Low density lipoprotein cholesterol (LDL-C) is the appropriate focus of primary and secondary prevention of coronary heart disease (CHD) in patients with hypercholesterolemia. Basic investigation and evidence from animal models and epidemiological studies lend robust support to its role as a major risk factor for CHD. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors reduce plasma concentrations of LDL-C and have consistently shown substantial benefits in primary and secondary prevention. However, although treatment has dramatically reduced the risk of recurrent CHD in secondary prevention trials, it is becoming increasingly evident that even reduction of LDL-C to 100 mg/dL may not be adequate to restore the risk levels of such patients to the risk levels of those individuals free of CHD. Despite mean on-treatment LDL-C concentrations ranging from 97 to 113 mg/dL, recurrent CHD event rates in 3 secondary prevention trials were all ≈2% per year.1–3 The CHD event rate in the 40% subset of participants in the Scandinavian Simvastatin Survival Study who lowered their LDL-C levels to <100 mg/dL (mean 95 mg/dL) was also 2% per year.4 These event rates are unacceptably high, and 2 approaches are being explored to determine whether there is room for improvement: (1) more aggressive lowering of LDL-C and (2) treatment of the “lipoprotein complex.”

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Although the first of these appears intuitively attractive, careful examination of curves relating CHD event rates to on-treatment LDL-C in the trials outlined above suggests an asymptotic relationship. The CHD risk appears to “flatten out” at 2% per year for LDL-C levels <120 mg/dL. In addition, although there are no data to show that dramatic reduction of LDL-C (eg, <50 mg/dL) might lead to increased risk of adverse events, subgroup analysis from the Multiple Risk Factor Intervention Trial (MRFIT) suggests an increased risk of hemorrhagic stroke in individuals with very low levels of LDL-C.5 Two ongoing clinical trials that are testing the “lower is better” hypothesis (the Treat to New Targets [TNT] trial with atorvastatin and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine [SEARCH] with simvastatin) will provide insight into this very important issue.

A second approach to reduce recurrent CHD events further might be to treat the lipoprotein complex rather than LDL-C alone. Patients with CHD often have not only elevated LDL-C levels but also elevated plasma concentrations of triglycerides and reduced HDL cholesterol (HDL-C) levels. The combination of elevated triglycerides and reduced HDL-C is particularly risky because it often reflects an underlying profound disturbance in glucose homeostasis, the insulin resistance syndrome, or frank diabetes.6

Although a recent meta-analysis suggests an association between plasma concentrations of triglycerides and incident CHD,7 this link has been hard to forge. In explanation, there may be subpopulations of triglyceride-rich particles (remnant lipoproteins and IDLs) that are particularly atherogenic. Each triglyceride-rich particle has a variable number of molecules of triglyceride but only 1 molecule of apoB, and the ratio of triglyceride to apoB in the nonatherogenic particles may be far greater than that for the atherogenic particles. For this reason, the triglyceride of the nonatherogenic particles may dwarf that of the atherogenic particles, whereas their apoB may be comparable, providing a partial rationale for use of apoB as a marker for risk. An additional rationale for use of apoB as a marker is derived from its better representation of LDL particle number than LDL-C concentrations, particularly in patients with small, dense, triglyceride-rich, cholesterol-poor LDLs.8

Recently, investigators have experienced a resurgence of interest in the role of HDL-C as a CHD risk factor and target for intervention. It is well established that reduced HDL-C is a powerful independent risk marker for CHD. However, 3 lines of evidence have lessened enthusiasm for considering HDL as a primary target for intervention. First, although long believed to be an important vehicle for “reverse cholesterol transport,” until recently, metabolism of HDL has been less well understood than that of LDL and/or triglyceride-rich particles. Sources of cellular cholesterol and mechanisms of hepatic uptake of HDL-C were poorly understood. Recent discovery of the ATP-binding cassette (ABC-A1) protein,9 of the scavenger receptor class B, type 1 (SR-B1) receptor,10 and of the hepatic uptake of apoA-I, the major apolipoprotein associated with HDL,11 has stimulated new research in HDL metabolism. Second, many examples exist of conditions in which low levels of HDL-C do not necessarily confer increased CHD risk and high levels do not necessarily confer protection. Low saturated fat–low cholesterol diets that improve plasma concentrations of LDL-C are recommended for reducing CHD risk, but they also cause reductions in plasma concentrations of HDL-C.12 In addition, patients with the

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Arterioscler Thromb Vasc Biol. 2000;20:2333-2335.)

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genetic variant of apoA-I (apoA-I Milano) have low levels of HDL-C as well as apoA-I but no increased CHD risk,13 whereas certain individuals with increased HDL-C may lack protection from CHD, dependent on the underlying phenotype.14 Third, earlier clinical trials were equivocal regarding CHD risk reduction associated with HDL-C–raising strategies. Although the data for risk reduction associated with niacin treatment (Coronary Drug Project) and gemfibrozil treatment (Helsinki Heart Study) were convincing, clofibrate trials were, in general, negative (Coronary Drug Project, World Health Organization).

