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Comparative Review of Cardiovascular Disease Risk Models: Bridging Evidence and Clinical Practice

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Abstract

The reviewed file provides a comprehensive comparative analysis of cardiovascular disease (CVD) risk prediction models, synthesizing evidence from over 100 studies and evaluating models' clinical performance, validation, and practical application across diverse settings. Cardiovascular disease remains the leading global cause of morbidity and mortality, making risk stratification vital for preventive care. The evolution in risk assessment has progressed from simple risk factor identification, exemplified by the foundational Framingham Risk Score, to advanced multivariable models such as QRISK3, SCORE2, ASCVD Pooled Cohort Equations, Reynolds Risk Score, PROCAM, and models developed specifically for country or region-specific populations. Innovations extend to recent models like PREVENT and machine learning-driven approaches, which integrate novel biomarkers, imaging data, and socio-demographic factors for improved risk stratification.

The review highlights that while established models generally demonstrate similar discrimination (C-statistics between 0.70 and 0.85), calibration and applicability vary significantly between populations, necessitating recalibration or development of tailored models for local contexts. Recent models also emphasize lifetime risk, integrate non-traditional risk factors, and deploy artificial intelligence to identify complex patterns, though challenges persist regarding transparency, equity, and generalizability. The paper underscores the need for continuous validation, recalibration, and inclusive model development to address disparities, as well as effective integration of risk assessment into electronic health records and clinical workflows. The ultimate goal of refined risk modeling remains to better guide preventive interventions, inform clinical guidelines, and reduce the global burden of CVD through targeted identification and management of high-risk individuals.

1.INTRODUCTION

Historical Development and Evolution of Cardiovascular Risk Prediction

The Framingham Legacy: Foundation of Modern Risk Assessment

The Framingham Heart Study, initiated in 1948, transformed cardiovascular epidemiology by introducing the notion of cardiovascular risk variables and their measurable correlation with disease outcomes. The Framingham Risk Score (FRS), first developed in 1998 and subsequently updated in 2008, represents the foundational model for cardiovascular risk prediction. The study includes thousands of participants from Framingham, Massachusetts, over multiple decades, identifying key risk factors including age, sex, total cholesterol, high-density lipoprotein cholesterol, smoking status, systolic blood pressure, and diabetes mellitus.[2][4][5][6]

The risk of coronary heart disease the original Framingham Risk Score, was 10-year. However, recognizing that CHD represents only a portion of cardiovascular morbidity, the 2008 Framingham model expanded its scope to estimate 10-year risk of developing any cardiovascular disease event, including coronary heart disease, cerebrovascular events, peripheral artery disease, and heart failure. This expanded cardiovascular disease endpoint provided a more comprehensive assessment of overall cardiovascular risk, better reflecting the true burden of atherosclerotic disease.[4][5][7][2]

The Framingham Risk Score is gender gender-specific algorithm and samples a point-based scoring system where risk factors are given a score based on their present cardiovascular risk. For example, in the Framingham CVD model, age carries substantial weight, with each decade of life contributing progressively more points to the total risk score. The final point total corresponds to an estimated 10-year probability of experiencing a cardiovascular event, typically ranging from less than 1% to greater than 30%.[5][4]

The Framingham Risk Score (FRS) emerged as the North American standard for cardiovascular risk assessment, influencing global models and guiding lipid-lowering therapy decisions under the NCEP ATP III guidelines. However, its continued use is tempered by significant limitations, including the potential for risk overestimation in modern populations, poor applicability to diverse ethnicities, and the omission of key risk factors like family history and inflammatory markers.[3][8][9][10][11][5]

Geographic and Population-Specific Model Development

The cardiovascular risk varies according to the geographical area and ethnic population, and different geographic regions. The researcher has developed risk prediction models according to their region-specific and country-specific. The systematic differences in cardiovascular disease incidence rates, risk factor distributions, and competing mortality risks across populations necessitate calibration or the development of new models tailored to specific demographic contexts.[12][13][14][15][16]

The European Society of Cardiology developed the SCORE (Systematic Coronary Risk Evaluation) project. It created cardiovascular risk charts specifically for European populations. The original SCORE model, based on data from 12 European cohort studies, predicted 10-year risk of fatal cardiovascular disease. However, focusing solely on cardiovascular mortality had limitations, particularly in younger individuals where non-fatal events may predominate and in populations with improving acute care where case-fatality rates have declined.[13][17][12]

To address these limitations, the European Society of Cardiology developed SCORE2, published in 2021, which represents a substantial advancement in European cardiovascular risk prediction. SCORE2 was derived from individual-participant data from 45 cohorts across 13 countries, encompassing 677,684 individuals and 30,121 cardiovascular disease events. The model predicts 10-year risk of fatal and non-fatal cardiovascular disease events including myocardial infarction and stroke in individuals aged 40-69 years without previous cardiovascular disease or diabetes.[18][12][13]

A key innovation of SCORE2 is its recalibration to four distinct European risk regions—low, moderate, high, and very high risk—based on country-specific cardiovascular mortality rates. This regional stratification acknowledges the substantial variation in cardiovascular disease burden across Europe, with estimated 10-year CVD risk for an identical risk factor profile varying several-fold between regions. For example, a 50-year-old male smoker with systolic blood pressure of 140 mmHg and specific cholesterol levels would have an estimated 10-year CVD risk ranging from 5.9% in low-risk countries to 14.0% in very high-risk countries. SCORE2 also incorporates competing risk adjustment, accounting for non-cardiovascular deaths, which prevents overestimation of cardiovascular risk particularly in older individuals and high-mortality populations.[19][17][12][13]

External validation in 25 additional European cohorts demonstrated good discrimination, with C-indices ranging from 0.67 to 0.81, confirming SCORE2's applicability across diverse European populations. The model has been integrated into European Society of Cardiology prevention guidelines and represents the current standard for cardiovascular risk assessment in Europe.[12][13][18]

Major Cardiovascular Risk Assessment Models

United Kingdom: QRISK Evolution and Innovation

The QRISK cardiovascular risk prediction algorithm was developed in 2007 using the United Kingdom's QResearch primary care database, marking a significant advancement in electronic health record-based risk prediction. The model has undergone continuous refinement, with QRISK2 released in 2008 and QRISK3 published in 2017, each iteration incorporating additional risk factors and expanding the applicable age range.[20][21][22][3]

QRISK3 represents one of the most comprehensive cardiovascular risk prediction tools currently available, incorporating a broader range of clinical variables than traditional models. The model includes conventional risk factors such as age, sex, ethnicity, smoking status, systolic blood pressure, total cholesterol, and HDL cholesterol, but additionally incorporates body mass index, chronic kidney disease (assessed by estimated glomerular filtration rate), atrial fibrillation, rheumatoid arthritis, systemic lupus erythematosus, severe mental illness, corticosteroid use, erectile dysfunction in men, migraine, and measures of blood pressure variability. The inclusion of chronic conditions and medications reflects the reality of contemporary clinical practice where patients often present with multiple comorbidities that influence cardiovascular risk.[21][23][9][22][3][20]

