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

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

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

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

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

4) Monounsaturated fatty acids

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

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

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

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

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

5) *Polyunsaturated fatty acids*

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

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

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

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

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

6) *Total fat*

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

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

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

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

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

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

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

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

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

7) *Carbohydrate*

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

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

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

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

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

8) Protein

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

b. Additional dietary options for LDL lowering

1) Increasing viscous fiber in the diet

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

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

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

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

2) Plant stanols/sterols

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

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

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

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

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

3) Soy protein

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2) Vitamins/antioxidants

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

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

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

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

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

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

b) Antioxidants

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

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

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

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

with established CHD failed to demonstrate a protective effect of vitamin E supplementation on subsequent cardiovascular events.[510,735,754]

Thus, in spite of the theoretical benefits of antioxidant vitamins for reducing risk for CHD, this potential has so far not been found in controlled clinical trials that have used a variety of antioxidant mixtures and doses. The failure to demonstrate benefit in controlled trials does not eliminate the possibility of benefit. It does, however, dilute confidence in benefit and stands in the way of a solid recommendation for high intakes of antioxidants for CHD prevention.

The Institute of Medicine has recently released recommendations for Dietary Reference Intakes (DRIs) for antioxidant vitamins. A specific recommendation was not made for beta-carotene because it has not been shown to be an essential nutrient nor have clinical trials demonstrated benefit for reduction in risk for either cardiovascular disease or cancer. The RDA for vitamin C was increased to 75 mg/day for women and 90 mg/day for men. The RDA for Vitamin E was set at 15 mg/day. Vitamin E supplementation was not recommended for prevention of chronic disease because of a lack of convincing evidence of benefit.

Evidence Statement: Oxidative stress and LDL oxidation appear to be involved in atherogenesis. However, clinical trials to date have failed to demonstrate that supplementation of the diet with antioxidants will reduce risk for CHD (A2).

Recommendation: Evidence of CHD risk reduction from dietary antioxidants is not strong enough to justify a recommendation for antioxidant supplementation to reduce CHD risk in clinical practice. ATP III supports current recommendations of the Institute of Medicine's RDAs for dietary antioxidants, i.e., 75 mg and 90 mg per day for women and men, respectively, for vitamin C and 15 mg per day for vitamin E.

3) *Moderate intakes of alcohol*

Observational studies consistently show a J-shaped relation between alcohol consumption and total mortality. Moderate alcohol consumption is associated with lower mortality, and higher consumption with higher mortality. The lower mortality appears to be related to CHD death, because CHD accounts for a significant proportion of total deaths. Case-control, cohort, and ecological studies indicate lower risk for CHD at low to moderate alcohol intake.[755] A moderate amount of alcohol can be defined as no more than one drink per day for women and no more than two drinks per day for men.[756,757] This gender distinction takes into account differences in both weight and metabolism. Moreover, any cardiovascular benefit occurs not in the young age groups but in middle-aged adults, men 45 years of age or older and women 55 years of age or older.[758] Mechanisms of putative risk reduction from moderate alcohol consumption are unknown; however, it could be due to an increase in HDL cholesterol and apo A-1 and modestly to an improvement in hemostatic factors.[759] Prospective cohort studies suggest a similar relationship with CHD regardless of the type of alcoholic beverages consumed.[760]

The dangers of overconsumption of alcohol are well known. At higher levels of intake, adverse effects include elevated blood pressure, arrhythmia, and myocardial dysfunction.[755,757] Alcohol excess also predisposes to acute pancreatitis. Rarely it can precipitate pancreatitis by accentuating a pre-existing hypertriglyceridemia and chylomicronemia.[761] A pooled analysis shows that alcohol intake increases the risk of breast cancer in women.[762] Since up to 10 percent of U.S. adults misuse alcohol, advice about alcohol intake should be given carefully with both advantages and negatives presented.[763] For some persons, the negatives of alcohol consumption will outweigh any advantage.

Evidence Statement: Moderate intakes of alcohol in middle-aged and older adults may reduce risk for CHD (C2). However, high intakes of alcohol produce multiple adverse effects (C1).

Recommendation: No more than two drinks per day for men and no more than one drink per day for women should be consumed. A drink is defined as 5 ounces of wine, 12 ounces of beer, or 1½ ounces of 80 proof whiskey. Persons who do not drink should not be encouraged to initiate regular alcohol consumption.

) Dietary sodium, potassium, and calcium

Many individuals with hypercholesterolemia also have ypertension (see Section VII.6). Evidence suggests nat even those with normal blood pressure levels can educe their chances of developing high blood pressure y consuming less salt.[160,161,657] Studies in diverse pop-lations have shown that a high sodium intake is asso-iated with higher blood pressure.[764] Also, a high salt ntake increases the amount of calcium excreted in the rine, and has been independently associated with one loss at the hip.[764] The Dietary Approaches to top Hypertension (DASH) trial has provided evidence hat a dietary pattern high in fruits, vegetables, low-fat airy products, whole grains, poultry, fish, and nuts nd low in fats, red meat, and sweets—foods that are ood sources of potassium, calcium, and magnesium–avorably influences blood pressure even when sodium evels are held constant,[765] but when these nutrients re consumed in combination with a low sodium ntake, 2400 mg or 1800 mg, blood pressure is owered even more.[766]

Evidence statement: JNC VI[160,161] provides a review of the evidence to support the concept that lower salt intake lowers blood pressure or prevents its rise. One clinical trial further shows that the effects of a dietary pattern high in fruits, vegetables, low-fat dairy products, whole grains, poultry, fish, and nuts and low in fats, red meat, and sweets—foods that are good sources of potassium, calcium, and magnesium—to reduce blood pressure are enhanced by a diet low in salt (A2).

Recommendation: The Diet and Health report[657] and JNC VI recommend a sodium intake of <2400 mg/d (no more than 100 mmol/day, 2.4g sodium or 6.0g sodium chloride). JNC VI further recommends maintaining adequate intakes of dietary potassium (approximately 90 mmol per day) and enough dietary calcium and magnesium for general health. ATP III affirms these recommendations for persons undergoing cholesterol management in clinical practice.

5) Herbal or botanical dietary supplements

The 10 top-selling herbal or botanical dietary supplements are cranberry, echinacea, evening primrose, garlic, ginkgo, ginseng, goldenseal, grape seed extract, St. John's wort, and saw palmetto.[767] These botanical supplements are available in health food stores, pharmacies, and many supermarkets. Several of the compounds have been promoted as agents to reduce the risk of CHD. Data from controlled trials regarding efficacy and safety are limited, in part because existing food and drug laws do not require demonstration of safety and efficacy to support legal marketing of dietary supplements. Dietary supplements are regulated according to different standards than are drugs. In addition to concerns about efficacy and safety, there is a lack of standardization among brands of botanical supplements. As a result, the amount of bioactive constituent, by which the supplements are hypothesized to influence disease, can differ widely among brands. In the case of garlic, a few randomized controlled studies are available, but the preponderance of available evidence fails to establish that garlic reduces LDL cholesterol levels. Biological plausibility supports use of some supplements, but there are few controlled clinical trials to document benefit. Studies designed to evaluate efficacy for disease endpoints, long-term safety, and drug interaction have not been reported.

Evidence statement: Despite widespread promotion of several herbal or botanical dietary supplements for prevention of CHD, a paucity of data exists on product standardization, controlled clinical trials for efficacy, and long-term safety and drug interactions. Clinical trial data are not available to support the use of herbal and botanical supplements in the prevention or treatment of heart disease.

Recommendation: ATP III does not recommend use of herbal or botanical dietary supplements to reduce risk for CHD. However, health care professionals should query patients to establish whether such products are being used because of the potential for drug interaction.

6) High protein, high total fat and saturated fat weight loss regimens

Periodically, weight-loss diets high in protein and fat and low in carbohydrate surge in popularity. Such diets will result in weight loss within a few weeks or months if calories are restricted. However, such diets have not been demonstrated to produce long-term weight loss in controlled trials. Although clinical trial data are lacking, several concerns have been expressed about the use of these diets in clinical weight reduction:

- Short-term, extreme diets rarely produce long-term weight reduction.
- High intakes of saturated fats can raise LDL cholesterol.
- Low intakes of fruits, vegetables, and grains can deprive persons of healthful nutrients and are not conducive to long-term health.

Diets popularized as low-carbohydrate, high-fat, high-protein regimens for rapid weight loss should not be confused with ATP III's easing restriction of the percentage of dietary fat for persons with the metabolic syndrome. The latter allows dietary fat to rise to 35 percent of total calories, provided it remains low in saturated fatty acids (<7 percent of total energy) and includes mostly unsaturated fats. This will reduce carbohydrate intake somewhat to prevent the actions of high-carbohydrate diets to raise triglycerides and reduce HDL cholesterol levels. The ATP III recommendation allows for the dietary variety outlined in the Dietary Guidelines for Americans (2000).[241]

Evidence statement: High protein, high total fat and saturated fat weight loss regimens have not been demonstrated in controlled clinical trials to produce long-term weight reduction. In addition, their nutrient composition does not appear to be conducive to long-term health.

Recommendation: High protein, high total fat and saturated fat weight loss regimens are not recommended for weight reduction in clinical practice.

4. Management of the metabolic syndrome through life habit changes

a. Weight control

ATP II[1,2] recommended increased emphasis on weight reduction as part of LDL-lowering therapy for overweight/obese persons who enter clinical guidelines for cholesterol management. ATP III confirms this recommendation. However, in ATP III, emphasis on weight reduction is delayed until after other dietary measures are introduced for LDL lowering (reduced intakes of saturated fatty acids and cholesterol and possibly other options for LDL lowering [plant stanols/sterols and increased dietary fiber]) (see Figure V.2–1). The delay in emphasizing weight reduction is to avoid overloading new patients with a multitude of dietary messages and to concentrate first on LDL reduction. After an adequate trial of LDL-lowering measures, attention turns to other lipid risk factors and the metabolic syndrome (see Figure V.2–1). Weight reduction then becomes a major focus of TLC. In 1998, the NHLBI published Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults from the Obesity Education Initiative (OEI).[78,79] This is an evidence-based report, and its recommendations for techniques of weight reduction are accepted by ATP III for persons undergoing management for cholesterol disorders. The ATP III report does not independently develop evidence statements beyond those in the OEI report. ATP III endorses the importance of weight control described in the OEI report. Indeed, weight control alone, in addition to lowering LDL cholesterol, favorably influences all of the risk factors of the metabolic syndrome.

b. Increased regular physical activity

ATP II also recommended increased emphasis on regular physical activity. In ATP III, the emphasis is reinforced with particular attention to its benefits for management of the metabolic syndrome. The recommendation for increased physical activity is introduced when TLC is initiated and the recommendation is reinforced when emphasis shifts to management of the metabolic syndrome (see Figure V.2–1). Physical inactivity is a major risk factor for CHD.[237,238] It raises risk for CHD in several ways, notably by augmenting the lipid and nonlipid risk factors of the metabolic

syndrome. It further enhances risk by impairing cardiovascular fitness and coronary blood flow. Regular physical activity can help reverse these adverse effects. It can have favorable effects on the metabolic syndrome and can reduce VLDL levels, raise HDL cholesterol and, in some persons, lower LDL levels. Regular physical activity lowers blood pressure and reduces insulin resistance. It also has been reported to reduce risk for CHD independently of standard risk factors. The evidence base for the recommendation of increased physical activity as part of cholesterol management is presented in the U.S. Surgeon General's Report on Physical Activity[238] and will not be detailed in this report. The purposes of regular exercise are to promote energy balance to maintain healthy body weight, to alleviate the metabolic syndrome, and to independently reduce baseline risk for CHD. In certain circumstances, a physician has the option of referring a patient to an exercise specialist for prescription and guidance in exercise training. Exercise specialists can complement nutrition professionals in implementation of TLC by guiding individuals in a healthy exercise program.

5. Practical approach to life habit changes

a. Role of the physician

The physician is crucial to initiating and maintaining the patient's dietary adherence. Physician knowledge, attitude, and motivational skills will strongly influence the success of dietary therapy. A positive attitude combined with effective dietary assessment, initiation of therapy, and followup are essential for initial and long-term adherence. The physician should try to determine the patient's attitude towards acceptance of and commitment to TLC. The physician's key responsibilities include: assessment of CHD risk, dietary assessment, explanation of the problem for the patient, decision about appropriate therapeutic plan, and description of the plan to the patient. The multiple benefits of lifestyle changes should be emphasized. The need for lifestyle change, even when drugs are prescribed, should be stressed. In this section, one model for the role of the physician in the institution and followup of dietary therapy will be described. This model can be modified according to the constraints of the practice setting. The key feature of this model is the introduction of dietary therapy in a stepwise manner, beginning with an emphasis on lowering LDL cholesterol and followed by a shift in emphasis to management of the metabolic syndrome, if the latter is present. The essential steps in this model are shown in Figure V.2–1.

1) Visit 1: Risk assessment, diet assessment, and initiation of therapeutic lifestyle change

Some persons do not qualify for immediate clinical management to lower LDL because their LDL level is not above the goal for their category of risk for CHD (see Section III). Nonetheless, the physican should appropriately control other risk factors, provide a public health message on overall risk reduction, and prescribe subsequent lipoprotein reevaluation as needed. Suggestions to assist the physician in conveying the public health message are outlined in Table V.1–3.

For persons who require dietary therapy, the first step is assessment of lifestyle habits. CAGE questions provide the physician with a way to rapidly assess current intakes of LDL-raising nutrients (Table V.2–4). A more detailed tool for both assessment and as a guide to TLC is available in Table V.2–6. Therapeutic change in the first visit should begin with the TLC diet. If the patient demonstrates a lack of basic knowledge of the principles of the TLC diet, the physician should consider referral to a nutrition professional for medical nutrition therapy.

2) Visit 2: Intensifying the TLC diet for LDL cholesterol lowering

Approximately 6 weeks after starting the TLC diet, lipoprotein analysis is repeated and assessed. If the LDL cholesterol goal is achieved by 6 weeks, the patient should be commended for his/her adherence and encouraged to continue lifestyle changes (Figure V.2–1). If the LDL goal has not been achieved, the LDL-lowering TLC should be intensified. Depending upon the patient's level of dietary adherence, various options exist. More vigorous reduction in saturated fats and cholesterol, adding plant stanols/sterols (2 g/day), increasing viscous fiber (see Table V.2–5), and referral to a nutrition professional can all enhance LDL lowering.

The physician should not ignore the power of TLC to reduce CHD risk. Despite the marked advances in drug therapy for elevated LDL cholesterol level,

ATP III places increased emphasis on nutrition and physical activity for cholesterol management and overall risk reduction. The low prevalence of CHD in populations that consume low intakes of saturated fats and cholesterol and high intakes of other healthful nutrients, and who maintain desirable body weight through balanced caloric intake and output, illustrate what can be achieved without drug therapy.[632] Moreover, specifically for LDL cholesterol reduction, the combination of several dietary modifications can produce a reduction in LDL levels that rivals reductions produced by standard doses of statins. LDL cholesterol responses shown in Table V.5–2 represent conservative estimates based on the literature. Although cumulative responses have not been documented by clinical trial, a sizable summed response from the multiple components of TLC is likely.

Table V.5–2. Approximate and Cumulative LDL Cholesterol Reduction Achievable By Dietary Modification

Dietary Component	Dietary Change	Approximate LDL Reduction
Major		
Saturated fat	<7% of calories	8–10%
Dietary cholesterol	<200 mg/day	3–5%
Weight reduction	Lose 10 lbs	5–8%
Other LDL-lowering options		
Viscous fiber	5–10 g/day	3–5%
Plant sterol/ stanol esters	2g/day	6–15%
Cumulative estimate		20–30%

Adapted From Jenkins et al.[768]

3) Visit 3: Decision about drug therapy; initiating management of the metabolic syndrome

If the LDL cholesterol goal has not been achieved after 3 months of TLC, a decision must be made whether to consider adding drug therapy. If drugs are started, TLC should be continued indefinitely in parallel with drug treatment. Although the apparent ease of drug use is appealing, the additive effect of TLC to drug therapy in LDL cholesterol lowering is substantial and should not be overlooked. For example, Hunninghake et al.[769] reported an extra 5 percent lowering of LDL cholesterol when lovastatin therapy was combined with dietary therapy. This additional LDL cholesterol lowering equates to doubling the dose of the statin, due to the log-dose characteristics of statin usage. Other studies revealed a much greater LDL reduction when dietary therapy plus plant stanols were combined with statin therapy.[709,770] These dietary options, if successfully implemented, are preferable to progressively increasing doses of LDL-lowering drugs.

A second purpose of Visit 3 is to initiate lifestyle therapies for the metabolic syndrome, if it is present. Emphasis in TLC shifts to weight control and increased physical activity. The principles of weight control are described in the Obesity Education Initiative report.[78,79]

Because of the complexities and frequent failures of long-term weight control in clinical practice, consideration should be given to referring overweight or obese individuals to a qualified nutrition professional for medical nutrition therapy.

A second element of treatment of the metabolic syndrome is to increase physical activity. The physician should provide specific recommendations for physical activity depending on the patient's physical well-being and social circumstances. Consideration also can be given to referral to an exercise specialist for guidance if this resource is available. Moderate, sustained exercise can cause a significant reduction in baseline risk for CHD. Examples of moderate intensity exercise that may be useful to individuals are listed in Tables V.2–6 and V.5–3. Moderate intensity physical activity should be promoted for most people. Moderate amounts of vigorous activity also can be beneficial for some individuals, provided safety is ensured. Suggestions to incorporate more exercise into daily life are shown in Table V.5–4.

Table V.5–3. Examples of Moderate* Physical Activity in Healthy Adults†

- Brisk walking (3–4 mph) for 30–40 minutes
- Swimming—laps for 20 minutes
- Bicycling for pleasure or transportation, 5 miles in 30 minutes
- Volleyball (noncompetitive) for 45 minutes
- Raking leaves for 30 minutes
- Moderate lawn mowing (push a powered mower) for 30 minutes
- Home care—heavy cleaning
- Basketball for 15–20 minutes
- Golf—pulling a cart or carrying clubs
- Social dancing for 30 minutes

* Moderate intensity defined as 4–7 kcal/minute or 3–6 METS. METS (work metabolic rate/resting metabolic rate) are multiples of the resting rates of oxygen consumption during physical activity. One MET represents the approximate rate of oxygen consumption of a seated adult at rest, or about 3.5 mL per min per kg.

† This table was adapted from the recommendations of the Surgeon General's Report on Physical Activity and Health[238] and the Centers for Disease Control and Prevention and American College of Sports Medicine.[771]

Table V.5–4. Suggestions to Incorporate More Physical Activity into the Day

- Walk more—look for opportunities!
  - Park farther away in parking lots near a mall so you have a longer walk
  - Walk or bike if your destination is just a short distance away
  - Walk up or down 1–2 flights of stairs instead of always taking the elevator
  - Walk after work for 30 minutes before getting in the car and sitting in traffic
  - Walk home from the train or bus—take a longer route so it takes 20 minutes instead of 5–10 minutes
  - Walk with a colleague or friend at the start of your lunch hour for 20 minutes
- Do heavy house cleaning, push a stroller, or take walks with your children
- Exercise at home while watching television
- Go dancing or join an exercise program that meets several times per week
- If wheelchair bound, wheel yourself for part of every day in a wheelchair

4) Visit N: Long-term follow-up and monitoring adherence to therapeutic lifestyle changes (TLC)

The patient who has achieved the goal LDL cholesterol as a result of TLC must be monitored for the long term. TLC is maintained indefinitely and reinforced by the physician and, as appropriate, by a nutrition professional if medical nutrition therapy is necessary. The patient can be counseled quarterly for the first year of long-term monitoring and twice yearly thereafter.

LDL cholesterol is measured prior to each visit, and the results are explained at the counseling session. When no lipoprotein abnormalities other than elevated LDL cholesterol are present, monitoring at 6-month intervals is appropriate. If elevated cholesterol level redevelops, the procedure outlined above for diet therapy of elevated LDL cholesterol should be reinstituted.

Persons who fail to achieve their goal LDL cholesterol by dietary therapy can be classified as having an inadequate response to diet. Such responses fall into four categories:

- *Poor adherence.* Some persons adhere poorly to diet modification despite intensive and prolonged dietary counseling. They are not ready to change for various reasons. Physician endorsement of the importance of diet is essential for facilitating increased interest on the part of the patient. If the patient admits a lack of willingness to change diet or other life habits, drug therapy may be the only reasonable option to effectively lower LDL.
- *Gradual change.* Some individuals modify eating habits only gradually. They may adhere poorly to diet in the first few months but eventually will modify their eating habits to meet the goals of therapy. Up to a year of instruction and counseling may be required for these persons. This is especially true for persons who are following a weight reduction plan. Ongoing follow-up and reinforcement is crucial for developing long-term adherence. A continued effort to achieve adherence to life-habit changes should not be abandoned if drug therapy is started.
- *Poor responders.* A minority of persons are non-responders to dietary therapy and will have high LDL cholesterol levels that are inherently resistant to dietary modification despite good

adherence.[772-774] The mechanisms for this resistance are not well understood. Recognition of such persons is important, and care must be taken not to accuse them of failing to adhere to diet when they are non-responders. Drug therapy may be the only effective means of treatment of high blood cholesterol in such persons, but continued adherence to TLC is helpful for maintaining an overall healthful dietary pattern.

- *Inadequate responders.* Persons with severe elevations of LDL cholesterol often do respond to dietary therapy, but the cholesterol lowering achieved is inadequate to reach the LDL cholesterol goal. For such persons, a 3-month period of intensive diet therapy before adding drugs is not necessary.

b. Role of nurses, physician assistants, and pharmacists

Other health professionals associated with the physician facilitate patient management. The role of nutrition professionals is addressed in more detail below. Other health professionals—nurses, physician assistants, nurse clinicians, pharmacists, and other professionals—can participate in patient education (e.g., explaining the rationale for dietary change, goal setting, selection of appropriate foods, diet adherence), promoting behavioral changes, and monitoring dietary changes. These health professionals should receive appropriate training in dietary assessment, dietary education, and counseling. Hospital nurses play a vital role in guiding patients during hospital admissions for acute coronary events. NCEP and AHA offer various educational materials to assist in training health professionals.

c. Specific role of registered dietitians and other qualified nutrition professionals

Registered and/or licensed dietitians are certified providers of medical nutrition therapy (MNT), and qualify for Medicare reimbursement. Individual state licensure laws have established credentials for determining qualifications for nutrition counselors. Dietitians with expertise and experience in dietary counseling for lipid lowering can be especially effective in facilitating adherence to TLC. Registered dietitians and other licensed nutritionists can be located through local hospitals and state and district affiliates of the American Dietetic Association. The American Dietetic Association (www.eatright.org; 216 W. Jackson Blvd., Suite 800, Chicago, IL 60606-6995; 312-899-0040) maintains a roster of dietitians and responds to requests in writing or e-mail for assistance in locating a registered dietitian in a given area. Dietitians with particular expertise in cholesterol management are available in most large medical centers where they are often part of a multidisciplinary lipid clinic or cardiac rehabilitation team.

Medical nutrition therapy provided by a registered dietitian is a service that involves a comprehensive assessment of a patient's overall nutritional status, medical data, and diet history, followed by intervention to prescribe a personalized course of treatment.

