

Clinical Pearl

The Impact of Recent Clinical Trials on National Cholesterol Education Program Adult Treatment Panel III Guidelines

Recent clinical trials have led to updates in the management of patients with high cholesterol.

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Introduction

The management of elevated cholesterol (which follows screening, as described in Case 2 of this issue) centers around a set of evidence-based guidelines put forth by the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, known as the Adult Treatment Panel III (ATP III). The ATP III published its final report in December 2002 [1,2]. The ATP III guidelines provide useful information for clinicians and clinical researchers, and address issues related to the detection, evaluation, and treatment of cholesterol disorders. The guidelines were based on randomized clinical trials, epidemiologic studies, and smaller clinical studies conducted since the ATP II guidelines were published in 1994 [3].

Five large randomized clinical trials have been conducted since the 2002 ATP III guidelines. The results of these trials led the NCEP to issue modifications to the ATP III guidelines in July 2004. This clinical pearl reviews the ATP III guidelines and the 5 randomized clinical trials with an emphasis on how these results might impact patient management.

ATP III Detection and Evaluation Guidelines

In the ATP III algorithm, the first step in analyzing a patient is determining the lipoprotein levels after a 9-12 hour fast. While the level of total cholesterol correlates with cardiovascular risk, the level of LDL-C determines the overall risk of adverse cardiovascular events. Higher HDL-C levels are protective against cardiovascular events. The ATP III classification is depicted in [Table 1](#).

Following lipid profile determination, patients are classified on the basis of risk factors. Patients who are determined to be *high risk* have coronary heart disease (CHD) or CHD risk equivalents. CHD risk equivalents are risk factors that pose a risk just as high as CHD. These include noncoronary forms of cardiovascular disease (CVD), such as symptomatic carotid artery disease, peripheral vascular disease, abdominal aortic aneurysm. Other risk equivalents are diabetes, or the combination of 2 or more of the following risk factors: smoking, hypertension, low HDL, a family history of premature CHD, or age (45+ for men; 55+ for women).

Lipid levels, medical history, and risk factors allow the classification of patients into different risk categories that are useful in determining the treatment strategy. Treatment consists of behavioral and pharmacological approaches. The behavioral approach is known as therapeutic lifestyle changes (TLC) and involves exercise, weight management, and diet modification. Pharmacological approaches include 4 main classes of drugs:

1. HMG Co-A reductase inhibitors (statins)
2. Bile acid sequestrants
3. Fibrates
4. Nicotinic acid

Of these drugs, statins cause the largest reductions in LDL-C and triglycerides and a significant elevation in HDL-C. Because of their dramatic effects and tolerable side effect profile, statins have become the focal point of cholesterol management, with the addition of the other drug categories as deemed necessary. A stratification of risk types along with the ATP III goals and treatment guidelines appears in [Table 2](#).

Summary of Recent Clinical Trials that Impact the ATP III Guidelines

Since the publication of the ATP guidelines in December 2002, 5 clinical trials have examined the role of statins in the treatment of cholesterol disorders [4-8]. The details of these trials are summarized in [Table 3](#).

The main conclusions of each trial follow.

1. *HPS*. This study had several important findings:

- Patients with LDL-C \geq 130 mg/dL benefited most from LDL-C reductions. If statins alone cannot achieve the goal of < 100 mg/dL, maximal dietary therapy and a drug from another class may help achieve this goal [9-11].
- In patients with LDL-C of 100-129 mg/dL, HPS demonstrated a substantial benefit of instituting a standard dose of statins to achieve a 30 to 40 percent reduction in LDL-C levels.
- In patients with low LDL-C < 100 mg/dL, HPS demonstrated an even greater risk reduction in high risk patients by lowering LDL-C < 70 mg/dL.
- In diabetic patients with CVD, statin administration to achieve an LDL-C goal < 70 mg/dL is reasonable, regardless of baseline LDL-C. In diabetic patients without CVD, HPS supports an LDL-C goal of < 100 mg/dL, although the benefit of statins in patients who are close to that endpoint may be less pronounced.

