VIEWPOINT

# Lifetime Perspectives on Primary Prevention of Atherosclerotic Cardiovascular Disease

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**Despite expanding primary prevention** efforts, the majority of individuals will develop cardiovascular disease (CVD) during their lifetime.[1,2] The discordance between short-term (10-year) and long-term (30-year to lifetime) cardiovascular risk is well established and is now reflected in the most recent clinical practice guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) on lipid-lowering treatment for primary prevention of atherosclerotic CVD (ASCVD).[3,4] Specifically, these guidelines recommend that lifetime risk estimation can be used as a communication strategy for adults younger than 60 years who are free of ASCVD and not candidates for lipid-lowering therapy. Although a high lifetime ASCVD risk has not been recommended as a class I indication for lipid-lowering treatment, the acknowledgment of lifetime risk in the guidelines indicates a more comprehensive awareness of the importance of prevention of ASCVD over a life span.

Risk estimation remains an imperfect science. However, by focusing on the key elements of risk prediction over a lifetime—the treatment thresholds, risk factor trajectories, and predicted outcome—advances can be made to more accurately identify individuals at an increased lifetime ASCVD risk to tailor optimal primary prevention strategies.

## Treating a "Lifetime Risk Equivalent"

For decades, guidelines have recommended lipid-lowering therapy for individuals with a low-density lipoprotein cholesterol (LDL-C) level of 190 mg/dL (4.9 mmol/L) or higher, irrespective of short-term risk, because these individuals have a "high lifetime risk for ASCVD."[3] Treatment is recommended for these individuals because of the cumulative effects of a lifetime exposure to high LDL-C. This recommendation is not based on clinical trial data, as no primary prevention trial testing the effect of statin therapy on cardiovascular end points has included only individuals with LDL-C levels of 190 mg/dL or higher.[3] In addition, this recommendation is also not based on a strategy to identify patients with heterozygous familial hypercholesterolemia.

Although a high lifetime risk represents the primary rationale for treatment of an LDL-C level of 190 mg/dL or higher, an elevated LDL-C level is not the only cause of a high lifetime risk. Hypertension, diabetes, and smoking are also associated with substantial differences in risk of ASCVD across the life span.[1] This well-established fact creates a dilemma. For example, a 45-year-old nonsmoking white man with a systolic blood pressure of 120 mm Hg, no diabetes, and normal high-density lipoprotein cholesterol (HDL-C; 40 mg/dL [1.0 mmol/L]) but with an LDL-C level of 190 mg/dL (corresponding to a total cholesterol level of 260 mg/dL [6.7 mmol/L]) would have a 10-year risk of hard ASCVD events (coronary death, myocardial infarction, stroke) of just 3.7%.[4] However, current guidelines would indicate a class I recommendation for statin therapy because of this patient's LDL-C level.[3] In contrast, another 45-year-old nonsmoking white man with a systolic blood pressure of 138 mm Hg, no diabetes, normal HDL-C, and an LDL-C level of 150 mg/dL (3.9 mmol/L; corresponding to a total cholesterol level of 220 mg/dL [5.7 mmol/L]) would have a similar 10-year risk of hard ASCVD events of 3.6%, but current guidelines would not recommend lipid-lowering therapy for this patient.[3]

However, using the Framingham Heart Study 30-year risk calculator, these individuals have identical 30-year risks of hard ASCVD events, approximately 24%.[5] Given the clinical trial evidence of a similar relative benefit of lipid-lowering therapy across a broad range of LDL-C in the short term, it would be reasonable that lipid-lowering therapy should be considered in both cases, and the second patient should be treated because of the presence of a "lifetime risk equivalent."

## Lifetime Risk Factor Trajectories

Understanding lifetime risk of ASCVD not only requires a measure of current risk factor levels but also should account for accumulated long-term exposure to risk factors. However, current CVD risk prediction algorithms are limited to single, cross-sectional measures of risk factor levels including current blood pressure, smoking, and lipids. Most often these risk prediction algorithms are applied for patients later in life, at the time of increasing absolute ASCVD risk. The adverse effects of these risk factors accumulate over the lifetime and, thus, long-term patterns in risk factor levels provide greater ability to identify individuals at high risk of experiencing a cardiovascular event. Given the rapid expansion of electronic health records, the increasing use of data within the electronic health record, and clinical decision support systems to calculate an individual's ASCVD risk, addition of these long-term risk factor patterns into risk prediction algorithms has now become feasible.

