INTERNATIONAL ATHEROSCLEROSIS SOCIETY

Unmet Needs and the Evolving Landscape of Primary Prevention in Atherosclerosis

A Clinical Proceedings White Paper

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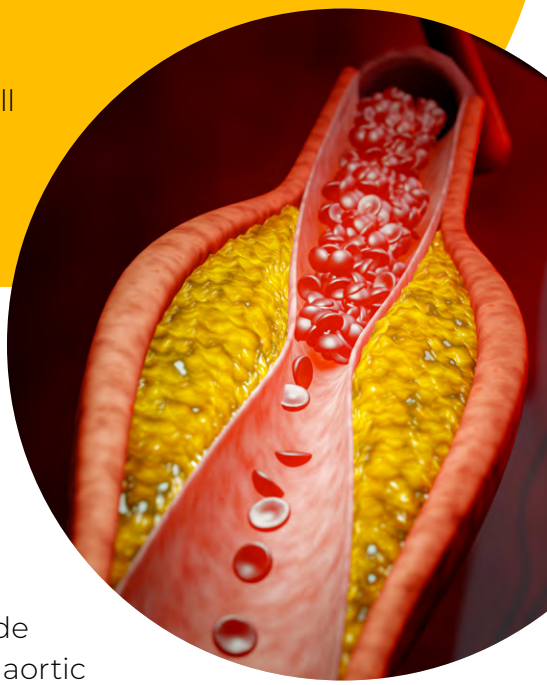
Introduction

This paper presents a summary of primary prevention measures for atherosclerotic cardiovascular disease (ASCVD) caused by elevated low-density lipoprotein cholesterol (LDL-C), and other cardio-metabolic risk factors such as obesity and diabetes, as well as hypertension.[1] Although LDL indubitably contributes causally to the development of ASCVD, there are many gaps in screening, diagnosis, and management of elevated LDL-C. This paper highlights these gaps in primary prevention, a crucial issue given the modifiability of many ASCVD risk factors.

Addressing these unmet needs benefits from a multidisciplinary approach from a variety of stakeholders: from researchers, professional organizations, primary care providers, specialists, and health systems to community leaders and policymakers. This paper will also discuss ways to move the needle in primary prevention and will highlight promising therapies on the horizon.



Defining ASCVD

Atherosclerosis, or the process of arterial plaque formation, results from buildup of intimal lesions, provoking thrombosis or progressing to stenoses, which when advanced can limit blood flow.[2, 3] Atheromata can also become calcified. ASCVD refers to a bundle of cardiovascular disease (CVD) conditions that can include coronary artery disease (CAD), ischemic cerebrovascular disease, aortic atherosclerotic disease, and peripheral artery disease (PAD).[4] Heart attack and ischemic stroke are the two most devastating events resulting from ASCVD.[1]

LDL-C level relates the risk of ASCVD onset as well as its severity and progression, making it both a causal and lifetime cumulative risk factor.[5] The results of the Framingham Heart Study demonstrated the relationship between serum cholesterol and coronary heart disease in the 1960s.[6] Since then, extensive evidence has supported this association, yet achieving targeted reductions in LDL-C levels has remained low in high-risk patients, and cardiovascular morbidity and mortality is on the rise worldwide.[5]

High LDL-C concentrations depend on genetics but also lifestyle behaviors, including unhealthy diet, smoking, older age, inadequate sleep, and low physical activity.[7, 8, 9] Although ASCVD usually manifests clinically in middle age, the development of atherosclerosis can begin early in life.[7] Elevated LDL-C levels from birth can be due to genetic causes such as forms of familial hypercholesterolemia (FH), and figure among the most common monogenic disorders worldwide.[5]

Prevalence

Globally, 18 million people die of CVD per year, of which 85% is due to ASCVD. It is also the leading cause of death and disability worldwide.[5, 11] Almost half of the United States (U.S.) adult population now has some form of CVD.[12] ASCVD is increasing among younger people around the world, and the elderly bear a large burden of ASCVD. Many countries now have a substantial population above the age of 65. The elderly will outnumber the younger populations in most countries in the next 40-60 years.[13] The primary prevention of ASCVD can help maintain health throughout the lifespan.

ASCVD requires particular attention in developing regions. Out of all cardiovascular deaths, 80% occur in low-and middle-income countries (LMICs), reflecting large shifts in demographics and epidemiology.[5, 14] Latin American individuals have higher cholesterol values compared with other regions of the world.[14] Latin America also has high proportion of people with undiagnosed and untreated FH, due to a lack of awareness of the disease.[14]

Asian countries, especially South Asian, have a high burden of ASCVD, and a growing rate of premature cardiovascular events. For example, the average age of myocardial infarction is around 53 years in India, compared to 62-63 years in China.[15] A major cause of premature ASCVD may be the high prevalence of type 2 diabetes in South Asian countries, as well as poor metabolic tolerance of visceral adiposity.

African countries, especially in Sub-Saharan Africa, have similar trends.[16, 17] The burden of CVD in Africa has increased almost 50% in the past 30 years due to rapid urbanization, which increased key traditional risk factors, and the exposure to air pollution. Hypertension has also driven the increasing prevalence of ASCVD in black populations.[17]

CVD Prevalence in 2021 by Country[10]