The applicable age range for QRISK3 extends from 25 to 84 years, broader than many competing models, allowing risk assessment in younger adults where lifetime risk considerations are particularly relevant. The model was derived from a cohort of 9.98 million patients and validated in 6.79 million individuals, representing one of the largest datasets used for cardiovascular risk prediction model development. This extensive derivation and validation enhances the model's generalizability and precision across diverse demographic subgroups.[9][22][3][20]

Studies comparing QRISK3 with other risk prediction models have demonstrated favorable performance characteristics. In a study of patients with systemic lupus erythematosus, QRISK3 outperformed the Framingham Risk Score, modified Framingham Risk Score, and ASCVD risk calculator in predicting cardiovascular events, with superior discrimination (area under the receiver operating characteristic curve of 0.60 for QRISK3 versus 0.52-0.56 for other models). Among patients with type 2 diabetes mellitus, QRISK3 demonstrated superior discrimination compared to the Framingham Risk Score, with C-statistics of 0.765 versus 0.757 respectively. The model's inclusion of systemic lupus erythematosus and corticosteroid use as explicit risk factors makes it particularly valuable for patients with autoimmune conditions, a population where traditional risk calculators significantly underestimate cardiovascular risk.[3][20][21][9]

QRISK3 is recommended by the National Institute for Health and Care Excellence (NICE) as the primary cardiovascular risk assessment tool for the United Kingdom National Health Service. The calculator is freely available online and integrated into electronic health record systems, facilitating its use in routine clinical practice. However, external validation studies in populations outside the United Kingdom have shown variable performance, suggesting that recalibration may be necessary when applying QRISK3 to different healthcare systems and ethnic populations.[24][25][23][21][9][3]

The most recent iteration, QRISK4, introduced in 2024, further expands the model by incorporating additional risk factors and utilizing even larger datasets for derivation. Early validation studies suggest QRISK4 demonstrates improved discrimination and calibration compared to widely used models including the Pooled Cohort Equations and SCORE2, although further external validation across diverse populations is necessary.[22]

United States: Pooled Cohort Equations and ASCVD Risk Assessment

The 2013 American College of Cardiology and American Heart Association guidelines introduced the Pooled Cohort Equations for estimation of 10-year atherosclerotic cardiovascular disease

risk, replacing the Framingham-based risk assessment used in previous cholesterol guidelines. The Pooled Cohort Equations were developed using data from multiple National Heart, Lung, and Blood Institute-funded cohort studies including the Atherosclerosis Risk in Communities study, Cardiovascular Health Study, and Framingham original and offspring cohorts.[10][26][27][9]

The equations are sex-specific and race-specific, with separate models for non-Hispanic white and non-Hispanic black men and women, representing an important advancement in addressing racial disparities in cardiovascular risk assessment. The primary outcome is 10-year risk of "hard" atherosclerotic cardiovascular disease events, defined as nonfatal myocardial infarction, fatal coronary heart disease, or fatal or nonfatal stroke. This composite outcome provides a clinically relevant endpoint encompassing the major manifestations of atherosclerotic disease.[26][9][10]

Risk factors included in the Pooled Cohort Equations comprise age, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication use, diabetes status, and current smoking. The model does not include family history, chronic kidney disease, inflammatory markers, or other novel risk factors, maintaining relative simplicity while focusing on well-established, readily measurable parameters.[27][9][10][26]

The 2013 ACC/AHA cholesterol guidelines recommended statin therapy for primary prevention in adults aged 40-75 years with an estimated 10-year ASCVD risk of 7.5% or greater, making accurate risk prediction critical for guiding treatment decisions. Subsequent guidelines adjusted this threshold, with current recommendations considering statin therapy for individuals with 10-year ASCVD risk between 5% and 7.5% based on shared decision-making and evaluation of additional risk-enhancing factors.[9][10][27]

Early concerns about the Pooled Cohort Equations centered on potential overestimation of cardiovascular risk when applied to contemporary populations, which could result in overtreatment with statin medications. Several external validation studies demonstrated variable performance across different populations and risk strata. In a comprehensive pooled analysis of eight longitudinal cohort studies including 37,311 adults, the Pooled Cohort Equations demonstrated acceptable discrimination but significantly overestimated risk in individuals with higher body mass index categories, particularly in overweight and obese individuals. The equations showed better calibration near clinical decision thresholds but less optimal calibration for groups at highest estimated risk.[28][10][26]

Performance varied by race and sex, with some studies suggesting better discrimination among Black individuals compared to White individuals, although calibration differed. These findings underscore the importance of continuous validation and potential recalibration of risk prediction models as populations evolve and treatment practices change.[26][28]

Despite these limitations, the Pooled Cohort Equations remain widely used in United States clinical practice and have been incorporated into numerous clinical decision support tools and mobile applications. The American Heart Association provides an online ASCVD Risk Estimator Plus tool that includes additional features such as calculation of lifetime risk for individuals aged 20-59 years and estimation of risk reduction with specific interventions.[29][30][27]

Reynolds Risk Score: Incorporating Inflammation and Family History

The Reynolds Risk Score, developed by Ridker and colleagues in 2007, represents an important advancement in incorporating inflammatory biomarkers and family history into cardiovascular risk prediction. The model was initially developed and validated in the Women's Health Study cohort of approximately 25,000 initially healthy American women, with subsequent adaptation for men.[31][32][11][33]

The Reynolds Risk Score calculates 10-year risk of cardiovascular disease events including myocardial infarction, ischemic stroke, coronary revascularization, and cardiovascular death. In addition to conventional risk factors (age, systolic blood pressure, total cholesterol, HDL cholesterol, smoking status, and hemoglobin A1c for those with diabetes), the Reynolds score uniquely incorporates high-sensitivity C-reactive protein (hsCRP) and parental history of premature myocardial infarction before age 60.[32][11][33][31]

The inclusion of hsCRP reflects accumulating evidence that inflammation plays a central role in atherosclerosis development and plaque vulnerability. Multiple large-scale prospective studies have demonstrated that hsCRP provides prognostic information beyond traditional risk factors, particularly for individuals at intermediate risk. Family history of premature cardiovascular disease captures genetic susceptibility and shared environmental factors that influence cardiovascular risk but are not fully accounted for by measured risk factors.[11][33][34][35][32]

In direct comparison studies with Framingham-based models, the Reynolds Risk Score demonstrated improved discrimination and reclassification. In the Women's Health Initiative Observational Cohort comprising 1,722 major cardiovascular disease cases and 1,994 controls, the Reynolds Risk Score showed superior calibration compared to both the Framingham ATP-III and Framingham CVD models. The Reynolds model achieved better discrimination through a higher C-statistic (0.765 versus 0.757 for ATP-III, p=0.03) and positive net reclassification improvement. The greatest clinical impact appeared among women with 5-10% estimated 10-year risk according to ATP-III, a group including many women destined to experience cardiovascular events in whom trial data indicate statin efficacy.[33][11]

