National Cholesterol
Education Program

Second Report of the Expert Panel on

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

I. Classification, Prevalence, Detection, Evaluation

A. Background and Introduction

There are two major strategies for preventing coronary heart disease (CHD) by lowering blood cholesterol. One is a clinical or patient-based approach that seeks to identify individuals at high risk who will benefit from intensive intervention efforts.[1,2] The goal of this approach is to detect, treat, and monitor high-risk patients who have elevated blood cholesterol. Guidelines for this approach were developed by the first Adult Treatment Panel and published in 1988.[1] The other strategy is the population or public health approach that attempts to lower blood cholesterol levels in the whole population by promoting changes in dietary habits and physical activity levels.[2-7] These two strategies are complementary, and both are incorporated in the National Cholesterol Education Program. This report focuses on the clinical approach and updates the guidelines from the 1988 report of the Adult Treatment Panel.[1]

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. These particles are called lipoproteins. The cholesterol level in the blood is determined partly by inheritance and partly by acquired factors such as diet, calorie balance, and level of physical activity.

Three major classes of lipoproteins are found in the blood of a fasting individual: low density lipoproteins (LDL), high density lipoproteins (HDL), and very low density lipoproteins (VLDL).[8-11] The LDL typically contain 60-70 percent of the total serum cholesterol and both are directly correlated with risk for CHD.[12-21] The HDL normally contain 20-30 percent of the total cholesterol, and HDL levels are inversely correlated with CHD risk.[22-26] The VLDL contain 10-15 percent of the total serum cholesterol along with most of the triglyceride in fasting serum; VLDL are precursors of LDL, and some forms of VLDL, particularly VLDL remnants, appear to be atherogenic.[8,27-30]

Since most cholesterol in serum is contained in LDL, the concentration of total cholesterol in most people is highly correlated with the concentration of LDL-cholesterol. Whereas LDL-cholesterol is the major atherogenic lipoprotein and thus is the primary target of cholesterol-lowering efforts, total cholesterol can be used in initial testing for detecting a possible elevation of LDL-cholesterol. Initial testing for serum total cholesterol has several advantages: it is more readily available and less expensive, and does not require that the patient be fasting. On the other hand, LDL-cholesterol offers more precision for risk assessment and is the primary target of interventions to lower blood cholesterol.

B. Rationale for Intervention

1. Primary Prevention: Patients Without Established CHD

a. The evidence that elevated LDL-cholesterol is a cause of CHD

- **Epidemiology.** A large body of epidemiologic evidence supports a direct relationship between the level of serum LDL-cholesterol (or total cholesterol) and the rate of CHD. This evidence includes within-population studies[12-14,31,32] as well as

between-population studies[33] showing that CHD is more common in countries whose inhabitants consume diets high in saturated fat and cholesterol and have relatively high levels of blood cholesterol. Indeed, in populations that have low levels of LDL-cholesterol (e.g., rural Japan and China) rates of CHD are quite low even when other known CHD risk factors are present.[34,35] In addition, migration studies that show that within a generation of immigration both blood cholesterol levels and CHD rates rise in parallel to resemble those of the new country of residence.[36,37] Finally, for both males and females, cohort studies[38] within populations consistently show an association between blood cholesterol levels and CHD rates; this association is continuous throughout the whole range of cholesterol levels in the population[14] and becomes particularly strong at higher levels of serum cholesterol. **Figure 1-1** indicates that men with cholesterol levels near the top of the population distribution have CHD mortality rates that are five times those near the bottom. This observed difference in fact is an underestimate: after adjustment for the effects of variability of cholesterol measurements, the true risk ratio

between higher and lower cholesterol levels is even higher.[2] A high blood cholesterol is thus a powerful risk factor for CHD.

- **Genetic disorders.** Premature CHD can result from high LDL-cholesterol levels even in the absence of any other risk factors. A striking example is found in children who have the homozygous form of familial hypercholesterolemia, a rare disorder characterized by the virtual absence of the specific cell-surface receptors that normally remove LDL from the circulation.[40] The consequence is an increase in the blood cholesterol occurring predominantly in the LDL fraction. LDL-cholesterol levels are extremely high, 500 to 1,000 mg/dL, and severe atherosclerosis and CHD often develop during the first two decades of life.[41] Patients with the more common heterozygous form of familial hypercholesterolemia have half the normal number of functioning LDL receptors; they have approximately twice-normal levels of LDL-cholesterol and commonly develop CHD in the middle decades of life.[41] Further evidence that LDL-cholesterol is atherogenic in humans comes from the genetic disorder called familial defective apolipoprotein B-100,[42,43] in which cholesterol elevation is limited to LDL; this disorder likewise is accompanied by premature CHD.[44,45]
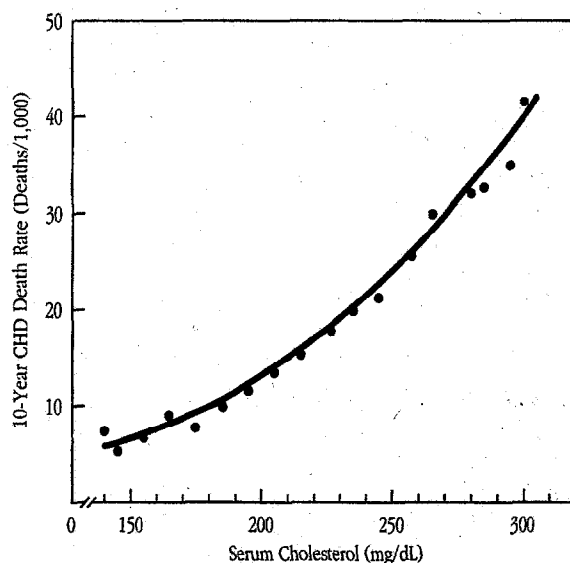
- **Animal evidence.** In many animal species, both spontaneous and diet-induced hypercholes-terolemias cause a form of atherosclerosis.[46-54] Moreover, in several species of primates, diets that raise mainly serum LDL-cholesterol levels induce arterial lesions resembling human atheroscle-rosis.[55-57] These lesions regress when the serum cholesterol is lowered by diet or drugs, suggesting that atherosclerosis may be reversible under certain circumstances.[58-66]

b. The evidence that reducing LDL-cholesterol levels prevents CHD

The evidence cited above from epidemiologic, genetic, and animal investigations strongly supports a causal link between elevated LDL-cholesterol and risk of CHD. In addition, clinical trials have demonstrated that this risk can be reduced; they have shown specifically that lowering LDL-cholesterol levels in men with high levels decreases the incidence of CHD. A number of randomized blinded trials have examined whether lowering LDL-cholesterol levels by dietary and

Figure 1-1

Relationship Between Serum Cholesterol Level and CHD Death Rate

From 361,662 Men Screened for MRFIT Program[39]

drug interventions can reduce CHD incidence in the primary prevention setting, i.e., in patients without evidence of CHD. One of the largest, the Lipid Research Clinics (LRC)-Coronary Primary Prevention Trial,[67,68] found that the cholesterol-lowering drug cholestyramine, compared with a placebo, significantly reduced the incidence of CHD. A similar reduction in CHD events was obtained with the lipid-lowering drug gemfibrozil in the Helsinki Heart Study.[69,70] Meta-analyses that pool the results of the major primary prevention trials of cholesterol lowering also demonstrate that reduction of cholesterol levels will reduce CHD rates;[71] these meta-analyses suggest that dietary therapy alone also is effective for reducing CHD rates.[71-73]

Finally, several recent trials[74-79] employing angiographic assessment have revealed that cholesterol-lowering therapy slows progression in a substantial portion of both men and women and produces regression of coronary atherosclerosis in some individuals.

Thus a large and diverse set of studies provides convincing evidence that reducing LDL-cholesterol levels will decrease the subsequent incidence and mortality from CHD events. The data from clinical trials are available chiefly for middle-aged men with initially high cholesterol levels. Since clinical and epidemiologic studies indicate that high blood cholesterol is accompanied by increased risk for CHD in various groups—young adults with genetic hypercholesterolemia,[41] young adult men,[32,80] postmenopausal women,[38] and the elderly[13]—it is reasonable to project that reduction in cholesterol levels in primary prevention will reduce CHD rates in these groups as well. However, each age and sex group has its own particular risk characteristics that may modify the approach to primary prevention, and each will be considered later in this section.

2. Secondary Prevention: Patients With CHD

The presence of established CHD confers a high risk for the occurrence of subsequent coronary events and CHD death. Men with CHD have about five to seven times the risk of developing a myocardial infarction as men with no prior clinical manifestations of coronary disease.[81] Women with a history of myocardial infarction resemble men in their high risk for reinfarction.[82] Past hesitancy to reduce cholesterol

levels in patients with clinically manifest CHD has been due largely to the belief that cholesterol levels are no longer an important risk factor in such patients. However, many recent observational studies[81,83,84] have shown that LDL-cholesterol (and total cholesterol) levels are significant predictors of future myocardial infarction in patients with established CHD. This relationship holds for CHD patients with cholesterol levels in the relatively low range.[83] Thus reduction of serum cholesterol in patients with established CHD might be expected to decrease subsequent CHD events.

Randomized blinded trials in patients with established CHD in fact have shown that lowering LDL-cholesterol levels reduces rates of recurrent CHD events along with a strong trend towards decreased total mortality rates; this was the finding of the large Coronary Drug Project trial[85] comparing nicotinic acid with a placebo. In addition, a meta-analysis[73,81] of several secondary prevention trials showed that cholesterol-lowering therapy reduced recurrent CHD events by approximately 26 percent and total mortality by about 9 percent (table 1-1). Angiographic studies[74-79] further have shown that, in patients with coronary atherosclerosis, intensive cholesterol lowering—often to LDL-cholesterol levels of 100 mg/dL or below—retards the rate of progression and in some patients leads to regression of atherosclerotic lesions. Favorable results have been observed whether cholesterol lowering was achieved by lifestyle modification (dietary therapy and physical activity),[78] drug therapy,[75-77,79] or ileal bypass surgery.[74] The significant decline in the incidence of clinical CHD events that has been observed in the treated group in a period of only 2 years makes it probable that the instability of plaques (which leads to fissuring, thrombosis, and intramural hemorrhage) is reduced as well;[86] in major primary prevention trials[67-69] up to 5 years have been required to show benefit. A reduction in CHD events resulting from cholesterol intervention has been observed even in patients who were not selected because of high cholesterol levels but had pretreatment levels in the so-called "normal" range.[87]

3. Magnitude of Reduction in CHD Risk

CHD is the leading cause of death for both men and women in the United States and accounts for about 500,000 deaths each year.[88] Clinical trials of relatively short-term duration indicate that a 2-percent reduction

Table 1-1

Morbidity and Mortality in Secondary Prevention Trials*†

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

* Meta-analysis by Rossouw based on Rossouw et al., 1990, 1991.[73,81]

† Trials include Medical Research Council's low-fat diet trial;[91] Medical Research Council's soya-bean oil trial;[92] Scottish Society of Physician's clofibrate trial;[93] Stockholm Ischaemic Heart Disease Secondary Prevention Study;[94] Coronary Drug Project's clofibrate trial;[85,95] Coronary Drug Project's niacin trial;[85,95] and Program on the Surgical Control of Hyperlipidemias.[74]

in CHD rates results from each 1-percent reduction in serum cholesterol level, and epidemiologic studies[2,89,90] suggest that the reduction in CHD rates achievable with long-term cholesterol lowering may be even greater—perhaps as much as 3 percent for each 1-percent reduction in serum cholesterol.

