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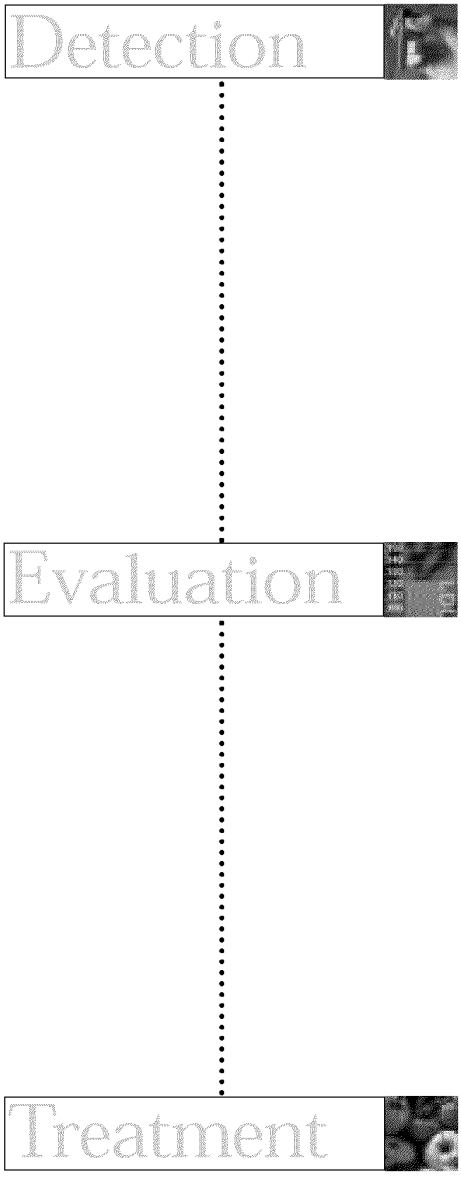

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Final Report

National Cholesterol Education Program

National Heart, Lung, and Blood Institute

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Acknowledgments

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

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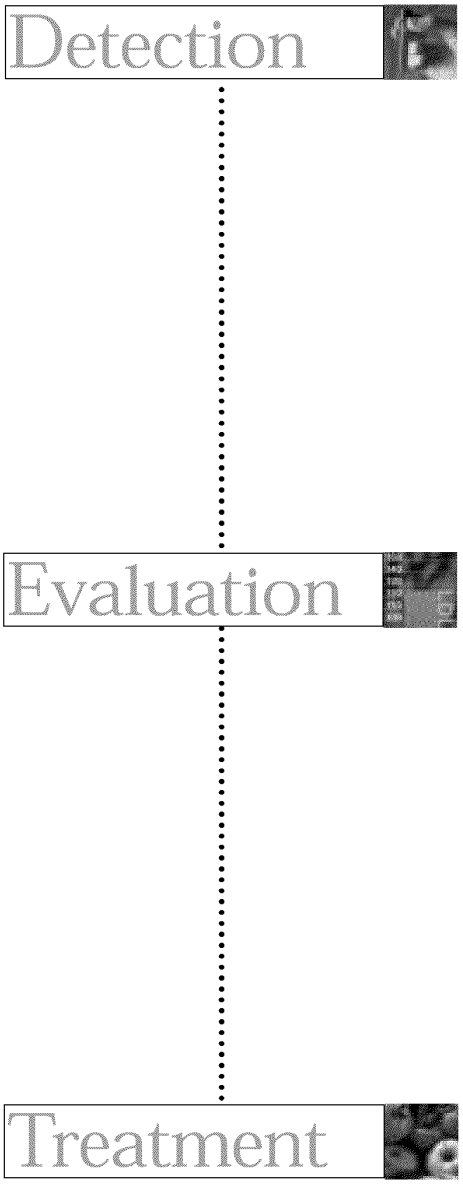

I. Background and Introduction

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The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) presents the National Cholesterol Education Program's (NCEP's) updated recommendations for cholesterol testing and management. It is similar to Adult Treatment Panel II (ATP II)[1,2] in general outline and fundamental approach to therapy. It focuses on the role of the clinical approach to prevention of coronary heart disease (CHD).* This report continues to identify low-density lipoprotein (LDL) as the primary target of cholesterol-lowering therapy. Since ATP II, a number of controlled clinical trials with newer cholesterol-lowering drugs have been reported. These trials demonstrated remarkable reductions in risk for CHD, in both primary and secondary prevention. Their results enrich the evidence base upon which the new guidelines are founded.

1. Development of an evidence-based report

The ATP III panel extensively analyzed the results of recent clinical trials whose findings strongly influenced the development of the new guidelines. The panel's major goals were to review the literature objectively and to document and display the scientific evidence for ATP III recommendations. Prior to the appointment of the ATP III panel, the NCEP Coordinating Committee developed a list of important issues for the panel's consideration. This list was presented to the panel, discussed, and modified appropriately. The literature pertaining to each defined issue was identified by the panel members and by a MEDLINE search. Panel members produced a series of issue papers that carefully reviewed the literature; these issue papers became the foundation for writing the first draft of the report. Modifications of drafts were made following review and discussion of additional evidence arising from the literature search. ATP III contains both evidence statements and specific recommendations based on these statements. Each evidence statement is qualified according to category of evidence (A–D) and strength of evidence (1–3), as follows:

Type of Evidence

Category of Type of Evidence	Description of Type of Evidence
A	Major randomized controlled clinical trials (RCTs)
B	Smaller RCTs and meta-analyses of other clinical trials
C	Observational and metabolic studies
D	Clinical experience

Strength of Evidence

Category of Strength of Evidence	Description of Strength of Evidence
1	Very strong evidence
2	Moderately strong evidence
3	Strong trend

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, ATP III recommendations are based on the panel's 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.

* In ATP III, CHD is defined as symptomatic ischemic heart disease, including myocardial infarction, stable or unstable angina, demonstrated myocardial ischemia by noninvasive testing, and history of coronary artery procedures.

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 ATP 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.

The 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.

2. Features of ATP III similar to those of ATP I and II

ATP III represents an update of recommendations for clinical management of high blood cholesterol and related abnormalities. It is constructed on the foundation of previous reports, ATP I[3,4] and ATP II.[1,2] The NCEP periodically produces ATP clinical updates as warranted by advances in the science of cholesterol management. Each report has a major thrust. ATP I outlined a strategy for primary prevention of CHD in persons with high LDL cholesterol (≥160 mg/dL) or in those with borderline-high LDL cholesterol (130–159 mg/dL) and multiple (2+) other risk factors. ATP II affirmed the importance of this approach and added a new feature: the intensive management of LDL cholesterol in persons with established CHD. For CHD patients, ATP II set a new, lower LDL-cholesterol goal of ≤100 mg/dL. ATP III maintains continuity with ATP I and ATP II. Before considering the new constituents of ATP III, some of the important features shared with previous reports are shown in Table I.2–1.

Table I.2–1. Shared Features of ATP III and ATP II

- Continued identification of LDL cholesterol lowering as the primary goal of therapy
- Consideration of high LDL cholesterol (≥160 mg/dL) as a potential target for LDL-lowering drug therapy, specifically as follows:
  - For persons with multiple risk factors whose LDL levels are high (≥160 mg/dL) after dietary therapy, consideration of drug therapy is recommended
  - For persons with 0–1 risk factor whose LDL levels are 160–189 mg/dL after dietary therapy, drug treatment is optional; if LDL levels are ≥190 mg/dL after dietary therapy, drug treatment should be considered
- Emphasis on intensive LDL-lowering therapy in persons with established CHD
- Identification of three categories of risk for different LDL goals and different intensities of LDL-lowering therapy:
  - CHD and CHD risk equivalents* (other forms of clinical atherosclerotic disease)
  - Multiple (2+) risk factors†
  - 0–1 risk factor
- Identification of population groups, besides middle-aged men, for detection of high LDL cholesterol (and other lipid risk factors) and for clinical intervention. These include:
  - Young adults
  - Postmenopausal women
  - Older persons
- Emphasis on weight loss and physical activity to enhance risk reduction in persons with elevated LDL cholesterol

* A CHD risk equivalent is a condition that carries an absolute risk for developing new CHD equal to the risk for having recurrent CHD events in persons with established CHD.

† Risk factors that continue to modify the LDL goal include cigarette smoking, hypertension, a low level of high-density lipoprotein (HDL) cholesterol, family history of premature CHD, age, and diabetes. Note that in ATP III, diabetes is regarded as a CHD risk equivalent. A high HDL cholesterol remains a "negative" risk factor: its presence subtracts one risk factor from the risk factor count.

3. New features of ATP III

While ATP III maintains attention to intensive treatment of patients with CHD, its major new feature is a focus on primary prevention in persons with multiple risk factors. Many of these persons have a relatively high risk for CHD and will benefit from more intensive LDL-lowering treatment than is recommended in ATP II. Table I.3–1. shows the new features of ATP III.

Table I.3–1. New Features of ATP III

Focus on Multiple Risk Factors

- Raises persons with diabetes without CHD (most of whom display multiple risk factors) to the risk level of CHD risk equivalent
- Uses Framingham projections of 10-year absolute CHD risk (i.e., the percent probability of having a CHD event in 10 years) to identify certain patients with multiple (2+) risk factors for more intensive treatment
- Identifies persons with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes

Modifications of Lipid and Lipoprotein Classification

- Identifies LDL cholesterol <100 mg/dL as optimal
- Raises categorical low HDL cholesterol from <35 mg/dL to <40 mg/dL because the latter is a better measure of a depressed HDL
- Lowers the triglyceride classification cutpoints to give more attention to moderate elevations

Support for Implementation

- Recommends lipoprotein analysis (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) as the preferred initial test, rather than screening for total cholesterol and HDL alone
- Encourages use of plant stanols/sterols and viscous (soluble) fiber as therapeutic dietary options to enhance lowering of LDL cholesterol
- Presents strategies for promoting adherence to therapeutic lifestyle changes and drug therapies
- Recommends treatment beyond LDL lowering for persons with triglycerides ≥200 mg/dL

4. Relation of ATP III to NCEP's public health approach

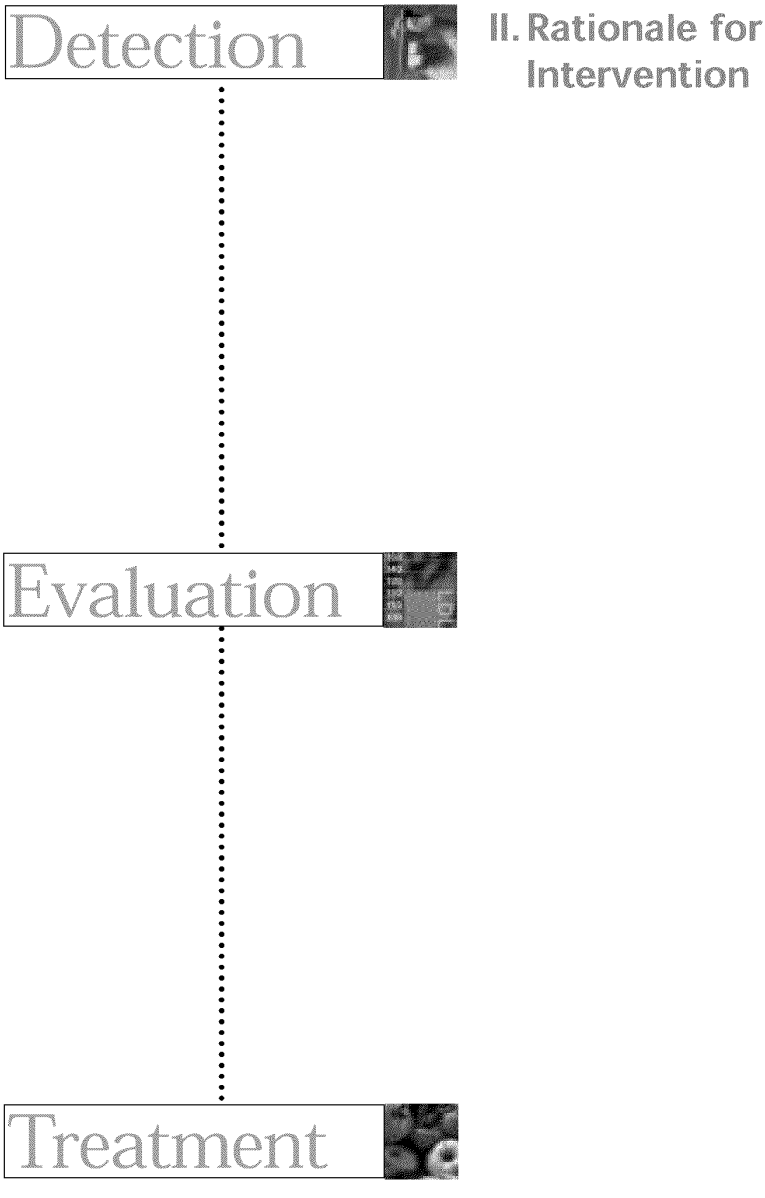
To reduce the burden of coronary atherosclerosis in society, LDL-cholesterol concentrations and other CHD risk factors must be kept as near to an optimal level as possible through the *public health (population) approach*. Lowering LDL-cholesterol levels in the whole population and keeping them low requires adoption of a low saturated fat and low cholesterol diet, maintenance of a healthy weight, and regular physical activity. NCEP has separately produced a Population Panel Report[5,6] that outlines a strategy for the public health approach. The population approach for controlling CHD risk factors will, in the long term, have the greatest impact on reducing the magnitude of cardiovascular disease in the United States. Nonetheless, for persons in whom LDL-cholesterol concentrations are significantly elevated, a *clinical strategy* is also required. NCEP's recommendations for the clinical approach are contained in the Adult Treatment Panel reports. The clinical and population approaches are complementary.[7] ATP III updates NCEP's clinical guidelines for cholesterol management. It also attempts to provide a bridge between clinical management and population strategy. Clinical professionals are integral to the public health approach. The clinical approach alone cannot overcome the burden of atherosclerotic disease in the general population. A parallel and simultaneous effort must be made to promote changes in population life habits to retard atherogenesis. The clinical approach can, however, delay or prevent the onset of CHD and prolong the lives of many persons at increased risk.

5. Relation of ATP III to other clinical guidelines

Since the publication of ATP II, other bodies have published guidelines for CHD risk reduction. For persons with established CHD, ATP III recommendations largely match other guidelines. Recent clinical trials confer a strong scientific base for the benefit of cholesterol-lowering therapy in secondary prevention, making it easier to achieve common ground with other guidelines. There is less congruence on guidelines for primary prevention through clinical therapy. Several recent guidelines place almost exclusive priority for treatment on persons at high risk in the short term, (i.e., ≤10 years). This priority is dictated largely by cost considerations, particularly the costs of cholesterol-lowering drugs. ATP III likewise identifies individuals at high short-term risk who need intensive intervention. However, an important feature of the ATP III guidelines (as in ATP I and ATP II) is extension of the clinical approach to the reduction of long-term (i.e., >10-year) risk. By so doing, ATP III links clinical therapy to the public health approach and goes beyond the more restrictive recommendations of some guideline committees. The panel concluded that clinical guidelines should not be truncated to include only persons at high short-term risk. High serum cholesterol itself is a major cause of the build-up of coronary atherosclerosis, and hence of the development of CHD in the long term. For this

reason, ATP III stresses the need for long-term prevention of coronary atherosclerosis, as well as short-term prevention of acute coronary syndromes resulting from advanced atherosclerosis.

A comment is required about the relationship of ATP III to what is commonly called *global risk assessment* for CHD. In recent clinical guidelines, assessment of absolute risk (global risk) for experiencing acute coronary syndromes over the short term (≤10 years) has assumed increasing importance for primary prevention. These estimates provide a guide for selecting persons for clinical intervention. Accordingly, ATP III can be considered the "cholesterol component" of integrated, short-term risk reduction. At the same time, ATP III can be viewed as a broad-based approach to reducing CHD risk through short-term and long-term control of high serum cholesterol and related disorders of lipid and lipoprotein metabolism. Thus, on the one hand, high serum cholesterol can be identified in the context of global risk assessment that employs all other risk factors. Alternatively, risk assessment can be performed for persons in whom high serum cholesterol and related lipid disorders are detected independently. Thus, ATP III guidelines are designed to be flexible for use in various approaches to primary prevention.



II. Rationale for Intervention

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1. Basic description of lipids and lipoproteins

Cholesterol is a fat-like substance (lipid) that is present in cell membranes and is a precursor of bile acids and steroid hormones. Cholesterol travels in the blood in distinct particles containing both lipid and proteins (lipoproteins). Three major classes of lipoproteins are found in the serum of a fasting individual: low density lipoproteins (LDL), high density lipoproteins (HDL), and very low density lipoproteins (VLDL). Another lipoprotein class, intermediate density lipoprotein (IDL), resides between VLDL and LDL; in clinical practice, IDL is included in the LDL measurement.

LDL cholesterol typically makes up 60–70 percent of the total serum cholesterol. It contains a single apolipoprotein, namely apo B-100 (apo B). LDL is the major atherogenic lipoprotein and has long been identified by NCEP as the primary target of cholesterol-lowering therapy. This focus on LDL has been strongly validated by recent clinical trials, which show the efficacy of LDL-lowering therapy for reducing risk for CHD.

HDL cholesterol normally makes up 20–30 percent of the total serum cholesterol. The major apolipoproteins of HDL are apo A-I and apo A-II. HDL-cholesterol levels are inversely correlated with risk for CHD. Some evidence indicates that HDL protects against the development of atherosclerosis, although a low HDL level often reflects the presence of other atherogenic factors.

The VLDL are triglyceride-rich lipoproteins, but contain 10–15 percent of the total serum cholesterol. The major apolipoproteins of VLDL are apo B-100, apo Cs (C-I, C-II, and C-III), and apo E. VLDL are produced by the liver and are precursors of LDL; some forms of VLDL, particularly VLDL remnants, appear to promote atherosclerosis, similar to LDL. VLDL remnants consist of partially degraded VLDL and are relatively enriched in cholesterol ester. Strictly speaking, IDL belongs to remnant lipoproteins although, in clinical practice, IDL is included in the LDL fraction.

A fourth class of lipoproteins, chylomicrons, are also triglyceride-rich lipoproteins; they are formed in the intestine from dietary fat and appear in the blood after a fat-containing meal. The apolipoproteins of chylomicrons are the same as for VLDL except that apo B-48 is present instead of apo B-100. Partially degraded chylomicrons, called chylomicron remnants, probably carry some atherogenic potential.

Although LDL receives primary attention for clinical management, growing evidence indicates that both VLDL and HDL play important roles in atherogenesis. In this report, therefore, VLDL and HDL receive consideration after LDL in the overall management of persons at risk for CHD.

2. LDL cholesterol as the primary target of therapy

ATP I and ATP II identified LDL as the primary target for cholesterol-lowering therapy, and ATP III continues this emphasis. This designation is based on a wide variety of observational and experimental evidence amassed over several decades from animal, pathological, clinical, genetic, and different types of population studies. Many earlier studies measured only serum total cholesterol, although most of total cholesterol is contained in LDL. Thus, the robust relationship between total cholesterol and CHD found in epidemiological studies strongly implies that an elevated LDL is a powerful risk factor. Subsequent studies have shown that LDL is the most abundant and clearly evident atherogenic lipoprotein. The role of LDL in atherogenesis is confirmed by genetic disorders in which serum LDL cholesterol is markedly increased in the absence of other CHD risk factors. Notable examples of such genetic disorders are homozygous and heterozygous forms of familial hypercholesterolemia; in both, atherogenesis is markedly accelerated. Finally, a causal role for LDL has been corroborated by controlled clinical trials of LDL lowering; recent trials especially have revealed a striking reduction in incidence of CHD. Evidence for LDL being both a major cause of CHD and a primary target of therapy will be examined in some detail.

a. Serum LDL cholesterol as a major cause of CHD

The induction of hypercholesterolemia is a prerequisite for atherogenesis, and sometimes myocardial ischemia, in various experimental animals. In addition, certain species have hereditary forms of hypercholesterolemia and develop atherosclerosis spontaneously; a classical example is the WHHL rabbit, which carries the same molecular defect as human familial hypercholesterolemia. In contrast, low LDL-cholesterol levels are well tolerated. LDL cholesterol as low as 25–60 mg/dL is physiologically sufficient.[8] Animal species that do not develop atherosclerosis generally have LDL-cholesterol levels below 80 mg/dL. The LDL-cholesterol concentration in the newborn infant is approximately 30 mg/dL, indicating that such low levels are safe. Moreover, persons who have extremely low levels of LDL throughout life due to familial hypobetalipoproteinemia have documented longevity.[9]

Epidemiological investigations of human populations incriminate high levels of LDL cholesterol as being atherogenic. In population studies, the serum total cholesterol is a good surrogate for LDL-cholesterol levels. The Framingham Heart Study,[10] the Multiple Risk Factor Intervention Trial (MRFIT),[11] and the Lipid Research Clinics (LRC) trial[12,13] found a direct relationship between levels of LDL cholesterol (or total cholesterol) and the rate of new-onset CHD in men and women who were initially free of CHD. The same relation holds for recurrent coronary events in people with established CHD.[14-16] Any LDL cholesterol above 100 mg/dL appears to be atherogenic. The prevalance of elevated levels in large part accounts for the near-universal development of coronary atherosclerosis in the United States and the high attendant risk for developing CHD over a lifetime—49 percent for men and 32 percent for women.[17]

Studies across different populations reveal that those with higher cholesterol levels have more atherosclerosis and CHD than do those having lower levels.[18-20] People who migrate from regions where average serum cholesterol in the general population is low to areas with high cholesterol levels show increases in their cholesterol levels as they acculturate. These higher levels in turn are accompanied by more CHD.[21,22]

The positive relationship between serum cholesterol levels and the development of first or subsequent attacks of CHD is observed over a broad range of LDL-cholesterol levels; the higher the level, the greater the risk.[11] Early prospective data suggested that the risk of CHD plateaued at lower cholesterol levels, but this apparent plateau has disappeared in larger studies.[11,23,24] Only in populations that maintain very low levels of serum cholesterol, e.g., total cholesterol <150 mg/dL (or LDL cholesterol <100 mg/dL) throughout life do we find a near-absence of clinical CHD.[19,23-28]

Atherosclerosis generally can first be identified by gross pathological examination of coronary arteries in adolescence or early adulthood.[29-31] The subsequent rate of atherogenesis is proportional to the severity of ambient risk factors including serum cholesterol levels. Moreover, the cholesterol level in young adulthood predicts development of CHD later in life. In three prospective studies with long-term followup,[32-34] detection of elevated serum cholesterol in early adulthood predicted an increased incidence of CHD in middle-age.

The power of elevated LDL to cause CHD is shown most clearly in persons with genetic forms of hypercholesterolemia.[8] In these persons, advanced coronary atherosclerosis and premature CHD occur commonly even in the complete absence of other risk factors. These disorders provide the strongest evidence that LDL is a powerful atherogenic lipoprotein.

Since LDL-cholesterol levels <100 mg/dL throughout life are associated with a very low risk for CHD in populations, they can be called *optimal*. Even when LDL-cholesterol concentrations are *near optimal* (100–129 mg/dL), atherogenesis occurs; hence, such levels must also be called *above optimal*. At levels that are *borderline high* (130–159 mg/dL), atherogenesis proceeds at a significant rate, whereas at levels that are *high* (160–189 mg/dL) and very high (≥190 mg/dL) it is markedly accelerated. These relationships are confirmed by the log-linear relationship between serum cholesterol levels and CHD risk observed in many populations.[23,24]

The relation of elevated LDL cholesterol to the development of CHD must be viewed as a multi-step process beginning relatively early in life.[35-37] The first stage of atherogenesis is the fatty streak, which consists largely of cholesterol-filled macrophages; most of the

cholesterol in fatty streaks is derived from LDL cholesterol. The second stage consists of fibrous plaques in which a layer of scar tissue overlies a lipid-rich core. Other risk factors contribute to plaque growth at this phase. The third stage is represented by the development of unstable plaques that are prone to rupture and formation of luminal thrombosis. Plaque rupture (or erosion) is responsible for most acute coronary syndromes (myocardial infarction, unstable angina, and coronary death).[38-41] Elevated LDL cholesterol plays a role in the development of the mature coronary plaque, which is the substrate for the unstable plaque. Recent evidence also indicates that elevated LDL cholesterol contributes to plaque instability as well; conversely, LDL cholesterol lowering stabilizes plaques and reduces the likelihood of acute coronary syndromes. Clinical intervention with LDL-lowering therapy in patients with advanced coronary atherosclerosis (short-term risk reduction) thus aims to stabilize plaques and to prevent acute coronary sydromes.[42,43] In contrast, LDL lowering earlier in life slows atherosclerotic plaque development, the foundation of the unstable plaque. This fact provides a rationale for long-term lowering of LDL cholesterol using both public-health and clinical approaches.

b. Serum LDL cholesterol as target of therapy

Notwithstanding this diverse evidence, the ultimate proof of the benefits of lowering LDL cholesterol is through clinical trial. A large number of clinical trials of cholesterol-lowering therapy have been carried out over the past four decades.[44] The history of cholesterol-lowering trials records one of the major advances in modern medicine.[44] The initial encouraging findings of earlier trials have recently been reinforced by the robust findings of a large number of studies, especially those using HMG CoA reductase inhibitors (statins). Clinical outcomes in terms of CHD incidence and CHD mortality are summarized in Table II.2–1 for pre-statin and statin trials in which LDL-cholesterol reduction was the major lipid response. The pre-statin trials provided strong evidence that CHD incidence is reduced by cholesterol-lowering therapy; statin trials extend the benefit to reduction of CHD mortality, and even to total mortality (see Section II.9).

Additional evidence of the benefit of LDL lowering is provided by study of coronary lesion architecture through coronary angiography. A summary of the evidence from different categories of angiographic trials reveals that LDL-lowering therapy produces favorable outcomes for coronary lesions, with a strong trend for a beneficial outcome for major coronary events (Table II.2–2).

Both clinical trials and angiographic studies show reductions in CHD risk that are broadly consonant with what was projected from cohort studies. The issue of whether cholesterol-lowering therapy reduces total mortality is considered in detail subsequently (see Section II.9).

In recent trials, statin therapy reduced risk for CHD in men and women, in those with or without heart disease, in older and younger subjects, in those with diabetes and hypertension, and at most levels of cholesterol. These benefits for different subgroups are shown by meta-analysis prepared for ATP III by panel members and statistical consultants at NHLBI (Table II.2–3) and by a recent analysis from two combined secondary prevention trials (CARE and LIPID).[47,48]

Table II.2–1.* CHD Outcomes in Clinical Trials of LDL-Cholesterol-Lowering Therapy†

Intervention	No. trials	No. treated	Person-years	Mean cholesterol reduction (%)	CHD Incidence (% change)	CHD Mortality (% change)
Surgery	1	421	4,084	22	**-43**	-30
Sequestrants	3	1,992	14,491	9	**-21**	-32
Diet	6	1,200	6,356	11	**-24**	-21
Statins	12	17,405	89,123	20	**-30**	**-29**

* This table is adapted from the meta-analysis of Gordon.[45]

† Not included among these clinical trials are those employing fibrates, nicotinic acid, and hormones. The major actions of fibrates and nicotinic acid are on triglyceride and HDL, whereas hormone trials have effects beyond serum lipids.

Table II.2–2. Odds Ratios for Coronary Lesion Regression vs. Progression and for Cardiovascular Event Rates in Angiographic Trials of LDL-Lowering Therapy (Including Comparison with Placebo and Trials of Calcium Channel Blockers)

Trials	Coronary Lesion Regression vs. Progression Odds Ratio (Number >1 means greater regression than progression)	Cardiovascular Event Rates Odds Ratio (Number <1 means fewer events on therapy)
Statins	2.1 (1.6, 2.7)* (p<0.0001)(vs. placebo)† (p<0.0001) vs. (calcium blocker)‡	0.67 (0.57, 0.80)* (p<0.0001)† (p=0.012)‡
Ileal Exclusion (POSCH)	4.7 (2.5, 9.0)* (p<0.0001)† (p=0.002)‡	0.57 (0.41, 0.78)* (p<0.0005)† (p=0.0082)‡
Sequestrants	3.2 (0.9, 11.4)* NS† NS‡	0.41 (0.17, 1.00)* NS† NS‡
Lifestyle	10.7 (4.0, 29.0)* (p<0.0001)† (p=0.0004)‡	0.57 (0.23, 1.46)* NS† NS‡
Combination Therapy	3.0 (1.8, 5.1)* (p<0.0001)† (p=0.03)‡	0.54 (0.36, 0.81)* (p=0.0031)† (p=0.021)‡
Calcium Channel Blockers	1.0 (0.6, 1.4)* NS†	1.33 (0.94, 1.89)* NS†

* Confidence intervals.
† Statistical significance compared to placebo.
‡ Statistical significance compared to calcium channel blocker trials.
NS Not significant.
This table was modified from a recently published meta-analysis provided by G.B.J. Mancini.[46] In this analysis, to assess trends and to synthesize the results of disparate trials, the reported trial results were examined with respect to the main angiographic and clinical endpoints. Odds ratios were calculated comparing progression and regression as dichotomous responses, excluding mixed or no-change responses. Odds ratios also were calculated for reported events. Tests of homogeneity were performed and were not significant, i.e., it may be assumed that the different trials in each category estimate a common odds ratio even though definitions of progression and regression and of clinical events differ somewhat among the trials. The significance of the calculated pooled odds ratios as well as 95 percent confidence intervals (CI) were calculated. Paired comparisons between combined odds ratios for different trial groups were carried out using Bonferroni's correction for multiple comparisons. The clinical trials compared in these studies were the following:
Statin trials:Δ LCAS, CIS, CARS, Post-CABG, REGRESS, PLAC I, CCAIT, MAAS, MARS
Surgical therapy:Δ POSCH
Sequestrant trials:Δ STARS, NHLBI Type II
Lifestyle intervention:Δ Heidelberg, STARS, Lifestyle Heart Trial
Combination drug therapy:Δ HARP, SCRIP, SCOR, FATS (lovastatin/colestipol), FATS (nicotinic acid/colestipol), CLAS
Calcium channel blocker monotherapy trialsΔ: Montreal Heart Institute Study, INTACT

Δ See List of Studies appendix for listing of the full names of these clinical trials.

Results of clinical trials of LDL lowering find support from a review of world-wide prospective studies on the relation between serum cholesterol levels and CHD incidence. In fact, Law et al.[23,24] reported a high congruence between results of prospective epidemiology studies and clinical trials. One advantage of epidemiological studies is their ability to examine and predict long-term influences. Earlier clinical trials found that a 1 percent reduction in serum total cholesterol level reduces risk for CHD by about 2 percent. Recent clinical trials with statins indicate that a 1 percent decrease in LDL cholesterol reduces risk by about 1 percent. However, across-country epidemiological studies strongly suggest that maintaining a lower serum cholesterol for periods longer than the duration of clinical trials yields a greater reduction in risk than is predicted from clinical trials. In populations that maintain very low cholesterol levels throughout life, the population risk for CHD is much lower than in populations that habitually carry higher cholesterol levels.[19,20] In contrast, in high-risk populations, the reduction in CHD attained with aggressive cholesterol-lowering therapy still leaves absolute CHD rates far above those in low-risk populations. From another point of view, epidemiological studies suggest that beginning cholesterol-lowering therapy at an earlier age will lead to a greater risk reduction than starting later in life. For example, using data from a large number of cohort studies, Law et al.[23,24] found that a 10 percent reduction in serum cholesterol level attained at age 40 yields a reduction in relative risk for CHD of 50 percent at age 40, whereas a 10 percent cholesterol reduction gives only a 20 precent reduction in risk if begun at age 70. This finding implies that the greatest long-term benefit is attained by early intervention; conversely, later intervention yields lesser benefit in risk reduction.

Evidence statement: Multiple lines of evidence from experimental animals, laboratory investigations, epidemiology, genetic forms of hypercholesterolemia, and controlled clinical trials indicate a strong causal relationship between elevated LDL cholesterol and CHD (A1, B1, C1).

Recommendation: LDL cholesterol should continue to be the primary target of cholesterol-lowering therapy.

Table II.2–3. CHD Risk Reduction (RR) in Cholesterol Trial Subgroups

CHD Risk Reduction in Cholesterol Trial Subgroups						
Trait	**Subgroup**	**N**	**Mean RR**	**95% CI**	**P-Interaction***	**Trials†**
Gender	Male Female	21651 4147	32% 34%	26–36% 20–45%	0.759	AFCAPS, POSCH, CARE, LIPID, PLAC1, 4S, CCAIT
Age	Younger Older	19119 16549	33% 30%	27–39% 24–36%	0.514	AFCAPS, POSCH, Upjohn, VAHIT, WOSCOPS, CARE, LIPID, PLAC1, CCAIT
Hypertension	No Yes	14623 8520	33% 22%	25–39% 12–31%	0.068	AFCAPS, POSCH, VAHIT, CARE, LIPID
Smoker	No Yes	18343 12193	23% 32%	16–30% 25–39%	0.075	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Newcastle, CCAIT
Diabetes	No Yes	25147 2443	27% 31%	21–32% 17–42%	0.596	AFCAPS, POSCH, VAHIT, CARE, LIPID, 4S
Cholesterol	Lower Higher	14180 7519	27% 32%	20–34% 22–40%	0.480	POSCH, Upjohn, WOSCOPS, CARE, LIPID
LDL	Lower Higher	11715 16071	29% 40%	22–36% 35–45%	0.012	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Helsinki
HDL	Lower Higher	16739 17021	33% 34%	27–38% 28–39%	0.865	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Helsinki
TG	Lower Higher	10791 12192	30% 27%	22–38% 20–34%	0.567	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Helsinki

* P-Interaction refers to the difference in treatment effect between the subgroups for each trait. The higher the number, the less is the difference in risk reduction between the two subgroups. The P-interaction term provides a statistical interpretation of the difference in relative risk reduction noted for the two subgroups. In statistical terms, the higher the number, the more homogeneous is the effect between the two subgroups. The dichotomous categories shown in this table vary in cutpoints depending on the results reported for each of the individual studies.

† See List of Studies appendix for listing of the full names of these clinical trials.

c. Categories and classification of total cholesterol and LDL cholesterol

ATP III maintains a classification of serum total cholesterol and LDL cholesterol similar to that in ATP II[1,2] with some minor modifications. The ATP III classification is shown in Table II.2–4.

Table II.2–4. ATP III Classification of Total Cholesterol and LDL Cholesterol

Total Cholesterol (mg/dL)		**LDL 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

3. Other lipid risk factors

a. Triglycerides

1) Elevated serum triglycerides (and triglyceride-rich lipoproteins) as a risk factor

Many prospective epidemiological studies have reported a positive relationship between serum triglyceride levels and incidence of CHD.[49,50] However, early

multivariate analyses generally did not identify serum triglycerides as an independent risk factor for CHD.[51] This failure results from the large number of intercorrelated variables associated with elevated triglycerides. Lipoprotein metabolism is integrally linked, and elevations of serum triglycerides can be confounded by significant correlations with total, LDL, and HDL-cholesterol levels. Nonlipid risk factors of obesity, hypertension, diabetes, and cigarette smoking are also interrelated with triglycerides[52] as are several emerging risk factors (insulin resistance, glucose intolerance, and prothrombotic state [see Section II.5]). Thus, many persons with elevated triglycerides are at increased risk for CHD, even when this greater risk cannot be independently explained by triglycerides. Still, renewed interest in the importance of elevated triglycerides has been stimulated by the publication of meta-analyses that found that raised triglycerides are in fact an *independent risk factor* for CHD.[49,50] This independence suggests that some triglyceride-rich lipoproteins (TGRLP) are atherogenic.

2) Lipoprotein remnants as atherogenic lipoproteins

The most likely candidates for atherogenic TGRLP are remnant lipoproteins. These lipoproteins include small very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL). They are cholesterol-enriched particles and have many of the properties of LDL. Reviews of several independent lines of evidence support the atherogenicity of remnants.[52-54] Specific evidence can be cited. In experimental animals, cholesterol-enriched remnants definitely cause atherosclerosis.[55,56] Genetic hyperlipidemias characterized by the accumulation of lipoprotein remnants commonly produce premature CHD and peripheral vascular disease in humans.[57,58] In several clinical studies in which remnants were specifically identified, their elevations emerged as strong predictors of coronary atherosclerosis or CHD.[59-69] This relation of remnants to CHD was also noted in several reviews.[52,54] Finally, drug therapies that reduce remnant lipoproteins (fibrates, nicotinic acid, and statins) are accompanied by reduced risk for CHD (see Section II.3.d).

3) VLDL cholesterol as a marker for remnant lipoproteins

Although a variety of methods have been developed to identify lipoprotein remnants, most are not applicable to clinical practice; the most readily available measure for clinical practice is VLDL cholesterol. Some cholesterol in VLDL may reside in non-atherogenic TGRLP, but most of it apparently occurs in atherogenic remnants.[59,70-72] Thus, VLDL cholesterol, as a marker for remnant lipoproteins, is a potential target of cholesterol-lowering therapy.

4) Causes of elevated serum triglycerides

Several causes underlie elevated triglycerides in the general population.[73,74]

- Overweight and obesity
- Physical inactivity
- Cigarette smoking
- Excess alcohol intake
- Very high-carbohydrate diets (>60 percent of total energy)
- Other diseases (type 2 diabetes, chronic renal failure, nephrotic syndrome)
- Certain drugs (corticosteroids, protease inhibitors for HIV, beta-adrenergic blocking agents, estrogens)
- Genetic factors

In persons with none of these factors, serum triglyceride levels typically are less than 100 mg/dL.[75] As some of these triglyceride-raising factors develop, levels commonly rise into the range of 150 to 199 mg/dL.[76,77] Although several factors can elevate triglycerides (see above), most common are overweight/obesity and physical inactivity.[76-81] When triglycerides rise to ≥200 mg/dL, these latter factors may contribute, but genetic influences play an increasing role as well.[82]

5) Categories of serum triglycerides

ATP II[1,2] adopted conservative definitions of serum triglyceride ranges based on the perceived weak independent relationship of triglycerides to CHD. Multivariate analysis of prospective studies at that time suggested that higher triglycerides carry little independent risk for CHD. After review of more recent evidence, the ATP III panel concluded that the link between serum triglycerides and CHD is stronger than previously recognized. Elevated triglycerides are widely recognized as a marker for increased risk, as revealed in univariate analysis.[49-51] In this context elevations in serum triglycerides can be considered a marker for atherogenic remnant lipoproteins, for other lipid risk factors (small LDL particles and low HDL), for other

Table II.3–1. Classification of Serum Triglycerides

Triglyceride Category	ATP II Levels	ATP III Levels
Normal triglycerides	<200 mg/dL	<150 mg/dL
Borderline-high triglycerides	200–399 mg/dL	150–199 mg/dL
High triglycerides	400–1000 mg/dL	200–499 mg/dL
Very high triglycerides	>1000 mg/dL	≥500 mg/dL

nonlipid risk factors (elevated blood pressure), and for emerging risk factors (insulin resistance, glucose intolerance, prothrombotic state).[52] Thus, the finding of elevated serum triglycerides helps to identify persons who are at risk and who need intervention for risk reduction. In addition, when triglyceride levels are ≥200 mg/dL, the presence of increased quantitites of atherogenic remnant lipoproteins can heighten CHD risk substantially beyond that predicted by LDL cholesterol alone.[60,83] For these reasons, ATP III modified the triglyceride classification to give more attention to moderate elevations.

Table II.3–1 compares the older ATP II classification with the new ATP III classification for serum triglycerides.

6) Elevated serum triglycerides and triglyceride-rich lipoproteins as targets of therapy

Elevated triglycerides represent one factor within a set of risk-factor targets in persons who are overweight, obese, sedentary, or cigarette smokers. Life-habit changes—weight control, exercise, and smoking cessation—will favorably modify multiple risk factors including elevated triglycerides.[78,79] Thus, elevated serum triglycerides are a potential target for therapeutic lifestyle changes.

Among triglyceride targets, remnant lipoproteins are the strongest candidates for direct clinical intervention designed to reduce risk for CHD. Atherogenic remnants can be lowered by weight reduction in overweight and obese persons[84] and by lipid-lowering drugs (statins, fibrates, and nicotinic acid).[85-88] However, none of these therapies reduce only remnants; they modify either concentrations or characteristics of all lipoprotein species. This makes it difficult to confirm the efficacy of lowering remnants per se through clinical trials. Nonetheless, the strong evidence for independent atherogenicity of elevated remnants makes them appropriate targets for cholesterol-lowering therapy.[60,83,89]

Evidence statements: Elevated serum triglycerides are associated with increased risk for CHD (C1). In addition, elevated triglycerides are commonly associated with other lipid and nonlipid risk factors (C1).

Recommendation: Greater emphasis should be placed on elevated triglycerides as a marker for increased risk for CHD. First-line therapy for elevated serum triglycerides should be therapeutic lifestyle changes.

Evidence statement: Some species of triglyceride-rich lipoproteins, notably, cholesterol-enriched remnant lipoproteins, promote atherosclerosis and predispose to CHD (C1).

Recommendation: In persons with high serum triglycerides, elevated remnant lipoproteins should be reduced in addition to lowering of LDL cholesterol.

b. Non-HDL cholesterol

1) Non-HDL cholesterol as a risk factor

Since VLDL cholesterol is highly correlated with atherogenic remnant lipoproteins, it can reasonably be combined with LDL cholesterol to enhance risk prediction when serum triglycerides are high. The sum of VLDL+LDL cholesterol is called non-HDL cholesterol. It is calculated routinely as total cholesterol minus HDL cholesterol. Non-HDL cholesterol includes all lipoproteins that contain apo B. In persons with high triglycerides (200–499 mg/dL) most cholesterol occurring in the VLDL fraction is contained in smaller (remnant) VLDL.[59,60,70-72] Few prospective studies have explicitly examined the predictive power of non-HDL-cholesterol levels versus LDL-cholesterol levels in a large group of persons with hypertriglyceridemia. However, Gordon et al.[90] reported that because non-HDL cholesterol and HDL cholesterol are

intercorrelated, they overlap in prediction, whereas LDL cholesterol is independent of HDL cholesterol as a predictor. Thus, some of the predictive power usually attributed to HDL cholesterol could be explained by elevations of non-HDL cholesterol. Frost and Havel[91] proposed that existing data actually favor use of non-HDL cholesterol over LDL cholesterol in clinical evaluation of risk. This proposal is strengthened by a recent report from the follow-up of the Lipid Research Clinic cohort which showed a stronger correlation with coronary mortality for non-HDL cholesterol than for LDL cholesterol.[92] Moreover, non-HDL cholesterol is highly correlated with total apolipoprotein B (apo B);[93,94] apolipoprotein B is the major apolipoprotein of all atherogenic lipoproteins. Serum total apo B also has been shown to have a strong predictive power for severity of coronary atherosclerosis and CHD events.[63,95-105] Because of the high correlation between non-HDL cholesterol and apolipoprotein B levels,[93,94] non-HDL cholesterol represents an acceptable surrogate marker for total apolipoprotein B in routine clinical practice; standardized measures of apolipoprotein B are not widely available for routine measurement. Potential uses of non-HDL cholesterol are for initial testing or for monitoring of response in the nonfasting state; the measurement is reliable in nonfasting serum, whereas calculated LDL cholesterol can be erroneous in the presence of postprandial hypertriglyceridemia.

In most persons with triglyceride levels <200 mg/dL, VLDL cholesterol is not substantially elevated,[106] and further, non-HDL cholesterol correlates highly with LDL cholesterol;[93,94] therefore, adding VLDL cholesterol to LDL cholesterol at lower triglyceride levels would be expected to provide little additional power to predict CHD. When triglyceride levels are ≥200 mg/dL, VLDL cholesterol levels are distinctly raised,[106] and LDL-cholesterol concentrations are less well correlated with VLDL and LDL (non-HDL) cholesterol levels;[93,94] consequently, LDL cholesterol alone inadequately defines the risk associated with atherogenic lipoproteins. In the presence of high serum triglycerides, non-HDL cholesterol therefore will better represent the concentrations of all atherogenic lipoproteins than will LDL cholesterol alone. On the other hand, when triglyceride levels become very high (e.g., ≥500 mg/dL) some of the cholesterol in TGRLP resides in nonatherogenic forms of larger VLDL and chylomicrons, and non-HDL cholesterol may be less reliable as a predictor of CHD risk.

