Protease-inhibitor induced dyslipidemia. Although protease inhibitors have improved morbidity and mortality in patients with human immunodeficiency virus (HIV), these drugs unfortunately can cause serious metabolic disorders.[997-999] The latter include peripheral lipodystrophy, increased visceral fat, hyperlipidemia, insulin resistance, and diabetes. The lipid pattern typically is that of atherogenic dyslipidemia (elevated triglyceride and low HDL-cholesterol levels). The mechanisms underlying the metabolic complications are unknown, although they resemble those of a genetic disorder called familial partial lipodystrophy.[1000] To date there is limited experience with lipid-lowering drugs for treatment of protease-inhibitor induced lipodystrophy. However, clinical experience indicates that both fibrates and statins will reduce serum triglycerides and cholesterol in this condition.[997] Fibrates may be especially useful to prevent the occurrence of acute pancreatitis associated with severe hypertriglyceridemia.

6. Persons with high blood cholesterol and concomitant hypertension

In 1990, NHLBI published a report of a working group on management of patients with concomitant high blood cholesterol and hypertension.[172,173] The major findings of this report are reviewed and updated in this section. Both high blood cholesterol and high blood pressure are common in U.S. adults, and these two conditions frequently coexist. Persons with high blood cholesterol have a higher than expected prevalence of hypertension, and persons with hypertension have a higher than expected prevalence of high blood cholesterol. According to unpublished data from NHANES II, 40 percent of the 51 million individuals with hypertension (blood pressure ≥140/90 mmHg or currently taking antihypertensive medications) have cholesterol levels ≥240 mg/dL, and 46 percent of those with cholesterol levels ≥240 mg/dL have hypertension. The risk gradient for blood pressure (systolic and diastolic) is similar to that for serum cholesterol; the higher the blood pressure, the greater the risk of CHD.[1001] In persons with both elevated cholesterol and high blood pressure, CHD risk is synergistically increased. Conversely, reducing blood pressure, like cholesterol lowering, decreases risk for cardiovascular disease.[1002]

a. Therapeutic considerations

In persons with concomitant hypertension and hypercholesterolemia, both conditions should be treated aggressively, especially in persons with known CHD. Diet and other lifestyle therapies are the essential first steps of therapy for elevations of both blood pressure and cholesterol. The principles of dietary therapy are similar in both cases and include reductions of calories, saturated fat, cholesterol, and alcohol consumption; sodium reduction and ample potassium intake are also important for control of hypertension. The recommended diet should emphasize fruits, vegetables, and low-fat dairy products.[766,1003] In overweight persons, weight reduction is very important and essential to the management of elevated blood pressure[1004] as well as for high blood cholesterol. Persons should be reminded that weight reduction and control is a chronic rather than an acute treatment and that successful weight control will be achieved only through long-term lifestyle modification that emphasizes both nutritional balance and physical activity.[78,79,1005] Exercise is also important because of its benefits on cardiovascular fitness and weight reduction as well as lowering of blood pressure and cholesterol.[238] Smoking cessation should also be included in the life habit changes required to improve cholesterol and blood pressure levels.

b. Effects of antihypertensive agents on serum lipids

Several antihypertensive agents affect serum lipid levels, whereas others do not.[1006,1007] For example, calcium channel antagonists, angiotensin converting enzyme inhibitors, hydralazine, minoxidil, potassium-sparing diuretics, and reserpine have minimal if any effects on serum lipids. Higher doses of thiazide diuretics can cause modest and often transient elevations (5–10 mg/dL) in serum total and LDL cholesterol and serum triglycerides with little or no adverse effects on HDL cholesterol. The effects of loop diuretics are similar to those of thiazides with increases in total and LDL cholesterol, whereas HDL-cholesterol levels are generally lower in persons on furosemide. Data regarding indapamide are inconclusive, but suggest a neutral effect. Alpha-1-adrenergic blockers and centrally acting alpha-2-receptor agonists have a slight beneficial effect on blood lipids by decreasing total and LDL cholesterol. In general, beta-blockers without intrinsic sympathomimetic activity (ISA) or alpha-blocking properties tend to reduce HDL cholesterol, increase serum

triglycerides, and have variable effects on total serum cholesterol. These effects are very modest and should not play a role in the selection of specific antihypertensive agents. Beta-blockers with ISA and the beta-blocker labetalol (which has alpha-1-adrenergic blocking properties) produce no appreciable changes in lipid levels.

The effects of antihypertensive drugs on the efficacy of lipid-lowering agents have not been carefully evaluated, but among participants in the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), those who were taking thiazide diuretics did not reduce LDL cholesterol as much as those who were not using thiazide diuretics.[13,1008] Regardless of the potential of thiazide diuretics to raise serum cholesterol levels, they are still considered to be first-line therapies for hypertension.[160,161] Moreover, lower doses of thiazides appear to have less of a cholesterol-raising action as well as few other side effects.[1009,1010] For these reasons, use of lower doses of thiazides need not be excluded in antihypertension regimens in persons undergoing clinical cholesterol management.

c. Selection of antihypertensive therapy

When lifestyle measures alone do not achieve desired goals, the addition of drug therapy may be required. Selection of drug therapy requires consideration of benefits, effects of therapy on quality of life, concomitant diseases, and costs. In general, selection of specific antihypertensive drugs for persons with elevated LDL-cholesterol levels should follow the guidelines outlined in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[160,161] Selection of lipid-lowering agents in persons with elevated blood pressure should follow the guidelines listed elsewhere in this report.

Drug therapy for uncomplicated hypertension should begin with a diuretic or beta-blocker. In older patients, a diuretic is preferred and a dihydropyridine (DHP) calcium antagonist can be considered. In certain comorbidities (such as CAD, heart failure, renal disease, and diabetes), angiotensin converting enzyme inhibitors or calcium antagonists have special indications. Alpha blockers should not be used as monotherapy or in those at risk for developing heart failure.[1011] Diuretics may slightly raise LDL-cholesterol levels and some beta-blockers may depress HDL-cholesterol levels, but these drugs should not be avoided if their non-use means less than optimal blood pressure control; further, their possible adverse effects on lipids should be balanced by considerations of efficacy, tolerability, cost, and adherence. Some persons will have strong indications for one of these medications (for example, beta-blockers in the post-myocardial infarction patient and diuretics in persons with salt-dependent hypertension). Therefore, they are not contraindicated even in the presence of the dyslipidemia. Some persons are not sensitive to the adverse effects of diuretics on lipids, and in others a low-saturated-fat, low-cholesterol diet will blunt or negate these effects. It should be noted that in the Systolic Hypertension in the Elderly Program,[171] use of low doses of thiazides and/or beta-blockers reduced both stroke and CHD in older persons and in fact had limited adverse effects on lipids.[1012] Thus any adverse effect on plasma lipids in this trial did not offset their net beneficial effect.

d. Selection of lipid-lowering therapy

Selection of drug therapy for persons with elevated cholesterol is discussed in depth elsewhere in this document. Several potential adverse effects on blood pressure control may occur and should be kept in mind. Bile acid sequestrants may decrease absorption of thiazide diuretics and propranolol, and medications should be given 1 hour before or 4 hours after the bile acid sequestrant. Nicotinic acid may enhance the fall in blood pressure due to antihypertensive vasodilators. Fibric acids are more likely to produce myopathy in persons with renal failure; therefore, dosage should be decreased and persons carefully monitored. The FDA lists no specific drug interactions between statins and antihypertensive agents; however, patients with some forms of renal disease may be at increased risk for myopathy with statin therapy.[1013-1015]