The greatest short-term benefit from cholesterol reduction is to be expected in patients who are at high risk for future CHD events either because of established CHD or multiple risk factors. This is because cholesterol intervention has a similar relative benefit in both primary and secondary prevention (a 2-percent decrease in CHD events for every 1-percent decrease in blood cholesterol), but the fivefold higher event rate among those with established CHD makes the near-term benefit of cholesterol intervention larger in this group. On the other hand, over a lifetime, a large percentage of all men and women will develop CHD,[88] and approximately one-quarter to one-third of individuals who have a first coronary event will die of it. Thus in the long run the greatest benefit in CHD reduction lies in primary prevention measures. This makes primary prevention an important element in both the public health and clinical approaches.

4. Mortality Considerations

Several primary prevention trials[67-69,96-100] have demonstrated that blood cholesterol lowering leads to reduction in rates of myocardial infarction and death from CHD. This conclusion from individual trials has been strengthened by the results of meta-analysis of pooled data from the available trials.[71] From these trials the hypothesis that cholesterol lowering will prevent CHD has been confirmed. The demonstration that cholesterol lowering prevents CHD is the cornerstone of both the public health and clinical approach to controlling high blood cholesterol. Beyond the beneficial effect of cholesterol lowering on CHD rates, however, lies the question of whether reduction of blood cholesterol levels extends the life span. The number of subjects, duration, and resulting costs of a single controlled clinical trial designed to demonstrate an impact on total mortality have been considered prohibitive, and thus investigators have to address the issue of total mortality indirectly in the absence of a definitive clinical trial. Two lines of evidence are available that bear on the total mortality issue—epidemiologic studies and clinical trials.

a. Epidemiologic evidence

Several types of epidemiologic data provide evidence on the total mortality question. It has been noted for example that Japanese have lower serum cholesterol levels than Americans, and on average, the Japanese have a lower age-adjusted mortality and a longer life expectancy than Americans.[34,101] Greater longevity in Japanese appear to be due mainly to less CHD. Within the United States, Seventh Day Adventists as a group have lower cholesterol levels than the population average and they too have lower age-adjusted mortality and a longer life expectancy.[102] These population comparisons are suggestive, but a solid conclusion that a lower cholesterol level per se is responsible must be tempered by the possibility of confounding factors.

Further information comes from the 30-year followup of the Framingham Heart Study;[32] in this analysis, young individuals with the lowest cholesterol levels at entry were found to have lower age-adjusted total mortality rates than those with the highest cholesterol levels. Similar findings were reported from the Johns Hopkins Precursors Study[80] in which young adult men were followed for 30.5 years after initial cholesterol measurement at mean age 22. This study reported a strong association between the serum cholesterol levels measured in the early twenties and development of CHD in midlife. A recent review of a large number of prospective cohort studies[38] reported that the lowest total mortality apparently occurred in men having total cholesterol levels below 200 mg/dL, specifically in the range of 160 to 199 mg/dL, whereas men with higher cholesterol levels had higher age-adjusted total mortality rates. However, the relation between cholesterol levels and total mortality appeared to be J-shaped, as found previously for hypertension and obesity. Higher total mortality occurred with high levels of cholesterol, but a relatively higher mortality also was noted in men with very low total cholesterol levels. The lowest category of cholesterol levels analyzed was that below 160 mg/dL, and it appeared that higher total mortality rates were associated with cholesterol values below this level. In this report, the Multiple Risk Factor Intervention Trial (MRFIT) screenees constituted 83 percent of U.S. men and two-thirds of the total number of men in the entire review. In a more detailed analysis of the followup of MRFIT men,[103] it was reported that cholesterol levels well below 160 mg/dL were still accompanied by decreasing total mortality rates. In this study there was no trend for an increase in total mortality until the total cholesterol level fell to below 140 mg/dL, and a distinct increase was noted only in the very small portion of the population below 120 mg/dL. Thus, it appears that any increase in total mortality in American men occurs only at quite low cholesterol levels, at least below 140 mg/dL. About 4 percent of U.S. men have serum cholesterol levels below 140 mg/dL. When all cohort data were pooled in the previous report of Jacobs et al.,[38] increases in mortality rates at low levels of cholesterol were statistically significant for each of a variety of conditions (e.g., some cancers, chronic respiratory disease, liver disease, hemorrhagic stroke, and trauma). The available evidence is insufficient to determine whether the association between very low cholesterol levels and increased mortality in this small segment of the population is due to confounding factors or biologic causation. A definite possibility is that some of these disorders cause low cholesterol levels, and not that low cholesterol levels cause disease. For example, in older adults of the Cardiovascular Health Study,[104] very low cholesterol levels were often present in individuals having several other biochemical abnormalities suggestive of impaired health.

There is little concrete support for the concept that total cholesterol levels below 160 mg/dL (or even lower) are inherently dangerous. In general, however, for primary prevention in patients with elevated serum cholesterol, it is neither necessary nor practical to attempt to lower total cholesterol to below the range of 160 to 200 mg/dL, which corresponds to LDL-cholesterol levels of 100 to 130 mg/dL. The pooling of cohort studies[38] suggests that decreasing elevated total cholesterol levels into the range of 160 to 200 mg/dL will reduce total mortality in men, and this is a reasonable goal for primary prevention in the United States. Moreover, according to the data from MRFIT screenees,[103] there is little likelihood of an increase in total mortality should total cholesterol fall below the 160 mg/dL level in some people in the course of primary prevention.

The pooling of cohort data in women produced a more uncertain result for the association between total cholesterol levels and disease or mortality for women.[38] The correlation between total cholesterol level and CHD death was strong and positive in

women as well as men. By contrast, total mortality was not increased at higher cholesterol levels in women as it was in men; indeed, the pooled estimate of risk for all causes of death was essentially flat across all levels of total cholesterol. The full reasons that higher CHD death rates at increased total cholesterol levels did not translate into higher total mortality rates in this pooled analysis are not understood, but one factor is the relatively low rates of CHD in women of the age group studied. The authors of this analysis indicated that "to obtain more precise information about total cholesterol-mortality associations in women, a screening and mortality followup study should be undertaken, comparable in size to the MRFIT Screening Study. Such a study should measure HDL-cholesterol as well as total cholesterol and should include older women, for example, up to age 79." In the absence of such a study, the relationship between total cholesterol levels and total mortality in women is unproven.

b. Clinical trial evidence

Primary prevention clinical trials of cholesterol lowering

Primary prevention trials have been designed to detect effects on CHD incidence (chiefly nonfatal myocardial infarction), and because of their relatively small size and duration, it is not surprising that none has provided an answer to the question of total mortality. In an attempt to obtain a better grasp on the effects of primary prevention on total mortality, the results of clinical trials have been pooled and analyzed together. The meta-analysis technique has the advantage of providing a larger number of subjects, which may enhance the power to detect a true result. However, meta-analysis may be misleading if there is heterogeneity between studies in the nature of the population or the interventions. For example, data from a trial using a drug producing serious adverse effects could obscure a favorable effect of a safer drug. Likewise, the inclusion of data from trials with less efficacious cholesterol-lowering drugs may obscure a beneficial effect of more effective agents and the mixing of trials having different endpoints can make interpretation difficult. With these limitations in mind, it should be noted that several meta-analyses of cholesterol-lowering drug trials[105-107] for primary prevention of CHD reveal a significant increase in aggregate non-CHD mortality, made up of multiple small and nonsignificant numerical increases in various causes. This increase in non-CHD mortality appeared to offset a significant decrease in CHD mortality such that total mortality was not reduced. Nonetheless, variability from study to study in the apparent causes of increased non-CHD death—i.e., cancers and other diseases of liver, biliary tract, and intestine in one trial and accidents, suicide, and homicide in others—makes it difficult to postulate a plausible biological mechanism whereby cholesterol lowering per se imparts specific adverse effects that increase mortality. Thus, the precise nature of any adverse effects and, if they are real, whether they are limited chiefly to one class of drugs or extend to all types of cholesterol-lowering drugs, remain to be determined. One meta-analysis[107] noted a numerical increase in non-CHD deaths in primary prevention studies using drugs, but not in those employing diet. In another meta-analysis[71] of primary and secondary prevention drug trials that was weighted for response in cholesterol lowering, a favorable trend in total mortality was noted when cholesterol reduction was substantial but not when it was small.

Thus, results of meta-analysis of primary prevention trials suggesting that drug intervention carries increased non-CHD mortality that offsets the beneficial effects of cholesterol lowering cannot be taken as definitive. At present, the evidence that blood cholesterol lowering reduces CHD mortality and morbidity is much more consistent and reliable than the evidence that certain cholesterol-lowering drugs may increase the non-CHD death rate, which may be an association due to chance. Nonetheless, experience has shown that almost all drugs have side effects, and this holds for cholesterol-lowering drugs as well; by treating high-risk patients with highly efficacious cholesterol-lowering drugs that have few side effects, the chances are increased that reduction in CHD death rates will more than offset any adverse effects.

Secondary prevention trials of cholesterol lowering

The principle that a reduction in total mortality by cholesterol lowering is possible can be demonstrated most readily in very high-risk patients in secondary prevention trials. In patients with established CHD, over 80 percent of deaths are from cardiovascular causes,[81] and thus any treatment that lowers CHD death rates can be expected to have a favorable effect

on total mortality. Indeed, a recent meta-analysis of secondary prevention trials observed a favorable trend in the total death rate (odds ratio 0.91).[73] Moreover, this analysis, which contained a large number of patients, showed *no* significant increase in noncardiovascular deaths including those from injury, homicide, suicide, or cancer, as might have been expected if cholesterol-lowering drug therapy *is* inherently dangerous.

c. Implications for cholesterol-lowering therapy

These considerations strongly imply that treatment of high blood cholesterol in patients with established CHD has the potential to prolong life by reducing new CHD events, because CHD deaths are by far the most common cause of death in these patients. Likewise, a reduction in total mortality by highly efficacious drug therapy probably can be achieved for patients who do not have established CHD but are at high risk for developing it. Although epidemiologic data suggest that long-term cholesterol lowering in individuals with moderately high cholesterol levels will prolong life, life extension by drug therapy in patients without severe hypercholesterolemia and who are otherwise at low risk will be difficult to demonstrate in a controlled clinical trial even if drug therapy has few side effects.