The following medical nutrition therapy CPT Codes can be found in the American Medical Association Current Procedural Terminology: CPT 2001:[775]

- 97802 Medical nutrition therapy; initial assessment and intervention, individual face-to-face with the patient, 15 minutes each.
- 97803 Reassessment and intervention, individual face-to-face with the patient, 15 minutes each.
- 97804 Group (2 or more individual(s), 30 minutes each.

(For medical nutrition therapy assessment and/or intervention performed by a physician, see Evaluation and Management or Preventive Medicine service codes.)

CPT codes currently cover consideration of MNT for management of diabetes mellitus and renal disease.

1) Role of the nutrition professional in LDL-lowering therapy

When the physician chooses to consult a nutrition professional at Visits 1 or 2 for medical nutrition therapy, the goal is to enhance adherence to TLC. Medical nutrition therapy should start with dietary assessment, including the patient's motivational level and willingness to change. A dietary assessment questionnaire, MEDFICTS, which was originally developed for and printed in ATP II[1,2] is included in Diet Appendix A. Other cardiovascular dietary assessment tools are also available.[776-782] Proper assessment leads to a tailored dietary prescription. This

›rescription then goes to the physician, who can encourge adherence and monitor progress.

) First: dietary assessment

\ thorough and detailed assessment of the patient's :nowledge, attitudes, and behavior regarding diet is ssential for effective nutrition counseling. Assessment equires attention to dietary history, cultural influences, nd current eating habits. It also includes recording the ›atient's weight and weight history, BMI, and waist ircumference. The presence of abdominal obesity ›oints to the metabolic syndrome. To assess current ating habits, the following information is needed:

- What times of the day does the patient usually eat?
- Are some meals routinely skipped?
- At what time does the patient eat his/her largest meal?
- Where are meals typically prepared and eaten (e.g., in a restaurant, work cafeteria, fast-food restaurant, deli, at home, or in the homes of others)?
- Are there occasions when stress increases food consumption?
- Are meals eaten at home purchased out and brought in, prepared from processed pre-packaged foods, or prepared fresh from the market?
- Which are favorite foods and what foods are disliked?
- Who is responsible for food shopping and preparation?
- What foods will be most difficult to increase or decrease?
- How well does the patient recognize serving sizes?

The nutrition professional should assess the patient's general knowledge of nutrition as it relates to elevated LDL cholesterol, the ability to read labels, educational level, motivation, attitudes toward diet, and the extent to which family members can facilitate dietary changes.

) Dietary guidance on adopting the TLC Diet

To help patients adapt to the TLC Diet, the dietitian can:

- Focus on dietary patterns to facilitate LDL lowering. These patterns are consistent with the Dietary Guidelines for Americans (2000)[241] to achieve overall health and to further reduce baseline risk for CHD. This eating pattern is recommended for the entire family.
- Seek mutual agreement on an overall plan for diet modification as well as specific foods and eating habits that need to be changed. Emphasis goes first to dietary habits that affect LDL cholesterol levels. Highest on the list are foods rich in saturated fatty acids and cholesterol. The dietitian can review options for choosing preferred foods that lower LDL levels. The need for self-monitoring is reinforced; and simple approaches to tracking saturated fat, fiber, fruit, and vegetable intake are provided. Weight reduction includes learning how to control portion sizes. Also, documenting preparation and the quantities of different foods helps in long-term adherence. Practical teaching with measuring cups, spoons, food models, or even a food scale will enhance patient understanding. Keeping a food record during weekends and weekdays can facilitate discussion with the dietitian. Electronic (e-mail) links between dietitian and patient may enhance checking food records or reporting self-monitoring activities.
- Help patients identify sources of saturated fat in their usual diet, especially "hidden" fats in foods, such as baked goods, cheese, salad dressings, and other processed foods. Advice on alternative food choices, including snack foods, should be provided. For persons willing to prepare foods at home, appropriate techniques and cooking methods can be addressed. For those who eat out regularly, guidance on how to select from a menu and purchase premade take-out food should also be given.
- Apply motivational interviewing techniques to provide encouragement and to empower patients to choose wisely on different eating occasions. Gradual, step-wise changes in current eating habits are more likely to achieve long-term adherence than drastic changes. Starting with a specific food or food group, such as the type of milk used, how to reduce portion size of meats, how to substitute egg whites for whole eggs in baking, or how to use margarines and oils in the place of fats rich in saturated fatty acids are excellent topics to pursue. The dietitian should involve other individuals of significance (e.g., parents, spouse, and children) in dietary instructions.
- Recommend a variety of foods from all food groups to help achieve adequate nutrient intake: vegetables, fruits, grain products, potatoes and

legumes, dairy products, and lean meat, poultry, and fish. Use of specially prepared processed foods, fat-free or fat modified snacks, desserts, etc. is not necessary, although some persons find these food choices appealing.

- Promote use of the Nutrition Facts food label to help patients learn to gauge saturated fat and cholesterol intakes. Saturated fat amounts listed on the Nutrition Facts food label correspond to 10 percent of calories; still lower intakes are needed to attain <7 percent. Persons should should be taught to routinely read the labels of all processed foods.

c) Specific foods and preparation techniques

Recommended food choices for the TLC Diet are summarized in Table V.2–6. This diet can be both tasty and nutritious. Many choices of high-quality and recommended foods are available in supermarkets, restaurants and as take-out options.

To decrease intake of saturated fat, total fat, and cholesterol, the emphasis of the diet should be on consumption of vegetables; fruits; breads, cereals, rice, legumes, and pasta; skim milk and skim milk products; and poultry, fish, and lean meat. There are many different eating styles in the United States that reflect diverse cultures and practices. Special attention to unique dietary preferences based on diverse cultures and eating habits can facilitate adoption of the TLC Diet. Sample menus are presented in Diet Appendix B.

Food preparation techniques should emphasize lower fat cooking and preparation methods (broiling, baking, grilling, steaming, poaching without added fat, trimming fat from meat, draining fat after cooking, and removing skin from poultry). Liquid vegetable oils high in unsaturated fatty acids (e.g. canola, corn, olive, rice bran, safflower, soybean, sunflower) are recommended in moderation. Since the major sources of saturated fat and total fat in the American diet are meat and high-fat dairy products, and since these foods as well as eggs are the major sources of dietary cholesterol, persons should limit consumption of foods containing butterfat such as whole milk (3.5 percent fat) and even reduced fat (2 percent) milk, butter, cheese, ice cream, cream, and pizza; fatty meats such as regular ground beef (hamburger), processed meats (hot dogs, sausage, bacon), and high-fat luncheon meats (bologna, salami, chopped ham products), as well as poultry skin. Low-saturated-fat substitutes, such as fat-free or 1 percent milk, soft margarine, low-fat cottage cheese, or low-fat or fat-free "ice cream" can be used. Egg yolks should be limited to 2 per week. Organ meats (liver, brain, sweetbreads) are rich sources of cholesterol and should be limited. Of the shellfish, only shrimp is moderately high in cholesterol and inclusion in the diet should be guided by the daily dietary cholesterol allowance. The vegetable oils rich in saturated fat—coconut oil, palm kernel oil, and palm oil—are used in some commercial foods and food products. Choose products that are labeled low saturated fat, e.g., 1 gram of saturated fat per serving, and meats that are labeled as lean.

Although persons need not purchase special foods for implementation of the TLC Diet, many new fat-modified products on the market may facilitate adherence to the TLC Diet.

d) Recommendations by food group

The following information about specific food choices can help persons adopt the TLC Diet.

- Breads, cereals, pasta, whole grains, potatoes, rice, dry peas, and beans (6 or more servings per day). These foods are high in complex carbohydrates and fiber, provide protein, and also are generally low in saturated fat, cholesterol, and total fat. Dry beans and peas are good sources of plant protein and are fiber-rich. They should be substituted for foods high in saturated fat, cholesterol, and total fat. Cereals can be eaten as snacks as well as for breakfast. Dry peas, beans, and legumes can be used in nutritious, tasty, lower fat entrees or accompaniments. Pasta, potatoes, rice, and vegetables can be combined with smaller amounts of lean meat, fish, or poultry for a tasty main dish that can provide less saturated fat and calories.
- Fruits and vegetables (5 or more servings per day). Fruits, vegetables, or both should be emphasized at each meal. They are major sources of vitamins C, E, and A, beta-carotene, other vitamins, fiber, and some minerals, and contribute to achieving the recommended allowances of these nutrients. Snacks and desserts that feature fruits and/or vegetables can be low in saturated fat, total fat, and cholesterol, and very nutritious.

- Fat-free or 1 percent dairy products (2–3 servings per day). Dairy products are important sources of protein, calcium, phosphorus, and vitamin D. Fat-free milk and other fat-free or low-fat dairy products provide as much or more calcium and protein than whole milk dairy products, with little or no saturated fat. Fat-free milk or 1 percent fat milk, fat-free or low-fat cheese (e.g., ≤3g per 1 oz serving), 1 percent fat cottage cheese or imitation cheeses made from vegetable oils, and fat-free or low-fat yogurt are good choices. It should be noted that 2 percent fat dairy products are still rich in saturated fat. Evaporated fat-free milk can be used in recipes calling for heavy cream. Low-fat or fat-free yogurt, 1 percent fat cottage cheese, and fat-free sour cream substitutes can replace sour cream in dips and salad dressings.
- Lean meats (beef, pork, and lamb), poultry, and fish (up to 5 oz per day). Lean cuts of beef include sirloin tip, round steak, rump roast, arm roast and, for pork, center-cut ham, loin chops, and tenderloin. All visible fat should be trimmed before cooking. Ground meat should be extra-lean and drained well after cooking. Meat can be ground at home or a butcher can grind very lean, well trimmed cuts of meat such as those that come from the round. Ground turkey, which can be seasoned and used like ground beef, is very lean if it does not contain turkey skin and fat. Both lean ground meat and ground turkey can be incorporated into soups, stews, and casseroles that contain grain products and vegetables. Special reduced-fat ground meat products (e.g., with carrageenan) may be selected. It is not necessary to eliminate or drastically reduce lean red meat consumption. Lean meat is rich in protein, contains a highly absorbable iron (Fe^{++}), and is a good source of zinc and vitamin B_{12}. Lean meat can contribute to maintenance of iron stores in premenopausal women.
  - Soy products. Foods containing soy-based meat analogues can be substituted in part for meat products.
  - Processed meats. Processed meats, such as lunch meat, bacon, bologna, salami, sausage, and frankfurters generally have a high content of saturated fat and sodium. Several new processed meat products are lower in saturated fat, total fat, and cholesterol. Read the Nutrition Facts food label to choose foods low in saturated fat, cholesterol, and sodium.
  - Organ meats. Liver, sweetbreads, kidneys, and brain have a high cholesterol content and should be used only occasionally.
  - Chicken and turkey. These are good sources of lean protein. Removing the skin and underlying fat layers substantially reduces the fat content. Chicken and turkey can be substituted for some of the lean red meat in the diet, but they do not contain as much iron. Chicken and other poultry should be prepared in ways that minimize the addition of saturated fat.
  - Fish. Fish are low in saturated fat, some are high in n-3 fatty acids (see Diet Appendix C), and they are a good source of lean protein. The preparation of fish is important. Like chicken and turkey, it should be prepared to limit additional saturated fat.
  - Shellfish. Shellfish are low in saturated fat. The cholesterol content of shellfish is variable (see Diet Appendix C). Shrimp are relatively high in cholesterol, but can be eaten occasionally.

About 5 ounces of fish, poultry, or meat per day can be included on the TLC Diet as 2 servings, each serving about the size of a deck of playing cards. A serving of meat in a restaurant often exceeds 5 ounces. (The saturated fat, total fat, and cholesterol content of various cooked meats are presented in Diet Appendix C).

- Fats and oils (including fats and oils used in food preparation). Fats high in saturated fat, *trans* fat, and cholesterol must be limited. This includes lard and meat fat. Some vegetable fats—coconut oil, palm kernel oil, and palm oil—are high in saturated fat and should be avoided; they often are used in bakery goods, processed foods, popcorn oils, and nondairy creamers. The Nutrition Facts food label is a guide for choosing fats and oils lowest in saturated fat. Hydrogenated shortenings and hard margarines are sources of *trans* fat and should be reduced. Vegetable oils and fats high in unsaturated fat do not raise blood cholesterol, but they have a high caloric density. These include canola oil, corn oil, olive oil, safflower oil, soybean oil, and sunflower oil. Margarine contains some *trans* fat but has less cholesterol-raising potential than butter, and thus is preferable to butter. In general, the softer the

margarine, the less LDL-cholesterol-raising potential it has. Hydrogenated shortening contains *trans* fat, resembles hard margarines, and should be limited. Hydrogenated shortenings are found in many commercially prepared baked foods, such as crackers, cookies, doughnuts, and desserts. There are many reduced fat margarines, vegetable oil spreads, and low-fat and fat-free salad dressings on the market. The Nutrition Facts food label provides the amount of fat and saturated fat per serving.

- Nuts. Nuts are high in fat, but in most nuts the predominant fats are unsaturated. The intake of nuts should fit within the calorie and fat goal.
- Eggs. Egg yolks are high in cholesterol (~215 mg/egg) and should be limited to no more than two egg yolks per week. Egg yolks often are found in cooked and processed foods. Egg whites contain no cholesterol, and they can be eaten often. Egg whites or commercial egg substitutes or reduced-cholesterol egg products can replace whole eggs in many recipes.

e) *Other eating tips*

- Snacks. Some choices for snacks that are low in saturated fat are graham crackers, rye crisp, melba toast, pretzels, low-fat or fat-free crackers, bread sticks, bagels, English muffins, fruit, ready-to-eat cereals, and vegetables; fat-free corn chips and potato chips can be made at home or purchased in some stores. Popcorn should be air popped or cooked in small amounts of vegetable oil. Low-fat cookies include animal crackers, fig and other fruit bars, ginger snaps, and molasses cookies.
- Desserts and sweets. Moderate amounts of sweets and modified-fat desserts (low in saturated fat) may be chosen. For example, fruits, low-fat or fat-free fruit yogurt, fruit ices, sherbet, angel food cake, jello, frozen low-fat or fat-free yogurt, and low-fat ice cream. Cookies, cakes, and pie crusts can be made using unsaturated oil or soft margarines, egg whites or egg substitutes, and fat-free milk. Candies with little or no fat include hard candy, gumdrops, jelly beans, and candy corn. Read the Nutrition Facts food label to choose those products lowest in saturated fat and calories.
- Cooking methods. Methods that use little or no fat include steaming, baking, broiling, grilling, or stir frying in small amounts of fat. Cook foods in the microwave or in a nonstick pan without added fat. Foods may be pan fried with limited fat. Soups and stews should be chilled for a few hours, and the congealed fat removed. Salt should be limited in the preparation of soups, stews, and other dishes. Herbs and spices can often be used instead of salt to help prevent or control high blood pressure.
- Eating away from home. Choose entrees, potatoes, and vegetables prepared without sauces, cheese, or butter when eating away from home. Eat only a small portion of meat. Choose vegetable or fruit salads, with salad dressings on the side. Limit toppings, such as chopped eggs, crumbled bacon, and cheese. Request soft margarine instead of butter, and use it sparingly.

A reference work on food and nutrition may be useful to patients. One available reference is the USDA's Home and Garden Bulletin No. 72, Nutritive Value of Foods.[783] In addition, a typical 1-day menu for TLC Diets for both men and women which displays different eating patterns is included in Diet Appendix B.

2) *Role of the dietitian in management of the metabolic syndrome*

After LDL cholesterol is controlled, medical nutrition therapy turns attention to the metabolic syndrome. Strategies for weight reduction described in the Obesity Education Initiative report (also see www.nhlbi.nih.gov) are helpful.[78,79] Weight reduction and dietary change introduced in medical nutrition therapy aim to achieve and maintain goals for LDL cholesterol as well as glucose and blood pressure. Hypocaloric diets, increased physical activity, and weight loss usually improve levels of LDL cholesterol, glycemic levels, and blood pressure and have the potential to improve long-term metabolic control. The distribution of calories from total fat and carbohydrate can vary (see Table V.2–2) and can be individualized based on the nutrition assessment and treatment goals.

6. Improving patient adherence to life habit changes

Outpatient studies show that variability in lipoprotein responsiveness to diet is often due to poor compliance. Good compliance is hampered in part by increased consumption of foods prepared away from home. In 1995 about 40 percent of the food budget was spent on food prepared away from home, compared with 25 percent in 1970.[784] The consumer has less knowledge of and less control over the nutritional content of food prepared away from home. Moreover, calories, saturated fat, and cholesterol tend to be higher in premade food than food prepared at home.[784] Food prepared away from home usually does not carry nutrition labeling. Barriers to adherence to dietary therapy must be addressed and reasonable solutions provided. Physicans in general report little confidence in the patients' ability to adhere to dietary change. In one survey, 17 percent of physicians reported that most patients complied, 59 percent reported that some complied, and 22 percent estimated that few patients complied.

Lack of adequate nutrition education in medical schools has been a contributing factor to low adherence to dietary therapy that fortunately is now being addressed. The newly implemented NHLBI-funded Nutrition Academic Award Program is now underway in 21 U.S. medical schools. This program provides training in nutritional assessment and counseling for medical students and other health professionals in training.[785] Other barriers, such as lack of time, lack of adequate referral strategies, lack of third party reimbursement, and competition with pharmacological intervention are also being addressed.[786]

Beyond these systemic problems, a validated methodology related to effective nutritional assessment and intervention is lacking. Ready access to a brief dietary assessment tool and accompanying follow up assessments are as yet not standard practice for most physicians. Advances have been made in the past decade regarding the combined use of behavioral strategies along with standardized diet assessment and intervention approaches.[776-782] (See Appendix A for an example of a validated assessment tool.)

There is growing evidence from the behavioral therapy literature that strategic approaches to lifestyle intervention can achieve better and more consistent long-term adherence.[787-789] These strategies are based on learning principles that address the need to overcome barriers to adherence with lifestyle change and reinforce newly adopted behaviors.[789-791] The vast majority of these studies appear in the weight management field.[792] The Obesity Guidelines panel reviewed 36 randomized clinical trial reports to determine potential benefits of behavioral therapy.[78,79] Key findings from these studies are summarized below:

- Multimodal strategies work better than a single approach.
- More frequent contact is associated with better adherence.
- Adherence declines with discontinued intervention or followup.
- Greater intensity of intervention, especially initially, is associated with faster and more sustained adherence.
- Motivation is enhanced when the patient sets achievable goals.

Further lessons learned from the behavioral literature emphasize the importance of baseline assessment of dietary intake, use of self-monitoring to improve adherence, and use of health messages that are matched to level of readiness to change, culturally sensitive, interactive, address prior knowledge, come from reliable sources, and recommend reasonable, gradual, and easily implemented change. Additional research is needed with measures of the efficacy and effectiveness of office-based dietary assessment methodology, especially as this relates to behavioral strategies enhancing dietary adherence.

Diet Appendix A

Sample Dietary Assessment Questionaire
MEDFICTS*

In each food category for both Group 1 and Group 2 foods check one box from the "Weekly Consumption" column (number of servings eaten per week) and then check one box from the "Serving Size" column. If you check Rarely/Never, do not check a serving size box. See next page for score.

Food Category	Weekly Consumption				Serving Size			Score
	Rarely/ never	3 or less	4 or more		Small <5 oz/d 1 pt	Average 5 oz/d 2 pts	Large >5 oz/d 3 pts	
Meats								
■ Recommended amount per day: ≤5 oz (equal in size to 2 decks of playing cards). ■ Base your estimate on the food you consume most often. ■ Beef and lamb selections are trimmed to 1/8" fat.								
Group 1. 10g or more total fat in 3 oz cooked portion **Beef –** Ground beef, Ribs, Steak (T-bone, Flank, Porterhouse, Tenderloin), Chuck blade roast, Brisket, Meatloaf (w/ground beef), Corned beef **Processed meats –** 1/4 lb burger or lg. sandwich, Bacon, Lunch meat, Sausage/knockwurst, Hot dogs, Ham (bone-end), Ground turkey **Other meats, Poultry, Seafood –** Pork chops (center loin), Pork roast (Blade, Boston, Sirloin), Pork spareribs, Ground pork, Lamb chops, Lamb (ribs), Organ meats†, Chicken w/skin, Eel, Mackerel, Pompano	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Less than 10g total fat in 3 oz cooked portion **Lean beef –** Round steak (Eye of round, Top round), Sirloin‡, Tip & bottom round‡, Chuck arm pot roast‡, Top Loin‡ **Low-fat processed meats –** Low-fat lunch meat, Canadian bacon, "Lean" fast food sandwich, Boneless ham **Other meats, Poultry, Seafood –** Chicken, Turkey (w/o skin)§, most Seafood†, Lamb leg shank, Pork tenderloin, Sirloin top loin, Veal cutlets, Sirloin, Shoulder, Ground veal, Venison, Veal chops and ribs‡, Lamb (whole leg, loin, fore-shank, sirloin)‡	☐	☐	☐	x	☐	☐	☐ ¥ 6 pts	
Eggs – Weekly consumption is the number of times you eat eggs each week					Check the number of eggs eaten each time			
					≤1	2	≥3	
Group 1. Whole eggs, Yolks	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Egg whites, Egg substitutes (1/2 cup)	☐	☐	☐		☐	☐	☐	
Dairy								
Milk – Average serving 1 cup **Group 1.** Whole milk, 2% milk, 2% buttermilk, Yogurt (whole milk)	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Fat-free milk, 1% milk, Fat-free buttermilk, Yogurt (Fat-free, 1% low fat)	☐	☐	☐		☐	☐	☐	
Cheese – Average serving 1 oz **Group 1.** Cream cheese, Cheddar, Monterey Jack, Colby, Swiss, American processed, Blue cheese, Regular cottage cheese (1/2 cup), and Ricotta (1/4 cup)	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Low-fat & fat-free cheeses, Fat-free milk mozzarella, String cheese, Low-fat, Fat-free milk & Fat-free cottage cheese (1/2 cup) and Ricotta (1/4 cup)	☐	☐	☐		☐	☐	☐	
Frozen Desserts – Average serving 1/2 cup **Group 1.** Ice cream, Milk shakes	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Low-fat ice cream, Frozen yogurt	☐	☐	☐		☐	☐	☐	

FIG MEDFICTS assessment tool.

