

## EXPEDITED REVIEW

# Optimal Low-Density Lipoprotein Is 50 to 70 mg/dl Lower Is Better and Physiologically Normal

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The normal low-density lipoprotein (LDL) cholesterol range is 50 to 70 mg/dl for native hunter-gatherers, healthy human neonates, free-living primates, and other wild mammals (all of whom do not develop atherosclerosis). Randomized trial data suggest atherosclerosis progression and coronary heart disease events are minimized when LDL is lowered to <70 mg/dl. No major safety concerns have surfaced in studies that lowered LDL to this range of 50 to 70 mg/dl. The current guidelines setting the target LDL at 100 to 115 mg/dl may lead to substantial undertreatment in high-risk individuals. (J Am Coll Cardiol 2004;43:2142-6) © 2004 by the American College of Cardiology Foundation

According to the National Cholesterol Education Program-Adult Treatment Panel-III (NCEP-ATP-III), the target low-density lipoprotein (LDL) level for patients with established coronary disease or coronary heart disease (CHD) risk equivalents (such as diabetes, peripheral or cerebral vascular disease, or predicted 10-year CHD risk of >20%) is <100 mg/dl (1). The European guidelines set the LDL target at <115 mg/dl (2). Accumulating data from multiple lines of evidence consistently demonstrate that the physiologically normal LDL level and the thresholds for atherosclerosis development and CHD events are approximately 50 to 70 mg/dl.

## WHY AVERAGE IS NOT OPTIMAL

Atherosclerosis development is a complex process influenced by a myriad of risk factors, although the LDL level is among the most important. In an atherogenic milieu, oxidized LDL infiltrates the intima where it stimulates inflammation, endothelial dysfunction, and eventually atherosclerosis. Although it is true that very high LDL levels (>200 mg/dl) are strongly associated with CHD risk, atherosclerosis is not uncommon even in those with relatively "normal" LDL levels (90 to 130 mg/dl) (3,4). Moreover, the 10% of the population with the highest LDL levels account for only 20% of the CHD events (3). Thus, focusing treatment only on those with very high cholesterol levels will ignore 80% of the people destined to suffer a CHD event (4). The mega-trials using statin therapy have demonstrated remarkable reductions in CHD events and in all-cause mortality among patients with baseline LDL levels generally from 120 to 180 mg/dl and on-treatment values between 100 and 140 mg/dl (5-11). Whereas cardiovascular

events were reduced by 25% in these studies, approximately three out of four CHD events occurred despite the statin therapy. This 25% reduction in LDL represents only partial treatment, and more robust reductions appear to provide more impressive improvements in prognosis (12).

The average total cholesterol level in American adults today is 208 mg/dl (corresponding to an LDL of approximately 130 mg/dl) (13). In this case, average is not normal because atherosclerosis is present in up to 40% to 50% of women and men by age 50 (14). Atherosclerosis is endemic in our population in part because the average person's LDL level is approximately twice the normal physiologic level (Fig. 1).

We live in a world very different from that for which we are genetically adapted. Profound changes in our environment began with the introduction of agriculture and animal husbandry 10,000 years ago, too recent on an evolutionary time scale for the human genome to adjust. As a result of this ever-worsening discordance between our ancient genetically determined biology and the nutritional, cultural, and activity patterns in modern populations, many of the so-called diseases of civilization, including atherosclerosis, have emerged. Evidence from hunter-gatherer populations while they were still following their indigenous lifestyles showed no evidence for atherosclerosis, even in individuals living into the seventh and eighth decades of life (15,16). These populations had total cholesterol levels of 100 to 150 mg/dl with estimated LDL cholesterol levels of about 50 to 75 mg/dl. The LDL levels of healthy neonates are even today in the 30 to 70 mg/dl range. Healthy, wild, adult primates show LDL levels of approximately 40 to 80 mg/dl (17). In fact, modern humans are the only adult mammals, excluding some domesticated animals, with a mean LDL level over 80 mg/dl and a total cholesterol over 160 mg/dl (15,16) (Fig. 1). Thus, although an LDL level of 50 to 70 mg/dl seems excessively low by modern American standards, it is pre-

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#### Abbreviations and Acronyms

CHD	= coronary heart disease
LDL	= low density lipoprotein
NCEP-ATP-III	= National Cholesterol Education Program-Adult Treatment Panel-III

