Is lowering low-density lipoprotein an effective strategy to reduce cardiac risk?

Lipid Management to Reduce Cardiovascular Risk

A New Strategy Is Required

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“It is not good to settle into a set of opinions. At first putting forth great effort to be sure that you have grasped the basics, then practicing so that they may come to fruition is something that will never stop for your whole lifetime. Do not rely on following the degree of understanding that you have discovered, but simply think...This is not enough.”

Hagakure, Yamamoto Tsunetomo, September 10, 1716 (a Samurai)1

For the past 22 years, substantial national efforts have been directed toward reducing the average blood low-density lipoprotein cholesterol (LDL-C) level of the American population. This initiative was initially prompted by the successful results of the Lipid Research Clinic–Coronary Primary Prevention Trial (LRC-CPPT), which first proved that reducing LDL-C resulted in a statistically significant reduction in cardiovascular events.2 The intent of these efforts has been to reduce the human suffering and economic cost of cardiovascular disease. In the subsequent 2 decades, a plethora of monotherapy cholesterol-lowering drug trials has consistently reported a statistically significant 25% relative risk reduction for cardiovascular events. These findings form the basis for the current Adult Treatment Panel (ATP) III guidelines and the recent call to adjust the LDL-C goal even lower.3

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Although this level of success in the fight against heart disease is laudable, a great danger for our patients’ future health lies in the assumption that cholesterol reduction alone will stem the tide of coronary heart disease (CHD). It is wise and prudent to remember the words of Yamamoto Tsunetomo that “this is not enough.” The purpose of this article is to challenge healthcare workers to consider the possibility that the cholesterol-lowering program has in large part failed to stem the epidemic of CHD and that the well-meaning focus on LDL-C reduction has deflected interest in other therapeutic aspects of lipoprotein treatment that provide equal or greater benefit. This myopic focus on LDL alone is not surprising because, so far, guidelines have not adequately addressed other evidence. This article reviews the knowledge supporting this concept that has been acquired since 1996.4 At that time, it was noted that despite significant LDL-C reduction, large numbers of subjects in the treatment groups continued to have cardiovascular events despite achieving significant LDL-C reduction. In the subsequent 10 years, important advances have been made in the understanding of lipoproteins that have clinical relevance for patient management and improved clinical outcomes beyond LDL-C reduction alone.
Blood Cholesterol–Lowering History

In the 21st century, atherosclerosis is well established as the leading cause of death in most industrialized nations. Large population-based studies have identified several risk factors as targets of intervention that may reduce cardiovascular disease. This approach for identifying “high-risk” populations was used to focus efforts on a population subset that could derive the most benefit from a treatment targeted to disorders such as hypertension or elevated blood cholesterol.

In the field of cholesterol and heart disease research, early efforts provided some evidence that cholesterol lowering was of benefit but were marred by adverse drug interactions such as that seen with thyroid, estrogen, and clofibrate treatments. It was not until the completion of the LRC-CPPT, which used a combination of moderately low-fat diet and cholestyramine in men with hypercholesterolemia, that it was established that reducing elevated LDL-C resulted in fewer CHD events (significant by a 1-tailed test). After the success of the LRC-CPPT, hydroxymethyl glutaryl coenzyme A reductase inhibitor medications (statins) became available that achieved greater LDL-C reduction with fewer side effects. These remarkable compounds made achieving reduced LDL-C values relatively easy, and their success forms the basis of the paradox that easily achieved LDL-C reduction may, in part, be responsible for the failure to substantially stem the tide of CHD.

On the basis of multiple clinical trials, the ATP-I recommended an LDL-C goal of <130 mg/dL to assist CHD risk reduction. Since the publication of ATP-I in 1988, multiple other clinical trials have reported that even greater LDL-C reduction in both primary and secondary prevention populations can achieve even greater reductions in CHD relative risk. The success of these trials prompted ATP-II and ATP-III to adjust LDL-C goals downward to the current recommendations. At the same time that large LDL-C–lowering trials were being conducted, several National Institutes of Health (NIH) trials that combined LDL-C lowering with high-density lipoprotein cholesterol (HDL-C) raising were successfully concluded. The results of these trials challenge the concept that LDL-C reduction alone is sufficient to stem the tide of CHD.