* MEDFICTS was orginally developed for and printed in ATP II[1,2]

Sample Dietary Assessment Questionaire (Continued)
MEDFICTS*

Food Category	Weekly Consumption: Rarely/never	3 or less	4 or more	Serving Size: Small <5 oz/d 1 pt	Average 5 oz/d 2 pts	Large >5 oz/d 3 pts	Score
Frying Foods – Average servings: see below. This section refers to method of preparation for vegetables and meat.							
Group 1. French fries, Fried vegetables (1/2 cup), Fried chicken, fish, meat (3 oz)	☐	☐ 3 pts	☐ 7pts	x ☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Vegetables, not deep fried (1/2 cup), Meat, poultry, or fish—prepared by baking, broiling, grilling, poaching, roasting, stewing: (3 oz)	☐	☐	☐	☐	☐	☐	
In Baked Goods – 1 Average serving							
Group 1. Doughnuts, Biscuits, Butter rolls, Muffins, Croissants, Sweet rolls, Danish, Cakes, Pies, Coffee cakes, Cookies	☐	☐ 3 pts	☐ 7pts	x ☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Fruit bars, Low-fat cookies/cakes/pastries, Angel food cake, Homemade baked goods with vegetable oils, breads, bagels	☐	☐	☐	☐	☐	☐	
Convenience Foods							
Group 1. Canned, Packaged, or Frozen dinners: e.g., Pizza (1 slice), Macaroni & cheese (1 cup), Pot pie (1), Cream soups (1 cup), Potato, rice & pasta dishes with cream/cheese sauces (1/2 cup)	☐	☐ 3 pts	☐ 7pts	x ☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Diet/Reduced calorie or reduced fat dinners (1), Potato, rice & pasta dishes without cream/cheese sauces (1/2 cup)	☐	☐	☐	☐	☐	☐	
Table Fats – Average serving: 1 Tbsp							
Group 1. Butter, Stick margarine, Regular salad dressing, Mayonnaise, Sour cream (2 Tbsp)	☐	☐ 3 pts	☐ 7pts	x ☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Diet and tub margarine, Low-fat & fat-free salad dressing, Low-fat & fat-free mayonnaise	☐	☐	☐	☐	☐	☐	
Snacks							
Group 1. Chips (potato, corn, taco), Cheese puffs, Snack mix, Nuts (1 oz), Regular crackers (1/2 oz), Candy (milk chocolate, caramel, coconut) (about 1 1/2 oz), Regular popcorn (3 cups)	☐	☐ 3 pts	☐ 7pts	x ☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Pretzels, Fat-free chips (1 oz), Low-fat crackers (1/2 oz), Fruit, Fruit rolls, Licorice, Hard candy (1 med piece), Bread sticks (1–2 pcs), Air-popped or low-fat popcorn (3 cups)	☐	☐	☐	☐	☐	☐	

† Organ meats, shrimp, abalone, and squid are low in fat but high in cholesterol.
‡ Only lean cuts with all visible fat trimmed. If not trimmed of all visible fat, score as if in Group 1.
¥ Score 6 pts if this box is checked.
§ All parts not listed in group 1 have <10g total fat.

Total from page 1 _____

Total from page 2 _____

Final Score _____

To Score: For each food category, multiply points in weekly consumption box by points in serving size box and record total in score column. If Group 2 foods checked, no points are scored (except for Group 2 meats, large serving = 6 pts).

Example:

☐	☐ 3 pts	☑ 7 pts	x	☐ 1 pt	☐ 2 pts	☑ 3 pts

21 pts

Add score on page 1 and page 2 to get final score.

Key:
≥70 Need to make some dietary changes
40–70 Heart-Healthy Diet
<40 TLC Diet

FIG. MEDFICTS assessment tool.
* MEDFICTS was orginally developed for and printed in ATP II[1,2]

TLC Sample Menu
Traditional American Cuisine
Male, 25–49 Years

Breakfast
- Oatmeal (1 cup)
  - Fat-free milk (1 cup)
  - Raisins (1/4 cup)
- English muffin (1 medium)
  - Soft margarine (2 tsp)
  - Jelly (1 Tbsp)
- Honeydew melon (1 cup)
- Orange juice, calcium fortified (1 cup)
- Coffee (1 cup) with fat-free milk (2 Tbsp)

Lunch
- Roast beef sandwich
  - Whole-wheat bun (1 medium)
  - Roast beef, lean (2 oz)
  - Swiss cheese, low fat (1oz slice)
  - Romaine lettuce (2 leaves)
  - Tomato (2 medium slices)
  - Mustard (2 tsp)
- Pasta salad (1 cup)
  - Pasta noodles (3/4 cup)
  - Mixed vegetables (1/4 cup)
- Olive oil (2 tsp)
- Apple (1 medium)
- Iced tea, unsweetened (1 cup)

Dinner
- Orange roughy (3 oz) cooked with olive oil (2 tsp)
  - Parmesan cheese (1 Tbsp)
- Rice* (1 1/2 cup)
- Corn kernels (1/2 cup)
  - Soft margarine (1 tsp)
- Broccoli (1/2 cup)
  - Soft margarine (1 tsp)
- Roll (1 small)
  - Soft margarine (1 tsp)
- Strawberries (1 cup) topped with low-fat frozen yogurt (1/2 cup)
- Fat-free milk (1 cup)

Snack
- Popcorn (2 cups) cooked with canola oil (1 Tbsp)
- Peaches, canned in water (1 cup)
- Water (1 cup)

Nutrient Analysis

Calories	2523
Cholesterol (mg)	139
Fiber (g)	32
Soluble (g)	10
Sodium (mg)	1800
Carbohydrates, % calories	57

Total fat, % calories	28
Saturated fat, % calories	6
Monounsaturated fat, % calories	14
Polyunsaturated fat, % calories	6
Trans fat (g)	5
Omega 3 fat (g)	0.4
Protein, % calories	17

***Higher Fat Alternative**

Total fat, % calories	34

No salt is added in recipe preparation or as seasoning. The sample menu meets or exceeds the Daily Reference Intake (DRI) for nutrients.

** For a higher fat alternative, substitute 1/3 cup of unsalted peanuts, chopped (to sprinkle on the frozen yogurt) for 1 cup of the rice.*

TLC Sample Menu
Traditional American Cuisine
Female, 25–49 Years

Breakfast
- Oatmeal (1 cup)
  - Fat-free milk (1 cup)
  - Raisins (1/4 cup)
- Honeydew melon (1 cup)
- Orange juice, calcium fortified (1 cup)
- Coffee (1 cup) with fat-free milk (2 Tbsp)

Lunch
- Roast beef sandwich
  - Whole-wheat bun (1 medium)
  - Roast beef, lean (2 oz)
  - Swiss cheese, low fat (1 oz slice)
  - Romaine lettuce (2 leaves)
  - Tomato (2 medium slices)
  - Mustard (2 tsp)
- Pasta salad (1/2 cup)
  - Pasta noodles (1/4 cup)
  - Mixed vegetables (1/4 cup)
  - Olive oil (1 tsp)
- Apple (1 medium)
- Iced tea, unsweetened (1 cup)

Dinner
- Orange roughy (2 oz) cooked with olive oil (2 tsp)
  - Parmesan cheese (1 Tbsp)
- Rice* (1 cup)
  - Soft margarine (1 tsp)
- Broccoli (1/2 cup)
  - Soft margarine (1 tsp)
- Strawberries (1 cup) topped with low-fat frozen yogurt (1/2 cup)
- Water (1 cup)

Snack
- Popcorn (2 cups) cooked with canola oil (1 Tbsp)
- Peaches, canned in water (1 cup)
- Water (1 cup)

Nutrient Analysis

Calories	1795	Total fat, % calories	27
Cholesterol (mg)	115	Saturated fat, % calories	6
Fiber (g)	28	Monounsaturated fat, % calories	14
Soluble (g)	9	Polyunsaturated fat, % calories	6
Sodium (mg)	1128	Trans fat (g)	2
Carbohydrates, % calories	57	Omega 3 fat (g)	0.4
		Protein, % calories	19

***Higher Fat Alternative**

Total fat, % calories	33

No salt is added in recipe preparation or as seasoning. The sample menu meets or exceeds the Daily Reference Intake (DRI) for nutrients.

** For a higher fat alternative, substitute 2 Tbsp of unsalted peanuts, chopped (to sprinkle on the frozen yogurt) for 1/2 cup of the rice.*

TLC Sample Menu
Lacto Ovo Vegetarian Cuisine
Male, 25–49 Years

Breakfast
- Egg white omelet, cooked with canola oil (2 tsp)
  - Liquid egg substitute (1/2 cup)
  - Tomato, chopped (1 medium slice)
  - Mushrooms, chopped (2 medium)
  - Green pepper, chopped (1/4 cup)
  - Cheddar cheese, low fat, grated (2 Tbsp)
- English muffin (1 whole)
  - Jelly (1 Tbsp)
- Honeydew melon (1/2 cup)
- Orange juice, calcium fortified (1 cup)
- Coffee (1 cup) with fat-free milk (2 Tbsp)

Lunch
- Vegetable sandwich
  - Onion roll (1 medium)
  - Tomato (2 medium slices)
  - Avocado slices, dark skin, California type (1/3 of small fruit)
  - Romaine lettuce (2 leaves)
  - Carrots, grated (1/2 cup)
  - Cheddar cheese, low fat (1 slice, 1 oz)
  - Mustard (1 Tbsp)
- Salad
  - Romaine lettuce (2 cups)
  - Kidney beans* (3/4 cup)
  - Tomato, cherry (1/2 cup)
  - Cucumber (1/3 cup)
  - Carrots, shredded (1/3 cup)
  - Dressing, homemade vinegar and olive oil (2 Tbsp)
- Fat-free milk (1 cup)

Dinner
- Pasta and Vegetables
  - Spaghetti, cooked (2 cups), with olive oil (1 Tbsp)
  - Broccoli (1 cup)
  - Marinara sauce, low sodium (3/4 cup)
  - Parmesan cheese (1 1/2 Tbsp)
- Angel food cake (2x3 inch piece)
  - Frozen yogurt (1/4 cup)
  - Chocolate sauce (1 Tbsp)
- Iced tea, unsweetened (1 cup)

Snack
- Bagel (1/2 medium)
  - Peanut butter, reduced fat, unsalted (1/2 Tbsp)
- Apple (1 medium)
- Water (1 cup)

Nutrient Analysis

Calories	2499
Cholesterol (mg)	24
Fiber (g)	44
Soluble (g)	17
Sodium (mg)	2282
Carbohydrates, % calories	60
Total fat, % calories	29
Saturated fat, % calories	5
Monounsaturated fat, % calories	16
Polyunsaturated fat, % calories	5
Trans fat (g)	0.4
Protein, % calories	15

***Higher Fat Alternative**

Total fat, % calories	33

No salt is added in recipe preparation or as seasoning. The sample menu meets or exceeds the Daily Reference Intake (DRI) for nutrients.

**For a higher fat alternative, substitute 1/3 cup of unsalted almond slices for 1/2 cup of the kidney beans in the salad.*

TLC Sample Menu
Lacto Ovo Vegetarian Cuisine
Female, 25–49 Years

Breakfast
- Egg white omelet, cooked with canola oil (2 tsp)
  - Liquid egg substitute (1/2 cup)
  - Tomato, chopped (1 medium slice)
  - Mushrooms, chopped (2 medium)
  - Green pepper, chopped (1/4 cup)
  - Cheddar cheese, low fat, grated (2 Tbsp)
- Whole-wheat toast (1 slice)
  - Jelly (2 tsp)
- Honeydew melon (1/2 cup)
- Coffee (1 cup) with fat-free milk (2 Tbsp)

Lunch
- Vegetable Sandwich
  - Onion roll (1 medium)
  - Tomato (2 medium slices)
  - Romaine lettuce (2 leaves)
  - Carrots, grated (1/2 cup)
  - Cheddar cheese, low fat (1 slice, 1 oz)
  - Mustard (1 Tbsp)
- Salad
- Romaine lettuce (2 cups)
- Kidney beans* (1/2 cup)
  - Tomato, cherry (1/2 cup)
  - Cucumber (1/3 cup)
  - Carrots, shredded (1/3 cup)
  - Dressing, homemade—vinegar and olive oil (2 Tbsp)
- Fat-free milk (1 cup)

Dinner
- Pasta and Vegetables
  - Spaghetti, cooked (1 cup), with olive oil (1/2 Tbsp)
  - Broccoli (1 cup)
  - Marinara sauce, low sodium (1/2 cup)
  - Parmesan cheese (1 Tbsp)
- Angel food cake (2x3 inch piece)
  - Frozen yogurt (1/4 cup)
  - Chocolate sauce (1 Tbsp)
- Iced tea, unsweetened

Snack
- Bagel (1/2 medium)
  - Peanut butter, reduced fat, unsalted (1/2 Tbsp)
- Water (1 cup)

Nutrient Analysis

Calories	1812
Cholesterol (mg)	26
Fiber (g)	30
Soluble (g)	12
Sodium (mg)	2205
Carbohydrates, % calories	58
Total fat, % calories	27
Saturated fat, % calories	5
Monounsaturated fat, % calories	15
Polyunsaturated fat, % calories	4
Trans fat (g)	1
Protein, % calories	18

***Higher Fat Alternative**

Total fat, % calories	33

No salt is added in recipe preparation or as seasoning. The sample menu meets or exceeds the Daily Reference Intake (DRI) for nutrients.

** For a higher fat alternative, substitute 1/4 cup of unsalted almond slices for all of the kidney beans in the salad.*

TLC Sample Menu
Southern Cuisine
Male, 25–49 Years

Breakfast
- Bran cereal (3/4 cup)
  - Banana (1 medium)
  - Fat-free milk (1 cup)
- Biscuit, made with canola oil (1 medium)
  - Jelly (1 Tbsp)
  - Soft margarine (2 tsp)
- Honeydew melon (1 cup)
- Orange juice, calcium fortified (1 cup)
- Coffee (1 cup) with fat-free milk (2 Tbsp)

Lunch
- Chicken breast (3 oz), sautéed with canola oil (2 tsp)
- Collard greens (1/2 cup)
  - Chicken broth, low sodium (1 Tbsp)
- Black-eyed peas (1/2 cup)
  - Corn on the cob* (1 medium)
  - Soft margarine (1 tsp)
- Rice, cooked (1 cup)
  - Soft margarine (1 tsp)
- Fruit cocktail, canned in water (1 cup)
- Iced tea, unsweetened (1 cup)

Dinner
- Catfish (3 oz) coated with flour and baked with canola oil (1/2 Tbsp)
- Sweet potato (1 medium)
  - Soft margarine (2 tsp)
- Spinach (1/2 cup)
  - Vegetable broth, low sodium (2 Tbsp)
- Corn muffin (1 medium), made with fat-free milk and egg substitute
  - Soft margarine (1 tsp)
- Watermelon (1 cup)
- Iced tea, unsweetened (1 cup)

Snack
- Bagel (1 medium)
  - Peanut butter, reduced fat, unsalted (1 Tbsp)
- Fat-free milk (1 cup)

Nutrient Analysis

Calories	2504	Total fat, % calories	30
Cholesterol (mg)	158	Saturated fat, % calories	5
Fiber (g)	52	Monounsaturated fat, % calories	13
Soluble (g)	10	Polyunsaturated fat, % calories	9
Sodium (mg)	2146	Trans fat (g)	6
Carbohydrates, % calories	59		
		Protein, % calories	18

***Higher Fat Alternative**

Total fat, % calories	34

No salt is added in recipe preparation or as seasoning. The sample menu meets or exceeds the Daily Reference Intake (DRI) for nutrients.

** For a higher fat alternative, substitute 1/4 cup of unsalted almond slices for the corn on the cob. Sprinkle the almonds on the rice.*

TLC Sample Menu
Southern Cuisine
Female, 25–49 Years

Breakfast
- Bran cereal (3/4 cup)
  - Banana (1 medium)
  - Fat-free milk (1 cup)
- Biscuit, low sodium and made with canola oil (1 medium)
  - Jelly (1 Tbsp)
  - Soft margarine (1 tsp)
- Honeydew melon (1/2 cup)
- Coffee (1 cup) with fat-free milk (2 Tbsp)

Lunch
- Chicken breast (2 oz) cooked with canola oil (2 tsp)
- Corn on the cob* (1 medium)
  - Soft margarine (1 tsp)
- Collards greens (1/2 cup)
  - Chicken broth, low sodium (1 Tbsp)
- Rice, cooked (1/2 cup)
- Fruit cocktail, canned in water (1 cup)
- Iced tea, unsweetened (1 cup)

Dinner
- Catfish (3 oz), coated with flour and baked with canola oil (1/2 Tbsp)
- Sweet potato (1 medium)
  - Soft margarine (2 tsp)
- Spinach (1/2 cup)
  - Vegetable broth, low sodium (2 Tbsp)
- Corn muffin (1 medium), made with fat-free milk and egg substitute
  - Soft margarine (1 tsp)
- Watermelon (1 cup)
- Iced tea, unsweetened (1 cup)

Snack
- Graham crackers (4 large)
- Peanut butter, reduced fat, unsalted (1 Tbsp)
- Fat-free milk (1/2 cup)

Nutrient Analysis

Calories	1823	Total fat, % calories	30
Cholesterol (mg)	131	Saturated fat, % calories	5
Fiber (g)	43	Monounsaturated fat, % calories	14
Soluble (g)	8	Polyunsaturated fat, % calories	8
Sodium (mg)	1676	Trans fat (g)	3
Carbohydrates, % calories	59	Omega 3 fat (g)	0.4
		Protein, % calories	18

***Higher Fat Alternative**

Total fat, % calories	35

No salt is added in recipe preparation or as seasoning. The sample menu meets or exceeds the Daily Reference Intake (DRI) for nutrients.

** For a higher fat alternative, substitute 1/4 cup of unsalted almond slices for the corn on the cob. Sprinkle the almonds on the rice.*

TLC Sample Menu
Asian Cuisine
Male, 25–49 Years

Breakfast
- Scrambled egg whites (3/4 cup liquid egg substitute)
  - Cooked with fat-free cooking spray*
- English muffin (1 whole)
  - Soft margarine (2 tsp)
  - Jam (1 Tbsp)
- Strawberries (1 cup)
- Orange Juice, calcium fortified** (1 cup)
- Coffee (1 cup) with fat-free milk (2 Tbsp)

Lunch
- Tofu Vegetable stir-fry
  - Tofu (3 oz)
  - Mushrooms (1/2 cup)
  - Onion (1/4 cup)
  - Carrots (1/2 cup)
  - Swiss chard (1 cup)
  - Garlic, minced (2 Tbsp)
  - Peanut oil (1 Tbsp)
  - Soy sauce, low sodium (2 1/2 tsp)
- Rice, cooked (1 cup)
- Vegetable egg roll, baked (1 medium)
- Orange (1 medium)
- Green Tea (1 cup)

Dinner
- Beef stir-fry
  - Beef tenderloin (3 oz)
  - Soybeans, cooked (1/4 cup)
  - Broccoli, cut in large pieces (1/2 cup)
  - Carrots, sliced (1/2 cup)
  - Peanut oil (1 Tbsp)
  - Soy sauce, low sodium (2 tsp)
- Rice, cooked (1 cup)
- Watermelon (1 cup)
- Almond cookies (2 cookies)
- Fat-free milk (1 cup)

Snack
- Chinese noodles, soft (1 cup)
  - Peanut oil (2 tsp)
- Banana (1 medium)
- Green tea (1 cup)

Nutrient Analysis

Calories	2519
Cholesterol (mg)	108
Fiber (g)	37
Soluble (g)	15
Sodium (mg)	2268
Carbohydrates, % calories	57
Total fat, % calories	28
Saturated fat, % calories	5
Monounsaturated fat, % calories	11
Polyunsaturated fat, % calories	9
Trans fat (g)	3
Protein, % calories	18

***Higher Fat Alternative**

Total fat, % calories	32

No salt is added in recipe preparation or as seasoning. The sample menu meets or exceeds the Daily Reference Intake (DRI) for nutrients.

** For a higher fat alternative, cook egg whites with 1 Tbsp of canola oil.*
***If using higher fat alternative, eliminate orange juice because canola oil adds calories.*

TLC Sample Menu
Asian Cuisine
Female, 25–49 Years

Breakfast
- Scrambled egg whites (1/2 cup liquid egg substitute)
  - Cooked with fat-free cooking spray*
- English muffin (1 whole)
  - Soft margarine (2 tsp)
  - Jam (1 Tbsp)
- Strawberries (1 cup)
- Orange Juice, calcium fortified** (1 cup)
- Coffee (1 cup) with fat-free milk (2 Tbsp)

Lunch
- Tofu Vegetable stir-fry
  - Tofu (3 oz)
  - Mushrooms (1/2 cup)
  - Onion (1/4 cup)
  - Carrots (1/2 cup)
  - Swiss chard (1/2 cup)
  - Garlic, minced (2 Tbsp)
  - Peanut oil (1 Tbsp)
  - Soy sauce, low sodium (2 1/2 tsp)
- Rice, cooked (1/2 cup)
- Orange (1 medium)
- Green tea (1 cup)

Dinner
- Beef stir-fry
  - Beef tenderloin (3 oz)
  - Soybeans, cooked (1/4 cup)
  - Broccoli, cut in large pieces (1/2 cup)
  - Peanut oil (1 Tbsp)
  - Soy sauce, low sodium (2 tsp)
- Rice, cooked (1/2 cup)
- Watermelon (1 cup)
- Almond cookie (1 cookie)
- Fat-free milk (1 cup)

Snack
- Chinese noodles, soft (1/2 cup)
  - Peanut oil (1 tsp)
- Green tea (1 cup)

Nutrient Analysis

Calories	1829	Total fat, % calories	28
Cholesterol (mg)	74	Saturated fat, % calories	6
Fiber (g)	26	Monounsaturated fat, % calories	11
Soluble (g)	10	Polyunsaturated fat, % calories	9
Sodium (mg)	1766	Trans fat (g)	3
Carbohydrates, % calories	56		
		Protein, % calories	18

***Higher Fat Alternative**

Total fat, % calories	33

No salt is added in recipe preparation or as seasoning. The sample menu meets or exceeds the Daily Reference Intake (DRI) for nutrients.

** For a higher fat alternative, cook egg whites with 1 Tbsp of canola oil.*
***If using higher fat alternative, eliminate orange juice because canola oil adds extra calories.*

TLC Sample Menu
Mexican-American Cuisine
Male, 25–49 Years

Breakfast
- Bean Tortilla
  - Corn tortilla (2 medium)
  - Pinto beans* (1/2 cup)
  - Onion (1/4 cup), tomato, chopped (1/4 cup)
  - Jalapeno pepper (1 medium)
  - Sauté with canola oil (1 tsp)
- Papaya** (1 medium)
- Orange Juice, calcium fortified (1 cup)
- Coffee (1 cup) with fat-free milk (2 Tbsp)

Lunch
- Stir-fried beef
  - Sirloin steak (3 oz)
  - Garlic, minced (1 tsp)
  - Onion, chopped (1/4 cup)
  - Tomato, chopped (1/4 cup)
  - Potato, diced (1/4 cup)
  - Salsa (1/4 cup)
  - Olive oil (2 tsp)
- Mexican rice
  - Rice, cooked (1 cup)
  - Onion, chopped (1/4 cup)
  - Tomato, chopped (1/4 cup)
  - Jalapeno pepper (1 medium)
  - Carrots, diced (1/4 cup)
  - Cilantro (2 Tbsp)
  - Olive oil (1 Tbsp)
- Mango (1 medium)
- Blended fruit drink (1 cup)
  - Fat-free milk (1 cup)

Lunch (continued)
  - Mango, diced (1/4 cup)
  - Banana, sliced (1/4 cup)
  - Water (1/4 cup)

Dinner
- Chicken fajita
  - Corn tortilla (2 medium)
  - Chicken breast, baked (3 oz)
  - Onion, chopped (2 Tbsp)
  - Green pepper, chopped (1/4 cup)
  - Garlic, minced (1 tsp)
  - Salsa (2 Tbsp)
  - Canola oil (2 tsp)
- Avocado salad
  - Romaine lettuce (1 cup)
  - Avocado slices, dark skin, California type (1 small)
  - Tomato, sliced (1/4 cup)
  - Onion, chopped (2 Tbsp)
  - Sour cream, low fat (1 1/2 Tbsp)
- Rice pudding with raisins (3/4 cup)
- Water (1 cup)

Snack
- Plain yogurt, fat free, no sugar added (1 cup)
  - Mixed with peaches, canned in water (1/2 cup)
- Water (1 cup)

Nutrient Analysis

Calories	2535
Cholesterol (mg)	158
Fiber (g)	48
Soluble (g)	17
Sodium (mg)	2118
Carbohydrates, % calories	58
Total fat, % calories	28
Saturated fat, % calories	5
Monounsaturated fat, % calories	17
Polyunsaturated fat, % calories	5
Trans fat (g)	<1
Protein, % calories	17

***Higher Fat Alternative**

Total fat, % calories	33

No salt is added in recipe preparation or as seasoning. The sample menu meets or exceeds the Daily Reference Intake (DRI) for nutrients.

