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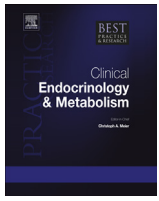

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Should low high-density lipoprotein cholesterol (HDL-C) be treated?

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The first observations linking a low serum level of HDL-C to increased risk for cardiovascular disease were made over 50 years ago. High serum levels of HDL-C appear to protect against the development of atherosclerotic disease, while low serum levels of this lipoprotein are among the most important predictors of atherosclerotic disease in both men and women and people of all racial and ethnic groups throughout the world. It has long been assumed that therapeutic interventions targeted at raising HDL-C levels would lower risk for such cardiovascular events as myocardial infarction, ischemic stroke, and death. Even after five decades of intensive investigation, evidence to support this assumption has been fleeting. A number of *post hoc* analyses of randomized controlled trials and meta-analyses suggest that HDL-C raising, particularly when coupled with aggressive LDL-C reduction, impacts risk for cardiovascular events and rates of progression of atherosclerotic disease. Unfortunately, four recent prospective trials

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performed with the intent of testing the "HDL hypothesis" (ILLUMINATE, dal-OUTCOMES, AIM-HIGH, and HPS2-THRIVE) failed to meet their primary composite endpoints. These results have lead many clinicians and investigators to question the validity of the assumption that HDL-C raising reduces risk for cardiovascular events. Additional trials with other drugs are underway. In the meantime, HDL-C cannot be considered a target of therapy. Given the complexity of the HDL proteome and lipidome, there is biological plausibility for how HDL particles might exert atheroprotection. We explore the evidence supporting the inverse relationship between HDL-C and cardiovascular disease risk, documented mechanisms by which HDL particles may exert atheroprotection, and the findings either supporting or negating specific therapeutic interventions in patients afflicted with low HDL-C.

Introduction

The etiologic role of low-density lipoprotein cholesterol (LDL-C) in atherosclerotic disease and the reduction in risk for cardiovascular (CV) events associated with lipid-modifying therapies that lower LDL-C are highly established. It is also recognized that low serum levels of high-density lipoprotein cholesterol (HDL-C) are among the most important predictors of risk for developing coronary artery disease (CAD) and its sequelae, such as myocardial infarction (MI), stroke, and death [1]. In contrast, high serum levels of HDL-C appear to be atheroprotective and correlate with reduced risk for CV morbidity and mortality. Considerable basic scientific research has suggested that HDL particles may possibly exert a number of antiatherogenic effects. From a clinical perspective, it would seem to be self-evident that simply raising HDL-C by pharmacologic or lifestyle means would reduce risk for developing CAD and sustaining CV events. Unlike the narrative for LDL-C, that for HDL-C has not played out quite so simply. A number of recent clinical trials that purportedly tested the "HDL hypothesis" failed to meet their primary composite endpoints. In addition, a Mendelian randomization study showed that a variety of alleles associated with serum HDL-C levels do not correlate significantly with risk for CAD [2].

Newer studies demonstrate that the roles of HDL in lipid and lipoprotein metabolism are far more complex than previously thought. Punctuating this complexity, over the last five years the literature on HDL has become populated with inconsistencies and contradictions. There is much about this lipoprotein and its range of activity that we still do not adequately understand. For years, many investigators have argued that serum levels of HDL-C should be a therapeutic target. Given the totality of evidence that has accrued over the last five decades, the primary questions explored herein are: (1) is there demonstrable clinical benefit treating patients with low serum levels of HDL-C with lipid-modifying drugs; and (2) more specifically, should drugs be used to raise low serum levels of HDL-C? These are distinct and mutually exclusive questions.

There is evidence from subgroup analyses in multiple clinical trials that treating patients with low serum levels of HDL-C with lipid modifying drugs is efficacious. Although there is suggestive evidence that raising HDL-C*per se* impacts CV risk and reduces rates of atherosclerotic disease progression in both the carotid and coronary vasculature, this is based on *post hoc* secondary analyses and a number of meta-analyses. There is no primary evidence to date from randomized controlled clinical trials that HDL-C is a target of therapy or that raising HDL-C to some threshold level either through lifestyle modification or pharmacologic intervention reduces risk for CV events. A more comprehensive evaluation of the controversies surrounding HDL-C and its role in patient management was recently published [3].

Epidemiology

Prospective cohorts evaluated around the world consistently demonstrate that there is an inverse relationship between HDL-C and risk for CV events in both men and women and people irrespective of