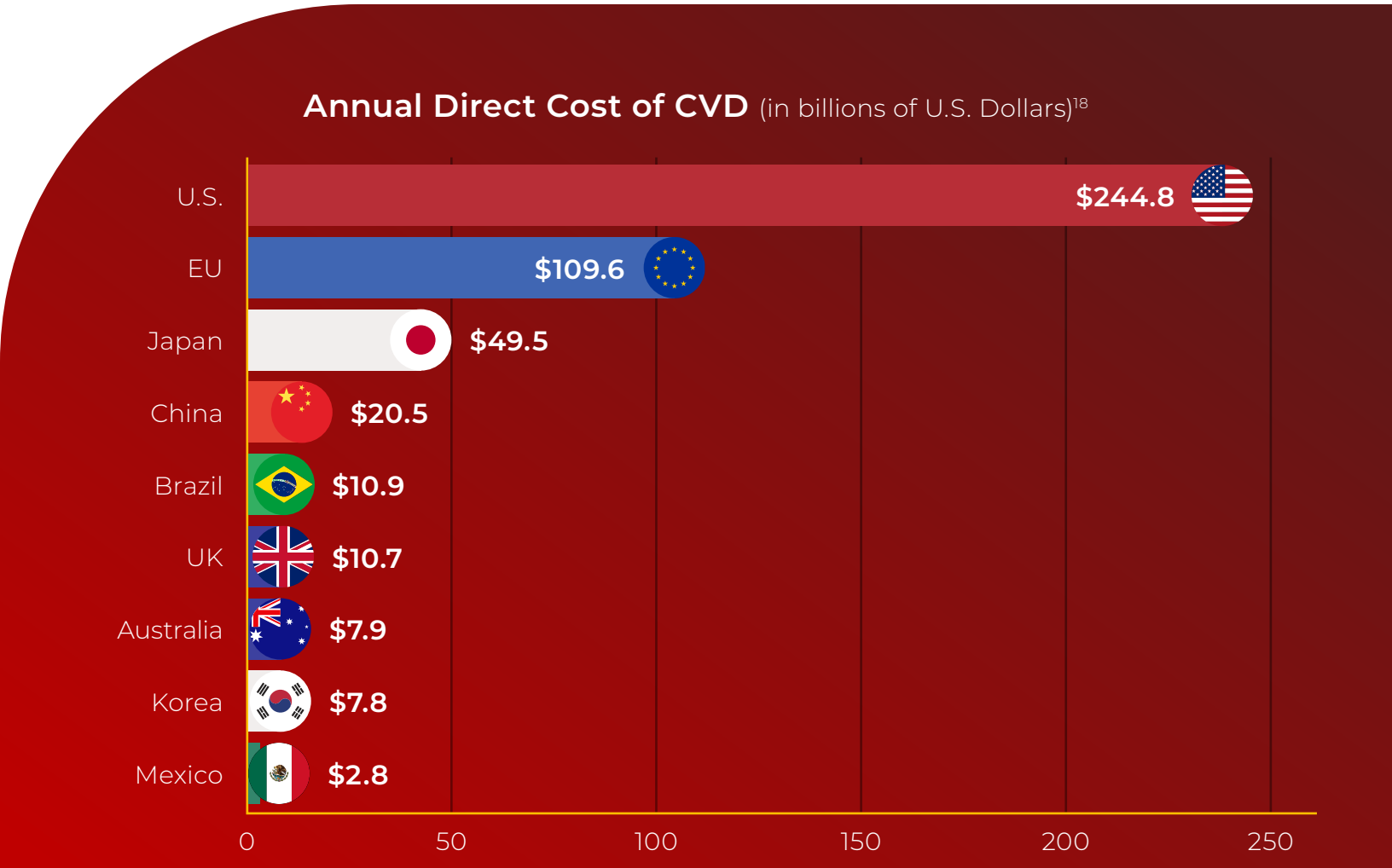
All Ages Total Cardiovascular Disease

Costs

Annually, in the U.S., ASCVD costs approximately $200 billion from loss of productivity, medications, and healthcare services.[19] By 2035, these costs will reach up to an estimated $309 billion.[20] The annual U.S. costs for ASCVD exceed $20,000 per patient, and almost half of adults with ASCVD in the U.S. face financial hardship due to medical expenses.[21, 22]

Other high-income countries also have notable indirect costs from loss of productivity attributable to ASCVD. In the European Union, ASCVD costs €210 billion per year.[23] A large retrospective study of more than 200,000 people with ASCVD in Sweden revealed that people with ASCVD incurred two-and-a-half times higher annual costs, were three times more likely to retire early, and missed twice as many workdays as those in a similarly sized cohort without ASCVD.[24]

Globally, the economic burden of CVD will reach an estimated $1,044 billion by 2030.[25]



**Direct costs refer to personal health care for CVD for China, Japan, the EU, Mexico, and the U.S. (curative care, long-term care, medical goods, rehabilitative care, and ancillary services) and personal healthcare and personal collective services for CVD (prevention and public health services) for all other countries.*

Primary Prevention

Although ASCVD risk exists across a continuum, the term “primary prevention” conventionally denotes interventions that limit or reduce risk factors in healthy or susceptible individuals before clinical manifestations of ASCVD occur. Clinical ASCVD is defined by the American College of Cardiology and the American Heart Association (ACC/AHA) as stable/unstable angina, transient ischemic attack, PAD, coronary or arterial revascularization, stroke, history of acute coronary syndrome, or history of myocardial infarction.[26]

Primary prevention has particular importance for ASCVD due to the modifiability of much risk. Both the duration and magnitude of high LDL-C levels determine risk, thus early interventions can prevent or slow ASCVD progression.[26] Primary prevention of ASCVD emphasizes screening, risk assessment, addressing modifiable risk factors through a healthy diet and lifestyle, and LDL-lowering medications for high-and very-high risk groups.

Screening

A routine blood test can assess LDL-C levels. Apolipoprotein-B measurements offer some incremental value in risk assessment over LDL concentrations, but require a more specialized assay, seldom required in general practice. Non-HDL-C, calculated by simple subtraction of HDL from total cholesterol concentration, captures the information for all apolipoprotein-B-containing lipoproteins. This parameter, sanctioned in several guidelines, furnishes an alternative to apolipoprotein-B measurements and avoids additional expense and the need for specialized testing.

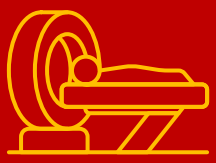
Lipoprotein(a), or Lp(a), an independent and inherited risk factor for ASCVD, requires a more specialized test, which is becoming more readily available. A single lifetime measurement suffices to establish risk due to Lp(a), as it is largely genetically determined.[5] Healthy adults should have cholesterol screening every 4-6 years. Older adults, at-risk patients, or those with a family history of high cholesterol may merit more LDL assessment.[4] South Asians may develop ASCVD at younger ages than Caucasians and thus may merit particularly early screening for lipid abnormalities including Lp(a).[80]

Healthcare providers should discuss with the patient his or her family history, lifestyle, any symptoms present, and may perform additional tests such as an electrocardiogram or ankle-brachial index test. Imaging studies can also aid in screening those with elevated estimated risk or with symptoms raising concerns of ischemia, and include Coronary Artery Calcium (CAC) scan, or computed coronary artery angiography.[27, 28] Carotid Intima-Media Thickness (CIMT), which uses ultrasonography, requires specialized skills and is less widely used as direct coronary artery imaging has become more available.[29] The application of artificial intelligence to analyze such studies promises to provide additional progress and standardization of interpretation. Genetic testing may aid management if there is a family history of ASCVD or cardiovascular events.

Types of Screening Tests

Lipid Panel

ECG or EKG



Imaging Tests

Genetic Tests

Because individuals can lack symptoms despite a considerable burden of ASCVD, screening should not await its manifestations. One-third of adults in the U.S. lack awareness of their risk before their first ASCVD event.[29] Many asymptomatic men in middle age manifest signs of atherosclerosis in multiple arterial beds upon advanced imaging.[30] Hence the importance of early screening for those at-risk patients, particularly those with non-lipid risk factors such as positive family history, hypertension, diabetes, or smoking.

CAC scores can powerfully predict ASCVD events and can outperform traditional risk factors in this regard.[1] Some argue that imaging can lead to more accurate treatment and enhance patient awareness and compliance.[31] Yet, calcification can be modifiable, increasing with statin treatment and vigorous exercise. Moreover, rigorous clinical trials have not demonstrated that targeting therapy based on CAC improves ASCVD outcomes.

Risk Assessment

Risk assessment is an important tool in primary prevention of ASCVD, as recommended in many guidelines. Risk equations can predict the probability of ASCVD, create population groups stratified by risk scores, and identify treatment intensity according to guidelines. Common risk assessment tools in current use include the ACC/AHA's Pooled Cohort Equation (PCE) and the European Society of Cardiology's (ESC's) Systematic Coronary Risk Evaluation-2 (SCORE2).[33, 34] Imaging test-based risk scores include the CAC score and the Multi-Ethnic Study of Atherosclerosis (MESA) CHD score, which also uses CAC.[34] Certain biomarkers, including C-reactive protein measured with a highly sensitive assay (high-sensitivity C-reactive protein [hsCRP]), can improve risk predictions, as shown in the Reynold's Risk Score, and is now recommended for aiding risk estimation in several guidelines,[35] as shown in the chart on the next page. Successive generations of polygenic risk scores (PRS) have emerged that also promise to add to traditional models.[36] PRS may prove particularly valuable to guide primary prevention interventions in youth, as genetic complement is determined at conception, and many standard risk factors increase only in adulthood.

Challenges surround the selection of risk factors, and which to include or exclude. For example, some argue that diabetes should be a major risk factor in the European SCORE2 equation, because adults with type 2 diabetes are four times more likely to develop ASCVD.[37] Commonly used risk equations can also incorporate psychosocial factors, since the presence of risk factors such as stress, anxiety, and/or depression, and adversity can associate with cardiovascular events.

