UNTOLD STORY OF HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL

SUMMARY

Majority of patients in both the primary and secondary prevention settings continue to experience significant residual risk for acute cardiovascular events even when their LDL cholesterol is lowered aggressively with combinations of lifestyle modification and pharmacologic intervention. As a result, there has been increased focus on targeting and treating low serum levels of high-density lipoprotein (HDL) cholesterol in an effort to further reduce risk for cardiovascular events. But now accumulating evidence suggests that simply increasing the amount of circulating high density lipoprotein cholesterol does not necessarily confer cardiovascular benefits. High density lipoprotein cholesterol particles vary substantially in size, density, composition, and functional properties. The varying functionality of different high density lipoprotein cholesterol subfractions most likely affects their relation to atherosclerosis. There is still much to be learned about HDL and its affect on CHD risk. The protectiveness of elevated HDL-C against CHD and its long-term sequelae is a subject of intense investigation throughout the world. HDL has the capacity to modulate a large number of atherogenic mechanisms, such as inflammation, oxidation, thrombosis, and cell proliferation. It is likely that the modulation of HDL function and its concentrations in serum will significantly impact future approaches to the management of cardiovascular disease in both the primary and secondary prevention settings. We have not understood the whole gamut of HDL completely. It is untold so far.

High-density lipoproteins (HDLs) have been well established to protect against the development of atherosclerotic cardiovascular disease. Decades of research on the function of HDL have yielded considerable insights and confusion. Recently, it has been appreciated that plasma HDL-C levels, while an important predictor of cardiovascular risk, do not tell the whole story. The story of HDL-C is still untold. The issue of HDL functionality has assumed major importance.[1] HDL is among the most fascinating and complex molecular assemblies yet to evolve in mammalian systems. Among lipoproteins HDL-C is also unique, in that it promotes the mobilization and clearance of excess lipid via the series of reactions collectively termed “reverse cholesterol transport.”[Figure-1] Numerous therapeutic agents are being developed in an attempt to modulate serum levels of HDL-C as well as its functionality. This article reviews the latest thinking.
Untold Story of High-Density Lipoprotien (HDL) Cholesterol

161

ester transfer protein (CETP) are associated with marked elevations in HDL-C levels but not necessarily with protection against coronary heart disease. The CETP inhibitors became the focus of a large drug discovery program in several pharmaceutical companies. The first CETP inhibitor (compound JTT705) used in clinical trials produced elevations in HDL-C on the order of 35% at the highest (900-mg) dose. The second such compound, torcetrapib, proved toxic despite causing a large increase in HDL-C levels and was withdrawn from clinical use. The significant and consistent finding with two new studies (IDEL and EPIC-Norfolk studies and Treating to New Targets study) is that elevated levels of HDL-C are no longer cardioprotective and may confer additional risk once corrected for apoA-I and apoB levels. [9,10]. This apparently counterintuitive finding may have important clinical implications: first, naturally occurring high levels of HDL-C may not protect against heart disease, and second, and herein lies the most important and provocative finding, HDL-C as a therapeutic goal may be fraught with potential dangers. This was the case in the torcetrapib trials (Illuminate, Illustrate, Radiance 1 and 2) [11,12]. One potential explanation may be that large cholesterol-enriched HDL particles lose some of their biological functions (cellular cholesterol efflux via the adenosine binding cassette transporters ABCA1, ABCG1; vascular endothelial vasomotor function modulation via SR-B1; antioxidant, antithrombotic, and anti-inflammatory properties). The finding that apoA-I, even when corrected for HDL-C and apoB, remains cardioprotective suggests that the means by which HDL particles are increased may be far more important than the cholesterol mass in HDL particles. Very recent data which appeared in February 09 issue of BMJ (British Medical Journal) by Briel et al suggest that simply increasing the amount of circulating high density lipoprotein cholesterol does not reduce the risk of coronary heart disease events, coronary heart disease deaths, or total deaths. [13] The results support reduction in low density lipoprotein cholesterol as the primary goal for lipid modifying interventions. Design of this study was systematic review and meta-regression analysis of randomised controlled trials and was sponsored by pharmaceutical house. Many researchers have raised their voice and LDL based strategies have been linked with statin marketing which is profitable at present. As the Briel et al point out, this is not a result of an intervention study aiming at different LDL-targets, but

