



Complete Summary

GUIDELINE TITLE

(1)Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). (2)Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines.

BIBLIOGRAPHIC SOURCE(S)

Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004 Jul 13;110(2):227-39. [45 references] [PubMed](#)

National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute; 2001 May. Various p. [1274 references]

GUIDELINE STATUS

2001 Guideline

This is the current release of the guideline. This guideline updates a previously released version: Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute; 1993 Sep. 180 p.

2004 Update

This version of the guideline updates selected recommendations presented in the 2001 version of the guideline: National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute; 2001 May. Various p.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

- High blood cholesterol (hypercholesterolemia)
- Coronary heart disease
- Metabolic syndrome

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine
Nursing
Nutrition
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Dietitians
Nurses
Patients
Pharmacists
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

2001 Guideline

- To examine the available evidence on coronary heart disease (CHD) and high blood cholesterol, especially the evidence that has emerged since the second report of the Expert Panel was published in 1993 (Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel II]. Bethesda [MD]: U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung and Blood Institute; 1993 Sep. 180 p.)
- To update, where appropriate, the existing recommendations for management of high blood cholesterol in adults

2004 Update

- To review the results of five recent clinical trials and assess their implications for cholesterol management
- To translate the scientific evidence into guidance that helps professionals and the public take appropriate action to reduce the risk for coronary heart disease and cardiovascular disease

TARGET POPULATION

- **Risk Assessment:** All adults aged 20 years or older
- **Treatment/Management:** Adults with high blood cholesterol

INTERVENTIONS AND PRACTICES CONSIDERED

Risk Assessment/Diagnosis:

1. Measurement of fasting lipoprotein (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides)
2. Identification of major risk factors as well as life-habit and emerging risk factors
3. Estimation of 10-year coronary heart disease (CHD) risk with Framingham scoring

Primary and Secondary Prevention of Coronary Heart Disease with Low-Density Lipoprotein Cholesterol-Lowering Therapy:

1. Therapeutic lifestyle changes including diet therapy, weight reduction, and increased physical activity
2. Drug therapy including HMG CoA reductase inhibitors (statins), bile acid sequestrants, nicotinic acid, and fibric acids

MAJOR OUTCOMES CONSIDERED

- Serum cholesterol levels
- Morbidity and mortality due to coronary heart disease (CHD)

- Total mortality (coronary heart disease and non-coronary heart disease mortality)
- Risk of coronary heart disease event

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
 Hand-searches of Published Literature (Secondary Sources)
 Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

2001 Guideline

The literature pertaining to each defined issue was identified by the panel members and by a MEDLINE (U.S. National Library of Medicine) search.

2004 Update

Since the publication of ATP III, 5 major clinical trials of statin therapy with clinical end points have been published and were reviewed for this addendum. The working group conducted a critical scientific review of the 5 relevant trials and assessed the implications of the trials for the ATP II guidelines.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Type of Evidence:

- A. Major randomized controlled trials
- B. Smaller randomized controlled trials and meta-analyses of other clinical trials
- C. Observational and metabolic studies
- D. Clinical experience

Strength of Evidence:

1. Very strong evidence
2. Moderately strong evidence
3. Strong trend

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Adult Treatment Panel III (ATP III) panel played four important roles in forging this evidence-based report. First, it systematically reviewed the literature and judged which reports provided relevant information. Second, it synthesized the existing literature into a series of evidence statements. This synthesis also required a judgment as to the category and strength of evidence. Third, the panel developed recommendations based on the evidence statements; these recommendations represent a consensus judgment about the clinical significance of each evidence statement. Lastly, the panel created an integrated set of recommendations and guidelines based on individual recommendations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Cost-effectiveness is directly related to baseline population risk and inversely related to drug cost per unit of low density lipoprotein (LDL) lowering. As baseline risk increases and effective drug cost decreases, cholesterol lowering with statins becomes more cost-effective. Cost-effectiveness also is a function of the time course of outcomes and costs. Cost-effectiveness becomes progressively more attractive as the overall risk of coronary heart disease (CHD) events increases. Secondary prevention is clearly cost-effective, and almost always more cost-effective than primary prevention, except when the latter is applied to people whose risk of experiencing a first CHD event, e.g., diabetics, is equivalent to that of a recurrent event in those who already have clinical manifestations of CHD. Using common reference standard criteria, LDL lowering using statin therapy is very cost-effective for people with symptomatic CHD. Cost-effectiveness is similar for those with CHD risk comparable to that of people with prior CHD events (CHD risk equivalents). Cholesterol lowering certainly is cost-effective, and perhaps even cost saving, in the highest risk CHD populations (diabetes mellitus with prior CHD events) and in high-risk populations with access to low acquisition cost drugs (as commonly negotiated by large managed care organizations and pharmacy benefit managers).

As baseline population risk declines, so does cost-effectiveness. LDL lowering is cost-effective for primary prevention in higher-risk persons; at lower ranges of 10-year risk, it is not. Regardless, cost-effectiveness is highly dependent on drug prices. This is illustrated by the projected progressive reduction of costs per Quality of Life Year (QALY) saved at each decrement in costs (Table II.14-4 in the original guideline document). Estimates shown in Table II.14-4 are based on cost-effectiveness analysis of recent clinical trials of LDL-lowering therapy described in the preceding discussion. They assume that costs per QALY gained are largely dependent on the costs of drugs. They also show an exponential rise in costs at lower absolute-risk levels as described by a team of researchers (Hay and colleagues).

Specific Adult Treatment Panel III (ATP III) guidelines for LDL-lowering therapy are influenced by cost-effectiveness analysis. However, they are made with the recognition that drug prices vary widely under different health care payment plans in the United States. In addition, it is noted that drug costs will likely decline in the future. For these reasons, guidelines for the American population cannot be as rigidly cost-dependent as in some other countries where there is a single-payment health care system and where costs of medication are relatively fixed and highly regulated.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

2001 Guideline

The "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)" was approved by the National Cholesterol Education Program Coordinating Committee, composed of representatives from 41 organizations (for a complete list of participating organizations, see the NGC Complete Guideline Summary field labeled "Guideline Developer Comment").

2004 Update

Once the updated had been drafted, it was subjected to multiple layers of scientific review, first by the Coordinating Committee of the National Cholesterol Education Program, consisting of 35 representatives of leading medical, public health, voluntary, community, and citizen organizations and Federal agencies, and then by the scientific and steering committees of the American Heart Association and the American College of Cardiology. Altogether approximately 90 reviewers scrutinized the draft. Their review was the basis for the endorsement of the update by the National Heart, Lung, and Blood Institute, American College of Cardiology, and American Heart Association.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): On July 13, 2004, the National Cholesterol Education Program (NCEP) updated their Adult Treatment Panel (ATP) III guidelines with evidence derived from 5 major clinical trials of statin therapy published since the release of the 2001 guideline. The updated recommendations are endorsed by the National Heart, Lung, and Blood Institute (NHLBI), the American College of Cardiology Foundation (ACC), and the American Heart Association (AHA). A summary of the updated recommendations, including modifications to ATP III treatment algorithm follows. Readers are referred to the full document published in *Circulation* for more information.

2004 Update

Summary of Implications of Recent Clinical Trials for ATP III Treatment Algorithm

From the evidence of previous statin trials, the ATP III panel was able to expand both the scope and intensity of low-density lipoprotein (LDL) lowering therapy for higher-risk individuals beyond that recommended in ATP II. The number of Americans for whom LDL-lowering drugs are considered was significantly increased by ATP III. Recent statin trials have provided new information on benefits of LDL-lowering therapy applied to persons in categories in which ATP III could not make definitive recommendations about drug therapy. In general, these new trials have strongly reinforced ATP III recommendations. In particular, they support ATP III recommendations for the benefit of LDL-lowering therapy for patients with diabetes and in older persons. Moreover, they provide new information on the efficacy of risk reduction in high-risk persons with relatively low LDL-cholesterol (C) levels. Although the full benefit of LDL-C reduction in higher-risk patients with low or very low LDL-C levels is still under investigation, the recent results open the door to use of cholesterol-lowering drugs in such patients with very high absolute risk who are most likely to benefit from added therapy.

Table 2 below shows the ATP III goals and cutpoints and proposed modifications in the treatment algorithm for LDL cholesterol based on evidence from recent clinical trials. Essential modifications are highlighted in footnotes to Table 2 and are summarized in Table 3 below.

Table 2: ATP III LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy⁹
<i>High risk:</i> CHD ¹ or CHD risk equivalents ² (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL) ⁶	≥100 mg/dL ⁸	≥100 mg/dL ¹⁰ (<100 mg/dL: consider drug options) ⁹
<i>Moderately high risk:</i>	<130 mg/dL ⁷	≥130	≥130 mg/dL

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy⁹
2+ risk factors ³ (10-year risk 10% to 20%) ⁴		mg/dL ⁸	(100-129 mg/dL; consider drug options) ¹¹
<i>Moderate risk</i> : 2+ risk factors ³ (10-year risk <10%) ⁴	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
<i>Lower risk</i> : 0-1 risk factor ⁵	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

¹Coronary heart disease (CHD) includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

²CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.

³Risk factors include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low high-density lipoprotein (HDL) cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥55 years).

⁴Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

⁵Almost all people with zero or 1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.

⁶Very high risk favors the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.

⁷Optional LDL-C goal <100 mg/dL.

