instance, large prospective studies have established that people with elevated hsCRP or IL-6 are at higher risk for adverse cardiovascular events (myocardial infarction, stroke, etc.), even if their LDL cholesterol and other risk factors are "normal." In the Women's Health Study and others, CRP and IL-6 levels were independently associated with future cardiovascular risk [16]. In fact, the Reynolds Risk Score was developed to incorporate hsCRP (and family history) into risk calculation for women, and it demonstrated improved calibration and risk prediction over Framingham in validation cohorts. As a proof-of-concept, the JUPITER trial selected individuals with low LDL (<3.4 mmol/L) but high hsCRP (≥2 mg/L) and showed that treating these ostensibly lower-risk patients with a statin led to a significant 44 % reduction in heart attacks, strokes, and cardiovascular death [17]. This outcome emphasises that hsCRP testing can identify a subset of patients with "hidden" inflammatory risk who benefit from preventive therapy beyond what traditional risk screening would indicate. Likewise, the CANTOS trial demonstrated that targeting inflammation (with an IL-1β inhibitor) in patients with prior MI and elevated CRP reduced recurrent events, with the greatest benefit seen in those who achieved the largest reductions in IL-6 and CRP [74]. Such findings bolster the case for inflammatory biomarkers as tools to stratify patients by residual inflammatory risk and guide therapy.

Cardiac-derived biomarkers also enhance risk stratification. NT-proBNP, for example, has strong prognostic value even in general populations without heart failure. Analyses from Atherosclerosis Risk In Communities (ARIC) study show that elevated NT-proBNP is an independent predictor of all-cause and cardiovascular mortality across all blood pressure categories [18]. Individuals with higher NT-proBNP (even within "normal" range) are more likely to develop heart failure, atrial fibrillation, or ischemic events over time than those with low levels [75-77]. This is because NT-proBNP may detect subclinical ventricular dysfunction or high wall stress that is not apparent from outward risk factors. Similarly, high-sensitivity cardiac troponins, though traditionally used for acute MI diagnosis, have emerged as chronic risk

predictors: a detectable hs-troponin T in an apparently healthy person signifies a higher risk of cardiac events and mortality (likely reflecting silent microinjury or occult CAD) [78]. When multiple biomarkers are used together, they can markedly improve risk discrimination. For example, in one study, a multi-marker panel of hs-troponin, NT-proBNP, CRP, and cystatin C significantly improved the prediction of death and major cardiac events compared to traditional risk factors alone [19]. The combination yielded a greater c-statistic and better reclassification of patients into correct risk categories. In patients with diabetes or renal disease, adding such biomarkers can help stratify those with much higher cardiovascular risk than would be expected from risk equations.

Biomarkers of endothelial dysfunction and arterial health also have diagnostic/prognostic utility for subclinical disease. A prime example is microalbuminuria – it strongly predicts cardiovascular events in diabetics and hypertensives, reflecting systemic endothelial dysfunction (though not a circulating marker per se) [79]. Another example, as mentioned, is arterial stiffness: measuring PWV or augmentation index can uncover early vascular ageing. An individual with an unexpectedly high PWV for their age likely has advanced arterial injury (due to cumulative risk factor exposure or genetic predisposition), flagging them for aggressive risk factor control. For instance, adding PWV to standard risk factors yielded a net reclassification improvement of 15 % for coronary heart disease events and 27 % for CVD death in intermediate-risk individuals [20]. Soluble ICAM-1 and other adhesion molecules, while not used routinely in practice, have been shown to predict the presence of coronary atherosclerosis and future coronary events independent of standard risk factors [67]. They may help identify individuals with active vascular inflammation who might benefit from early intervention.

Overall, the integration of vascular biomarkers into clinical practice is improving our ability to detect subclinical cardiovascular disease and more precisely estimate risk. These biomarkers can unmask pathophysiological processes (inflammation, myocardial strain, endothelial injury) that are not captured by traditional risk scoring. In doing so, they allow for patient stratification beyond traditional models, such as identifying which "intermediate-risk" patients are actually high-risk and should be treated more aggressively. For instance, measuring hsCRP can refine risk in a middle-aged patient with borderline risk factor levels, or checking NT-proBNP in an older hypertensive patient might reveal high heart failure risk warranting closer follow-up. Outcome-based studies consistently demonstrate that incorporating biomarkers like CRP, NT-proBNP, or troponin improves risk prediction metrics (C-index, net reclassification) over models based on

demographics and risk factors alone [18,80]. Importantly, such improved risk stratification has clinical ramifications: it enables personalised preventive strategies (e.g., deciding on statin use, tighter blood pressure targets, etc.) and motivates searching for latent disease (such as silent left ventricular dysfunction or inflammatory disorders). As always, clinical judgment is needed – for example, an elevated biomarker should prompt consideration of remediable causes (poorly controlled risk factors, occult disease) – but the trend in cardiovascular medicine is toward leveraging these biomarkers to tailor risk management to the individual, moving beyond the one-size-fits-all approach.

2.3.5 Potential Integration into Prediction Algorithms

With the advent of machine learning and big data, there is a growing interest in integrating vascular biomarkers into advanced risk prediction algorithms to enable personalised cardiovascular risk assessment. Traditional risk calculators use a handful of variables, but artificial intelligence models can incorporate dozens of biomarkers (proteins, metabolites, genetic factors) simultaneously and detect complex, non-linear interactions among them. Recent studies provide proof that such integration can significantly improve predictive accuracy [81]. For example, advanced lipidomic profiling was used to derive a lipid-based risk score that outperformed the Framingham Risk Score in predicting coronary events: by integrating 153 lipid species into an ML model, researchers achieved a notable improvement in AUC (area under the curve) from 0.545 to 0.659 for risk prediction, with robust external validation [25]. This lipidomic risk score captured subtle contributions of triglyceride and phospholipid subclasses that traditional cholesterol measurements miss, thus enhancing risk discrimination. Similarly, proteomics has been leveraged: Hoogeveen et al. showed that adding a panel of protein biomarkers – including growth differentiation factor-15 (GDF-15) and IL-6 – to a clinical model raised the predictive AUC to 0.754 for short-term cardiovascular risk [82]. Notably, GDF-15 and IL-6 reflect inflammatory and metabolic pathways, indicating that ML algorithms identified these as influential features for risk, consistent with our understanding of inflammation's role in CVD. These examples mark a shift from reliance on a few clinical factors to a more comprehensive inclusion of molecular data in risk prediction.

Furthermore, AI-based models can incorporate genetic risk scores alongside classical and biomarker data. Polygenic risk scores, derived from aggregating the small risk contributions of numerous DNA variants, have

shown incremental value in stratifying individuals by lifetime cardiovascular risk. Studies like Lauber et al. demonstrated that integrating a polygenic risk score with biomarker-enhanced models improved the prediction of coronary artery disease beyond either alone [83]. The combined approach can identify, for instance, a person with both high genetic susceptibility and high inflammatory biomarkers as extremely high-risk, meriting aggressive prevention, whereas someone with high genetic risk but low biomarker levels might be at intermediate risk. Machine learning algorithms excel at handling such multilayered data, finding patterns that clinicians cannot easily see. They can also adapt to new data modalities – for example, combining imaging biomarkers (like coronary calcium scores or retinal vessel analytics) with blood biomarkers to further refine risk estimates [84]. A notable 2018 study even showed that an AI could predict cardiovascular risk factors (age, smoking status, blood pressure) just from retinal photographs [85], highlighting the potential of digital biomarkers; these could eventually be merged with circulating biomarkers in an integrated risk model.

Early results of these multimodal AI models are promising. For instance, one study used an ensemble ML approach on a broad panel of inflammatory markers to predict cardiovascular events and found it outperformed traditional regression-based risk scores, especially in certain subgroups (e.g., younger individuals or women, where traditional scores often underperform) [86]. The integration of novel biomarkers underscores the role of AI in bridging the gap between molecular research and clinical application – translating the flood of data from genomics, proteomics, and metabolomics into actionable risk information [87]. This approach aligns with the goals of precision medicine: tailoring risk prediction and prevention strategies to an individual's unique biological profile.

Moving forward, it is anticipated that risk algorithms will increasingly incorporate panels of vascular biomarkers (e.g., inflammatory cytokines, cardiac peptides, adhesion molecules), perhaps updated in real-time through wearable or point-of-care devices, and combine them with genetic and lifestyle data. AI-based platforms could then output a highly individualised risk score and even suggest which component of risk (inflammation, cholesterol, blood pressure, etc.) is most prominent for a given patient, guiding targeted interventions. There are ongoing pilot initiatives to validate such AI models in diverse populations and to ensure they provide incremental value over simpler models before widespread clinical adoption. Challenges remain, including the need for large, well-annotated datasets for model training, the cost-effectiveness of extensive biomarker panels, and the interpretability of complex ML predictions for clinicians. Nevertheless, the trajectory is clear:

integrating vascular biomarkers into AI-driven prediction models holds great potential to improve early cardiovascular risk detection and enable personalised prevention [81]. By harnessing these innovations, healthcare can move toward more proactive and individualised cardiovascular care, where a person's risk is quantified not just by age and risk factors, but by the very molecular and functional signals emanating from their vascular system.

2.4 Concept and Measurement of Vascular Ageing

2.4.1 Definitions and Clinical Relevance

Vascular ageing refers to the progressive deterioration in arterial structure and function that occurs with advancing age, a process that can be accelerated by cardiovascular risk factors or disease [69]. This concept encompasses multifactorial changes in the arterial wall, notably endothelial dysfunction, vascular remodelling, and loss of arterial elasticity, which manifest as increased arterial stiffness and elevated systolic and pulse pressures [88]. In essence, ageing vessels become thicker, stiffer, and less reactive, impairing their ability to cushion pulsatile blood flow and regulate circulation. These structural and functional changes can lead to end-organ damage in the heart, brain, kidneys, and other tissues, underlining why age is one of the strongest risk factors for cardiovascular disease [89].

Importantly, individuals do not all age at the same rate – there is high inter-individual variability in vascular ageing. This has given rise to the concept of "biological" vascular age versus chronological age [89]. For example, some people exhibit early vascular ageing (EVA) – their arteries behave "older" (stiffer, more diseased) than expected for their chronological age – whereas others (so-called "supernormal vascular ageing" phenotypes) retain unusually preserved arterial flexibility even in old age [90]. Such phenotypic extremes highlight that factors like genetics, lifestyle, and chronic conditions can accelerate or decelerate vascular ageing beyond what calendar age alone would predict [90]. From a clinical perspective, this is critical: chronological age alone is a suboptimal surrogate for vascular health, and recognising accelerated vascular ageing can help target individuals for early preventive interventions [89].

In clinical practice, measures of vascular ageing are emerging as valuable markers of cardiovascular risk [69]. Vascular ageing represents the cumulative effect of lifelong exposure to risk factors (e.g., hypertension, hyperlipidaemia, smoking), and its subclinical markers can predict cardiovascular events independently of traditional risk factors [91]. In

asymptomatic individuals – those with no overt cardiovascular disease – evidence of advanced vascular ageing (such as high arterial stiffness or carotid wall thickening) may flag elevated risk of heart attack or stroke before any symptoms occur. Indeed, studies show that these vascular ageing indicators improve risk stratification: they help identify high-risk patients who might otherwise appear low-risk by conventional scoring [91]. For instance, arterial stiffness has been described as a mediating step between risk factors and cardiovascular events, and its assessment captures early target-organ damage that is prognostically important [91]. Ultimately, incorporating vascular ageing assessments could enhance preventive cardiology – guiding lifestyle or pharmacologic therapies to promote healthy vascular ageing (e.g., exercise, diet, antihypertensives), which have been shown to improve arterial function and reduce stiffness [92]. It should be noted that while research into vascular age has advanced, routine clinical evaluation of vascular ageing is not yet standard practice, pending further evidence and the development of convenient assessment tools [69]. Nonetheless, the clinical relevance is clear: vascular age provides a nuanced understanding of cardiovascular risk, complementing chronological age and helping to explain why some "younger" patients suffer cardiovascular events while some "older" individuals remain disease-free.

2.4.2 Surrogate Measures of Vascular Ageing

Because vascular ageing is not directly measurable by a single test, clinicians and researchers rely on surrogate markers that reflect arterial structure and function. Three widely used surrogate measures of vascular ageing are carotid-femoral pulse wave velocity (cfPWV), augmentation index (AIx), and carotid intima-media thickness (cIMT). Each of these provides a window into arterial health – capturing aspects of stiffness, wave reflection, or atherosclerotic burden – and each has been validated as a predictor of cardiovascular events and overall vascular ageing [69].

2.4.2.1 Carotid-Femoral Pulse Wave Velocity: Arterial Stiffness

Pulse wave velocity is the speed at which the arterial pulse propagates through the circulation, and cfPWV (measured along the carotid and femoral arterial pathway) is the reference standard for assessing central arterial stiffness [93]. As arteries stiffen with age or disease, the pulse wave travels faster. To measure cfPWV, synchronised pressure waveforms are recorded at the carotid and femoral arteries (commonly via applanation tonometry or

pressure sensors), and the transit time between the wave fronts is divided by the distance between the measurement sites [94]. The result, typically expressed in meters/second, increases with age and blood pressure – for example, a young, healthy adult might have a PWV of ~6 m/s, whereas an older hypertensive patient might have values exceeding 10 m/s. A higher cfPWV indicates increased aortic stiffness, meaning the aorta is less compliant and cannot dampen pulsatile pressure effectively. Clinically, this has significant implications: cfPWV is a robust independent predictor of cardiovascular outcomes, including heart attacks, strokes, and mortality [70]. A landmark meta-analysis demonstrated that individuals with higher aortic PWV have substantially greater risk of future cardiovascular events; for each 1 m/s increase in PWV, cardiovascular event risk rises by ~14–15 % (after adjusting for age, sex, and risk factors) [70]. These findings have been confirmed across diverse populations (hypertensives, diabetics, renal disease, and general populations alike) [95-98]. Owing to this strong prognostic evidence, cfPWV is often regarded as the single best index of "arterial age" – essentially how old or "stiff" an individual's arteries are relative to normal [99]. It has been recommended by expert consensus as a tool for risk stratification, and while not yet routine in primary care, it is frequently utilised in research and speciality cardiovascular clinics to gauge vascular ageing and the effect of interventions on arterial health.

2.4.2.2 Augmentation Index: Wave Reflections and Arterial Function

Augmentation index is a composite measure derived from the arterial pulse waveform that reflects the degree of wave reflection from the periphery and the timing of that reflection. In healthy, elastic arteries, the pulse wave sent out by the heart returns (as a reflected wave) during diastole, whereas in stiffer arteries the reflected wave arrives earlier (during late systole), boosting central systolic pressure. AIx quantifies this by expressing the augmentation of central pressure (caused by the reflected wave) as a percentage of the central pulse pressure [100]. Put simply, AIx = (ΔP_aug / pulse pressure) × 100 %, where ΔP_aug is the rise in pressure due to the returning wave. Conventionally, AIx is measured non-invasively using applanation tonometry: a pressure sensor is applied over a superficial artery (often the radial artery at the wrist or the carotid artery) to record the waveform, and a generalised transfer function is used to derive the corresponding central aortic pressure wave. The AIx is calculated from the central waveform as the ratio of the late systolic pressure increment (augmented pressure) to the total pulse pressure [101]. Because heart rate strongly influences AIx (faster heart rates

tend to reduce AIx by shortening systole), AIx is often reported normalised to a standard heart rate (e.g., AIx@75 bpm).

Clinically, AIx provides insight into arterial stiffness and peripheral resistance – a higher AIx implies that arteries are stiffer or that wave reflections from the periphery are more pronounced. Elevated AIx has been observed in younger individuals with risk factors (e.g., those with hypercholesterolemia or hypertension tend to have a higher AIx than healthy peers, indicating early vascular ageing [102]. Moreover, AIx has been correlated with the presence and extent of cardiovascular disease. Studies have shown that AIx is higher in patients with coronary artery disease and correlates with the burden of risk factors [103]. Notably, some investigations report that AIx can be an independent predictor of cardiovascular events and mortality in certain populations [104]. For example, in patients with end-stage renal disease or those undergoing coronary angiography, a high aortic AIx was associated with increased risk of adverse outcomes [105,106]. However, the prognostic value of AIx has been less consistent across studies compared to cfPWV; AIx is influenced by multiple factors (heart rate, age, height, etc.), and its predictive power may be weaker in older populations where very stiff arteries cause the augmentation waveform to merge with the primary wave (making AIx measurement challenging). Nonetheless, AIx remains a useful research tool and surrogate of vascular ageing, especially in younger or middle-aged cohorts. It captures an aspect of arterial function (wave reflection dynamics) not provided by PWV alone. In practice, AIx is often measured alongside PWV when performing advanced pulse wave analysis, providing complementary information on central hemodynamics and arterial health. A high AIx in an otherwise asymptomatic patient could signal augmented load on the heart and potentially earlier vascular ageing, requiring risk factor management.

2.4.2.3 Carotid Intima-Media Thickness: Arterial Wall Structure (Subclinical Atherosclerosis)

Carotid intima–media thickness is a structural marker of vascular ageing obtained via B-mode ultrasound of the carotid arteries. It measures the thickness of the intima and media layers of the carotid artery (usually the common carotid, just proximal to the bifurcation). As individuals age – and particularly if they have atherosclerotic risk factors – the carotid intima-media layer gradually thickens due to lipid deposition, fibrosis, and smooth muscle hyperplasia. cIMT is typically reported as the mean or maximum thickness (in millimetres) of the arterial wall. Elevated cIMT is interpreted as an early sign

of atherosclerosis and arterial ageing, even before overt plaque formation. It is a non-invasive, widely used surrogate because ultrasound is safe and relatively inexpensive, and serial cIMT measurements can track the progression or regression of atherosclerosis over time.

Clinically, cIMT has been well-established as a predictor of future cardiovascular events. Numerous epidemiological studies and meta-analyses have confirmed that individuals with thicker cIMT are at higher risk for myocardial infarction and stroke. For example, a recent meta-analysis reported that for every 1-standard deviation increase in common cIMT, the hazard of future stroke increases by about 32 % and myocardial infarction by about 27 % [107]. In fact, cIMT has been widely used as an indicator of cardiovascular risk in research [107]. Its appeal lies in directly visualising arterial wall changes: unlike PWV or AIx, which infer risk from hemodynamic properties, cIMT provides an anatomic measure of subclinical atherosclerosis. This makes it particularly relevant for identifying asymptomatic individuals with hidden atherosclerotic disease. Still, the presence of an abnormally high cIMT or carotid plaque on ultrasound strongly suggests advanced vascular ageing relative to one's peers. Such findings often prompt more aggressive management of risk factors. It's worth noting that cIMT progression over time can also be used as a surrogate end-point in trials of preventive therapies (e.g., statins or blood pressure drugs) – the premise being that slowing cIMT progression reflects slowed vascular ageing and reduced future risk.

In summary, cfPWV, AIx, and cIMT are key surrogate measures of vascular ageing, each capturing a different facet of arterial health: cfPWV quantifies central arterial stiffness, AIx reflects pressure wave reflections and composite arterial function, and cIMT gauges structural atherosclerotic changes in the arterial wall. All three have demonstrated value as predictors of cardiovascular events, independent of and additive to classic risk factors [70,100,107]. They are extensively used in clinical research and increasingly in practice to assess vascular age. By applying these measures, clinicians can better identify patients with "arteries older than their years," even if those patients have not yet experienced symptoms – enabling more tailored prevention strategies aimed at mitigating cardiovascular risk and promoting healthier vascular ageing. Each measure has practical considerations (equipment, expertise, patient factors), but together they underscore a fundamental principle: how "old" your blood vessels are biologically can be quantified, and this vascular age is intimately linked to your future cardiovascular destiny. Monitoring and improving these surrogate markers is thus an emerging paradigm in cardiovascular risk reduction and personalised preventive cardiology.

2.5 Artificial Intelligence and Machine Learning in Cardiovascular Risk Prediction

2.5.1 Overview of AI/ML Methods Used for CVD Risk Prediction

Machine learning and artificial intelligence techniques have been increasingly applied to cardiovascular disease risk prediction. Unlike traditional risk scores that rely on predefined linear equations, ML models learn patterns from data and can capture complex relationships between predictors and outcomes. Common supervised ML algorithms explored in recent CVD risk studies include decision tree ensembles (e.g., random forests and gradient boosting methods like XGBoost), support vector machines (SVM), and artificial neural networks (including deep learning architectures) [81]. Advanced deep learning techniques (e.g., convolutional and recurrent neural networks) enable analysis of high-dimensional data such as medical images or longitudinal electronic health records [81]. Ensemble approaches (bagging and boosting) combine multiple weak learners to enhance predictive accuracy [81]. In practice, many studies compare multiple algorithms; for example, recent work has evaluated logistic regression (as a baseline), tree-based methods, boosting algorithms, and multilayer neural networks for risk prediction [23]. The choice of method may depend on the data modality (tabular clinical data vs. imaging vs. omics data) and the need for interpretability. Notably, deep learning models can automatically extract features from raw data (e.g., imaging pixels or genomic sequences), whereas methods like random forests or SVM typically use predefined variables. Overall, a wide range of AI/ML methods have been applied, reflecting the diverse data types and predictive tasks in CVD risk assessment.

2.5.2 Advantages of AI/ML-based Over Traditional Risk Models

AI and ML approaches offer several advantages over traditional regression-based risk models. First, they capture non-linear relationships between risk factors and outcomes that linear models (like Framingham or SCORE equations) may miss [22]. CVD risk is influenced by many interacting variables; ML algorithms can automatically model high-order interactions and complex risk factor patterns without requiring manual specification of interaction terms. Second, ML models can handle high-dimensional data and leverage rich, multi-modal datasets. Modern CVD datasets may include hundreds to thousands of variables – from clinical demographics and labs to imaging, genomics, proteomics, and wearable sensor data. ML methods are

well-suited to process such large, multidimensional inputs and uncover subtle patterns within them [108]. This scalability enables a more holistic risk assessment: for example, combining electronic health records (EHR) data with imaging or genetic markers in one model. Third, ML models are data-driven "self-learning" systems, meaning they optimise their predictive functions based on the training data, rather than relying on a priori assumptions about linearity. This flexibility can improve predictive accuracy as fewer restrictive assumptions are imposed [109]. In practice, AI-based models have demonstrated superior discrimination in some cases, thanks to their robust data-processing capability and ability to fit complex relationships [109]. They can continuously update or be retrained as new data becomes available, potentially improving over time (whereas traditional scores are usually static once developed). Additionally, AI models can integrate new types of risk predictors that traditional tools do not accommodate – for instance, imaging findings or biomarker panels – thereby expanding the scope of risk stratification beyond conventional factors [110-112]. Taken together, these features (non-linearity, interaction modelling, scalability, and flexibility) allow ML-based risk prediction to potentially yield more personalised and accurate CVD risk assessments than the older generation of risk equations [108,111,113].

Empirical evidence supports these advantages. A 2023 meta-analysis found that across 16 studies, the top-performing ML models achieved a slightly higher average C-statistic (≈0.773) for CVD risk discrimination than traditional risk scores (≈0.759), a statistically significant difference [24]. Although the improvement in AUC/C-statistic is often modest, ML models tend to net reclassification improvements and better identification of high-risk individuals in diverse populations [23]. Furthermore, ML algorithms can be trained to incorporate dynamics and updates in patient data – for example, using repeated measurements or time-series data – whereas most traditional models consider a single snapshot of risk factors. This ability to handle time-varying data means AI-driven risk tools could enable real-time or longitudinal risk monitoring rather than one-off risk calculation [81,114]. In summary, AI/ML methods provide a more flexible and powerful framework for risk prediction, addressing many limitations of conventional models (such as linearity and limited inputs) and thus hold promise for improving CVD preventive strategies.

2.5.3 Examples of AI-Based Risk Models

Recent years have seen a number of AI-driven CVD risk models, especially for primary prevention cohorts, that illustrate the capabilities of these methods. Below are representative examples (post-2020) of such models, including those using standard risk factors and those incorporating novel biomarkers:

ML models with traditional risk factors: Ward et al. developed ML models for 5-year atherosclerotic CVD (ASCVD) risk in a large multi-ethnic EHR-derived cohort (over 260,000 patients) [115]. They trained logistic regression (with L1/L2 (lasso/ridge) regularisation), random forest, gradient boosting machine (GBM), and XGBoost models using demographics and routine clinical risk factors. The best model achieved an AUC of 0.835 in the full cohort, significantly outperforming the guideline-standard Pooled Cohort Equations (PCE), which had AUC 0.775 in the same population [115]. Notably, the ML approach was able to make risk predictions for individuals who were "PCE-ineligible" (due to missing or out-of-range inputs), thereby extending risk assessment to a broader patient group [115]. Similarly, in a study of 222,998 Korean adults free of CVD, Cho et al. found that an artificial neural network model modestly but significantly outperformed established risk scores (C-statistic 0.751 vs 0.738 for the PCE) and had better calibration [23]. Other ML methods (random forests, bagged trees, AdaBoost) in that study also showed performance on par or slightly better than traditional scores, and improvements were also observed over Framingham, SCORE, and QRISK3 algorithms [23]. These examples underscore that ML-based models using conventional clinical predictors can incrementally improve risk discrimination and especially improve inclusivity (covering patients often omitted by rigid traditional tools) [115].

Models integrating novel biomarkers: A major advantage of AI models is the ability to incorporate biomarker data and other non-traditional risk factors. Proteomics-based risk models have shown particularly promising results. Hoogeveen et al. constructed a CVD risk model based on 50 circulating proteins (selected from an initial panel of 368 measured via a proteomics assay) in a primary prevention cohort [82]. Using tree-based ensemble and boosting algorithms, their protein-only model significantly improved risk prediction for myocardial infarction compared to an optimised clinical factor model. For example, over a 20-year follow-up in the EPIC-Norfolk study, the proteomic model achieved an AUC of 0.754 vs 0.730 for the clinical model ($p < 0.001$), and importantly, for near-term (3-year) risk, AUC was 0.803 with the protein model vs 0.732 with clinical factors [82].

More recently, Climente-González et al. (2025) leveraged the large-scale UK Biobank proteomics dataset to build an interpretable ML risk model. They trained an Explainable Boosting Machine (EBM) on 50,000 individuals using 2,923 protein biomarkers plus 55 traditional risk factors [116]. The resulting model achieved a 10-year CVD event AUC of 0.785 when combining proteomics with clinical factors, outperforming conventional risk equations (e.g., the PREVENT score) and providing a substantial improvement in precision-recall metrics. Notably, the model maintained robust accuracy across sexes and ethnic subgroups and offered interpretable insights (via feature importance in the EBM) into how specific proteins and risk factors contributed to individual risk [116]. This illustrates how ML can integrate "big data" biomarker profiles to refine risk stratification.

Inclusion of novel "omics" and exposome variables: Beyond proteomics, other studies have combined standard risk factors with newer predictors such as genomics, metabolomics, and environmental exposures. For instance, Atehortúa et al. developed an "exposome-based" ML model for CVD risk using 109 lifestyle and environmental variables (e.g., physical activity, pollution exposure, psychosocial factors) from the UK Biobank [117]. Using an XGBoost ensemble, they predicted 13-year risk of CVD (and diabetes) and compared it to an integrative model with clinical/biological factors and to the Framingham risk score. The exposome-only model achieved an Receiver operating characteristic (ROC)-AUC of 0.78 for CVD, which was comparable to the full integrative model and significantly better than the Framingham score on the same cohort [117]. Importantly, the authors assessed fairness: the model showed no performance bias across sex, ethnicity, or age groups, meeting their criteria for a "fair" algorithm. They also employed SHAP (SHapley Additive Explanations) to interpret the model, identifying novel risk factors (e.g., daytime napping, educational attainment, fatigue levels, work status) as influential predictors of CVD risk [117]. This example highlights how AI can incorporate unconventional risk determinants (the exposome) and potentially reveal new modifiable risk factors.

AI using imaging biomarkers: AI/ML models have been created to predict CVD risk from medical imaging and other vascular biomarkers that were not part of traditional risk scores. A noteworthy development is the use of retinal fundus imaging as a window into cardiovascular risk. Recent deep learning models can analyse retinal photographs to predict future CVD events by detecting microvascular changes. In a 2023 pivotal trial, Lee et al. validated an AI system called Reti-CVD for risk stratification using retinal images [118]. In a cohort of 1,106 individuals, the Reti-CVD algorithm stratified subjects into low, moderate, and high-risk tiers for 5-year incident CVD; those

categorised as high-risk by the retinal AI had a hazard ratio 3.56 for future events compared to the low-risk group [118]. Even after accounting for traditional risk factors and measures of subclinical atherosclerosis (coronary calcium score, cIMT, pulse-wave velocity), the retinal AI's risk categorisation remained an independent predictor of outcomes. This tool effectively functions as a non-invasive "imaging biomarker" risk score. Its successful validation led to regulatory authorisation of Reti-CVD in South Korea, making it one of the first AI Software-as-Medical-Device tools for CVD risk approved for clinical use [118]. Similarly, other studies have used deep learning to integrate coronary CT angiography findings or arterial imaging with clinical data, improving risk prediction for events by identifying high-risk plaque features invisible to traditional factor models [119]. These examples underscore the expanding frontiers of CVD risk assessment when AI is applied – ranging from molecular biomarkers to retinal scans – and demonstrate improved predictive power in multiple contexts.

2.5.4 Challenges to Adoption in Clinical Practice

Despite the promise of AI/ML in cardiovascular risk prediction, several challenges impede their routine adoption in clinical practice. Data quality and generalizability are major concerns. ML models are highly dependent on the data used for training, and issues such as noisy or incomplete EHR data, inconsistent outcome definitions, and limited cohort diversity can undermine model reliability [109]. Systematic reviews have found that most published CVD ML models have a high risk of bias – for example, a 2024 review noted all identified models (n=486) were at high risk of bias under PROBAST criteria, often due to problems like inappropriate patient selection, predictor measurement flaws, and inadequate handling of model overfitting [109]. This indicates many ML models may not be as robust as reported, especially when applied to new populations. A related issue is the lack of external validation: many AI risk models are developed on a single dataset and not validated elsewhere. Without rigorous external (and preferably prospective) validation, clinicians justifiably remain cautious about trusting these models in practice [24].

Bias and equity: AI models can inadvertently perpetuate or even amplify healthcare disparities if the training data are not representative. Traditional risk scores have known shortcomings in certain subgroups (e.g., underestimating risk in women or minorities) [120,121], and ML is not immune to these issues. If an AI model is trained predominantly on one demographic group, its predictions may be less accurate for others, raising

concerns about fairness. Ensuring diverse, high-quality training data is therefore critical [81]. Researchers are increasingly aware of this and now often evaluate algorithm performance across subgroups (as in the UK Biobank exposome study that checked for sex/ethnicity bias [117]). Nonetheless, addressing bias remains a challenge, and regulatory guidance is still evolving on how to audit and mitigate bias in AI tools.

Interpretability and transparency: Many powerful ML models (e.g., gradient boosted ensembles or deep neural networks) operate as "black boxes," providing a risk prediction without an explanation that a clinician or patient can easily understand. Lack of interpretability is frequently cited by clinicians as a barrier to trusting and adopting AI systems [109]. Clinicians are accustomed to well-known risk factors and clear rationale (e.g., "patient has high risk because of age, smoking, cholesterol, etc."). In contrast, an opaque ML model might output a risk score derived from dozens of variables and complex interactions, making it hard to know why the risk is what it is. This lack of transparency can hinder clinical acceptance and raise concerns for accountability (how to justify treatment decisions based on an unreadable algorithm). To address this, newer approaches incorporate explainability techniques – for instance, using SHAP values or other methods to highlight which features drove a given prediction [122]. The emergence of inherently interpretable models (like the Explainable Boosting Machine used in the proteomic study [116]) is another response, aiming to balance accuracy with interpretability. Still, achieving broad clinician comfort with AI will require continued focus on making model outputs and decision logic transparent.

Integration into clinical workflow: Even a well-validated, interpretable model faces practical integration hurdles. Technical integration with health IT systems can be non-trivial – the model needs to reliably pull patient data from the electronic record, compute risk in real-time, and present results within the clinician's workflow. Many current models are not deployed in user-friendly software or lack regulatory approval to be used as clinical decision support. The example of Reti-CVD shows that regulatory clearance is possible [118], but regulatory pathways for AI are still emerging. Additionally, clinicians would need training on how to use and act on AI risk predictions. There may be workflow disruptions or additional time required, which can be a barrier in busy practice settings. Ensuring that an AI risk tool provides actionable information (e.g., improved risk stratification that clearly maps to guideline-recommended interventions) is key for uptake. Otherwise, even an accurate model might be ignored if it doesn't seamlessly fit into decision-making processes.

