High Blood Cholesterol and ATP III: Guidelines for Health Benefit and Health Care Providers

by Marcus C. Ravnan and Linda L. Norton

Hyperlipidemia is well established as a major risk factor for the development of coronary heart disease (CHD). Elevated levels of cholesterol, in particular elevated levels of low-density lipoprotein cholesterol (LDL-C) are of great concern as elevated LDL-C has been linked to cardiovascular events resulting in significant morbidity and mortality not only in the United States (U.S.) but worldwide. As a result, the NCEP has developed guidelines for the detection, evaluation and treatment of high blood cholesterol in adults—the adult treatment panel (ATP). These guidelines are based on the cumulative outcomes of large clinical trials and expert recommendations. The ATP I, ATP II and, most recently, the ATP III have been designed not only to provide appropriate detection, evaluation and management of high blood cholesterol, but also to emphasize the extreme importance of cholesterol management. The thrust of all of these guidelines has been a focused strategy for the primary prevention of CHD in patients with high and borderline high LDL-C cholesterol, >160mg/dL and between 130-159mg/dL, respectively. The ATP II focused on risk minimization for patients with established CHD and added a new lower therapeutic goal for CHD patients, <100mg/dL. In addition to primary prevention and the focus on intensive management of patients with CHD, the ATP III has added a new focus that is directed towards primary prevention in patients with specific risk factors for the development of CHD such as non-CHD atherosclerosis and diabetes.

Before reviewing the new ATP III guidelines, it is important to consider two questions: “What is the result of chronic high blood cholesterol?” and the associated question, “Why is cholesterol management so important?”

What is the result of chronic high blood cholesterol?

In order to design therapy and a drug benefit for a covered disease state and then evaluate the efficacy and costs of that coverage and therapy, the course of the disease in patients with and without treatment must be understood. For high blood cholesterol, the primary concern is the relationship among chronic high blood cholesterol, particularly elevated LDL-C, the development of an atherosclerotic plaque, endothelial dysfunction, and events associated with the formation and/or the ultimate rupture of the atherosclerotic plaque which include acute coronary syndrome (ACS), stroke and peripheral vascular disease (PVD).

Atherosclerosis has been thought by many to be a process of chronic lipid accumulation within an artery wall. However, the accumulation or deposition of cholesterol in the artery wall may lead to narrowing of the artery lumen and thus reducing blood flow within the artery.
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**Table 1** Landmark Lipid Lowering Outcome Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>LDL-C Reduction</th>
<th>Total Mortality Reduction</th>
<th>Event Reduction</th>
<th>Reduced Need for CABG &amp; PTCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>35%</td>
<td>30% (p=0.003)</td>
<td>34% (p&lt;0.0001)</td>
<td>37% (p&lt;0.0001)</td>
</tr>
<tr>
<td>CARE</td>
<td>32%</td>
<td>9% (n.s.)</td>
<td>24% (p=0.003)</td>
<td>27% (p&lt;0.001)</td>
</tr>
<tr>
<td>LIPID</td>
<td>25%</td>
<td>22% (p&lt;0.0001)</td>
<td>24% (p&lt;0.0001)</td>
<td>22% (p&lt;0.001)</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>26%</td>
<td>22% (p=0.051)</td>
<td>31% (p=0.001)</td>
<td>37% (p=0.009)</td>
</tr>
<tr>
<td>AFCAPS/TEXCAPS</td>
<td>25%</td>
<td>n.p.</td>
<td>37% (p&lt;0.001)</td>
<td>33% (p=0.001)</td>
</tr>
</tbody>
</table>

Note: n.s. is not statistically significant, n.p. is not powered to detect.