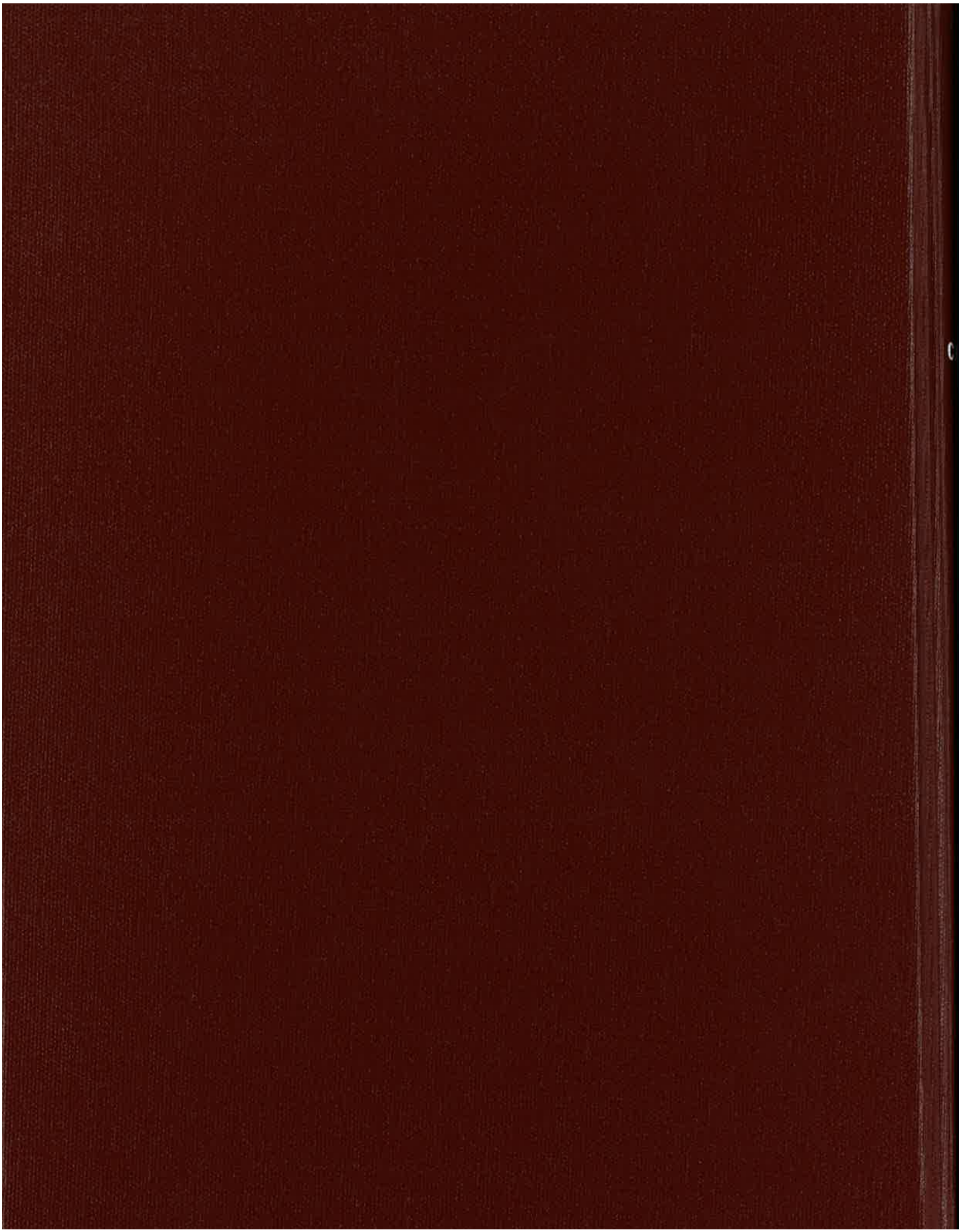
e. Compliance with therapy

Although the risks of elevated blood pressure and cholesterol levels are well-known, and the benefits of treatment well established, many persons are not adequately controlled. In the case of hypertension, more than half of persons are either untreated or inadequately treated. Poor adherence to therapy is a major reason for inadequate control of high blood pressure. Approximately 50 percent of persons with hypertension fail to keep

followup appointments, and only 60 percent take their medications as prescribed. Efforts aimed at improving control of hypertension and hypercholesterolemia must address barriers to effective adherence. These include poor doctor-patient communication, cost of therapy, and side effects of medications. Lack of attention (complacency) to achieving treatment goals by health care providers is another important reason for inadequate control rates of hypertension.[1016] Physicians and patients must be mutually committed to the goals of therapy and achieving control of the risk factor. Physicians must communicate instructions clearly and prescribe therapies that are effective, affordable, and have minimal or no adverse effects on the patient's quality of life or overall cardiac risk profile. Persons must follow recommendations and alert their physicians to any problems with their medications—particularly those relating to side effects and cost.

ATTACHMENT 1 (Part 8)

(ATP-III)



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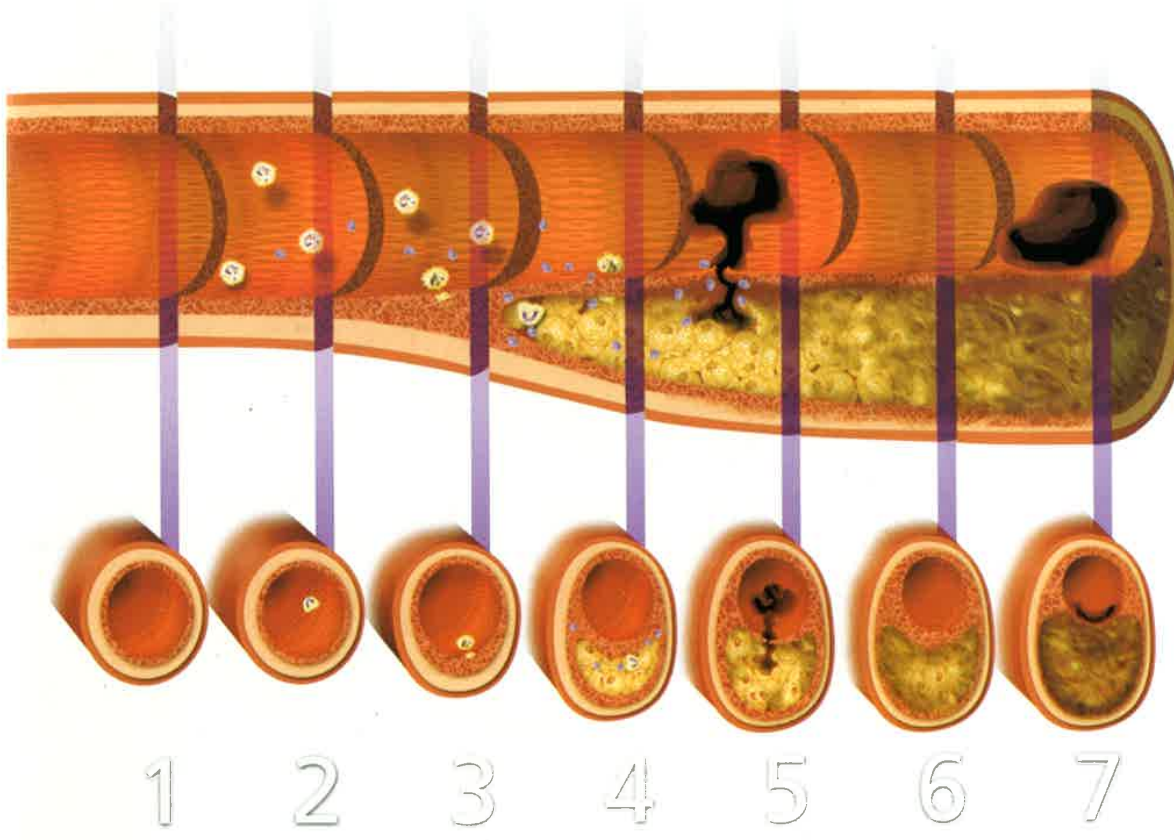

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection

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

Evaluation

Final Report

Treatment

National Cholesterol Education Program

National Heart, Lung, and Blood Institute

National Institutes of Health

NIH Publication No. 02-5215
September 2002

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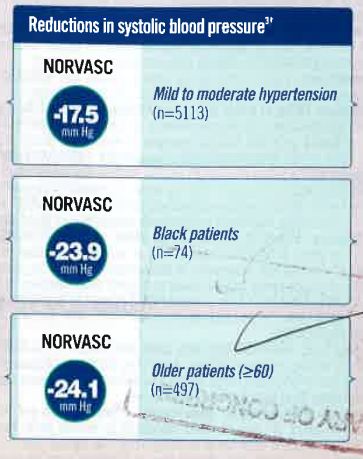

Reductions in DBP were 12.3, 17.1, and 10.8 mm Hg, respectively[3]

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In clinical trials, the most common side effects versus placebo were edema (8.3% vs 2.4%), headache (7.3% vs 7.8%), fatigue (4.5% vs 2.8%), and dizziness (3.2% vs 3.4%)

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001 for all NORVASC patients vs placebo.