⁸Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

⁹When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

¹⁰If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

¹¹For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.

Table 3: Recommendations for Modifications to Footnote the ATP III Treatment Algorithm for LDL-C

- Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.
- In high-risk persons, the recommended LDL-C goal is <100 mg/dL.
 - An LDL-C goal of <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk.
 - If LDL-C is ≥ 100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.
 - If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug to achieve an LDL-C level <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
 - If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When triglycerides are ≥ 200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.
- For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL; an LDL-C goal <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence. When LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
- Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.
- When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy.

Several modifications offer therapeutic options with regard to LDL-C goals lower than those in ATP III and choice of therapies. Recent clinical trials provide greater rationale for more intensive LDL-lowering therapy, but they do not resolve all issues surrounding very low LDL levels. At these levels, physicians must ultimately rely on clinical judgment to weigh patient risk and the efficacy, safety, and cost of different therapies. These issues can be discussed in the following context.

For high-risk patients, the recommended LDL-C treatment goal remains at <100 mg/dL. However, a target of <70 mg/dL represents a therapeutic option (i.e., a reasonable clinical strategy, for persons considered to be at very high risk, on the basis of emerging clinical trial data). TLC is recommended in high-risk patients whenever the LDL-C level is ≥ 100 mg/dL. Furthermore, any person at high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglycerides, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level. As before, whenever the baseline LDL-C concentration is ≥ 130 mg/dL, simultaneous initiation of an LDL-lowering drug and dietary therapy is recommended. If LDL-C is 100 to 129 mg/dL, the

same now holds. If baseline LDL-C is <100 mg/dL and the patient is considered to be at very high risk, initiation of an LDL-lowering drug to achieve an LDL-C level of <70 mg/dL is a therapeutic option that has clinical trial support. For those high risk patients who have elevated triglycerides or low HDL-C levels, addition of a fibrate or nicotinic acid to LDL-lowering therapy can be considered.

For patients at moderately high risk (10-year risk 10% to 20%), the LDL-C goal remains <130 mg/dL. However, a goal of <100 mg/dL represents a therapeutic option on the basis of evidence of efficacy in risk reduction from primary prevention trials. TLC should be initiated in all such persons whose LDL-C level is \geq 130 mg/dL. Again, any person at moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglycerides, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level. If the LDL-C concentration is \geq 130 mg/dL after TLC, consideration should be given to initiating an LDL-lowering drug, to achieve and sustain the LDL-C goal of <130 mg/dL. For LDL-C levels of 100 to 129 mg/dL at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of clinical trial evidence of additional efficacy.

When initiating LDL-lowering therapy in a person at high risk or moderately high risk, the efficacy of therapeutic lifestyle change both to lower LDL-C levels and to reduce risk through other mechanisms must not be overlooked. Lifestyle change must be an integral part of risk reduction therapy. When an LDL-lowering drug is employed in a person at high risk or moderately high risk, a reduction in LDL-C levels of at least 30% to 40% beyond dietary therapy should be achieved if feasible. For people in lower risk categories, there are no proposed changes to the treatment goals and cutpoints.

2001 Guideline

Low-Density Lipoprotein (LDL) Cholesterol: the Primary Target of Therapy

Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that elevated low-density lipoprotein (LDL) cholesterol is a major cause of coronary heart disease (CHD). In addition, recent clinical trials robustly show that low-density lipoprotein-lowering therapy reduces risk for coronary heart disease. For these reasons, the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) continues to identify elevated low-density lipoprotein cholesterol as the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cutpoints for initiating treatment are stated in terms of low-density lipoprotein cholesterol.

Risk Assessment: First Step in Risk Management

A basic principle of prevention is that the intensity of risk-reduction therapy should be adjusted to a person's absolute risk. Hence, the first step in selection of low-density lipoprotein-lowering therapy is to assess a person's risk status. Risk

assessment requires measurement of low-density lipoprotein cholesterol as part of lipoprotein analysis and identification of accompanying risk determinants.

In all adults aged 20 years or older, a fasting lipoprotein profile (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein [HDL] cholesterol, and triglycerides) should be obtained once every 5 years. If the testing opportunity is nonfasting, only the values for total cholesterol and high-density lipoprotein cholesterol will be usable. In such a case, if total cholesterol is ≥ 200 mg/dL or high density lipoprotein is < 40 mg/dL, a follow-up lipoprotein profile is needed for appropriate management based on low density lipoprotein. The relationship between low-density lipoprotein cholesterol levels and coronary heart disease risk is continuous over a broad range of low-density lipoprotein levels from low to high. Therefore, the Adult Treatment Panel III adopts the classification of low-density lipoprotein cholesterol levels shown in Table 1, below; this also shows the classification of total and high-density lipoprotein cholesterol levels.

Table 1. Adult Treatment Panel III Classification of Low-Density Lipoprotein, Total, and High-Density Lipoprotein Cholesterol

Total Cholesterol (mg/dL)		Low Density Lipoprotein Cholesterol (mg/dL)	
		< 100	Optimal
< 200	Desirable	100-129	Near optimal/above optimal
200-239	Borderline high	130-159	Borderline high
≥ 240	High	160-189	High
		≥ 190	Very high

High Density Lipoprotein Cholesterol (mg/dL)	
< 40	Low
≥ 60	High

Risk determinants in addition to low density lipoprotein-cholesterol include the presence or absence of coronary heart disease, other clinical forms of atherosclerotic disease, and the major risk factors other than low density lipoprotein (see Table 2, below) (low density lipoprotein is not counted among the risk factors in Table 2 because the purpose of counting those risk factors is to modify the treatment of low density lipoprotein.)

Table 2. Major Risk Factors (Exclusive of Low-Density Lipoprotein Cholesterol) That Modify Low-Density Lipoprotein Goals*

- Cigarette smoking
- Hypertension (blood pressure $\geq 140/90$ mmHg or on antihypertensive medication)
- Low high-density lipoprotein cholesterol (<40 mg/dL)[#]
- Family history of premature coronary heart disease (coronary heart disease in male first degree relative <55 years; coronary heart disease in female first degree relative <65 years)
- Age (men ≥ 45 years; women ≥ 55 years)*

* In the Adult Treatment Panel III guidelines, diabetes is regarded as a coronary heart disease risk equivalent.

[#] High-density lipoprotein cholesterol ≥ 60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

Based on these other risk determinants, the Adult Treatment Panel III identifies three categories of risk that modify the goals and modalities of low-density lipoprotein-lowering therapy. Table 3, below, defines these categories and shows the corresponding low-density lipoprotein cholesterol goals.

Table 3. Three Categories of Risk that Modify Low-Density Lipoprotein Cholesterol (mg/dL) Goals

Risk Category: Coronary heart disease and coronary heart disease risk equivalent

- *Low-density Lipoprotein Cholesterol Goal:* <100

Risk Category: Multiple (2+) risk factors*

- *Low-density Lipoprotein Cholesterol Goal:* <130

Risk Category: Zero to one risk factor

- *Low-density Lipoprotein Cholesterol Goal:* <160

* Risk factors that modify the low-density lipoprotein goal are listed in Table 2, above.

The category of highest risk consists of coronary heart disease and coronary heart disease risk equivalents. The latter carry a risk for major coronary events equal to that of established coronary heart disease (i.e., $>20\%$ per 10 years, more than 20 of 100 such individuals will develop coronary heart disease or have a recurrent coronary heart disease event within 10 years). Coronary heart disease risk equivalents comprise:

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease);
- Diabetes;

- Multiple risk factors that confer a 10-year risk for coronary heart disease >20%.

Diabetes counts as a coronary heart disease risk equivalent because it confers a high risk of new coronary heart disease within 10 years, in part because of its frequent association with multiple risk factors. Furthermore, because persons with diabetes who experience a myocardial infarction have an unusually high death rate either immediately or in the long term, a more intensive prevention strategy is warranted. Persons with coronary heart disease or coronary heart disease risk equivalents have the lowest low-density lipoprotein cholesterol goal (<100 mg/dL).

The second category consists of persons with multiple (2+) risk factors in whom 10-year risk for coronary heart disease is \leq 20%. Risk is estimated from Framingham risk scores (see the section titled "Estimating 10-year Risk for Men and Women" found in the Appendix to the guideline's [Executive Summary](#)). The major risk factors, exclusive of elevated low-density lipoprotein cholesterol, are used to define the presence of multiple risk factors that modify the goals and cutpoints for low-density lipoprotein-lowering treatment (see Table 2, above). The low-density lipoprotein cholesterol goal for persons with multiple (2+) risk factors is <130 mg/dL.

The third category consists of persons having 0 to 1 risk factor; with few exceptions, persons in this category have a 10-year risk <10 %. Their low-density lipoprotein cholesterol goal is <160 mg/dL.

Method of Risk Assessment: Counting Major Risk Factors and Estimating 10-Year Coronary Heart Disease Risk

Risk status in persons *without* clinically manifest coronary heart disease or other clinical forms of atherosclerotic disease is determined by a 2-step procedure.