The derivation of risk algorithms has largely used cohorts in higher income countries, yet the greatest global burden of CVD occurs in LMICs.[38] Some of the risk factors vary between countries and regions. The INTERHEART study in China demonstrated that Northern Chinese had higher rates of smoking and hypertension, and Southern Chinese had lower fruit and vegetable consumption.[39]

Strong associations between risk factors and disease can apply on the population level, for example saturated fat intake and serum cholesterol levels, but not always to individuals.[40] Thus, dietary fat intake does not always identify high-risk people.[40] Although LDL indubitably causes atherosclerosis, a 2009 U.S. study showed that of 136,000 emergency room patients with CAD, 77% had LDL-C levels accepted as "normal."[39]

Comparing Two Common CVD Guidelines: ACC/AHA and ESC[32]

	2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease (U.S.A)	2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Europe)
Risk Assessment Tool	Pooled Cohort Equation (PCE): calculates the 10-year risk of developing ASCVD for individuals 40-75 years of age; includes non-fatal myocardial infarction or coronary heart disease (CHD) death and fatal or non-fatal stroke; creates high, intermediate, borderline, and low risk categories For those older than 75 years, risk discussions are recommended for treatment of high cholesterol, T2D, and hypertension	Systemic Coronary Risk Estimation 2 (SCORE2 for ages 40-69 years) and SCORE2-OP (for those 70 years of age or older): calculates a 10-year risk assessment of total cardiovascular events Unlike the PCE, SCORE2 stratifies into region-specific and age-specific risk groups
Screening Recommendations	Includes biomarkers such as C-reactive protein, Apo-B, lipoprotein(a) or Lp(a), and triglycerides Includes imaging screening recommendations such as CAC score if the decision about statin treatment is uncertain in intermediate and borderline-risk groups	Does not include biomarkers Recommends CAC imaging test Other imaging tests not included (based on concerns around availability and cost-effectiveness)
Diet Recommendations	DASH, Mediterranean, or plant-based diet	DASH, Mediterranean, or plant-based diet
Lifestyle Recommendations	Physical Activity: At least 150 minutes of moderate intensity or 75 minutes of vigorous-intensity aerobic physical activity per week Smoking: smoking cessation counseling and pharmacologic options Overweight/Obesity: caloric restriction	Physical Activity: At least 150-300 minutes of moderate intensity or 75-150 minutes of vigorous intensity aerobic activity per week; also recommends resistance training 2–3 days a week Smoking: smoking cessation counseling and pharmacologic options Overweight/Obesity: caloric restriction and pharmacologic options
Major Risk Factors	Smoking, dyslipidemia, family history of premature ASCVD, chronic inflammatory diseases, hypertension, or T2D	Non-HDL cholesterol, smoking, blood pressure, T2D, or adiposity
Risk Enhancers & Risk Modifiers	Age >65 years, high-risk ethnicities (South Asian), biomarkers associated with very high-risk, metabolic syndrome, family history, CKD, inflammatory conditions, infections, premature menopause (before age of 40), pregnancy-associated conditions	Ethnicity (ESC provides risk adjustments for certain ethnicities) Socioeconomic status, physical inactivity, frailty, social deprivation, obesity and central obesity, psychological stress, environmental exposure, atrial fibrillation, major psychiatric disorders, treatment for HIV, left ventricular hypertrophy, CKD, obstructive sleep apnea, non-alcoholic fatty liver disease, cancer, migraine, pregnancy-related hypertension, premature menopause, preeclampsia, polycystic ovary syndrome, erectile dysfunction
Treatment Recommendations	ACC/AHA uses a risk decision tree to guide treatment: Statin treatment recommended for the following groups: Patients ages 20-75 years and LDL-C ≥190 mg/dl or T2DM and age 40-75 years For those ages 40-75 years and LDL-C between 70 mg/dl and 190 mg/dl without diabetes, use of risk enhancing factors and risk discussions to determine best course For those 75 years and older, clinical assessment and/or risk discussions must occur	ESC uses more stringent LDL-C targets based on level of ASCVD risk Statin treatment for primary prevention in older people >_70 years of age may be considered, if at high risk or above Statins may be considered in people 40 years of age or below with type 1 or type 2 diabetes and/or an LDL-C level >100 mg/dL

In 2023, the AHA released a scientific statement on the need to move beyond individual risk factor management into a more comprehensive risk framework that would address the gaps from pooled cohort equations.[41] This statement advised consideration of cardiovascular-kidney-metabolic (CKM) cluster to assess CVD risk. People with chronic kidney disease (CKD) are more likely succumb to a CVD event than progress to end-stage kidney failure.[41]

The management of risk factors provides a proven approach to prevention of ASCVD events. Recent research has shown that the successful management of multiple risk factors can reduce risk of CVD events by > 50%, yet only 20% of patients reach the targeted reduction in key risk factors such as lipid levels, blood pressure, and blood sugar levels.[42] Indeed, the management of risk factors applies across the spectrum of inherited, genetically determined risk. Hence the urgency of addressing risk factor control through lifestyle management as well as introducing first-line therapies as needed.

Other Guidelines for CVD Prevention

- **2023 Chinese Guideline for Lipid Management**
- **2023 Statement from Lipid Association of India**
- **2023 National Institute for Health and Care Excellence (NICE)**
- **2022 U.S. Preventive Services Task Force (USPSTF) Statement**
- **2021 Canadian Cardiovascular Society Guidelines**
- **2021 PoLA/CFPiP/PCS/PSLD/PSD/PSH Guideline (Poland)**

Diet and Lifestyle

Diet and lifestyle management furnish the foundation of primary prevention of ASCVD. Lifestyle interventions apply to all, but particularly to those with greater ASCVD risk. Ninety percent of cardiovascular risks arise from modifiable risk factors, and more than half of these involve lifestyle behaviors including alcohol consumption, smoking, a sedentary lifestyle, stress, and an unhealthy diet.[43]

Lifestyle measures can mitigate CVD risk even in those genetically predisposed to conditions such as CAD. For example, adhering to a lifestyle by not smoking, partaking in physical activity, and consuming a healthy diet was associated with a decreased risk of coronary events, and a decreased subclinical burden of CAD, across all genetic risk categories.[9]

Engaging in regular physical activity can also trigger other changes in salutary lifestyle behaviors such as improving sleep, preventing future weight gain, and reducing anxiety. Lifestyle interventions have better efficacy when combined; for example, nutrition education plus physical activity demonstrated more weight reduction in patients.[44]

Gaping gaps exist between lifestyle guidelines and their implementation. Population-level interventions do not always work for individuals, and can depend on variables such as partner status, age, sex, and socioeconomic status. Maintaining a healthy weight is also difficult for many patients, and long-term weight reduction by diet has proven difficult to

sustain. The advent of effective weight loss drugs, such as the incretin mimetics, which appear to exert beneficial effects beyond reduced weight, may commit individuals to long-term pharmacotherapy, a prospect with daunting medical, societal, financial, and equity challenges. A proposed “Food is Medicine” approach offers a potential solution to this conundrum.[45]

The public needs a heightened awareness of the association between lifestyle and ASCVD risk. Developing prevention activities to include patient outreach and education can address some of these challenges. Confronting the increasing rates of childhood obesity through non-pharmacologic interventions such as health literacy and control of sugar-sweetened beverage may prove effective. Improving access to healthy foods and developing spaces for physical activity in workplaces and in other areas are also feasible solutions. Community-level programs such as peer-support groups can include information on physical activity, diet, and education on risk factors.[6] Other programs could include improving availability of fresh fruits and vegetables in "food desert" neighborhoods.

Diet and lifestyle interventions should consider both regional/population and individual characteristics, include multidisciplinary methods, a long-term outlook, and sustainable ways to measure progress.

> “Lifestyle is a key to prevention of atherosclerotic cardiovascular disease.”
>
> **~Peter Libby, MD**

Pharmacologic Approaches to Risk Reduction in Primary Prevention

To mitigate risk in many high-risk individuals, lifestyle measures alone may not suffice to achieve optimum avoidance of ASCVD events and have proven difficult to sustain in many cases. Statins furnish the first-line drug treatment for the primary prevention of ASCVD and have repeatedly shown overwhelming net benefits in individuals with broad categories of risk including in primary prevention. Overall, statins are well tolerated and can successfully reduce high LDL-C levels. Although risk reduction depends on the baseline LDL-C level, the ACC/AHA guidelines have given a rough estimate that a 1% lowering of LDL-C concentration corresponds to a 1% reduction in ASCVD risk.[8]

Statins have also proven cost effecting using the $50,000 threshold commonly used in high-income countries. A study of U.S. adults aged 45-75 years with a 10-year ASCVD risk threshold of 7.5% demonstrated a cost of $37,000 per quality-adjusted life year (QALY) gained.[45]

Statin prescribing patterns in primary prevention depend upon many factors, and can change based on variables such as ethnicity, CKD, HIV, age, and sex. Of note, pregnant women are advised against taking statins.[46]

Some considerations limit statin use. Guidelines vary on statin use for certain groups even after risk discussions, especially for younger people and people over the age of 75. Some call for more evidence on the benefits of statin therapy in the elderly and for titration to achieve target lipid levels.[47, 48]

Low statin adherence is common and more pronounced in women, minorities, younger adults, and older adults. Many people remain undiagnosed or untreated for high LDL-C for a variety of reasons. Unaware and untreated groups are more commonly younger adults, people with lower education attainment, lower income, and those who lack insurance coverage or ready access to primary care services.