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Contents

VIII. Special Considerations for Different Population Groups

Therapeutic recommendations in this report are based heavily on evidence from controlled clinical trials. Nonetheless, randomized clinical trials have not been carried out to address all therapeutic questions pertaining to all age groups, both sexes, and different racial/ethnic groups. Consequently, ATP III recommendations for various groups often must be made by combining what has been learned from clinical trials with other lines of evidence such as epidemiological findings. Fortunately, a large number of clinical trials have produced a very large set of consistent results that allow for considerable confidence in projections of benefits and drawbacks of cholesterol-lowering therapy in groups that have not been subject to clinical trials. In the discussion to follow, the ATP III panel has crafted its recommendations for different population groups from general evidence statements and general recommendations developed in previous sections. No attempt will be made to grade the category and strength of evidence for all recommendations made in this section.

1. Middle-aged men

Men of middle-age (35–65 years) are at increasing risk for CHD as they progressively age. Up to one-third of all new CHD events and about one-fourth of all CHD deaths occur in middle-aged men.[1017] Most of the excess risk for CHD morbidity and mortality in middle-aged men can be explained by the major risk factors—cholesterol disorders, hypertension, and cigarette smoking.[10,11] Men are predisposed to abdominal obesity, which makes them particularly susceptible to the metabolic syndrome. Consequently, metabolic risk factors (elevated cholesterol and triglycerides, low HDL cholesterol, and elevated blood pressure) appear earlier in men than women. Table VIII.1–1 summarizes factors to consider when applying ATP III guidelines to middle-aged men.

Table VIII.1–1. Special Considerations for Cholesterol Management in Middle-Aged Men

Risk Level	Special Considerations
CHD and CHD risk equivalents 10-year risk >20% LDL-C goal <100 mg/dL	■ Strong evidence of risk reduction from LDL lowering with statin therapy ■ Strong trend for risk reduction from drug treatment of atherogenic dyslipidemia (see section II.3.d) ■ Consider fibrates or nicotinic acid as a second lipid-lowering drug in persons with low HDL and atherogenic dyslipidemia ■ High prevalence of metabolic syndrome (requires intensive life-habit changes)
Multiple (2+) risk factors 10-year risk 10–20% LDL-C goal <130 mg/dL	■ Strong evidence of risk reduction from LDL lowering with statins (WOSCOPS/AFCAPS) and bile acid sequestrants (LRC-CPPT) ■ Consider LDL-lowering drugs when LDL-C is >160 mg/dL ■ Consider LDL-lowering drugs when LDL-C remains at 130–159 mg/dL after TLC Diet ■ Emerging risk factors: testing optional to raise risk level
Multiple (2+) risk factors 10-year risk <10% LDL-C goal <130 mg/dL	■ Strong evidence of risk reduction from LDL lowering with statins (AFCAPS) ■ Consider LDL-lowering drugs when LDL-C is >160 mg/dL ■ Emphasize TLC when LDL-C is 130–159 mg/dL – Consider nondrug therapeutic options—plant stanols/sterols and increased viscous fiber – Intensify weight control and physical activity when metabolic syndrome is present ■ Emerging risk factors: testing optional to raise risk level
0–1 risk factor 10-year risk <10% LDL-C goal <160 mg/dL	■ Consider LDL-lowering drugs when LDL-C is ≥190 mg/dL ■ LDL-lowering drug is optional when LDL-C is 160–189 mg/dL – Factors favoring drug therapy: higher end of age range, presence of emerging risk factors (if measured), obesity, cigarette smoking, positive family history, very low HDL-C ■ Emphasize public health message (including heart healthy diet) when LDL-C <160 mg/dL

2. Women

CHD is a major cause of death in women as well as men and it ultimately kills as many women as men.[1017] However, the onset of CHD is delayed by some 10–15 years in women compared to men; thus ATP III defines age as a risk factor in women at age 55, compared to age 45 for men. Since the onset of CHD is delayed by 10–15 years in women compared to men, it seems appropriate to include comments on treatment of women up to age 45 under younger adults (see VIII.4 below) and to restrict comments for older persons to women age >75 years (see VIII.3 below). Thus comments in this section will apply to women in the age range of 45 to 75 years. It is only at age 75 and above that CHD rates of women approximate those of men.[1017] Because there are more older women than older men, the lifetime risk of CHD is almost as high in women as in men. The reasons for the disparity in ages of onset of CHD between women and men are not fully understood. The Framingham Heart Study could not explain the gender disparity solely on the basis of the major risk factors. Nonetheless, patterns of risk factors often differ between men and women. For example, blood pressure, LDL cholesterol, and triglycerides rise at an earlier age in men than in women. Moreover, HDL-cholesterol levels are on average some 10 mg/dL lower in adult men than in women. This latter difference is established at puberty when HDL-cholesterol levels decrease in males but not in females. Since a 10-mg/dL difference in HDL cholesterol is projected to account for a 20–30 percent difference in CHD event rates over the short term,[90] this difference over the adult lifespan could account for a significant portion of the gender disparity between men and women.

Although the magnitude of risk factors on average may vary between women and men, all of the major risk factors raise the risk for CHD in women.[10] This is true for lipid risk factors including LDL cholesterol and HDL cholesterol. Moreover, triglycerides appear to be an even more powerful risk factor in women than in men.[89,1018-1021]

A commonly cited reason for the gender difference is a protective effect of estrogen in women. Data in support, however, are open to varying interpretations. For example, while oral estrogens increase HDL cholesterol and decrease LDL cholesterol, they also increase the potential for coagulation and possibly for inflammation.[889,1022-1024] Oral estrogens do not mimic the physiologic role of endogenous estrogen, which is released into the systemic rather than the portal circulation. When given through the transcutaneous route, estrogen does not in fact increase HDL cholesterol and has a more modest effect on LDL cholesterol and on coagulation factors than oral estrogen.[1025-1028] There is no acceleration of CHD rates at about the age of menopause as endogenous estrogen levels wane; but as in males, the rates simply increase in a log-linear fashion with age. There is very little or no decrease in HDL cholesterol in cohorts followed across the transition through the menopause.[1029] Observational studies have consistently suggested that postmenopausal estrogen users are at lower risk of CHD than non-users. However, these studies are confounded by a number of powerful biases that may account for a large overestimation of potential benefit.[1030-1032]

Special considerations for management of serum cholesterol in women (ages 45–75 years) are presented in Table VIII.2–1. ATP III does not recommend different guidelines for men and women, but several nuances of difference are noted by comparison of Tables VIII.1–1 and VIII.2–1 for middle-aged men and women, respectively.

3. Older persons (men ≥65 years; women ≥75 years)

Most new CHD events and most coronary deaths occur in older persons.[1033] This is because older persons have accumulated more coronary atherosclerosis than younger age groups. Clinical trial data indicate that older persons with established CHD show benefit from LDL-lowering therapy.[206,435,436] Therefore, benefits of intensive LDL lowering should not be denied to persons with CHD solely on the basis of their age.

To reduce the prevalence of CHD in older persons, risk factors should be controlled throughout life. Nonetheless, a high level of LDL cholesterol and low HDL cholesterol still carry predictive power for the development of CHD in older persons. ATP III reaffirms the position taken in ATP II that older persons who are at higher risk and in otherwise good health are candidates for cholesterol-lowering therapy. The difficulty in selection of older persons for LDL-lowering drugs lies in the uncertainties of risk assessment. Risk factors, particularly LDL cholesterol, decline in predictive power.[1034-1036] For this reason, risk assess-

Table VIII.2–1. Special Considerations for Cholesterol Management in Women (Ages 45–75 years)