One danger of a medical therapy, deemed to be statistically significant in large clinical trials, is the tendency to assume that almost all patients will benefit in a similar manner from that single therapy and thus to ignore other potentially beneficial treatments. Recently, the results of a series of statin-induced cholesterol-lowering trials have been used to suggest that a new LDL-C goal of <70 mg/dL should be embraced nationally. A major conclusion of the 1996 article “Beyond LDL Cholesterol” was that a large number of patients taking cholesterol-lowering medications, and achieving lower LDL-C values, continued to have clinical events. This continues to be true even with the substantially greater absolute LDL-C reduction achieved in recent trials. At this point in the history of cholesterol reduction, it is important to pause and discuss the possibility that statistical (mathematical) significance does not necessarily equate to clinical relevance.

Relative Risk Reduction and Professional/Public Confusion

Clinical trials using monotherapy have consistently reported an ~25% relative risk reduction in cardiovascular events regardless of the lipid-lowering medication class (statin, fibrate, niacin) used. This 25% reduction in risk is the “relative risk,” i.e., the difference between the number of events in the treated group relative to the number of events in the control group. To achieve this degree of relative risk reduction, in cholesterol-lowering studies, it is necessary to treat ~30 individuals to prevent 1 event. This amount of “success” requires that a huge number of individuals be treated yet leaves a large number of patients in the treatment group experiencing a myocardial infarction or CHD death even with aggressive LDL-C reduction (Figure 1).

It is not uncommon for the public to interpret this 25% risk reduction as meaning that 25% of the entire population was saved from an event as a result of the treatment. In fact, if there were 1000 subjects in the treatment group and 1000 subjects in the placebo group and if 100 events were experienced in the placebo group and 75 events in the treatment group, the difference between 100 and 75 is the 25% relative risk reduction in events (n = 25), not 25% of 1000 subjects (n = 250). What clinicians must now consider is the possibility that LDL-C reduction alone is not adequate to...
stem the epidemic of CHD events when LDL-C values are below “hypercholesterolemic” levels. Although laudable, a 25% relative risk reduction is insufficient to treat this disease; rather, relative risk reductions of 90% should be the goal and have been achieved in some NIH combination lipid drug trials.

Statistical Significance Does Not Necessarily Mean Clinical Relevance

Statistical, or mathematical, significance is a tool useful in calculating how likely it is that the results of an experiment are due to chance alone and not really due to the intervention. Achieving statistical significance generally means that the results observed probably were not due to chance alone and probably were the result of the intervention used in the clinical trial. A value of \( P=0.05 \) indicates that there is still a 1 in 20 chance that the results were due to chance alone and not the intervention. Thus, statistical significance is a mathematical tool to test the hypothesis that the results observed were probably due to the intervention, but it does not necessarily mean the results are clinically significant or even meaningful.

Small absolute change can be mathematically (statistically) significant and indicate that the intervention achieved some result. In blood cholesterol–lowering trials, however, large numbers of people achieving statistically significantly lower LDL-C did not benefit from the intervention; thus, clinical relevance may be weak despite an impressive probability value. In a meta-analysis of 5 statin clinical trials, in 30 817 men and women, a 27% relative risk reduction in CHD events was reported. However, this represents the difference between 2042 events in the placebo group and 1490 events continuing to occur in the statin treatment group. To achieve this degree of event reduction, \( \approx 30 \) subjects had to be treated to prevent 1 event.

Another example of debatable clinical relevance is the argument to reduce LDL-C goals even further, which has been in part on the results of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVEIT) trial. In PROVEIT, 40 mg/d pravastatin was tested against 80 mg/d atorvastatin for 2 years in subjects who had been hospitalized for the acute coronary syndrome. The group randomized to atorvastatin achieved a mean LDL-C of 62 mg/dL; the pravastatin group achieved 95 mg/dL. A statistically significant 16% relative risk reduction in clinical events (\( P=0.005 \)) was reported, and it was concluded that in acute coronary syndrome patients, an intensive lipid-lowering statin regimen provided greater protection than a standard statin regimen and indicated that such patients benefit from lowering of LDL-C to levels substantially below current target levels. This statistically significant 16% relative risk reduction represents a primary event rate of 26.3% in the pravastatin group compared with 22.4% in the atorvastatin group (Figure 2). However, the conclusion that the data are evidence that intensive lipid lowering will provide protection against early recurrent cardiovascular events, although true for a small group, ignores the 22.4% of subjects in the intensively treated group who achieved a low LDL-C yet experienced a clinical event. Thus, intensive lipid lowering with a statin only did not successfully prevent an event in a large group of acute coronary syndrome patients.