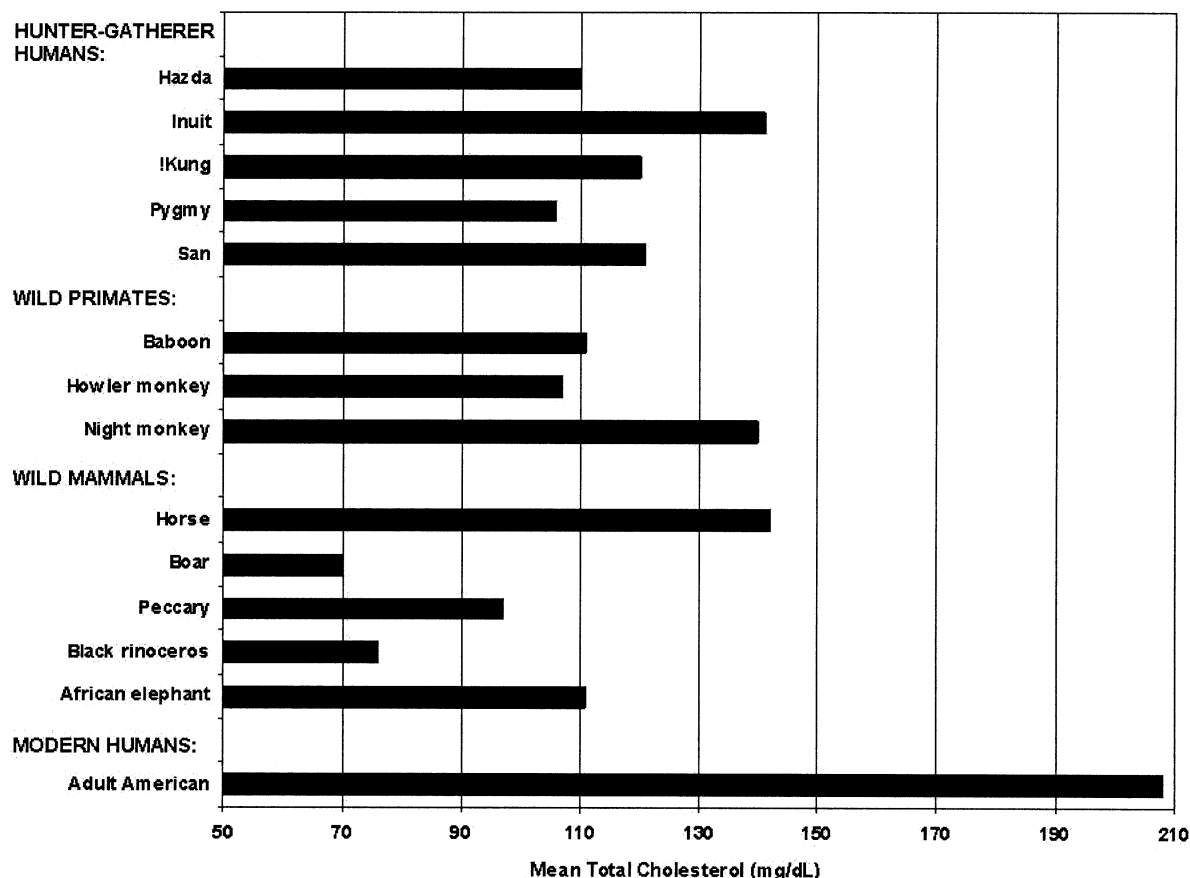
cisely the normal range for individuals living the lifestyle and eating the diet for which we are genetically adapted.

### LDL AND ATHEROSCLEROSIS PROGRESSION

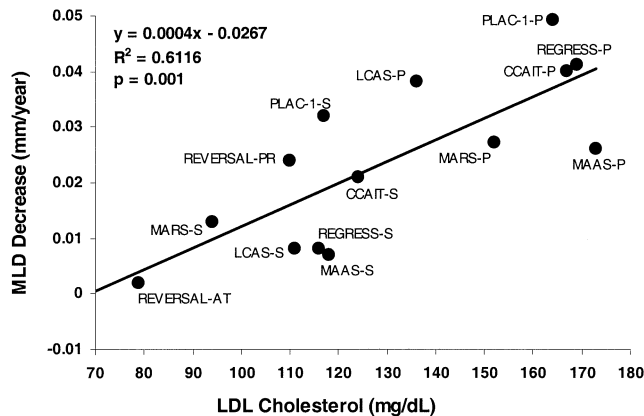
Abundant data from prospective trials reveal a strong and direct relationship between on-treatment LDL level and rate of atherosclerotic progression. These randomized controlled trials show that whether patients were on statin therapy or placebo, the rate of angiographic progression of atherosclerosis was closely related to the chronic LDL level (18-24). Figure 2 indicates that the threshold for atherosclerotic progression may be at an LDL level of approximately 67 mg/dl. The strongest data on atherosclerotic progression come from the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial (24). In this randomized study of 654 patients with symptomatic coro-