The Reynolds Risk Score reclassified 40-50% of women at intermediate risk by traditional models into higher or lower risk categories, with improved accuracy compared to ATP-III predictions. This enhanced risk stratification enables more targeted preventive interventions, potentially identifying individuals who would benefit from treatment but would be missed by traditional risk assessment, while avoiding unnecessary medication in those truly at lower risk.[32][11]

Despite its advantages, the Reynolds Risk Score has not been as widely adopted as other models, partly because measurement of hsCRP is not routinely performed in all clinical settings and adds cost to risk assessment. Additionally, the model was developed primarily in white American populations, and external validation in diverse ethnic groups is more limited compared to other widely used models.[36][11]

PROCAM: European Perspective on Acute Coronary Risk

The Prospective Cardiovascular Münster (PROCAM) study, conducted in Germany, provides an important European perspective on cardiovascular risk prediction focused specifically on acute coronary events. The PROCAM score was developed by Assmann and colleagues in 2002 using data from 5,389 men aged 35-65 years followed for 10 years, during which 325 acute coronary events occurred.[37][38][39][40]

The PROCAM score predicts 10-year risk of acute coronary events including sudden cardiac death and fatal or nonfatal myocardial infarction. The score differs from many other models by focusing exclusively on coronary events rather than broader cardiovascular disease outcomes, making it particularly relevant

for assessment of myocardial infarction risk. Risk factors included are age, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, smoking status, presence of diabetes mellitus, and family history of premature myocardial infarction.[38][39][40][37]

The detailed lipid profile in PROCAM, including both LDL cholesterol and triglycerides rather than total cholesterol alone, provides more comprehensive assessment of lipid-related risk. Elevated triglycerides represent an independent cardiovascular risk factor, particularly when accompanied by low HDL cholesterol in the metabolic syndrome pattern commonly observed in type 2 diabetes and obesity.[40][37]

PROCAM demonstrated excellent calibration in its derivation cohort, with estimated risk showing very good agreement with observed incidence across all score categories (Hosmer-Lemeshow $x^2=6.5$, $p>0.3$). Risk categories range from less than 1% 10-year risk (score ≤20) to greater than 40% risk (score ≥62), enabling clear stratification for treatment decisions. The score performed favorably compared to the European SCORE system, showing more appropriate identification of high-risk patients while avoiding overestimation that could lead to overtreatment.[39][37]

Comparative studies with other risk prediction models have shown that PROCAM provides useful discrimination for coronary artery disease in European populations. In a study comparing Framingham, PROCAM, SCORE, and Diamond Forrester pre-test probability in patients with stable chest pain undergoing cardiac computed tomographic angiography, PROCAM demonstrated reasonable but slightly lower discrimination (area under the curve 0.64) compared to Framingham (0.68) and SCORE (0.69). However, PROCAM's focus on myocardial infarction rather than total cardiovascular disease makes direct comparisons challenging.[41][40]

PROCAM has been widely used in European cardiovascular prevention programs and clinical practice, particularly in German-speaking countries. The model provides country-appropriate risk estimation for populations with lower absolute cardiovascular risk compared to American populations used to derive Framingham-based models.[37][40][41]

Global and Regional Models: WHO, Globorisk, and Beyond

Recognizing the need for cardiovascular risk prediction tools applicable to low- and middle-income countries, where the majority of global cardiovascular disease burden occurs, the World Health Organization and independent research groups have developed globally applicable risk prediction models.[15][16][42][43][44]

The WHO cardiovascular disease risk prediction charts, updated in 2019, were developed using data from the Emerging Risk Factors Collaboration comprising 376,177 individuals from 85 cohorts across 21 Global Burden of Disease regions. The models predict 10-year risk of fatal and nonfatal cardiovascular disease events including myocardial infarction and stroke in individuals aged 40-80 years. Risk factors included are age, sex, smoking status, systolic blood pressure, total cholesterol, and history of diabetes. The WHO risk charts are available in both laboratory-based versions (requiring cholesterol measurement) and non-laboratory versions (using body mass index instead of cholesterol), recognizing resource constraints in many settings.[45][16][15]

A critical innovation of the WHO risk charts is their recalibration for 21 specific geographic regions, accounting for substantial variation in baseline cardiovascular disease rates and risk factor distributions globally. For an identical risk factor profile, estimated 10-year cardiovascular disease risk ranged from 11% in Andean Latin America to 30% in central Asia, demonstrating the importance of region-specific calibration. External validation in 19 cohorts from diverse regions showed good discrimination, with Harrell's C-indices ranging from 0.685 to 0.833.[16][15]

When applied to survey data from 79 countries, predominantly low- and middle-income nations, the proportion of individuals aged 40-64 years with greater than 20% 10-year risk varied from less than 1% in Uganda to more than 16% in Egypt, highlighting substantial global heterogeneity in cardiovascular disease burden. The WHO risk charts enable identification of high-risk individuals in resource-limited settings where comprehensive risk factor assessment may not be feasible, supporting targeted preventive interventions where they can have greatest impact.[46][15][16]

Globorisk, developed by Hajifathalian and colleagues in 2015, represents the first cardiovascular risk prediction tool calibrated for all 182 countries worldwide. The model predicts 10-year risk of fatal or nonfatal cardiovascular disease (myocardial infarction or stroke) in individuals without prior cardiovascular disease. Globorisk exists in both laboratory-based and office-based versions, with the office-based model using body mass index instead of cholesterol and diabetes status, enhancing its applicability in settings with limited laboratory capacity.[42][43][44][47][48]

Country-specific calibration of Globorisk accounts for differences in baseline cardiovascular disease incidence, risk factor distributions, and competing mortality risks. Validation studies have compared Globorisk with WHO risk charts and other models, finding substantial agreement and strong positive correlations between country-specific Globorisk predictions and region-specific WHO predictions (correlation coefficients >0.9). In comparative assessments with the Framingham Risk Score in metabolic syndrome populations, Globorisk classified a higher proportion of individuals in moderate to high-risk categories compared to Framingham, potentially identifying additional individuals who would benefit from preventive interventions.[8][43][44][48][42]

Country-Specific Models: Italy, Scotland, and National Approaches

Several countries have developed nation-specific cardiovascular risk prediction models calibrated to their unique population characteristics and healthcare contexts. These models often outperform internationally derived tools when applied to their target populations, underscoring the importance of appropriate geographic calibration.[49][50][51][52][53][54][55][56][57]

The CUORE (CUore, Ore, urea, REpertorio) Project in Italy has developed cardiovascular risk charts specifically for the Italian adult population. Initiated in 1998 and continuously updated, the CUORE project uses data from Italian cohort studies to predict 10-year risk of fatal and nonfatal major cardiovascular events. Risk factors include age, sex, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, diabetes, and antihypertensive therapy.[53][54][55][56][57]

The CUORE risk functions have been validated against the European SCORE mortality charts, showing that SCORE charts reflect Italian cardiovascular mortality reasonably well, with Lin's concordance coefficients of 0.929 for men and 0.935 for women. However, CUORE provides more accurate risk stratification for the Italian population by accounting for country-specific baseline risk and risk factor distributions. Recent health examination surveys using CUORE risk assessment show that approximately 57% of Italian men and 88% of women have less than 5% 10-year CVD risk, with 22% of men and 9% of women at 10-15% risk.[54][55][56][57][53]