**Table 2** ATP III Cost Effectiveness Information for LDL-C Lowering Therapies*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>LDL-C Level for Lifestyle Changes</th>
<th>LDL-C Level for Drug Therapy</th>
<th>Comments: Drug Therapy Cost Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or risk equivalents</td>
<td>Z100 mg/dL</td>
<td>Z130 mg/dL</td>
<td>LDL-C lowering therapy results in significant CHD risk reduction and has very favorable ratios.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100–129 mg/dL</td>
<td>Drug therapy optional. Clinical judgment required for decision.</td>
</tr>
<tr>
<td>Two or more risk factors, but Framingham 10-yr risk &lt;20%</td>
<td>Z130 mg/dL</td>
<td>If 10 year risk 10%–20% then, Z130 mg/dL</td>
<td>If LDL-C Z130 mg/dL after three months of lifestyle change, LDL-C lowering drugs can be started to reach LDL-C goal and are cost effective.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If 10 year risk &lt;10% then, Z160 mg/dL</td>
<td>If LDL-C Z160 mg/dL after three months of lifestyle change, LDL-C lowering drugs can be considered to reduce LDL-C to &lt;130 mg/dL—a “strong case can be made for using drugs...”</td>
</tr>
<tr>
<td>Zero or one risk factor</td>
<td>Z160 mg/dL</td>
<td>Z190 mg/dL</td>
<td>If LDL-C Z190 mg/dL after three months of lifestyle change, LDL-C lowering drugs can be considered to reduce LDL-C to &lt;160 mg/dL—a “strong case can be made for using drugs...”</td>
</tr>
</tbody>
</table>

Note: *ATP III cutpoints for drug therapy were, for the most part, risk-benefit based, but were checked for cost effectiveness. Therapeutic lifestyle changes - decreased saturated fat and cholesterol intake, increased activity and weight loss when appropriate—are the heart of primary prevention, are recommended as first line therapy and considered the most cost-effective methods to reduce CHD risk.

atherosclerotic process starts with injury to the endothelium and a state of chronic inflammation. Further investigation has led to the formulation of the response-to-injury hypothesis of atherosclerosis. Plaque formation and endothelial dysfunction are part of a continuum that involve not only cellular injury but also cellular immune responses. Under normal circum-

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stages endothelial cells function to maintain homeostasis. These cells line the blood vessels, are in direct contact with blood and synthesize and release substances such as nitric oxide (NO). Elevated levels of modified LDL-C can increase oxidant stress within the endothelium and as a result activate cytokine production. The endothelial wall and cellular debris in the area attract monocytes that engulf the modified LDL-C and permeate the endothelial wall, the result of which is "foam cell" formation. Accumulation of modified LDL-C, foam cells and lipid fragments form a lipid core within the artery that is covered by a fragile cap, what is referred to as a vulnerable plaque.

In an effort to stabilize the plaque and to protect the core from exposure to vascular active substances and platelet activators, smooth muscle cells are recruited to the site. However, the ensuing inflammatory state decreases smooth muscle cell proliferation and collagen synthesis, and the vulnerable plaque and the inflammatory state remain uninterrupted. This process can continue indefinitely; or, based on the extent of the plaque and inflammation and local factors, it can trigger an acute event. The resulting endothelial dysfunction is characterized by increased platelet and leukocyte adhesion, pro-coagulation and deregulation of vasoactive substances and growth factors. This chronic state of inflammation and cellular damage results in elevation of C-reactive protein (CRP). Elevated levels of CRP is now considered a systemic marker and an independent risk factor for cardiovascular disease. As mentioned, ATP III continues the guidelines for primary prevention and for patients with existing CHD and adds guidelines for patients with specific and multiple risk factors. These additions include: 1) raising the risk level for persons with CHD risk factors; 2) reducing risk for persons with clinical CHD, diabetes or CHD equivalents or for those with high blood pressure; and 3) improving levels of high density lipoproteins (HDL-C) for persons with existing CHD, diabetes or CHD equivalents or for those with high blood pressure. However, the question remains: Why manage high blood cholesterol?