First, the number of risk factors is counted (see Table 2, above). Second, for persons with multiple (2+) risk factors, 10-year risk assessment is carried out with Framingham scoring (see the section titled "Estimating 10-year Risk for Men and Women" found in the Appendix to the guideline's [Executive Summary](#)) to identify individuals whose short-term (10-year) risk warrants consideration of intensive treatment. Estimation of the 10-year coronary heart disease risk adds a step to risk assessment beyond risk factor counting, but this step is warranted because it allows better targeting of intensive treatment to people who will benefit from it. When 0 to 1 risk factor is present, Framingham scoring is not necessary because 10-year risk rarely reaches levels for intensive intervention; a very high low-density lipoprotein level in such a person may nevertheless warrant consideration of drug therapy to reduce long-term risk. Risk factors used in Framingham scoring include age, total cholesterol, high-density lipoprotein cholesterol, blood pressure, and cigarette smoking. Total cholesterol is used for 10-year risk assessment because of a larger and more robust Framingham database for total than for low-density lipoprotein cholesterol, but low-density lipoprotein cholesterol is the primary target of therapy. Framingham scoring divides persons with multiple risk factors into those with 10-year risk for coronary heart disease of >20%, 10% to 20%, and <10%. It should be noted that this 2-step sequence can be reversed with essentially the same results.* Initial risk

assessment in the Adult Treatment Panel III guidelines uses the major risk factors to define the core risk status. Only after the core risk status has been determined should any other risk modifiers be taken into consideration for adjusting the therapeutic approach.

* If Framingham scoring is carried out *before* risk factor counting, persons with <10 percent risk are then divided into those with 2+ risk factors and 0 to 1 risk factor by risk factor counting to determine the appropriate low-density lipoprotein goal (see Table 3, above).

Role of Other Risk Factors in Risk Assessment

The Adult Treatment Panel III guidelines recognize that risk for coronary heart disease is influenced by other factors not included among the major, independent risk factors (see Table 2, above). Among these are *life-habit risk factors* and *emerging risk factors*. The former include obesity, physical inactivity, and atherogenic diet; the latter consist of lipoprotein (a), homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease. The *life-habit risk factors* are direct targets for clinical intervention, but are not used to set a lower low-density lipoprotein cholesterol goal of therapy. The *emerging risk factors* do not categorically modify low-density lipoprotein cholesterol goals; however, they appear to contribute to coronary heart disease risk to varying degrees and can have utility in selected persons to guide intensity of risk-reduction therapy. Their presence can modulate clinical judgment when making therapeutic decisions.

Metabolic Syndrome

Many persons have a constellation of major risk factors, life-habit risk factors, and emerging risk factors that constitute a condition called the *metabolic syndrome*. Factors characteristic of the metabolic syndrome are abdominal obesity, atherogenic dyslipidemia (elevated triglyceride, small low-density lipoprotein particles, low high-density lipoprotein cholesterol), raised blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. The Adult Treatment Panel III recognizes the metabolic syndrome as a secondary target of risk-reduction therapy, after the primary target--low-density lipoprotein cholesterol. Diagnosis and treatment of the metabolic syndrome is described below (see the section titled "Benefit Beyond Low-Density Lipoprotein Lowering: the Metabolic Syndrome as a Secondary Target," below).

The Link Between Risk Assessment and Cost Effectiveness

In the Adult Treatment Panel III guidelines, a primary aim is to match intensity of low-density lipoprotein-lowering therapy with absolute risk. Everyone with elevated low-density lipoprotein cholesterol is treated with lifestyle changes that are effective in lowering low-density lipoprotein levels. Persons at relatively high risk are also candidates for drug treatment, which is very effective but entails significant additional expense. The cutpoints for drug treatment are based primarily on risk-benefit considerations: those at higher risk are likely to get greater benefit. However, cutpoints for recommended management based on therapeutic efficacy are checked against currently accepted standards for cost effectiveness. Lifestyle changes are the most cost-effective means to reduce risk

for coronary heart disease. Even so, to achieve maximal benefit, many persons will require low-density lipoprotein-lowering drugs. Drug therapy is the major expense of low-density lipoprotein-lowering therapy, and it dominates cost-effectiveness analysis. However, the costs of low-density lipoprotein-lowering drugs are currently in flux and appear to be declining. This report recognizes that as drug prices decline it will be possible to extend drug use to lower risk persons and still be cost effective. In addition, the Adult Treatment Panel III recognizes that some persons with high long-term risk are candidates for low-density lipoprotein-lowering drugs even though use of drugs may not be cost effective by current standards.

Note from the National Guideline Clearinghouse (NGC): Readers are referred to the summary of the 2004 update (above) for proposed modifications to the following treatment guidelines.

Primary Prevention With Low-Density Lipoprotein-Lowering Therapy

Primary prevention of coronary heart disease offers the greatest opportunity for reducing the burden of coronary heart disease in the United States. The clinical approach to primary prevention is founded on the public health approach that calls for lifestyle changes, including: (1) reduced intakes of saturated fat and cholesterol, (2) increased physical activity, and (3) weight control, to lower population cholesterol levels and reduce coronary heart disease risk, but the clinical approach intensifies preventive strategies for higher risk persons. One aim of primary prevention is to reduce long-term risk (>10 years) as well as short-term risk (≤ 10 years). Low-density lipoprotein goals in primary prevention depend on a person's absolute risk for coronary heart disease (i.e., the probability of having a coronary heart disease event in the short term or the long term); the higher the risk, the lower the goal. Therapeutic lifestyle changes are the foundation of clinical primary prevention. Nonetheless, some persons at higher risk because of high or very high low-density lipoprotein cholesterol levels or because of multiple risk factors are candidates for low-density lipoprotein-lowering drugs. Recent primary prevention trials show that low-density lipoprotein-lowering drugs reduce risk for major coronary events and coronary death even in the short term.

Any person with elevated low-density lipoprotein cholesterol or other form of hyperlipidemia should undergo clinical or laboratory assessment to rule out secondary dyslipidemia before initiation of lipid-lowering therapy. Causes of secondary dyslipidemia include:

- Diabetes
- Hypothyroidism
- Obstructive liver disease
- Chronic renal failure
- Drugs that increase low-density lipoprotein cholesterol and decrease high-density lipoprotein cholesterol (progestins, anabolic steroids, and corticosteroids)

Once secondary causes have been excluded or, if appropriate, treated, the goals for low-density lipoprotein-lowering therapy in primary prevention are established according to a person's risk category (see Table 3, above).

Secondary Prevention With Low-Density Lipoprotein-Lowering Therapy

Recent clinical trials demonstrate that low-density lipoprotein-lowering therapy reduces total mortality, coronary mortality, major coronary events, coronary artery procedures, and stroke in persons with established coronary heart disease. As shown previously (see Table 1, above), a low-density lipoprotein cholesterol level of <100 mg/dL is *optimal*; therefore, the Adult Treatment Panel III specifies a low-density lipoprotein cholesterol <100 mg/dL as the goal of therapy in secondary prevention. This goal is supported by clinical trials with both clinical and angiographic endpoints and by prospective epidemiological studies. The same goal should apply for persons with coronary heart disease risk equivalents. When persons are hospitalized for acute coronary syndromes or coronary procedures, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of low-density lipoprotein-lowering therapy before or at discharge. Adjustment of therapy may be needed after 12 weeks.

Low-Density Lipoprotein Lowering Therapy in Three Risk Categories

The two major modalities of low-density lipoprotein-lowering therapy are *therapeutic lifestyle changes* and *drug therapy*. Both are described in more detail in further sections, below. The "Therapeutic Lifestyle Changes Diet" stresses reductions in saturated fat and cholesterol intakes. When the metabolic syndrome or its associated lipid risk factors (elevated triglyceride or low high-density lipoprotein cholesterol) are present, therapeutic lifestyle changes also stresses weight reduction and increased physical activity. Table 4, below, defines low-density lipoprotein cholesterol goals and cutpoints for initiation of therapeutic lifestyle changes and for drug consideration for persons with three categories of risk: coronary heart disease and coronary heart disease risk equivalents; multiple (2+) risk factors (10-year risk 10% to 20% and <10%); and 0 to 1 risk factor.

Table 4. Low-Density Lipoprotein Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories (See Table 2 in the summary of the 2004 Update (above) for proposed modifications based on recent clinical trial evidence.)

Risk Category	LDL-C Goal	LDL Level at which to Initiate TLC	LDL Level at which to Consider Drug Therapy
Coronary Heart Disease or Coronary Heart Disease Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug options)*
2+ Risk Factors (10-year risk ≤ 20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0 to 1 Risk Factor [#]	<160	≥160 mg/dL	≥190 mg/dL

Risk Category	LDL-C Goal	LDL Level at which to Initiate TLC	LDL Level at which to Consider Drug Therapy
	mg/dL		(160-189 mg/dL: low-density lipoprotein-lowering drug optional)

* Some authorities recommend use of low-density lipoprotein-lowering drugs in this category if a low-density lipoprotein cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and high-density lipoprotein, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

Almost all people with 0 to 1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0 to 1 risk factor is not necessary.

Coronary Heart Disease and Coronary Heart Disease Risk Equivalents

For persons with coronary heart disease and coronary heart disease risk equivalents, low-density lipoprotein-lowering therapy greatly reduces risk for major coronary events and stroke and yields highly favorable cost-effectiveness ratios. The cutpoints for initiating lifestyle and drug therapies are shown in the Table 4, above.

