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High-density lipoproteins: A consensus statement from the National Lipid Association

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Abstract: For >4 decades it has been recognized that elevated serum levels of high-density lipoprotein cholesterol (HDL-C) are associated with reduced risk of cardiovascular disease (CVD) and its sequelae. Many prospective observational studies performed around the world have confirmed an inverse relationship between HDL-C and cardiovascular risk in people irrespective of sex, race, or ethnicity. Consequently, it was assumed that, by extension, raising HDL-C through lifestyle modification and pharmacologic intervention would reduce risk of CVD. Animal studies are consistent with this assumption. Lipid treatment guidelines around the world promoted the recognition of HDL-C as a therapeutic target, especially in high-risk patients. Some post hoc analyses from randomized controlled trials also suggest that raising HDL-C beneficially affects the risk of CVD. However, a number of recent randomized studies putatively designed to test the "HDL hypothesis" have failed to show benefit. The results of these trials have caused many clinicians to question whether HDL-C is a legitimate therapeutic target. In response to the many questions and uncertainties raised by the results of these trials, the National Lipid Association convened an expert panel to evaluate the current status of HDL-C as a therapeutic target; to review the

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current state of knowledge of HDL particle structure, composition, and function; and to identify the salient questions yet to be answered about the role of HDL in either preventing or contributing to atherosclerotic disease. The expert panel's conclusions and clinical recommendations are summarized herein. The panel concludes that, although low HDL-C identifies patients at elevated risk, and much investigation suggests that HDL may play a variety of antiatherogenic roles, HDL-C is not a therapeutic target at the present time. Risk stratified atherogenic lipoprotein burden (low-density lipoprotein cholesterol and non–HDL-C) should remain the primary and secondary targets of therapy in patients at risk, as described by established guidelines. The National Lipid Association emphasizes that rigorous research into the biology and clinical significance of low HDL-C should continue. The development of novel drugs designed to modulate the serum levels and functionality of HDL particles should also continue. On the basis of an enormous amount of basic scientific and clinical investigation, a considerable number of reasons support the need to continue to investigate the therapeutic effect of modulating HDL structure and function.

The proposition that high-density lipoproteins (HDLs) protect against the development of cardiovascular disease (CVD) is based on a number of robust and consistent observations. (1) Human population studies have shown consistently that plasma concentrations of both HDL cholesterol (HDL-C) and the major HDL apolipoprotein (apo), apoA-I, are statistically independent, inverse predictors of the risk of having a CVD event in multivariate models that adjust for established risk factor covariates.[1] (2) HDLs possess several properties with the potential to protect against CVD.[2,3] (3) Interventions that increase the HDL concentration in a variety of animal models inhibit the development of atherosclerosis.[4–7] (4) In proof-of-concept studies in humans, infusions of reconstituted HDLs (rHDL) and mutant forms of HDL (apoA-I_{Milano}) promote regression of coronary atheroma as assessed by intravascular ultrasound (IVUS).[8,9]

However, interventions that increase the concentration of HDL-C in statin-treated humans have not yet been shown to translate into a reduction in clinical CVD events. Indeed, recent human clinical trials that investigated the effects of HDL-C–raising agents have failed to find any clinical CVD benefit,[10,11] and in one case the treatment caused harm.[12]

The question arises: why has the robust evidence from the human population studies, the animal intervention studies, and the HDL functional studies not translated into a reduction in clinical CVD events in 4 recent trials with agents that increase the concentration of HDL-C? At this time it is not possible to provide a definitive answer to the question of whether it is too soon to abandon the HDL hypothesis. In this consensus statement, we advocate that much more research is needed to understand the reasons for the unexpected results in these failed clinical trials. This document reviews much of what we know about HDL particles and identifies many areas where more research is required.

Epidemiology

HDL-C as an independent risk factor for CVD

The epidemiologic evidence in support of HDL-C as an inverse predictor of CVD has been appreciated for >50 years. Gofman et al[13] first reported an inverse association between HDL-C levels and risk of ischemic heart disease. Subsequently, an inverse association between HDL-C and CVD risk was found in the Norwegian Tromsø Heart Study,[14] and this was soon followed by US longitudinal data available from the Honolulu Heart Study and the Framingham Heart Study (FHS).[15,16] Both of those studies found low HDL-C to be either highly prevalent in patients with CVD or to increase the risk of myocardial infarction (MI), independent of other CVD risk factors. In fact, low HDL-C has been repeatedly found to be associated with increased CVD risk worldwide in both men and women. For example, observational studies in Germany (Fig. 1) and Israel (Fig. 2)[17–20] identified low HDL-C as the strongest predictor of incident MI, especially in men older than 50 years. Epidemiologic data are consistent with arteriographic studies that found low HDL-C to be prevalent in patients with left main coronary artery disease (CAD)[21] as well as a dose-response relationship between HDL-C and extent of arteriographically defined CAD.[22]

On the basis of the aforementioned studies, there was general acceptance by the mid-1980s that HDL-C was important to CVD risk factor assessment. It was, therefore, quite surprising, when the Adult Treatment Panel (ATP) of the National Cholesterol Education Program issued the inaugural guidelines for the identification and management

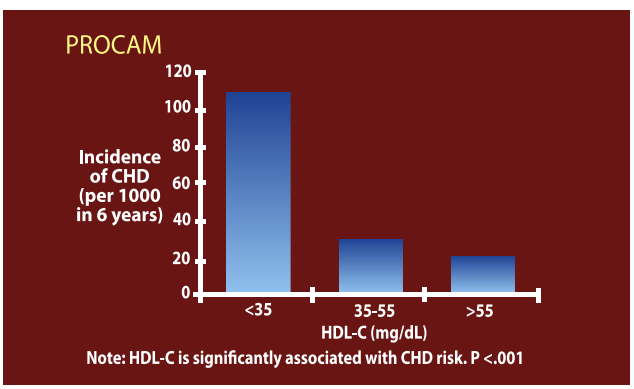

Figure 1 Incidence of CHD according to concentration of HDL-C in the Prospective Cardiovascular Münster study.[20] CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol.