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High-Density Lipoprotein Cholesterol in Atherosclerotic Cardiovascular Disease Risk Assessment: Exploring and Explaining the "U"-Shaped Curve

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Abstract

Purpose of Review—Review updates for the association of HDL-cholesterol with atherosclerotic cardiovascular disease (ASCVD) and discuss the approach to incorporating HDL-cholesterol within risk assessment.

Recent Findings—There is a U-shaped relationship between HDL-cholesterol and ASCVD. Both low HDL-cholesterol (< 40 mg/dL in men, < 50 mg/dL in women) and very-high HDL-cholesterol (≥ 80 mg/dL in men) are associated with a higher risk of all-cause and ASCVD mortality, independent from traditional risk factors. There has been inconsistency for the association between very-high HDL-cholesterol and mortality outcomes in women. It is uncertain whether HDL-cholesterol is a causal ASCVD risk factor, especially due to mixed results from Mendelian randomization studies and the collinearity of HDL-cholesterol with established risk factors, lifestyle behaviors, and socioeconomic status.

Summary—HDL-cholesterol is a risk factor or risk enhancer in primary prevention and high-risk condition in secondary prevention when either low (men and women) or very-high (men). The contribution of HDL-cholesterol to ASCVD risk calculators should reflect its observed U-shaped association with all-cause and ASCVD mortality.

Keywords

HDL cholesterol; Lipids; Cardiovascular disease; Risk

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Introduction

Measurement of high-density lipoprotein-cholesterol (HDL-C) level is important in primary and secondary atherosclerotic cardiovascular disease (ASCVD) risk assessment because reduced HDL-C is one of the most common lipid abnormalities in patients with clinical ASCVD [1]. Early observational studies have demonstrated a strong, independent, and inverse relationship between HDL-C and ASCVD risk [2, 3], as initial findings from the Framingham Heart Study found that each 5 mg/dL lower HDL-C below the median for men and women is associated with a 25% higher risk for myocardial infarction [4]. These data have supported the role of HDL-C in protection from atherosclerosis, predominantly mediated through the process of reverse cholesterol transport [5].

Despite the important role of HDL-C in reverse cholesterol transport, emerging evidence from randomized controlled clinical trials and more recent prospective cohort studies has suggested a more nuanced contribution of HDL-C to ASCVD risk. The intentional raising of HDL-C in primary and secondary prevention with niacin [6], fibrates [7], and/or cholesteryl ester transfer protein (CETP) inhibitors [8] has not resulted in reduced ASCVD risk, while contemporary observational cohort studies have found that very-high HDL-C (≥ 80 mg/dL in men, ≥ 100 mg/dL in women) may be associated with higher all-cause and ASCVD mortality [9••, 10••]. Taken together, these findings underline that our understanding of HDL-C in ASCVD is continuing to evolve and how to optimally incorporate HDL-C within routine clinical risk assessment is thus of great interest [11].

In this review, we aim to predominantly focus on the role of HDL-cholesterol in ASCVD risk by discussing (1) genomics involving HDL-C, (2) implications of HDL-C and very-high HDL-C in primary and secondary prevention, (3) potential mechanisms underlying the association of very-high HDL-C and adverse outcomes, and (4) propose an alternative approach for evaluating the contribution of HDL-C to current clinical ASCVD risk prediction.

HDL-C Genomics and Inherited Deficiencies

Genetic profile plays a critical role in HDL-C levels, supported by a high estimated heritability of 40–60% [12, 13]. While genome-wide association studies (GWAS) have identified many single nucleotide polymorphisms (SNPs) that can serve as robust genetic instrumental variables of HDL-C [14, 15], these SNPs account for relatively small variation in HDL levels [9••]. The most recent large-scale multi-ancestry GWAS that included ~ 1.6 million individuals have identified 562 genomic loci associated with HDL-C at a stringent genome-wide association level [16]. Multiple Mendelian randomization models have been widely used for causal effect estimation of HDL-C, including the inverse variance weighting, Egger, as well as the pleiotropy residual sum and outlier models [17–20].