- If *baseline low-density lipoprotein cholesterol* is ≥ 130 mg/dL, intensive lifestyle therapy and maximal control of other risk factors should be started. Moreover, for most patients, a low-density lipoprotein-lowering drug will be required to achieve a low-density lipoprotein cholesterol <100 mg/dL; thus a low-density lipoprotein cholesterol lowering drug can be started simultaneously with therapeutic lifestyle changes to attain the goal of therapy.
- If *low-density lipoprotein cholesterol levels* are 100-129 mg/dL, either at baseline or on low-density lipoprotein-lowering therapy, several therapeutic approaches are available:
 - Initiate or intensify lifestyle and/or drug therapies specifically to lower low-density lipoprotein.
 - Emphasize weight reduction and increased physical activity in persons with the metabolic syndrome.
 - Delay use or intensification of low-density lipoprotein-lowering therapies and institute treatment of other lipid or nonlipid risk factors; consider use of other lipid-modifying drugs (e.g., nicotinic acid or fibric acid) if the patient has elevated triglyceride or low high-density lipoprotein cholesterol.
- If *baseline low-density lipoprotein cholesterol* is <100 mg/dL, further low-density lipoprotein-lowering therapy is not required. Patients should nonetheless be advised to follow the "Therapeutic Lifestyle Changes Diet" on their own to help keep the low-density lipoprotein level optimal. Several clinical trials are currently underway to assess benefit of lowering low-density lipoprotein cholesterol to well below 100 mg/dL. At present, emphasis should be placed on controlling other lipid and nonlipid risk factors and on treatment of the metabolic syndrome, if present.

Multiple (2+) Risk Factors and 10-year Risk \leq 20%

For persons with multiple (2+) risk factors and 10-year risk \leq 20%, intensity of therapy is adjusted according to 10-year risk and low-density lipoprotein cholesterol level. The treatment approach for each category is summarized in Table 4, above.

- *Multiple (2+) risk factors and a 10-year risk of 10-20%.* In this category, the goal for low-density lipoprotein cholesterol is <130 mg/dL. The therapeutic aim is to reduce short-term risk as well as long-term risk for coronary heart disease. If baseline low-density lipoprotein cholesterol is ≥ 130 mg/dL, therapeutic lifestyle changes is initiated and maintained for 3 months. If low-density lipoprotein remains ≥ 130 mg/dL after 3 months of therapeutic lifestyle changes, consideration can be given to starting a low-density lipoprotein-lowering drug to achieve the low-density lipoprotein goal of <130 mg/dL. Use of low-density lipoprotein-lowering drugs at this risk level reduces coronary heart disease risk and is cost-effective. If the low-density lipoprotein falls to less than 130 mg/dL on therapeutic lifestyle changes alone, therapeutic lifestyle changes can be continued without adding drugs. In older persons (≥ 65 years), clinical judgment is required for how intensively to apply these guidelines; a variety of factors, including concomitant illnesses, general health status, and social issues may influence treatment decisions and may suggest a more conservative approach.
- *Multiple (2+) risk factors and a 10-year risk of $<10\%$.* In this category, the goal for low-density lipoprotein cholesterol also is <130 mg/dL. The therapeutic aim, however, is primarily to reduce longer-term risk. If baseline low-density lipoprotein cholesterol is ≥ 130 mg/dL, the "Therapeutic Lifestyle Changes Diet" is initiated to reduce low-density lipoprotein cholesterol. If low-density lipoprotein is <160 mg/dL on therapeutic lifestyle changes alone, it should be continued. Low-density lipoprotein-lowering drugs generally are not recommended because the patient is not at high short-term risk. On the other hand, if low-density lipoprotein cholesterol is ≥ 160 mg/dL, drug therapy can be considered to achieve a low-density lipoprotein cholesterol <130 mg/dL; the primary aim is to reduce long-term risk. Cost-effectiveness is marginal, but drug therapy can be justified to slow development of coronary atherosclerosis and to reduce long-term risk for coronary heart disease.

Zero to One Risk Factor

Most persons with 0 to 1 risk factor have a 10-year risk $<10\%$. They are managed according to Table 4, above. The goal for low-density lipoprotein cholesterol in this risk category is <160 mg/dL. The primary aim of therapy is to reduce long-term risk. First-line therapy is therapeutic lifestyle changes. If after 3 months of therapeutic lifestyle changes the low-density lipoprotein cholesterol is <160 mg/dL, therapeutic lifestyle changes is continued. However, if low-density lipoprotein cholesterol is 160-189 mg/dL after an adequate trial of therapeutic lifestyle changes, drug therapy is *optional* depending on clinical judgment. Factors favoring use of drugs include:

- A severe single risk factor (heavy cigarette smoking, poorly controlled hypertension, strong family history of premature coronary heart disease, or very low high-density lipoprotein cholesterol);

- Multiple life-habit risk factors and emerging risk factors (if measured);
- 10-year risk approaching 10% (if measured; see the section titled "Estimating 10-year Risk for Men and Women" found in the Appendix to the guideline's [Executive Summary](#)).

If low-density lipoprotein cholesterol is ≥ 190 mg/dL despite therapeutic lifestyle changes, drug therapy should be considered to achieve the low-density lipoprotein goal of < 160 mg/dL.

The purpose of using low-density lipoprotein-lowering drugs in persons with 0 to 1 risk factor and elevated low-density lipoprotein cholesterol (≥ 160 mg/dL) is to slow the development of coronary atherosclerosis, which will reduce long-term risk. This aim may conflict with cost-effectiveness considerations; thus, clinical judgment is required in selection of persons for drug therapy, although a strong case can be made for using drugs when low-density lipoprotein cholesterol is ≥ 190 mg/dL after therapeutic lifestyle changes.

For persons whose low-density lipoprotein cholesterol levels are already below goal levels upon first encounter, instructions for appropriate changes in life habits, periodic follow-up, and control of other risk factors are needed.

Therapeutic Lifestyle Changes in Low-Density Lipoprotein-Lowering Therapy

The Adult Treatment Panel III recommends a multifaceted lifestyle approach to reduce risk for coronary heart disease. This approach is designated *therapeutic lifestyle changes* (therapeutic lifestyle changes). Its essential features are:

- Reduced intakes of saturated fats ($< 7\%$ of total calories) and cholesterol (< 200 mg per day) (see Table 5, below, for overall composition of the therapeutic lifestyle changes diet)
- Therapeutic options for enhancing low-density lipoprotein lowering such as plant stanols/sterols (2 g/day) and increased viscous (soluble) fiber (10 to 25 g/day)
- Weight reduction
- Increased physical activity

Table 5. Nutrient Composition of the Therapeutics Lifestyle Changes Diet

Saturated Fat*

- *Recommended Intake:* Less than 7% of total calories

Polyunsaturated Fat

- *Recommended Intake:* Up to 10% of total calories

Monounsaturated Fat

- *Recommended Intake:* Up to 20% of total calories

Total Fat

- *Recommended Intake:* 25% to 35% of total calories

Carbohydrate[#]

- *Recommended Intake:* 50% to 60% of total calories

Fiber

- *Recommended Intake:* 20 to 30 g/day

Protein

- *Recommended Intake:* Approximately 15% of total calories

Cholesterol

- *Recommended Intake:* Less than 200 mg/day

Total Calories (Energy)^{\$}

- *Recommended Intake:* Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

* Trans fatty acids are another low-density lipoprotein-raising fat that should be kept at a low intake.

Carbohydrate should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.

\$ Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 Kcal per day).

A model of steps in therapeutic lifestyle changes is shown in Figure 1 titled "A Model of Steps in Therapeutic Lifestyle Changes (TLC)" (found in the guideline's [Executive Summary](#)).

To initiate therapeutic lifestyle changes, intakes of saturated fats and cholesterol are reduced first to lower low-density lipoprotein cholesterol. To improve overall health, the Adult Treatment Panel III's "Therapeutic Lifestyle Changes Diet" generally contains the recommendations embodied in the "Dietary Guidelines for Americans 2000" (for a summary of these dietary guidelines, see Table V.2-3. "Dietary Guidelines for Americans 2000 [U.S. Department of Agriculture, 2000]" in the original guideline document). One exception is that total fat is allowed to range from 25% to 35% of total calories provided saturated fats and trans fatty acids are kept low. A higher intake of total fat, mostly in the form of unsaturated fat, can help to reduce triglycerides and raise high-density lipoprotein cholesterol in persons with the metabolic syndrome. In accordance with the "Dietary Guidelines for Americans 2000," moderate physical activity is encouraged. After 6

weeks, the low-density lipoprotein response is determined; if the low-density lipoprotein cholesterol goal has not been achieved, other therapeutic options for low-density lipoprotein lowering such as plant stanols/sterols and viscous fiber can be added.

After maximum reduction of low-density lipoprotein cholesterol with dietary therapy, emphasis shifts to management of the metabolic syndrome and associated lipid risk factors. The majority of persons with these latter abnormalities are overweight or obese and sedentary. Weight reduction therapy for overweight or obese patients will enhance low-density lipoprotein lowering and will provide other health benefits including modifying other lipid and nonlipid risk factors.

Assistance in the management of overweight and obese persons is provided by the National Heart, Lung and Blood Institute (NHLBI) Obesity Education Initiative guideline titled "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (1998)." Additional risk reduction can be achieved by simultaneously increasing physical activity.

At all stages of dietary therapy, physicians are encouraged to refer patients to registered dietitians or other qualified nutritionists for *medical nutrition therapy*, which is the term for the nutritional intervention and guidance provided by a nutrition professional.