In Scotland, the ASSIGN (Assessing Cardiovascular Risk using Scottish Intercollegiate Guidelines Network) cardiovascular risk score was developed in 2006 specifically for the Scottish population. ASSIGN estimates 10-year risk of first atherosclerotic cardiovascular disease including coronary heart disease, stroke, and transient ischemic attack. The model includes conventional risk factors (age, sex, systolic blood pressure, total cholesterol, HDL cholesterol, smoking, diabetes, family history of cardiovascular disease) plus the Scottish Index of Multiple Deprivation (SIMD), a socioeconomic deprivation measure.[50][51][52][58][59][60][49]

The inclusion of social deprivation represents an important innovation, recognizing that socioeconomic factors substantially influence cardiovascular risk through mechanisms including access to healthcare, health behaviors, psychosocial stress, and environmental exposures. Studies have demonstrated that social deprivation predicts cardiovascular disease independent of traditional risk factors.[51][58][49]

ASSIGN was recalibrated in 2024 (ASSIGN v2.0) using contemporary data from UK Biobank and the Generation Scotland Scottish Family Health Study to account for declining cardiovascular disease rates in Scotland. The original ASSIGN substantially overestimated contemporary ASCVD risk, with median predicted 10-year risks of 10.6% for females and 15.1% for males compared to observed risks of 6% and 11.4% respectively. The recalibrated ASSIGN v2.0 provides more accurate contemporary risk estimation and adjusts the risk threshold from 20% to 10% to maintain appropriate sensitivity for identifying individuals who would benefit from preventive interventions.[52][59][49][50]

American Heart Association PREVENT: Next-Generation Risk Assessment

The American Heart Association's PREVENT (Predicting Risk of cardiovascular disease EVENTs) equations, released in 2023, represent the most recent advancement in United States cardiovascular risk prediction. PREVENT was developed using contemporary data from more than 6.5 million diverse adults in the United States, making it more representative of the current American population than previous tools.[61][62][63][64][65]

PREVENT estimates both 10-year and 30-year risk of total cardiovascular disease, encompassing atherosclerotic cardiovascular disease and heart failure, in individuals aged 30-79 years without known cardiovascular disease. This expanded age range and longer-term risk prediction enables assessment of lifetime risk burden, particularly relevant for younger adults where short-term risk may be low despite substantial long-term risk from modifiable factors.[62][63][65][61]

A major innovation of PREVENT is the inclusion of kidney and metabolic health measures in the risk equations. In addition to traditional risk factors (age, sex, race, systolic blood pressure, total and HDL cholesterol, smoking status, diabetes, body mass index), PREVENT incorporates estimated glomerular filtration rate (eGFR) as a measure of kidney function. The model can additionally incorporate optional predictors including urine albumin-creatinine ratio, hemoglobin A1c, and social deprivation index to further personalize risk estimates.[63][65][61][62]

The inclusion of kidney function reflects growing recognition that chronic kidney disease substantially increases cardiovascular risk through multiple mechanisms including endothelial dysfunction, arterial calcification, activation of inflammatory and thrombotic pathways, and altered metabolism. Studies have consistently demonstrated that declining kidney function predicts cardiovascular events independent of traditional risk factors. Similarly, measures of metabolic health including glycemic control provide important prognostic information beyond simple diabetes status.[65][61][62]

PREVENT represents an integrated approach to cardiovascular-kidney-metabolic syndrome, acknowledging the interconnected nature of these conditions. The prognostic performance demonstrates good discrimination and calibration in the overall derivation population and among demographic subgroups, with C-statistics for 10-year atherosclerotic cardiovascular disease prediction ranging from 0.74 to 0.81. External validation studies are ongoing to assess performance in independent cohorts and diverse populations.[64][61][62][63][65]

The PREVENT calculator is freely available through the American Heart Association website and is expected to be incorporated into clinical practice guidelines and electronic health record systems. Early commentary suggests PREVENT addresses limitations of previous tools including the Pooled Cohort Equations by using contemporary data, broader cardiovascular endpoints, and additional risk factors relevant to current medical practice.[61][62][63][64]

JBS3 and Heart Age: Communicating Lifetime Risk

The Joint British Societies' Consensus Recommendations for the Prevention of Cardiovascular Disease (JBS3), published in 2014, introduced a paradigm shift in cardiovascular risk communication through the concept of "heart age" and emphasis on lifetime rather than only 10-year risk. JBS3 was developed by experts from 11 UK professional societies and charities involved with cardiovascular disease prevention, synthesizing evidence on risk assessment and preventive strategies.[66][67][68][69][70]

The JBS3 risk calculator estimates both 10-year cardiovascular disease risk and lifetime risk, defined as the probability of developing cardiovascular disease over an individual's remaining lifespan. Risk factors include age, sex, ethnicity, systolic blood pressure, total cholesterol, HDL cholesterol, smoking status, diabetes, and family history of premature cardiovascular disease. The calculator presents risk estimates in multiple formats including conventional percentage risk, "heart age," and years of cardiovascular disease-free survival expected.[67][68][70][66]

"Heart age" represents the age of an individual with the same estimated cardiovascular risk who has optimal risk factor levels (non-smoker, ideal blood pressure and cholesterol). This metric provides an intuitive way to communicate risk, enabling patients to understand how their cardiovascular health compares to what would be expected for their chronological age. For example, a 35-year-old female smoker with elevated blood pressure and cholesterol might have a heart age of 47, immediately conveying that her cardiovascular system has aged prematurely due to modifiable risk factors.[68][71][66][67]

The calculator also demonstrates the potential benefits of risk factor modification, showing how interventions such as smoking cessation, blood pressure reduction, or cholesterol lowering would reduce heart age and extend cardiovascular disease-free survival. In the example above, if the woman stopped smoking and achieved target cholesterol and blood pressure levels, her heart age could drop to 30 (below her chronological age) and her projected cardiovascular disease-free survival could extend from age 71 to 85.[66][67][68]

Evidence suggests that communicating cardiovascular risk using heart age results in greater emotional impact and better risk factor modification compared to traditional percentage-based risk estimates. A Spanish randomized trial demonstrated that heart age communication resulted in superior smoking cessation rates, blood pressure reduction, and weight loss over 12 months compared to standard 10-year risk estimates. The intuitive nature of heart age resonates with patients and facilitates

shared decision-making between clinicians and patients regarding preventive interventions.[71][67][66]

JBS3 emphasizes lifetime risk assessment to address the limitation that many younger individuals, particularly women, have low 10-year risk despite high lifetime risk due to modifiable factors. Traditional 10-year risk assessment dominated by age may miss opportunities for early intervention that could substantially reduce cumulative lifetime cardiovascular disease burden. The JBS3 calculator has been integrated into the NHS Health Check programme in England for adults aged 40-74 years, with the goal of identifying individuals who would benefit from lifestyle modification and, when appropriate, preventive medications.[67][68][71][66]