Validation and evidence for clinical benefit: Thus far, most AI CVD risk models have been evaluated retrospectively. There is a lack of prospective clinical trials demonstrating that using an ML-based risk tool leads to better patient outcomes (e.g., by preventing more heart attacks or targeting therapy more effectively). Guideline committees and practitioners tend to wait for such evidence before changing practice. As noted by Weber et al., it remains "uncertain whether [ML models] can be implemented in clinical settings" and further research is needed on how to integrate them into primary prevention workflows [24]. This points to the need for implementation science: studying how an AI tool performs in real-world practice, how clinicians interact with it, and whether it actually improves decision-making or patient adherence.

In summary, while AI and machine learning have demonstrated technical advantages and promising performance in CVD risk prediction, several challenges must be overcome for widespread clinical adoption. Ensuring high-quality, representative data and external validations will improve model reliability and generalizability. Improving explainability and transparency will foster clinician trust and acceptance. Addressing ethical and bias concerns is critical to deploy AI in an equitable manner. Finally, practical aspects of integration into healthcare systems and workflows, along with evidence of real clinical benefit, will determine how quickly these AI-driven risk models transition from research studies to routine patient care. Continued efforts in these areas are needed to unlock the full potential of AI/ML in cardiovascular risk prevention.

3. METHODS

3.1 Study Population/Inclusion and Exclusion Criteria

The dataset encompassed individuals enrolled in the LitHiR (Lithuanian High Cardiovascular Risk primary prevention program), a government-funded program launched in Lithuania in 2006, aimed at the multifactorial reduction of cardiovascular (CV) risk among middle-aged individuals to avert the early onset of atherosclerosis [123,124]. The program targeted men aged 40–54 years and women aged 50–64 years, without evident CVD, but diagnosed with metabolic syndrome (MetS), and these subjects were assessed from 2006 to 2023 at the tertiary care facility—Vilnius University Hospital Santaros Klinikos, located in Vilnius, Lithuania. Metabolic Syndrome was defined according to the updated criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), which necessitated the presence of three or more of the following criteria: systolic blood pressure (SBP) of ≥ 130 mmHg or diastolic blood pressure (DBP) of ≥ 85 mmHg, or an existing hypertension diagnosis; a waist circumference of ≥ 88 cm for females and ≥ 102 cm for males; high-density lipoprotein (HDL) cholesterol levels of <1.29 mmol/L in females and < 1.03 mmol/L in males; triglyceride (TG) levels of ≥ 1.7 mmol/L or special treatment is administered to reduce TG concentration; and diagnosed type 2 diabetes mellitus or fasting plasma glucose levels of ≥ 5.6 mmol/L [36].

Data for the present study were derived from the LitHiR program's prospectively and uniformly collected dataset, which constituted the foundation for extracting the vital variables necessary for analysis. Inclusion criteria for subjects entailed having documented measures for key parameters including low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose levels, creatinine, C-reactive protein, the urine albumin-creatinine ratio, femoral pulse wave velocity, along with detailed family and medication history. Any subject lacking records for these crucial indicators was omitted from the analysis, a measure taken to maintain the integrity and accuracy of the risk assessment process.

For this research, the exclusion criteria encompassed individuals with a history of silent myocardial ischemia, coronary artery disease, transient ischemic attacks, peripheral artery disease, both ischemic and haemorrhagic strokes, oncological conditions, chronic or persistent arrhythmias, severe renal or liver dysfunction, significant psychiatric conditions, gout, as well as those who were pregnant, were undergoing therapy with xanthine oxidase inhibitors

or had drug addiction issues. This approach was adopted to eliminate confounding factors and ensure the study population was representative of individuals primarily at risk for metabolic syndrome without the influence of these complex comorbid conditions.

For outcome analyses, a subset of the LitHiR population was used, consisting of 5,812 individuals with complete adjudicated follow-up data on cardiovascular outcomes. This outcome-specific dataset was smaller than the overall cohort, as outcome events were systematically recorded only up to the year 2021. To preserve analytical validity, only participants with fully available outcome information and baseline risk variables were included. This ensured consistency in follow-up time and minimised potential bias related to incomplete endpoint ascertainment.

3.2 Risk Prediction Models

3.2.1 Systematic Coronary Risk Evaluation 2 (SCORE2)

SCORE2 is a risk assessment tool created to estimate the 10-year risk of both fatal and non-fatal CVD in individuals aged 40 to 69 years in Europe who have no prior history of CVD. This score represents a refinement of the original SCORE model, updated to include more recent data [8]. The SCORE2 model factors in various risk determinants such as age, gender, systolic blood pressure, non-HDL cholesterol levels, and smoking status. The calculation of the risk score was performed using a specific calculator available at: https://u-prevent.com/calculators/score2 (accessed on June 2, 2023). For this analysis, we employed a recalibrated version of the risk score tailored for use in areas identified as 'very high risk' by pertinent guidelines, without any alterations to the original computation process.

3.2.2 Predicting Risk of Cardiovascular Disease EVENTs (PREVENT)

PREVENT equations provide 10-year risk estimates for individuals 30-79 years of age and provide 30-year risk estimates for individuals 30-59 years of age. The algorithms were developed by the American Heart Association Cardiovascular-Kidney-Metabolic Scientific Advisory Group. The risk equation was derived and validated in a large, diverse sample of over 6 million individuals [7,37]. The calculation of the risk score was performed using a specific calculator available at: https://professional.heart.org/en/guidelines-and-statements/prevent-calculator (accessed on 1 March 2024). The 10-year

risk of CVD was calculated. During the computation procedure, the inclusion of the Zip Code was not applicable.

3.2.3 Pooled Cohort Equations (PCE) Cardiovascular Risk Score

PCE is designed to estimate an individual's likelihood of experiencing atherosclerotic CVD (ASCVD) over a decade, utilising data gathered from diverse community-based cohorts. This tool is relevant for both African-American and non-Hispanic White males and females within the age bracket of 40 to 79 years [3]. It integrates common cardiovascular risk elements including sex, age, SBP, HDL-cholesterol, total cholesterol (TC), the presence of hypertension treatment, diabetes status, racial background, and smoking habits into the risk assessment. The calculation of the risk score was performed using a specific calculator available at: https://static.heart.org/riskcalc/app/index.html#!/baseline-risk (accessed on June 1, 2023). No changes were made to the computation procedure.

3.2.4 Multi-Ethnic Study of Atherosclerosis (MESA) Risk Score

The Multi-Ethnic Study of Atherosclerosis (MESA) risk score is formulated to calculate the 10-year likelihood of cardiovascular events in individuals aged 45 to 85 years who have no diagnosed CVD [6]. This score is derived from the extensive data collected in the MESA study, encompassing over 6,800 participants from diverse racial and ethnic backgrounds. The findings from the MESA study confirm the score's accuracy in assessing CVD risk across a broad spectrum of races and ethnic groups. The calculation of the risk score was performed using a specific calculator available at: https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx (accessed on June 2, 2023). The coronary artery calcification index was excluded from the computation procedure as this variable was not present in our dataset.

3.2.5 QRISK3 Risk Calculator (QRISK3)

Introduced in 2017, the QRISK3 calculator serves as a revision of the QRISK2 algorithm, first launched in 2008 and established as the primary risk assessment tool for estimating a 10-year cardiovascular event risk within the English population aged 25 to 84 years [9]. The updated model enhances its predictive capability by incorporating an additional eight risk factors that have been recognised in various studies as potential contributors to CVD. These include the use of corticosteroids, migraine, treatment with atypical

antipsychotic drugs, systemic lupus erythematosus, severe mental illness, blood pressure variability, and erectile dysfunction. The calculation was performed using a specific calculator available at: https://qrisk.org/ (accessed on June 2, 2023). No changes were made to the computation procedure.

3.2.6 Assessing Cardiovascular Risk Using SIGN (ASSIGN)

The ASSIGN model is tailored to calculate the 10-year likelihood of cardiovascular events in individuals without pre-existing CVD, incorporating measures of social deprivation (via the Scottish Index of Multiple Deprivation) and family history alongside traditional variables [10]. This approach has demonstrated enhanced accuracy compared to other CVD risk scores in forecasting CVD risk within the Scottish population. Moreover, the ASSIGN score is the recommended tool for CVD risk assessment by the Scottish Government Health Directorates and the Scottish Intercollegiate Guidelines Network (SIGN). The calculation of the risk model was performed using a specific calculator available at: https://www.assign-score.com/estimate-the-risk/visitors/ (accessed on June 2, 2023). The Scottish Index of Social Deprivation was not applicable during the computation procedure.

3.2.7 Australian CVD Risk Score (AusCVDRisk)

The AusCVDRisk model is developed to predict the 5-year probability of cardiovascular events, specifically for individuals aged 30 to 79 years without established CVD and who do not fulfil criteria for high risk. This tool is based on the NZ PREDICT-1 equation, originating from an extensive and modern primary care cohort study in New Zealand [11]. The equation has undergone recalibration to suit the Australian demographic and has been adjusted to align with the Australian healthcare framework. The calculation of the risk score was performed using a specific calculator available at: https://www.cvdcheck.org.au/calculator (accessed on August 2, 2023). The inclusion of a postcode variable was not applicable during the computation procedure.

3.2.8 Framingham Risk Score for Hard Coronary Heart Disease (FRS-hCHD)

The risk score is formulated to predict the risk of coronary heart disease (CHD) events in 10 years, including coronary death and myocardial infarction. It evaluates various risk factors such as sex, age, HDL cholesterol, TC, SBP,

smoking status, and hypertension treatment. The FRS-hCHD tool is specifically designed for non-diabetic individuals between the ages of 30 and 79 who have no previous diagnosis of intermittent claudication or coronary heart disease [36]. The calculation was performed using a specific calculator available at: https://www.mdcalc.com/calc/38/framingham-risk-score-hard-coronary-heart-disease (accessed on June 1, 2023). No changes were made to the computation procedure.

3.2.9 Reynolds Risk Score (RRS)

The RRS is aimed at predicting the 10-year likelihood of a major cardiovascular event, including stroke, myocardial infarction, or other significant heart conditions. This score integrates conventional risk determinants like sex, age, cholesterol levels, smoking habits, and blood pressure, along with supplementary biomarkers, including high-sensitivity C-reactive protein and a history of premature atherosclerosis in the family [4]. While initially formulated for female populations, the model has subsequently been adjusted to apply to male demographics as well. The calculation of the risk score was performed using a specific calculator available at: http://www.reynoldsriskscore.org/ (accessed on June 2, 2023). No changes were made to the computation procedure.

3.3 Definitions of Variables

3.3.1 Risk Prediction Model Agreement Analysis

Every Risk Prediction Model (RPM) features distinct risk categories and scoring ranges, requiring the adoption of a standardised methodology to ensure analytical uniformity. Figure 1 graphically depicts these risk categories and their corresponding intervals among the various models. In certain RPMs, the categorisation boundaries were maintained, but the terminology was modified for consistency. For example, the ASSIGN risk score initially classified some individuals as "non-high risk," which was later segmented into low- and intermediate-risk categories to achieve analytical harmony. Similarly, in scores like PREVENT, the term "borderline risk" was redefined as "intermediate risk" to conform to the uniform categorisation scheme used in this analysis. This standardisation of risk categories enables a more detailed and nuanced comparison.

Native risk score categorization					Harmonized risk score categorization			
Predicting Risk of cardiovascular disease EVENTs (PREVENT)								
Low risk	*Borderline risk*	*Intermediate risk*	*High risk*	→	*Low risk*	*Intermediate risk*	*High risk*	
<5	5–<7.5	≥7.5–<20	≥20		<7.5	≥7.5–<20	≥20	
Systematic Coronary Risk Evaluation 2 (SCORE2)								
Age Group	*Low-moderate risk*	*High risk*	*Very high risk*	→	*Age Group*	*Low risk*	*Intermediate risk*	*High risk*
<50	<2.5	2.5–7.49	≥7.5		<50	<2.5	2.5–7.49	≥7.5
50-69	<5	5–9.99	≥10		50-69	<5	5–9.99	≥10
≥70	<7.5	7.5–14.99	≥15		≥70	<7.5	7.5–14.99	≥15
Pooled Cohort Equation (PCE)								
Low risk	*Borderline risk*	*Intermediate risk*	*High risk*	→	*Low risk*	*Intermediate risk*	*High risk*	
<5	5–<7.5	≥7.5–<20	≥20		<7.5	≥7.5–<20	≥20	
QRISK3 cardiovascular risk calculator (QRISK3)								
Low risk	*Moderate risk*	*High risk*		→	*Low risk*	*Intermediate risk*	*High risk*	
<10	≥10–≤20	>20			<10	≥10–≤20	>20	
Framingham Risk Score for Hard Coronary Heart Disease (FRS-hCHD)								
Low risk	*Intermediate risk*	*High risk*		→	*Low risk*	*Intermediate risk*	*High risk*	
<10	≥10–<20	≥20			<10	≥10–<20	≥20	
Reynolds Risk Score (RRS)								
Very low risk	*Low-intermediate*	*Intermediate-high risk*	*High risk*	→	*Low risk*	*Intermediate risk*	*High risk*	
<5	≥5–<10	≥10–<20	≥20		<10	≥10–<20	≥20	
Assessing cardiovascular risk using SIGN (ASSIGN)								
Non-high risk		*High risk*		→	*Low risk*	*Intermediate risk*	*High risk*	
0-19		≥20			<10	≥10–<20	≥20	
Australian CVD risk score (AusCVDRisk)								
Low risk	*Intermediate risk*	*High risk*		→	*Low risk*	*Intermediate risk*	*High risk*	
<5	≥5–<10	≥10			<5	≥5–<10	≥10	
Multi-Ethnic Study of Atherosclerosis risk score (MESA)								
Low risk	*Intermediate risk*	*High risk*		→	*Low risk*	*Intermediate risk*	*High risk*	
<5	≥5–<7.5	≥7.5			<5	≥5–<7.5	≥7.5	

Figure 1. Comparative presentation of native and harmonised cardiovascular risk categorisations after adjustment

3.3.2 Statin eligibility analysis

Cardiovascular (CV) risk prediction models (RPM) are essential tools for guiding statin therapy decisions, yet variations across models can lead to inconsistent recommendations and impact patient outcomes. Understanding the level of agreement among these models is crucial for optimising risk assessment and ensuring effective clinical decision-making. Therefore, this analysis aimed to evaluate the levels of statin eligibility across nine CV RPMs. Cardiovascular risk was estimated using the nine RPMs, and based on model-specific treatment thresholds, statin eligibility rates were calculated for each model. Figure 2 graphically depicts these thresholds among the various models.

Statin eligibility threshold			
Systematic Coronary Risk Evaluation 2 (SCORE2)			
Age Group	*Low-moderate risk*	*High risk*	*Very high risk*
<50	<2.5	2.5–7.49	**≥7.5**
50-69	<5	5–9.99	**≥10**
≥70	<7.5	7.5–14.99	**≥15**
Predicting Risk of cardiovascular disease EVENTs (PREVENT)			
Low risk	*Borderline risk*	*Intermediate risk*	*High risk*
<5	5–<7.5	**≥7.5–<20**	**≥20**
Pooled Cohort Equation (PCE)			
Low risk	*Borderline risk*	*Intermediate risk*	*High risk*
<5	5–<7.5	**≥7.5–<20**	**≥20**
QRISK3 cardiovascular risk calculator (QRISK3)			
Low risk	*Moderate risk*	*High risk*	
<10	**≥10–≤20**	**>20**	
Framingham Risk Score for Hard Coronary Heart Disease (FRS-hCHD)			
Low risk	*Intermediate risk*	*High risk*	
<10	**≥10–<20**	**≥20**	
Reynolds Risk Score (RRS)			
Very low risk	*Low-intermediate*	*Intermediate-high risk*	*High risk*
<5	≥5–<10	**≥10–<20**	**≥20**
Assessing cardiovascular risk using SIGN (ASSIGN)			
Non-high risk		*High risk*	
0-19		**≥20**	
Australian CVD risk score (AusCVDRisk)			
Low risk	*Intermediate risk*	*High risk*	
<5	≥5–<10	**≥10**	
Multi-Ethnic Study of Atherosclerosis risk score (MESA)			
Low risk	*Intermediate risk*	*High risk*	
<5	≥5–<7.5	**≥7.5**	

Figure 2. Presentation of statin eligibility thresholds among different prediction models. Variables in **bold** indicate eligibility for antilipid treatment

3.4 Statistical Analysis

In the quantitative evaluation, agreement among nine cardiovascular risk prediction models was rigorously examined utilising a multifaceted methodology. An initial analysis employing descriptive statistics mapped out the frequency distributions of risk categories across each algorithm, establishing a baseline for comprehending the segmentation of patient populations into distinct risk levels. Concordance among model pairs was quantitatively ascertained using Cohen's Kappa statistics, a robust measure for evaluating categorical agreement, offering a scale from -1 to 1, with higher values denoting greater agreement.

A heatmap was created to enhance the interpretability of the Kappa coefficients. Additional analysis of the model interrelations was facilitated by hierarchical clustering. Utilising the pairwise Kappa coefficients, a dendrogram was synthesised via the Ward method, aimed at reducing within-cluster variance, thereby categorising models with similar risk differentiation patterns.

An overarching analysis of score agreement was conducted via Collective Model Agreement Analysis, calculating the frequency of patients categorised consistently across models, thus offering comprehensive insights into agreement levels in a clinical setting.

Additionally, model discrimination was evaluated as follows: receiver operating characteristic (ROC) analyses were generated per outcome with all nine models overlaid, and area under the ROC curve (AUC) was estimated non-parametrically with 95 % confidence intervals obtained via stratified bootstrap resampling. For each outcome, pairwise differences in AUC between the per-outcome top model and each comparator were tested using two-sided bootstrap p-values (unadjusted).

Statistical analyses were conducted using IBM SPSS software version 25.0 (SPSS, Chicago, IL, USA) or Python, employing libraries such as Pandas for data management, scikit-learn for statistical analysis, and Matplotlib and Seaborn for graphical visualisations. The significance threshold for statistical inferences was established at 0.05.

3.5 Machine Learning–Based Predictive Modelling

To evaluate the potential of incorporating vascular biomarkers into cardiovascular risk prediction, a supervised machine learning approach was employed. The analysis utilised a Random Forest classifier, selected for its

robustness to multicollinearity, capacity to model complex non-linear relationships, and ability to quantify feature importance.

Data preprocessing was conducted within a scikit-learn pipeline framework to ensure reproducibility and minimise data leakage. Missing values were imputed using the mean imputation strategy (SimpleImputer), followed by standardisation (StandardScaler). Model training and evaluation were performed using a stratified train–test split, allocating 70 % of the data to training and 30 % to testing, with random state fixed at 42 to ensure replicability. The Random forest (RF) used 100 trees (n_estimators = 100) with default splitting parameters; probability outputs were obtained by averaging tree votes.

Analysis population. All modelling and evaluation were conducted on an outcome-specific dataset (n = 5,812), a subset of the full registry restricted to records with adjudicated outcomes for the composite endpoint. After the stratified split and alignment of rows across specifications, the held-out test set comprised N = 1,744 individuals with 58 Composite CV events (3.3 %) and 1,686 non-events. All between-model comparisons were restricted to these exact test rows.

Model specifications. Four specifications were evaluated on the same test instances:

- RF (7 var) model's variables: age; gender; diastolic blood pressure; total cholesterol; triglycerides; fasting glucose; C-reactive protein;
- RF (7 var+PWV) model's variables: age; gender; diastolic blood pressure; total cholesterol; triglycerides; fasting glucose; C-reactive protein; carotid-femoral pulse wave velocity;
- SCORE2: calculated without training on the identical test individuals (for probability-based metrics, the SCORE2 risk was scaled to [0,1] by dividing by 100; this scaling does not affect discrimination/AUC);
- RF (6 var) model's variables: age; diastolic blood pressure; triglycerides; fasting glucose; C-reactive protein; smoking status (parsimony analysis).

Performance assessment. Discrimination was summarised by the area under the receiver operating characteristic curve (AUC-ROC) on the held-out test set. Ninety-five percent confidence intervals for AUC were obtained via non-parametric bootstrap (4,000 resamples; percentile method). Between-model differences in AUC (ΔAUC) were evaluated using a paired bootstrap (the same resamples applied across models) with two-sided p-values.

Threshold-based operating points. To contextualise discrimination with clinically relevant trade-offs, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were reported at prespecified

targets of approximately 0.80 and 0.90 specificity on the test set. Thresholds were chosen from the empirical ROC to achieve the closest attainable specificity.

Calibration. Overall accuracy was quantified using the Brier score.

Explainability. Global feature attribution was examined using model-based importances and SHAP (SHapley Additive exPlanations) applied to the fitted RF models.

Software. All analyses were conducted in Python (pandas, numpy, scikit-learn, matplotlib, shap).

3.6 Author's Methodological Contributions

As part of this doctoral research, I was responsible for the complete analytical pipeline, beginning with data preparation and curation of the LitHiR registry. I extracted and cleaned the dataset, performed consistency and range checks, harmonised units, and excluded records with missing values for key parameters, thereby constructing the final analysis-ready cohort. I derived all relevant variables, including lipid fractions, blood pressure indices, glycemic measures, renal function, CRP, urine albumin-creatinine ratio, femoral pulse wave velocity, as well as family and treatment histories.

I calculated risk estimates for all nine conventional cardiovascular risk prediction models (SCORE2, PREVENT, PCE, MESA, QRISK3, ASSIGN, AusCVDRisk, FRS-hCHD, and RRS), ensuring fidelity to original computation procedures, and standardised risk categories across models to enable direct comparison. Using these data, I conducted all statistical analyses, including descriptive statistics, agreement analyses using Cohen's κ, hierarchical clustering, and collective model agreement summaries. I assessed discrimination through ROC curves and AUC estimation with stratified bootstrap resampling, and I performed decision-curve analyses to evaluate clinical utility across relevant treatment thresholds.

In addition, I developed and evaluated machine learning–based models. These analyses were implemented within reproducible scikit-learn pipelines, incorporating preprocessing, stratified train–test splits, and Random Forest classifiers. Multiple specifications were tested, including models with traditional risk factors, with and without vascular biomarkers (PWV), as well as a parsimonious variable set. I assessed predictive performance using AUC with bootstrap confidence intervals, sensitivity and specificity at prespecified operating points, calibration metrics, and explainability analyses with SHAP values.

In summary, I was directly responsible for dataset preparation, implementation of all conventional risk prediction models, statistical analyses, and machine-learning modelling, as well as the generation of all results and figures presented in this thesis.

3.7 Ethical Considerations

The research was authorised by the Vilnius Regional Biomedical Research Ethics Committee (permission No. 2019/3-1104-603).

The author acknowledges the use of OpenAI's GPT large language models, which were employed exclusively to assist in language refinement and ensure textual consistency throughout the manuscript.

4. RESULTS

4.1 Descriptive Statistics

In the current study, a total of 11,174 participants were evaluated within the LitHiR cohort. The subjects were predominantly female (*n* = 6527, 58.4 %), with a mean age of 53.49 ± 6.47 years. Key cardiovascular risk factors were notably present; the mean body mass index (BMI) was 31.57 ± 4.46 kg/m^2, and the mean TC level was 6.17 ± 1.37 mmol/L. The lipid profile further indicated a mean LDL cholesterol of 3.98 ± 1.21 mmol/L and a mean HDL cholesterol of 1.23 ± 0.31 mmol/L. Additionally, the study population exhibited a mean SBP of 137.16 ± 15.41 mmHg and a mean DBP of 82.99 ± 10.69 mmHg. Comorbidities were also prevalent, with 18.5 % (*n* = 2063) of the participants having diabetes mellitus and 26.3 % (*n* = 2939) receiving treatment for hypertension. Notably, 11.2 % (*n* = 1248) were on dyslipidaemia treatment with statins. The cohort included current smokers (*n* = 2305, 20.6 %) and ex-smokers (*n* = 686, 6.1 %), underlining the complexity of cardiovascular risk in this population. This comprehensive baseline characterisation provided the groundwork for the comparative analysis of nine cardiovascular risk prediction models (Table 1).

Table 1. Baseline characteristics of the study cohort (n = 11,174)

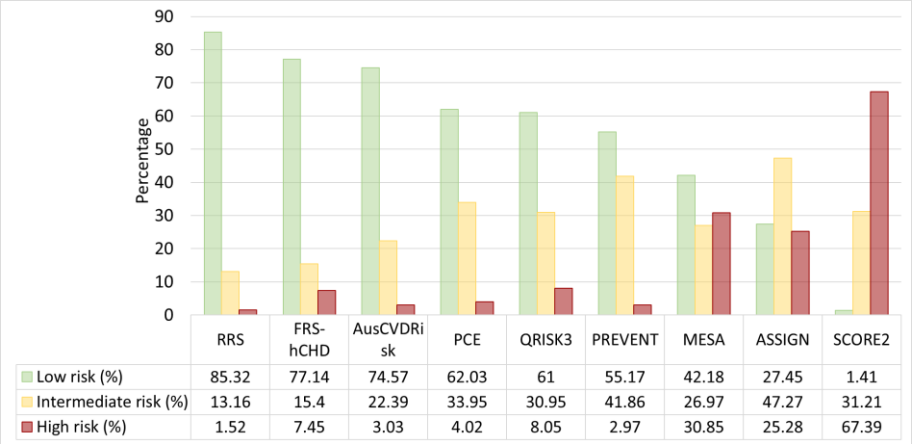
	Characteristics			**p-value**
	Total	Female 6527 (58.41)	Male 4647 (41.59)	<0.001
Age, years: mean (SD)	53.49 (6.47)	57.62 (4.21)	47.69 (4.27)	<0.001
Body mass index, kg/m^2: mean (SD)	31.47 (4.18)	31.76 (4.68)	31.24 (3.85)	<0.001
Systolic blood pressure, mmHg: mean (SD)	137.16 (15.40)	137.15 (15.96)	137.17 (14.59)	0.939
Diastolic blood pressure, mmHg: mean (SD)	82.99 (10.69)	80.99 (10.38)	85.79 (10.48)	<0.001
Total cholesterol, mmol/L: mean (SD)	6.17 (1.37)	6.33 (1.40)	5.96 (1.31)	<0.001
Triglycerides, mmol/L: mean (SD)	2.11 (1.5)	1.88 (1.15)	2.43 (1.84)	<0.001
Low-density lipoprotein cholesterol, mmol/L: mean (SD)	3.98 (1.21)	4.13 (1.23)	3.76 (1.14)	<0.001
High-density lipoprotein cholesterol, mmol/L: mean (SD)	1.23 (0.31)	1.33 (0.31)	1.09 (0.26)	<0.001
Estimated glomerular filtration rate, ml/min/1.73m^2: mean (SD)	92.44 (11.83)	88.97 (10.74)	97.32 (11.56)	<0.001
C-reactive protein, mg/L: mean (SD)	2.81 (3.18)	3.09 (3.98)	2.56 (3.06)	<0.001
Creatinine, µmol/L: mean (SD)	71.69 (12.79)	65.60 (8.93)	80.25 (12.48)	<0.001
Fasting glucose, mmol/L: mean (SD)	6.31 (1.49)	6.30 (1.51)	6.32 (1.45)	0.463
Diabetes mellitus: *n* (%)	2063 (18.46)	1325 (20.3)	738 (15.89)	<0.001
Dyslipidaemia treatment (statins): *n* (%)	2183 (19.54)	764 (11.7)	814 (17.52)	<0.001
Hypertension treatment: *n* (%)	2939 (26.3)	1861 (28.5)	1078 (23.2)	<0.001
Antiplatelet treatment: *n* (%)	30 (0.27)	19 (0.29)	11 (0.24)	0.584
Current smoker: *n* (%)	2305 (20.63)	841 (12.9)	1464 (31.5)	<0.001
Ex-smoker: *n* (%)	686 (6.14)	189 (2.9)	497 (10.7)	<0.001

SD—standard deviation.

4.2 Risk Prediction Model Agreement Analysis

4.2.1 Risk Category Distribution

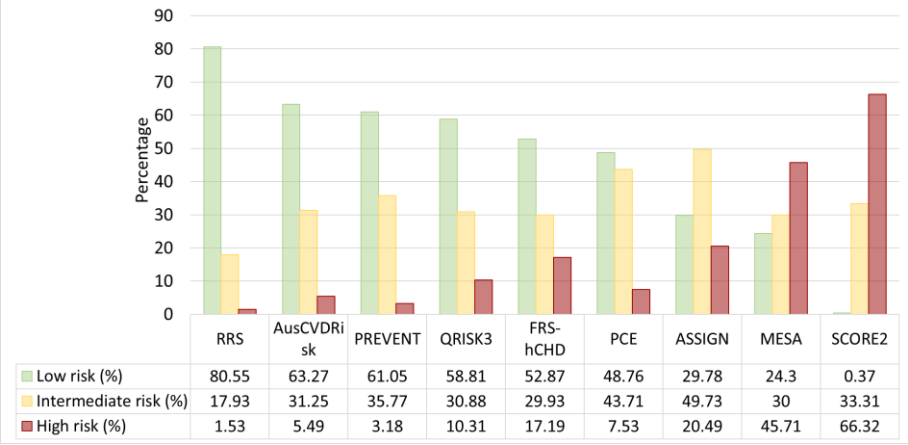
In the overall cohort, the distribution of cardiovascular risk categories varied markedly across the nine evaluated prediction models. The RRS model was notably conservative, classifying 85.32 % (n = 9,534) of individuals as low risk, while SCORE2 assigned only 1.41 % (n = 157) to this category and instead designated a striking 67.39 % (n = 7,530) of subjects as high risk. Models such as FRS-hCHD and AusCVDRisk also tended to yield lower-risk classifications, with 77.14 % (n = 8,620) and 74.57 % (n = 8,333) of individuals in the low-risk group, respectively, and relatively modest proportions identified as high risk (7.45 % [n = 833] for FRS-hCHD and 3.03 % [n = 339] for AusCVDRisk). In contrast, the PCE and QRISK3 models stratified approximately 62.03 % (n = 6,931) and 61 % (n = 6,816) of participants as low risk, accompanied by intermediate risk percentages of 33.95 % (n = 3,794) and 30.95 % (n = 3,458) and high-risk proportions of 4.02 % (n = 449) and 8.05 % (n = 900), respectively. The PREVENT model demonstrated a shift toward the intermediate category, classifying 55.17 % (n = 6,165) as low risk and 41.86 % (n = 4,677) as intermediate risk, whereas the MESA and ASSIGN models displayed more balanced distributions—with MESA classifying 42.18 % (n = 4,713) as low risk and 30.85 % (n = 3,447) as high risk, and ASSIGN assigning 27.45 % (n = 3,067) to low risk, 47.27 % (n = 5,282) to intermediate risk, and 25.28 % (n = 2,825) to high risk. These overall discrepancies in risk stratification are illustrated in Figure 3.



	RRS	FRS-hCHD	AusCVDRisk	PCE	QRISK3	PREVENT	MESA	ASSIGN	SCORE2
Low risk (%)	85.32	77.14	74.57	62.03	61	55.17	42.18	27.45	1.41
Intermediate risk (%)	13.16	15.4	22.39	33.95	30.95	41.86	26.97	47.27	31.21
High risk (%)	1.52	7.45	3.03	4.02	8.05	2.97	30.85	25.28	67.39

Figure 3. Distribution of cardiovascular risk categories across nine cardiovascular risk prediction models

When stratified by sex, the differences among models became even more pronounced. Among male subjects, the RRS model maintained its conservative approach by designating 80.55 % (n = 3,743) as low risk, whereas SCORE2 again produced an extreme profile, classifying only 0.37 % (n = 17) as low risk and 66.32 % (n = 3,082) as high risk. The AusCVDRisk and PREVENT models assigned 63.27 % (n = 2,940) and 61.05 % (n = 2,837) of males to the low-risk category, respectively, with corresponding high-risk proportions of 5.49 % (n = 255) and 3.18 % (n = 148). Intermediate risk estimates varied considerably, with PCE assigning 43.71 % (n = 2,031) and QRISK3 30.88 % (n = 1,435) of males to this category. Notably, FRS-hCHD and MESA classified 17.19 % (n = 799) and 45.71 % (n = 2,124) of males as high risk, respectively, while the ASSIGN model exhibited a near-equitable distribution—29.78 % (n = 1,384) low, 49.73 % (n = 2,311) intermediate, and 20.49 % (n = 952) high risk. These sex-specific variations among male subjects are presented in Figure 4.