Drug Therapy to Achieve Low-Density Lipoprotein Cholesterol Goals

A portion of the population whose short-term or long-term risk for coronary heart disease is high will require low-density lipoprotein-lowering drugs in addition to therapeutic lifestyle changes to reach the designated goal for low-density lipoprotein cholesterol (see Table 4, above). When drugs are prescribed, attention to therapeutic lifestyle changes should always be maintained and reinforced. Currently available drugs that affect lipoprotein metabolism are HMG CoA reductase inhibitors (statins), bile acid sequestrants, nicotinic acid, and fibric acids (for details, see Table 7 titled "Drugs Affecting Lipoprotein Metabolism" found in the guideline's [Executive Summary](#)).

Some cholesterol-lowering agents are currently available over-the-counter (OTC) (e.g., nicotinic acid), and manufacturers of several classes of low-density lipoprotein-lowering drugs (e.g., statins, bile acid sequestrants) have applied to the U.S. Food and Drug Administration (FDA) to allow these agents to become over-the-counter medications. At the time of publication of the Adult Treatment Panel III guidelines, the U.S. Food and Drug Administration had not granted permission for over-the-counter status for statins or bile acid sequestrants. If an over-the-counter cholesterol-lowering drug is or becomes available, patients should continue to consult with their physicians about whether to initiate drug treatment, about setting the goals of therapy, and about monitoring for therapeutic responses and side effects.

Secondary Prevention: Drug Therapy for Coronary Heart Disease and Coronary Heart Disease Risk Equivalents

For persons with coronary heart disease and coronary heart disease risk equivalents, the goal is to attain a low-density lipoprotein cholesterol level <100 mg/dL. The cutpoints for initiating lifestyle and drug therapies are shown in the Table 4, above), and the approach to treatment is discussed immediately after this table. Most coronary heart disease patients will need low-density lipoprotein-lowering drug therapy. Other lipid risk factors may also warrant consideration of drug treatment. Whether or not lipid-modifying drugs are used, nonlipid risk factors require attention and favorable modification.

In persons admitted to the hospital for a major coronary event, low-density lipoprotein cholesterol should be measured on admission or within 24 hours. This value can be used for treatment decisions. In general, persons hospitalized for a coronary event or procedure should be discharged on drug therapy if the low-density lipoprotein cholesterol is ≥ 130 mg/dL. If the low-density lipoprotein is 100 to 129 mg/dL, clinical judgment should be used in deciding whether to initiate drug treatment at discharge, recognizing that low-density lipoprotein cholesterol levels begin to decline in the first few hours after an event and are significantly decreased by 24 to 48 hours and may remain low for many weeks. Thus, the initial low-density lipoprotein cholesterol level obtained in the hospital may be substantially lower than is usual for the patient. Some authorities hold drug therapy should be initiated whenever a patient hospitalized for a coronary heart disease-related illness is found to have a low-density lipoprotein cholesterol >100 mg/dL. Initiation of drug therapy at the time of hospital discharge has two advantages. First, at that time patients are particularly motivated to undertake and adhere to risk-lowering interventions; and second, failure to initiate indicated therapy early is one of the causes of a large "treatment gap," because outpatient follow-up is often less consistent and more fragmented.

Low-density Lipoprotein-Lowering Drug Therapy for Primary Prevention

Table 4, above, shows the cutpoints for considering drug treatment in primary prevention. The general approach to management of drug therapy for primary prevention is outlined in Figure 2 titled "Progression of Drug Therapy in Primary Prevention" found in the guideline's [Executive Summary](#).

When drug therapy for primary prevention is a consideration, the third visit of dietary therapy (see Figure 1 titled "A Model of Steps in Therapeutic Lifestyle Changes (TLC)" (found in the guideline's [Executive Summary](#)) will typically be the visit to initiate drug treatment. Even if drug treatment is started, therapeutic lifestyle changes should be continued. As with therapeutic lifestyle changes, the first priority of drug therapy is to achieve the goal for low-density lipoprotein cholesterol. For this reason, a low-density lipoprotein-lowering drug should be started. The usual drug will be a statin, but alternatives are a bile acid sequestrant or nicotinic acid. In most cases, the statin should be started at a moderate dose. In many patients, the low-density lipoprotein cholesterol goal will be achieved, and higher doses will not be necessary. The patient's response should be checked about 6 weeks after starting drug therapy. If the goal of therapy has been achieved, the current dose can be maintained. However, if the goal has not been achieved, low-density lipoprotein-lowering therapy can be intensified, either by increasing the dose of statin or by combining a statin with a bile acid sequestrant or nicotinic acid.

After 12 weeks of drug therapy, the response to therapy should again be assessed. If the low-density lipoprotein cholesterol goal is still not achieved, consideration can be given to further intensification of drug therapy. If the low-density lipoprotein goal cannot be attained by standard lipid-lowering therapy, consideration should be given to seeking consultation from a lipid specialist. Once the goal for low-density lipoprotein cholesterol has been attained, attention can turn to other lipid risk factors and nonlipid factors. Thereafter, patients can be monitored for response to therapy every 4 to 6 months, or more often if considered necessary.

Benefit Beyond Low-Density Lipoprotein Lowering: the Metabolic Syndrome as a Secondary Target of Therapy

Evidence is accumulating that risk for coronary heart disease can be reduced beyond low-density lipoprotein-lowering therapy by modification of other risk factors. One potential secondary target of therapy is the metabolic syndrome, which represents a constellation of lipid and nonlipid risk factors of metabolic origin. This syndrome is closely linked to a generalized metabolic disorder called *insulin resistance* in which the normal actions of insulin are impaired. Excess body fat (particularly abdominal obesity) and physical inactivity promote the development of insulin resistance, but some individuals also are genetically predisposed to insulin resistance.

The risk factors of the metabolic syndrome are highly concordant; in aggregate they enhance risk for coronary heart disease at any given low-density lipoprotein cholesterol level. For purposes of the Adult Treatment Panel III guidelines, the diagnosis of the metabolic syndrome is made when three or more of the risk determinants shown in Table 6, below, are present. These determinants include a combination of categorical and borderline risk factors that can be readily measured in clinical practice.

Table 6. Clinical Identification of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal Obesity* Men Women	Waist Circumference# >102 cm (>40 in) >88 cm (>35 in)
Triglycerides	≥150 mg/dL
High-density lipoprotein cholesterol Men Women	<40 mg/dL <50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

* Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased (e.g., 94 to 102 cm [37 to 39 inches]). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

Management of the metabolic syndrome has a two-fold objective: (1) to reduce underlying causes (i.e., obesity and physical inactivity), and (2) to treat associated nonlipid and lipid risk factors.

Management of Underlying Causes of the Metabolic Syndrome

First-line therapies for all lipid and nonlipid risk factors associated with the metabolic syndrome are weight reduction and increased physical activity, which will effectively reduce all of these risk factors. Therefore, after appropriate control of low-density lipoprotein cholesterol, therapeutic lifestyle changes should stress weight reduction and physical activity if the metabolic syndrome is present.

Weight control. In the Adult Treatment Panel III guidelines, overweight and obesity are recognized as major, underlying risk factors for coronary heart disease and identified as direct targets of intervention. Weight reduction will enhance low-density lipoprotein lowering and reduce all of the risk factors of the metabolic syndrome. The recommended approaches for reducing overweight and obesity are contained in the National Heart, Lung and Blood Institute (NHLBI) Obesity Education Initiative guideline titled "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (1998)."

Physical activity. Physical inactivity is likewise a major, underlying risk factor for coronary heart disease. It augments the lipid and nonlipid risk factors of the metabolic syndrome. It further may enhance risk by impairing cardiovascular fitness and coronary blood flow. Regular physical activity reduces very low-density lipoprotein (VLDL) levels, raises high-density lipoprotein cholesterol, and in some persons, lowers low-density lipoprotein levels. It also can lower blood pressure, reduce insulin resistance, and favorably influence cardiovascular function. Thus, the Adult Treatment Panel III recommends that regular physical activity become a routine component in management of high serum cholesterol. The evidence base for this recommendation is contained in the "U.S. Surgeon General's Report on Physical Activity" (Physical activity and health: a report of the Surgeon General. Atlanta [GA], Georgia: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996, 300 p.).

Specific Treatment of Lipid and Non-Lipid Risk Factors

Beyond the underlying risk factors, therapies directed against the lipid and nonlipid risk factors of the metabolic syndrome will reduce coronary heart disease risk. These include treatment of hypertension, use of aspirin in patients with

coronary heart disease to reduce the prothrombotic state (guidelines for aspirin use in primary prevention have not been firmly established), and treatment of elevated triglycerides and low high-density lipoprotein cholesterol as discussed below under the section titled "Management of Specific Dyslipidemias."

Special Issues

Management of Specific Dyslipidemias

Very high low-density lipoprotein cholesterol (≥ 190 mg/dL). Persons with very high low-density lipoprotein cholesterol usually have genetic forms of hypercholesterolemia: monogenic familial hypercholesterolemia, familial defective apolipoprotein B, and polygenic hypercholesterolemia. Early detection of these disorders through cholesterol testing in young adults is needed to prevent premature coronary heart disease. Family testing is important to identify similarly affected relatives. These disorders often require combined drug therapy (statin + bile acid sequestrant) to achieve the goals of low-density lipoprotein-lowering therapy.

