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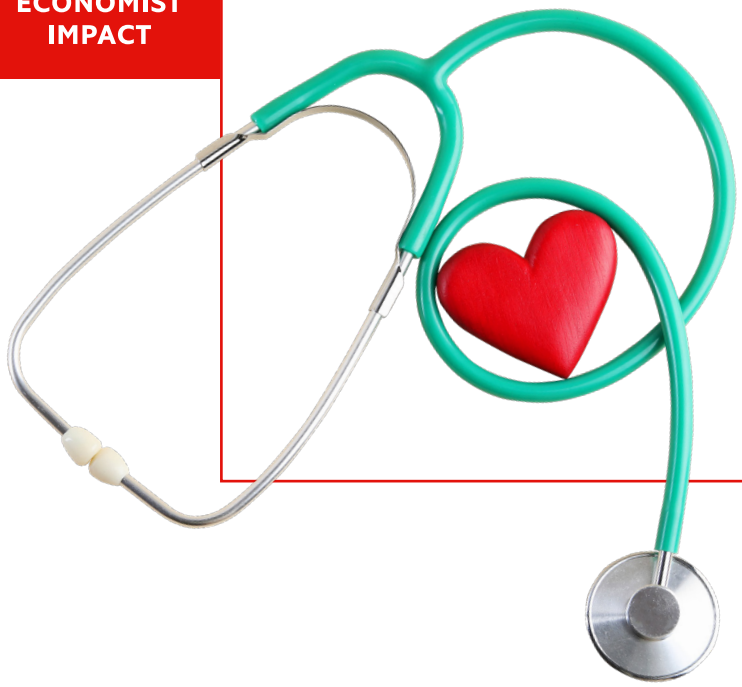

Know Your Heart: Exploring the Role of Laboratory Testing for Cardiovascular Disease Prevention

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About this article

This article, supported by Abbott and created by Economist Impact, is an educational resource that aims to raise awareness of international guidelines and empower patients to engage in informed discussions with their doctors about cardiovascular disease.

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- **Dr Salim Hayek**, Vice President, Chief Transformation Officer, and Chair of the Department of Internal Medicine at the University of Texas Medical Branch; Former Medical Director of the Frankel Cardiovascular Center Clinics and Director of the Hayek Cardiac Biomarkers Laboratory at the University of Michigan

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Introduction

Over half a billion people worldwide have cardiovascular diseases (CVD) – an umbrella term that encompasses disorders of the heart and blood vessels, such as coronary heart disease, peripheral arterial disease or rheumatic heart disease, deep vein thrombosis, and pulmonary embolism[1,2] – resulting in 20.5m deaths in 2021, representing almost a third of the global death toll.[2] Atherosclerotic CVD (ASCVD), which causes a thickening of the arteries, is responsible for nearly two-thirds of CVD deaths.[3] The burden of CVD is growing, significantly impacting low- and middle-income countries (LMICs) (*see* Figure 1). The number of deaths caused by CVD has risen globally over the past 30 years, mainly due to an aging and growing population.[2] Estimates suggest that by 2030, more than 23.3m people will die annually from CVD.[4]

In addition to its effects on health and mortality, CVD imposes significant economic costs on healthcare systems and society at large, thereby highlighting the urgent need for prevention and management strategies to mitigate its impact. The economic impact is a result of both direct costs such as hospitalization, medications, and medical procedures, as well as indirect costs due to lost productivity and long-term care. Between 2019 and 2020, direct and indirect costs totaled $422.3bn ($254.3bn in direct costs and $168bn in lost productivity/mortality).[5]

The burden on families is high; in the United States (US), the annual out-of-pocket healthcare costs amounted to $4,423 on average between 2014 and 2018. Overall, 14% of families experienced a high burden, and for 5%, the costs were catastrophic. Among low-income families, 24% experienced a high financial burden and 10% experienced a catastrophic burden. Low-income families of patients with CVD are disproportionately affected, with a significant proportion encountering financial challenges due in part to the large out-of-pocket healthcare expenses.[6]

According to the American Heart Association (AHA), the annual cost of CVD in the US is projected to reach $1.1trn by 2035, driven by an aging population and increasing prevalence of risk factors such as obesity and diabetes.[7] A 2023 study reported that in the European Union (EU), CVD costs €282bn ($305bn) annually, with health and long-term care accounting for 55% of the total cost, productivity losses accounting for 17%, and informal care costs accounting for 28%.[8]

$168bn

Loss caused by productivity loss and mortality from 2019-2020.

$4,423

Average annual CVD out-of-pocket expenses.

$1.1trn

Cost of CVD in the US by 2035.