** For a higher fat alternative, cook beans with canola oil (1 Tbsp).*
***If using higher fat alternative, reduce papaya serving to 1/2 medium fruit because canola oil adds extra calories.*

TLC Sample Menu
Mexican-American Cuisine
Female, 25–49 Years

Breakfast
- Bean Tortilla
  - Corn tortilla (1 medium)
  - Pinto beans (1/4 cup)
  - Onion (2 Tbsp), tomato, chopped (2 Tbsp), Jalapeno pepper (1 medium)
  - Sauté with canola oil (1 tsp)
- Papaya** (1 medium)
- Orange juice, calcium fortified (1 cup)
- Coffee (1 cup) with fat-free milk (2 Tbsp)

Lunch
- Stir-fried Beef
  - Sirloin steak (2 oz)
  - Garlic, minced (1 tsp)
  - Onion, chopped (1/4 cup)
  - Tomato, chopped (1/4 cup)
  - *Potato, diced (1/4 cup)
  - Salsa (1/4 cup)
  - Olive oil (1 1/2 tsp)
- Mexican rice (1/2 cup)
  - Rice, cooked (1/2 cup)
  - Onion, chopped (2 Tbsp)
  - Tomato, chopped (2 Tbsp)
  - Jalapeno pepper (1 medium)
  - Carrots, diced (2 Tbsp)
  - Cilantro (1 Tbsp)
  - Olive oil (2 tsp)
- Mango (1 medium)
  - Blended fruit drink (1 cup)
  - Fat-free milk (1 cup)

Lunch (continued)
- Mango, diced (1/4 cup)
- Banana, sliced (1/4 cup)
- Water (1/4 cup)

Dinner
- Chicken fajita
  - Corn tortilla (1 medium)
  - Chicken breast, baked (2 oz)
  - Onion, chopped (2 Tbsp)
  - Green pepper, chopped (2 Tbsp)
  - Garlic, minced (1 tsp)
  - Salsa (1 1/2 Tbsp)
  - Canola oil (1 tsp)
- Avocado salad
  - Romaine lettuce (1 cup)
  - Avocado slices, dark skin, California type (1/2 small)
  - Tomato, sliced (1/4 cup)
  - Onion, chopped (2 Tbsp)
  - Sour cream, low fat (1 1/2 Tbsp)
- Rice pudding with raisins (1/2 cup)
  - Water (1 cup)

Snack
- Plain yogurt, fat free, no sugar added (1 cup)
  - Mixed with peaches, canned in water (1/2 cup)
- Water (1 cup)

Nutrient Analysis

Calories	1821
Cholesterol (mg)	110
Fiber (g)	35
Soluble (g)	13
Sodium (mg)	1739
Carbohydrates, % calories	61
Total fat, % calories	26
Saturated fat, % calories	4
Monounsaturated fat, % calories	15
Polyunsaturated fat, % calories	4
Trans fat (g)	<1
Protein, % calories	17

***Higher Fat Alternative**

Total fat, % calories	34

No salt is added in recipe preparation or as seasoning. The sample menu meets or exceeds the Daily Reference Intake (DRI) for nutrients.

* *For a higher fat alternative, substitute 1/2 cup of unsalted peanut halves for the potatoes.*
** *If using higher fat alternative, eliminates papaya because the peanuts add extra calories*

Detection 

Diet Appendix C

Evaluation 

Treatment 

Saturated Fat, Total Fat, Cholesterol, and Omega-3 Content of Meat, Fish, and Poultry in 3-Ounce Portions Cooked Without Added Fat

Source	Saturated Fat g/3 oz	Total Fat g/3 oz	Cholesterol mg/3 oz	Omega-3 g/3 oz
Lean Red Meats				
Beef (rump roast, shank, bottom round, sirloin)	1.4	4.2	71	–
Lamb (shank roast, sirloin roast, shoulder roast, loin chops, sirloin chops, center leg chop)	2.8	7.8	78	–
Pork (sirloin cutlet, loin roast, sirloin roast, center roast, butterfly chops, loin chops)	3.0	8.6	71	–
Veal (blade roast, sirloin chops, shoulder roast, loin chops, rump roast, shank)	2.0	4.9	93	–
Organ Meats				
Liver				
Beef	1.6	4.2	331	–
Calf	2.2	5.9	477	–
Chicken	1.6	4.6	537	–
Sweetbread	7.3	21.3	250	–
Kidney	0.9	2.9	329	–
Brains	2.5	10.7	1,747	–
Heart	1.4	4.8	164	–
Poultry				
Chicken (without skin)				
Light (roasted)	1.1	3.8	72	–
Dark (roasted)	2.3	8.3	71	–
Turkey (without skin)				
Light (roasted)	0.9	2.7	59	–
Dark (roasted)	2.0	6.1	72	–
Fish				
Haddock	0.1	0.8	63	0.22
Flounder	0.3	1.3	58	0.47
Salmon	1.7	7.0	54	1.88
Tuna, light, canned in water	0.2	0.7	25	0.24
Shellfish				
Crustaceans				
Lobster	0.1	0.5	61	0.07
Crab meat				
Alaskan King Crab	0.1	1.3	45	0.38
Blue Crab	0.2	1.5	85	0.45
Shrimp	0.2	0.9	166	0.28
Mollusks				
Abalone	0.3	1.3	144	0.15
Clams	0.2	1.7	57	0.33
Mussels	0.7	3.8	48	0.70
Oysters	1.3	4.2	93	1.06
Scallops	0.1	1.2	56	0.36
Squid	0.6	2.4	400	0.84

VI. Drug Therapy

VI. Drug Therapy

1. Thresholds and goals for drug treatment

a. Drug therapy to achieve treatment goals: overview

LDL cholesterol is the primary target of treatment in clinical lipid management. The use of therapeutic lifestyle changes (TLC), including LDL-lowering dietary options (plant stanols/sterols and increased viscous fiber) will achieve the therapeutic goal in many persons. Nonetheless, a portion of the population whose short-term and/or long-term risk for CHD, will require LDL-lowering drugs to reach the prescribed goal for LDL cholesterol. The availability of HMG CoA reductase inhibitors (statins) allows attainment of the LDL goal in most higher risk persons. Other agents—bile acid sequestrants, nicotinic acid, and some fibrates—also can moderately lower LDL levels.

If TLC alone fails to achieve the goal for LDL cholesterol, consideration can be given to adding drug therapy. In such cases, the third visit of dietary therapy (Figure V.2–1) will be the visit to initiate drug treatment. When drugs are used, however, TLC also should always be used concomitantly. Dietary therapy provides additional CHD risk reduction beyond drug efficacy. Suggestions for combined use of TLC and drug therapy are given in Table VI.1–1.

The general scheme for initiation and progression of LDL-lowering drug therapy is outlined in Figure VI.1–1. As with dietary therapy, the first priority of drug therapy is to achieve the goal for LDL cholesterol. For this reason an LDL-lowering drug should be started. The usual drug will be a statin, but alternatives are a bile acid sequestrant or nicotinic acid. The starting dose of statin will depend on the baseline LDL-cholesterol level. In persons with only moderate elevations of LDL cholesterol, the LDL-cholesterol goal will be achieved with low or standard doses, and higher doses will not be necessary. The response to drug therapy should be checked in about 6 weeks. If the treatment goal has been achieved, the current dose can be maintained; if not, LDL-lowering therapy can be intensified, either by increasing the statin dose or by combining a statin with a bile acid sequestrant.

Although LDL cholesterol is the primary target of therapy, other lipid risk factors besides elevated LDL affect CHD risk. Among these are low HDL cholesterol, elevated triglyceride (especially VLDL remnants), and possibly small LDL particles. This "lipid triad" has been called *atherogenic dyslipidemia.* It commonly occurs as one component of the metabolic syndrome. Weight reduction and increased physical activity constitute first-line therapy for atherogenic dyslipidemia, and three classes of drugs—statins, nicotinic acid, and fibrates—favorably modify the lipid abnormalities of atherogenic dyslipidemia. Many persons with atherogenic dyslipidemia have high triglycerides (≥200 mg/dL). Such persons usually have an increase in atherogenic VLDL remnants, which can be estimated clinically by measuring VLDL cholesterol. In persons with high triglycerides, the combination of LDL cholesterol + VLDL cholesterol (non-HDL cholesterol) represents *atherogenic cholesterol.* Non-HDL cholesterol thus represents a secondary target of therapy (after LDL cholesterol) when triglycerides are elevated. Statins alone will be sufficient to attain the non-HDL-cholesterol goal in some persons, but a combination of statins and nicotinic acid (or fibrates) can be helpful in others.

The general strategy for initiation and progression of drug therapy is outlined in Figure VI.1–1. Consideration of drug therapy often occurs simultaneously with the decision to initiate TLC therapy for the metabolic syndrome (Figure V.2–1). Thus weight reduction and increased physical activity may begin at the same time as drug treatment.

After another 6 weeks, the response to therapy should be assessed. If the LDL-cholesterol goal is still not achieved, further intensification of therapy should be considered, with re-evaluation in another 6 weeks. Once the LDL-cholesterol goal has been attained, attention turns to other lipid risk factors when present. If triglycerides are high (≥200 mg/dL), the secondary target of treatment becomes non-HDL cholesterol. If the LDL-cholesterol goal has been attained but not the non-HDL-cholesterol goal, there are two alternative approaches: (a) the dose of the LDL-lowering drug can

Table VI.1–1. Suggestions for Combined Use of TLC and Drug Therapy

- Intensive LDL lowering with TLC, including therapeutic dietary options (plant stanols/sterols and/or increased viscous fiber)
  - May obviate need for drug therapy
  - Can augment LDL-lowering drug therapy
  - May allow for lower doses of drugs
- Weight control plus increased physical activity
  - Reduces risk beyond LDL-cholesterol lowering
  - Constitutes primary management of the metabolic syndrome
  - Raises HDL-cholesterol levels
  - Enhances reduction of non-HDL cholesterol
- Initiating TLC before drug consideration
  - For most persons, a trial of dietary therapy of about 3 months is advised before initiating drug therapy
  - Unsuccessful trials of dietary therapy without drugs should not be prolonged indefinitely if goals of therapy are not approached in a reasonable period; drug therapy should not be withheld if it is needed to reach targets in persons with a short-term and/or long-term CHD risk that is high.
- Initiating drug therapy simultaneously with TLC
  - For severe hypercholesterolemia in which dietary therapy alone cannot achieve LDL targets
  - For those with CHD or CHD risk equivalents in whom dietary therapy alone will not achieve LDL targets

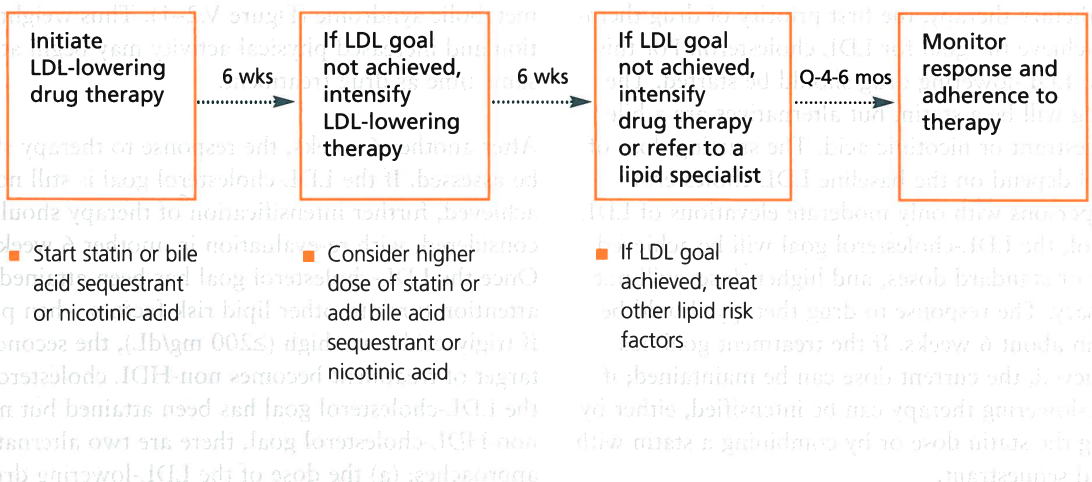
be increased to reduce both LDL and VLDL, or (b) consideration can be given to adding a triglyceride-lowering drug (fibrate or nicotinic acid) to LDL-lowering therapy, which will mainly lower VLDL (see Section VII). The latter approach has the advantage of raising HDL cholesterol in addition to lowering non-HDL cholesterol. Thereafter, persons can be monitored for response to therapy every 4 or 6 months, or more often if considered necessary.

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

b. Cholesterol management in persons with CHD or CHD risk equivalents

The general approach to drug therapy in persons with CHD or CHD risk equivalents is shown in Figure IV.2–1. The LDL-cholesterol goal is <100 mg/dL. Most persons with CHD or CHD risk equivalents should be

Figure VI.1–1. Progression of Drug Therapy



treated to achieve this goal. Special considerations for LDL-lowering therapy with drugs are given for the following subcategories of persons with CHD or CHD risk equivalents.

1) Baseline LDL cholesterol ≥130 mg/dL

Secondary prevention trials consistently show benefit from LDL-lowering drugs when baseline LDL cholesterol is ≥130 mg/dL. Thus, most persons with baseline LDL cholesterol ≥130 mg/dL should be started on LDL-lowering drugs simultaneously with TLC since many such persons cannot achieve the LDL-cholesterol goal of <100 mg/dL on dietary therapy alone. Nonetheless, the use of dietary therapy is essential because it provides benefits not available through drugs. In some persons, to achieve the LDL goal, relatively high doses of LDL-lowering drugs will be required. Statins typically are the drug of first choice. In persons whose baseline LDL cholesterol is very high, drugs in combination (e.g., statins + bile acid sequestrants) will be necessary to reduce the LDL cholesterol to <100 mg/dL.

2) On-treatment LDL cholesterol 100–129 mg/dL

If the LDL-cholesterol level is reduced to <100 mg/dL, current drug therapy can be continued. However, even in controlled clinical trials, less than half of persons with CHD achieved an LDL-cholesterol goal of <100 mg/dL on standard doses of statins (i.e., simvastatin 20–40 mg/day in the 4S trial[435] or pravastatin 40 mg/day in CARE[436] and LIPID[206]). In the majority of participants, on-treatment LDL cholesterol was in the range of 100–129 mg/dL. For such persons, several therapeutic options are available (Table VI.1–2).

First, dietary options for LDL lowering can be intensified. These include reinforcement of lifestyle therapies (reduced intakes of saturated fat and cholesterol and weight reduction); referral to a dietitian for medical nutrition therapy is advisable. These changes in eating habits, combined with other dietary therapies (plant stanols/sterols and increased viscous fiber), often will reduce LDL-cholesterol levels to near 100 mg/dL. *Second,* LDL-lowering drug therapy can be intensified. The dose of statins can be increased, or a second LDL-lowering drug (bile acid sequestrant or nicotinic acid) can be combined with statin therapy. *Third,* if the patient has the metabolic syndrome, attention can turn to managing this condition through weight loss and increased physical activity; besides improvement of lipid and nonlipid risk factors of this syndrome, further LDL lowering often is obtained. *Fourth,* if the patient has atherogenic dyslipidemia, other drugs (nicotinic acid or fibric acids) can be added to the regimen, or LDL-lowering therapy can be intensified. Nicotinic acid not only will improve atherogenic dyslipidemia, but it also can lower LDL-cholesterol levels. If elevated triglycerides are present, addition of one of these drugs will assist in reaching the non-HDL-cholesterol goal. And *fifth,* treatment of nonlipid risk factors can be intensified. Finally, a combination of these options is advisable for some persons.

Table VI.1–2. Therapeutic Options for Clinical Management of Persons with On-Treatment LDL-Cholesterol Levels of 100–129 mg/dL

#1	■ Increase intensity of TLC for LDL lowering to achieve LDL-cholesterol goal <100 mg/dL – Reinforce reduction of saturated fats and cholesterol – Add other dietary therapies ➤ Plant stanols/sterols ➤ Increase viscous fiber – Promote weight loss in overweight/obese persons
#2	■ Intensify LDL-lowering drug therapy to achieve LDL-cholesterol goal <100 mg/dL – Increase dose of statin – Add a second LDL-lowering drug (bile acid sequestrant or nicotinic acid)
#3	■ Introduce lifestyle therapies for treatment of the metabolic syndrome, if present – Promote weight loss in overweight/obese persons – Recommend increased physical activity
#4	■ Employ drug therapy for treatment of atherogenic dyslipidemia, if present – Nicotinic acid – Fibric acids
#5	■ Intensify treatment of nonlipid risk factors – Hypertension – Hyperglycemia – Prothrombotic state (antiplatelet drugs/anticoagulants)

3) Baseline LDL cholesterol 100–129 mg/dL

NHANES III data showed that more than 30 percent of people with CHD have baseline LDL-cholesterol levels in the 100–129 mg/dL range. In clinical practice, however, misclassification of LDL-cholesterol levels from single measurements in individuals will be high. Many persons will have true baseline LDL-cholesterol

levels ≥130 mg/dL. Baseline levels of LDL cholesterol are labile from one measurement to another. Regardless of apparent baseline level, the LDL-cholesterol goal for all CHD patients and CHD risk equivalents is <100 mg/dL. The various options outlined in Table VI.1–2 can be applied to this category. Many persons with baseline LDL-cholesterol levels between 100 and 129 mg/dL will be able to attain LDL cholesterol <100 mg/dL through TLC especially if it includes plant stanols/sterols and increased viscous fiber. Others will require cholesterol-lowering drugs to reach this target. Clinical judgment is required as to when to initiate a cholesterol-lowering drug. If the LDL cholesterol falls near 100 mg/dL on dietary therapy alone, the physician has the option to forego a cholesterol-lowering drug for the present. This is particularly so if other lipid or nonlipid risk factors seem to need greater attention.

Once adequate LDL-lowering therapy has been attained, other lipid risk factors deserve attention. For example, if the patient has an elevated triglyceride or low-HDL cholesterol, a different lipid-lowering drug can be considered (e.g., nicotinic acid or fibric acid). The positive results of the VA-HIT trial showing the efficacy of gemfibrozil therapy alone in CHD patients have led some authorities to favor fibrates over statins in low-LDL patients with CHD.[48] Overall, however, for monotherapy, clinical trials with statins have been more robust in their favorable outcomes than have fibrates. In addition, combined drug therapy (low-dose statin + fibrate [or nicotinic acid]) remains an option in such persons, provided that precautions are taken to prevent and monitor for side effects of lipid-lowering drugs used in combination.

4) Baseline LDL cholesterol <100 mg/dL

Some patients with CHD or CHD risk equivalent will have a baseline LDL cholesterol <100 mg/dL. These patients are already at their LDL-cholesterol goal. For them, further LDL lowering is not required. Attention shifts to other lipid or nonlipid risk factors. If triglycerides are elevated (≥200 mg/dL), the non-HDL cholesterol remains a secondary target of therapy. Alternative therapies to reduce VLDL-cholesterol levels to attain the non-HDL-cholesterol goal are statins or triglyceride-lowering drugs (nicotinic acid or fibrate). Furthermore, nonlipid risk factors may be largely responsible for the patient's CHD and thus may deserve intensive modification.

5) Initiating cholesterol-lowering drugs in hospitalized patients

Hospitalization for a coronary event or procedure provides a unique opportunity to initiate LDL-lowering therapy. Physicians should take advantage of this opportunity. In the past, this opportunity has often been lost due to confusion about the meaning of LDL-cholesterol levels obtained during hospitalization. Although it is true that LDL levels can change during an acute illness, this should not stand in the way of starting needed therapy. A few simple recommendations can guide initiation of LDL-lowering therapy during hospitalization. The guiding principle is that LDL cholesterol should be measured in all patients, preferably on admission, but in any case at some time during hospitalization, and can be used as a guide to start treatment.[793] Thus, the first 24 hours of hospital admission should be considered a "window of opportunity" during which a fasting lipoprotein profile should be obtained. Whereas as much as a 10 percent fall in LDL cholesterol may occur during this first day (due to heparinization, stress, diet, and other factors), a value quite close to the actual baseline for that individual will be obtained and will be crucial in the decision to initiate early cholesterol-lowering therapy.

If this first 24-hour "window" is missed, a fasting lipoprotein profile should still be obtained during hospitalization since an elevated LDL cholesterol in that setting will identify persons with even higher baseline LDL cholesterol. The following summarizes the ATP III position on initiation of LDL-lowering drugs during hospitalization of CHD-related events or procedures.

First, persons hospitalized with a coronary event or procedure should be discharged on *both* dietary therapy and drug therapy if the LDL cholesterol is ≥130 mg/dL.

Second, if the LDL is 100–129 mg/dL during hospitalization, clinical judgment should be used in deciding whether to initiate drug treatment at discharge. The initial LDL-cholesterol level obtained in the hospital may be the lowest value seen for this patient. LDL-cholesterol levels are decreased beginning in the first 24–48 hours after an event and may remain low for many weeks. Later, if necessary, therapy can be adjusted according to the LDL response.

Initiation of both TLC and LDL-lowering drugs at the time of hospital discharge has several advantages. First, at this time persons are particularly motivated to undertake and adhere to risk-lowering interventions. Second, failure to initiate indicated therapy early is one of the causes of a large "treatment gap" as outpatient follow up is often less consistent and more fragmented. Finally, new and ongoing studies suggest a very early benefit of LDL-cholesterol-lowering therapy.[471,794-797] Recent support for this approach comes from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Trial of over 3,000 persons hospitalized with non-Q myocardial infarction or unstable angina, with a mean hospital LDL-cholesterol level of 124 mg/dL. Statin treatment, initiated in the hospital, was safe and resulted in a 16 percent relative risk reduction in subsequent coronary events at 16 weeks.[469] Finally, a large observational study from Sweden showed an adjusted 25 percent reduction in total mortality at one year for myocardial infarction patients started on statins in-hospital.[471]

These latter trials,[469,471] while suggesting benefit from starting LDL-lowering therapy at time of acute coronary syndrome, do not preclude the need for further research on efficacy of drug therapy started at this time.

6) Special considerations for drug therapy in CHD patients

In most persons with CHD, goals for LDL-lowering therapy can be achieved with lifestyle therapies and drug monotherapy. The benefits of intensive LDL reduction with the use of drugs apparently extend to those with advanced age and poor cardiac prognosis; nonetheless, some persons with severe co-existing medical conditions that severely impair quality of life or life expectancy will not benefit.