nary disease and a baseline stenosis of 20% or more on coronary angiography, patients were randomized to high-dose atorvastatin, 80 mg daily, or pravastatin, 40 mg daily. Coronary atherosclerosis, as documented by intravascular ultrasound, was virtually halted in the atorvastatin group where a 48% LDL reduction led to a mean on-treatment LDL of 79 mg/dl. The pravastatin group experienced a 28% decline to a mean on-treatment LDL of 110 mg/dl. These differing regimens resulted in 0.4% regression of atheroma volume in the atorvastatin versus a 2.7% mean progression in the pravastatin group over the 18-month trial. Systemic inflammation was also reduced at lower LDL levels as reflected by the C-reactive protein levels, which were reduced by 36% in the group treated to a mean LDL of 79 mg/dl compared to a 5% decrease when the LDL was 110 mg/dl (24).

Two recent studies using ultrasound determined carotid intima-media thickness also found that aggressive LDL reduction halted atherosclerosis, whereas moderate LDL lowering allowed for continued progression. The Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) trial compared atorvastatin 80 mg/day to simvastatin 40 mg/day in 325 patients with familial hypercholesterolemia (25). Carotid intima-media thickness regressed



**Figure 1.** Total cholesterol levels for hunter-gatherers, wild primates, and wild mammals, generally range from about 70 to 140 mg/dl (corresponding to low-density lipoprotein levels of about 35 to 70 mg/dl [24,25]). The mean cholesterol levels of modern Westernized humans are almost twice these normal values (13).

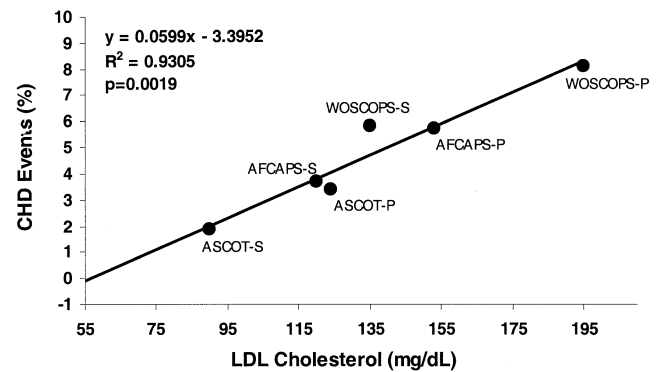


**Figure 2.** Atherosclerosis progression varies directly with low-density lipoprotein (LDL) cholesterol. This regression line indicates that atherosclerosis does not progress when LDL is 67 mg/dl or below (18–24). Data from randomized placebo-controlled trials using statins for preventing atherosclerosis progression (analysis for Fig. 2) or preventing coronary heart disease events in primary (analysis for Fig. 3) or secondary (analysis for Fig. 4) prevention were utilized for computation of the univariate regression lines correlating LDL with outcomes. Regression estimates, model  $R^2$ , and p values for LDL effect were obtained from the unweighted regression lines. AT = atorvastatin; CCAIT = Canadian Coronary Atherosclerosis Intervention Trial; LCAS = Lipoprotein and Coronary Atherosclerosis Study; MAAS = Multicentre Anti-Atheroma Study; MARS = Monitored Atherosclerosis Regression Study; MLD = mean luminal diameter; P = placebo; PLAC = Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study; PR = pravastatin; REGRESS = Regression Growth Evaluation Statin Study; REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid Lowering; S = statin.

0.031 mm over two years in the atorvastatin group compared with a 0.036-mm progression in the simvastatin group. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trial used 80 mg/day atorvastatin versus 40 mg/day pravastatin in 161 patients with a mean baseline LDL of 150 mg/dl (26). Atorvastatin reduced LDL by 50% to a mean LDL of 76 mg/dl compared with a 27% drop to a mean of 110 mg/dl on pravastatin. Again, the carotid intima-media thickness regressed 0.038 mm in the atorvastatin group compared with a mean progression of 0.026 mm in the pravastatin group ( $p = 0.021$ ). Both of these trials demonstrated the inadequacy of LDL reduction to current goals.