10.8m

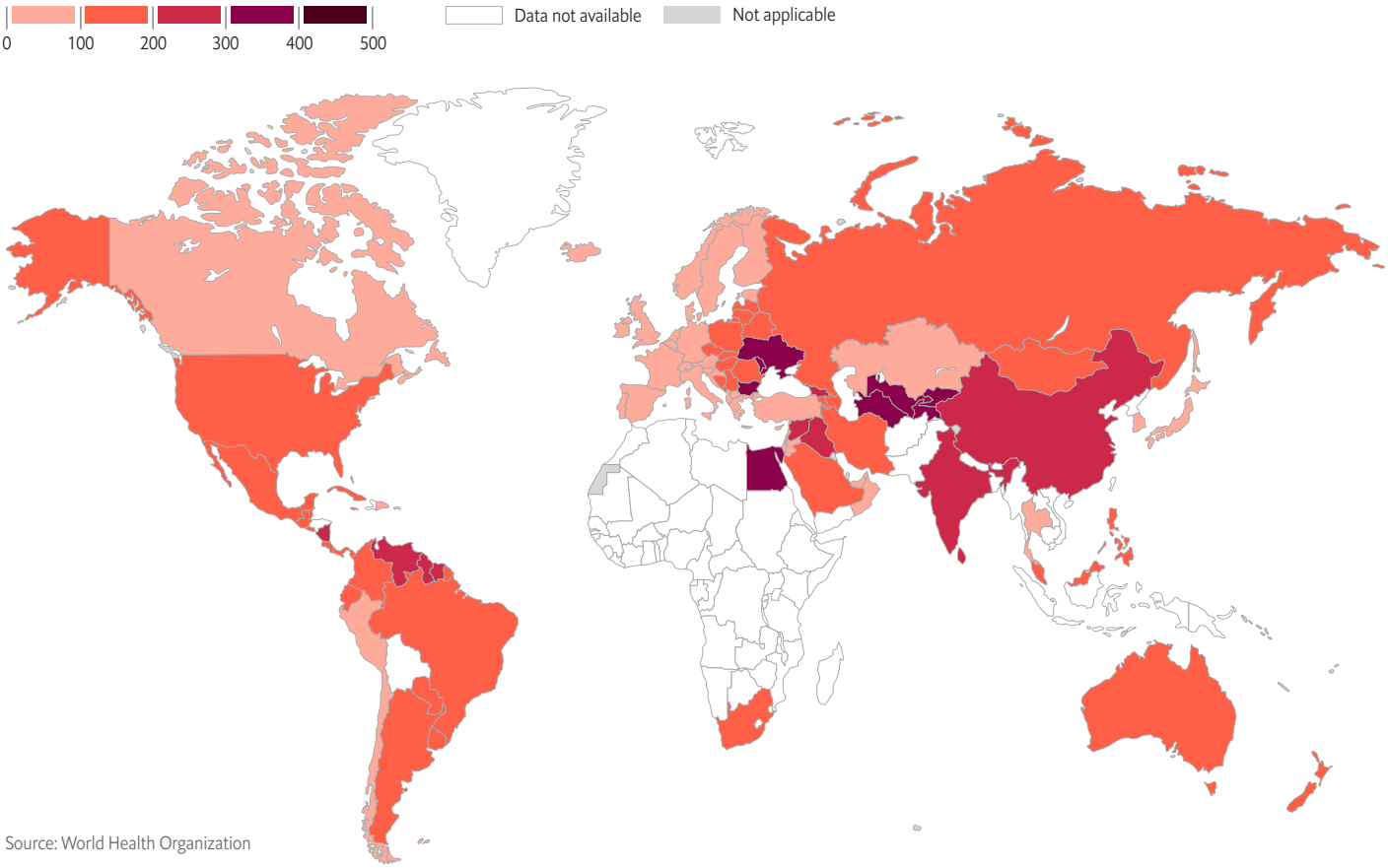
Number of deaths caused by hypertension.

These health and economic costs could be largely prevented. High blood pressure, or hypertension, is one of the most critical risk factors for the development of CVD. In 2021, hypertension caused 10.8m deaths, making it the most significant modifiable risk factor associated with CVD.[2] In the US, approximately 73m adults, or 60% of the adult population, have hypertension; the prevalence in six European countries (Germany, Finland, Sweden, England, Spain, Italy) is found to be 44% in adults aged 19-64 years.[9,10]

India accounts for one-fifth of CVD deaths in the world, with a significant proportion occurring among younger individuals. According to a 2020 study, the age-standardized CVD mortality rate in India is 272 per 100 000, higher than the global average of 235.[11] Similar numbers are noted for China – in 2020, the age-standardized mortality rate for CVD was approximately 245.39 per 100,000, down from 286.85 per 100,000 in 2005. A total of 4.58m CVD deaths was estimated to have occurred in China in 2020.[12]

It is estimated that up to 80% of premature heart attacks and strokes could be averted with healthier life choices. Besides high blood pressure, the modifiable risk factors that contributed to CVD deaths in 2021 included air pollution (4.8m deaths), low-density lipoprotein (LDL) cholesterol (3.8m deaths), high fasting blood glucose (2.3m deaths), higher body mass index (2m deaths) and physical inactivity (~400 000 deaths).[2] These high death toll numbers highlight the urgent need for preventive measures to address risk factors such as smoking and obesity.