2. *PROSPER*. The PROSPER study demonstrated decreased composite endpoint, major coronary events, and CHD mortality as a result of LDL-lowering therapy in older patients with or without established CHD. Although an increased cancer risk was noted, this is the only trial to date that describes an increased risk of cancer.

3. *ALLHAT-LLT*. Unlike others, this study did not demonstrate a decreased risk in hypertensive patients. This could have been due, however, to the large crossover of higher-risk subjects to the lipid-lowering treatment arm, the unblinded nature of the study, and the difference in cholesterol between patients on pravastatin and those receiving usual care. The significant reduction in cardiovascular events in African Americans supports the ATP III recommendation that the goals of LDL-lowering therapy should not be modified on the basis of ethnicity [12].

4. *ASCOT-ALL*. This study supported the therapeutic option of administering LDL-lowering therapy to reach a goal LDL-C < 100 mg/dL in patients at moderately high risk with an LDL-C 100-129 mg/dL. (The study was cut short because of the pronounced risk reduction of cardiovascular events in patients with multiple CVD risk factors.)

5. *PROVE IT*. This study tested the effects of intensive LDL-C lowering beyond standard targets on the incidence of major coronary events. High levels of atorvastatin caused an even greater reduction in composite endpoint, which was correlated with a 35 percent lower LDL-C level in patients treated with high levels of atorvastatin. This study lent support to the HPS study, suggesting an optional therapeutic threshold for LDL-C < 70 mg/dL in high risk patients. It also demonstrated the benefit of LDL-C < 70 mg/dL after acute coronary syndromes.

Modifications to ATP III Guidelines after Recent Clinical Trials

Given these results, modifications to the ATP III guidelines are now proposed. These modifications are summarized in [Table 4](#).

The guidelines recommend the initiation of TLC in (a) high-risk patients with LDL-C \leq 100 mg/dL, (b) moderately high or moderate-risk patients with LDL-C \leq 130 mg/dL, or (c) low risk patients with LDL-C \leq 160 mg/dL. In patients with high risk or moderately high risk who have lifestyle-related risk factors like obesity, metabolic syndrome, elevated triglycerides, or decreased HDL-C, TLC is recommended regardless of LDL-C levels.

The recommendations for modifications to the ATP III treatment algorithm impact patients with *high risk* the most. While the LDL treatment goal is still LDL-C $<$ 100 mg/dL, HPS and PROVE IT support an optional treatment goal of LDL-C $<$ 70 mg/dL in high risk patients, especially diabetics, even when the baseline or on-treatment LDL-C is already $<$ 100 mg/dL. Adding nicotinic acid or fibrates to statin therapy can also help reach the therapeutic goal. The studies demonstrate benefits of lowering LDL-C by 30 to 40 percent, even in patients whose baseline LDL-C is 100-129 mg/dL. These data support lowering the threshold at which to consider pharmacologic therapy from \geq 130 mg/dL to \geq 100 mg/dL in high-risk patients.

For patients with *moderately high risk*, the LDL treatment goal is still LDL-C $<$ 130 mg/dL. For patients with baseline or on-TLC levels of 100-129 mg/dL, initiation of an LDL-lowering drug is an appropriate therapeutic option to achieve a goal of LDL-C $<$ 100 mg/dL. The goal with statin administration should be a 30 to 40 percent reduction in LDL-C.

The guidelines for patients with *moderate* or *low risk* have not changed.

Conclusions

The results of recent clinical trials, including HPS, PROSPER, ALLHAT-LLT, ASCOT-LLA, and PROVE IT, support the modification of the ATP III guidelines for treatment of cholesterol disorders. The modifications suggest that, for some patients, more intensive lowering of LDL-C is beneficial for reducing cardiovascular event risk. The revised guidelines offer alternative therapeutic goals of LDL-C $<$ 70 in high risk patients and LDL-C $<$ 100 in moderately high risk patients. Further studies will help determine if this therapeutic option should be incorporated into the guidelines for all patients.

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