Lack of clinical trial data proving that cholesterol-lowering therapy reduces age-adjusted mortality in individuals with moderately high blood cholesterol and without other CHD risk factors, however, does not preclude efforts to reduce cholesterol levels in this group. The evidence that cholesterol lowering will reduce the incidence of CHD is strong, whereas the possibility that cholesterol lowering per se causes adverse effects is relatively weaker. Increases in the incidence of adverse events (e.g., cancer, accidents, suicide, and violence) observed in association with cholesterol-lowering trials[105] have not been found to be statistically significant when taken as individual effects, and apparent increases in these events may have been due to chance. Even if total mortality accompanying cholesterol lowering in low-risk populations is unchanged, substantial benefit will still be derived from a reduction of CHD morbidity. For this reason, primary prevention receives a high priority in this document. The possibility of adverse effects that accumulate during several decades of drug therapy, which may offset CHD risk reduction, nonetheless must be kept in mind when making a decision to use cholesterol-lowering drugs on a lifetime basis. Therefore, primary prevention in low- and moderate-risk populations should emphasize modification of dietary and exercise habits. Drug therapy should be reserved for patients considered to be at high risk, as will be discussed in detail later in this report.

5. Other Lipid Risk Factors for CHD

a. High density lipoproteins (HDL)

Many epidemiologic studies in high-risk populations have shown that low HDL-cholesterol levels are a significant risk factor for CHD, independent of LDL-cholesterol and other risk factors. Because of the increasing evidence linking HDL to CHD, the National Institutes of Health sponsored a Consensus Development Conference in February 1992 to review new data on low HDL (and high triglycerides) and to make recommendations on their management.[108] The current report takes account of these recommendations.

The precise basis for the inverse association between HDL-cholesterol and CHD is not understood, but recent studies suggest several possible mechanisms, most likely the promotion of cholesterol efflux from foam cells in atherosclerotic lesions.[109] Several studies in laboratory animals likewise support a protective role of HDL against atherogenesis.[110,111] Moreover, in patients deficient in HDL and its major apolipoprotein, early CHD often is present.[112-114]

Epidemiologic surveys indicate that HDL-cholesterol levels are inversely correlated with CHD rates over a broad range of HDL levels.[22,23,115,116] Available evidence shows that for every 1-mg/dL decrease in HDL-cholesterol the risk for CHD is increased by 2-3 percent.[26] Likewise, higher HDL-cholesterol levels appear to afford a degree of protection against CHD. The strength and independence of this association warrants calling a low HDL-cholesterol level (i.e., <35 mg/dL) a risk factor for assessing the risk status of individual patients and for influencing the vigor of treatment directed at high levels of LDL-cholesterol. The protective effect of a high HDL-cholesterol conversely warrants calling a high level (i.e., ≥60 mg/dL) a "negative" risk factor.[117] These considerations justify measurement of HDL-cholesterol at initial cholesterol testing.

A variety of factors contribute to low HDL-cholesterol levels. Genetic influences undoubtedly are important in many patients.[118] These inherited influences can be accentuated by life habits—cigarette smoking, lack of exercise, and excessive caloric intake leading to obesity.[119-121] Certain drugs, including beta-adrenergic blocking agents (beta-blockers), anabolic steroids, and progestational agents, likewise reduce HDL-cholesterol. A moderately strong, inverse relation also exists between HDL-cholesterol and triglyceride levels, and the various hypertri-glyceridemic states frequently are accompanied by low HDL-cholesterol concentrations.[122]

Fortunately, the factors cited above that contribute to low HDL-cholesterol levels are reversible through weight reduction in overweight patients, exercise, and smoking cessation. Most lipid-lowering drugs have the potential to raise HDL-cholesterol levels. The most potent agent is nicotinic acid, but fibric acids, statins, and even bile acid sequestrants can have a mild-to-moderate HDL-raising action. Thus, it may be difficult to distinguish the relative contributions of LDL lowering and HDL raising to CHD risk reduction. Nonetheless, in several drug trials of both primary and secondary prevention, a rise in HDL-cholesterol levels appeared to contribute to the overall reduction in CHD risk.[26,70,76] To date, however, no clinical trials have been reported that specifically test the efficacy of raising HDL in prevention of CHD. This fact militates against recommendations to use drugs specifically to raise HDL-cholesterol levels in patients with isolated low HDL levels. In patients with CHD or a strong family history of CHD, drug use may be considered. Nevertheless, the link between low HDL and CHD may influence the choice of drugs used for LDL lowering. Specific recommendations for management of patients with low HDL-cholesterol are covered in section IV.

Several epidemiologic studies reveal that total cholesterol/HDL-cholesterol ratios (or LDL/HDL ratios) are strong predictors of CHD events.[13,123] Although some investigators advocate the use of such ratios both for predicting risk and as targets for therapy, this approach has drawbacks. For one thing, LDL and HDL are independent risk factors, and each requires individual attention. In addition, whether ratios accurately predict CHD risk at extremes of high and low LDL-cholesterol levels is uncertain. The use of

ratios may have utility for summarizing the importance of *both* LDL and HDL to patients, but it is preferable for the physician to focus on LDL and HDL separately for risk assessment and therapy. For these reasons, cholesterol ratios are not made a part of the specific algorithms in these guidelines.

b. Triglycerides

In most case-control and prospective studies, serum triglyceride levels are positively correlated with CHD rates by univariate analysis.[124,125] However, when total cholesterol and HDL-cholesterol are included in a multivariate analysis, triglycerides have been reported to lose their power to predict CHD in several studies,[126-129] but not in all.[17,18,130] In the view of some workers,[124,131] the statistical methods used to assign independent relationships to CHD risk among the different lipid fractions are of limited value because of high intercorrelations among various lipoprotein fractions and the greater variability in triglyceride measurements. In fasting plasma, most triglycerides are carried in VLDL of hepatic origin. Postprandially, there is the addition of dietary triglycerides carried in intestinal chylomicrons. Catabolism of these triglyceride-rich lipoproteins produces remnant particles that appear to be atherogenic,[8,27-30] whereas newly secreted VLDL and chylomicrons, which are rich in triglycerides and low in cholesterol esters, apparently are less atherogenic. Disorders characterized by high levels of smaller, cholesterol-enriched VLDL are accompanied by increased risk for CHD; examples include familial dysbetalipo-proteinemia[30,132] and familial combined hyperlipidemia.[133-136] By contrast, when VLDL particles are large and enriched in triglycerides (e.g., in severe hypertriglyceridemia due to primary lipoprotein lipase deficiency,[137] or in some kinships of familial hypertriglyceridemia,[135,136] high triglyceride does not appear to raise CHD risk. These associations between different forms of VLDL and atherogenesis appear to hold in animal models as well.[138] Unfortunately, the triglyceride level per se does not distinguish between VLDL particles that are and are not atherogenic.

Independent of the question of atherogenicity of the various types of triglyceride-rich lipoproteins is the observation that elevated triglycerides are often associated with reduced HDL-cholesterol levels,[23,139-141] and to the extent that low HDL levels are atherogenic,

elevated triglycerides likewise might be considered atherogenic,[131] although one step removed. Still, there is debate whether low HDL-cholesterol levels induced by high triglycerides are atherogenic. In some families with familial hypertriglyceridemia, HDL-cholesterol levels are reduced and yet the risk for CHD apparently is not increased.[135,136]

No large-scale clinical trials have specifically addressed the question of whether reducing triglyceride levels per se in hypertriglyceridemic patients will decrease risk for CHD. This adds an element of uncertainty about the utility of treatment of elevated triglycerides.[142,143] In the Helsinki Heart Study, which recruited hypercholesterolemic patients, the initial data analysis found no relation between the fall in triglyceride levels on gemfibrozil therapy and reduction in CHD risk.[69,144] On subgroup analysis, however, the greatest decrease in CHD was found to occur in patients who had high triglycerides combined with high total cholesterol and reduced HDL.[70] In the Stockholm Ischemic Heart Disease Study,[94] a secondary prevention trial, the combination of nicotinic acid and clofibrate was used, and the greatest reduction in CHD mortality occurred in patients with elevated triglycerides. The results of these two trials, although suggestive, are not sufficient to prove that triglyceride lowering in general will reduce risk for CHD. Nonetheless, the 1992 NIH Consensus Conference indicated that triglyceride reduction should be part of the therapy of certain dyslipidemias that carry an increased risk for CHD (see section IV C).

c. Other lipoprotein risk factors

Beyond the lipid parameters provided by the lipoprotein profile, several additional components of the lipoprotein system have been identified and are under intense evaluation. At present, however, the knowledge of each is insufficient to recommend that they be used in clinical practice. Some of the more important of these components include apolipoproteins B[145-149] and AI;[150-153] HDL subclasses (HDL$_2$ and HDL$_3$)[154-156] and LP-AI and LP-AI/AII;[157] small, dense LDL particles;[158-160] remnants of chylomicrons and VLDL; intermediate density lipoproteins (IDL);[161] and lipoprotein (a) [Lp(a)].[122,162-164] Because accurate and reliable measurements of these various fractions are not widely available and because we lack definitive

clinical trial data showing that their modification reduces risk for CHD, more research is required to determine their clinical utility.

6. CHD and Other Atherosclerotic Diseases as Risk Indicators

Patients with established CHD or clinical atherosclerotic disease of the aorta, arteries to the limbs, or carotid arteries are at high risk for subsequent myocardial infarction or CHD death.[83,165,166] Indeed, about 50 percent of all myocardial infarctions and at least 70 percent of CHD deaths occur in individuals with prior manifestations of cardiovascular disease. There are approximately 12 million people in the United States with symptomatic CHD, and many others with other forms of atherosclerotic vascular disease. If progression of atherosclerotic disease and its complications could be arrested in these patients, the potential for reduction in both morbidity and mortality from CHD would be substantial. The positive results obtained in secondary prevention trials indicate that cholesterol lowering should be a valuable component of the overall treatment regimen for CHD patients.