Figure 1: CVD mortality, 2020 age-standardized per 100,000 population[13]



Source: World Health Organization

However, it should be noted that significant progress has been made in CVD outcomes. While the absolute number of deaths due to CVD has increased, the age-standardized death rate, which accounts for population size and age distribution, has decreased by one-third from 1990 to 2019.[2] Shahed Ahmad, Medical Director for System Improvement and Professional Standards, South East Region, NHS England and Former National Clinical Director for Cardiovascular Disease Prevention at NHS England, highlighted this achievement: "Over the past 50 years, we have substantially reduced mortality rates. Much of this success can be attributed to notable reductions in smoking rates and better management of risk factors such as hypertension and lipid levels."

Prevention and early detection saves lives by allowing for improved management of CVD with counseling and medications. Yet, screening, medical therapies, and lifestyle interventions are still underused globally. For example, only half of the patients use recommended ACE inhibitors to manage their hypertension; whereas about 80% of patients use antiplatelet therapy, and 70% take statins to lower their cholesterol levels.[14]

Health inequities in CVD care

The reduction in death rates over the past three decades, while laudable, has largely been uneven. High-income countries (HICs) have experienced faster declines as compared to LMICs. Four out of five CVD deaths occur in LMICs, where access to effective and equitable healthcare is limited.[2] Late detection and diagnosis mean that many individuals die at a younger age, often during their most productive years, which imposes a significant economic burden – both on families due to high out-of-pocket expenses and catastrophic spending, as well as on society due to productivity losses and preventable mortality.[1]

Outcome disparities also exist within countries according to sex, ethnicity, and socioeconomic status. Despite high-quality universal healthcare in Nordic countries, the gap in life expectancy between highly educated men and those with a lower level of education varies between 4.0 years in Sweden and 5.1 years in Finland.[15]

Similar disparities exist in Britain, as noted by Dr Ahmad: "Although cardiovascular disease mortality has fallen quite significantly, we still have deprived populations and ethnic minority populations that often have higher rates of cardiovascular mortality than the national average. Our biggest challenge now is tackling inequalities in cardiovascular mortality," he said.

"In the US, where there is no universal healthcare system, the disparities are also due to access; as Dr Salim Hayek, Vice President, Chief Transformation Officer, and Interim Chair of Internal Medicine at the University Texas Medical Branch (UTMB) explained: "I truly believe that the main contributors to disparities in health are the large differences in socioeconomic status and access to health. He argues that "if people do not have access to or cannot afford their medications or the healthy food they need, it becomes difficult to make a dent in the treatment and prevention of cardiovascular disease."

Prevention, diagnosis, and management

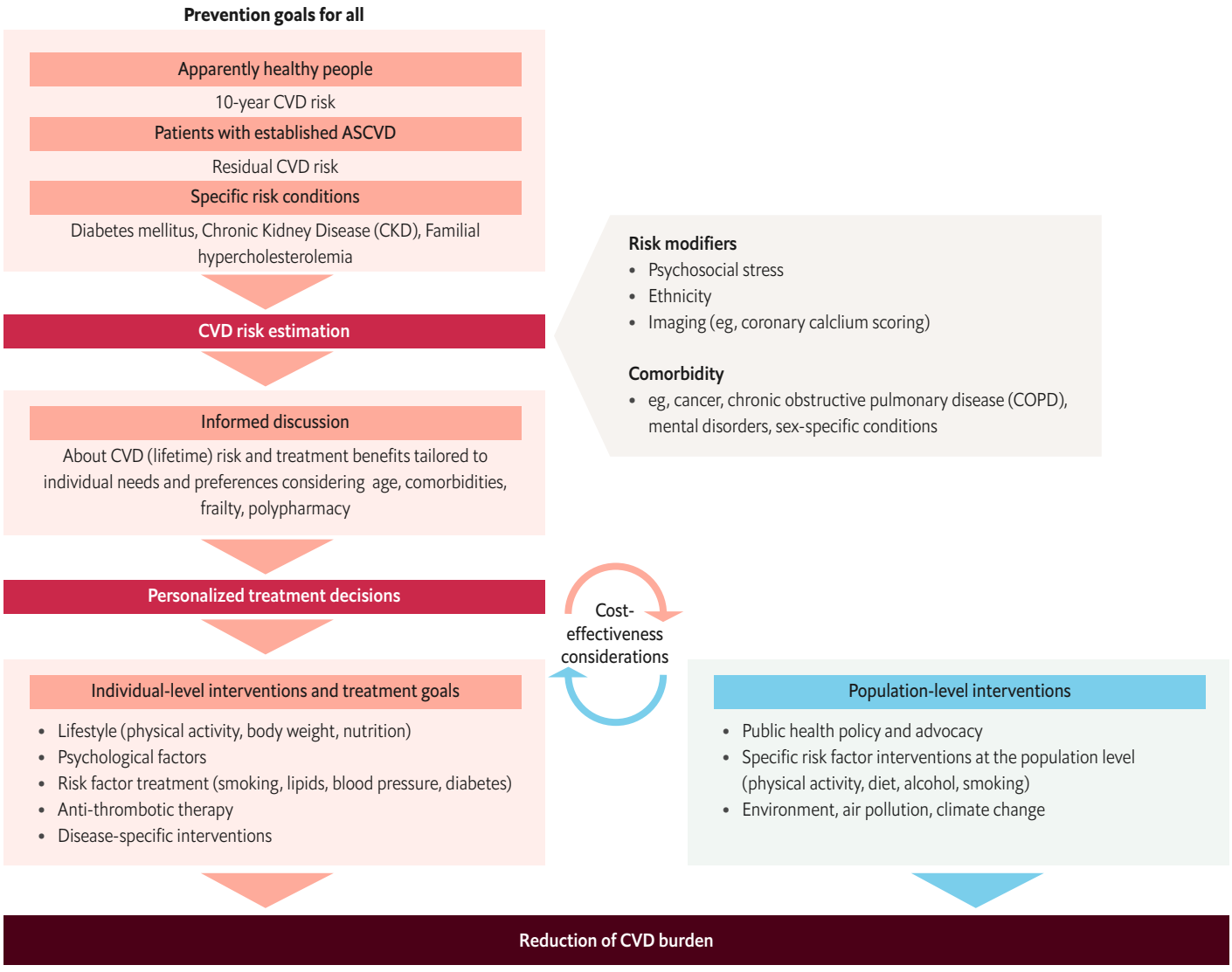
There is no one-size-fits-all approach for improving cardiovascular health globally because risk factors vary depending on the lifestyles of different populations. However, there are baseline approaches that can be universally implemented by nations and then tailored according to their specific CVD burden and needs.[2]