Risk Level	Special Considerations
CHD and CHD risk equivalents 10-year risk >20% LDL goal <100 mg/dL	■ All secondary prevention trials with statins have included women ■ Meta-analysis (pooled data) of statin trials show 29% (CI 13–42%) reduction in CHD events (vs. 31% reduction in men)[489] ■ Statins appear to be cholesterol-lowering drugs of first choice in secondary prevention ■ Diabetes counteracts lower risk usually present in women ■ Other therapeutic modalities are effective in secondary prevention – Antihypertensive treatment (SHEP/HOPE) – Aspirin – Beta-blockers ■ Estrogen replacement therapy NOT found to be effective in secondary prevention in women (HERS)
Multiple (2+) risk factors 10-year risk 10–20% LDL goal <130 mg/dL	■ Clinical trials of LDL lowering generally are lacking for this risk category; rationale for therapy is based on extrapolation of benefit from men of similar risk ■ A large proportion of new onset CHD occurs in women who have clustering of risk factors and fall into this risk level ■ LDL-lowering drugs should be considered when LDL-C is ≥160 mg/dL after TLC ■ LDL-lowering drugs can be used when LDL-C remains at 130–159 mg/dL after TLC ■ Estrogen replacement therapy is not recommended for LDL lowering in post-menopausal women
Multiple (2+) risk factors 10-year risk <10% LDL goal <130 mg/dL	■ Primary purpose of LDL-lowering therapy at this risk level is to reduce long-term (>10-year) risk for CHD ■ LDL-lowering drugs can be considered when LDL-C is ≥160 mg/dL after TLC diet. The aim is to reduce long-term risk for CHD ■ LDL-lowering drugs generally are not indicated when LDL-C is 130–159 mg/dL after TLC diet ■ Measurement of emerging risk factors in women with LDL-C 130–159 mg/dL that may raise risk to a higher level is optional ■ Estrogen replacement therapy is not recommended for LDL lowering in post-menopausal women
0–1 risk factor 10-year risk <10% LDL goal <160 mg/dL	■ LDL-lowering drugs can be used when LDL-C is ≥190 mg/dL; the purpose is to reduce long-term risk ■ Drug therapy for LDL lowering is optional when LDL-C is 160–189 mg/dL after TLC diet ■ Because of low long-term risk, drugs may not be necessary when LDL-C is 160–189 mg/dL after TLC diet ■ Measurement of emerging risk factors that may raise risk to a higher level is optional ■ Estrogen replacement therapy is not recommended for LDL lowering in post-menopausal women

ment by Framingham scoring may be less reliable in older persons. A partial solution to this problem is the measurement of subclinical atherosclerosis by noninvasive techniques. If an older person is found to have advanced coronary or systemic atherosclerosis, LDL-lowering therapy can be intensified even in the absence of clinical coronary symptoms.[1037]

Beyond risk assessment, many other factors come into play in older persons that can affect the decision to employ LDL-lowering drugs. These include coexisting diseases, social and economic considerations, and functional age. If Framingham scoring is used to estimate risk in older persons, a more rational decision about initiation of cholesterol-lowering drugs may derive from an examination of the number needed to treat for benefit rather than from a given risk cutpoint (see Section II.7). Some special considerations that apply to different risk categories in older persons are summarized in Table VIII.3–1.

4. Younger adults (men 20–35 years; women 20–45 years)

Special considerations when applying ATP III guidelines to young adults are outlined in Table VIII.4–1. In this age group, CHD is rare except for persons with severe risk factors, e.g., familial hypercholesterolemia,

Table VIII.3–1. Special Considerations for Cholesterol Management in Older Persons (Men ≥65 years; Women ≥75 years)

Risk Level	Special Considerations
CHD and CHD risk equivalents 10-year risk >20% LDL Goal <100 mg/dL	■ Sizable number of older persons were included in secondary prevention statin trials ■ Older persons respond similarly in risk reduction as do middle-aged persons ■ Guidelines for use of LDL-lowering drugs thus are similar in older and middle aged persons for secondary prevention ■ Prevalence of diabetes, a CHD risk equivalent, rises markedly in the older population ■ Clinical judgment assumes increased importance in choice of LDL-lowering therapies in older persons (see Section II.7; NNT for benefit in older persons)
Multiple (2+) risk factors 10-year risk 10–20% LDL Goal <130 mg/dL	■ Risk assessment by standard risk factors probably less reliable in older persons; emerging risk factors (e.g., noninvasive assessment of subclinical atherosclerosis) may assist in risk estimation ■ LDL-lowering drugs can be considered in older persons when multiple risk factors are present and when LDL-C is ≥130 mg/dL on TLC diet ■ Management of other risk factors (e.g., smoking, hypertension, diabetes) has priority in older persons ■ Clinical judgment assumes increased importance in choice of LDL-lowering therapies in older persons (see Section II.7; NNT for benefit in older persons)
Multiple (2+) risk factors 10-year risk <10% LDL Goal <130 mg/dL	■ LDL-C can be a target of drug therapy when LDL-C is ≥160 mg/dL to reduce short-term risk ■ However, risk assessment by standard risk factors probably less reliable in older persons; emerging risk factors (e.g., noninvasive assessment of subclinical atherosclerosis) may assist in risk estimation ■ Emphasis should be given to dietary changes that promote overall good health ■ Clinical judgment assumes increased importance in choice of LDL-lowering therapies in older persons (see Section II.7; NNT for benefit in older persons)
0–1 risk factor 10-year risk <10% LDL Goal <160 mg/dL	■ Persons in this category have no risk factors other than age ■ Absolute short-term risk is relatively low ■ Very high LDL-C (≥190 mg/dL), after TLC diet, justifies consideration of drug therapy ■ High LDL-C (160–189 mg/dL) makes drug therapy optional ■ Clinical judgment assumes increased importance in choice of LDL-lowering therapies in older persons (see Section II.7; NNT for benefit in older persons)

heavy cigarette smoking, and diabetes. Even though clinical CHD is relatively rare in young adults, coronary atherosclerosis in its early stages may be progressing rapidly. The rate of development of coronary atherosclerosis in young adulthood has been shown to correlate with the major risk factors. Long-term prospective studies further note that elevated serum cholesterol first observed in young adults predicts a higher rate of premature CHD in middle age.[32-34] Thus, risk factor control in young adults represents an attractive aim for primary prevention.[1038,1039]

ATP III recommends testing for lipids and lipoproteins beginning at age 20. There are several reasons for this recommendation.[1038] First, early testing provides physicians with the opportunity to link clinical management with the public health approach to primary prevention; the finding of any risk factors in their early stages calls for the reinforcement of the public health message. Second, every young adult has the right to be informed if they are at risk for the development of premature CHD, even though clinical disease may be several decades away. Third, individuals with cholesterol levels in the upper quartile for the population are definitely at higher long-term risk, and life-habit intervention to control risk factors is fundamental.

Most young adults with very high LDL-cholesterol levels (≥190 mg/dL) are candidates for cholesterol-lowering drugs, even when they are otherwise at low risk with 0–1 risk factor and 10-year risk <10 percent. Although their 10-year risk may not be high, long-term risk will be high enough to justify a more aggressive approach to LDL lowering. ATP II set a higher cut-point for initiation of cholesterol-lowering drugs (LDL cholesterol ≥220 mg/dL) in young adults than is being recommended in ATP III. The apparent safety of cholesterol-lowering drugs and growing evidence of the dangers of early onset LDL-cholesterol elevations have led the ATP III panel to recommend consideration of

Table VIII.4–1. Special Considerations for Cholesterol Management in Younger Adults (Men 20–35 years; Women 20–45 years)

Risk Level	Special Considerations
CHD and CHD risk equivalents 10-year risk >20% LDL Goal <100 mg/dL	■ CHD is rare in this age group in the general population ■ Persons with heterozygous familial hypercholesterolemia (FH) may develop very premature CHD and deserve intensive LDL-lowering therapy; however, an LDL-C <100 mg/dL is often difficult to achieve in FH persons (combined LDL-lowering drugs usually are indicated) ■ CHD can occur in this age range in persons with type 1 diabetes or in very heavy cigarette smokers ■ In persons with type 1 diabetes without CHD, clinical judgment is required whether to set LDL-C goal <100 mg/dL
Multiple (2+) risk factors 10-year risk 10–20% LDL Goal <130 mg/dL	■ Most younger adults without CHD will not reach a 10-year risk of 10–20% ■ In rare cases when this level of risk is achieved, LDL-lowering drugs can be employed to reach the LDL-C goal ■ Other risk factors should be vigorously controlled
Multiple (2+) risk factors 10-year risk <10% LDL Goal <130 mg/dL	■ Two non-LDL-risk factors in a younger adult carry a high long-term risk ■ LDL-lowering drugs can be considered when LDL-C is ≥160 mg/dL after TLC diet ■ When LDL-C is <160 mg/dL, TLC should be applied intensively, combined with control of other risk factors
0–1 risk factor 10-year risk <10% LDL Goal <160 mg/dL	■ In otherwise low-risk, younger adults who qualify for clinical management of elevated LDL-C, primary therapy is TLC ■ LDL-lowering drugs can be considered when LDL-C is ≥190 mg/dL after trial of TLC diet ■ When LDL-C is 160–189 mg/dL, drug therapy is optional; however, drug therapy should be avoided if the LDL-C can be reduced to near goal with TLC

cholesterol-lowering drugs at an LDL cholesterol of ≥190 mg/dL in young adults. However, prudence in the initiation of cholesterol-lowering drugs is still indicated. In otherwise low-risk young adults it is acceptable to maximize TLC and to delay initiation of cholesterol-lowering drugs when the LDL cholesterol is in the range of 190 to 220 mg/dL, particularly in premenopausal women. Through the use of LDL-lowering dietary options, possibly combined with bile acid sequestrants, elevated LDL cholesterol in young adult men before age 35 and in premenopausal women usually can be normalized.