2) Non-HDL cholesterol as a secondary target of therapy

Clinical trials of cholesterol-lowering therapy have not specifically identified non-HDL cholesterol (independent of LDL) as a target of therapy; thus, it has been difficult to isolate the impact of lowering non-HDL cholesterol per se on CHD risk. However, the same statement could be made about LDL itself. For example, it has been widely assumed from primary and secondary prevention trials of statin therapy that risk reduction is a response to LDL cholesterol lowering. Of interest, however, the percentage reductions of LDL cholesterol and VLDL cholesterol on statin therapy are similar.[93]

Consequently, it is not possible to differentiate risk reduction due to LDL lowering from non-HDL cholesterol lowering. Most clinical trials have not specifically included persons with hypertriglyceridemia; thus it can be assumed that lowering of VLDL cholesterol was a minor contributor to risk reduction in statin trials. However, in clinical practice, the situation may be different; when triglycerides are high, a significant fraction of non-HDL cholesterol is contained in VLDL. Here LDL cholesterol may not be the only significant lipid risk factor. Consequently, when triglycerides are high, non-HDL cholesterol (including VLDL cholesterol) can serve as a secondary target of therapy.

A "normal" VLDL cholesterol can be defined as that present when triglycerides are <150 mg/dL; this value typically is ≤30 mg/dL.[106] Conversely, when triglyceride levels are >150 mg/dL, VLDL cholesterol usually is >30 mg/dL. Thus, a reasonable goal for non-HDL cholesterol is one that is 30 mg/dL higher than the LDL-cholesterol goal. A specific goal of therapy for serum triglycerides is not identified in ATP III for two reasons: (a) triglyceride levels have more day-to-day variability than non-HDL-cholesterol levels and thus are less reliable, and (b) non-HDL cholesterol as a target allows more flexibility in choice of therapies to reduce atherogenic lipoproteins contained in the combined LDL+VLDL fraction. Non-HDL cholesterol was chosen as a preferred secondary target of therapy over total apo B for three other reasons:

(a) standardized measures of total apo B are not widely available in clinical practice; (b) measures of total apo B have not been shown in a large number of prospective studies to carry greater predictive power than non-HDL cholesterol in persons with elevated triglycerides; and (c) measurement of total apo B will constitute an added expense beyond the usual lipoprotein profile.

Evidence statements: Some species of triglyceride-rich lipoproteins are independently atherogenic; notable among these are cholesterol-enriched remnant lipoproteins (C1). Moreover, VLDL cholesterol is a marker for atherogenic VLDL remnants (C1).

Recommendation: In persons with high triglycerides (≥200 mg/dL), VLDL cholesterol should be combined with LDL cholesterol, yielding non-HDL cholesterol. The latter constitutes "atherogenic cholesterol" and should be a secondary target of therapy.

c. High density lipoproteins (HDL)

1) *Low HDL cholesterol as an independent risk factor for CHD*

Strong epidemiological evidence links low levels of serum HDL cholesterol to increased CHD morbidity and mortality.[10,90,107] High HDL-cholesterol levels conversely convey reduced risk. Epidemiological data taken as a whole signify that a 1 percent decrease in HDL cholesterol is associated with a 2–3 percent increase in CHD risk.[90] Epidemiological studies consistently show low HDL cholesterol to be an *independent risk factor* for CHD. Its independent relationship holds after correction for other risk variables in multivariate analysis. In fact, in prospective studies,[108,109] HDL usually proves to be the lipid risk factor most highly correlated with CHD risk. ATP II specified low HDL cholesterol (<35 mg/dL) as one of several major risk factors used to modify the therapeutic goal for LDL cholesterol. The definition of a low HDL was set to be the same for both men and women because of the view that a given level of HDL would impart the same risk for men and women.

The mechanistic relationship between low HDL-cholesterol levels and occurrence of CHD has not been fully elucidated. One theory holds that HDL directly participates in the atherogenic process. Some research in laboratory animals backs a direct action. In genetically modified animals, high levels of HDL appear to protect against atherogenesis.[110-112] In vitro, HDL promotes efflux of cholesterol from foam cells in atherosclerotic lesions (reverse cholesterol transport).[113] Recent studies indicate that the antioxidant and anti-inflammatory properties of HDL also inhibit atherogenesis.[114-116] Further, some genetic forms of HDL deficiency are accompanied by increased risk for CHD;[117,118] others appear not to be.[119-121] This latter finding raises the possibility that some subspecies of HDL affect atherogenesis whereas others do not. Although there are conflicting data, multiple lines of evidence strongly intimate that HDL plays a direct role in the atherogenic process. If so, it is a potential target for therapy.

The direct role of HDL in atherogenesis probably cannot fully account for the strong predictive power of HDL in epidemiological studies. A low HDL level correlates with the presence of other atherogenic factors.[122] In many persons, a low HDL level correlates with elevations of serum triglycerides and remnant lipoproteins;[123,124] in addition, low HDL commonly shows linkage with small, dense LDL particles.[125-128] The tight association among low HDL, small LDL particles, and elevated triglycerides has evoked the term *lipid triad.* Moreover, a low HDL level can be a sign of insulin resistance and its associated metabolic risk factors[122] (see Section II.6 Metabolic Syndrome). Because of the association of low HDL with other atherogenic factors (some of which are not included among standard risk factors), a low HDL cholesterol is not as strongly *independent* in its prediction of CHD as suggested by usual multivariate analysis, i.e., its independence is partially confounded by some risk factors that are not routinely measured, e.g., *emerging risk factors* (see Section II.5). This confounding raises the possibility that therapeutic raising of HDL-cholesterol levels will not reduce CHD risk as much as might be predicted from prospective epidemiological studies.[122]

Evidence statement: A low HDL-cholesterol level is strongly and inversely associated with risk for CHD (C1).

2) Causes of low HDL cholesterol

There are several factors that contribute to low HDL-cholesterol levels that need to be identified in clinical practice.[73,74,129] These include:

- Elevated serum triglycerides
- Overweight and obesity
- Physical inactivity
- Cigarette smoking
- Very high carbohydrate intakes (>60 percent of total energy intake)
- Type 2 diabetes
- Certain drugs (beta-blockers, anabolic steroids, progestational agents)
- Genetic factors

In the general population, about 50 percent of the variability of serum HDL-cholesterol levels derives from genetic factors;[130] the other 50 percent presumably comes from the acquired factors listed above. Moreover, when a person has a genetic predisposition to reduced HDL, acquired factors often drive HDL cholesterol to categorically low levels. Among these acquired factors, overweight and obesity appear to be most important.[78,79,131] Part of the effect of overweight and obesity can be explained by their action to raise serum triglycerides, which lowers HDL-cholesterol levels, but they probably reduce HDL cholesterol through other mechanisms as well.[132-134]

3) Classification of serum HDL cholesterol

The inverse association between HDL-cholesterol concentrations and CHD risk is a continuous variable; no threshold relationship has been identified.[10] For this reason, any categorical definition of low HDL cholesterol must be arbitrary. In ATP II,[1,2] a low HDL cholesterol was defined as a level <35 mg/dL; the setting of this cutpoint was influenced by the concept that low HDL is primarily a direct cause of atherosclerotic disease. More recently, the role of HDL as an indicator of other risk correlates has been emphasized.[122,135-137] This shift in perception requires a re-examination of the appropriate cutpoint for low HDL. Clearly, low HDL levels predict CHD at levels above 35 mg/dL;[10] this fact combined with the moderate reductions of HDL cholesterol caused by obesity and physical inactivity led the ATP III panel to recognize a somewhat higher HDL-cholesterol level as a categorical risk factor. The level <40 mg/dL was set as a low HDL cholesterol, both in men and women. Women typically have higher HDL cholesterol levels than men, and a cutpoint of <40 mg/dL will identify more men than women with low HDL cholesterol, i.e., approximately one-third of men and about one-fifth of women in the general population. Setting a different cutpoint for categorical low HDL cholesterol for men and women was rejected because it would make many women who are otherwise at low risk eligible for LDL-lowering drugs. On the other hand, as will be discussed subsequently, a higher level of HDL cholesterol (<50 mg/dL) is defined as a marginal risk factor in women, which will mandate more intensive lifestyle therapies (weight reduction and increased physical activity) (see Section II.6 Metabolic Syndrome).

In prospective studies, including the Framingham Heart Study,[10] a high HDL cholesterol is associated with reduced risk for CHD. In ATP II, this level *(high HDL cholesterol)* was also called a *negative risk factor,* and its presence evoked removal of one risk factor from the risk factor count used for setting treatment goals for LDL cholesterol. ATP III affirms the validity of this assignment. The ATP III classification of HDL cholesterol thus is given in Table II.3–2.

Table II.3–2. ATP III Classification of HDL Cholesterol

Serum HDL Cholesterol (mg/dL)	
<40 mg/dL	Low HDL cholesterol
≥60 mg/dL	High HDL cholesterol

Evidence statement: Population studies show a continuous rise in risk for CHD as HDL-cholesterol levels decline (C1). Higher risk for CHD at lower HDL levels is multifactorial in causation (C1). Although the inverse relationship between HDL cholesterol and CHD shows no inflection points, any reduction in HDL cholesterol from population means is accompanied by increased risk for CHD (C1).

Recommendation: A categorical low HDL cholesterol should be defined as a level of <40 mg/dL, in both men and women.

4) Low HDL cholesterol as a potential target of therapy

Persons with low HDL-cholesterol levels benefit similarly to those with higher HDL cholesterol during LDL-lowering therapy (See Table II.2–3). Whether raising HDL per se will reduce risk for CHD has not been resolved. Nonetheless, HDL levels are raised to varying degrees with lipid-modifying drugs, e.g., nicotinic acid,[138] fibrates,[48,139] and statins[140]. Furthermore, clinical trials with nicotinic acid[141] and fibrates[48,139] provide suggestive evidence that HDL raising provides one component of risk reduction with these drugs. Whether the small rise in HDL-cholesterol levels accompanying statin therapy accounts for any of the risk reduction from these drugs is uncertain. Since currently available drugs have multiple actions, it is difficult to dissect fully the benefit of HDL raising from that of reducing atherogenic lipoproteins. Regardless, use of drugs that favorably modify multiple inter-related lipid risk factors appears to reduce risk for CHD (see Section II.3.d Atherogenic Dyslipidemia). Finally, raising HDL levels by reversal of the major acquired causes of low HDL levels—overweight and obesity, physical inactivity, and smoking—provides the opportunity for further risk reduction in persons with low HDL-cholesterol levels. In addition, modifying these causes will be beneficial for other reasons besides raising HDL-cholesterol concentrations.

Evidence statements: Clinical trials provide suggestive evidence that raising HDL-cholesterol levels will reduce risk for CHD (A2). However, it remains uncertain whether raising HDL-cholesterol levels per se, independent of other changes in lipid and/or nonlipid risk factors, will reduce risk for CHD.

Recommendation: A specific HDL-cholesterol goal level to reach with HDL-raising therapy is not identified. However, nondrug and drug therapies that raise HDL-cholesterol levels and are part of management of other lipid and nonlipid risk factors should be encouraged.

d. Atherogenic dyslipidemia

A common form of dyslipidemia is characterized by three lipid abnormalities: elevated triglycerides, small LDL particles, and reduced HDL cholesterol.[49,52,54] Often the lipoprotein concentrations in this *lipid triad* are not categorically abnormal, but are only marginally deranged. More sophisticated methodology than that used in routine clinical practice can identify these multiple interrelated abnormalities. Still, in some persons, low HDL-cholesterol levels can occur in the absence of other lipoprotein abnormalities. These persons are said to have *isolated low HDL*. They are not common in the general population, however; more often, low HDL cholesterol occurs as a component of the lipid triad. Because of the common occurrence of the lipid triad, the relation of the lipid triad as a whole to CHD risk will be considered, and whether the entire triad is a target for therapy.

1) Atherogenic dyslipidemia as a "risk factor"

The lipid triad occurs commonly in persons with premature CHD,[125,142] hence the designation *atherogenic lipoprotein phenotype* or *atherogenic dyslipidemia*. Typical characteristics of persons with atherogenic dyslipidemia are obesity, abdominal obesity, insulin resistance, and physical inactivity.[78,79] Many persons with type 2 diabetes have atherogenic dyslipidemia.[143-145] In epidemiological studies in high-risk populations, the contributions of individual components of atherogenic dyslipidemia to CHD risk cannot reliably be dissected from the sum of lipid risk factors. Although there is evidence that each component of the lipid triad—low HDL, small LDL, and remnant lipoproteins—is individually atherogenic, the relative quantitative contribution of each cannot be determined. For this reason, it is reasonable to view the lipid triad as a whole as a "risk factor."

2) Atherogenic dyslipidemia as a target of therapy

Most therapies that lower triglyceride or raise HDL cholesterol actually modify all of the components of the lipid triad. Weight reduction in overweight and obese subjects favorably modifies atherogenic dyslipidemia;[78,79] so does increased physical activity.[146] Among lipid-lowering drugs, fibrates and nicotinic acid specifically improve all of the elements of the lipid triad.[87,138,147,148] Therefore, in considering clinical trial evidence of benefit from therapeutic modification of atherogenic dyslipidemia, all therapeutic responses together rather than individual responses in individual lipoprotein species likely determine efficacy. Although attempts have been made to dissect apart the

Table II.3–3. Primary Prevention Clinical Trials with CHD Endpoints Using Drugs that Modify Triglyceride-Rich Lipoproteins

Primary prevention

Trial/Drug/ Duration of Intervention	Number of Subjects	Baseline or Placebo Lipid and Lipoprotein Values and On-Treatment Lipid and Lipoprotein in Drug Treatment Group					% Change in Coronary Event Rate (Drug vs. Placebo Groups)
		Group	TC (mg/dL)	TG (mg/dL)	Non-HDL-C (mg/dL)	HDL-C (mg/dL)	
WHO trial[149] Clofibrate 5 yrs	15,745 men lipids from Edinburgh (Subsets: n = 4935)	Placebo	257	210	—	—	-20% (p=0.05)
		On-Treatment	229	160	—	—	
Helsinki Heart Study[139] Gemfibrozil 5 yrs	4,081 men	Baseline	289	175	242	47	-34% (p<0.02)
		On-Treatment	247	115	196	51	

TC = total cholesterol; TG = triglycerides; non-HDL-C = non-HDL cholesterol; HDL-C = HDL cholesterol.

Table II.3–4. Secondary Prevention Clinical Trials with CHD Endpoints Using Drugs that Modify Triglyceride-Rich Lipoproteins

Trial/Drug/ Duration of Intervention	Number of Subjects	Baseline or Placebo Lipid and Lipoprotein Values and On-Treatment Lipid and Lipoprotein in the Drug-Treatment Group					% Change in Coronary Event Rate (Drug vs. Placebo Groups)
		Group	TC (mg/dL)	TG (mg/dL)	Non-HDL-C (mg/dL)	HDL-C (mg/dL)	
Coronary Drug Project[141] Clofibrate 5 yrs	1,103 men on Clofibrate Treatment vs. 2,789 placebo	Baseline	250	177	—	—	-5% (NS)
		On-Treatment	234	149	—	—	
Coronary Drug Project[141] Nicotinic acid 5 yrs	1,119 Rx men; 2,789 placebo	Baseline	250	177	—	—	-22% p<0.05
		On-Treatment	226	143	—	—	
Newcastle Trial[150]	400 men	Baseline	245	337	—	—	-49% p<0.01
		On-Treatment	217	215	—	—	
Clofibrate 5 yrs	97 women	Baseline	270	—	—	—	
		On-Treatment	229	—	—	—	
Scottish Trial[151]	593 men	Baseline	264	—	—	—	-44% (NS)
		On-Treatment	229	—	—	—	
Clofibrate 6 yrs	124 women	Baseline	280	—	—	—	
		On-Treatment	228	—	—		
Stockholm Study[152] Clofibrate+ Nicotinic acid 5 yrs	219 men 60 women lipoproteins on subset	Baseline	251	208	203	48	-36% p<0.01
		On-Treatment	218	166	—	—	
VA-HIT Trial[48] Gemfibrozil 5 yrs	2,531 men	Baseline	175	161	143	32	-22% p<0.006
		On-Treatment	170	115	136	34	
BIP[153] Bezafibrate 6 yrs	2,825 men 265 women	Baseline	212	145	177	35	-9.4% p=0.26
		On-Treatment	202	115	161	41	

Table II.3–5. Clinical Trials with Angiographic Endpoints Using Drugs that Modify Triglyceride-Rich Lipoproteins in Persons with Established Coronary Disease or CHD Equivalent

Trial/Drug/ Duration of Intervention	N	Baseline and Rx Lipid and Lipoprotein Values					Mean change, minimum lesion diameter (mm)*
		Group	Total Chol	TG	LDL	HDL	
BECAIT[154] Bezafibrate 600 mg 5 yr	92 men; 80% had mixed dyslipidemia	Baseline	266	216	180	34	-0.17 placebo -0.06 bezafibrate
		On-Treatment	229	159	173	37	p<0.05
LOCAT[155] Gemfibrozil 1200 mg 2–3 yr	395 men with Low HDL, all s/p CABG	Baseline	199	146	139	31	-0.04 placebo -0.01 gemfibrozil
		On-Treatment	186	92	130	38	p=0.009
DAIS[156] Fenofibrate	305 men 113 women with Type 2 Diabetes	Baseline	216	214	133	40	-0.06 placebo -0.01 fenofibrate
		On-Treatment	~194	~154	~125	~43	p<0.029

* Lower numbers signify less progression of lesions.

Table II.3–6. Treatment of Atherogenic Dyslipidemia with Drugs in Combination with LDL-Lowering Sequestrants or Statins

Trial/Drug/ Duration of Intervention	N	Baseline and Rx Lipid and Lipoprotein Values in Drug Group					Mean change, minimum lesion diameter (mm)*
		Group	Total Chol	TG	LDL	HDL	
CLAS[157] Niacin 3–12g + Colestipol 30g 2 yrs	162 male non-smokers s/p CABG	Baseline	246	151	171	45	-0.06 placebo +0.02 N+C
		On-Treatment	180	110	97	61	p<0.01
FATS[158] Niacin 4–6g + Colestipol 30g 2 yrs	146 men with CAD and high Apo B levels	Baseline	270	194	190	39	-0.05 usual care +0.04 N+C
		On-Treatment	209	137	129	55	p=0.005
HATS[159] Niacin 2–4g + Simvastatin 10–20 mg	160 (24 women, 136 men) with CAD, low HDL, normal LDL	Baseline	201	213	125	31	-0.14 -0.01
		On-Treatment	139	126	75	40	p<0.001

* Positive numbers indicate net regression, compared to negative numbers which denote progression of lesions.
N = niacin; C = colestipol.

contributions of changes in individual lipoprotein species, the conclusions are always dubious. Tables II.3–3 and II.3–4 summarize the results of clinical trials in which drugs that modify atherogenic dyslipidemia—fibrates and nicotinic acid—were used. Table II.3–3 shows results of primary prevention trials, whereas Table II.3–4 summarizes secondary prevention trials. The trials taken as a whole show a strong trend towards reduction in CHD risk through therapeutic modification of atherogenic dyslipidemia.

In addition to the endpoint trials shown in Tables II.3–3 and II.3–4, three trials of fibrate therapy have been carried out in which the endpoints are coronary

atherosclerosis as assessed by angiography. The results of these trials are summarized in Table II.3–5. They show that fibrate therapy on average causes a reduction in minimum lesion diameter of coronary arteries, without appreciably reducing LDL cholesterol.

Finally, two trials of combined drug therapy have assessed changes in coronary lumen diameter; in these trials, one drug was an LDL-lowering drug and another targeted atherogenic dyslipidemia (Table II.3–6). In both, drug therapy produced favorable changes in coronary lesions.

Taken together, these various clinical trials support a beneficial effect of drugs that favorably modify atherogenic dyslipidemia on coronary lesions and major coronary events.

Evidence statements: Atherogenic dyslipidemia commonly occurs in persons with premature CHD (C1). Moreover, atherogenic dyslipidemia strongly associates with abdominal obesity, obesity, and physical inactivity (C1). Weight reduction and increased physical activity will mitigate atherogenic dyslipidemia (A1).

Recommendation: For management of atherogenic dyslipidemia, emphasis in management should be given to life-habit modification—weight control and increased physical activity.

Evidence statement: Drugs that modify atherogenic dyslipidemia yield a moderate reduction in CHD risk (A2, B2).

Recommendation: Consideration should be given to treatment of atherogenic dyslipidemia with specific drug therapy, i.e., fibrates or nicotinic acid, in higher risk persons.

4. Nonlipid risk factors

A number of nonlipid risk factors are associated with increased CHD risk and must be considered in preventive efforts. Some of these factors are modifiable and are appropriate targets for intervention efforts in themselves (Table II.4–1). Several fixed risk factors cannot be modified; their presence signals the need for more intensive lowering of LDL cholesterol. ATP I/II and other guidelines have advocated adjusting the intensity of LDL-cholesterol therapy in the primary prevention setting according to the absolute risk for CHD. In addition, emerging risk factors promise to provide new insights into the atherosclerotic process and potentially refine risk assessment. Certainly not all of coronary risk can be explained by the major independent risk factors. Other risk factors, some of which are yet to be identified, undoubtedly influence risk independently of the major risk factors. Some of these other factors contributing to CHD risk include the life-habit risk factors (obesity, physical inactivity, and atherogenic diet), emerging risk factors, male sex, and genetic/racial/ethnic characteristics. This section will review the established nonlipid risk factors including the life-habit risk factors. The emerging risk factors are reviewed in Section II.5. The influence of racial/ethnic characteristics on risk are discussed in more detail in Section VIII.

Table II.4–1. Nonlipid Risk Factors for CHD

Modifiable Risk Factors	Nonmodifiable Risk Factors
Hypertension*	Age*
Cigarette Smoking*	Male Sex*
Thrombogenic/ Hemostatic State†	Family History of Premature CHD*
Diabetes‡	
Obesity	
Physical Inactivity	
Atherogenic Diet	

* Risk factors that are included in the ATP III CHD risk assessment algorithm.
† This risk factor is inferred from observations that antiplatelet drugs and anticoagulants have been shown to reduce risk for CHD.
‡ Modification of blood pressure and lipids in people with diabetes has been shown to reduce CHD risk. Clinical trials of improved glucose control show a trend to CHD risk reduction, but not a statistically significant reduction.

A first aim for people with modifiable nonlipid risk factors is to alter them to reduce CHD risk. Risk reduction therapies consist of smoking cessation, control of hypertension, weight reduction, increased physical activity, and improved nutrition. Control of diabetic hyperglycemia will prevent microvascular complications, although clinical trials have not unequivocally

demonstrated that improved glucose control lowers CHD events. Modification of blood pressure and lipids in people with diabetes, however, does reduce CHD risk (see discussion below). In addition, the recommendations for cholesterol management operationally take selected factors into account by setting lower thresholds for initiating treatment and lower goal levels for LDL cholesterol for those at higher risk (Table II.4–2). A low HDL cholesterol (<40 mg/dL) also counts as a major risk factor for setting lower LDL goals, whereas a higher HDL cholesterol (≥60 mg/dL) takes away one other risk factor. Evidence relating the nonlipid risk factors to CHD is summarized below (Sections II.4.a and II.4.b).

Table II.4–2.

Primary Prevention: Risk Status Based on Presence of CHD Risk Factors Other Than LDL Cholesterol

Positive Risk Factors

- Age

  Male: ≥45 years

  Female: ≥55 years
- Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative)
- Current cigarette smoking
- Hypertension (≥140/90 mmHg,* or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL*)

Negative (protective) Risk Factor†

- High HDL cholesterol (≥60 mg/dL)

High risk, defined as a net of two or more CHD risk factors, leads to more vigorous intervention in primary prevention. Age (defined differently for men and for women) is treated as a risk factor because rates of CHD are higher in the older than in the young, and in men than in women of the same age. Obesity is not listed as a risk factor because it operates through other risk factors that are included (hypertension, hyperlipidemia, and decreased HDL cholesterol, as well as diabetes mellitus, which is treated as a CHD equivalent—see section II.12.b), but it should be considered a target for intervention. Physical inactivity is not listed as a risk factor to modify treatment goals for LDL cholesterol, but it too should be considered a target for intervention, and physical activity is recommended as desirable for everyone. High risk due to CHD or its equivalents is addressed directly in the algorithm.

* Confirmed by measurements on several occasions.

† If the HDL-cholesterol level is ≥60 mg/dL, subtract one risk factor (because high HDL-cholesterol levels decrease CHD risk).

a. Modifiable risk factors

1) Hypertension

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[160,161] defines categorical hypertension as a blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic or current use of antihypertensive medication. Numerous observational studies have demonstrated unequivocally a powerful association of high blood pressure with risk for CHD.[162-167] This association holds for men and women and younger and older persons. Even below categorical hypertension, subjects with high-normal blood pressure (130–139 mmHg systolic and/or 85–89 mmHg diastolic) are at increased risk for CHD compared with those with optimal values.[168,169] Clinical trials have established that blood pressure reduction in people with hypertension reduces risk for a variety of blood pressure-related endpoints including CHD.[170] This is true even for older people with isolated systolic hypertension.[165,171] Following the approach taken in ATP II,[1,2] JNC VI[160,161] employed the level of blood pressure and the concomitant presence of risk factors, coexisting cardiovascular disease (CVD), or evidence of target-organ damage to classify blood pressure severity and to guide treatment. Hypertension and high serum cholesterol often occur concomitantly.[172-174] Approaches to their joint management are considered in more detail under Section VII.6.

Evidence statements: Hypertension is a major, independent risk factor for CHD (A2, B1, C1). Treatment of hypertension does not remove all of the CHD risk accompanying elevated blood pressure (A2, B1).

Recommendation: Elevated blood pressure is a risk factor that should modify goals of LDL-lowering therapy in primary prevention (Table II.4–2). Treated hypertension should also count as a risk factor for setting goals of LDL cholesterol in primary prevention. Hypertension should be treated in all affected people according to JNC guidelines.

2) Cigarette smoking

Cigarette smoking has been established as a powerful contributor to risk for CHD and other forms of CVD.[175-186] The relationship of smoking to CVD risk is dose dependent and observed in men and women. Observational data suggest that smoking cessation reduces the risk for CVD events and that the decline in risk begins within months after quitting.[186] Randomized clinical trials of smoking cessation in primary prevention settings have revealed substantial reductions in risk for cardiac events in those who quit.[187-189] Cigarette smoking features prominently in the risk assessment component of ATP III because of the CVD risks associated with it and the substantial benefits to be derived from smoking cessation. Moreover, smokers benefit as much, if not more, from LDL-lowering therapy as do nonsmokers (Table II.2–3).

Evidence statements: Cigarette smoking is a strong, independent risk factor for CHD (C1). Smoking cessation is accompanied by a reduction in CHD risk (C1).

Recommendation: Prevention of smoking and smoking cessation should receive prime emphasis in the clinical strategy to reduce CHD risk.

3) Diabetes

Diabetes is defined as a fasting blood glucose of 126 mg/dL or greater.[190] Risk for all forms of CVD, including CHD is increased substantially with type 1 and type 2 diabetes mellitus.[191-195] Furthermore, the mortality rate in diabetic subjects who have experienced CHD is much higher than in non-diabetic subjects.[107,196,197] The increase in risk attributed to hyperglycemia per se is independent of the overweight/obesity and dyslipidemia commonly observed in persons with diabetes. Tighter glycemic control reduces risk for microvascular complications of diabetes such as renal impairment and retinopathy.[198-200] Thus far, however, improved glucose control in diabetic people has not been definitively shown to reduce macrovascular disease (CHD), although a trend toward benefit has been observed.[198-200] Importantly, management of other risk factors effectively reduces the incidence of major coronary events in persons with diabetes. This has been shown for tight blood pressure control.[201,202] Analyses of diabetic subgroups within large placebo-controlled trials of cholesterol- and triglyceride-lowering therapy have indicated that the benefits of treatment are comparable among diabetics and non-diabetics[48,203-209] (see also Table II.2–3).

A growing body of literature reveals that higher-risk people with diabetes carry an absolute risk for major coronary events similar to that of non-diabetic people with established CHD.[210-213] Although some populations with diabetes do not reach this risk level,[214] the very high morbidity and mortality after onset of CHD makes it appropriate to place most people with diabetes in a separate category of risk (see Section II.12.b).

Evidence statements: Diabetes is a major, independent risk factor for CHD and other forms of CVD (B1). Reducing cholesterol levels in people with diabetes reduces risk for CHD (see Section II.12.b).

Recommendation: The presence of diabetes should modify treatment goals for LDL cholesterol. Because of growing evidence that many people with diabetes carry a risk for CHD similar to that of people with established CHD, diabetes should be removed from the list of other risk factors that modify LDL-cholesterol goals. Instead, diabetes should be treated as a separate category of higher risk (see Section II.12.b).

4) Overweight/obesity

An estimated 97 million adults in the United States are overweight or obese.[78,79] *Obesity* is defined as a body mass index (BMI) (weight in kg divided by the square of height in meters) of ≥30 kg/m^2 and *overweight* as 25–29.9 kg/m^2.[78,79] Although some people classified as overweight actually have a large muscle mass, most persons with BMIs of 25 to 29.9 kg/m^2 have excess body fat. Overweight and obesity not only predispose to CHD, stroke, and numerous other conditions, they also are associated with a greater all-cause mortality.[215-218] People who are overweight or obese have a high burden of other CHD risk factors including dyslipidemia (high LDL cholesterol, low HDL cholesterol, and high VLDL and triglycerides),[76,77,219-221] type 2 diabetes[222,223] and hypertension.[224-226]

Obese individuals who do not yet have these risk factors are at increased risk for developing them. The Framingham Heart Study confirms that obesity is strongly predictive of CHD. Risk for CVD is particularly raised when abdominal obesity is present; *abdominal obesity is defined* by a waist circumference greater than 102 cm (40 inches) in men or 88 cm (35 inches) in women.[78,79]

Despite the strong association between various indicators of obesity and risk for CHD, ATP III does not list obesity among the risk factors that modify the treatment goals for LDL cholesterol. Much of the risk associated with overweight and obesity appears to be mediated through the major risk factors. The independent component of risk has not been quantified. Furthermore, the prevalence of overweight and obesity in the U.S. population is so high that counting them as risk factors to modify LDL goals would enormously expand the population having multiple risk factors, causing an even greater increase in usage of LDL-lowering drugs than will result from the intensified management of persons with multiple risk factors outlined in ATP III. Instead, ATP III identifies overweight and obesity as direct targets of weight-reduction intervention; this approach will achieve more overall risk reduction than will LDL lowering without an emphasis on weight control.

Evidence statement: Obesity is a major, modifiable risk factor for CHD (C1). Nevertheless, the incremental risk imparted by obesity independently of accompanying risk factors is uncertain.

Recommendation: Obesity should be considered a direct target for clinical intervention rather than an indicator for lipid-modifying drug treatment. Because of the association of obesity with other risk factors, obesity should not be included as a factor influencing treatment goals of LDL cholesterol in primary prevention.

5) Physical inactivity

Physical inactivity is associated with increased risk for CHD. Conversely, physical activity favorably modifies several risk factors; it has been reported to lower LDL and triglyceride levels, raise HDL cholesterol, improve insulin sensitivity, and lower blood pressure.[227-230] Evidence that physical activity can reduce risk for CHD comes from multiple observational studies.[231-236] Therefore, physical inactivity is widely designated to be a major risk factor for CHD.[1,2,237,238] In ATP III, physical inactivity also is listed as a major modifiable risk factor. The mechanisms whereby physical inactivity raises risk for CHD are not fully understood and are probably multifactorial. Physical inactivity reduces caloric expenditure and probably contributes to obesity and to its associated lipid and nonlipid risk factors,[239] as well as to insulin resistance.[240] Beyond its effects on standard risk factors, physical inactivity may have adverse effects on cardiovascular fitness and function. Many of the adverse effects of a sedentary lifestyle that raise CHD risk can be inferred from the actions of increased physical activity, which include reduction in insulin resistance, lowering of blood pressure, reducing serum triglycerides, raising HDL cholesterol, and improving cardiovascular risk.[238]

Although ATP III specifies physical inactivity as a major modifiable risk factor, it does not list it as a risk factor that modifies LDL-cholesterol goals. Because of the collinearity of physical inactivity with other independent risk factors, there is some confounding between physical inactivity and the risk factors that modify LDL goals. Nonetheless, physical inactivity is designated as a major target of intervention for therapeutic lifestyle changes. Undoubtedly some of the benefit of increased physical activity is mediated through mechanisms other than the measured risk factors. In addition, after setting LDL-cholesterol goals with standard risk factors, a physician can take into account a person's levels of physical activity and fitness when adjusting the intensity of LDL-lowering therapy.

It has been suggested that a history of regular physical activity should count as a "negative risk factor," similarly to high HDL cholesterol. Although regular physical activity undoubtedly reduces baseline risk for CHD and should be encouraged, ATP III does not specifically count it as a negative risk factor for setting the goal level for LDL cholesterol.

Evidence statements: Physical inactivity is a major, modifiable risk factor for CHD (C1). However, a portion of the increased risk for CHD accompanying physical inactivity can be explained by associated major risk factors (C2). Regardless of mechanism, increased physical activity will reduce risk for CHD (B2, C1).

Recommendations: Physical inactivity should be a direct target for clinical intervention. Increased physical activity in accord with a person's overall health status should be encouraged as part of lifestyle therapies to reduce risk for CHD. Patients undergoing clinical cholesterol management should be provided with guidance for safe forms of physical activity that will reduce CHD risk beyond LDL-lowering therapy.

A history of physical inactivity should not be counted as a risk factor for setting goals for LDL cholesterol in primary prevention. However, clinical judgment can be used to decide whether to intensify LDL-lowering therapy in physically inactive persons, or to reduce intensity of therapy in physically active persons.

6) Atherogenic diet

Prospective studies in populations show that dietary patterns modify the baseline CHD risk of populations.[241,242] In high-risk populations, some of the adverse effects of diet composition undoubtedly relate to established risk factors, e.g., effects of high intakes of saturated fatty acids and cholesterol on LDL-cholesterol levels and of high salt intakes on blood pressure. Moreover, dietary patterns appear to influence baseline risk beyond the known risk factors. For example, populations that consume diets high in fruits, vegetables, whole grains, and unsaturated fatty acids appear to be at a lower baseline risk than can be explained by standard risk factors. The particular nutrients that impart this lower risk have not been adequately defined, but strong candidates include antioxidant nutrients, folic acid, other B-vitamins, omega-3 fatty acids, and other micronutrients.[242]

Evidence statements: An atherogenic diet is a major, modifiable risk factor for CHD (C1). High intakes of saturated fatty acids and cholesterol directly raise LDL-cholesterol concentrations (see Section V.5). Further, certain dietary patterns appear to modify baseline risk for CHD, independently of effects on LDL cholesterol (see Sections V.1, V.4, and V.5.c).

Recommendation: Modification of an atherogenic diet should be employed to reduce CHD risk as part of overall therapeutic lifestyle changes for CHD risk reduction (see Section V). However, consumption of an atherogenic diet should not be included among risk factors to modify LDL-cholesterol goals in primary prevention.

b. Nonmodifiable risk factors

1) Age

Risk for coronary disease increases steeply with advancing age in men and women. At any given level of LDL cholesterol, risk for CHD is higher in older than in younger people.[10] The principal reason that risk rises with age is that age is a reflection of the progressive accumulation of coronary atherosclerosis, which in turn reflects the cumulative exposure to atherogenic risk factors, both known and unknown. On average, older persons have more coronary atherosclerosis than do younger persons. Once atherosclerosis develops, the coronary plaque itself becomes a "risk factor" for development of clinical CHD. This is because plaque ruptures produce acute coronary events (unstable angina or myocardial infarction), or when plaques grow large, coronary obstructive symptoms (angina pectoris) occur. Recent clinical trials indicate that older persons benefit from LDL-lowering therapy similarly to middle-aged individuals (Table II.2–3).

Evidence statement: Advancing age is a major, independent risk factor for CHD (C1).

Recommendation: Age should count as a risk factor to modify LDL-cholesterol goals in primary prevention.

2) Male sex

The rise in absolute risk with aging becomes most clinically significant in men in their mid-forties and in women about the time of the menopause. At any given age men are at greater risk for coronary disease than are women.[10] Risk in women lags about 10 to 15 years behind that of men. The reasons for a gender difference in CHD risk are not fully understood. Part of the difference can be explained by the earlier onset of risk factors in men, e.g., elevations of LDL cholesterol and blood pressure, and lower HDL cholesterol. However, the Framingham Heart Study has shown that the differences in absolute risk between the sexes cannot be explained entirely by standard risk factors. Nonetheless, women respond to LDL-lowering therapy with a reduction in relative risk similarly to men (Table II.2–3).

Evidence statement: Men have a higher baseline risk for CHD than do women at all ages, except perhaps in the oldest age group (>80 years) (C1).

Recommendation: An age cutpoint at which age becomes a risk factor to modify goals for LDL cholesterol should be set lower in men (≥45 years) than in women (≥55 years) in primary prevention (Table II.4–2).

3) Family history of premature CHD

CHD tends to cluster in families, and a positive family history of premature CHD counts as a risk factor. Several prospective studies[243-255] indicate that a family history of premature CHD is an *independent* risk factor even when other risk factors are taken into account. Relative risk for CHD in first-degree relatives has been reported to range from two to as high as 12 times that of the general population.[256-258] Risk increases with the number of primary relatives affected and at younger ages of onset in the probands.[259,260] The clustering of CHD risk in families most closely resembles diseases of polygenic origin and does not follow a Mendelian recessive or dominant pattern that suggests a single gene locus.[261] Among primary relatives, it appears that siblings of probands have the highest relative risk, probably due to shared sociocultural environment, exposures, and genetics. Many prospective cohort and case-control investigations, including the recent Atherosclerosis Risk In Communities Study (ARIC) in four U.S. communities, show this risk to be independent of known risk factors.[253,262] Many risk factors are under genetic control (e.g., blood pressure, lipids and lipoproteins, Lp(a), and obesity), but they account for only a portion of the aggregation of CHD seen in families.[263,264] While family history is immutable, a large number of modifiable risk factors are found in people with a history of premature CHD in a first-degree relative.[265,266] This has been demonstrated in both genders and in most races. The Framingham Heart Study family history analysis does not demonstrate sufficient incremental risk for family history to be included in risk assessment equations. Nonetheless, a body of compelling case-control and cohort studies has found family history to be independently associated with higher risk status. The variance across studies depends on the way in which family history is assessed. In the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study and in the Newcastle Family History Study, self-report of a family history of premature CHD in a first degree relative has been found to be reasonably accurate with sensitivity above 80 percent and specificity about 90 percent.[253,267,268]

Evidence statements: A positive family history for CHD in a first-degree relative (parent, sibling, or offspring) is a major risk factor for CHD. Often a positive family history is associated with a high prevalence of modifiable risk factors (C1); however, a positive family history carries excess risk beyond standard measurements of risk factors (C1). Risk for CHD is higher the younger the age of onset in the affected family member and the greater the number of affected first degree relatives (C1).

Recommendation: The presence and age of onset of CHD in all first-degree relatives should be assessed. The family history should be considered positive for premature CHD if clinical CHD or sudden death can be documented in first degree male relatives younger than 55 years of age and in first degree female relatives younger than 65 years of age. Because a positive family history of premature CHD is immutable but bears information about the risk for CHD and the probability of having modifiable risk factors, it should serve as a factor in making treatment decisions relative to setting and reaching LDL-cholesterol goals in primary prevention (Table II.4–2).

5. Emerging risk factors

The major risk factors listed in Table II.4–2, along with elevated LDL cholesterol, are powerfully associated with the development of CHD. Although several of them are directly atherogenic, their power to predict CHD is still limited. Most of the *excess* risk for CHD can be explained by the major risk factors; this is shown by the very low risk in persons who have optimal levels of all of these risk factors (see Primary Prevention [Section II.7]). Nonetheless, when major risk factors are present, they account for only about half of the *variability* in CHD risk in the U.S. population; other factors, yet to be identified, seemingly influence how much the major risk factors affect absolute CHD risk. Consequently there has been intensive research to identify new risk factors that will enhance predictive power in individuals. These newer factors can be called *emerging risk factors.* For present purposes, these can be conveniently divided into three categories: lipid risk factors, nonlipid risk factors, and subclinical atherosclerotic disease (see below).

To determine the clinical significance of the emerging risk factors, they must be evaluated against the following criteria used to identify the major risk factors:

- Significant predictive power that is independent of the other major risk factors
- A relatively high prevalence in the population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population-reference values, and be relatively stable biologically
- Preferably, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk

In the discussion to follow, the *emerging risk factors* are evaluated against these criteria. Even when a factor does not qualify as a major risk factor for routine measurement, its association with CHD risk deserves some consideration. A review of the key literature is required to determine whether the putative risk factor deserves to be elevated to the level of a major risk factor, and if not, whether it can still be used in selected persons as an adjunct to risk assessment. Even if neither is the case, the risk factor often remains a direct target of therapy, unrelated to modifying LDL-cholesterol goals. If the emerging risk factor is a lipid parameter, its treatment will be considered in more detail elsewhere in this report. If it is a nonlipid risk factor, the reader will be referred to other sources for information on therapy.

A foundation of ATP III is that the major risk factors define absolute risk and thereby modify LDL-cholesterol goals. An initial assessment of risk is made on the basis of these risk factors before any consideration is given to whether emerging risk factors should influence goals or therapies. The same reasoning holds for underlying risk factors: obesity, physical inactivity, and atherogenic diet. On the other hand, ATP III does not discount the influence of underlying or emerging risk factors. *They can be taken into consideration according to clinical judgment as optional modifiers of therapy, but they should be used only as an adjunct to adjust the estimate of absolute risk status obtained with the major risk factors.*

a. Emerging lipid risk factors

1) Triglycerides

Elevated serum triglycerides have long been considered a risk factor by some investigators. The status of triglycerides as a risk predictor is reviewed in other sections of this report (Sections II.3.a and VII.2). Two questions about triglycerides persist: (a) whether they constitute an independent risk factor for CHD and (b) whether they should be a direct target for therapy. Although recent data point to some independence in risk prediction, their close association with other lipid risk factors (remnant lipoproteins, small LDL, low HDL cholesterol) and nonlipid risk factors makes the issue of their "independence" open to considerable question. In this report, elevated triglycerides are viewed as a marker for other lipid and nonlipid risk factors that themselves raise risk; however, elevated triglycerides per se are not designated a major risk factor to modify goals for LDL cholesterol. Nonetheless, ATP III gives increased weight to elevated triglycerides in cholesterol management in two ways: (a) as a marker for atherogenic remnant lipoproteins and (b) as a marker for other lipid and nonlipid risk factors in the metabolic syndrome (see Section II.6). The former leads to non-HDL cholesterol as a secondary target of therapy when triglycerides are high, whereas the latter calls for more intensive lifestyle therapies (see Section V).

2) Lipoprotein remnants

Many lines of evidence point to the atherogenic potential of lipoprotein remnants (see Section II.3.a.2). Although no single finding confirms remnant lipoproteins as an independent risk factor, circumstantial evidence is strong. Lipoproteins called beta-VLDL, which are apolipoprotein E-enriched remnants and are typical of dysbetalipoproteinemia, almost certainly are atherogenic, because dysbetalipoproteinemia is accompanied by increased risk for CHD (see Section VII). High serum levels of lipoproteins enriched in apolipoprotein C-III, another form of VLDL remnants, appear to be atherogenic as well.[64,65,68,69,269] Several assays are available for identification and measurement of remnant lipoproteins; these include ultracentrifugation, electrophoresis, and immunological techniques. Remnant-like particles (RLP) measured immunologically appear to be a promising risk predictor.[270-273] Even so, prospective studies relating various remnant measures to CHD risk are limited, and measurement with specific assays cannot be recommended for routine practice. Nonetheless, as discussed earlier (see Section II.3.a), ATP III identifies elevated VLDL cholesterol as the surrogate for elevated atherogenic remnants in persons with triglycerides ≥200 mg/dL.

