

Introduction: Missing the Target With Lipid-Lowering Therapy

Based on presentations by Donald B. Hunninghake, MD; and James M. McKenney, PharmD

Hypercholesterolemia is a well-established risk factor for coronary heart disease (CHD) and myocardial infarction. Several large clinical trials show that lowering low-density lipoprotein cholesterol (LDL-C) significantly reduces morbidity and mortality. Yet only a third of those individuals who should be treated with drug therapy are actually treated—with fewer than half being treated to the appropriate target levels.

Why? This is the simple yet exceedingly complex question around which the discussions reported in this supplement to *The American Journal of Managed Care* revolve. Leading researchers in hyperlipidemia were assembled to help define the current unmet needs in cholesterol therapy and to provide insight and guidance for managed care organizations (MCOs) that are struggling to improve their CHD prevention approaches.

In addition to reporting on the roundtable discussion, this supplement summarizes formal presentations by James M. McKenney, PharmD, who focused on combination therapy as an emerging strategy to attain cholesterol treatment targets. Abstracts of the most relevant and recent articles on cholesterol management can also be found in this issue. As a starting point, this introduction explores the evidence, assumptions, and guidelines on which most clinicians and healthcare managers now base their decisions.

The Value of LDL-C Reduction

In the United States, 13 million people have clinically evident cardiovascular disease, and more than 500,000 die each year as a result of CHD.¹ Hospitalization and nursing home costs for CHD are approximately \$39 billion in the United States, with another \$38 billion accounted for by lost productivity and mortality and about \$3 billion for drug treatment.²

Decades of experimental, epidemiologic, and clinical data have documented that hypercholesterolemia is a major preventable risk factor for CHD. Lipids are now known to be central in the pathogenesis of plaque, and the physiologic benefits of reducing LDL-C levels include decreased lesion size and increased lesion stability.

The first definitive evidence of clinical benefits with LDL-C reduction came in the Lipid Research Clinics Program, which documented an 11% cholestyramine-related reduction in LDL-C and an associated 24% drop in CHD death as well as a 19% reduction in nonfatal myocardial infarction.³ The benefits of reducing LDL-C levels with more powerful systemic agents, such as the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), have become irrefutable.⁴⁻⁶

Recently, the benefits of LDL-C reduction have even been demonstrated at the lowest continuum of risk: for example, in healthy older men and women (including smokers and those with diabetes) with average

cholesterol levels. In the important Air Force/Texas Coronary Atherosclerosis Prevention Study, only 17% of such patients would have received drug therapy under current National Cholesterol Education Program (NCEP) guidelines, and yet treatment with lovastatin significantly reduced the risk of a first major coronary event.⁷ Based on these results, the authors estimated that about 6 million more individuals in the United States who do not have documented cardiovascular disease may require treatment.

This evidence of value in lower risk patients indicates the population that is likely to benefit from lipid-lowering therapy may be expanding. Eventually, to increase the cost effectiveness of primary prevention, noninvasive diagnostic tests may be needed to identify risk in those patients without a history of CHD.

Defining Targets: NCEP and HEDIS

Even before the results of the large statin trials were known, the NCEP had issued recommendations for reducing LDL-C below 100 mg/dL in patients with established CHD. These NCEP recommendations were reiterated in 1994, along with specific testing and treatment recommendations for those with risk factors (Table).⁸ The guidelines called for aggressive dietary and/or pharmacologic therapy to lower LDL-C in mild-to-severe hypercholesterolemia. These NCEP guidelines are scheduled to be updated within the next year.

In addition to these widely accepted clinical targets for the management of individual patients, the National Committee for Quality Assurance (NCQA) has now implemented a special performance measure for evaluating lipid-related care in an entire population. The NCQA Health Plan Employer and Data Information Set (HEDIS) performance measure for LDL-C is higher (≤ 130 mg/dL) than that of the NCEP

target (≤ 100 mg/dL) for persons with coronary disease, mainly because the NCQA recognizes the current reluctance of many physicians to use higher doses of cholesterol-lowering drugs to achieve the NCEP target.^{9,10}

In some cases, this reluctance is a conscious decision made by clinicians or organizations based on their perceived balance of risk factors, safety, and costs. For example, some clinicians may choose not to increase the dose of therapy or add medications in an otherwise healthy male exsmoker with single-vessel disease whose LDL-C already has been reduced from 150 mg/dL to 110 mg/dL. If the patient had diabetes, however, most clinicians would be more likely to pursue the NCEP target (LDL-C ≤ 100 mg/dL).¹¹

As a result, despite near universal agreement that patients with CHD should lower their cholesterol, the precise lipid goal is still being debated. The HEDIS guidelines, while encouraging physicians to aim for the NCEP goal in secondary prevention, establish a more permissive goal that reflects both the theoretical debate and the practical difficulties in aggressively lowering LDL-C.

The Treatment Gap

To a large degree, the call for greater attention to LDL-C as a treatable CHD risk factor has been heard. From 1991 to 1997, the volume of

Table. Guidelines of the National Cholesterol Education Program

Patient Assessment Criteria	Initiation Level	Minimum Goal
Without CHD and < 2 risk factors	≥ 190 mg/dL	< 160 mg/dL
Without CHD and > 2 risk factors	≥ 160 mg/dL	< 130 mg/dL
With CHD	≥ 130 mg/dL	≤ 100 mg/dL

CHD = coronary heart disease.
Source: Reference 8.

cholesterol-lowering medication dispensed in US retail pharmacies more than doubled.¹² Still, only about one third of the estimated 26 to 28 million individuals in the United States who require drug therapy (based on NCEP criteria) actually receive a prescription.¹ And most of those treated with drugs fail to attain the plasma LDL-C goal, as defined by the NCEP.^{13,14}

In the most recent documentation of this treatment gap, the therapeutic results of 4888 adult patients from 5 regions of the United States were assessed.¹⁵ Overall, only 38% of these patients who were treated by primary care physicians achieved the NCEP LDL-C target. Although drug therapy was significantly more effective than nondrug therapy, many patients taking lipid-lowering drugs still did not achieve the target LDL-C level.