"It is important for populations to get the best access to preventative treatments now," said Dr Ahmad.

Prevention guidelines

The first step in creating primary prevention programs is to reference clinical guidelines. The European Society of Cardiology (ESC) recommends an interdisciplinary approach that addresses lifestyle modifications, psychosocial factors, treatment of risk factors, and social determinants (*see* Figure 2). It lists the main risk factors associated with ASCVD as blood apolipoprotein-B-containing lipoproteins (of which LDL is most abundant), high blood pressure, cigarette smoking, and diabetes mellitus.[16]

Figure 2: Primary prevention of CVD[16]



"It is important for populations to get the best access to preventative treatments now."

Dr Shahed Ahmad, Medical Director for System Improvement and Professional Standards, South East Region, NHS England and Former National Clinical Director for Cardiovascular Disease Prevention at NHS England

The AHA's recommendations are similar. It finds that the best way to prevent coronary disease is to promote a healthy lifestyle, noting that clinicians should evaluate how social determinants affect their patients' health and modify their treatment accordingly. It also recommends that adults aged 40-75 years who are being assessed for CVD should undergo a risk assessment every decade, and notes that statin therapy should be a first-line treatment for CVD.[17] A comparison of the different associations' clinical guidelines for lipid tests is shown in Table 1.[18]

The primary approach for all the associations' guidelines is to clarify a patient's risk level and base recommendations on that.

In Europe, the risk is calculated using the Systematic Coronary Risk Evaluation 2 (SCORE2) algorithm, which assesses the 10-year risk of total CV events based on the incidence of comorbidities such as ASCVD, diabetes mellitus, and chronic kidney disease (CKD). American guidelines calculate risk using Pooled Cohort Equations (PCE), which assess the 10-year risk of developing CVD by including data on both fatal and non-fatal stroke and myocardial infarction among people who do not have CVD.

Table 1: Recommended lipid panel according to the ESC Guidelines, AHA, American College of Cardiology (ACC), Multisociety (MS Guidelines), and American Diabetes Association (ADA) Guidelines[18-21]

Biomarkers	ESC Guidelines	AHA/ACC/MS Guidelines	ADA Guidelines
LDL-C	Primary target, goal <55 mg/dL for very high-risk individuals and <70 mg/dL for high-risk individuals	Primary target, thresholds for initiating treatment, goal <70 mg/dL for high-risk individuals and <100 mg/dL for moderate-risk individuals	Monitored annually, <100 mg/dl
High-density lipoprotein (HDL)-C	Monitored, not a primary target	Monitored, not a primary target	Monitored annually, >40 mg/dl
Total Cholesterol (TC)	Secondary target, goal <175 mg/dL	Monitored, not a primary target	Monitored annually, <150 mg/dl
Triglycerides (TG)	Monitored, goal <150 mg/dL	Monitored, goal <150 mg/dL	Monitored annually, <150 mg/dl
Non-HDL-C	Secondary target, goal <85 mg/dL	Monitored in specific cases	Monitored annually, <130 mg
Apolipoprotein B (ApoB)	Optional, considered in high-risk individuals	Optional, for more precise risk stratification	Recognized, not directly mentioned
Lipoprotein (a) [Lp(a)]	Optional, considered in high-risk individuals	Optional, particularly in those with a family history	Recognized, not directly mentioned
High-sensitivity CRP (hs-CRP)	Not routinely recommended	Optional, in conjunction with other risk factors	Refers to AHA guidelines, not routinely recommended
Apolipoprotein A1 (ApoA1)	Not routinely recommended	Not routinely recommended	Recognized, not directly mentioned

Each guideline accounts for differences in risk-modifying/enhancing factors among the various ethnic groups based on population studies of their varying risk for CVD events (*see* Table 2).[18] Dr Ahmad explained the reasons for different approaches for different ethnicities. "There is information to suggest that certain groups with the highest mortality rates might be having their [CVD] events at an earlier age," he said. "We might need to look at threshold levels for treatment for groups who suffer more mortality; that should be part of the research agenda going forward."