The risk for subsequent myocardial infarction and death in patients with established CHD or other atherosclerotic disease is five to sevenfold higher than for the general population.[83,165,166] The presence of CHD can be established on the basis of definite clinical and laboratory evidence of myocardial infarction or clinically significant myocardial ischemia, history of coronary artery surgery, or coronary angioplasty. This report does not recommend that angiography be carried out specifically for the purpose of classifying patients for cholesterol-lowering therapy. However, in the presence of clinical symptoms of coronary disease, an angiogram that shows substantial coronary atherosclerosis can be considered sufficient for establishing the diagnosis of CHD.

Several recent reports have indicated that the presence of peripheral arterial or carotid disease also confers a four to sixfold increase in risk of subsequent CHD events.[165,166] The presence of peripheral arterial disease is established on the basis of finding abdominal aortic aneurysm, or clinical signs and symptoms of ischemia to the extremities, accompanied by substantial atherosclerosis on angiograms or abnormalities of segment-to-arm pressure ratios or flow

velocities. Substantial carotid atherosclerosis is documented by cerebral symptoms (transient ischemic attacks or stroke) accompanied by the demonstration of significant atherosclerosis on sonogram or angiogram.

For patients with established CHD or other clinical atherosclerotic disease that puts them at equivalent risk, it is reasonable to set a lower target value for LDL-cholesterol lowering than is recommended for primary prevention. Angiographic studies taken as a whole[74-79] suggest that net regression of coronary atherosclerosis is proportional to the decrease in LDL-cholesterol levels, even to levels below 100 mg/dL. This finding provides a rationale for reducing LDL-cholesterol in CHD patients to 100 mg/dL or lower. Several secondary prevention trials are currently underway,[167] and the panel emphasizes that secondary prevention trials are ethical and are needed to refine the initiation and target levels for LDL-cholesterol in CHD patients. Nonetheless, the concept that LDL-cholesterol should be reduced more in secondary prevention than in primary prevention appears valid. With available combinations of diet and drugs, a target of 100 mg/dL or lower is attainable for a great many CHD patients. Many of these patients also have low concentrations of HDL-cholesterol and will benefit from a therapeutic regimen that will simultaneously lower LDL and raise HDL levels. It must be emphasized that not all patients with CHD will be candidates for cholesterol-lowering therapy; factors that militate against the use of such therapy include very advanced age, cardiac conditions that impart a poor prognosis (e.g., very low ejection fraction and chronic congestive heart failure), deterioration of mental function, and coexisting diseases that impair quality of life or reduce longevity.

7. Nonlipid Risk Factors for CHD

A number of nonlipid risk factors must be considered in preventive efforts. Some of these factors are modifiable and are appropriate targets for intervention efforts. There also are several fixed risk factors that cannot be modified, but since they increase CHD risk, their presence signals the need for more aggressive cholesterol lowering. The following lists the two types of risk factors.

NONLIPID RISK FACTORS

Modifiable Risk Factors	Nonmodifiable Risk Factors
• Cigarette smoking	• Age
• Hypertension	• Male sex
• Obesity	• Family history of premature CHD
• Physical inactivity	
• Diabetes mellitus	

The first aim of therapy in patients with modifiable nonlipid risk factors is to alter them to reduce CHD risk. This means a major effort towards smoking cessation, control of hypertension, weight reduction, and increased physical activity. Control of hyperglycemia in diabetic patients is prudent, although clinical trials have not been carried out to prove that glucose lowering per se reduces CHD events. In addition, the recommendations for cholesterol management operationally take selected factors into account (**table 1-2**) by setting lower thresholds for initiating treatment and lower goal levels for LDL-cholesterol for those at higher risk. These initiation and goal levels for LDL-cholesterol also are modified by the level of HDL-cholesterol. Evidence relating these nonlipid risk factors to CHD risk is summarized here.

a. Cigarette smoking

Cigarette smoking is a strong risk factor for CHD[168-173] and other atherosclerotic diseases,[174-177] and smoking cessation is one of the most effective ways to reduce risk for these diseases.[172,174,178] A major reduction in CHD risk occurs even within the first year after stopping smoking. Changing to low-tar or low-nicotine cigarettes does not appear to reduce the risk for CHD. Thus, patients who smoke should be given advice and specific followup care designed to promote quitting. Smoking cessation is particularly important not only because it reduces risk for CHD and stroke but also because it can prevent cancer and chronic lung disease.

b. Hypertension

Sustained elevations of systolic or diastolic blood pressure are associated with increased rates of cardiovascular disease. An update on current treatment of hypertension is available in the Fifth Report of the Joint National Committee on Detection,

Table 1-2

Risk Status Based on Presence of CHD Risk Factors Other Than LDL-Cholesterol

Positive Risk Factors

- Age:
    - Male: ≥45 years
    - Female: ≥55 years or premature menopause without estrogen replacement therapy

- 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 (<35 mg/dL*)

- Diabetes mellitus

Negative 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 figures 1-2 and 1-3. Age (defined differently for men and for women) is treated as a risk factor because rates of CHD are higher in the elderly 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, decreased HDL-cholesterol, and diabetes mellitus), but it should be considered a target for intervention. Physical inactivity is similarly not listed as a risk factor, but it too should be considered a target for intervention, and physical activity is recommended as desirable for everyone. High risk due to coronary or peripheral atherosclerosis is addressed directly in figure 1-4.

* 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).

Evaluation and Treatment of High Blood Pressure (JNC V).[179] The definition of hypertension used in this document is that of JNC V, i.e., a blood pressure ≥140/90 mmHg (confirmed by measurements on several occasions), or on medication for hypertension. In several early studies treatment of hypertension could not be shown to reduce the risk for CHD imparted by elevated blood pressure; more recent data, however, indicate that treatment of hypertension significantly reduces risk for CHD, but does not completely reverse it. Moreover, the physician may have difficulty determining how long the blood pressure has been adequately controlled versus how long it has been uncontrolled. For these reasons, hypertension, whether or not it is under treatment with medication, is included in the list of factors that modify the therapeutic approach to LDL-cholesterol. Hypertension and high serum cholesterol can occur concomitantly, and approaches to their joint management are considered in more detail under section IV F.

c. Obesity

- **Whole-Body Obesity**

Obesity, defined as a body mass index (weight in kilograms/height in meters squared) of more than 27, is accompanied by increased risk for CHD in men and women.[31,180-182] This elevated risk appears to be mediated chiefly through the metabolic consequences of obesity: glucose intolerance and diabetes mellitus,[183,184] hypertension,[185-189] decreased levels of HDL-cholesterol,[120,190,191] and increased levels of LDL-

and VLDL-cholesterol.[120,192-195] The incremental risk imparted by obesity independently of these associated conditions is uncertain, and for this reason, obesity is not defined in table 1-2 as a separate risk factor that specifically modifies therapy for high LDL-cholesterol levels. Nonetheless, the fact that weight reduction in obese patients affects these other risk factors makes it important in treatment of high blood cholesterol (see section II) and obesity is a major target for intervention in CHD prevention.

- **Visceral Obesity**

Visceral obesity is a common form of moderate obesity characterized by excessive accumulation of adipose fat within the abdomen. In many people its presence is manifested by an increase in the ratio of waist-to-hip circumference.[196,197] This pattern of obesity appears particularly to be associated with other risk factors (glucose intolerance, lipid disorders, and hypertension);[183,188,196,198-205] these may be due in part to hyperinsulinemia and increased insulin resistance induced by visceral obesity.[206] Visceral obesity also has been shown to be associated with increased risk of cardiovascular disease.[197,207-209] Available data indicate that a desirable waist-to-hip ratio for men is less than 0.9, whereas for middle-aged and elderly women, it is less than 0.8.[208,210] Thus, a greater effort should be made to achieve weight reduction in patients having visceral obesity.

d. Physical inactivity

Longitudinal studies indicate that regular physical activity of moderate intensity (such as walking briskly for 30 minutes a day or running for 30 minutes three times a week) affords an element of protection against CHD.[211-222] Therefore in this report physical inactivity is identified as a modifiable risk factor for CHD. In part the protection afforded by exercise may be due to direct effects of regular physical activity on the heart and arteries, and in part, it may result from favorable effects on HDL-cholesterol, blood pressure, body weight, and insulin resistance.[121,223-228] Increased physical activity is an important therapeutic modality for patients with high blood cholesterol (see section II).

e. Diabetes mellitus

Diabetes, whether insulin dependent or non-insulin dependent, increases the risk for CHD.[229-234] To some extent this increment in risk may be explained by

alterations in serum lipoproteins, and the management of this association is addressed under section IV D. However, there is something about the diabetic state, independent of serum lipoproteins, that contributes to CHD.[235,236] In men, diabetes increases risk for CHD by about threefold,[237] whereas in women the increase in risk may be even greater.[223,229,238,239] Although diabetes certainly increases the risk for CHD in women, whether it completely eliminates the protection against CHD afforded to women is uncertain.[230,240,241]

f. Age

Advancing age increases risk for CHD and can be called a risk factor. For example, the chances that a 62-year-old man will die of CHD in the next year is 500 times that of a 22-year-old man. This relationship has implications for therapeutic strategies. Since middle-aged and elderly adults are at much greater short-term risk for CHD than younger adults at the same LDL-cholesterol concentration, the former are more likely to benefit in the near future from aggressive cholesterol-lowering intervention. Although risk for CHD increases continuously with age, CHD events are relatively rare until men reach their middle forties; such events increase progressively thereafter, which accounts for the designation of age over 45 in men as a risk factor to modify therapy of high LDL-cholesterol. The corresponding age for women is older, as will be discussed below.

Clinical trials demonstrating benefit from cholesterol lowering have been carried out mainly in middle-aged men; only limited data are available in older people. Whether results in middle-aged men can be extrapolated to the elderly is not entirely resolved. However, LDL-cholesterol levels are still correlated with CHD rates in the elderly,[13] and the clinical trial evidence for the effectiveness of intervention after myocardial infarction suggests that lowering LDL-cholesterol could be beneficial even in patients who already have advanced atherosclerotic disease (table 1-1). Indeed, in view of the high-risk status of older persons, intervention may actually be more effective than in middle-aged patients in terms of number of lives preserved per year per 1,000 patients treated. The approach to cholesterol management in elderly patients requires special considerations, and these are discussed under section IV A.

g. Gender

The sex of an individual is another important determinant of risk. Men in their forties are four times more likely to die from CHD than women of the same age, but this relationship diminishes to a factor of two by age 70.[13] After the menopause, the incidence of CHD increases progressively in women until ultimately as many women as men die of CHD;[242] this accounts for the designation of age over 55 in women as a risk factor to modify therapy of high LDL-cholesterol. Premenopausal women in general are at very low risk for CHD,[243] and even severe genetic forms of high LDL-cholesterol usually do not produce CHD before the menopause except in the presence of other CHD risk factors[244] (see table 1-2). This has therapeutic implications. Primary prevention with diet is certainly appropriate, but based on their low short-term risk of developing CHD, drug therapy of elevated blood cholesterol in most premenopausal women should be delayed, except for those at high risk because of multiple risk factors or those with severe elevations of LDL-cholesterol.