Among the 30% of the patient group with established CHD, only 18% reached the LDL-C target whereas the success rate in the low-risk group (ie, < 2 risk factors, no CHD) was 68% (Figure). In other words, the aggressiveness of therapy was inversely related to risk, a situation that ideally would be reversed.

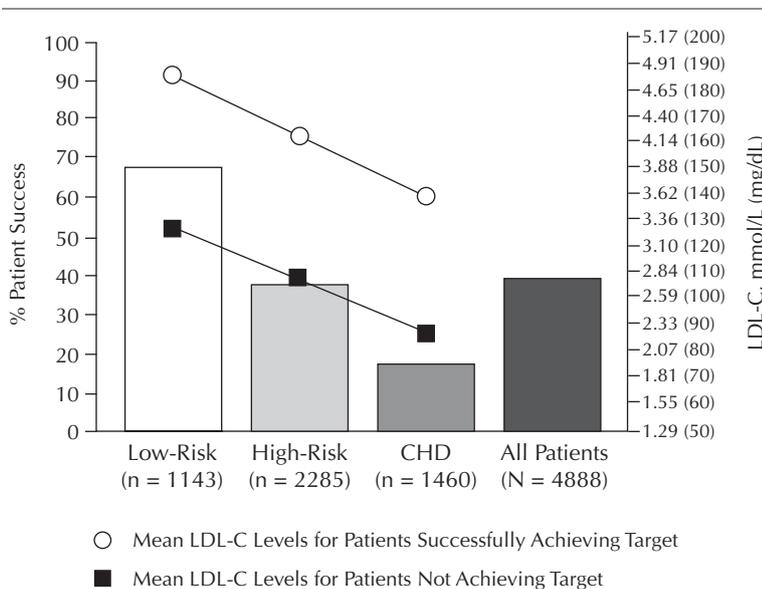
A review of cholesterol treatment success in the setting of health maintenance organizations indicates an even worse situation, with lipid-lowering drugs exhibiting rates of discontinuance ranging from 15% to 46%, depending on the drug class.¹⁶ Thus, clinical trial results may even underestimate the actual intolerability of antihyperlipidemic drugs—as seen for example in typical primary care situations.

Possible explanations for the treatment gap include drug discontinuation, poor patient adherence, and drug intolerance or side effects. However, as described in the most recent survey of treatment failures, poor patient compliance is an unlikely cause for the high proportion of dyslipidemic patients whose LDL-C levels remain above NCEP targets.¹⁵ Instead, these patients are probably not receiving adequate lipid-lowering treatment, or perhaps the lipid-lowering treatments themselves are not adequate. Therefore, an inadequate regimen—caused by physician reluctance to increase doses because of costs or side effects—seems to be the major contributor to the low success rates.

Defining Current Needs

With currently available lipid-lowering options, the lack of aggressiveness in pursuing NCEP targets may be the result of barriers related to drug intolerance, side effects, and costs. Treatment alternatives are needed for many patients with hypercholesterolemia. In particular, those who do not tolerate other drugs (especially niacin and statins) and those with only mild-to-moderate elevations of LDL-C

Figure. Achievement of Target LDL-C Related to Risk



CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol. Source: Pearson TA, Laurora I, Chue H, Kafonek S. The Lipid Treatment Assessment Project (L-TAP). *Arch Intern Med* 2000;160:459-467. Reprinted with permission from the American Medical Association.

would benefit from a drug with improved tolerability and an enhanced side-effect profile.

An alternative agent would also be welcome in that large population of patients who have been started on a statin but are unable to tolerate the dose escalation required to reach NCEP goals. Finally, safer agents with indications in pediatric patients and premenopausal women also would be useful.

Various strategies aimed at increasing the percentage of treated patients who attain target LDL-C levels are now being developed. Switching from one statin to milligram-equivalent doses of another statin, for example, has been associated with greater reductions in LDL-C.¹⁷ Certain statins may in fact help achieve NCEP goals more quickly than others.¹⁸ However, trade-offs in terms of potentially increased costs and side effects of the newer statins need to be considered in this switching strategy.¹⁷

Another option that is emerging to fill the treatment gap is combination therapy. As described by Dr. McKenney in this supplement, combinations may often provide the necessary final push of LDL-C levels toward the NCEP target. A thoughtful combination may also allow clinicians to target other lipid risks, such as high triglycerides or low high-density lipoprotein cholesterol (HDL-C). Niacin in combination with bile acid sequestrants or statins, for example, can help increase HDL-C and lower LDL-C.¹⁹ As an alternative to doubling or tripling statin doses to reach the LDL-C target, adding the nonsystemic bile acid-binding agent colesevelam, which has not been associated with the severe constipating effects of the older bile acid sequestrants, to the regimen may allow patients to attain the target with a minimum of side effects.²⁰

The emerging options for improved cholesterol treatment will require

long-term demonstrations of sustained efficacy, safety, tolerance, and compliance. The balancing of costs with these long-term clinical outcomes will determine whether national professional committees and MCOs can adopt such new options in the renewed drive toward more successful cholesterol treatment.

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