In young adults with LDL <190 mg/dL, ATP III guidelines applied to all adults are appropriate. Favorable changes in life habits should receive highest priority for management of elevated LDL cholesterol in young adults. Because of long-term risk, judicious use of drug therapy may be warranted in those who have LDL levels of 160–189 mg/dL and other risk factors. Nonetheless, the high costs and potential for side effects in the long term must always be kept in mind when considering cholesterol-lowering drugs.

5. Racial and ethnic groups

a. African Americans

African Americans have the highest overall CHD mortality rates and the highest out-of-hospital coronary death rates of any ethnic group in the United States, particularly at younger ages.[1040-1043] The earlier age of onset of CHD in African Americans creates particularly striking African American/white differences in years of potential life lost for both total and ischemic heart disease. Although the reasons for the excess CHD mortality among African Americans have not been fully elucidated, these can be accounted for, at least in part, by the high prevalence and suboptimal control of coronary risk factors.

Hypertension, left ventricular hypertrophy, diabetes mellitus, cigarette smoking, obesity, physical inactivity, and multiple CHD risk factors all occur more frequently in African Americans than in whites.[1044,1045] The predictive value of most conventional risk factors for CHD appears to be similar for African Americans and

Table VIII.5–1. Special Features of CHD Risk Factors in African Americans

Risk Factor	Special Features
LDL	■ Mean LDL levels slightly lower and high LDL levels slightly more common in African American men compared to white men ■ LDL levels similar in African American and white women ■ Relationship between total cholesterol levels and CHD risk similar between African American and white men (MRFIT study) ■ African American men often have a relatively high baseline but still normal level of creatine kinase that should be documented before starting statin therapy
HDL	■ Mean HDL levels are higher in African American men than in white men. Whether higher HDL levels in African American men protect against CHD is not known ■ HDL levels are similar between African American and white women
Triglycerides	■ Triglyceride levels are lower in African American men and women than in white men and women
Lipoprotein (a)	■ Lp(a) levels are higher in African American men and women than in white men and women ■ Whether higher Lp(a) in African Americans increases risk for CHD is not known
Hypertension	■ Hypertension is more common in African Americans than in whites ■ Hypertension is a more powerful risk factor for CHD and CVD in African Americans than in whites* ■ Left ventricular hypertrophy (LVH) is more common in African Americans ■ LVH is a powerful predictor of cardiovascular deaths in African Americans† ■ LVH is considered to be a direct target of therapy and does not modify the LDL goal in ATP III‡
Obesity	■ Obesity and abdominal obesity are twice as common in African American women compared to white women ■ Obesity is similar in African American and white men
Diabetes	■ Type 2 diabetes is more common in African Americans than in whites ■ The higher prevalence of type 2 diabetes in African Americans appears related to more obesity and to genetic propensity
Multiple Risk Factors	■ African Americans are 1.5 times more likely to have multiple risk factors than are whites—possibly related to more obesity in African Americans

* Hypertension is not given extra weight in Framingham scores in African Americans despite its greater power to predict CHD. Clinical judgment should be used to correct for this difference.[400,1049]

† LVH is not included in Framingham scoring because of difficulty in estimation and confounding with hypertension.

‡ For ATP III, it is uncertain that LDL lowering will offset the high risk accompanying LVH.

whites.[1046] However, the risk of death and other sequelae attributable to some risk factors (i.e., hypertension, diabetes) is disproportionately greater for African Americans.[1046-1048] The Framingham risk assessment algorithm appears to have the same predictive value in African Americans as in whites. Nonetheless, among the risk factors, some differences have been observed between African Americans and whites. These differences are highlighted in Table VIII.5–1. Although ATP III guidelines generally are applicable equally to African Americans and whites, differences in risk factors and/or genetic constitution call for special attention to certain features of risk management in African Americans (Table VIII.5–2).

b. Hispanic Americans

The Hispanic population in the United States is a heterogeneous group with national origins or ancestry that may be Puerto Rican, Cuban, Mexican/Mexicano, Mexican American, Chicano, other Latin American, or other Spanish. Hispanics are the second largest minority group in the continental United States, comprising 22.4 million people, and increasing at a rate five times that of the rest of the United States. It has been estimated that by the early 21st century, Hispanics will become the largest minority group in the United States. CHD and cardiovascular disease mortality are approximately 20 percent lower among adult Hispanics than

Table VIII.5–2. Special Considerations for Cholesterol Management in African Americans

Risk Level	Special Considerations
CHD and CHD risk equivalents 10-year risk >20% LDL Goal <100 mg/dL	■ African Americans with established CHD are at particularly high risk for cardiac death (reasons: LVH, more diabetes, and lack of access to health care) ■ Goals for LDL-lowering therapy same for African Americans and whites
Multiple (2+) risk factors 10-year risk 10–20% LDL Goal <130 mg/dL	■ Hypertension is a particularly powerful risk factor for CHD in African Americans ■ If hypertension is present, check for LVH ■ Risk factor clustering more prevalent in African Americans than whites ■ LDL-lowering drugs warranted when LDL-C is >130 mg/dL after trial of TLC diet
Multiple (2+) risk factors 10-year risk <10% LDL Goal <130 mg/dL	■ Particular attention should be given to detection and control of hypertension ■ Goals for LDL lowering are those outlined in ATP III for this category
0–1 risk factor 10-year risk <10% LDL Goal <160 mg/dL	■ Goals for LDL lowering are those outlined in ATP III for this risk category

among whites in the United States.[1050-1052] This is true despite a less favorable cardiovascular risk profile among Hispanics, who on average have a greater prevalence of diabetes, more obesity, a tendency towards central obesity, and lower HDL-cholesterol and higher triglyceride levels.[1053-1055] Hispanics on average have higher CHD risk scores than non-Hispanic whites,[1054] but the Framingham algorithm has not been validated in this group. A comparison with Puerto Rican Hispanics indicates that Framingham scoring overestimates actual risk.[400,1049] Some have referred to this as the "Hispanic paradox."[1056] However, even though Hispanics appear to have lower than expected mortality from CHD and CVD, the proportion of total deaths due to these two diseases is similar to that for whites in the United States and one cannot conclude that Hispanics are protected from CHD or that they should be treated less aggressively than other groups. The reasons for these differences are unclear.

In summary, despite limited data suggesting some differences in baseline risk between Hispanic and white populations, the ATP III panel concludes that the evidence for differences is not strong enough to justify separate guidelines for Hispanic populations. For this reason, no separate algorithm for lipid management is recommended and the same guidelines and risk stratification groupings are appropriate for Hispanics as for other populations.

c. Native Americans (American Indians)

When the Strong Heart Study was initiated in 1988 to investigate cardiovascular disease and its risk factors in diverse groups of Native Americans (American Indians) in the United States, prevalence data from the initial examination suggested that at least some Native American tribal groups had lower rates of myocardial infarction and CHD than other U.S. groups.[1057-1059] However, recent data from the Indian Health Service indicate that CVD mortality rates vary among the American Indian communities and appear to be increasing.[1057-1060] CHD incidence rates among Native American men and women were almost twice as high as those in the biracial Atherosclerosis Risk in Communities Study[1059] and CHD appeared more often to be fatal. The significant independent predictors of CVD in Native American women were diabetes, age, obesity, LDL, albuminuria, triglycerides, and hypertension. In men the significant predictors of CVD were diabetes, age, LDL, albuminuria, and hypertension. Interestingly, and unlike other ethnic groups, Native Americans appear to have an increasing incidence of CHD, possibly related to the high and increasing prevalence of diabetes in these communities. At a recent NHLBI workshop on risk assessment, the cardiovascular risk score in Native American women appeared to overestimate actual risk.[400,1049] Although no separate algorithm for lipid management should be recommended for Native Americans, efforts to reduce cholesterol and other CHD risk factors in this

population are especially important because of the higher CHD incidence and the suggestion of apparently higher associated mortality rates. The importance of LDL cholesterol as a contributor to CHD in this group should not be underestimated merely because total and LDL-cholesterol levels are lower than the U.S. average. Moreover, because of the high frequency of type 2 diabetes, many Native Americans will have an even lower LDL goal.