A low HDL cholesterol (<40 mg/dL) is common in patients with CHD. A low HDL level can be secondary to other modifiable risk factors such as cigarette smoking, obesity, or physical inactivity. Beta-blockers can also lower HDL-cholesterol levels in CHD patients, but have been shown to be efficacious for reducing subsequent CHD events after myocardial infarction. Therefore, their benefit in CHD patients outweighs the drawback of HDL lowering. Secondary prevention trials show that statin therapy significantly reduces risk for major coronary events even in patients with low HDL cholesterol; therefore in these patients, LDL remains the primary target of therapy. The VA-HIT study[48] suggests that fibrate therapy also may be beneficial for patients with low HDL levels in whom LDL-cholesterol levels are near optimal.

c. General principles of primary prevention with drug therapy

Primary prevention pertains to individuals without clinically evident CHD. For those with CHD risk equivalents, primary and secondary prevention merge. The guidelines for consideration of drug therapy and target goals for primary prevention are shown in Table VI.1–3.

d. Drug considerations for persons with multiple (2+) risk factors

1) 10-year risk >20 percent

Persons with multiple (2+) risk factors whose 10-year risk for hard CHD is >20 percent are included in the category of CHD risk equivalent. As discussed in section VI.1.b, they are managed similarly to other CHD risk equivalents that include non-coronary forms of clinical atherosclerotic disease and diabetes. The LDL cholesterol goal in these patients is <100 mg/dL, and when LDL cholesterol is ≥130 mg/dL, an LDL-lowering drug can be started together with theraputic lifestyle changes. When baseline LDL cholesterol is 100–129 mg/dL, TLC is indicated and concomitant use of drugs is optional. Drug options include statins, bile acid sequestrants, fibrates, and nicotinic acid.

2) 10-year risk 10–20 percent

Here the LDL-cholesterol goal is <130 mg/dL. TLC should be introduced first. If this goal is not achieved after 3 months of TLC, drug therapy should be considered. A low dose of drug may suffice if TLC drops the LDL cholesterol to near 130 mg/dL. If not, a higher dose can be used. At the same time, if the metabolic syndrome is present, weight reduction and physical activity should be emphasized. Later, consideration can be given to modifying other lipid risk factors with nicotinic acid or fibrates if they have not been adequately controlled by TLC.

Table VI.1–3. Drug Therapy Consideration and Goals of Therapy for Primary Prevention

Risk Category	10-Year Risk for CHD	LDL cholesterol	
		Level at Which to Consider Drug Therapy	Primary Goal of Therapy
Multiple (2+) risk factors	>20% (includes all CHD Risk Equivalents*)	>100 mg/dL†	<100 mg/dL
	10–20%	≥130 mg/dL‡	<130 mg/dL
	<10%	≥160 mg/dL	<130 mg/dL
0–1 risk factor	<10%	≥190 mg/dL¥	<160 mg/dL

* Most patients with CHD risk equivalents have multiple risk factors and a 10-year risk >20 percent. They include patients with non-coronary forms of clinical atherosclerosis, diabetes, and multiple (2+) risk factors with a 10-year risk >20 percent by Framingham scoring.

† When LDL cholesterol is ≥130 mg/dL, a cholesterol-lowering drug can be started concomitantly with TLC. If baseline LDL cholesterol is 100–129 mg/dL, TLC should be started immediately. Concomitant use of drugs is optional; several options for drug therapy are available (e.g., statins, bile acid sequestrants, fibrates, nicotinic acid).

‡ When LDL cholesterol is in the range of 130–159 mg/dL, drug therapy can be used if necessary to reach the LDL-cholesterol goal of <130 mg/dL, after an adequate trial of TLC.

¥ When LDL cholesterol is in the range of 160–189 mg/dL, use of cholesterol-lowering drugs is optional, depending on response to TLC diet.

3) 10-year risk <10 percent

The LDL-cholesterol goal for multiple risk factors and 10-year risk <10 percent also is <130 mg/dL. However, LDL-lowering drugs are not to be considered unless LDL cholesterol remains ≥160 mg/dL on TLC. When 10-year risk is <10 percent, cost-effectiveness of drug therapy begins to erode, especially when the LDL-cholesterol level remains in the range of 130 to 159 mg/dL and other risk factors are appropriately controlled. On the other hand, when LDL-cholesterol concentrations ≥160 mg/dL occur with multiple (2+) risk factors, long-term (>10-year) risk for CHD is relatively high. Thus, drug therapy deserves consideration. Of course, costs and side effects of drugs must also be taken into account when contemplating lifetime drug therapy.

e. Drug considerations for persons with 0–1 risk factor, 10-year risk <10 percent

The LDL-cholesterol goal in this risk category is <160 mg/dL. For adults with severe elevations of LDL cholesterol (e.g., ≥220 mg/dL), drug therapy can be started simultaneously with TLC. When baseline LDL cholesterol is in the range of 190–219 mg/dL, a 3-month trial of TLC is indicated. If the LDL-cholesterol level remains ≥190 mg/dL after TLC, drug therapy should be considered for most persons. However, if LDL cholesterol falls to the range of 160–189 mg/dL on TLC, drug therapy is optional, depending on clinical judgment. Similarly, if baseline LDL cholesterol is 160–189 mg/dL, a 3-month trial of TLC is indicated; again, if the LDL level persists ≥160 mg/dL on TLC, drug therapy is optional. In either case, factors that favor drug therapy are severe, single risk factors, such as heavy smoking, a family history of premature CHD, very low HDL-cholesterol levels, and the presence of other emerging risk factors (see Section II). Likewise, if triglycerides are high (≥200 mg/dL), non-HDL cholesterol will be a secondary target of therapy.

2. Available drug therapies

a. Overview and general approach

The major classes of drugs for consideration are:

- HMG CoA reductase inhibitors (statins)—lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin
- Bile acid sequestrants—cholestyramine, colestipol, colesevelam
- Nicotinic acid—crystalline, timed-release preparations, Niaspan®
- Fibric acid derivatives (fibrates)—gemfibrozil, fenofibrate, clofibrate

Hormones are also discussed below:

- Estrogen replacement
- Selective estrogen receptor modulators

b. Major drugs

1) *HMG CoA reductase inhibitors (statins*)—lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin*

These drugs are summarized in Table VI.2–1. The HMG CoA reductase inhibitors are the most effective and practical class of drugs for reducing LDL-cholesterol concentrations. Results from five clinical trials with a mean duration of 5.4 years have documented a decrease in CHD and total mortality, reductions in myocardial infarctions, revascularization procedures, stroke, and peripheral vascular disease.[206,207,416,435,436,489] These trials documented benefits in men and women, in middle-aged and older persons, and in primary and secondary prevention. Approximately 30,000 individuals were randomized to either placebo or statin therapy in these five clinical outcome trials. Statin therapy proved remarkably safe, with no major or unexpected adverse effects observed. Several other types of clinical trials with statin therapy also showed favorable results.[434,456] Beneficial outcomes in CHD parameters have been reported with almost all of the statins. Thus, statins are highly effective in lowering LDL-cholesterol levels (the primary target of therapy). Statin therapy reduces the risk of essentially every clinical manifestation of the atherosclerotic process; they are easy to administer with good patient acceptance. They have few drug-drug interactions, and they have a good record for safety.

* Cerivastatin was voluntarily withdrawn from the market by the manufacturer following reports of fatal rhabdomyolysis to the FDA. A substantial proportion of the deaths occurred in patients taking both cerivastatin and gemfibrozil. Rhabdomyolysis associated with cerivastatin use has been reported significantly more frequently than for other statin drugs. Myopathy associated with other statin drugs occurs infrequently, and in most cases, stopping the drug reverses the problem. The significant benefits of statins—lowering cholesterol and reducing the risk for MI and death from CHD—outweigh the risk of developing myopathy or rhabdomyolysis. For additional information on statin side effects, see the ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins, *J Am Coll Cardiol* 2002;40:567-72; *Circulation* 2002;106:1024-8; www.nhlbi.nih.gov/guidelines/cholesterol/statins.htm.

Table VI.2–1. Summary of HMG CoA Reductase Inhibitors

Available Drugs*	Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin	
Lipid/lipoprotein effects	LDL cholesterol	- ↓ 18–55%
	HDL cholesterol	- ↑ 5–15%
	Triglycerides	- ↓ 7–30%
Major use	To lower LDL cholesterol	
Contraindications		
■ **Absolute**	Active or chronic liver disease	
■ **Relative**	Concomitant use of cyclosporine, macrolide antibiotics, various anti-fungal agents and cytochrome P-450 inhibitors (fibrates and nicotinic acid should be used with appropriate caution)	
Efficacy	Reduce risk for CHD and stroke	
Safety	Side effects minimal in clinical trials	
Major side/adverse effects	Myopathy, increased liver transaminases	
Usual starting dose	Lovastatin	- 20 mg
	Pravastatin	- 20 mg
	Simvastatin	- 20 mg
	Fluvastatin	- 20 mg
	Atorvastatin	- 10 mg
Maximum FDA-approved dose	Lovastatin	- 80 mg
	Pravastatin	- 80 mg
	Simvastatin	- 80 mg
	Fluvastatin	- 80 mg
	Atorvastatin	- 80 mg
Available preparations	Lovastatin	- 10, 20, 40 mg tablets
	Pravastatin	- 10, 20, 40 mg tablets
	Simvastatin	- 5, 10, 20, 40, 80 mg tablets
	Fluvastatin	- 20, 40 mg capsules, 80 mg XL tablets
	Atorvastatin	- 10, 20, 40, 80 mg tablets

* Cerivastatin was withdrawn from the market by the manufacturer in August, 2001.

Statins inhibit HMG CoA reductase, the rate-limiting step in cholesterol biosynthesis.[798] This change produces a lowering of LDL-cholesterol levels.[799-802] Inhibition of cholesterol synthesis reduces hepatic cholesterol content, resulting in increased expression of LDL receptors, which lowers serum LDL-cholesterol levels.[803] Intermediate density lipoprotein (IDL) and VLDL remnants also are removed via the LDL receptor. The latter effect contributes to lowering of triglyceride-rich lipoproteins (TGRLP) by statins.[86,804,805] Statins also appear to reduce hepatic release of lipoproteins into the circulation;[806,807] this effect may be due in part to enhanced removal of lipoproteins by LDL receptors within hepatocytes or in the space of Disse.[808] In some persons with homozygous familial hypercholesterolemia, high doses of statins lower LDL-cholesterol levels.[809-811] This latter action is mediated either by increased expression of residual LDL-receptor activity or by inhibition of lipoprotein assembly.

The statins are generally administered with the evening meal or at bedtime. Somewhat greater LDL-cholesterol reductions occur when they are administered at night than in the morning. Most statins have a high first-pass clearance by the liver and a short half-life. Atorvastatin and its metabolites, in contrast, have very long half-lives and thus morning administration is equally effective. Depending upon the specific statin and the dose administered, reductions in LDL cholesterol of 18–55 percent are observed.[812,813] The reductions in LDL cholesterol are dose-dependent and log-linear, so that with each doubling of the dose of statin, LDL-cholesterol levels fall by about 6 percent. HDL cholesterol generally rises by 5–10 percent, but greater increases usually occur in persons with low HDL and elevated triglycerides.[206,207,435,436,489,813-815]

The reductions in triglycerides with the statins generally range from 7–30 percent.[206,207,416,435,436,489,813,815] In individuals with triglyceride levels of <150 mg/dL, triglyceride responses are inconsistent. But when triglyceride levels are >200 mg/dL, triglycerides fall in direct proportion to LDL-cholesterol lowering.[812] With very high triglyceride levels, however, LDL-cholesterol lowering is less than that observed with low triglyceride levels. The statins reduce the concentration of all LDL particles, including the small LDL particles, as well as IDL and VLDL remnants.[86,804] The combined lowering of LDL and TGRLP with the statins makes them efficacious for reducing non-HDL cholesterol in persons with atherogenic dyslipidemia or combined hyperlipidemias.

The statins are well-tolerated by most persons. Elevated hepatic transaminases generally occur in 0.5–2.0 percent of cases and are dose-dependent.[816,817] Bradford et al.[818] reported that the 2-year incidence of serum transaminase elevation with lovastatin therapy was 0.1 percent for 20 mg/day and 1.9 percent for 80 mg/day. Whether transaminase elevation with statins constitutes true hepatotoxicity has not been determined. In fact, the incidence of clinically important (>3 times upper limit of normal) transaminase elevations in the large statin trials is the same for statin as for placebo. Progression to liver failure is exceedingly rare, if it ever occurs; this observation has led some authorities to conclude that statins do not carry clinically significant hepatotoxicity. Reversal of transaminase elevation is frequently noted with reduction of dose or even continued administration of the same dose. Nonetheless, persons who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in transaminase levels of >3 times upper limit of normal or greater persist, discontinuation of therapy is recommended by the FDA. According to the clinical experience of ATP III panel experts, if the statin has been discontinued, transaminase elevations often do not recur with either rechallenge or selection of another statin.[819,820] Cholestasis and active liver disease are listed by the FDA as contraindications to statins. It is not known whether statins worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C. There is no evidence that they are harmful in patients with fatty liver due to obesity. Their use in persons with various forms of chronic liver disease depends on clinical judgment that balances proven benefit against risk.

That statins can produce myopathy under some circumstances is well established. An elevation of creatine kinase is the best indicator of statin-induced myopathy. Unfortunately, statins have often been discontinued for suspected myopathy which in fact is not present. A common complaint is non-specific muscle aches or joint pains that may be falsely attributed to statin therapy; these symptoms are usually not accompanied

by significant increases in creatine kinase. In placebo-controlled trials, the incidence of these complaints is similar between placebo and active drug therapy, suggesting that statins are not responsible in many cases.[816] Sometimes, nonetheless, persons can develop clinically significant myopathy, which is characterized by muscle aches, soreness, or weakness, and elevated creatine kinase levels, generally greater than ten times the upper limit of normal. Overall, the incidence of myopathy with elevations in serum creatine kinase during statin therapy is low.[818,821,822] Failure to recognize myopathy and to discontinue drug therapy can lead to rhabdomyolysis, myoglobinuria, and acute renal necrosis.[823] Myopathy is most likely to occur in persons with complex medical problems and/or who are taking multiple medications. Older patients may also be more susceptible. It occurs less frequently with statin monotherapy, but more frequently when statins are used in combination with a variety of medications including cyclosporine, fibrates, macrolide antibiotics, certain anti-fungal drugs, and nicotinic acid.[824-826] Some of the drug-drug interactions involve specific interactions with the cytochrome P-450 drug metabolizing system, especially those involving the 3A4 isozyme.[827,828] Routine laboratory monitoring of creatine kinase is of little value in the absence of clinical signs or symptoms. Therefore, all persons started on statins should be instructed to immediately report muscle pain and weakness or brown urine, and a creatine kinase measurement should be done. If myopathy is present or strongly suspected, the statin should be discontinued immediately.

Evidence statements: HMG CoA reductase inhibitors (statins) are powerful LDL-lowering drugs (A1). Statin therapy reduces risk for acute coronary syndromes, coronary procedures, and other coronary outcomes in both primary and secondary prevention (A1). It also reduces risk for stroke in secondary prevention (A1). Treatment with statins is generally safe, although rarely persons experience myopathy (D1). Myopathy is more likely in persons with complex medical problems or in those who are taking multiple medications (D1).

Recommendation: Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.

2) Bile acid sequestrants—cholestyramine, colestipol, colesevelam

These drugs are summarized in Table VI.2–2. The major action of bile acid sequestrants is to lower LDL cholesterol.[12,13,829-832] Therapy with cholestyramine reduced the risk of CHD in the Lipid Research Clinics Coronary Primary Prevention Trial.[12,13] Beneficial outcomes also occurred in other clinical trials in which sequestrants were combined with other lipid-modifying drugs.[157,158] Sequestrants add to the LDL-lowering effects of other drugs, notably statins.[833-835] They remain unabsorbed in their passage through the gastrointestinal tract and lack systemic toxicity. Their disadvantages are two-fold. Because of their bulk, they lack convenience of administration; they also cause various gastrointestinal symptoms, notably constipation.

The sequestrants bind bile acids in the intestine through anion exchange; this binding reduces the enterohepatic recirculation of bile acids, which releases feedback regulation on conversion of cholesterol to bile acids in the liver. The resulting decrease in hepatocyte cholesterol content enhances LDL-receptor expression, which in turn lowers serum LDL-cholesterol concentrations.[836] In some persons, sequestrants increase hepatic VLDL production,[837] thereby raising serum triglyceride levels.[838]

Cholestyramine and colestipol are both administered as powders that must be mixed with water or juice. They usually are given once or twice daily with meals. Colestipol also comes in 1g tablets. The LDL-cholesterol-lowering effect of 4g of cholestyramine equals that of 5g of colestipol. Eight to 10 g/day cholestyramine or 10–20 g/day colestipol reduce LDL-cholesterol concentrations by 10–20 percent. Smaller doses of sequestrants (8–10 g/day) generally are well-tolerated; higher doses (16–20 g/day) are less well-tolerated. Colesevelam, a recently marketed drug, is a much more potent bile acid sequestrant. It has been primarily evaluated at doses of 2.6–3.8g/day, and reductions in LDL cholesterol of 12–18 percent are reported.[831] Colesevelam is more easily administered and better tolerated than other sequestrants.

Sequestrants add to LDL lowering when combined with other cholesterol-lowering drugs. Whereas doubling the dose of a statin produces only a 6 percent further reduction in LDL cholesterol, adding a

Table VI.2–2. Summary of Bile Acid Sequestrants

Available drugs	Cholestyramine, colestipol, colesevelam	
Lipid/lipoprotein effects	LDL cholesterol	- ↓ 15–30%
	HDL cholesterol	- ↑ 3–5%
	Triglycerides	- no effect or increase
Major use	To lower LDL cholesterol	
Contraindications		
■ **Absolute**	Familial dysbetalipoproteinemia Triglycerides >400 mg/dL	
■ **Relative**	Triglycerides >200 mg/dL	
Efficacy	Clinical trial evidence of CHD risk reduction	
Safety	Clinical trial evidence of lack of systemic toxicity; GI side effects common	
Major side/adverse effects	Upper and lower gastrointestinal complaints common Decrease absorption of other drugs	
Usual daily dose	Cholestyramine	- 4–16g
	Colestipol	- 5–20g
	Colesevelam	- 2.6–3.8g
Maximum daily dose	Cholestyramine	- 24g
	Colestipol	- 30g
	Colesevelam	- 4.4g
Available preparations	Cholestyramine	- 9g packets (4g drug) - 378g bulk
	Cholestyramine "light"	- 5g packets (4g drug) - 210g bulk
	Colestipol	- 5g packets (5g drug) - 450g bulk - 1g tablets
	Colesevelam	- 625 mg tablets

moderate dose of a sequestrant to a statin can further lower LDL cholesterol by 12–16 percent.[839-841] Thus, sequestrants are useful in combined drug therapy with statins. Further, sequestrants combined with plant stanol esters apparently enhance LDL lowering.[842,843] Thus, sequestrants in combination with TLC, including other dietary options for lowering LDL cholesterol (plant stanols/sterols and viscous fiber), should enable many persons to achieve their LDL-cholesterol goal without the need for an agent that is systemically absorbed.

Since sequestrants tend to raise serum triglycerides, they are contraindicated as monotherapy in persons with high triglycerides (>400 mg/dL) and in familial dysbetalipoproteinemia.[844] They generally should be used as monotherapy only in persons with triglyceride levels of <200 mg/dL. Bile acid sequestrants are not contradicted in patients with type 2 diabetes.[845]

Sequestrant therapy can produce a variety of gastrointestinal symptoms, including constipation, abdominal pain, bloating, fullness, nausea, and flatulence.[12] These symptoms often can be lessened by moderate doses of standard sequestrants or use of colesevelam. Sequestrants are not absorbed from the intestine, but can decrease the absorption of a number of drugs that are administered concomitantly. The general recommendation is that other drugs should be taken either an hour before or 4 hours after administration of the sequestrant. Colesevelam, which apparently does not decrease absorption of co-administered drugs, need not be administered separately from other drugs.

Evidence statements: Bile acid sequestrants produce moderate reductions in LDL cholesterol (A1). Sequestrant therapy reduces risk for CHD (A1). They are additive in LDL-cholesterol lowering in combination with other cholesterol-lowering drugs (C1). They lack systemic toxicity (A1).

Recommendation: Bile acid sequestrants should be considered as LDL-lowering therapy for persons with moderate elevations in LDL cholesterol, for younger persons with elevated LDL cholesterol, for women with elevated LDL cholesterol who are considering pregnancy, for persons needing only modest reductions in LDL cholesterol to achieve target goals, and for combination therapy with statins in persons with very high LDL-cholesterol levels.

3) Nicotinic acid

This drug is summarized in Table VI.2–3. Nicotinic acid or niacin favorably affects all lipids and lipoproteins when given in pharmacological doses. Nicotinamide, which is sometimes confused with niacin or nicotinic acid, has only vitamin functions and does not affect lipid and lipoprotein levels. Nicotinic acid lowers serum total and LDL-cholesterol and triglyceride levels and also raises HDL-cholesterol levels. Smaller doses often increase HDL-cholesterol levels, but doses of 2–3 g/day are generally required to produce LDL-cholesterol reductions of 15 percent or greater.[87,147,846-849] Nicotinic acid can also lower Lp(a) up to 30 percent with high doses.[283] Whether Lp(a) lowering by nicotinic acid therapy reduces risk for CHD is not known. Nicotinic acid was shown to reduce the risk of recurrent myocardial infarction in the Coronary Drug Project,[141] and total mortality was decreased in a 15-year followup of the persons who had originally received nicotinic acid.[444] Decreased

Table VI.2–3. Summary of Nicotinic Acid

Available drugs	Crystalline nicotinic acid Sustained-release (or timed-release) nicotinic acid Extended-release nicotinic acid (Niaspan®)
Lipid/lipoprotein effects	LDL cholesterol - ↓ 5–25% HDL cholesterol - ↑ 15–35% Triglycerides - ↓ 20–50%
Major use	Useful in most lipid and lipoprotein abnormalities
Contraindications	
■ **Absolute**	Chronic liver disease, severe gout
■ **Relative**	Hyperuricemia; high doses in type 2 diabetes
Efficacy	Clinical trial evidence of CHD risk reduction
Safety	Serious long-term side effects rare for crystalline form; serious hepatotoxicity may be more common with sustained-release form
Major side/adverse effects	Flushing, hyperglycemia, hyperuricemia or gout, upper gastrointestinal distress, hepatotoxicity, especially for sustained-release form
Usual daily dose	Crystalline nicotinic acid - 1.5–3g Sustained-release nicotinic acid - 1–2g Extended-release nicotinic acid (Niaspan®) - 1–2g
Maximum daily dose	Crystalline nicotinic acid - 4.5g Sustained-release nicotinic acid - 2g Extended-release nicotinic acid (Niaspan®) - 2g
Available preparations	Many OTC preparations by various manufacturers for both crystalline and sustained-release nicotinic acid. The extended-release preparation (Niaspan®) is a prescription drug.

rates of atherosclerotic progression were also observed in three quantitative angiographic trials: FATS,[158] HATS,[159] and CLAS[157]. In all of these trials, nicotinic acid was combined with other LDL-lowering drugs and effects were compared to placebo.

Many crystalline preparations of nicotinic acid are available without a prescription and are inexpensive. Some preparations and a new formulation, Niaspan®, are available by prescription. Niaspan® is a proprietary extended-release formulation of nicotinic acid; its use is associated with less flushing than occurs with usual crystalline preparations.