Artificial Intelligence and Machine Learning in Cardiovascular Risk Prediction

The Promise of Advanced Computational Approaches

Recent years have witnessed rapid advancement in the application of artificial intelligence and machine learning methodologies to cardiovascular risk prediction, with numerous studies demonstrating potential advantages over traditional statistical models. Machine learning algorithms can identify complex, nonlinear relationships between risk factors and outcomes, incorporate high-dimensional data from multiple sources, and potentially improve discrimination and calibration compared to conventional approaches.[72][73][74][75][76][77][78][22]

A systematic review and meta-analysis of machine learning-based prediction models for cardiovascular disease risk using electronic health records data, encompassing 20 studies, found that machine learning models demonstrated superior performance compared to traditional risk scores. Random forest and deep learning models achieved the highest pooled areas under the curve of 0.865 and 0.847 respectively, significantly outperforming conventional risk scores with pooled AUC of 0.765. These findings suggest machine learning approaches may enhance calibration and discrimination for CVD risk assessment.[72]

Multiple specific algorithms have shown promise in cardiovascular risk prediction. Random forest-based models, which use ensemble learning techniques combining multiple decision trees, have demonstrated particular success. Petrazzini and colleagues used random forest algorithms applied to electronic health record data from multiethnic cohorts to predict coronary artery disease risk, achieving 12% improvement in 1-year risk prediction compared to Pooled Cohort Equations, with particularly notable gains (20% discrimination improvement, 34.4% reclassification improvement) in subgroups with lower baseline coronary artery disease risk.[78][22]

Deep learning models, which utilize artificial neural networks with multiple layers to learn hierarchical representations of complex data, have shown especially impressive performance. The Dynamic-DeepHit model, which incorporated 8 years of longitudinal data from four cardiovascular disease cohorts analyzing temporal changes in traditional risk factors, demonstrated superior discrimination compared to Pooled Cohort Equations (AUROC 0.815 versus 0.792) with better overall performance (Brier score 0.0514 versus 0.0542). Notably, the model showed enhanced performance in specific demographic groups including Black women and individuals aged less than 60 years, potentially addressing health care disparities through more nuanced risk stratification.[76][22][72]

Integration of machine learning with clinical and imaging data has further advanced prediction of major adverse cardiac events. Studies combining machine learning algorithms with myocardial perfusion imaging data showed significant improvements predicting major adverse cardiac events compared to traditional visual or automated assessments. Deep learning analysis of echocardiography data in multicenter studies accurately predicted in-hospital death, outperforming established prediction scores.[22]

The QRISK4 model, introduced in 2024, represents an evolution of traditional cardiovascular risk prediction incorporating machine learning approaches applied to massive datasets from UK primary care. Early validation suggests QRISK4 demonstrates improved discrimination and calibration compared to widely used models including Pooled Cohort Equations and SCORE2, although widespread external validation is still needed.[22]

Challenges and Limitations of AI-Based Risk Prediction

Despite the promise of artificial intelligence and machine learning approaches, significant challenges and limitations temper enthusiasm and restrict current clinical applicability. A primary concern is the "black box" nature of many machine learning algorithms, particularly deep learning models, which may achieve superior predictive performance but provide limited interpretability regarding which factors drive individual risk predictions. This lack of transparency creates barriers to clinical acceptance and implementation, as clinicians and patients may be reluctant to base treatment decisions on models they cannot understand or validate.[74][76][72][22]

Data quality issues represent another major challenge for AI-based cardiovascular risk prediction. Machine learning models are highly dependent on the quality, completeness, and representativeness of training data. Electronic health record data, frequently used for model development, may contain missing values, measurement errors, inconsistent coding, and biases in who receives certain tests or diagnoses. Models trained on data with these limitations may perpetuate or amplify existing disparities and biases.[74][72][22]

Standardization across healthcare systems poses additional difficulties. Electronic health record structures, coding systems, and clinical workflows vary substantially across institutions and countries, potentially limiting generalizability of models developed in specific settings. Geographic variability in disease prevalence, risk factor distributions, and healthcare delivery further complicate model transportability.[22]

The heterogeneity noted in the systematic review of machine learning cardiovascular risk prediction models (I^2 > 99%) indicates substantial variability in model performance across studies, raising concerns about reliability and reproducibility. Publication bias, with preferential reporting of positive results, may inflate perceived model performance.[72]

Validation and recalibration requirements represent practical barriers to implementation. While machine learning models may demonstrate excellent performance in derivation datasets, their performance in independent external validation cohorts is often substantially lower. Continuous validation and recalibration are necessary to ensure model performance remains adequate as populations evolve and treatment practices change.[72][22]

Regulatory and ethical considerations add complexity to deployment of AI-based risk prediction tools in clinical practice. Questions remain regarding liability when algorithmic predictions inform treatment decisions, particularly if errors or biases lead to adverse outcomes. Ensuring equity and avoiding algorithmic discrimination requires careful attention to model development, validation across diverse populations, and monitoring for disparate impact.[74][22]

Current consensus suggests that AI and machine learning approaches show substantial promise for enhancing cardiovascular risk prediction but require further development, rigorous validation, improved interpretability, and careful

integration into clinical workflows before widespread adoption. These tools should complement rather than replace clinical judgment, with clinicians maintaining ultimate decision-making authority.[73][76][74][22][72]

Model Performance: Discrimination, Calibration, and Clinical Utility

Understanding Risk Model Performance Metrics

Evaluation of cardiovascular risk prediction models requires assessment of multiple performance dimensions including discrimination, calibration, and clinical utility. These metrics provide complementary information about model performance and suitability for clinical application.[79][80][81][82][28]

Discrimination refers to a model's ability to distinguish individuals who will develop cardiovascular disease from those who will not. The most commonly reported discrimination metric is the C-statistic (concordance statistic), equivalent to the area under the receiver operating characteristic curve. A C-statistic of 0.5 indicates no discrimination beyond chance, while 1.0 represents perfect discrimination. Most contemporary cardiovascular risk prediction models demonstrate C-statistics between 0.70 and 0.85, considered acceptable to good discrimination.[80][81][82][79][28][72]

However, recent analyses have highlighted that discrimination metrics may be relatively insensitive to the addition or removal of important risk factors. A study comparing age-only risk models with full multivariable models found that while individual risk estimates differed substantially between the models (for example, 4.9% versus 16.1% for one woman), the C-statistics were similar (0.773 versus 0.814). This finding raises important questions about relying primarily on discrimination measures to compare model performance.[81][79]

Calibration assesses the agreement between predicted risk and observed outcomes across the spectrum of predicted risk levels. Well-calibrated models accurately estimate absolute risk, with predicted probabilities matching observed event rates. Calibration is typically evaluated using calibration plots comparing predicted versus observed risk across risk deciles, calibration slopes, and goodness-of-fit statistics such as the Hosmer-Lemeshow test.[82][79][80][81][28]