**Why is cholesterol management so important?**

Cholesterol management is important because managed cholesterol should mean lower cholesterol; and, lower cholesterol means a lower risk of a variety of pathogenic conditions such as those mentioned above and a host of diseases including CHD. However, a quick review of the 2001 Heart and Stroke Statistical Update published by the American Heart Association provide additional detail in terms of human morbidity and mortality. The effects of cardiovascular disease account for approximately one million deaths annually in the U.S. 20% of these deaths, 48% are the direct result of CHD. As one of the major results of CHD, patients who suffer an ACS, which includes unstable angina, non-Q-wave myocardial infarction (NQWMI) and Q-wave myocardial infarction (QWMI), often experience a fatal event. Other data show that approximately 1.1 million Americans experience a recurrent or new myocardial infarction each year, and of these sufferers one-third will die, the majority within the first hour of symptom onset. It is estimated that 99.5 million Americans have total cholesterol levels in excess of 200mg/dl, and that 39.9 million have levels in excess of 240mg/dl, levels that are associated with great risk and mortality.

Furthermore, in the U.S. the cost of CHD and the events associated with CHD accrued an estimated $118 billion in health care and related costs in 2000. This figure includes $55 billion in direct costs associated with treatment and $63 billion in indirect costs resulting from morbidity and mortality. Moreover, CHD accounts for 19% of the disability allowances reported by the Social Security Administration.

When considering management, data from landmark trials involving both primary and secondary prevention have demonstrated that lipid management, in particular management with statins (i.e., lovastatin, pravastatin, and simvastatin), results in significant reduction in morbidity and mortality as well as reduction in the need for invasive procedures (Table 1, page 483). Data from these trials has shown that for approximately every 1% decrease in LDL-C there is approximately a 1% decrease in cardiovascular disease-related mortality. In addition, statin therapy has been demonstrated to achieve coronary plaque stabilization, and recently atorvastatin has been demonstrated to reduce recurrent ischemic events in patients with ACS. All taken into consideration strongly supports the importance of aggressive blood cholesterol management.

**Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III)**

As mentioned, ATP III continues the guidelines for primary prevention and for patients with existing CHD and adds guidelines for patients with specific and multiple risk factors. These additions include: 1) raising the risk level for persons with CHD risk factors; 2) reducing risk for persons with clinical CHD, diabetes or CHD equivalents or for those with high blood pressure; and 3) improving levels of high density lipoproteins (HDL-C) for persons with existing CHD, diabetes or CHD equivalents or for those with high blood pressure. However, the question remains: Why manage high blood cholesterol?
equivalents (i.e., diabetes, non-CHD atherosclerosis, or a 10 year risk of CHD >20%) to the same level of risk as those with CHD; 2) using of Framingham projections of CHD risk to identify which patients with two or more risk factors are candidates for more aggressive therapy; and 3) indicating persons with metabolic syndrome as candidates for preventive therapeutic lifestyle changes. Additionally, ATP III defines the optimal LDL-C level at <100mg/dL, increases the high designation for low HDL-C from <35mg/dL to <40mg/dL and lowers the cutoff points for triglycerides. The ATP III continues the focus on LDL-C as a major cause and indicator of risk of CHD. The guidelines also acknowledge that there are a number of other independent risk factors (e.g., elevated homocysteine levels) and suggest that other measurements may, under selected circumstances, be targets for therapy, especially in individuals with additional metabolic abnormalities.

A primary principle of ATP III is the concept of matching the aggressiveness of LDL-C lowering therapy to the individual’s absolute risk. To accomplish this, risk assessment is the first step in using the guidelines. To begin the risk assessment process the guidelines suggest that everyone over the age of 20 years should complete a fasting lipoprotein profile (i.e., total, LDL and HDL cholesterol and triglyceride) at least every five years.

**ATP III blood lipid classifications are:**

- LDL-C levels in mg/dL:
  - optimal <100, near optimal 100–129, borderline high 130–159, high 160–189, and very high >190.
  - Total cholesterol levels are defined in mg/dL as:
    - desirable <200, borderline high 200–239, and high >240.
  - HDL-C are described in mg/dL as:
    - low <40 and high >60.

Setting LDL-C goals for patients with CHD is simple. Their goal, as shown above, is an LDL-C of <100mg/dL. For patients without clinical CHD or CHD risk equivalents (e.g., atherosclerotic disease or diabetes) the number of major risk factors is determined.