3) Lipoprotein (a)

Several studies[274-277] report a strong association between Lp(a) levels and CHD risk. Indeed, a recent meta-analysis of reported prospective studies supports an independent predictive power for elevated Lp(a).[278] In addition, concomitant elevations of Lp(a) and LDL cholesterol have been reported to have synergy in elevating risk in both men and women with hypercholesterolemia. On the basis of these studies, some authorities hold that an elevation of Lp(a) is an independent risk factor for CHD. It must be noted nonetheless that several prospective studies[279,280] do not confirm independent prediction. Of note, Lp(a) levels are higher in African Americans than in Caucasians, but an increased risk for CHD associated with higher Lp(a) levels in African Americans has not been documented.[279] Thus, the quantitative contribution of elevated Lp(a) to CHD risk beyond the major risk factors is uncertain. This uncertainty extends both to individuals and populations; in the latter, the frequency of elevated Lp(a) is not as high as for the major risk factors.

Moreover, issues related to measurement of Lp(a) in clinical practice have not been fully resolved.[281,282] Measurement of Lp(a) is made by immunological methods, and standardized methods are available only in a few reference laboratories. Population reference levels are available from these laboratories, but they are not widely available in clinical practice. Accurate methodology has not yet been established in most clinical chemistry laboratories; samples generally must be sent to special laboratories for measurement. As a result, extra expense in measurement is required. Serum Lp(a) is relatively resistant to therapeutic lowering. Statin drugs are ineffective. Among currently available drugs, only nicotinic acid reduces Lp(a) concentrations, and only moderately.[283,284] In postmenopausal women, estrogen therapy also causes some reduction in Lp(a) concentrations.[285] Although these therapies typically lower elevated Lp(a) levels, they have not been widely adopted. At present no clinical trial evidence supports a benefit from lowering Lp(a) levels with particular agents.

Despite limitations in measurement and therapy, some authorities believe that Lp(a) measurement is a useful addition to the major risk factors for identifying persons at still higher risk than revealed by those factors. According to advocates for Lp(a), the option of measurement is best reserved for persons with a strong family history of premature CHD or those with genetic causes of hypercholesterolemia, such as familial hypercholesterolemia.[281,282] An elevated Lp(a) thus presents the option to raise a person's risk to a higher level. For example, if a person has a high LDL cholesterol and only one other risk factor, the finding of a high Lp(a) could count as a second risk factor to justify a lower goal for LDL cholesterol. ATP III did not find strong evidence to support this approach, but accepts it as an option for selected persons.

4) Small LDL particles

One component of atherogenic dyslipidemia is small LDL particles. They are formed in large part, although not exclusively, as a response to elevations of triglycerides. Their presence is associated with an increased risk for CHD;[125,286,287] however, the extent to which they predict CHD independently of other risk factors is unresolved.[288] Moreover, standard and inexpensive methodologies are not available for their measurement. For these reasons, ATP III does not recommend

measurement of small LDL particles in routine practice. If the clinical decision is made to detect and measure small LDL, their presence is best used as an indicator for atherogenic dyslipidemia and the metabolic syndrome. Their elevation also supports intensified therapeutic lifestyle changes. If small LDL particles accompany elevated triglycerides or low HDL cholesterol in high-risk persons, consideration can be given to using nicotinic acid or fibric acid as components of lipid-lowering therapy. Nonetheless, LDL cholesterol remains the primary target of treatment in persons with small LDL particles.

5) HDL subspecies

HDL comprises several components and subfractions that also have been related to CHD risk. While HDL cholesterol is the risk indicator most often used, HDL subfractions (LpAI and LpAI/AII and/or HDL_3 and HDL_2) have also been used for risk prediction. Although small studies suggest greater predictive power of one or another HDL component, their superiority over HDL cholesterol has not been demonstrated in large, prospective studies. Moreover, measures of HDL subspecies are not readily available in clinical practice. Consequently, ATP III does not recommend the routine measurement of HDL subspecies in CHD risk assessment.

6) Apolipoproteins

a) Apolipoprotein B

Apolipoprotein B is a potential marker for all atherogenic lipoproteins. It has been proposed as an alternative to LDL cholesterol as a risk factor (see Section II.3.b). Limited epidemiological and clinical trial evidence supports its superiority over LDL cholesterol in risk prediction.[289,290] Nonetheless, the body of evidence in favor of apolipoprotein B has not been developed sufficiently to justify replacing LDL cholesterol, which itself is a powerful independent predictor of CHD (see Section II.2). In addition, from the viewpoint of ATP III, the question is whether apolipoprotein B is preferred as a target of therapy, not as a factor in risk assessment. Although LDL cholesterol and apolipoprotein B are highly correlated in persons with normal triglyceride levels, the apolipoprotein B level typically is disproportionately higher in persons with hypertriglyceridemia. ATP III takes this difference into account and sets a secondary target, non-HDL cholesterol, in persons with hypertriglyceridemia. Non-HDL cholesterol is significantly correlated with apolipoprotein B and can serve as a "surrogate" for it. The non-HDL-cholesterol measure is readily available in clinical practice, whereas standardized apolipoprotein B measures are not widely available, and in any case, would add expense beyond routine lipoprotein analysis.

b) Apolipoprotein A-I

Apolipoprotein A-I is carried in HDL, and it is usually low when HDL is reduced. A low apolipoprotein A-I thus is associated with increased risk for CHD, but not independently of low HDL. Whether it has independent predictive power beyond HDL cholesterol is uncertain. In any case, standardized methodology for estimating apolipoprotein A-I is not widely available. Its measurement thus is not recommended for routine risk assessment in ATP III.

7) Total cholesterol/HDL-cholesterol ratio

Many studies show that the total cholesterol/HDL-cholesterol ratio is a powerful predictor of CHD risk. Some investigators[291-294] propose that this "cholesterol ratio" is a simple approach for lipid risk assessment. This ratio reflects two powerful components of risk. A high total cholesterol is a marker for atherogenic lipoproteins, whereas a low HDL cholesterol correlates with the multiple risk factors of the metabolic syndrome and probably imparts some independent risk. In fact, however, the total cholesterol/HDL-cholesterol ratio is subsumed in the Framingham global risk equations that are the basis of the 10-year risk assessment used in ATP III. In this way, ATP III incorporates cholesterol ratios into risk assessment. If risk assessment is done using Framingham risk factors as continuous variables (e.g., by risk equations), then the ratio is essentially incorporated. If risk assessment is made using total cholesterol and HDL cholesterol in graded, incremental steps (see Section III), then the ratio is applied approximately. Regardless, ATP III does not define the total cholesterol/HDL-cholesterol ratio as a specified lipid target of therapy. Instead, LDL cholesterol is retained as the primary target of lipid-lowering therapy. Nor is the total cholesterol/HDL-cholesterol ratio recommended as a secondary target of therapy. Treatment of ratios will divert priority from specific lipoprotein fractions as targets of therapy.

b. Emerging nonlipid risk factors

1) Homocysteine

Elevations of serum homocysteine are positively correlated with risk for CHD.[295-303] The mechanism of the link between homocysteine and CHD is not well understood, although persons with inherited forms of severe homocysteinemia have premature vascular injury and atherosclerosis. In any case, the strength of association between homocysteine and CHD is not as great as that for the major risk factors. Moreover, an elevation of homocysteine is not as common as that of the major risk factors. For these reasons, ATP III does not list elevated homocysteine as a major risk factor to modify LDL-cholesterol goals.

Even though elevated homocyteine is not classified as a major risk factor, some investigators hold that the association with CHD is strong enough to make it a direct target of therapy. The available intervention for elevated homocysteine is dietary folic acid, perhaps combined with other B vitamins (B_6 and B_{12}).[298] Measurement of homocysteine is an option favored by some authorities, with the aim of treating with supplemental B vitamins. Others, however, contend that measurement of homocysteine adds little to risk reduction provided that persons are consuming recommended dietary allowances of folic acid. Several clinical trials are underway to test whether homocysteine lowering will reduce CHD risk.[304] It had been predicted that the recent institution of folate fortification of foods would reduce average levels of homocysteine in the U.S. population.[305,306] Recent data show that this has occurred.[307] Substantial increases in serum folate in young women have also been documented.[308]

ATP III does not recommend routine measurement of homocysteine as part of risk assessment to modify LDL-cholesterol goals for primary prevention. This lack of recommendation is based on uncertainty about the strength of the relation between homocysteine and CHD, a lack of clinical trials showing that supplemental B vitamins will reduce risk for CHD, and the relatively low prevalence of elevated homocysteine in the U.S. population. Measurement of homocysteine nonetheless remains an option in selected cases, e.g., with a strong family history of premature CHD in an otherwise low-risk patient. If elevated, the clinical approach favored by ATP III is to determine vitamin B_{12} level and, if this is normal, to ensure adequate folate intake rather than modifying the LDL-cholesterol goal.

2) Thrombogenic/hemostatic factors

Thrombosis plays a key role in acute coronary syndromes, including myocardial infarction.[309] Both platelets and coagulation factors are involved in the thrombotic process. Although the precise hemostatic or prothrombotic mechanisms that predispose to myocardial infarction have not been worked out, the evidence that aspirin and other antiplatelet therapy can reduce risk is compelling and suggests a role for platelet hyperaggregability.[310-312] Another hemostatic factor associated with CHD risk is fibrinogen.[313-316] A high fibrinogen level associates significantly with increased risk for coronary events, independent of cholesterol level; and conversely, a low fibrinogen level indicates a reduced risk, even in the presence of high total cholesterol levels. Other hemostatic factors that have been found to be associated with increased coronary risk include activated factor VII, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA), von Willebrand factor, factor V Leiden, protein C, and antithrombin III. Studies have shown that some of these prothrombotic factors are elevated as a component of the metabolic syndrome.

ATP III does not recommend measurement of prothrombotic factors as part of routine assessment of CHD risk. The strength of the association between any of these factors and CHD risk has not been defined. Specific therapeutic interventions, other than aspirin or warfarin therapy, are not available in clinical practice. Clinical trials have not been carried out that target specific prothrombotic factors. Laboratory measurements for prothrombotic factors are not widely available, nor have they been standardized. This said, it is worth noting that the metabolic syndrome is often accompanied by a prothrombotic state, and life-habit intervention to reverse the metabolic syndrome reduces serum levels of prothrombotic factors.

3) Inflammatory markers

The increasing recognition that atherosclerosis involves a chronic inflammatory process has brought greater attention to arterial "inflammation" as a risk factor for major coronary events. In fact, recent reports indicate that serum inflammatory markers, such as C-reactive protein (CRP), carry predictive power for coronary events.[317-322] High sensitivity (hs) CRP appears to be the most reliable inflammatory marker available at present. Cigarette smoking, which apparently promotes arterial inflammation and predisposes to major coronary events, is associated with higher levels of CRP.[323] Because of the growing evidence that inflammation within coronary plaques predisposes to plaque rupture, one theory holds that an elevation of hs-CRP reflects the presence of "unstable" plaques. The recent observations that obesity and the metabolic syndrome are commonly accompanied by increases in CRP also suggest a close link between metabolic derangement and inflammation.[324-326] Although adverse metabolism could activate immune mechanisms and predispose to major coronary events, some investigations suggest that chronic, low-grade infections of the arterial wall accelerate atherogenesis and lead to CHD. Infectious agents that have been implicated are Chlamydia pneumoniae and cytomegalovirus.

ATP III does not recommend routine measurement of inflammatory markers for the purpose of modifying LDL-cholesterol goals in primary prevention. A growing body of literature nonetheless suggests that inflammatory markers such as hs-CRP carry some independent predictive power beyond lipid risk factors.[321] The extent to which they provide extra prediction beyond all the major risk factors combined is uncertain. Nonetheless, in the opinion of some investigators,[321] in persons with elevated hs-CRP, consideration can be given to more aggressively lowering LDL-cholesterol levels than indicated by the goals set by the major risk factors in ATP III.

4) Impaired fasting glucose

A common metabolic abnormality in the metabolic syndrome is an impaired fasting glucose (glucose 110–125 mg/dL). According to the Framingham Heart Study, the association between elevated plasma glucose and CHD risk is a continuous variable; some investigators thus view impaired fasting glucose to be an independent risk factor.[327,328] However, to other researchers, the strong association between impaired fasting glucose and other risk factors of the metabolic syndrome casts doubt on the independent predictive power of impaired fasting glucose.[329-332] Moreover, at present, impaired fasting glucose cannot be considered a direct target for drug therapy, although weight reduction and increased physical activity will often correct it. Thus, ATP III identifies impaired fasting glucose as one component of the metabolic syndrome that signifies the need for more intensive lifestyle therapies, i.e., weight reduction and increased physical activity. However, its presence does not place a person in the same high-risk category as does overt diabetes; neither does it count as a risk factor to modify the LDL-cholesterol goal.

c. Subclinical atherosclerotic disease

A large body of data indicates that persons with advanced subclinical coronary atherosclerosis are at greater risk for major coronary events than are persons with less severe atherosclerosis. Although the precise relationship between subclinical atherosclerotic disease and CHD risk has not been defined, subclinical disease must be classified as an emerging risk factor. The American Heart Association recently held a conference (Prevention Conference V) to assess the current status of subclinical atherosclerosis as a predictor of major coronary events.[333-336] The major findings of this report represent current understanding of the predictive power of subclinical disease. The conclusions of the Prevention Conference V report are represented in the position of ATP III on subclinical atherosclerotic disease.

1) Ankle-brachial blood pressure index (ABI)

The ABI is a simple, inexpensive, noninvasive test to confirm the clinical suspicion of lower extremity peripheral arterial disease (PAD). It is performed by measuring the systolic blood pressure (by Doppler probe) in brachial, posterior tibial, and dorsalis pedis arteries. An ABI of <0.9, found in either leg, is diagnostic of PAD, and prospective studies indicate that risk for major coronary events is in the range of that of persons with established CHD.[337,338] The test is most likely to be positive in persons over age 50 who have other risk factors. A strong case can be made that a positive ABI essentially constitutes a *diagnosis* of PAD. Consequently the ABI can be considered a diagnostic test to identify persons at high risk for CHD (see Section II.12.a).

2) Tests for myocardial ischemia

Tests available in this category include standardized exercise electrocardiogram (ECG) testing, myocardial perfusion imaging, and stress echocardiography. Exercise ECG testing has been extensively studied. A positive exercise ECG in asymptomatic, middle-aged men with traditional risk factors carries independent predictive power for major coronary events; thus, exercise testing carries the potential to identify middle-aged men who are at higher risk than revealed by the major risk factors. Consequently a positive test could call for more aggressive risk-reduction therapies. The same predictive power apparently does not hold for young adults and middle-aged or older women; a "positive" test is much less predictive of major coronary events. In these groups, the likelihood of inappropriate application of aggressive preventive measures is increased. Myocardial perfusion imaging and stress echocardiography have been less extensively evaluated for their predictive power, although they appear to contain independent prognostic information. Certainly a positive perfusion imaging result obtained in middle-aged men with multiple risk factors and men ≥45 years with a strong family history of CHD is strongly indicative of obstructive coronary atherosclerosis and carries a high risk for acute coronary syndromes. The decision to employ perfusion imaging in appropriately selected persons depends on clinical judgment. The expense of the test and its low yield of positive outcomes makes it unsuitable for routine risk assessment in asymptomatic persons, but does not exclude its clinical utility in selected persons. In ATP III, the presence of myocardial ischemia appropriately identified by stress testing qualifies as a diagnosis of CHD.

3) Tests for atherosclerotic plaque burden

a) Carotid intimal medial thickening

One test in this category is *carotid sonography* used to measure intimal medial thickness (IMT) of the carotid arteries.[336] The extent of carotid atherosclerosis correlates positively with the severity of coronary atherosclerosis. Furthermore, recent studies show that severity of IMT independently correlates with risk for major coronary events.[336,339-341] Thus, measurement of carotid IMT theoretically could be used as an adjunct in CHD risk assessment. For instance, the finding of an elevated carotid IMT (e.g., ≥75th percentile for age and sex) could elevate a person with multiple risk factors to a higher risk category. However, its expense, lack of availability, and difficulties with standardization preclude a current recommendation for its use in routine risk assessment for the purpose of modifying intensity of LDL-lowering therapy. Even so, if carried out under proper conditions, carotid IMT could be used to identify persons at higher risk than that revealed by the major risk factors alone.

b) Coronary calcium

Another indication of subclinical coronary atherosclerosis is coronary calcium as detected by *electron beam computed tomography (EBCT)* or *spiral CT*. Amounts of coronary calcium correlate positively with coronary plaque burden. Therefore, a high coronary calcium score should carry predictive power for major coronary events.[333,336] Several studies indicate that, in persons with multiple risk factors, a concomitantly high coronary calcium score places persons in the range of a CHD risk equivalent.[342-346] A recent report by the American College of Cardiology/American Heart Association (ACC/AHA) acknowledged the potential power of coronary calcium to predict major coronary events.[347,348] At the same time, this report emphasized the limitations of the technique as a tool to diagnose obstructive coronary disease for the purpose of coronary revascularization. Despite these limitations, both the Prevention V report and the ACC/AHA report affirmed that use of EBCT for risk prediction can be an option, provided its use is limited to patients referred by physicians. Under these circumstances, when used appropriately, measurement of coronary calcium could be of value for persons whose absolute risk is greater than that revealed by the major risk factors. Thus, a high coronary calcium score in a patient with multiple risk factors is consistent with a still higher risk state.

In accord with recent reports,[334,347,348] ATP III does not recommend EBCT for indiscriminate screening for coronary calcium in asymptomatic persons, particularly in persons without multiple risk factors. Its predictive power for persons without multiple risk factors has not been determined in prospective studies. Testing is relatively expensive and not widely available. It should be used primarily as an adjunct to modify risk assessment based on the major risk factors. Only in exceptional cases should it evoke further invasive diagnostic tests and interventions. Despite uncertainties as to the predictive power of coronary calcium, ATP III supports the conclusions of AHA's Prevention Conference V

and the ACC/AHA report that high coronary calcium scores signify and confirm increased risk for CHD when persons have multiple risk factors. Therefore, measurement of coronary calcium is an option for advanced risk assessment in appropriately selected persons, provided the test is ordered by a physician who is familiar with the strengths and weaknesses of noninvasive testing. In persons with multiple risk factors, high coronary calcium scores (e.g., ≥75th percentile for age and sex) denotes advanced coronary atherosclerosis and provides a rationale for intensified LDL-lowering therapy. Moreover, measurement of coronary calcium is promising for older persons in whom the traditional risk factors lose some of their predictive power.[349] For example, a high coronary calcium score could be used to tip the balance in favor of a decision to introduce LDL-lowering drugs for primary prevention in older persons.

6. Metabolic syndrome

a. Metabolic syndrome as multiple, interrelated factors that raise risk

This syndrome has become increasingly common in the United States. It is characterized by a constellation of metabolic risk factors in one individual.[350-352] The root causes of the metabolic syndrome are overweight/obesity, physical inactivity, and genetic factors. The metabolic syndrome is closely associated with a generalized metabolic disorder called *insulin resistance,* in which tissue responsiveness to the normal action of insulin is impaired.[353-355] Some individuals are genetically predisposed to insulin resistance; in these persons, acquired factors (excess body fat and physical inactivity) elicit insulin resistance and the metabolic syndrome. Most persons with insulin resistance have abdominal obesity.[356-358] The mechanistic connections between insulin resistance and metabolic risk factors are not fully understood and appear to be complex. Various risk factors have been included in the metabolic syndrome; the following list contains those factors that are generally accepted as being characteristic of this syndrome:

- Abdominal obesity
- Atherogenic dyslipidemia
- Raised blood pressure
- Insulin resistance ± glucose intolerance
- Prothrombotic state
- Proinflammatory state

Because of the high degree of association of these risk factors in persons with the metabolic syndrome, it has proven difficult to dissect the individual contributions of each factor to CHD risk. However, there is little doubt that this syndrome taken in aggregate enhances the risk for CHD at any given LDL-cholesterol level. From a population viewpoint, the increasing prevalence of the metabolic syndrome threatens to partially reverse the reduction in CHD risk that has resulted from a decline in serum LDL cholesterol levels in the U.S. population, which has occurred over the past three decades. The metabolic syndrome and its associated risk factors have emerged as a coequal partner to cigarette smoking as contributors to premature CHD.[10,78,79,238,359,360] In addition, the insulin resistance accompanying the metabolic syndrome is one of the underlying causes of type 2 diabetes.[361,362] For these reasons, ATP III places increased emphasis on the metabolic syndrome as a risk enhancer.

There are two general approaches to the treatment of the metabolic syndrome. The first strategy modifies root causes, overweight/obesity and physical inactivity, and their closely associated condition, insulin resistance. Weight reduction[363-365] and increased physical activity[240,366] both lower insulin resistance and indirectly mitigate the metabolic risk factors. The second approach directly treats the metabolic risk factors—atherogenic dyslipidemia, hypertension, the prothrombotic state, and underlying insulin resistance. At present, most success in clinical practice comes from pharmacological modification of the associated risk factors. However, the greatest potential for management of the syndrome lies in reversing its root causes. ATP III promotes this latter approach, which is a major new initiative for persons entering clinical cholesterol management.

Evidence statements: The presence of the metabolic syndrome accentuates the risk accompanying elevated LDL cholesterol (C1). This increase in risk appears to be mediated through multiple risk factors—major and emerging risk factors (C1).

Clinical trials show that modifying three major components of the metabolic syndrome—atherogenic dyslipidemia (B2), hypertension (A2, B1),[160,161] and the prothrombotic state (A2, B1)—will reduce risk for CHD.

Recommendations: Increased emphasis should be placed on therapeutic modification of the metabolic syndrome in persons undergoing LDL-lowering therapy. Primary management of the metabolic syndrome should be to reverse its root causes—overweight/obesity and physical inactivity. In addition, other lipid and nonlipid risk factors associated with the metabolic syndrome should be appropriately treated.

The presence of the metabolic syndrome provides the option to intensify LDL-lowering therapy after LDL-cholesterol goals are set with the major risk factors. Primary emphasis nonetheless should be given to modifying the underlying risk factors (overweight/obesity and physical inactivity) and other risk factors associated with the metabolic syndrome.

b. Diagnosis of metabolic syndrome

There are no well-accepted criteria for the diagnosis of the metabolic syndrome. Nonetheless, many persons seen in clinical practice are readily recognized as having multiple metabolic risk factors. Most persons with the metabolic syndrome are overweight or obese; clinical studies have noted a high correlation between abdominal obesity and the risk factors characteristic of the metabolic syndrome.[356,358,367,368] For example, closely associated with abdominal obesity is an elevation of serum triglycerides.[369-371] The elevation can be either borderline high (150–199 mg/dL) or high (≥200 mg/dL). A higher triglyceride level is usually accompanied by lower HDL-cholesterol concentrations.[124,372] HDL-cholesterol levels <40 mg/dL occur commonly in men with insulin resistance.[135] Further, moderate (marginal) reductions of HDL-cholesterol levels are observed commonly in women with the syndrome;[373,374] thus for women, HDL cholesterol <50 mg/dL counts as one indicator in the diagnosis of the metabolic syndrome. A moderately strong association exists between insulin resistance and hypertension.[375-377] Insulin resistance also is associated with high-normal blood pressure.[378,379]

Impaired fasting glucose (110–125 mg/dL) usually is an indicator of insulin resistance and is frequently accompanied by other metabolic risk factors;[380,381] measurement of fasting glucose in overweight and obese persons is a reasonable option.[78,79] A portion of persons with impaired fasting glucose will eventually develop type 2 diabetes,[382,383] which further enhances risk for CHD. Type 2 diabetes is the epitome of the metabolic syndrome. Other components of the metabolic syndrome (insulin resistance, proinflammatory state, and prothrombotic state) cannot be identified by routine clinical evaluation. However, in the presence of abdominal obesity, they often are present. For present purposes, the metabolic syndrome is identified by the presence of three or more of the components listed in Table II.6-1.

Table II.6–1. Clinical Identification of the Metabolic Syndrome*

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

* The ATP III panel did not find adequate evidence to recommend routine measurement of insulin resistance (e.g., plasma insulin), proinflammatory state (e.g., high-sensitivity C-reactive protein), or prothrombotic state (e.g., fibrinogen or PAI-1) in the diagnosis of the metabolic syndrome.

† Some male persons can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94–102 cm (37–39 in). Such persons 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.

c. Metabolic syndrome as a target of therapy

In persons entering clinical management of elevated LDL cholesterol, the full benefit of risk reduction will be lost if the metabolic syndrome is ignored. To achieve maximal benefit from modification of multiple metabolic risk factors, the underlying insulin resistant state must become a target of therapy. The safest, most effective, and preferred means to reduce insulin resistance is weight reduction in overweight and obese persons and increased physical activity. Both weight control[363-365] and exercise[240,366,384,385] reduce insulin resistance and favorably modify the metabolic risk factors. ATP III thus places increased emphasis on the metabolic syndrome and on its favorable modification through changes in life habits.

Drug treatment of several of the individual risk factors of the metabolic syndrome will reduce risk for CHD. The strong trend for benefit of drug treatment of atherogenic dyslipidemia is discussed in Section II.3. Risk reductions by lowering blood pressure with antihypertensive drugs[160,161] and treating the prothrombotic state with aspirin[310] are well established. However, lowering serum glucose with drugs has not yet been documented to reduce risk for CHD. Although drugs are available to reduce insulin resistance, there is no clear evidence yet that they will reduce risk for CHD in persons with the metabolic syndrome.

7. Primary prevention: persons without established CHD

a. Scope of primary prevention

Primary prevention aims to prevent new onset CHD. If prevention is delayed until advanced coronary atherosclerosis has developed, the U.S. public will continue to suffer from a heavy burden of CHD. The essential approach to primary prevention is to reduce risk factors for CHD. Waiting until a diagnosis of CHD is made before beginning risk factor reduction will miss the opportunity to prevent CHD in people whose first presentation is sudden cardiac death or disability.[386-389] One-third of people who experience a myocardial infarction will die within 24 hours and many survivors will have serious morbidity including congestive heart failure, angina, arrhythmias, and an increased risk of sudden death.[389] One-third of all new cardiovascular events occurs in individuals under age 65.[389] These observations argue strongly for primary prevention of CHD.

Elevations of serum LDL cholesterol contribute importantly to the high prevalence of CHD in the United States. International studies find that CHD is uncommon in cultures with low levels of serum cholesterol even when the prevalence of hypertension and cigarette smoking is relatively high.[19,25,390] Migration studies reveal that persons who emigrate from low-risk to high-risk cultures show a rise in LDL-cholesterol levels and assume the risk of the new culture.[391] Mass elevations of serum LDL cholesterol result from the habitual diet in the United States, particularly diets high in saturated fats and cholesterol.[19,241,392,393] When these diets are combined with a relatively heavy burden of other CHD risk factors, a high prevalence of premature CHD results.

b. Clinical strategy in primary prevention effort

NCEP supports two complementary approaches to primary prevention: (1) population strategies and (2) clinical strategies.[1,2,5,6] NCEP encourages dietary and other behavioral interventions for all Americans to reduce the population burden of atherosclerosis. The clinician has the opportunity to bridge the gap between the public health population strategy and clinical primary prevention. The population approach is augmented when physicians reinforce the public health message (see Section V). The clinical approach is needed to identify higher risk persons in whom risk factor modification is more urgently required. It further extends to the identification of relatives of affected persons who also are at higher risk and who need clinical intervention to modify risk factors.

c. Concepts of short-term and long-term prevention

Clinical primary prevention can be categorized into long-term and short-term prevention. Long-term prevention aims to reduce risk for CHD over a lifetime; its goal is to prevent the initiation and progression of coronary atherosclerosis, the underlying cause of CHD. It is directed towards persons who are not in imminent danger of suffering a major coronary event, but instead have a high probability of developing CHD sometime during their lives. Lifetime prevention places priority on modifying adverse life habits that are the underlying causes of risk factors and coronary atherosclerosis.

In some persons, however, when risk factors are categorically abnormal drug therapy is required in addition to life-habit changes to reduce long-term risk.

Short-term prevention is designed to reduce risk for new onset CHD, mostly acute coronary syndromes, over the next few years (e.g., ≤10 years). It is directed towards persons who in all probability already have advanced coronary atherosclerosis and who are at high risk of suffering acute coronary syndromes. Such higher risk persons deserve more intensive intervention. Modification of life habits remains an important component of risk reduction in the short term, but more persons will require the addition of pharmacological therapy to reduce risk factors than in long-term prevention.

d. Role of LDL lowering in short-term and long-term primary prevention

Several general comments can be made about the role of LDL lowering in short-term and long-term prevention before addressing specific issues in these areas. A broad base of evidence indicates that elevations in LDL cholesterol are a direct cause of atherosclerosis. Long-term elevations of LDL cholesterol lead to a progressive accumulation of coronary atherosclerosis, which is essential to development of clinical CHD. Recent clinical trials demonstrate that LDL-lowering therapy reduces CHD risk in both primary and secondary prevention. In fact, LDL lowering reduces risk even when LDL-cholesterol levels are not categorically high. For this reason, LDL-lowering therapy represents a powerful modality for reducing both short-term and long-term risk.

Persons at higher risk in the short term (i.e., ≤10 years) deserve highest priority in clinical intervention. Identification of higher risk persons thus becomes a critical issue. This identification is based largely on algorithms that take into account the interaction of multiple risk factors that raises CHD risk multiplicatively. These short-term risk estimates are less reliable for selection of candidates for long-term prevention in clinical practice. Long-term prevention begins with a fundamental principle: all categorical risk factors should be managed clinically regardless of projected short-term risk. All of the major risk factors for CHD—cigarette smoking, hypertension, elevated LDL cholesterol, and diabetes—can produce CHD or other cardiovascular disease even in the absence of other risk factors. Each deserves clinical intervention. In the case of LDL cholesterol, a categorical elevation for ATP III is defined as a level ≥160 mg/dL. Many persons with persistent levels of LDL cholesterol in this range will ultimately require LDL-lowering drugs to reduce risk, although therapeutic lifestyle changes are first-line management. For persons with LDL-cholesterol levels ≥160 mg/dL, categorization of absolute risk can help guide the type and intensity of therapy. Furthermore, some persons with lower levels of LDL cholesterol, e.g., 130–159 mg/dL, will nonetheless have a short-term risk high enough to justify LDL-lowering drugs because of other risk factors. Absolute risk assessment will assist in identification of the latter persons.

e. Risk assessment in primary prevention

In accord with the preceding comments, clinical risk assessment has two goals: to identify persons who are at risk for accelerated atherogenesis, and to identify those persons who are at higher risk for experiencing an acute coronary syndrome because of established advanced atherosclerosis. Long-term prevention in clinical practice is designed for the former, whereas short-term prevention is intended for the latter. Short-term risk reduction (i.e., prevention of coronary plaque rupture and acute coronary syndromes) depends almost exclusively on absolute-risk assessment for its selection of persons for intense clinical intervention. For short-term prevention, absolute risk can be estimated by the summed interaction of multiple coronary risk factors.

NCEP originally introduced a simple system of risk assessment that employed counting of categorical risk factors (Table II.4–2). Treatment goals for LDL cholesterol were set according to the number of risk factors. This system represented a blending of the concepts of relative and absolute risk in an effort to effectively institute both long-term and short-term prevention. The major intervention in NCEP recommendations has been lifestyle changes; LDL-lowering drugs were reserved for persons with categorical elevations of LDL cholesterol who were projected to be at highest risk. After release of ATP II, several major clinical trials reported results showing the efficacy and safety of LDL-lowering drugs for primary prevention (as well as for secondary prevention). These reports opened the door to wider use of LDL-lowering drugs, both for short-term and long-term prevention. In particular, there is a growing consensus that higher risk persons

should not be denied the proven short-term benefits of LDL-lowering drugs, even when LDL-cholesterol levels are <160 mg/dL. Consequently, the selection of persons for short-term prevention to reduce plaque rupture and acute coronary syndromes has assumed increased importance. Moreover, there has been a growing view that a more quantitative assessment of short-term risk is required for the selection of persons who will benefit most from intensive risk-reduction intervention.

The Framingham Heart Study provides an algorithm for assessing risk for CHD in the short term (≤10 years).[10] This algorithm, which is based on robust risk factors, has been adopted by European cardiovascular societies for their treatment guidelines,[394,395] the British cardiovascular societies[396-398] and the American Heart Association.[399] In 1999, the National Heart, Lung, and Blood Institute sponsored a workshop to evaluate the applicability of Framingham risk scores to other population groups in the United States.[400] Framingham projections for "hard" CHD (myocardial infarction and CHD deaths) were found to be similar to those found in other prospective studies in both Caucasian and African American populations in the United States. Comparisons also showed that Framingham scoring led to some overestimation of absolute risk in certain population groups, e.g., Japanese men in Hawaii (Honolulu Heart Program) and Hispanic persons in Puerto Rico.[400] Nonetheless the broad "transportability" of Framingham risk scores within the U.S. population makes it possible for ATP III to employ the Framingham algorithm for quantitative risk assessment to assist in matching intensity of therapy with absolute risk. It must be noted, however, that other published risk assessment algorithms are available.[401] All algorithms do not contain the same factors, nor are risk predictions entirely congruent. Moreover, Framingham scoring itself has been undergoing modification over the past few years. Therefore, absolute risk estimation must be viewed as an evolving science. This is particularly the case as emerging risk factors and measures of subclinical atherosclerosis are added to risk assessment algorithms.

The ATP III panel was faced with the need to reconcile its previous method of counting risk factors with the developing field of integrated, "global" risk assessment. There are advantages and disadvantages to each approach. For example, risk factor counting provides continuity with previous ATP guidelines; it allows for a history of detected risk factors to be included in risk assessment; it includes family history of premature CHD; and it provides a focus on the individual risk factors, each of which requires clinical intervention. However, risk factor counting alone also has disadvantages: it does not provide a quantitative estimate of absolute risk in the short term; it does not allow for variability in risk factor level or intensity (i.e., it uses only categorical risk factors); and it may underestimate the progressive impact of advancing age on absolute risk in older persons. Integrated models of risk estimation (e.g., Framingham risk scoring) counter several of these disadvantages. For instance, they give a more quantitative absolute risk prediction for short-term risk; they account for variability in risk factor intensity, including the progressive impact of advancing age on risk; and they can include corrections for the interactions of risk factors. Even so, there are disadvantages or potential disadvantages to quantitative models for risk estimation: they introduce an approach that has not been widely field tested for practicality in clinical practice; they do not account for variability of risk factor level from one clinic visit to another (and no historical information on variable risk factors is included); they require extra steps in risk assessment (either manual or computer-based assessment); they tend to focus primary attention on short-term risk (to the exclusion of long-term risk); their transportability to all populations is uncertain; and there are remaining uncertainties due to competing and evolving risk-assessment models. All of these factors were taken into account in the ATP III choice of risk assessment methods.

The final method chosen attempts to capitalize on the advantages of both approaches. Risk factor counting is retained for initial assessment, but Framingham risk scoring, updated for ATP III (see Section III), is layered over risk factor counting to improve risk estimation for refining decisions about goals, intensity, and types of LDL-lowering therapy in persons with multiple risk factors. In the final analysis, however, ATP III risk assessment allows physicians to begin with either approach; ultimately the two give similar results. The method of risk assessment therefore depends on physician preference. These methods are described in detail in Section III.

f. Primary prevention with lifestyle changes

1) *Basis for lifestyle recommendations for primary prevention*

A broad base of evidence supports recommendations for lifestyle changes for LDL-lowering therapy in primary prevention.

2) *Dietary clinical trials of cholesterol lowering*

A sizable number of clinical trials have been carried out to test whether lowering serum cholesterol levels with dietary modification will reduce risk for CHD. Some of these were primary prevention trials,[187,402-405] and others were secondary prevention trials.[406-408] None of these trials provided convincing proof of the efficacy of serum cholesterol lowering by dietary means to reduce CHD risk. Most of the trials, however, showed positive trends. In a meta-analysis of dietary trials, Gordon[45,409,410] found that dietary lowering of serum cholesterol produces as much CHD risk reduction as do drugs, commensurate with their respective degree of cholesterol lowering.

3) *Linkage of public health approach and clinical approach in primary prevention*

A strong case exists for the efficacy and safety of primary prevention through lifestyle changes. Primary prevention efforts extend to both public health and clinical arenas. The essential changes in life habits include smoking avoidance or cessation, modifying intakes of foods and nutrients, weight control, and physical activity. Evidence to support each of these changes has been presented in the NCEP Population Report[5,6] U.S. Surgeon General's Reports on Smoking[186] and on Physical Activity;[238] the Obesity Clinical Guidelines Report,[78,79] and Dietary Guidelines for Americans (2000).[241] ATP III affirms the validity of lifestyle changes as first-line therapy for primary prevention. It places priority on LDL-lowering modifications because of the identification of LDL cholesterol as the primary target of therapy; however, ATP III also urges the use of a broad approach to lifestyle changes for CHD risk reduction in primary prevention.

g. Effectiveness of LDL-lowering drugs in primary prevention

Clinical trials of cholesterol-lowering drugs support the efficacy of clinical primary prevention in higher risk persons. In the era before statin drugs, several primary prevention trials of cholesterol lowering were carried out with drug intervention.[44] Landmark trials among these were the World Health Organization clofibrate trial,[149] the Helsinki Heart Study gemfibrozil trial,[139,411,412] and the Lipid Research Clinics cholestyramine trial.[12,13] All of these trials of lipid-lowering therapy reduced major coronary events. However, they were underpowered to address the issue of total mortality; hence, in the minds of many, the benefits of lipid modification in primary prevention remained uncertain.[413-415] The availability of more efficacious cholesterol-lowering drugs (statins) made it possible to definitively test whether LDL lowering would reduce CHD risk. Two major primary prevention trials with statins were the West of Scotland Coronary Prevention Study (WOSCOPS)[416] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[207]. Their results are summarized in Table II.7–1. In both trials, statin therapy significantly reduced relative risk for major coronary events. WOSCOPS also showed a very strong trend towards a

Table II.7–1. Major Primary Prevention Trials with Statins

Study	Persons	Duration	Statin Drug (dose/d)	Baseline LDL-C (mg/dL)	LDL-C Change	Major Coronary Events	Revascularization	Coronary Mortality	Total Mortality
WOSCOPS	6595	4.9 yrs	Pravastatin 40 mg	192	-26%*	-31%*	-37%*	-33%*	-22%*
AFCAPS/TexCAPS	6605	5 yrs	Lovastatin 20/40 mg	150	-25%*	-37%*	-33%*	NS	NS

* Changes significant at p<0.05 or lower.

reduction in total mortality. In AFCAPS/TexCAPS, the numbers of deaths in both placebo and treatment groups were so small that no conclusions could be drawn about effects of cholesterol-lowering therapy on total mortality; however, no significant adverse effects of statin therapy were detected.

WOSCOPS and AFCAPS/TexCAPS have important differences that reveal the potential spectrum of use of drugs for primary prevention. WOSCOPS participants, on average, had high LDL-cholesterol levels at baseline, and they often had multiple risk factors. AFCAPS/TexCAPS participants, in contrast, had only borderline high LDL-cholesterol levels and fewer other risk factors, except for relatively low HDL-cholesterol levels. Because of higher LDL cholesterol and more risk factors, WOSCOPS participants had a relatively high absolute risk. AFCAPS/TexCAPS is important because it showed that LDL-lowering therapy in persons with only borderline-high LDL-cholesterol levels produces a large reduction in relative risk. Nevertheless, absolute risk reduction was lower than in WOSCOPS participants, so that more persons had to be treated to receive the benefits of treatment. The implications of these two studies for use of LDL-lowering drugs in primary prevention are considered briefly below.

h. Selection of persons for short-term risk reduction with LDL-lowering drugs

The major reason for using LDL-lowering drugs in short-term, primary prevention is to reduce the likelihood of major coronary events in persons who presumably have advanced coronary atherosclerosis. Primary prevention trials with LDL-lowering drugs provide the rationale for this approach. The most robust primary prevention trial for evaluating benefits of LDL-lowering therapy was WOSCOPS. Its participants generally had elevated LDL cholesterol along with other CHD risk factors. In the WOSCOPS placebo group, 10-year risk for major coronary events (myocardial infarction and CHD death) was approximately 15 percent. Statin therapy reduced this risk by about one-third (Table II.7–1). In AFCAPS/TexCAPS, the estimated 10-year risk for major coronary events in the placebo group was 10.9 percent, but almost half of these events were unstable angina; risk for hard CHD (myocardial infarction + CHD death) was only about 7 percent. Thus, absolute risk in WOSCOPS participants was approximately twice that of AFCAPS/TexCAPS participants. Statin therapy in AFCAPS/TexCAPS produced reductions in relative risk similar to those in WOSCOPS; nonetheless, because of lower absolute risk in AFCAPS/TexCAPS, the number needed to treat (NNT) for every event prevented was higher than in WOSCOPS.

In these two primary prevention studies, statin therapy proved to be remarkably safe as well as efficacious. Since safety does not appear to be an issue for short-term risk reduction in primary prevention with LDL-lowering drugs, the determining factor for the lower risk cutpoint for drug recommendation will be cost-effectiveness (see Section II.14). As noted in Section II.14, the lower cutpoint for selection of drug therapy at current prices of LDL-lowering drugs is a risk for myocardial infarction and coronary death of about 1 percent per year (or 10 percent per 10 years). By this criterion many persons entering AFCAPS/TexCAPS were below accepted cost-effectiveness for short-term risk reduction with statins.

It must be emphasized that the ATP III clinical guidelines do not advocate the attainment of LDL goals exclusively through drug therapy. The aim of therapy is to achieve the LDL goals that are set according to absolute risk criteria. ATP III recommendations call for achieving the goals of therapy by the safest and most cost-effective means. Use of dietary therapy to attain the targets of therapy is emphasized, and if drugs are required, cost-effective agents should be used in the lowest doses needed to achieve the recommended goals of therapy.

i. Selection of older persons for short-term, primary prevention

Approximately two-thirds of first major coronary events occur in persons ≥65 years. Many asymptomatic older persons have advanced coronary atherosclerosis. Recent clinical trials have revealed that aggressive LDL-lowering therapy is effective in reducing risk for CHD (see Table II.2–3). Therefore, the prospects for reducing clinical CHD in the United States by intensive LDL lowering are good. To maximize this benefit, LDL-lowering drugs will be needed for many persons at higher risk. However, to fully implement widespread use of LDL-lowering drugs in older populations, several major problems will have to be overcome. For example, the most effective LDL-lowering drugs (statins) are often expensive; at current prices, statin therapy can cost up to $500–$1,500 per year.

At present, Medicare does not pay for prescription drugs, and many older Americans do not have other private insurance to cover this high cost. Moreover, techniques to assess absolute risk in older persons are less reliable than for middle-aged persons. In particular, serum cholesterol is less robust as a predictor of CHD events in the elderly than in the middle aged.[417] Measurements of subclinical atherosclerosis are promising,[418,419] but currently are not widely available, nor have evidence-based guidelines been produced for their use (see Section II.5.c). Thus, selection of older persons for intensive LDL-lowering therapy with drugs requires a considerable degree of clinical judgment and may be less open to a specific guideline. Nonetheless, several factors can be taken into account when selecting older persons for intensive LDL-lowering therapy, particularly for drug therapy.

Framingham risk scoring remains the primary means of identifying older persons at higher risk. Even so, one factor that may add perspective in the selection of older persons for LDL-lowering drugs at different levels of risk projected from risk factors is an estimate of the number of persons needed to treat (NNT) to achieve benefit. Table II.7–2 gives an estimate of the benefit of statin therapy in older persons over a 15-year period at different levels of projected 10-year risk, assuming that therapy is applied continuously between ages 65 and 80. The assumption is also made that statin therapy reduces risk for all CHD categories by approximately one-third and that for older persons, CHD deaths account for 50 percent of all hard CHD events. No published data provide the ratio of CHD deaths/hard CHD events in older persons, but considering the high mortality in this large group, an estimate of 50 percent appears reasonable.

Table II.7–2. Number Needed to Treat (NNT) with Statin Therapy for 15 Years to Prevent CHD Events by Age 80 Starting at Age 65*[10]

10-Year Risk for Hard CHD†	NNT to Prevent CHD Events (15 Years of Drug Therapy)		
	CHD Death	Hard CHD†	Total CHD‡
10%	42	21	10
20%	20	10	5
30%	13	7	3
40%	10	5	1–2

* The results in this table assume that statin therapy reduces relative risk for all CHD events by one-third (see Table II.2–3).
† Hard CHD includes myocardial infarction + CHD death.
‡ Total CHD includes myocardial infarction, CHD death, unstable angina, and coronary procedures (angioplasty and coronary bypass surgery).