A large Mendelian randomization study of over 20,000 myocardial infarction cases investigated the causal effect of HDL-C using the endothelial lipase gene *LIPG* and 14 common SNPs associated with HDL-C exclusively and suggested that genetic mechanisms that raise HDL-C may not necessarily lead to a decreased risk of myocardial infarction [21]. A study investigating the lecithin-cholesterol acyltransferase (*LCAT*) gene similarly

found that genetically decreased HDL-C levels did not result in lower myocardial infarction rates [22]. In over 12,000 coronary heart disease (CHD) cases, although a causal effect of triglycerides was recognized, there was no clear evidence of causal effect for HDL-C [23]. Another multivariable Mendelian randomization study identified a small magnitude inverse association between HDL-C and coronary artery disease after adjustment for other lipids, concluding that interventions targeting HDL-C as compared to low-density lipoprotein cholesterol (LDL-C) levels may have a modest impact on CHD risk [19]. Overall, the current evidence regarding the causal effect of HDL-C on ASCVD demonstrates limited impact or non-causality.

Several inherited disorders that lead to major reductions in HDL-C are associated with a heightened risk factor for ASCVD. For example, familial hypoalphalipoproteinemia is an autosomal dominant disorder associated with premature ASCVD. These individuals have reduced levels of apolipoprotein A-1, the main protein component of HDL, due to a compromise in protein production, increased breakdown, or enzymatic alterations [24]. Similarly, mutations in the adenosine triphosphate-binding cassette transporter (ABCA1) gene encoding the cholesterol efflux regulatory protein contribute to the higher HDL catabolism found in familial HDL deficiency and Tangier disease which are also associated with premature CHD [25–27]. However, the association between mutations in ABCA1 and CHD is independent of serum HDL-C levels [28] and there appears to be notable heterogeneity among individuals with inherited causes of low HDL-C, such that not all develop premature atherosclerosis [27]. These observations may corroborate with Mendelian randomization studies and underline that a more nuanced approach beyond measurement of HDL-C itself may be beneficial to understanding its association with ASCVD.

HDL-C as a Protective Risk Marker for ASCVD

Many observational cohort studies have demonstrated that HDL-C shares a linear, inverse association with ASCVD. Among the most notable and initial findings were derived from nearly 3,000 men and women free of clinical ASCVD from the Framingham Heart Study. Here, investigators found that individuals with HDL-C > 65 mg/dL had an eight-fold lower incidence of ASCVD compared to those with HDL-C < 35 mg/dL over a median follow-up time of 4 years [3]. Similar findings were subsequently discovered across an independent collection of observational cohort studies, suggesting that each 10 mg/dL higher increment in HDL-C was associated with up to a 3% lower incidence of ASCVD [29]. Thereafter, the association of HDL-C with ASCVD was studied in larger and more diverse cohorts, including the ARIC (Atherosclerosis Risk in Communities), Cardiovascular Health, the CARDIA (Coronary Artery Risk Development in Young Adults), and the Framingham Original and Offspring Study cohorts, which contributed to the 2013 Pooled Cohort Equations (PCE) risk calculator [30]. The 2013 PCE calculator includes HDL-C as a negative risk factor in risk equations and remains as the guideline-based first-line tool for risk assessment to guide eligibility for statin therapy in primary prevention patients [30].

The protective association between higher HDL-C and ASCVD outcomes appears to be stronger among those with known CHD. For example, among nearly 2200 patients with stable CHD, those in the highest quintile of HDL-C values (≥ 48 mg/dL) have a one-third

lower crude rate of myocardial infarction and all-cause mortality compared to patients in the lowest quintile of HDL-C (< 35 mg/dL) after adjusting for age, sex, body mass index, hypertension, diabetes, current cigarette smoking, LDL-C, and serum triglycerides [31]. Furthermore, meta-analysis of large randomized controlled trials involving statins has demonstrated that the inverse association between HDL-C and ASCVD outcomes is not attenuated or modified by statin therapy [32]. However, not all studies among patients with clinical CHD have identified an independent inverse association between HDL-C and ASCVD outcomes, especially among patients treated with high-intensity statins [33], and after adjusting for LDL-cholesterol particle concentration [34].