The potential harm in the assumption that mathematical significance is equivalent to clinical significance is that many public and professional individuals have the misleading impression that if they just get their LDL-C low enough, they will be free of CHD risk. The results of 5 large statin trials show that this is a dangerous misconception in that it leaves large numbers of patients still at risk for cardiovascular events.

Investigations using coronary arteriography as an end point also have been revealing in regard to possible misinterpretation of statistical significance and clinical relevance. Multiple LDL-C–lowering only arteriographic trials have documented a statistically significant reduction in the rate of arteriographic progression but no mean regression. This supports the concept that LDL-C reduction alone can slow the rate of progression but that mean arteriographic regression is difficult to achieve. In comparison, arteriographic investigations using combination drug therapy that both lowers LDL-C and raises HDL-C have frequently achieved evidence of arteriographically defined “regression” (Table 1). The Reversal of Atherosclerosis With Lipitor (REVERSAL) trial and A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound–Derived Coronary Atheroma Burden (ASTEROID) are the LDL-C-lowering only exceptions that used intravascular ultrasound and achieved some degree of intravascular ultrasound–determined regression: −0.4% in REVERSAL and −1.0% in ASTEROID for percent atheroma volume. The trial design for ASTEROID used each subject as his or her own control, not a control group as in previous investigations. In ASTEROID, the 53% reduction in LDL-C also was associated with a 15% increase in HDL-C. It is of interest to note that a small combination LDL-C lowering plus HDL-C

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**Figure 2.** Results of PROVEIT indicating the statistically significant reduction in clinical events with atorvastatin 80 mg/d vs pravastatin 40 mg/d. Arrow indicates the relatively large group of patients who continuing to suffer cardiovascular (CV) events despite treatment with atorvastatin. Reprinted from Cannon et al, with permission from the Massachusetts Medical Society.
Number Needed to Treat

The number needed to treat (NNT) represents the number of patients who need to be treated to prevent 1 cardiovascular event and reflects the efficiency of the treatment modality.22 The smaller the number is, the more efficient the treatment is. Table 2 lists a number of clinical end-point and arteriographic investigations that used LDL-C–lowering only therapy or LDL-C–lowering plus HDL-C–raising drug therapy. The results of these trials must be interpreted in light of the different types of patient populations and duration of treatment, so a direct 1-to-1 comparison is difficult. Nevertheless, NNT can be used to assess relative differences in efficiency. The duration of the studies also varies, and to adjust for the duration variable, the NNT per year of treatment was calculated.

Some LDL-C–lowering clinical end-point studies achieved a low NNT per year such as the Scandinavian Simvastatin Survival Study (SSSS), which achieved an NNT of 11.7 and an NNT per year of 2.2.23 This efficiency was achieved in part by treating a high-risk population with very elevated LDL-C (baseline mean, 188 mg/dL) with a relatively powerful drug designed to reduce LDL-C. However, the 6 clinical end-point LDL-C–lowering statin studies (Table 2) achieved an average NNT of 41.0 and an average NNT per year of 8.5, reflecting an overall less efficient therapeutic approach. Three recent trials have compared 1 statin brand or dose against another.18,24,25 In these “statin versus statin” trials, the average NNT was 64.6, and the average NNT per year was 19.1. Arteriographic LDL-C–lowering statin studies achieved an average NNT of 64.3 and an average NNT per year of 28.7.

In comparison, LDL-C–lowering and HDL-C–raising drug studies have been more efficient, achieving an average NNT of 9.6 and an average NNT per year of 3.4. The LDL-C–lowering plus HDL-C–raising studies have primarily used arteriographic outcomes as primary end points. The rather inefficient results of the LDL-C–lowering only trials compared with LDL-C–lowering combined with HDL-C–raising trials should be considered in view of the recent call to lower LDL-C goals even further because this may detract attention from the beneficial aspects of lipoprotein metabolism not directly linked to LDL-C reduction. This is relevant because the combination drug therapy used in the NIH trials is readily available and relatively inexpensive.

