Facts, myths and misconceptions about LDL-C and HDL-C

By Michael B. Clearfield, DO

Many asymptomatic individuals will succumb to cardiovascular disease (CVD), which is the leading cause of death and loss of disability-adjusted life-years worldwide.1

One of the major advances in the treatment and prevention of CVD involves lowering elevated low-density lipoprotein cholesterol (LDL-C) to current goals. In addition to being aggressive at treating LDL-C, osteopathic physicians must also be aggressive at treating other risk factors such as hypertension, cigarette smoking and diabetes. If we believe we are treating more people more effectively, why isn’t the rate of CVD decreasing to a greater extent? The answer is very complex but lies partly in the facts, myths and misconceptions about two lipoproteins: LDL-C and HDL-C.

A series of large randomized endpoint trials have established statins as a primary therapy for the prevention of the first major fatal and non-fatal cardiovascular events in people at moderate high and high risk for cardiovascular disease.2-10

These statin trials have contributed the majority of the evidence on which the National Cholesterol Education Program’s Adult Treatment Panels III (NCEP-ATP III) guidelines and 2004 update have been formulated.2-3 The evolution of these primary prevention trials demonstrates that aggressive LDL-C lowering therapy with statins in individuals with average or even below average LDL-C levels but with other coexisting risk factors can significantly reduce the number of coronary events.

The next question in primary prevention is how do we select whom to treat in lower-risk groups, how aggressively should their LDL-C be lowered, and should additional therapy to raise HDL-C be added to the regime?

The treatment of elevated total and LDL cholesterol originated in patients with documented cardiovascular disease. Such treatment has evolved over the years into more aggressive strategies that further lower LDL-C to a minimum goal below 100 mg/dl and to LDL-C levels of less than 70 mg/dl in very high risk patients.2-3 Since CV events continue to occur even in those reaching the goal of an LDL-C < 70 mg/dl, the next question is whether even further lowering of LDL-C is of any additional benefit, or should raising HDL-C be the next primary objective in these patients?

Facts about LDL-C in primary prevention statin trials

1. Lowering LDL-C has consistently been found to improve cardiovascular endpoints.

In 2005 the Cholesterol Treatment Trialists’ (CTT) Collaborators published a meta-analysis of 90,056 participants in 14 randomized trials using statin therapy, of which 47% had previous CHD.11 The CTT analysis revealed that those without previous myocardial infarction (MI) or CHD had 18 fewer major coronary events per 1,000 treated with statins for each mmol/L (39 mg/dl) of LDL-C reduction. The CTT meta-analysis concluded that statin therapy, irrespective of lipid profile or presenting risk factors, can safely reduce the five-year incidence of major coronary events, coronary revascularizations and stroke by about 20% per mmol/L (39 mg/dl) reduction of LDL-C.
Lowering LDL-C in secondary prevention statin trials improves both cardiovascular events and mortality.

In the Cholesterol Treatment Trialists’ (CTT) Collaborators meta-analysis, participants with previous MI or CHD were found to have 30 fewer major coronary events per 1,000 treated with statins for each mmol/L of LDL-C reduction. The CTT meta-analysis concluded that statin therapy in secondary prevention was even more effective than in primary prevention in safely reducing the five-year incidence of major coronary events, coronary revascularizations and stroke.

Myths about LDL-C

1. Lowering LDL-C has not been shown to be beneficial in women, diabetics or the elderly.

The meta-analysis by CTT demonstrated that lowering LDL-C with statins was beneficial in all the groups listed above.

2. Lowering LDL-C increases the risk of stroke.

The CTT meta-analysis showed a significant reduction in ischemic stroke. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial that randomized patients with prior Transient Ischemic Attacks (TIAs) or strokes but no evident CHD, atorvastatin significantly reduced incidence of ischemic stroke but non-significantly increased risk of hemorrhagic stroke.12