After menopause, LDL-cholesterol levels rise more rapidly,[245,246] possibly because of loss of estrogens, and on the average, postmenopausal women have higher LDL-cholesterol levels than men of the same age.[247] These higher levels probably accelerate coronary atherosclerosis and contribute to relatively high rates of CHD in older women. Estrogens may protect women from CHD in other ways as well, and because of this apparent protective effect, premature menopause without estrogen replacement therapy is designated a risk factor in women (table 1-2). Several points must be considered in the decision to use drug therapy in postmenopausal women. First, CHD in women typically occurs later in life than in men. Second, epidemiologic data do not show as strong a relation between cholesterol levels and cardiovascular or total mortality as they do in men.[38,248] Third, many older women have high levels of HDL-cholesterol that appear to afford an element of protection in the presence of elevated LDL-cholesterol.[26] Fourth, only limited clinical trial data are available in postmenopausal women to document the benefit of cholesterol lowering. And fifth, use of estrogen replacement in postmenopausal women may extend the protection of the premenopausal state (see section III). These factors speak in favor of a somewhat more conservative approach to the use of cholesterol-lowering drugs in postmenopausal women than in men of the same age and LDL-cholesterol levels. Furthermore, the possibility of using estrogen replacement therapy as an alternative to cholesterol-lowering drugs in postmenopausal women is considered in more detail under sections III and IV A.

h. Family history of premature CHD

CHD tends to cluster in families, and a positive family history of premature CHD is an important risk factor. The reason for this is that in epidemiologic studies a family history for premature CHD emerges as an independent risk factor for CHD even when other risk factors are taken into account.[249-255] The family history is considered positive if clinical CHD or sudden death can be documented in first-degree male relatives before age 55 or in first-degree female relatives before age 65. The family history should document the presence or absence of high cholesterol levels, CHD or other cardiovascular disease, and nonlipid risk factors (cigarette smoking, hypertension, and diabetes mellitus) in first-degree relatives (biologic parents, siblings, and offspring). The age of onset of each risk factor should be noted. Elevated LDL-cholesterol levels in the presence of a positive family history suggests the presence of an inherited lipoprotein disorder. Expanding the family tree to include second-degree relatives (grandparents, uncles, and aunts) often provides additional useful information about genetic lipid disorders. Recording the family history is facilitated by using a simple family tree and can be performed in a few minutes.

8. Race

CHD death rates are 3 to 70 percent higher among blacks than among whites of the same age up through age 74, and the current decline in age-adjusted CHD death rate in the United States is less striking in blacks than in whites. Reasons for these differences are not entirely clear. Differences in the prevalence of hypertension may be one factor. Although LDL-cholesterol levels are similar in blacks and whites, HDL-cholesterol levels actually are higher in blacks.[25] Blacks often have high Lp(a) levels that may increase their risk for CHD. No separate algorithm for lipid management based on race is recommended, but efforts to reduce cholesterol and other CHD risk factors in the black population are especially important because of the higher rates of CHD and of

hypertension, diabetes mellitus, and cigarette smoking. The current guidelines are also applicable to people of Hispanic, Asian and Pacific Islander, and Native American origin in the United States.

9. The Importance of a Multidisciplinary Team Approach

This report presents guidelines for interventions that are the responsibility not only of physicians, but also of dietitians, nurses, pharmacists, and other health professionals who must work together as a team in educating, treating, and following up each patient. Ultimately, the interventions are the responsibility of the patient, who must make the dietary and lifestyle changes needed for reducing CHD risk.

10. Cost Considerations

The aggregate cost of CHD in the United States is enormous. These costs include physician visits, hospitalizations for ischemic coronary syndromes, expensive diagnostic evaluations, coronary artery surgery and angioplasty, often multiple medications, and chronic coronary care. In addition, income is lost due to chronic illness and disability. The total burden of CHD costs the nation between $50 to $100 billion per year, including $20 to $40 billion for direct medical care costs. These amounts do not take into account psychosocial costs that likewise are enormous. Therefore, if the burden of CHD in our society could be reduced significantly, the potential for cost savings would be great.

The least expensive way to reduce CHD rates is through the population or public health approach.[2] This approach targets the general population in attempts to reduce the major risk factors for CHD—smoking, hypertension, and high blood cholesterol—by public education, governmental policy, and industry commitment. In the long term, the public health approach promises the greatest impact on CHD with the least cost; this is true for cholesterol control as well as for other risk factors.

The clinical high-risk strategy, which aims to identify and treat individuals at greatest risk for CHD, complements the public health approach because it has an educational "spinoff" for public education. It helps to spread the message about the importance of cholesterol control throughout the public. The benefit-to-cost ratio of this spinoff of the high-risk strategy is

difficult to quantify, but its benefit may be substantial. Once an individual becomes a patient in the health care system, costs will inevitably rise. These costs may be partially offset if prevention efforts mitigate the costs of hospitalization, heart operations, or medications required for long-term care. The remaining net expense may be justified if one can avoid the personal and family toll of heart attack, cardiac disability, or premature death.

For individuals who enter active medical therapy for high cholesterol levels, the costs will include laboratory assessment and monitoring, professional fees, and in some cases, medications. The longer a person is maintained in such a program, therefore, the greater will be the total cost. Likewise, the health benefits (increased longevity and improved quality of life) and offsetting cost savings will be greatest in groups with the highest near-term risk of CHD. Patients at the highest risk are those who already have CHD, and benefit-to-cost ratios have been estimated to be greatest for this category. The next highest benefit-to-cost ratio accrues for patients with multiple risk factors or very high cholesterol levels who likewise have a high risk for developing CHD in the near future. The lowest benefit-to-cost ratios occur for medical treatment of individuals at lower short-term risk, most notably, younger adults without severe hypercholesterolemia or other CHD risk factors. The higher costs of primary prevention in patients with only moderately high cholesterol levels and no other risk factors by no means preclude the use of preventive measures in these patients, but it does indicate the need to keep costs down as much as possible. (See section IV G for details of cost-effectiveness calculations.)

The largest component of expense in preventive therapy of high-risk patients is cholesterol-lowering medication.[256] For patients with CHD or middle-age and older adults with multiple risk factors, use of cholesterol-lowering drugs appears to be cost-effective compared to accepted therapies for other diseases (see section IV G). On the other hand, for young adults having high cholesterol levels, but who are unlikely to develop CHD for many years, benefit-to-cost ratios tend to be low. This is the product of the high cost of prolonged drug therapy and the fact that a portion of treated patients who are without other risk factors will never develop overt CHD and thus will not have their lives extended by cholesterol lowering.

These concepts about costs versus benefits parallel those for risk-benefit considerations developed under section I B 4—Mortality Considerations. Therefore, *aggressive* drug therapy of moderately high blood cholesterol in young adults otherwise at low risk who are unlikely to develop CHD for many years can be questioned on both economic and safety grounds. For these patients, long-term drug therapy will be expensive and could have offsetting side effects. Certainly young adults with high cholesterol levels deserve continuing medical attention and monitoring to promote changes in life habits, especially diet and physical activity, but their management should be carried out at the lowest possible cost. The goal is to establish habits that maximally lower cholesterol levels without the need for frequent and costly followup and monitoring on a long-term basis. As indicated before, drug therapy in young adults should be limited to those who are considered to be at unusually high risk.

The issue of costs versus benefits in treatment of high blood cholesterol in middle-aged and elderly adults who are at moderately high risk for CHD also must be addressed. Here again, the principles of maximizing lifestyle intervention and minimizing the use of expensive cholesterol-lowering drugs should be observed. However, drug therapy is more cost-effective in these patients than in younger adults because of their higher short-term risk.

C. Detection and Evaluation

1. Who Should Be Tested

Total cholesterol should be measured at least once every 5 years in all adults 20 years of age and over. HDL-cholesterol should be measured at the same time if accurate results are available; reasons for adding HDL-cholesterol to routine testing were discussed before (see section I B 5a). Although screening programs that have the specific purpose of inviting the public to receive this test can be used (provided that care is taken to assure that the screening determination is accurate and that there is appropriate followup for further tests and treatment), the preferred approach is case finding. In this document, case finding means using the opportunity presented by a visit to the physician to perform a total and HDL-cholesterol blood test in the setting of a medical examination that also inquires about other CHD risk factors, i.e., prior CHD

and other atherosclerotic disease, age, gender, family history, cigarette smoking, high blood pressure, diabetes mellitus, obesity, and physical inactivity.

2. Measurement Methods

Serum total cholesterol and HDL-cholesterol levels can be measured at any time of day in the nonfasting state because total cholesterol concentrations do not change appreciably after a fat-containing meal, and HDL-cholesterol levels drop only slightly. Patients who are acutely ill, however, or those with recent trauma, surgery, acute infection, a change in usual diet, weight loss, or pregnancy should be rescheduled for lipid testing because the lipid levels in such patients may not be representative of their usual levels. Cholesterol levels for up to 12 weeks after acute myocardial infarction may be lower than usual, but a preliminary measurement during the acute phase provides an approximation, which if elevated can assist with initial management decisions. To minimize the problem that posture can alter the cholesterol value by changing plasma volume, venipuncture should be carried out in patients who have been sitting for at least 5 minutes, and the tourniquet should be used for as brief a period as possible. It is preferable to collect the blood in tubes without anticoagulant (for serum), but it is possible to use tubes containing EDTA (for plasma, which produces values that are about 3 percent lower than serum).

LDL-cholesterol is estimated from measurements of total cholesterol, total fasting triglycerides, and HDL-cholesterol.[257] If the triglyceride value is below 400 mg/dL, then this value can be divided by 5 to estimate the VLDL-cholesterol level. Since the total cholesterol level is the sum of LDL-cholesterol, HDL-cholesterol, and VLDL-cholesterol, LDL-cholesterol can be calculated as follows:

$$\text{LDL Cholesterol} = \text{Total Cholesterol} - \text{HDL Cholesterol} - \frac{\text{Triglycerides}}{5}$$

where all quantities are in mg/dL.

Because the LDL-cholesterol value is estimated from measurements that include triglyceride, blood samples should be collected from patients who have fasted for at least 9 to 12 hours, i.e., nothing by mouth of caloric value. For patients with triglyceride values over 400 mg/dL, estimation of LDL-cholesterol in this way is not

accurate, and ultracentrifugation in a specialized laboratory is required for accuracy. Furthermore, patients with triglycerides over 400 mg/dL constitute a special group in whom considerations of therapy go beyond the management of LDL-cholesterol (see section IV C).

