Shedding Light on High-Density Lipoprotein Cholesterol

The Post-ILLUMINATE Era*

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Although age-adjusted mortality rates from coronary heart disease (CHD) have decreased by nearly 70% during the past half-century, cardiovascular disease still remains the number one killer in the U.S. (1). During this time period, numerous public health efforts, pharmacologic advances, and interventional strategies have contributed to the dramatic decline in CHD. In the past 20 years, substantial lipid intervention directed at lowering levels of low-density lipoprotein cholesterol (LDL-C) with a statin medication has contributed to the decline in CHD events (2). Continued advancements against CHD, however, will likely require therapeutic targets beyond LDL-C (3).

Epidemiologic Evidence

During the last several years, substantial enthusiasm has been directed toward the importance of low levels of high-density lipoprotein cholesterol (HDL-C), particularly regarding the potential for aggressive pharmacologic elevation (4). Certainly, epidemiologic evidence has supported a powerful inverse relationship between levels of HDL-C and CHD events. Based on data from the Framingham Heart Study, the risk of major CHD events increased by nearly 25% for every 5-mg/dl decrease in HDL-C below the median values (5). In a meta-analysis of 4 large population-based studies, every 1% increase in HDL-C corresponded to a nearly 3% reduction in CHD risk (6). In epidemiologic studies, including Framingham, CHD events have correlated more strongly with HDL-C than with either total or LDL-C levels. These data are particularly relevant, because low levels of HDL-C are present in over one-fourth of adults and over one-half of patients with CHD in the U.S. (4,7,8). Although lowering LDL-C, typically with statins, is well established to reduce major CHD events, several trials that demonstrated particularly marked CHD event reduction were associated with more significant HDL-C raising (9,12).

Mechanisms of HDL-C

Although much of the antiatherosclerotic properties of HDL-C is considered to be mediated by reverse cholesterol transport (RCT), a process in which excess cholesterol in cells and, particularly, atherosclerotic plaque is removed, HDL-C has other beneficial effects, including reducing endothelial dysfunction, as well as antiinflammatory, antioxidant, and antithrombotic effects (13,14). Despite these potential theoretical benefits and the substantial epidemiologic and limited pharmacologic data that would support clinical event reduction with HDL-C raising interventions, several trials with fibrates (15–17), estrogens (18,19), and, particularly, cholesterol ester transport protein (CETP) inhibition with torcetrapib (20) have demonstrated neutral effects or even harm related to HDL-C–elevating interventions. Disappointment in HDL-C intervention reached its pinnacle when the major morbidity and mortality trial, ILLUMINATE (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events), was halted owing to excess mortality in the torcetrapib group (20).

The CETP Inhibition “Bust”

Despite substantial enthusiasm directed toward CETP inhibition and the first agent in its class, torcetrapib, the failure of this agent to reduce CHD events and possibly cause harm were partly predictable (4,13). Although a possible contributing factor to torcetrapib’s downfall was that it increased blood pressure in some patients, its major failure was likely due to producing HDL-C elevation without RCT augmentation (4,20). In fact, subsequent to the termination of all torcetrapib trials after ILLUMINATE, results of 2 major trials were published showing no significant effects of this therapy on coronary or carotid atherosclerosis progression despite marked increases in HDL-C (21,22). Although these data have resulted in the “death” of torcetrapib and pessimism toward the entire field of CETP inhibition, it should be noted that the relationship among CETP levels, CETP polymorphism, HDL-C concentrations and activity, and CHD appears to be complex and certainly additional research is needed.

When Good Cholesterol Goes Bad?

Although it is not clear if the negative data with torcetrapib was due to CETP inhibition in general or adverse effects of the particular agent used, likely both the blood pressure increases and production of an “inactive” HDL that lacks significant RCT contributed to the poor results with this agent (4,20). Complicating the clinical relevance of raising...
HDL-C is the recent suggestion that in systemic inflammatory states, including acute coronary syndrome (ACS), HDL-C may convert from anti-inflammatory to proinflammatory (23–27). Augmenting the inflammatory response may be beneficial in connective tissue diseases and combating infection, but in atherosclerotic disease such as ACS, this effect is likely detrimental (26,27). It has been suggested that HDL-C normally supports an anti-inflammatory state, but in the acute inflammatory environment, as in ACS, HDL's antioxidant enzymes are inactivated and accumulate elevated levels of oxidized lipids, making HDL-C proinflammatory (25–27). Therefore, HDL-C may actually lower CHD risk in chronic atherosclerosis but possibly potentiate risk in the setting of ACS. Although this concept deserves further study, clinical trials with other HDL-raising therapies (i.e., niacin, exercise) have not demonstrated clinical harm, including an increase in CHD death or ACS events.