## LDL CHOLESTEROL AND CHD EVENT REDUCTION

Observational studies show a continuous positive relationship between CHD risk and LDL levels that extends well below the average range seen in modern populations without any definite threshold where lower LDL concentrations are not associated with lower risk (27). Over 100,000 patients have been randomized to statin therapy in CHD event reduction trials. When examined in aggregate, these studies also demonstrate a direct relationship between on-treatment LDL cholesterol and absolute risk of CHD events (5–12). Trials from both the setting of primary prevention (Fig. 3) and secondary prevention (Fig. 4) show that the risk of suffering a CHD event during the course of the study was closely correlated with on-treatment LDL.

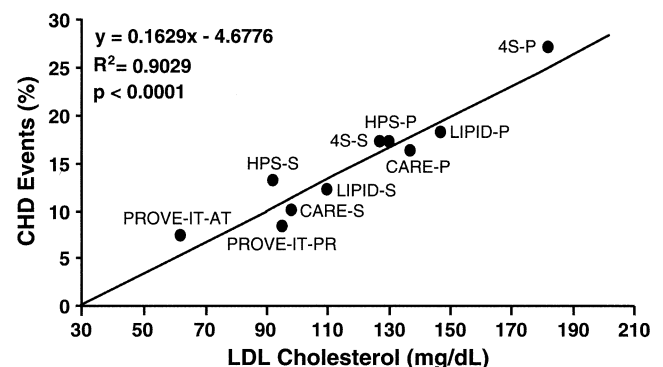


**Figure 3.** Coronary heart disease (CHD) event rates in primary prevention trials (4 to 5 years duration) are directly proportional to the on-treatment low-density lipoprotein (LDL) cholesterol levels. The event rate is predicted to approach 0 at an LDL level of about 57 mg/dl (5–7). AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; ASCOT = Anglo-Scandinavian Cardiac Outcome Trial; WOSCOPS = West of Scotland Coronary Prevention Study. Other abbreviations as in Figure 2.

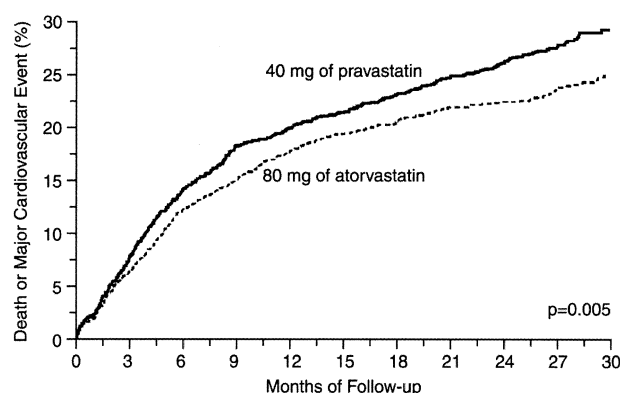
Interestingly, the LDL level at which the cardiovascular event rate is predicted to approach 0 is 57 mg/dl for primary prevention and 30 mg/dl for secondary prevention. These data implicate LDL as a requisite catalyst in the atherosclerosis process whereby extremely low LDL may prevent CHD events regardless of the other risk factors.

In the Heart Protection Study (8), approximately 3,500 of the 20,536 (17%) participants presented with a baseline LDL measurement that was below the “target” level of 100 mg/dl even before initiating simvastatin or placebo. In this subset, the mean LDL reduction from 97 mg/dl to 65 mg/dl on statin therapy produced a 25% reduction in relative risk of CHD, which was similar to the benefits seen in the patients presenting with baseline LDL levels >100 mg/dl.

The recently published PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) trial is the strongest verification of the lower is better hypothesis (12). This study randomized 4,162 acute coronary syndrome



**Figure 4.** Coronary heart disease (CHD) event rates in secondary prevention trials (5 years in duration except the PROVE-IT study, which was 2 years) were directly proportional to low-density lipoprotein (LDL) cholesterol levels. The event rate is predicted to approach 0 at LDL of 30 mg/dl (8–12). 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol And Recurrent Events trial; HPS = Heart Protection Study; LIPID = Long-term Intervention with Pravastatin In Ischemic Disease trial; PROVE-IT = PRavastatin Or atorVastatin Evaluation and Infection Therapy trial. Other abbreviations as in Figure 2.



