Commentary

Debate: “How low should LDL cholesterol be lowered?”

Viewpoint: “It doesn’t need to be very low”

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Abstract

The importance of low-density lipoprotein (LDL) control in the management of patients at high risk of cardiovascular events is unquestionable. The major statin trials have shown that the benefits of LDL lowering extend throughout the range of risk and the range of serum cholesterol, and have indicated that the protective effects of the intervention are mostly related to the baseline risk. Statin therapy is, for this reason, currently seen as an anti-atherogenic approach for the majority of high risk individuals and possibly all coronary heart disease patients. This debate is not about the value of statin therapy or the importance of LDL reduction, but about the goals to be set once we decide that LDL cholesterol must be reduced. With the National Cholesterol Education Program (NCEP) guidelines representing a solid middle ground, the two viewpoints in this debate try to argue, on one hand, that the LDL goals should be substantially lower than our current standards or, on the other, that a specific on-treatment LDL value may not be the most important goal to pursue. We defend the latter position by presenting the case that the most effective LDL intervention in high risk patients is to achieve a reduction of at least 30%. This strategy complies with the NCEP guidelines, as most of the high risk patients treated with an average dose of an average statin would experience a 30–40% LDL reduction that would put on-treatment LDL levels safely below goal. Our position differs from both the guidelines and the proponents of more aggressive LDL goals in the management of the two extremes of the cholesterol distribution, where our lack of interest in a predefined on-treatment LDL concentration would make us more aggressive than guidelines on low baseline LDL patients and less aggressive than guidelines on high baseline LDL patients.

Keywords: atherosclerosis, clinical trials, coronary disease prevention, coronary heart disease risk, low-density lipoprotein cholesterol, meta-analyses, statins

Introduction

In a debate to discuss whether LDL cholesterol should be decreased to very low levels to achieve optimal cardiovascular risk reduction, the viewpoint defending aggressive intervention is usually considered the most logical stance and is by far the most popular position. We defend the opposite viewpoint in this paper; that is, not all high risk patients should have the objective to reach a low LDL concentration (defined as any prespecified number substantially lower than 130 or 100 mg/dl). We will present, in this brief discussion, the case that the most important lipid maneuver in high risk patients with inappropriate LDL...
is a significant reduction from baseline (approximately 30–40%), rather than the attainment of a specific on-treatment level. Not only is this approach largely in agreement with the goals set by the NCEP guidelines [1], as it drives the majority of high risk patients to a LDL level of less than 130 or 100 mg/dl, but it is even more aggressive than the guidelines for the high risk patients with low baseline LDL (130 mg/dl or lower). For the small population of high risk patients with high baseline LDL (200 mg/dl and higher), debating on the appropriate lipid goal is a frivolous exercise because the high prevalence of genetic dyslipidemias in this group attenuates the response to treatment. The most reasonable position is to accept the results of high dose lipid-lowering therapy, whether achieved with a single drug or a combination regimen when necessary.

Among the frequently cited arguments in favor of low targets for LDL are, first, the fact that coronary heart disease (CHD) rates correlate with average plasma cholesterol levels within and between countries, with the lowest rates shown by people with a total cholesterol lower than 150 mg/dl [2,3]. Second, secondary prevention trials have shown a direct correlation between degree of LDL lowering and the extent of angiographic or clinical benefits [4,5]. Finally, the incomplete successes of the statin trials might have been amplified had larger proportions of study subjects reached their LDL goal. On the contrary, the proponents of a less aggressive approach to LDL management question the safety of very low LDL levels [6], cite data from statin trials showing reduced or absent benefits in patients with baseline low LDL [7] or in any patients after the initial 25% drop in LDL [8–10], and invoke the possibility that the impressive results obtained with statins are partly due to direct effects of the drug on the vascular wall and are therefore somewhat independent of LDL changes [11].