The choice of a laboratory is an important issue because there is variability in the accuracy and reliability with which laboratories measure cholesterol. The physician should seek a laboratory that participates in a reliable standardization program, preferably one that has its lipid assays standardized through one of the National Network Laboratories of the Centers for Disease Control and Prevention. Rapid capillary blood (fingerstick) methodology for cholesterol measurement, as well as triglyceride and HDL-cholesterol determinations, can produce satisfactory results provided they are standardized in the same fashion as serum or plasma measurements. More detailed information is provided in "Recommendations for Improving Cholesterol Measurement" from the Laboratory Standardization Panel of the NCEP and in papers on the standardization of LDL, HDL, and triglyceride measurements from the NCEP Working Group on Lipoprotein Measurement.

3. Classification of Patients Without Evidence of CHD

a. Initial classification based on total cholesterol level

The classification system begins with a measurement of the total and HDL-cholesterol level.* The prime purpose of the HDL-cholesterol measurement is to help determine risk status (see table 1-2). These measurements can be made in the nonfasting state. An LDL-cholesterol estimation, which requires the fasting state, will provide still more information if it can be performed at the initial analysis. This analysis will save an extra visit and blood test for those with high blood cholesterol who need subsequent measurements. Serum is most frequently used for this measurement, and cholesterol levels in this report are stated as serum values.

Total cholesterol levels below 200 mg/dL (5.2 mmol/L) are classified as *desirable blood cholesterol*, those 200-239 mg/dL (5.2-6.2 mmol/L) as *borderline-high blood cholesterol*, and those 240 mg/dL (6.2 mmol/L) and above as *high blood cholesterol* (**figure 1-2**). Because the relationship between serum cholesterol level and CHD risk is a continuous and steadily increasing one (figure 1-1), these cutpoints (like those for high blood pressure) are somewhat arbitrary. The 240 mg/dL cutpoint for total serum cholesterol is a level at which CHD risk is roughly double that at 200 mg/dL and rising steeply.

Patients with a *desirable blood cholesterol* level at the initial test (<200 mg/dL) and in whom HDL-cholesterol is over 35 mg/dL do not need a second blood test. They can be given advice and educational materials on the eating pattern recommended for the general population, and advised to have another serum cholesterol test in 5 years. As with all patients, these patients should also be given other forms of preventive medical care for cigarette smoking, hypertension, and other risk factors as appropriate.

b. Subsequent classification based on LDL-cholesterol level for patients without evidence of CHD (or other clinical atherosclerotic disease)

Patients with serum total cholesterol of 200 mg/dL or greater or HDL-cholesterol less than 35 mg/dL on initial testing should have a fasting lipoprotein analysis that provides measures of total cholesterol, HDL-cholesterol, triglycerides, and an estimate of LDL-cholesterol. The classification of patients based on LDL-cholesterol is shown in **figure 1-3**. LDL-cholesterol levels are classified as desirable (below 130 mg/dL [3.4 mmol/L]), borderline-high-risk (130-159 mg/dL [3.4-4.1 mmol/L]), or high-risk (160 mg/dL [4.1 mmol/L] or greater). If the LDL-cholesterol level is below 130 mg/dL, patients can be given advice and educational material on the eating pattern recommended for the general population, and advised to have another serum cholesterol test in 5 years, just as for those with total cholesterol levels below 200 mg/dL. They likewise should be given other forms of preventive care for cigarette smoking, hypertension,

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* Population distributions for serum total cholesterol, LDL-cholesterol, and HDL-cholesterol levels in the United States are provided in appendix I-A. To convert serum values to plasma, multiply by 0.97. To convert cholesterol values in mg/dL to millimoles per liter, divide by 38.7. To convert triglyceride values in mg/dL to millimoles per liter, divide by 88.6. See Appendix I-B for corresponding levels of lipids in mg/dL and mmol/L.

Figure 1-2

Primary Prevention in Adults Without Evidence of CHD: Initial Classification Based on Total Cholesterol and HDL-Cholesterol

```
┌─────────────────────────────────┐
│ Measure nonfasting total blood  │
│ cholesterol and HDL-cholesterol │                          ┌──────────────────────────────┐
│                                 │                          │ Repeat total cholesterol and │
│ Assess other nonlipid CHD risk  │                          │ HDL within 5 years or with   │
│ Factors                         │                          │ physical exam                │
└─────────────────────────────────┘                          │                              │
                                      ┌──────────────────┐    │ Provide education on general │
                                      │ HDL ≥35 mg/dL    │──→ │ population eating pattern,    │
          ┌──────────────────────┐    └──────────────────┘    │ physical activity, and       │
          │ Desirable blood      │                            │ risk factor reduction        │
          │ cholesterol          │                            └──────────────────────────────┘
          │ <200 mg/dL           │    ┌──────────────────┐
          └──────────────────────┘    │ HDL <35 mg/dL    │
                                      └──────────────────┘    ┌──────────────────────────────┐
                                                              │ Provide information on dietary│
                                                              │ modification, physical activity,│
                                      ┌──────────────────────┐│ and risk factor reduction    │
                                      │ HDL ≥35 mg/dL and    ││                              │
                                      │ fewer than 2 risk    ││ Reevaluate patient in 1-2 years│
          ┌──────────────────────┐    │ factors              ││ − Repeat total and           │
          │ Borderline-high      │    └──────────────────────┘│   HDL-cholesterol            │
          │ blood cholesterol    │                            │   measurement                │
          │ 200-239 mg/dL        │    ┌──────────────────────┐│ − Reinforce nutrition and    │
          └──────────────────────┘    │ HDL <35 mg/dL or     ││   physical activity education│
                                      │ 2 or more risk factors│└──────────────────────────────┘
                                      └──────────────────────┘
                                                              ┌──────────────────────────────┐
          ┌──────────────────────┐                           │                              │
          │ High blood cholesterol│                           │ Do lipoprotein analysis      │
          │ ≥240 mg/dL           │──────────────────────────→│                              │
          └──────────────────────┘                           │ (Go to figure 1-3)           │
                                                              │                              │
                                                              └──────────────────────────────┘
```

┌───┐
│ CHD Risk Factors   │
│   │
│ **Positive**   │
│ • Age: Male ≥45 years   │
│   Female ≥55 years or   │
│   premature menopause   │
│   without estrogen   │
│   replacement therapy   │
│ • Family history of premature CHD   │
│ • Smoking   │
│ • Hypertension   │
│ • HDL-cholesterol <35 mg/dL   │
│ • Diabetes   │
│   │
│ **Negative**   │
│ • HDL-cholesterol ≥60 mg/dL   │
└───┘

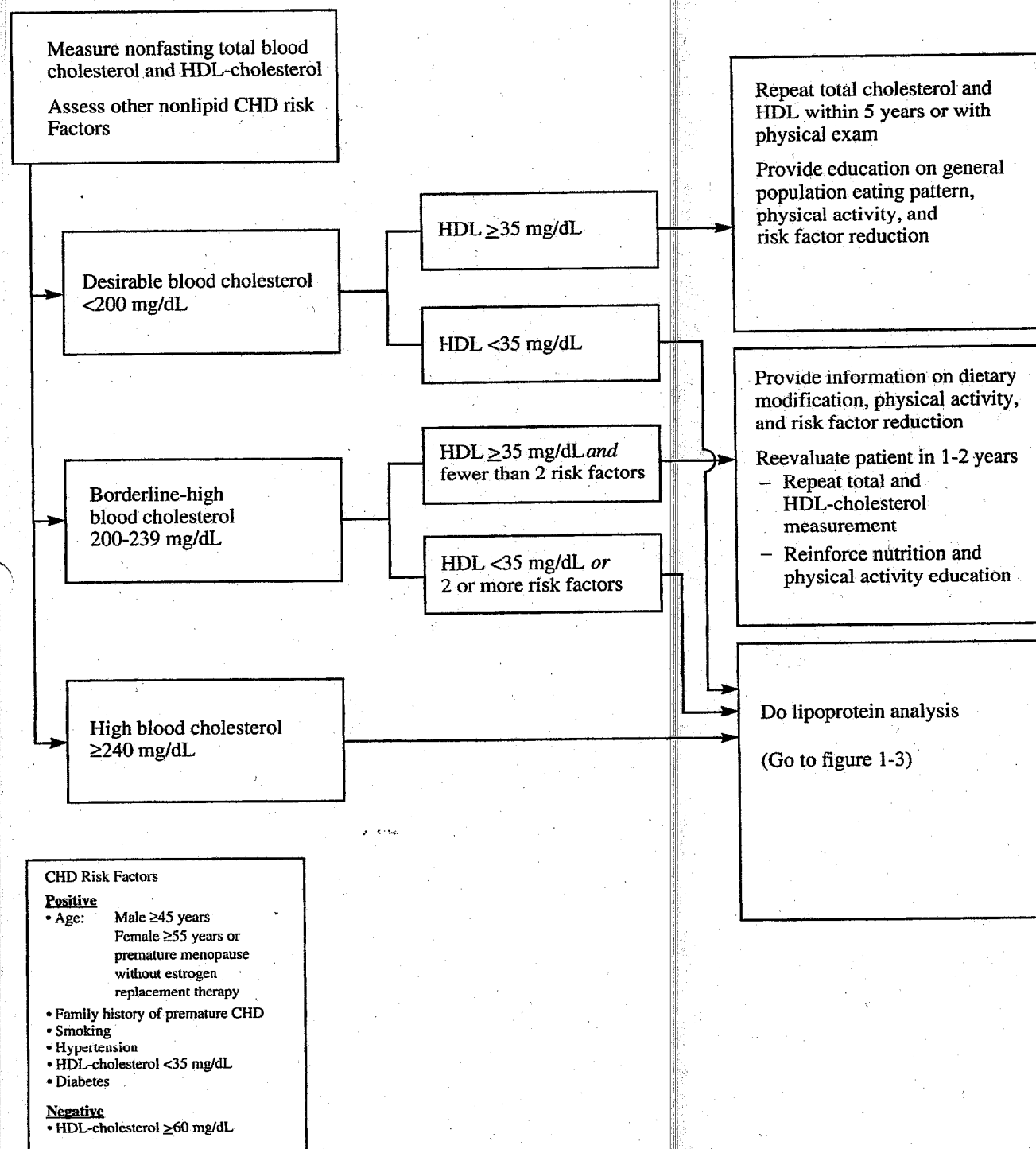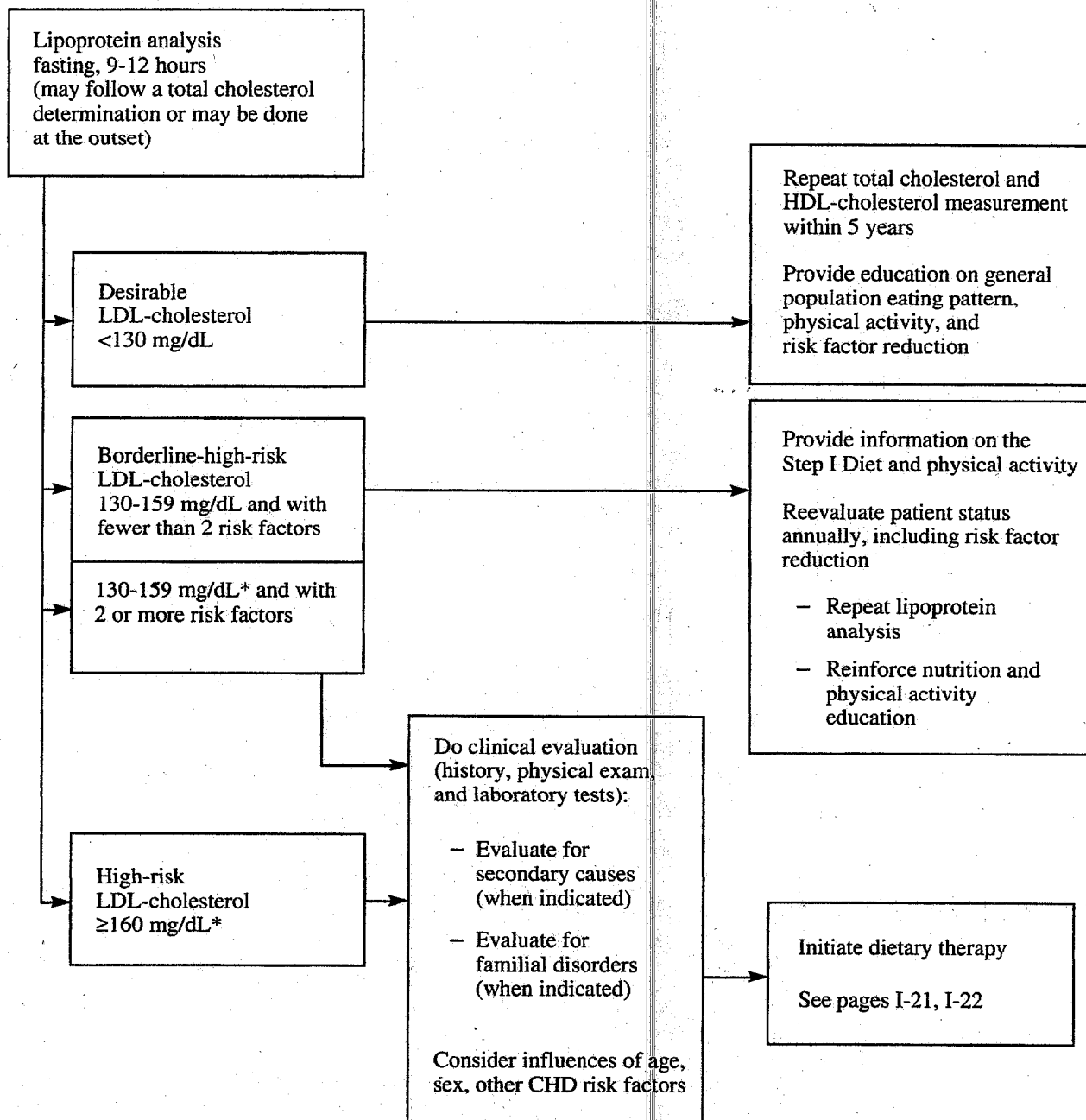*Figure 1-3*