Factors other than the 10-year risk score based on major risk factors may further aid in selection of older persons for intensive LDL-lowering therapy. Since the relative risk accompanying some risk factors declines with advancing age, measures of subclinical atherosclerosis may assist in the identification of older persons who are at high absolute risk and who should benefit from more intensive therapy (see Section II.5.c). For example, a positive ankle-brachial blood pressure index places an older person in a high-risk category (see Section II.5.c.1), as does identification of myocardial ischemia (Section II.5.c.2). The same is true for older persons with advanced subclinical atherosclerosis identified by increased carotid artery thickening or coronary calcium (e.g., ≥75th percentile for age or sex) (see Section II.5.c.3). Thus, use of noninvasive measures of myocardial ischemia or subclinical atherosclerosis may be helpful in the selection of older persons who are good candidates for intensive LDL-lowering therapy including drug therapy. Beyond these approaches to risk assessment, however, many other medical and social factors must be taken into account in the selection of older persons for aggressive short-term risk reduction. These are discussed in more detail in Section VIII.3.

j. Selection of persons for long-term primary prevention in the clinical setting

The essential reason for using clinical resources for long-term primary prevention of CHD is to slow the development of coronary atherosclerosis. Long-term prevention in the clinical setting thus represents an extension of the public health approach. Unless coronary atherosclerosis is prevented (or greatly reduced), the total burden of CHD in society will not be substantially reduced. The lion's share of the effort to prevent coronary atherosclerosis falls to the population (public health) approach; nonetheless, modification of risk factors in persons with a high lifetime risk requires attention by health professionals. A considered judgment is needed for how best to manage such persons. The physician is obliged to identify underlying risk factors (atherogenic diet, overweight/obesity, and physical inactivity) and to introduce risk reduction therapies for them. For the major risk factors, smoking cessation intervention is indicated for cigarette smokers, blood pressure lowering is required for persons with hypertension, and elevated LDL cholesterol should be

lowered in those with high levels (≥160 mg/dL) regardless of the presence or absence of other risk factors. Lifestyle intervention is the preferred approach, but in some cases, drug therapy is optional or needed. ATP III outlines approaches to treatment of elevated LDL-cholesterol levels; if clinical management is needed, the report favors therapeutic options that will be robust even for long-term prevention. The absence of other risk factors does not obviate the need to treat elevated LDL cholesterol to reduce build-up of coronary atherosclerosis in the long term.

The concept of long-term prevention highlights the need for early detection of lipid disorders. Early detection links clinical and population approaches to primary prevention at an age when intervention can retard the early stages of atherogenesis. NCEP has long recommended that all adults, starting at age 20, undergo periodic testing for serum cholesterol levels. Some guidelines[394-397,420-422] have recommended that cholesterol testing be delayed until later in life. This recommendation is predicated on the belief that risk can be largely reversed by clinical intervention later in life. A vast body of information on the evolution and natural history of atherosclerosis, however, contradicts this belief. As shown by recent clinical trials with statin therapy, clinical intervention in high-risk populations later in life still leaves many persons with an unacceptably high risk. In other words, if primary atherogenesis is ignored until atherosclerosis has become advanced, intervention to stabilize existing lesions can never reduce risk to the level of a person with minimal coronary lesions. Early detection of cholesterol disorders provides the opportunity to curtail development of coronary atherosclerosis from young adulthood, a time when atherogenesis is beginning to accelerate. Persons at highest long-term risk are those in the upper quartile of cholesterol levels during young adulthood.[32-34] Elevated serum cholesterol belongs among a constellation of risk factors (cigarette smoking, elevated blood pressure, obesity, physical inactivity, and an atherogenic diet) that contributes to build up of coronary atherosclerosis throughout life.[30,76,77,423-427] Early detection of these risk factors, including elevated cholesterol, affords an opportunity to initiate interventions that will arrest or slow the progression of atherogenesis during young adulthood.

An additional important reason to test serum cholesterol in young adults is to identify genetic disorders of lipid and lipoprotein metabolism. Persons with heterozygous familial hypercholesterolemia are at particularly high risk, even in the short term. Although this disorder is not common, it is highly dangerous not only for the affected person, but potentially for first-degree relatives as well. Screening the relatives of persons with heterozygous familial hypercholesterolemia is important in identifying new cases and increasing the number of these high-risk patients who are subsequently treated with LDL-lowering drug therapy.[428] Moreover, there are other causes of severe hypercholesterolemia (e.g., polygenic hypercholesterolemia) that are more common and also are accompanied by increased risk for premature CHD. These genetic forms of hypercholesterolemia can now be treated effectively, which increases the need for their early detection. For more detail, see Section VII Management of Specific Dyslipidemias.

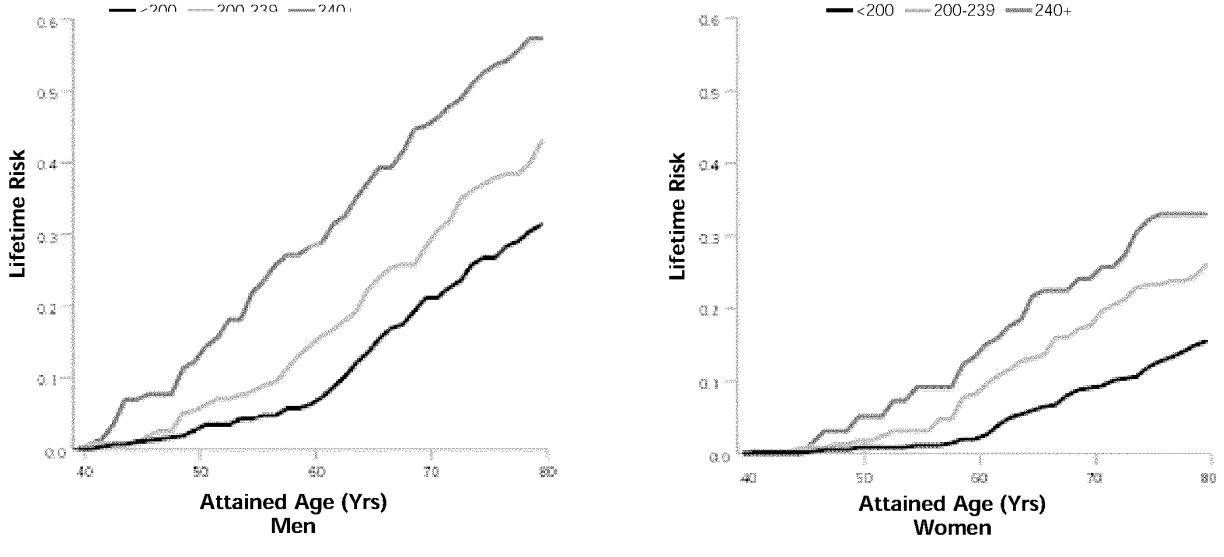
The relationship between serum cholesterol levels and lifetime risk for CHD has been evaluated in the Framingham Heart Study. The lifetime risk for total CHD (i.e., all clinical manifestations of CHD) for men and women free of CHD at age 40 years is 1 in 2 for men and 1 in 3 for women; it decreases only slightly with advancing age attained free of CHD.[17] Even at age 70 the lifetime risk for CHD remains high: 1 in 3 for men and 1 in 4 for women. The lifetime risk for men and women free of CHD at various ages varies according to total cholesterol levels as shown in Table II.7–3. Three ranges of total cholesterol are compared: <200, 200–239 mg/dL, and ≥240 mg/dL; these ranges approximately correspond to LDL-cholesterol ranges of <130, 130–159 mg/dL, and ≥160 mg/dL. For men at age 40, the risk of developing CHD in any form over the next 40 years for the three ranges is 31 percent, 43 percent, and 57 percent respectively. Corresponding risks in women are 15 percent, 26 percent, and 33 percent. This is in sharp contrast to the low 10-year risks at age 40. The figures below present the plots of lifetime risk at age 40 (Figure II.7–1) and age 70 (Figure II.7–2) for men (left panel) and women (right panel) at different total cholesterol levels.

These time-dependent risks have implications for ATP III guidelines. Increased lifetime risks associated with high total cholesterol levels (≥240 mg/dL), which correspond to categorically high LDL cholesterol (≥160 mg/dL), are clearly evident and justify clinical therapies to reduce long-term risk. But even borderline-high total cholesterol (200–239 mg/dL) carries significant long-

Table II.7–3. Short-Term and Lifetime Risk of CHD by Cholesterol Levels Obtained at Various Ages (modified from Lloyd-Jones et al.[17])

	Total Cholesterol Level (mg/dL)					
	Men			Women		
	<200	200–239	240+	<200	200–239	240+
Age 40						
10-year risk	3%	5%	12%	1%	2%	5%
40-year risk	31%	43%	57%	15%	26%	33%
Age 50						
10-year risk	8%	10%	15%	2%	4%	8%
40-year risk	40%	42%	63%	19%	30%	39%
Age 60						
10-year risk	16%	15%	21%	5%	8%	11%
Lifetime risk	34%	41%	51%	20%	24%	36%
Age 70						
10-year risk	18%	22%	28%	5%	7%	13%
Lifetime risk	27%	36%	42%	14%	20%	29%
Age 80						
10-year risk	14%	23%	29%	14%	16%	17%
Lifetime risk	17%	23%	34%	17%	18%	21%

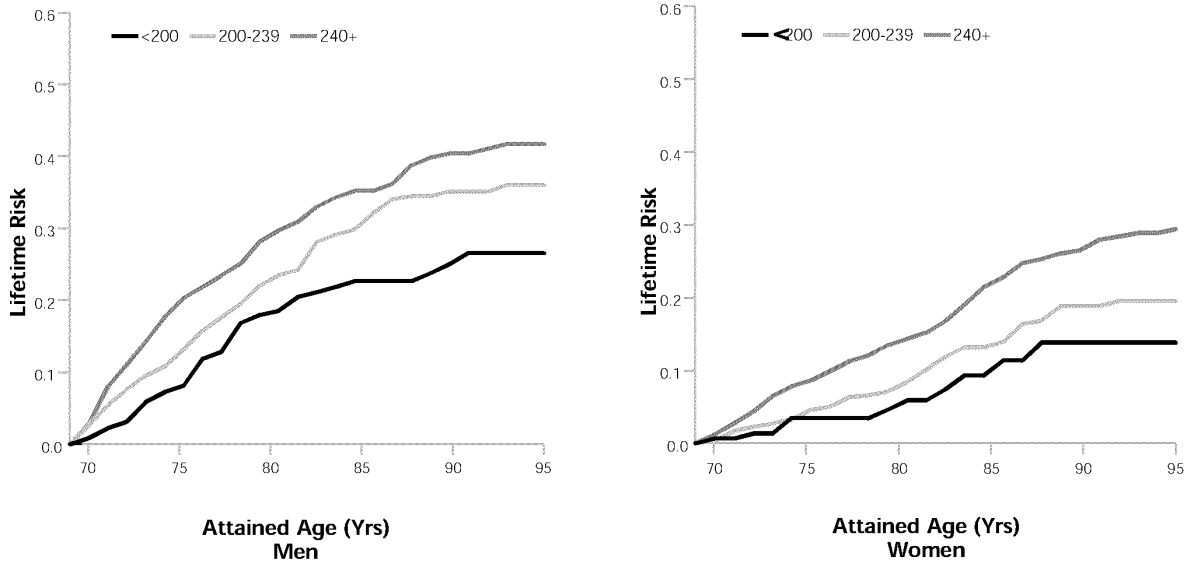
Figure II.7–1. Lifetime Risk of CHD by Total Cholesterol Level for Men (left) and Women (right) at Age 40 Years (derived from Lloyd-Jones et al.[17])



term risk, and it deserves clinical intervention, albeit not necessarily with LDL-lowering drugs.

The major impediment to long-term primary prevention in clinical practice is the cost of therapy. Costs are incurred in all aspects of clinical intervention, e.g., physician time, dietary therapy, drugs, and monitoring. At present, the cost of drugs appears to predominate. This fact has led some guideline committees in other countries to recommend restricting use of LDL-lowering drugs to persons at high short-term risk.[394-398] This restriction is considered necessary because of financial

Figure II.7–2. Lifetime Risk of CHD by Total Cholesterol Level for Men (left) and Women (right) at Age 70 Years



constraints that require a conservative allocation of national medical resources. Certainly persons at higher risk in the short term (≤10 years) deserve priority in intervention including use of LDL-lowering drugs. Still, the advantages of preventing coronary atherosclerosis in the first place cannot be ignored. Lifetime prevention of CHD by retarding atherogenesis remains an important goal. Consequently, persons with above-average long-term risk deserve attention by physicians; they are not necessarily candidates for cholesterol-lowering drugs, but at the very least, deserve intervention on life habits. Physicians can use their influence to advocate and support long-term risk reduction.

The issue of long-term prevention with LDL-lowering drugs deserves comment. Elevated LDL cholesterol is the primary driving force for coronary atherogenesis. When LDL-cholesterol levels are high (≥160 mg/dL), atherosclerosis progresses at a relatively high rate. Persons with very high LDL-cholesterol levels (≥190 mg/dL) can develop premature CHD even in the absence of other risk factors. Those with high LDL-cholesterol levels (160–189 mg/dL) can experience premature CHD when other risk factors are present, even when absolute risk at a younger age is <10 percent per 10 years. There is little doubt that LDL-lowering drugs will curtail atherogenesis in these persons. Therefore, use of LDL-lowering drugs in such persons can be justified to achieve the benefits of long-term risk reduction even when drugs are not considered "cost-effective" by conventional analysis. As patents on initial statins expire and competition increases, it is highly likely that costs of LDL-lowering drugs will decline substantially. Nonetheless, ATP III emphasizes that its goals for LDL cholesterol should be achieved by the most cost-effective means, i.e., by use of maximal dietary therapy before drugs and by choosing the most cost-effective drug regimens. ATP III considers the judicious use of LDL-lowering drugs in long-term prevention to be an "adjunct" to lifestyle changes—and not first-line therapy. For a more detailed discussion of the cost-effectiveness of LDL-lowering therapy, see Section II.14.

k. LDL goals in primary prevention

Prospective epidemiological studies show that the incidence of CHD is proportional to serum total cholesterol and LDL-cholesterol levels. When LDL-cholesterol levels are <100 mg/dL, CHD risk likewise is low, even in the presence of other risk factors. [10,19,20,25] Thus, an LDL cholesterol <100 mg/dL can be called *optimal*. Moreover, when other coronary risk factors are largely absent and LDL-cholesterol concentrations are above but near optimal, i.e., 100–129 mg/dL, the 10-year risk for CHD is relatively low[11,429] (see Table II.7–4).

Despite the low risk for CHD accompanying LDL-cholesterol levels that are optimal (<100 mg/dL) or above but near optimal (100–129 mg/dL), the intensity of clinical intervention required to achieve such levels for everyone in the population would financially over-

Table II.7–4. 10-Year Risk for CHD in the Framingham Population for Low Risk and Lowest Risk Persons with LDL Cholesterol Levels 100–129 mg/dL (modified from Wilson et al.[10])

Age Group (Years)	Average Risk*		Low Risk†		Lowest Risk‡	
	Men	Women	Men	Women	Men	Women
30–39	3%	<1%	1%	0%	0%	0%
40–49	6%	1.5%	2%	1%	1%	0%
50–59	11%	5%	3%	1%	2%	1%
60–69	20%	8%	4%	2%	2%	1%
70–74	25%	11%	6%	3%	3%	1%

* Average 10-year risk for hard CHD (myocardial infarction and CHD death) in the Framingham population regardless of LDL-cholesterol levels.
† Low risk level = 10-year absolute risk for hard CHD (myocardial infarction and CHD death) in a subject with LDL cholesterol 100–129 mg/dL, blood pressure <130/<85 mmHg, no treatment for hypertension, HDL cholesterol 45–59 mg/dL, nondiabetic and nonsmoker.
‡ Lowest risk level = 10-year absolute risk for hard CHD in a subject with LDL cholesterol 100–129 mg/dL, blood pressure <120/<80 mmHg, no treatment for hypertension, HDL cholesterol ≥60 mg/dL, nondiabetic and nonsmoker.

load the health care system. Drug usage would rise enormously. Selection of persons for clinical intervention depends on the principle of adjusting intensity of therapy to absolute risk. Persons at higher risk require more intensive therapy to attain the goal of a lower risk LDL level. In ATP III the decision was made to set the primary LDL-cholesterol goals according to the number of major risk factors, as was done in ATP II.

In ATP II,[1,2] the LDL-cholesterol goal for persons with multiple (2+) risk factors was <130 mg/dL. This goal is maintained in ATP III. Therapeutic lifestyle changes can be recommended for all such persons whose LDL cholesterol is ≥130 mg/dL at baseline. These changes include an LDL-lowering diet, weight reduction, and increased physical activity. As in ATP II, for persons with multiple risk factors, ATP III continues to recommend consideration of LDL-lowering drugs when LDL-cholesterol levels are ≥160 mg/dL after therapeutic lifestyle changes. However, new evidence outlined in this section supports more intensive therapy to achieve this goal for some persons whose LDL-cholesterol levels are borderline high (130–159 mg/dL) after therapeutic lifestyle changes. Thus, when multiple risk factors are present and 10-year risk for CHD is relatively high (i.e., ≥10 percent), consideration of LDL-lowering drugs is warranted when LDL cholesterol is ≥130 mg/dL after lifestyle changes. Not only is consideration justified by clinical trials that showed that drug therapy is efficacious, but it was found to be cost-effective as well (see Section II.14.f). Indeed, for those at highest 10-year risk (i.e., >20 percent), an optimal LDL cholesterol is a suitable target goal. On the other hand, when 10-year risk is low to moderate (<10 percent), restricting LDL-lowering drugs to those with LDL cholesterol ≥160 mg/dL still seems appropriate on grounds of both efficacy and cost-effectiveness.

When 0–1 risk factor is present, LDL-lowering therapy need not be as intense because absolute risk is not as high as when multiple risk factors are present. Most persons with 0–1 risk factor have a 10-year risk for CHD <10 percent. In such persons, an LDL-cholesterol goal of <160 mg/dL is allowable. Although a lower level (<130 mg/dL) is nearer to optimal, introduction of drug therapy to treat LDL-cholesterol levels of 130–159 mg/dL when 10-year risk is <10 percent is unrealistic. An enormous number of people would then be drug-eligible. They would require many years of drug therapy before realizing any discernible population benefit; any unrecognized long-term side effects of drugs would be magnified in this large group of lower risk persons; and drug therapy would not be cost-effective by current standards. Whether to consider drug therapy in persons with 0–1 risk factor and LDL cholesterol 160–189 mg/dL after lifestyle changes is more problematic. Their short-term risk is relatively low, and drug therapy is of marginal cost-effectiveness at current drug prices (see Section II.14.f). However, atherogenesis undoubtedly is accelerated, and use of drugs must be deemed optional if other factors (e.g., severe single-risk factors, a family history of premature CHD, life-habit risk factors, or emerging risk factors) are present beyond the count of major risk factors. Finally, when LDL cholesterol is ≥190 mg/dL after lifestyle changes, drug therapy should be considered even in persons with 0–1 risk factor because of accelerated atherogenesis and high long-term risk.

Evidence statements: A strong relationship exists between LDL-cholesterol levels and CHD risk (C1). An elevated serum total cholesterol contributes to coronary atherosclerosis throughout life; serum total cholesterol levels measured in young adulthood correlate with CHD rates later in life and over a lifetime (C1). For persons without other CHD risk factors, risk for CHD is relatively low when LDL-cholesterol levels are <130 mg/dL (C1). Moreover, for persons with higher LDL-cholesterol levels (≥130 mg/dL), clinical trials document the efficacy of LDL lowering to reduce risk for CHD in primary prevention (A1, B1), particularly when LDL-cholesterol levels are reduced to <130 mg/dL (A1).

Recommendation: LDL-lowering therapy should play an important role in primary prevention of CHD in persons at increased risk. For persons at increased risk because of the presence of multiple risk factors, the LDL-cholesterol goal should be <130 mg/dL. Therapeutic lifestyle changes should be initiated in all such persons. Persons with multiple risk factors whose short-term (10-year) risk is low to moderate (<10 percent) generally should not receive LDL-lowering drugs when LDL-cholesterol concentrations are only borderline high (130–159 mg/dL), but drugs should be considered when LDL levels are high (≥160 mg/dL). For higher risk persons with multiple risk factors (10-year risk 10–20 percent), consideration should be given to drug therapy when the LDL goal (<130 mg/dL) cannot be achieved by lifestyle therapies. Finally, multiple-risk-factor persons at highest risk (10-year risk >20 percent) need to attain even lower LDL-cholesterol levels (LDL goal <100 mg/dL), and consideration should be given to starting drug therapy simultaneously with therapeutic lifestyle changes when LDL-cholesterol levels are ≥130 mg/dL.

Recommendation: For persons who are otherwise at lower risk (0–1 risk factor), an effort should be made to lower LDL-cholesterol levels to <160 mg/dL. In such persons, lifestyle changes should be emphasized when the LDL-cholesterol level is in the range of 130–159 mg/dL to minimize the risk of any marginal (subcategorical) risk factors. Drug therapy at these LDL levels generally should be avoided, because of lack of long-term data on safety and because of relatively low cost-effectiveness ratios. In persons with 0–1 risk factor, if LDL-cholesterol levels cannot be reduced to <160 mg/dL by therapeutic lifestyle changes, LDL-lowering drugs can be viewed as optional when levels are in the range of 160–189 mg/dL, and should be strongly considered when levels persist at ≥190 mg/dL. Physicans should opt for drug therapy at former levels (160–189 mg/dL) when persons appear to have risk that is greater than that revealed by 0–1 standard risk factor, i.e., because of a severe single-risk factor, a family history of premature CHD, or the presence of life-habit or emerging risk factors.

Recommendation: Routine cholesterol testing should begin in young adulthood (≥20 years of age). In young adults, above-optimal LDL-cholesterol levels deserve attention. When LDL-cholesterol concentrations range from 100–129 mg/dL, young adults should be encouraged to modify life habits to minimize long-term risk. In those with borderline high LDL cholesterol (130–159 mg/dL), clinical attention through therapeutic lifestyle changes is needed both to lower LDL cholesterol and to minimize other risk factors. If LDL cholesterol is high (160–189 mg/dL), more intensive clinical intervention should be initiated, with emphasis on therapeutic lifestyle changes. However, if LDL cholesterol remains elevated despite therapeutic lifestyle changes, particularly when LDL cholesterol is ≥190 mg/dL, consideration should be given to long-term management with LDL-lowering drugs.

8. Secondary prevention: persons with CHD

a. Secondary prevention of recurrent CHD

Persons with established CHD are at very high risk for recurrent CHD. A growing body of evidence indicates that LDL-lowering therapy reduces recurrent coronary events in persons with existing CHD. The results of earlier secondary prevention trials, which were the basis of ATP II recommendations, are summarized in Table II.8–1. As shown, even before introduction of statins, cholesterol-lowering therapy was found to reduce CHD events without evidence of an increase in noncardiovascular mortality.[14,430] Subsequent secondary prevention trials with statins documented a reduction in cardiovascular morbidity and mortality and total mortality. These latter trials included those with both angiographic outcomes[46,158,431-434] and clinical endpoints[206,435,436]. In several of the angiographic trials, a significant decline in the incidence of clinical CHD events was observed in the treated group in a period of only two years (Table II.2–2). This finding makes it probable that the instability of plaques (which leads to fissuring, thrombosis, and intramural hemorrhage) is reduced as well.[437-441] The three major secondary prevention trials with statins were the Scandinavian Simvastatin Survival Study (4S),[435] Cholesterol and Recurrent Events (CARE) Study,[436] and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study.[206] Results of these trials are summarized in Table II.8–2. All three showed reductions in recurrent myocardial infarction and coronary death, coronary artery procedures, and stroke. Two of the trials reported a reduction in total mortality with statin therapy. Thus, secondary prevention trials provide strong evidence for the benefit of cholesterol-lowering therapy in persons with established CHD.

Table II.8–1. Earlier Secondary Prevention Trials: Morbidity and Mortality Results*†

Event	Proportion of Deaths	Relative Risk	Confidence Interval
Nonfatal myocardial infarction	—	0.74	0.66–0.84
Fatal myocardial infarction	73%	0.86	0.77–0.96
Cardiovascular deaths	90%	0.89	0.79–1.00
Cancer deaths	5%	0.89	0.59–1.39
Other deaths	4%	1.14	0.71–1.82
All deaths	100%	0.91	0.81–1.01

* Meta-analysis by Rossouw based on Rossouw et al.;[14] Rossouw[442].
† Trials include Medical Research Council's low-fat diet trial,[407] Medical Research Council's soya-bean oil trial,[443] Scottish Society of Physician's clofibrate trial,[151] Stockholm Ischaemic Heart Disease Secondary Prevention Study,[152] Coronary Drug Project's clofibrate trial,[141,444] Coronary Drug Project's niacin trial,[141,444] and Program on the Surgical Control of Hyperlipidemias[445].

Recent statin trials also reveal the impact of LDL lowering on selected populations and on additional clinical endpoints. LDL lowering has been shown to produce marked benefit regardless of gender, age, and the presence of diabetes, smoking, and hypertension.[203,205,436,446-449] Furthermore, in CHD patients, LDL lowering decreases stroke rates,[206,435,436,450,451] improves angina and myocardial perfusion,[448,452-455] and decreases the need for subsequent revascularization.[206,434-436,456]

Table II.8–2. Major Secondary Prevention Trials with Statins: Morbidity and Mortality Results

Study	Persons	Duration	Drug (dose/d)	Baseline LDL-C (mg/dL)	LDL-C Change	Major Coronary Events	Revascularization	Coronary Mortality	Total Mortality	Stroke
4S[435]	4444	5.4 yrs	Simvastatin 10/40 mg	188	-35%*	-35%*	-37%*	-42%*	-30%*	-27%*
CARE[436]	4159	5 yrs	Pravastatin 40 mg	139	-27%*	-25%*	-27%*	-24%*	-9%	-31%*
LIPID[206]	9014	5 yrs	Pravastatin 40 mg	150	-25%*	-29%*	-24%*	-24%*	-23%*	-19%*

* Statistically significant changes at $p<0.05$ or lower.

ATP II[1,2] identified the LDL-cholesterol goal for secondary prevention to be a level ≤100 mg/dL. Recent clinical trials provide an opportunity for reexamination of this goal. Epidemiological data strongly suggest that the prevalence of CHD is lowest when the LDL-cholesterol level is <100 mg/dL. Large studies and meta-analyses have revealed that CHD rates decrease with declining cholesterol levels down to a total cholesterol of 150 mg/dL, corresponding to an LDL cholesterol of about 100 mg/dL.[11,23,24,457] Epidemiological data demonstrate a continuous (log-linear) relationship between LDL cholesterol (and total cholesterol) and CHD risk.[23,24] The log-linear relationship holds to levels of LDL cholesterol below 100 mg/dL.[458] Factors that increase risk (e.g., presence of CHD) shift the curvilinear relationship, increasing the risk impact of LDL cholesterol at lower ranges.[459] Models based upon epidemiological data support the concept that LDL-lowering treatment at baseline total cholesterol levels >200 mg/dL (comparable to baseline LDL of approximately 130 mg/dL) will lower mortality and morbidity.[460] Finally, Law et al.[23,24] reported that results of epidemiological studies and clinical trials are highly congruent, providing additional support for the applicability of epidemiological data for setting LDL-cholesterol goals in secondary prevention.

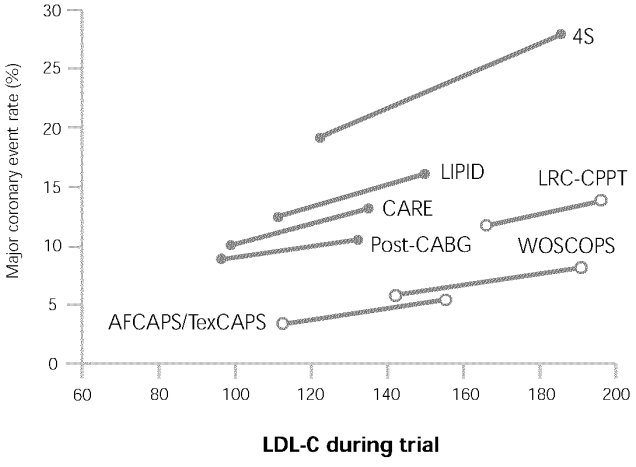
Angiographic studies on the whole are consistent with maximal CHD reduction in secondary prevention occurring at LDL levels <100 mg/dL. Three studies are particularly noteworthy: POSCH,[445,461] FATS,[158] and Post-CABG[434]. POSCH (using surgery) and FATS (using nicotinic acid and a statin or sequestrant) achieved LDL levels near 100 mg/dL and showed favorable changes in coronary lesions. The Post-CABG trial tested the concept that a lower LDL is better by examining the benefits of moderate versus aggressive LDL lowering on progression of atherosclerosis in saphenous vein grafts. Using a statin and sequestrant if needed, the moderate treatment group was treated to maintain LDL levels between 130–140 mg/dL, and the aggressive treatment group was titrated to a target LDL of <95 mg/dL. The aggressively treated group had less progression, fewer new lesions, and needed less revascularization.[434,456]

Post-hoc analyses of statin trials clearly show benefit from LDL cholesterol lowering to the range of 100 to 125 mg/dL.[462-465] Not all of the studies confirm that an optimal LDL cholesterol is <100 mg/dL; however, in subgroup analysis the statistical power to reliably define the lower limit of benefit may be lacking. In the 4S trial,[464] lowering of LDL levels gave proportional and continuous but progressively smaller absolute decrements in CHD risk down to an LDL cholesterol of 100 mg/dL. In CARE[436,463] benefit with statin treatment was seen with mean on-therapy LDL-cholesterol levels in the range of 100 mg/dL throughout the study (Figure II.8–1). Although CARE and LIPID could not rule out a threshold relation at LDL cholesterol less than 125 mg/dL, the combined data from epidemiological, angiographic,[43,466-468] and other clinical trials support an LDL-cholesterol goal of <100 mg/dL for secondary prevention.

Recently, clinical trials have examined the effect of treatment to lower LDL cholesterol goals, and earlier treatment of patients. Although no single trial conclusively confirms a specific LDL-cholesterol goal lower than 100 mg/dL, several studies showed a clinical benefit in the treatment group with on-treatment LDL cholesterol from 72 mg/dL to 98 mg/dL (MIRACL,[469] AVERT,[470] MARS,[466] LAARS,[468] Post-CABG,[434] FATS extension,[467] HATS[159]). The totality of this data suggests that further benefit accrues in patients treated to an LDL-cholesterol level below 100 mg/dL. It is not known whether LDL levels markedly below 100 mg/dL versus marginally below 100 mg/dL confer any additional benefit. Trials with clinical endpoints (AVERT, MIRACL) and other endpoints, including vascular function, confirm an early (1 week to 3 months) benefit of statin treatment for patients with atherosclerosis or acute coronary syndromes. In this regard MIRACL is noteworthy, demonstrating that statin treatment initiated in hospital (in patients with non-Q MI or unstable angina) was safe and was associated with a 16 percent relative risk reduction at 16 weeks. Also supporting the concept of early treatment is a recently published, very large observational study from Sweden. In-hospital initiation of statin treatment was associated with an adjusted 25 percent lowering of total mortality at 1 year.[471]

The recent VA-HIT trial,[48] however, revealed that modification of other lipid risk factors could reduce risk for CHD when LDL cholesterol is in the range of 100 to 129 mg/dL (Tables II.8–3a–b). In this trial, persons with low LDL (mean 112 mg/dL) were treated with gemfibrozil for 5 years. Gemfibrozil therapy, which raised HDL and lowered triglyceride, reduced

Figure II.8–1. Relation of CHD Events to LDL Levels in Treatment and Placebo Groups: Statin Trials[472]



the primary endpoint of fatal and non-fatal myocardial infarction by 22 percent without significantly lowering LDL-cholesterol levels. This study thus raises the possibility of efficacy from optional use of non-statin drugs when LDL-cholesterol levels in CHD patients are in the range of 100–129 mg/dL.

Despite the strongly positive result of gemfibrozil therapy in the VA-HIT trial, less striking results have been reported for other fibrate trials in secondary prevention. For example, the clofibrate arm of the early Coronary Drug Project[141] produced no evidence of benefit. Another early secondary prevention trial[151] with clofibrate gave more favorable outcomes, but the reduction in CHD events was not statistically significant. Results from the recent BIP trial with bezafibrate therapy were essentially negative.[153] This secondary prevention study recruited patients with a mean LDL cholesterol >130 mg/dL; in similar CHD patients, both CARE and LIPID trial results were strongly positive with statin therapy. Thus, statin therapy is clearly preferred over fibrates in patients with borderline high or high LDL cholesterol (≥130 mg/dL). Nonetheless, VA-HIT findings support the potential for significant additional risk reduction in patients with low LDL cholesterol (<130 mg/dL). VA-HIT results also support a positive trend for CHD events (although not for all-cause mortality) when all fibrate trials are considered together.[45]

Table II.8–3a. Veterans Affairs HDL Intervention Trial (VA-HIT): Lipids and Lipoproteins

Persons	Drug/Duration	Total Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	Triglyceride (mg/dL)	Non-HDL Cholesterol (mg/dL)
2531 men	Gemfibrozil (1200 mg/day) 5.1 years	175*	111*	32*	161*	143*
	% Difference (Treatment minus Control)	-4%	0%	+6%	-31%	-6%

* Baseline levels.

Table II.8–3b. Veterans Affairs HDL Intervention Trial (VA-HIT): Cardiovascular Events: Percent Risk Reduction (95 percent Confidence Intervals)

Non-Fatal Myocardial Infarction + CHD Death	CHD Death	Non-Fatal Myocardial Infarction	Stroke	Revascularization	Total Mortality
22%*	22%	23%†	31%‡	9%	11%
(7 to 35%)	(-2 to 41%)	(4 to 38%)	(2 to 52%)	(-8 to 23%)	(-8 to 27%)

* Primary endpoint, p = 0.006.
†, ‡ Secondary endpoints, p = 0.02 and 0.036, respectively.

Evidence statements: Secondary prevention trials demonstrate that reduction of LDL-cholesterol levels significantly reduces risk for recurrent major coronary events in persons with established CHD (A1). Evidence from endpoint trials with cholesterol-lowering drugs, angiographic trials, and epidemiological studies indicates that maximal CHD reduction occurs when LDL cholesterol is <100 mg/dL (A2, B1, C1).

Recommendation: Persons with established CHD should receive intensive LDL-lowering therapy. The goal of therapy in persons with established CHD should be LDL cholesterol <100 mg/dL.

Evidence statement: Persons with established CHD who have a baseline LDL cholesterol ≥130 mg/dL receive benefit from institution of LDL-cholesterol-lowering drugs (A1).

Recommendation: Persons with established CHD who have a baseline LDL cholesterol ≥130 mg/dL should be started on a cholesterol-lowering drug simultaneously with therapeutic lifestyle changes and control of nonlipid risk factors (therapeutic lifestyle changes alone are unlikely to achieve the LDL-cholesterol goal of <100 mg/dL).

Evidence statements: Persons with established CHD who have a baseline LDL cholesterol of 100–129 mg/dL likely will benefit from reducing LDL cholesterol to <100 mg/dL (A2, B2, C1). These persons also appear to benefit from therapy that modifies atherogenic dyslipidemia (A2, B2).

Recommendation: Several options should be considered for treatment of CHD patients with baseline LDL-cholesterol levels of 100–129 mg/dL. These include use of a cholesterol-lowering drug, maximization of therapeutic lifestyle changes, use of a drug to modify atherogenic dyslipidemia, and intensified control of nonlipid risk factors.

b. Effects of lipid-lowering therapy on stroke

Recent clinical trials in patients with established CHD indicate that lipid-lowering therapy, especially with statins, reduces risk for stroke. A significant reduction in stroke was reported in all three major clinical trials with statins—4S,[454] CARE,[473] and LIPID[206,474]. A similar result was obtained with a meta-analysis of several smaller clinical trials with pravastatin.[446] Subsequent meta-analysis of all statin trials revealed that statin therapy reduces stroke in patients with established CHD by 27–31 percent.[451,475,476] Subsequent analyses of pooled pravastatin studies confirm benefit of statin therapy on strokes.[477] The mechanisms whereby statin therapy reduces stroke in CHD patients are not well understood but probably involve retardation of plaque progression, plaque stabilization, and reduction of the risk for coronary events.[478] Regardless, reduction in stroke is definitely an added benefit of statin therapy in secondary prevention. Besides statin therapy, treatment with gemfibrozil in patients with established CHD in the VA-HIT trial reduced investigator-designated stroke by 25 percent, confirmed stroke by 25 percent, and transient ischemic attacks by 59 percent.[48] In summary, lipid lowering, particularly with statins, reduces risk for stroke in patients with established CHD. The question of whether LDL-lowering therapy in primary prevention also reduces stroke has not been adequately tested, although one meta-analysis[451] showed a strong trend towards benefit.

Evidence statement: In persons with established CHD, LDL-lowering therapy reduces risk for stroke (A1, B1).

Recommendation: For persons with established CHD, LDL-lowering therapy should be carried out to reduce the risk for stroke and for recurrent coronary events.

9. Total mortality considerations and therapeutic safety

Beyond the striking reduction in CHD rates accompanying lowering of LDL cholesterol lies the question of whether cholesterol-lowering therapy will actually extend the life span. At the time of publication of ATP II (1993), the net impact of cholesterol lowering on

mortality was an area of controversy. Previous clinical trials generally had not been designed with sufficient power to address all-cause mortality. In the early 1990s, several meta-analyses found that mortality from all causes was essentially identical in treated and control persons, despite a significant reduction in CHD mortality.[14,414,415,479-482] This finding raised concerns that cholesterol lowering per se might be causing an increase in non-CHD mortality that offset the reduction in CHD. This concern was reinforced by reports that total mortality rates in populations are relatively high in subgroups with the lowest cholesterol levels.

Further analysis of earlier trials yielded possible explanations for a failure of reduced CHD event rates to translate into reduced mortality rates.[45] For example, drugs such as estrogen, dextrothyroxine, and possibly clofibrate, may have had toxicity that obscured the benefit of other drugs. Also, a reduction in all-cause mortality is difficult to detect when total deaths from CHD in clinical trials are relatively low. For instance, all-cause mortality was reduced in secondary prevention trials (where 80 percent of deaths were due to CHD) but were increased in primary prevention trials that included potentially toxic drugs (where only 37 percent of deaths were due to CHD). Finally, the modest degree of cholesterol lowering in most of the earlier trials probably was insufficient to test the hypothesis that treatment reduced total mortality. Analyses of the earlier trials indicated that the crossover point where the reduction in CHD mortality began to outstrip the increase in non-CHD mortality was at an 8–10 percent reduction in serum cholesterol.[455,457]

Since the ATP II report, trials using statins have been reassuring for total mortality considerations. Five large long-term cholesterol-lowering trials using statins, as well as 11 smaller trials of 2–4 years duration, were published between 1993 and 1999.[206,207,416,432,434-436,483-487] In these trials, which encompass more than 17,000 statin treated persons followed for an average of 5 years, statin drugs have consistently produced reductions of 18 percent or more in serum cholesterol levels, and have been remarkably free of adverse effects. Two of the large secondary prevention trials, 4S[435] and LIPID,[206] demonstrated significant reductions in mortality by themselves, and several others showed clear trends in the same direction. Meta-analysis of these trials shows an overall 29 percent reduction in CHD mortality ($p<0.001$) and an 11 percent reduction in non-CHD mortality ($p=0.06$). All-cause mortality was reduced by 22 percent ($p<0.001$). Finally, a global meta-analysis incorporating 40 trials using statins, fibrates, sequestrants (or partial ileal bypass surgery), nicotinic acid, and/or diet to lower cholesterol now shows a 12 percent reduction in all-cause mortality ($p<0.001$) (Table II.9–1). The results in Table II.9–1 constitute a refinement of a recent meta-analysis reported by Gordon.[45] Results were prepared for ATP III by panel members D. Gordon and M.A. Proschan.

Beyond the recent clinical trials showing a reduction in total mortality from LDL-lowering therapy, questions remain about short-term and long-term safety of specific LDL-lowering modalities. The dispute about the safety of lowering of LDL per se has been resolved, at least for the short term; net benefits in high-risk

Table II.9–1. Meta-Analysis of Mortality in Cholesterol-Lowering Trials by Treatment Modality

Treatment Modality	Number of Trials	Number (Treatment/ Control)	% Change Cholesterol	Mortality	
				Deaths	OR (p)
Statins	17	18494/18449	20%	1107/1381	.78 (<.001)
Fibrates	7	10654/12999	9%	859/1277	1.03 (.58)
		CHD Mortality for Fibrates ➔		495/884	.93 (.24)
		Non-CHD Mortality for Fibrates ➔		364/393	1.19 (.02)
Sequestrants	5	3562/3530	12%	159/191	.81 (.06)
Other*	14	4025/5801	10%	789/1293	.93 (.19)
All trials†	42	36775/37321	15%	2914/3420	.88 (<.001)

* Nicotinic acid, diet, and various combinations of drugs.
† Multi-armed trials (CDP[141], STARS[488]) are counted only once in the totals although their arms can contribute to more than one row.

persons exceed any adverse effects. Furthermore, no evidence for adverse effects of dietary therapy has been uncovered for the short term; in contrast, the optimal diet for long-term prevention of CHD remains an issue under investigation (see Section V). The fact that all drugs potentially carry side effects must be kept in mind when using them for prevention of CHD. Consideration can first be given to short-term side effects. Bile acid sequestrants cause a variety of gastrointestinal side effects, although none of these is apparently life threatening.[12,13] Nicotinic acid has numerous short-term side effects, and some persons can develop severe liver toxicity.[141] Overall, however, clinical experience does not suggest an increase in non-CHD mortality from use of nicotinic acid. Statins have proven to be remarkably free of short-term side effects, although occasionally persons develop severe myopathy. Controversy persists about the short-term safety of fibrates. Therapy with these drugs can cause myopathy and gallstones. Moreover, in the WHO clofibrate trial,[149] the treatment group showed an increase in total mortality, compared to the placebo group. The reasons for the higher mortality were never identified. Otherwise, a statistically significant higher mortality from non-CHD causes has never been observed in other clinical trials using fibrate therapy. Nonetheless, when all fibrate trials are combined in meta-analysis, the results of the large WHO trial overshadow other trials and lead to a persistent increase in non-CHD mortality. Many investigators, however, doubt that fibrate therapy carries an increased risk for fatal side effects in the short term. But the results of the WHO trial remain a reminder that fibrates should be limited to persons in whom they will provide the greatest benefit, such as those with hypertriglyceridemia[411] or the metabolic syndrome[48].

The issue of long-term safety of LDL-lowering drugs cannot be resolved by short-term clinical trials. There is always the possibility that chronic administration of drugs will lead to unanticipated side effects. There is no evidence that currently used cholesterol-lowering drugs promote development of cancer or induce subtle neurological diseases. Moreover, clinical experience with these drugs over periods of 30 years for fibrates and bile acid sequestrants and 15 years for statins has uncovered no long-term side effects. Nonetheless, the possibility of long-term side effects, albeit remote, should be one factor to consider when recommending lifetime therapy with a cholesterol-lowering drug.

Evidence statements: Overall Benefit of Cholesterol Lowering on Mortality. LDL-lowering therapy reduces total mortality, i.e., extends life, by decreasing CHD mortality (A1, B1). This therapeutic benefit was unclear in earlier trials using interventions with limited cholesterol lowering (10 percent), some of which showed adverse non-CHD effects. However, in trials using statins, in which cholesterol levels were reduced by 20 percent and non-CHD mortality was not increased, the reduction in mortality is incontrovertible.

Evidence statements: Benefit of Cholesterol Lowering on Mortality in Secondary Prevention. The benefits of cholesterol lowering on longevity are particularly clear in CHD 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 CHD (A1, B1). In persons with established CHD, a reduction in CHD deaths by effective cholesterol-lowering therapy more than outweighs any side effects of drug therapy.