Biomarkers

Lipid biomarkers

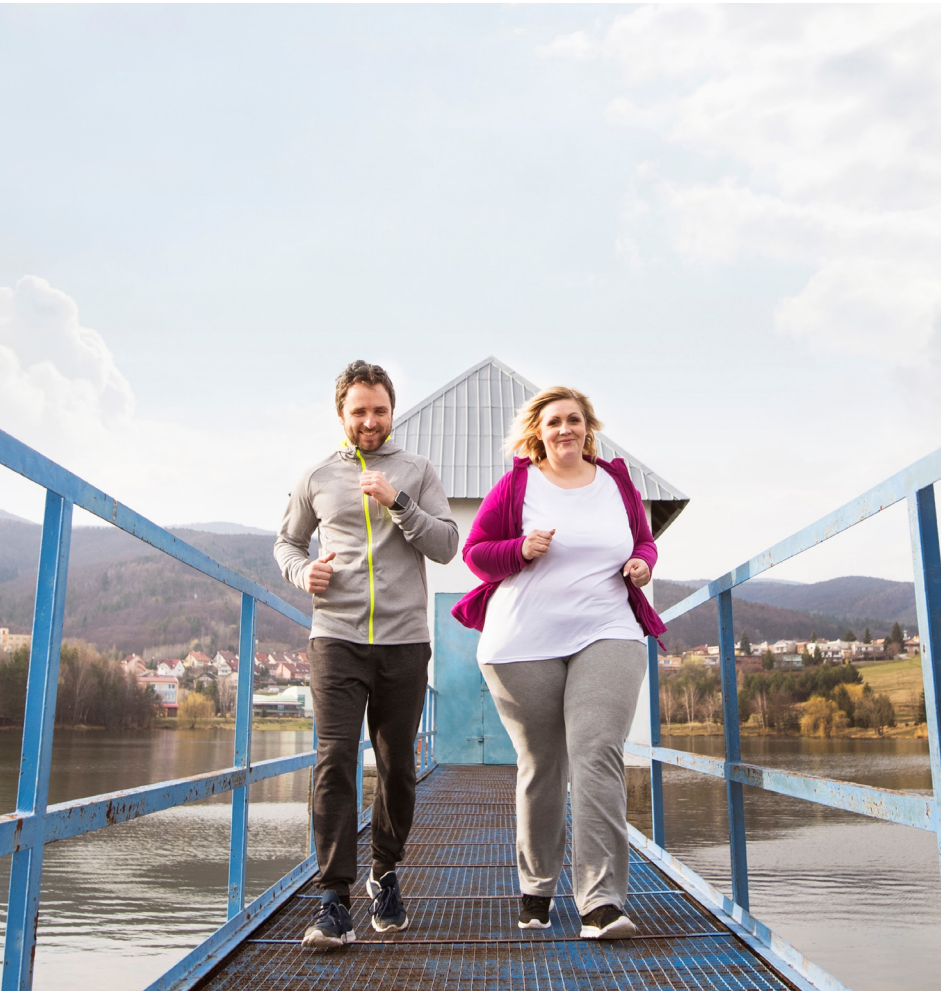
Cholesterol is a significant risk factor for CVD, and assessing and managing plasma lipids plays a pivotal role in preventing ASCVD.22 Prolonged lower LDL (commonly known as bad cholesterol) is associated with a lower risk of ASCVD, while HDL is inversely associated with ASCVD risk.[16] Conventional lipid panels comprising total cholesterol, HDL, LDL, and triglycerides remain a prominent method for evaluating risk.

New insights into the mechanisms of atherosclerosis have led to the introduction of innovative lipid and non-lipid biomarkers that provide enhanced predictive capabilities. ApoB is present in all lipoproteins except for HDL. It may be a better measure of harmful serum LDL than LDL concentration; LDL particles vary widely in size and cholesterol content, but each contains one molecule of ApoB, which, therefore, better reflects the total number of LDL particles.[23]

Table 2: Comparison of scoring systems[18]