**The major risk factors (not LDL-C based) identified in ATP III include:**

1. Cigarette smoking
2. Hypertension (blood pressure ≥140/90 mmHg or taking a blood pressure medication)
3. Low HDL-C (note: HDL-C ≥60 mg/dL is considered a "negative risk factor")
4. Family history–early onset CHD in 1st degree relative (male <55 years old, female <65 years old)
5. Age (males ≥45 years old, females ≥55 years old)

In persons with two or more risk factors Framingham scoring is used to determine a 10-year risk. Once the 10-year risk is determined, goals for LDL-C are set.

**LDL-C goals and suggested therapies based on risk categories are:**

1. **Goal <100mg/dL:** For patients with CHD or similar risks including other forms of atherosclerotic disease, diabetes or a combination of risk factors that yield a 10-year risk for CHD >20%.
   - Therapeutic Lifestyle Changes started if LDL-C >goal.
   - Drug therapy considered if LDL-C ≥130 mg/dL. (Some recommendations suggest initiating drug therapy if LDL-C >100mg/dL.)

2. **Goal <130 mg/dL:** For patients with two or more risk factors, and risk factors yield a 10-year risk for CHD <20% as estimated from Framingham risk scores.
   - Therapeutic Lifestyle Changes started if LDL-C >goal.
   - Drug therapy considered if LDL-C >130 mg/dL for persons with a 10-year risk of 10–20%, or if LDL-C >160 mg/dL for those with a 10-year risk <10%.

3. **Goal <160 mg/dL:** For patients with zero or one risk factor. These are generally persons with a 10-year risk of <10%.
   - Therapeutic Lifestyle Changes started if LDL-C >goal.
   - Drug therapy considered if LDL-C >190 mg/dL, drug therapy optional if LDL-C is 160–189 mg/dL.

For persons with less than two risk factors, Framingham risk assessment is not necessary unless there are factors that, with the use of clinical judgement, suggest that the assessment should be completed.

In the ATP III, metabolic syndrome (i.e., abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance and pro-thrombotic or pro-inflammatory conditions) is considered a secondary target for lowering CHD risk. However, these factors are targeted after LDL-C therapy has been addressed. In contrast, persons with high blood cholesterol should be screened for secondary causes of dyslipidemia such as diabetes, hypothyroidism, liver and kidney disease or adverse effects of medications before LDL-C lowering therapy is started.

In addition to the treatment guidelines for lowering LDL-C, the ATP III presents models for instituting therapeutic lifestyle changes and for the progression of drug therapy in primary prevention. Both models are developed around multiple visits (i.e., one visit every six weeks for 12 weeks then visits every four to six months), adequate follow up and referral to specialists as needed. The model for therapeutic lifestyle changes also emphasizes ongoing teaching and encouragement. Commentary on the progression of drug therapy suggests that the drug of choice for most patients will be a statin, but that other medications such as bile acid sequestrants or nicotinic acid are alternatives. Additional information and guidelines for a number of specific conditions and age groups are also presented in the ATP III.
the NCEP ATP II guidelines, an estimated 12.7 million Americans are eligible for drug therapy but are not currently receiving it.\textsuperscript{15,30} This is a staggering statistic as the ATP III guideline recommends aggressive therapy not only in patients with CHD and multiple risk factors as in ATP II, but also in patients at increased risk due to CHD risk equivalents (i.e., diabetes, non-CHD atherosclerosis, or a 10-year risk of CHD $>20\%$).

Following the recommendations of the ATP III, more patients would be eligible for aggressive medication intervention than ever before. However, even when eligibility is confirmed and drug therapy is received, appropriate and optimal management and outcomes do not always occur. Data published recently from The Lipid Treatment Assessment Project (L-TAP) has demonstrated that for those patients who are on lipid-lowering therapy, large portions are not achieving NCEP LDL-C target levels.\textsuperscript{31} The L-TAP evaluated lipid management in a total of 4,888 patients, reporting that overall only 38\% of patients achieved NCEP-specified LDL-C target levels. However, for patients with CHD, only 18\% achieved the recommended goal of LDL-C levels of 100 mg/dL or less. These findings indicate that more aggressive management is needed especially in patients at great risk of experiencing cardiovascular events.