The recent publication of the VA-HDL Intervention Trial (VA-HIT) has changed our thinking regarding the potential role of the lipoprotein complex in cardiovascular disease. Gemfibrozil raised HDL-C 6%, lowered triglycerides 31%, and had no effect on LDL-C in men with a prior history of CHD, low LDL-C (111 mg/dL), and low HDL-C (32 mg/dL).15 Risk of recurrent CHD was reduced by 22%. Post hoc analyses of the data support the view that increases in HDL-C and/or reductions in remnant-like particles17 associated with gemfibrozil therapy were primarily responsible for risk reduction. The recently reported data from the Bezafibrate Infarction Prevention (BIP) study contradict those of VA-HIT. Bezafibrate raised HDL-C 18%, lowered triglycerides 21%, and did not affect LDL-C in men with CHD, low HDL-C (35 mg/dL), and high LDL-C (148 mg/dL). Coronary risk was not reduced except in the subset with triglycerides >200 mg/dL at baseline.18 However, the BIP study was conducted in individuals with higher levels of LDL-C than those in VA-HIT, and it is possible that at higher levels, LDL-C determines CHD event rates (BIP), whereas when LDL-C is lower (<120 mg/dL), HDL-C becomes the primary determinant of events (VA-HIT). In support of this concept, recent analysis of the data of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) shows that baseline LDL-C, HDL-C, and apoB were significant predictors of first acute major coronary events but that only on-treatment apoB and the ratio of apoB/apoA-I were predictive of subsequent risk.19 On-treatment LDL-C was 115 mg/dL and did not predict events.

The observations of van Lennep et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology support the concept that at low on-treatment levels, LDL-C is only loosely related to CHD risk.20 CHD patients who responded to statin treatment with LDL-C reductions of at least 30% and attained mean LDL-C levels of 97 mg/dL had an average recurrent CHD event rate of 4% per year. At this low level of LDL-C, on-treatment levels of total cholesterol, LDL-C, and triglycerides did not predict subsequent events. By contrast, on-treatment apoA-I and apoB were predictive of future events in men and women, and on-treatment HDL-C was predictive in women. ApoB in these patients may better capture a larger panoply of atherogenic particles than LDL-C and may thus indeed be a better marker of risk, particularly in patients with low levels of LDL-C. Furthermore, at low levels of LDL-C, HDL-C may grow in importance as a risk factor. The high CHD event rate and the residual predictability of on-treatment apoB and apoA-I suggest room for further treatment improvement.

The present study leaves us with important remaining questions. First, if apoA-I and/or HDL-C remains independently related to risk after treatment of LDL-C, does this argue for use of statins with particular benefit for apoA-I? Recent head-to-head comparisons have uncovered differences between statins in the effects on HDL-C and apoA-I. In 1 study, simvastatin increased HDL-C and apoA-I more than atorvastatin at high doses that were equipotent for lowering LDL-C.21 There is evidence for a negative dose-response effect of atorvastatin on HDL-C and apoA-I.22 Whether these differences between statins in effects on HDL-C and apoA-I will translate into differences in clinical outcome is unknown. Alternatively, should we consider further beneficial modulation of the lipoprotein complex through, for instance, use of a fibrate or niacin in combination with statin? Are there increased risks associated with this combination, and will the benefits outweigh any increased risks? The Lipids in Diabetes Study (LDS) is an ongoing 2×2 factorial trial of primary prevention of CHD (to be completed in 2004) that is randomizing type 2 diabetic patients to cerivastatin and/or fenofibrate.

Second, should we routinely use apoproteins rather than LDL-C and HDL-C to risk-stratify individuals? This issue has been hotly debated for over a decade, and although there are attractive features to using apoproteins (as mentioned above), consistency of data supporting this approach is lacking, and there are many alternative candidate “nontraditional” lipid parameters, eg, Lp(a), LDL-C size, and non–HDL-C, that might also be considered. The Quebec Cardiovascular Study supports apoB as an important risk factor.23 However, recent data in diabetics do not suggest any increased predictive power of apoB and/or apoA-I for coronary events beyond that provided by conventional lipid profiles.24 Standardization of measurement of apoproteins remains far less advanced than that for lipoprotein cholesterol, and for the general population, there are strong correlations between apoB and LDL-C and between apoA-I and HDL-C. Nonetheless, in certain cases in which risk is uncertain (eg, in patients with normal lipid profiles who have very unfavorable family history or manifest coronary disease), measurement of these nontraditional lipid moieties may have a role.

Finally, what is the mechanism of risk reduction associated with increased HDL-C? Recent growth in understanding of metabolism of HDL is gratifying. However, perplexities remain regarding the direct role of HDL in coronary disease. Is the absolute level of HDL or its metabolic fate more important for CHD risk? Do metabolic parameters that appear to correlate with its level in plasma (eg, hepatic lipase and cholesterol ester transfer protein) bear unique roles in CHD risk? To what extent is the association of HDL with the metabolic syndrome responsible for its apparent risk?

In summary, we have made great strides in the treatment of CHD through lipid-lowering therapy, particularly through the use of statins. However, treatment does not fully reduce the excess risk of recurrent events associated with dyslipidemia. Thus, there is room for further improvement. Secondary prevention strategies focusing on the lipoprotein complex rather than LDL-C alone may further reduce risk, and clinical trials to evaluate the efficacy of such strategies are important. In addition, advances in understanding of the role of HDL and its apoproteins in cardiovascular disease are important to provide rationale for adequate secondary prevention of CHD over the years to come.
References


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Arterioscler Thromb Vasc Biol. 2000;20:2333-2335
doi: 10.1161/01.ATV.20.11.2333
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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