Current data have generally not supported aspirin use in routine primary prevention, as stated by both ACC/AHA guidelines and the United States Preventive Services Task Force and is not recommended for adults >70 years or adults at increased risk of bleeding. Low-dose aspirin (75-100 mg orally daily) may be considered among adults 40-70 years of age who have higher risk ASCVD.[48, 49]

> “Several published studies report that compared to Caucasians, Chinese have a higher blood concentration of statins for a given dose and higher rate of side effects. Thus, Asian populations may require lower starting doses of statins than Western people, particularly in the elderly and frail.[50, 51, 52]”
>
> **~Dong Zhao, MD, PhD**

Therapies for Statin Intolerance and Statin Resistance

Some patients do not take statins due to side effects or due to an aversion or reluctance. Statin intolerance often arises from muscle symptoms (statin associated muscle symptoms, SAMS) such as pain or cramps. Randomized double blind studies have shown that many of these perceived SAMS result from the nocebo effect.[53, 54, 55]

Statins may accelerate the development of diabetes in those already prone to this condition, but as institution of statin therapy should be part of the preventive regimen of people with diabetes, this concern should not limit appropriate allocation of this drug class. Although there are effective alternatives, many statin intolerant patients do not receive treatment or adequate doses. The statin intolerant population also faces a higher risk of non-fatal cardiovascular events, and statin intolerance is associated with increased health care expenditures.[56] The non-statin ezetimibe lowers LDL-C by limiting absorption of cholesterol from the gut, and thus combines well with statins affording incremental event reduction.[57]

Nonstatin Agents for Management of LDL-C Related ASCVD Risk[58-61]

Bempedoic Acid

- Inhibits adenosine triphosphate citrate lyase, a liver enzyme involved in cholesterol synthesis
- Lowers risk of major adverse cardiac events including non-fatal stroke, non-fatal myocardial infarction and cardiovascular death
- 15-25% reduction in LDL-C

Ezitimibe

- Reduces cholesterol absorption in small intestine
- 18% (alone), 25% (when combined with statin therapy)

Bempedoic Acid & Ezetimibe

- Inhibits both cholesterol synthesis in the liver and cholesterol absorption in the intestine
- Up to 38% (when combined with statin therapy)

PCSK9 Inhibitors

- Monoclonal antibodies that bind to PCSK9 thereby increasing the number of LDL receptors
- 45-60%

Inclisiran

- siRNA that targets PCSK9 and inhibits its production in liver
- 48-52% (when combined with statin therapy)

Bile Acid Sequestrants (BAS)

- Non-absorbed polymer that binds to bile acids in the intestine, which increases hepatic metabolism of cholesterol and thereby lowers LDL-C levels
- 10-20% (alone), providing an additional 10-16% LDL-C lowering when combined with statins

> Whenever I have a patient complaining of muscle symptoms, I first question whether the symptoms are compatible with those usually associated with statins, and if there are other possible causes."
>
> **~Viviane Z. Rocha, MD**

Bempedoic acid is a novel non-statin LDL-C lowering therapy, which acts on the same pathway as statins. It is a pro-drug that requires metabolism to attain activity. Skeletal muscle lacks the activating enzyme, thus bempedoic acid offers an effective alternative for LDL-C lowering in individuals with statin intolerance or reluctance due to SAMS.[58] Bempedoic acid also lowers inflammation, a contributor to residual risk in statin-treated patients, as gauged by the biomarker of hsCRP.[59] The CLEAR outcomes trial for high-risk cardiovascular patients has shown that bempedoic acid can lower LDL-C by 20–30% and reduce events in those who won't take high dose statins. Combined with ezetimibe, bempedoic acid lowers LDL-C by 40–50%.[62]

The pre-specified analysis of the primary prevention cohort within CLEAR outcomes showed a mortality reduction and a striking preventive effect in women.[63]

Many patients experience CVD events or have a persistently high LDL-C level despite statin treatment. These patients can benefit from statin alternatives or combination therapies. The addition of ezetimibe or proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors to statins can effectively lower LDL-C in statin-treated patients and provide incremental reduction of CVD events, as shown by large studies with the anti-PCSK9 antibodies alirocumab or evolocumab.[62]

> The prescription of a PCSK9 inhibitor has been an effective alternative for some of my high-risk patients who cannot take a statin. I think it is important to avoid inertia and reinforce to the patient the proper prescription of lipid-lowering therapy in every consultation."
>
> **~Viviane Z. Rocha, MD**

The field of lipid management has recently witnessed many innovations and developments. Bempedoic acid tablets and bempedoic acid/ezetimibe combination tablets were recently approved for primary prevention by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) with expanded indications for adults with primary hyperlipidemia.[64] Other new therapies include inclisiran, a hepatocyte-targeted small interfering RNA directed against PCSK9 messenger RNA. This agent can be given only twice a year, or even once a year in primary prevention, and affords a sustained lowering of LDL-C.[65] Its efficacy in event reduction is under evaluation in a large phase 3 study underway. Novel therapies are also emerging including gene editing approaches and an orally active PCSK9 inhibitor, which might improve adherence.[66, 67] Other novel biological agents that improve the lipid profile target apolipoprotein C3 or angiopoietin-like 3 or 4.[66]

Genetic editing using CRISPR technology could take this one step further with a single lifetime treatment through editing specific genes, such as the PCSK9 gene.[67] Therapies based on RNA technology that target the independent risk factor Lp(a) are in advanced clinical development.[68]

Thus, the future of lipid therapies holds considerable promise, and emerging evidence supports their efficacy in lowering LDL-C levels when used as alternatives or adjuncts to statin therapy. Practitioners can seek to improve access to these treatments, especially for vulnerable and disadvantaged populations. Programs aimed at expanding access to innovative therapies have proven successful in the past; for example, providing medication against drug-resistant tuberculosis or HIV in low-income countries. Programs and policies can also emphasize the use of less expensive generics along with a healthy lifestyle, as an alternative to the newer and more expensive treatments for which payers and health systems can limit access.

Reaching Primary Prevention Targets

Most countries fail to reach risk factor targets, such as lowering LDL-C levels, and fall short of implementing guideline recommendations. Four cross-sectional surveys evaluated guideline implementation in Europe: The European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EuroAspire). The most recent survey, EuroAspire IV, showed persistent high rates of smoking, low rates of physical activity, prevalent obesity, and inadequate control of blood pressure, glucose, and lipids, even with cardioprotective drugs.[89] The survey also showed variations in lifestyle, risk factor prevalences, and medication usage across European countries.[90] There is a large unmet need to update the guidelines and effectively apply them in a systematic and comprehensive manner for at-risk populations.

Formulation of guidelines across countries should reflect awareness of epidemiological data relevant to the specific population in question. As noted previously, certain Asian populations may require lower doses of pharmacologic agents. Compared to similar at-risk populations in the U.S., Asian Indians develop ASCVD a decade earlier, although they have lower LDL-C levels and therefore may merit lower LDL-C goals.[80, 91] South Asians also tolerate visceral adiposity more poorly than Western populations, thus the International Diabetes Foundation has promulgated lower cutoffs for waist circumference in Asians than in Caucasians.