Primary Prevention in Adults Without Evidence of CHD: Subsequent Classification Based on LDL-Cholesterol

```
┌─────────────────────────┐
│ Lipoprotein analysis    │
│ fasting, 9-12 hours     │
│ (may follow a total     │
│ cholesterol             │
│ determination or may be │
│ done at the outset)     │
└─────────────────────────┘
```

```
┌──────────────────────┐                              ┌────────────────────────────┐
│ Desirable            │                              │ Repeat total cholesterol   │
│ LDL-cholesterol      │ ──────────────────────────►  │ and HDL-cholesterol        │
│ <130 mg/dL           │                              │ measurement within 5 years │
└──────────────────────┘                              │                            │
                                                       │ Provide education on       │
                                                       │ general population eating  │
                                                       │ pattern, physical          │
                                                       │ activity, and              │
                                                       │ risk factor reduction      │
                                                       └────────────────────────────┘
```

```
┌──────────────────────────┐                          ┌────────────────────────────┐
│ Borderline-high-risk     │                          │ Provide information on the │
│ LDL-cholesterol          │ ───────────────────────► │ Step I Diet and physical   │
│ 130-159 mg/dL and with   │                          │ activity                   │
│ fewer than 2 risk factors│                          │                            │
├──────────────────────────┤                          │ Reevaluate patient status  │
│ 130-159 mg/dL* and with  │                          │ annually, including risk   │
│ 2 or more risk factors   │                          │ factor reduction           │
└──────────────────────────┘                          │                            │
                                                       │  –  Repeat lipoprotein     │
                                                       │     analysis               │
                                                       │                            │
                                                       │  –  Reinforce nutrition    │
                                                       │     and physical activity  │
                                                       │     education              │
                                                       └────────────────────────────┘
```

```
                          ┌────────────────────────────┐
                          │ Do clinical evaluation     │
                          │ (history, physical exam,   │
                          │ and laboratory tests):     │
                          │                            │
                          │  –  Evaluate for           │
                          │     secondary causes       │
                          │     (when indicated)       │       ┌──────────────────────┐
┌──────────────────────┐  │                            │       │ Initiate dietary     │
│ High-risk            │  │  –  Evaluate for           │ ────► │ therapy              │
│ LDL-cholesterol      │─►│     familial disorders     │       │                      │
│ ≥160 mg/dL*          │  │     (when indicated)       │       │ See pages I-21, I-22 │
└──────────────────────┘  │                            │       └──────────────────────┘
                          │ Consider influences of     │
                          │ age, sex, other CHD risk   │
                          │ factors                    │
                          └────────────────────────────┘
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* On the basis of the average of two determinations. If the first two LDL-cholesterol tests differ by more than 30 mg/dL, a third test should be obtained within 1-8 weeks and the average value of three tests used.

and other risk factors as appropriate. If the average of the two HDL-cholesterol levels is below 35 mg/dL in a patient with LDL-cholesterol less than 130 mg/dL, consult section IV B for the approach to such a patient. If the triglyceride level is over 200 mg/dL in a patient with LDL-choles-terol below 130 mg/dL, consult section IV C.

Individuals with LDL-cholesterol in the range of 130-159 mg/dL and fewer than two other CHD risk factors should be given advice on diet modification and physical activity and should be retested by lipoprotein analysis in 1 year. If low HDL-cholesterol or high triglyceride levels are present in such an individual, consult section IV B or C. Individuals with LDL-cholesterol in the range of 130-159 mg/dL who have two (or more) risk factors (see table 1-2) or an LDL-cholesterol level ≥160 mg/dL should have a second lipoprotein analysis for LDL-cholesterol estimation within 1-8 weeks. Treatment decisions should always be based on the mean of two or more LDL-cholesterol levels. If the two values differ by more than 30 mg/dL, a third test should be carried out and the average of all three used.

On the basis of their average values, patients with borderline-high-risk LDL-cholesterol (130-159 mg/dL) who do have two or more other risk factors, as well as patients in the high-risk LDL-cholesterol group (≥160 mg/dL), undergo the clinical evaluation described below and then enter a more intensive lipid intervention program.

4. Patients With Evidence of CHD (or Other Clinical Atherosclerotic Disease)

All men and women who have established CHD (or other clinical atherosclerotic disease) as defined earlier should have a lipoprotein analysis for LDL-cholesterol determination after an overnight fast on two occasions 1-8 weeks apart (**figure 1-4**). As usual, if the two LDL-cholesterol values differ by more than 30 mg/dL, a third test is performed and the average of all three is used. If lipoprotein analysis is carried out during recovery from an acute coronary event (myocardial infarction or unstable angina), the results must be interpreted with caution. Levels typically fall during the event and may not be restored to baseline for several weeks.[258,259] Even during the acute event, LDL-cholesterol levels frequently are above the target value for a CHD patient, and the period of

hospitalization is a propitious time to begin dietary therapy. In most cases, however, drug therapy should be withheld until a new baseline of LDL-cholesterol is established on dietary therapy in 6 to 12 weeks. However, in patients who have distinct elevations of LDL-cholesterol, prompt initiation of drug therapy is acceptable.

Because patients with CHD or other atherosclerotic disease are at particularly high risk of myocardial infarction and death, an LDL-cholesterol greater than 100 mg/dL is higher than optimal and defines the need for therapy. Most such patients will meet this criterion and require treatment to lower LDL-cholesterol levels. In addition, many patients with clinical CHD in this category have low levels of HDL-cholesterol (<35 mg/dL). This can be secondary to other modifiable factors such as cigarette smoking, obesity, or physical inactivity. Beta-blockers also can lower HDL-cholesterol levels in CHD patients but nonetheless have been shown to be efficacious for reducing subsequent CHD events after myocardial infarction; therefore their benefit in many high-risk patients may outweigh their drawback of HDL-cholesterol lowering. Management of low HDL-cholesterol levels is considered in detail under section IV B, and management of hypertriglyceridemia is discussed in section IV C.
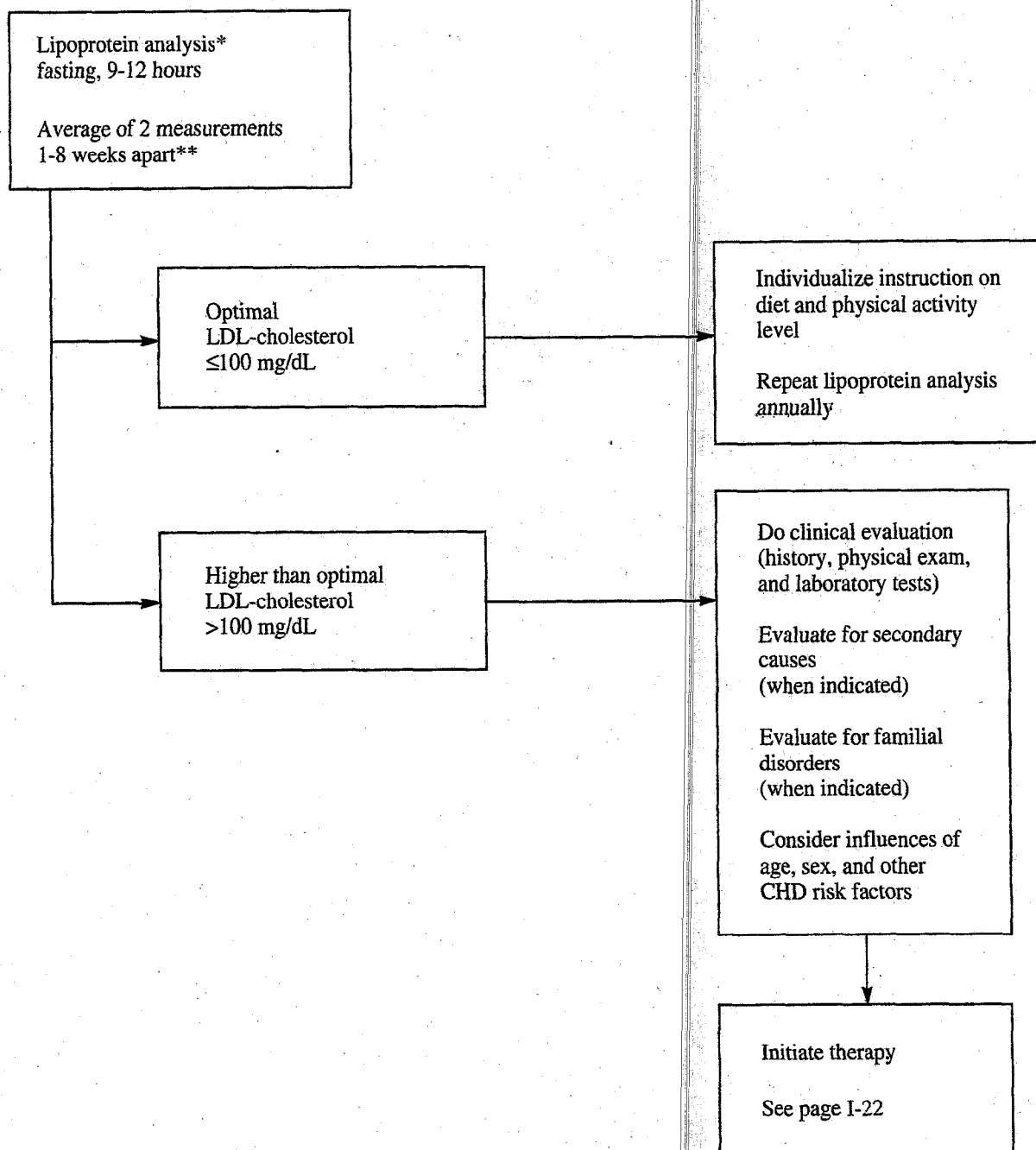
5. Clinical Evaluation

All patients with an LDL-cholesterol level ≥160 mg/dL, those with a level of 130-159 mg/dL and two (or more) other CHD risk factors, and those with CHD (or other clinical atherosclerotic disease) and an LDL-cholesterol >100 mg/dL should be evaluated thoroughly to guide cholesterol management.

The clinical evaluation, which includes a history, physical examination, and basic laboratory tests, has three aims. The first is to determine whether the high LDL-cholesterol level is caused by a disease, diet, or drug that can be altered. The second is to determine whether a genetic disorder may underlie the elevated LDL-cholesterol, indicating a need to take a family history and to measure cholesterol in other family members. Evaluation of the family may uncover additional patients who need therapy for high LDL-cholesterol prior to their developing clinical disease. The third aim is to better characterize the risk status of the patient, the presence or absence of CHD and other