HDL-C FUNCTIONALITY: MAJOR FOCUS OF RESEARCH NOW

When the clinical laboratory gives a report, it refers to the mass of cholesterol within the specific particle (i.e., the HDL-C level). Relatively little used is the measurement of serum apoA-I levels, the major protein moiety of HDL particles, which may reflect the number of circulating HDL particles. Given the extraordinary biological diversity of HDL particles, these measurements, HDL-C and apoA-I levels, do not provide much functional information. [2]

The cardioprotective effects of HDL seem to be multiple: prevention of low-density lipoprotein oxidation and of vascular wall inflammation and of thrombosis [3]; preservation of endothelial vasomotor, proliferative, and survival functions [4]; possible prevention of macropage apoptosis [5]; increase in endothelial progenitor cells [6]; and the well-characterized role in reverse cholesterol transport. It is this latter mechanism (i.e., removal of macropage cholesterol from the plaque) that is considered to be the most potent antiatherosclerotic mechanism of HDL.

BENEFIT OF RAISING HDL-C HAS BECOME CONTROVERSIAL

Evidence that raising high density lipoprotein cholesterol will reduce cardiovascular adverse outcomes remains controversial. Three decades ago, the first reports linking a low HDL-C level with the presence of coronary artery disease were reported and subsequently confirmed in multiple epidemiologic studies. On the basis of these studies, the HDL-C level became a categorical cardiovascular risk factor in the National Cholesterol Education Program guidelines [7], but not a therapeutic target. This epidemiologic association was thought to work in reverse: raising HDL should prevent coronary artery disease. This simple paradigm remains unproven to date.

With the discovery of ApoA-I Milano once firmly held belief that with HDL-C, more was better came into controversy. ApoA-I Milano, a naturally occurring variant of apoA-I, causes very low HDL-C levels without an increase in coronary heart disease events [8]; carriers of the mutation seem to enjoy a healthy life. It was also found that mutations that impair the function of cholesteryl
rather an observational meta-regression which risks bias by confounding and cannot support causal interpretation. Data by Goldenberg I et al demonstrate that, in this high-risk patient subset, 5 mg/dL increments in HDL-C were independently associated a significant 27% (p<0.001) reduction in cardiac mortality, whereas on-treatment reductions in LDL-C did not contribute to outcome after adjustment for HDL-C changes. The long-term survival benefit associated with of HDL-C modification was also substantiated in an extended 16-year follow-up study of the BIP trial. [14] Furthermore, in a recent analysis of the BIP population [15] they have shown that the benefit of raising HDL-C is related to baseline serum levels of LDL-C. Thus, HDL-C modification was associated with an enhanced survival benefit among patients with low baseline LDL-C (<130 mg/dL), whereas a significant benefit of LDL-C modification was evident only among patients with elevated baseline LDL-C (>130 mg/dL). These results further demonstrate the substantial benefit associated with increasing HDL-C, provided appropriate selection of patients and therapeutic modalities. These apparently conflicting data can be attributed to important differences in the selected populations among the studies. Findings by Briel et al may provide erroneous and misleading implications for an important proportion of currently treated patients with the common raised triglycerides-low HDL-C dyslipidaemia, who have a high risk for major cardiac events even when their LDL-C levels are in the normal- or low-range. [14] This important subset of patients should receive a more comprehensive lipid modifying therapeutic approach, designed also to raise HDL-C and reduce triglycerides, rather than a narrow approach that is based solely on LDL-C modification as suggested by Briel et al.