Risk Category	ESC Guidelines	AHA/ACC/MS Guidelines
Scoring System	SCORE2/SCORE2-OP (Systematic Coronary Risk Evaluation)	PCE (Pooled Cohort Equations)
Low Risk	<2.5% (under 50 years), <5% (50-69 years), <7.5% (70 years and older)	<5% 10-year risk of ASCVD events
Moderate Risk	2.5-7.5% (under 50 years), 5-10% (50-69 years), 7.5-15% (70 years and older)	5-7.5% 10-year risk of ASCVD events
High Risk	≥7.5% (under 50 years), ≥10% (50-69 years), ≥15% (70 years and older)	≥20% 10-year risk of ASCVD events
Very High Risk	Automatically includes ASCVD, diabetes with target organ damage, severe CKD (eGFR < 30 mL/min/1.73 m^2), SCORE ≥ 10%	Two or more major ASCVD events or one major event and multiple high-risk conditions
Risk Modifiers/Enhancing Factors	Family history of premature CVD, obesity, central obesity, physical inactivity, social deprivation, immune-mediated disorders, CKD, atrial fibrillation, OSA, metabolic syndrome, non-alcoholic fatty liver disease, coronary artery calcium (CAC) score > 0, elevated biomarkers (e.g., hs-CRP, Lp(a), ApoB)	Family history of premature ASCVD, high-risk race/ethnicities, CKD, chronic inflammatory conditions, high hs-CRP, elevated Lp(a) or ApoB, conditions like metabolic syndrome and primary hypercholesterolemia

Note: For ESC Guidelines, the percentages represent the 10-year risk of fatal and non-fatal CVD events. For AHA/ACC/MS Guidelines, the percentages represent the 10-year risk of ASCVD events, which include non-fatal myocardial infarction, coronary heart disease death, and fatal or non-fatal stroke.



Similarly, ApoA1 is proposed as a more accurate measurement for HDL, as HDL contains two associated apolipoproteins. The ratio of ApoB to ApoA1 has also been proposed as a superior measure of bad to good cholesterol ratio. Lp(a), a genetically determined and time-stable biomarker, is an independent risk factor for coronary artery disease and improves risk evaluation. Dr Hayek described these biomarkers as more refined measurements of cholesterol. "We have seen that these measurements only modestly improve risk prediction compared to regular LDL cholesterol (LDL-C)," he said. However, he does not think they are helpful for patients who are already known to be at risk of cardiovascular disease.

The ACC recommends some lipids and other biomarkers to determine risk-enhancing factors in patients. These are hs-CRP ≥2.0 mg/L, Lp(a), which constitutes a risk-enhancing factor at values ≥50 mg/L and especially at higher levels, and ApoB at concentrations ≥130 mg/dL. The guideline suggests that an indication for measuring ApoB would be triglyceride levels above 200 mg/dL. Elevated ApoB ≥ 130 mg/dL corresponds to an LDL-C > 160 mg/dL, which is a risk-enhancing factor.[24]

Several strategies have been proposed for managing cholesterol and reducing the risk of ASCVD. First, educational initiatives can increase awareness about the links between cholesterol levels and ASCVD-risk among the public and healthcare professionals. A second solution could be to deploy population-wide strategies to prevent ASCVD through better lifestyle choices. Other proposals include improving population screening to reduce the under-diagnosis of genetic dyslipidemias, enhancing access to cholesterol-lowering medications, and establishing national or regional monitoring systems to track treatment adherence and outcomes. These approaches are designed to tackle the complex challenges associated with cholesterol management and ASCVD prevention and redesign health systems for better outcomes.[25]

Non-lipid biomarkers

Non-lipid biomarkers have also become essential in evaluating CVD risk. Pro B-type Natriuretic Peptide (proBNP) is produced by the heart's ventricles when under strain and is a marker for the likelihood of heart failure. It is cleaved into B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), both of which are used to aid diagnosis of heart failure.[26]

Besides their role in the diagnosis of heart failure, natriuretic peptides have been shown to improve risk prediction of both cardiac events and mortality in asymptomatic patients.[27] A study of

96,000 people investigating whether NT-proBNP concentrations could improve prediction of heart attacks, strokes, and heart failure found that higher levels of this biomarker were linked to a greater risk of heart issues. Measurement of NT-proBNP, alongside measurement of traditional risk factors such as age and smoking, improved the accuracy of predicting heart problems.[28] Elevated levels have been associated with adverse outcomes after some cardiac surgeries[29], and a recent meta-analysis showed a strong relationship between circulating levels of natriuretic peptides and CVD risk in patients with end-stage kidney disease.[30]

Although risk prediction for patients with type 2 diabetes mellitus (T2DM) is normally considered inaccurate, recent research suggests that NT-proBNP is a reliable tool to improve outcomes prediction when used alongside multivariate models. Even as a single variable, this biomarker has shown the ability to predict death and cardiovascular events in patients with diabetes.[31]

Cystatin C assesses kidney function and is linked to cardiovascular risk; fibrinogen is a clotting factor and is associated with the future onset of CVD; and leptin is a protein that fat cells secrete, which is elevated in heart disease.23 Cystatin C was investigated alongside NT-proBNP as a dual-marker strategy to look at cardiorenal syndrome, which is characterized by cardiac and renal dysfunction. Cardiorenal patients with elevated concentrations of NT-proBNP and cystatin C had a worse prognosis than those with low concentrations of these biomarkers.[32]