There are several possible explanations for a lack of association between low HDL-C and a higher risk of ASCVD after considering adjacent risk factors, lifestyle, demographics, and socioeconomic status. First, low HDL-C is often found among persons with metabolic syndrome [35], and/or type 2 diabetes [36]—which have also been identified to be independent risk factors for incident ASCVD. Second, low HDL-C is associated with both unhealthy (suboptimal physical activity) [37] and healthy lifestyle behaviors (low-fat, plant-based dietary pattern) [38]. Ethnicity also appears to modify the association between HDL-C and ASCVD, as low HDL-C has been recently observed to confer a 22% higher risk of ASCVD events in White, but not Black, adults [39•]. Lastly, low HDL-C has been associated with a lower median income [40]. While the inverse association between HDL-C and ASCVD risk is important within both primary and secondary prevention, clinicians and population health scientists should also consider the company that low HDL-C keeps, including accompanying metabolic disorders, lifestyle habits, and socioeconomic status.

Very-High HDL-C and ASCVD Risk

In the past decade, observational evidence has indicated that very-high HDL-C level is paradoxically associated with a higher risk for all-cause and ASCVD mortality in patients with and without clinical ASCVD [9••, 10••, 40–53]. In particular, the association between very-high HDL-C and adverse outcomes has been most notable in men compared to women. Despite this rapidly evolving evidence, no universal definition of very-high HDL-C exists, though spline analyses suggest that elevated risk begins at approximately 80 mg/dL in men and 100 mg/dL in women [46]. Using these clinical thresholds, initial estimates suggest that the prevalence of very-high HDL-C would range between 2 and 11% based on the sample studied [9••, 40, 49]. While very-high HDL-C may be associated with certain underlying genetic polymorphisms, alcohol consumption is also higher in this subset [9••, 50], which may help explain a certain proportion of the downstream risk attributable to very-high HDL-C.

In one of the most recent studies among 415,416 participants without clinical ASCVD enrolled in the UK Biobank, very-high HDL-C (≥ 80 mg/dL in men [2%], ≥ 100 mg/dL in women [11%]) conferred an 80% higher risk of all-cause and ASCVD mortality in men, but not women over nearly one decade of follow-up [9••]. The reference/comparator group in this study were men and women with HDL-C values between 40 and 60 mg/dL, and covariables adjusted for included traditional risk factors and an HDL-specific genetic risk score. This study underlines the U-shaped relationship between HDL-C and ASCVD

mortality, especially among men, in a primary prevention sample (Fig. 1). Similar findings have been observed in large, independent cohort of individuals without known ASCVD, suggesting that the association of very-high HDL-C with all-cause mortality is more pronounced in men compared to women [40, 47, 50, 52]. For example, among a pooled cohort of nearly 43,000 individuals without clinical ASCVD, men with HDL-C ≥ 90 mg/dL had a 2.6-fold higher risk of ASCVD mortality after adjustment for traditional risk factors and current alcohol consumption, whereas no significant association was identified in women [50]. Given the high burden of hypertension in primary prevention, the association of very-high HDL-C has also been studied specifically among participants who have not had an ASCVD event but who have hypertension [41]. Here, men with HDL-C ≥ 80 mg/dL had a 35% higher risk of ASCVD events compared to those with HDL-C 40–79 mg/dL, and a similar magnitude risk was found for individuals with low HDL-C (< 40 mg/dL) [41]. While not all studies involving very-high HDL-C have observed sex differences [40, 49] or significant associations [48, 53] of very-high HDL-C with all-cause or ASCVD mortality, the general summary of current literature is that very-high HDL-C may be a marker of excess downstream risk, more strongly in men compared to women.