Elevated serum triglycerides. Recent meta-analyses of prospective studies indicate that elevated triglycerides are also an independent risk factor for coronary heart disease. Factors contributing to elevated (higher than normal) triglycerides in the general population include: obesity and overweight, physical inactivity, cigarette smoking, excess alcohol intake, high carbohydrate diets (>60% of energy intake), several diseases (e.g., type 2 diabetes, chronic renal failure, nephrotic syndrome), certain drugs (e.g., corticosteroids, estrogens, retinoids, higher doses of beta-adrenergic blocking agents), and genetic disorders (familial combined hyperlipidemia, familial hypertriglyceridemia, and familial dysbetalipoproteinemia).

In clinical practice, elevated serum triglycerides are most often observed in persons with the metabolic syndrome, although secondary or genetic factors can heighten triglyceride levels. The Adult Treatment Panel III adopts the following classification of serum triglycerides:

- Normal triglycerides: <150 mg/dL
- Borderline-high triglycerides: 150 to 199 mg/dL
- High triglycerides: 200 to 499 mg/dL
- Very high triglycerides: ≥ 500 mg/dL

The finding that elevated triglycerides are an independent coronary heart disease risk factor suggests that some triglyceride-rich lipoproteins are atherogenic. The latter are partially degraded very low-density lipoproteins, commonly called *remnant lipoproteins*. In clinical practice, very low-density lipoproteins cholesterol is the most readily available measure of atherogenic remnant lipoproteins. Thus, very low-density lipoproteins cholesterol can be a target of cholesterol-lowering therapy. The Adult Treatment Panel III guidelines identify the sum of low-density lipoprotein + very low-density lipoproteins cholesterol [termed *non-high-density lipoprotein cholesterol* (total cholesterol minus high density lipoprotein cholesterol)] as a secondary target of therapy in persons with high triglycerides (≥ 200 mg/dL). The goal for non-high-density lipoprotein cholesterol in persons with high serum triglycerides can be set at 30 mg/dL higher than that for low-

density lipoprotein cholesterol (see Table 7, below) on the premise that a very low-density lipoproteins cholesterol level ≤ 30 mg/dL is normal.

Table 7. Comparison of Low-Density Lipoprotein Cholesterol and Non-High-Density Lipoprotein Cholesterol Goals for Three Risk Categories

Risk Category	Low-density Lipoprotein Goal (mg/dL)	Non-high-density Lipoprotein Cholesterol Goal (mg/dL)
Coronary heart disease and coronary heart disease risk equivalent (10-year risk for coronary heart disease 20%)	<100	<130
Multiple (2+) risk factors and 10-year risk $\leq 20\%$	<130	<160
0 to 1 risk factor	<160	<190

The treatment strategy for elevated triglycerides depends on the causes of the elevation and its severity. For all persons with elevated triglycerides, the primary aim of therapy is to achieve the target goal for low-density lipoprotein cholesterol. When triglycerides are *borderline high* (150 to 199 mg/dL), emphasis should also be placed on weight reduction and increased physical activity. For *high triglycerides* (200 to 499 mg/dL), non-high-density lipoprotein cholesterol becomes a secondary target of therapy. Aside from weight reduction and increased physical activity, drug therapy can be considered in high-risk persons to achieve the non-high-density lipoprotein cholesterol goal. There are two approaches to drug therapy. First, the non-high-density lipoprotein cholesterol goal can be achieved by intensifying therapy with a low-density lipoprotein-lowering drug; or second, nicotinic acid or fibrate can be added, if used with appropriate caution, to achieve the non-high-density lipoprotein cholesterol goal by further lowering of very low-density lipoproteins cholesterol. In rare cases in which triglycerides are *very high* (≥ 500 mg/dL), the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering. This approach requires very low fat diets ($\leq 15\%$ of calorie intake), weight reduction, increased physical activity, and usually a triglyceride-lowering drug (fibrate or nicotinic acid). Only after triglyceride levels have been lowered to < 500 mg/dL should attention turn to low-density lipoprotein lowering to reduce risk for coronary heart disease.

Low high-density lipoprotein cholesterol. Low high-density lipoprotein cholesterol is a strong independent predictor of coronary heart disease. In the Adult Treatment Panel III guidelines, low high-density lipoprotein cholesterol is defined categorically as a level < 40 mg/dL, a change from the level of < 35 mg/dL in the Adult Treatment Panel II guidelines. In the present guidelines, low high-density lipoprotein cholesterol both modifies the goal for low-density lipoprotein-lowering therapy and is used as a risk factor to estimate 10-year risk for coronary heart disease.

Low high-density lipoprotein cholesterol levels have several causes, many of which are associated with insulin resistance (i.e., elevated triglycerides, overweight and obesity, physical inactivity, type 2 diabetes). Other causes are cigarette smoking, very high carbohydrate intakes (>60% of calories), and certain drugs (e.g., beta-blockers, anabolic steroids, progestational agents).

The Adult Treatment Panel III does not specify a goal for high-density lipoprotein raising. Although clinical trial results suggest that raising high-density lipoprotein will reduce risk, the evidence is insufficient to specify a goal of therapy. Furthermore, currently available drugs do not robustly raise high-density lipoprotein cholesterol. Nonetheless, a low high-density lipoprotein should receive clinical attention and management according to the following sequence. In all persons with low high-density lipoprotein cholesterol, the primary target of therapy is low-density lipoprotein cholesterol; the Adult Treatment Panel III guidelines should be followed to achieve the low-density lipoprotein cholesterol goal. Second, after the low-density lipoprotein goal has been reached, emphasis shifts to weight reduction and increased physical activity (when the metabolic syndrome is present). When a low high-density lipoprotein cholesterol is associated with high triglycerides (200 to 499 mg/dL), secondary priority goes to achieving the non-high-density lipoprotein cholesterol goal, as outlined before. Also, if triglycerides are <200 mg/dL (isolated low high-density lipoprotein cholesterol), drugs for high-density lipoprotein raising (fibrates or nicotinic acid) can be considered; however, treatment for isolated low high-density lipoprotein is mostly reserved for persons with coronary heart disease and coronary heart disease risk equivalents.

Diabetic dyslipidemia. This disorder is essentially atherogenic dyslipidemia (high triglycerides, low high-density lipoprotein, and small dense low-density lipoprotein) in persons with type 2 diabetes. Although elevated triglycerides and/or low high-density lipoprotein cholesterol are common in persons with diabetes, clinical trial results support the identification of low-density lipoprotein cholesterol as the primary target of therapy, as it is in those without diabetes. Since diabetes is designated a coronary heart disease risk equivalent in the Adult Treatment Panel III guidelines, the low density lipoprotein cholesterol goal of therapy for most persons with diabetes will be <100 mg/dL. Furthermore, when low density lipoprotein cholesterol is ≥ 130 mg/dL, most persons with diabetes will require initiation of low-density lipoprotein-lowering drugs simultaneously with therapeutic lifestyle changes to achieve the low-density lipoprotein goal. When low-density lipoprotein cholesterol levels are in the range of 100 to 129 mg/dL at baseline or on treatment, several therapeutic options are available: increasing intensity of low-density lipoprotein-lowering therapy, adding a drug to modify atherogenic dyslipidemia (fibrate or nicotinic acid), or intensifying control of other risk factors including hyperglycemia. When triglyceride levels are ≥ 200 mg/dL, non-high-density lipoprotein cholesterol becomes a secondary target of cholesterol-lowering therapy. Several ongoing clinical trials (e.g., Antihypertensive and Lipid Lowering Heart Attack Trial [ALLHAT]) will better quantify the magnitude of the benefit of low-density lipoprotein-lowering treatment in older individuals with diabetes. In older persons (≥ 65 years of age) with diabetes but no additional coronary heart disease risk factors other than age, clinical judgment is required for how intensively to apply these guidelines; a variety of factors, including concomitant illnesses, general health status, and social issues may influence treatment decisions and may suggest a more conservative approach.

Special Considerations for Different Population Groups

Middle-aged men (35 to 65 years). In general, men have a higher risk for coronary heart disease than do women. Middle-aged men in particular have a high prevalence of the major risk factors and are predisposed to abdominal obesity and the metabolic syndrome. A sizable fraction of all coronary heart disease in men occurs in middle age. Thus, many middle-aged men carry a relatively high risk for coronary heart disease, and for those who do, intensive low-density lipoprotein-lowering therapy is needed.

Women (ages 45 to 75 years). In women, onset of coronary heart disease generally is delayed by some 10 to 15 years compared with that in men; thus most coronary heart disease in women occurs after age 65. All risk factors contribute to coronary heart disease in women, and most premature coronary heart disease in women (<65 years) occurs in those with multiple risk factors and the metabolic syndrome. Despite the previous belief that the gender difference in risk for coronary heart disease reflects a protective effect of estrogen in women, recent secondary and primary prevention trials cast doubt on the use of hormone replacement therapy to reduce coronary heart disease risk in postmenopausal women. In contrast, the favorable effects of statin therapy in women in clinical trials make a cholesterol-lowering drug preferable to hormone replacement therapy for coronary heart disease risk reduction. Women should be treated similarly to men for secondary prevention. For primary prevention, the Adult Treatment Panel III's general approach is similarly applicable for women and men. However, the later onset of coronary heart disease for women in general should be factored into clinical decisions about use of cholesterol-lowering drugs.