Misconceptions about LDL-C

1. Continued lowering of LDL-C has been definitively proven to decrease cardiovascular events.

In 2004, following the publication of the aforementioned trials, the National Cholesterol Education Program-Adult Treatment panel recommended a modification to the 2001 guidelines relative to primary prevention.3 Individuals free of CVD but with two or more risk factors and a 10-20% 10-year Framingham risk for CHD, classified as moderate high risk, could be treated to an optional LDL-C goal < 100 mg/dl. A strong contributor to this recommendation came from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) data where treatment with atorvastatin was effective in hypertensive subjects with LDL-C levels both above and below the mean of 132 mg/dl.9 This approach recently received additional support from a re-analysis of the Airforce/Texas Coronary Atherosclerosis Prevention Study (AF-CAPS/TexCAPS) where 35% of the participants did not meet ATP III criteria for treatment with lipid-lowering medication and yet were responsible for 21% of the acute major coronary events.13 Of the subgroup who did not meet ATP III criteria for a lipid-lowering medication, 334 (5.1%) were at moderately high risk and had an LDL-C <130 mg/dl yet benefited from lovastatin therapy—with a 68% reduction in acute major coronary events (95% CI 12% to 88%, p = 0.027). These results support the ATP III recommendation for more aggressive treatment for primary prevention patients at moderate high risk with a baseline LDL-C < 130 mg/dl. Although not specifically analyzed in primary prevention patients, the concept of lowering LDL-C more aggressively was once again supported in CTT meta-analysis, which found similar benefits from statin therapy independent of baseline LDL-C.11

The updated guidelines now recommend an optional goal of LDL-C < 100 mg/dl in those with moderate high risk.3 However, questions still exist as to how far and in whom should LDL-C be lowered in primary prevention? In a review by O’Keefe et al, it was noted that the optimal LDL-C may be 50-70 mg/dl, which is the normal range for native hunter-gatherers and healthy neonates.14 O’Keefe also suggested that CHD event rates in a primary prevention...
tion scenario could approach zero at an LDL-C of 55 mg/dl.

Although no randomized trial has directly evaluated this premise, the on-going JUPITER trial will help answer this question. JUPITER is a primary prevention study of 15,000 subjects with a baseline LDL-C < 130 mg/dl and high-sensitivity C-reactive protein (hsCRP) > 2 mg/L randomized to either rosvastatin 20 mg or placebo. The utility of combining CRP with LDL-C as a dual goal in primary prevention was first suggested in AFCAPS/TexCAPS where the subgroup with LDL-C < 150 mg/dl and CRP > 1.6 mg/L had a similar CHD risk and benefit from lovastatin therapy to those with baseline LDL-C > 150 mg/dl, where those with LDL-C < 150 and CRP < 1.6 mg/L had a much lower CHD risk and minimal benefit from statin therapy. The results from JUPITER should address whether aggressive LDL-C reduction to levels well below the optional goal of 100 mg/dl in those with CRP levels greater than 2 mg/L has further efficacy in primary prevention.

2. Further lowering of LDL-C in secondary prevention has been definitively proven to decrease cardiovascular events and mortality.

Since publication of the CTT analysis, several additional large-scale secondary prevention trials including a meta-analysis in which intensive high-dose statins were used, the result should reduce CV events by about 40% and stroke by 33% in high-risk patients. To that end, the PROVE-IT trial showed a continued significant 16% reduction of events in patients with acute coronary syndrome who were aggressively treated to an LDL-C of 62 with 80 mg of atorvastatin when compared to a less aggressive lowering of LDL-C to 95 mg/dl with pravastatin 40 mg. This data supports that lowering LDL-C even below the suggested optional goal of 70 mg/dl may be beneficial. In addition, LDL-C levels did not increase any adverse events from statins even when LDL-C levels were less than 40 mg/dl.

Facts about HDL-C in the prevention of CHD

1. A low HDL-C is considered a risk factor for CHD and metabolic syndrome.

As part of the Framingham Risk HDL-C, levels less than 40 mg/dl are considered an independent risk factor for both men and women. In the ATP III guidelines, an HDL-C < 40 mg/dl in men and < 50 mg/dl in women are considered a risk factor relative to the diagnosis of metabolic syndrome. The AFCAPS/TexCAPS trial showed that lowering LDL-C with lovastatin negated the added risk found with a low HDL-C, suggesting that one of the best ways to treat the risk associated with a low HDL-C is to lower the LDL-C.

2. A high HDL-C is considered a negative risk factor for CHD by Framingham Guidelines.

As part of the NCEP-ATP III guidelines, an HDL-C > 60 mg/dl is considered protective and essentially negates one other CHD Framingham risk fac-
HDL-C increased only 1.2% compared to the control group.21

2. All patients with a low HDL-C are at high CHD risk.

Although a low HDL-C is a risk factor for CHD, there are some individuals with genetic predisposition to low HDL-C who do not appear to have increased CV risk. For example, individuals with apoA1 Milano mutation may have very low HDL-C levels but generally are not at any increased risk for CHD events.

Individuals with apoA1 Milano represent a small group of patients who usually have a family history of longevity with a concomitant family history of low HDL-C.