> We have this barrier in Europe; very clear data from clinical practice that show the rate of success in reaching LDL-C targets still remains quite low."
>
> **~Manfredi Rizzo, MD, PhD**

Examples of Barriers

	BRAZIL	INDIA	ITALY
Health Systems	The health system consists of Sistema Único de Salud (SU.S.) or the Unified Health System, which is the largest government run public health care system in the world and offers universal healthcare access. However, this is largely underfunded. There is also a supplementary private healthcare system used by a smaller percentage of the population, mostly older adults. Both the public and private systems have little focus on CVD prevention.[84, 85] There is minimal integration between public and private health sectors and poor knowledge sharing about patient risks and treatment within these systems.[85]	Treatment of key CVD risk factors (hypertension and diabetes) is very poor, and only one-fifth of those diagnosed with either condition have their blood pressure or glucose levels under control.[76] There are competing priorities in health systems with limited resources, and a greater focus on older public health concerns of infectious diseases and maternal/child health, and a growing burden of chronic diseases such as diabetes, obesity, and hypertension.[78] There is a lack of early and aggressive primary prevention interventions and from which Indians would greatly benefit.[76]	High- and very-high-risk populations are under-treated by providers, and those that are treated with a lipid-lowering therapy (LLT) are not reaching LDL-C targets set forth by the ESC Guidelines. There is also large underutilization of combination therapies in high- and very-high-risk groups and underestimation of overall risk in these groups.[70] There is no national plan or strategy to specifically address CVD and its risk factors, despite advances made by public programs such as banning smoking in public places and regulating amount of salt in bread.[71, 72] The National Health Services (NHS) offers universal coverage free of charge and includes cardiovascular prevention, but there are large discrepancies in standard-of-care across different regions. Care can also be politicized and bureaucratic based on the size of the hospital.[69]
Awareness	CVD is not recognized as critical on the national level, and emphasis is on hypertension, diabetes, obesity, and smoking with little focus on high cholesterol levels. There is also minimal attention on lifestyle changes for either prevention or management.[87, 88]	There is little awareness from both the public and from healthcare practitioners on the lifetime risk of ASCVD and the efficacy of statins.[77] There is conflicting evidence on which molecule offers accurate prediction of ASCVD/CVD risk in Indians, especially in people already on statins. Commonly used risk scores poorly estimate ASCVD risk in Indians.[77, 79, 80] There is a lack of CVD knowledge especially in lower income and in youth populations.[82, 83]	There is a low perception of cardiovascular risk in Italy, especially among women.[73]
Affordability & Availability	The public health system is poorly funded.[85] Health care providers are distributed unevenly across the country and between the public and private systems, making prevention services difficult to access.[85] Cost of many recommended statins for ASCVD are only affordable for 3% of Brazilian households.[14]	India has a very wide range of socioeconomic levels and an uneven distribution of providers and facilities.[78] Most CVD care is provided by private secondary and tertiary centers that are accessible only to the small number of patients who can afford it; most of the preventive services are in urban areas, and only 13% of the rural population has access to a primary care facility.[78] There is a lack of cardiologists, and a huge shortage of nurses in rural areas, which affects preventive CVD services.[78]	Screening and testing equipment are widely available but are often obsolete and underused.[69]
Adherence	Adherence to treatment and lifestyle changes are low both before and after a CVD event, and SU.S. has no clear guidelines on statin use.[86] Adherence issues partly stem from limited access and physician scarcity in poorer regions.[87]	Statins are widely available at a low-cost but are under prescribed and under used.[79, 80] There are concerns of statin side effects in the general population.[77] High-dose statins are under-utilized in India, and there is a misconception that because of low baseline LDL-C levels in Indians, that only low-intensity statins are required.[81]	Italy has relatively low statin use compared to other European countries.[74, 75] Statin adherence has been negatively affected by Italian reimbursement policies in the past.[74] There is a higher adherence with high-intensity statin use versus low-to-moderate intensity statins.[74]

The Role of Healthcare Providers

Healthcare providers have a leading role in ASCVD prevention through screening and risk assessments, diet and lifestyle recommendations, and treatment regimens. They should also convey risk to individuals. Clear and culturally sensitive communication between providers and patients calibrated to educational level can foster trust and facilitate more effective management and follow-up.

Many healthcare providers do not prescribe statins for patients with diagnosed elevated LDL-C levels in a timely manner. For example, a large retrospective study of a health system showed that in patients with severe hyperlipidemia (LDL-C > 190 mg/dL), 41% were not prescribed or recommended for statin or another lipid-lowering treatment within three months of an LDL-C measurement.[92] The same study also revealed that only 13% of these patients were referred to a specialist within three months of their elevated LDL-C result. Among those with LDL-C values >220 mg/dL who had not previously seen a specialist, only 16% received such a referral.[92]

A multidisciplinary approach can address many of these gaps. Using a multidisciplinary care team, which can include cardiologists, endocrinologists, primary care providers, nurses and other health professionals, can emphasize and help implement comprehensive lifestyle and risk factor management. Pediatricians and adolescent medicine specialists have a particularly integral role in this framework in the context of primary prevention, as childhood obesity is a major risk factor for ASCVD. These providers should participate pivotally in the early identification of genetically determined LDL-C elevations. This approach can also strengthen long-term monitoring and follow-up of patients.

> Patients must be evaluated regularly with follow-up. In the care of these patients, each provider has a role, and we are a team altogether."
>
> **~Manfredi Rizzo, MD, PhD**

Recommendation for best practices in screening and treatment vary and can overlook certain groups.[93] For example, younger populations from 18-39 years of age with elevated LDL-C have magnified risk for ASCVD later in life, yet most do not receive treatment or lifestyle interventions.[94]

> For risk factor management in childhood obesity, lipid profiles are seldom ordered. It is important to start monitoring very early since we're talking about duration of exposure."
>
> **~Viviane Z. Rocha, MD**

People with FH also receive inadequate treatment, especially women and children.[95] Some physicians view prevention guidelines as too complex and cumbersome for stratifying patient risk in daily practice.[37] Efforts to streamline risk assessments and flag overlooked groups can leverage electronic medical records or using other technologies.[96] Large electronic medical record datasets can serve to collate information on race, ethnicity, socioeconomic level, biomarkers, and geography for risk models.[97] EMRs can also help identify children and adolescents with FH, as well as their relatives.[97]

Providers can offer educational resources and empower patients to take an active role in managing their cardiovascular health. They can also emphasize individualized lifestyle recommendations tailored to the patient based on tobacco and alcohol use, physical activity and sleep levels, socioeconomic status, and stress levels. The challenges of screening and treating all at-risk individuals, and long-term monitoring and follow-up require reinforced patient-provider communication and implementation by a multidisciplinary care team.

A Multidisciplinary ASCVD Team Can Include Many Providers

- Primary Care Physicians
- Cardiologist
- Pediatrician
- Nutritionist or Physiologist
- Nurse & EMR Staff
- Endocrinologist
- Geriatician
- OB/GYN
- Therapist or Psychologist

Conclusion

ASCVD prevalence is increasing globally and emerging earlier and in younger populations. ASCVD places a large burden on health care systems, economies, and reduces quality of life and longevity through its many complications and cardiovascular events. Effective management of this lifelong condition extends from prevention strategies in youth to the elderly. ASCVD often remains asymptomatic until an acute event, mandating an emphasis on early prevention and management of modifiable risk factors. Health systems and CVD organizations worldwide should strive to improve implementation and adherence of these preventive measures. The entire health care community should mobilize to close the gap in effective identification and treatment of individuals with ASCVD risk across the lifespan.

ASCVD has a cumulative lifetime risk, and at-risk patients merit ongoing evaluation. A multidisciplinary approach should enhance communication, trust, and follow-up for long-term prevention and treatment. EMR systems can help identify at-risk patients. Statins are generally well tolerated and affordable. For those unwilling or unable to take statins, fortunately an expanding palette of therapies has become available. Achievement of desirable LDL-C goals in high-risk individuals may require more advanced and hence expensive therapies. All stakeholders should strive to enable the availability of and access to these therapies in an equitable manner. Evolving primary prevention measures could enable major inroads in combatting ASCVD, if healthcare providers globally could integrate new treatments with standard care and policymakers could make them available to all who could benefit.

