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Scientific Update™

NCEP Guidelines for cholesterol lowering: The clinical evidence

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Cholesterol assessment and lowering is a simple, noninvasive, universally available intervention that is associated with significant improvement in the well-being and longevity of patients with cardiovascular disease, as well as of those at risk for ischemic heart disease. Overwhelming evidence has accumulated to indicate the importance of early diagnosis and intervention with respect to lowering low-density lipoprotein cholesterol. Some of this evidence and its importance to a goal-oriented approach are discussed in this brief review centered around the symposium on coronary heart disease risk reduction that was presented at the 47th Annual Scientific Session of the American College of Cardiology.

Introduction

The importance of individual cholesterol assessment with a view towards lowering low-density lipoprotein cholesterol (LDL-C) is underscored by the recent and somewhat surprising report that ischemic heart disease has been the most important cause of death worldwide since 1992, followed by stroke.[1] The key role of cholesterol metabolism in initiation and advancement of atherosclerotic disease has long been understood. More recently, overwhelming evidence in support of primary (WOSCOPS, AFCAPS, TEXCAPS studies) and secondary (4S, CARE, LIPID, POSTCABG studies) prevention has become available. It is clear that effective LDL-C lowering is associated with a significant reduction in mortality, fatal and non-fatal myocardial infarction, need for revascularization procedures, stroke, occurrence of new angina, detectable bruits, as well as symptomatic claudication.

LDL-C can be lowered most effectively with HMG-CoA reductase inhibitors. This effect is associated not only with improved clinical outcome from cardiovascular events but also with more basic evidence of atherosclerotic disease regression, plaque stabilization, and improvement in endothelial function. More recent evidence suggests that HMG-CoA reductase inhibitors influence multiple steps in atherogenesis, including monocyte adhesion, proliferation, and activation, as well as smooth-muscle cell proliferation. These changes likely account for the plaque-stabilizing effect thought to be responsible for reduction in cardiovascular events.

Goal-oriented therapy

This overwhelming evidence of benefit associated with lowering LDL-C notwithstanding, only 25–30% of suitable patients actually receive cholesterol-lowering treatment.

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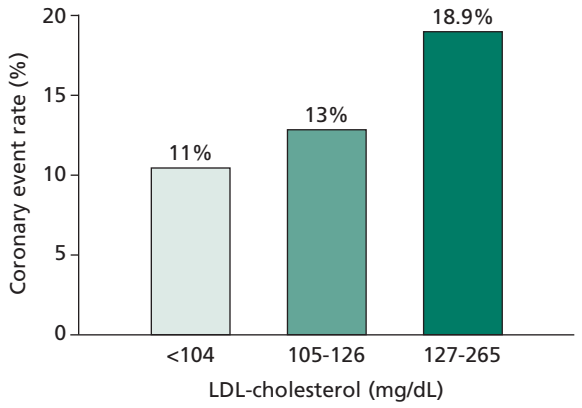
Figure 1: Event rate and cholesterol lowering.



This is due, in part, to a less-than-optimal screening and detection approach, high discontinuation rates, and compliance issues, as well as to the use of fixed-dose rather than goal-oriented therapy.

The National Cholesterol Expert Panel (NCEP) has produced target levels for LDL-C (table 1) that are lower than ever. Support for such aggressive, "the-lower-the-better" therapy comes from a number of investigations. In the Scandinavian Simvastatin Survival Study (4S),[2] reduction of coronary events was in direct relation ($p<0.05$) to the LDL-C lowering achieved with simvastatin treatment (figure 1). In similar fashion, the change in LDL-C cholesterol was linked ($p<0.05$) to the coronary event rate (figure 2). Not surprisingly, the greatest benefit from LDL-C lowering was derived by those at greatest risk for development of atherosclerotic disease: diabetic patients (figure 3).

Table 1: NCEP guidelines for LDL-C levels

Primary prevention	<3.33 mmol/L (130 mg/dL)
Secondary prevention	<2.56 mmol/L (100 mg/dL)

Figure 2: Event rate and change in cholesterol.

