J Lipid Atheroscler. 2021 Jan;10(1):57-61
https://doi.org/10.12997/jla.2021.10.1.57
pISSN 2287-2892·eISSN 2288-2561

JLA Journal of Lipid and Atherosclerosis

Editorial

HDL-C and Cardiovascular Risk: You Don't Need to Worry about Extremely High HDL-C Levels

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▸ See the article "High-Density Lipoprotein Cholesterol and the Risk of Myocardial Infarction, Stroke, and Cause-Specific Mortality: a Nationwide Cohort Study in Korea" in volume 10 on page 74.

Received: Dec 31, 2020
Revised: Jan 7, 2021
Accepted: Jan 11, 2021

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Funding
None.

Conflict to Interest
The authors have no conflicts of interest to declare.

Author Contributions
Conceptualization: Cho YK, Jung CH; Writing - original draft: Cho YK; Writing - review & editing: Jung CH.

Dyslipidemia is an established risk factor for the development of cardiovascular disease (CVD). Cardiovascular (CV) outcome trials have consistently proven that reducing low-density lipoprotein cholesterol (LDL-C) with statins and/or ezetimibe significantly lowered the rates of CVD events.[1,2] However, despite these advances in the treatment of high LDL-C levels, CV risk remains high in a significant number of patents, demanding novel approaches to modulate other forms of cholesterol associated with CV risk. Targeting high-density lipoprotein cholesterol (HDL-C) represents one such approach, as it has been widely accepted that HDL-C plays an important role in the development of CV mortality and morbidity.[3-7] Early epidemiological studies have consistently demonstrated a linear inverse association between HDL-C levels and CVD events. For example, studies have shown that every 1 mg/dL rise in HDL-C levels was related to a 3% to 4% reduction in CV mortality,[4,8,9] indicating that attaining high HDL-C levels could reduce the risk of CVD events. However, major clinical trials have reported disappointing results that therapeutic approaches to increase HDL-C levels with niacin and cholesteryl ester transfer protein (CETP) inhibitors have failed to prove benefits for lowering incident CVD.[10-12] Furthermore, several recent genetic and epidemiological studies have suggested that HDL-C levels might not be predictive of CV outcomes in all populations, and have reported inverse associations with a plateau or even a U-shaped curve from sub-analyses, whereby very high levels of HDL-C may be related to increased CV risk.[13-15]

In this issue of the *Journal of Lipid and Atherosclerosis*, Yang et al.[16] presented evidence supporting a protective link between HDL-C and clinical CV risk. Studying 343,687 individuals from a large-scale nationwide cohort who underwent routine health examinations, the researchers reported that lower HDL-C levels were closely related to a greater risk of mortality and CVD events including myocardial infarction (MI) and stroke, whereas extremely high HDL-C levels were not associated with poor outcomes. They did not observe a U-shaped risk pattern between HDL-C level and mortality or CVD events. In particular, regarding CV mortality and MI, the lowest risk was observed at the extreme high end of HDL-C levels, which implies a strong inverse relationship between HDL-C level and CV risk. According to the results, the higher the HDL-C level, the better for lowering CV mortality and MI risk.

A major strength of this study is its ability to analyze a number of clinical data points from a large population-based cohort, allowing the identification of factors that could contribute to adverse clinical outcomes. This also expands the spectrum of clinical investigations spanning the continuum from case series and small healthcare center audits to large multicenter studies. The big data approaches used in this study provided the opportunity for a fundamental identification of factors affecting the prognosis of the disease with a sufficient power of discrimination.

Previously, Ko et al.[7] found a U-shaped dose-response association between HDL-C levels and cause-specific mortality outcomes, which is reversed by the current results of Yang et al.[16] In the study of Ko et al.,[7] individuals whose HDL-C levels were very low (<50 mg/dL in women and <40 mg/dL in men) or extremely high (>80 to 90 mg/dL) faced a higher risk of death than individuals who had HDL-C levels that fell within intermediate ranges.[7] They concluded that HDL-C levels are unlikely to represent a CV-specific risk factor, although they were unsure why there was a higher risk of non-cardiac/non-cancer mortality among individuals with very high HDL-C levels. Now, based on the findings of Yang et al.,[16] HDL-C levels have again emerged as a predictor of CV outcomes; lower HDL-C levels were significantly correlated with higher CV mortality and MI event rates, consistent with the generally accepted relationship between HDL-C levels and CV risk. Although the mechanism underlying the cardioprotective effect of HDL-C was not established in this paper, previous experimental studies have shown that HDL promotes cholesterol efflux from macrophage foam cells in atheromatous vessels, thereby reducing the cholesterol burden and macrophage-driven inflammation.[17,18] It is worth noting that administration of recombinant lipid-depleted forms of HDL produced significant regression of coronary atherosclerosis in patients with acute coronary syndrome.[19] In light of those previous reports, HDL-C certainly has the potential as a protective factor in CVD.