Nicotinic acid appears to alter lipid levels by inhibiting lipoprotein synthesis and decreasing the production of VLDL particles by the liver. It inhibits the peripheral mobilization of free fatty acids, reducing hepatic secretion of VLDL.[850,851] It decreases the plasma concentration of triglyceride, VLDL remnants, and IDL;[88,138] and it causes a shift in LDL composition from the small, denser LDL particles to the larger, more buoyant LDL particles.[852] Nicotinic acid also is the most effective lipid-lowering drug for raising HDL levels.[87] The changes in HDL cholesterol and triglyceride concentrations tend to be curvilinear (log-linear); thus, smaller doses of nicotinic acid still produce significant increases in HDL or reductions in triglyceride with fewer side effects. The increases in HDL cholesterol are generally in the range of 15–30 percent,[87] but increases of 40 percent have been noted with very high doses.[846,849,853,854] The sustained-release preparations usually increase HDL cholesterol levels by only 10–15 percent[853,854] with the exception of Niaspan® which retains the HDL-raising potential of the crystalline form. Nicotinic acid typically reduces triglyceride levels by 20 to 35 percent, but reductions of 50 percent have been noted with high doses in hypertriglyceridemic persons.[87,147,846-849] Among lipid-lowering agents, nicotinic acid appears to be the most effective for favorably modifying all of the lipoprotein abnormalities associated with atherogenic dyslipidemia.

The degree of LDL-cholesterol lowering by nicotinic acid has varied in different studies. Some studies report little or no change in LDL levels.[87] However, in one carefully controlled study in patients with hypercholesterolemia,[855] reductions in LDL cholesterol of 5 percent, 16 percent, and 23 percent were noted with daily doses of 1.5, 3.0 and 4.5 grams, respectively.

Extended-release nicotinic acid (Niaspan®), which is administered as a single bedtime dose, has been shown to reduce LDL cholesterol by 15 percent at 2 g/day.[147,847,853,856] Because many persons cannot tolerate higher doses, nicotinic acid is typically not used primarily to lower LDL levels. Instead, it is generally used in combination with other drugs, especially the statins.[857]

Nicotinic acid therapy can be accompanied by a number of side effects. Flushing of the skin is common with the crystalline form and is intolerable for some persons. However, most persons develop tolerance to the flushing after more prolonged use of the drug. Less severe flushing generally occurs when the drug is taken during or after meals, or if aspirin is administered prior to drug ingestion. A newer preparation, Niaspan®, is reported to cause less flushing than crystalline nicotinic acid. A variety of gastrointestinal symptoms, including nausea, dyspepsia, flatulence, vomiting, diarrhea, and activation of peptic ulcer may occur. Three other major adverse effects include hepatotoxicity, hyperuricemia and gout, and hyperglycemia. The risk of all three is increased with higher doses, especially at doses of 2g or higher. The risk of hepatotoxicity appears to be greater with the sustained-release preparations, although not with Niaspan®. Impending hepatotoxicity should be considered if there is a dramatic reduction in plasma lipids.[858] Nicotinic acid reduces insulin sensitivity, and higher doses (>3 g/day) often worsen hyperglycemia in persons with type 2 diabetes.[859] Recent studies suggest that lower doses do not unduly worsen hyperglycemia.[860,861] Other adverse effects include conjunctivitis, nasal stuffiness, acanthosis nigricans, ichthyosis, and retinal edema (toxic amblyopia).

Nicotinic acid is usually administered in two or three doses a day, with the exception of Niaspan®, which is administered as a single dose at bedtime. Crystalline nicotinic acid is the least expensive drug, and small doses are especially useful for increasing HDL-cholesterol levels or lowering triglycerides. The timed-release (sustained-release) preparations are designed to minimize cutaneous flushing. When switching from crystalline nicotinic acid to a sustained-release preparation, smaller doses should be used to reduce the risk of hepatotoxicity. The dose can then be carefully titrated upward, generally to a level not exceeding 2 g/day. Rare cases of fulminant hepatitis have been reported with sustained-release preparations.[862-864] Considerable

variation exists among different sustained-release preparations, and persons should be advised not to switch from one preparation to another. Niaspan® is an extended-release preparation; however, its more rapid-release than sustained-release preparation appears to reduce the risk of hepatotoxicity. Niaspan® also is associated with less flushing than with crystalline nicotinic acid. Since many nicotinic acid preparations are available without a prescription, persons should be instructed that nicotinic acid is associated with many severe adverse effects and regular monitoring by a health professional is essential.

Although nicotinic acid can be highly efficacious and favorably modify the lipoprotein profile, especially in patients with atherogenic dyslipidemia, its long-term use is limited for many patients by side effects.[865] For this reason, the drug is generally reserved for patients at higher short-term risk, i.e., for those with CHD, CHD risk equivalents, or multiple (2+) risk factors with 10-year risk for CHD of 10–20 percent. Its use for long-term prevention of CHD in persons with 10-year risk <10 percent is not well established, and in such persons, should be used more cautiously. For example, it is not known whether long-term use of nicotinic acid for lower-risk persons with isolated low HDL cholesterol is beneficial.

Evidence statements: Nicotinic acid effectively modifies atherogenic dyslipidemia by reducing TGRLP, raising HDL cholesterol, and transforming small LDL into normal-sized LDL (C1). Among lipid-lowering agents, nicotinic acid is the most effective HDL-raising drug (C1). Nicotinic acid usually causes a moderate reduction in LDL-cholesterol levels (C1), and it is the most effective drug for reducing Lp(a) levels (C1).

Evidence statements: Nicotinic acid therapy is commonly accompanied by a variety of side effects, including flushing and itching of the skin, gastrointestinal distress, glucose intolerance, hepatotoxicity, hyperuricemia, and other rarer side effects (C1). Hepatotoxicity is more common with sustained-release preparations (D1).

Evidence statement: Nicotinic acid therapy produces a moderate reduction in CHD risk, either when used alone or in combination with other lipid-lowering drugs (A2, B2).

Recommendation: Nicotinic acid should be considered as a therapeutic option for higher-risk persons with atherogenic dyslipidemia. It should be considered as a single agent in higher-risk persons with atherogenic dyslipidemia who do not have a substantial increase in LDL-cholesterol levels, and in combination therapy with other cholesterol-lowering drugs in higher-risk persons with atherogenic dyslipidemia combined with elevated LDL-cholesterol levels.

Recommendation: Nicotinic acid should be used with caution in persons with active liver disease, recent peptic ulcer, hyperuricemia and gout, and type 2 diabetes. High doses of nicotinic acid (>3 g/day) generally should be avoided in persons with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia.

4) Fibric acid derivatives (fibrates): gemfibrozil, fenofibrate, clofibrate

These drugs are summarized in Table VI.2–4. There are three fibrates—gemfibrozil, fenofibrate, and clofibrate—currently available in the United States. Other fibrate preparations, including bezafibrate and ciprofibrate, are available outside the United States. The fibrates are primarily used for lowering triglycerides because the LDL-cholesterol-lowering effects of gemfibrozil and clofibrate are generally in the range of 10 percent or less in persons with primary hypercholesterolemia. Only slight changes in LDL cholesterol are noted in persons with combined hyperlipidemia, and LDL-cholesterol levels generally rise on fibrate therapy in persons with hypertriglyceridemia.[866,867] Fenofibrate frequently reduces LDL-cholesterol levels by 15 to 20 percent when triglycerides are not elevated; other fibrates not available in the United States are also more effective in lowering LDL cholesterol.[868-870] Therapy with clofibrate and gemfibrozil reduced risk of fatal and non-fatal myocardial infarction in two large primary prevention trials,[139,149] and gemfibrozil therapy reduced CHD death and non-fatal myocardial infarction and stroke in a recently reported secondary prevention trial.[48] However, this beneficial effect on cardiovascular outcomes has not been observed in all large fibrate trials.[141,153]

Table VI.2–4. Summary of Fibric-Acid Derivatives

Available drugs	Gemfibrozil, fenofibrate, clofibrate	
Lipid/lipoprotein effects	LDL cholesterol	- ↓ 5–20% (in nonhypertriglyceridemic persons); may be increased in hypertriglyceridemic persons
	HDL cholesterol	- ↑ 10–35% (more in severe hypertriglyceridemia)
	Triglycerides	- ↓ 20–50%
Major uses	Hypertriglyceridemia, atherogenic dyslipidemia	
Contraindications	Severe hepatic or renal insufficiency	
Efficacy	Clinical trials indicate a moderate reduction in CHD risk	
Safety	Serious side effects seemingly do not occur in the long term, although early studies suggested an increase in non-CHD mortality	
Major side/adverse effects	Dyspepsia, various upper gastrointestinal complaints, cholesterol gallstones, myopathy	
Usual daily dose	Gemfibrozil	- 600 mg bid
	Fenofibrate	- 200 mg daily
	Clofibrate	- 1000 mg bid
Maximum daily dose	Gemfibrozil	- 1200 mg
	Fenofibrate	- 200 mg
	Clofibrate	- 2000 mg
Available preparations	Gemfibrozil	- 600 mg tablets
	Fenofibrate	- 67 and 200 mg tablets
	Clofibrate	- 500 mg capsules

There has been some concern about the short-term safety of the fibrates. Although nonfatal myocardial infarction fell by 25 percent in the WHO Clofibrate Study, a primary prevention study, total mortality was significantly higher in the clofibrate group, due to an increase in non-CHD deaths.[149] The use of clofibrate in general medical practice decreased markedly after this study. The Helsinki Heart Study, a primary prevention trial employing gemfibrozil, demonstrated a 37 percent reduction in fatal and non-fatal myocardial infarctions and no change in total mortality during the course of the study.[139] After 8.5–10 years of followup, non-cardiac death and all cause mortality were numerically higher in the group that had received gemfibrozil during the study.[412] However, this increase was *not* statistically significant. Moreover, after 10 years of followup, no difference in cancer rates was observed between those who had received gemfibrozil or placebo. In the Veterans Administration HDL Intervention Trial (VA-HIT),[48] a secondary prevention trial, gemfibrozil therapy reduced risk for CHD death and nonfatal myocardial infarction by 22 percent; stroke rates also were reduced by gemfibrozil therapy. In this study, there was no suggestion of an increased risk of non-CHD mortality. Neither was there an increase in non-CHD mortality from fibrate therapy in the recently reported Bezafibrate Infarction Prevention (BIP) study.[153] Furthermore, worldwide clinical experience with various fibrates is vast. No evidence of specific toxicity that enhances non-CHD mortality has emerged. This experience, taken in the light of all the clinical trials, provides little support for the concern that fibrates carry significant short-term toxicity that precludes their use for appropriately selected persons.

The mechanism of action of the fibrates is complex and there may be some variation among the drugs in this class. Recent research shows fibrates to be agonists for the nuclear transcription factor *peroxisome proliferator-activated receptor-alpha (PPAR-alpha)*.[871] Through this mechanism, fibrates downregulate the apolipoprotein C-III gene and upregulate genes for apolipoprotein A-I, fatty acid transport protein, fatty acid oxidation, and possibly lipoprotein lipase.[872] Its effects on

lipoprotein lipase and apolipoprotein C-III (an inhibitor of lipoprotein lipase) enhance the catabolism of TGRLP, whereas increased fatty acid oxidation reduces formation of VLDL triglycerides. These effects account for serum triglyceride lowering, which is the major action of fibrates. Serum triglyceride lowering combined with increased synthesis of apolipoprotein A-I and A-II tend to raise HDL-cholesterol levels.[873] Triglyceride lowering also transforms small, dense LDL into normal-sized LDL.[874] The effect of PPAR activity on other atherogenic mechanisms is now being evaluated.[875,876]

The fibrates typically reduce triglyceride by 25–50 percent; the greater reductions generally occur in severely hypertriglyceridemic individuals.[867] Fibrates usually raise HDL cholesterol by 10–15 percent, but greater increases can occur in persons with very high triglyceride levels and very low HDL-cholesterol levels. Thus fibrates, like nicotinic acid, primarily target atherogenic dyslipidemia. In addition, the ability of fibrates to lower triglycerides has led to their wide usage in persons having very high triglyceride levels and chylomicronemia.[867] The purpose of fibrate therapy in such persons is to reduce the risk for acute pancreatitis. Their value for this purpose is well recognized. Finally, fibrates are highly effective for reducing beta-VLDL concentrations in persons with dysbetalipoproteinemia.[877]

Whether fibrate modification of atherogenic dyslipidemia reduces risk for CHD is an important issue. Results of clinical trials with fibrates are summarized in Tables II.3–3 and II.3–4. The major primary prevention trials were the WHO clofibrate trial and the Helsinki Heart Study gemfibrozil trial.[139,149] In both trials, CHD incidence was significantly reduced by fibrate therapy. Early secondary prevention trials with clofibrate therapy gave suggestive evidence of CHD risk reduction. In another secondary prevention trial, the Coronary Drug Project, clofibrate therapy failed to significantly reduce risk for CHD.[141] Likewise, in the BIP trial, bezafibrate therapy did not significantly reduce recurrent major coronary events in persons with established CHD.[153] In contrast, gemfibrozil therapy in the VA-HIT[48] trial showed wide benefit by significantly reducing CHD events and strokes in persons with established CHD (Table II.3–4 and Table II.8–3b). Thus, taken as a whole, clinical trials of fibrate therapy strongly suggest a reduction in CHD incidence, although results are less robust than with statin therapy. Further, a reduction in total mortality, which would have required a greater reduction in CHD mortality than observed, has not been demonstrated with fibrate therapy (see Table II.9–1). This failure does not rule out a benefit of fibrate therapy but certainly suggests less efficacy than with statin therapy.

Several studies have employed fibrates in combination with LDL-lowering drugs in persons with combined hyperlipidemia (elevated LDL + atherogenic dyslipidemia). Combination therapy improves the overall lipoprotein profile compared to either fibrates or LDL-lowering drugs alone. This finding has led to a movement for considering use of fibrates in combination with statins in high-risk individuals whose triglyceride levels are still elevated. In some persons, this combination may better achieve the secondary target for non-HDL cholesterol than will statins alone. Nonetheless, to date no clinical trials have been published that compare statins vs. statins + fibrates on CHD outcomes.

The fibrates are generally well-tolerated in most persons. Gastrointestinal complaints are the most common complaints. All drugs in this class appear to increase the lithogenicity of bile, increasing the likelihood of cholesterol gallstones.[878] A portion of the excess deaths reported in the WHO Clofibrate Study was related to gallstone disease.[879] The fibrates bind strongly to serum albumin and so may displace other drugs that bind with albumin. For example, fibrates displace warfarin from its albumin-binding sites, thereby increasing the latter's anticoagulant effect. Fibrates are excreted primarily by the kidney; consequently, elevated serum levels occur in persons with renal failure and risk for myopathy is greatly increased. The combination of a fibrate with a statin also increases the risk for myopathy, which can lead to rhabdomyolysis.[823,880] None of these well-established side effects can account for the increased total mortality observed in the WHO clofibrate study.[881,882] The increase in non-CHD deaths remains unexplained. An increase in non-CHD mortality has not been confirmed by subsequent trials with fibrate therapy.

Evidence statements: Fibrates are effective for modifying atherogenic dyslipidemia, and particularly for lowering serum triglycerides (C1). They produce moderate elevations of HDL cholesterol (C1). Fibrates also are effective for treatment of dysbetalipoproteinemia (elevated beta-VLDL) (C1). They also can produce some lowering of LDL, the degree of which may vary among different fibrate preparations (C1). Fibrates also can be combined with LDL-lowering drugs in treatment of combined hyperlipidemia to improve the lipoprotein profile, although there is no clinical-trial evidence of efficacy for CHD risk reduction with combined drug therapy (C1, D1).

Evidence statements: Fibrate therapy moderately reduces risk for CHD (A2, B1). It may also reduce risk for stroke in secondary prevention (A2).

Evidence statements: Evidence for an increase in total mortality due to an increased non-CHD mortality, observed in the first large primary prevention trial with clofibrate, has not been substantiated in subsequent primary or secondary prevention trials with other fibrates (gemfibrozil or bezafibrate) (A2, B1). Nonetheless, fibrates have the potential to produce some side effects. Fibrate therapy alone carries an increased risk for cholesterol gallstones (A2), and the combination of fibrate and statin imparts an increased risk for myopathy (B2).

Recommendations: Fibrates can be recommended for persons with very high triglycerides to reduce risk for acute pancreatitis. They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-VLDL). Fibrate therapy should be considered an option for treatment of persons with established CHD who have low levels of LDL cholesterol and atherogenic dyslipidemia. They also should be considered in combination with statin therapy in persons who have elevated LDL cholesterol and atherogenic dyslipidemia.

c. Other drugs

Probucol is no longer available in the United States and in most other countries. This drug has powerful antioxidant properties, which is theoretically beneficial. In one angiographic trial, probucol therapy failed to retard femoral atherogenesis; neither was a reduction in CHD risk observed. There is some current interest in reports that probucol reduced the restenosis rates following angioplasty.[883,884]

d. n-3 (omega) fatty acids

n-3 fatty acids (linolenic acid, DHA, and EPA) have two potential uses. In higher doses, DHA and EPA lower serum triglycerides by reducing hepatic secretion of triglyceride-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. They are available in capsules of fish oil, and doses of 3–12 g/day have been used depending on tolerance and severity of hypertriglyceridemia.

Recent clinical trials also suggest that relatively high intakes of n-3 fatty acids (1–2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce risk for major coronary events in persons with established CHD (see Section V.3.c). Although this usage falls outside the realm of "cholesterol management," the ATP III panel recognizes that n-3 fatty acids can be a therapeutic option in secondary prevention. The n-3 fatty acids are recommended only as an option because the strength of the clinical trial evidence is moderate at present. The n-3 fatty acids can be derived from either foods (n-3 rich vegetable oils or fatty fish) or from fish-oil supplements. In the view of the ATP III panel, more definitive clinical trials are required before relatively high intakes of n-3 fatty acids (1–2 g/day) can be strongly recommended for either primary or secondary prevention.

e. Hormone replacement therapy (HRT)

Risk for CHD is increased in postmenopausal women whether the menopause is natural, surgical, or premature.[885-887] Loss of estrogen has been proposed as a cause for increased risk. This putative mechanism was strengthened by results of numerous case-control and epidemiological studies which suggested that either

Table VI.2–5. Major Characteristics and Outcomes of HERS Trial

Patient Characteristics	Study Design	Clinical Outcomes (E+P vs. Placebo)	Side Effects
2,763 postmenopausal women	Randomized, double-blind	CHD events 172 vs. 176	Thromboembolic events (E+P ≥ placebo)
Age <80 years (mean age 67 years)	Placebo vs. 0.625 mg of conjugated equine estrogens and 2.5 mg medroxyprogesterone acetate (E+P)	CHD death 71 vs. 58	Gallbladder disease (E+P ≥ placebo)
History of CHD	Duration: 4.1 years	Non-fatal MI 116 vs. 129	
Absent hysterectomy			
BMI >27 kg/m2			
45% on lipid-lowering drugs at entry			

estrogen alone, or in combination with progestin, reduces risk for CHD in primary and secondary prevention. However, benefit of estrogen replacement was not confirmed in a secondary prevention trial, the Heart and Estrogen/progestin Replacement Study (HERS).[493] A subsequent angiographic study also revealed no apparent benefit from HRT.[888] The major features of the HERS trial are shown in Table VI.2–5.

As shown in the table, estrogen/progestin replacement produced no overall benefit for the entire duration of the trial. Moreover, both CHD death and non-fatal myocardial infarction were increased, especially during the first year. Estrogen/progestin (E+P) replacement increased risk for thromboembolic events and caused more gallbladder disease.[493,889] Thus, E+P produced no overall benefit for the entire study and increased risk for CHD events, thromboembolic events, and gallbladder disease in the early phase of the trial. There was a suggestion, however, that E+P reduced non-fatal myocardial infarction in the latter years of the trial. A 3-year followup study is currently in progress. The overall interpretation of the trial by the investigators was that HRT should not be initiated in postmenopausal women with CHD for the purpose of reducing risk of CHD, but if women had already been on HRT for a period of time, they could continue, with the expectation that there may be some later benefit. The mechanism for the early increase in CHD events and increased thromboembolic events has not been clearly defined, but it appears that E+P administration was associated with a prothrombotic tendency.

Estrogen therapy favorably influences lipid and lipoprotein levels, but this did not translate into a reduction in CHD risk in the HERS trial. In postmenopausal women, orally administered estrogen preparations (0.625 mg of conjugated estrogen or 2 mg of micronized estradiol) reduce LDL-cholesterol levels by 10–15 percent and increase HDL-cholesterol levels up to 15 percent.[890-892] Co-administration of progestin may decrease the HDL-cholesterol-raising effect of estrogen. In the HERS trial, the mean difference between E+P minus placebo was an 11 percent decrease in LDL cholesterol, a 10 percent increase in HDL cholesterol and an 8 percent increase in triglycerides.

There is no definitive explanation for why the epidemiologic/observational studies provided markedly different results from the HERS trial. The HERS trial clearly demonstrates the need for controlled clinical trials. Some investigators postulate that if lower doses of estrogen, different progestins, younger age group, estrogen only, or women without CHD had been employed, the results may have been different. The NHLBI Women's Health Initiative is utilizing the same hormonal preparation in a wide range of ages in an estrogen-only and in an estrogen/progestin group in women without CHD.[683] This trial may answer some of the questions, but the results will probably not be available before 2003. There is also a possibility of an increased risk of breast cancer with prolonged HRT.[893-897]

Evidence statements: Hormone replacement therapy in postmenopausal women does not reduce risk for major CHD events or coronary deaths in secondary prevention (A2). Moreover, hormone replacement therapy carries an increased risk for thromboembolism and gallbladder disease (A2).

Recommendation: Hormonal replacement therapy cannot be recommended for the express purpose of preventing CHD. Instead, control of risk factors should be the primary approach to reducing CHD risk in women. There may be other valid reasons for hormonal replacement therapy, such as for management of perimenopausal and postmenopausal symptoms or for treatment or prevention of osteoporosis.

1) Selective estrogen receptor modulators (SERM)—Raloxifene

A number of SERMs are under development. Raloxifene imparts benefits similar to those of HRT on bone density in postmenopausal women. Raloxifene also has an LDL-cholesterol-lowering effect similar to that of estrogen, but the HDL-raising effect appears to be less.[898] Clinical trials to evaluate its effect on CHD risk are underway. Again, until controlled clinical trials are available that demonstrate a reduction in CHD risk, this class of drugs should not be considered for the purpose of CHD prevention. SERMs also increase the risk of thromboembolic events.

f. Miscellaneous drugs and therapeutic approaches

1) Investigational drugs

Many new cholesterol-lowering drugs with a wide range of mechanistic actions are currently in various phases of development. It is still too early to predict which drugs will be approved by the FDA and what their long-term toxicities may be. They will also have the near-term disadvantage of lacking clinical trials documenting a reduction in CHD clinical events.

2) Other approaches

With the advent of statins, effective control of LDL-cholesterol levels can now be achieved in the majority of persons with either monotherapy or drug combinations. Persons with severe forms of hypercholesterolemia or other hyperlipidemias who cannot be adequately controlled should be referred to a center specializing in lipid disorders. LDL apheresis is now available for persons with very high LDL levels, but the procedure is costly and time-consuming. The FDA recently approved two commercial techniques for this purpose: (1) a heparin-induced extracorporeal lipoprotein precipitation, and (2) a dextran sulfate cellulose adsorbent for removal of lipoproteins.