In summary, despite limited data suggesting some differences in baseline risk between Native American and white populations, the ATP III panel concludes that the evidence for differences is not strong enough to justify separate guidelines for Native American populations. Consequently no separate algorithm for lipid management is recommended and the same guidelines and risk stratification groupings are appropriate for Native Americans as for other populations.

d. Asian and Pacific Islanders

There is limited information on the risks and benefits of lipid management for reduction of CHD and CVD in this population. The Honolulu Heart Program is an ongoing prospective study of CHD and stroke in a cohort of Japanese American men living in Hawaii.[1061,1062] In this study, CHD and CVD mortality rates are lower than in the general U.S. population, and the Framingham risk scoring system appears to overestimate actual risk.

Even so, despite limited data suggesting some differences in baseline risk between Asian and Pacific Islanders and American white populations, the ATP III panel concludes that the evidence for differences is not strong enough to justify separate guidelines for Asian Americans and Pacific Islander populations. Therefore, no separate algorithm for lipid management should be recommended and the same guidelines and risk stratification groupings are appropriate for Asian Americans and Pacific Islanders as for other populations.

e. South Asians

South Asians are a rapidly growing population in the United States. There has been some special interest in this group because they have been reported to have very high prevalence rates of coronary disease at younger ages in the absence of traditional risk factors.[1063] The higher CHD risk in this population may be related in part to a higher prevalence of insulin resistance, the metabolic syndrome, and diabetes. Lipoprotein (a) levels have also been reported to be elevated[1064] although its contributions to the observed increased CHD risk are unclear. Efforts to reduce cholesterol and other CHD risk factors in this group with South Asian Indian ancestry appear to be especially important.

In summary, a growing body of evidence indicates that South Asians are at high baseline risk for CHD, compared to American whites. They are particularly at risk for the metabolic syndrome and type 2 diabetes. For this reason, the ATP III panel advises that special attention should be given to detection of CHD risk factors in South Asians. Also, increased emphasis should be given to life habit changes to mitigate the metabolic syndrome in this population. Otherwise, cholesterol management guidelines are the same as those for other population groups.

IX. Adherence

Despite accumulating evidence of the benefits of LDL lowering over the past two decades, initiation of treatment and long-term adherence to therapy remain far from optimal. Lack of adherence is causing persons to miss the risk-reducing benefit of treatment, and is creating enormous costs in the health system to treat cardiovascular events that could have been prevented. Clinical trials have demonstrated that LDL-lowering therapy can reduce all major adverse manifestations of CHD. Clinical trials also have shown that the amount of risk reduction achieved[13,1065,1066] is related to the level of adherence with treatment. Adherence to lipid management in the United States, as well as cardiovascular preventive therapy in general, is less than desirable, as reflected in the following findings:

- Less than half of persons who qualify for any kind of lipid-modifying treatment for CHD risk reduction are receiving it.[1067-1071]
- Less than half of even the highest-risk persons, those who have symptomatic CHD, are receiving lipid-lowering treatment.[1067-1071]
- Only about a third of treated persons are achieving their LDL goal; less than 20 percent of CHD patients are at their LDL goal.[1069,1070]
- Only about half of the persons who are prescribed a lipid-lowering drug are still taking it six months later; after 12 months this falls to 30–40 percent of persons.[1072] This is especially disconcerting, since it takes 6 months to 1 year before a benefit from treatment becomes apparent.

Unfortunately, guidance from the available literature as to what should be done about the adherence problem is sparse. A recent, rigorous search of the world's literature to identify interventions proven to help persons follow prescription medications uncovered a total of 4,762 citations.[1073] Of these, just 19 met the criteria of an unconfounded randomized clinical trial, a standard to which all of our important decisions in health care are held. The panel of experts that reviewed this data concluded that current methods of improving adherence with chronic health problems are not very effective, and that there is little evidence that medication adherence can be improved consistently.

Poor adherence with lipid-modifying therapy threatens the success of any set of recommendations. The recommendations contained in this document are being made on the premise that a sustained reduction in serum LDL cholesterol levels will be accompanied by a reduction in CHD events. For this benefit to be realized, treatment will have to be continued for years and probably for the duration of the patient's life. Thus, paying attention to ways of improving adherence with treatment is just as important to the ultimate success of these guidelines as are the rudiments of the guidelines themselves. Health professionals are encouraged to review the material that follows for guidance on how they may address adherence issues in their daily practice.

1. Recurrent themes and perspectives

A review of the adherence literature reveals recurrent themes and perspectives that provide insights about the adherence problem and suggest ways of dealing with it effectively. Some of these perspectives are listed below:

1. Most people do not successfully self-administer medical treatments as prescribed without some intervention designed to enhance adherence.
2. Adherence is not related to gender, age, ethnic or socioeconomic characteristics of patients. The young are just as likely to be as non-adherent as the elderly; the wealthy just as likely as the poor; males as much as females. There are no differences in adherence rates among African Americans, Hispanic Americans, Asian Americans, and Anglo-Saxon Americans. The causes of non-adherence transcend these differences among people.
3. There is no one cause of poor adherence. Different causes are invariably operating in any group of persons given the same regimen for the same reason. For example, for some persons the cost of the prescription is critically important in determining adherence, but for the majority it is not. Some people forget to take their doses. Others do not believe that they are sick enough to require drug treatment. Still others fear side effects from their treatment. The list of reasons goes on. Since there is no single cause of poor adherence, there is

not likely to be any one intervention that will improve adherence in all persons.
4. Patient counseling and written instructions appear to have the greatest impact on improving short-term adherence (e.g., with antibiotic drug regimens) but less impact on long-term regimens.
5. Poor adherence is just as much of a problem in persons with symptomatic illnesses (e.g., epilepsy and diabetes) as it is with asymptomatic disorders (e.g., hypertension and hyperlipidemia).
6. Initial good adherence with therapy does not mean that the patient will continue to be adherent.
7. If a patient admits non-adherence with therapy, he/she is usually telling the truth, but if a patient denies non-adherence, he/she is telling the truth about half the time.
8. A certain consistent proportion of persons (probably about one-third) will be adherent with therapy just by being given a prescription and asked to take it by their physicians. Another proportion of individuals (probably about 15–25 percent) will be non-adherent with therapy, even with the most vigorous interventions. Interventions to improve adherence, then, are optimally aimed at the middle 50 percent of individuals who may adhere if given support and encouragement.
9. Practically any intervention appears to improve adherence. Rarely are interventions not effective in improving medication adherence, at least for a while. This suggests that the increased attention paid to adherence and/or to the patient by a provider may be as important as the intervention itself.
10. Medication-taking is a behavior that must be learned. Not all individuals have the skills, support structure, or belief system to adopt this behavior without help.
11. Physicians and other health providers have little training in behavioral modification techniques, and do not naturally apply behavioral change principles to improving medication-taking behavior. That is, physicians and other professionals need training in adherence-improving strategies.
12. Many primary care providers and other health professionals spend little time in their practices to provide interventions to encourage adherence with therapy.
13. There are too few incentives built into the health delivery system (e.g., compensation) to encourage and support health professionals to address poor adherence among patients.
14. Interventions to improve adherence must be sustained and reinforced. Interventions to improve adherence last only as long as they are provided. If the intervention is discontinued, even if the patient is fully adherent at the time, adherence will deteriorate.
15. Most successful interventions, especially for long-term drug therapies, use multiple approaches simultaneously.
16. The more patients are asked to do, the less likely they will be to do it all. Rather, they will choose what they are willing to do. This may not be the optimal choice.
17. Adherent behavior reduces morbidity and mortality, even among placebo-treated individuals.[1074] This suggests that the patient who takes steps to improve his/her health achieves a better outcome than the patient who does not.

2. Interventions to improve adherence

The list of evidence-based approaches for improving adherence has been organized under interventions focused on the patient, health professionals, and the health delivery system. In the final analysis, the most successful plan to improve adherence will likely use approaches from all three categories.