The Need To Go Beyond LDL-C Reduction and Incorporate Aspects of Reverse Cholesterol Transport

It is important for clinicians to appreciate the need for additional treatment other than simple LDL-C reduction for 3 important reasons. First, an LDL-C central focus allows many patients to experience a CHD event even with adequately controlled LDL-C values. Second, disorders that contribute to CHD risk other than LDL-C are common in the coronary artery disease population even with LDL-C <100 mg/dL (Table 3). Third, effective therapies currently exist to treat these other disorders, and new therapies under development will greatly expand the armamentarium. A key component of
the most successful arteriographic “regression” trials has been the combination of LDL-C reduction with enhanced reverse cholesterol transport as reflected by substantially increased HDL-C and HDL2 levels.

Understanding the reverse cholesterol transport process is a clinically important topic because current and future pharmacological treatments can have a beneficial effect on reverse cholesterol transport and play an important therapeutic role that amplifies the benefit of LDL-C reduction.26 There are 5 components of reverse cholesterol transport that are useful for the clinician to understand: enzyme activity, transfer proteins, membrane modulators, apoproteins, and HDL subclasses.27

Table 2. Clinical Event Reduction (Fatal and Nonfatal Myocardial Infarction) in Investigations Using LDL-C Reduction Alone Versus LDL-C Reduction Plus HDL-C Elevation

<table>
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<th>Drug</th>
<th>Duration, y</th>
<th>Patient Type</th>
<th>Baseline Mean LDL-C, mg/dL</th>
<th>Control, n</th>
<th>Treatment, n</th>
<th>Events Control Group, n</th>
<th>Events Treatment Group, n</th>
<th>RRR, %</th>
<th>Absolute, %</th>
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| Chol indicates cholesterol; Asympto, asymptomatic; ACS, acute coronary syndrome; HyperapoB, hyperapolipoprotein B; FHC, familial heterozygous hypercholesterolemia; and CABG, coronary artery bypass graft surgery. Other abbreviations as in Table 1. Relative risk reduction (RRR) is presented with the absolute risk reduction. The NNT to prevent 1 event is listed, as well as the NNT per year of study.22 LOCAT revealed no clinical event difference between groups, and the NNT is represented as not applicable. Clinical events were selected to be fatal and nonfatal myocardial infarction for purposes of comparison. To convert cholesterol from milligrams per deciliter to millimoles per liter, multiply millimoles per liter by 0.0259.
HDL-C–Raising Therapy

On the eve of new treatments designed to increase HDL-C, it is important to emphasize that an effective HDL-C–raising medication has been used clinically for >50 years. Nicotinic acid has been the lipidologists’ drug of choice for increasing HDL-C since the first demonstration that it improves lipid profiles in 1955, followed by successful clinical trial results in 1964. This time-proven medication can achieve substantial elevations in HDL-C and HDL2; reductions in LDL-C, high-sensitivity C-reactive protein, and fibrinogen; and reductions in clinical events and all-cause mortality. It also can help induce arteriographic regression.

The mechanism of action of nicotinic acid has been clarified with the elucidation of the nicotinic acid receptor, which is a G protein–coupled receptor called HM74, and the gene that codes for the protein has been cloned. It also has recently been demonstrated that nicotinic acid stimulates a critical step in the reverse cholesterol transport scheme. The ATP-binding cassette promotes transfer of cholesterol out of macrophages for uptake by HDL and is stimulated by nicotinic acid. This attribute of nicotinic acid helps drive cholesterol out of fatty plaque and onto HDL3 for eventual removal. This nicotinic acid–induced promotion of cholesterol efflux out of plaque helps to explain the success of atherosclerosis regression trials that used nicotinic acid as 1 component of combination drug therapy. Contrary to popular belief, with appropriate clinical support, high compliance rates can be achieved with nicotinic acid.

LDL-C–Lowering Only Therapy Versus LDL-C–Lowering Plus HDL-C–Raising Therapy Trials

For purposes of this discussion, combination therapy is defined as ≥2 pharmacological treatments designed to affect lipoprotein metabolism in 2 different directions. The most common example is 1 drug to reduce LDL-C and another to increase HDL-C.