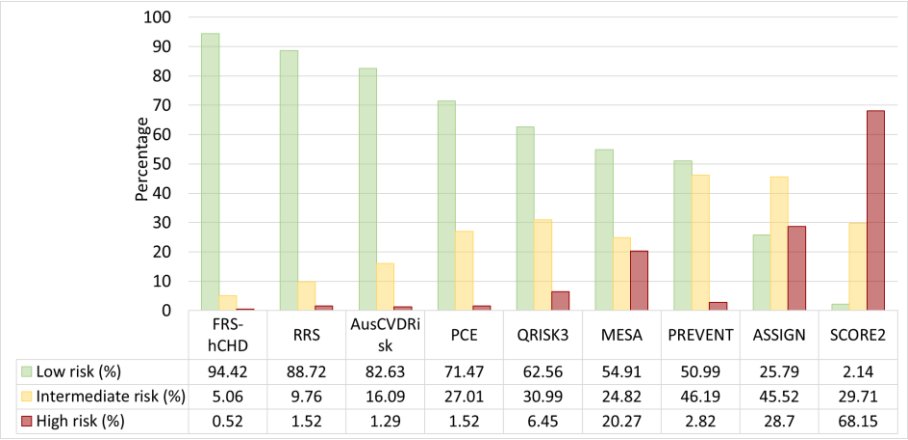


	RRS	AusCVDRisk	PREVENT	QRISK3	FRS-hCHD	PCE	ASSIGN	MESA	SCORE2
Low risk (%)	80.55	63.27	61.05	58.81	52.87	48.76	29.78	24.3	0.37
Intermediate risk (%)	17.93	31.25	35.77	30.88	29.93	43.71	49.73	30	33.31
High risk (%)	1.53	5.49	3.18	10.31	17.19	7.53	20.49	45.71	66.32

Figure 4. Distribution of cardiovascular risk categories across nine cardiovascular risk prediction models among males

Conversely, female subjects were predominantly categorised into lower risk groups by most models. The FRS-hCHD model was the most conservative, classifying 94.42 % (n = 6,163) of females as low risk, followed by the RRS (88.72 %, n = 5,791) and AusCVDRisk (82.63 %, n = 5,393) models. However, SCORE2 deviated considerably from this pattern, with only 2.14 % (n = 140) of females classified as low risk and a dominant 68.15 % (n = 4,448) assigned to the high-risk category. The PCE model identified 71.47 % (n = 4,665) of females as low risk, while QRISK3 allocated 6.45 % (n = 421) to high risk. In contrast, the MESA model stratified 54.91 % (n =

3,584) of females as low risk with 20.27 % (n = 1,323) in the high-risk group, and the PREVENT model tended toward an intermediate-risk classification by categorizing 46.19 % (n = 3,015) of females as intermediate risk, with only 50.99 % (n = 3,328) in the low-risk group. The ASSIGN model yielded a more balanced risk distribution among females, with 25.79 % (n = 1,683) classified as low risk, 45.52 % (n = 2,971) as intermediate risk, and 28.7 % (n = 1,873) as high risk. These distinct patterns for female subjects are depicted in Figure 5.



	FRS-hCHD	RRS	AusCVDRisk	PCE	QRISK3	MESA	PREVENT	ASSIGN	SCORE2
Low risk (%)	94.42	88.72	82.63	71.47	62.56	54.91	50.99	25.79	2.14
Intermediate risk (%)	5.06	9.76	16.09	27.01	30.99	24.82	46.19	45.52	29.71
High risk (%)	0.52	1.52	1.29	1.52	6.45	20.27	2.82	28.7	68.15

Figure 5. Distribution of cardiovascular risk categories across nine cardiovascular risk prediction models among females

4.2.2 Pairwise Agreement Analysis

In the overall cohort, the heatmap of Cohen's Kappa statistics revealed that the degree of pairwise agreement among the nine cardiovascular risk prediction models varied considerably (Figure 6). The range of values extends from -1 to 1, with higher values indicative of stronger concordance. Notably, the PREVENT model demonstrated moderate agreement with both PCE (κ = 0.53) and QRISK3 (κ = 0.54), suggesting similar patient categorisations between these models. In stark contrast, SCORE2 exhibited minimal to negative agreement with PREVENT (κ = -0.08) and with PCE (κ = -0.09). Additionally, the PCE model displayed strong concordance with AusCVDRisk (κ = 0.640), while moderate agreements were observed between MESA and ASSIGN (κ = 0.40) as well as between QRISK3 and AusCVDRisk (κ = 0.51).

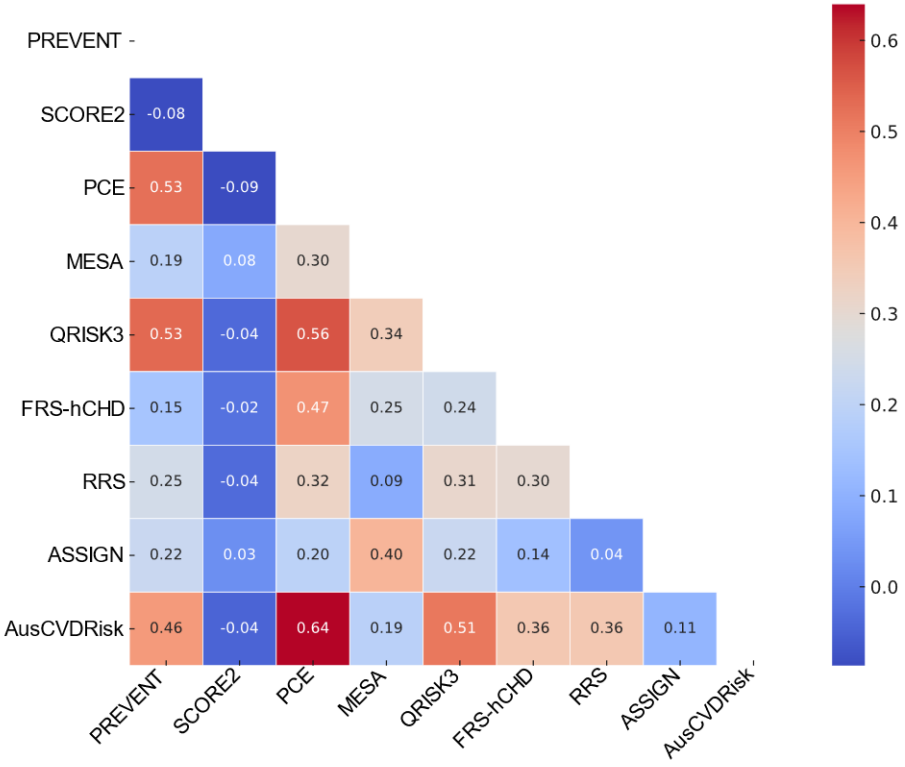


Figure 6. Heatmap illustrating pairwise agreement across nine cardiovascular risk prediction models

Among male subjects, the pairwise agreement analysis similarly revealed notable patterns (Figure 7). The PREVENT model achieved moderate agreement with PCE (κ = 0.55) and QRISK3 (κ = 0.51), while SCORE2 again demonstrated negligible agreement with PREVENT (κ = -0.08). Furthermore, PCE and AusCVDRisk maintained strong concordance (κ = 0.61), with additional moderate agreements observed between PCE and QRISK3 (κ = 0.54) and between MESA and ASSIGN (κ = 0.43).

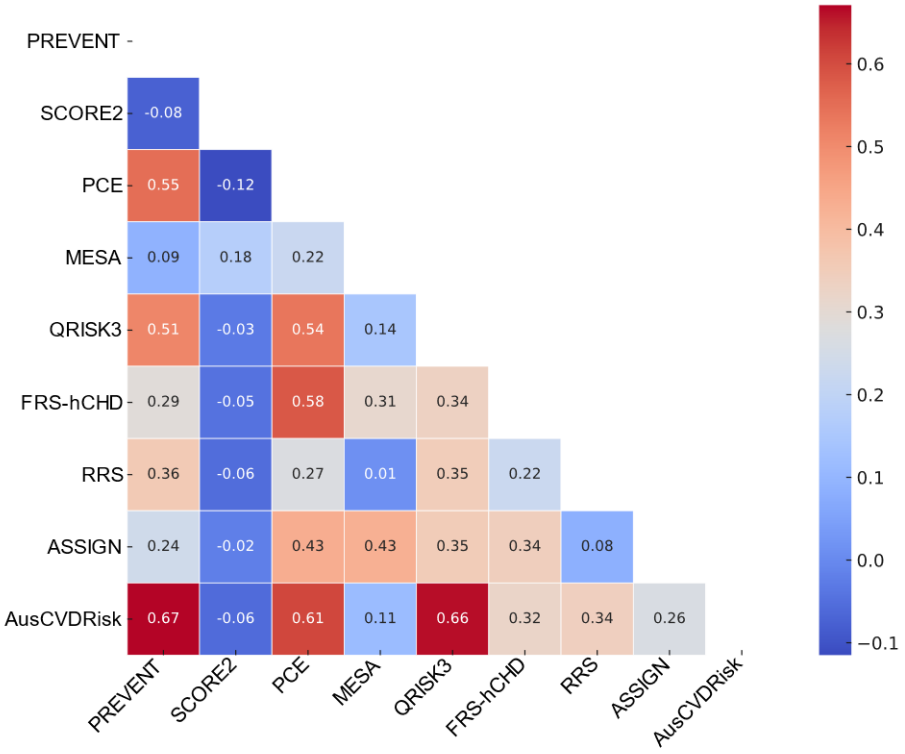


Figure 7. Heatmap illustrating pairwise agreement across nine cardiovascular risk prediction models among males

Conversely, in the female subgroup, distinct agreement patterns were observed (Figure 8). PREVENT exhibited moderate concordance with both PCE ($\kappa = 0.52$) and QRISK3 ($\kappa = 0.55$), whereas SCORE2 showed slight negative agreement with PREVENT ($\kappa = -0.09$). The strongest agreement was observed between PCE and AusCVDRisk ($\kappa = 0.64$), with further moderate concordance noted between PREVENT and MESA ($\kappa = 0.30$) and between PCE and MESA ($\kappa = 0.33$). These findings underscore the variability in risk categorisation methodologies across the models and highlight sex-specific differences in pairwise agreement.

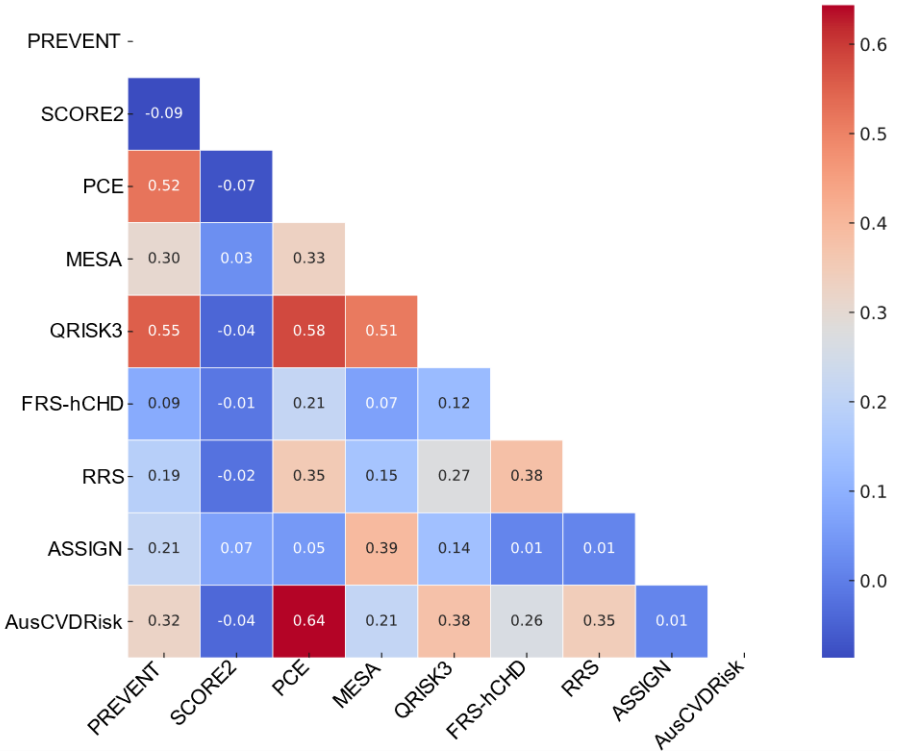


Figure 8. Heatmap illustrating pairwise agreement across nine cardiovascular risk prediction models among females

4.2.3 Cluster Analysis: Hierarchical Clustering

We performed hierarchical agglomerative clustering of nine cardiovascular risk-prediction models using pairwise agreement (Cohen's κ) transformed to a dissimilarity metric (distance = 1 – κ). The resulting dendrograms (overall cohort; male and female subgroups) reveal stable, interpretable groupings that reflect concordance in risk stratification.

Two coherent constellations and one consistently distant triad were observed (Figure 9):

- Constellation A (highest internal similarity): PCE clusters tightly with AusCVDRisk, to which PREVENT and then QRISK3 are subsequently linked at low linkage distances. This indicates broadly congruent risk categorisation among these four tools.
- Constellation B (moderate internal similarity): RRS pairs with FRS-hCHD, forming a compact subcluster that ultimately joins Constellation A at a higher distance—consistent with partial, but weaker, alignment to the PCE/AusCVDRisk/PREVENT/QRISK3 group.

- Distant triad: MESA and ASSIGN form a close pair that then clusters with SCORE2 only at a relatively large distance. This late fusion underscores the divergent behaviour of SCORE2 with respect to the models in Constellation A.

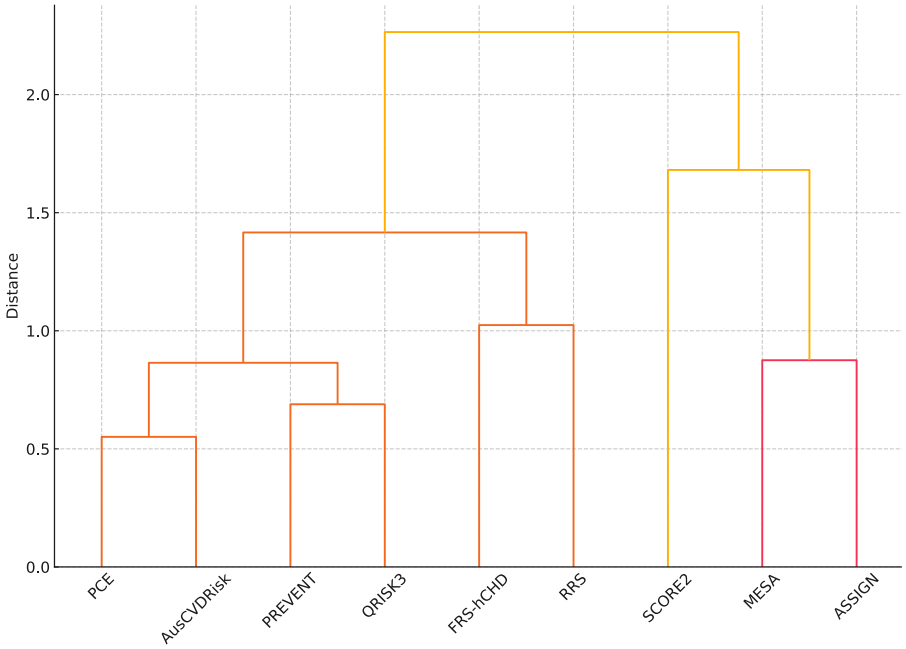


Figure 9. Dendrogram of hierarchical clustering demonstrating similarities across nine cardiovascular risk prediction models

Sex-stratified clustering in males (Figure 10) preserves the global structure with subtle shifts:

- Left-sided cluster: RRS links early with QRISK3, which then merges with PREVENT, AusCVDRisk, PCE, and subsequently FRS-hCHD—again indicating a broad zone of agreement across these models in men.
- Right-sided cluster (distant): MESA and ASSIGN remain a tight pair and cluster with SCORE2 only at high distance, reinforcing SCORE2's relative discordance in male risk classification.

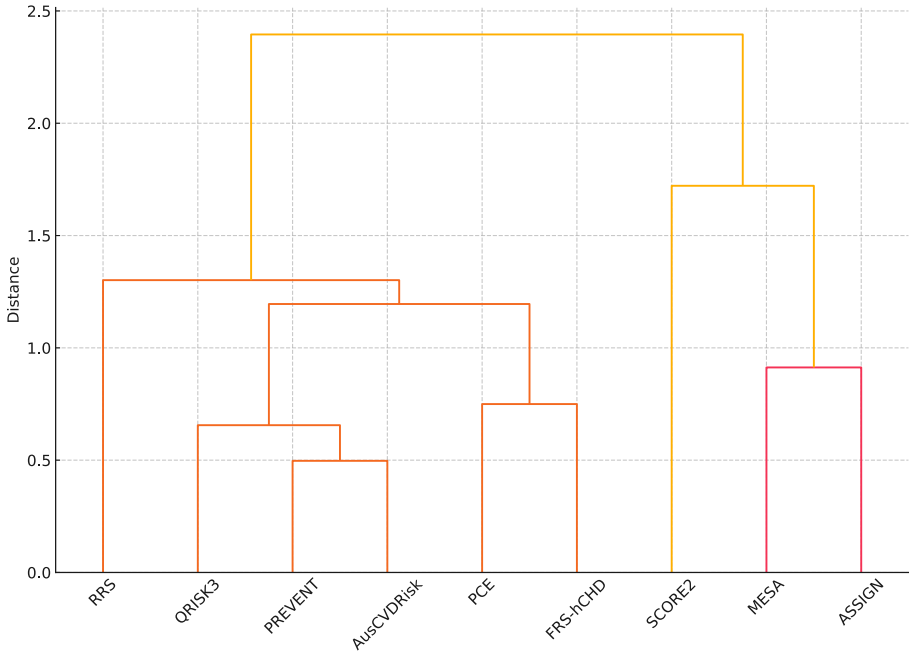


Figure 10. Dendrogram of hierarchical clustering demonstrating similarities across nine cardiovascular risk prediction models among males

Among women (Figure 11), the same macro-pattern is evident, with a clearer separation between the two main constellations:

- Concordant cluster: PCE, AusCVDRisk, and PREVENT again cluster closely, and QRISK3 joins this group at a modest distance—suggesting stable agreement among these tools in female risk stratification.
- RRS–FRS-hCHD pairing: RRS forms a compact pair with FRS-hCHD and subsequently affiliates with the concordant cluster at a higher distance, mirroring the overall cohort.
- Distant triad (most separated in females): SCORE2 joins the MESA–ASSIGN pair only at a high linkage distance, highlighting pronounced divergence of SCORE2 from the PCE/AusCVDRisk/PREVENT/QRISK3 cluster in women.

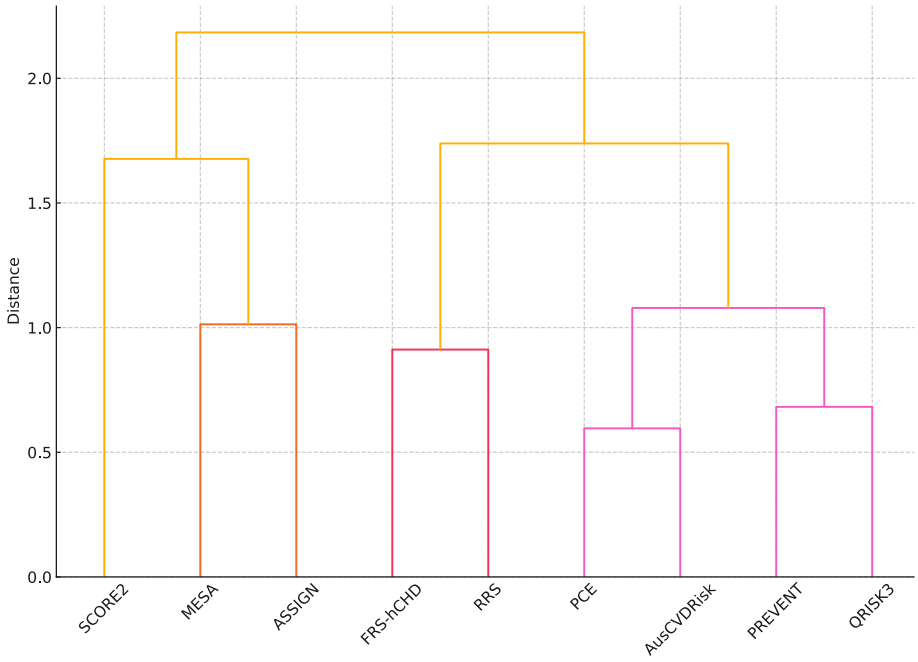


Figure 11. Dendrogram of hierarchical clustering demonstrating similarities across nine cardiovascular risk prediction models among females

Across the full cohort and both sex strata, three features are consistent:

1) A stable, high-similarity cluster comprising PCE, AusCVDRisk, PREVENT, and QRISK3, indicating broadly concordant risk categorisation.
2) A compact RRS–FRS-hCHD pair that aligns with the above cluster only at intermediate distances, denoting partial concordance.
3) A distinct, late-merging triad in which SCORE2 clusters with MESA–ASSIGN only at large distances, signifying methodological divergence from the more concordant group—particularly evident in females.

These patterns corroborate substantial inter-model heterogeneity and, specifically, the relative discordance of SCORE2 with several contemporary tools, supporting the use of multi-model risk ranges and adjudication by vascular markers in clinical decision-making.

4.2.4 Collective Model Agreement Analysis

Finally, we quantified the frequency of agreement among all nine cardiovascular risk prediction models in assigning patients to a specific risk category, thereby offering an overall perspective on model concordance

(Table 2). In the overall cohort, the highest concordance was observed when eight models agreed, which occurred in 2,524 patients (22.59 %). This was closely followed by six-model agreement in 2,316 patients (20.73 %) and five-model agreement in 2,047 patients (18.32 %). In contrast, complete consensus—where all nine models concurred—was relatively rare, affecting only 147 patients (1.32 %), while agreement among only three models was noted in 246 patients (2.2 %).

Among male subjects, a similar pattern was observed. The highest frequencies of agreement were found with five-model and six-model concordance, which were observed in 1,008 (21.69 %) and 1,006 (21.65 %) patients, respectively. Eight-model agreement was also substantial, being recorded in 973 patients (20.94 %). In contrast, complete consensus among all nine models was uncommon among males, occurring in only 18 patients (0.39 %), with four-model agreement present in 797 patients (17.15 %), seven-model agreement in 776 patients (16.70 %), and three-model agreement in 69 patients (1.48 %).

Conversely, in the female subgroup, the highest level of model concordance was observed when eight models agreed, which occurred in 1,551 patients (23.76 %). This was followed by six-model agreement in 1,310 patients (20.07 %) and seven-model agreement in 1,107 patients (16.96 %). Complete consensus across all nine models was achieved in 129 females (1.98 %), while agreement among only three models was seen in 177 patients (2.71 %). Additionally, four-model and five-model agreements were observed in 1,214 (18.6 %) and 1,039 (15.92 %) patients, respectively.

Table 2. The frequency and percentage of occurrences where a designated count of models agree regarding the risk category for a particular patient

Number of Models Agreeing	Number of Patients	Percentage of Patients (%)
Total		
3	246	2.2
4	2011	18
5	2047	18.32
6	2316	20.73
7	1883	16.85
8	2524	22.59
9	147	1.32
Males		
3	69	1.48
4	797	17.15

Number of Models Agreeing	Number of Patients	Percentage of Patients (%)
5	1008	21.69
6	1006	21.65
7	776	16.7
8	973	20.94
9	18	0.39
	Females	
3	177	2.71
4	1214	18.6
5	1039	15.92
6	1310	20.07
7	1107	16.96
8	1551	23.76
9	129	1.98

4.3 Statin Eligibility Analysis

4.3.1 Eligibility Rate Analysis

In the statin eligibility analysis, substantial variability was observed across the nine cardiovascular risk prediction models in categorising patients as eligible for statin therapy (Figure 12). In the overall cohort, the SCORE2 model identified the highest eligibility rate with 7,530 patients (67.39 %), whereas the AusCVDRisk model reported the lowest, classifying only 339 patients (3.03 %) as eligible. Intermediate eligibility rates were noted for the other models: PREVENT identified 5,009 patients (44.83 %), PCE 4,243 (37.97 %), MESA 3,447 (30.85 %), QRISK3 4,358 (39 %), FRS-hCHD 2,554 (22.86 %), RRS 1,640 (14.68 %), and ASSIGN 2,825 (25.28 %).

These findings underscore significant heterogeneity in statin eligibility determination across different models, revealing considerable discrepancies that may have important implications for clinical decision-making in cardiovascular risk management.

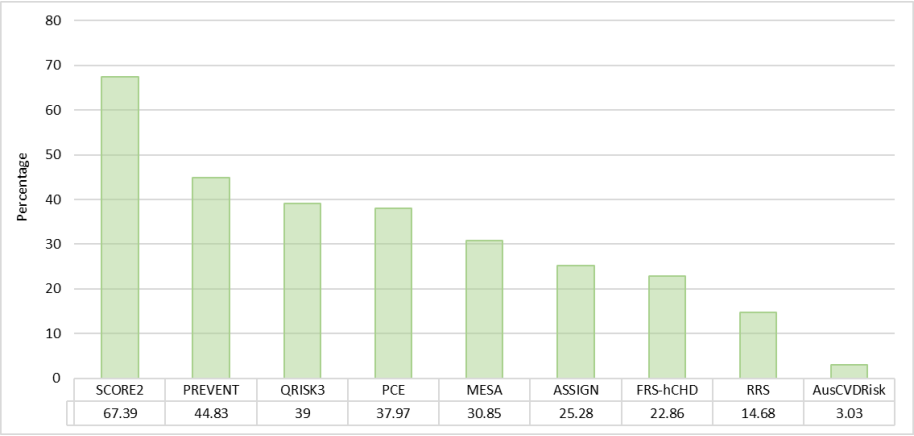


Figure 12. Distribution of statin eligibility across nine cardiovascular risk prediction models

4.3.2 Eligibility Overlap Analysis

In the overall cohort, the heatmap of Cohen's Kappa statistics revealed a wide spectrum of pairwise concordance among the nine cardiovascular risk prediction models in terms of statin treatment eligibility (Figure 13). Kappa values ranged from as low as 0.03 (SCORE2 vs. AusCVDRisk) to as high as 0.67 (QRISK3 vs. ASSIGN), indicating minimal to moderate agreement across different model pairings. Notably, QRISK3 exhibited relatively strong concordance with PCE ($\kappa \approx 0.65$) and MESA ($\kappa \approx 0.64$), whereas PREVENT and AusCVDRisk showed only limited agreement ($\kappa \approx 0.07$). These findings suggest that certain models share more similar criteria for recommending statin therapy, while others diverge considerably in their patient classifications.

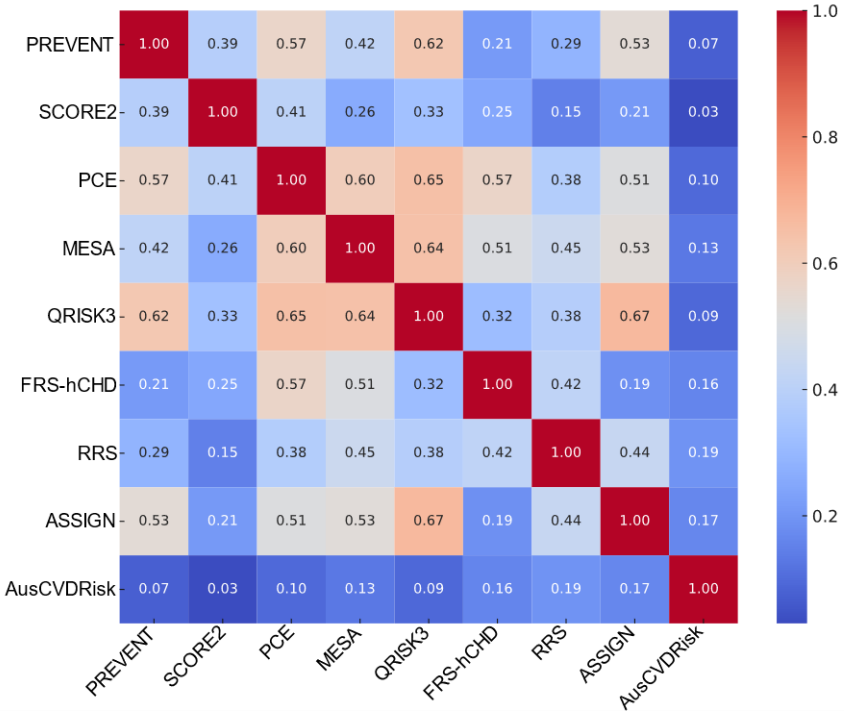


Figure 13. Heatmap illustrating pairwise statin eligibility overlap across nine cardiovascular risk prediction models

4.4 Predictive Performance of Traditional Cardiovascular Risk Prediction Models

We evaluated the predictive performance of nine cardiovascular risk prediction models—SCORE2, PCE, QRISK3, FRS-hCHD, RRS, ASSIGN, AusCVDRisk, MESA, and PREVENT—across five outcomes on outcome-specific dataset (n = 5,812): all-cause mortality (events = 169; prevalence = 2.9 %), cardiovascular (CV) death (events = 41; prevalence = 0.7 %), myocardial infarction (MI) (events = 46; prevalence = 0.8 %), stroke (events = 117; prevalence = 2.0 %), and composite CV event outcome that included CV death, MI, and stroke (events = 192; prevalence = 3.3 %). ROC curves were generated per outcome with all models overlaid, and AUCs were estimated non-parametrically with 95 % confidence intervals (CIs) from stratified bootstrap resampling (B = 200).

Pairwise AUC differences were evaluated with a paired, stratified bootstrap (events and non-events resampled separately; same resamples

applied to both models). For each outcome we first compared the per-outcome best AUC model against the second-best model to assess whether the apparent leader was statistically superior (primary comparison). We also compared the best model against each remaining model and reported the number of comparators that were significantly inferior at α=0.05. Reported p-values are two-sided and unadjusted for multiplicity.

Discrimination (AUC with 95 % CI and pairwise comparisons).

All-cause mortality: PREVENT and AusCVDRisk were co-leaders with AUC = 0.677 (95 % CI 0.634–0.718) and AUC = 0.677 (95 % CI 0.636–0.720), respectively; p (best vs second) = 0.99, with 3 comparators significantly inferior to the best model at α = 0.05 (Figure 14).

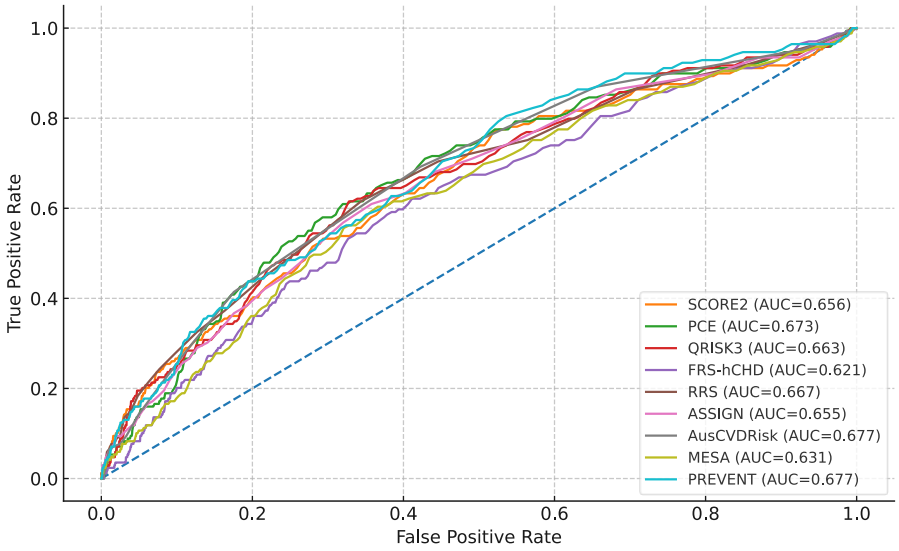


Figure 14. ROC curves for all-cause mortality: comparison of nine risk prediction models

CV death: PCE was highest with AUC = 0.824 (95 % CI 0.766–0.876); AusCVDRisk was second with AUC = 0.814 (95 % CI 0.760–0.871); p = 0.46, with 4 comparators significantly inferior (Figure 15).

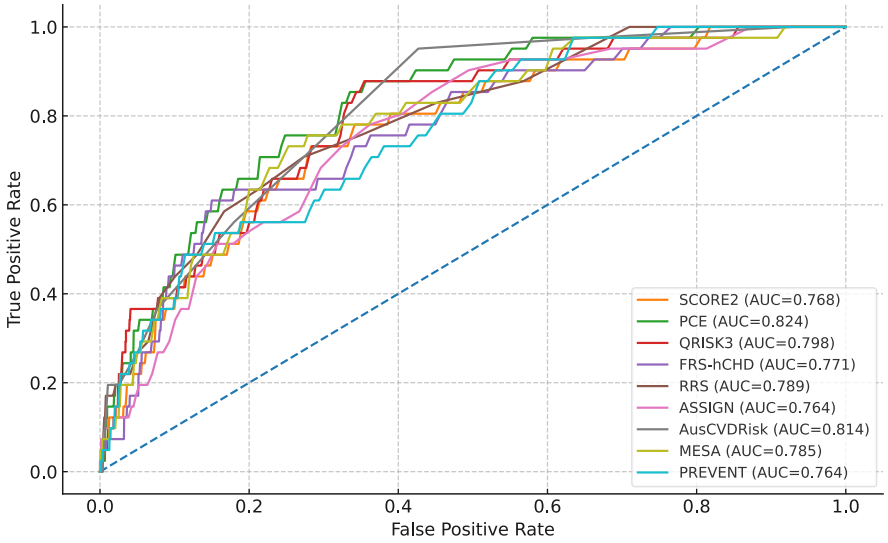


Figure 15. ROC curves for CV death: comparison of nine risk prediction models

MI: PCE led with AUC = 0.785 (95 % CI 0.730–0.842); FRS-hCHD was second with AUC = 0.784 (95 % CI 0.724–0.849); p = 0.96, with 6 comparators significantly inferior (Figure 16).