Evidence statements: Benefit of Cholesterol Lowering on Mortality in Primary Prevention. Primary prevention trials using statins show a significant reduction in CHD mortality, no increase in non-CHD mortality, and a strong trend towards lower overall mortality (A2). Because of the lower proportion of deaths that are due to CHD 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 (C1). 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 percent) and in some instances by adverse non-CHD effects not seen with the statins.

10. Magnitude of reduction in CHD risk

Clinical trials[13,206,207,416,435,436,464] provide the best estimate of the actual reduction in CHD risk that can be achieved by treating high blood cholesterol. However, the trials reflect the impact of short-term cholesterol lowering only; more benefit should accrue with longer treatment. In most trials, treatment duration was 5 years and the average time to event was 2–3 years (assuming that about half the events occur after the midpoint of the trial). Despite the relatively short exposure to treatment, regression analyses relating the percent cholesterol reduction to risk of CHD predict that for every 10 percent reduction in serum cholesterol, there will be a 15 percent reduction in CHD events.[455] In the major statin trials the absolute reduction in serum cholesterol (and LDL cholesterol) averaged 45 mg/dL. This corresponds to a 20 percent lowering in serum cholesterol and resulted in a 30 percent reduction in CHD risk.[45,489] The average reduction in LDL cholesterol was 28 percent; thus in the short-term CHD risk will be reduced by 10 percent for every 10 percent that LDL cholesterol is lowered. This relationship holds true for primary and secondary prevention, largely unrelated to baseline levels of serum cholesterol in the trials.

It is conceivable that a longer duration of treatment will result in a further reduction in CHD risk. Ecologic studies (i.e., international comparisons)[11,23,24] suggest that differences in levels of serum cholesterol explain almost all of the differences in CHD rates between populations, and a lifelong exposure to a lower average cholesterol level has a marked effect on lowering CHD risk. Regression equations indicate that a difference in total cholesterol level of 23 mg/dL, or approximately 10 percent for a typical Western population, is accompanied by a 30 percent difference in CHD rates.[23,24,27] Cohort studies relating individual serum cholesterol levels to future risk over several decades indicate that a 23 mg/dL (10 percent) decrease in serum cholesterol is associated with a 25 percent reduction in CHD risk.[23,24,490] Thus, both ecologic studies and cohort studies suggest a more powerful long-term effect on CHD risk than that found in clinical trials. For a 10 percent reduction in serum cholesterol, the ecologic studies suggest a 30 percent reduction in CHD risk, the cohort studies a 25 percent reduction, and the clinical trials actually found 15 percent. The main reason for this difference is likely to be the duration of exposure to a given cholesterol level. In addition, other favorable lifestyle attributes (especially related to diet and physical activity) that are associated with lower cholesterol levels can reduce risk.

Evidence statements: In short-term, controlled clinical trials, a 1 percent reduction in LDL-cholesterol levels on average reduces risk for hard CHD events (myocardial infarction and CHD death) by approximately 1 percent (A1). Cohort studies suggest that a more prolonged reduction in LDL-cholesterol levels will produce an even greater reduction in CHD risk (C1). In the absence of long-term clinical trials, maximal long-term risk reduction cannot be estimated with certainty.

11. CHD as a risk indicator

The older literature suggested that having coronary disease increased future CHD event risk approximately 7 fold compared to healthy individuals, with an absolute risk of 50–60 percent per decade.[14,442] CHD rates and case-fatality rates in the United States and in most other developed countries have fallen considerably over the last two decades.[491,492] Extrapolating from the in-trial experience, the placebo groups in two recent secondary prevention trials (CARE, LIPID) of persons with "average" cholesterol levels had absolute risks for CHD of about 26 percent per decade.[206,436] In 4S, the placebo group had high cholesterol levels and an absolute risk of about 56 percent per decade, while in the VA-HIT population with low HDL-cholesterol levels it was about 43 percent per decade.[48,435] In women with existing CHD, rates were similar to men, and older persons had higher rates than younger persons.[489,493] Given that clinical trial participants are likely to have event rates lower than that of similar persons in the general population (due to the healthy volunteer effect), and that the event rates likely will increase as the participants age beyond the typical 5–6 year trial periods, an event rate of 20 percent per decade in persons with CHD represents a minimum estimate of the absolute annual risk associated with existing CHD. A subgroup of the WOSCOPS men with prior evidence of vascular disease (angina, claudication, stroke, TIA, or ECG abnormalities) had an annual rate of CHD of approximately 26 percent per decade, similar to that observed in the secondary prevention trials

of persons with prior myocardial infarction or unstable angina.[416] Persons with stable angina pectoris and persons who have had coronary revascularization procedures also have a 20 percent risk of CHD events over 10 years.[456,494,495] Thus, it appears that evidence of coronary disease short of clinical MI carries the same future risk for CHD as does MI. In most studies, the minimal rate of recurrent, major coronary events in persons with any clinical evidence of CHD appears to be >20 percent over 10 years.

Evidence statement: Persons with established CHD in the United States have a risk for recurrent myocardial infarction and CHD death (hard CHD) that exceeds 20 percent per 10 years (C1).

12. Concept of CHD risk equivalents

Some persons without established CHD will have an absolute, 10-year risk for developing major coronary events (myocardial infarction and coronary death) equal to that of persons with CHD, i.e., >20 percent per 10 years. Such persons can be said to have a *CHD risk equivalent.* These persons belong in a high-risk category for primary prevention. Three groups of persons with CHD risk equivalents are identified.

a. Other forms of clinical atherosclerotic disease

Atherosclerosis is a generalized macrovascular disease. Population-based autopsy studies have demonstrated that atherosclerotic disease in one region of the arterial tree is associated with and predicts disease in other arterial regions. The pathobiology and predisposing risk factors are similar for atherosclerosis in coronary, peripheral, and carotid arteries. Further, there is growing evidence that clinical atherosclerotic disease in non-coronary arteries is a powerful predictor of CHD. However, the conclusion that non-coronary forms of atherosclerosis represent a CHD risk equivalent must be derived from the totality of prospective studies because few if any studies were designed specifically to test this hypothesis. The available data relating non-coronary forms of atherosclerosis to CHD are reviewed in the following discussion.

1) Peripheral arterial disease (PAD)

In Table II.12–1, crude rates of CHD are shown for five studies of persons with atherosclerotic peripheral arterial disease (PAD). The Edinburgh Artery Study[496] included 1,592 middle-aged men and women. One third of the persons had established CHD. PAD was diagnosed by the ankle/brachial blood pressure index (ABI). Those with a categorical abnormality (ABI <0.9) had an annual event rate for major coronary events of 2.4–3.8 percent per year. In the Multicenter Study of Osteoporotic Fractures,[497] ABI was measured in 1,027 women without CHD. Those with ABI <0.9 had an annual rate for *total CHD mortality* of 2.9 percent per year. The outcome was similar to that for 495 women with pre-existing CHD. In the San Diego cohort of the Lipid Research Clinic Study,[337,338] persons with documented PAD (without CHD) had a *total CHD mortality* of 2 percent per year. In another cohort of persons of whom 40 percent had co-existing CHD, McKenna et al.[498] reported a very high CHD mortality for persons with categorically low ABI (≤0.85). A similarly high mortality also was reported by Poulias et al.[499] in 1,000 persons undergoing aortofemoral bypass. These studies taken together support the concept that PAD, whether diagnosed by ABI, lower limb blood flow studies, or clinical symptoms, is a CHD risk equivalent.

2) Carotid artery disease

The association between symptomatic carotid disease and future coronary morbidity and mortality derived from sizable reported studies is shown in Table II.12–2a. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET),[500] symptomatic patients undergoing carotid endarterectomy had an average 10-year CHD mortality of 19 percent. Since coronary mortality is typically 2 to 3 times that of major coronary events, this high mortality is indicative of a CHD risk equivalent. Similarly, in the ECST study,[501] symptomatic patients had very high death rates from nonstroke vascular disease, regardless of the percent of carotid artery stenosis at the outset. Finally, Norris et al.[502] reported a much worse outcome in 696 persons with carotid bruits who were referred for Doppler studies for carotid stenosis. When persons had >75 percent carotid stenosis, rates of transient ischemic attacks (TIAs), stroke, and CHD events were very high (8.3 percent per year for CHD events), and were high even

Table II.12–1. Crude CHD Event Rate in Persons with Atherosclerotic Peripheral Artery Disease by Study

Study and Design	Number of Subjects; Ages	Subsequent CHD mortality or event rate
Edinburgh Artery Study[496] Ankle/brachial blood pressure index (ABI) in randomly selected population 5 yr follow-up	1592 men and women 614 had CHD Ages: 55–74	During follow-up, 137 fatal and nonfatal CHD events occurred. CHD event outcomes per year were: 1.4% in those with ABI >1.1 1.4% in those with ABI 1.1–1.01 1.8% in those with ABI 1.0–0.91 2.4% in those with ABI 0.9–0.71 3.8% in those with ABI <0.7
Multicenter Study of Osteoporotic Fracture[497] ABI testing 4.3 yr follow-up	1027 women without CHD; 495 women with CHD Ages: 65–93	During follow-up, 15 CHD deaths occurred in women without CHD. CHD mortality outcomes per year were: 0.2% for women with normal ABI (>0.9) 2.9% for women with ABI <0.9 During follow-up, 17 CHD deaths occurred in women with CHD. CHD mortality outcomes per year were: 0.7% for women with ABI >0.9 3.0% for women with ABI <0.9
LRC San Diego cohort[337,338] Noninvasive testing lower limb blood flow 4 yr follow-up[337] 10 yr follow-up[338]	257 men 310 women 31 men and 28 women had CHD Ages: 38–82	During 4 yr follow-up of entire cohort, 17 died of CHD. CHD mortality outcomes per year were: 159 subjects had peripheral vascular disease 2% CHD mortality 408 subjects had normal noninvasive testing 0.1% CHD mortality During 10 yr follow-up of those without baseline CHD, 12 men and 6 women died of CHD. CHD mortality outcomes per year were: 0.4% in men without vascular disease 2.5% in men with peripheral vascular disease 0.2% in women without vascular disease 0.4% in women with peripheral vascular disease
McKenna et al.[498] Persons underwent ABI for evaluation of peripheral artery disease Average 3 yr follow-up (2–10 yr)	744 men and women Ages: 19–89	40% of persons with ABI <0.85 had history of CHD 29% of persons with ABI >0.85 had history of CHD During follow-up, 101 CHD deaths occurred. CHD mortality outcomes per year were: 2% in persons with ABI >0.85 6% in persons with ABI <0.85
Poulias et al.[499] Persons undergoing aortofemoral bypass Follow-up: 1 mo to 20 yr (average 8 yr)	941 men and 59 women Ages: 35–87	During follow-up, 192 CHD deaths occurred. CHD mortality outcome: 2.4%/yr

Table II.12–2a. CHD incidence in Symptomatic Carotid Disease

Subjects	Disease severity (% Carotid Stenosis)	CHD Deaths	Estimated 10-yr CHD risk
NASCET[500] Cohort of 1,415 patients randomized to carotid endarterectomy Mean age 66 33% current smokers	≥70% (n = 326) 50–69% (n = 858) <50% (n = 1368)	8-yr follow-up all-cause mortality: ≥70% 17% <70% 17% Most of deaths due to CHD	10-yr CHD death = 19%
ECST[501,503] Entire cohort of 3,024 patients randomized to surgical vs. medical management Mean age 62 72% males 23% had Hx CAD 53% current smokers	0–19% (n = 140) 20–29% (n =279) 30–39% (n = 339) 40–49% (n = 312) 50–59% (n = 590) 60–69% (n = 369) 70–79% (n = 401) 80–89% (n = 410) 90–100% (n = 178)	All-cause mortality 6 yr follow-up was 27% for both treatment groups. All-cause mortality did not differ by % stenosis: 0–19% (24%) 20–29% (28%) 30–39% (28%) 40–49% (22%) 50–59% (27%) 60–69% (24%) 70–79% (28%) 80–89% (30%) 90–100% (31%)	Since 72% deaths were due to non-stroke vascular disease, 10-yr CHD death is estimated at 30%
Norris et al.[502] Persons with carotid bruits 327 men 369 women 235 had CHD Ages 45–90 Follow-up: 0.5–8 yr (mean 3.4 yr)		During follow-up, 132 CHD events occurred. CHD event rates were: 2.7%/yr for stenosis <50% 6.6%/yr for stenosis 50–75% 8.3%/yr for stenosis ≥75%	

when stenosis was >50 percent. These studies taken together show that persons with symptomatic carotid artery disease are at high risk for major coronary events and so can be considered CHD risk equivalents.

Similarly, high CHD event rates have been documented in asymptomatic patients with advanced carotid artery stenosis. The natural history of this association is best illustrated by data from controlled clinical trials evaluating the effectiveness of carotid endarterectomy in these patients. When considering the CHD event or death rates reported for all subjects in the trials listed in Table II.12–2b, it is clear that patients with stenosis >50 percent, even if asymptomatic, have historically high CHD event rates thereby classifying them as a CHD risk equivalent.

Finally, other studies[339-341,508] have reported that carotid intimal-medial thickening of the carotid arteries in asymptomatic persons in whom carotid narrowing is <50 percent is still associated with increased risk for CHD. Although asymptomatic thickening of carotid arteries (<50 percent stenosis), in contrast to symptomatic disease and asymptomatic bruits of ≥50 percent stenosis, does not raise risk to the level of a CHD risk equivalent, these studies show that carotid artery atherosclerosis is accompanied by increased risk for new-onset CHD. Therefore measurements of carotid intimal-medial thickening represent an option for adjusting risk and therapies in persons with multiple risk factors (see Section II.5 Emerging Risk Factors).

Table II.12–2b. Asymptomatic Carotid Disease

Subjects	Disease severity	CHD events	Estimated 10-yr CHD risk
ACAS trial[504] Entire cohort of 1,662 patients randomized to carotid surgery or medical management; 69% Hx CHD 28% smokers 25% diabetics	Asymptomatic Stenosis ≥60%	2.7 yr follow-up: 84 deaths from MI (n =45) or other cardiac disease	10-yr MI mortality rate 10%; CHD mortality rate 19%
Veterans Affairs Cooperative Study Group[505] Entire cohort of 444 men Mean age 60 27% Hx MI 50% smokers 30% diabetics All received aspirin therapy	Asymptomatic Stenosis ≥50%	4 yr follow-up: 91 deaths from cardiac causes	10-yr CHD mortality rate 51%
Mayo Asymptomatic Carotid Endarterectomy Study[506] 158 patients 40% Hx CAD 15% diabetics	Asymptomatic Stenosis ≥50% Trial stopped due to high event rate in surgical arm secondary to cessation of medical therapy (aspirin)	2.5 yr follow-up: 12 CHD events	10-yr CHD event rate 30%
CASANOVA[507] 410 patients 42% Hx CAD 26% smokers 30% diabetics	Asymptomatic Stenosis ≥50%	3.5 yr follow-up: 50 deaths due to CHD	10-yr CHD mortality rate 35%

3) Abdominal aortic aneurysm (AAA)

Limited data are available on the CHD risk in persons with atherosclerotic abdominal aortic aneurysm (AAA). The most complete study is that from Hertzer[509] who reported the incidence of myocardial infarction following AAA resection in 343 persons followed 6–11 years postoperatively (Table II.12–3). The persons were separated into four groups according to pre-operative history of coronary disease. For persons with no evidence of previous CHD events, CHD mortality averaged 1.9 percent per year. Since the rate of CHD events is at least twice that of CHD mortality, even those without established CHD at time of operation would fall into the category of CHD risk equivalent. An even higher CHD death rate occurs in persons with prior CHD. This study thus supports the concept that AAA is a CHD risk equivalent.

Evidence statement: Clinical forms of non-coronary atherosclerosis carry a risk for clinical CHD approximately equal to that of established CHD and hence constitute a CHD risk equivalent (C1). These conditions include peripheral arterial disease, carotid artery disease (transient ischemic attack or stroke of carotid origin, or >50% stenosis on angiography or ultrasound), and abdominal aortic aneurysm.

Recommendation: Persons with clinical forms of non-coronary atherosclerosis should have the same LDL-cholesterol goal (<100 mg/dL) as those for persons with established CHD and should be managed similarly (see Section IV.1).

b. Diabetes as a CHD risk equivalent

Persons with type 1 or type 2 diabetes are at increased risk for CHD.[191-194] In women with diabetes, relative risk, but seemingly not absolute risk, exceeds that in men with diabetes.[194] Some of the increased CHD risk in persons with diabetes can be attributed to the major risk factors;[191,192,195] other metabolic abnormalities, e.g., hyperglycemia and insulin resistance, probably contribute additional risk. Most literature relating diabetes to CHD risk considers type 2 diabetes, although cardiovascular complications are important for persons with type 1 diabetes as well. Because of the many differences between the two forms of diabetes, it seems appropriate to consider them separately.

Type 2 diabetes. This form of diabetes is characterized by insulin resistance, variable levels of endogenous insulin, and typically, by overweight/obesity and the metabolic syndrome. As hyperglycemia worsens, insulin therapy will become necessary. Persons with type 2 diabetes who are treated with insulin should not be confused with persons having type 1 diabetes who uniformly require insulin. Three lines of evidence support the concept that persons with type 2 diabetes from populations with high-average risk for CHD should be managed as if they have a CHD risk equivalent. But first it should be pointed out that hyperglycemia by itself does not raise risk to the level of a CHD risk equivalent. Instead, type 2 diabetes generally is accompanied by a constellation of metabolic risk factors that combine with hyperglycemia to impart a high risk. Furthermore, beyond having a high risk for first coronary events, persons with diabetes who develop CHD have a relatively poor prognosis for recurrent CHD events and coronary death. It is this constellation of

Table II.12–3. Crude CHD Event Rate in Persons with Abdominal Aortic Aneurysm

Study population	N	Subsequent CHD mortality or event rate
Hertzer[509] Persons operated on for abdominal aortic aneurysm (AAA) Persons separated into four groups based on preoperative CHD history and EKG Endpoint: incidence of fatal MI after surgical recovery: 6–11 yrs follow-up	300 men 43 women with AAA Ages: 45–89y	On follow-up, 62 CHD deaths occurred among the 286 operative survivors. CHD mortality rates per year were: 1.9% in persons with no symptoms, no prior history of CHD, and normal EKG (31%) 2.0% in persons with no symptoms but previous MI by EKG (33%) 3.9% in persons with prior MI by history and EKG (23%) 3.9% in persons with angina/prior MI history but normal EKG (7%)

factors rather than a single risk projection that justifies classifying most persons with type 2 diabetes in the United States as CHD risk equivalents. The evidence to support this recommendation will be reviewed.

First, several studies have shown that absolute risk for first major coronary events for persons with type 2 diabetes in high-risk populations approximates that for recurrent events in non-diabetic persons with clinical CHD. For example, in a Finnish population-based study, the seven-year incidence of myocardial infarction (fatal and nonfatal) among 1,373 non-diabetic subjects (ages 45–65 years) with and without prior myocardial infarction at baseline was 18.8 percent and 3.5 percent, respectively ($p<0.001$).[210] In contrast, in 1,059 persons with type 2 diabetes, the seven-year incidence rates of myocardial infarction with and without prior myocardial infarction at baseline were 45.0 percent and 20.2 percent, respectively ($p<0.001$). The hazard ratio for CHD death for diabetic subjects without prior myocardial infarction as compared with non-diabetic subjects with prior myocardial infarction was not significantly different from 1.0 (hazard ratio, 1.4; 95 percent confidence interval, 0.7 to 2.6) after adjustment for age and sex, suggesting similar risk in the two groups. After further adjustment for total cholesterol, hypertension, and smoking, this hazard ratio remained close to 1.0 (hazard ratio, 1.2; 95 percent confidence interval, 0.6 to 2.4). Thus, in the Finnish population, which is known to be a high-risk population, persons with type 2 diabetes without prior CHD have as high a risk for a myocardial infarction as do persons without diabetes with previous myocardial infarction.

Similar results were obtained from the recent OASIS study.[212] In this study, persons with type 2 diabetes without CHD, average age 65, had rates of CHD events equal to that of persons with established CHD. Moreover, in the HOPE trial,[510] persons with type 2 diabetes without prior cardiovascular disease, but with one or more cardiovascular risk factors, had an annual event rate for CHD of 2.5 percent. The results of these two trials further support the concept that persons with type 2 diabetes, even without clinical CHD, belong in the category of CHD risk equivalent.

In a major clinical trial, the United Kingdom Prospective Diabetes Study (UKPDS), the absolute 10-year risk for hard CHD was between 15 and 20 percent, depending on the subgroup.[199,200,202] Although this percentage was below 20 percent in some subgroups, it must be recognized that the persons in this trial had a diagnosis of diabetes made relatively recently; also, on average they were less obese than most persons with type 2 diabetes in the United States. In those with higher BMIs (>30 kg/m^2), 10-year risk exceeded 20 percent. Finally, it is well known that persons participating in clinical trials manifest a lower risk during the trial than does the population at large. Thus, UKPDS results are consistent with the concept that persons with type 2 diabetes belong in the category of CHD risk equivalent.

Since many persons develop type 2 diabetes after age 65, the question arises whether older persons with diabetes deserve the designation of CHD risk equivalent. Prospective studies[191,192] show that the relative risk for CHD for persons with diabetes versus without diabetes declines with age. Indeed, in a population-based study of older subjects with small numbers of diabetic subjects from Australia, the risk for CHD in non-diabetic subjects with preexisting CHD was greater than in diabetic subjects without preexisting CHD.[214] Nonetheless, the combined risk factors of age plus diabetes appear to raise absolute risk for CHD to above 20 percent per decade.

Some persons with type 2 diabetes will not attain a 10-year risk for hard CHD of >20 percent when scored with algorithms from either Framingham[10,399] or the International Task Force for Prevention of Coronary Heart Disease.[401] Such persons usually are younger and do not manifest multiple major risk factors. However, if their risk is projected to age 65, most of them will attain a risk of 20 percent. This high risk for premature CHD justifies more intensive risk reduction therapy earlier in life. On the other hand, in some populations where the baseline risk of coronary heart disease is very low, the presence of adult hyperglycemia weakly predicts CHD. One example includes persons of East Asian ancestry, e.g., China and Japan.[20] In contrast, type 2 diabetes is accompanied by a very high risk for CHD in persons of South Asian origin.

A second reason for regarding persons with type 2 diabetes as having a CHD risk equivalent is that they have an increased case fatality rate with a myocardial infarction.[107,196,197] Prevention of myocardial infarction thus becomes a high priority. In one study,[197] the one-year case fatality rate for a first myocardial infarction

(from the onset of symptoms, including pre-hospitalization mortality) was 45 percent in men with diabetes and 39 percent in women with diabetes, compared to 38 percent and 25 percent for men and women without diabetes, respectively. Of the persons with diabetes who died, 50 percent of men and 25 percent of women died before hospitalization. Clearly, secondary prevention strategies are inadequate in these persons, and primary prevention is essential.

A third reason to aggressively prevent onset of CHD in persons with diabetes is that their overall prognosis for survival is much worse once they develop CHD than it is for CHD patients without diabetes.[210,511-516]

Classification of diabetes as a CHD risk equivalent in ATP III implies that enhanced benefit will be achieved from aggressive LDL-lowering therapy. Four studies have examined the benefits of cholesterol lowering with statins on CHD events in subgroups with diabetes[203-207] (see Table II.12–4). All of these studies have shown as much benefit in those with diabetes as in those without diabetes. The 4S, CARE, and LIPID studies were all secondary prevention trials. There were 202 subjects in the 4S with a clinical diagnosis of diabetes.[203] In this small group of subjects, simvastatin therapy was associated with a 55 percent reduction in major CHD (fatal and nonfatal CHD) (p=0.002) as compared with a 32 percent reduction in major CHD in non-diabetic subjects. In a further study of the 4S results[204] using the current American Diabetes Association criteria (fasting plasma glucose ≥126 mg/dL) an additional 281 diabetic subjects (without a previous diagnosis of diabetes) were identified. In this group simvastatin therapy was associated with a 42 percent reduction in major CHD (p=0.001). In the CARE study,[205] 586 subjects with a clinical diagnosis of diabetes were identified. Pravastatin therapy reduced the risk for CHD (fatal plus non-fatal myocardial infarction, CABG and PTCA) by 25 percent in the diabetic group (p=0.05) as compared to 23 percent in the non-diabetic group (p<0.001). In the LIPID study,[206] pravastatin reduced the incidence of fatal and nonfatal CHD by 19 percent in 792 diabetic subjects (p=NS) and 25 percent in the non-diabetic subjects (p<0.001). Although the reduction in CHD events in diabetic subjects was not significant with pravastatin, the test for heterogeneity in response between diabetic and non-diabetic subjects was not statistically significant. In AFCAPS/TexCAPS,[207] a primary prevention study, only 155 subjects had a clinical diagnosis of diabetes. Among this small number of diabetic subjects, a 42 percent reduction in CHD was seen (p=NS) which was similar to the 37 percent reduction in CHD seen in the overall study population. Thus, in post-hoc analysis of all statin trials, there was a strong and consistent trend for benefit of LDL lowering in persons with diabetes.

With the growing prevalence of severe obesity and physical inactivity in the United States, type 2 diabetes has been observed to occur more frequently in young adults and even teenagers.[517] It can be expected that early onset of type 2 diabetes will result in premature CHD. Clinical judgment is required to decide whether to manage these persons intensively with LDL-lowering drugs. LDL-lowering drugs need not always be started in young adults with type 2 diabetes. However, once LDL-cholesterol levels reach borderline high levels (130–159 mg/dL) or higher, LDL-lowering drugs become an option for reducing long-term risk. This is particularly so if other risk factors are present.

Persons with type 2 diabetes typically have atherogenic dyslipidemia, which represents a risk factor beyond elevated LDL cholesterol. This form of dyslipidemia in persons with diabetes is often called *diabetic dyslipidemia* which is described in detail in Section VII, Specific Dyslipidemias, along with recommendations for its management.

Type 1 diabetes. Although persons with type 1 diabetes are clearly at increased risk for CHD,[518,519] no study has specifically examined whether type 1 diabetic subjects have a risk of CHD as high as age- and sex-matched non-diabetic subjects with pre-existing CHD. This analysis is difficult to perform because persons with type 1 diabetes often develop diabetes at an early age. The intensity of LDL-lowering therapy therefore depends on clinical judgment. However, the ATP III panel favored starting LDL-lowering drug therapy in persons with type 1 diabetes when LDL-cholesterol levels are ≥130 mg/dL.

Table II.12–4. CHD Prevention Trials with Statins in Diabetic Subjects: Subgroup Analysis

Study	Drug	No.	CHD Risk Reduction (Diabetes)	Baseline LDL-C mg/dL (mmol/L)	LDL-C Lowering	CHD Risk Reduction (Overall)
Primary Prevention						
AFCAPS/ TexCAPS[207]	Lovastatin	239	-43%	150 (3.9)	-25%	37%
Secondary Prevention						
CARE[205]	Pravastatin	586	-25% (p=0.05)	136 (3.6)	-28%	-23%
4S[203]	Simvastatin	202	-55% (p=0.002)	186 (4.8)	-36%	-32%
LIPID[206]	Pravastatin	782	-19%	150* (3.9)	-25%*	-25%
4S-Extended[204]	Simvastatin	483	-42% (p=0.001)	186 (4.8)	-36%	-32%

* Values for whole group.

Evidence statements: Persons with type 2 diabetes have a 10-year risk for major coronary events (myocardial infarction and CHD death) that approximates the risk in CHD patients without diabetes (A2, C1). This high risk can be explained by the combination of hyperglycemia plus lipid and nonlipid risk factors of the metabolic syndrome. In addition, persons with type 2 diabetes have a high incidence of death at time of acute myocardial infarction as well as a relatively poor prognosis for long-term survival after myocardial infarction (C1). Thus type 2 diabetes constitutes a CHD risk equivalent.

Recommendations: Persons with type 2 diabetes should be managed as a CHD risk equivalent. Treatment for LDL cholesterol should follow ATP III recommendations for persons with established CHD (see Section IV.2a). For younger persons with type 2 diabetes, who otherwise are at lower risk, clinical judgment is required as to the intensity of LDL-lowering therapy. However, consideration should be given to using LDL-lowering drugs when LDL-cholesterol levels are ≥130 mg/dL.

Evidence statements: Persons with type 1 diabetes have increased risk for coronary heart disease. However, some persons with type 1 diabetes have a 10-year risk for CHD less than 15–20 percent (i.e., young persons without other risk factors [A2, C1]). Such persons will nevertheless have a high long-term risk for CHD (C1). Moreover, there is no reason to believe that the benefits of LDL reduction are different in persons with type 1 and type 2 diabetes (D1).

Recommendations: The intensity of LDL-lowering therapy in persons with type 1 diabetes should depend on clinical judgment. Recent-onset type 1 diabetes need not be designated a CHD risk equivalent; hence reduction of LDL cholesterol to <130 mg/dL is sufficient. With increasing duration of disease, a lower goal (<100 mg/dL) should be considered. Regardless of duration, LDL-lowering drugs should be considered in combination with lifestyle therapies when LDL-cholesterol levels are ≥130 mg/dL.

c. High-risk persons with multiple risk factors

Many persons without clinical atherosclerotic disease or diabetes are still at high risk because of advanced coronary atherosclerosis. Those asymptomatic persons who have an absolute, 10-year risk as high as that of persons with established CHD, i.e., >20 percent, can be classified as having a *CHD risk equivalent.* When they are identified, it is appropriate to employ intensive risk-reduction therapy, similar to that used in persons with established CHD. The most reliable method currently available to identify these high-risk persons is assessment of absolute risk with Framingham risk scoring. Persons with CHD risk equivalents will be near the top of the risk spectrum, as determined by the presence of multiple risk factors.

Evidence statement: Some persons with multiple CHD risk factors have an absolute 10-year risk for major coronary events (myocardial infarction and CHD death) of >20 percent (CHD risk equivalent) (C1).

Recommendation: For persons with CHD risk equivalents, the same recommendations should apply as for persons with established CHD (see Section IV.2).*

13. Models for clinical intervention: role of multidisciplinary team

Although epidemiology and clinical trials reveal the power of clinical intervention for both primary and secondary prevention, implementation of prevention guidelines has been less than optimal.[520,521] This deficiency is due in part to a structure of clinical management that is not designed for optimal preventive strategies. Successful prevention in clinical practice requires a multi-disciplinary team of health care professionals. The optimal organization of this team may well be a "lipid clinic" or "preventive cardiology clinic," but ATP III guidelines are designed so that primary care physicians can implement them in office practice.

Regardless of the clinical structure, implementation of ATP III guidelines is the responsibility not only of physicians, but also of registered dietitians and other qualified nutritionists, nurses, physician assistants, pharmacists, and other health professionals who must work together as a team in educating, treating, and following up each patient. There is consistent evidence from randomized trials demonstrating that approaches using a multidisciplinary team for the management of high serum cholesterol improve patient compliance, enlarge the scope of the population served, and improve the effectiveness of the guidelines.[266,522-531] There are an estimated 70,000 nutrition professionals (75 percent registered dietitians), 2.6 million registered nurses, and 190,000 pharmacists (80 percent in practice settings), and an increasing number of health educators. A team approach can be used to optimize education, monitoring, and follow-up. Physicians should identify a management strategy and work in concert with a health professional team to address the areas of diet, physical activity, and assistance with adherence enhancement. The multiple intervention strategies that can be employed when a multidisciplinary team approach is used offer persons optimal support for life-habit change. Finally, the success of ATP III's recommendations requires full participation of the patient, who must adopt and adhere to therapeutic modalities—whether life habit changes or drug therapy.

Evidence statement: Use of a multidisciplinary team for management of high serum cholesterol improves patient compliance, enlarges the scope of the population served, and improves compliance to treatment guidelines (A2).

Recommendation: Physicians have a primary responsibility for implementing ATP III guidelines. In addition, a multidisciplinary team, potentially including nurses, dietitians, nurse practitioners, pharmacists, and health educators, should be utilized whenever possible.

14. Cost-effectiveness issues

This section examines the issue of cost-effectiveness of LDL-lowering therapy in the United States at the present time, and it considers changes that are likely to occur in the next few years. Costs and cost-effectiveness of LDL-lowering therapy must be put into the context of the total costs of CHD and CVD. At present, direct medical costs for diagnosis and management of CVD in the United States exceed $100 billion

*See footnote, page II–61, regarding the Heart Protection Study.

annually. Similar amounts are lost in reduced productivity. Prevention of CHD with LDL-lowering therapy will reduce some of these costs. The most cost-effective approach to prevention of CHD is population intervention: diet modification, exercise, and weight control combined with smoking avoidance and cessation.[532] These approaches are safe, incur few direct costs, and offer benefits beyond CHD reduction. Clinical interventions to reduce LDL-cholesterol levels, the subject of ATP III, are less cost-effective, but can be justified on other grounds in higher risk persons. The introduction of safe and effective LDL-lowering drugs makes clinical intervention attractive for higher risk persons. Nonetheless, the costs of drug therapy are the dominant factor determining cost-effectiveness of the clinical approach to cholesterol reduction.

Another major factor influencing cost-effectiveness of LDL-lowering therapy for individuals is absolute risk for CHD. Cost-effectiveness is greater for those at highest short-term risk and decreases progressively as risk of suffering a coronary event falls. Recently, clinical trials have revealed that LDL-lowering therapy will reduce relative risk for CHD at all absolute-risk levels. This fact heightens the importance of cost-effectiveness analysis for selection of appropriate persons for clinical intervention. Whereas LDL-lowering therapy is efficacious to further reduce relative risk in lower risk persons, it is not necessarily cost-effective by current standards.

a. Purpose of cost-effectiveness analysis of LDL-lowering therapy

Relative-risk reduction accompanying reduction of LDL levels at all levels of absolute risk opens the door to widespread use of LDL-lowering drugs. In fact, use of these drugs could easily rival that of drug therapy for hypertension in the United States. At present approximately 50 million Americans are candidates for antihypertensive drugs and approximately 25 million of these people are taking antihypertensive drugs.[160,161] The widespread use of LDL-lowering drugs, although potentially effective in reducing the burden of CHD in the United States, would be costly. The fundamental rationale for assessment of economic consequences of LDL-lowering drugs is the reality that resources are limited, whereas demand for medical therapies always exceeds available public resources. Consequently, difficult choices often must be made among potentially beneficial interventions. Resources are best allocated according to potential alternative uses. Evidence of efficacy and safety of drug therapy, a requirement for clinical intervention, is insufficient to make recommendations for drug use in a cost-constrained society. This is particularly true when many millions of persons are potential recipients of the therapy. Limited resources should be targeted to where they provide the greatest health benefits. One of the major objectives of cost-effectiveness analysis is to facilitate patient selection so that incremental benefits are greatest relative to incremental costs. Thus, for LDL-lowering therapy to be widely used in the U.S. population, it must be cost-effective by current standards.

Cost-effectiveness analysis of LDL-lowering therapy compares its incremental costs with alternative interventions and their incremental benefits. Assessment of cost-effectiveness is inherently relative, i.e., it requires comparison of costs and health outcomes among alternative interventions (including no intervention). The metric used is incremental cost-effectiveness, which is the additional cost required to attain an additional unit of benefit. The reason for assessing cost-effectiveness is not that a particular health benefit is not worth paying for in an absolute sense; instead, spending money for medical, health care, and other societal needs in other ways might benefit individuals or society more. Although intensive LDL-lowering therapy is attractive because it clearly reduces risk for CHD, cholesterol-lowering drugs are relatively expensive. For this reason, drug therapy is a prime subject for cost-effectiveness analysis, and for comparison with other accepted modalities of medical practice. For comparison, cost-effectiveness estimates of currently used diagnostics and therapies in medical practice are shown in Table II.14–1.

b. Approaches to estimating cost-effectiveness of cholesterol-lowering therapies

Effectiveness analysis assesses net health benefit. For CHD prevention, effectiveness consists of extended survival, reduced morbidity, and enhanced quality of life. Effectiveness is generally expressed in terms of years of life gained or, preferably, quality adjusted years of life (QALY) gained. With the QALY measure, length of survival is weighted by the quality of survival. Aspects of quality of life attributable to cholesterol reduction include improvements in functional status and reductions in the anxiety and disutility that accompany all CHD events.

Table II.14–1. Cost-Effectiveness of Common Diagnostic or Therapeutic Modalities*

Diagnostic or Therapeutic Modality	Cost-Effectiveness Range† (dollars per year of life saved)
Antihypertensive therapy	$4,000 to $93,000
Screening mammography	$1,000 to $190,000
Renal dialysis	$20,000 to $79,000
Coronary artery bypass surgery (left main disease/ three-vessel disease)	$2,300 to $27,000
Exercise to prevent CHD	Cost-saving to $38,000
Aspirin to prevent CHD	Cost-saving to $5,000
Smoking cessation to prevent CHD	Cost-saving to $13,000

* *Major source references:*
Neumann et al.;[533] Stone et al.;[534] Tengs et al.[535]
Other references:
Barosi et al.;[536] Boer et al.;[537] Bulgin;[538] Buxton and West;[539] Christie;[540] Churchill et al.;[541] Croghan et al.;[542] Cromwell et al.;[543] Cummings et al.;[544] de Koning et al.;[545] Douzdjian et al.;[546] Eccles et al.;[547] Eddy et al.;[548] Edelson et al.;[549] Fiscella and Franks;[550] Gyrd-Hansen;[551] Harvald et al.;[552] Hatziandreu et al.;[553] Hlatky et al.;[554] Hristova and Hakama;[555] Johannesson et al.;[556] Johannesson et al.;[557] Johannesson et al.;[558] Johannesson;[559] Johannesson;[560] Jones and Eaton;[561] Kerlikowske et al.;[562] Klarman et al.;[563] Knox;[564] Kodlin;[565] Kristein;[566] Krumholz et al.;[567] Lai et al.;[568] Leivo et al.;[569] Lindfors and Rosenquist;[570] Lindholm and Johannesson;[571] Littenberg et al.;[572] Ludbrook;[573] Mandelblatt et al.;[574] Marks et al.;[575] Meenan et al.;[576] Moskowitz and Fox;[577] Munro et al.;[578] Okubo et al.;[579] Oster et al.;[580] Pearson et al.;[581] Roberts et al.;[582] Rosenquist and Lindfors;[583] Salzmann et al.;[584] Secker-Walker et al.;[585] Shepard et al.;[586] Simon;[587] Simpson and Snyder;[588] Smith;[589] Sollano et al.;[590] Stange and Sumner;[591] Stason and Weinstein;[592] Streitz et al.;[593] Tsevat;[594] van der Maas et al.;[595] Warner et al.;[596] Wasley et al.;[597] Weinstein and Stason;[598] Williams[599].

† Rounded to closest thousands

Cost refers to net cost of health care resources consumed. LDL reduction includes the costs of physician services, counseling, tests for screening, case finding and monitoring, drugs, and the treatment of side effects. Subtracted from these costs are savings from reductions in medical care resources utilized to manage CHD sequelae. For LDL lowering, these cost offsets include savings from decreased hospital and ambulatory services for angina, myocardial infarction, revascularization procedures, stroke, and heart failure. Cost offsets also include savings from decreased economic losses secondary to increased gainful employment and productivity resulting from reduced CHD morbidity and mortality. The benefits of reducing LDL cholesterol are reflected in cost-effectiveness analyses in three ways: (1) direct economic savings offset costs of LDL reduction, (2) avoidance of CHD mortality means a gain in survival, and (3) avoidance of the disability, distress, and pain from CHD counts as an increase in quality-adjusted life expectancy.

Several approaches to cost-effectiveness analysis of LDL lowering have been taken. Raw data for these analyses include estimates of risk based on Framingham risk scores and the results of clinical trials of cholesterol-lowering therapy in different population groups. Some investigators use sophisticated, complex, state-transition models to simulate the natural history of disease.[532] This approach attempts to incorporate and integrate data from the best available sources, including observational cohorts and health care administrative data in addition to clinical trials. Many factors are taken into account when developing the economic model (Table II.14–2). An alternate approach is to simplify the analyses to include only the essential factors.[600] Here the major costs (e.g., drugs) are compared to savings from prevention of disease.

Table II.14–2. Assumptions Used in Cost-Effectiveness Analyses of LDL-lowering Drugs[532]

- Efficacy of drug therapy
- Price of drugs (with or without wholesale discounts)
- Lag time between institution of therapy and first benefit (e.g., two years)
- Baseline risk of population
- Impact of individual risk factors on CHD risk
- Extrapolation of clinical trial results to the general population
- Prior dietary therapy before initiation of drug therapy (lessening cost-effectiveness of drugs)
- Prior treatment with less expensive drugs (e.g., nicotinic acid) before starting more expensive drugs (e.g., statins) (lessening cost-effectiveness of more expensive drugs)
- Endpoints selected for cost-effectiveness analysis (e.g., morbidity reduction, life years gained, quality adjusted life years [QALY] gained)
- Projections of efficacy of secondary prevention measures (to extend life) after failure of primary prevention
- Coexisting primary and secondary prevention measures (e.g., aspirin prophylaxis)
- Quality of life adjustments
- Time discounting of benefits, risks and costs
- Methods adjustments for quality of life years
- Costs of treating new-onset CHD and sequelae
- Projected morbidity and mortality outcomes after onset of CHD
- Frequency and costs of physician visits for monitoring
- Adherence/compliance characteristics of population
- Thresholds for acceptable costs per year of life saved
- Country-specific costs

Although the latter analysis does not include all the "hidden costs" of therapy, they show the "bare-bones" cost-effectiveness of the simplest model for clinical intervention, namely, identification of the person at risk for CHD and initiation of life-time drug therapy without follow-up or monitoring. Of course, if the intervention algorithm of ATP III were to be followed rigorously, many of these factors shown in Table II.14–2 would have to be taken into account in the analysis. Nonetheless, in many cases, realities of clinical practice will constrain intervention over time towards the simplest model. These variations in actual practice account for some of the difficulties in making reliable estimates of cost-effectiveness of LDL-lowering drugs.

Cost-effectiveness analysis is complicated by variability in the health care delivery system, including drug prescription plans. Individuals with similar biological risk and clinical benefit face very different cost-effectiveness scenarios depending on resource prices, financial structure of medical plans, and subjective valuation of health resources. On the basis of the aggregate clinical experience of the clinicians on the panel, it was noted that, depending on the payment scheme, the annual costs of statin drugs can vary from $100 to $1000. This difference alone imparts an almost 10-fold difference in cost-effectiveness for cholesterol-lowering therapy.