Studies using such a combination of lipid medications have consistently demonstrated better clinical and arteriographic results compared with LDL-C–lowering only studies. Most combination lipoprotein drug studies have used arteriographic end points and consequently smaller groups compared with clinical end-point trials. However, in addition to arteriographic change, the HDL Atherosclerosis Treatment Study (HATS) investigated the effect of combination treatment on clinical events as a primary hypothesis. The results of the combination drug studies are informative and clinically important to achieve the best clinical outcome for CHD patients. Table 2 compares clinical event reduction in LDL-C–lowering only versus LDL-C–lowering plus HDL-C–raising trials. In Table 2, combination therapy trials have achieved an average 71.6% relative risk reduction compared with 27.2% in monotherapy clinical end-point trials and 29.6% in monotherapy arteriographic trials. It is also helpful to appreciate that long-term follow-up of combination drug
trials has revealed dramatic reduction in events and mortality. A 10-year follow-up of Familial Atherosclerosis Treatment Study (FATS) and a 7-year follow-up of the Cholesterol Lowering and Atherosclerosis Study (CLAS) have reported 93% and 62% reductions in death and myocardial infarction.41,42 Table 1 compares arteriographic outcomes from LDL-C–lowering only versus LDL-C–lowering plus HDL-C–raising trials. It is noteworthy that although LDL-C–lowering only drug studies have slowed the rate of arteriographic progression, arteriographic regression is uncommon. In contrast, 3 of the 5 LDL-C–lowering plus HDL-C–raising combination drug therapy arteriographic trials have demonstrated mean arteriographic regression.

The NNT reflects the improved efficiency of combination LDL-C–lowering and HDL-C–raising drug therapy compared with LDL-C–lowering drug therapy alone. In general, LDL-C–lowering only trials require that 20 to 60 subjects be treated to prevent 1 event, and this has been argued to be “cost-effective.”43 However, in NIH-funded combination LDL-C–lowering plus HDL-C–raising studies, the NNT was on average 9.6.44–46 This illustrates the greatly enhanced efficiency in reducing clinical events of LDL-C–lowering plus HDL-C–raising therapy compared with LDL-C–lowering therapy alone.

Conclusions

It is clear that although a focus on LDL-C reduction has benefited some patients by reducing CHD risk, large numbers of patients remain at elevated risk despite substantial reductions in LDL-C. The well-intentioned focus on LDL-C reduction alone ignores the multiple other lipoprotein disorders contributing to CHD risk and the better clinical and arteriographic outcomes when combination LDL-C–lowering plus HDL-C–raising therapy is used compared with LDL-C lowering alone. Combination LDL-C–lowering and HDL-C–raising lipid treatment drug studies have been shown to be more efficacious than LDL-C lowering alone in reducing CHD events, inducing arteriographic regression, and improving efficiency, as noted by the substantially lower NNT. On the eve of new therapies designed to increase HDL-C, it is important to appreciate that currently available LDL-C–lowering and HDL-C–raising lipid drug therapy has convincingly demonstrated a superior clinical benefit compared with LDL-C lowering alone in NIH-funded clinical trials. Furthermore, clinicians can use this approach at the present time and not delay treatment of reverse cholesterol transport in appropriate patient populations.

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References


Response to Superko and King

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Superko and King argue that lowering of low-density lipoprotein (LDL) is inadequate to stem the cardiovascular epidemic and that other lipid targets (eg, high-density lipoprotein [HDL]) could provide additional risk reduction. First, the authors underestimate the benefit of LDL lowering in secondary prevention. When clinical trial data are combined, including the Treating to New Targets (TNT) and Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) studies, maximal LDL lowering can be calculated to reduce cardiovascular events by 45% to 50%. Moreover, epidemiological studies imply that prolonged LDL lowering in primary prevention will reduce risk even more. Of course, modifying other lipid targets (eg, other apolipoprotein B–containing lipoproteins or HDL) might produce more benefit. In particular, lowering of atherogenic triglyceride-rich lipoproteins likely will be efficacious. Whether raising HDL by pharmacological intervention that directly targets HDL will reduce cardiovascular risk remains to be proven. This idea is attractive to many investigators because of the known association between low HDL levels and cardiovascular risk. On the other hand, it is possible that a low HDL is primarily a marker of risk caused by other factors (eg, metabolic syndrome) and that direct HDL raising will not substantially modify risk. To resolve this question, 2 things are needed: development of a drug that will effectively raise HDL (without a confounding lowering of apolipoprotein B–containing lipoproteins) and demonstration of the efficacy of such a drug in a morbidity/mortality outcome trial. Until these have been accomplished, the benefit of raising HDL per se remains in the arena of speculation. See article p 569.
Lipid Management to Reduce Cardiovascular Risk: A New Strategy Is Required
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