Each health professional should use this list to develop a plan for encouraging adherence by patients in their practice and managing poor adherence by those who fail to achieve treatment goals. An important component of the plan will be to identify what the primary care provider will do to encourage adherence, and how other health professionals, resources and systems can support and augment this initiative. Another important component of the plan will be how to weave adherence-improving approaches into the ongoing daily process of caring for patients.

a. Interventions focused on the patient

Following is a list of practical recommendations for improving adherence that are focused on the patient. (See Table IX.2–1 and the discussion below). A combination of approaches shown in Table IX.2–1 can be used for maximal effectiveness. For maximal efficiency,

the health professional should focus the greatest attention on individuals whose lipid control is inadequate due to poor adherence.

1) Simplify medication regimens

Taking medications once daily, rather than three to four times a day, enhances adherence with the regimen.[467,1075] As well, keeping the number of drugs in the regimen to a bare minimum is important. This may be particularly important in the patient with multiple risk factors or CHD where 6–12 medications are often prescribed. In these circumstances, the clinician should thoughtfully consider what therapy is a must and then negotiate with the patient about what they are willing to take. Compromise here may not provide optimal therapy, but prescribing too many medications will lead to poor adherence with all medications and not achieve any of the therapy goals.

2) Provide explicit patient instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment

Persons must understand what is expected of them in order to do it. A number of studies affirm this principle and have illustrated that patient instruction is far more than just giving patients some information.[1076-1078] If the goal is to change or reinforce adherence behavior, the instruction needs to be constructed with this goal in mind. Following are suggestions to impart behaviorally-based instruction:

- Begin with an assessment of the patient's current understanding. Identify the patient's concerns and misunderstandings. Determine what the patient has already tried to do about their cholesterol problem, what problems they encountered, and how they sought to overcome these problems.
- Determine what benefit the patient expects to receive from the treatment. Reinforce or amplify these expectations.
- Negotiate cholesterol and dietary goals with the patient. Select short- and long-term goals, and set timelines for achieving the short-term goals.
- Provide explicit instruction on a low-fat diet, including how to shop for foods, how to select foods when eating out, and how to order foods while traveling. This is often best accomplished by a dietitian or a nurse.
- Provide explicit instruction on how to take lipid-modifying medications. Emphasize the need for continued treatment for CHD risk reduction. Reassure the patient about the safety of the regimen (if appropriate). Emphasize the potential benefits of treatment. Attempt to link these benefits to the LDL level, which provides the patient with a measure with which to track progress.
- Make adherence with therapy an ongoing topic of discussion. Inform the patient that you will be asking about this at each visit and will want to explore ways to help overcome any problems encountered.
- Make instructions concise and reinforce them with written materials or Web-based information.
- Take time to answer the patient's questions. Verify that the patient understands the instructions.

3) Encourage the use of prompts to help persons remember treatment regimens

Forgetfulness is one of the most common reasons given by patients for not taking medications. Most persons will have to identify ways to prompt them to take medications.[1077-1081] Following are a few approaches that have been tried and proven successful:

- Integrate medication doses with other daily activities, such as meals and bedtime.
- Use alarms on clocks or watches to signal dosing times.
- Use special medication packing (e.g., pill boxes) to organize medications.
- Phone persons to remind them of medication refills.
- Phone persons or send postcards to remind them of return appointments.

4) Use systems to reinforce adherence and maintain contact with the patient

A variety of systems have been used to enhance adherence with low-fat diets as well as lipid-modifying medications.[1082-1087] One simple and inexpensive way is to have the office nurse or dietitian phone the patient between appointments to review information on the treatment regimen, solve problems being experienced

by the patient, answer questions, and reinforce adherence behavior. Telemedicine is particularly important to use when the time between appointments is protracted. Another option is a computer link via the patient's phone so that patients can report their home blood pressure recording. Health professionals can also check with patients about their understanding of medication regimens, inquire about adherence, and provide information and instructions. It is quite conceivable that Web-based systems and e-mail can be effectively used to send and receive messages with the patient that reinforce adherence and maintain contact with the patient.

5) Encourage the support of family and friends

The power of the "significant other" in influencing the patient's behavior is substantial and can be used to advantage in encouraging adherence with a treatment regimen. A spouse or special friend who is taught about the patient's therapy, and becomes an advocate to reinforce adherence behavior and help solve problems, has been shown to be effective.[1088-1090] Obviously, this must be done with the patient's permission and acceptance. In some circumstances, getting the family or friends involved can have adverse effects.

6) Reinforce and reward adherence

Reinforcing the importance of lipid control and providing rewards for progress are two of the most powerful methods of achieving treatment goals.[1077,1079] Most commonly, reinforcement is accomplished by asking about adherence at each visit, reviewing lipid results at followup visits, and charting the patient's progress toward achieving their treatment goals. It is best to avoid giving negative feedback in these settings; rather, recognizing even small positive changes is more likely to encourage larger positive changes. When persons achieve short-term goals, it is important to acknowledge (i.e., reward) it. Most often, reward is simply the praise of the health professional. In some cases, rewards may be tangible, such as points toward a free cholesterol evaluation or home test system. Studies have shown these to be powerful methods for encouraging adherence behavior as well as achieving improved outcomes.[1079]

7) Increase patient visits for persons unable to achieve treatment goal

See patients more often when they are struggling to get their cholesterol under control, and less often when their control is good. Always call patients who miss appointments.

8) Increase the convenience and access to care

Although it may be impractical to many providers, studies have shown that when care is provided at the worksite or during home visits to improve access and convenience of care, adherence with therapy is improved.[1077,1079,1080,1089]

9) Involve patients in their care through self-monitoring

Involving the patient in their treatment through self-monitoring is another powerful way to improve adherence.[1091-1093] In this manner persons can follow firsthand their response to treatment and their progress toward achieving and maintaining treatment goals. They can also observe the consequences of nonadherence.

b. Interventions focused on the physician and medical office

As indicated above, many persons with a lipid disorder who qualify for treatment are not receiving it from their physicians. Generally this is not due to the physician's lack of familiarity or agreement with the NCEP guidelines, their interest, or their intent to successfully implement them.[1094,1095] Instead, barriers exist which impede treatment, including the physician's lack of confidence in treating certain lipid disorders and implementing certain elements of treatment—especially diet and exercise therapy; inertia in making fundamental changes in current practice patterns; contradictory patient preferences; and time constraints.[1095]

Generally, when given assistance, physicians are receptive to making changes in their practice and improving preventive health services.[1094,1096-1099] They are especially motivated to change if their patients request these services, if they perceive a legal liability, if peers or thought-leaders advocate these services, and if they perceive that treatment is cost-effective.[1096] Given a

readiness to change, the question is what the more effective ways are to encourage physicians to make changes in their daily practices to improve adherence with therapy. Some of the more important interventions are summarized below and listed in Table IX.2–1.

1) Teach physicians to implement lipid treatment guidelines

Although traditional CME programs that use lectures and conferences to teach physicians rarely change professional practice,[1100] they can increase awareness and motivate physicians to learn more specific approaches to therapy. Moreover, when physician-training programs supply important background material (i.e., science) and guidance on ways to implement treatment guidelines into everyday practice, they are more likely to influence practice. For example, when training programs provide the physician with enabling strategies (e.g., office reminders), reinforcing strategies (e.g., feedback) and predisposing strategies (e.g., practice guidelines), improvements in the quality of practice are more commonly seen. Some of these strategies are reviewed below.[1096]

2) Use reminders to prompt physicians to attend to lipid management

Reminders have been used successfully to prompt physicians to attend to lipid issues.[1100,1101] This may be as simple as placing a brightly-colored sticker identifying the patient as a cholesterol patient or a sheet of paper on the front of the chart with information about the patient's lipid results, treatment status, or a definitive recommendation for care.[1102] Electronic medical records have the potential to prompt (i.e., require) the physician to act on lipid results or needed treatment issues as a part of each office visit.

3) Identify a patient advocate in the office to help deliver or prompt care

Many studies have demonstrated the value of assigning an individual in the office the responsibility of keeping track of the patient's progress, and prompting or augmenting the care provided.[1094,1097-1099,1101,1103] In fact, this organizational change may be one of the more powerful ways of advancing preventive care in the average busy office setting. This individual is usually an office nurse who is able to work additional hours to assume this new role; occasionally, new part-time personnel will need to be hired. The advocate reviews the patient chart, extracts critical information, summarizes it and prompts the physician to attend to certain issues, provides patient information and consultation, reinforces treatment plans, and follows up with patients between scheduled visits by phone or e-mail. Most physicians who have worked with a patient advocate recognize the vital importance of this role in providing preventive services.