In general, very-high HDL-C has most strongly conferred a higher risk for all-cause mortality compared to other ASCVD outcomes in analyses that have also included individuals with CHD. To our knowledge, in the only study performed exclusively among individuals with clinical CHD, those with HDL-C ≥ 80 mg/dL (2% of individuals) experienced a 96% and 71% higher risk for all-cause mortality and ASCVD mortality when compared to persons with HDL-C values between 40 and 60 mg/dL after adjustment for traditional risk factors, alcohol consumption, medications, kidney function, and genetic polymorphisms associated with higher HDL-C [10••]. In this study, individuals with HDL-C ≥ 30 mg/dL also had an adjusted 33% and 42% higher risk of all-cause and ASCVD mortality. In sensitivity analyses, the risk associated with very-high HDL-C was replicated and significant only for men and the outcome of all-cause mortality [10••]. Thus, there is evidence for very-high HDL-C as a high-risk condition and risk enhancer among individuals who have and have not experienced an index ASCVD event, respectively, which may have implications for routine risk assessment and current clinical risk calculators.

Potential Mechanisms Underlying Very-High HDL-C and Adverse Outcomes

There are several possible explanations for the observed associations between very-high HDL-C and adverse outcomes. With respect to atherosclerosis, very-high HDL-C may be associated with reduced cholesterol efflux. However, measurement of serum ApoA-I concentrations, the main HDL-C component that facilitates reverse cholesterol transport, does not seem to provide additional value beyond measurement of HDL-C itself as both ApoA-I and HDL-C have identical U-shaped associations with ASCVD outcomes [54].

Measurement of peripheral HDL-C is not a precise measure of HDL function, specifically cholesterol efflux capacity. Instead, current evidence suggests that a mass effect underlies cholesterol efflux capacity, such that both the number and size of HDL particles may be most important. Previous studies have shown that cholesterol efflux capacity is positively associated with large- and medium-sized HDL particles, while being inversely associated

with small HDL particles [55, 56]. Independent of traditional risk factors, including HDL-C, individuals in the highest tertile of cholesterol efflux capacity have a 36% lower risk of CHD compared to individuals in the lowest tertile of cholesterol efflux capacity [57]. Similar findings have been replicated in independent cohorts including patients with and without clinical CHD. Cholesterol efflux assays thus may provide clinical value for individuals with very-high HDL-C as they measure the total efflux cholesterol from macrophages [56, 58]. In the first trial of its kind, the AEGIS-II trial is currently ongoing and will report on whether augmenting cholesterol efflux capacity with ApoA-I infusion in high-risk patients post myocardial infarction can reduce risk for recurrent CHD events [59]. Furthermore, while CETP inhibitors substantially increase HDL-C levels (as much as two-fold), there is an ongoing trial of CETP inhibition with obicetrapib in combination with ezetimibe for additional LDL-C and apolipoprotein-B (ApoB) lowering for patients who are already on high-intensity statin therapy [60].

Additionally, inflammation modifies the protective association between HDL-C and incident CHD, such that C-reactive protein and interleukin-6 are more strongly associated with CHD events among individual with lower (< 40 mg/dL) versus higher HDL-C (≥ 60 mg/dL) [61]. Thus, concomitant measurement of select inflammatory markers may be helpful to guide ASCVD risk assessment among individuals with very-high HDL-C; however, future studies in this research space are required.

As noted earlier, alcohol consumption is an important environmental factor potentially underlying the U-shaped relationship between HDL-C and adverse outcomes. Genetic epidemiology studies suggest that habitual alcohol consumption is linearly associated with both hypertension and CHD [62]. Given the dose-dependent association between alcohol consumption and HDL-C levels [63], the association between very-high HDL-C and mortality may in part be mediated through or explained by alcohol consumption patterns.