Beyond theoretical analyses, natural tensions exist at the level of the individual—both physician and patient. Health insurance programs seek to minimize payer costs, individuals desire to maximize their benefits relative to their health insurance and out-of-pocket payments, and physicians must make treatment decisions that optimize benefits to individuals without exceeding the bounds imposed by the insurance plan. In some cases, clinical judgment will push beyond payer controls; clinical treatment decisions must be individualized and guided by local conditions and patient preferences. Moreover, cost-effectiveness constraints need to be reassessed as either clinical or economic data change.

c. Criteria for cost-effectiveness therapies

There are no explicit criteria for what is or is not cost-effective.[535,601,602] Acceptable thresholds for cost-effectiveness are a reflection of available resources and cultural, social, political and individual values. The best situation occurs when an intervention both improves health and saves money. However, most commonly the costs of interventions that improve health outcomes are only partially offset by such savings. Empirically, the literature on cost-effectiveness indicates that most commonly accepted medical interventions in the United States have incremental cost per QALY gained below $50,000–$75,000 (Table II.14–1). Generally, interventions are considered highly cost-effective when the cost per QALY gained is below $20,000–$25,000, moderately high in cost-effectiveness when the cost per QALY is between $25,000–$50,000, borderline cost-effective when the cost per QALY is between $50,000–$100,000, and generally not cost-effective as the cost per QALY further increases. Clinical trial information on the impact of LDL lowering on functional status and quality of life is limited. Thus, it is difficult to directly weigh non-fatal outcomes and thereby assess cost per QALY. Economic analyses of persons with elevated cholesterol are further limited by restriction of measured resource use to a subset of cardiac services (most commonly revascularization procedures and CHD-related hospitalizations).

d. Cost-effectiveness analysis for LDL lowering for secondary prevention (persons with established CHD)

Individuals with CHD are at high risk for subsequent major coronary events. They have a >2 percent annual risk for experiencing myocardial infarction or CHD death and approximately 4 percent annual risk for these events plus unstable angina and coronary revascularization. Cost-effectiveness of secondary prevention has been estimated largely from the results of large, randomized clinical trials.[603-608] Among these trials, the very high risk of participants in the 4S trial made statin therapy highly cost-effective.[608] In the 4S placebo group, estimated 10-year risk for hard CHD events (myocardial infarction and CHD death) was about 36 percent. Several independent analyses applied to the trial as a whole indicated that costs per QALY average at current retail prices of drugs to be about $10,000.[532,603,606,608,609] Some investigators note nonetheless that even among persons with CHD, inherent risk for future CHD varies. Although cost-effectiveness analysis of subgroups of clinical trials is always problematic, ranges in cost-effectiveness have been reported, as exemplified by the recent analysis of the 4S trial by Prosser et al.[532] (Table II.14–3). In two other secondary prevention trials (CARE, LIPID), 10-year risk for hard CHD was lower than that for

Table II.14–3. Cost-Effectiveness Estimates of the 4S Trial by Gender and Age[532]

Costs ($) Per QALY Gained					
Group	Age 35–44	Age 45–54	Age 55–64	Age 65–74	Age 75–84
Men	4,500	1,800	3,900	6,700	9,900
Women	40,000	8,100	8,400	9,500	11,000

the 4S trial, i.e., about 26 percent. It can be expected that cost-effectiveness analysis of these trials will reveal a higher cost per QALY gained than for the 4S trial.[532,610] For example, in other trials of pravastatin therapy (PLAC I and PLAC II), one analysis[611] estimated costs per QALY saved in populations similar to that of CARE and LIPID to average about $25,000 at 1997–1998 drug prices. Also, Tsevat et al.[607] report for the CARE study that treatment with pravastatin increased quality-adjusted life expectancy at an incremental cost of $16,000 to $32,000 (average $24,000) per QALY gained. This value also is consistent with the variable cost-effectiveness within subgroups of persons with established CHD reported by Goldman et al.[610] and Prosser et al.[532]

e. Cost-effectiveness analysis in persons with CHD risk equivalents

Direct evidence of cost-effectiveness from randomized clinical trials is not available for persons with CHD risk equivalents. However, randomized trials and economic decision models consistently have confirmed that clinical benefit and cost-effectiveness are a function of population baseline risk. Models indicate that the cost-effectiveness of treating CHD risk equivalent populations is similar to that of those with symptomatic CHD.[532,610,612] Thus, although the strength of evidence is somewhat less, cholesterol reduction in CHD risk equivalent populations is expected to exhibit the same degree of cost-effectiveness as observed in the clinical trials of secondary prevention.

f. Cost-effectiveness of primary prevention

1) Cost-effectiveness of dietary therapy for primary prevention

According to the analysis performed by Prosser et al.,[532] dietary therapy is more cost-effective than drug therapy for primary prevention. When the same assumptions are applied to dietary as to statin drug therapy, the costs per QALY gained usually are below $50,000 for persons with elevated LDL cholesterol and multiple risk factors. Prosser et al.[532] also examined the cost-effectiveness of combining dietary therapy with an inexpensive drug (nicotinic acid). This combination enhanced the cost-effectiveness of therapy and eroded the incremental cost-effectiveness of statin therapy. A similar improvement in cost-effectiveness likely would result from combining dietary therapy with other therapeutic dietary options for LDL lowering (e.g., plant stanols/sterols and increased viscous fiber [see Section V]).

2) Cost-effectiveness of drug therapy for short-term primary prevention

All interventions with drugs incur costs and have the potential for risk as well as benefit. Thus, evidence of demonstrated benefit is especially important before recommending primary prevention on a population basis, where individual benefits are reduced relative to secondary prevention. Primary prevention encompasses an extremely broad spectrum of CHD risk, and cost-effectiveness of drug therapy declines in direct relation to baseline population risk. Evidence of the cost-effectiveness of drugs in primary prevention among people at moderate-to-high risk for CHD events is available from two sources: WOSCOPS and a series of economic decision models.

3) Cost-effectiveness for primary prevention based on WOSCOPS results

The West of Scotland Coronary Prevention Study (WOSCOPS) provides the best source of data from which to estimate cost-effectiveness for primary prevention among individuals at higher risk for CHD events. As indicated by the event rate in the placebo group, WOSCOPS participants had an estimated 10-year risk for myocardial infarction and CHD death (hard CHD) of about 15 percent. A cost-effectiveness analysis was performed based on clinical resource use and costs observed in the WOSCOPS trial.[600] As with the cost-effectiveness analyses of the other large statin trials, a Markov model was used to estimate the effects of alternative assumptions regarding long-term benefit of pravastatin therapy and a range of discount rates on expected number of people making the transition to symptomatic cardiovascular disease, survival, and

recurrent coronary heart disease events for each treatment strategy beyond the trial period. Impact on quality of life was not estimated. Costs and benefits were discounted at 6 percent per year in the base case analysis. Incremental cost per year of life gained for the WOSCOPS cohort as a whole was estimated to be approximately $30,000 (UK costs and currency converted to dollars), ranging from approximately $19,000–$55,000, depending on assumptions used in various sensitivity analyses. These analyses incorporated only the initial management of CHD events; consideration of subsequent costs resulting from a CHD event would have resulted in somewhat improved estimates of cost-effectiveness. Based on analysis of the WOSCOPS trial, a reasonable estimate of costs per QALY saved at current retail drug prices of subjects with a 10-year risk of 15 percent would be about $50,000. A similar result was obtained by Morris.[613]

Estimates of cost-effectiveness from clinical trials in subgroups that are at variable risk are less reliable than for the whole cohort, but can be informative nonetheless. In WOSCOPS, restriction of statin therapy to the 25 percent of participants with a risk for hard CHD of >2 percent per year, who incurred 45 percent of all CHD events, revealed an incremental cost per additional year of life gained of approximately $20,000.[600,614] This estimate clearly differs from that of the lowest-risk quartile of subjects, which had a risk for hard CHD of about 1 percent per year. A formal cost-effectiveness analysis has not been presented for this study population subgroup. However, extrapolation of the published WOSCOPS cost-effectiveness analysis to this subgroup yields an incremental cost per additional year of life gained of approximately $100,000, assuming statin therapy costs of about $1,000 per year.

4) Cost-effectiveness of primary prevention based on the AFCAPS/TexCAPS trial

The AFCAPS/TexCAPS trial[207] studied the effectiveness of statins for risk reduction in participants with only borderline-high risk. Although statin therapy proved to be efficacious for reducing major coronary events, a comparison of AFCAPS/TexCAPS with other trials is hampered by the fact that the primary endpoint included unstable angina in addition to myocardial infarction and CHD death. Thus, the primary clinical endpoint differed from those of other trials in which major coronary events included only myocardial infarction and CHD death. In AFCAPS/TexCAPS, CHD rates in the placebo group were about 1.09 percent per year, with unstable angina accounting for a significant half of all "major coronary events." From a purely economic point of view, differences between unstable angina and myocardial infarction are not substantial; costs incurred by hospitalization for unstable angina are similar in magnitude to those for myocardial infarction. However, total CHD events were incorporated into the WOSCOPS cost-effectiveness analysis described above rather than hard CHD only. Using WOSCOPS criteria for analysis, incremental cost per additional year of life gained would be >$100,000 for the whole cohort of AFCAPS/TexCAPS. For the higher risk subgroups, however, costs could be lower.

5) Cost-effectiveness in long-term primary prevention

Primary prevention aims to reduce risk for CHD in the long term as well as in the short term. The public health approach to long-term primary prevention generally is considered to have a favorable incremental cost-effectiveness ratio. However, at current retail drug prices, drug treatment for primary prevention in persons whose 10-year risk is <10 percent may not be considered cost-effective, i.e., it would exceed $100,000 per QALY saved.[532,600,610] Nonetheless, ATP III recommends consideration of drug therapy in lower risk persons (0–1 risk factor) whose LDL-cholesterol levels are very high (≥190 mg/dL) and in persons with multiple risk factors whose LDL-cholesterol concentrations are high (≥160 mg/dL); these recommendations include a trial of dietary therapy before drug consideration. The recommendation represents the attempt to achieve an appropriate balance between risk and costs. CHD is the foremost killer of Americans. Moreover, persons with elevated LDL cholesterol are at high long-term risk for CHD (see Table II.7–3 and Figure II.7–1). These facts must weigh against the costs of long-term drug therapy. In addition, the costs of drug therapy are difficult to judge. Many payment plans provide LDL-lowering drugs at prices below retail prices. Further, loss of patent protection and increased market competition likely will markedly reduce the prices of drugs over the long term. With each price reduction, cost-effectiveness will increase. ATP III recommendations for long-term primary prevention reflect the considered judgment of the expert panel for the optimal management of persons with elevated LDL cholesterol. The recommendations attempt to balance benefit against

costs, and it must be noted that several other approaches that were potentially beneficial but still more costly were rejected.

g. Summary

Cost-effectiveness is directly related to baseline population risk and inversely related to drug cost per unit of 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 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 QALY saved at each decrement in costs (Table II.14–4). 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 Hay et al.[615]

Specific 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.

Table II.14–4. Dependence of Cost-Effectiveness on Costs of LDL-Lowering Drugs*

	Estimated Cost-Effectiveness of LDL-Lowering Therapy (costs per QALY gained) at Different Costs of LDL-Lowering Drugs			
10-year risk†	$1000 per year	$500 per year	$250 per year	$125 per year
35%	10,000	5,000	2,500	1,250
25%	25,000	12,500	6,250	3,125
15%	50,000	25,000	12,500	6,250
10%	100,000	50,000	25,000	12,500
5%	200,000	100,000	50,000	25,000

* Table developed from aggregate data available in existing literature[532,600,603-609,613,615]
† Risk expressed as 10-year risk for hard CHD (myocardial infarction + coronary death).

Evidence statement: At current retail drug prices, LDL-lowering drug therapy is highly cost-effective in persons with established CHD (A1).

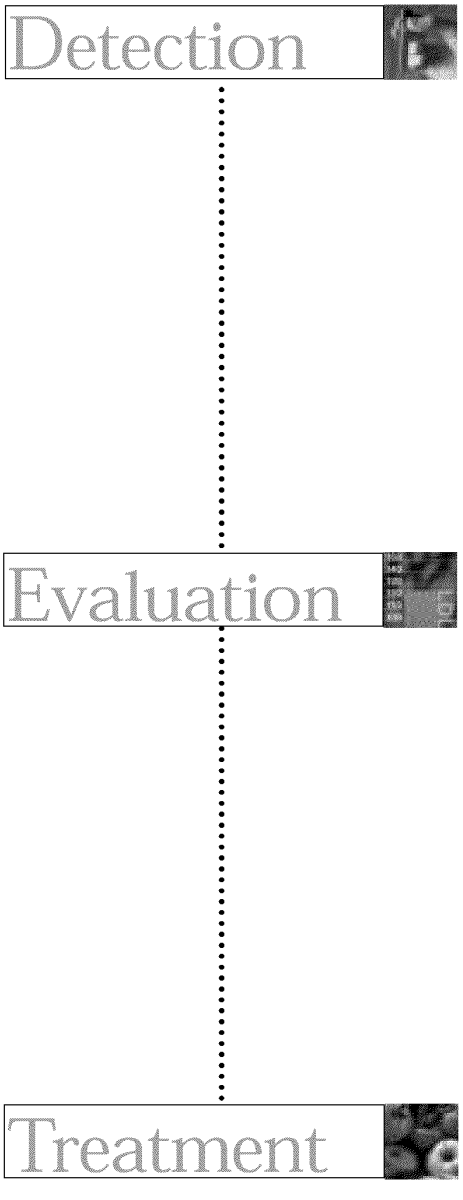
Evidence statement: LDL-lowering drug therapy is cost-effective for primary prevention in persons with CHD risk equivalents (C1).

Evidence statement: At current retail drug prices, when 10-year risk for hard CHD (myocardial infarction + CHD death) is in the range of 10–20 percent per year, LDL-lowering drug therapy carries an acceptable cost-effectiveness (by current cost-effectiveness standards in the United States) (B1).

Evidence statement: At current retail drug prices, when 10-year risk for hard CHD (myocardial infarction + CHD death) is <10 percent per year, the cost-effectiveness of LDL-lowering drug therapy exceeds current cost-effectiveness standards in the United States (A2).

Recommendation: When 10-year risk for hard CHD is <10 percent per year, LDL-lowering drugs should be used judiciously. Priority should be given to dietary therapy, which is more cost-effective. However, if LDL-cholesterol levels remain ≥160 mg/dL after dietary therapy in persons with 10-year risk <10 percent, LDL-lowering drugs should be considered if long-term risk for CHD is deemed to be high, i.e., if multiple major risk factors are present. When LDL-cholesterol levels are ≥190 mg/dL after dietary therapy, long-term risk is considered to be high regardless of other risk factors; thus LDL-lowering drugs should be considered. The need to reduce long-term risk in some circumstances can override the need to stay within currently acceptable cost-effectiveness criteria.

Footnote:
As this ATP III report was being prepared for printing, the results of the Heart Protection Study (HPS) were reported (Heart Protection Study Collaborative Group, *Lancet*, 2002;360:7-22). This randomized, double-blind, 5-year trial in the United Kingdom studied the effects of simvastatin for LDL cholesterol lowering vs. placebo in 20,536 adults aged 40-80 years who were at high risk for CHD death because they had CHD, other occlusive arterial disease, or diabetes. In the treatment group, LDL cholesterol was lowered by 29%, all-cause mortality was reduced by 13%, CHD events (non-fatal myocardial infarction or CHD death) by 27%, strokes by 25%, revascularizations by 24%, and any major vascular event (non-fatal myocardial infarction or CHD death, stroke, or revascularization) by 24%. The benefit of treatment was seen in both men and women, and in both the younger and older participants (even in those 75-80 years old at entry, who were 80-85 years old at the end of the trial). The HPS results provide additional strong scientific support for the ATP III recommendation to lower LDL cholesterol intensively in individuals with CHD or a CHD risk equivalent. The implications of the HPS results for patients with low and very low LDL cholesterol levels, as well as other implications, will be explored in a paper to be prepared for the Coordinating Committee of the National Cholesterol Education Program.



III. Detection and Evaluation

III. Detection and Evaluation

ATP III recognizes that detection of cholesterol disorders and other coronary heart disease (CHD) risk factors occurs primarily through clinical case finding. Risk factors can be detected and evaluated as part of a person's work-up for any medical problem. Alternatively, public screening programs can identify risk factors, provided that affected individuals are appropriately referred for physician attention. The identification of cholesterol disorders in the setting of a medical examination has the advantage that other cardiovascular risk factors—including prior CHD, PVD, stroke, age, gender, family history, cigarette smoking, high blood pressure, diabetes mellitus, obesity, physical inactivity—co-morbidities, and other factors can be assessed and considered prior to treatment.

At the time of physician evaluation, the person's overall risk status is assessed. Thus, detection and evaluation of cholesterol and lipoprotein problems should proceed in parallel with risk assessment for CHD. The approach to both is described below.

1. Identification of risk categories for setting of LDL-cholesterol goals

The guiding principle of ATP III is that the intensity of LDL-lowering therapy should be adjusted to the individual's absolute risk for CHD. In applying this principle, ATP III maintains that both short-term (≤10-year) and long-term (>10-year) risk must be taken into consideration. Thus, treatment guidelines are designed to incorporate risk reduction for both short-term and long-term risk (composite risk). ATP III identifies three categories of risk for CHD that modify goals and modalities of LDL-lowering therapy: established CHD and CHD risk equivalents, multiple (2+) risk factors, and 0–1 risk factor (Table III.1–1).

Table III.1–1. Categories of Risk for Coronary Heart Disease (CHD)

Risk Categories
Established CHD & CHD risk equivalents
Multiple (2+) risk factors
0–1 risk factor

a. Identification of persons with CHD and CHD risk equivalents

Coronary heart disease. Persons with CHD are at very high risk for future CHD events (10-year risk >20 percent). Several clinical patterns constitute a diagnosis of CHD; these include history of acute myocardial infarction, evidence of silent myocardial infarction or myocardial ischemia, history of unstable angina and stable angina pectoris, and history of coronary procedures (coronary angioplasty and coronary artery surgery).

Other clinical atherosclerotic diseases. Persons in this subcategory have a CHD risk equivalent. Included are those with peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease (symptomatic [e.g., transient ischemic attack or stroke of carotid origin] or >50 percent stenosis on angiography or ultrasound), and likely other forms of clinical atherosclerotic disease (e.g., renal artery disease).

Diabetes mellitus. ATP III counts diabetes as a CHD risk equivalent. The current criteria for the diagnosis of type 2 diabetes from the American Diabetes Association (ADA) are a fasting plasma glucose ≥126 mg/dL and/or 2-hour plasma glucose (after a standard 75 mg glucose load) ≥200 mg/dL.[616] The current ADA recommendations de-emphasize the oral glucose tolerance test in routine clinical care, so it is expected that most people with diabetes will be diagnosed by a fasting glucose level.

Multiple risk factors and 10-year risk for CHD >20 percent. Based on 10-year risk assessment using Framingham scoring (see below), a person in this category can be said to have a CHD risk equivalent.

b. Risk assessment in persons without CHD or CHD risk equivalents (starting with risk factor counting)

ATP III's primary approach to risk assessment for persons without CHD or CHD risk equivalents is to count the number of major risk factors for CHD. For persons with multiple (2+) risk factors, a second step is to carry out 10-year risk assessment for CHD. There are two essential reasons for estimating 10-year risk in persons

with multiple risk factors: (a) to identify those who have a 10-year risk >20 percent (CHD risk equivalent), and (b) to identify those with borderline high LDL cholesterol who have a 10-year risk of 10–20 percent. Both groups are candidates for more intensive LDL-lowering therapy than was recommended in ATP II.

An alternative approach, which gives similar though not identical results, is to begin with 10-year risk assessment, followed by counting of risk factors in persons with a 10-year risk for CHD <10 percent. This sequence is recommended by advocates of "global risk assessment." The sequence of risk assessment depends on personal choice. It should be noted that beginning with 10-year risk assessment is consistent with approaches recently proposed in other guidelines. Nevertheless, ATP III stratifies risk below 10 percent on the basis of the number of risk factors and not on projected 10-year risk.

The major independent risk factors identified in risk factor counting include:

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)
- Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)

If a person has a high HDL cholesterol (≥60 mg/dL), one risk factor is subtracted from the count. If the person has type 2 diabetes, this person is classified as having a CHD risk equivalent (see Section II.12.b).

1) Identification of persons with multiple (2+) risk factors

The second risk category that modifies LDL goals includes persons with multiple (2+) risk factors. Approaches to clinical evaluation of risk factors that define the person with multiple (2+) risk factors are shown in Table III.1–2.

Table III.1–2. Clinical Evaluation to Identify Persons with Multiple (2+) Risk Factors

Risk factor	Definition	Comments
Cigarette smoking	Any cigarette smoking in the past month	
Hypertension	Blood pressure ≥140/90 mmHg or taking antihypertensive medications	Multiple measures of blood pressure required for diagnosis (see JNC VI for further clinical evaluation)[160,161]
Low HDL cholesterol	HDL cholesterol <40 mg/dL	
Family history of premature CHD	Clinical CHD or sudden death documented in 1st–degree male relative before age 55 or in 1st–degree female relative before age 65	

2) Calculation of 10-year CHD risk

The person with multiple risk factors is assigned to one of three categories according to 10-year risk for hard CHD (myocardial infarction + CHD death): >20 percent, 10–20 percent, and <10 percent (see Table III.1–3). A person with 10-year risk >20 percent is elevated to the category of CHD risk equivalent.

Table III.1–3. Categories of 10-Year Risk for Persons with Multiple (2+) Risk Factors

Risk Categories
>20% (CHD risk equivalents)
10–20%
<10%

Risk assessment for determining 10-year risk is carried out according to Framingham risk scoring (Tables III.1–5 for men and III.1–6 for women). Risk factor scoring in ATP III derives from an update of the Framingham database and methodology reported by Wilson et al.;[10] the revised scoring applies specifically to hard CHD. The risk factors included in the Framingham calculation of 10-year risk are: age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. The first step is to calculate the number of points for each risk factor. For initial assessment, values for total cholesterol and HDL cholesterol are required. Because

of a larger database, Framingham estimates are more robust for total cholesterol than for LDL cholesterol. Note that the LDL-cholesterol level is the primary target of therapy. Total cholesterol and HDL-cholesterol values should be the average of at least two measurements obtained from lipoprotein analysis. The average of several blood pressure measurements, as recommended by JNC VI,[160,161] is needed for an accurate measure of baseline blood pressure. The blood pressure value used in the risk score is the average of several recent values, regardless of whether the person is on antihypertensive therapy. However, if the person is on antihypertensive treatment, an extra point is added beyond points for the blood pressure reading because treated hypertension carries residual risk. The designation "smoker" means any cigarette smoking in the past month. The total risk score sums the points for each risk factor. The 10-year risk for myocardial infarction and coronary death is estimated from total points, and the person is categorized according to absolute 10-year risk as indicated above.

The primary endpoint for 10-year risk assessment in ATP III is "hard CHD" (myocardial infarction + CHD death). However, previous Framingham risk scoring provided estimates of total CHD (stable angina, unstable angina, myocardial infarction, and CHD death). Generally, estimates for hard CHD are about two-thirds to three-fourths of those for total CHD. An exception is for women whose 10-year risk is <10 percent. Estimates of hard CHD for these women can be significantly lower than for total CHD because of the high prevalence of angina pectoris in middle-aged women without evident coronary atherosclerotic disease. Although ATP III does not recommend use of Framingham risk scores for total CHD, it has been adopted in various European countries in accord with guidelines of European cardiovascular societies. Should Framingham scores for total CHD be employed, the approximate equivalency for the three subcategories of risk for persons with multiple (2+) risk factors is listed in Table III.1–4.

Ten-year risk for hard CHD can be estimated for men and women from Tables III.1–5 and III.1–6, respectively (note that charts for men and women have different scales, so point scores for the two sexes cannot be directly compared). Tables III.1–5 and III.1–6, which approximate the Framingham equations, are provided as a convenient way to estimate 10-year CHD risk using a "paper-and-pencil" approach. Electronic calculators to determine 10-year risk are available on the ATP III page of the NHLBI Web site (www.nhlbi.nih.gov/guidelines/cholesterol). The electronic calculators give a more precise value for 10-year risk because they use continuous variables as opposed to the discrete cutpoints used in the tables. However, the tables provide a result that is accurate for clinical purposes. Improved methods of assessing 10-year CHD risk will undoubtedly be developed in the future.

Table III.1–4. Approximate Equivalency of Subcategories of Hard and Total CHD According to Framingham Risk Scoring (modified from Wilson et al.[10])

Hard CHD*	Total CHD†
>20% (CHD Risk Equivalent)	>25% (CHD Risk Equivalent)
10–20%	15–25%
<10%	<15%

* Hard CHD endpoints: myocardial infarction + CHD death.
† Total CHD endpoints: myocardial infarction + CHD death + "coronary insufficiecy" (unstable angina) + angina pectoris.

It should be noted that the Framingham equations for 10-year CHD risk are not intended to be used to track changes in risk over time as risk factors are modified. The 10-year risk calculation is intended to be performed at the outset to help guide decisions about the intensity of therapy. Thereafter, the clinical trial results are the best guide to the change in risk that accompanies reductions in the risk factors.

In Tables III.1–5 and III.1–6, note that the points for total cholesterol and cigarette smoking decline with age. At face value, this decline is in accord with reports that relative risk for CHD for these two parameters decreases with advancing age. However, this decline is more apparent than real because of the exponential rise in risk with mounting Framingham points. Thus, in older persons who have several points due to age alone, the addition of fewer points for high total cholesterol or smoking increases absolute risk as much or more as do more points at a younger age. Thus, the data in Tables III.1–5 and III.1–6 should not be misconstrued to mean that these risk factors decline in importance with advancing age. The correctness of this conclusion is shown by the same relative benefit in risk reduction obtained with LDL-lowering therapy or smoking cessation in older persons as in younger persons.

Table III.1–5. Estimate of 10-Year Risk for Men (Framingham Point Scores)

Age	Points
20–34	-9
35–39	-4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

Total Cholesterol	Points at Ages 20–39	Points at Ages 40–49	Points at Ages 50–59	Points at Ages 60–69	Points at Ages 70–79
<160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
≥280	11	8	5	3	1

	Points at Ages 20–39	Points at Ages 40–49	Points at Ages 50–59	Points at Ages 60–69	Points at Ages 70–79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL	Points
≥60	-1
50–59	0
40–49	1
<40	2

Systolic BP	If Untreated	If Treated
<120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
≥160	2	3

Point Total	10-Year Risk	Point Total	10-Year Risk
<0	<1%	11	8%
0	1%	12	10%
1	1%	13	12%
2	1%	14	16%
3	1%	15	20%
4	1%	16	25%
5	2%	≥17	≥30%
6	2%		
7	3%		
8	4%		
9	5%		
10	6%		

Table III.1–6. 10-Year Risk Estimates for Women (Framingham Point Scores)

Age	Points
20–34	-7
35–39	-3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	16

Total Cholesterol	Points at Ages 20–39	Points at Ages 40–49	Points at Ages 50–59	Points at Ages 60–69	Points at Ages 70–79
<160	0	0	0	0	0
160–199	4	3	2	1	1
200–239	8	6	4	2	1
240–279	11	8	5	3	2
≥280	13	10	7	4	2

	Points at Ages 20–39	Points at Ages 40–49	Points at Ages 50–59	Points at Ages 60–69	Points at Ages 70–79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL	Points
≥60	-1
50–59	0
40–49	1
<40	2

Systolic BP	If Untreated	If Treated
<120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
≥160	4	6

Point Total	10-Year Risk	Point Total	10-Year Risk
<9	<1%	20	11%
9	1%	21	14%
10	1%	22	17%
11	1%	23	22%
12	1%	24	27%
13	2%	≥25	≥30%
14	2%		
15	3%		
16	4%		
17	5%		
18	6%		
19	8%		

2. Determination and classification of LDL cholesterol

a. Who should be tested for cholesterol and lipoproteins?

A fasting lipoprotein profile including major blood lipid fractions, i.e., total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride, should be obtained at least once every 5 years in adults age 20 and over. The rationale for starting cholesterol testing in young adults is described in Sections II.7.j and VIII.4. Since risk categories change slowly over time, the panel judged that lipoprotein measurements once every 5 years are adequate in otherwise low-risk persons. More frequent measurements are required for persons with multiple risk factors or, in those with 0–1 risk factor, if the LDL level is only slightly below the goal level, as will be described subsequently (see Table IV.2–5). If the testing opportunity is nonfasting, only the values for total cholesterol and HDL will be usable. In otherwise low-risk persons (0–1 risk factor), further testing is not required if the HDL-cholesterol level is ≥40 mg/dL and total cholesterol is <200 mg/dL. However, for persons with multiple (2+) risk factors, lipoprotein measurement is recommended as a guide to clinical management.

b. Procedures of measurement

A lipoprotein profile involving measurement of triglycerides and the indirect calculation of LDL cholesterol (the common method) requires a 9- to 12-hour fast. Individuals should be seated for at least five minutes prior to phlebotomy to avoid hemoconcentration. Blood should be collected in tubes without anticoagulant for serum or with EDTA for plasma. Plasma produces values approximately 3 percent lower than serum.

The measurement of any lipid is preferably performed with the person in a baseline stable condition, that is, in the absence of acute illnesses including stroke, trauma, surgery, acute infection, weight loss, pregnancy, or recent change in usual diet. These conditions often result in values that are not representative of the person's usual level.

In persons admitted to the hospital for acute coronary syndromes or coronary procedures, lipid measurements should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy at discharge. LDL cholesterol levels begin to decline in the first few hours after a coronary event and are significantly decreased by 24–48 hours and may remain low for many weeks. Thus, the initial LDL cholesterol level obtained in the hospital may be substantially lower than is usual for the patient. Nevertheless, values obtained during the acute phase provide guidance for initiating LDL-lowering therapy.

LDL cholesterol is routinely estimated from measurements of total cholesterol, total triglycerides, and HDL cholesterol in the fasting state. If the triglyceride level is below 400 mg/dL, this value can be divided by five to estimate the VLDL-cholesterol level. Since total cholesterol is the sum of LDL cholesterol, HDL cholesterol, and VLDL cholesterol, LDL cholesterol can be calculated as follows:[617]

$$\text{LDL-C}^{*} = \text{TC}^{**} - \text{HDL-C}^{\dagger} - \text{TG}^{\ddagger}/5$$

(where all measures are in mg/dL)

For persons with triglycerides over 400 mg/dL, estimation of LDL cholesterol by this method is not accurate. A more complex ultracentrifugation method in a specialized laboratory is required for accuracy. In addition, individuals with significantly elevated triglycerides need further evaluation.

The practical difficulties of obtaining fasting blood samples have resulted in a search for methods that directly measure LDL cholesterol in the nonfasting state. In recent years, several methods have been developed and standardized. Such methods will grow in use but still require careful quality control and monitoring. These methods do not require separation of LDL cholesterol and can be performed rapidly on automated machines. For initial testing, fasting triglycerides provide additional important information.

Most measurements are performed on venous samples from a phlebotomy. However, finger-stick methods are also widely available for total cholesterol, triglyceride, and HDL-cholesterol measurements. Careful attention must be paid to sample collection to minimize tissue

* LDL-C=LDL Cholesterol
** TC=Total Cholesterol
† HDL-C=HDL Cholesterol
‡ TG=Triglycerides

fluid dilution. Sample handling is critical in obtaining accurate values from finger-stick samples. They can produce accurate results when standardized by the same methods described for other laboratories.

The choice of laboratories is important to ensure accuracy and reliability in lipid measurements. Clinicians should seek a laboratory that participates in a recognized standardization program, preferably one standardized by the National Network Laboratories of the Centers for Disease Control and Prevention. More detailed information is provided in "Recommendations for Improving Cholesterol Measurement" from the Laboratory Standardization Panel of the NCEP[618] and in "Recommendations on Lipoprotein Measurement" from the NCEP Working Group on Lipoprotein Measurement.[619]

c. Classification of lipid and lipoprotein levels

In ATP II, initial classification for primary prevention was based on measurement of total cholesterol and HDL cholesterol. Because of increased availability of lipoprotein testing and to achieve more efficient evaluation, ATP III recommends measurement of LDL cholesterol for initial classification. This measurement requires a fasting lipoprotein analysis that includes total cholesterol, HDL cholesterol, triglycerides, and an estimate of LDL cholesterol. ATP III classifications of these four lipid and lipoprotein parameters were shown in Tables II.2–4, II.3–2, II.3–1, and II.2–4, respectively.* Persons with very high LDL-cholesterol concentrations can have one of several familial forms of hypercholesterolemia (see Section VII).

d. Secondary dyslipidemias (see Section VII)

Any person who presents with elevated LDL cholesterol or other form of hyperlipidemia must undergo evaluation to rule out secondary dyslipidemia. The major causes of secondary dyslipidemia are shown in Table III.2–1. They include diabetes, hypothyroidism, nephrotic syndrome, obstructive liver disease, chronic renal failure, and certain drugs that raise LDL cholesterol or triglyceride levels or lower HDL-cholesterol levels—particularly progestins, anabolic steroids, corticosteroids, and certain antihypertensive agents—and protease inhibitors (for persons with HIV infections). The family, drug, and diet history may reveal clues to secondary causes of dyslipidemia. Patient history and physical examination can provide clues to diabetes, hypothyroidism, nephrotic syndrome, or liver disease. If a secondary dyslipidemia is suspected, urinalysis (for proteinuria), serum thyroid stimulating hormone (TSH) (for LDL cholesterol ≥160 mg/dL to rule out a masked form of hypothyroidism), and alkaline phosphatase (to detect obstructive biliary disease) should be measured. Glycosylated hemoglobin is a standard method for assessing the status of glucose control.

Table III.2–1. Major Causes of Secondary Dyslipidemia

- Diabetes
- Hypothyroidism
- Nephrotic syndrome
- Obstructive liver disease
- Chronic renal failure
- Drugs (that may raise LDL cholesterol or cause other dyslipidemias)
  - Progestins
  - Anabolic steroids
  - Corticosteroids
  - Protease inhibitors for treatment of HIV infections

3. Atherogenic dyslipidemia and the metabolic syndrome

a. Atherogenic dyslipidemia and classification of serum triglycerides

Atherogenic dyslipidemia is defined by elevation of serum triglycerides, presence of small LDL particles, and low HDL-cholesterol levels. For clinical purposes, elevated triglyceride (≥150 mg/dL) plus low HDL cholesterol (<40 mg/dL) define atherogenic dyslipidemia. As previously discussed (Section II.6), these levels frequently denote the presence of the metabolic syndrome. Serum triglycerides are measured in the fasting state as part of lipoprotein analysis. The ATP III classification of fasting serum triglycerides was given in Table II.3–1. The various categories of elevated triglycerides are described in more detail in Section VII. Triglyceride levels ≥200 mg/dL indicate the need to identify non-HDL cholesterol as a secondary target of lipid-lowering therapy (see Section VII).

* Population distributions for serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels in the United States are provided in Appendix III-A. To convert cholesterol values in mg/dL to mmol/L, divide by 38.7. To convert triglyceride values in mg/dL to mmol/L, divide by 88.6.

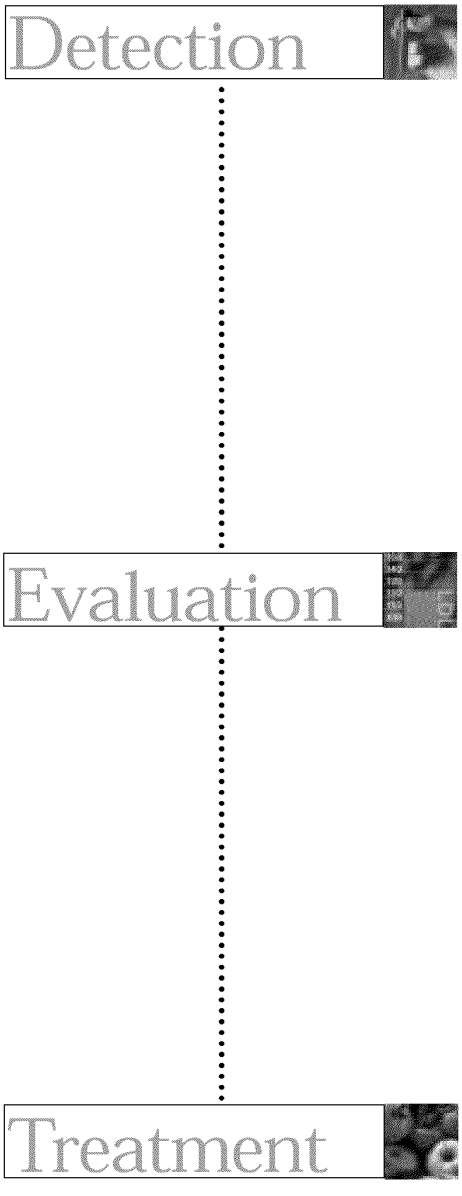
b. Diagnosis of the metabolic syndrome

As stated in Section II.6, the metabolic syndrome is identified in ATP III by the presence of three or more marginal or categorical risk factors (see Table II.6–1). Other components of the metabolic syndrome (insulin resistance and prothrombotic state) cannot be identified by routine clinical evaluation. However, in the presence of abdominal obesity, they can be assumed to be present to some degree.

4. Role of emerging risk factors in risk assessment

The relationship of emerging risk factors to CHD risk is considered in detail in Section II.5. Some of these factors are potential adjuncts to risk assessment, but they should not take priority over the major risk factors. Risk evaluation should first be carried out as described for the major risk factors. Measurement of emerging risk factors is optional. Emerging risk factors that can be measured include elevations of Lp(a), remnant lipoproteins, small LDL, fibrinogen, homocysteine, high-sensitivity C-reactive protein, impaired fasting plasma glucose (110–125 mg/dL), and measures of subclinical atherosclerosis (myocardial ischemia by exercise testing, carotid intimal-medial thickness, and/or coronary calcium). Among these factors, measures of subclinical atherosclerosis appear to have the most potential usefulness for risk assessment in middle-aged or older persons in whom standard risk factors decline in predictive power for individuals. If measurements are made and if abnormalities are detected, physician judgment is needed whether to modify the risk assessment. Examples of where emerging risk factors might be integrated into ATP III risk assessment are the following: (a) to elevate persons with multiple risk factors and 10-year risk ≤20 percent to the category of CHD risk equivalent, and (b) to guide a decision about use of LDL-lowering drugs—after lifestyle changes—in persons with 0–1 risk factor who have an LDL cholesterol in the range of 160–189 mg/dL (see Section IV.2.c).

ATP III does not recommend routine measurement of any of the emerging risk factors for the purpose of risk assessment. They should be used for this purpose only in selected persons and then only on the basis of considered clinical judgment. Several of these tests are not readily available, not well standardized, and are relatively expensive. Therefore, if these tests are used to adjust risk estimates, the physician should be fully cognizant of their limitations; above all, they should not be given undue weight relative to the major risk factors.



Appendix III-A

Distributions of Total Cholesterol, LDL Cholesterol, HDL Cholesterol, and Triglycerides in the U.S. Adult Population, NHANES III Data (1988-1994)(Serum)

Serum total cholesterol (mg/dL) levels for persons 20 years of age and older. United States, 1988-94

Sex, Age and Race/Ethnicity	Number of Examined Persons	Mean	Selected percentile								
			5th	10th	15th	25th	50th	75th	85th	90th	95th
Men*											
20 years and older	7,531	202	139	151	160	173	200	228	244	255	273
20-34	2,298	186	131	142	148	161	183	209	223	233	253
35-44	1,323	206	143	154	163	180	205	232	247	257	267
45-54	904	216	154	167	178	191	214	242	255	266	283
55-64	1,004	216	154	167	174	189	214	243	258	270	282
65-74	1,058	212	149	163	175	186	209	237	248	263	284
75+	944	205	145	155	164	176	203	230	246	255	273
Women*											
20 years and older	8,531	206	143	153	161	175	201	233	251	265	284
20-34	2,651	184	132	141	148	158	181	205	219	231	248
35-44	1,645	195	144	153	160	171	192	215	234	243	257
45-54	1,013	217	157	166	174	187	212	243	259	274	298
55-64	1,045	235	167	184	191	204	229	261	276	286	307
65-74	1,075	233	170	181	189	204	232	258	276	289	308
75+	1,102	229	161	174	185	198	228	258	274	286	305
Mexican American											
Men	2,175	199	137	150	157	171	197	224	241	253	272
Women	2,165	198	139	148	156	167	193	223	238	249	274
Non-Hispanic black											
Men	1,923	198	136	147	155	169	195	222	239	251	275
Women	2,360	201	136	148	157	170	196	226	246	261	284
Non-Hispanic white											
Men	3,161	203	141	153	162	174	201	229	244	256	272
Women	3,645	208	144	155	163	177	203	235	252	267	284

* Total sample of men and women includes racial/ethnic groups other than those shown.

Serum LDL cholesterol (mg/dL) levels for persons 20 years of age and older. United States, 1988-94

Sex, Age and Race/Ethnicity	Number of Examined Persons	Mean	Selected percentile								
			5th	10th	15th	25th	50th	75th	85th	90th	95th
Men*											
20 years and older	3,154	130	76	87	93	105	128	153	166	177	194
20-34	970	119	72	81	87	97	119	139	151	156	170
35-44	546	135	82	91	96	111	132	156	171	186	205
45-54	388	140	76	95	106	117	140	164	178	188	195
55-64	428	138	82	90	99	115	135	162	174	182	200
65-74	468	136	83	92	103	113	133	158	171	182	196
75+	354	132	86	92	97	109	128	151	167	177	194
Women*											
20 years and older	3,641	125	69	81	89	98	121	147	162	172	190
20-34	1,190	111	63	71	79	90	109	130	142	152	170
35-44	741	118	70	83	90	96	115	137	147	159	171
45-54	444	131	70	85	93	106	129	153	166	177	190
55-64	457	144	80	93	107	121	143	167	184	192	209
65-74	417	143	76	95	106	119	144	166	182	188	203
75+	392	145	83	102	106	119	144	167	186	196	209
Mexican American											
Men	913	124	71	78	85	98	121	144	160	171	188
Women	943	117	67	75	83	93	115	137	152	161	178
Non-Hispanic black											
Men	802	127	71	79	86	100	124	149	165	179	200
Women	1,012	122	63	77	84	97	119	145	161	172	193
Non-Hispanic white											
Men	1,317	131	79	88	95	106	129	154	167	177	194
Women	1,539	126	70	81	89	98	122	149	164	173	189

* Total sample of men and women includes racial/ethnic groups other than those shown.

Serum HDL cholesterol (mg/dL) levels for persons 20 years of age and older. United States, 1988-94

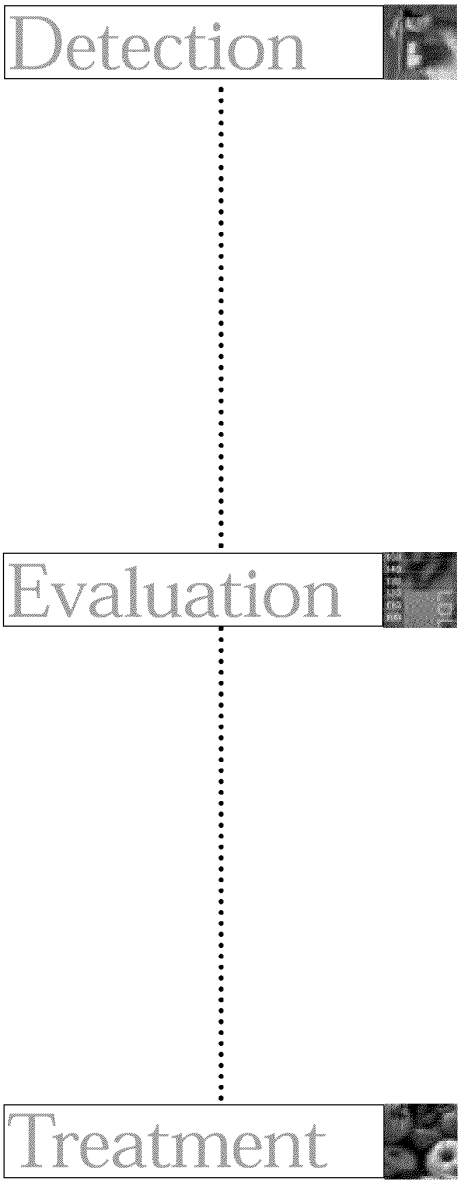
Sex, Age and Race/Ethnicity	Number of Examined Persons	Mean	Selected percentile								
			5th	10th	15th	25th	50th	75th	85th	90th	95th
Men*											
20 years and older	7,473	46	28	30	34	37	44	53	58	62	72
20-34	2,285	46	28	32	34	38	45	53	59	62	69
35-44	1,306	45	28	30	32	36	43	52	57	61	73
45-54	893	45	26	30	32	35	42	52	58	66	75
55-64	999	45	28	31	34	36	42	51	57	61	71
65-74	1,052	46	28	30	32	36	43	54	58	64	73
75+	938	47	28	31	34	37	44	54	61	66	75
Women*											
20 years and older	8,478	55	34	38	41	44	53	64	70	75	83
20-34	2,640	55	34	38	41	45	53	64	69	74	83
35-44	1,628	54	34	38	41	44	53	64	68	72	79
45-54	1,004	56	36	38	41	45	55	65	72	77	84
55-64	1,039	56	33	37	40	44	53	65	73	78	89
65-74	1,071	56	33	37	40	45	54	65	71	76	84
75+	1,096	56	32	37	40	44	55	65	71	76	86
Mexican American											
Men	2,151	46	28	32	34	37	44	52	58	61	67
Women	2,156	52	33	36	38	42	51	60	66	71	77
Non-Hispanic black											
Men	1,916	52	32	35	37	41	50	60	68	74	85
Women	2,348	57	35	39	42	46	55	66	73	79	86
Non-Hispanic white											
Men	3,138	45	27	30	33	36	43	52	57	61	71
Women	3,615	56	34	38	41	45	54	64	70	76	84

* Total sample of men and women includes racial/ethnic groups other than those shown.