Older adults (men ≥ 65 years and women ≥ 75 years). Overall, most new coronary heart disease events and most coronary deaths occur in older persons (≥ 65 years). A high level of low-density lipoprotein cholesterol and low high-density lipoprotein cholesterol still carry predictive power for the development of coronary heart disease in older persons. Nevertheless, the finding of advanced subclinical atherosclerosis by noninvasive testing can be helpful for confirming the presence of high risk in older persons. Secondary prevention trials with statins have included a sizable number of older persons, mostly in the age range of 65 to 75 years. In these trials, older persons showed significant risk reduction with statin therapy. Thus, no hard-and-fast age restrictions appear necessary when selecting persons with established coronary heart disease for low-density lipoprotein-lowering therapy. For primary prevention, therapeutic lifestyle changes are the first line of therapy for older persons. However, low-density lipoprotein-lowering drugs can also be considered when older persons are at higher risk because of multiple risk factors or advanced subclinical atherosclerosis.

Younger adults (men 20 to 35 years; women 20 to 45 years). Coronary heart disease is rare except in those with severe risk factors (e.g., familial hypercholesterolemia, heavy cigarette smoking, or diabetes). Even though clinical coronary heart disease is relatively rare in young adults, coronary atherosclerosis in its early stages may progress rapidly. The rate of development of coronary atherosclerosis earlier in life correlates with the major risk factors. In particular, long-term prospective studies reveal that elevated serum cholesterol detected in young adulthood predicts a higher rate of premature coronary heart disease in middle age. Thus, risk factor identification in young adults is an important aim for

low-density lipoprotein cholesterol with life-habit changes offers the opportunity for delaying or preventing onset of coronary heart disease later in life. For young adults with low-density lipoprotein cholesterol levels ≥ 130 mg/dL, therapeutic lifestyle changes should be instituted and emphasized.

Particular attention should be given to young men who smoke and have a high low-density lipoprotein cholesterol (160 to 189 mg/dL); they may be candidates for low-density lipoprotein-lowering drugs. When young adults have very high low-density lipoprotein cholesterol levels (≥ 190 mg/dL), drug therapy should be considered, as in other adults. Those with severe genetic forms of hypercholesterolemia may require low-density lipoprotein-lowering drugs in combination (e.g., statin + bile acid sequestrant).

Racial and ethnic groups. African Americans have the highest overall coronary heart disease mortality rate and the highest out-of-hospital coronary death rates of any ethnic group in the United States, particularly at younger ages. Although the reasons for the excess coronary heart disease mortality among African Americans have not been fully elucidated, it can be accounted for, at least in part, by the high prevalence of coronary risk factors. Hypertension, left ventricular hypertrophy, diabetes mellitus, cigarette smoking, obesity, physical inactivity, and multiple coronary heart disease risk factors all occur more frequently in African Americans than in whites. Other ethnic groups and minority populations in the United States include Hispanics, Native Americans, Asian and Pacific Islanders, and South Asians. Although limited data suggest that racial and ethnic groups vary somewhat in baseline risk for coronary heart disease, this evidence did not appear sufficient to lead the Adult Treatment Panel III panel to modify general recommendations for cholesterol management in these populations.

Adherence to Low Density Lipoprotein-Lowering Therapy

Adherence to the Adult Treatment Panel III guidelines by both patients and providers is a key to approximating the magnitude of the benefits demonstrated in clinical trials of cholesterol lowering. Adherence issues have to be addressed in order to attain the highest possible levels of coronary heart disease risk reduction. Thus, the Adult Treatment Panel III recommends the use of state-of-the-art multidisciplinary methods targeting the patient, providers, and health delivery systems to achieve the full population effectiveness of the guidelines for primary and secondary prevention (see Table 8, below).

Table 8. Interventions to Improve Adherence

Focus on the Patient

- Simplify medication regimens
- Provide explicit patient instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment
- Encourage the use of prompts to help patients remember treatment regimens
- Use systems to reinforce adherence and maintain contact with the patient
- Encourage the support of family and friends
- Reinforce and reward adherence
- Increase visits for patients unable to achieve treatment goal
- Increase the convenience and access to care

- Involve patients in their care through self-monitoring

Focus on the Physician and Medical Office

- Teach physicians to implement lipid treatment guidelines
- Use reminders to prompt physicians to attend to lipid management
- Identify a patient advocate in the office to help deliver or prompt care
- Use patients to prompt preventive care
- Develop a standardized treatment plan to structure care
- Use feedback from past performance to foster change in future care
- Remind patients of appointments and follow-up missed appointments

Focus on the Health Delivery System

- Provide lipid management through a lipid clinic
- Utilize case management by nurses
- Deploy telemedicine
- Utilize the collaborative care of pharmacists

CLINICAL ALGORITHM(S)

The following algorithms are provided in the original guideline document:

1. Physician responsibilities for visit 1
2. Therapeutic approaches to persons with coronary heart disease or coronary heart disease risk equivalent
3. Therapeutic approaches to persons with multiple risk factors, 10-year risk 10% to 20%
4. Therapeutic approaches to the patient with multiple (2+) risk factors, 10-year risk <10 percent
5. Therapeutic approaches to persons with 0 to 1 risk factor
6. A model of steps in therapeutic lifestyle changes
7. Progression of drug therapy

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

2001 Guideline

The type of supporting evidence came from results of clinical trials, prospective epidemiological studies, the "U. S. Surgeon General's Report on Physical Activity" (Physical activity and health: a report of the Surgeon General. Atlanta [GA], Georgia: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996, 300 p.), and meta-analyses of prospective studies. Graded evidence statements are provided in the original guideline document. (For details on the rating scheme used, see the National Guideline Clearinghouse [NGC] Complete Summary field labeled "Rating Scheme.")

2004 Update

The type of supporting evidence came from five recent clinical trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Effective detection, evaluation, and treatment of high blood cholesterol in adults may result in reduced morbidity and mortality from coronary heart disease.

Total Mortality Considerations and Therapeutic Safety

- *Overall Benefit of Cholesterol Lowering on Mortality.* Low-density lipoprotein-lowering therapy reduces total mortality (i.e., extends life, by decreasing coronary heart disease mortality). This therapeutic benefit was unclear in earlier trials using interventions with limited cholesterol lowering (10%), some of which showed adverse non-coronary heart disease effects. However, in trials using statins, in which cholesterol levels were reduced by 20% and non-coronary heart disease mortality was not increased, the reduction in mortality is incontrovertible.
- *Benefit of Cholesterol Lowering on Mortality in Secondary Prevention.* The benefits of cholesterol lowering on longevity are particularly clear in coronary heart disease patients and other high-risk populations due to their high short-term mortality rates when left untreated and to the high proportion of those deaths caused by coronary heart disease. In persons with established coronary heart disease, a reduction in coronary heart disease deaths by effective cholesterol-lowering therapy more than outweighs any side effects of drug therapy.
- *Benefit of Cholesterol Lowering on Mortality in Primary Prevention.* Primary prevention trials using statins show a significant reduction in coronary heart disease mortality, no increase in non-coronary heart disease mortality, and a strong trend towards lower overall mortality. Because of the lower proportion of deaths that are due to coronary heart disease in primary prevention trials (relative to secondary prevention), the latter trend is not significant. The statin trials lasted an average of five years; longer-term observational studies offer a better indication of the potential lifelong impact of cholesterol reduction on mortality. The lack of overall reduction in mortality in primary prevention trials performed before the advent of the statins can be explained by their modest cholesterol reduction (<10%) and in some instances by adverse non-coronary heart disease effects not seen with the statins.

POTENTIAL HARMS

Side Effects of Drug Therapy

1. HMG CoA reductase inhibitors (statins)
 - Myopathy
 - Increased liver enzymes
2. Bile acid sequestrants
 - Gastrointestinal distress

- Constipation
 - Decreased absorption of other drugs
3. Nicotinic acid
 - Flushing
 - Hyperglycemia
 - Hyperuricemia (or gout)
 - Upper gastrointestinal distress
 - Hepatotoxicity
 4. Fibric acids
 - Dyspepsia
 - Gallstones
 - Myopathy
 - Unexplained non-coronary heart disease deaths seen in a World Health Organization (WHO) study

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindications to Drug Therapy

1. HMG CoA reductase inhibitors (statins)

Absolute:

- Active or chronic liver disease

Relative:

- Concomitant use of certain drugs (cyclosporine, macrolide antibiotics, various antifungal agents and cytochrome P-450 inhibitors [fibrates and niacin should be used with appropriate caution])

2. Bile acid sequestrants

Absolute:

- Dysbetalipoproteinemia
- Triglycerides >400 mg/dL

Relative:

- Triglycerides >200 mg/dL

3. Nicotinic acid

Absolute:

- Chronic liver disease
- Severe gout

Relative:

- Diabetes
 - Hyperuricemia
 - Peptic ulcer disease
4. Fibrin acids

Absolute:

- Severe renal disease
- Severe hepatic disease

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Empirical data provide the foundation for recommendations; but research in the cholesterol field, as in almost any other, generally has addressed large questions and has not necessarily provided answers to every specific question of clinical intervention. Thus, in the panel's view, the general evidence (including type and strength) often fails to carry a one-to-one correspondence with needed specific recommendations. Consequently, the Adult Treatment Panel III recommendations are based on the panels' best interpretation of the relation between empirical evidence and issues of clinical intervention. The recommendations are crafted in language that best links general evidence to specific issues; they are not qualified quantitatively according to category and strength of evidence, which is implicit in the language of the recommendation. Finally, for complex issues, several evidence statements or recommendations may be grouped together.
- This evidence-based report should not be viewed as a standard of practice. Evidence derived from empirical data can lead to generalities for guiding practice, but such guidance need not hold for individual patients. Clinical judgment applied to individuals can always take precedence over general management principles. Recommendations of the Adult Treatment Panel III thus represent general guidance that can assist in shaping clinical decisions, but they should not override a clinician's considered judgment in the management of individuals.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm
 Patient Resources
 Personal Digital Assistant (PDA) Downloads
 Quality Measures
 Slide Presentation
 Tool Kits

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004 Jul 13;110(2):227-39. [45 references] [PubMed](#)

National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute; 2001 May. Various p. [1274 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1993 Sep (updated 2004)

GUIDELINE DEVELOPER(S)

National Cholesterol Education Program - Federal Government Agency [U.S.]
National Heart, Lung, and Blood Institute (U.S.) - Federal Government Agency [U.S.]