Poor calibration can occur through systematic overestimation or underestimation of risk. Many cardiovascular risk models demonstrate calibration challenges when applied to populations different from their derivation cohorts. For example, SCORE2 significantly underestimated cardiovascular disease risk in Dutch primary care populations, with observed 10-year risk of 10.1% versus predicted risk of 6.2%, resulting in approximately 35% of patients potentially missing preventive treatments. Recalibration can address these issues by adjusting baseline risk estimates to match the target population.[19][5][80][81][28][82][12][26]

A systematic review comparing laboratory-based and non-laboratory-based cardiovascular risk prediction equations found that calibration measures between the two model types were similar, although non-calibrated equations often overestimated risk. Many models showed poor calibration during external validation, emphasizing the need for recalibration when applying CVD risk equations to new populations.[80][81]

Clinical utility extends beyond discrimination and calibration to consider the impact of risk prediction on clinical decision-making and patient outcomes. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) quantify the extent to which a new model correctly reclassifies individuals into more appropriate risk categories compared to an existing model. Decision curve analysis evaluates the net benefit of using a prediction model to guide treatment decisions across different risk thresholds.[11][79][28][82]

Number needed to treat (NNT) and number needed to screen provide clinically interpretable metrics of model utility. A study comparing artificial intelligence cardiovascular risk prediction models found that AI models required treatment of only 9-10 patients to prevent one CVD event, compared to 38 patients using conventional models, demonstrating superior clinical efficiency.[73]

Comparative Performance Across Major Models

Direct comparisons of major cardiovascular risk prediction models have yielded important insights into their relative performance and optimal applications. These comparisons must account for differences in target populations, outcomes, time horizons, and risk factors between models, making head-to-head comparisons challenging.[44][8][21][40][28][82][3][9][11]

In studies comparing Framingham, PROCAM, SCORE, and Diamond Forrester models in European populations with stable chest pain, Framingham and SCORE demonstrated superior discrimination for significant coronary artery disease (areas under the curve 0.68 and 0.69) compared to PROCAM (0.64) and Diamond Forrester (0.65). Framingham showed the lowest number of low-risk patients with significant coronary artery disease or events, suggesting safer risk stratification.[40]

Comparisons of QRISK3 versus Framingham Risk Score and ASCVD Pooled Cohort Equations in diverse populations have generally favored QRISK3, particularly in specific subgroups. In patients with systemic lupus erythematosus, QRISK3 and the disease-specific PREDICTS score both outperformed Framingham, modified Framingham, and ASCVD models, with QRISK3 achieving area under the receiver operating characteristic curve of 0.60 versus 0.52-0.56 for other models. Among patients with type 2 diabetes mellitus, QRISK3 demonstrated superior discrimination and calibration compared to Framingham Risk Score.[21][3][9]

The Reynolds Risk Score showed improved discrimination over Framingham ATP-III in the Women's Health Initiative, with C-statistic of 0.765 versus 0.757 (p=0.03) and positive net reclassification improvement of 4.9%. The Reynolds score was better calibrated than Framingham-based models and demonstrated superior performance across white and Black women.[11]

External validation studies comparing Globorisk and WHO risk prediction models found substantial agreement and very strong positive correlations between laboratory-based models (κ=0.58, r=0.94) and between non-laboratory-based models (κ=0.70, r=0.92). Both models showed good discrimination in diverse populations, though calibration varied and often required adjustment for specific populations.[44]

Comparisons of newer models including PREVENT, SCORE2, and QRISK4 are emerging but remain limited as these models have only recently been introduced. Early evidence suggests these models may outperform older tools through incorporation of contemporary data, additional risk factors, and advanced methodologies, but extensive external validation across diverse populations is needed to confirm these advantages.[63][65][9][61][22]

Novel Biomarkers and Advanced Risk Assessment

Inflammatory and Metabolic Markers

Beyond traditional risk factors, numerous novel biomarkers have been investigated to enhance cardiovascular risk prediction. Inflammatory markers have received particular attention given inflammation's central role in atherosclerosis development and plaque instability.[83][34][35][84][85][31][32]

High-sensitivity C-reactive protein (hsCRP) represents the most extensively studied inflammatory biomarker for cardiovascular risk prediction. Large-scale prospective studies including the Women's Health Study, Physicians' Health Study, and others have consistently demonstrated that hsCRP predicts cardiovascular events independent of traditional risk factors. The Reynolds Risk Score's incorporation of hsCRP demonstrated improved risk classification, particularly for individuals at intermediate risk by traditional assessment.[34][35][31][32][11]

Additional inflammatory markers showing promise include growth differentiation factor-15 (GDF-15), fibrinogen, and uric acid, all of which predict myocardial infarction and death in prospective studies. Pregnancy-associated plasma protein A, myeloperoxidase, and matrix metalloproteinases predict acute coronary syndrome risk. Lipoprotein-associated phospholipase A2 and secretory phospholipase A2 predict incident and recurrent cardiovascular events.[35][85][34]

Recent research has identified epigenetic biomarkers that may improve cardiovascular disease risk prediction beyond traditional factors. An epigenome-wide association study across five cohorts totaling over 10,000 participants identified 609 DNA methylation markers significantly associated with cardiovascular health, of which 141 were potentially causal for cardiovascular disease including stroke, heart failure, and gestational hypertension. Individuals with favorable methylation profiles had up to 32% lower risk of incident cardiovascular disease, 40% lower cardiovascular mortality, and 45% lower all-cause mortality. These findings suggest epigenetic markers may capture biological pathways not reflected in traditional risk factors.[84][83]

Metabolic biomarkers beyond standard glucose and lipid measures offer additional prognostic information. Lipoprotein(a) [Lp(a)], a genetically determined risk factor for atherosclerotic disease, provides risk stratification information although targeted therapies remain under development. Heart-type fatty acid-binding protein (H-FABP) shows promise as an early marker of myocardial injury in acute coronary syndromes. Thioredoxin-interacting protein (TXNIP) links metabolic dysfunction and oxidative stress, emerging as a biomarker of ischemic and metabolic cardiovascular disease.[85][34][35][61]

Cardiac Biomarkers and Imaging

Cardiac-specific biomarkers and advanced imaging techniques provide complementary approaches to risk stratification beyond traditional risk factors. High-sensitivity cardiac troponin assays detect subclinical myocardial injury and predict future cardiovascular events even in apparently healthy individuals. Elevated troponin levels in the absence of acute myocardial infarction signal underlying cardiovascular pathology and increased risk.[34][35][85]

Natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal pro-BNP [NT-proBNP]) reflect myocardial stretch and neurohormonal activation, providing powerful prognostic information particularly for heart failure risk. Studies have validated elevated natriuretic peptides as predictors of death and heart failure following myocardial infarction and for risk stratification in stable populations. Other cardiac biomarkers including ST2, endothelin-1, mid-regional-pro-adrenomedullin, copeptin, and galectin-3 have been validated for predicting adverse cardiovascular outcomes, particularly in heart failure populations.[35][85][34]