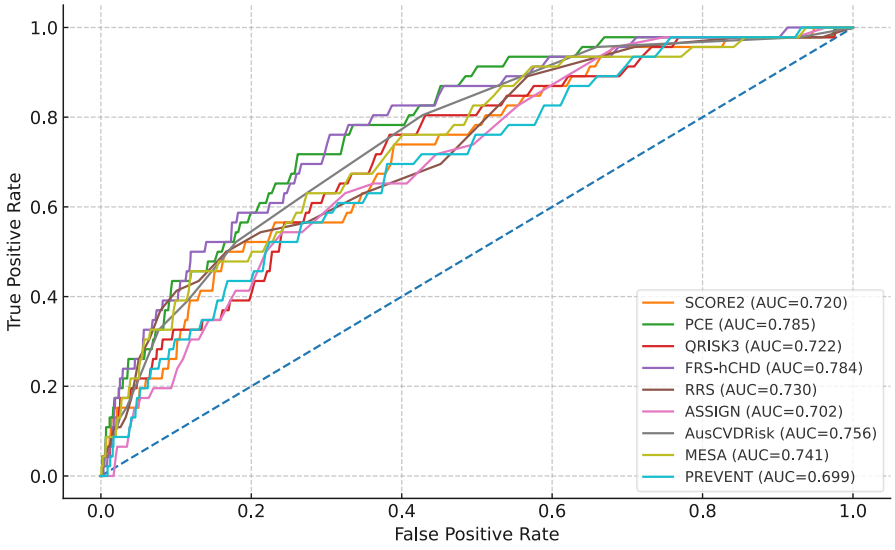


Figure 16. ROC curves for myocardial infarction: comparison of nine risk prediction models

Stroke: PREVENT was highest with AUC = 0.566 (95 % CI 0.512–0.632); SCORE2 was second with AUC = 0.557 (95 % CI 0.508–0.615); p = 0.65, with 2 comparators significantly inferior (Figure 17).

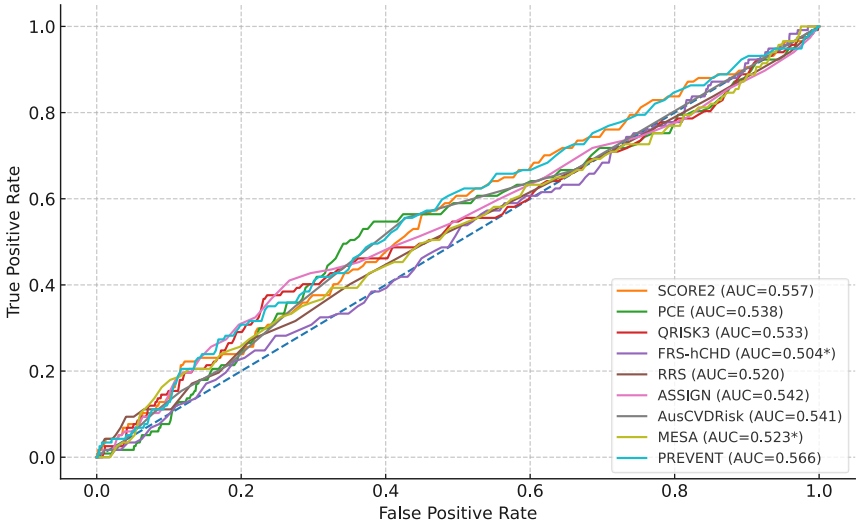


Figure 17. ROC curves for stroke: comparison of nine risk prediction models ("*" indicates sign-flipped scale)

Composite CV event (CV death/MI/stroke): PCE was highest with AUC = 0.647 (95 % CI 0.603–0.691); AusCVDRisk was second with AUC = 0.639 (95 % CI 0.591–0.683); p = 0.29, with 4 comparators significantly inferior (Figure 18).

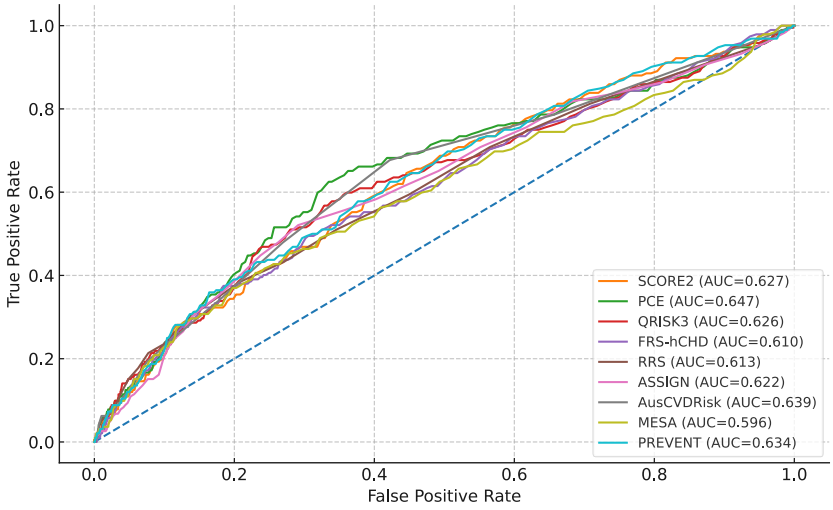


Figure 18. ROC curves for composite CV event: comparison of nine risk prediction models

Overall, between-model AUC differences were modest, and top-two comparisons were not statistically distinguishable across outcomes in this dataset (all $p \geq 0.29$), underscoring the need to consider calibration and clinical utility alongside discrimination.

Clinical utility (decision-curve analysis). Decision curve analysis (DCA) was performed for five endpoints—composite cardiovascular events, all-cause mortality, stroke, myocardial infarction, and cardiovascular death—across clinically plausible decision thresholds (5 %, 7.5 %, 10 %, and 20 %). Outcome prevalences in the analytic cohort were 3.30 % (composite), 2.91 % (all-cause mortality), 2.01 % (stroke), 0.79 % (MI), and 0.71 % (CV death):

- At the 5 % threshold, two outcomes exhibited small but positive net benefit (NB) surpassing both reference strategies ("treat none," NB = 0; "treat all," negative NB):
  - Composite: best model AusCVDRisk, NB = 0.0021; treat-all NB = −0.0179. This corresponds to ≈2 avoided interventions per 100 patients versus "treat all."
  - All-cause mortality: best model AusCVDRisk, NB = 0.0014; treat-all NB = −0.0220, or ≈2.3 avoided interventions per 100 versus "treat all."
  - For MI, stroke, and CV death at 5 %, NB ≤ 0, indicating no net clinical utility relative to "treat none."
- At 7.5 %, only the Composite endpoint retained positive NB: AusCVDRisk, NB = 0.0005; treat-all NB = −0.0454, implying ≈4.6 avoided interventions per 100 versus "treat all." All other outcomes had NB ≤ 0.
- At 10 %, no outcome achieved NB > 0; the best-model NB across outcomes ranged from −0.0031 to −0.0006, so "treat none" dominated at this threshold. At 20 %, no outcome showed positive NB (best-model NB ≈ −0.0001).

In this cohort with low event prevalences, limited clinical utility was observed at low thresholds—notably for composite (5 % and 7.5 %) and all-cause mortality (5 %)—while no model provided net benefit at 10 % or 20 % for any outcome. These findings are consistent with increasing penalties for false positives at higher thresholds, which push NB below zero unless discrimination and calibration are sufficiently strong (Figures 19; 20; 21; 22; 23).

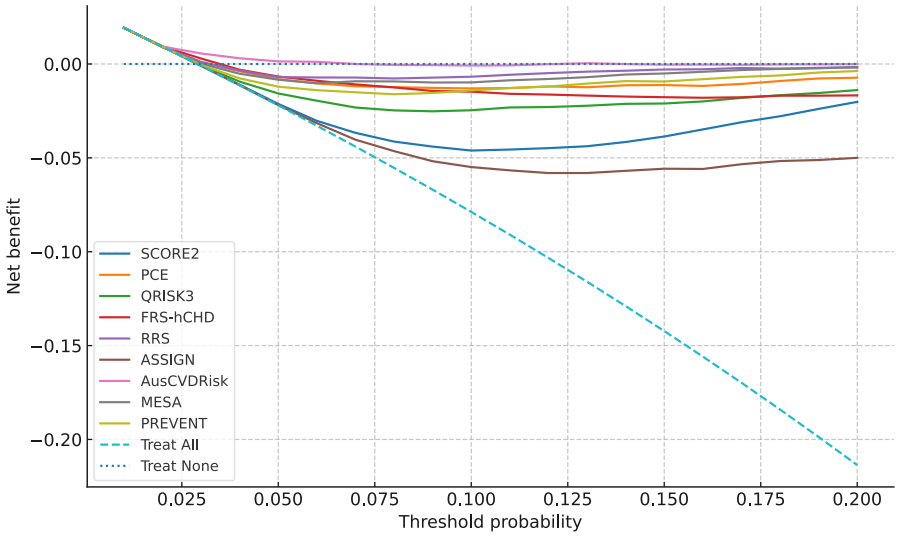


Figure 19. Decision curve analysis for all-cause mortality (n = 5,812)

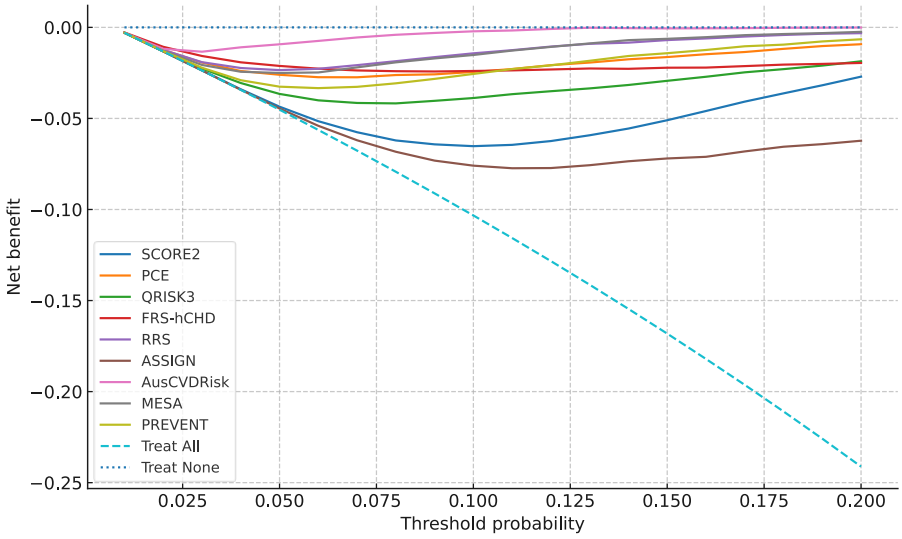


Figure 20. Decision curve analysis for cardiovascular mortality (n = 5,812)

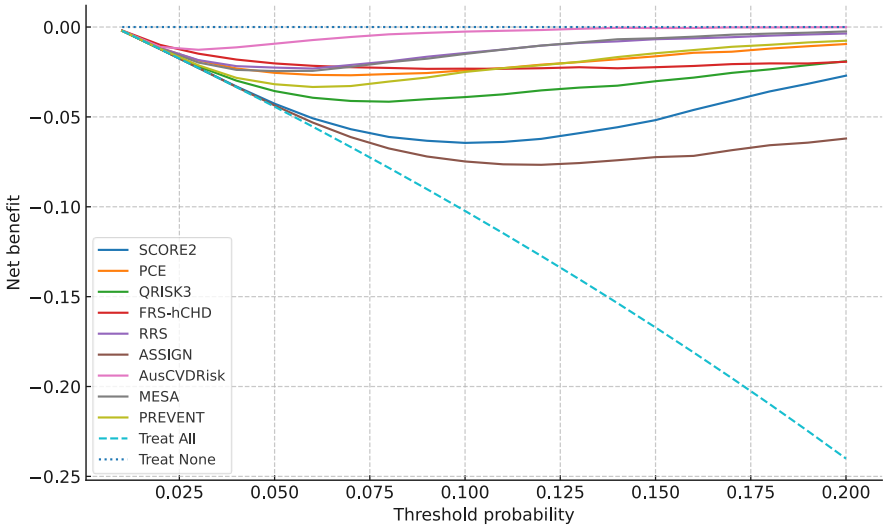


Figure 21. Decision curve analysis for myocardial infarction (n = 5,812)

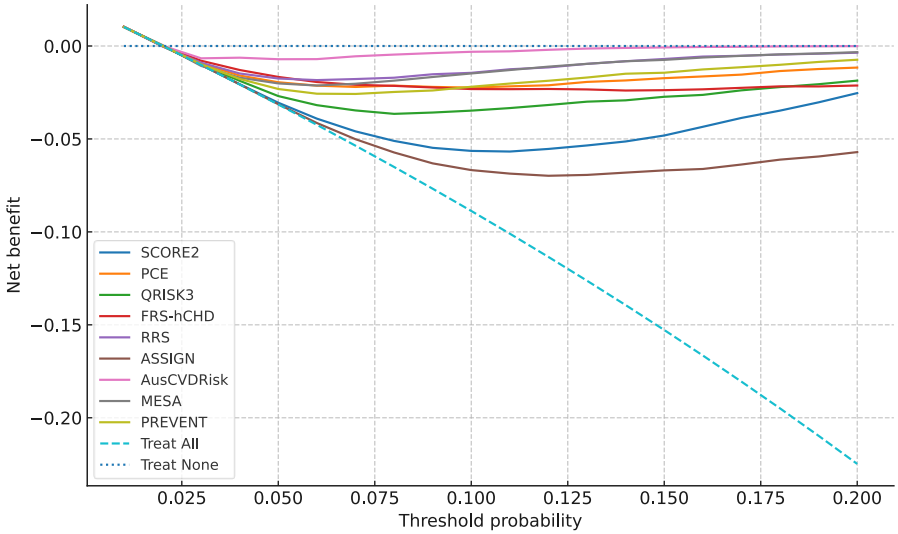


Figure 22. Decision curve analysis for stroke (n = 5,812)

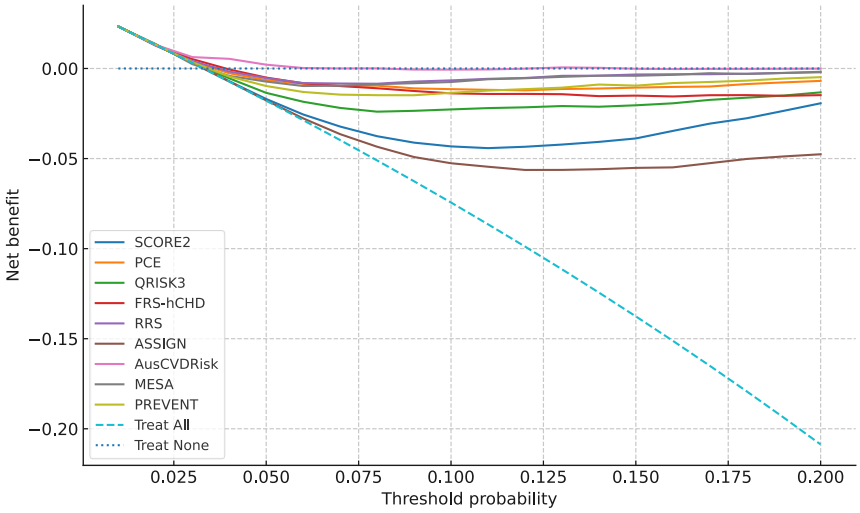


Figure 23. Decision curve analysis composite CV event: comparison of nine risk prediction models

The above results suggest a performance ceiling of conventional RPMs within this cohort. Together with heterogeneous threshold-dependent net benefit, these findings motivate the integration of vascular biomarkers and development of personalised, multiparametric, AI-based models to enhance discrimination, improve absolute risk accuracy, and yield greater net clinical benefit at decision-relevant thresholds.

4.5 Machine Learning–Based Cardiovascular Risk Prediction Incorporating Vascular Biomarkers

To quantify the incremental predictive utility of a vascular ageing biomarker, we developed three supervised models using a unified preprocessing–modelling pipeline. All analyses were conducted on an outcome-specific dataset (n = 5,812), a subset of the full registry; the full database is larger but lacks complete outcome ascertainment for all records, hence only patients with adjudicated outcomes for the composite endpoint were retained. Because the number of events for individual outcomes was limited, all machine-learning analyses were prespecified to target the composite cardiovascular endpoint aggregating cardiovascular (CV) death, myocardial infarction, and stroke (composite CV events). Focusing on this aggregated outcome increased the number of events available for evaluation and improved the stability of out-of-sample estimates.

Further, preprocessing and modelling were standardised across all ML specifications: mean imputation → z-score standardisation → Random Forest classifier with 100 trees, evaluated on a fixed 70/30 stratified split (random_state = 42). The resulting test set comprised N = 1,744 individuals with 58 events (3.3 %) and 1,686 non-events; all between-model comparisons were restricted to these exact rows. Three primary comparators were evaluated on the same test instances:

- RF (7 var) model's variables: age; gender; diastolic blood pressure; total cholesterol; triglycerides; fasting glucose; C-reactive protein;
- RF (7 var+PWV) model's variables: age; gender; diastolic blood pressure; total cholesterol; triglycerides; fasting glucose; C-reactive protein; femoral pulse wave velocity;
- SCORE2: calculated without training on the identical test individuals (for probability-based metrics, the SCORE2 risk was scaled to [0,1] by dividing by 100; this scaling does not affect discrimination/AUC);

In addition, for context of parsimony, we also report a compact RF (6 var)—age; diastolic blood pressure; triglycerides; fasting glucose; C-reactive protein; smoking status—to illustrate that more features do not necessarily yield superior discrimination in low-event settings.

AUCs were estimated on the held-out test set with non-parametric bootstrap 95 % CIs (4,000 resamples). Paired bootstrap (same resamples across models) provided two-sided p-values for ΔAUC between models.

4.5.1 Model Performance, Operating Points, Calibration, and Parsimony

On the common test set, RF (7 var+PWV) achieved an AUC = 0.614 (95 % CI 0.542–0.682), which was higher than SCORE2 (AUC = 0.600, 95 % CI 0.518–0.674) and the RF (7 var) baseline (AUC = 0.545, 95 % CI 0.465–0.625) (Figure 24). In paired bootstrap comparisons, adding PWV yielded a ΔAUC = +0.070 for RF (7 var+PWV) vs RF (7 var) with a borderline p = 0.053, indicating a directionally favourable and nearly significant improvement in discrimination attributable to the vascular biomarker. In contrast, RF (7 var) vs SCORE2 gave ΔAUC = −0.055 (p = 0.228), i.e., the seven-feature RF without PWV underperformed the established score. Although RF (7 var+PWV) was numerically superior to SCORE2 (ΔAUC = +0.015), this difference was not statistically significant (p = 0.722). These results support the inference that PWV contributes incremental predictive signal for Composite CV events in this cohort, while also illustrating that not all ML specifications surpass traditional scores when evaluated fairly on the same rows.

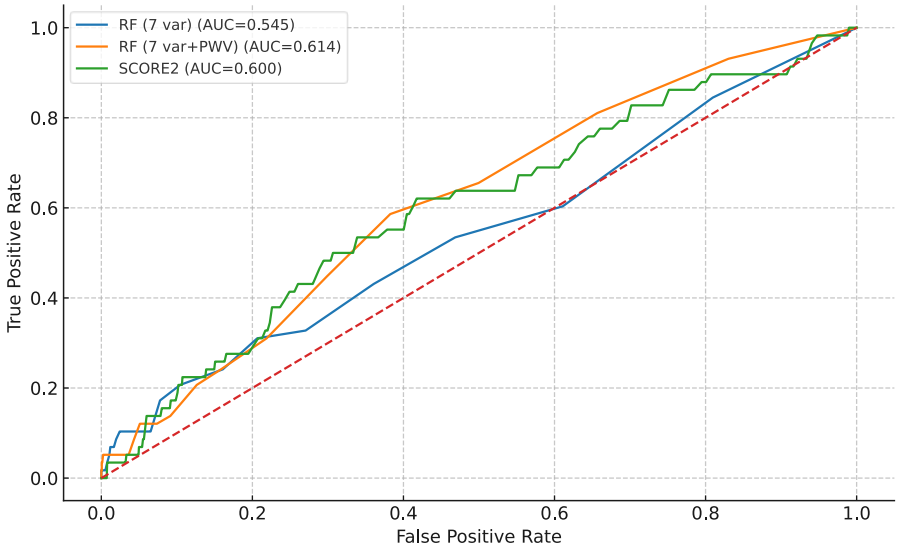


Figure 24. ROC curves for composite cardiovascular events: RF (7 var), RF (7 + PWV), and SCORE2

To complement threshold-free AUC summaries with operating-point performance, we examined sensitivity–specificity trade-offs at ≈80 % and ≈90 % specificity on the test set:

- At a target of ~80 % specificity: RF (7 var+PWV) achieved specificity = 0.781 with sensitivity = 0.310 (TP/FP/TN/FN = 18/369/1317/40; PPV = 0.047, NPV = 0.971), while RF (7 var) achieved specificity = 0.794 with sensitivity = 0.310 (18/348/1338/40; PPV = 0.049, NPV = 0.971). SCORE2 at ~80 % specificity (specificity = 0.805) yielded sensitivity = 0.276 (16/328/1358/42; PPV = 0.047, NPV = 0.970).
- Tightening to ~90 % specificity: RF (7 var+PWV) operated at specificity = 0.909 with sensitivity = 0.138 (8/154/1532/50; PPV = 0.049, NPV = 0.968), RF (7 var) at specificity = 0.896 with sensitivity = 0.207 (12/176/1510/46; PPV = 0.064, NPV = 0.970), and SCORE2 at specificity = 0.899 with sensitivity = 0.190 (11/170/1516/47; PPV = 0.061, NPV = 0.970).
- As expected with 3.3 % prevalence, PPV values were low across all models and thresholds, while NPV was uniformly high (>0.968). These operating-point results echo the AUC-based ranking and show that PWV does not worsen false-positive burden at comparable specificity.

We further quantified calibration on the held-out test set. Brier scores were 0.0329 for RF (7 var), 0.0325 for RF (7 var+PWV), and 0.0440 for SCORE2

(the latter computed after scaling the SCORE2 risk to a 0–1 probability). Logistic calibration regressing the observed outcome on the logit of predicted risk yielded calibration-in-the-large (intercept) and calibration slope, respectively: RF (7 var) intercept −3.20, slope 0.033; RF (7 var+PWV) intercept −2.82, slope 0.125; SCORE2 intercept −2.17, slope 0.633. In absolute terms, all three models overpredicted risk in this cohort (negative intercepts) and were under-confident in slope (<1), consistent with probability shrinkage in the RFs and systematic overestimation by SCORE2 given the observed 3.3 % event rate. As a practical matter, these findings argue for post-hoc recalibration (e.g., intercept/slope adjustment) prior to deployment, while noting that recalibration would not alter the relative ordering by AUC.

Finally, a deliberately examined a parsimonious variant, RF (6 var) with age, CRP, DBP, fasting glucose, smoking status, TG, achieved AUC = 0.624 (95 % CI 0.547–0.701) on the same test set—numerically higher than both RF (7 var) and RF (7 var+PWV) here (Figure 25; Table 3). This observation underscores that adding more variables does not guarantee better out-of-sample discrimination, particularly in low-event settings where redundancy and sampling variability can dominate. Regarding robustness, across 4,000 paired bootstrap resamples the PWV-augmented model exceeded the seven-feature baseline in the vast majority of resamples (directionally consistent improvement), and the primary RF (7 var+PWV) vs RF (7 var) comparison remained borderline significant ($p \approx 0.053$). Taken together, these results suggest that vascular ageing measures such as PWV warrant further exploration in CV risk prediction; however, parsimony and recalibration should be prioritised alongside the inclusion of additional biomarkers, and traditional scores like SCORE2 remain difficult to surpass without sufficient event counts and external validation on independent cohorts.

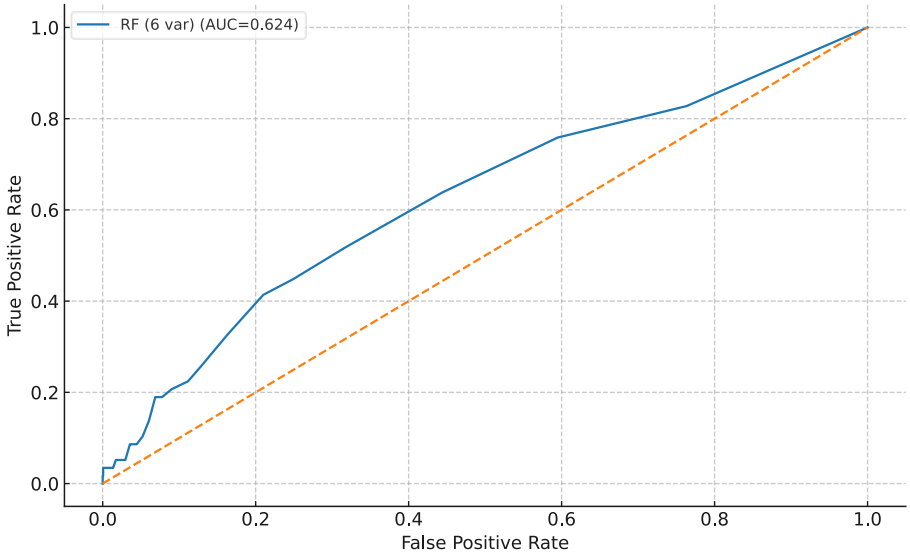


Figure 25. ROC curve for composite cardiovascular events: RF (6 var)

Table 3. Test-set AUC and 95 % confidence intervals for composite cardiovascular events: Random Forest models (7 vars, 7 + PWV, 6 vars) versus SCORE2

Model	AUC	95 % CI (Lower)	95 % CI (Upper)
RF (7 var)	0.544842	0.46541	0.625234
RF (7 var+PWV)	0.614462	0.542142	0.68204
SCORE2	0.599532	0.518196	0.674114
RF (6 var)	0.6241	0.547404	0.701087

4.5.2 Global Explainability of the Random-Forest Models

Global explainability, assessed with model-based feature importance and corroborated by SHAP on the fitted Random-Forest models, indicated that age contributed the largest share of predicted risk across specifications. In the RF (7 var) model, the next most influential features were diastolic blood pressure and fasting glucose, followed by CRP; total cholesterol and triglycerides showed smaller but non-negligible contributions, while the male sex indicator contributed the least. Upon adding femoral PWV (RF (7 var+PWV)), PWV emerged as a mid-to-high–rank contributor—approximately comparable to diastolic blood pressure and fasting glucose—which is directionally consistent with the observed improvement in discrimination (AUC 0.614 vs. 0.545; ΔAUC = +0.070, paired bootstrap p = 0.053). Taken together, the attribution

patterns support the incremental signal carried by vascular ageing, while also illustrating that traditional covariates (age, blood pressure, glycaemia, inflammation) remain the dominant determinants of model output in this cohort.

5. DISCUSSION

This study delivers a systematic head-to-head evaluation of nine widely used cardiovascular risk-prediction models in a large Lithuanian, metabolic-syndrome–enriched primary-prevention middle-age cohort, revealing marked inter-model heterogeneity in risk categorisation and calibration—thereby underscoring the need for cautious, context-specific application and motivating the development of locally validated, biomarker-informed machine-learning approaches.

5.1 Comparison of Risk Prediction Models: Agreement, Statin Eligibility, and Predictive Performance

The present analysis provides a head-to-head evaluation of nine widely used cardiovascular risk prediction models in a Lithuanian primary prevention cohort. We found substantial variation in how these models stratify patients into risk categories and qualify individuals for statin therapy, underscoring the need for circumspect application in practice. For example, the SCORE2 algorithm categorised an overwhelming majority of participants (≈67 %) as high-risk, whereas the RRS labelled most individuals as low-risk (over 85 % in the lowest-risk group). Models like ASSIGN yielded a more balanced distribution across risk tiers, while tools such as the PREVENT and QRISK3 identified far fewer high-risk individuals compared to SCORE2 or MESA. These disparities in risk categorisation are clinically consequential, as they translate into markedly different management recommendations for the same patient population.

Consistent with these distribution differences, the models showed only moderate agreement with one another in classifying individual patients' risk. Pairwise Cohen's κ statistics revealed that certain clusters of models behave similarly. Notably, the PCE and the Australian CVD risk score (AusCVDRisk) had a high concordance (κ ~0.64), suggesting they often identified the same persons as high- or low-risk. The new PREVENT equations aligned closely with PCE and QRISK3 (κ ~0.53), indicating that this contemporary AHA model yields a similar risk stratification to those established tools. In contrast, SCORE2 showed negligible or even negative agreement with several others – for instance, κ ~–0.08 versus PREVENT and –0.09 versus PCE – highlighting a fundamentally divergent classification approach. Moderate agreements were observed in a few other pairings (e.g., QRISK3 with AusCVDRisk, κ ~0.51; MESA with ASSIGN, κ ~0.40), but on the whole, there was no single pair of models that consistently classified

patients alike. Indeed, complete consensus (all nine models agreeing on the same risk category for a patient) was exceedingly rare (under ~2 % of cases, per a prior subset analysis), underscoring how differently these tools can view the same individual. Hierarchical clustering of the agreement data reinforced these findings: PCE, AusCVDRisk, PREVENT, and QRISK3 formed a tight group (Constellation A), RRS paired with FRS-hCHD as a secondary cluster, and SCORE2 remained an outlier that only joined the others at a distant linkage – especially among women, where SCORE2's late fusion with the MESA–ASSIGN pair was most pronounced. This "SCORE2 vs. the rest" pattern suggests that SCORE2's risk assignments are uniquely high in many cases where the other models concur, which raises concern given SCORE2's prominence in European practice.

Several factors likely contribute to the poor concordance among RPMs. Differences in risk classification thresholds and predictive time intervals are one obvious cause. Some tools target 10-year risk (e.g., SCORE2, PCE, QRISK3), while others use 5-year risk (AusCVDRisk) or even lifetime risk projections; what one model deems "high-risk" (e.g., ≥10 % 5-year risk in Australian guidelines) may not align with a 10-year risk threshold in another tool. Likewise, the outcomes and endpoints considered vary: FRS-hCHD predicts hard coronary events, SCORE2 emphasises total (fatal + non-fatal) atherosclerotic CVD, and QRISK3 and PREVENT incorporate an even broader range of cardiovascular outcomes. A model focused narrowly on fatal events or CHD will naturally classify fewer people as high-risk than one predicting any vascular event. Additionally, each algorithm uses a unique set of predictors and cohort-derived coefficients. For example, PREVENT includes kidney function (estimated glomerular filtration rate (eGFR)), QRISK3 integrates socioeconomic factors and certain comorbidities (like atrial fibrillation or rheumatoid arthritis), and ASSIGN adds a Scottish deprivation index and family history. These tailored inputs lead to different risk estimates for the same individual. It is also worth noting that our agreement analysis was based on risk ranks/categories rather than absolute risk values, which minimises the impact of baseline risk calibration differences – yet substantial disagreement persisted, pointing to deeper methodological discrepancies. Another critical factor is the population origin of each model. The tools we examined were derived in diverse settings: SCORE2 from pooled European cohorts [8], ASSIGN from a Scottish cohort with unique social risk profiles [10], AusCVDRisk from an Australasian recalibration of the New Zealand PREDICT study, FRS-hCHD from the historic Framingham U.S. cohort, MESA from a modern multi-ethnic American cohort [6], PCE from multiple U.S. cohorts (ARIC, CHS, CARDIA

etc.) used to create race- and sex-specific equations, QRISK3 from a large contemporary UK primary care database [9], and RRS from a U.S. women's cohort enriched with biomarkers (hsCRP) and family history [4]. These disparate derivation cohorts and design intents mean each model is "tuned" to a different context. Thus, when applied to the same Lithuanian patients, they naturally yield discrepant predictions, as we observed. In our study, for instance, the RRS – originally developed in women – showed a distinctive pattern in females (pairing closely with FRS-hCHD and remaining separate from the PCE cluster), whereas in males the RRS aligned more with the PCE/QRISK constellation, reflecting how a model's developmental lineage (in this case, a female-focused cohort) can influence its behavior across sexes. Likewise, SCORE2's emphasis on European high-risk populations led it to over-classify risk in our sample, whereas AusCVDRisk (calibrated to generally lower-risk Australians) was far more conservative – a clear demonstration of how regional epidemiology and guideline thresholds drive model outputs.