Considering the data summarized in the L-TAP, care and benefit providers must acknowledge the need for comprehensive education and disease management if target cholesterol goals are to be achieved.\textsuperscript{31} Taking into consideration the expanded number of patients in need of lower blood lipid levels and the need for aggressive education and counseling to improve adherence to prescribed therapy, overall costs of chronic, preventive care, especially care related to lifestyle and drug therapy, will mostly likely continue to escalate. Conversely, if therapeutic goals are achieved and the catastrophic events associated with high blood cholesterol and CHD are avoided, the acute care costs associated with high blood cholesterol and CHD would be expected to decrease. The ATP III cost-effectiveness information for select treatment groups is presented in Table 2.

In most patients, statins are considered the treatment of choice for risk reduction in high blood cholesterol. However, it is possible that all statins are not created equal. These agents do more than just lower cholesterol. Large clinical endpoint trials have involved only the first-generation statins which include simvastatin, pravastatin and lovastatin.\textsuperscript{35} Based on their mechanism of action, the primary observed effect of a statin is lowering lipid levels, in particular significant lowering of LDL-C. However, the exact mechanism by which statins decrease cardiovascular events and ultimately mortality has not been fully elucidated. Studies have demonstrated that statins promote coronary plaque regression and plaque stability resulting in a less susceptible and less vulnerable fibrous cap preventing fissure or rupture.\textsuperscript{15,32-34} Statins have been suggested to improve endothelial function, increase myocardial perfusion in patients with CHD and decrease platelet aggregation and thromboxane synthesis.\textsuperscript{15,32-34} Considering the evidence and evolving data, statins cannot be evaluated clinically or from a cost-effective standpoint solely based on each product’s ability to lower cholesterol. These observations lead to the conclusion that each product may not be equally efficacious in terms of event prevention and, based on recent events (the market removal of cerivastatin), product safety.

### Summary

The new strategy as described in the ATP III guideline will represent a long-term investment. Based on clinical studies and economic evaluation of these studies both in primary and secondary risk prevention, this long-term investment should result in cost savings through event reduction in the future.\textsuperscript{35-39} However, when considering risk and event reduction, comprehensive management involves more than just lipid management. Comprehensive risk reduction involves the cost and outcome of treating modifiable risk factors, which include hypertension and its management, smoking and smoking cessation programs, diabetes and its control, and obesity. Finally it must be stated that pharmacoeconomic analyses has demonstrated that statins are the treatment of choice for hyperlipidemia both in primary and secondary prevention, and they result in very effective and moderately cost-effective outcomes, respectively.\textsuperscript{36}

However, in order to achieve optimal cost effectiveness, managed care organizations must institute quality disease management and outcome projects designed to reduce independent risk factors as well as high blood cholesterol. These projects should consist of comprehensive problem identification, acceptance and/or development of proven guidelines for management, provider education, intervention and follow-up, all of which require considerable resources and effort to achieve optimal patient outcome.\textsuperscript{40}

### References


Upon completion of this article, the successful participant should be able to:
1. Explain the results of chronic high blood cholesterol.
2. Discuss the need for aggressive lipid management.
4. List suggested options for lipid lowering therapy.
5. Describe the application of information from the ATP III guidelines to improve the health care and health benefits of patients receiving care through managed care pharmacy organizations.

SELF-ASSESSMENT QUESTIONS

1. The primary health concern with high blood cholesterol is the relationship between chronic high blood cholesterol, primarily LDL-C, and:
   A. Developing atherosclerotic plaques.
   B. Endothelial dysfunction.
   C. Events associated with the rupture of a plaque.
   D. All of the above.

2. Causes of endothelial dysfunction include:
   A. Diabetes, hypertension, smoking, high LDL-C and others.
   B. Diabetes, pneumonia, chlamydia, fungal infections and others.
   C. Hypertension, high homocysteine levels, pregnancy and others.
   D. High LDL-C, hypertension, helicobacter and others.

3. Based on data presented from the American Heart Association, the effects of cardiovascular disease account for approximately:
   A. 500,000 deaths annually in the United States.
   B. 750,000 cases of disability annually in the United States.
   C. 1,000,000 deaths annually in the United States.
   D. 2,500,000 cases of disability monthly in the United States.