IAS' Clinical Proceedings

Established in 1979, the International Atherosclerosis Society is a global network of the world's leading atherosclerotic cardiovascular disease experts who collaborate to develop mission-centered programming that spans geographical and generational boundaries. IAS' Clinical Proceedings — a white paper series — are informational resources intended to raise awareness and address unmet needs in atherosclerosis.

IAS recognizes the expert panel members who contributed to the development of this white paper.

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References

1. Naghavi M, Maron DJ, Kloner RA, et al. Coronary artery calcium testing: A call for universal coverage. *Preventive Medicine Reports*. 2019;15:100879. doi:10.1016/j.pmedr.2019.100879
2. National Institutes of Health (NIH). What is atherosclerosis? National Heart Lung and Blood Institute. Published March 24, 2022. Accessed June 1, 2024. https://www.nhlbi.nih.gov/health/atherosclerosis
3. Libby P. Inflammation during the life cycle of the atherosclerotic plaque. *Cardiovascular Research*. 2021;117(13):2525-2536. doi:10.1093/cvr/cvab303
4. American Heart Association. Accessed June 1, 2024. https://www.heart.org/en/health-topics/cholesterol
5. Ray KK, Ference BA, Séverin T, et al. World Heart Federation Cholesterol Roadmap 2022. *Global Heart*. 2022;17(1):75. doi:10.5334/gh.1154
6. Libby P, Pinkosky SL, Nissen SE. Conquering cholesterol: a report from the front lines. *Cardiovascular Research*. 2023;119(17):e160-e163. doi:10.1093/cvr/cvad152
7. Mann HK, Magnani JW, Johnson AE. Health Literacy is Essential to ASCVD Prevention in Youth. *Current Atherosclerosis Reports*. 2023;25(4):113-118. doi:10.1007/s11883-023-01086-2
8. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2019;73(24):3168-3209. doi:10.1016/j.jacc.2018.11.002
9. Khera AV, Emdin CA, Drake I, et al. Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. *New England Journal of Medicine*. 2016;375(24):2349-2358. doi:10.1056/NEJMoa1605086
10. Lindstrom M, DeCleene N, Dorsey H, et al. Global Burden of Cardiovascular Diseases and Risks Collaboration, 1990-2021. *Journal of the American College of Cardiology*. 2022;80(25):2372-2425. doi:10.1016/j.jacc.2022.11.001
11. Wright RS, Ray KK, Raal FJ, et al. Pooled Patient-Level Analysis of Inclisiran Trials in Patients with Familial Hypercholesterolemia or Atherosclerosis. *Journal of the American College of Cardiology*. 2021;77(9):1182-1193. doi:10.1016/j.jacc.2020.12.058
12. Angell SY, McConnell MV, Anderson CAM, et al. The American Heart Association 2030 Impact Goal: A Presidential Advisory from the American Heart Association. *Circulation*. 2020;141(9):e120-e138. doi:10.1161/CIR.0000000000000758
13. Fuster V. Changing Demographics: A New Approach to Global Health Care Due to the Aging Population. *Journal of the American College of Cardiology*. 2017;69(24):3002-3005. doi:10.1016/j.jacc.2017.05.013
14. Corral P, Pavia Lopez A, Giunta G, et al. ASCVD in LATAM: A Call for Action on LDL-C Reduction. *Authorea*. 2021. doi: 10.22541/au.161548923.32347892/v1
15. Gupta K, Modi S, Ananthasubramaniam K. Toward Understanding Cardiovascular Risk Burden in South Asians: A Major Step Forward. *JACC Asia*. 2022;2(7):912-915. doi:10.1016/j.jacasi.2022.10.005
16. Kassam N, Surani S, Hameed K, et al. Magnitude, Distribution and Contextual Risk Enhancing Predictors of High 10-Year Cardiovascular Risk Among Diabetic Patients in Tanzania. *Patient Related Outcome Measures*. 2023;14:87-96. doi:10.2147/PROM.S405392
17. Minja NW, Nakagaayi D, Aliku T, et al. Cardiovascular diseases in Africa in the twenty-first century: Gaps and priorities going forward. *Front Cardiovascular Medicine*. 2022;9:1008335. doi:10.3389/fcvm.2022.1008335
18. Rittiphairoj T, Reilly A, Reddy CL, et al. The State of Cardiovascular Disease in G20+ countries. Health Systems Innovation Lab, Harvard University, May 2022. doi:10.54111/0001/HSIL/cvdg20
19. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646. doi:10.1161/CIR.0000000000000678
20. Sikand G, Severson T. Top 10 dietary strategies for atherosclerotic cardiovascular risk reduction. *American Journal of Preventive Cardiology*. 2020;4:100106. doi:10.1016/j.ajpc.2020.100106
21. Khera R, Valero-Elizondo J, Nasir K. Financial Toxicity in Atherosclerotic Cardiovascular Disease in the United States: Current State and Future Directions. *Journal of the American Heart Association*. 2020;9(19):e017793. doi:10.1161/JAHA.120.017793
22. Valero-Elizondo J, Khera R, Saxena A, et al. Financial Hardship from Medical Bills Among Nonelderly U.S. Adults with Atherosclerotic Cardiovascular Disease. *Journal of the American College of Cardiology*. 2019;73(6):727-732. doi:10.1016/j.jacc.2018.12.004
23. Chapman MJ, Zamorano JL, Parhofer KG. Reducing residual cardiovascular risk in Europe: Therapeutic implications of European medicines agency approval of icosapent ethyl/eicosapentaenoic acid. *Pharmacology & Therapeutics*. 2022;237:108172. doi:10.1016/j.pharmthera.2022.108172
24. Steen Carlsson K, Nilsson K, Wolden ML, et al. Economic burden of atherosclerotic cardiovascular disease: a matched case-control study in more than 450,000 Swedish individuals. *BMC Cardiovascular Disorders*. 2023;23(1):483. doi:10.1186/s12872-023-03518-y
25. Ferrara P, Di Laura D, Cortesi PA, et al. The economic impact of hypercholesterolemia and mixed dyslipidemia: A systematic review of cost of illness studies. *PLoS One*. 2021;16(7):e0254631. doi:10.1371/journal.pone.0254631
26. Garshick M, Underberg JA. The Use of Primary Prevention Statin Therapy in Those Predisposed to Atherosclerosis. *Current Atherosclerosis Reports*. 2017;19(12):48. doi:10.1007/s11883-017-0685-7
27. Underberg J, Toth PP, Rodriguez F. LDL-C target attainment in secondary prevention of ASCVD in the United States: barriers, consequences of nonachievement, and strategies to reach goals. *Postgraduate Medicine*. 2022;134(8):752-762. doi:10.1080/00325481.2022.2117498

28. McDermott M, Meah MN, Khaing P, et al. Rationale and Design of SCOT-HEART 2 Trial: CT Angiography for the Prevention of Myocardial Infarction. *JACC Cardiovascular Imaging*. 2024;17(9):1101-1112. doi:10.1016/j.jcmg.2024.05.016

29. Chan K, Wahome E, Tsiachristas A, et al. Inflammatory risk and cardiovascular events in patients without obstructive coronary artery disease: the ORFAN multicentre, longitudinal cohort study. *Lancet*. 2024;403(10444):2606-2618. doi:10.1016/S0140-6736(24)00596-8

30. Weber LA, Cheezum MK, Reese JM, et al. Cardiovascular Imaging for the Primary Prevention of Atherosclerotic Cardiovascular Disease Events. *Current Cardiovascular Imaging Reports*. 2015;8(9):36. doi:10.1007/s12410-015-9351-z

31. Grant JK, Orringer CE. Coronary and Extra-coronary Subclinical Atherosclerosis to Guide Lipid-Lowering Therapy. *Current Atherosclerosis Reports*. 2023;25(12):911-920. doi:10.1007/s11883-023-01161-8

32. Fegers-Wustrow I, Gianos E, Halle M, et al. Comparison of American and European Guidelines for Primary Prevention of Cardiovascular Disease: JACC Guideline Comparison. *Journal of the American College of Cardiology*. 2022;79(13):1304-1313. doi:10.1016/j.jacc.2022.02.001