Beyond categorisation agreement, we evaluated each model's discrimination, calibration, and clinical utility. Overall, discrimination was modest and fairly similar across the traditional RPMs. No model achieved what would be considered excellent predictive power in our cohort; most C-statistics (AUCs) for 10-year hard outcomes hovered in the 0.65–0.75 range. For example, PCE, PREVENT, and AusCVDRisk each attained an AUC ~0.67 for all-cause mortality, marginally outperforming older scores like Framingham (AUC ~0.62) and MESA (~0.63) in that outcome. For hard atherosclerotic outcomes (e.g., CV death or MI), some models performed a bit better – PCE reached ~0.78–0.82 for CV mortality, and for MI prediction, PCE was also among the leaders (AUC ~0.78) – but differences between the top contenders were small. In no single outcome was SCORE2 the top performer; in fact, SCORE2's discrimination was often on the lower end (e.g., AUC ~0.72 for MI vs. ~0.78 for the best model). This is notable given SCORE2's endorsement in European practice, and it suggests that at least in this Lithuanian middle-aged sample, the newer SCORE2 algorithm did not confer an advantage in ranking individuals by risk. We also observed sex-specific performance patterns: generally, discrimination was slightly higher in men (not surprising, as many models were derived in mixed-sex or male-dominated cohorts), whereas in women the same models tended to have lower AUCs and wider confidence intervals (reflecting fewer events). This aligns with broader evidence that traditional scores often underperform in women – for instance, some studies report C-statistics in women below 0.65 for tools that perform well in men [125]. Such underperformance can lead to

underestimation of risk in women [126-128], reinforcing calls for sex-specific calibration or models. In terms of calibration, as expected, applying these RPMs without local recalibration led to systematic miscalibration of absolute risk. All nine models over-predicted events in our cohort, evidenced by calibration intercepts well below 0 and slopes far under 1 (ideal=1). For instance, logistic calibration of SCORE2 indicated an intercept of about –2.2 and slope ~0.63 on our data (meaning it was substantially overestimating risk and not scaling perfectly to observed outcomes). Other models showed a similar trend of overestimation, likely because the base event rate in our cohort (3.3 % composite event rate over ~10 years) was lower than what their original populations experienced or assumed. This has practical implications: a 10 % 10-year risk per these models may actually correspond to a much lower realised risk in Lithuanian patients, which could lead to over-treatment if guidelines are followed to the letter. Finally, our decision-curve analysis found that no model provided a large net benefit advantage across a range of risk thresholds. Many of the curves for different RPMs intersected or ran close to the "treat-all" strategy, especially at lower thresholds (e.g., 5–7.5 % 10-year risk), indicating that in this primary-prevention setting with low event rates, the clinical utility of these scores is limited. There were hints of sex differences here: for example, in women, models that aggressively assign high risk (like SCORE2) actually showed negative net benefit at lower thresholds – essentially performing worse than treating all women with preventive therapy – due to identifying so many false-positive "high-risk" individuals. Men tended to have slightly higher net benefit for the same models at equivalent thresholds (owing to higher event incidence), but overall, the rank order of models' net benefit was similar between sexes. Importantly, no single risk calculator consistently dominated the net benefit; even the best discriminators provided only modest incremental benefit (<5 % absolute) over simpler approaches. This emphasises that improving model calibration and specificity (to avoid unnecessary treatment of low-risk people) is just as crucial as improving raw discrimination.

Our findings both align with and add to the existing literature on RPM performance. Multiple external validation studies have documented miscalibration and misclassification by these models in various populations. For example, the original SCORE (2003) was reported to underestimate CVD risk in certain high-risk countries and subgroups, prompting recalibrations in multiple regions [12,129]. Framingham-based scores, on the other hand, notoriously overestimate risk when applied outside the U.S. (by as much as 30–50 % in some European cohorts) [12]. The ACC/AHA PCE has drawn scrutiny for divergent performance across ethnic groups: it over-predicted 10-

year ASCVD risk in Chinese Americans while under-predicting in South Asian Americans [13,14], reflecting how a one-size-fits-all model can misfire in minority populations. Likewise, PCE equations have been found to underpredict events in individuals of lower socioeconomic status and those with chronic inflammatory conditions (e.g., HIV, rheumatoid arthritis, systemic lupus), who experience higher actual event rates than their calculated risk would suggest [130-132]. Our observation that RRS categorised far fewer patients as high-risk than many other models is consistent with its design: RRS was intended to reclassify intermediate-risk women by incorporating hsCRP, and indeed, prior work showed RRS can better identify women at risk who were missed by Framingham (improving classification of women in the 5–20 % 10-year risk range) [5]. The RRS (and its men's version) has also proven useful in cohorts with inflammatory disorders, predicting long-term CVD risk more accurately than traditional scores in patients with rheumatoid arthritis and other autoimmune diseases [133]. Meanwhile, the newer models in our study illustrate both the promise and the challenges of "next-generation" risk tools. PREVENT, an equation derived from contemporary U.S. cohorts, performed very similarly to PCE and QRISK3 in our analysis, which mirrors a recent finding from Switzerland that PREVENT did not outperform SCORE2 in an external comparison [134]. This indicates that simply updating cohort data (as PREVENT did relative to PCE) doesn't automatically yield a more transportable model. Similarly, QRISK3, despite its rich risk factor list and excellent performance in UK derivation (C-statistic ~0.86 in women, ~0.83 in men on internal validation [125], may require recalibration abroad – one study found QRISK3's C-index fell to ~0.72 for women in an external cohort [135]. The ASSIGN score, though tailored for Scotland, included a deprivation score we could not implement; this highlights how missing or inapplicable inputs can hinder a model's use in new settings (a limitation we faced with ASSIGN, AusCVDRisk, and PREVENT due to a lack of certain region-specific variables). Lastly, the stark contrast in statin eligibility yielded by these models cannot be overlooked. In our cohort, the proportion of patients deemed statin-eligible ranged from as low as 3 % (AusCVDRisk) up to 67 % (SCORE2) – a more than 20-fold difference. Most models clustered in the intermediate range (e.g., ~38–45 % for PCE, QRISK3, PREVENT; ~23–25 % for FRS-hCHD, ASSIGN), but the extremes are telling. AusCVDRisk's very low eligibility rate stems from its shorter prediction time (5 years), whereas SCORE2 (using "very-high-risk region" calibration in our case) flags nearly everyone with metabolic syndrome as deserving intensive therapy. Such variability has been echoed in the literature: in a recent analysis by Mortensen et al., applying different international guidelines to the same population led to

only 4 % of individuals qualifying for statins under the 2021 ESC/SCORE2 criteria versus 34 % under U.S. (ACC/AHA) criteria and 20 % under UK (National Institute for Health and Care Excellence (NICE) QRISK3) criteria [15]. Our results reaffirm that depending on which risk calculator is chosen, a large fraction of patients could be started on lifelong statin therapy or, conversely, not treated at all – a concerning roulette that could impact outcomes. Taken together, prior studies and our head-to-head comparison paint a consistent picture of inter-model heterogeneity. Even when statistical methodologies and cohorts differ, the recurring theme is low agreement and frequent miscalibration among competing risk tools [15,136]. This lack of concordance can lead to conflicting clinical decisions – from who gets medication or more aggressive counselling to who doesn't – highlighting an urgent need to improve risk assessment strategies. Overall, these findings reveal marked inter-model heterogeneity in risk categorisation and calibration—thereby underscoring the need for cautious, context-specific application and motivating the development of locally validated, biomarker-informed machine-learning approaches.

5.2 Toward Locally Adapted ML-Based Risk Prediction

The clear limitations of existing RPMs in our cohort – from miscalibrated absolute risks to discordant treatment recommendations – motivate exploration of new approaches. In particular, our results support a turn toward machine-learning-based models that can be trained on local data and augmented with novel biomarkers. Traditional risk equations, while well-established, cannot easily adjust to population shifts or incorporate emerging risk factors without a lengthy guideline revision process. In contrast, ML models offer flexibility to learn patterns from local epidemiology (thereby inherently recalibrating to the host population) and to integrate non-linear interactions or additional inputs (e.g., inflammatory or vascular biomarkers) that most classical scores omit. The heterogeneity observed between the nine compared models serves as a cautionary tale: if one model can label two-thirds of patients high-risk while another labels the vast majority low-risk, clearly no single "out-of-the-box" tool is universally reliable. This is precisely where a data-driven, locally-trained ML model could add value – by tailoring risk predictions to Lithuania's unique risk factor distribution and outcome rates, rather than relying entirely on extrapolation from foreign cohorts. Moreover, the inclusion of biomarkers like high-sensitivity CRP or measures of arterial stiffness (which current scores treat, at best, as optional modifiers) could meaningfully improve risk stratification in cases where conventional factors

paint an incomplete picture. In short, the next generation of risk models for our setting will likely require both local customisation and broader information inputs, goals that an ML framework is well-suited to achieve.

Our exploratory machine learning analyses, though preliminary, provided some insights into the potential and pitfalls of this approach. We trained several random forest models using a limited set of readily available clinical variables, with and without a vascular biomarker, and tested their performance on held-out data. Interestingly, the most complex model (RF with 7 variables, mimicking the core Framingham risk factors) did not perform best – in fact, it had the lowest discrimination (test AUC ≈0.545). This counterintuitive result likely reflects overfitting and class imbalance in our sample: with relatively few events (~3 % incidence) and no regularisation, an unconstrained RF can learn spurious patterns that don't generalise. Indeed, without careful hyperparameter tuning or larger data, adding more predictors can introduce noise and instability rather than improving accuracy. When we incorporated carotid-femoral pulse wave velocity as an additional feature – motivated by its role as a biomarker of vascular ageing – the RF's performance improved notably (AUC ↑ ~0.07 to ~0.614, borderline p≈0.05). This suggests that PWV carries an incremental prognostic signal, aligning with our expectation that arterial stiffness indicates cumulative vascular damage beyond what traditional risk factors capture. Perhaps most intriguingly, a parsimonious RF using only 6 variables (age, smoking, diastolic blood pressure, fasting glucose, triglycerides, and hs-CRP) achieved the highest discrimination of the three ML models (AUC ≈0.62). Despite using one fewer variable than the full model – notably excluding sex and total cholesterol – this streamlined model slightly outperformed both the 7-factor model and the PWV-augmented model. While the differences were small, this outcome reinforces an important principle: more features do not guarantee a better model, especially in limited datasets. Irrelevant or redundant variables (or those with unstable importance) can hurt generalisation when event rates are low. The superior performance of the 6-variable model likely arose from focusing on the strongest predictors (several of which coincide with metabolic syndrome components and inflammation) and implicitly reducing overfit. It is also a testament to the value of biomarkers like CRP – which was among the top contributors in the RF models – in capturing risk that may be missed by traditional cholesterol-focused metrics. Notably, even with its small advantage, the best ML model's AUC (~0.62) was still in the same ballpark as the better traditional models (and within the confidence interval of, say, PCE or QRISK3 in our dataset). This underscores that ML is not a magical solution – at least not with the sample size and variables at hand. Other groups have likewise found that ML-

based CVD risk models offer only modest discrimination gains over established scores in external comparisons (often on the order of +0.01–0.02 in C-statistic) [23]. For instance, a recent meta-analysis reported that contemporary ML models achieved an average C-index of ~0.773 versus ~0.759 for traditional scores, a statistically significant ($P < 0.0001$) but clinically modest difference [24]. Similarly, Cho et al. showed in a large Korean cohort that an ANN model slightly but significantly outperformed the PCE (C-statistic 0.751 vs 0.738) and had better calibration [23]. Our experience mirrors these findings: incremental improvement is possible with ML (especially when adding novel markers like PWV or CRP), but dramatic leaps in accuracy were not observed, likely owing to fundamental limitations of the data (e.g., unmeasured risk factors, inherent unpredictability of who develops events, and the low event base rate). The key takeaway is that any ML model must be rigorously validated and probably recalibrated before use – we saw that our RF models, like the published scores, overestimated absolute risk and would require intercept/slope adjustments for calibration-in-the-large. Without external validation, there is also risk of optimism; thus, these exploratory ML results primarily illustrate feasibility and guide future development rather than provide a deployable tool just yet.

Despite these cautions, ML-based risk prediction holds several practical advantages that we believe warrant further pursuit. First, ML can seamlessly incorporate new predictors (such as the biomarker panel mentioned above) and complex interactions between them, which could help in adjudicating discordant cases. For example, consider a patient whom SCORE2 classifies as high-risk but QRISK3 as low-risk – measuring an additional factor like PWV and inputting it into a more flexible ML model might tilt the risk estimate one way or the other with better justification, potentially resolving the ambiguity. In our cohort, incorporating PWV reclassified some individuals to higher predicted risk (those with advanced arterial stiffness), which could target intensive therapy to those who truly need it among seemingly low-risk profiles. Second, ML algorithms can be updated continuously as new data accrue. Traditional models require formal recalibration studies or new editions (e.g., the jump from SCORE to SCORE2 took nearly two decades); an ML model could be periodically retrained on emerging local outcome data, ensuring it stays calibrated to current trends in risk factors and event rates. This is particularly relevant in Lithuania and Eastern Europe, where CVD epidemiology is evolving and may not mirror the historical data underlying Western risk scores. Third, although often criticised for opacity, ML models can be made interpretable – for instance, using techniques like SHAP values or adopting inherently explainable algorithms (e.g., Explainable Boosting

Machines). In our analysis, we employed SHAP-based global explanations, which confirmed that age, blood pressure, glycemia, and CRP were dominant drivers of risk in the RF models – reassuringly, the same factors that any clinician would recognise as critical, thus building trust that the model is leveraging meaningful signals rather than noise. We also saw that adding PWV increased the importance of this feature to a mid-level contributor, consistent with its known role, which provides face validity to the model's behaviour. By pruning less important features (as in the 6-var model), we inherently improved interpretability and reduced complexity. This highlights a counter-intuitive point: an ML model need not be a black box using hundreds of predictors – it can be designed to be parsimonious and transparent, with the added benefit of potentially outperforming over-engineered models in small-data settings.

Across primary-prevention cohorts, supervised ML has most commonly been implemented with penalised linear models (L1/L2 logistic or Cox), tree ensembles (random forests, gradient boosting, XGBoost/GBMs), and—less frequently but increasingly—neural network models, including feed-forward ANNs and survival-aware architectures (e.g., DeepSurv and other neural survival models). In a large UK primary-care dataset (n≈378k; 10-year CVD), Weng et al. compared four ML approaches with a guideline score and reported modest but statistically significant gains in discrimination: AUC rose from 0.728 for the reference score to 0.745–0.764 for ML models, with the best performance from a neural network and small absolute improvements in sensitivity/PPV at the 7.5 % statin threshold [137]. Using a multi-ethnic EHR cohort (n≈263k; 5-year ASCVD), Ward et al. likewise found that gradient-boosted trees achieved AUC ~0.835 versus ~0.775 for PCE in eligible patients, while also enabling risk estimation in "PCE-ineligible" individuals with missing/out-of-range inputs—an important pragmatic advantage of ML pipelines over fixed-form equations [115]. At an evidence-synthesis level, a 2023 systematic review and meta-analysis (16 studies; ≈3.3 million participants) concluded that ML models outperform traditional risk scores by ~0.014 C-statistic on average (0.773 vs. 0.759), but also emphasized limited external validation and frequent risk-of-bias concerns [24]. Complementing these findings, survival-aware neural networks have shown parity or small advantages over PCE with good internal calibration but still tend to overestimate risk on external cohorts, underscoring the need for recalibration before deployment [138].

Despite these encouraging signals, several cautions recur. In a BMJ longitudinal analysis of 3.6 million patients across 19 modelling approaches, Li et al. found that while population-level performance was similar (C-

statistics ≈0.87 across methods), individual-level risk estimates varied widely between models (e.g., a patient at 9.5–10.5 % 10-year risk by QRISK3 could be 2.4–7.2 % by a neural network), and methods that ignored censoring underestimated risk. The authors argued for survival-appropriate modelling and routine consistency checks before clinical use [139]. Methodological reviews further note that many published AI/ML CVD models lack independent external validation, often report incomplete calibration, and are at high risk of bias by PROBAST criteria; newer checklists (e.g., IVS/PROBAST+AI) have been proposed to standardise appraisal and replication [109,140]. A recent EHR-focused systematic review similarly concludes that while modest discrimination gains are plausible, transparent reporting, calibration-in-the-large/slope adjustment, and external validation remain prerequisites for implementation [141].

A parallel strand of work explores biomarker-augmented or imaging-derived ML risk models. Targeted proteomics panels (≈50 proteins) added to conventional risk factors improved prediction of first major CVD events in primary prevention, outperforming clinical models alone; subsequent work with expanded panels and modern ML methods has replicated these gains and suggested portability across cohorts (with careful recalibration) [82,142]. Large-scale studies in UK Biobank using thousands of proteins and gradient-boosting frameworks reported incremental AUROC improvements for 10-year major events when proteomic signatures were added to standard predictors—again reinforcing a "parsimonious-plus-biomarker" strategy rather than wholesale feature proliferation [143]. Beyond blood-based markers, retinal image–derived deep-learning biomarkers (Reti-CVD) have demonstrated externally validated CVD risk stratification and regulatory authorisation in Korea, illustrating a feasible translational pathway for ML-based digital biomarkers; related systems predict CAC or composite vascular risk directly from fundus photographs [118].

Taken together, contemporary evidence suggests that (i) tree ensembles and neural networks can deliver small but consistent discrimination gains over traditional scores in well-curated EHR cohorts; (ii) calibration and external validity are the dominant barriers to clinical adoption, with many models requiring local recalibration and rigorous out-of-sample testing; (iii) parsimonious feature sets augmented by select biomarkers (e.g., hsCRP, proteomic panels, arterial stiffness proxies) tend to generalize better than "kitchen-sink" models in limited-event settings; and (iv) explainability (e.g., SHAP, monotonic GAMs/EBMs) and workflow integration are increasingly emphasized by reviews and regulators to ensure reproducibility, fairness, and clinician trust. These points align with our exploratory findings—namely, that

adding a vascular biomarker (PWV) yielded a measurable signal while unconstrained addition of variables without robust tuning/validation did not—and reinforce our proposed next steps around local registries, periodic recalibration/drift monitoring, subgroup audits, and EHR-embedded multi-model adjudication [24,139].

Looking ahead, a number of pragmatic steps would be necessary to translate these findings into improved clinical practice. A top priority would be to establish a prospective, multicenter Lithuanian CVD registry or cohort that enrols a broad, representative sample of patients, with standardised data collection and long-term follow-up for cardiovascular events. This would create a rich dataset for both external validation of existing models and the development of a new Lithuania-specific risk model if needed. Efforts should be made to include diverse regions (primary care and speciality centres) and to capture variables of local importance (such as dietary patterns or genetic factors prevalent in this population). Such a registry would enable direct recalibration of tools like SCORE2 or PREVENT on local outcome data, and provide a testing ground for any machine-learning models under consideration. Indeed, given our results, an argument could be made for either recalibrating an established model (e.g. adjusting SCORE2's baseline risk and perhaps its coefficients to better fit Lithuanian cohorts) or creating a new hybrid model that starts with a proven risk equation but layers on additional biomarkers via ML. Any new model or recalibrated score should be developed with openness and rigour – publishing the methods and coefficients openly, and subjecting it to independent external validation prior to adoption in national guidelines. Alongside development, continuous model monitoring and periodic updates must be instituted. If a risk calculator is implemented in practice, its performance (discrimination, calibration, net benefit) should be re-assessed every few years using fresh data, and adjustments made if it drifts – much like one would periodically update software. Another crucial consideration is fairness and equity in prediction. Our cohort was relatively homogeneous ethnically, but as Lithuania's population diversifies and as we consider global implementations, we must ensure that the model does not unduly favour or penalise any subgroup. Fairness evaluations (checking for equal error rates or calibration across sexes, age groups, and ethnic minorities) should be an integral part of the validation pipeline. It is encouraging that some recent ML risk models (using large UK datasets) have demonstrated minimal performance bias across demographic subgroups, and our future models should be held to the same standard. Lastly, for any risk prediction advances to make a difference at the patient level, they need to be effectively integrated into clinical workflows. We would recommend developing

clinician-friendly decision support tools that incorporate the chosen risk model into the electronic health record. For example, a point-of-care risk calculator that automatically pulls a patient's latest data (labs, blood pressure, etc.) and computes their updated risk can facilitate shared decision-making during clinic visits. If a machine-learning model is used, its output could be accompanied by an explanation (e.g. "patient's risk is elevated primarily due to high CRP and blood pressure") to aid understanding. By embedding these predictions in EHR systems, alongside guideline-recommended management prompts, clinicians can more readily translate risk estimates into action (such as starting preventive medications or ordering further tests for those at high predicted risk). In summary, embracing a locally adapted, ML-based risk prediction approach – supported by robust local data infrastructure, continuous validation, attention to fairness, and seamless clinical integration – offers a path to overcome the heterogeneity and miscalibration we observed. Such steps would ensure that cardiovascular prevention in Lithuania (and similar settings) is guided by risk assessment tools that are both more accurate and more personalised, ultimately improving identification of those most in need of intervention.

5.3 Limitations of the Study

This work has several methodological and contextual limitations that should be considered when interpreting the findings.

Study setting and population. The analysis was conducted in a single tertiary-care centre, within the LitHiR primary prevention program, and targeted middle-aged adults with metabolic syndrome. While this ensures uniform data capture, it limits external validity beyond Lithuanian, tertiary-care, high-risk primary-prevention populations and may not generalise to community or multi-ethnic cohorts. The outcome-analysis subset restricted the sample to records with adjudicated endpoints, potentially compounding selection effects.

Applicability of risk models to the local context. Several benchmark risk equations were developed and calibrated for non-Lithuanian settings (e.g., U.S./U.K./Australian cohorts). Except for SCORE2 (evaluated with the "very-high-risk" European calibration), most models were applied without local recalibration to Lithuanian baseline hazards. Consequently, absolute-risk calibration and downstream decision thresholds may be misaligned for this population, even if discrimination is acceptable. In addition, specific model inputs were unavailable or inapplicable (e.g., coronary artery calcium for MESA; postcode/area-level deprivation variables for AusCVDRisk; Scottish

deprivation index for ASSIGN; U.S. ZIP code for PREVENT), necessitating omissions or default handling that can bias both calibration and treatment eligibility estimates.

Outcome ascertainment and statistical power. Comparative performance analyses requiring outcomes were conducted in a reduced subset (n≈5,812) with adjudicated endpoints; event rates for individual outcomes were low, limiting statistical power, widening confidence intervals, and increasing the risk of unstable threshold-based metrics and decision-curve estimates.

Machine-learning specification. Absence of external validation constrains generalizability and increases the risk of optimism or instability—particularly given class imbalance and the modest number of events.

Collectively, these limitations suggest that while cross-model comparisons and exploratory ML analyses are informative within this setting, caution is warranted when extrapolating absolute risks, treatment eligibility, or net clinical utility to other populations or care contexts. Future work should prioritise local recalibration/validation, prospective longitudinal follow-up with hard outcomes in the full registry, richer biomarker integration, rigorous cross-validated and externally validated ML pipelines.

6. CONCLUSIONS

1. Inter-model variability: Substantial differences among nine cardiovascular risk models in risk stratification (3 %–67 % classified as high-risk), leading to major discrepancies in statin recommendations.
2. Predictive performance: No universally superior model; performance varied by outcome, with modest discrimination across all tools (c-statistics 0.6–0.8).
3. Calibration issues: All models overestimated absolute cardiovascular risk in the Lithuanian cohort, underscoring the need for local recalibration or population-specific algorithms.
4. Biomarker contribution: Adding vascular ageing markers, particularly carotid–femoral pulse wave velocity, improved predictive accuracy and risk differentiation without inflating false positives.
5. Machine learning insights: ML models performed comparably to established scores; simple models with a few key predictors were as effective as complex ones. While ML enables integration of novel biomarkers, advancing beyond conventional scores will require larger datasets, longer follow-up, and external validation.

7. PRACTICAL RECOMMENDATIONS

1. We recommend not relying solely on risk prediction models (RPMs) when assessing an individual's cardiovascular risk; whenever feasible, incorporate additional risk modifiers to refine risk estimation and guide therapy—for example, high-sensitivity C-reactive protein, carotid–femoral pulse wave velocity, lipoprotein(a), apolipoprotein B, family history of premature ASCVD, and chronic inflammatory disorders.
2. Use arterial stiffness as an adjudication tool in discordant or intermediate-risk cases. Incorporate PWV measurement when risk prediction models disagree or when risk is intermediate; PWV provided an incremental signal and directionally improved discrimination in ML analyses, supporting its role as a refinement test rather than a universal screen.
3. We propose convening a national, multidisciplinary working group (cardiology, primary care, epidemiology/biostatistics, and health IT) to deliver a validated, Lithuania-appropriate cardiovascular risk prediction model: either (a) recalibration and external validation of SCORE2 or PREVENT on multicentre Lithuanian outcomes, or (b) development of a new national RPM. Methods and coefficients should be open and transparent, with periodic recalibration and performance monitoring, and independent external validation prior to guideline adoption.
4. We recommend leveraging machine learning in the development of future cardiovascular risk models, complementing established clinical tools and biomarkers. Emphasis should be placed on interpretability, transparency, and rigorous validation (including external testing) before clinical adoption, with ongoing monitoring and recalibration thereafter.
5. We recommend establishing a prospective, multicentre Lithuanian registry encompassing primary care, regional, and tertiary centres, with standardised variable definitions and adjudicated hard cardiovascular outcomes, to enable robust external validation and underpin future CVD prevention initiatives.

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11. SUMMARY

SANTRAUKA

ĮVADAS

Širdies ir kraujagyslių ligos (ŠKL) tebėra pagrindinė mirtingumo priežastis visame pasaulyje, o tai kelia didžiulę naštą sveikatos priežiūros sistemai [1]. Nepaisant pažangos prevencijos ir gydymo srityje, mirčių nuo ŠKL skaičius pasaulyje išaugo nuo maždaug 12 milijonų 1990 m. iki 18,6 milijono 2019 m. [1]. Ši našta yra ypač didelė Rytų Europoje: Lietuvoje ŠKL sudaro daugiau nei pusę visų mirčių – tai didžiausias procentas Europos Sąjungoje [2]. Šie statistiniai duomenys pabrėžia skubų poreikį taikyti veiksmingas širdies ir kraujagyslių ligų rizikos vertinimo ir prevencijos strategijas.

Per pastaruosius dešimtmečius buvo sukurta daug širdies ir kraujagyslių ligų rizikos prognozavimo modelių, skirtų didelės rizikos asmenims nustatyti, kad būtų galima laiku imtis prevencinių priemonių. Vienas iš pirmųjų ir geriausiai žinomų modelių – „Framingham Risk Score for hard coronary heart disease“ (FRS-hCHD) – buvo sukurtas remiantis ilgalaikiu „Framingham Heart“ tyrimu, siekiant įvertinti 10 metų išeminės širdies ligos riziką pagal amžių, lytį, kraujospūdį, cholesterolio koncentraciją ir rūkymą. Vėlesni modeliai buvo sukurti remiantis didesnėmis ir įvairesnėmis kohortomis ir įtraukiant papildomų veiksnių. Pavyzdžiui, 2013 m. pristatytas „Pooled Cohort Equations“ (PCE) modelis išplėtė JAV rizikos paradigmą, į jį įtrauktos rasei specifinės lygtys ir nauji veiksniai, pavyzdžiui, cukrinis diabetas [3]. „Reynolds Risk Score“ (RRS) buvo pirmasis modelis, į kurį įtraukti biožymenys, prie tradicinių rizikos veiksnių jame pridėtas didelio jautrumo C reaktyvusis baltymas (djCRB) ir šeiminė anamnezė [4]. Tai pagerino rizikos prognozavimą moterims, palyginti su Framingham [5]. Kitas JAV modelis, sukurtas remiantis daugiatautine „Multi-Ethnic Study of Atherosclerosis“ (MESA) studija, apima pasirinktinius subklinikinius aterosklerozės matavimus (pvz., vainikinių arterijų kalcio indeksą), siekiant pagerinti įvairių populiacijų diagnostinį tikslumą [6]. Naujausios „Predicting Risk of cardiovascular disease EVENTs (equations)“ (PREVENT) lygtys (2023 m.) buvo sudarytos remiantis šiuolaikinėmis kohortomis, siekiant atnaujinti 10 metų ŠKL rizikos įvertinimą, ir jos yra naujausios kartos rizikos skaičiuoklės, pagrįstos šiuolaikine epidemiologija [7].

Tuo pačiu metu atsirado rizikos įverčių, pritaikytų kitoms populiacijoms. Europoje 2003 m. įdiegta „Systematic Coronary Risk Evaluation“ (SCORE) sistema buvo skirta 10 metų mirtinos ŠKL rizikai, o 2021 m. ji atnaujinta kaip

SCORE2, įtraukiant nemirtinus įvykius. SCORE2 dabar rekomenduojama Europos gairėse (ir naudojama Lietuvoje) pirminės prevencijos tikslais [8]. Jungtinėje Karalystėje QRISK3 (2017 m.) buvo sukurta naudojant visos šalies pirminės sveikatos priežiūros duomenis ir įtraukiant daugelį gretutinių ligų ir socialinių veiksnių [9]. Škotijos ASSIGN skaičiuoklė papildyta nepritekliaus indeksu, siekiant pagerinti jo kalibravimą pagal gyventojų ekonominę padėtį [10], o Australijos ŠKL rizikos vertinimo skaičiuoklė (AusCVDRisk) perkalibruota pagal Australijos duomenis, remiantis Naujosios Zelandijos modeliu [11]. Nepaisant dizaino skirtumų, šios skaičiuoklės remiasi pagrindiniais rizikos veiksniais ir yra pagrindinės pagalbinės priemonės prevencinėje kardiologijoje.

Vis dėlto tradicinės rizikos vertinimo skaičiuoklės turi svarbių ribotumų, ypač kai jos taikomos ne jų pirminėse kohortose. Daugybė tyrimų patvirtino **netinkamą kalibravimą** – sistemingą rizikos pervertinimą arba nepakankamą įvertinimą – ir sumažėjusį šių modelių tikslumą išorinėse populiacijose [12]. Pavyzdžiui, Framingham skaičiuokle pagrįsti sprendimai Europos kohortose riziką linkę pervertinti 30–50 proc., o originalus SCORE riziką tam tikrose šalyse, kuriose sergamumas yra didelis, įvertino nepakankamai, todėl reikėjo atlikti regioninį perkalibravimą. JAV PCE taip pat rodo skirtingus įvairių etninių grupių rezultatus [13, 14]. Be to, vienas tyrimas parodė, kad tik apie 4 proc. žmonių atitiktų ESC/SCORE2 kriterijus gydymui statinais, palyginti su maždaug 20–30 proc. pagal JAV ar JK gaires [15]. Toks rizikos įvertinimų (ir dėl to priimtų gydymo sprendimų) skirtumas pabrėžia būtinybę pagerinti rizikos stratifikaciją, nes dabartiniai modeliai gali praleisti tikrai didelės rizikos asmenis, o kitus klaidingai klasifikuoti kaip didelės rizikos.

Šie trūkumai paskatino domėjimąsi rizikos prognozavimo tobulinimu naudojant naujus biologinius žymenis, atspindinčius pagrindinius ligos vystymosi kelius. Uždegimo, endotelio disfunkcijos ir širdies pažeidimų biologiniai žymenys gali užfiksuoti „paslėptą“ riziką, kuri nėra akivaizdi pagal tradicinius veiksnius. Pavyzdžiui, perspektyvinės kohortos parodė, kad žmonės, turintys padidėjusius uždegimo žymenis (pvz., djCRB arba interleukiną-6), turi didesnę širdies ir kraujagyslių ligų riziką, net jei jų MTL cholesterolis yra normalus [16]. Atitinkamai, įtraukus djCRB į rizikos vertinimą – kaip padaryta RRS – pagerėjo didesnę riziką turinčių pacientų identifikavimas (ypač perklasifikuojant daugelį moterų, kurios pagal įprastą vertinimo sistemą buvo priskirtos mažos rizikos grupei) [5]. Klinikinėje praktikoje šią likutinę riziką iliustravo JUPITER tyrimas: akivaizdžiai sveikų asmenų, turinčių aukštą djCRB, gydymas statinais sumažino didžiųjų ŠKL įvykių dažnį 44 proc. [17]. Be uždegimo, širdies perkrovos ar pažeidimo žymenys (pvz., N- terminalinis pro-B tipo natriuretinis peptidas ir didelio

jautrumo troponinas T) suteikia nepriklausomą prognostinę vertę: net ir besimptomiams suaugusiesiems padidėjęs NT-proBNP arba troponino lygis prognozuoja didesnį širdies nepakankamumo bei širdies ir kraujagyslių mirtingumo rodiklį laikui bėgant [18]. Be to, naudojant kelis biožymenis kartu galima pagerinti stratifikaciją – pavyzdžiui, djCRB, troponino, NT-proBNP ir cistatino C derinys gerokai pagerino rizikos vertinimą, palyginti su tradiciniais veiksniais [19].

