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Commentary

Debate: "How low should LDL cholesterol be lowered for optimum prevention of vascular disease?" Viewpoint: "Below 100 mg/dl"

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Abstract

Arteriosclerotic vascular disease manifests as heart disease, stroke, aortic aneurysms, and peripheral vascular disease, and is a growing problem world-wide. The preventive efforts made so far have demonstrated that lowering LDL-C is one action that individuals and populations can do with significant success in delaying the onset of clinical events. Epidemiological studies and small clinical trials suggest that more aggressive and sustained lowering to LDL-C below 100 mg/dl could result in 50 to 70% reductions in vascular death. The full benefit of reducing LDL-C is only now being tested in adequate clinical trials.

Keywords: arteriosclerosis, cholesterol, clinical trials, LDL, vascular disease

The rationale

In this debate, the author takes the position that LDL cholesterol is a major causative factor in the huge prevalence and incidence of arteriosclerotic disease that has plagued the Western World and which is now growing rapidly in developing countries [1]. In examining population data, the risk of clinical vascular disease is a continuous function of rising plasma cholesterol, which is attributable to a rise in LDL cholesterol [2]. Those cultures estimated to have lifelong LDL cholesterol values at or below 100 mg/dl have previously experienced myocardial infarction and coronary death rates that are 70 to 90% below those in Eastern Europe where LDL has been 50 to 70% higher [3]. As economic changes have brought about dietary changes, plasma cholesterol levels have risen, as have other major risk factors such as obesity and diabetes. Even in societies with low total cholesterol levels, preliminary evidence indicates that declining risk extends to values below 160 mg/dl (4.2 mmol/l), which is equivalent to an LDL level of approximately 100 mg/dl (2.6 mmol/l) [4]. Lowering plasma cholesterol by a variety of means – including diet, surgical bypass of the distal ileum, bile acid sequestrants, fibric acid derivatives and most recently statins – has led to a reduction in events both in patients with known clinical vascular disease as well in those without [5–13]. It is highly probable that reducing the population distribution curve of LDL cholesterol values to a mean of around 100 mg/dl (total cholesterol of approximately 150–160 mg/dl) would cause a major change in the incidence of this problem. Furthermore, reductions well below 100 mg/dl, where feasible and cost effective, are predicted to give an additional margin of protection that could save millions of lives.

AVERT = Atorvastatin Versus Revascularization Treatments; CAD = coronary artery disease; CARE = Cholesterol And Recurrent Events; IDEAL = Incremental Decrease in Endpoints through Aggressive Lipid; MI = myocardial infarction; PDAY = Pathobiological Determinants of Atherosclerosis in Youth; Post-CABG = Post-Coronary Artery Bypass Graft; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TNT = Treating to New Targets; WOSCOPS = West of Scotland Coronary Prevention Study.

Expert opinion

The National Cholesterol Education Program (NCEP) in the US and the Joint European Commission have taken the position that health care providers should set the most aggressive treatment goals in those at highest risk [14,15]. The NCEP has chosen the LDL-C target of less than 100 mg/dl for all patients with clinically evident arteriosclerotic vascular disease. Furthermore, this organization is considering using other indicators of impending events, such as diabetes mellitus, reduced ankle/arm blood pressure ratios, and integrated risk analysis ('global risk'), to define additional populations that should be included in this LDL-C goal. The European recommendations suggest setting an LDL-C goal of 115 mg/dl (3.0 mmol/l), or less, in those patients with a global risk analysis that predicts a 20% probability of having a myocardial infarction (MI) or coronary artery death (CAD) in the next 10 years [15]. Accordingly, we will attempt to develop the argument for reducing the LDL cholesterol to values below 100 mg/dl (2.6 mmol/l) by sequentially focusing on defined populations ranked by increasing risk of suffering a major cardiovascular event.

Clinical trial evidence

Those at highest risk are patients who have suffered a recent major spontaneous event such as a myocardial infarction or hospitalization for unstable angina. Recurrent hospitalization for CAD or coronary death occurs in 12 to 20% of this group within 1 year [16]. The recently reported Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial (MIRACL) [17, 18] selected 3080 patients in hospital for non-Q wave MI or unstable angina and randomly assigned them to receive atorvastatin (80 mg/d) or placebo for four months. Initially the LDL-C was only 124 mg/dl. By the end of the study, it had risen to 135 mg/dl in the control group but had been reduced to 72 mg/dl in those on the statin. Those treated with atorvastatin had experienced 16% fewer endpoints defined as 'primary' (14.8% versus 17.4%). These included total death, nonfatal acute MI, cardiac arrest with resuscitation, and urgent hospitalization for angina (with objective evidence of ischemia). The hospitalizations for angina, when considered alone, were reduced by 26% (6.2% versus 8.4%). In addition, a reduction in non-fatal stroke of 50% was observed. All of these differences were statistically significant.