Contribution of HDL-C to ASCVD Risk Assessment and Prediction

In primary prevention, the PCE calculator to quantify 10-year ASCVD risk and guide statin therapy incorporates HDL-C as a strictly negative risk factor [30]. While it is certainly reasonable to consider low HDL-C as a risk factor for incident ASCVD events, this approach may be overly simplistic to guide ASCVD risk assessment for several reasons. First, ethnicity is known to modify the association between low HDL-C and ASCVD risk, as observational analyses from the REGARDS (REasons for Geographic and Racial Differences in Stroke) have found low HDL-C is associated with a higher risk of incident CHD in White but not Black men and women [39•]. Second, several other HDL metrics, including density, apolipoprotein content, particle number, and particle size also, contribute to function and may thus not be captured by simply measuring absolute HDL-C [11]. Lastly, carefully conducted observational evidence over the past decade has shown that very-high HDL-C may be a marker of elevated risk when compared to normal HDL-C values, more consistently in men versus women and patients with versus without clinical ASCVD [9••, 10••].

In the setting of such evidence, we propose to use HDL-C as both a traditional risk factor and a risk enhancer/high-risk condition in ASCVD risk assessment (Fig. 2). Here, low

HDL-C (< 40 mg/dL in men, < 50 mg/dL in women) and very-high (≥ 80 mg/dL in men) would contribute as a risk-enhancing factor (risk enhancer) or high-risk condition (secondary prevention) to global risk assessment for the consideration of diagnostic (e.g., Lp(a) testing or coronary artery calcium scoring) and therapeutic (e.g., statin and aspirin therapy) decision-making in primary prevention, and inform treatment intensification (e.g., combination lipid-lowering therapy) in secondary prevention. In the situation when HDL-C values are between 40–80 mg/dL in men and 50–100 mg/dL in women, HDL-C would not necessarily contribute to higher or lower risk unless there was clinical suspicion for a functional HDL-C abnormality, which could prompt more in-depth assessments including measurement of HDL particle number and/or cholesterol efflux capacity assays. For women, while very-high HDL-C (≥ 100 mg/dL) has not consistently conferred an increased for ASCVD or all-cause mortality, there does not appear to be a lower ASCVD risk for HDL-C ≥ 100 versus 50–100 mg/dL. Importantly, a normal or high HDL-C should not be used as a rationale to discourage the use of statins in a patient who meets statin eligibility criteria based on calculated 10-year risk, LDL-C, ApoB levels, and/or presence of coronary artery calcium.

Conclusion

The current summary of evidence indicates a U-shaped relationship between HDL-C values and ASCVD risk. Both low HDL-C (< 40 mg/dL in men, < 50 mg/dL in women) and very-high HDL-C (≥ 80 mg/dL in men) are associated with an increased risk of ASCVD and all-cause mortality, independent from traditional risk factors. For women, while very-high HDL-C (≥ 100 mg/dL) has not consistently conferred an increased risk for ASCVD or all-cause mortality, there does not appear to be added protection for HDL-C ≥ 100 versus 50–100 mg/dL. It is likely that HDL-C is not a causal risk factor for ASCVD based on the overwhelming evidence from Mendelian randomization studies and the collinearity of HDL-C with established ASCVD risk factors, lifestyle behaviors, and socioeconomic status. In the setting of these findings, it is important to continue evolving current risk assessment approaches that involve HDL-C to help facilitate more precise diagnostic and therapeutic decision-making in the primary and secondary prevention of ASCVD.