Worth mentioning is also a very recent systematic MEDLINE literature search which concluded that association between HDL-C and CVD risk is significant and strong, although further evidence may be needed to establish whether this association is consistent across other lipid risk factors. Furthermore, uncertainties remain regarding the mechanism in which HDL-C exerts its effects, suggesting a need for further research focused on new methods for reliable measurement. [16]

HDL AS A MODULATOR OF SYSTEMIC INFLAMMATION: THE DOUBLE JEOPARDY OF HDL

High-density lipoprotein (HDL) is conventionally believed to possess many features that protect against atherosclerosis. However, these lipoproteins may be modified in certain individuals and/or circumstances to become pro-inflammatory. 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 [17-20]. Augmenting the inflammatory response may benefit in connective tissue diseases and combating infection, but in atherosclerotic disease such as ACS, this effect is likely detrimental [19,20]. 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 [19,20]. Therefore, HDL-C may actually lower CHD risk in chronic atherosclerosis but possibly potentiate risk in the setting of ACS.

APO-A-I MILANO – (KNOWN AS THE “LONGEVITY PROTEIN”): THE MYSTERY OF HDL

Story of Apo-a-I Milano is something a little more complicated than just raising HDL-C. About 20 years ago in Limone sul Garda, a small village near Milan, Italy, about 40 villagers were found to be carriers of a naturally occurring variant of apo A-I now known as apo A-I Milano. Apo A-I is the major constituent of HDL-C. It appears from church birth records, each patient was traceable to a common ancestor in 1780. Genetic studies identified a point mutation in the apolipoprotein A-I gene at position 173, in which cysteine is substituted for arginine. This mutation causes the formation of apolipoprotein A-I Milano homodimers (A1 Milano/A1 Milano) and apolipoprotein A-II heterodimers. In addition to very low plasma concentration of HDL, other major factors in reverse cholesterol transport, including LCAT and CETP, are also markedly reduced in carriers. Apolipoprotein A-I Milano markedly accelerates reverse cholesterol transport in transgenic mice and in humans. Recombinant apolipoprotein A-I Milano has been formulated into liposomes that reduce macrophage volume, aortic atherosclerosis, and the proapoptotic effect of oxysterols (produced during LDL cholesterol oxidation) in hypercholesterolemic rabbits and apolipoprotein E-deficient mice.
The history of the "elixir of long life", which fortuitously began centuries ago due to the geographic isolation of the village, continues, passing from one generation to another. ApoA-I is a large protein comprising 243 amino acids, which means that venous administration is necessary. In addition, manufacture of apoA-I is difficult and expensive. Research has, therefore, been directed towards finding smaller peptide mimetics that produce similar results to apoA-I, but that are easier to manufacture and administer. A potent peptide, 4F, which was synthesized wholly from D-amino acids, could be given orally. Use of 4F significantly improved the function of HDL in mice and monkeys. Importantly, D-4F stimulates the conversion of proinflammatory HDL to anti-inflammatory HDL. If ultimately successful, D-4F offers an appealing and more cost-effective way of delivering an apoA-I mimetic to patients with low HDL-C and/or compromised capacity for RCT. A number of other apoA-I mimetic peptides are also in development.[21]

TARGETTING CETP AS A POTENTIAL METHOD FOR CARDIOVASCULAR RISK REDUCTION [FIGURE-2]

The potential importance of cholesteryl ester transfer protein (CETP) was recognized when it was noted that mice and rats lacked plasma CETP activity, had HDL as their major plasma lipoprotein, and were resistant to diet-induced atherosclerosis. In contrast, rabbits were found to have very high CETP activity levels and to develop marked elevations of apoB-containing lipoproteins and significant atherosclerosis when fed diets rich in saturated fat and cholesterol. In 1990 Inazu and colleagues reported very high HDL cholesterol, increased large HDL, decreased CAD risk, and potentially enhanced longevity in Japanese kindreds associated with CETP deficiency. Later Japan Tobacco (JTT-705; Japan Tobacco Inc. Tokyo, Japan) and Pfizer (torcetrapib; Pfizer Inc, New York, NY) began development of CETP inhibitors. However, excess mortality, increased blood pressure, and no benefit on coronary or carotid atherosclerosis have been associated with the use of one of these compounds, torcetrapib. [11] This compound has been reported to bind to CETP on HDL particles and to form a nonproductive complex that prevents transfer of all neutral lipids and phospholipids between HDL and other lipoproteins. Not only is HDL involved in reverse cholesterol transport but it also has anti-inflammatory and antioxidant properties. Torcetrapib may interfere with some of these functions. Now that the structure of CETP is known, it should be possible to design CETP inhibitors that do not interfere with any of these functions, do not bind to HDL or raise blood pressure, and promote regression of coronary atherosclerosis and CAD risk reduction. Another view would be that all CETP inhibition is unfavorable, and that development of this class of compounds should be abandoned.[22] Torcetrapib 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.[2]