Coronary artery calcium (CAC) scoring using computed tomography has emerged as a powerful risk stratification tool, particularly for reclassifying individuals at intermediate risk by traditional assessment. CAC scores directly measure coronary atherosclerosis burden and consistently predict cardiovascular events across diverse populations. Integration of CAC with traditional risk factors and other biomarkers may further refine risk assessment.[22]

Advanced cardiac imaging including coronary computed tomographic angiography, cardiac magnetic resonance imaging, and echocardiography provides detailed anatomic and functional information useful for risk stratification. Machine learning applied to cardiac imaging data has shown particular promise, with studies demonstrating accurate prediction of cardiovascular events and mortality exceeding traditional approaches.[22]

MicroRNAs (miRNAs), small non-coding RNA molecules that regulate gene expression, represent an emerging area for cardiovascular biomarker development. Circulating miRNAs reflect cellular stress, apoptosis, and pathological processes, with potential utility for identifying early plaque instability and subclinical cardiac dysfunction. However, standardization of measurement methods and validation in large prospective studies are needed before clinical implementation.[85][34][35]

Integration and Multimarker Approaches

While individual novel biomarkers demonstrate associations with cardiovascular risk, their incremental predictive value beyond traditional risk factors has often been modest. C-statistics typically improve by only 0.01-0.03 when single novel biomarkers are added to comprehensive traditional risk factor models. This limited improvement has raised questions about the clinical utility of individual biomarkers for risk prediction, as opposed to their value for mechanistic understanding or as therapeutic targets.[86][34][35]

Multimarker panels combining multiple biomarkers reflecting different pathophysiological pathways (inflammation, thrombosis, myocardial stress, metabolism) have shown more promising results for risk prediction than individual markers alone. The rationale is that cardiovascular disease results from multiple interacting processes, and panels capturing this complexity may provide superior risk assessment. Studies using panels of 3-10 biomarkers have achieved better discrimination and reclassification compared to traditional risk factors alone or traditional risk factors plus single biomarkers.[86][34][35]

However, challenges remain for multimarker approaches including increased cost, complexity of measurement and interpretation, and questions about whether the incremental predictive value justifies these burdens. Standardization of biomarker measurements across laboratories and validation in diverse populations are necessary before routine clinical implementation.[34][35][86]

The PREVENT equations' incorporation of kidney function (eGFR) and metabolic measures (hemoglobin A1c) represents a pragmatic approach to multimarker risk assessment using readily available clinical tests. This integration of biomarkers reflecting cardiovascular-kidney-metabolic health may provide a model for practical implementation of enhanced risk prediction in routine clinical practice.[65][61][63]

Clinical Implementation and Guidelines

Translation Into Clinical Practice

The ultimate value of cardiovascular risk prediction models lies in their ability to guide clinical decision-making and improve patient outcomes through targeted preventive interventions. Major cardiovascular disease prevention guidelines from organizations including the American Heart Association, American College of Cardiology, European Society of Cardiology, and National Institute for Health and Care Excellence have incorporated risk assessment tools into their recommendations

for identifying individuals who would benefit from preventive therapies.[5][18][10][9][61][63]

In the United States, the 2013 ACC/AHA cholesterol guidelines introduced the Pooled Cohort Equations as the primary tool for estimating atherosclerotic cardiovascular disease risk and guiding statin therapy decisions. The guidelines recommended moderate- to high-intensity statin therapy for adults aged 40-75 years with 10-year ASCVD risk of 7.5% or greater. Subsequent iterations of the guidelines have refined these recommendations, incorporating additional "risk-enhancing factors" for shared decision-making in individuals with intermediate risk (5-7.5% 10-year risk). The introduction of the PREVENT equations in 2023 may lead to further evolution of U.S. prevention guidelines as the new model undergoes validation and gains acceptance.[10][27][9][61][63]

European cardiovascular prevention guidelines have incorporated SCORE and subsequently SCORE2 as the primary risk assessment tools. The European Society of Cardiology recommends targeting individuals at high risk (≥10% 10-year risk of fatal and non-fatal CVD by SCORE2) for intensive risk factor modification including lifestyle interventions and preventive medications. The four-region stratification of SCORE2 (low, moderate, high, very high risk) enables country-appropriate application across diverse European populations.[17][13][18][12]

In the United Kingdom, NICE guidelines recommend QRISK3 for cardiovascular risk assessment in primary prevention. The current threshold for offering statin therapy is 10% 10-year CVD risk, though guidelines emphasize shared decision-making considering individual patient preferences, comorbidities, and potential treatment benefits and harms. The NHS Health Check programme provides systematic cardiovascular risk assessment for adults aged 40-74 years, incorporating QRISK3 and, in some implementations, JBS3 heart age tools.[23][71][66][67]

Barriers and Facilitators to Implementation

Despite guideline recommendations and availability of validated risk prediction tools, barriers persist to widespread implementation in clinical practice. Time constraints during clinical encounters, complexity of risk calculation, lack of integration with electronic health record systems, and limited patient understanding of risk estimates all impede effective risk assessment.[5][67][72][22]

Electronic health record integration and clinical decision support tools can facilitate risk assessment by automatically calculating risk scores using available clinical data and presenting results at point of care. Web-based and mobile application calculators provide accessible platforms for risk calculation. However, ensuring data quality, maintaining model updates, and addressing interoperability across different electronic health record systems present ongoing challenges.[25][30][24][27][29][72][22]

Risk communication represents a critical but often underappreciated aspect of effective implementation. Traditional communication of risk as percentage probabilities may not resonate with patients or effectively motivate behavior change. Alternative approaches including heart age, expected cardiovascular disease-free survival years, and visual representations of risk have shown promise for enhancing patient understanding and engagement.[68][71][66][67]

Studies have demonstrated that communicating risk using heart age results in better smoking cessation, blood pressure control, and weight loss compared to percentage-based risk estimates. The JBS3 calculator's ability to show potential risk reduction with specific interventions helps patients visualize the benefits of behavior change or medical therapy, potentially enhancing motivation and adherence.[66][67][68]

Clinician education and training in risk assessment and communication are essential for effective implementation. Many clinicians report limited confidence in interpreting and explaining risk estimates to patients. Professional society educational programs, continuing medical education, and integration of risk assessment training into medical school and residency curricula can address these gaps.[67][5][22]

Limitations, Controversies, and Future Directions

Model Limitations and Generalizability

All cardiovascular risk prediction models have inherent limitations that constrain their applicability and performance. Models are typically derived from specific populations and may not perform well when applied to populations with different demographics, risk factor distributions, healthcare systems, or disease prevalence. External validation consistently demonstrates that discrimination and particularly calibration decline when models are transported to new populations.[81][28][3][12][19][26][40][80][5][22]

The exclusion of certain risk factors from models, whether due to measurement challenges, cost considerations, or statistical decisions, means that important contributors to cardiovascular risk may not be captured. For example, most widely used models do not include chronic kidney disease, detailed measures of glycemic control, inflammatory markers, genetic risk scores, environmental exposures, or social determinants of health, all of which influence cardiovascular risk.[3][21][10][61][5][34]