Cardiac troponin (isoforms cTnI and cTnT) is a biomarker of myocyte injury and provides valuable information on the risk of cardiovascular events. Described as the most successful cardiac-specific biomarker in cardiovascular medicine, it has contributed to accurate diagnosis of acute coronary syndromes.[33] Both isoforms show strong associations with heart failure and death due to CVD, and may help inform future clinical care and research.[34] High-sensitivity cardiac

troponin (hs-cTn) assays can accurately detect low concentrations of cTnI and cTnT in asymptomatic individuals, allowing for the early detection of elevated troponin levels and the ruling out of CVD, while also noting that statin therapy can reduce troponin concentration.[35] The high-sensitivity assays also detect minimal myocardial injury in cardiovascular re-stratification for non-cardiac surgery patients, cardiotoxicity, and COVID-19 infection.[36-38] Levels are responsive to preventive interventions and have been shown to reflect a parallel reduction in CVD risk.[33,39,40]

In patients with diabetes, CVD is the leading cause of hospitalization, morbidity, and mortality in US adults, responsible for over 30% of deaths.[1,41,42] A recent study of NT-proBNP and hs-cTnT in adults, with no prior history of CVD and with and without diabetes, found that elevation of both biomarkers was associated with CVD mortality, while elevated hs-cTnT was more prevalent in those who had poorer glycemic control and had had diabetes for a longer period of time. Those with diabetes had double the prevalence of both biomarkers as compared to those without diabetes, suggesting twice the prevalence of subclinical CVD.[43] In older patients with diabetes, elevation of hs-cTn was associated with prevalent comorbidities including coronary heart disease and heart failure, and both biomarkers stratified mortality risk beyond comorbidity levels, suggesting a means of guiding clinical care of this patient group.[44]

To date, the most frequently studied marker of inflammatory vascular processes is C-reactive protein or CRP, a marker that can identify patients with inflammatory cardiovascular risk despite good control of their LDL-C levels. Reducing levels of both LDL-C and CRP has been associated with a greater reduction in the risk of adverse cardiovascular events when compared to control of LDL-C alone.[45]

Since chronic, low-grade inflammation plays an important role in the development of atherosclerosis, CRP as a cardiovascular biomarker needs to be detected using highly sensitive assays or high-sensitivity CRP (hs-CRP), which could detect lower levels of CRP in uninfected persons[46] hs-CRP is elevated in most patients after myocardial infarction, and patients with hs-CRP ≥ 2mg/L showed a higher risk of major adverse cardiovascular events. In contrast to this, patients with previous percutaneous coronary intervention, and those on statins and ACE inhibitors or angiotensin II receptor blockers (ARBs), were associated with lower hs-CRP.[47] Despite evidence of its clinical usefulness, use of this biomarker remains low in clinical practice, and very little information exists outside the controlled setting of clinical trials.

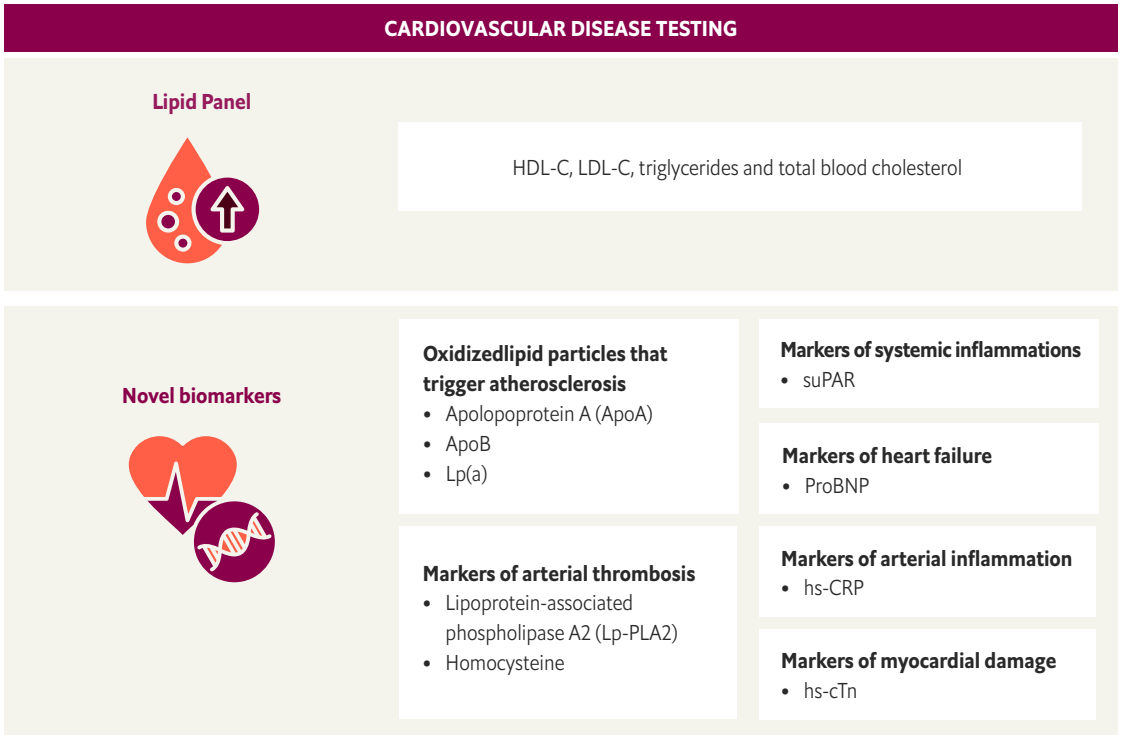
Another promising biomarker is soluble urokinase plasminogen activator receptor (suPAR), which is related to immune activation that is linked to

atherosclerosis and other diseases.[48] Although promising, suPAR is still undergoing clinical trials, with Phase I completed and Phase II underway, requiring further research to confirm its efficacy.