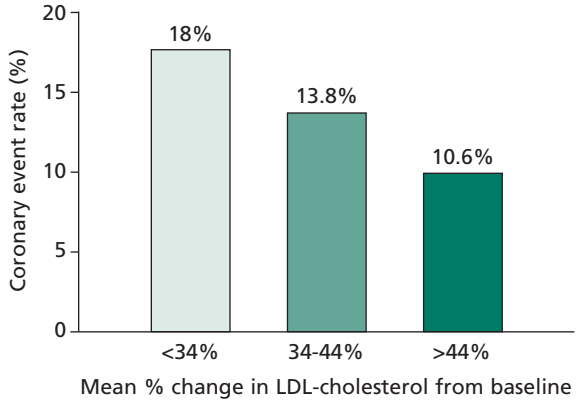
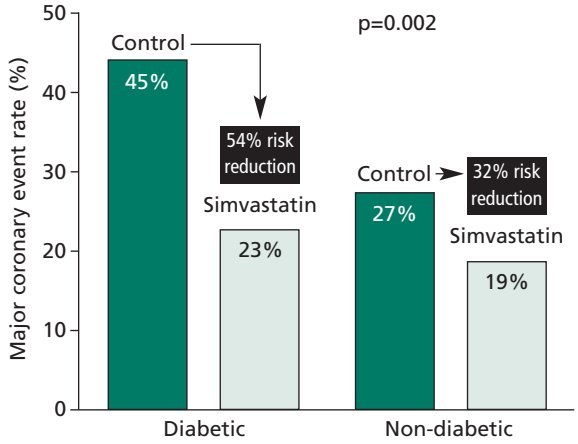


Figure 3: Benefit of LDL-cholesterol lowering in diabetics from 4S. (*AJC* 1995;76:64C-88C)



The percent decrease in LDL-C required for optimal therapy is clearly related to the baseline LDL-C measurement. Table 2 outlines the necessary decrease in LDL-C levels for several baseline readings.

The POSTCABG[3] study was specifically designed to test whether lower LDL-C is better. This was an angiographic trial of 1,351 subjects who had previously undergone coronary artery bypass grafting (CABG). The moderate-treatment

Table 2: Baseline LDL-C and percent reduction necessary

Baseline LDL-C (mg/dL)	(mmol/L)	Decrease necessary
130	3.3	24%
160	4.1	38%
190	4.9	48%
>220	>5.6	>50%

Table 3: Reduction in rates of angiographically-documented disease progression

HDL (mg/dL)	Moderate LDL-C lowering (mean 135 mg/dL)	Aggressive LDL-C lowering (mean 95 mg/dL)
<35	47%	30%
35-39	39.8%	27.6%
40-44	37%	24.7%
>45	29.9%	27.0%

group levels were titrated to an LDL-C level of 130–140 mg/dL (mean 135 mg/dL), and the aggressive-treatment group had a mean LDL-C of 85 mg/dL (the actual achieved was 95 mg/dL). The more aggressively treated group had 30–50% less progression, new occlusions, new lesions, lumen narrowing, and revascularization. Atherosclerosis progression in the POSTCABG trial directly correlated with the in-trial LDL-C levels, and achieving the lowest levels was associated with the greatest benefit.

Lowering LDL-C levels to significantly below 100 mg/dL might also be a worthwhile goal. This is now being evaluated in a number of clinical-event trials, including ALLIANCE, which is comparing standard care with atorvastatin treatment aimed at lowering LDL-C levels to <80 mg/dL.

LDL-C lowering in relation to HDL and TG

Pronounced lowering of LDL-C can have a beneficial impact even in the presence of other metabolically unfavorable factors such as low high-density lipoprotein cholesterol (HDL-C) or raised triglycerides (TG). The POSTCABG trial revealed that aggressively reducing LDL-C attenuates the risk associated with unfavorable HDL-C and TG profiles.

Table 4: Relationship between TG levels and risk reduction by lowering LDL-C levels.

Baseline TG (mg/dL)	LDL lowering	
	Moderate	Aggressive
<110	31.6%	25.4%
110–144	36.1%	29.0%
145–199	46.7%	26.6%
>200	43.6%	30.3%

Table 3 illustrates two important points. First, angiograms show that, even when HDL-C levels are low, reducing LDL-C can reduce the rate of disease progression. Second, and more important, aggressively lowering LDL-C essentially eliminates the "gradient of disease" related to HDL-C levels that is seen with moderate treatment.