**Present Study**

In this issue of the Journal, a large Veterans Administration study by deGoma et al. (28) demonstrated a strong inverse relationship between HDL-C and CHD risk even among patients with very low levels of LDL-C <60 mg/dl (mean <50 mg/dl). In fact, in these patients with very low levels of LDL-C (well below the aggressive “optimal” guidelines), every 10-mg/dl reduction in HDL-C was associated with a 10% increase in major CHD events. Other studies have also supported this relationship. In 2 post-ACS pravastatin studies of 13,173 patients, low HDL-C was a significantly stronger predictor of CHD events in patients with LDL-C <125 mg/dl compared with those with LDL-C >125 mg/dl (29). For every 10-mg/dl increase in HDL-C with pravastatin, CHD event rate decreased by 29% in those with LDL-C <125 mg/dl compared with only 10% reduction in those with LDL-C >125 mg/dl. In a recent large intensity trial of low-dose (10 mg) versus high-dose (80 mg) atorvastatin in patients with stable CHD, HDL-C remained a potent predictor of CHD risk even in those who achieved LDL-C levels of <70 mg/dl (30). In fact, according to the Framingham Heart Study, a patient with HDL-C of 25 mg/dl and LDL-C of only 100 mg/dl has the same CHD risk as does a patient with LDL-C of 220 mg/dl and HDL-C of 45 mg/dl (31).

The U-shaped relationship between HDL-C and all-cause mortality in the current study may be slightly surprising, with those in the highest quartile of HDL-C having higher mortality than those in the second and, especially, those in the third quartile; this effect was at least partly explained by alcohol abuse or dependence (suggesting that this relationship may be partly an association and not necessarily causal) (28,32). As the authors mentioned (28), previous epidemiologic studies from the U.S., Norway, Finland, and, especially, Russia noted a similar U-shaped relationship between HDL-C and total mortality, including deaths from excess alcohol, violence, or accidents. On the other hand, HDL-C levels above 75 mg/dl had been associated with prolonged life (the “longevity syndrome”) and freedom from CHD events (33). In fact, in a review by Glueck et al. (33) of 18 kindred with functional hyperalphalipoproteinemia and very high levels of HDL-C, men and women lived 5 and 7 years longer, respectively, compared with those in the general U.S. population.

**Conclusions**

Based on the conflicting data that we currently have regarding the risk of low HDL-C and therapies to increase HDL-C, how should clinicians and researchers proceed at present? As illustrated in the present report by deGoma et al. (28) in the Veterans Administration study, low levels of HDL-C are certainly potent predictors of CHD risk, even in the setting of quite low and desirable levels of LDL-C. We believe that HDL-C remains a viable target for reduction of CHD, particularly when using proven therapies (e.g., exercise training [34–36], weight reduction [36,37], moderate doses of alcohol [32], niacin [38–41], and certain fibrates [10–12,42]) that not only raise HDL-C but also stimulate RCT, translating into a reduction in CHD risk. At times, however, epidemiologic and preclinical studies (e.g., hormone replacement regimens, antioxidant vitamins, and so on), including that with a new and previously untested HDL-C intervention, torcetrapib (20), have not lived up to their promises and, in fact, have led us astray. However, it should be emphasized that raising HDL-C by all other means has been shown to be safe and effective, and, as yet, the only exception has been CETP inhibition. Therefore, we should not throw out the baby with the bath water. The “bust” with CETP inhibition (at least with torcetrapib) does not mean that we should abandon other HDL-C-elevating therapies. Nevertheless, future new classes of HDL-C therapies should focus on the quality (especially that which stimulates RCT), not just the quantity of HDL-C, and will require absolute proof of benefit and safety from large-scale randomized, controlled trials assessing CHD events, noncardiovascular morbidity and mortality, and all-cause mortality.

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