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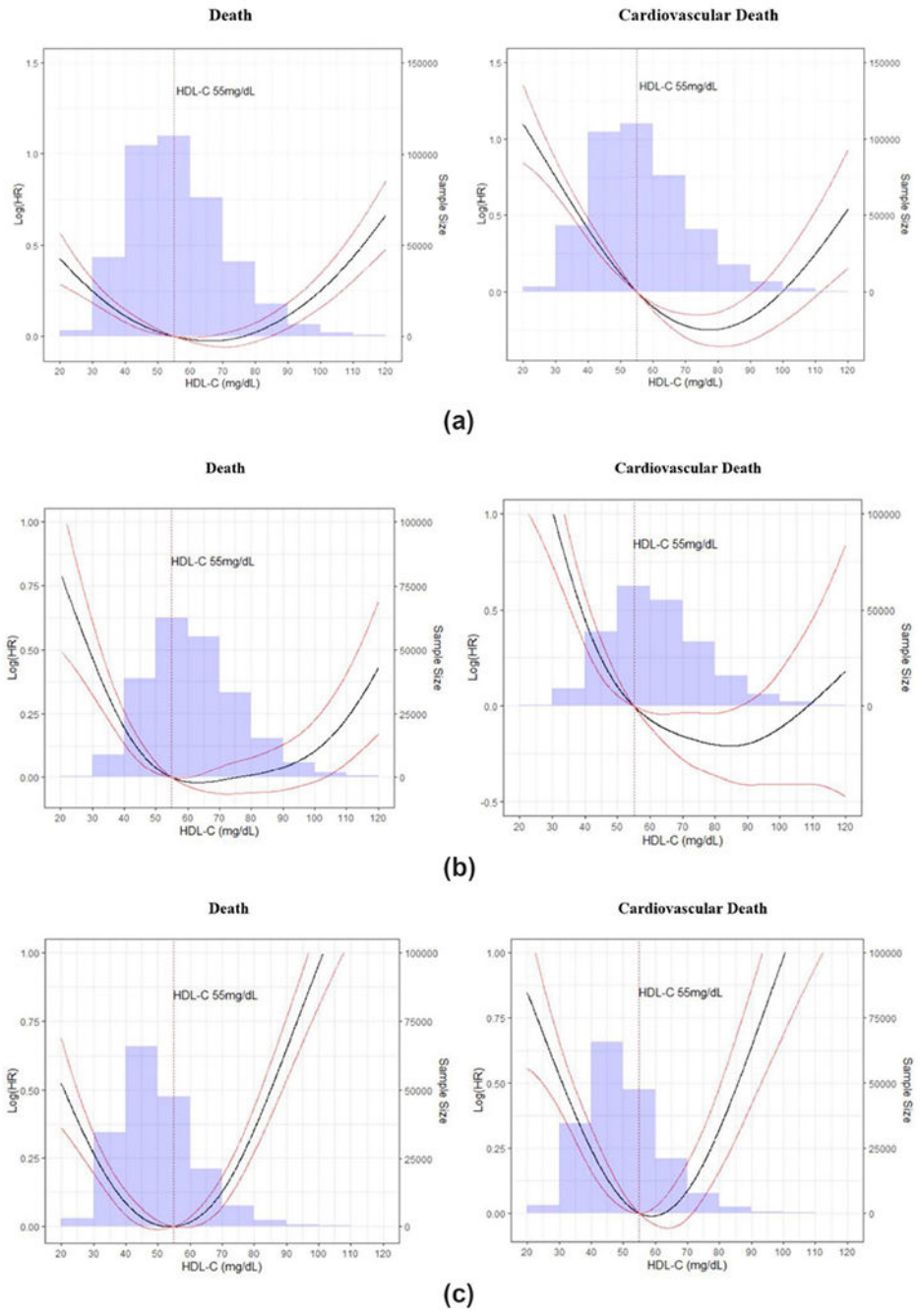

Fig. 1.

Association of very-high HDL-C with death and ASCVD mortality in the overall sample (**a**), women (**b**), and men (**c**). ASCVD, atherosclerotic cardiovascular disease; HDL-C, high density lipoprotein-cholesterol. (From Liu, C et al. Am J Cardiol. 2022;167(188):120–1, with permission from Elsevier) [9••]. ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein-cholesterol