Figure 1-4

Secondary Prevention in Adults With Evidence of CHD: Classification Based on LDL-Cholesterol

Lipoprotein analysis*
fasting, 9-12 hours

Average of 2 measurements
1-8 weeks apart**

Optimal
LDL-cholesterol
≤100 mg/dL

Individualize instruction on
diet and physical activity
level

Repeat lipoprotein analysis
annually

Higher than optimal
LDL-cholesterol
>100 mg/dL

Do clinical evaluation
(history, physical exam,
and laboratory tests)

Evaluate for secondary
causes
(when indicated)

Evaluate for familial
disorders
(when indicated)

Consider influences of
age, sex, and other
CHD risk factors

Initiate therapy

See page I-22

* Lipoprotein analysis should be performed when the patient is not in the recovery phase from an acute coronary or other medical event that would lower their usual LDL-cholesterol level.

** If the first two LDL-cholesterol tests differ by more than 30 mg/dL, a third test should be obtained within 1-8 weeks and the average value of the three tests used.

CHD risk factors, as well as age and sex, in order to se this information in decisions about treatment directed at LDL-cholesterol.

a. Secondary high blood cholesterol

The clinical evaluation for secondary (and possibly reversible) forms of high LDL-cholesterol includes consideration of, and where appropriate ruling out, the following conditions:

- Diabetes mellitus

- Hypothyroidism

- Nephrotic syndrome

- Obstructive liver disease

- Drugs that may raise LDL-cholesterol levels or lower HDL-cholesterol levels, particularly progestins, anabolic steroids, corticosteroids, and certain antihypertensive agents (see section IV F2)

Secondary high blood cholesterol can be detected by clinical evaluation and, when indicated, by the following laboratory tests: urinalysis, serum thyroid stimulating hormone, glucose, and alkaline phosphatase. When one of the causes of secondary high cholesterol is present, the usual approach is to treat the disease or discontinue the drug (if possible) and then to reevaluate the LDL-cholesterol level.

b. Familial disorders

High blood cholesterol is often familial. Family testing is essential to the diagnosis of familial hyperlipidemias. All available first-degree relatives (children, siblings, and parents) should be tested for plasma lipids and lipoproteins when a patient has documented high-risk LDL-cholesterol or premature CHD. Diagnosing genetic disorders helps clarify the etiology and management of LDL-cholesterol elevations in affected patients, and it may uncover additional patients who need therapy for high cholesterol levels. The genetic hyperlipidemias are described in detail under section IV E, Severe Forms of Hypercholesterolemia.

c. Risk status

Information on whether CHD or its other risk factors are present is used to assess whether the patient has reasons other than LDL-cholesterol for being at high risk of a CHD event or death. The search is important because modifiable risk factors such as hypertension and cigarette smoking are themselves important targets for intervention. In addition, the presence of any of the risk factors in table 1-2, whether modifiable or not, influences clinical decisions about LDL-cholesterol because the increased absolute level of risk increases the potential benefit from lowering the level of LDL-cholesterol, and these guidelines therefore provide for a lower intervention threshold and therapeutic goal for LDL-cholesterol.

D. General Approach to Treatment

Patients with high-risk LDL-cholesterol levels ($\geq$160 mg/dL), those with borderline-high-risk LDL-cholesterol (130-159 mg/dL) who have two or more risk factors (see table 1-2), and those with CHD or other clinical atherosclerotic disease and an LDL-cholesterol >100 mg/dL should enter into a program of therapy initiated by the physician. The first two groups qualify for primary prevention and the latter for secondary prevention.

1. Primary Prevention

For the patient without CHD or other atherosclerotic disease, the target goals for LDL-cholesterol lowering depend on the risk status of the patient and include the following:

- <160 mg/dL if fewer than two other risk factors are present (see table 1-2)

- <130 mg/dL if two (or more) CHD risk factors are present (see table 1-2)

In primary prevention, most patients who qualify for medical treatment should receive dietary therapy and should increase physical activity. The levels of LDL-cholesterol for initiation of dietary therapy are:

- $\geq$160 mg/dL in patients who have fewer than two other CHD risk factors

- $\geq$130 mg/dL in patients who have two (or more) CHD risk factors

The LDL-cholesterol levels at which drug therapy can be considered *after* an adequate trial of dietary therapy are:

- $\geq$190 mg/dL in patients without two other CHD risk factors

- $\geq$160 mg/dL in patients with two (or more) CHD risk factors

Drug therapy in primary prevention generally should be reserved for middle-age and older patients who are at high risk. Such patients include those with multiple CHD risk factors (see table 1-2), severe forms of hypercholesterolemia (see section IV E), and severe secondary dyslipidemias (see section IV D). Some patients who have LDL-cholesterol levels in the range of 160 to 220 mg/dL and one powerful risk factor, like diabetes mellitus or family history of premature CHD, also may be candidates for drug therapy. *For most patients without severe hyperlipidemias, a 6-month trial of dietary therapy is indicated before considering drugs,* whereas for those with LDL-cholesterol levels well above 220 mg/dL, drug therapy can be started once intensive dietary therapy has been initiated.

In young adult men (<35 yrs) and premenopausal women without other risk factors, the general approach when LDL-cholesterol is in the range of 190-220 mg/dL is to delay drug therapy to an older age. Certainly these patients deserve a thorough risk evaluation, intensive dietary therapy, and frequent monitoring. In many of these young adults, intensive dietary therapy will reduce their LDL-cholesterol levels to below 190 mg/dL, the cutpoint for drug consideration. Only 1-2 percent of the young adult population will remain with LDL-cholesterol levels in the range of 190 to 220 mg/dL after dietary therapy. If a decision is made to use drugs, safer drugs should be employed at the lowest effective doses. Even so, use of drugs for many years could produce unanticipated and offsetting side effects, and cost-effectiveness ratios likely will be high. Therefore, it may be prudent to delay drug therapy and to monitor the patient closely.

The younger the patient, the longer it should be possible to delay use of drugs. If other risk factors develop during monitoring, a decision to employ drugs can be made earlier. If LDL-cholesterol levels are even higher (i.e., consistently over 220 mg/dL), most patients are candidates for drug therapy; safer drugs should nevertheless be used at the lowest effective doses.

2. Secondary Prevention

For the patient with CHD or other clinical atherosclerotic disease, the target goal for LDL-cholesterol reduction is:

* 100 mg/dL or lower

Maximal dietary therapy should be initiated in patients in this category; but if and when it becomes apparent that the target LDL-cholesterol cannot be reached by diet alone, drug therapy should be considered. Whether to initiate drug therapy for patients with CHD (or other atherosclerotic disease) whose LDL-cholesterol is in the range of 100 to 129 mg/dL after intensive dietary therapy depends on a variety of factors and must be left to the judgment of the physician. Many authorities believe it is prudent to do so to maximize reduction of LDL-cholesterol levels. However, if the LDL-cholesterol level is 100 to 129 mg/dL with maximal dietary therapy, the physician may deem it inappropriate to subject a patient to the potential side effects and costs of drug therapy. Likewise, if the LDL-cholesterol level is between 100 and 129 mg/dL after single-drug therapy, raising the dose or adding a second drug may be considered unsuitable for the same reasons.