In like manner, the importance of elevated TG levels is diminished when LDL-C levels are lowered markedly (table 4).

LDL-C lowering and atorvastatin

HMG-CoA reductase inhibitor efficacy is measured by its ability to lower LDL-C. The recently published CURVES study[4] is the first trial to compare the lipid-lowering efficacy of all marketed HMG-CoA reductase inhibitors across their dose ranges. An open-label design was chosen for the study because of the impracticality of blinding 15 treatment arms; however, efficacy endpoints were based on objective laboratory measurements. In CURVES, atorvastatin lowered LDL-C 38-54%, the other statins 17-48%. Triglycerides were reduced 13-32% with atorvastatin, while with the other statins the reduction was in the range of 2-17%.

Table 5: Relationship of serum lipids and subsequent risk of major coronary events.

Variable	Increment	Risk reduction %	95% CI	p value
TG	-1 mmol/L	-3.1	-22.8 to -21.7	0.788
TC	-1 mmol/L	-22.5	-31.9 to -11.9	0.002
HDL-C	0.1 mmol/L	-3.7	-7.5 to 0.3	0.07
LDL-C	-1 mmol/L	-27.8	-36.8 to -17.6	<0.00001
non–HDL-C	-1 mmol/L	-24.9	-33.7 to -14.9	0.00006

NCEP guidelines: Impact on clinical events

Analysis of the 4S investigation revealed a near-linear relationship between LDL-C at one year and major coronary events ($p<0.0001$). After the simvastatin group's first year, the relationship of serum lipids and the subsequent risk of major coronary events were assessed in a Cox proportional-hazards regression model with age, sex, myocardial infarction, smoking, hypertension, and diabetes as covariates with findings. These are summarized in table 5.

These results suggest that the larger the reduction of LDL-C the greater the risk reduction and—therefore—that current guidelines to reduce LDL-C to 2.56 mmol/L (<100 mg/dL) in patients with ischemic heart disease are valid.

A recent meta-analysis[5] of over 10,000 patients randomized in secondary prevention trials to treatment with either HMG-CoA reductase inhibitors or placebo also reveals a 31% risk reduction in stroke, from 7.3 events/thousand to 5.1 events/thousand. Thus, successful LDL-C lowering with HMG-CoA reductase inhibitors is associated with significant impact on the outcome of two leading global causes of mortality: ischemic heart disease and stroke.

Table 6: Reducing the risk of coronary death[2]

LDL-C lowering	0.585
CABG[6]	0.616

Based on the results of the 4S study, the clinical impact of LDL-C lowering compares very favorably to, for example, the risk reduction achieved with coronary artery bypass surgery (CABG) (table 6). The soon to be completed AVERT study will provide a similar comparison of angioplasty (n=178) and therapy with 80 mg of atorvastatin (n=163).

Conclusion

Coronary artery disease is humankind's most common cause of death. Given the demographics of the aging population worldwide, the favorable impact of lowering LDL-C is significant and extends beyond mortality or important morbidity such as myocardial infarction and stroke. Atherosclerotic plaque formation and development, as well as the pathophysiology of endothelial dysfunction, are favorably modified by falling LDL-C levels. This implies long-term benefits from not only secondary but also primary prevention.

Not all patients benefit from cholesterol reduction, although clearly it needs to be attempted by everyone with or at significant risk of coronary artery disease. It is also important to modify other risk factors, including smoking, hypertension, glucose intolerance, and other lipid abnormalities. The importance of yet more risk factors—homocysteine, for instance—is also emerging. Aggressive and goal-oriented LDL-C lowering should be a routine part of risk-factor modification.

References

1. Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997;349:1269.
2. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383.
3. The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous vein coronary artery bypass grafts. *N Engl J Med* 1997;336:153-162.
4. Jones P, Kafonek S, Laurora I, Hunninghake D, for the CURVES Investigators. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (The CURVES study). *Am J Cardiol* 1998; 81:582-587.
5. Crouse JR III, Byington RP, Hoen HM, Furberg CD. Reductase inhibition monotherapy and stroke prevention. *Arch Intern Med* 1997; 157:1305.
6. Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: Overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialist Collaboration. *Lancet* 1994;344:563.