Serum Triglyceride (mg/dL) levels for persons 20 years of age and older. United States, 1988-94

Sex, Age and Race/Ethnicity	Number of Examined Persons	Mean	Selected percentile								
			5th	10th	15th	25th	50th	75th	85th	90th	95th
Men*											
20 years and older	3,251	148	53	62	69	83	118	173	218	253	318
20-34	987	118	46	55	60	70	94	139	171	204	256
35-44	570	150	53	62	70	82	126	180	213	242	307
45-54	415	182	62	72	82	100	135	201	269	296	366
55-64	446	176	64	80	87	101	144	228	276	311	396
65-74	476	160	64	76	83	99	137	190	226	256	319
75+	357	144	64	71	82	96	125	175	200	220	304
Women*											
20 years and older	3,707	128	48	56	61	72	102	152	193	226	273
20-34	1,201	101	43	49	55	61	84	117	147	177	226
35-44	754	123	46	53	57	67	93	132	170	215	288
45-54	457	136	49	59	66	76	114	163	201	239	277
55-64	470	166	62	72	82	96	135	203	251	313	396
65-74	426	157	70	76	85	99	134	182	228	253	283
75+	399	150	64	74	79	94	130	178	211	235	274
Mexican American											
Men	955	152	53	60	69	83	120	184	225	259	361
Women	962	140	55	63	72	85	118	170	210	237	293
Non-Hispanic black											
Men	815	114	45	51	56	64	89	135	164	192	245
Women	1,021	96	41	46	51	58	79	113	142	162	207
Non-Hispanic white											
Men	1,357	152	55	64	71	85	123	181	223	258	319
Women	1,573	130	49	56	63	75	104	156	196	229	274

* Total sample of men and women includes racial/ethnic groups other than those shown.



IV. General Approach to Treatment—Goals and Thresholds

IV. General Approach to Treatment—Goals and Thresholds

The basic principle that guides cholesterol-lowering intervention is that the intensity of treatment is directly related to the degree of risk for CHD events. Both short-term (10-year) risk and long-term risk must be considered for treatment decisions. Persons with existing CHD (or a CHD risk equivalent) are at the highest risk; for this reason, they have the lowest goal level for LDL cholesterol and receive the most intensive treatment. For persons without CHD, classification and treatment goals are based on the category of risk, of which there are two—multiple (2+) risk factors other than LDL, and 0–1 risk factor. Persons with 2+ risk factors have an LDL goal that is not quite as low as that for persons with CHD (or CHD risk equivalents). ATP III differs from ATP II in that it distinguishes three subcategories of risk among persons with multiple (2+) risk factors: 10-year risk for hard CHD >20 percent, 10–20 percent, and <10 percent. Among the group with multiple risk factors, those at highest risk receive the most intensive LDL-lowering therapy, and those with the lowest risk receive the least intensive therapy. For persons with 0–1 risk factor, LDL goal levels are not as low as for persons with multiple risk factors, and intensive LDL-lowering therapy is not required unless LDL cholesterol levels are very high.

1. Therapeutic goals for LDL cholesterol

ATP III recommends that LDL cholesterol be the primary target of therapy. The LDL cholesterol goals for each risk category are shown in Table IV.1–1.

Table IV.1–1. LDL Cholesterol Goals for Three Risk Levels

Risk Level	LDL-C Goal
CHD and CHD Risk Equivalent	<100 mg/dL
Multiple (2+) Risk Factors	<130 mg/dL*
0–1 Risk Factor	<160 mg/dL

* LDL-C goal for multiple-risk-factor persons with 10-year risk >20 percent = <100 mg/dL.

Persons with CHD or CHD risk equivalent have an LDL cholesterol goal of <100 mg/dL. Those with multiple risk factors have an LDL cholesterol goal of <130 mg/dL; an exception is the patient with a CHD risk equivalent (>20 percent per 10 years) who has an LDL cholesterol goal <100 mg/dL. Finally, those with 0–1 risk factor have a goal LDL cholesterol of <160 mg/dL. These goals are set to maximize reduction in both short-term and long-term risk.

For persons whose LDL cholesterol levels are above the goal for the category, the goal of therapy is achieved through the judicious use of lifestyle and drug therapies. Lifestyle therapy in clinical management is designated Therapeutic Lifestyle Changes (TLC). TLC includes the following: (a) reduced intakes of saturated fats and cholesterol, (b) therapeutic dietary options to enhance LDL lowering (plant stanols/sterols and increased viscous fiber), (c) weight control, and (d) increased physical activity (see Section V). The drugs available for LDL-cholesterol-lowering are presented in Section VI.

ATP III recommends a two-step approach to cholesterol management. Priority goes to attaining the goal for LDL cholesterol; thereafter emphasis shifts to management of the metabolic syndrome and other lipid risk factors. Figure IV.1–1 shows the physician's responsibility at the first visit. Once the lipoprotein analysis is evaluated, risk factor counting and, if necessary, 10-year risk assessment are carried out to determine risk status. The patient is then started on dietary therapy or discharged with instructions for appropriate life-habit modifications. If the patient has CHD or a CHD risk equivalent, LDL-lowering drug therapy can be started simultaneously with dietary therapy if the LDL level warrants.

After an appropriate trial of dietary therapy to reduce LDL cholesterol (~ 3 months), two additional therapeutic decisions may be required. First, if the LDL cholesterol goal has not been achieved, consideration may be given to initiating drug therapy. Second, if the metabolic syndrome is present, additional lifestyle changes (i.e., weight reduction and increased physical activity) will be needed. Later, if lifestyle therapies do not alleviate the metabolic syndrome, drug therapy for treatment of the metabolic risk factors may be required.

2. Management of LDL Cholesterol

The following summarizes the ATP III approach to management of persons in the three categories of risk.

a. CHD and CHD risk equivalents

For persons with CHD and CHD risk equivalents, the type and intensity of LDL-lowering therapy are adjusted according to baseline LDL cholesterol level, i.e., whether ≥130 mg/dL, 100–129 mg/dL, or <100 mg/dL (Table IV.2–1 and Figure IV.2–1). Each subcategory of LDL cholesterol is discussed below.

1) Baseline LDL cholesterol ≥130 mg/dL

Persons with LDL cholesterol ≥130 mg/dL generally will require an LDL-lowering drug to achieve LDL cholesterol <100 mg/dL. Therefore, a cholesterol-lowering drug should be initiated simultaneously with TLC and maximal control of other risk factors. If the LDL cholesterol falls to the range of 100–129 mg/dL on cholesterol-lowering therapy, several options are available depending on circumstances:

- LDL lowering can be intensified with dietary therapy to achieve an LDL cholesterol level <100 mg/dL.
- LDL lowering can be intensified with drug therapy to achieve an LDL cholesterol level <100 mg/dL.
- If the on-treatment LDL cholesterol level is near the goal of therapy, the physician can maintain the current LDL-lowering therapy unchanged.
- If the metabolic syndrome is present, dietary therapy is intensified by increased efforts to reduce excess weight and increase physical activity.
- If the patient has elevated triglycerides or low HDL, a different lipid-lowering drug can be considered (e.g., nicotinic acid or fibric acid) for combination therapy with an LDL-lowering drug (see Section VI).

2) Baseline LDL cholesterol 100–129 mg/dL

When baseline LDL cholesterol is 100–129 mg/dL, several therapeutic options likewise are available. All approaches include TLC as initial therapy. Depending on circumstances, the following options are available:

- Inclusion of therapeutic dietary options (e.g., plant stanol/sterols and increased viscous fiber) can help to achieve the LDL goal.
- If LDL cholesterol levels remain appreciably above 100 mg/dL after 3 months of maximal dietary therapy, consideration can be given to adding an LDL-lowering drug.
- If the patient has an elevated triglyceride or low HDL cholesterol level, another lipid-lowering drug can be considered (e.g., nicotinic acid or fibric acid).
- If the LDL cholesterol level falls to near the goal on dietary therapy alone, the physician can choose to forgo use of a lipid-lowering drug for the present.

Because other risk factors may have contributed importantly to development of CHD in persons with low LDL levels, maximal control of nonlipid risk factors is necessary.

Table IV.2–1. Therapeutic Approaches to LDL Cholesterol Lowering in Persons with CHD or CHD Risk Equivalents

Subcategory of LDL Cholesterol Level	LDL Cholesterol Goal	Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	Level at Which to Initiate LDL-Lowering Drugs
≥130 mg/dL	<100 mg/dL	≥100 mg/dL	Start drug therapy simultaneously with dietary therapy
100–129 mg/dL	<100 mg/dL	≥100 mg/dL	Consider drug options*
<100 mg/dL	<100 mg/dL	TLC & emphasize weight control and physical activity	LDL-lowering drugs not required

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by TLC. Others prefer use of drugs that primarily modify other lipoprotein fractions, e.g., nicotinic acid and fibrate. Clinical judgment also may call for withholding drug therapy in this subcategory.

3) Baseline LDL cholesterol <100 mg/dL

If baseline LDL cholesterol is below the goal of therapy, further LDL-lowering therapy is not currently recommended. Emphasis should be placed on controlling other risk factors and the metabolic syndrome. The TLC diet should be recommended to the person to help maintain a low LDL.

b. Multiple (2+) risk factors

ATP III differs from ATP II in that it distinguishes three subcategories of risk among persons with multiple risk factors, depending on 10-year risk: >20 percent, 10–20 percent, and <10 percent. Within this category of multiple (2+) risk factors, intensity of therapy is adjusted according to 10-year risk and LDL cholesterol level. The treatment approach for each subcategory is shown below in Table IV.2–2.

The following reviews the approach to each subcategory in more detail.

1) Multiple risk factors, and 10-year risk >20 percent

Persons with multiple risk factors and 10-year risk >20 percent have a CHD risk equivalent and are treated as described in the previous section (See Figure IV.2–1).

2) Multiple risk factors, and 10-year risk 10–20 percent

The goal for LDL cholesterol in this risk category is <130 mg/dL. The therapeutic aim is to reduce short-term risk as well as long-term risk for CHD. If baseline LDL cholesterol is ≥130 mg/dL, persons are started on TLC for a 3-month trial of dietary therapy, possibly augmented by options for further LDL lowering (plant stanols/sterols and increased viscous fiber). After 6 weeks and again after three months of dietary therapy, lipoprotein analysis is repeated. If LDL remains ≥130 mg/dL after three months, consideration can be given to starting an LDL-lowering drug to achieve the LDL goal <130 mg/dL. Should the LDL be less than 130 mg/dL on dietary therapy alone, it can be continued without adding drug treatment. If the metabolic syndrome is present, more attention should be given to weight control and increased physical activity. See Figure IV.2–2 for the treatment algorithm for this subcategory.

3) Multiple risk factors, 10-year risk <10 percent

The goal for LDL cholesterol in this risk category likewise is <130 mg/dL. The therapeutic aim, however, is primarily to reduce longer-term risk. If baseline LDL cholesterol is ≥130 mg/dL, persons are started on dietary therapy for reducing LDL cholesterol. Options for enhancing LDL lowering can be employed if needed to achieve the goal of therapy. After three months of dietary therapy, lipoprotein analysis is repeated. If LDL is <160 mg/dL on dietary therapy alone, the dietary therapy should be continued. LDL-lowering drugs generally are not recommended because the patient is not at high short-term risk. On the other hand, if LDL cholesterol is ≥160 mg/dL, drug therapy can be considered to achieve an LDL cholesterol <130 mg/dL. See Figure IV.2–3 for the treatment algorithm for this subcategory.

c. Zero to one risk factor

Most persons with 0–1 risk factor have a 10-year risk <10 percent. Guidelines for this category are given in Table IV.2–3.

Table IV.2–2. Management of LDL Cholesterol in Persons with Multiple (2+) Risk Factors

10-Year Risk	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy (After TLC)
>20%	<100 mg/dL	≥100 mg/dL	See CHD and CHD risk equivalent
10–20%	<130 mg/dL	≥130 mg/dL	≥130 mg/dL
<10%	<130 mg/dL	≥130 mg/dL	≥160 mg/dL

Table IV.2–3. Management of LDL Cholesterol in Persons with Zero to One (0–1) Risk Factor

Risk Category	LDL Goal	LDL Level at Which to Initiate TLC	LDL Level at Which to to Consider Drug Therapy (After TLC)
0–1 Risk Factor*	<160 mg/dL	≥160 mg/dL	≥190 mg/dL†

* Most persons with 0–1 risk factor have a 10-year risk for CHD <10 percent.
† Drug therapy optional for LDL-C 160–189 mg/dL (after dietary therapy).

The goal for LDL cholesterol in this risk category is <160 mg/dL. The primary aim of therapy is to reduce long-term risk. When baseline LDL cholesterol is ≥160 mg/dL, persons are started on dietary therapy for three months. After 6 weeks, the LDL response is evaluated and dietary enhancers of LDL lowering (plant stanols/sterols and increased viscous fiber) may be added if necessary to reach the LDL goal. After 3 months, lipoprotein analysis is repeated. If LDL cholesterol is <160 mg/dL, dietary therapy is continued. For LDL cholesterol 160–189 mg/dL, drug therapy is optional depending on clinical judgment. Factors that favor use of drugs in this category include:

- A severe single risk factor (heavy cigarette smoking, poorly controlled hypertension, strong family history of premature CHD, or very low HDL cholesterol).
- Multiple life-habit risk factors and emerging risk factors (if measured).
- 10-year risk approaching 10 percent (if measured).

If LDL cholesterol is ≥190 mg/dL despite dietary therapy in persons with 0–1 risk factor, drug therapy can be considered to achieve the goal of therapy in all adults. For persons with severe elevations of LDL cholesterol (e.g., ≥220 mg/dL), drug therapy can be started together with dietary therapy. Most such patients will have genetic forms of hypercholesterolemia that cannot be adequately treated with dietary therapy alone.

d. Management of LDL cholesterol when risk assessment begins with Framingham scoring (Table IV.2–4)

If clinicians choose to begin risk assessment with Framingham risk scoring, the treatment algorithm is similar to that beginning with risk factor counting. The only difference occurs for persons whose 10-year risk is 10–20 percent and who have 0–1 risk factor; if one begins with risk factor counting, such persons would not have their 10-year risk calculated. This difference occurs in only 2.6 percent of the U.S. population that has 0–1 risk factor.

Table IV.2–4. Management of LDL Cholesterol in Persons Beginning with 10-year Risk Assessment

10-Year Risk	LDL Goal	LDL Level at Which to Initiate TLC	LDL Level at Which to Consider Drug Therapy (After TLC)
>20%	<100 mg/dL	≥100 mg/dL	See CHD and CHD risk equivalent
10–20%	<130 mg/dL	≥130 mg/dL	≥130 mg/dL
<10%:			
Multiple (2+) risk factors	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
0–1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL*

* Drug therapy optional for LDL-C 160–189 mg/dL (after dietary therapy).

e. Recommendations for persons whose LDL cholesterol levels are below goal

For persons whose LDL cholesterol levels are already below goal levels upon encounter, instructions for appropriate changes in life habits, periodic follow-up, and control of other risk factors are required (upper portions of Figures IV.1–1, IV.2–2, IV.2–3, and IV.2–4). For all persons without CHD or CHD risk equivalents whose LDL is below goal, the diet for the general public and a physical activity regimen should be recommended. For those with CHD or CHD risk equivalent, the therapeutic diet (TLC diet, see Section V) should be recommended even if the LDL is below goal. Follow-up lipoprotein analysis should be carried out according to Table IV.2–5.

Table IV.2–5. Schedule for Follow-Up Lipoprotein Analysis for Persons Whose LDL Cholesterol Levels are Below Goal Levels

Risk Level	LDL Goal (mg/dL)	LDL Level Observed (mg/dL)	Repeat Lipoprotein Analysis
CHD or CHD risk equivalents	<100	<100	<1 year
2+ risk factors	<130	<130	≤2 years
0–1 risk factor	<160	130–159	≤2 years
0–1 risk factor	<160	<130	≤5 years

f. LDL-lowering therapy in older persons

For primary prevention in persons ≥65 years of age, clinical judgment plays an increasingly important role in decisions about LDL-lowering therapy. Framingham risk scores are less robust for predicting risk in older individuals, and measurements of subclinical atherosclerosis, when available, can assume increasing importance. Rather than routinely applying the algorithms described for persons with multiple risk factors, physician judgment may rely more heavily on the estimated NNT to achieve a reduction in CHD events for the different risk categories (Table II.7–2). Other factors including concomitant chronic diseases, social circumstances, chronological and functional age, and financial considerations must be taken into account when making decisions about therapy, especially about use of LDL-lowering drugs, in older persons.

3. Management of atherogenic dyslipidemia and the metabolic syndrome

After an adequate trial of dietary therapy for LDL lowering, attention should turn to atherogenic dyslipidemia and the metabolic syndrome. Treatment of these conditions usually begins after an initial 3-month period of dietary therapy to lower LDL cholesterol. Therapy for atherogenic dyslipidemia and metabolic syndrome thus begins after the LDL goal has been achieved with TLC alone or simultaneously with initiation of more intensive LDL-lowering therapy with drugs.

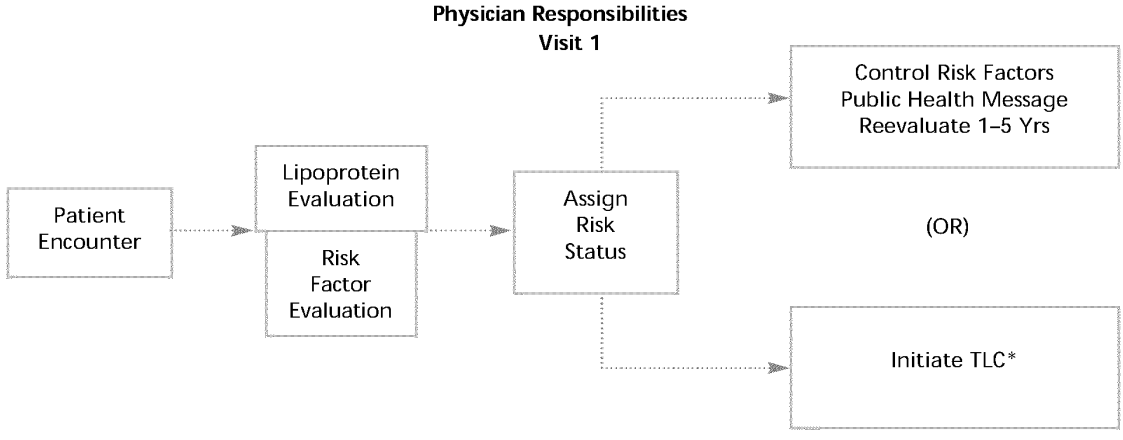
a. Atherogenic dyslipidemia

For atherogenic dyslipidemia, treatment strategy focuses on triglycerides. If triglycerides are ≥150 mg/dL and HDL cholesterol is <40 mg/dL, a diagnosis of atherogenic dyslipidemia is made. The patient likely has the metabolic syndrome (see below); if triglycerides are <200 mg/dL, and specific drug therapy to reduce triglyceride-rich lipoproteins (TGRLP) is not indicated. However, if the patient has CHD or CHD risk equivalents, consideration can be given to using a drug to raise HDL cholesterol (fibrate or nicotinic acid), as outlined above under LDL-lowering therapy. On the other hand, if triglycerides are 200–499 mg/dL, non-HDL cholesterol becomes a secondary target of therapy. Goals for non-HDL cholesterol are 30 mg/dL higher than those for LDL cholesterol. First the LDL cholesterol goal is attained, and if non-HDL remains elevated, additional therapy may be required to achieve the non-HDL goal. Alternative approaches for treatment of elevated non-HDL cholesterol that persists after the LDL goal has been achieved are (a) higher doses of statins, or (b) moderate doses of statins + triglyceride-lowering drug (nicotinic acid or fibrate) (see Sections VI and VII). If triglycerides are very high (≥500 mg/dL), attention turns first to prevention of acute pancreatitis, which is more likely to occur when triglycerides are >1000 mg/dL. Triglyceride-lowering drugs (fibrate or nicotinic acid) become first line therapy; although statins can be used to lower LDL cholesterol to reach the LDL goal, in these patients it is often difficult (and unnecessary) to achieve a non-HDL cholesterol goal of only 30 mg/dL higher than for LDL cholesterol.

b. Metabolic syndrome

Beyond treatment of elevated triglycerides, with drugs if necessary, first-line therapy for the metabolic syndrome is change in life habits, especially reducing weight and increasing physical activity. The approach to treatment of the metabolic syndrome with life-habit modification is presented in Section V.

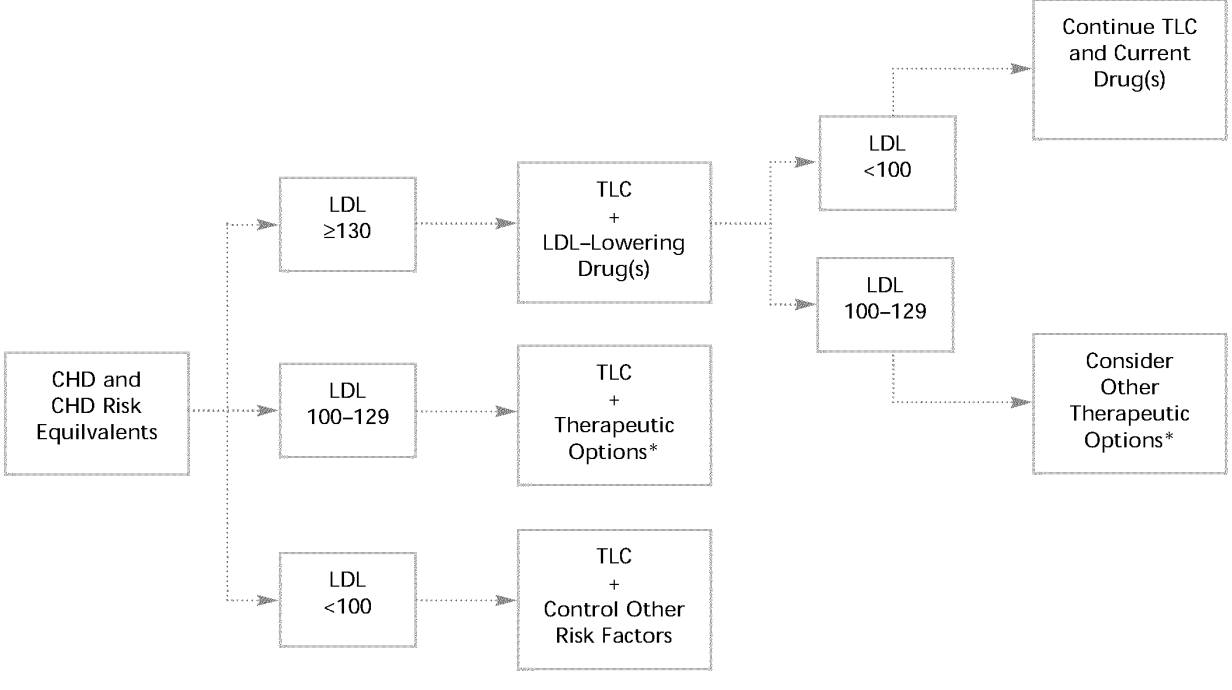
Figure IV.1–1. Physician responsibilities for Visit 1



* If CHD or CHD risk equivalent is present, drug therapy can be started simultaneously with TLC when LDL-C is ≥130 mg/dL.

Figure IV.2–1. Therapeutic approaches to persons with CHD or CHD risk equivalents

The LDL cholesterol goal is <100 mg/dL.



* Therapeutic options include intensifying LDL-lowering dietary or drug therapies, emphasizing weight reduction and increased physical activity, adding drugs to lower triglycerides or raise HDL cholesterol (nicotinic acid or fibrates), and intensifying control of other risk factors.

Figure IV.2–2. Therapeutic approaches to persons with multiple risk factors, 10-year risk 10–20 percent

The LDL cholesterol goal is <130 mg/dL. Drugs can be considered if necessary to attain the LDL cholesterol goal if the LDL cholesterol level is ≥130 mg/dL after a trial of TLC.

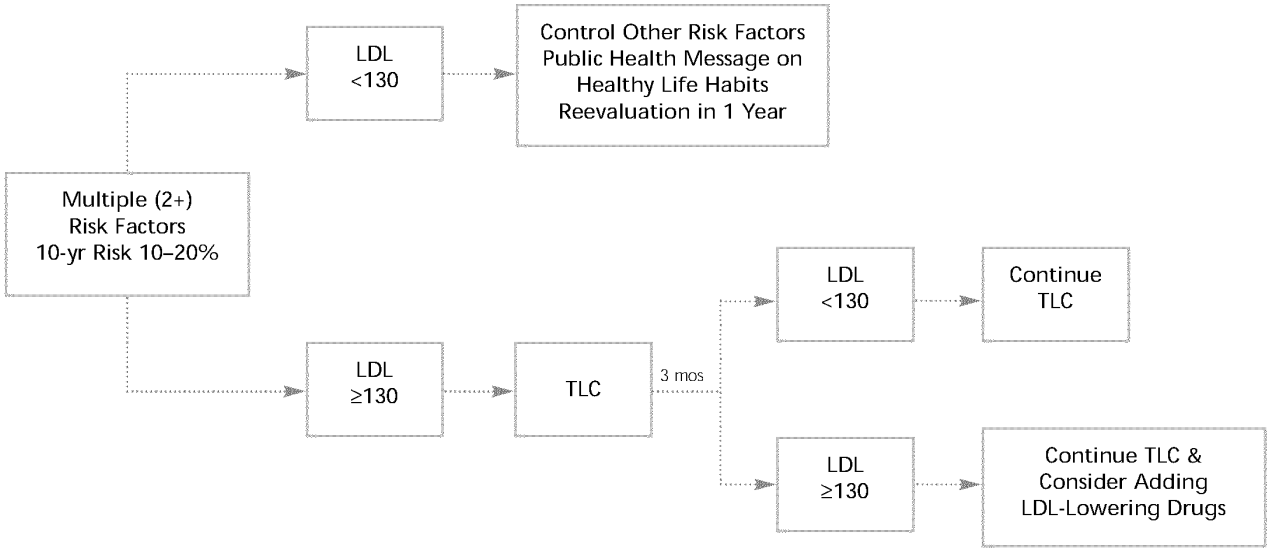


Figure IV.2–3. Therapeutic approaches to the patient with multiple (2+) risk factors, 10-year risk <10 percent

The LDL cholesterol goal is <130 mg/dL. Drug therapy can be considered if LDL cholesterol is ≥160 mg/dL after a trial of TLC.

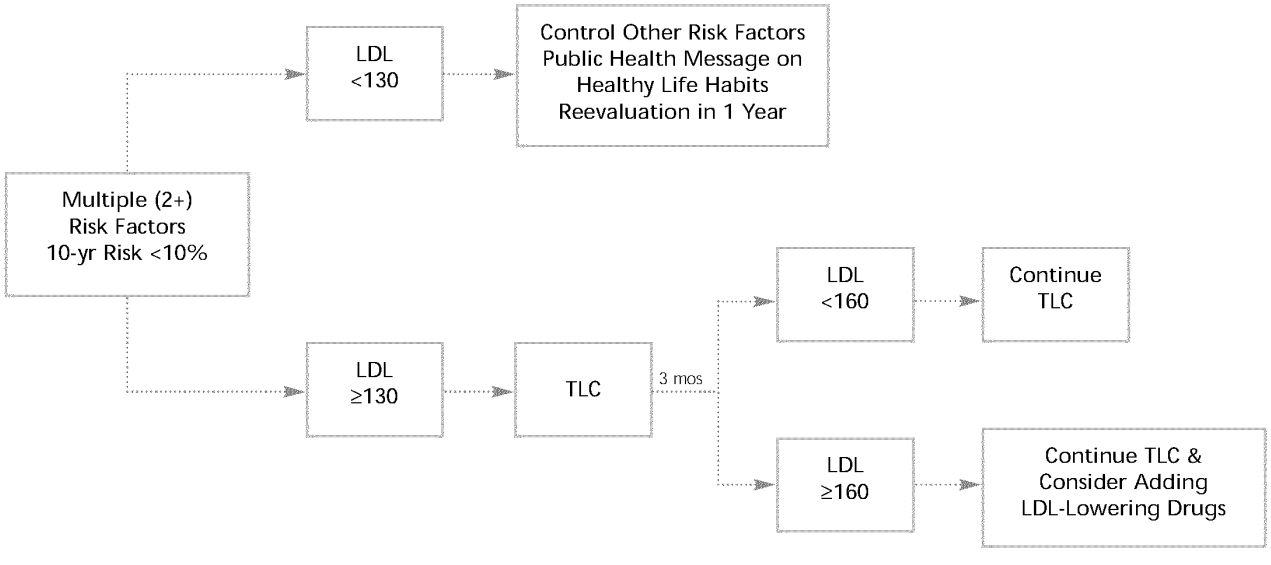
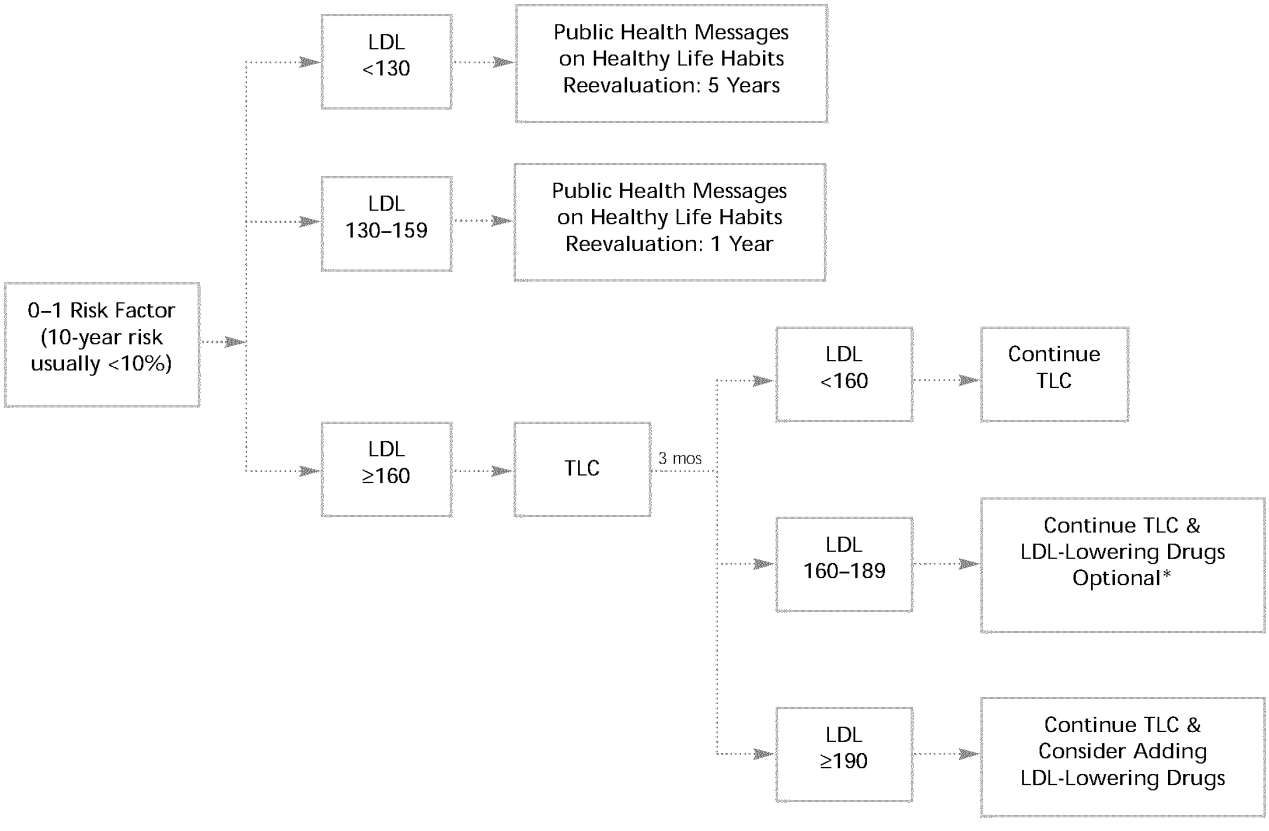
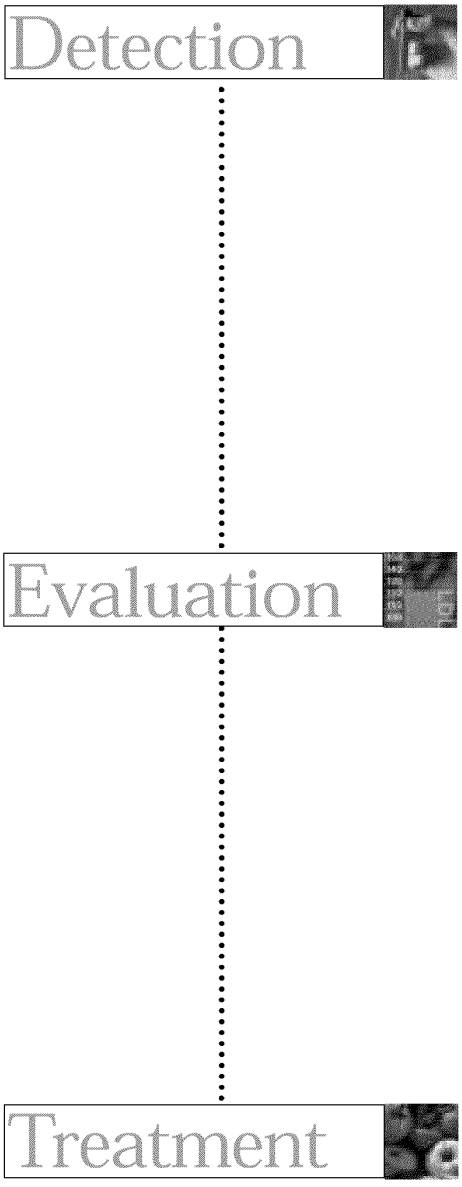


Figure IV.2–4. Therapeutic approaches to persons with 0–1 risk factor

The LDL cholesterol goal is <160 mg/dL. Drug therapy can be considered if the LDL cholesterol level is ≥190 mg/dL after a trial of TLC. If LDL cholesterol is 160–189 mg/dL, drug therapy is optional depending on clinical judgment.



* Factors favoring drug use are a severe single risk factor, a family history of premature CHD, and/or underlying or emerging risk factors in addition to a single major risk factor.



V. Adopting Healthful Lifestyle Habits to Lower LDL Cholesterol and Reduce CHD Risk

V. Adopting Healthful Lifestyle Habits to Lower LDL Cholesterol and Reduce CHD Risk

1. Population approach: promoting a base of healthy life habits

NCEP advocates a two-pronged approach for reducing CHD risk: the population approach and the clinical strategy. The two are closely linked. The population approach, which is outlined in the 1990 report of the Population Panel,[5,6] is designed to lower risk in the whole population through adoption of healthy life habits including a healthy diet, weight control, and increased physical activity. The clinical strategy is described in the ATP reports. This section summarizes the population approach and connects it to the clinical strategy. The clinical management team must recognize that they are an integral part of the population approach and contribute to it by providing education and guidance to the patient with high serum cholesterol and the patient's family.

The health community has provided the American public with consistent messages on cardiovascular risk reduction for the past four decades. These messages have encouraged avoidance or cessation of cigarette smoking, reduction of intakes of saturated fats and cholesterol, achieving and maintaining a healthy body weight, regular physical activity, and routine medical check-ups for blood pressure and cholesterol. Table V.1–1 (derived from the Healthy People 2010 publication)[620] reports the current status of the U.S. population on various healthy lifestyle habits and compares it with the goals for 2010.

Although progress has been made, it is clear that much more is needed to bring about the changes required to achieve the goals for 2010. The physician has an important role to play in this effort to help attain these goals.

The NHLBI, American Heart Association, and other organizations have mounted a major effort to reduce risk factors for CHD in the United States. Not only is there continuing research on improved methods for risk reduction, but national educational programs have also been put into effect. Table V.1–2 lists some of the Web sites of the programs sponsored by the U.S. Government.

Table V.1–1. Status Report on Healthy Lifestyle Habits: Healthy People 2010

Lifestyle Habit	Status in the 1990s	Goal for 2010
Healthy weight (BMI <25 kg/m^2)	42%	60%
Saturated fat intake <10% calories	36%	75%
Vegetable intake of at least 3 servings/day with at least 1/3 dark green or orange	3%	50%
Fruit intake of at least 2 servings/day	28%	75%
Grain intake of at least 6 servings/day with at least 1/3 whole grain	7%	50%
Smoking cessation by adult smokers	41%	75%
Regular physical activity of moderate intensity	15%	30%

Table V.1–2. Government-Sponsored Web Sites for Public Information: An Effective Way to Implement the Public Health Approach

Diet	www.nhlbi.nih.gov/chd www.nhlbi.nih.gov/subsites/index.htm—then click Healthy Weight www.nhlbi.nih.gov/hbp www.nutrition.gov
Physical activity	www.fitness.gov
Body weight	www.nhlbi.nih.gov/subsites/index.htm—then click Healthy Weight
Cholesterol	www.nhlbi.nih.gov/chd
Blood pressure	www.nhlbi.nih.gov/hbp
Smoking cessation	www.cdc.gov/tobacco/sgr_tobacco_use.htm

Physicians and other health professionals have the opportunity to implement the public health and clinical approaches to risk reduction through interaction with patients and their families. Even in persons who are not candidates for clinical management of high serum cholesterol, control of other risk factors and preventive efforts convey the broader public health message to the patient. The physician's advice is valued and considered more credible than mass media or non-targeted educational campaigns. The physician can affect the public health arena in many ways. Table V.1–3 compares the role of the physician and other health professionals in the implementation of the public health approach with their role in the clinical management of risk factors through lifestyle changes.

2. General approach to therapeutic lifestyle changes (TLC)

ATP III recommends a multifactorial lifestyle approach to reducing risk for CHD. This approach is designated *therapeutic lifestyle changes* (TLC) and includes the following components (see Table V.2–1):

- Reduced intakes of saturated fats and cholesterol
- Therapeutic dietary options for enhancing LDL lowering (plant stanols/sterols and increased viscous [soluble] fiber)
- Weight reduction
- Increased regular physical activity

Reduced intakes of saturated fats and cholesterol and other therapeutic dietary options for LDL-lowering (plant stanols/sterols and increased viscous fiber) are introduced first for the purpose of achieving the LDL cholesterol goal. After maximum reduction of LDL cholesterol is achieved with dietary therapy, emphasis shifts to management of the metabolic syndrome and its associated lipid risk factors (elevated triglycerides and low HDL cholesterol). A high proportion of patients with the metabolic syndrome are overweight/obese and sedentary; for them, weight reduction therapy and

Table V.1–3. The Role of the Physician and Other Health Care Professionals in Implementing the Population and Clinical Approaches to Lifestyle Modification

	Population Approach	Clinical Approach
Principles	Promote change in lifestyle habits by serving as a role model to patients.	Promote targeted changes in individual lifestyle to produce significant reductions in an individual patient's risk.
	Provide general advice and access to credible sources of information regarding healthy lifestyle habits.	Initiate outcome measurements that will be tracked during scheduled follow-up visits.
		Physicians, dietitians, and other relevant health professionals should go beyond monitoring adherence to actively helping individuals overcome barriers and promote new behaviors.
Diet	Briefly assess dietary intake of saturated fat and cholesterol.	Promote ATP III TLC diet using:
	Promote U.S. Dietary Guidelines (population diet) using pamphlets/handouts and Food Guide Pyramid.	▪ Individualized diet counseling that provides acceptable substitutions for favorite foods contributing to a patient's elevated LDL level – counseling often best performed by a registered dietitian
	Provide shopping and food preparation pamphlets/handouts highlighting low saturated fat foods including reduced fat dairy products, leaner meats, lower fat ground meat, and reduced fat baked goods.	▪ Reinforcement of dietary principles during follow-up visits at which LDL response to diet is assessed
	Make full use of office personnel to promote public health message.	▪ Consideration of readiness to change and level of motivation
Physical activity	Promote regular physical activity by taking a physical activity history.	Follow Surgeon General recommendations for physical activity.[238]
	Provide pamphlets/advice regarding general principles of physical activity.	Promote regular physical activity for individuals using:

Table V.1–3. The Role of the Physician and Other Health Care Professionals in Implementing the Population and Clinical Approaches to Lifestyle Modification (continued)

	Population Approach	Clinical Approach
Physical activity *(continued)*	Recommend 30 minutes of regular moderate intensity activity on most, if not all, days of the week.	▪ Specific recommendations to increase physical activity based on a patient's cardiac status, age, and other factors ▪ Specific advice regarding how physical activity could be integrated into the patient's lifestyle ▪ Follow-up visits to monitor physical activity level, and follow-up counseling regarding barriers to daily physical activity
Body Weight	Ensure that weight, height, and waist circumference are measured at every visit. Promote prevention of weight gain: ▪ Provide access to tables identifying height/weight categories for BMI in waiting room or exam room ▪ Provide literature relating BMI to health outcomes ▪ Provide literature explaining use of Nutrition Facts labeling to identify calorie content and recommended portion sizes of foods	Follow Obesity Education Initiative (OEI) guidelines for weight management.[78,79] Promote prevention of weight gain: ▪ Calculate BMI for every patient at every visit ▪ Anticipate high-risk times for weight gain (peri-menopausal years, times of significant life stress) and counsel patient on ways to prevent weight gain ▪ Follow-up visits to discuss success of weight gain prevention strategies Discuss 10% weight loss goals for persons who are overweight: ▪ Discuss lifestyle patterns that promote weight loss ▪ Portion control ▪ Daily physical activity ▪ Follow-up visits to examine weight/BMI and discuss barriers to adherence
Cholesterol	Ensure that all adults age 20 and over have their blood cholesterol measured and their results explained in keeping with ATP III guidelines. Ensure children and first degree relatives of adults in whom a genetic lipoprotein disorder is suspected have cholesterol screening performed.	Follow ATP III guidelines for detection, evaluation, and treatment of persons with lipid disorders.
Blood Pressure	Ensure that all adults have their blood pressure measured and their results explained in keeping with JNC VI guidelines.	Follow JNC VI guidelines for the detection, evaluation, and treatment of persons with high blood pressure.[160,161]
Smoking Cessation	Ensure that all persons are aware of the health hazards of cigarette smoking by using posters/handouts in the waiting room. Query all persons regarding their smoking habits on every visit.	Follow U.S. Department of Health and Human Services Clinical Practice Guideline: Treating Tobacco Use and Dependence.[621] Promote smoking cessation: ▪ Query regarding smoking habits ▪ Provide targeted advice according to patient's knowledge base, e.g., dangers of smoking, benefits of quitting, and tips to quit ▪ Schedule follow-up visits to discuss patient's progress in addressing smoking cessation

Table V.2–1. Essential Components of Therapeutic Lifestyle Changes (TLC)

Component	Recommendation
LDL-raising nutrients	
Saturated fats*	Less than 7% of total calories
Dietary cholesterol	Less than 200 mg/day
Therapeutic options for LDL lowering	
Plant stanols/sterols	2 grams per day
Increased viscous (soluble) fiber	10–25 grams per day
Total calories (energy)	Adjust total caloric intake to maintain desirable body weight/prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal per day

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

Table V.2–2. Macronutrient Recommendations for the TLC Diet

Component	Recommendation
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25–35% of total calories*
Carbohydrate†	50–60% of total calories*
Dietary fiber	20–30 grams per day
Protein	Approximately 15% of total calories

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat.

† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.

Table V.2–3. Dietary Guidelines for Americans (2000)[241]

Aim for Fitness

- Aim for a healthy weight
- Be physically active each day

Build a Healthy Base

- Let the pyramid guide your food choices
- Choose a variety of grains daily, especially whole grains
- Choose a variety of fruits and vegetables daily
- Keep foods safe to eat

Choose sensibly

- Choose a diet that is low in saturated fat and cholesterol and moderate in total fat
- Choose beverages and foods to moderate your intake of sugars
- Choose and prepare foods with less salt
- If you drink alcoholic beverages, do so in moderation

physical activity guidance is required to obtain further CHD risk reduction beyond that achieved by LDL lowering. 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 nutrition intervention and guidance provided by a nutrition professional.