Prospective epidemiologic studies have consistently found that risk factor levels measured early in life are more strongly associated with cardiovascular outcomes compared with contemporary levels later in life. Recently, a growing body of evidence demonstrates that the long-term patterns of risk factor levels, including blood pressure and cholesterol levels, provide additional information above and beyond single measurements to identify individuals at increased risk of future CVD.[6,7] This cumulative exposure over a lifetime is not captured in current risk prediction algorithms and, as a consequence, risk estimates may be overestimated or underestimated, depending on whether risk factors were

accrued recently or earlier in life. Incorporating long-term risk factor patterns into risk prediction algorithms may improve the performance of these equations and would provide patients with a more accurate estimate of their future risk.

## CVD Manifestations Over a Lifetime

Traditional cardiovascular prediction algorithms were limited to predicting the risk of CVD mortality or coronary heart disease (CHD). The most recent iteration of the ACC/AHA prevention guidelines adds stroke to hard CHD events to form a composite ASCVD outcome of the 10-year risk calculators.[4] This is a major step forward, as this better reflects the overall burden of CVD in women and African Americans, among whom the stroke-to-CHD ratio is known to be greater.[2] However, limiting predicted ASCVD risk to end points of hard CHD and stroke does not reflect the entire risk of developing ASCVD over a lifetime. Most first manifestations of ASCVD are not hard end points with fatal or incapacitating consequences and include angina, transient ischemic attacks, or intermittent claudication.[2] These "soft" end points should be incorporated in global ASCVD risk prediction algorithms as they represent a greater portion of the events in women and, particularly, younger individuals.[2] The latter is also reflected by the substantially greater case fatality of a first CVD event with increasing age.[2] Therefore, the effect of age on the overall burden of ASCVD in risk prediction algorithms is greater when solely predicting hard outcomes or CVD mortality compared with a broader outcome.

Incorporating soft atherosclerotic outcomes (and potentially also ischemic heart failure) into the outcome of risk calculators would generate higher lifetime risks than calculators restricted to hard outcomes.[2,5] Calculators with more inclusive outcomes would yield more realistic estimates for patients on their risk of ASCVD, as, on average, 2 of 3 will develop some form of ASCVD during their life span, whereas less than 1 of 3 will die of ASCVD.[1,2] Experiencing an ASCVD event and its consequences during life may be of greater importance to patients than their mode of death when balancing the risks and benefits of preventive measures.

## Existing Resources

For decades, short-term risk estimation strategies have emphasized the value of considering the additive effect of multiple risk factors. A similar evolution is needed for a longitudinal lifetime perspective by moving away from single measurements of risk factors to a broader appreciation of the influence of the entire range of risk factor burden on lifetime risk of a broad spectrum of ASCVD. All of the suggested modifications to more accurately identify asymptomatic individuals at increased ASCVD risk over a lifetime can be made using existing resources. Most high-quality population-based studies to date have collected outcome data on a wide range of cardiovascular outcomes over decades with repeated measurement of traditional and novel risk factors. Therefore, creativity, commitment, and persistence of researchers and clinicians will be instrumental in finding and implementing optimal strategies to quantify lifetime risk and subsequent potential benefit from preventive treatment to further lower the burden of ASCVD.


### ARTICLE INFORMATION

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### REFERENCES


1. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366(4):321-329.

2. Leening MJG, Ferket BS, Steyerberg EW, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. *BMJ*. 2014;349:g5992.

3. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25)(suppl 2):S1-S45.

4. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25)(suppl 2):S49-S73.

5. Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009;119(24):3078-3084.

6. Allen NB, Siddique J, Wilkins JT, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. *JAMA*. 2014;311(5):490-497.

7. Navar-Boggan AM, Peterson ED, D'Agostino RB Sr, Neely B, Sniderman AD, Pencina MJ. Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease. *Circulation*. 2015;131(5):451-458.