3. Selection of drugs for elevated LDL cholesterol

Reduction in serum concentrations of LDL cholesterol is the primary approach to lowering the risk of CHD in both primary and secondary prevention. In persons whose triglycerides are elevated along with LDL cholesterol, it may also be desirable to lower triglycerides and increase HDL-cholesterol concentrations. Several factors influence the selection of initial drug therapy in individual persons. These include the lipoprotein profile and magnitude of change needed to attain goals of therapy, concurrent drug therapies that may increase the risk of side effects with specific drugs, and the presence of other medical disorders that may influence drug metabolism or be adversely influenced by a specific hypolipidemic drug.

Statins are the most effective class of drugs for reducing LDL-cholesterol concentrations: they are well tolerated, easy to administer, and they are usually the first drugs used. Five statins (lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin) are approved for clinical use in the United States.* Available statins differ somewhat in the degree of LDL-cholesterol lowering that can be achieved per mg dose. In addition, the metabolic clearance of these drugs also vary. Simvastatin and lovastatin undergo metabolic inactivation by the 3A4 isozyme of cytochrome P-450 (CYP 3A4); atorvastatin is also a substrate for CYP 3Y4, though some of its metabolites remain active; and fluvastatin is metabolized by CYP 2C9. Pravastatin appears not to be metabolized by the P-450 system. These differences can have implications for drug-drug interactions, particularly where the concern is myopathy related to elevated systemic levels of the statin. Statins vary in the dose required to produce a given degree of LDL lowering. Whether different doses that

* Cerivastatin was withdrawn from the market by the manufacturer in August, 2001.

produce the same degree of LDL lowering differ in side effect profiles is unknown because of a lack of direct comparison studies. For all statins, the incidence of side effects increases with higher doses. The degree of LDL lowering that is required to achieve target goals and the percent of LDL lowering that is seen with the usual starting dose and maximum dose of the statins are illustrated in Table VI.3–1. In general, for every doubling of the dose of a statin, LDL levels fall by approximately 6 percent.

The dose of statin required to achieve target goals can be extrapolated from Table VI.3–1. However, the response of an individual may vary considerably and cannot be predicted. The LDL response may be influenced by a number of factors, including diet and drug compliance, the genetic cause of hypercholesterolemia, gender and hormonal status, apo E phenotype, and differences in drug absorption and metabolism. There is a tendency in current clinical practice to initiate therapy with the usual starting dose, but the dose often is not titrated upwards to achieve target goals. Persons requiring large LDL reductions will never achieve target goals with the starting dose of some statins. Since the absolute incidence rates of side effects are not much greater at higher doses of currently available preparations, persons requiring major LDL-cholesterol lowering should be started on doses (or their equivalents) used in most clinical trials. Doses can then be increased as needed to achieve the recommended LDL goal. Alternatively, a second LDL-lowering drug (e.g., bile acid sequestrant or nicotinic acid) can be added to standard doses of statin.

Table VI.3–1. Achieving Target LDL-Cholesterol (LDL-C) Goals (mg/dL)

Baseline LDL-C	130	160	190	220
(Percent Reduction to Achieve Target Goals)				
Target LDL-C <100	23	38	47	55
Target LDL-C <130	—	19	32	41
Target LDL-C <160	—	—	16	27

Average Percent Reduction in LDL Cholesterol With Usual Starting Dose and Maximal Statin Dose*

		Starting Dose	Maximum Dose
Lovastatin	20, 80 mg	24%	40%†
Pravastatin	20, 80 mg	24%	34%†
Simvastatin	20, 80 mg	35%	46%
Fluvastatin	20, 80 mg	18%	31%
Atorvastatin	10, 80 mg	37%	57%

* Maximum dose currently approved by the FDA.
† Administered in divided doses.

The bile acid sequestrants are the second most effective class of drugs for lowering LDL-cholesterol levels. They are particularly useful in combination with statins to achieve major reductions in LDL-cholesterol levels. They can either be added to a statin when maximal doses of statin have not achieved target goals, or they can be added to lower doses of statin if there are concerns about the tolerability and side effects of higher doses. Cholestyramine (8–16 g/day) or colestipol (10–20 g/day) usually produce 10–20 percent reductions in LDL cholesterol when administered as monotherapy, and colesevelam lowers LDL cholesterol by 12–18 percent. Similar reductions in LDL cholesterol are noted when the sequestrants are added to low doses of statins, but the additional LDL-cholesterol lowering is less when added to statins given at higher doses. For purposes of drug safety, bile acid sequestrants can be considered as monotherapy in younger persons, women considering pregnancy, and when only modest LDL lowering is needed.

The LDL-cholesterol-lowering effects of nicotinic acid are usually modest and can be quite variable. Reductions in LDL of 5–23 percent have been noted with doses of 1.5–4.5g of crystalline nicotinic acid and 10–20 percent at 2.0–3.0g of Niaspan®.[147,856,899,900] Nicotinic acid should be considered if additional LDL-cholesterol lowering is required after statin administration, especially in persons who do not tolerate sequestrants or who prefer to take medication in tablet form. Nicotinic acid is also considered if, in addition to LDL-cholesterol lowering, increases in HDL cholesterol and decreases in triglycerides and Lp(a) are needed.

The fibrates usually do not significantly enhance LDL-cholesterol lowering when added to a statin. However, if a patient is not at LDL target level and has not tolerated a bile acid sequestrant or nicotinic acid, addition of fenofibrate may enhance LDL lowering in some patients;[901] it may also be useful if the patient has concomitant atherogenic dyslipidemia.[902]

The use of drugs for treatment of other forms of dyslipidemia (severe hypercholesterolemias, isolated low HDL, hypertriglyceridemias, diabetic dyslipidemia, and other secondary forms of hyperlipidemia) are considered in Section VII.

a. Practical advice on combined drug therapy

Some persons will require combined drug therapy to reach ATP III treatment goals. Combination therapy may be needed to provide additional reduction of LDL cholesterol, to achieve the goal for non-HDL cholesterol, to treat severe hypertriglyceridemia, and if it seems advisable, to raise HDL-cholesterol levels. Although it seems desirable to improve the overall lipoprotein profile with combined drug therapy, major randomized controlled trials have not been carried out to test for efficacy and safety in large numbers of persons. Nonetheless, several smaller trials and angiographic trials have provided evidence of positive benefit from combined drug therapy.

1) Statin—bile acid sequestrant combination

In the majority of persons who are treated with a statin, the LDL-cholesterol goal can be reached. However, in persons with severe polygenic or familial hypercholesterolemia, a statin alone may not be enough. In these cases, combination therapy with a bile acid sequestrant or nicotinic acid added to the statin, or a sequestrant-nicotinic acid combination, should be considered for additional LDL-cholesterol lowering. Of these, the statin-sequestrant combination may be the most effective, reducing LDL cholesterol by as much as 70 percent. The alternative combinations are generally less effective.

Following are practical considerations when utilizing statins and sequestrants in combination.

- The dose of the sequestrant in the statin-sequestrant combination can be low or moderate. Higher doses do not appear to add signficiantly to LDL-cholesterol-lowering efficacy.[903-905]
- Since the statin-sequestrant combination may more effectively lower LDL than a maximum dose of statin, consideration should be given to use of a combination approach early in the course of treating persons with very high LDL-cholesterol levels.[841,905]
- The LDL-cholesterol lowering achieved with the statin-sequestrant combination appears to have a ceiling beyond which there is little if any additional LDL lowering even if the statin or sequestrant doses are further increased. In these cases, consideration can be given to adding a third agent, such as nicotinic acid. Bile acid sequestrants will reduce the bioavailability, but not the LDL-lowering action, of the statin when administered together. Thus, the drugs may be given together. However, it is probably best to give the statin at night (bedtime) and the sequestrant with each meal. It is not necessary to separate the time of administration of colesevelam and statins.
- If the statin-sequestrant combination is not successful in achieving the LDL-cholesterol goal, addition of nicotinic acid to the combination can be considered.[467] Studies have shown that the use of Niaspan® provides equivalent effect on lipid parameters and is better tolerated than immediate release of nicotinic acid.[863]

2) Statin—fibrate combination therapy

The combination of statins and fibrates has proven to be highly effective for improvement of the lipoprotein profile in patients with combined hyperlipidemia.[902,906-908] It also may be useful for patients with elevated LDL cholesterol and atherogenic dyslipidemia. A statin + fibrate can reduce both LDL cholesterol and VLDL cholesterol (i.e., non-HDL cholesterol) in patients with elevated triglycerides. Since the primary aim of cholesterol management is LDL reduction, statin therapy usually will be introduced before fibrates. In some patients with high triglycerides, both LDL and non-HDL goals can be attained with higher doses of statins. However, an alternative approach is to use a statin + fibrate. To date no clinical trials have been carried out in patients with hypertriglyceridemia to document the relative value of these two approaches.

The major concern about this combination is the potential for occurrence of myopathy. In the past, this combination was widely thought to be "contraindicated" because of the potential danger of myopathy. More recently, statin-fibrate combination therapy has been used with apparent safety in the majority of persons. It should be noted that the specific combination of cerivastatin and gemfibrozil caused

more clinical myopathy than is noted with other statin drugs. This is one factor that led to the voluntary withdrawl of cerivastatin from the market. Several key points must be kept in mind when using statin-fibrate combination therapy.

- Ensure that the patient has normal renal function.
- Ensure that there are no potential drug interactions that could increase the systemic blood levels of either the statin or fibrate.
- Limit the initial dose of the statin to a starting or intermediate dose when combining it with a fibrate. The dose of statin can then be increased cautiously.
- Teach the patient to recognize and report symptoms of muscle soreness, tenderness, and pain.
- Obtain a creatine kinase (CK) blood level prior to beginning combination therapy to document the patient's baseline level. Repeat this measurement if the patient reports muscle symptoms suggestive of myopathy.
- If the patient experiences muscle soreness, tenderness, or pain, with or without CK elevations, rule out common causes such as exercise or strenuous work. Advise moderation in activity for persons who experience this finding during combination therapy.
- Discontinue combination therapy if a CK greater than ten times the upper limit of normal (ULN) is encountered in a patient with muscle soreness, tenderness, or pain. Wait for symptoms to vanish and CK levels to return to normal before reinitiating therapy with either drug and use a lower dose of the drug(s).

If the patient experiences muscle soreness, tenderness, or pain with either no CK elevation or a moderate elevation (i.e., between three and ten times the upper limit of normal), monitor the patient's symptoms and CK levels until symptoms resolve and the CK returns to normal or until the clinical situation worsens to the point described above, mandating discontinuation of therapy. Following are summary comments reflecting current experience with these issues.

- Although not consistent in the literature, the general terminology used to describe muscle toxicity with these agents includes *myalgia* to reflect muscle symptoms without CK elevations, *myositis* for increased CK levels without muscle symptoms, and *myopathy* for muscle symptoms with CK elevations. Severe myopathy *(rhabdomyolysis)* may subsequently occur. Technically, all of these terms fall under the category of *myopathy*.
- Statin therapy appears to carry a small but definite risk of myopathy when used alone. According to several large databases, the incidence of myopathy is reported to be 0.08 percent with lovastatin and simvastatin.[816,820,909] Elevations of CK greater than ten times the ULN have been reported in 0.09 percent of persons treated with pravastatin. All currently marketed statins appear to have a similar potential for causing this adverse effect.
- Fibrate treatment alone appears to be associated with some risk of muscle toxicity, although probably less than that of statins.
- Of the nearly 600 persons who have participated in controlled clinical trials of a statin and fibrate combination, 1 percent have experienced a CK greater than three times ULN without muscle symptoms and 1 percent have been withdrawn from therapy because of muscle pain.[814,902,910-915] None of these events were considered serious. No cases of rhabdomyolysis or myoglobinuria have been encountered in these clinical trials. The experience in these trials is predominantly with lovastatin and gemfibrozil. Other statin-fibrate combinations may well give similar results. A prior report from FDA surveillance of a 30 percent incidence of myopathy associated with a statin-fibrate combination and a 5 percent incidence of myopathy associated with a statin-nicotinic acid combination appears to be a gross overestimate of the problem.[823]

3) Statin—nicotinic acid combination therapy

This combination is attractive because of the favorable effects of nicotinic acid on atherogenic dyslipidemia. Combining the powerful LDL-lowering action of statins with the triglyceride-lowering and HDL-raising actions of nicotinic acid offers the potential to correct most forms of complex dyslipidemias. The relative inexpensiveness of nicotinic acid also makes for an attractive combination. Several small-scale clinical trials speak to the efficacy of this combination for

modifying an abnormal lipoprotein pattern and even for favorably affecting coronary outcomes.[158] The disadvantages of the combination lie mainly in the side effect profile of nicotinic acid. There is little evidence that the combination is synergistic in producing side effects. Whether the statin-nicotinic acid combination increases the risk for myopathy is uncertain. Some investigators have found that combining relatively small doses of nicotinic acid with a statin produces an improvement in the lipoprotein profile comparable to that obtained with a statin-fibrate combination, and probably with a lower risk for myopathy.[916] This potential advantage, however, may be offset by the inability of some persons to tolerate the side effects of nicotinic acid.

4) Fibrate—nicotinic acid combination therapy

This combination has not been studied extensively, but it is attractive for atherogenic dyslipidemia. In the Stockholm Ischaemic Heart Disease study, a fibrate (clofibrate) + nicotinic acid significantly reduced CHD events in persons with established CHD.[152] Otherwise, it is largely untried.

4. Initiation, monitoring and followup of drug treatment

a. Initiation of LDL-lowering drug therapy

Consideration should be given to starting statin therapy for LDL reduction simultaneously with TLC in persons with CHD or a CHD equivalent who have LDL ≥130 mg/dL (see previous discussion on drug options when LDL-cholesterol levels are in the range of 100–129 mg/dL). Initiation of drug therapy seems especially advisable when the patient is hospitalized for an acute coronary event or intervention. When therapy is begun in this setting, persons have demonstrated a very high adherence rate, presumably because of the associated importance of the treatment in preventing recurring events. Early initiation of statin therapy also takes advantage of effects of LDL lowering on endothelial function and plaque stabilization.

Consideration may also be given to starting statin therapy simultaneously with TLC in primary prevention persons who have marked hypercholesterolemia, where it is clear that diet alone will not reduce the patient's LDL cholesterol to goal.

In all other persons, a period of lifestyle modification should precede initiation of drug therapy. This period should be long enough for persons to integrate TLC into their routine and for the effects of this intervention to be manifest. Generally, no more than 3 months is required.

b. Baseline measurements

Prior to initiating drug therapy, baseline lipid and lipoprotein measurements that will be used to follow the drug's efficacy and safety should be documented. Except for acute hospitalization, the initial lipoprotein profile upon which treatment decisions are based should be the average of two measurements done one to four weeks apart while the patient is consistently following a low-fat diet. Baseline measurements also include liver function tests (i.e., ALT or AST), CK and appropriate medical history. Table VI.4–1 lists selected baseline and followup measures for other lipid-modifying drug therapy.

c. Interval of follow up

With good adherence, maximum LDL lowering, as well as lowering of triglyceride and raising of HDL cholesterol, is achieved within 6 weeks of initiating drug therapy. Thus, the first followup visit should occur 6–8 weeks after initiating drug therapy. In the case of nicotinic acid, where doses must be titrated by the patient to a therapeutic level, the first followup visit should occur 6–8 weeks after the patient has reached the initial targeted dose, generally 1,000–1,500 mg daily. If the dose is increased, monitoring should be continued at 6–8 weeks until the final dose is determined.

If the initial dose of the drug must be increased or another drug added in an effort to reach the treatment goal(s), the patient should be seen in another 6–8 weeks for followup evaluation of the new drug regimen. This process should be repeated until the patient has reached his/her treatment goal(s).

Once the patient has achieved the treatment goal(s), followup intervals may be reduced to every 4–6 months. The primary focus of these visits is encouragement of long-term adherence with therapy. Lipoprotein profiles should be assessed at least annually, and preferably at each clinic visit to promote compliance.

Table VI.4–1. Monitoring Parameters and Followup Schedule

Drug	Monitoring Parameters	Followup Schedule
Bile Acid Sequestrants	Indigestion, bloating, constipation, abdominal pain, flatulence, nausea	Evaluate symptoms initially, and at each followup visit. Also check time of administration with other drugs.
Nicotinic Acid	Flushing, itching, tingling, headache, nausea, gas, heartburn, fatigue, rash	Evaluate symptoms initially, and at each followup visit.
	Peptic ulcer	Evaluate symptoms initially, then as needed.
	Fasting blood sugar (FBS) Uric acid	Obtain an FBS and uric acid initially, 6–8 weeks after starting therapy, then annually or more frequently if indicated to monitor for hyperglycemia and hyperuricemia.
	ALT and AST	Obtain an ALT/AST initially, 6–8 weeks after reaching a daily dose of 1,500 mg, 6–8 weeks after reaching the maximum daily dose, then annually or more frequently if indicated.
Statins	Muscle soreness, tenderness or pain	Evaluate muscle symptoms and CK initially. Evaluate muscle symptoms at each followup visit. Obtain a CK when persons have muscle soreness, tenderness, or pain.
	ALT, AST	Evaluate ALT/AST initially, approximately 12 weeks after starting, then annually or more frequently if indicated.
Fibrates	Abdominal pain, dyspepsia, headache, drowsiness	Evaluate symptoms initially, and at each followup visit.
	Cholelithiasis	Evaluate history and symptoms initially, and then as needed.

d. Followup treatment decisions

Followup visits are used to enhance adherence and to determine whether persons have achieved their treatment goal(s). If they have not, changes in the drug regimen should be made to attempt to reach these goals. In most cases, LDL goals can be achieved by titrating doses of the statin or bile acid sequestrant upward to the maximum recommended dose. This may be done systematically one step at a time. For example, the dose of a statin may be doubled at each visit to achieve an additional 6–7 percent LDL lowering with each dose titration. However, when the difference between the patient's on-treatment LDL cholesterol and his/her goal is great, consideration may be given to making larger changes in the drug dose. Alternatively, another LDL-lowering drug may be added (e.g., adding a bile acid sequestrant to a statin), as described above. If the decision is made to replace a less efficacious statin with a more efficacious one to achieve the LDL goal, one statin may be discontinued and the new statin started the next day. A dose titration scheme for commonly used lipid-modifying drugs is presented in Table VI.3–1.

If a patient has high triglycerides (≥200 mg/dL) the non-HDL-cholesterol goal should be addressed. If the patient was earlier treated with a statin to achieve the LDL goal, increasing its dose beyond that used to reach the LDL goal may assist in reaching the non-HDL-cholesterol goal. In many instances, however, reaching the non-HDL-cholesterol goal will require the addition of a triglyceride-lowering drug such as nicotinic acid or a fibrate to the LDL-lowering drug. Clinical experience suggests that if nicotinic acid is selected, the immediate release and polygel sustained-release dosage form (Niaspan®) should be titrated to 1,000–1,500 mg daily by the patient before a followup assessment visit is scheduled. If needed, immediate release nicotinic acid may be further titrated to 3,000 mg daily. If a fibrate is selected, dose titrations are not needed as the initial dose is also the maximum dose. Followup visits for these assessments may also be scheduled 6–8 weeks apart.

Detection

VII. Management of Specific Dyslipidemias

Evaluation

Treatment

VII. Management of Specific Dyslipidemias

Randomized clinical trials generally have not focused on specific dyslipidemias. Yet these disorders are common enough to deserve specific attention in ATP III. In this section, the major dyslipidemias will be reviewed. Recommendations for their management are derived from the considered judgment of the ATP III panel. Recommendations are based in part on the sizable body of literature that describes changes in serum lipid and lipoprotein levels produced by dietary and drug therapies. In some dyslipidemias, combined drug therapy is required to obtain optimal lipoprotein profiles. In general, improvements in lipoprotein profiles rather than favorable clinical outcomes are the endpoints that serve as the basis for recommendations. These recommendations are made with the recognition that some induced changes in the lipoprotein profile have not been proven through clinical trial to reduce risk for CHD. Instead, they generally represent a synthesis of several lines of indirect evidence.

1. Very high LDL cholesterol

Severe forms of elevated LDL cholesterol are defined as those in which LDL concentrations are persistently ≥190 mg/dL after TLC. Most elevations of this degree have a strong genetic component. Table VII.1–1 identifies three familial forms of elevated LDL cholesterol, i.e., familial hypercholesterolemia (heterozygous and

Table VII.1–1. Familial Disorders That Cause Very High LDL-Cholesterol Levels (≥190 mg/dL)

Clinical Condition	Clinical Features and Clinical Outcomes	Therapeutic Considerations
Heterozygous familial hypercholesterolemia (FH)	■ Due to mutated LDL receptor (half normal-expression) ■ Prevalence: 1/500 in United States ■ LDL-C levels: twice normal (e.g., 190–350 mg/dL) ■ Tendon xanthomas common ■ Premature CHD common – 30–40's in men – 40–50's in women	■ Begin LDL-lowering drugs in young adulthood ■ TLC indicated for all persons ■ Statins: first line of therapy (start dietary therapy simultaneously) ■ BAS* (if necessary in combination with statins) ■ If needed, consider triple-drug therapy (statins + BAS + nicotinic acid)
Homozygous familial hypercholesterolemia (FH)	■ Due to two mutated LDL receptors ■ Prevalence: 1/1,000,000 in United States ■ LDL-C levels: 4-fold increase (e.g., 400–1000 mg/dL) ■ Xanthomas: tendinous, tuberous, dermal ■ Widespread, severe atherosclerosis (multiple arterial beds affected) ■ Very severe clinical atherosclerotic disease ■ Aortic valve disease	■ Dietary therapy not effective ■ BAS not effective ■ Nicotinic acid mildly effective ■ Statins may be moderately effective in some persons ■ Ileal exclusion operation not effective ■ Liver transplant effective, but impractical ■ LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia)
Familial defective apolipoprotein B-100 (FDB)	■ Due to mutated apo B-100 (position 3500 A→G) ■ Prevalence 1/700–1000 ■ LDL-C levels: 1.5–2-fold increase (e.g., 160–300 mg/dL) ■ Xanthomas: tendon ■ Premature CHD – CHD 40–65yr common in men – Uncertain in women	■ TLC indicated ■ All LDL-lowering drugs are effective ■ Combined drug therapy required less often than in heterozygous FH
Polygenic hypercholesterolemia	■ Due to multiple gene polymorphisms (often combined with dietary excesses) ■ Prevalence: 1/10–20 (depending on age) ■ LDL-C: ≥190 mg/dL ■ Prevalence of CHD: 3–4-fold increase (above average)	■ TLC indicated for all persons ■ Consider for drug therapy (if LDL-C ≥190 mg/dL after dietary therapy [all persons]) ■ All LDL-lowering drugs are effective ■ If necessary to reach LDL-C goals, consider combined drug therapy

* BAS=bile acid sequestrants.

homozygous forms), familial defective apolipoprotein B-100, and polygenic hypercholesterolemia. Clinical features, clinical outcomes, and therapeutic considerations are listed in the table and are discussed in more detail below.

a. Familial hypercholesterolemia (FH)

Heterozygous familial hypercholesterolemia. This autosomal-dominant disorder occurs in 1 of every 500 people.[917] The defect is a mutation in the gene for the LDL receptor;[8] a large number of mutations affecting LDL receptor function has been reported.[918,919] In all of these, half the normal number of receptors are expressed. Hypercholesterolemia often is detectable at birth or shortly thereafter, and total cholesterol levels eventually rise to 350–500 mg/dL in many persons. Tendon xanthomas, especially in the Achilles tendons and the extensor tendons of the hands, are typical. FH carries increased risk of premature CHD; CHD commonly occurs in men by the fourth or fifth decade, and about 10 years later in women. Treatment for FH heterozygotes should begin with TLC, but drug therapy is generally required as well. For adults with heterozygous FH, LDL-lowering drugs should be initiated as soon as it is recognized that the LDL-cholesterol goal cannot be achieved with TLC alone. Persons with milder forms of heterozygous FH may respond sufficiently to therapy with a bile acid sequestrant or a statin. More severe cases require two-drug therapy (e.g., statin plus bile acid sequestrant)[800,803] or even triple-drug therapy (statin plus bile acid sequestrant plus nicotinic acid)[920,921]. Because of the high risk of premature CHD accompanying heterozygous FH, drug therapy is cost-effective.