3. All patients with a high HDL-C are protected from CHD.

There appears to be different types of HDL-C. For example, HDL-C may change during the acute phase period and may actually be pro-inflammatory and pro-atherogenic rather than protective. Likewise, some individuals with very high HDL-C may actually have an increased risk of CV events due to a dysfunctional HDL-C particle.22

Misconceptions about HDL-C

1. All HDL-C particles are the same.

In deference to LDL-C, the results are consistent in that the lower the LDL-C level achieved the better the decrease in major acute coronary events. When HDL-C is evaluated the results are not as consistent. HDL-C particles that are pro-inflammatory are generally smaller particles that have an increased capacity to induce mono-cyte chemotactic activity (MCA).23

2. Raising HDL-C in conjunction with lowering LDL-C has been shown to have an additive effect on CV events.

In several smaller studies such as FATS, HATS, ARBITER, the ability of raising HDL-C with the addition of niacin, while lowering LDL-C with a statin, has resulted in some of the best outcomes found in statin-based trials. It is therefore speculated that the combination of lowering LDL-C while raising HDL-C may have a significantly better effect than either alone. However, the recent results from ILLUMINATE, which has generated the greatest HDL-C increases to date, actually increased the event rates. The medication used in ILLUMINATE was torcetrapib, a blocker of CETP, suggesting that different medications raising HDL-C may have far different clinical outcomes. To date there has been no study that has selectively raised HDL-C to determine whether raising HDL-C independent of lowering LDL-C will improve CV outcomes.

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Myths about HDL-C

1. Raising HDL-C by any means will lower CHD events.

Unfortunately, several medications that raise HDL-C did not result in lowering CV event rates. Estrogen therapy in women, while raising HDL-C and lowering LDL-C, has not been shown as beneficial in post-menopausal women, especially when started several years after menopause.

Torcetrapib, a newer experimental medication which inhibits cholesterol ester transfer protein (CETP), has been shown to markedly increase HDL-C by > 50%. Recently the ILLUMINATE study, which was comparing the efficacy of a torcetrapib/atorvastatin combination compared to atorvastatin alone, was discontinued because of increased mortality and CV events with the combination treatment, despite a marked increase in HDL-C levels with the combination.

Raising HDL-C with fibrate therapy may also have some benefit. For example, in Helsinki Heart Trial in primary prevention and in VA-HIT in secondary prevention there were benefits noted by raising HDL-C by 11% and 6% respectively while having little effect on LDL-C.19 20 However, the recent FIELD trial with fenofibrate did not demonstrate any significant benefit in reducing CV events; however, the HDL-C increased only 1.2% compared to the control group.21

2. All patients with a low HDL-C are at high CHD risk.

Although a low HDL-C is a risk factor for CHD, there are some individuals with genetic predisposition to low HDL-C who do not appear to have increased CV risk. For example, individuals with apoA1 Milano mutation may have very low HDL-C levels but generally are not at any increased risk for CHD events.

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Torcetrapib is currently unavailable for clinical use. However, an elevated HDL-C itself does not preclude one from treating other risk factors. A family history is critical for all patients and in those with a high HDL-C, it can help in predicting how protective the HDL-C would be for them.
Statin therapy has been shown to be effective in multiple prospective, randomized trials for both primary and secondary prevention of cardiovascular events. With each progressive trial the cutpoint for LDL-C continues to drop, currently resulting in the updated guidelines which recommend an optional LDL-C goal of less than 100 mg/dl for those at moderate high risk for CHD in primary prevention and less than 70 mg/dl in those with very high risk.

Post-hoc analyses of several primary prevention trials suggest that individuals with associated metabolic syndrome, especially when combined with either a family history of premature CHD or an elevated CRP, may portend a higher risk than predicted by the Framingham risk score and therefore may be strong candidates for treating to the optional LDL-C goal.

In secondary prevention, especially in those post-acute coronary syndrome (ACS), LDL-C levels that reached the optional goal < 70 mg/dl to about 62 mg/dl revealed continued reduction in CV events.

Raising HDL-C is a more complicated issue. Since there are no studies that isolate the raising of HDL-C, the best data suggests that a statin in combination with niacin and possibly a fibrate may result in the best CV outcomes. The strongest data are from statin/niacin combinations, which in small groups of patients have shown the best outcomes. The AIM-HIGH study will hopefully clarify this issue of comparing simvastatin monotherapy with simvastatin/fenofibrate combination in 6,000 diabetics.

Lastly, a regime that includes a global risk reduction strategy appears to have the best potential outcome for individuals with multiple risk factors to prevent their first or a recurrent major coronary event.

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References


