# Editorial

# Is It Time for New Thinking About High-Density Lipoprotein?

Christian M. Madsen, Børge G. Nordestgaard

The perception of high-density lipoprotein (HDL) cholesterol as the good cholesterol that protects against atherosclerotic cardiovascular disease (ASCVD) has persisted for decades based largely on the countless observational studies showing high risk of ASCVD in individuals with low concentrations of HDL cholesterol.[1] The notion has been the higher the better and the faith in HDL cholesterol–elevating drugs as a new treatment option for ASCVD so great, that >70 000 patients worldwide have been randomized in phase III outcome trials with the 4 major cholesteryl ester transfer protein inhibitors.[2–5] Cholesteryl ester transfer protein inhibitors effectively increase HDL cholesterol, but to date none of these compounds have been marketed because of disappointing effects on the risk of ASCVD, and one drug even increased ASCVD risk as well as all-cause mortality.[2] Despite the failures of HDL cholesterol–elevating drugs, which in addition to cholesteryl ester transfer protein inhibitors include niacin,[6] and genetic studies showing that genetically elevated HDL cholesterol does not confer lower risk of ASCVD,[7–12] the perception of HDL cholesterol as the good cholesterol is still deeply believed among many physicians, scientists, and individuals in the general public.

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In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Hamer et al[13] provide further data to show that higher is not necessarily better when it comes to HDL cholesterol. Using data on 36 059 individuals from the general population participating in the Health Survey for England and the Scottish Health Survey, the authors confirm findings from a recent study of the general population[14] and 2 studies based on routinely collected healthcare data,[15,16] showing that the association between HDL cholesterol and all-cause mortality is U shaped. The lowest mortality was observed for those with HDL cholesterol between 1.50 and 1.99 mmol/L (58–77 mg/dL), and similar risks of any death were observed for those with HDL cholesterol above or below this interval. The authors do not provide evidence as to what drives the high mortality with high HDL cholesterol because neither cardiovascular nor cancer mortality was increased with high HDL cholesterol. The main strength of the study is the large number of included individuals from the general population with long-term follow-up. The main limitations include the inherent inability of observational studies to address the question of causality and the lack of included information on additional lipid biomarkers, such as triglycerides, which are inversely associated with HDL cholesterol.[17]

Two main questions arise from this[13] and the recent similar studies[14–16]:

1. What is the cause of the high mortality in individuals with high concentrations of HDL cholesterol?
2. What are the clinical implications, if any?

One possible explanation for the findings is of course the presence of unmeasured confounders in those with high HDL cholesterol, confounders which lead to both high mortality and high HDL cholesterol (Figure). However, in the study of Hamer et al[13] and similar previous studies, the findings seem robust after different sensitivity analyses with adjustments and stratifications for potential confounders.

Alternative explanations include the presence of genetic variants that cause high HDL cholesterol and at the same time have unfavorable pleiotropic health effects or unfavorable effects on the HDL particles themselves (Figure). Several such variants, in for example, *CETP*, *ABCA1*, *LIPC*, and *SCARB1*, are known.[7,8,10,12] Individuals with high HDL cholesterol might have HDL particles that are compositionally and functionally altered, perhaps even leading them to become harmful (Figure); however, the exact mechanism can only be speculated about.

Theoretically, it is possible that at high HDL cholesterol concentrations, the HDL particle sizes become so large that these particles like low-density lipoproteins[18] gets trapped in the arterial intima, leading to cholesterol deposition and atherosclerosis development. Concerning the function of HDL, this has predominantly revolved around the so-called reverse cholesterol transport.[19] Although there seem to be no doubt that HDL is involved in cholesterol transport from peripheral tissues to the liver, the narrow interpretation of reverse cholesterol transport, where HDL particles are believed to be able to remove cholesterol from the arterial intima and thereby protect against atherosclerosis, seems less and less plausible in humans. In fact, we are not aware of any convincing human data showing that removal of cholesterol from human atherosclerotic intima occurs through reverse cholesterol transport, a mechanism that is difficult to envision would have developed through evolution as cardiovascular disease typically kill people after the reproductive age.

From an evolutionary standpoint, HDL must nevertheless have an important role in human and animal physiology because HDL is the predominant lipoprotein in plasma in

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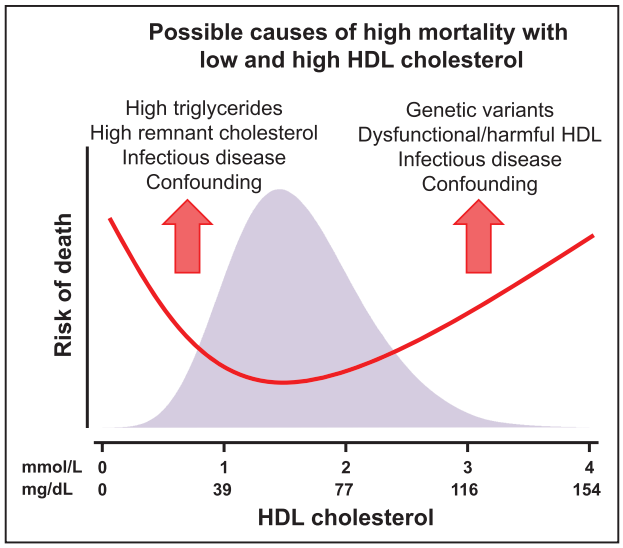


**Figure.** Possible causes of the U-shaped relationship between high-density lipoprotein (HDL) cholesterol and all-cause mortality. The purple area indicates the distribution of HDL cholesterol in the general population. Data in the figure is derived from Hamer et al[13] and Madsen et al.[14]

most species. Therefore, HDL function is an important area of research and will continue to be so for decades to come. The recent negative HDL-related results within cardiovascular disease in randomized trials as well as in genetics hopefully will inspire research into new areas where HDL might be of importance. One of these could be in relation to normal function of the immune system and protection against infectious disease, where a similar U-shaped association, as observed for mortality,[13–16] seems to be present between HDL cholesterol concentrations and risk of infectious disease (Figure).[20]

Clinically, it is widely recommended that HDL cholesterol is measured as part of ASCVD risk prediction and in relation to treatment with lipid-lowering therapy.[21,22] Most clinicians will, therefore, be aware of the HDL cholesterol results of their patients. The results from Hamer et al[13] and similar studies[14–16] imply that physicians should pay close attention to individuals with high HDL cholesterol: it is no longer relevant to simply assume that these individuals will have a good prognosis because of their high HDL cholesterol. Rather, great care should be taken, also in individuals with high HDL cholesterol, to minimize the impact of other risk factors.

Hamer et al[13] should be complemented for their focus on a timely topic. Our understanding of HDL is changing, and there is a need for new and innovative research focusing on the role of HDL with respect to many diseases, not just in relation to cardiovascular disease. Yes, it is indeed high time for new thinking about HDL.

## Disclosures

None.

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