A second high-risk group consists of those symptomatic patients who are evaluated by coronary angiography and who are found to be suitable for treatment with percutaneous transluminal coronary angioplasty. The Atorvastatin Versus Revascularization Treatments (AVERT) study [19] randomly assigned 341 such patients to receive either the angioplasty and usual medical care, or to forego the angioplasty and instead begin immediately on atorvastatin (80 mg/dl). After eighteen months, 21% of those receiving standard care had had a major vascular event compared to only 13% of those with more aggressive LDL-C reduction. This represents a difference of 36% in the incidence of recurrent events. The time to the first ischemic event after randomization was significantly longer in those given atorvastatin but no angioplasty. At the close of the trial, the mean LDL-C was 77 mg/dl in the atorvastatin treated group compared to 119 mg/dl with usual care. It is of note that over 70% of the latter group had received various lipid-lowering medications during the trial but at low doses, and that these were often started later in the study.

Patients who have undergone coronary artery bypass surgery are at high risk of worsening disease in native arteries as well as new lesions in the vein grafts. The Post-Coronary Artery Bypass Graft study (Post-CABG) [20] selected 1351 patients who had undergone this procedure one to eleven years earlier, had LDL-C levels of 130 to 175 mg/dl, and who had patent vein grafts. The cohort was randomly divided into two groups, one to be aggressively treated, and the other to have more modest LDL-C reduction. Diet and drug regimens containing lovastatin and cholestyramine were used to titrate the LDL-C to values of 95 to 97 mg/dl in an aggessively treated group. These were compared to a second randomly selected group in which the LDL-C was reduced to only 135 to 137 mg/dl, thus leaving them some 40 mg/dl higher for the duration of the study. The major question was the relative protection of the vein grafts. After 4.3 years, the mean luminal diameter, the number of new lesions, and the percentage narrowing at major stenoses were all significantly better in the group with the greater reduction of LDL-C. Furthermore, the incidence of new revascularization procedures was reduced by 29%. The number of major clinical events was also reduced in the aggressively treated group after an additional three years of monitoring [21].

Large long-term clinical trials using statins have achieved reductions in LDL-C of 26 to 35% with concomitant reductions in major vascular disease events of 24 to 37% [9–13]. When considered separately, the cohorts with known CHD and those without demonstrated a strong trend to lower event rates with lower group mean LDL-C during treatment with either drug (simvastatin) or placebo. In the 4S study, this high-risk group of coronary patients experienced a stepwise lower incidence of clinical events when ranked by tertiles of LDL-C while on treatment [22]. The lowest tertile on simvastatin, with LDL-C of less than 104 mg/dl, had an incidence of MI and CAD of 10.8% compared to rates of 13.3% in the middle (LDL-C 105 to 126 mg/dl) and 18.9% for the upper tertile (>126 mg/dl). Other studies, particularly those using pravastatin such as Cholesterol And Recurrent Events (CARE) and West of Scotland Coronary Prevention Study (WOSCOPS), have not reported similar findings. Those groups on treatment, who demonstrated a fall in LDL-C of more than approximately 25%, did not appear to enjoy any additional benefits [23,24]. It should be kept in mind,

however, that comparisons of subgroups within study cohorts are often distorted by various biases that are generated by the assumptions and selection criteria of the study and by the study procedures themselves. The only scientifically valid method to measure the benefits of further reduction in LDL-C is to perform a randomized and blinded comparison of groups treated to various LDL-C values. Fortunately, such studies are underway with interesting names such as Treating to New Targets (TNT), Incremental Decrease in Endpoints through Aggressive Lipid lowering trial (IDEAL), Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), and Heart Protection. A definitive answer to whether leaving LDL-C just above 100 mg/dl is adequate or whether a significant further risk reduction can be achieved by lowering LDL-C by an additional 30 to 50%, will be available within the next five years. However, it should be recognized that these studies address the middle aged and older individuals who already have clinically evident disease. The extremely important question of the optimum LDL-C for children, young adults, and those without clinical disease will remain with us for some time.

The future

For the next decade it will be necessary to compromise our efforts in an attempt to use our current resources to give the greatest gain in controlling the clinical disease. The cost of screening, monitoring, and current drugs adds unwanted economic burdens to most societies. It is in this context that a rational argument can be made for more relaxed goals than those medically possible today. However, we should not be satisfied with the status quo since studies, such as Pathobiological Determinants of Atherosclerosis in Youth (PDAY) [25], demonstrate that after 30 years of age the majority of adult patients in the USA already have the disease of arteriosclerosis and we are only delaying its clinical appearance. The result is a growth in the number of elderly patients whose lives are compromised by vascular disease. Gaining knowledge of the effects of lowering LDL-C to much lower levels (ie around 50 mg/dl) is extremely important and relevant to practical issues. Setting targets at this level will soon be feasible for most patients as new and more powerful statins appear and as new drugs with totally different mechanisms of action (eg reducing bile acid absorption, cholesterol absorption and or lipoprotein synthesis) are developed. Clearer concepts of the total societal costs, as well as the potential economic benefits of various preventive measures and treatments, must evolve so that the best policies can be developed to take advantage of the demonstrated efficacy of such drugs. With a world already experiencing approximately 11,000,000 deaths annually from CHD and stroke [1], the potential volume of usage will put major pressure on those attempting to reduce costs and improve efficiency of drug and health care delivery systems. Current trends strongly indicate that earlier treatment and more aggressive goals for LDL-C reduction will be targets for the future.

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