Taip pat perspektyvūs yra kraujagyslių senėjimo ir subklinikinės aterosklerozės žymenys. Arterijų standumas, dažnai matuojamas kaip miego ir šlaunies arterijų pulsinės bangos greitis (PBG), rodo arterijų pažeidimą ir „biologinį“ kraujagyslių amžių. Didesnis nei tikėtasi PBG rodo pažengusį kraujagyslių senėjimą ir yra susijęs su padidėjusia ŠKL rizika, net jei standartinis rizikos veiksnių profilis atrodo palankus [20]. PBG įtraukimas į rizikos modelius pagerino predikciją: pridėjus PBG prie tradicinių rizikos veiksnių, maždaug 15–20 proc. vidutinės rizikos pacientų buvo perklasifikuoti į aukštesnės rizikos kategorijas [20]. Kitas naujas veiksnys yra lipoproteinas (a), genetiškai nulemta MTL tipo dalelė, kuri savarankiškai padidina aterosklerozės riziką. Lp(a) lygis, viršijantis ~105 nmol/L arba 50 mg/dL, dabar prevencijos gairėse laikomas riziką didinančiu veiksniu [21]. Integruojant biožymenis, rodančius uždegimą, kraujagyslių senėjimą ir genetinį polinkį, galima tiksliau suskirstyti asmenis, kurie kitaip galėtų būti nepakankamai arba pernelyg gydomi pagal įprastus algoritmus.

Kitas tobulinimo būdas yra dirbtinio intelekto ir mašininio mokymosi (MM) metodų taikymas. Šiuolaikiniai MM algoritmai gali įtraukti kur kas daugiau prognostinių veiksnių nei tradicinės rizikos skaičiuoklės ir užfiksuoti sudėtingas netiesines kintamųjų sąveikas [22]. Ši galimybė yra ypač naudinga integruojant kelis biožymenis ir klinikinius parametrus, siekiant gauti individualizuotas rizikos prognozes. MM modeliai taip pat gali būti perkalibruoti remiantis vietiniais duomenimis, taip potencialiai pagerinant kalibravimą konkrečioms populiacijoms. Ankstyvieji tyrimai rodo, kad MM pagrįsti modeliai pasiekia panašų, o kartais ir geresnį prognozavimo tikslumą nei tradicinės skaičiuoklės. Pavyzdžiui, dirbtinis neuroninis tinklas šiek tiek pranoko AKK/AŠA PCE (cstatistika ~0,75 prieš ~0,74) [23]; o metaanalizė parodė, kad MM algoritmai pasiekė šiek tiek aukštesnį vidutinį C indeksą (~0,77) nei standartiniai rizikos vertinimo modeliai (~0,75) [24]. Pažymėtina, kad mašininis mokymasis puikiai tinka aukštos dimensijos duomenims: viename tyrime, integravus išsamų lipidomikos profilį (153 lipidų rūšys) į MM modelį, AUC pagerėjo nuo ~0,55 (naudojant Framingham pagrįstą modelį) iki ~0,66 [25]. Šie pavyzdžiai iliustruoja duomenimis pagrįstų metodų potencialą atskleisti subtilius rizikos prognozės veiksnius ir

pagerinti individualią rizikos stratifikaciją, viršijantį tai, ką gali pasiūlyti tradiciniai modeliai.

Šis darbas yra pirmasis, kuriame tiesiogiai vertinami devyni plačiai naudojami ŠKL rizikos modeliai (įskaitant naująją 2023 m. PREVENT skaičiuoklę [7]) remiantis viena kohorta, suteikiant unikalią įžvalgą į jų lyginamąjį tikslumą Lietuvoje. Tai taip pat yra vienas iš pirmųjų tyrimų, kuriame išoriškai patvirtinami šie naujausi rizikos vertinimo modeliai, be to, jame pristatytos naujos modelių „sutapimo“ analizės (naudojant Koheno κ ir klasterizavimą), siekiant ištirti, kaip panašiai modeliai klasifikuoja pacientus. Be to, buvo sukurtas naujas MM pagrįstas rizikos modelis, integruojantis kraujagyslių biožymenį (PBG), ir palygintas su tradicine rizikos vertinimo skaičiuokle, pademonstruojant panašų tikslumą ir predikcijos pagerėjimą integruojant PBG. Rezultatai taip pat parodė, kad daugelis rizikos modelių (pvz., SCORE2) yra netinkamai kalibruoti šioje populiacijoje (pervertinant absoliučią riziką) ir kad rizikos skaičiuoklės pasirinkimas gali iš esmės pakeisti gydymo sprendimus (pvz., gydymą statinais), o tai yra įrodymas, kuris padės ateityje tobulinti rizikos vertinimą.

TYRIMO HIPOTEZĖ

Tikimasi, kad integravus kraujagyslių senėjimo biožymenis su pažangiais mašininio mokymosi algoritmais bus galima tiksliau prognozuoti širdies ir kraujagyslių ligų riziką nei naudojant įprastus rizikos vertinimo modelius.

TYRIMO UŽDAVINIAI

1. Atlikti plačiai taikomų širdies ir kraujagyslių ligų rizikos prognozavimo modelių tiesioginę lyginamąją analizę, įvertinti jų gebą stratifikuoti pacientų riziką, taikymo padarinius klasifikuojant tinkamumą statinų terapijai ir bendrą prognostinį tikslumą tiriamojoje kohortoje.
2. Išanalizuoti pagrindinius kraujagyslinius biožymenis, susijusius su kraujagyslių senėjimu ir kardiometaboline rizika, bei įvertinti šių biožymenų integravimo į rizikos prognozavimo algoritmus įgyvendinimo galimybę ir potencialią naudą.
3. Panaudojant mašininio mokymosi metodus sukurti ir įvertinti personalizuotą, daugiaparametrį širdies ir kraujagyslių ligų rizikos prognozavimo modelį, kuris integruotų tradicinius rizikos veiksnius ir atrinktus kraujagyslinius biožymenis, ir palyginti jo tikslumą su tradiciniais rizikos vertinimo modeliais.

1. Širdies ir kraujagyslių ligų rizikos prognozavimo modeliai labai skiriasi klasifikuojant pacientų riziką ir nustatant gydymo statinais indikacijas, todėl šiais modeliais grindžiamos gydymo rekomendacijos labai skiriasi.
2. Tradicinių širdies ir kraujagyslių ligų rizikos modelių predikcinės savybės skiriasi priklausomai nuo prognozuojamų baigčių, ir nėra vieno modelio, kuris būtų pranašesnis visais atvejais.
3. Taikant tradicinius rizikos modelius Lietuvos pirminės prevencijos kohortai, jie yra netiksliai kalibruoti – paprastai pervertinama absoliuti rizika – todėl reikalinga jų rekalibracija arba populiacijai specifinio modelio adaptacija.
4. Įtraukiant kraujagyslių senėjimo biožymenis, ypač miego ir šlaunies arterijų pulsinės bangos greitį, į rizikos vertinimą, gaunama papildoma predikcinė vertė, viršijanti tradicinius rizikos veiksnius.
5. Mašininio mokymosi prognozavimo modeliai, kurie sujungia tradicinius rizikos veiksnius su atrinktais kraujagysliniais biožymenimis, pasiekia panašų tikslumą kaip ir nusistovėję rizikos vertinimo modeliai.

METODAI

Tyrime buvo analizuojami Lietuvos pirminės prevencijos programos „LitHiR“ dalyviai – 40–54 metų vyrų ir 50–64 metų moterų (be klinikinės ŠKL) kohorta, įtraukta 2006–2023 m. [123, 124]. Visi tiriamieji turėjo metabolinį sindromą (pagal NCEP-ATPIII kriterijus: padidėjęs kraujospūdis ≥130/85 mmHg, pilvinis nutukimas ≥102 cm vyrų arba ≥88 cm moterų, žemas DTL, aukštas trigliceridų lygis ir (arba) padidėjusi gliukozės koncentracija nevalgius) [36]. Buvo surinkti kiekvieno dalyvio baziniai duomenys (lipidų profilis, kraujospūdis, gliukozė, inkstų funkcija, C reaktyvusis baltymas, albumino ir kreatinino santykis šlapime, miego ir šlaunies arterijų pulsinės bangos greitis ir kt.). Asmenys, turintys širdies ir kraujagyslių ligų ar kitų sunkių gretutinių ligų anamnezę (ankstesnė nebyli išemija, vainikinių arterijų liga, insultas ar PSIP, periferinė arterijų liga, aktyvus onkologinis susirgimas, sunkus organų funkcionavimo sutrikimas ir kt.). Taip pat baigčių analizei buvo atrinktas n = 5 812 dalyvių pogrupis, turintis išsamius širdies ir kraujagyslių ligų įvykių stebėsenos duomenis (iki 2021 m.). Tai užtikrino vienodą visų įtrauktų dalyvių stebėjimo laikotarpį.

Kiekvieno tyrimo dalyvio riziką sirgti širdies ir kraujagyslių ligomis apskaičiavome pagal skirtingus rizikos vertinimo modelius: SCORE2 („Systematic Coronary Risk Evaluation 2“) [8]; PREVENT („Predicting Risk

of cardiovascular disease EVENTs (equations)“) [7, 37]; PCE („Pooled Cohort Equations“) (2013 m. AKK/AŠA 10 metų ŠKL rizikos skaičiuoklė suaugusiems JAV gyventojams) [3]; MESA rizikos balas (10 metų vainikinių arterijų ligos rizikos modelis iš „Multi-Ethnic Study of Atherosclerosis“, 45–85 metų amžiaus grupė) [6]; QRISK3 (2017 m. JK 10 metų rizikos algoritmas, apimantis tradicinius veiksnius ir keletą papildomų rizikos veiksnių) [9]; ASSIGN (Škotijos 10 metų ŠKL rizikos numatymo modelis, apimantis socialinės atskirties indeksą ir šeiminę anamnezę) [10]; AusCVDRisk (Australijos 5 metų ŠKL rizikos skaičiuoklė 30–79 metų amžiaus žmonėms, perkalibruota pagal Naujosios Zelandijos kohortą) [11]; FRS-hCHD („Framingham Risk Score for hard coronary heart disease“) (10 metų MI arba koronarinės mirties rizika, cukriniu diabetu nesergantiems asmenims) [36]; ir RRS („Reynolds Risk Score“) (10 metų didžiųjų kardiovaskulinių įvykių rizika, įtraukiant amžių, lytį, cholesterolio kiekį, kraujospūdį, rūkymą, taip pat djCRB ir šeiminę ankstyvos aterosklerozinės ŠKL riziką) [4]. Visi skaičiuoklių įverčiai buvo apskaičiuoti naudojant jų originalias paskelbtas lygtis arba oficialias priemones (prieinamas 2023 m.), be jokių pakeitimų (išskyrus atitinkamą regioninį kalibravimą SCORE2 ir neįtraukiant jokių mūsų duomenų rinkinyje nesančių kintamųjų, pavyzdžiui, vainikinių arterijų kalcio indekso MESA skaičiuoklės atveju). Kadangi kiekvienas modelis skirtingai apibrėžia „mažos“, „vidutinės“ ir „didelės“ rizikos kategorijas, siekdami nuoseklumo, standartizavome visų skaičiuoklių rizikos kategorijas. Pavyzdžiui, jei modelis turėjo „ribinės rizikos“ kategoriją, mes tuos asmenis perklasifikavome į vidutinės rizikos kategoriją pagal mūsų schemą, o rezultatas „neaukšta rizika“ buvo suskirstytas į atitinkamai žemos arba vidutinės rizikos kategorijas. Šis suvienodinimas (1 pav.) užtikrino, kad lygindami modelius naudojome lygiaverčius rizikos kategorijų apibrėžimus. Panašiai apibrėžėme antilipidinio gydymo slenksčius kiekvienam iš pasitelktų modelių ir apskaičiavome kohortos dalį, kuriai pagal kiekvieną algoritmą būtų indikuotinas gydymas statinais (2 pav.).

Pirminis rizikos įverčio kategorizavimas					Harmonizuotas rizikos įverčio kategorizavimas		
Predicting Risk of cardiovascular disease EVENTs (PREVENT)							
Maža rizika	Ribinė rizika	Vidutinė rizika	Didelė rizika	→	*Maža rizika*	*Vidutinė rizika*	*Didelė rizika*
<5	5–<7,5	≥7,5–<20	≥20		<7,5	≥7,5–<20	≥20
Systematic Coronary Risk Evaluation 2 (SCORE2)							
Amžiaus grupė	Maža-vidutinė rizika	Didelė rizika	Labai didelė rizika		Amžiaus grupė	Maža rizika	Vidutinė rizika	Didelė rizika
<50	<2,5	2,5–7,49	≥7,5	→	<50	<2,5	2,5–7,49	≥7,5
50-69	<5	5–9,99	≥10		50-69	<5	5–9,99	≥10
≥70	<7,5	7,5–14,99	≥15		≥70	<7,5	7,5–14,99	≥15
Pooled Cohort Equation (PCE)							
Maža rizika	Ribinė rizika	Vidutinė rizika	Didelė rizika	→	Maža rizika	Vidutinė rizika	Didelė rizika
<5	5–<7,5	≥7,5–<20	≥20		<7,5	≥7,5–<20	≥20
QRISK3 cardiovascular risk calculator (QRISK3)							
Maža rizika	Vidutinė rizika	Didelė rizika		→	Maža rizika	Vidutinė rizika	Didelė rizika
<10	≥10–≤20	>20			<10	≥10–≤20	>20
Framingham Risk Score for Hard Coronary Heart Disease (FRS-hCHD)							
Maža rizika	Vidutinė rizika	Didelė rizika		→	Maža rizika	Vidutinė rizika	Didelė rizika
<10	≥10–<20	≥20			<10	≥10–<20	≥20
Reynolds Risk Score (RRS)							
Labai maža rizika	Maža-vidutinė rizika	Vidutinė-didelė rizika	Didelė rizika	→	Maža rizika	Vidutinė rizika	Didelė rizika
<5	≥5–<10	≥10–<20	≥20		<10	≥10–<20	≥20
Assessing cardiovascular risk using SIGN (ASSIGN)							
Ne didelė rizika		Didelė rizika		→	Maža rizika	Vidutinė rizika	Didelė rizika
0-19		≥20			<10	≥10–<20	≥20
Australian CVD risk score (AusCVDRisk)							
Maža rizika	Vidutinė rizika	Didelė rizika		→	Maža rizika	Vidutinė rizika	Didelė rizika
<5	≥5–<10	≥10			<5	≥5–<10	≥10
Multi-Ethnic Study of Atherosclerosis risk score (MESA)							
Maža rizika	Vidutinė rizika	Didelė rizika		→	Maža rizika	Vidutinė rizika	Didelė rizika
<5	≥5–<7,5	≥7,5			<5	≥5–<7,5	≥7,5

1 paveikslas. Pirminių (modeliuose apibrėžtų) ir harmonizuotų širdies ir kraujagyslių ligų rizikos kategorijų palyginimas po standartizacijos

Statinų skyrimo slenksčiai			
Systematic Coronary Risk Evaluation 2 (SCORE2)			
Amžiaus grupė	*Maža-vidutinė rizika*	*Didelė rizika*	*Labai didelė rizika*
<50	<2,5	2,5–749	**≥7,5**
50-69	<5	5–9,99	**≥10**
≥70	<7,5	7,5–14,99	**≥15**
Predicting Risk of cardiovascular disease EVENTs (PREVENT)			
Maža rizika	*Ribinė rizika*	*Vidutinė rizika*	*Didelė rizika*
<5	5–<7,5	**≥7,5–<20**	**≥20**
Pooled Cohort Equation (PCE)			
Maža rizika	*Ribinė rizika*	*Vidutinė rizika*	*Didelė rizika*
<5	5–<7,5	**≥7,5–<20**	**≥20**
QRISK3 cardiovascular risk calculator (QRISK3)			
Maža rizika	*Vidutinė rizika*	*Didelė rizika*	
<10	**≥10–≤20**	**>20**	
Framingham Risk Score for Hard Coronary Heart Disease (FRS-hCHD)			
Maža rizika	*Vidutinė rizika*	*Didelė rizika*	
<10	**≥10–<20**	**≥20**	
Reynolds Risk Score (RRS)			
Labai maža rizika	*Maža-vidutinė rizika*	*Vidutinė-didelė rizika*	*Didelė rizika*
<5	≥5–<10	**≥10–<20**	**≥20**
Assessing cardiovascular risk using SIGN (ASSIGN)			
Ne didelė rizika		*Didelė rizika*	
0-19		**≥20**	
Australian CVD risk score (AusCVDRisk)			
Maža rizika	*Vidutinė rizika*	*Didelė rizika*	
<5	≥5–<10	**≥10**	
Multi-Ethnic Study of Atherosclerosis risk score (MESA)			
Maža rizika	*Vidutinė rizika*	*Didelė rizika*	
<5	≥5–<7,5	**≥7,5**	

2 paveikslas. Statinų skyrimo indikacijų pasiskirstymas pagal devynis širdies ir kraujagyslių ligų rizikos prognozavimo modelius. Paryškintos vertės rodo gydymo statinais tinkamumą

Statistinė analizė: Naudojome daugialypį metodą modelių rezultatams ir tikslumui palyginti. Pirmiausia apibendrinome atvejų pasiskirstymą pagal rizikos kategorijas kiekvienam iš devynių modelių, kad nustatytume, kaip kiekvienas modelis klasifikavo kohortą. Toliau kiekybiškai įvertinome porinę modelių rizikos klasifikacijų sutaptį naudodami Koheno κ statistiką, kurią vizualizavome kaip spalvomis koduotą šilumos žemėlapį. Taip pat atlikome hierarchinį klasterizavimą κ verčių matricoje (naudodami 1–κ kaip atstumą), kad sugrupuotume modelius su panašiomis rizikos stratifikavimo savybėmis. Be to, apskaičiavome pacientų, kurie buvo priskirti tai pačiai rizikos kategorijai pagal visus modelius, dažnį, kad įvertintume bendrą sutaptį.

Tada įvertinome kiekvieno modelio **prognozavimo savybes** panaudojant kohortos pogrupį su širdies ir kraujagyslių sistemos baigčių rezultatais. Kiekvienam tiriamam rezultatui (pvz., mirtingumas dėl visų priežasčių, mirtingumas dėl širdies ir kraujagyslių sistemos ligų, miokardo infarktas, insultas ir sudėtiniai didieji širdies ir kraujagyslių sistemos įvykiai) sukūrėme visų modelių imtuvo veikimo charakteristikų kreives ir apskaičiavome kiekvieno modelio plotą po ROC kreive (AUC) kaip diskriminacijos matą. 95 proc. pasikliautinieji intervalai AUC buvo apskaičiuoti naudojant „bootstrap“ pakartotinį atrankos metodą, o tiksliausiai prognozuojančius modelius statistiniu būdu palyginome su kitais, naudodami porinius „bootstrap“ testus (dvipusis $p < 0,05$ reikšmingumui). Taip pat ištyrėme modelio kalibravimą, palygindami prognozuojamą absoliučią riziką su stebėtais įvykių dažniais (įskaitant Brier balų skaičiavimą, siekiant apibendrinti bendrą tikslumą). Visoms analizėms skaičiuoti naudota IBM SPSS (v25) ir „Python“ (su tokiomis bibliotekomis kaip *scikit-learn*, *pandas* ir *numpy*).

Mašininio mokymosi modelių kūrimas: siekdami ištirti naujų biožymenų integravimą, naudodami atsitiktinių miškų klasifikatorių sukūrėme prižiūrimą mašininio mokymosi modelį. Taip pat sukūrėme duomenų išankstinio apdorojimo sistemą (trūkstamų verčių vidurkio įrašymas ir kintamųjų standartizavimas) ir panaudojome sluoksniuotą 70/30 mokymo ir testavimo padalijimą (išlaikydami tą patį įvykių paplitimą abiejuose rinkiniuose). Modelio hiperparametrai buvo palikti numatyti, o „Random Forest“ buvo konfigūruotas su 100 sprendimų medžiais. MM analizė buvo atlikta baigčių duomenis turinčiame pogrupyje ($n = 5812$), o išskirtame testavimo pogrupyje buvo 1 744 asmenys (iš kurių 58 patyrė didįjį širdies ir kraujagyslių įvykį, ~3,3 proc.). Įvertinome keturis modelius toje pačioje testavimo kohortoje: (1) RF (7 var) – atsitiktinių miškų modelis, naudojantis septynis tradicinius rizikos veiksnius (amžių, lytį, diastolinį kraujospūdį, bendrąjį cholesterolį, trigliceridų koncentraciją, gliukozės koncentraciją

nevalgius ir C reaktyvųjį baltymą); (2) RF (7 var + PWV) – tas pats modelis, papildytas pulsinės bangos greičiu kaip papildomu prognostiniu veiksniu; (3) RF (6 var) – supaprastintas atsitiktinių miškų modelis, naudojantis šešis pagrindinius požymius (amžius, diastolinis kraujospūdis, trigliceridai, gliukozė nevalgius, CRB ir rūkymas), siekiant patikrinti, ar paprastesnis modelis gali veikti taip pat gerai; ir (4) tradicinė SCORE2 rizikos vertinimo skaičiuoklė (taikoma tiesiogiai tiriamiesiems asmenims palyginti). Kiekvieno modelio diskriminacinę galią vertinome pagal jo testų rinkinio AUC (su 95 proc. PI, apskaičiuotu pakartotinės atrankos (angl. bootstrap) metodu, iš 4000 atrankų). Taip pat ištyrėme jautrumą ir specifiškumą dviejuose klinikiniu požiūriu svarbiuose veikimo taškuose (~80 proc. specifiškumas ir ~90 proc. specifiškumas) ir užregistravome atitinkamą teigiamą prognostinę vertę (TPV) bei neigiamą prognostinę vertę (NPV), kad suprastume atitiktį tarp klaidingai teigiamų ir klaidingai neigiamų rezultatų. Modelio kalibracija testiniame rinkinyje buvo vertinamas naudojant Brier įvertį (prognozuojamų tikimybių vidutinė kvadratinė paklaida). Galiausiai, norėdami interpretuoti MM modelius, analizavome savybių svarbos reitingus ir naudojome SHAP („Shapley Additive Explanations“) metodą, kad įvertintume kiekvienos savybės indėlį į atsitiktinių miškų prognozes.

Visi tyrimo komponentai buvo atlikti gavus atitinkamą etinį patvirtinimą. Tyrimo protokolas buvo patvirtintas Vilniaus regiono biomedicininių tyrimų etikos komiteto (Nr. 2019/3-1104-603).

REZULTATAI

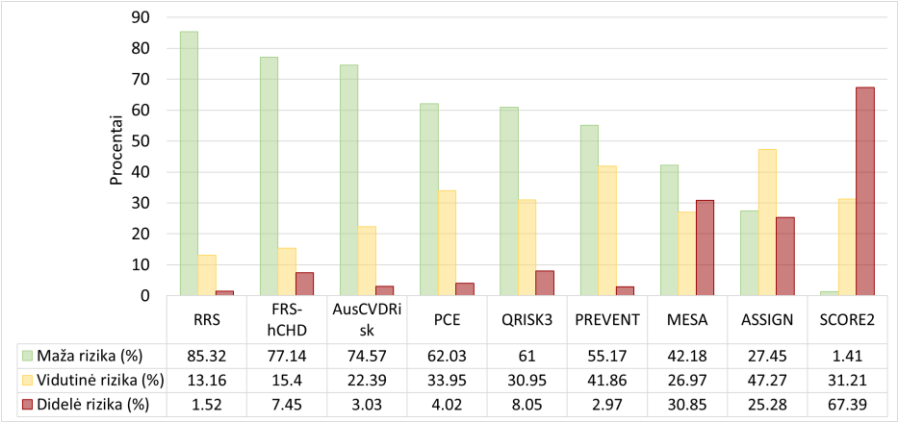
Pradinės charakteristikos: Iš viso į LitHiR registrą buvo įtraukti 11 174 dalyviai. Dauguma dalyvių buvo moterys (58,4 proc.), o bendras vidutinis amžius buvo ~53,5 metų. Atsižvelgiant į tarp įtraukimo kriterijų esantį metabolinį sindromą, nutukimas ir susiję rizikos veiksniai buvo dažni: vidutinis kūno masės indeksas buvo ~31,6 kg/m², o vidutinis bendras cholesterolis buvo 6,17 mmol/l. Vidutinis MTL cholesterolis buvo 3,98 mmol/l, o DTL – 1,23 mmol/l. Kohortos vidutinis kraujospūdis buvo 137/83 mmHg. Gretutinės būklės apėmė cukrinį diabetą, kuris stebėtas 18,5 proc. dalyvių, o 26,3 proc. buvo gydoma arterinė hipertenzija. Tik 11,2 proc. pradiniame etape vartojo statinus (dėl dislipidemijos). Rūkymas buvo gana paplitęs (20,6 proc. dabartinių rūkančiųjų ir 6,1 proc. buvusių rūkančiųjų), o tai pabrėžia daugialypį šios pacientų grupės rizikos veiksnių spektrą. Tiriamosios grupės savybės pateikiamos 1 lentelėje.

1 lentelė. Tyrimo kohortos pagrindiniai demografiniai ir klinikiniai rodikliai (n = 11,174)

	Požymiai			**p-vertė**
	Bendrai	Moterys 6527 (58.41)	Vyrai 4647 (41.59)	<0.001
Amžius, metai: vidurkis (SN)	53,49 (6,47)	57,62 (4,21)	47,69 (4,27)	<0,001
Kūno masės indeksas, kg/m^2: vidurkis (SN)	31,47 (4,18)	31,76 (4,68)	31,24 (3,85)	<0,001
Sistolinis kraujospūdis, mmHg: vidurkis (SN)	137,16 (15,40)	137,15 (15,96)	137,17 (14,59)	0,939
Diastolinis kraujospūdis, mmHg: vidurkis (SN)	82,99 (10,69)	80,99 (10,38)	85,79 (10,48)	<0,001
Bendrasis cholesterolis, mmol/L: vidurkis (SN)	6,17 (1,37)	6,33 (1,40)	5,96 (1,31)	<0,001
Trigliceridai, mmol/L: vidurkis (SN)	2,11 (1,5)	1,88 (1,15)	2,43 (1,84)	<0,001
Mažo tankio lipoproteinų cholesterolis, mmol/L: vidurkis (SN)	3,98 (1,21)	4,13 (1,23)	3,76 (1,14)	<0,001
Didelio tankio lipoproteinų cholesterolis, mmol/L: vidurkis (SN)	1,23 (0,31)	1,33 (0,31)	1,09 (0,26)	<0,001
Apskaičiuotas glomerulų filtracijos greitis, ml/min/1.73m^2: vidurkis (SN)	92,44 (11,83)	88,97 (10,74)	97,32 (11,56)	<0,001
C reaktyvusis baltymas, mg/L: vidurkis (SN)	2,81 (3,18)	3,09 (3,98)	2,56 (3,06)	<0,001
Kreatininas, µmol/L: vidurkis (SN)	71,69 (12,79)	65,60 (8,93)	80,25 (12,48)	<0,001
Gliukozė nevalgius, mmol/L: vidurkis (SN)	6,31 (1,49)	6,30 (1,51)	6,32 (1,45)	0,463
Cukrinis diabetas: *n* (%)	2063 (18,46)	1325 (20,3)	738 (15,89)	<0,001
Dislipidemijos gydymas (statinai): *n* (%)	2183 (19,54)	764 (11,7)	814 (17,52)	<0,001
Arterinės hipertenzijos gydymas: *n* (%)	2939 (26,3)	1861 (28,5)	1078 (23,2)	<0,001
Antitrombocitinis gydymas: *n* (%)	30 (0,27)	19 (0,29)	11 (0,24)	0,584
Šiuo metu rūkantys: *n* (%)	2305 (20,63)	841 (12,9)	1464 (31,5)	<0,001
Anksčiau rūkę: *n* (%)	686 (6,14)	189 (2,9)	497 (10,7)	<0,001

SN—standartinis nuokrypis.

Rizikos stratifikacijos skirtumai: pagal devynis rizikos vertinimo modelius asmenų, priskirtų mažos, vidutinės ar didelės rizikos grupei, dalis labai skyrėsi. Konservatyviausias modelis – RRS – pagal jį apie 85 proc. dalyvių priskirta mažos rizikos grupei, o remiantis SCORE2 (kalibruotas labai didelės rizikos Europos gyventojams) tik apie 1,4 proc. priskirta tai pačiai rizikos grupei ir apie 67 proc. kohortos didelės rizikos grupei. Kitų modelių vertinimas buvo tarp šių dviejų kraštutinių variantų: pavyzdžiui, pagal FRS-hCHD ir AusCVDRisk skaičiuokles mažos rizikos kategorijai priskirta apie 74–77 proc. asmenų (ir atitinkamai labai nedaug didelės rizikos: ~3–7 proc.). PCE ir QRISK3 modelių rezultatas tarpinis: remiantis kiekvienu modeliu priskirta apie 60 proc. tiriamųjų mažos rizikos grupei ir tik apie 4–8 proc. didelės rizikos grupei. Remiantis PREVENT skaičiuokle linkstama klasifikuoti didesnę dalį asmenų kaip turinčių vidutinę riziką (apie 55 proc. mažos, 42 proc. vidutinės, 3 proc. didelės rizikos). Tuo tarpu pagal MESA ir ASSIGN modelius teikiamas labiau subalansuotas pasiskirstymas – pavyzdžiui, MESA klasifikavo ~42 proc. kaip mažos rizikos ir ~31 proc. kaip didelės rizikos, o ASSIGN ~27 proc. kaip mažos rizikos ir ~25 proc. kaip didelės rizikos (~47 proc. kaip vidutinės rizikos). Šie skirtumai vaizduojami 3 paveiksle. Praktiniu požiūriu, tas pats asmuo gali būti laikomas didelės rizikos pagal vieną modelį, bet mažos rizikos pagal kitą.

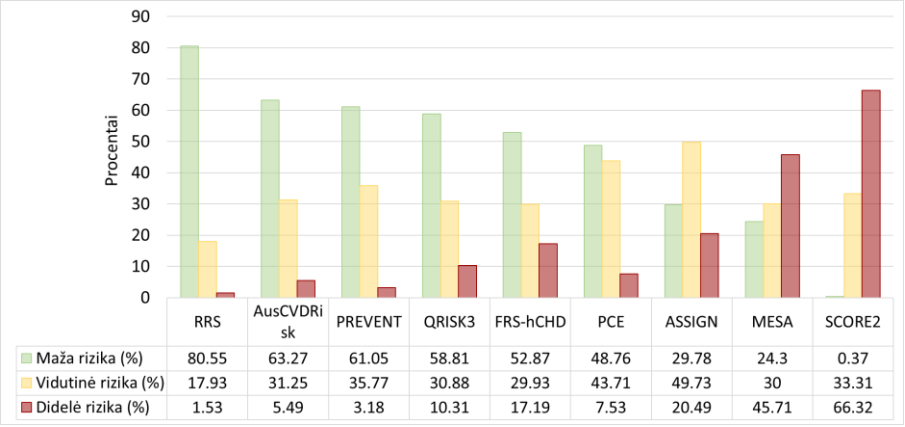


	RRS	FRS-hCHD	AusCVDRisk	PCE	QRISK3	PREVENT	MESA	ASSIGN	SCORE2
Maža rizika (%)	85.32	77.14	74.57	62.03	61	55.17	42.18	27.45	1.41
Vidutinė rizika (%)	13.16	15.4	22.39	33.95	30.95	41.86	26.97	47.27	31.21
Didelė rizika (%)	1.52	7.45	3.03	4.02	8.05	2.97	30.85	25.28	67.39

3 paveikslas. Širdies ir kraujagyslių ligų rizikos kategorijų pasiskirstymas pagal devynis rizikos vertinimo modelius

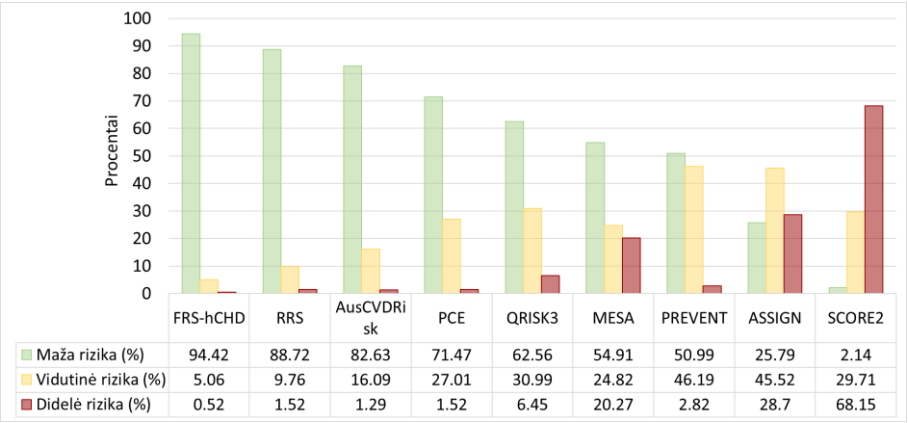
Stratifikacija taip pat reikšmingai skyrėsi pagal lytį (4; 5 pav.). Vertinant vyrų rizikos kategorijas, SCORE2 buvo išskirtinis – praktiškai nė vienas vyras

pagal šį modelį neklasifikuotas kaip mažos rizikos (~0,4 proc.), o daugiau nei 66 proc. vyrų priskirta didelės rizikos grupei, tuo tarpu pagal RRS vis dar dauguma vyrų (~81 proc.) priskirti prie mažos rizikoskategorijos. Kitų modelių teikiami vyrų rizikos prognozavimo rezultatai tarpiniai. Vertinant moterų širdies ir kraujagyslių ligų riziką dauguma modelių buvo konservatyvesni (pavyzdžiui, pagal FRS-hCHD 94 proc. moterų priskirta mažos rizikos grupei, o RRS – ~89 proc.), tačiau SCORE2 rezultatai vėl kraštutiniai – tik ~2 proc. moterų pagal SCORE2 buvo priskirta mažos rizikos grupei, o net 68 proc. moterų priskirta didelės rizikos grupei. Taigi, pagal SCORE2 tendencingai pateikiami gerokai didesnę riziką atitinkantys įvertinimai, ypač moterų, palyginti su kitomis skaičiuoklėmis. Šie skirtumai rodo, kad modelio pasirinkimas gali turėti didelę įtaką rizikos sirgti minėtomis ligomis tiek vyrams, tiek moterims stratifikacijai.