4) Use patients to prompt preventive care

Physicians typically respond to a patient's request for health services.[1096] Using this premise, several programs have given the patient access to information about their lipid disorder not only to inform them, but also to motivate them to request preventive health services.[1100] This approach also has the advantage of transferring responsibility for health-seeking behavior into the hands of the patient. An important part of this approach is to identify sources of accurate information the patient can use to learn more about their health. The Web sites of the NCEP and American Heart Association are recommended.

5) Develop a standardized treatment plan to structure care

Some physicians work better if they follow a structured plan or treatment algorithm when providing risk factor management.[1104] One advantage of following such a plan is that it is standardized, and should therefore assure consistency and completeness in the care delivered. It should prompt the physician to attend to all key issues during routine follow-up appointments, including evaluation of the patient's adherence with treatment. Of course, following a standardized treatment plan does not mean that the physician cannot deviate from it when needed.

6) Use feedback from past performance to foster change in future care

Routine review of a select number of patient charts can provide important feedback about the care being provided to lipid patients, and prompt improvements in care if needed. Charts selected for this review should be those of high-risk patients, such as individuals with a history of myocardial infarction or diabetes. The audit

may be another way of using the services of a patient advocate (discussed above). Key issues to extract from the charts include:

- Did the patient have a recent lipid profile?
- If the patient qualifies for treatment, was treatment provided?
- If treatment was given, is the patient at their LDL goal?
- Did the physician document his/her assessment and plans?

Routinely receiving feedback such as this serves to inform the physician about how well he/she is doing with lipid management, and directs attention to ways of enhancing this service. It may also serve as important information for marketing the physician's services to health insurance plans and employer groups.

7) Remind patients of appointments and follow-up missed appointments

Many lipid patients are lost to followup, and thus do not receive the services they require to successfully reduce CHD risk. Every physician's office should have a system of tracking patients to assure that all have return appointments and that follow up is provided to persons who miss appointments. It is important to give patients a followup appointment before they depart the office and to send a reminder card or call about a week before the appointment. It is also recommended that the office nurse or patient advocate be given the opportunity to schedule followup visits with the patient to reinforce education and support treatment adherence. When a patient misses a followup appointment, someone in the office should be given the responsibility of trying to reschedule the patient.

c. Interventions focused on the health delivery system

Interventions that are focused on the health delivery system have also been shown to improve patient adherence. Compared with interventions focused on the patient and physician, these interventions have produced the greatest improvement in patient adherence and have sustained this improvement for a long period of time. Further, they have improved both adherence with treatment and outcomes. Some of the more important of these interventions are summarized below and listed in Table IX.2–1.

1) Provide lipid management through a lipid clinic

Establishment of a lipid clinic makes the most sense in health systems where there are a large number of persons, some of whom have very complicated and unique lipid disorders, such as may be found in large primary care group practices and institutions. For example, lipid clinics are commonplace in many Department of Veterans Affairs Medical System institutions. Lipid clinics are typically run by a supervising physician who has often obtained additional training in managing lipid disorders, and are staffed by pharmacists, nurses, and/or dietitians who provide patient care in a multidisciplinary fashion. Other physicians in the health care system refer selected patients for lipid management. The process of care is frequently well defined by a protocol, and a quality control system gives health care providers feedback on their performance. Patient care goals are clear: get referred patients an effective treatment, give them support to adhere to it, and achieve NCEP treatment goals. Perhaps it is this simplicity of purpose and focus that have resulted in reports of very good adherence by persons with prescribed therapy and achievement of treatment goals.[527-529,1105,1106] For example, one lipid clinic which provided care exclusively to CHD patients reported that 100 percent of persons were on lipid-lowering therapy, 97 percent had lipid levels documented in medical records, and 71 percent met their LDL goal of <100 mg/dL.[1106] Lipid clinics have easily outperformed the usual care models in lowering LDL and getting persons to their NCEP goal.[527,528,1105] However, the lipid clinic is a more expensive model of care[527] that may not be available to all patients, but these clinics can be especially valuable for patients with complex lipid disorders.

2) Utilize case management by nurses

Closely related to the lipid clinic concept is case management by nurses. A number of such models have been described in the literature, and compare very favorably to other models of care in terms of treatment outcomes, lipid control, and patient adherence.[266,523,525,1080,1107-1109] In these models, some (or all) of the elements of care are provided by specially-trained nurses. In some instances, care is delivered by nurses at the worksite, in the home, or in the community; and in other cases, a clinic or hospital outpatient setting. Often, there is a strong emphasis on lifestyle modification (i.e., smoking cessation, exercise

training, weight loss, and nutrition counseling) in addition to lipid-modifying drug therapy. Treatment is often guided by a written protocol. Nurses in these settings deliver care that is typically provided by physicians, including conducting medical histories and physical exams; collecting and interpreting laboratory tests; and selecting and titrating medications. All case management models describe strong patient counseling and follow-up monitoring components. Comparison of nurse case management versus usual care models have shown the nurse care model to be at least equivalent, and in some cases superior, in terms of LDL lowering and achievement of treatment goals. No cost-effectiveness comparisons have been made.

3) Deploy telemedicine

As noted above, phone follow-up of patients between scheduled physician visits has been successfully used to improve adherence.[1082,1083,1087] This is a very accessible, relatively inexpensive way to maintain a link with the patients and to manage problems that deter adherence as they arise. Reports indicate that groups using this approach have seen improvement in LDL reduction and achievement of treatment goals.

4) Utilize the collaborative care of pharmacists

Collaborative care by pharmacists is a model in which community pharmacists, working in their pharmacies, collaborate with primary care providers to augment the care provided to persons with lipid disorders. In this model, pharmacists see persons during medication refills or by appointment, to reinforce the importance and purpose of therapy, provide patient education on lifestyle and pharmacologic therapy, emphasize the need for adherence, identify and resolve barriers to adherence, and provide long-term monitoring of drug response and feedback to the patient between visits to the primary care provider. During these visits, pharmacists commonly measure the patient's blood pressure or blood lipids utilizing desktop analyzers. This allows pharmacists to give the patient feedback on their progress and reinforce the steps to achieving treatment goals. Services are documented, and summaries are sent to the patient's primary provider to inform him/her of the pharmacists findings and actions. These models have proved to be among the strongest for maintaining persons on treatment and achieving treament goals.[1110-1112] For example, one study of pharmacists' collaborative care reported that 94 percent of persons persisted on therapy (i.e., stayed on lipid-lowering treatment at least to some degree), 90 percent of persons were considered adherent with prescribed medications, and 63 percent had reached and were maintained at their NCEP LDL goal for a period of two years.[1111]

5) Execute critical care pathways in hospitals

Use of clinical pathways or other management protocols in hospital settings has resulted in improved adherence to therapy by CHD patients and better cholesterol control.[524] The Cardiac Hospitalization Atherosclerosis Management Program (CHAMP) focused on the initiation of therapy with aspirin, beta blocker, ACE inhibitor, statin, diet, and exercise in persons with established CHD prior to hospital discharge.[524] The program used post-discharge follow-up visits to titrate the statin dose to achieve an LDL of <100 mg/dL. One year after discharge, 91 percent of persons were being treated with cholesterol-lowering therapy and 58 percent were at treatment goals; these results suggest that initiating treatment during hospitalization for CHD adds needed emphasis to the importance of cholesterol-lowering treatment alongside other cardiac medications.

Table IX.2–1. Interventions to Improve Adherence

Focus on the Patient (utilize as many as possible)

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

Focus on the Physician and Medical Office

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

Focus on the Health Delivery System

- Provide lipid management through a lipid clinic
- Utilize case management by nurses
- Deploy telemedicine
- Utilize the collaborative care of pharmacists
- Execute critical care pathways in hospitals

Table IX.2–2. The Clinicians Abridged Pocket Guide to Enhancing Adherence

- Keep the regimen as simple as possible
- Give the patient clear instructions
- Discuss adherence for at least a few seconds at each visit
- Concentrate on those who don't reach treatment goals
- Always call patients who miss visit appointments
- Use 2 or more strategies for those who miss treatment goals

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ATTACHMENT 1 (Part 9)

(ATP-III)

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

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

Final Report

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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