ATP III recommendations for ranges of other macronutrient intakes in the TLC Diet are given in Table V.2–2. Note that the recommendation for total fat ranges from 25 percent to 35 percent of total calories. To improve overall health, ATP III's lifestyle therapies generally contain the recommendations embodied in the Dietary Guidelines for Americans (2000).[241]

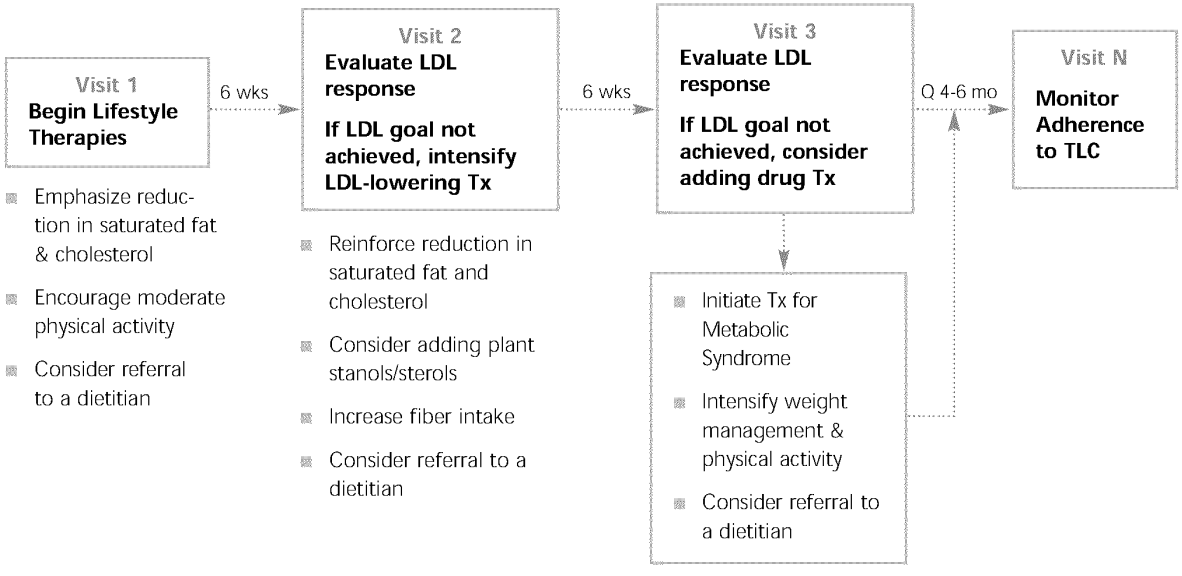
The overall composition of the TLC Diet is consistent with the recommendations of the Dietary Guidelines for Americans (2000) (Table V.2–3). The dietary principles delineated in the Dietary Guidelines need not and should not be sacrificed for the purpose of LDL lowering. Furthermore, adherence to Dietary Guidelines recommendations should contribute to a reduction in risk beyond LDL lowering.

Figure V.2–1 presents one model illustrating the general approach to dietary therapy.

During the first three months of dietary therapy, priority is given to lowering LDL cholesterol. In the first visit, the physician should address a few key questions and obtain an overall assessment of the individual's current life habits:

- Does the patient consume excess calories in the form of LDL-raising nutrients?

Figure V.2–1. A Model of Steps in Therapeutic Lifestyle Changes (TLC)



- Is the patient overweight or obese? Is abdominal obesity present?
- Is the patient physically active or inactive?
- If the patient is overweight/obese and/or physically inactive, is the metabolic syndrome present? (See Table II.6–1.)

To assess intakes of LDL-raising nutrients, the ATP III panel devised a brief Dietary CAGE that may be helpful (Table V.2–4). These questions are not a substitute for a systematic dietary assessment, which is usually carried out by a nutrition professional. CAGE questions can be used to identify the common food sources of LDL-raising nutrients—saturated fat and cholesterol—in the patient's diet. Also in the first visit, advice is given to begin moderate physical activity, but serious attempts to achieve weight loss can be delayed briefly to concentrate first on reducing intakes of LDL-raising nutrients. At any and every stage of dietary therapy, effective dietary modification will be facilitated by consultation with a registered dietitian or other qualified nutritionist for *medical nutrition therapy.* (Subsequently, the term *nutrition professional* will refer to a registered dietitian or qualified nutritionist.)

After approximately 6 weeks, the physician should evaluate the LDL cholesterol response. If the LDL cholesterol goal has been achieved, or if progress in LDL lowering has occurred, dietary therapy should be continued. If the LDL goal is not achieved, the physician has several options to enhance LDL lowering. First, dietary instructions can be reexplained and reinforced. The assistance of a nutrition professional for more formal instruction and counseling (medical nutrition therapy) is especially valuable at this time. Second, therapeutic dietary options for LDL lowering (plant stanols/sterols and increased viscous fiber) will also enhance LDL lowering. Plant stanols/sterols are currently incorporated into special margarines, which are available directly to consumers. The stanol/sterol contents are listed on the food label. They may be available in other products in the future. Viscous fiber can be increased by emphasizing certain foods: cereal grains, fruits, vegetables, and dried beans, peas, and legumes (see Table V.2–5).

Table V.2–4. Dietary CAGE Questions for Assessment of Intakes of Saturated Fat and Cholesterol

- **C**—Cheese (and other sources of dairy fats—whole milk, 2% milk, ice cream, cream, whole fat yogurt)
- **A**—Animal fats (hamburger, ground meat, frankfurters, bologna, salami, sausage, fried foods, fatty cuts of meat)
- **G**—Got it away from home (high-fat meals either purchased and brought home or eaten in restaurants)
- **E**—Eat (extra) high-fat commercial products: candy, pastries, pies, doughnuts, cookies

After another 6 weeks, the response to dietary therapy should be evaluated. If the LDL cholesterol goal is achieved, the current intensity of dietary therapy should be maintained indefinitely. If the patient is approaching the LDL goal, consideration should be given to continuing dietary therapy before adding LDL-lowering drugs. If it appears unlikely that the LDL goal will be achieved with dietary therapy alone, drug therapy should be considered (see Section IV).

Thereafter, the metabolic syndrome, if present, becomes the target of therapy (see Section II). First-line therapy for the metabolic syndrome is weight control and increased physical activity. Again, referral to a nutrition professional for medical nutrition therapy to assist in weight reduction is recommended.

Finally, long-term monitoring for adherence to TLC is required. Revisits are indicated every 4–6 months during the first year of therapy and every 6–12 months in the long term. If a person is started on drug therapy, more frequent visits are advised.

The information shown in Table V.2–6 may be helpful for the physician both for dietary and lifestyle assessment and for guidance of the patient adopting TLC recommendations. The table is compiled from current ATP III dietary recommendations, Dietary Guidelines for Americans (2000),[241] Obesity Education Initiative (OEI) guidelines for weight reduction,[78,79] and the Surgeon General's Report on Physical Activity.[238]

3. Components of the TLC Diet

a. Major nutrient components

The major LDL-raising dietary constituents are saturated fat and cholesterol. A reduction in intakes of these components is the core of the TLC Diet. The scientific foundation for the relationship between high intakes of saturated fat and increased LDL levels dates back several decades and consists of several lines of evidence: observational studies, metabolic and controlled feeding studies, and clinical studies, including randomized clinical trials. These data have been reviewed in detail in previous reports of the NCEP,[1,2,5,6] the U.S. Dietary Guidelines Committees,[241] and the American Heart Association.[393] The other major nutrients—unsaturated fats, protein, and carbohydrates—do not raise LDL cholesterol levels. In developing an LDL-lowering diet

Table V.2–5. Food Sources of Viscous (Soluble) Fiber

Food Source	Soluble Fiber (g)	Total Fiber (g)
Cereal Grains (½ cup cooked)		
Barley	1	4
Oatmeal	1	2
Oatbran	1	3
Seeds		
– Psyllium Seeds, Ground (1 Tbsp)	5	6
Fruit (1 medium fruit)		
Apples	1	4
Bananas	1	3
Blackberries (½ cup)	1	4
Citrus Fruit (orange, grapefruit)	2	2–3
Nectarines	1	2
Peaches	1	2
Pears	2	4
Plums	1	1.5
Prunes (¼ cup)	1.5	3
Legumes (½ cup cooked)		
Beans		
– Black Beans	2	5.5
– Kidney Beans	3	6
– Lima Beans	3.5	6.5
– Navy Beans	2	6
– Northern Beans	1.5	5.5
– Pinto Beans	2	7
Lentils (yellow, green, orange)	1	8
Peas		
– Chick Peas	1	6
– Black Eyed Peas	1	5.5
Vegetables (½ cup cooked)		
Broccoli	1	1.5
Brussels Sprouts	3	4.5
Carrots	1	2.5

Table V.2–6. Guide to Therapeutic Lifestyle Changes (TLC)

Healthy Lifestyle Recommendations for a Healthy Heart

Food Items to Choose More Often	Food Items to Choose Less Often	Recommendations for Weight Reduction	Recommendations for Increased Physical Activity
Breads and Cereals ≥6 servings per day, adjusted to caloric needs Breads, cereals, especially whole grain; pasta; rice; potatoes; dry beans and peas; low fat crackers and cookies **Vegetables** 3–5 servings per day fresh, frozen, or canned, without added fat, sauce, or salt **Fruits** 2–4 servings per day fresh, frozen, canned, dried **Dairy Products** 2–3 servings per day Fat-free, ½%, 1% milk, buttermilk, yogurt, cottage cheese; fat-free & low-fat cheese **Eggs** ≤2 egg yolks per week Egg whites or egg substitute **Meat, Poultry, Fish** ≤5 oz per day Lean cuts loin, leg, round; extra lean hamburger; cold cuts made with lean meat or soy protein; skinless poultry; fish **Fats and Oils** Amount adjusted to caloric level: Unsaturated oils; soft or liquid margarines and vegetable oil spreads, salad dressings, seeds, and nuts **TLC Diet Options** Stanol/sterol-containing margarines; viscous fiber food sources: barley, oats, psyllium, apples, bananas, berries, citrus fruits, nectarines, peaches, pears, plums, prunes, broccoli, brussels sprouts, carrots, dry beans, peas, soy products (tofu, miso)	**Breads and Cereals** Many bakery products, including doughnuts, biscuits, butter rolls, muffins, croissants, sweet rolls, Danish, cakes, pies, coffee cakes, cookies Many grain-based snacks, including chips, cheese puffs, snack mix, regular crackers, buttered popcorn **Vegetables** Vegetables fried or prepared with butter, cheese, or cream sauce **Fruits** Fruits fried or served with butter or cream **Dairy Products** Whole milk/2% milk, whole-milk yogurt, ice cream, cream, cheese **Eggs** Egg yolks, whole eggs **Meat, Poultry, Fish** Higher fat meat cuts: ribs, t-bone steak, regular hamburger, bacon, sausage; cold cuts: salami, bologna, hot dogs; organ meats: liver, brains, sweetbreads; poultry with skin; fried meat; fried poultry; fried fish **Fats and Oils** Butter, shortening, stick margarine, chocolate, coconut	**Weigh Regularly** Record weight, BMI, & waist circumference **Lose Weight Gradually** Goal: lose 10% of body weight in 6 months. Lose ½ to 1 lb per week **Develop Healthy Eating Patterns** ▪ Choose healthy foods (see Column 1) ▪ Reduce intake of foods in Column 2 ▪ Limit number of eating occasions ▪ Select sensible portion sizes ▪ Avoid second helpings ▪ Identify and reduce hidden fat by reading food labels to choose products lower in saturated fat and calories, and ask about ingredients in ready-to-eat foods prepared away from home ▪ Identify and reduce sources of excess carbohydrates such as fat-free and regular crackers; cookies and other desserts; snacks; and sugar-containing beverages	**Make Physical Activity Part of Daily Routines** ▪ Reduce sedentary time ▪ Walk, wheel, or bike-ride more, drive less; Take the stairs instead of an elevator; Get off the bus a few stops early and walk the remaining distance; Mow the lawn with a push mower; Rake leaves; Garden; Push a stroller; Clean the house; Do exercises or pedal a stationary bike while watching television; Play actively with children; Take a brisk 10-minute walk or wheel before work, during your work break, and after dinner **Make Physical Activity Part of Exercise or Recreational Activities** ▪ Walk, wheel, or jog; Bicycle or use an arm pedal bicycle; Swim or do water aerobics; Play basketball; Join a sports team; Play wheelchair sports; Golf (pull cart or carry clubs); Canoe; Cross-country ski; Dance; Take part in an exercise program at work, home, school, or gym

for ATP III, consideration was given not only to these long-established factors but also to new and emerging data that support the importance of the appropriate distribution of other nutrients that are related to cardiovascular health as well as general health. Therefore, the rationale for the recommendations for each component of the TLC diet will be described briefly.

1) Saturated fatty acids

Saturated fatty acids are a major dietary determinant of LDL cholesterol level.[241] The effects of saturated fatty acids on serum total cholesterol (and LDL cholesterol) levels have been studied extensively.[622] Several meta-analyses and reviews have been carried out to estimate the impact of saturated fatty acids on cholesterol levels.[623,624] These analyses indicate that for every 1 percent increase in calories from saturated fatty acids as a percent of total energy, the serum LDL cholesterol rises about 2 percent. Conversely, a 1 percent reduction in saturated fatty acids will reduce serum cholesterol by about 2 percent. Recent trials confirm the efficacy of diets low in saturated fatty acids for lowering LDL levels. For example, the DELTA Study[625] investigated the effects of reducing dietary saturated fatty acids from 15 percent of total calories to 6.1 percent of total calories. On the diet low in saturated fatty acids, LDL cholesterol was reduced by 11 percent. Another study, beFIT,[626,627] tested effects of an NCEP therapeutic diet in individuals with hypercholesterolemia with and without hypertriglyceridemia. Compared to the participants' baseline diet, LDL cholesterol levels were reduced on the therapeutic diet by approximately 8 percent. Large-scale randomized controlled trials have been carried out to assess the safety of reduced intakes of saturated fatty acids and cholesterol in children and have found no evidence for compromised growth or development.[628,629]

Evidence statements: There is a dose response relationship between saturated fatty acids and LDL cholesterol levels. Diets high in saturated fatty acids raise serum LDL cholesterol levels (A1). Reduction in intakes of saturated fatty acids lowers LDL cholesterol levels (A1, B1).

The beneficial effects of reducing saturated fatty acids and cholesterol in the diet can be enhanced by weight reduction in overweight persons. Several studies have shown that LDL cholesterol levels can be lowered through weight reduction in overweight persons.[78,79] And most important, as shown in the MRFIT study, weight reduction will enhance serum cholesterol lowering brought about by a reduction in intakes of saturated fatty acids and cholesterol.[630,631]

Evidence statements: Weight reduction of even a few pounds will reduce LDL levels regardless of the nutrient composition of the weight loss diet (A2), but weight reduction achieved through a calorie-controlled diet low in saturated fatty acids and cholesterol will enhance and sustain LDL cholesterol lowering (A2).

Recommendation: Weight loss through reduced caloric intake and increased levels of physical activity should be encouraged in all overweight persons. Prevention of weight gain also should be emphasized for all persons.

Epidemiological studies show that populations that consume high amounts of saturated fatty acids and cholesterol have a high risk for CHD.[19,632] The evidence that lowering serum cholesterol levels by decreasing intakes of saturated fatty acids reduces the risk for CHD has been demonstrated in the meta-analysis by Gordon.[409,410] This analysis included six robust dietary trials, in aggregate including 6,356 person-years of follow up. It showed that lowering serum cholesterol levels by reducing the intake of saturated fatty acids significantly decreased the incidence of CHD by 24 percent. There was also a trend toward a decrease in coronary mortality (21 percent) and total mortality (6 percent). No increase in non-CVD mortality was found.

The data from dietary trials, in combination with the results of controlled clinical trials with cholesterol-lowering medications,[455,633] document that reducing serum cholesterol and LDL cholesterol by diet alone or with pharmacological means will reduce CHD endpoints. The current American diet contains an average of about 11 percent of total calories as saturated fatty acids. The major sources of saturated fatty acids in the diet are high-fat dairy products (whole milk, cheese,

butter, ice cream, and cream); high-fat meats; tropical oils such as palm oil, coconut oil, and palm kernel oil; and baked products and mixed dishes containing dairy fats, shortening, and tropical oils. To maximize LDL cholesterol lowering by reducing saturated fatty acid intake in the therapeutic diet, it will be necessary to lower intakes from the population mean intake of approximately 11 percent to <7 percent of total energy.

Evidence statements: High intakes of saturated fatty acids are associated with high population rates of CHD (C2). Reduction in intake of saturated fatty acids will reduce risk for CHD (A1, B1).

Recommendation: The therapeutic diet to maximize LDL cholesterol lowering should contain less than 7 percent of total calories as saturated fatty acids.

2) *Trans* fatty acids

Trans fatty acids are those in which double bonds are in the *trans* configuration. They are generally produced by hydrogenation of vegetable oils but some are found naturally in animal fats. Substantial evidence from randomized clinical trials indicates that *trans* fatty acids raise LDL cholesterol levels, compared with unsaturated fatty acids.[634-646] These studies also show that when *trans* fatty acids are substituted for saturated fatty acids, HDL cholesterol levels are lower,[647] with a dose response effect observed. Recent United States data show that the use of liquid vegetable oil or semiliquid margarine results in the most favorable total and LDL cholesterol levels and ratios of total cholesterol to HDL cholesterol, whereas the use of butter or stick margarine results in the worst lipid levels.[634] In addition, evidence from some epidemiological cohort studies suggests that high intakes of *trans* fatty acids are associated with higher risk for CHD.[648-651] Whether this association is due to adverse effects of *trans* fatty acids on lipoproteins, to other adverse actions, or to confounding variables is uncertain.

The mean U.S. level of *trans* fatty acids intake is about 2.6 percent of total energy (compared with saturated fatty acids intake of ~11 percent of energy). Major sources of *trans* fatty acids in the diet include products made from partially hydrogenated oils such as baked products including crackers, cookies, doughnuts, breads, and products like french fries or chicken fried in hydrogenated shortening. Animal sources including dairy products provide smaller amounts of *trans* fatty acids. Soft margarines, tub and liquid, and vegetable oil spreads have low amounts of *trans* fatty acids. Some margarines and spreads are now *trans*-fatty acid free. Some hydrogenation of vegetable oils is the primary technology currently used to provide form to food products, so that they can be eaten out of the hand, rather than with a spoon.

Evidence statements: *Trans* fatty acids raise serum LDL cholesterol levels (A2). Through this mechanism, higher intakes of *trans* fatty acids should increase risk for CHD. Prospective studies support an association between higher intakes of *trans* fatty acids and CHD incidence (C2). However, *trans* fatty acids are not classified as saturated fatty acids, nor are they included in the quantitative recommendations for saturated fatty acid intake of <7 percent of calories in the TLC Diet.

Recommendation: Intakes of *trans* fatty acids should be kept low. The use of liquid vegetable oil, soft margarine, and *trans* fatty acid-free margarine are encouraged instead of butter, stick margarine, and shortening.

3) *Dietary cholesterol*

Dietary cholesterol causes marked hypercholesterolemia in many laboratory animals, including nonhuman primates. High intakes of cholesterol in humans, however, do not cause such a marked increase in serum cholesterol. Nonetheless, controlled metabolic studies in humans indicate that high cholesterol intakes raise LDL cholesterol levels. The degree of rise varies from person to person, as is true for all nutrients. Meta-analyses of studies done in controlled settings confirm the LDL-raising action of dietary cholesterol.[652,653] A recent meta-analysis showed that dietary cholesterol raises the ratio of total to HDL cholesterol, adversely affecting the serum cholesterol profile.[654] A lesser effect of dietary cholesterol has been found in studies carried out in the outpatient setting;[655] in this circumstance, failure to detect the full effect of dietary cholesterol is likely related to lack of tight metabolic

control. On average, the response of serum cholesterol to dietary cholesterol as revealed in tightly controlled studies is approximately 10 mg/dL per 100 mg dietary cholesterol per 1000 kcal.[656,657]

In the past 40 years, there has been a progressive decline in intakes of dietary cholesterol. This has been the result of decreased intakes of eggs, high-fat meat, and high-fat dairy products. This reduction in cholesterol intake, along with a substantial reduction in the proportion of calories from saturated fatty acids, corresponds with the decline in serum cholesterol levels that has occurred in the U.S. population over four decades.[658] At present, the average U.S. daily consumption of cholesterol is 256 mg, higher for men (331 mg) than for women (213 mg).[659] Eggs contribute about one-third of the cholesterol in the food supply and this fraction has increased somewhat in recent years.[660] Other sources of dietary cholesterol include animal products, dairy, meats, poultry, and shellfish.

Some epidemiological data, namely the Western Electric Study, suggest dietary cholesterol increases heart disease risk independently of its effect on serum LDL cholesterol levels.[661] In contrast, data from two prospective cohort studies, the Nurses Health Study and the Health Professionals Study, found no significant association between frequency of reported egg consumption and CHD, except among diabetic women.[662]

Evidence statements: Higher intakes of dietary cholesterol raise serum LDL cholesterol levels in humans (A2, B1). Through this mechanism, higher intakes of dietary cholesterol should raise the risk for CHD. Reducing cholesterol intakes from high to low decreases serum LDL cholesterol in most persons (A2, B1).

Recommendation: Less than 200 mg per day of cholesterol should be consumed in the TLC Diet to maximize the amount of LDL cholesterol lowering that can be achieved through reduction in dietary cholesterol.

4) Monounsaturated fatty acids

The most common form of monounsaturated fatty acids is oleic acid, which occurs in the cis form. Substitution of cis-monounsaturated fatty acids for saturated fatty acids results in a fall in LDL cholesterol levels.[624] Moreover, substitution of monounsaturated fatty acids for saturated fatty acids results in little or no decrease in HDL cholesterol and does not increase triglycerides as occurs with very high intakes of carbohydrates (>60 percent of total energy).[624,663-665]

Monounsaturated fatty acids—as part of a diet that is low in saturated fatty acids and cholesterol and rich in vegetables, fruits, and grain products—have received increased attention as being potentially beneficial for risk reduction because of their association with low rates of CHD in olive-oil consuming populations of the Mediterranean basin.[19,20,632] Despite epidemiological support for higher intakes of monounsaturated fatty acids, there are no controlled clinical trials that are designed to compare effects of monounsaturated and saturated fatty acids on CHD endpoints. This lack of data contrasts with several trials that replaced saturated fat with polyunsaturated fat.

Evidence statements: Monounsaturated fatty acids lower LDL cholesterol relative to saturated fatty acids (A2, B2). Monounsaturated fatty acids do not lower HDL cholesterol nor raise triglycerides (A2, B2).

Evidence statement: Dietary patterns that are rich in monounsaturated fatty acids provided by plant sources and rich in fruits, vegetables, and whole grains and low in saturated fatty acids are associated with decreased CHD risk (C1). However, the benefits of replacement of saturated fatty acids with monounsaturated fatty acids has not been adequately tested in controlled clinical trials.

Recommendations: Monounsaturated fatty acids are one form of unsaturated fatty acid that can replace saturated fatty acids. Intake of monounsaturated fatty acids can range up to 20 percent of total calories. Most monounsaturated fatty acids should be derived from vegetable sources, including plant oils and nuts.

5) Polyunsaturated fatty acids

Polyunsaturated fatty acids, consisting mainly of n-6 linoleic acid, reduce LDL cholesterol levels when substituted for saturated fatty acids. At high intakes, linoleic acid also can produce small reductions in HDL cholesterol and triglycerides, although these responses are variable. Compared to cis-monounsaturated fatty acids, polyunsaturated fatty acids often cause a slightly greater reduction in LDL cholesterol levels.[624]

Several controlled clinical trials have compared the effects of polyunsaturated fatty acids, as a replacement for saturated fatty acids, on coronary endpoints.[657] Meta-analysis of trial results indicates that substitution of polyunsaturated fatty acids for saturated fatty acids reduces risk for CHD.[409,410,624] This positive result is supported by research in primates that indicates that polyunsaturated fatty acids are antiatherogenic when substituted for saturated fatty acids.[666]

Despite evidence of CHD risk reduction from polyunsaturated fatty acids, there are no large populations that have consumed large quantities of polyunsaturated fatty acids for long periods. Thus, high intakes have not been proven safe in large populations; this introduces a note of caution for recommending high intakes.

Evidence statements: Linoleic acid, a polyunsaturated fatty acid, reduces LDL cholesterol levels when substituted for saturated fatty acids in the diet (A1, B1). Polyunsaturated fatty acids can also cause small reductions in HDL cholesterol when compared with monounsaturated fatty acids (B2). Controlled clinical trials indicate that substitution of polyunsaturated fatty acids for saturated fatty acids reduces risk for CHD (A2, B2).

Recommendations: Polyunsaturated fatty acids are one form of unsaturated fatty acids that can replace saturated fat. Most polyunsaturated fatty acids should be derived from liquid vegetable oils, semi-liquid margarines, and other margarines low in *trans* fatty acids. Intakes of polyunsaturated fat can range up to 10 percent of total calories.

6) Total fat

Among the fatty acids that make up the total fat in the diet, only saturated fatty acids and *trans* fatty acids raise LDL cholesterol levels.[657] Thus, serum levels of LDL cholesterol are independent of intakes of total fat per se. ATP II[1,2] advised limiting total fat in Step I and Step II diets to ≤30 percent of calories primarily as a means of achieving lower intakes of saturated fatty acids. The focus of the dietary approach to reducing CHD risk then and now is on dietary fatty acids that raise LDL cholesterol concentrations.

Evidence statement: Unsaturated fatty acids do not raise LDL cholesterol concentrations when substituted for carbohydrates in the diet (A2, B2).

Recommendation: It is not necessary to restrict total fat intake for the express purpose of reducing LDL cholesterol levels, provided saturated fatty acids are reduced to goal levels.

For many years, other public health groups have recommended low intakes of total fat in an effort to curtail obesity and to reduce the risk for some forms of cancer. These recommendations were based largely on experiments in laboratory animals and cross-cultural studies. Several short-term studies also suggest that higher fat intakes (>35 percent of calories) modify the body's metabolism in ways that favor fat accumulation.[667-672] However, isocaloric exchange of fat for carbohydrate does not produce weight gain over a period of many months.[673,674] Further, although some prospective studies have suggested a relationship between the percentage of dietary fat and obesity,[675,676] recent prospective studies (or meta-analysis of studies) have failed to detect a causative link between them.[677,678] Evidence related to these areas is reviewed in detail in the recent rationale report of the Dietary Guidelines for Americans (2000).[241]

Studies in laboratory animals and cross-cultural studies have suggested a relationship between fat intake and risk for certain cancers.[679-682] Moreover, a major clinical trial is presently underway to determine whether low-fat diets will reduce risk for breast cancer in women; this trial is a component of the Women's Health Initiative[683] and is scheduled to end in 2005.

Even so, recent prospective studies have not confirmed an association between fat intake and cancer.[684-687] Thus, a strong recommendation to reduce fat intake for the purpose of preventing cancer does not seem warranted at this time.[241]

The Dietary Guidelines for Americans (2000)[241] noted that some investigators are concerned that recommendations that emphasize lower total fat intakes (<30 percent of energy) may have led to an overconsumption of carbohydrates, contributing to an increased prevalence of obesity. Moreover, very high intakes of carbohydrates (>60 percent of calories) in overweight/-obese persons can aggravate some of the risk factors of the metabolic syndrome.[663,664,688-691] These latter responses have led some investigators to propose that populations with a high prevalence of insulin resistance and the metabolic syndrome should avoid very high-carbohydrate diets and should consume relatively more unsaturated fatty acids.[692]

Evidence statement: The percentage of total fat in the diet, independent of caloric intake, has not been documented to be related to body weight or risk for cancer in the general population.[241] Short-term studies suggest that very high fat intakes (>35 percent of calories) modify metabolism in ways that could promote obesity (C2). On the other hand, very high carbohydrate intakes (>60 percent of calories) aggravate some of the lipid and non-lipid risk factors common in the metabolic syndrome (A2, B2, C2).

Recommendations: Dietary fat recommendations should emphasize reduction in saturated fatty acids. Further, for persons with lipid disorders or the metabolic syndrome, extremes of total fat intake—either high or low—should be avoided. In such persons, total fat intakes should range from 25–35 percent of calories. For some persons with the metabolic syndrome, a total fat intake of 30–35 percent may reduce lipid and nonlipid risk factors.

7) Carbohydrate

When carbohydrates are substituted for saturated fatty acids, the fall in LDL cholesterol levels equals that with monounsaturated fatty acids. However, compared with monounsaturated fatty acids, substitution of carbohydrate for saturated fatty acids frequently causes a fall in HDL cholesterol and a rise in triglyceride.[624,663,689,693] This effect apparently persists in the long term, as suggested by differences in population lipid levels in the presence of different habitual diets.[694,695] When carbohydrate is consumed along with high-fiber diets, however, the rise in triglycerides or fall in HDL cholesterol has been reported to be reduced.[693,696,697]

Digestible carbohydrates include starches (complex carbohydrates) and sugar. Some foods, such as whole grains, vegetables, and some fruits, contain viscous fiber that helps to lower LDL cholesterol as well (see Table V.2–5). Sugars and starches occur naturally in many foods that also supply other important nutrients. Examples of these foods include fat-free and low-fat dairy products, fruits, some vegetables, breads, cereals, and grains. Inclusion of these foods helps provide daily recommended intakes of essential nutrients.[241]

An old concept receiving recent attention is the "glycemic" potential of different foods. Glycemic index refers to the value obtained by feeding a carbohydrate load and measuring the level of blood glucose. Study of this factor is complicated because there is a wide range in the glycemic index for each group of foods, attributed to factors such as its form when eaten, the way it is processed, how it is chewed, how it is emptied from the stomach, and an individual's physiologic and metabolic responses.[698] To date the glycemic index has not been widely accepted as a practical means by which to select specific carbohydrate-containing foods for dietary therapy.[241]

Evidence statement: When carbohydrate is substituted for saturated fatty acids, LDL cholesterol levels fall (A2, B2). However, very high intakes of carbohydrate (>60 percent of total calories) are accompanied by a reduction in HDL cholesterol and a rise in triglyceride (B1, C1). These latter responses are sometimes reduced when carbohydate is consumed with viscous fiber (C2); however, it has not been demonstrated convincingly that viscous fiber can fully negate the triglyceride-raising or HDL-lowering actions of very high intakes of carbohydrates.

Recommendation: Carbohydrate intakes should be limited to 60 percent of total calories. Lower intakes (e.g., 50 percent of calories) should be considered for persons with the metabolic syndrome who have elevated triglycerides or low HDL cholesterol. Regardless of intakes, most of the carbohydrate intake should come from grain products, especially whole grains, vegetables, fruits, and fat-free and low-fat dairy products.

8) Protein

Dietary protein in general has little effect on serum LDL cholesterol level or other lipoprotein fractions. However, substituting soy protein for animal protein has been reported to lower LDL cholesterol[699] (see Section V.3.b.3). Plant sources of protein are predominantly legumes, dry beans, nuts, and, to a lesser extent, grain products and vegetables, which are low in saturated fats and cholesterol. Animal sources of protein that are lower in saturated fat and cholesterol include fat-free and low-fat dairy products, egg whites, fish, skinless poultry, and lean meats.

b. Additional dietary options for LDL lowering

1) Increasing viscous fiber in the diet

Recent reports indicate that viscous (soluble) forms of dietary fiber can reduce LDL cholesterol levels. In contrast, insoluble fiber does not significantly affect LDL cholesterol.[700] On average, an increase in viscous fiber of 5–10 grams per day is accompanied by an approximately 5 percent reduction in LDL cholesterol.[701,702] In a meta-analysis of 67 trials related to oats, pectin, guar, and psyllium, a small but significant reduction in serum total and LDL cholesterol was noted for all sources of viscous fiber in ranges of 2–10 grams per day.[703] Thus, at present, there is general agreement that viscous fiber (e.g., oats, guar, pectin, and psyllium) decreases serum cholesterol and LDL cholesterol. Because of the favorable effect of viscous fiber on LDL cholesterol levels, the ATP III panel recommends that the therapeutic diet be enriched by foods that provide a total of at least 5–10 grams of viscous fiber daily (see Table V.2–5). Even higher intakes of 10–25 grams per day can be beneficial.

Some investigators report that the consumption of viscous (soluble) fiber (provided by oats, barley, psyllium, pectin-rich fruit, and beans) produces a reduction in HDL cholesterol concentration.[699] Other reviews report little, no, or inconsistent effect on HDL cholesterol.[704,705]

Evidence statement: 5–10 grams of viscous fiber per day reduces LDL cholesterol levels by approximately 5 percent (A2, B1).

Recommendation: The use of dietary sources of viscous fiber is a therapeutic option to enhance LDL cholesterol lowering.

2) Plant stanols/sterols

Recent studies have demonstrated the LDL-lowering effect of plant sterols, which are isolated from soybean and tall pine-tree oils. Plant sterols can be esterified to unsaturated fatty acids (creating sterol esters) to increase lipid solubility. Hydrogenating sterols produces plant stanols and, with esterification, stanol esters. The efficacy of plant sterols and plant stanols is considered to be comparable.[706,707] Because lipids are needed to solubilize stanol/sterol esters, they are usually available in commercial margarines. The presence of plant stanols/sterols is listed on the food label. When margarine products are used, persons must be advised to adjust caloric intake to account for the calories contained in the products.

Data show that plant-derived stanol/sterol esters at dosages of 2–3 g/day lower LDL-C levels by 6–15 percent with little or no change in HDL cholesterol or triglyceride levels.[707-713] The more recent among these studies indicate that maximal lowering of LDL cholesterol occurs at intakes of plant stanol/sterol esters of 2 g/day. LDL reductions also occur in individuals who have both hypercholesterolemia and type 2 diabetes[714] and in children with hypercholesterolemia.[715] A greater percent lowering of LDL occurs in older people than in younger people.[716] No studies have been conducted to determine the effect of plant stanols/sterols on CHD risk, although Law[716] has recently projected that their use should double the beneficial effect on CHD risk achieved by reducing dietary saturated fatty acids and cholesterol.

Plant sterols/stanols reduce absorption of dietary carotenoids, and decreased levels of plasma beta-carotene have been observed subsequent to consumption of margarines that contain either stanol ester or sterol ester.[706] Whether carotenoid decreases are deleterious is unknown, but prudence calls for adhering to current recommendations for intakes of fruits and vegetables with consumption of plant stanols/sterols.

Evidence statement: Daily intakes of 2–3 grams per day of plant stanol/sterol esters will reduce LDL cholesterol by 6–15 percent (A2, B1).

Recommendation: Plant stanol/sterol esters (2 g/day) are a therapeutic option to enhance LDL cholesterol lowering.

3) Soy protein

Soy protein included in a diet low in saturated fatty acids and cholesterol can lower levels of total cholesterol and LDL cholesterol in individuals with hypercholesterolemia. Recent reviews[717,718] gave particular weight to 16 well-controlled trials that reported intakes of saturated fatty acids and cholesterol. More than half of the studies used more than 40 g/day soy protein in some form. One report[719] indicated that 25 g/day soy protein in a diet low in saturated fatty acids and cholesterol lowers LDL cholesterol levels by about 5 percent.

The specific processing of the soybean determines the characteristics of soy protein, such as the content of isoflavones, fiber, and saponins. There is some evidence that an LDL-lowering effect is dependent upon isoflavone content[720] but conclusive data are lacking. Since there are inconsistent findings regarding both the dose and the potential benefit of soy protein, soy protein's major role in LDL-lowering may be to help reduce the intake of animal food products with their higher content of saturated fatty acids.

Evidence statement: High intakes of soy protein can cause small reductions in LDL cholesterol levels, especially when it replaces animal food products (A2, B2).

Recommendation: Food sources containing soy protein are acceptable as replacements for animal food products containing animal fats.

c. Other dietary factors that may reduce baseline risk for CHD

Epidemiological studies strongly suggest that other nutrient factors affect baseline risk for CHD. For example, in the Mediterranean region, where the diet is rich in fruits and vegetables, whole grains, ocean fish, and unsaturated fatty acids, the risk for CHD appears to be lower than predicted by the major risk factors. In contrast, in regions without this dietary pattern, such as Eastern Europe and Russia, CHD rates are higher than predicted by the prevalence of CHD risk factors. Such observational data provide a basis for a general recommendation for a dietary pattern that is consistent with a low baseline population risk. The Dietary Guidelines for Americans (2000),[241] were crafted to facilitate reduction in baseline risk for CHD (Table V.2–3).

In addition, nutritional research has focused on several specific factors that may have unique properties to reduce risk for CHD. The status of these emerging dietary factors are reviewed below and summarized in evidence statements.

1) n-3 (omega-3) polyunsaturated fatty acids

Polyunsaturated fatty acids of the n-3 (omega-3) type occur as alpha-linolenic acid (18:3), primarily in certain vegetable sources such as soybean, canola oil and

English walnuts, and in fish oils as eicosapentaenoic acid (EPA) (20:5) and docosahexaenoic acid (DHA) (22:6) *(marine n-3 fatty acids)*.

Moderate fish consumption has been associated with reduced sudden cardiac death or reduced CHD mortality in several prospective cohort studies[721-723] but not in others.[724,725] One study found a trend toward increased relative risk of CHD death with marine n-3 fatty acids. A nested, case-control study found an inverse relationship between risk for sudden cardiac death and both reported intake of marine n-3 fatty acids and red blood cell n-3 fatty acid level.[726] Postulated mechanisms for the effects of marine n-3 fatty acids on CHD risk include favorable effects on cardiac rhythm, platelet aggregation, inflammatory responses, and serum triglyceride levels. High intakes of marine n-3 fatty acids reduce triglyceride levels;[727] this effect appears to be secondary to decreased VLDL production.[728] Generally, marine n-3 fatty acids have no effect on LDL cholesterol levels, but large doses have been shown to reciprocally increase LDL cholesterol levels in persons with hypertriglyceridemia.[729] Recent data indicate that some fish have a high mercury content and the toxic effects of mercury could attenuate protective effects of fish.[730,731]

Four clinical trials suggest that n-3 fatty acids from marine or plant sources reduce sudden death and overall death in populations with pre-existing cardiovascular disease. The DART trial[732] was a relatively large secondary prevention trial in which subjects advised to eat fatty fish had a 29 percent reduction in 2-year all-cause mortality compared with those not so advised, although myocardial infarction and coronary death were not specifically reduced. The Lyon Heart Trial[733] included increased intakes of alpha-linolenic acid as part of a "Mediterranean" diet. Compared to the control group, subjects consuming the Mediterranean diet had fewer coronary events. The authors attributed some of the benefit to higher intakes of n-3 fatty acids. In a small supplement trial, Singh et al.[734] treated patients with suspected acute myocardial infarction with fish oil capsules (EPA 1.08 g/day) or mustard oil (alpha-linolenic acid 2.9 g/day) or placebo. After one year, total cardiac events were significantly less in the groups on fish oil and mustard seed oil supplements. Further, the large placebo-controlled, but unblinded Italian GISSI Prevention trial[735] administered fish oil supplements containing n-3 fatty acids (1 g/day fish oil, n = 2836 subjects) and compared coronary outcomes to controls (n = 2828). The group receiving fish-oil supplements had a 14 percent reduction in total death and a 17 percent reduction in cardiovascular death. Other clinical trials are less suggestive of benefit from n-3 fatty acids. Angiographic data fail to show that marine n-3 fatty acids modify coronary lumen size.[736,737] Also, fish oil administration apparently does not prevent restenosis after coronary angioplasty.[738] Additional studies are underway to determine the effect of n-3 fatty acids on CHD risk in the U.S. population.[241]

Based on these findings, the Dietary Guidelines for Americans (2000)[241] noted that some fish, such as salmon, tuna, and mackerel, contain omega-3 fatty acids that are being studied to determine if they offer protection against heart disease. No quantitative recommendations for n-3 fatty acids were made for the general public.

Evidence statement: The mechanisms whereby n-3 fatty acids might reduce coronary events are unknown and may be multiple. Prospective data and clinical trial evidence in secondary CHD prevention suggest that higher intakes of n-3 fatty acids reduce risk for coronary events or coronary mortality (A2, C2).

Recommendation: Higher dietary intakes of n-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of the evidence is only moderate at present. ATP III supports the American Heart Association's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective n-3 fatty acids. However, a dietary recommendation for a specific amount of n-3 fatty acids is not being made (See Section VI for ATP III recommendations on n-3 supplements for reducing risk for CHD.)

2) Vitamins/antioxidants

a) Folic acid and vitamins B_6 and B_{12}

Folic acid and vitamins B_6 and B_{12} play a role in the metabolism of homocysteine, and levels of these vitamins correlate inversely with homocysteine levels. Data from the Framingham Heart Study suggest that the mandated fortification of cereal grains with folic acid has lowered population mean homocysteine levels as well as the prevalence of hyperhomocysteinemia.[307] Many cross-sectional case-control studies and some prospective cohort studies show a positive association between plasma homocysteine levels and CVD risk[297,739-743] but other prospective cohort studies do not.[300,744-746]

Despite the fact that homocysteine levels can be reduced with supplements of folate, B_6, and B_{12}, it is not known whether reduction of plasma homocysteine levels by diet and/or vitamin supplements will reduce CVD risk.[743] Several randomized trials are underway to determine if folic acid, vitamin B_6, and vitamin B_{12} will be effective in reducing the risk of heart disease.[304]

The Institute of Medicine has recently published dietary recommendations for folate for the general population.[747] The recommended dietary allowance (RDA) for folate is 400 micrograms per day. This level of intake was deemed adequate to provide any reduction in risk for cardiovascular disease that can be obtained from dietary folate. An upper limit for folate derived from fortified food or supplements was estimated to be 1000 micrograms per day.

Evidence statement: According to the Institute of Medicine, the RDA for folate for adults is 400 micrograms per day, and the upper limit is 1000 micrograms per day. There are no published randomized controlled clinical trials to show whether lowering homocysteine levels through dietary intake or supplements of folate and other B vitamins will reduce the risk for CHD.

Recommendation: ATP III endorses the Institute of Medicine RDA for dietary folate, namely, 400 micrograms per day. Folate should be consumed largely from dietary sources.

b) Antioxidants

Oxidative stress is a putative cause of atherosclerotic disease. In experimental studies, oxidation of LDL is an important step in the development and progression of CHD. Thus, a large body of research has been directed towards the potential of antioxidants for reducing CHD risk. Antioxidants under investigation include ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), beta-carotene, ubiquinone (coenzyme Q10), bioflavonoids, and selenium.

Several studies in laboratory animals support the concept that antioxidants are antiatherogenic.[748] Some, but not all, epidemiological data lend additional support to the concept that dietary antioxidants can reduce risk for CHD.[748] Generally, in populations that consume a dietary pattern rich in fruits and vegetables and other foods high in antioxidants, there is a reduced risk of CHD.

Several controlled clinical trials have been carried out to determine whether supplementation with antioxidants reduces risk for CHD. The Linxian study in China found that supplements of beta-carotene (15 mg/d), vitamin E (30 mg/d), and selenium (15 mcg/d), given at levels obtained from foods, were associated with a non-significant 10 percent decrease in CVD mortality.[749] In the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study, supplementation with beta-carotene had no beneficial effect on the incidence of myocardial infarction.[750] Another trial,[751] found no benefit (or harm) for CHD incidence after 12 years of beta-carotene supplementation in 22,071 male physicians. Finally, in the CARET study, a non-significant 26 percent increase in cardiovascular mortality was reported in a group supplemented with beta-carotene.[752]

In the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study, supplementation with small doses of vitamin E in Finnish male smokers had only a marginal effect on incidence of fatal CHD, whereas it had no effect on incidence of nonfatal myocardial infarction.[750] In a secondary prevention trial among patients with CHD, vitamin E supplementation (400 or 800 IU per day during 1.5 years) in the Cambridge Heart Antioxidant Study (CHAOS), significantly reduced the risk for recurrent MI (77 percent). No effect was demonstrated for CVD mortality. A non-significant increase in total mortality was observed in the vitamin E group.[753] Two large-scale clinical trials in patients