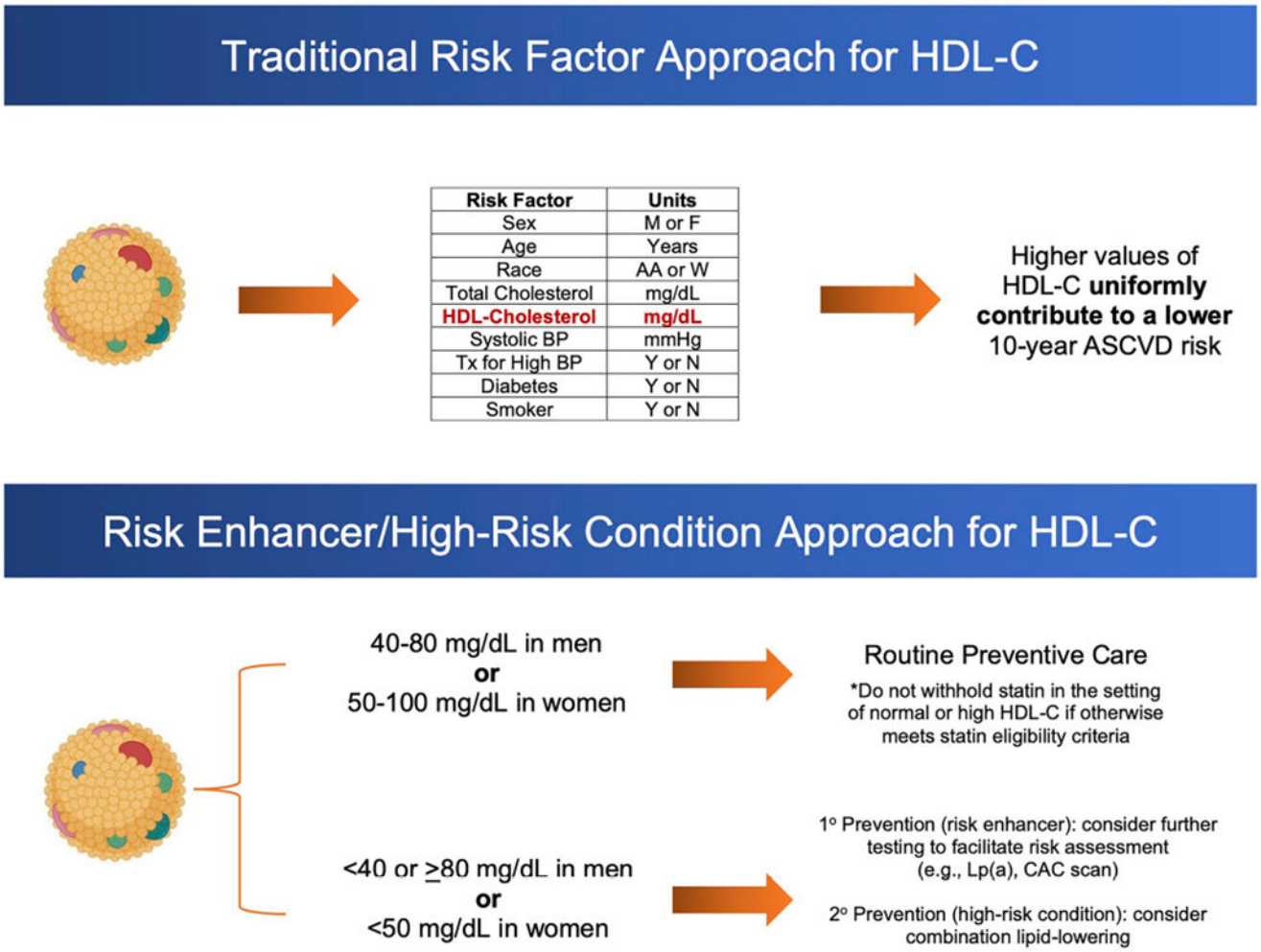

Fig. 2.

HDL-C as a traditional risk factor or risk enhancer in primary prevention and high-risk condition in secondary prevention. CAC, coronary artery calcium; HDL-C, high-density lipoprotein-cholesterol; Lp(a), lipoprotein(a)