Then, why have we observed conflicting results on the association between HDL-C and CV risk? First, a simple assessment of HDL-C levels might not be sufficient. Measurements of the functional activity of HDL would have a superior ability to predict CV risk; that is, qualitative measurements of HDL may be more important in the context of atheroprotection.[20,21] In this context, substantial research is being conducted to determine whether more qualitative approaches to targeting HDL will be favorable.[21] HDL-C subclasses could be one example; Martin et al. reported an analysis of HDL_2-C (larger, more buoyant) and HDL_3-C (smaller, denser) subclasses with clinical results in 2 cohorts for secondary prevention.[22] The analyses showed an increase of > 50% in both the mortality and MI risk in the individuals with lower HDL_3-C, whereas no significant relationships with outcomes were observed for HDL-C and HDL_2-C. These findings suggest that HDL-C levels alone might not adequately reflect the protective potential of HDL against atherogenesis and that we should shift our focus to differentiating HDL subspecies and evaluating their function, instead of simply measuring circulating HDL-C levels, to better understand the implications of HDL for CV risk assessment. Future studies will also need to explore which HDL-C subclasses are suitable for therapeutic purposes.[23] As a priority for future research, development and standardization of methodologies on fractionating HDLs based on their functional properties should be achieved.

Next, genetic factors in different populations could be another potential reason for different results; in particular, some genetic mutations contributing to extremely high HDL-C could simultaneously confer adverse CV risk.[24] For instance, genetic variants with opposing effects on expression of endothelial lipase caused an elevation in plasma HDL-C levels by reduced

https://doi.org/10.12997/jla.2021.10.1.57

phospholipolysis, but did not demonstrate the expected decreased CV risk.[25,26] Another example is *SCARB1*, which is the gene encoding scavenger receptor BI (SR-BI), the main receptor enabling circulating HDL to transport cholesterol to the liver for excretion.[27] Mice that have depleted *SCARB1* (SR-BI knockout mice) have markedly elevated HDL-C levels, but paradoxically, a higher susceptibility to atherosclerosis.[27] Additionally, large population-based studies demonstrated that heterozygous carriers of the P376L variant had significantly increased levels of plasma HDL-C, but paradoxically, an increased risk of CVD.[27] Finally, mutations in the gene encoding CETP resulted in elevated HDL-C levels, but inconsistent relationships with CVD.[24,28-30] Several CETP inhibitors have proven their HDL-C-increasing effect; however, the CV-protective effects were inconsistent, as anacetrapib decreased CV risk, dalcetrapib and evacetrapib had no effect, and torcetrapib even increased CV risk in randomized controlled trials.[11,31,32] In conclusion, genetic mutations or therapies leading to elevation in HDL-C have not consistently brought about the predicted decrease in CV risk, and some mutations have been associated with paradoxically increased risk. Since the populations included in HDL-related studies were diverse, the prevalence and pattern of genetic mutations may be substantially different, potentially explaining the conflicting patterns reported for the association between HDL-C and CV risk.

In addition, the association between HDL-C levels and mortality might be mediated through complex interactions of several established CV risk factors; the authors observed a pervasive trend for participants with high HDL-C levels to have lower body mass index, waist circumference, and glucose levels, as well as a lower prevalence of diabetes, hypertension, and metabolic syndrome. Individuals with high HDL-C levels had better lifestyle factors in terms of regular exercise; however, heavy alcohol consumption was observed. Each of these variables is considered to be associated with CV risk and/or mortality. In particular, HDL-C is one of the key components defining metabolic syndrome, a constellation of metabolic derangement that can contribute to poor CV outcomes. The interaction or coexistence of metabolic syndrome components with high HDL-C levels could influence study results; thus, differences in these components might lead to conflicting results.

Lastly, circulating HDL-C levels could be highly changeable over time, given the concept that metabolic health could be transient. Recently, researchers have tried new approaches to examine the effect of metabolic health on various outcomes by assessing its transitions. Our research team has also demonstrated that transitions in metabolic health—although we did not analyze HDL-C levels separately—affected the risk of CVD and all-cause mortality, as well as chronic kidney disease and colorectal cancer.[33-35] In this context, it would be necessary to investigate the impact of transitions of HDL-C levels on CVD. Additionally, by adopting this approach, researchers could investigate the effect of decreasing or increasing HDL-C in serial assessments, hopefully resulting in some hints regarding the future potential of HDL-C–targeting therapies.

In summary, future research on the evaluation of subclasses and functions of HDL-C and clinical studies on the effects of changing HDL-C levels would provide additional information on this issue; for the time being, we should not jump to hasty conclusions on the implications of HDL-C for CV risk assessment. We should await further data linking HDL-C to clinical endpoints.

https://doi.org/10.12997/jla.2021.10.1.57

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