33. Ibanez B, Fernández-Ortiz A, Fernández-Friera L, et al. Progression of Early Subclinical Atherosclerosis (PESA) Study: JACC Focus Seminar 7/8. *Journal of the American College of Cardiology*. 2021;78(2):156-179. doi:10.1016/j.jacc.2021.05.011

34. Navickas P, Lukavičiūtė L, Glaveckaitė S, et al. Navigating the Landscape of Cardiovascular Risk Scores: A Comparative Analysis of Eight Risk Prediction Models in a High-Risk Cohort in Lithuania. *Journal of Clinical Medicine*. 2024;13(6):1806. doi:10.3390/jcm13061806

35. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. 2007;297(6):611-619. doi:10.1001/jama.297.6.611

36. Natarajan P, Young R, Stitziel NO, et al. Polygenic Risk Score Identifies Subgroup with Higher Burden of Atherosclerosis and Greater Relative Benefit from Statin Therapy in the Primary Prevention Setting. *Circulation*. 2017;135(22):2091-2101. doi:10.1161/CIRCULATION AHA.116.024436

37. Banach M, Surma S, Reiner Z, et al. Personalized management of dyslipidemias in patients with diabetes-it is time for a new approach (2022). *Cardiovascular Diabetology*. 2022;21(1):263. doi:10.1186/s12933-022-01684-5

38. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):937-952. doi:10.1016/S0140-6736(04)17018-9

39. Teo KK, Liu L, Chow CK, et al. Potentially modifiable risk factors associated with myocardial infarction in China: the INTERHEART China study. *Heart*. 2009;95(22):1857-1864. doi:10.1136/hrt.2008.155796

40. Rose G. Sick individuals and sick populations. International *Journal of Epidemiology*. 2001;30(3):427-434. doi:10.1093/ije/30.3.427

41. Khan SS, Coresh J, Pencina MJ, et al. Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health: A Scientific Statement from the American Heart Association. *Circulation*. 2023;148(24):1982-2004. doi:10.1161/CIR.0000000000001191

42. Wong ND, Sattar N. Cardiovascular risk in diabetes mellitus: epidemiology, assessment and prevention. *Nature Reviews Cardiology*. 2023;20(10):685-695. doi:10.1038/s41569-023-00877-z

43. Van Trier TJ, Mohammadnia N, Snaterse M, et al. Lifestyle management to prevent atherosclerotic cardiovascular disease: evidence and challenges. *Netherlands Heart Journal*. 2022;30(1):3-14. doi:10.1007/s12471-021-01642-y

44. Kris-Etherton PM, Sapp PA, Riley TM, et al. The Dynamic Interplay of Healthy Lifestyle Behaviors for Cardiovascular Health. *Current Atherosclerosis Reports*. 2022;24(12):969-980. doi:10.1007/s11883-022-01068-w

45. Mozaffarian D, Aspry KE, Garfield K, et al. "Food Is Medicine" Strategies for Nutrition Security and Cardiometabolic Health Equity: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*. 2024;83(8):843-864. doi:10.1016/j.jacc.2023.12.023

46. Pandya A, Sy S, Cho S, et al. Cost-effectiveness of 10-Year Risk Thresholds for Initiation of Statin Therapy for Primary Prevention of Cardiovascular Disease. *JAMA*. 2015;314(2):142-150. doi:10.1001/jama.2015.6822

47. Nanna MG, Navar AM, Wojdyla D, et al. The Association Between Low-Density Lipoprotein Cholesterol and Incident Atherosclerotic Cardiovascular Disease in Older Adults: Results from the National Institutes of Health Pooled Cohorts. *Journal of the American Geriatrics Society*. 2019;67(12):2560-2567. doi:10.1111/jgs.16123

48. Leya M, Stone NJ. Statin Prescribing in the Elderly: Special Considerations. *Current Atherosclerosis Reports*. 2017;19(11):47. doi:10.1007/s11883-017-0683-9

49. U.S. Preventive Services Task Force, Mangione CM, Barry MJ, et al. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: U.S. Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;328(8):746-753. doi:10.1001/jama.2022.13044

50. Wang P. Statin dose in Asians: is pharmacogenetics relevant? *Pharmacogenomics*. 2011; 12(11):1605–1615. doi: 10.2217/pgs.11.98 PMID: 22044416

51. Liao J. Safety and efficacy of statins in Asians. *The American Journal of Cardiology*. 2007; 99(3):410–414. PMID: 17261409

52. Lee E, Ryan S, Birmingham B et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clinical Pharmacology & amp; Therapeutics*. 2005; 78(4):330–341

53. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab in statin-intolerant patients over 3 years: open-label treatment period of the ODYSSEY ALTERNATIVE trial. *Journal of Clinical Lipidology*. 2020 Jan-Feb;14(1):88-97. e2. doi: 10.1016/j.jacl.2020.01.001.

54. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients with Muscle-Related Statin Intolerance: The GAU.S.S-3 Randomized Clinical Trial. *JAMA*. 2016 Apr 19;315(15):1580-90. doi: 10.1001/jama.2016.3608

55. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New England Journal of Medicine*. 2008 Nov 20;359(21):2195-207. doi: 10.1056/NEJMoa0807646.

56. Graham JH, Sanchez RJ, Saseen JJ, et al. Clinical and economic consequences of statin intolerance in the United States: Results from an integrated health system. *Journal of Clinical Lipidology*. 2017;11(1):70-79.e1. doi:10.1016/j.jacl.2016.10.003

57. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *New England Journal of Medicine*. 2015;372(25):2387-2397. doi:10.1056/NEJMoa1410489

58. Writing Committee, Lloyd-Jones DM, Morris PB, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. *Journal of the American College of Cardiology*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

59. The ABC's of Bempedoic Acid for Cardiovascular Health. International Atherosclerosis Society. Published February 2024. Accessed June 1, 2024. https://athero.org/wp-content/uploads/2024/02/IAS_The-ABCs-of-Bempedoic-Acid_Infographic_February-2024.pdf

60. Esperion. Esperion Announces Pooled Analysis from Phase 3 LDL-C Lowering Clinical Development Program of NEXLETOL™ (Bempedoic Acid) Tablets Presented at the American Diabetes Association 80th Scientific Sessions. Published June 14, 2020. Accessed August 1, 2024. https://www.esperion.com/news-releases/news-release-details/esperion-announces-pooled-analysis-phase-3-ldl-c-lowering

61. Ross S, D'Mello M, Anand SS, et al. Effect of Bile Acid Sequestrants on the Risk of Cardiovascular Events: A Mendelian Randomization Analysis. *Circulation: Cardiovascular Genetics*. 2015;8(4):618-627. doi:10.1161/CIRCGENETICS.114.000952

62. Abrahams T, Nelson AJ, Nicholls SJ. How Will Our Practice Change After the CLEAR Outcomes Trial? *Current Atherosclerosis Reports*. 2024;26(3):83-89. doi:10.1007/s11883-024-01188-5

63. Nissen SE, Menon V, Nicholls SJ, et al. Bempedoic Acid for Primary Prevention of Cardiovascular Events in Statin-Intolerant Patients. *JAMA*. 2023;330(2):131-140. doi:10.1001/jama.2023.9696

64. Esperion. U.S. FDA Updates LDL-C Lowering Indication for Esperion's NEXLETOL® (bempedoic acid) Tablet and NEXLIZET® (bempedoic acid and ezetimibe) Tablet. Published December 13, 2023. Accessed June 1, 2024. https://www.esperion.com/news-releases/news-release-details/us-fda-updates-ldl-c-lowering-indication-esperions-nexletolr

65. Nishikido T. Clinical potential of inclisiran for patients with a high risk of atherosclerotic cardiovascular disease. *Cardiovascular Diabetology*. 2023;22(1):20. doi:10.1186/s12933-023-01752-4

66. Tokgözoğlu L, Libby P. The dawn of a new era of targeted lipid-lowering therapies. *European Heart Journal*. 2022;43(34):3198-3208. doi:10.1093/eurheartj/ehab841

67. American Heart Association. A single infusion of a gene-editing medicine may control inherited high LDL cholesterol. American Heart Association Scientific Sessions 2023. Published November 12, 2023. Accessed June 1, 2024. https://newsroom.heart.org/news/a-single-infusion-of-a-gene-editing-medicine-may-control-inherited-high-ldl-cholesterol.