**Figure 5.** The PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) trial randomized over 4,000 patients either to high-dose atorvastatin (low-density lipoprotein [LDL] = 62 mg/dl) or pravastatin (LDL = 95 mg/dl) (12). A 16% reduction in the primary end point was noted in the atorvastatin-treated group.

patients with a baseline total cholesterol of 200 mg/dl or less either to atorvastatin 80 mg or pravastatin 40 mg daily. The on-treatment LDL was 62 mg/dl (51% decrease) for the atorvastatin group versus 95 mg/dl (22% decrease) for the pravastatin group. At the end of two years, a highly significant 16% reduction ( $p < 0.001$ ) in adverse CHD events and a 28% reduction in death were noted in the atorvastatin group (Fig. 5). This trial is especially relevant because pravastatin-treated patients achieved a mean LDL (95 mg/dl) that was under the current target of 100 mg/dl, yet they continued to experience excess CHD events (Fig. 5).

## IS A TARGET LDL OF 50 TO 70 MG/DL PRACTICAL?

The newer and more potent statins are capable of dramatically reducing LDL cholesterol safely and tolerably in most patients. The Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial randomized more than 3,000 patients either to rosuvastatin, atorvastatin, simvastatin, or pravastatin (28). The rosuvastatin (10 mg/day), atorvastatin (80 mg/day), and simvastatin (80 mg/day) all achieved the NCEP ATP-III LDL goal in approximately 80% of patients. Higher doses of high-efficacy statins are more effective in reaching goals especially when combined with diet and agents, such as ezetimibe, niacin, or plant sterol and stanol esters. However, today only one in three CHD patients is at or below the more liberal current LDL goal of 100 mg/dl (29). Much work remains to be done in the development of treatment strategies to achieve the LDL goal of 50 to 70 mg/dl in most CHD patients.

Some investigators have proposed that any one specific LDL threshold is artificial, and if clinically significant atherosclerosis develops, the LDL cholesterol warrants treatment regardless of the absolute level (3). Using this approach, LDL reductions of 50% for secondary prevention patients and 30% for primary prevention can be supported by the cumulative randomized trial experience (5–12).

**How low is too low?** Cholesterol is an essential component of the cell membrane and an obligate precursor for bile acid, steroid hormone, and vitamin D synthesis. Consequently, it is likely that a physiologically ideal range of blood cholesterol exists above and below which adverse health consequences might be expected. Although individuals with serious chronic illnesses, such as cancer, often develop depressed LDL levels as a result of malnutrition, epidemiologic studies show that people with naturally low LDL levels are associated with improved longevity (27). The cumulative experience with statin therapy shows impressive cardiovascular benefits that are directly proportional to LDL lowering with no increase in adverse events such as malignancy or non-cardiovascular mortality (5–12,18–26). The incidence of the two principal adverse effects commonly attributed to statins—liver and muscle toxicity—rise modestly as a function of dose of statin utilized but not in relationship to the on-treatment LDL level (5–12).

People with heterozygous hypobetalipoproteinemia have total cholesterol levels as low as 80 mg/dl and LDL cholesterol levels as low as 30 mg/dl (30). This condition is associated with longevity (31), presumably due to the absence of atherosclerosis, but the lack of other adverse effects that might have accompanied a low LDL level suggests that such low levels of LDL are safe.

**Unintended benefits of LDL lowering.** Inflammation and endothelial dysfunction, both important markers of abnormal vascular biology, have been shown to be improved as LDL is lowered to  $<80$  mg/dl (12,24). Statin therapy has been associated with reductions in the incidence of symptomatic peripheral vascular disease (32), stroke (33), dementia (34), macular degeneration (35), aortic stenosis (36), and osteoporosis-related hip and vertebral fractures (37). Although the mechanisms responsible for these benefits are not known, it is possible that an elevated LDL cholesterol level may be a common denominator predisposing to a wide variety of chronic degenerative diseases seen in modern civilization. If our genetically determined ideal LDL is indeed 50 to 70 mg/dl, perhaps lowering the currently average but elevated levels closer to the physiologically normal range may improve not just CHD but also many other diseases commonly attributed to the aging process. For all of these reasons, and given the safety record of statins, some investigators have suggested that statins be considered for routine use in individuals over age 55 years (38).

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