Before emphasizing the basis for our position, we think it necessary to state what we do not consider valid arguments against aggressively low LDL goals. First, there is danger in achieving LDL levels between 50 and 75 mg/dl. Although LDL is an important vehicle to transport vitamin A and vitamin E as well as cholesterol to tissues, data from subjects with the heterozygous form of hypobetalipoproteinemia clearly indicate the safety of low LDL [12,13]. Untoward effects of low LDL may become evident for concentrations below 25 mg/dl [14], a value that is rarely reached with statin therapy in common high risk patients. Second, a small reduction in LDL may be just as good as a larger one. It is undeniable that, particularly in high risk patients, LDL reductions to extremely low levels should decrease the atherogenic pressure more than more moderate interventions would. The difference between benefits achieved with one approach versus the other may, however, be too small to too justify aggressive interventions, as clinical trials have indicated that up to 85% of the preventive effect of lipid lowering is collected after the initial 25% drop in LDL from baseline [15]. Finally, LDL reduction is not a therapeutic objective at all in some high risk patients. Although data showing significant clinical benefits in high risk patients with low HDL and low LDL treated with gemfibrozil are available [16], it is unquestionable that the mediator of risk in low HDL conditions is the level of the atherogenic lipoproteins. It is also unquestionable that LDL and remnant reduction in these patients represent the best approach to reducing the cholesterol/high-density lipoprotein (HDL) ratio as well as CHD risk.

**LDL lowering and atherosclerosis**

To prepare the ground for our argument, we need to revisit the biology of atherogenesis. Plaque development in the vessel wall depends always on the accumulation of lipid material in the subendothelial space, a phenomenon that directly or indirectly triggers all other aspects of lesion growth, including macrophage recruitment, foam cell formation, and the inflammatory response in the artery wall. After more than 90 years of studies on atherosclerosis, it is clear that the pathology of the lesion is dependent on cholesterol accumulation, and that no alternative pathways to the initiation of atherogenesis are in place [17,18]. This means that, even in subjects whose main CHD risk factors are not related to lipids, the atherogenic pressures are translated into a ‘permissive’ environment that allows lipid accumulation in the vessel wall. In other words, a diabetic hypertensive patient with a LDL level of 115 mg/dl and a HDL level of 34 mg/dl has increased risk because insulin resistance, hyperglycemia, and high blood pressure affect the endothelium, the intima, and the rest of the vessel wall so that the environment becomes permissive for lipid deposition, which initiates the atherosclerotic process. In this scenario, lowering LDL and raising HDL are clinically beneficial because they affect the plasma and tissue concentration of the ‘initiators’ of atherogenesis even if the ‘permissive’ factors are not modified. This hypothesis finds support in the data of clinical trials such as the United Kingdom Prospective Diabetes Study (UKPDS) [19,20], the Scandinavian Simvastatin Survival Study (4S) [21,22], the Cholesterol and Associated Events (CARE) study [7], or the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study [23], which together show that the strongest intervention to reduce the risk of heart attacks in diabetics may not be an improved glucose control or a more aggressive lowering of blood pressure, but rather a LDL reduction of 28–38%. The advantage of LDL lowering applies to the most common high risk phenotypes, because one of the most striking results of the major statin trials is the larger clinical benefits observed in individuals who have other risk factors in addition to the hypercholesterolemia (ie pre-existing CHD, smoking, hypertension, diabetes, or family history of CHD). Statins may, in this line of thinking, be seen as anti-atherogenic agents that will impact on the overall CHD risk even when the LDL component of the risk profile is not the most prominent problem in the patient.
**LDL goals in high risk patients**