	RRS	AusCVDRisk	PREVENT	QRISK3	FRS-hCHD	PCE	ASSIGN	MESA	SCORE2
Maža rizika (%)	80.55	63.27	61.05	58.81	52.87	48.76	29.78	24.3	0.37
Vidutinė rizika (%)	17.93	31.25	35.77	30.88	29.93	43.71	49.73	30	33.31
Didelė rizika (%)	1.53	5.49	3.18	10.31	17.19	7.53	20.49	45.71	66.32

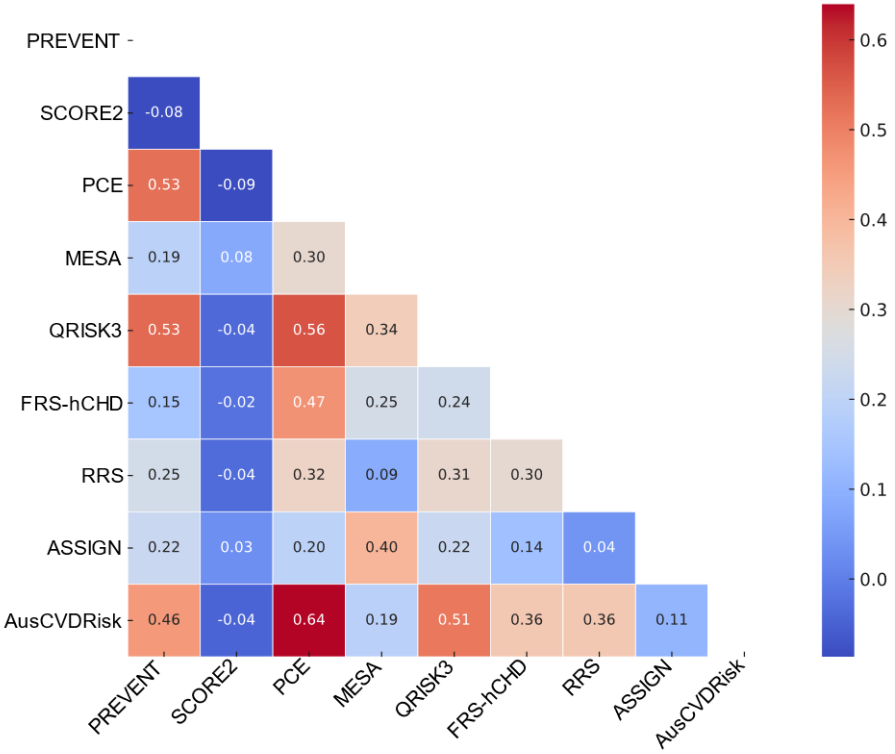
4 paveikslas. Širdies ir kraujagyslių ligų rizikos kategorijų pasiskirstymas pagal devynis rizikos vertinimo modelius: vyrų pogrupis



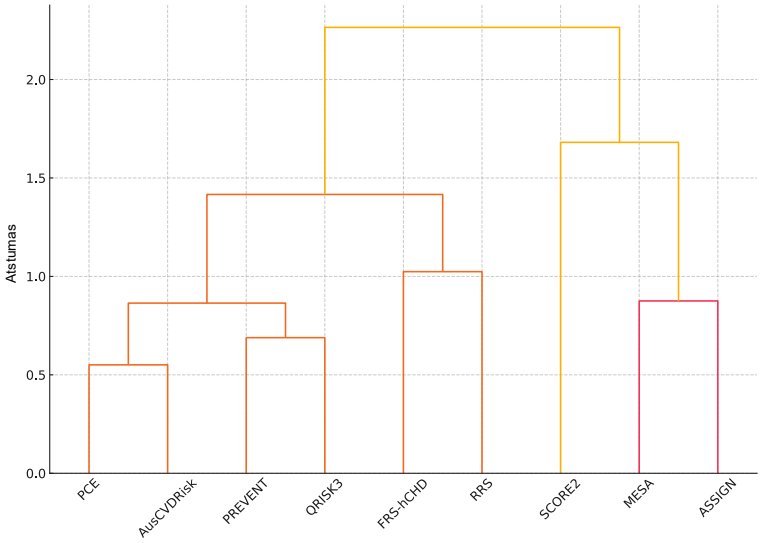
	FRS-hCHD	RRS	AusCVDRisk	PCE	QRISK3	MESA	PREVENT	ASSIGN	SCORE2
Maža rizika (%)	94.42	88.72	82.63	71.47	62.56	54.91	50.99	25.79	2.14
Vidutinė rizika (%)	5.06	9.76	16.09	27.01	30.99	24.82	46.19	45.52	29.71
Didelė rizika (%)	0.52	1.52	1.29	1.52	6.45	20.27	2.82	28.7	68.15

5 paveikslas. Širdies ir kraujagyslių ligų rizikos kategorijų pasiskirstymas pagal devynis rizikos vertinimo modelius: moterų pogrupis

Porinio sutapimo palyginimai patvirtino, kad skirtingų rizikos modelių klasifikacijos apskritai santykinai mažai sutampa. Koheno κ vertės tarp kiekvienos modelių poros reikšmingai skyrėsi – kai kurios buvo artimos nuliui (tai rodo, kad praktiškai nesutampa rizikos klasifikavimo ypatumai), o geriausiu atveju siekė vidutinę sutaptį nurodančias vertes (apie 0,5–0,6) (6 pav.). Pavyzdžiui, SCORE2 turėjo vieną iš mažiausių sutapčių su kitais ($\kappa \approx -0,08$ palyginti su PREVENT arba PCE, kas reiškia, kad modelių klasifikacija visiškai nesutapo), o skaičiuoklės su panašiais rezultatais parodė didesnį κ – pvz., PCE palyginti su AusCVDRisk pasiekė $\kappa \sim 0,64$ (stipriausia nustatyta sutaptis). Toliau modelių grupės buvo sugrupuotos pagal tai, kuriuos asmenis jos identifikavo kaip didelės rizikos. 7 paveikslo dendrogramoje matyti, kad, pvz., vieną iš atveju, PCE, AusCVDRisk, QRISK3 ir PREVENT sudarė vieną pogrupį (turėdami gana panašų rizikos pasiskirstymą), o SCORE2 išsiskyrė (pademonstruodamas išskirtinai didelę rizikos asimetriją). Šios analizės rodo didelį modelių tarpusavio skirtumą klasifikuojant pacientus, tai patvirtina, kad rizikos kategorizavimas labai priklauso nuo modelio.

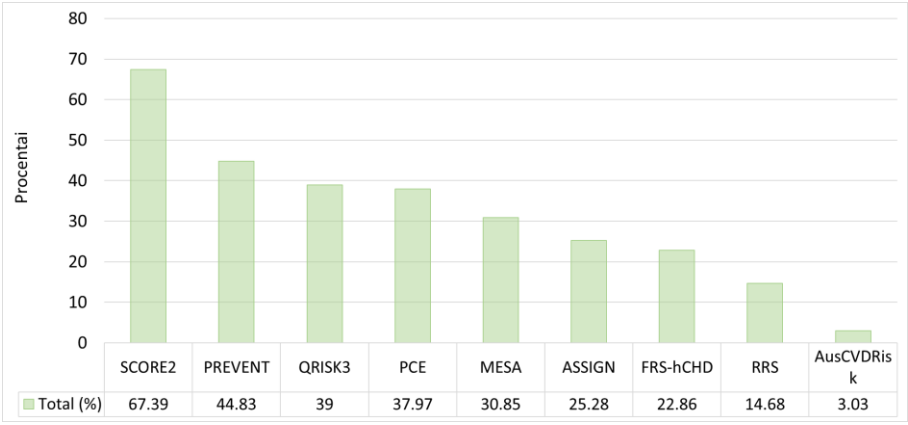


6 paveikslas. Šilumos žemėlapis, rodantis porinę (tarpusavio) devynių širdies ir kraujagyslių ligų rizikos vertinimo modelių atitiktį

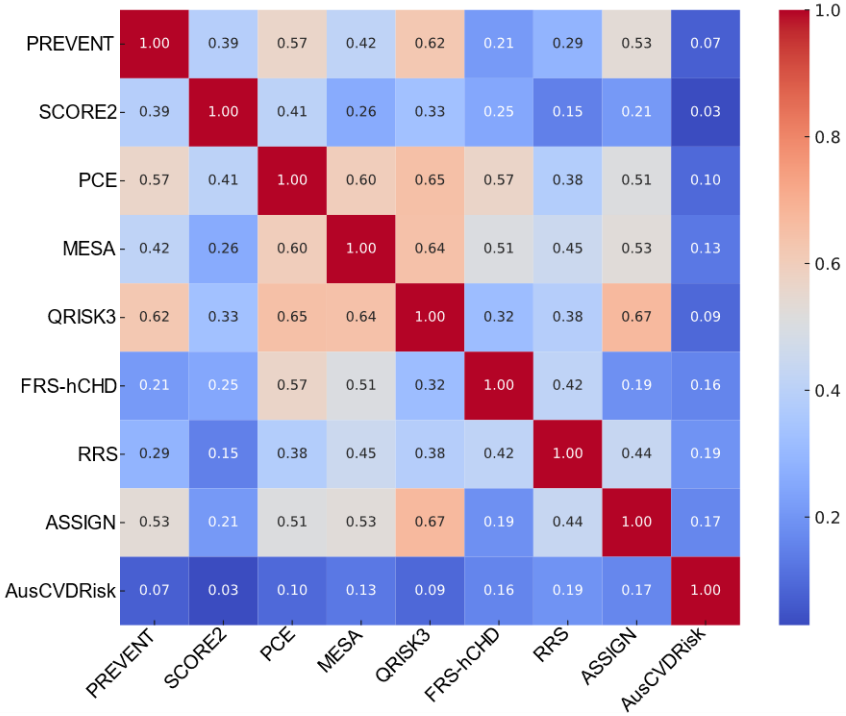


7 paveikslas. Hierarchinio klasterizavimo dendrograma, iliustruojanti devynių širdies ir kraujagyslių ligų rizikos vertinimo modelių panašumus

Kadangi kiekvienas modelis naudoja skirtingus slenksčius, kai neabejotinai rekomenduojamas lipidų koncentraciją mažinantis gydymas, pastebėjome didelius skirtumus ir vertinant gydymo statinais indikacijas. Dalyvių, kuriems būtų rekomenduojamas gydymas statinais, procentas svyravo nuo 3 proc. (pagal AusCVDRisk kriterijus) iki 67 proc. (pagal SCORE2 kriterijus). Kitaip tariant, pagal SCORE2 būtų rekomenduota gydyti daugiau nei du trečdalius šios kohortos dalyvių, o AusCVDRisk – praktiškai nė vieno. Dauguma kitų modelių buvo tarp šių dviejų: pagal PREVENT būtų rekomenduotas gydymas ~45 proc. asmenų, PCE – ~38 proc., QRISK3 – ~39 proc., ASSIGN – ~25 proc., FRS-hCHD – ~23 proc., o RRS – tik ~15 proc. Šie skirtumai (8 pav.) pabrėžia, kad priklausomai nuo to, kuris rizikos vertinimo modelis naudojamas, prevenciniam medikamentiniam gydymui būtų svarstoma dramatiškai skirtinga pacientų dalis. Atsižvelgiant į tai, modelių sutaptis vertinant gydymo statinais indikacijas buvo santykinai ribota: κ vertės svyravo nuo ~0,03 (iš esmės nėra sutapties – pvz., tarp SCORE2 ir AusCVDRisk) iki didžiausios sutapties ~0,67 (tarp QRISK3 ir ASSIGN) (9 pav.). Taigi, pagal vieną modelį galima klasifikuoti asmenį kaip tinkamą medikamentiniam gydymui, o pagal kitą modelį (taikomą tam pačiam asmeniui) bus siūloma netaikyti jokio gydymo – tai neatitiktis, kuris gali turėti įtakos klinikinei priežiūrai.



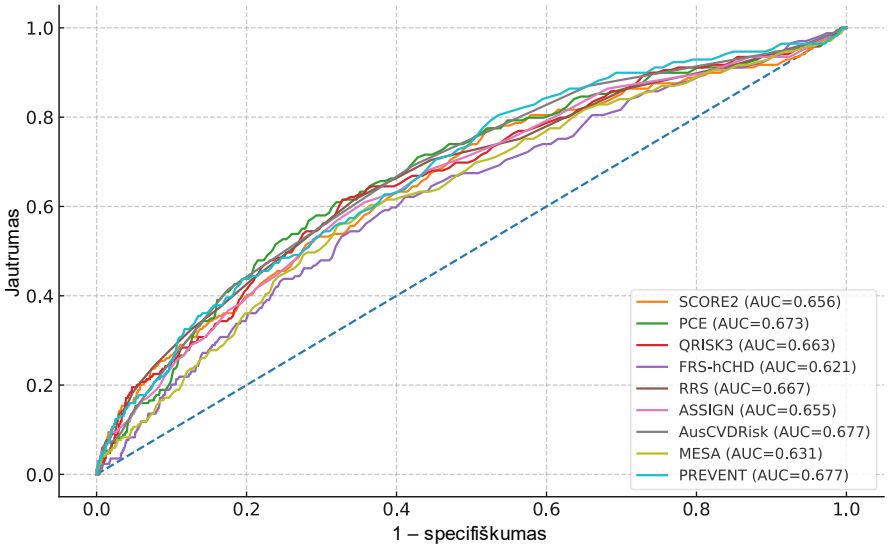
8 paveikslas. Statinų skyrimo indikacijų pagal devynis širdies ir kraujagyslių ligų rizikos vertinimo modelius pasiskirstymas



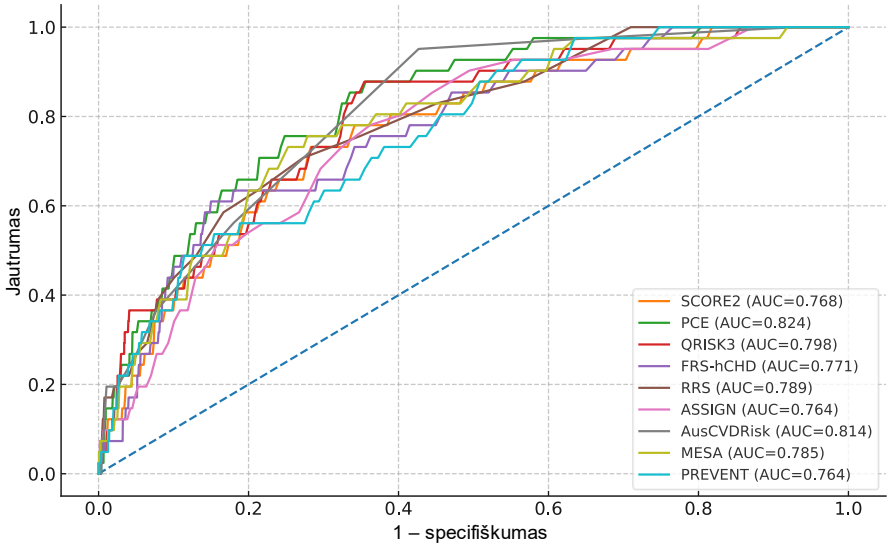
9 paveikslas. Šilumos žemėlapis: porinė gydymo statinais indikacijų sutaptis pagal devynis širdies ir kraujagyslių ligų rizikos vertinimo modelius

Modelių diskriminacinė galia ir prognostinės savybės: nė vienas rizikos modelis nebuvo pranašiausias prognozuojant faktinius širdies ir kraujagyslių ligų įvykius (10; 11; 12; 13; 14 pav.). Vertinant įvairias baigtis, skirtingi modeliai turėjo aukščiausią AUC – pavyzdžiui, PCE geriausiai pasirodė prognozuojant širdies ir kraujagyslių ligų mirtį (AUC ~0,82) ir miokardo infarktą (AUC ~0,785, praktiškai identiškas FRS-hCHD) atvejais, PREVENT buvo tiksliausias insulto (AUC ~0,57) atveju, o PCE pademonstravo geriausius rezultatus numatant sudėtinę ŠKL baigtį (AUC ~0,65). Vis dėlto nė vienas iš šių skirtumų nebuvo didelis: du pagal kiekvieną baigtį geriausi modeliai tarpusavyje statistiškai reikšmingai nesiskyrė ($p > 0,05$), o bendra visų priemonių diskriminacinė geba buvo ribota. Iš tiesų, visų modelių c statistika svyravo tik nuo 0,5 iki 0,7, o tai rodo, kad nė vienas modelis nepasiekė didelio prognozavimo tikslumo. Pavyzdžiui, prognozuojant 10 metų mirtingumą dėl širdies ir kraujagyslių ligų, PCE modelis turėjo didžiausią AUC (~0,824, 95 proc. PI 0,77–0,88), o AusCVDRisk buvo antras

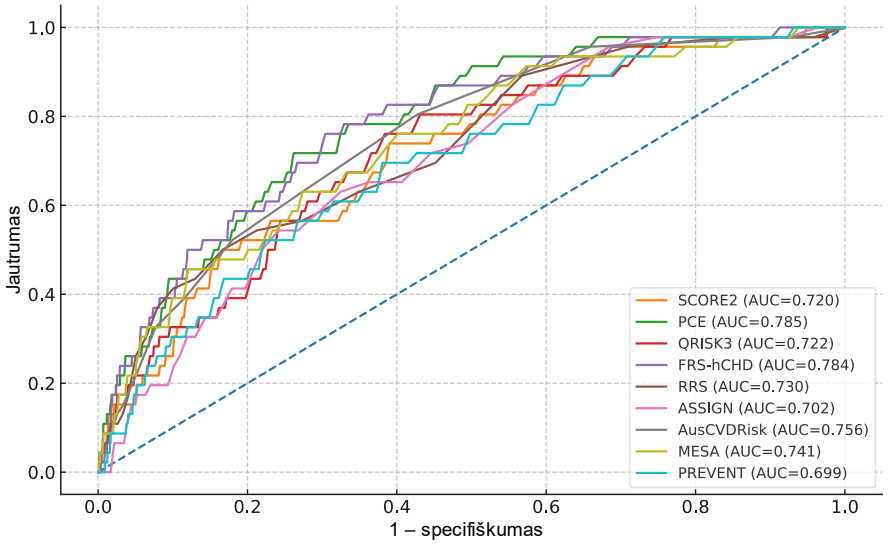
(~0,814); šis skirtumas nebuvo statistiškai reikšmingas (p = 0,46). Miokardo infarkto atveju PCE ir FRS-hCHD rezultatai buvo labai panašūs (AUC ~0,785). Tuo tarpu insulto atvejais visi modeliai prognozavo prastai (AUC vos viršijo 0,55 – iš esmės tik šiek tiek geriau nei atsitiktinumas). Sudėtinio širdies ir kraujagyslių ligų įvykio atveju (ŠKL mirtis + miokardo infarktas + insultas) PCE pasiekė aukščiausią AUC (~0,647), o AusCVDRisk buvo antras (~0,639), tačiau ir vėl šis nedidelis pranašumas nebuvo reikšmingas (p = 0,29). Apskritai modelių gebėjimas identifikuoti, kas patirs įvykius, o kas ne, buvo tik vidutinis. Atsižvelgdami į tai, toliau nagrinėjome sprendimų kreives ir paaiškėjo, jog nė vienas iš modelių nesuteikė didelės papildomos teigiamos prognostinės vertės – geriausiu atveju ~5–8 proc. tų, kurie buvo klasifikuoti kaip „didelės rizikos“, iš tikrųjų patyrė įvykį. Kita vertus, modelių neigiama prognostinė vertė buvo labai didelė (~97–99 proc. tų, kurie buvo klasifikuoti kaip mažos rizikos, išvengė įvykių). Visi modeliai buvo linkę pervertinti absoliučią riziką – pavyzdžiui, SCORE2 prognozavo gerokai didesnę įvykių tikimybę nei buvo stebėta – tai patvirtina ankstesnį teiginį, kad šios priemonės buvo netinkamai kalibruotos mūsų kohortoje. Šie rezultatai rodo, kad nors šiuolaikiniai rizikos modeliai ir atspindi riziką plačiąja prasme, jų kalibravimas ir tikslumas gali būti pagerinti, o vieno modelio pasirinkimas vietoj kito iš esmės nekeis prognozavimo gebėjimų, bet turės įtakos tam, ką mes gydysime.



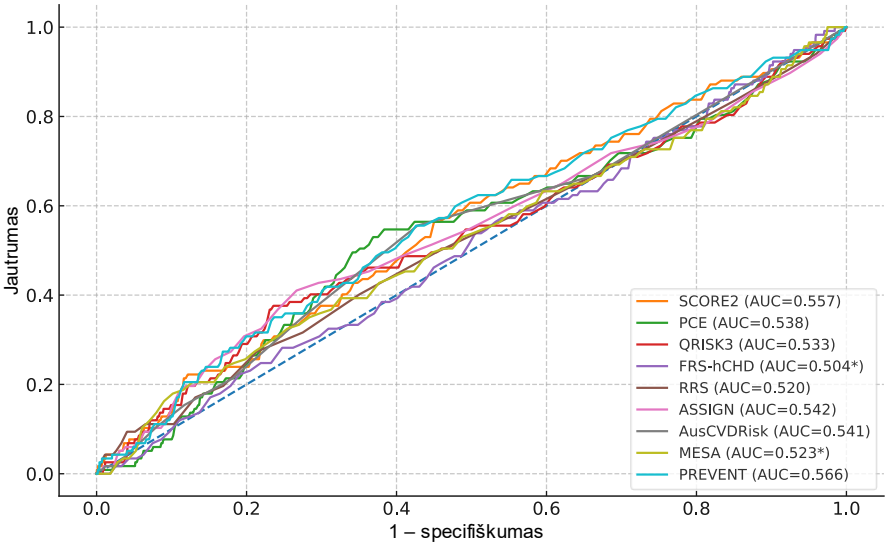
10 paveikslas. Rizikos prognozavimo modelių palyginimas: mirtingumo dėl visų priežasčių ROC kreivės



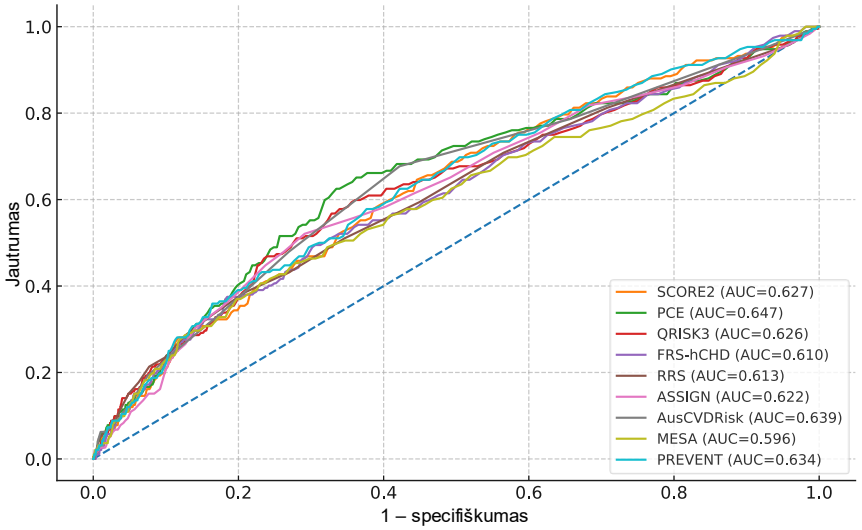
11 paveikslas. Rizikos prognozavimo modelių palyginimas: mirtingumo dėl širdies ir kraujagyslių ligų ROC kreivės



12 paveikslas. Rizikos prognozavimo modelių palyginimas: miokardo infarkto atvejų ROC kreivės



13 paveikslas. Rizikos prognozavimo modelių palyginimas: insulto atvejų ROC kreivės

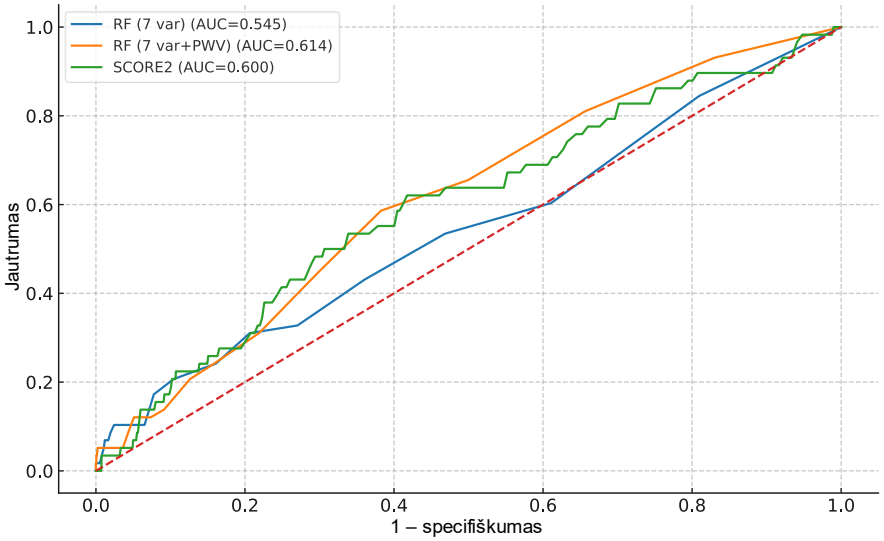


14 paveikslas. Rizikos prognozavimo modelių palyginimas: sudėtinė baigtis (ŠKL mirtis /MI /insultas) ROC kreivės

Pirmiau minėti rezultatai taip pat rodo, kad tradiciniai rizikos modeliai šioje populiacijoje pasiekė savo tikslumo ribą. Net geriausiai veikiantys algoritmai pasiekė tik nedidelį diskriminacinį tikslumą, o jų grynoji klinikinė

nauda (įvertinta sprendimų kreivių analizės principu) buvo ribota ir priklausė nuo pasirinktų slenksčių. Tai skatina įtraukti papildomus rizikos žymenis ir labiau individualizuotus metodus (pavyzdžiui, MM), siekiant išsiaiškinti, ar galima pasiekti tikslesnių rezultatų.

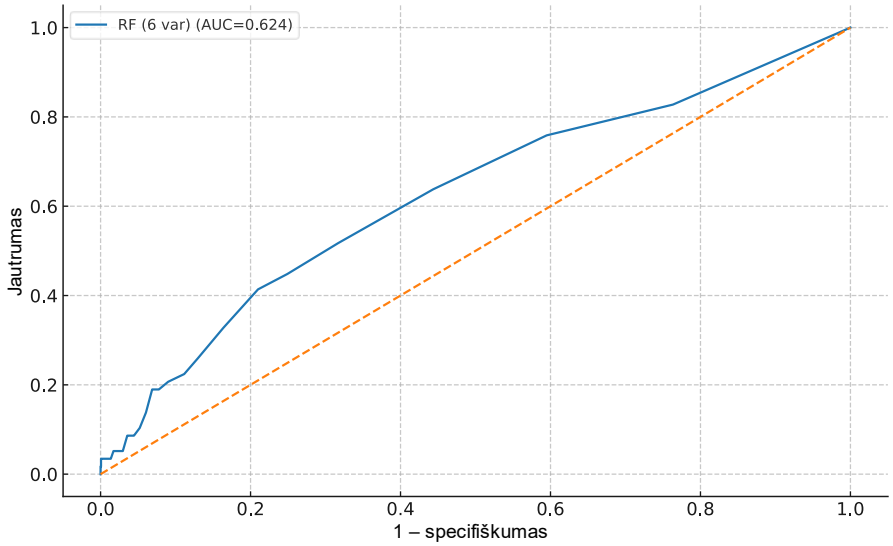
Mašininio mokymosi modelio rezultatai: Reikia pažymėti, kad gauti mūsų tiriamojo MM modelio ir tradicinių rizikos prognozavimo modelių naudojimo rezultatai buvo panašūs. Atsitiktinių miškų modelis, naudojantis septynis tradicinius rizikos veiksnius, turėjo AUC ~0,545 testiniame atvejų rinkinyje, kuris buvo mažesnis nei SCORE2 algoritmo AUC (~0,600) tiems patiems asmenims. Vis dėlto, kai PBG buvo pridėtas prie modelio (RF 7 var + PBG), diskriminacija pagerėjo: AUC padidėjo iki ~0,614. Šis ~0,07 AUC padidėjimas, įtraukus arterijų standumo žymenį, turėjo ribinį statistinį reikšmingumą (ΔAUC = +0,070, p ≈ 0,053), o tai rodo tendenciją pagerinti prognozavimą. Pažymėtina, kad RF modelis su PBG pranoko SCORE2 pagal AUC (0,614 palyginti su 0,600), nors šis skirtumas nebuvo reikšmingas (p = 0,72). Priešingai, RF modelis be PBG buvo prastesnis nei SCORE2 (AUC 0,545 palyginti su 0,600, ΔAUC = –0,055, p ~0,23), o tai rodo, kad MM metodas be naujojo biožymens nepranoko tradicinės skaičiuoklės (15 pav.).



15 paveikslas. Rizikos prognozavimo modelių palyginimas: sudėtinė baigtis (ŠKL mirtis /MI /insultas) ROC kreivės

Įdomu tai, kad supaprastintas RF modelis, turintis tik šešis požymius, iš tikrųjų pasiekė AUC ~0,624 – šiek tiek aukštesnį nei visas septynių kintamųjų

modelis ir su PBG papildytas modelis. Tai rodo, kad, įtraukiant per daug koreliuojančių kintamųjų (ypač ribotame duomenų rinkinyje su nedaug įvykių), gali atsirasti triukšmas ir tai nebūtinai pagerina modelio tikslumą. Kitaip tariant, mažiau kriterijų turintis modelis, kai sutelkiamas dėmesys į stipriausią prognostinę vertę turinčius veiksnius (amžių, kraujospūdį, gliukozės kontrolę, uždegimą ir kt.), šioje situacijoje gali būti toks pat veiksmingas (ar netgi veiksmingesnis) kaip sudėtingesnis modelis (16 pav.).



16 paveikslas. Rizikos prognozavimo modelių palyginimas: sudėtinė baigtis (ŠKL mirtis /MI /insultas) ROC kreivė

Tirdami konkrečius prognostinius slenksčius, nustatėme, kad PBG įtraukimas labai nepablogino sąsajos tarp klaidingai teigiamų ir klaidingai neigiamų rezultatų. Esant aukštam specifiškumo slenksčiui (apie 90 proc. specifiškumas), RF su PBG ir RF be PBG turėjo labai panašų specifiškumą (~0,90) ir beveik identiškas teigiamas prognostines vertes (~5–6 proc.), tačiau PBG modelis užfiksavo keletu daugiau tikrų įvykių (šiek tiek didesnis jautrumas). Praktiškai PBG kaip papildomo rizikos veiksnio panaudojimas nepadidino klaidingai teigiamų rezultatų skaičiaus nustatant didelės rizikos asmenis, tačiau padėjo nustatyti keletą papildomų įvykių atvejų, kurie kitaip būtų praleisti. Abu MM modeliai ir SCORE2 turėjo aukštą neigiamą prognostinę vertę (~96–97 proc.), o tai reiškia, kad visi jie buvo geri atmetant riziką tiems, kurie buvo klasifikuojami kaip turintys mažą riziką.