GUIDELINE DEVELOPER COMMENT

This guideline was approved by the National Cholesterol Education Program Coordinating Committee, which is comprised of representatives from the following organizations:

Member Organizations

- National Heart, Lung, and Blood Institute
- American Academy of Family Physicians
- American Academy of Insurance Medicine
- American Academy of Pediatrics
- American Association of Occupational Health Nurses
- American College of Cardiology
- American College of Chest Physicians
- American College of Nutrition
- American College of Obstetricians and Gynecologists
- American College of Occupational and Environmental Medicine
- American College of Preventive Medicine
- American Diabetes Association, Inc.
- American Dietetic Association
- American Heart Association
- American Hospital Association
- American Medical Association
- American Nurses Association
- American Osteopathic Association
- American Pharmaceutical Association
- American Public Health Association
- American Red Cross
- Association of Black Cardiologists
- Association of State and Territorial Health Officials
- Citizens for Public Action on Blood Pressure and Cholesterol, Inc.
- National Black Nurses Association, Inc.
- National Medical Association
- Society for Nutrition Education
- Society for Public Health Education

Associate Member Organization

- American Association of Office Nurses

U.S. Federal Agencies

- NHLBI Ad Hoc Committee on Minority Populations
- Agency for Healthcare Research and Quality
- Centers for Disease Control and Prevention
- Coordinating Committee for the Community Demonstration Studies
- Department of Agriculture
- Department of Defense
- Food and Drug Administration
- Health Resources and Services Administration
- National Cancer Institute
- National Center for Health Statistics
- Office of Disease Prevention and Health Promotion

- Department of Veterans Affairs

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

2001 Guideline

Committee Members: Scott M. Grundy, MD, PhD (Panel Chair); Diane Becker, RN, MPH, ScD; Luther T. Clark, MD; Richard S. Cooper, MD; Margo A. Denke, MD; Wm. James Howard, MD; Donald B. Hunninghake, MD; D. Roger Illingworth, MD, PhD; Russell V. Luepker, MD, MS; Patrick McBride, MD, MPH; James M. McKenney, PharmD; Richard C. Pasternak, MD, FACC; Neil J. Stone, MD; Linda Van Horn, PhD, RD

Ex-Officio Members: H. Bryan Brewer, Jr., MD; James I. Cleeman, MD (Executive Director of the Panel); Nancy D. Ernst, PhD, RD; David Gordon, MD, PhD; Daniel Levy, MD; Basil Rifkind, MD; Jacques E. Rossouw, MD; Peter Savage, MD

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2004 Update

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*Member of the Working Group until December 31, 2003

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

2001 Guideline

Not stated

2004 Update

Dr. Grundy has received honoraria from Merck, Pfizer, Sankyo, Bayer, Merck/Schering-Plough, Kos, Abbott, Bristol-Myers Squibb, and AstraZeneca; he has received research grants from Merck, Abbott, and Glaxo Smith Kline.

Dr. Cleeman has no financial relationships to disclose.

Dr. Bairey Merz has received lecture honoraria from Pfizer, Merck, and Kos; she has served as a consultant for Pfizer, Bayer, and EHC (Merck); she has received unrestricted institutional grants for Continuing Medical Education from Pfizer, Procter & Gamble, Novartis, Wyeth, AstraZeneca, and Bristol-Myers Squibb Medical Imaging; she has received a research grant from Merck; she has stock in Boston Scientific, IVAX, Eli Lilly, Medtronic, Johnson & Johnson, SCIE Insurance, ATS Medical, and Biosite.

Dr. Brewer has received honoraria from AstraZeneca, Pfizer, Lipid Sciences, Merck, Merck/Schering-Plough, Fournier, Tularik, Esperion, and Novartis; he has served as a consultant for AstraZeneca, Pfizer, Lipid Sciences, Merck, Merck/Schering-Plough, Fournier, Tularik, Sankyo, and Novartis.

Dr. Clark has received honoraria for educational presentations from Abbott, AstraZeneca, Bristol-Myers Squibb, Merck, and Pfizer; he has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Merck, and Pfizer.

Dr. Hunninghake has received honoraria for consulting and speakers bureau from AstraZeneca, Merck, Merck/Schering-Plough, and Pfizer, and for consulting from Kos; he has received research grants from AstraZeneca, Bristol-Myers Squibb, Kos, Merck, Merck/Schering-Plough, Novartis, and Pfizer.

Dr. Pasternak has served as a speaker for Pfizer, Merck, Merck/Schering-Plough, Takeda, Kos, BMS-Sanofi, and Novartis; he has served as a consultant for Merck, Merck/Schering-Plough, Sanofi, Pfizer Health Solutions, Johnson & Johnson-Merck, and AstraZeneca.

Dr. Smith has received institutional research support from Merck; he has stock in Medtronic and Johnson & Johnson.

Dr. Stone has received honoraria for educational lectures from Abbott, AstraZeneca, Bristol-Myers Squibb, Kos, Merck, Merck/Schering-Plough, Novartis, Pfizer, Reliant, and Sankyo; he has served as a consultant for Abbott, Merck, Merck/Schering-Plough, Pfizer, and Reliant.

ENDORSER(S)

American College of Cardiology Foundation - Medical Specialty Society
American Heart Association - Professional Association

GUIDELINE STATUS

2001 Guideline

This is the current release of the guideline. This guideline updates a previously released version: Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II).
Bethesda (MD): U.S. Department of Health and Human Services, Public Health

Service, National Institutes of Health, National Heart, Lung and Blood Institute; 1993 Sep. 180 p.

2004 Update

This version of the guideline updates selected recommendations presented in the 2001 version of the guideline: National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute; 2001 May. Various p.

GUIDELINE AVAILABILITY

Electronic copies of the 2001 guideline: Available from the [National Heart, Lung, and Blood Institute \(NHLBI\) Web site](#).

Electronic copies of the 2004 update: Available from the [NHLBI Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive summary. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute, 2001 May. 28 p. Also published in JAMA 2001 May 16;285(19):2486-97. Available from the [National Heart, Lung, and Blood Institute \(NHLBI\) Web site](#).
- ATP III At-a-glance: quick desk reference. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute, 2001 May. 6 p. Available from the [NHLBI Web site](#). See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).
- ATP III guidelines slide set. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute, 2001. Various pagings. Available from the [NHLBI Web site](#). See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).
- Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. Stroke. 2002 Sep;33(9):2337-41; Circulation. 2002 Aug 20;106(8):1024-8; J Am Coll Cardiol. 2002 Aug 7;40(3):567-72. Available from the [NHLBI Web site](#).
- ATP III cholesterol management implementation tool for Palm OS. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute, 2001. Available from the [NHLBI Web site](#). See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).

A complete list of related documents is available at the [NHLBI Web site](#).

Get With the Guidelines (GWTG) provides disease-specific process documents and tools for in-house quality improvement. See the [American Heart Association Web site](#) for more information. See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#) for this related tool set.

PATIENT RESOURCES

The following are available:

- High blood cholesterol. What you need to know. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute, 2001 May. 6 p. Available from the [National Heart, Lung and Blood Institute \(NHLBI\) Web site](#). See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).
- Risk assessment tool for estimating your 10-year risk of having a heart attack. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute, 2001. Available from the [NHLBI Web site](#). See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).
- Risk assessment tool for estimating 10-year risk of developing hard coronary heart disease (myocardial infarction and coronary death). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute, 2004. Available from the [NHLBI Web site](#). See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).
- National Cholesterol Education Program "[Live Healthier, Live Longer](#)" [Web site](#), based on the new Adult Treatment Panel (ATP) III guidelines. See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).
- Protect your heart - lower your cholesterol (also available in Spanish). National Institutes of Health, National Heart, Lung and Blood Institute, 1996. Available from the [NHLBI Web site](#). See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).
- Cholesterol-lowering medications and you. National Heart, Lung and Blood Institute, 2004. Available from the [National Heart, Lung and Blood Institute \(NHLBI\) Web site](#). See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).
- National Heart, Lung, and Blood Institute: high blood cholesterol, 2006 Feb. Available from the [National Heart, Lung and Blood Institute \(NHLBI\) Web site](#). See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on December 1, 1998. The information was verified by the guideline developer on January 11, 1999. The summary was updated on January 23, 2002 in response to the guideline update issued in September 2001. This summary was most recently updated on August 23, 2004 in response to the addendum to the guideline issued in June 2004.

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