68. Sosnowska B, Surma S, Banach M. Targeted Treatment against Lipoprotein (a): The Coming Breakthrough in Lipid Lowering Therapy. *Pharmaceuticals* (Basel). 2022;15(12):1573. doi:10.3390/ph15121573

69. Indolfi C, Esposito G. Universal Health Care System and Cardiovascular Disease Burden in Italy. *Circulation*. 2022;145(8):559-561. doi:10.1161/CIRCULATIONAHA.121.057496

70. Arca M, Calabro P, Solini A, et al. Lipid-lowering treatment and LDL-C goal attainment in high and very high cardiovascular risk patients: Evidence from the SANTORINI study—The Italian experience. *European Atherosclerosis Journal*. 2023;2(1).doi:10.56095/EAJ.V2I1.26

71. Giampaoli S, Palmieri L, Donfrancesco C, et al. Cardiovascular health in Italy. Ten-year surveillance of cardiovascular diseases and risk factors: Osservatorio Epidemiologico Cardiovascolare/Health Examination Survey 1998–2012. *European Journal of Preventive Cardiology*. 2015;22(2_suppl):9-37. doi:10.1177/2047487315589011

72. Cardiovascular Disease Scorecard. World Heart Federation. Published October 2022. https://world-heart-federation.org/wp-content/uploads/CVD-Scorecard-Italia.pdf

73. Maffei S, Meloni A, Deidda M, et al. Cardiovascular Risk Perception and Knowledge among Italian Women: Lessons from IGENDA Protocol. *Journal of Clinical Medicine*. 2022;11(6):1695. Published 2022 Mar 18. doi:10.3390/jcm11061695

74. Arca M, Ansell D, Averna M, et al. Statin utilization and lipid goal attainment in high or very-high cardiovascular risk patients: Insights from Italian general practice. *Atherosclerosis*. 2018;271:120-127. doi:10.1016/j.atherosclerosis.2018.02.024

75. Maggioni AP, Calabria S, Rossi E, et al. Use of lipid lowering drugs in patients at very high risk of cardiovascular events: An analysis on nearly 3,000,000 Italian subjects of the ARNO Observatory. *International Journal of Cardiology*. 2017;(246):62-67. doi:10.1016/j.ijcard.2017.02.108.

76. Kalra A, Jose AP, Prabhakaran P, et al. The burgeoning cardiovascular disease epidemic in Indians - perspectives on contextual factors and potential solutions. *Lancet Regional Health - Southeast Asia*. 2023;12:100156. doi:10.1016/j.lansea.2023.100156

77. Enas EA, Varkey B, Gupta R. Expanding statin use for prevention of ASCVD in Indians: Reasoned and simplified proposals. *Indian Heart Journal*. 2020;72(2):65-69. doi:10.1016/j.ihj.2020.03.015

78. Prabhakaran D, Jaacks LM. Reflections From India on Scaling Up Risk Factor Control for Cardiovascular Diseases to Reach 1 Billion Adults. *Circulation*. 2019;139(1):4-6. doi:10.1161/CIRCULATION AHA.118.035975

79. Menon AS, Kotwal N, Singh Y, et al. Statins: Cholesterol guidelines and Indian perspective. *Indian Journal of Endocrinology and Metabolism*. 2015;19(5):546-553. doi:10.4103/2230-8210.163105

80. Puri R, Bansal M, Mehta V, et al. Lipid Association of India 2023 update on cardiovascular risk assessment and lipid management in Indian patients: Consensus statement IV. *Journal of Clinical Lipidology*. Published online February 8, 2024. doi:10.1016/j.jacl.2024.01.006

81. Davidson MH. Intensive statin therapy in India: Demonstrating efficacy and safety. *Indian Heart Journal*. 2016;68(6):756-757. doi:10.1016/j.ihj.2016.09.006

82. Krupp K, Wilcox ML, Srinivas A, et al. Cardiovascular Risk Factor Knowledge and Behaviors Among Low-Income Urban Women in Mysore, India. *Journal of Cardiovascular Nursing*. 2020;35(6):588-598. doi:10.1097/JCN.0000000000000657

83. Bhat V, Coates R, Shanbhag D, et al. Impact of a simple educational intervention on awareness regarding cardiovascular disease among school-going adolescents in a rural area of Bengaluru district, India. *Journal of Education and Health Promotion*. 2023;12:19. Published 2023 Jan 31. doi:10.4103/jehp.jehp_965_22

84. de Araújo JM, Eufrosino de Alencar Rodrigues R, da Costa Pereira de Arruda Neta A, et al. The direct and indirect costs of cardiovascular diseases in Brazil. *PLoS One*. 2022;17(12):e0278891. doi:10.1371/journal.pone.0278891

85. Ribeiro AL, Duncan BB, Brant LC, et al. Cardiovascular Health in Brazil: Trends and Perspectives. *Circulation*. 2016;133(4):422-433. doi:10.1161/CIRCULATIONAHA.114.008727

86. do Nascimento RCRM, Guerra AA Jr, Alvares J, et al. Statin use in Brazil: findings and implications. *Current Medical Research Opinion*. 2018;34(10):1809-1817. doi:10.1080/03007995.2018.1451312

87. Mota D, Mattos AC, Oliveira G, et al. The Need for Brazil to Focus on CVD. *Global Heart*. 2016;11(4):439-440. doi:10.1016/j.gheart.2016.10.001

88. Bartlett ES, Flor LS, Medeiros DS, et al. Public knowledge of cardiovascular disease and response to acute cardiac events in three municipalities in Brazil. *Open Heart*. 2020;7(2):e001322. doi:10.1136/openhrt-2020-001322

89. Kotseva K, EUROASPIRE Investigators. The EUROASPIRE surveys: lessons learned in cardiovascular disease prevention. *Cardiovascular Diagnosis and Therapy*. 2017;7(6):633-639. doi:10.21037/cdt.2017.04.06

90. McEvoy JW, Jennings C, Kotseva K, et al. Variation in Secondary Prevention of Coronary Heart Disease: The INTERASPIRE Study. *European Heart Journal*. Published online August 30, 2024. doi:10.1093/eurheartj/ehae558

91. Sreeniwas Kumar A, Sinha N. Cardiovascular disease in India: A 360-degree overview. *Medical Journal Armed Forces India*. 2020;76(1):1-3. doi:10.1016/j.mjafi.2019.12.005

92. Jackson CL, Ahmad Z, Das SR, et al. The evaluation and management of patients with LDL-C ≥ 190 mg/dL in a large health care system. *American Journal of Preventive Cardiology*. 2020;1:100002. doi:10.1016/j.ajpc.2020.100002

93. Harris E. High LDL Cholesterol Has Decreased Since 1999. *JAMA*. 2023;330(21):2044. doi:10.1001/jama.2023.22354

94. Kohli-Lynch CN, Bellows BK, Zhang Y, et al. Cost-Effectiveness of Lipid-Lowering Treatments in Young Adults. *Journal of the American College of Cardiology*. 2021;78(20):1954-1964. doi:10.1016/j.jacc.2021.08.065

95. Watts GF, Gidding SS, Hegele RA, et al. International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia. *Nature Reviews Cardiology*. 2023;20(12):845-869. doi:10.1038/s41569-023-00892-0

96. Petrazzini BO, Chaudhary K, Márquez-Luna C, et al. Coronary Risk Estimation Based on Clinical Data in Electronic Health Records. *Journal of the American College of Cardiology*. 2022;79(12):1155-1166. doi:10.1016/j.jacc.2022.01.021

97. Pepplinkhuizen S, Ibrahim S, Vink R, et al. Electronic health records to facilitate continuous detection of familial hypercholesterolemia. *Atherosclerosis*. 2020;310:83-87. doi:10.1016/j.atherosclerosis.2020.07.022