4. Information presented from the American Journal of Medicine 2001 state that the direct costs associated with treatment of CHD in 2000 were:
   A. $34 billion.
   B. $55 billion.
   C. $72 billion.
   D. $100 billion.

5. Which of the following are correct?
   A. The optimal level for total cholesterol is >200 mg/dL.
   B. The desirable level for total cholesterol is <200 mg/dL.
   C. HDL-C is considered high when the level is >40 mg/dL.
   D. HDL-C is considered desirable when the level is <40 mg/dL

6. The ATP III cutpoints for drug therapy are based, for the most part, on:
   A. Risk-benefit, but were checked for cost effectiveness.
   B. Risk-benefit for developing CHD alone.
   C. Cost-effectiveness only.
   D. None of the above.

7. Currently, for the CHD or risk equivalents group, LDL-C lowering therapy has been recommended to start and has been shown to produce a significant reduction of CHD risk with very favorable ratios at what levels?
   A. For lifestyle changes 130 mg/dL or more and 160 mg/dL or more for drug therapy.
   B. For lifestyle changes 100 mg/dL or more and 130 mg/dL or more for drug therapy.
   C. For lifestyle changes 130 mg/dL or more and 160 mg/dL or more for drug therapy.
   D. For lifestyle changes 160 mg/dL or more and 190 mg/dL or more for drug therapy.

8. The heart of primary prevention of CHD and recommended first line therapy include:
   A. Decreased saturated fat and cholesterol intake.
   B. Weight loss when appropriate.
   C. Increased activity when feasible.
   D. All of the above.

9. Current evidence shows that in the U.S. high blood cholesterol is:
   A. No longer a public health problem.
   B. Slightly undertreated with regional fluctuations in levels of care.
   C. Vastly undertreated despite available treatment methods.
   D. None of the above.

10. Based on data from the L-TAP, what percentage of patients who are on lipid lowering therapy reach the recommended goal or target level:
    A. 94% of patients overall and 98% of CHD patients.
    B. 83% of patients overall and 56% of CHD patients.
    C. 38% of patients overall and 18% of CHD patients.
    D. 16% of patients overall and 24% of CHD patients.
INSTRUCTIONS

This test affords 1 hour (0.10 CEU) of continuing pharmaceutical education in all states that recognize the American Council on Pharmaceutical Education. To receive credit, you must score at least 70% of your test answers correctly. To record an answer, darken the appropriate block below. Mail your completed answer sheet to: Academy of Managed Care Pharmacy, 100 N. Pitt Street, Suite 400, Alexandria, VA 22314. If you score 70% or more, a certificate of achievement will be mailed to you within eight weeks. If you fail to achieve 70% on your first try, you will be allowed only one retake. The ACPE Provider Number for this lesson is 233-000-01-006-H01. This offer of continuing education credit expires December 31, 2002.

11. In what type of setting do you work? (Leave blank if none of the responses below applies.)
   a. HMO
   b. PPO
   c. Indemnity insurance
   d. Pharmacy benefits management
   e. Other

12. Did this program achieve its educational objectives?
   a. Yes  b. No

13. How many minutes did it take you to complete this program, including the quiz? (Fill in on answer sheet.)

14. Did this program provide insights relevant or practical for you or your work?
   a. Yes  b. No

15. Please rate the quality of this CE article.
   a. Excellent  c. Fair
   b. Good  d. Poor

A B C D

1.               6.               11.               ☐ A ☐ B ☐ C ☐ D ☐ E
2.               7.               12.               ☐ Yes ☐ No
3.               8.               13.               Minutes ____________
4.               9.               14.               ☐ Yes ☐ No
5.               10.              15.               ☐ A ☐ B ☐ C ☐ D

Participant Identification: Please type or print.

Social Security #: Work Phone #: Date:

Name:

Company:

Address: STREET (with Apt. No.) or P.O. Box CITY STATE ZIP

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Member Type: ☐ Active ☐ Supporting Associate ☐ Student ☐ Nonmember

Signature:

I verify by my signature above that I have completed this examination independently.

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