Kalibravimo atžvilgiu, kaip minėta anksčiau, visi MM modeliai (ir SCORE2) turėjo tendenciją pervertinti absoliučią riziką testiniame rinkinyje. Pavyzdžiui, bendras įvykių dažnis buvo 3,3 proc., o vidutinė SCORE2 prognozuojama rizika buvo didesnė (kalibravimo sankirta ~–2,17, o tai rodo rizikos pervertinimą). Atsitiktinių miškų modeliai taip pat turėjo neigiamus kalibravimo sankirtos taškus ir nuolydžius, kurie buvo gerokai mažesni nei 1, o tai rodo, kad jie buvo pernelyg pasitikintys savo prognozėmis ir būtų naudinga juos perkalibruoti, jei jie būtų naudojami absoliučios rizikos tikimybei prognozuoti. Vis dėlto, kadangi mūsų tyrime daugiausia dėmesio buvo skirta santykinei rizikos diskriminacijai, šias kalibravimo problemas prireikus galima išspręsti atlikus *post hoc* korekciją.

Galiausiai, atsitiktinių miškų kriterijų svarbos ir SHAP verčių analizė suteikė įžvalgų apie rizikos veiksnius MM modelyje. Kaip ir tikėtasi, amžius buvo didžiausią įtaką prognozei turintis veiksnys, turėjęs didžiausią svarbą modelio rizikos prognozei visose RF variantuose. Pagrindiniame 7 kintamųjų modelyje kiti svarbiausi požymiai buvo diastolinis kraujospūdis ir gliukozės koncentracija nevalgius, paskui – CRB; kraujo lipidai (bendrasis cholesterolis ir trigliceridai) turėjo mažesnę įtaką, o lytis suteikė mažiausiai informacijos (tikriausiai dėl to, kad rizika šioje homogeninėje MetS kohortoje jau buvo padidėjusi abiem lytims). Kai buvo pridėtas PBG, jis tapo vidutinės svarbos (2–3 pagal aktualumą) prognozės veiksniu – maždaug lygiaverčiu kraujospūdžiui ir gliukozės kiekiui. Tai atitinka nedidelį AUC pagerėjimą, pastebėtą su PBG. Tai patvirtina, kad nors PBG ir turi nepriklausomą prognostinę naudą (atspindintį kraujagyslių senėjimo aspektus), modelio rizikos prognozės vis dar daugiausia priklauso nuo tradicinių veiksnių: amžiaus, kraujospūdžio, gliukozės kiekio kraujyje ir sisteminio uždegimo. Apibendrinant reikia pažymėti, kad MM rezultatai rodo, jog, įtraukus kraujagyslių senėjimo biožymenį, pavyzdžiui, PBG, galima laipsniškai pagerinti rizikos prognozavimą, tačiau, norint pasiekti didesnį tikslumą nei naudojant tradicinius rizikos veiksnius, gali prireikti didesnių duomenų rinkinių arba papildomų naujų biožymenų. Mūsų teikiamo MM modelio rezultatai panašūs į nusistovėjusios rizikos skaičiuoklės, reikia pabrėžti tiek MM potencialą, tiek dabartinius ribotumus šiame kontekste.

IŠVADOS

1. **Modelių variabilumas**: labai skiriasi devynių širdies ir kraujagyslių ligų rizikos predikcijos modelių rizikos stratifikacija (3–67 proc. asmenų yra

klasifikuojami kaip didelės rizikos), todėl labai skiriasi ir antilipidinių vaistų skyrimo indikacijos.
2. **Prognozavimo tikslumas**: nėra visuotinai pripažįstamo pranašiausio minėtos rizikos vertinimo modelio; tikslumas skiriasi priklausomai nuo prognozuojamų baigčių, o visų modelių diskriminacinė galia yra ribota (c statistika 0,6–0,8).
3. **Kalibracijos problemos**: visi modeliai pervertina absoliučią Lietuvos didelės rizikos kohortos širdies ir kraujagyslių ligų riziką. Tai rodo vietinio perkalibravimo arba specifinių populiacijai pritaikytų algoritmų poreikį.
4. **Biožymenų indėlis**: įtraukiant į modelius kraujagyslių senėjimo biožymenis, ypač miego ir šlaunies arterijų pulsinės bangos greitį, pagerėjo širdies ir kraujagyslių ligų rizikos prognozavimo tikslumas ir rizikos diferencijavimas, o klaidingai teigiamų rezultatų skaičius nepadidėjo.
5. **Mašininio mokymosi įžvalgos**: mašininio mokymosi modelių naudojimo rezultatai panašūs kaip tradicinių rizikos skaičiuoklių; mažiau kriterijų įtraukiantys algoritmai buvo tokie pat tikslūs kaip ir sudėtingi, daugiau veiksnių naudojantys modeliai. Nors mašininis mokymasis leidžia integruoti naujus biožymenis, norint pranokti tradicines skaičiuokles, reikės didesnių aukštos kokybės duomenų rinkinių, ilgesnės stebėsenos ir išorinės validizacijos.

TYRIMO NAUJUMAS

1. Šioje disertacijoje pateikiamas pirmasis tai pačiai populiacijai taikomas devynių plačiai naudojamų širdies ir kraujagyslių ligų rizikos vertinimo modelių tiesioginis palyginimas. Vienu metu įvertinus visas šias skaičiuokles remiantis vietine kohorta, gaunama unikalių įžvalgų apie jų tikslumą ir taikymo Lietuvoje tinkamumą.
2. Tai yra vienas iš pirmųjų tyrimų, kuriame naujausi rizikos prognozavimo modeliai, pavyzdžiui, 2023 m. paskelbta PREVENT skaičiuoklė, išoriškai vertinami kartu su kitomis skaičiuoklėmis. Įtraukus tokius naujus modelius (dar plačiai neįvertintus už pradinės kūrimo imties ribų), gaunamas pažangus analizės aspektas ir užpildoma spraga, kaip šios naujai diegiamos priemonės veikia praktiškai.
3. Darbe pristatomi nauji būdai kiekybiškai įvertinti, kiek remiantis skirtingais modeliais sutariama dėl paciento rizikos kategorizavimo: modelių porinė sutaptis išmatuota taikant Koheno kapa (κ) rodiklį bei panaudota hierarchinio klasterizavimo analizė, skirta modeliams su panašiomis klasifikavimo savybėmis grupuoti. Toks daugiasluoksnis

suderinamumo vertinimas yra naujas ŠKL rizikos modelių palyginimo kontekste, teikia gilesnį supratimą, kurios skaičiuoklės linkusios klasifikuoti panašiai, o kurios – skirtingai.

4. Disertacijoje kiekvieno rizikos modelio predikcinės savybės vertinamos atskirai skirtingoms širdies ir kraujagyslių ligų baigtims (pvz., sudėtiniai ŠKL įvykiai, miokardo infarktas, insultas ir pan.), o ne apibendrinant visas baigtis kartu. Atlikus diskriminacinės galios analizę konkrečioms baigtims, nustatyta, kad nė vienas modelis nėra vienodai pranašus visoms baigtims. Toks detalus etaloninis palyginimas suteikia gilesnį supratimą apie kiekvieno modelio stiprybes ir ribotumus skirtingų įvykių atžvilgiu.
5. Esminis originalus indėlis – personalizuoto, mašininio mokymosi pagrindu sukurto ŠKL rizikos prognozavimo modelio sukūrimas ir įvertinimas. Šis naujas modelis sujungia tradicinius rizikos veiksnius su kraujagyslių senėjimo žymenimis (miego ir šlaunies arterijų pulsinės bangos greitis), siekiant pagerinti rizikos stratifikaciją. Parodoma, kad šių kraujagyslinių biožymenų įtraukimas į mašininio mokymosi algoritmą gali pagerinti modelio predikcines savybes, be to, šis modelis palyginamas su tradicine skaičiuokle, išryškinant potencialią naudą.
6. Tyrime nuodugniai įvertinta, kaip įsitvirtinę rizikos vertinimo modeliai yra kalibruoti Lietuvos populiacijoje. Nustatyta, kad daugelis plačiai naudojamų modelių (pvz., SCORE2) šioje kohortoje yra netiksliai kalibruoti – dažniausiai pervertina absoliučios rizikos lygį. Tai nauja, regionui specifinė įžvalga, rodanti vietinės rekalibracijos poreikį. Įvertinus tikslumą anksčiau netirtai populiacijai gaunama metodologinė vertė ir užtikrinamas tiesioginis radinių aktualumas vietinei klinikinei praktikai.
7. Lyginamieji rezultatai turi reikšmingas visuomenės sveikatos ir klinikines panaudas. Parodoma, kad pasirinktas rizikos modelis gali lemti visiškai skirtingus terapinius sprendimus – pavyzdžiui, asmenų, kuriems būtų tikslingas gydymas statinais, dalis dėl skirtingų rizikos slenksčių ir įverčių tarp algoritmų labai skiriasi. Kiekybiškai įvertinus šiuos skirtumus, atskleidžiami galimi gairėmis grindžiamos priežiūros nenuoseklumai ir pateikiami duomenys, galintys daryti įtaką būsimų gairių atnaujinimams.

PRAKTINĖS REKOMENDACIJOS

1. Vertinant individualią širdies ir kraujagyslių ligų riziką, reikėtų vengti remtis vien tik tradiciniais rizikos prognozavimo modeliais; kai įmanoma, vertinimas turėtų apimti patvirtintus rizikos modifikatorius, pavyzdžiui, didelio jautrumo C reaktyvųjį baltymą, miego ir šlaunies arterijų pulsinės

bangos greitį, lipoproteiną (a), apolipoproteiną B, ŠKL šeiminę anamnezę ir lėtinius uždegiminius sutrikimus, siekiant patikslinti rizikos įvertinimą ir pagrįsti gydymą.

2. Arterijų standumas galėtų būti naudojamas vertinti vidutinės ŠKL rizikos scenarijus. Pulsinės bangos greitis (PBG) turėtų būti įtrauktas, kai rizika yra ribinė; mašininio mokymosi analizėse PBG suteikė papildomos prognostinės informacijos ir pagerino diskriminaciją, patvirtindamas savo kaip patikslinančio riziką tyrimo vaidmenį, o ne kaip universalią atrankos priemonę.
3. Svarstytina įsteigti nacionalinę daugiadisciplininę darbo grupę (kardiologija, pirminė sveikatos priežiūra, epidemiologija/ biostatistika ir sveikatos IT), kad būtų sukurtas Lietuvai tinkamas širdies ir kraujagyslių ligų rizikos vertinimo modelis, atliekant (a) SCORE2 arba PREVENT perkalibravimą ir išorinę validizaciją remiantis daugiacentriais Lietuvos duomenimis arba (b) kuriant naują nacionalinį modelį. Metodai ir koeficientai turėtų būti atviri, periodiškai kalibruojami ir stebimi, o prieš patvirtinant gaires turėtų būti atliekama nepriklausoma išorinė validizacija.
4. Mašininis mokymasis turėtų būti naudojamas siekiant papildyti būsimus širdies ir kraujagyslių ligų rizikos vertinimo modelius kartu su įsitvirtinusiais klinikiniais įrankiais ir biožymenimis, teikiant pirmenybę interpretuojamumui, skaidrumui ir griežtai validizacijai (įskaitant išorinius tyrimus) prieš klinikinį diegimą, po kurio turėtų būti atliekama nuolatinė stebėsena ir kalibravimas.
5. Turėtų būti sukurtas perspektyvusis, daugiacentris Lietuvos registras, apimantis pirminės sveikatos priežiūros, antrinio ir tretinio lygio centrus, su standartizuotais kintamųjų apibrėžimais ir pritaikytomis širdies ir kraujagyslių ligų stebimomis baigtimis, kad būtų galima atlikti patikimą išorinę validizaciją bei koreguoti nacionalinę širdies ir kraujagyslių ligų priežiūros strategiją.

12. LIST OF PUBLICATIONS

The main findings of the doctoral dissertation were published in the following articles:

1. **Navickas, Petras**; Lukavičiūtė, Laura; Glaveckaitė, Sigita; Baranauskas, Arvydas; Šatrauskienė, Agnė; Badarienė, Jolita; Laucevičius, Aleksandras. Navigating the landscape of cardiovascular risk scores: a comparative analysis of eight risk prediction models in a high-risk cohort in Lithuania // Journal of clinical medicine. Basel: MDPI AG. eISSN 2077-0383. 2024, vol. 13, iss. 6, art. no. 1806, p. [1-13]. DOI: 10.3390/jcm13061806. [DB: Science Citation Index Expanded (Web of Science), Scopus, PubMed] (IF: 3.4)
2. **Navickas, Petras**; Lukavičiūtė, Laura; Glaveckaitė, Sigita; Baranauskas, Arvydas; Šatrauskienė, Agnė; Badarienė, Jolita; Laucevičius, Aleksandras. PREVENT equation: the black sheep among cardiovascular risk scores? A comparative agreement analysis of nine prediction models in high-risk Lithuanian women // Medicina: Special issue: Current advances in cardiovascular disease research. Basel: MDPI AG. ISSN 1010-660X. eISSN 1648-9144. 2024, vol. 60, iss. 9, art. No. 1511, p. [1-15]. DOI: 10.3390/medicina60091511. [DB: Science Citation Index Expanded (Web of Science), Scopus] [IF: 2.400; AIF: 3.000; Q1 (2024 InCities JCR SCIE)]

Other publications during the PhD period:

1. Slušnienė, Anžela; **Navickas, Petras**; Stankus, Albinas; Laucevičienė, Ieva; Ryliškytė, Ligita; Laucevičius, Aleksandras. Defining the nocturnal period in 24-h ambulatory blood pressure monitoring: a comparison of three methods // Blood pressure monitoring. Philadelphia: Lippincot Williams & Wilkins. ISSN 1359-5237. eISSN 1473-5725. 2021, vol. 26, iss. 3, p. 207-214. DOI: 10.1097/MBP.0000000000000509. [DB: Science Citation Index Expanded (Web of Science), Scopus, MEDLINE] [IF: 1.430; AIF: 6.292; Q4 (2021 InCities JCR SCIE)]
2. Gopcevic, Kristina R.; Gkaliagkousi, Eugenia; Nemcsik, Janos; Acet, Omur; Bernal-Lopez, M. Rosa; Bruno, Rosa M.; Climie, Rachel E.; Fountoulakis, Nikolaos; Fraenkel, Emil; Lazaridis, Antonios; **Navickas, Petras**; Rochfort, Keith D.; Šatrauskienė, Agnė; Zupkauskienė, Jūratė; Terentes-Printzios, Dimitrios. Pathophysiology of circulating biomarkers and relationship with vascular aging: a review of the literature from VascAgeNet group on circulating biomarkers, European Cooperation in Science and Technology Action 18216 // Frontiers in physiology.

Lausanne: Frontiers Media S.A. eISSN 1664-042X. 2021, vol. 12, art. no. 789690, p. [1-19]. DOI: 10.3389/fphys.2021.789690. [DB: Science Citation Index Expanded (Web of Science), Scopus, MEDLINE]

3. Laučytė-Cibulskienė, Agnė; Ryliškytė, Ligita; Badaras, Ignas; **Navickas, Petras**; Badarienė, Jolita; Laucevičius, Aleksandras. Arterial stiffness in regards to kidney function in middle-aged subjects with metabolic syndrome: Lithuanian high-risk cohort // Blood pressure monitoring. Philadelphia: Lippincott Williams & Wilkins. ISSN 1359-5237. eISSN 1473-5725. 2021, vol. 26, no. 3, p. 191-195. DOI: 10.1097/MBP.0000000000000510. [DB: Science Citation Index Expanded (Web of Science), Scopus] [IF: 1.430; AIF: 6.292; Q4 (2021 InCities JCR SCIE)]
4. Šerpytis, Rokas; Majauskienė, Eglė; **Navickas, Petras**; Lizaitis, Mindaugas; Glaveckaitė, Sigita; Ručinskas, Kęstutis; Petrulionienė, Žaneta; Valevičienė, Nomeda Rima; Samalavičius, Robertas Stasys; Berūkštis, Andrius; Baranauskas, Arvydas; Gargalskaitė, Urtė; Laucevičius, Aleksandras; Chen, Qin M; Alpert, Joseph S; Šerpytis, Pranas. Randomized pilot trial on optimal treatment strategy, myocardial changes, and prognosis of patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) // American journal of medicine. New York: Elsevier. ISSN 0002-9343. eISSN 1555-7162. 2022, vol. 135, iss. 1, p. 103-109. DOI: 10.1016/j.amjmed.2021.08.023. [DB: Science Citation Index Expanded (Web of Science), Scopus, PubMed, MEDLINE, Embase, Current Contents] [IF: 5.900; AIF: 6.700; Q1 (2022 InCities JCR SCIE)]
5. Zupkauskienė, Jūratė; Laucevičienė, Ieva; **Navickas, Petras**; Ryliškytė, Ligita; Puronaitė, Roma; Badarienė, Jolita; Laucevičius, Aleksandras. Changes in health-related quality of life, motivation for physical activity, the levels of anxiety and depression after individualized aerobic training in subjects with metabolic syndrome // Hellenic journal of cardiology. Athens: Hellenic Cardiological Society. ISSN 1109-9666. eISSN 2241-5955. 2022, vol. 66, p. 41-51. DOI: 10.1016/j.hjc.2022.04.003. [DB: Science Citation Index Expanded (Web of Science), Scopus] [IF: 4.100; AIF: 5.200; Q2 (2022 InCities JCR SCIE)]
6. Stankus, Vytautas; **Navickas, Petras**; Slušnienė, Anžela; Laucevičienė, Ieva; Stankus, Albinas; Laucevičius, Aleksandras. A novel adaptive noise elimination algorithm in long RR interval sequences for heart rate variability analysis // Sensors. Basel: MDPI. ISSN 1424-8220. 2022, vol. 22, iss. 23, art. no. 9213, p. 1-16. DOI: 10.3390/s22239213. [DB: Science

Citation Index Expanded (Web of Science), Scopus, MEDLINE] [IF: 3.900; AIF: 4.333; Q2 (2022 InCities JCR SCIE)]

7. Šerpytis, Rokas; Lizaitis, Mindaugas; Majauskienė, Eglė; **Navickas, Petras**; Glaveckaitė, Sigita; Petrulionienė, Žaneta; Valevičienė, Nomeda Rima; Laucevičius, Aleksandras; Chen, Qin M.; Alpert, Joseph S.; Šerpytis, Pranas. Type 2 myocardial infarction and long-term mortality risk factors: a retrospective cohort study // Advances in therapy. New York: Springer Healthcare Communications. ISSN 0741-238X. eISSN 1865-8652. 2023, vol. 40, no. 5, p. 2471-2480. DOI: 10.1007/s12325-023-02485-2. [DB: Science Citation Index Expanded (Web of Science), Scopus] [IF: 3.400; AIF: 4.250; Q2 (2023 InCities JCR SCIE)]
8. Zupkauskienė, Jūratė; Laucevičienė, Ieva; Ryliškytė, Ligita; **Navickas, Petras**; Kizlaitis, Romualdas Jonas; Laucevičius, Aleksandras. Ambulatory and successive home-based heart rate targeted aerobic training improves arterial parameters: a follow-up study in people with metabolic syndrome // Annals of medicine. Abingdon: Taylor & Francis Ltd. ISSN 0785-3890. eISSN 1365-2060. 2023, vol. 55, no. 2, art. no. 2250363, p. 1-13. DOI: 10.1080/07853890.2023.2250363. [DB: Science Citation Index Expanded (Web of Science), Scopus] [IF: 4.900; AIF: 3.300; Q1 (2023 InCities JCR SCIE)]
9. Lycholip, Valentinas; Puronaitė, Roma; Skorniakov, Viktor; **Navickas, Petras**; Tarutytė, Gabrielė; Trinkūnas, Justas; Burneikaitė, Greta; Kazėnaitė, Edita; Jankauskienė, Augustina. Assessment of the disease severity in patients hospitalized for COVID-19 based on the National Early Warning Score (NEWS) using statistical and machine learning methods: An electronic health records database analysis // Technology and health care. Amsterdam: IOS Press. ISSN 0928-7329. eISSN 1878-7401. 2023, vol. 31, no. 6, p. 2513-2524. DOI: 10.3233/THC-235016. [DB: Science Citation Index Expanded (Web of Science), Scopus] [IF: 1.400; AIF: 4.000; Q3 (2023 InCities JCR SCIE)]
10. Zanelli, Serena; Agnoletti, Davide; Alastruey, Jordi; Allen, John; Bianchini, Elisabetta; Bikia, Vasiliki; Boutouyrie, Pierre; Bruno, Rosa Maria; Climie, Rachel; Djeldjli, Djammaleddine; Gkaliagkousi, Eugenia; Giudici, Alessandro; Gopcevic, Kristina; Grillo, Andrea; Guala, Andrea; Hametner, Bernhard; Joseph, Jayaraj; Karimpour, Parmis; Kodithuwakku, Vimarsha; Kyriacou, Panicos A; Lazaridis, Antonios; Lønnebakken, Mai Tone; Martina, Maria Raffaella; Mayer, Christopher Clemens; Nabeel, P. M.; **Navickas, Petras**; Nemcsik, János; Orter, Stefan; Park, Chloe; Pereira, Telmo; Pucci, Giacomo; Rey, Ana Belen Amado; Salvi, Paolo; Seabra,

Ana Carolina Gonçalves; Seeland, Ute; van Sloten, Thomas; Spronck, Bart; Stansby, Gerard; Steens, Indra; Stieglitz, Thomas; Tan, Isabella; Veerasingham, Dave; Wassertheurer, Siegfried; Weber, Thomas; Westerhof, Berend E; Charlton, Peter H. Developing technologies to assess vascular ageing: a roadmap from VascAgeNet // Physiological measurement. Bristol: IOP Publishing. ISSN 0967-3334. eISSN 1361-6579. 2024, vol. 45, no. 12, art. no. 121001, p. [1-89]. DOI: 10.1088/1361-6579/ad548e. [DB: Science Citation Index Expanded (Web of Science), Scopus, IOP Science] [IF: 2.700; AIF: 4.000; Q2 (2024 InCities JCR SCIE)]

11. Šileikienė, Vaida; Dženkevičiūtė, Vilma; Čypienė, Alma; Smailytė, Urtė; Puronaitė, Roma; Badarienė, Jolita; Laucevičius, Aleksandras; Butkevičiūtė, Eglė; **Navickas, Petras**; Rinkūnienė, Egidija. Hypertension types and associated cardiovascular risk factors in Lithuanians aged 50–54 years // Journal of clinical medicine. Basel : MDPI. ISSN 2077-0383. 2025, vol. 14, iss. 9, art. no. 3177, p. 1-9. DOI: 10.3390/jcm14093177. [DB: Science Citation Index Expanded (Web of Science), Scopus, MEDLINE] (IF: 2.9)

Theses and presentations of the main findings of the doctoral dissertation:

1. **Petras Navickas**; Laura Lukavičiūtė; Agnė Šatrauskienė; Aleksandras Laucevičius. Deciphering cardiovascular risk in Lithuanian males: an inter-model agreement analysis of nine risk prediction models in a high-risk Lithuanian cohort. The 6th International Conference: Evolutionary Medicine: How Evolutionary Thinking Can Contribute To The Medical And Health Sciences. 18th – 21st of June, 2024, Vilnius University, Lithuania.
2. **Petras Navickas**, Laura Lukaviciute-Navickiene, Agne Satrauskiene, Aleksandras Laucevicius. Risky business: exploring statin eligibility across nine cardiovascular risk prediction models. ESC Preventive Cardiology 2025. 3rd – 5th April, 2025, Milan, Italy.

13. BRIEF INFORMATION ABOUT THE AUTHOR

Education and training

- **2008–2012** — Secondary education (Secondary School Leaving Certificate, *cum laude*), Vilnius Mykolas Biržiška Gymnasium.
- **2012–2018** — Master's degree in Medicine (*magna cum laude*), Faculty of Medicine, Vilnius University.
- **2018–2022** — Residency in Cardiology (residency diploma), Faculty of Medicine, Vilnius University.
- **2021–2025** — PhD candidate in Medical Sciences, Faculty of Medicine, Vilnius University.

Professional appointments

- **2022–present** — Cardiologist, Affidea Lietuva LLC.
- **2023–present** — Head of the Cardiology Centre, Affidea Lietuva LLC.
- **2022–present** — Cardiologist, Vilnius University Hospital Santaros Klinikos.

I am an interventional cardiologist with clinical and research interests in coronary interventions and cardiovascular imaging, particularly cardiac computed tomography. I hold an academic appointment at Vilnius University, where I teach medical students in the field of cardiology. I also serve as a researcher at the Centre for Innovative Medicine, focusing on applications of artificial intelligence and personalised digital medicine in cardiovascular care. My work spans a substantial portfolio of R&D projects across national schemes and EU frameworks (COST; Horizon Europe). I regularly contribute to Lithuanian and European cardiology conferences and congresses and am an active—and board—member of professional cardiology societies, supporting education and evidence-based practice.

14. ACKNOWLEDGEMENTS

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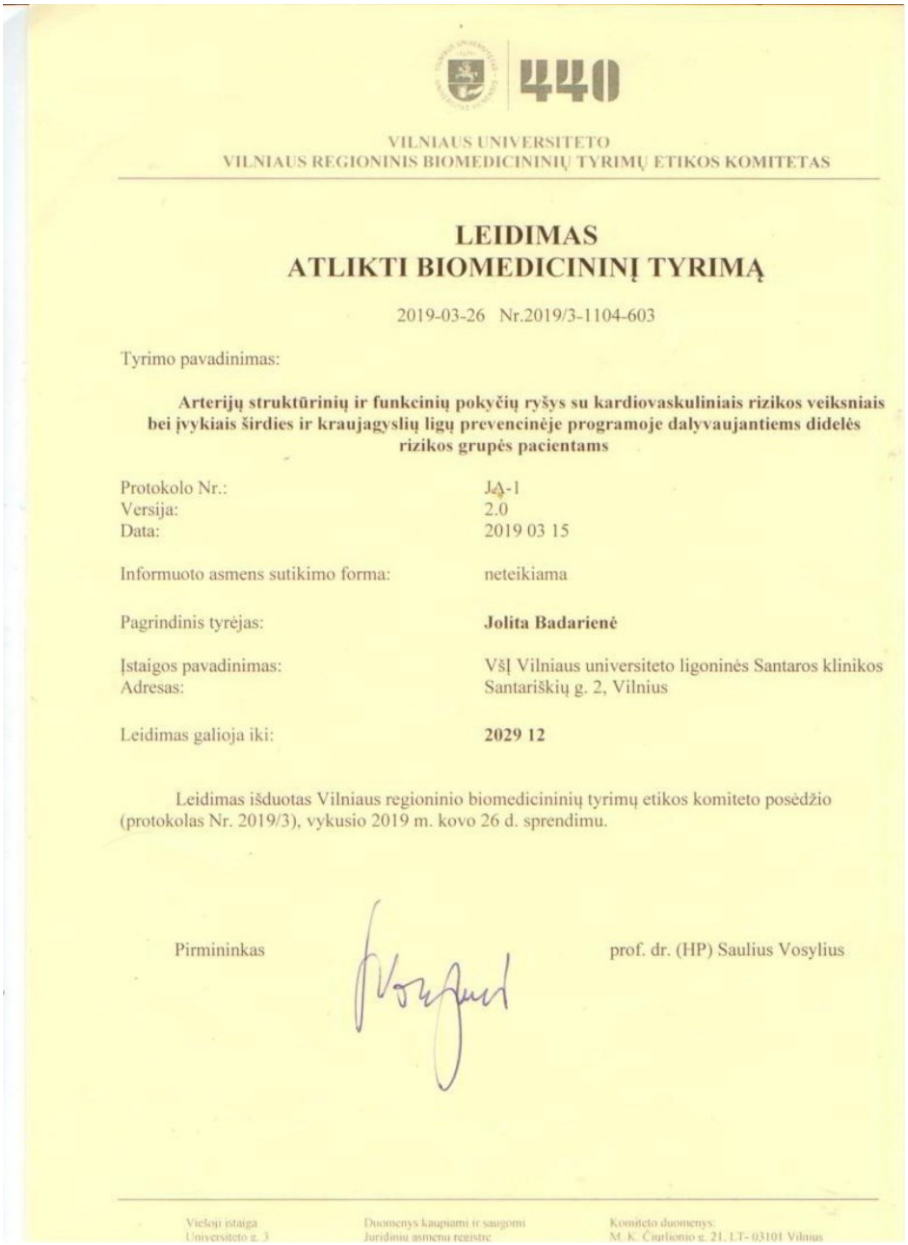
To all who, in ways both visible and unseen, contributed to this work—please accept my deepest thanks.

15. ANNEXES

15.1 Ethical Approval by the Vilnius Regional Bioethics Committee



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VILNIAUS UNIVERSITETO
VILNIAUS REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS

LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2019-03-26 Nr.2019/3-1104-603

Tyrimo pavadinimas:

Arterijų struktūrinių ir funkcinių pokyčių ryšys su kardiovaskuliniais rizikos veiksniais bei įvykiais širdies ir kraujagyslių ligų prevencinėje programoje dalyvaujantiems didelės rizikos grupės pacientams

Protokolo Nr.:	JA-1
Versija:	2.0
Data:	2019 03 15
Informuoto asmens sutikimo forma:	neteikiama
Pagrindinis tyrėjas:	**Jolita Badarienė**
Įstaigos pavadinimas:	VšĮ Vilniaus universiteto ligoninės Santaros klinikos
Adresas:	Santariškių g. 2, Vilnius
Leidimas galioja iki:	**2029 12**

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 2019/3), vykusio 2019 m. kovo 26 d. sprendimu.

Pirmininkas prof. dr. (HP) Saulius Vosylius

Viešoji įstaiga Universiteto g. 3 | Duomenys kaupiami ir saugomi Juridinių asmenų registre | Komiteto duomenys: M. K. Čiurlionio g. 21, LT- 03101 Vilnius

Pasibaigus tyrimui privaloma VRBTEK raštu informuoti apie tyrimo pabaigą bei pateikti tyrimo ataskaitos santrauką.

Lietuvos Respublikos sveikatos apsaugos ministro įsakymo "Dėl leidimų atlikti biomedicininį tyrimą išdavimo tvarkos aprašo patvirtinimo" *(Žin., 2008, Nr. 6-225, 2016 m. sausio 8 įsakymo Nr. V-27 redakcija (galiojanti suvestinė redakcija (nuo 2017-01-04)*

VII skyrius 40. Leidimas atlikti biomedicininį tyrimą galioja iki biomedicininio tyrimo paraiškoje nurodytos tyrimo pabaigos datos.

VII skyrius 41. Biomedicininių tyrimų užsakovas, jo įgaliotas atstovas ar pagrindinis tyrėjas per **30 kalendorinių dienų** nuo biomedicininio tyrimo pabaigos **privalo raštu pranešti** leidimą išdavusiam Lietuvos bioetikos komitetui ar regioniniam biomedicininių tyrimų etikos komitetui apie biomedicininio tyrimo pabaigą ir per **90 kalendorinių dienų** nuo biomedicininio tyrimo pabaigos **pateikti** biomedicininio tyrimo **vykdymo ataskaitos santrauką**.

Įsakymo nuostata taikoma visiems biomedicininiams tyrimams.

VILNIAUS REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS
sui generis darinys prie VILNIAUS UNIVERSITETO

Biomedicininio tyrimo „Arterijų struktūrinių ir funkcinių pokyčių ryšys su kardiovaskuliniais rizikos veiksniais bei įvykiais širdies ir kraujagyslių ligų prevencinėje programoje dalyvaujantiems didelės rizikos grupės pacientams“
pagrindinei tyrėjai Jolitai Badarienei

2022-10-18 Nr. 2022-LP-62

PRITARIMAS
BIOMEDICININIO TYRIMO DOKUMENTŲ PAKEITIMAMS

Leidimo Nr. 2019/3-1104-603 pakeitimas Nr. 4

Vilniaus regioninis biomedicininių tyrimų etikos komitetas išnagrinėjęs prašymą atlikti su vykdomu biomedicininiu tyrimu *„Arterijų struktūrinių ir funkcinių pokyčių ryšys su kardiovaskuliniais rizikos veiksniais bei įvykiais širdies ir kraujagyslių ligų prevencinėje programoje dalyvaujantiems didelės rizikos grupės pacientams“* (leidimas Nr. 2019/3-1104-603, išduotas 2019-03-26 d.) susijusių dokumentų pakeitimus nusprendė, kad pakeitimai **atitinka** Lietuvos Respublikos biomedicininių tyrimų etikos įstatymo II skyriuje nustatytus reikalavimus. Atsižvelgiant į tai **pritariama**, kad būtų:

- vadovaujamasi protokolu (Nr. JA-1, versijos Nr. 3.0, data 2022 01 12);
- teikiama informuoto asmens sutikimo forma (versijos Nr. JA-1, data 2022 01 12);
- įtraukiami į tyrimą papildomi tyrėjai - Agnė Laučytė – Cibulskienė, Petras Navickas ir kiti tyrimą atliekantys asmenys - Vaidota Maksimaitytė, Ieva Rudinskaitė, Augustė Kručaitė, Ignas Marčiukaitis, Viktorija Rinkevičiūtė.

Pirmininkas doc. dr. Alfredas Laurinavičius

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