

Are we lowering LDL cholesterol sufficiently?

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A positive causal relationship between the concentration of LDL cholesterol and the future risk of cardiovascular events is one of the best-proven cases in modern medicine. Major clinical trials have shown that interventions that lower LDL cholesterol levels reduce future cardiovascular risk, and that the magnitude of risk reduction is a direct function of the degree of LDL cholesterol reduction. So, based on available evidence, what LDL cholesterol target level should be recommended? Are there safety issues associated with achieving very low LDL cholesterol levels, and how feasible is it to achieve very low levels in all high-risk people?

What do the trials tell us about LDL cholesterol target levels? There is now a huge body of evidence supporting aggressive LDL cholesterol lowering to reduce cardiovascular risk. Intervention trials of LDL cholesterol reduction have been conducted in settings of primary and secondary prevention, in men and women spanning a wide range of ages, in those with and without diabetes, with and without hypertension and in individuals with a wide range of baseline LDL cholesterol levels. The results of these trials have been amazingly consistent.

A meta-analysis of data from 90,056 participants in 14 randomized trials of statins showed that for each 1.0 mmol/l reduction in LDL cholesterol, there is a 12% reduction in all-cause mortality, a 23% reduction in myocardial infarction risk or coronary-related mortality, a 24% reduction in the need for coronary revascularization and a 17% reduction in the fatal or nonfatal stroke rate.¹ All of these reductions were highly significant. This analysis also demonstrated that the reduction in major vascular events was proportional to the magnitude of LDL cholesterol reduction.

There is mounting evidence that the risk of having a cardiovascular event when treated with lipid-lowering agents is a direct function of the concentration of LDL cholesterol achieved. This relationship is independent of the pretreatment LDL cholesterol level, with significant benefits of lipid lowering seen in high-risk individuals

even when their baseline LDL cholesterol level is low.² To date, trials have not yet identified a threshold below which LDL cholesterol reduction is no longer of value.

Many guidelines recommend an LDL cholesterol target level of 2.6 mmol/l in people at high cardiovascular risk, although, in light of more recent evidence, the National Cholesterol Education Program Adult Treatment Panel III guidelines have been updated with the recommendation that an LDL cholesterol target of 1.8 mmol/l be seriously considered in high-risk individuals.³ Importantly, support for this view is mounting. The REVERSAL trial, for example, which included people with existing coronary artery disease, compared the effects of aggressive therapy that achieved LDL cholesterol levels of 2.05 mmol/l with the effects of more-moderate therapy that achieved LDL cholesterol levels of 2.85 mmol/l;⁴ there was significantly less progression of coronary atherosclerosis in the aggressively treated patients. The PROVE-IT trial of patients with acute coronary syndromes again compared aggressive and moderate LDL cholesterol lowering treatments.⁵ Treatment with 80 mg atorvastatin daily achieved an average LDL cholesterol level of 1.60 mmol/l, while 40 mg pravastatin daily achieved an average LDL cholesterol level of only 2.46 mmol/l; the aggressively treated group had a significant 16% lower rate of cardiovascular events ($P < 0.005$).

The 'lower LDL cholesterol is better' hypothesis received further support from the TNT trial of more than 10,000 patients with stable coronary heart disease.⁶ Atorvastatin at a dose of 10 mg or 80 mg per day achieved mean LDL cholesterol levels of 2.6 mmol/l and 2.0 mmol/l, respectively. The major cardiovascular event rate was 22% lower in the aggressively treated than in the less-aggressively treated group ($P < 0.001$). A similar result was observed in the IDEAL trial, in which the effects of low-dose simvastatin were compared with the effects of high-dose atorvastatin.⁷ The low-dose simvastatin group achieved an average LDL cholesterol level of 2.69 mmol/l compared with 2.17 mmol/l in the high-dose

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Received 25 January 2006

Accepted 23 March 2006

www.nature.com/clinicalpractice
doi:10.1038/npcardio0555

atorvastatin group. The difference in the reduction in major coronary events between the groups was not statistically significant ($P=0.07$); however, the occurrence of major cardiovascular events was 13% lower in the aggressively treated group than in the less-aggressively treated group ($P=0.02$).

The results of these trials support the clinical application of an LDL cholesterol target of less than 2.0 mmol/l in individuals at high risk of having a cardiovascular event. Whether targets should be even lower than this will have to await further research.

As with any drug class, there are well-recognized adverse effects associated with taking lipid-lowering agents. Severe adverse events are extremely rare, however, and tend to relate to individual susceptibility and the type and dose of the agent used rather than to the LDL cholesterol level achieved. While there is evidence that elderly patients and those with comorbidities might be at increased risk of developing muscle problems when taking higher statin doses,⁸ there is no direct evidence to prove that these problems relate to the low LDL cholesterol levels that are achieved. Indeed, the LDL cholesterol level in most mammals, bar humans, is approximately 1.0 mmol/l and is not associated with adverse effects. Furthermore, there is circumstantial evidence that this level could have been that found in humans throughout most of our evolution. More-direct evidence that low LDL cholesterol levels are safe has emerged from the TNT study findings.⁹ Compared with participants with higher LDL cholesterol levels, the 2,000 or more participants with LDL cholesterol levels less than 1.65 mmol/l had the lowest major cardiovascular event rate, without any evidence of increased incidence of noncardiovascular disease or death.⁹

How feasible is achieving very low LDL cholesterol levels? Monotherapy with higher doses of the more effective statins can reduce LDL cholesterol levels by almost 60%.¹⁰ Combining a statin with niacin or ezetimibe has the capacity to reduce LDL cholesterol even further, although it should be noted that the benefits of reducing LDL cholesterol with ezetimibe have not yet been tested in trials. Thus, achieving an LDL cholesterol target of 2.0 mmol/l in most people is feasible, even in those whose baseline LDL cholesterol level is as high as 6.0 mmol/l. It will be more difficult to achieve such a target in people with familial hypercholesterolemia whose LDL cholesterol levels are often greater than 6.0 mmol/l, although

it should be emphasized that any LDL cholesterol reduction is beneficial even if a recommended target is not achieved. Likewise, in circumstances in which health-care costs are a major barrier to using newer more-potent statins to achieve lower targets, there are undoubted benefits associated with any LDL cholesterol reductions such as those that can be achieved with less-costly generic forms of a less-potent agent (e.g. simvastatin).

Evidence that cardiovascular event rates are a direct function of the LDL cholesterol concentration is robust down to levels of 2.0 mmol/l. Furthermore, with currently available agents it is feasible to achieve such levels in most people. Thus, given that there are no apparent safety issues associated with maintaining LDL cholesterol at this level, it seems logical that an LDL cholesterol target of 2.0 mmol/l should be considered for minimizing cardiovascular events in high-risk individuals.

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Competing interests

The authors declared competing interests; go to the article online for details.