Competing risks from non-cardiovascular causes of death can lead to overestimation of cardiovascular risk, particularly in older populations and regions with high non-cardiovascular mortality. While newer models including SCORE2 incorporate competing risk adjustment, many established models do not.[13][12][19]

Temporal changes in cardiovascular disease incidence, risk factor distributions, and treatment practices mean that models require periodic recalibration to maintain accuracy. The decline in cardiovascular disease rates observed in many high-income countries over recent decades has led to substantial overestimation of risk by older models, necessitating updates such as ASSIGN v2.0 and the development of new models using contemporary data.[49][52][12][19][80][81]

Controversies in Risk Thresholds and Treatment Decisions

Substantial debate surrounds appropriate risk thresholds for initiating preventive therapies, particularly statins. The 2013 ACC/AHA guidelines' recommendation of a 7.5% 10-year risk threshold for statin therapy was controversial, with concerns about potential overtreatment and concerns that the Pooled Cohort Equations overestimated risk in some populations. Different guidelines recommend different thresholds, with European guidelines generally using 10% thresholds and UK guidelines also at 10% for QRISK3.[23][18][12][9][10][26][68][66]

The tension between short-term and lifetime risk creates additional complexity. Young individuals may have low 10-year risk despite substantial lifetime risk from modifiable factors, potentially missing opportunities for early intervention. Conversely, older individuals may have high short-term risk driven primarily by age even with well-controlled risk factors, raising questions about appropriate treatment intensity.[68][66]

Cost-effectiveness considerations influence threshold decisions, with the different thresholds appropriate depending on medication costs, healthcare system resources, and societal willingness to pay for health gains. The advent of lower-cost generic statins has shifted cost-effectiveness analyses toward lower treatment thresholds, though similar analyses for newer,

more expensive preventive therapies may yield different conclusions.[9][61][66]

Patient preferences regarding acceptance of preventive medications, tolerance of potential side effects, and values regarding quality versus quantity of life should inform treatment decisions through shared decision-making. Rigid application of risk thresholds without consideration of individual circumstances and preferences represents suboptimal care.[27][23][61][63]

Future Directions and Research Priorities

Multiple promising directions for advancing cardiovascular risk prediction include integration of genetic risk scores, incorporation of social determinants of health, enhanced inclusion of diverse populations in model development and validation, and application of artificial intelligence and machine learning methodologies.[76][61][63][74][72][22]

Genetic risk scores, which aggregate information from multiple genetic variants associated with cardiovascular disease, have demonstrated ability to predict cardiovascular events independent of traditional risk factors. Large-scale genome-wide association studies have identified hundreds of genetic variants associated with cardiovascular disease, and polygenic risk scores combining these variants show promise for risk stratification. However, questions remain about whether genetic information provides sufficient incremental predictive value beyond readily available clinical risk factors to justify the cost and complexity of genetic testing for risk prediction purposes.[76][22]

Social determinants of health including socioeconomic status, education, occupation, housing, food security, and environmental exposures substantially influence cardiovascular risk but are often not captured in risk prediction models. The inclusion of social deprivation in ASSIGN and the optional social deprivation index in PREVENT represent steps toward integrating these factors. Further research is needed to identify optimal approaches for measuring and incorporating social determinants into risk assessment.[51][49][61][63]

Enhanced representation of diverse populations in model development and validation is critical for ensuring equitable cardiovascular care. Many widely used models were derived primarily from white populations, with limited inclusion of racial and ethnic minorities, leading to questions about applicability and potential for exacerbating health disparities. The PREVENT equations' development using data from over 6.5 million diverse U.S. adults represents progress, though continued validation across populations is essential.[26][61][63][65][9][22]

Artificial intelligence and machine learning offer potential for incorporating high-dimensional data from multiple sources including clinical characteristics, biomarkers, imaging, genetics, environmental exposures, and social factors to create comprehensive risk profiles. Deep learning models that analyze temporal patterns in risk factors may capture disease trajectories more accurately than static models. However, addressing challenges of interpretability, validation, bias, and integration into clinical workflows remains essential before these advanced approaches can be widely implemented.[74][76][72][22]

The ultimate goal of cardiovascular risk prediction is not simply accurate risk estimation but improvement in patient outcomes through effective preventive interventions. Future research should focus on comparative effectiveness of different risk assessment strategies, optimal approaches for communicating risk and engaging patients, and demonstration that enhanced risk prediction translates into better cardiovascular outcomes. Implementation science investigating how to effectively integrate risk assessment into clinical workflows and optimize clinical decision support represents a crucial research priority.[61][63][5][67][22]

2. CONCLUSION

Cardiovascular disease risk prediction has evolved substantially over the past several decades from single risk factor assessment to sophisticated multivariable models incorporating diverse clinical, biological, and increasingly, imaging and genetic information. The Framingham Risk Score established the foundation for quantitative risk assessment and has been followed by numerous models including QRISK3, SCORE2, ASCVD Pooled Cohort Equations, Reynolds Risk Score, PROCAM, WHO cardiovascular risk charts, ASSIGN, PREVENT, CUORE, JBS3, Globorisk, and emerging artificial intelligence-based approaches. Each model has distinct characteristics including target populations, outcomes, time horizons, risk factors, and geographic applicability.

Comparative studies demonstrate that no single model is universally superior across all populations and applications. Model performance varies depending on the population, with models generally performing best in populations similar to their derivation cohorts. Discrimination, assessed by C-statistics, is generally similar across major models, typically ranging from 0.70 to 0.85. However, calibration—the agreement between predicted and observed risk—varies substantially, with many models requiring recalibration when applied to new populations. The choice of appropriate model should consider the target population, availability of required risk factor measurements, healthcare context, and guideline recommendations for the relevant geographic region.

Recent innovations including the incorporation of kidney function and metabolic measures (PREVENT), competing risk adjustment (SCORE2), inclusion of chronic conditions and medications (QRISK3), country-specific calibration (Globorisk), and heart age communication (JBS3) represent meaningful advances. Artificial intelligence and machine learning approaches show promise for enhancing risk prediction through identification of complex patterns and integration of high-dimensional data, though challenges of interpretability, validation, and bias must be addressed before widespread clinical implementation.

The ultimate value of risk prediction lies in its ability to guide effective preventive interventions that reduce cardiovascular disease burden. Evidence-based guidelines from major professional societies have incorporated validated risk assessment tools into recommendations for identifying individuals who would benefit from lifestyle interventions and preventive medications. However, barriers including time constraints, complexity, limited electronic health record integration, and challenges in risk communication impede consistent implementation in clinical practice.

Future directions should focus on developing more accurate, equitable, and actionable risk prediction tools through integration of genetic information, social determinants of health, artificial intelligence methodologies, and enhanced representation of diverse populations. Equally important is research on effective implementation strategies, optimal risk communication approaches, and demonstration that enhanced risk assessment

improves patient outcomes. As cardiovascular risk prediction continues to evolve, the goal remains reducing the global burden of cardiovascular disease through identification of high-risk individuals and delivery of effective preventive care.

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