This information brings us to the central point of our argument; that is, the most important objective in LDL lowering for high risk patients is the percentage change from baseline rather than the reaching of any predefined on-treatment goal. This view is corroborated by a large amount of clinical trial data showing, first, that on-treatment LDL levels do not predict CHD rates whereas baseline LDL levels do [24]. Second, the correlation between LDL reduction and CHD risk reduction within each study is at best curvilinear even in high risk, high cholesterol populations where the average on-treatment LDL is still significantly distant from the NCEP goal of 100 mg/dl [10]. Finally, the same percentage LDL reduction appears to be more effective in subjects with higher baseline LDL (and whose on-treatment LDL stays higher than 100 mg/dl) compared with those with a lower baseline LDL (and whose on-treatment LDL adjusts below 100 mg/dl) [7,21,25]. With regard to the last point, Cullen and Assmann propose the scenario in which higher doses of statins would be needed in high risk patients with ‘average cholesterol’ rather than in average risk patients with high cholesterol [26]. Since statin treatment produces the same relative reduction in cholesterol levels irrespective of baseline concentrations, it follows that to accomplish the same absolute reduction in cholesterol (e.g., 40 mg/dl), more aggressive intervention must be given to produce a cholesterol decrease from 200 to 160 mg/dl (20% reduction) than to decrease it from 260 to 220 mg/dl (15% reduction). It is interesting to note that when the correlation between LDL reduction and coronary events is analyzed on a large scale, including statin and non-statin trials, less additional clinical benefits are expected from cholesterol reductions larger than 15%, indicating that this relationship is governed by a law of diminishing returns [15,27]. Considering that each doubling of statin dose reduces LDL only by an additional 6–7% [28,29], the cost-effectiveness of high dose statin treatment in the long-term care of patients with common hypercholesterolemia remains to be evaluated. On the contrary, it is clear that high risk patients with high cholesterol (e.g., subjects with familial hypercholesterolemia) should be treated with the most aggressive regimens available and that they represent the best targets for the new ‘superstatins’ now in the experimental phase, which can reportedly reduce LDL cholesterol approximately 65–70% [30].

To state it simply, the proponents of aggressively low LDL goals would like to see every high risk patient reach a LDL level of 70–90 mg/dl. This position is flawed for the following reasons. First, many high risk patients with severe hypercholesterolemia (LDL level >200 mg/dl) will not be able to reach that goal even at the highest doses of more than one lipid-lowering agent. Setting unreasonable, nonevidence-based goals will affect patient compliance, the ultimate objective to make an impact on CHD risk. Second, the cyclical variations in LDL induce oscillations whose range often encompasses a predefined goal in high risk patients with moderate hypercholesterolemia, thus triggering unjustified dose adjustments or changes of drug. Finally, the high risk patients without hypercholesterolemia (LDL level <100 mg/dl) may be denied LDL lowering intervention because they are already ‘at goal’. Our position is also simple, but has the additional advantages of being feasible throughout the range of cholesterol distributions and being completely based on published clinical evidence. We support the concept that the most effective LDL intervention in high risk patients is to achieve a reduction of at least 30%. This concept is based on the knowledge that atherosclerosis initiation and progression depend on plasma cholesterol, and that the vast majority of LDL concentrations in western populations are sufficient to support plaque formation in the appropriate ‘permissive’ environment. Our strategy complies with the NCEP guidelines, as most of the high risk patients treated with an average dose of an average statin would experience a 30–40% LDL reduction that would put on-treatment LDL levels safely below goal. Our position differs from both the guidelines and the proponents of more aggressive LDL goals in the management of the two extremes of the cholesterol distribution, where our lack of interest in a predefined on-treatment LDL concentration would make us more aggressive than guidelines on low baseline LDL patients and less aggressive than guidelines on high baseline LDL patients.

**Conclusions**

If, at the end of this discussion, the two positions seem to have more similarities than differences, it is because they do. The controversy on which to set LDL goals in high risk patients is actually not a burning social or clinical issue, as little disagreement exists on the value of LDL lowering in high risk patients, and therapy is commonly limited to the use of one statin or another. Different statins at different doses provide, overall, a narrow range of LDL reductions accompanied with significant variation in individual responses, so that different philosophical viewpoints are not easily translated into different practical stances.

The greatest difference between the two viewpoints is in the use of cholesterol lowering as a means to reduce cardiovascular disease in the population. The proponents of aggressive LDL lowering intend to eradicate atherosclerosis by acting on its initiating factor, with the assumption that adequately low LDL levels will impede lesion growth in most individuals, irrespective of their underlying risk profile. We consider cholesterol lowering as one of the many battles in the war on atherosclerotic disease, a war that will not be won without a concerted attack against the other major players in the enemy camp, including inactive lifestyle, the western diet, obesity, cigarette smoking, diabetes, and hypertension.
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