Cohort studies and meta-analyses suggest all these biomarkers may improve CVD-risk prediction accuracy. Circulating cardiac markers, troponins and NT-proBNP may augment risk assessment for onset of CVD in primary care.[49] However, it is still unknown whether this improved accuracy is clinically essential or if it could lead to changes in the management of CVD. Overall, there is insufficient evidence that the use of these biomarkers leads to an improvement in health outcomes, and further work is required.[50]

Dr Hayek, who developed and studied several patient cohorts and biobanks totaling over 50,000 participants, explained that CVD is a complex process involving multiple pathways. "Cardiovascular disease isn't a one-size-fits-all condition. It's a complex interplay of various pathways, each of which can be the primary driver in different individuals. For instance, in one patient, elevated cholesterol might be the main culprit, while in another, smoking could be the major driving factor. Some patients might have multiple drivers, such as a combination of diabetes, high cholesterol and lifestyle factors like smoking. This complexity is why we're moving towards a multi-biomarker approach to assess risk and develop personalized treatment strategies. By identifying each patient's unique disease profile, we hope to be able to tailor our interventions more effectively," he said.

Figure 3: Biomarkers[51,52]



"The real promise of AI lies in its ability to process and provide unbiased, comprehensive feedback from vast amounts of patient data, potentially revolutionizing our approach to personalized risk prediction and treatment strategies."

Dr Salim Hayek, Vice President, Chief Transformation Officer, and Chair of the Department of Internal Medicine at the University of Texas Medical Branch; Former Medical Director of the Frankel Cardiovascular Center Clinics and Director of the Hayek Cardiac Biomarkers Laboratory at the University of Michigan

Future directions

Policies need to focus on preventing CVD by addressing behavioral risk factors and enabling early detection and treatment for high-risk individuals. Countries have set voluntary targets to reduce tobacco and alcohol use, increase physical activity, lower salt intake, improve access to medicines, and control blood glucose, blood pressure, and obesity.[53]

The AHA's 2030 Impact Goal prioritizes cardiovascular health promotion and CVD prevention, aiming to increase healthy life expectancy. This policy statement emphasizes the perspective needed for effective cardiovascular surveillance in the US in the coming decade and beyond. The 2030 Impact Goal, along with the Strategic Value Proposition, mandates the continuation of existing surveillance efforts and the inclusion of new dimensions such as health-adjusted life expectancy (HALE) and indicators of overall health and well-being.[54]

Statins are the mainstay for effectively reducing ASCVD risk by lowering LDL-C. However, they do not always reduce lipid levels to guideline targets. New treatments such as bempedoic acid, mipomersen, and olezarsen, which target new lipid biomarkers, are therefore emerging and show some promise, but require further research.[55,56]

Dr Ahmad pointed to the need for further research across the board to improve CVD outcomes: " We should ensure we have good quality research to inform policy. We may also want to repeat some of the past research that we relied on, but ensure it is significantly powered to also look at populations who suffer from health inequalities," he said.

Dr Hayek thinks that the promise of artificial intelligence (AI) will allow for a global assessment of risk prediction, elaborating that "Today, measuring biomarkers isn't the challenge; it's interpreting and applying that information effectively. Imagine AI algorithms analyzing a patient's complete electronic health record,

integrating diverse data points to refine risk assessment both retrospectively and prospectively. This technology could identify which data or variables are truly significant and which are less relevant. The real promise of AI lies in its ability to process and provide unbiased, comprehensive feedback from vast amounts of patient data, potentially revolutionizing our approach to personalized risk prediction and treatment strategies." Indeed, AI-driven advances in hardware have had a tremendous impact on optimizing patient care and outcomes in CVD.[57] Researchers have developed a new tool, QR4, which includes new risk factors to stratify risk, taking into account the impact of other diseases on heart health. These include learning disabilities, COPD, and factors specific to women's health, such as postpartum depression and pre-eclampsia.[58]

As we navigate the complexities of CVD prevention and management, leveraging collective insights and innovative approaches is imperative. The introduction of new technologies will not only improve risk assessments and identification but also enable us to tackle risk factors more effectively and develop personalized treatment plans post-diagnosis. By fostering collaboration across sectors and embracing a holistic approach to cardiovascular health, we can move towards a future where the devastating impact of these diseases is significantly mitigated, thereby enabling healthier lives for generations to come.

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