Early studies with other agents, such as Merck's anacetrapib, suggest that it may not be the CETP inhibition itself that causes toxicity—as has been feared—but an adverse effect of the Pfizer compound alone. Phase 3 trials are now ongoing with another CETP inhibitor, dalcetrapib (Roche), and an intensive phase 2 safety study with anacetrapib is also under way.

NOVEL THERAPIES FOR INCREASING HDL

Many recent advances are on the way. [Table-1]
10 POINTS OF UNTOLD STORY OF HDL-C

1. Current guidelines recognise high density lipoprotein cholesterol as an independent cardiovascular risk factor but the extent to which changes in high density lipoprotein cholesterol alter risk of coronary heart disease events remains controversial.

2. The study by Briel et al which showed that simply increasing the amount of circulating HDL-C does not reduce the risk of coronary heart disease events, coronary heart disease deaths, or total deaths was supported by an unrestricted educational grant from Pfizer. It is interesting how a statistical exercise financed by Pfizer about HDL-cholesterol winds up suggesting that raising HDL does not matter while lowering LDL-cholesterol does - in cardiovascular events and all-cause deaths. This study has flaws. It appears that bad cholesterol [LDL] is good marketing while good cholesterol[HDL] is not. There is still much to be learned about HDL and its affect on CHD risk.

3. Recently the issue of HDL functionality has assumed major importance. Available measures of the function of high density lipoprotein cholesterol include indices of inflammation, oxidation, monocyte chemotaxis, nitric oxide production, endothelial function, and thrombosis, as well as tests assessing the reverse cholesterol transport effects of treatments.

4. Recent updates of the NCEP guidelines confirmed low levels of high density lipoprotein cholesterol (<40 mg/dl) as a major cardiovascular risk factor. Although they refrained from making recommendations about specific targets for raising high density lipoprotein cholesterol concentrations.

5. The lack of association between treatment induced change in high density lipoprotein cholesterol and the risk of coronary heart disease events, coronary heart disease deaths, or total deaths in some studies raises questions about the rationale for development of therapeutic agents that increase high density lipoprotein cholesterol.

6. The discovery of ApoA-I Milano suggests that coronary-artery disease is much more dynamic than anyone had thought. The mystery of ApoA-I Milano when completely understood, will make a big shift in cardiovascular management. It will unravel an entirely new strategy for fighting heart disease.

7. The failure to improve intracoronary atheroma burden in ultrasound studies and the excess mortality seen in the LLUMINATE trial by torcetrapib does not mean that cholesteryl ester transfer protein inhibitors’ era is over.

8. Determination of HDL anti-inflammatory/proinflammatory function will likely yield important additional information beyond that available from simply knowing the quantitative level of HDL-C in an individual. This additional information will likely improve predictive accuracy for CHD and may also provide new strategies for the prevention and treatment of atherosclerosis.

9. Raising small HDL particles (often referred to as “nascent” HDL particles) may be more important than generating large, cholesterol-rich HDL particles. Drugs that modulate HDL-C levels can be conceptually seen as those that decrease catabolism (CEPTP inhibitors, possibly niacin) and those that increase the production rate (fibrate and possibly small molecules that increase apoA-I production, and agonists of the liver-specific receptor LxR to increase ABCA1-mediated cholesterol efflux from cells.

10. In future HDL-based strategies may be much better in cardiovascular risk reduction than today’s LDL-based scenario.

REFERENCES