Homozygous familial hypercholesterolemia occurs in only 1 in 1 million persons.[917] LDL-receptor activity is essentially absent, and total cholesterol levels commonly run between 700 and 1,200 mg/dL. Cutaneous xanthomas form at various sites within the first few months or years of life, whereas tendon and tuberous xanthomas develop later. Atherosclerosis is severe and widespread, affecting coronary, carotid, iliac, and femoral arteries, and the aortic root. Treating FH homozygotes is difficult because the persons express little or no LDL-receptor activity and therefore are resistant to the effects of therapeutic diets and most cholesterol-lowering medications. High doses of statins may produce some cholesterol reduction in a few FH homozygotes, as does nicotinic acid. In the past, various surgical procedures have been tested. Ileal bypass surgery is not effective. Portacaval shunt surgery only modestly lowers LDL levels.[922-924] Liver transplantation provides new LDL receptors that dramatically reduce LDL-cholesterol levels;[923] further, responsiveness to LDL-lowering drugs returns. However, transplantation requires continuous immunosuppression and is not a practical approach. Current accepted therapy consists of modified forms of plasmapheresis that selectively remove VLDL and LDL from the plasma. Early studies laid the foundation for this approach.[925-929] The FDA has more recently approved commercial techniques for this purpose: (a) heparin-induced extracorporeal lipoprotein precipitation, and (b) a dextran sulfate cellulose absorbent. Such treatment must be performed every 1 to 3 weeks, depending on the clinical state of the patient, in order to promote xanthoma regression and retard atheroma formation.

b. Familial defective apolipoprotein B-100 (FDB)

FDB is an autosomal dominant abnormality that causes elevated LDL cholesterol.[930-933] It results from a single nucleotide mutation that substitutes glutamine for arginine at amino acid position 3,500 in apolipoprotein B. This mutation reduces affinity of LDL particles for the LDL receptor; consequently, the LDL of affected individuals is cleared from plasma more slowly than normal. FDB prevalence varies among different populations. In the United States it occurs in about 1 in 700–1000 people.[932] Serum LDL levels are often similar to those described for persons with heterozygous FH. Affected individuals can manifest premature atherosclerosis and tendon xanthomas. However, other affected individuals have a more moderate form of hypercholesterolemia, indistinguishable from polygenic hypercholesterolemia (see below). The diagnosis requires molecular screening techniques available only in specialized laboratories. Treatment is similar to that of heterozygous FH; however, less intensive intervention may achieve the goals of therapy.[934]

c. Polygenic hypercholesterolemia

LDL-cholesterol levels ≥190 mg/dL characterize polygenic hypercholesterolemia. No unique genetic defect is responsible; rather the high LDL-cholesterol level is explained by a complex interaction of environmental and genetic factors. A variety of patterns of LDL

metabolism have been reported.[935] The disorder is associated with increased risk for premature CHD. In polygenic hypercholesterolemia, the elevation in plasma cholesterol is generally milder than in heterozygous FH, and tendon xanthomas are not observed. Only about 7 percent of the first-degree relatives of persons with polygenic hypercholesterolemia have high LDL-cholesterol levels. Treatment of polygenic hypercholesterolemia is essentially identical to that given for heterozygous FH, although drugs in combination are required in fewer cases.

2. Elevated triglycerides

a. Classification, causation, and clinical significance

1) Classification of serum triglycerides

Because of the growing evidence for a strong association between elevated triglycerides and CHD risk, ATP III adopts lower cutpoints for triglyceride abnormalities than did ATP II[1,2] (see Section II.3).

Category	Serum Triglyceride Levels (mg/dL)
Normal triglycerides	Less than 150
Borderline high triglycerides	150 to 199
High triglycerides	200 to 499
Very high triglycerides	≥500

Terminology for triglyceride levels is similar to that used for LDL cholesterol. Borderline high triglycerides (150–199 mg/dL) are a common component of the metabolic syndrome. The same is true for high triglycerides (200–499 mg/dL) except that genetic factors play a more important role. Very high triglycerides (≥500 mg/dL) also have a strong genetic component and are accompanied by increasing risk for acute pancreatitis. High triglycerides equate to the older definition of type 4 hyperlipoproteinemia, whereas very high triglycerides were called type 5 hyperlipoproteinemia.[936-940]

2) Causes of elevated triglycerides

The causes of raised serum levels of triglycerides in each category of elevated triglyceride are listed in Table VII.2–1.

Table VII.2–1. Classification and Causes of Elevated Serum Triglycerides

Classification of Serum Triglycerides	Causes of Elevated Serum Triglycerides
Normal Triglycerides (<150 mg/dL)	
Borderline High Triglycerides (150–199 mg/dL)	■ Acquired causes – Overweight and obesity – Physical inactivity – Cigarette smoking – Excess alcohol intake – High carbohydrate intake (>60% of total energy) ■ Secondary causes* ■ Genetic causes – Various genetic polymorphism
High Triglycerides (200–499 mg/dL)	■ Acquired causes – Same as for borderline high triglycerides (usually combined with foregoing causes) ■ Secondary causes* ■ Genetic patterns – Familial combined hyperlipidemia – Familial hypertriglyceridemia – Polygenic hypertriglyceridemia – Familial dysbetalipoproteinemia
Very High Triglycerides (≥500 mg/dL)	■ Usually combined causes – Same as for high triglycerides ■ Familial lipoprotein lipase deficiency ■ Familial apolipoprotein C-II deficiency

* Secondary causes of elevated triglycerides: diabetes mellitus (see VII.4 Diabetic dyslipidemia), chronic renal failure, nephrotic syndrome, Cushing's disease, lipodystrophy, pregnancy, and various drugs (corticosteroids, beta-blockers, retinoids, oral estrogens [not transcutaneous estrogen], tomoxifen, protease inhibitors for AIDS).

Borderline high triglycerides (150–199 mg/dL). In most persons, borderline high triglycerides derive from acquired factors (Table VII.2–1). Acquired factors include overweight and obesity, physical inactivity, excess alcohol intake, and in some persons, high-carbohydrate diets. Genetic factors play a lesser role.[941,942] It is also important to rule out secondary causes (see footnote Table VII.2–1).

High Triglycerides (200–499 mg/dL). Generally, genetic and acquired factors combine to produce high serum triglycerides. Many persons with high triglycerides

manifest insulin resistance and the metabolic syndrome. Abdominal obesity is especially common among those with high triglycerides.[370,371] With high triglycerides, genetic factors play an increasingly predominant role.[943-945] Patterns of dyslipidemia have been found to cluster in some families, suggesting a strong genetic component. Three patterns for family clustering of elevated triglycerides have been identified; they are called *familial combined hyperlipidemia, familial hypertriglyceridemia,* and *familial dysbetalipoproteinemia*. Each pattern is reviewed briefly.

In *familial combined hyperlipidemia,* affected persons and their first-degree relatives may at various times manifest high serum cholesterol, high triglycerides, or both.[82,946,947] Whether the underlying defect is monogenic or polygenic is not known. Metabolic studies suggest that the liver overproduces VLDL, but other metabolic defects may be present.[948-950] Many persons exhibit high levels of apo B-100 (hyperapobetalipoproteinemia).[951-953] There are no specific clinical features to diagnose this disorder. When total cholesterol is high, the level is typically in the range of 250–350 mg/dL. Triglyceride levels vary considerably, but about two-thirds of the persons have levels in the range of 200–500 mg/dL. Hyperlipidemia may or may not be present in childhood. Familial combined hyperlipidemia is associated with increased risk for premature CHD. In an early study, about 10 percent of persons with early onset myocardial infarction fell in the category of this disorder.[82,946,947]

Family clustering of elevated triglycerides without increased serum cholesterol levels characterizes *familial hypertriglyceridemia*.[82,946,947] Persons with familial hypertriglyceridemia seemingly do not carry as high a risk for premature CHD as do those with familial combined hyperlipidemia.[954,955] This is not surprising because the former generally have lower levels of LDL cholesterol than the latter. Many persons with familial hypertriglyceridemia also manifest obesity,[956] but in some, triglycerides are elevated without obesity or any other evidence of the metabolic syndrome. These latter persons may have a defect in catabolism of TGRLP (e.g., an abnormality in lipoprotein lipase activity).[957,958]

A third category of familial clustering of elevated triglycerides includes those with increased remnant lipoproteins (*familial dysbetalipoproteinemia*).[877] This condition also has been named type 3 hyperlipoproteinemia.[936-940] The defining defect in this disorder is an isoform variation in apolipoprotein E. Among the three major isoforms, E-2, E-3, and E-4, the one most often associated with dysbetalipoproteinemia is apo E-2. Affected persons usually are homozygous for apo E-2. Since apo E mediates binding of VLDL remnants and chylomicron remnants to their hepatic receptors, these remnants accumulate in plasma when the dysfunctional apo E-2 is present. The frequency of apo E-2 homozygosity in the general population is approximately 1 in 100, but the clinical syndrome of dysbetalipoproteinemia occurs much less frequently. The difference in frequency between the permissive genotype and the clinical syndrome is explained by the requirement for other factors, including age, hypothyroidism, obesity, diabetes mellitus, or the coincident presence of another genetic lipoprotein disorder, such as familial combined hyperlipidemia, to fully express the syndrome. Some persons have palmar xanthomas of the creases of the palms and fingers, but these may progress to nodules several millimeters in size. Tuberoeruptive xanthomas occur and vary from small papules to larger lesions. Premature atherosclerotic disease may present as myocardial infarction, stroke, or peripheral arterial disease. Hyperlipidemia is accentuated by concomitant glucose intolerance, diabetes mellitus, hyperuricemia, hypothyroidism, and obesity. The disorder is not commonly expressed in childhood.

Very high triglycerides (≥500 mg/dL). When serum triglycerides exceed 500 mg/dL, chylomicrons usually begin to appear in fasting plasma. Their presence typically denotes a catabolic defect for TGRLP.[959] Most frequently reported are genetic defects in lipoprotein lipase or apo C-II.[960] Impaired catabolism of TGRLP also is induced by overproduction of apo C-III, an inhibitor of lipoprotein lipase activity.[961-963] Excessive production of apo C-III can be a consequence of the insulin-resistance state.[964] Many persons with very high triglycerides have both overproduction and defective catabolism of TGRLP.[959] Sometimes very high triglycerides are found in families with familial combined hyperlipidemia or familial hypertriglyceridemia. Although some persons with very high triglycerides remain free from CHD throughout their lives, others develop premature CHD.[965,966] The latter may be due in part to the presence of atherogenic TGRLP, but the metabolic syndrome also is common in these persons. When triglycerides exceed 1000 mg/dL, persons are at

risk for acute pancreatitis.[967] Because of the danger of acute pancreatitis, persons with severely elevated triglycerides (>2000 mg/dL) should be treated as a medical urgency.

3) Relation of elevated triglycerides to CHD and other conditions

As shown in Table VII.2–2, triglycerides are related to CHD in several ways.

Borderline high triglycerides (150–199 mg/dL) are primarily a marker for other atherogenic factors—small LDL particles, low HDL cholesterol, and other components of the metabolic syndrome. High triglycerides (200–499 mg/dL) reflect the presence of atherogenic remnant lipoproteins as well as being a marker for atherogenic dyslipidemia and the metabolic syndrome. When remnants are enriched with cholesterol ester (dysbetalipoproteinemia), CHD risk is particularly high. Finally, some persons with very high triglycerides (≥500 mg/dL) carry other atherogenic factors—increased remnant lipoproteins, atherogenic dyslipidemia and the metabolic syndrome—and hence are at increased risk for CHD. However, a more urgent concern in such persons is an increased risk of acute pancreatitis.[967] This risk increases in proportion to the rise in triglyceride levels. When triglycerides exceed 2000 mg/dL, persons are subject to the chylomicronemia syndrome,[967] which is characterized by eruptive skin xanthomas, lipemia retinalis, mental changes and acute pancreatitis. If very high triglycerides are due exclusively to a catabolic defect of serum triglycerides (e.g., deficiencies of lipoprotein lipase or apo C-II), the patient may not be at increased risk for CHD.

Table VII.2–2. Relationship of Elevated Triglycerides to CHD and Other Conditions

Classification of Serum Triglycerides	Clinical Significance
Normal triglycerides (<150 mg/dL)	
Borderline High Triglycerides (150–199 mg/dL)	■ Marker for atherogenic dyslipidemia – Elevated small LDL particles – Low HDL cholesterol ■ Marker for the metabolic syndrome – Elevated blood pressure – Insulin resistance and glucose intolerance – Prothrombotic state – Proinflammatory state
High Triglycerides (200–499 mg/dL)	■ Elevated atherogenic remnant lipoproteins ■ Marker for other components of atherogenic dyslipidemia (see above) ■ Marker for the metabolic syndrome (see above)
Very High Triglycerides (≥500 mg/dL)	■ Metabolic syndrome, type 2 diabetes, and increased risk for CHD common ■ Increased risk for acute pancreatitis (risk proportional to triglyceride elevation above 1000 mg/dL) ■ Chylomicronemia syndrome (triglycerides >2000 mg/dL) – Eruptive skin xanthomas – Hepatic steatosis – Lipemia retinalis – Mental changes – High risk for pancreatitis

b. Therapeutic considerations for persons with elevated triglycerides

1) Non-HDL cholesterol: secondary target for persons with elevated triglycerides

Persons with elevated triglycerides typically have an associated increase in atherogenic VLDL remnants. Higher serum levels of VLDL cholesterol reflect this increase. Since VLDL remnants appear to have atherogenic potential similar to that of LDL, VLDL cholesterol can be added to LDL cholesterol to become a secondary target of therapy. VLDL + LDL cholesterol, termed non-HDL cholesterol, equals total cholesterol minus HDL cholesterol. Relations among the different lipoprotein fractions are as follows:

1) Total cholesterol = LDL + VLDL + HDL
2) Total cholesterol – HDL = LDL + VLDL = non-HDL

A normal VLDL cholesterol can be considered to be a level <30 mg/dL.[75] Thus, a therapeutic goal for non-HDL cholesterol can be 30 mg/dL higher than the goal for LDL cholesterol (Table VII.2–3). For persons with borderline high triglycerides (150–199 mg/dL), the VLDL cholesterol is not elevated enough to evoke non-HDL cholesterol as a secondary target. However, non-HDL cholesterol becomes an appropriate secondary target when triglycerides are in the range of 200–499

Table VII. 2–3. Non-HDL-Cholesterol Goal Corresponding to LDL-Cholesterol Goals

LDL-Cholesterol Goal	Non-HDL-Cholesterol Goal
<160 mg/dL	<190 mg/dL
<130 mg/dL	<160 mg/dL
<100 mg/dL	<130 mg/dL

mg/dL. When triglycerides are very high (≥500 mg/dL), some of the cholesterol in TGRLP may be present in nonatherogenic lipoproteins, e.g., large VLDL and chylomicrons. Moreover, current triglyceride-lowering therapies may not be sufficient to attain non-HDL-cholesterol goals for persons with very high triglycerides. Rather than risk possible side effects of combined therapy with lipid-lowering drugs it may be preferable to allow the non-HDL-cholesterol level to remain above the recommended goal.

2) Changes in life habits are primary therapy for elevated triglycerides

Elevated serum triglycerides in the general population are due principally to acquired life habits including overweight and obesity, physical inactivity, excess alcohol intake, cigarette smoking, and in some persons, high-carbohydrate diets. The goal of therapy is to reduce atherogenic VLDL remnants and to mitigate the associated lipid and nonlipid risk factors of the metabolic syndrome. The following changes in life habits are the foundation of therapy for elevated triglycerides:

- Body weight control
- Regular physical activity
- Smoking cessation
- Restriction of alcohol use (in selected persons)
- Avoidance of high-carbohydrate diets

Recommendations for the institution of each of these life-habit changes are discussed in Section V.

3) Special treatment considerations for different triglyceride categories (Table VII.2–4)

Borderline high triglycerides (150–199 mg/dL). Serum triglycerides in the range of 150–199 mg/dL often indicate adverse life habits, as noted in the previous section. Borderline high triglycerides should alert the physician to the possible presence of the metabolic syndrome and should signal the need for changes in life habits. When triglycerides are borderline high, LDL cholesterol remains the primary target of treatment and it is not necessary to evoke non-HDL cholesterol as a secondary target of therapy. Drug therapy to specifically reduce VLDL remnants is rarely needed for triglycerides in this range, although statins concomitantly lower LDL and VLDL remnants. Thus the general approach to management of elevated LDL cholesterol need not be modified when triglycerides are borderline high. Nonetheless, some persons with borderline high triglycerides have low HDL cholesterol, which may influence the choice of drugs as described in the previous section. Even so, when drug therapy is needed, LDL-lowering drugs generally take priority. In the presence of low HDL cholesterol, nicotinic acid represents an alternative therapy provided the goals for LDL cholesterol are achieved. Further, as previously noted, fibrate therapy is another option for persons with low HDL cholesterol, low LDL cholesterol, and borderline high triglycerides. The positive outcome with gemfibrozil therapy in the VA-HIT trial in persons with this profile places fibrates on the list of alternatives.[48]

High triglycerides (200–499 mg/dL). In persons with high serum triglycerides, LDL cholesterol remains the primary target of therapy. In addition, non-HDL cholesterol becomes a secondary target. Changes in life habits, as outlined before, represent first-line therapy, but it is also important to determine whether a patient is taking drugs known to exacerbate hypertriglyceridemia, and, if so, these should be modified. Among hypolipidemic agents, the statins are the most effective for lowering non-HDL cholesterol. Not only do statins reduce LDL cholesterol, but they also lower VLDL triglycerides and VLDL cholesterol.[8,12] For example, in persons with triglyceride levels between 200 and 499 mg/dL, the statins lower triglycerides by 20–40 percent, and VLDL cholesterol is lowered to a similar degree as LDL cholesterol.[8,6] On the other hand, the presence of hypertriglyceridemia of any magnitude is a relative contraindication to bile acid sequestrants when used as monotherapy since these drugs usually promote an increase in triglyceride levels.[8,44]

When LDL-cholesterol levels are not significantly elevated, the goal for non-HDL cholesterol with a triglyceride-lowering drug usually is within reach. Among these, nicotinic acid is usually the most effective; it reduces triglycerides by 30–50 percent usually without causing

Table VII.2–4. Treatment Considerations for Elevated Serum Triglycerides

Serum Triglyceride Category	Special Treatment Considerations
Borderline High Triglycerides (150–199 mg/dL)	■ Primary goal: achieve LDL-C goal ■ Life-habit changes: first-line therapy for borderline high triglycerides – Body weight control – Regular physical activity – Smoking cessation – Restriction of alcohol use (when consumed in excess) – Avoid high carbohydrate intakes (>60% of calories) ■ Drug therapy: – Triglycerides in this range not a direct target of drug therapy
High Triglycerides (200–499 mg/dL)	■ Primary goal: achieve LDL-C goal ■ Secondary goal: achieve non-HDL-C goal: 30 mg/dL higher than LDL-C goal ■ First-line therapy for high triglycerides: TLC-emphasize weight reduction and increased physical activity ■ Second-line therapy: drugs to achieve non-HDL-C goal – Statins: lowers both LDL-C and VLDL-C – Fibrates: lowers VLDL-triglycerides and VLDL-C – Nicotinic acid: lowers VLDL-triglycerides and VLDL-C ■ Alternate approaches to drug therapy for lowering non-HDL-C – High doses of statins (lower both LDL-C and VLDL-C) – Moderate doses of statins and triglyceride-lowering drug (fibrate or nicotinic acid): **Caution:** increased frequency of myopathy with statins + fibrates
Very High Triglycerides (≥500 mg/dL)	■ Goals of therapy: – Triglyceride lowering to prevent acute pancreatitis (first priority) – Prevention of CHD (second priority) ■ Triglyceride lowering to prevent pancreatitis: – Very low-fat diet when TG >1000 mg/dL (<15% of total calories as fat) – Medium-chain triglycerides when TG >1000 mg/dL (can replace long-chain triglycerides in diet) – Institute weight reduction/physical activity – Fish oils (replace some long-chain triglycerides in diet) – Triglyceride-lowering drugs (fibrate or nicotinic acid): most effective – Statins: not first-line agent for very high triglycerides (statins not powerful triglyceride-lowering drugs) – Bile acid sequestrants: contraindicated—tend to raise triglycerides ■ Triglyceride lowering to prevent CHD: – Efficacy of drug therapy to prevent CHD in persons with very high triglycerides not demonstrated by clinical trials

a reciprocal increase in LDL concentrations.[138] At the same time, nicotinic acid therapy commonly raises HDL-cholesterol concentrations by 20–30 percent. In persons with contraindications to nicotinic acid or in whom this drug is poorly tolerated, fibric acid derivatives (gemfibrozil 600 mg twice daily, fenofibrate 200 mg once daily) reduce triglycerides by 40–60 percent, and cause a 15–25 percent increase in HDL-cholesterol concentrations. Nevertheless, fibrates often raise LDL-cholesterol levels by 5–30 percent (by forming larger LDL particles). This reciprocal increase in LDL cholesterol usually means that fibrates alone do not lower non-HDL-cholesterol levels.[968] Therefore, if fibrates are employed it is usually necessary to combine them with a statin to attain the non-HDL-cholesterol goal.[908] Supplements of long chain n-3 polyunsaturated fatty acids present in fish oil, particularly eicosapentaenoic acid at doses of 3 g/day, have been shown to reduce plasma triglycerides by up to 30 percent, and at higher doses (9 g/day) by up to 50 percent.[969,970] They represent an alternative for use in combination with statins.

Rarely, persons with high triglycerides have familial dysbetalipoproteinemia. In this condition, excess triglycerides are transported in cholesterol-enriched VLDL remnants (beta-VLDL). The same therapeutic approaches are effective as in those with other genetic

forms of high triglycerides. Weight reduction is effective in lowering beta-VLDL in overweight/obese persons. Fibrates and nicotinic acid are particularly efficacious for reducing beta-VLDL,[971,972] but statins also can be effective[973].

Very high triglycerides (≥500 mg/dL). When triglycerides are very high (≥500 mg/dL), drugs that raise triglycerides should be identified and preferably discontinued. Alcohol should be eliminated. If hyperglycemia is present, insulin or oral hypoglycemic drugs may be started or increased in dosage. When triglyceride levels are >1000 mg/dL, very low-fat diets (<15 percent of total calories as fat) should be started immediately to lessen chylomicronemia that contributes importantly to very high triglycerides. Weight reduction and increased physical activity as components of TLC should be emphasized. Triglyceride-lowering drugs (fibrates or nicotinic acid) are usually required and are efficacious in persons with very high triglycerides and often can prevent acute pancreatitis. Fibrates generally are the most practical choice.[974] Gemfibrozil (600 mg twice daily) has been reported to reduce serum triglycerides by a mean of 74 percent in persons with severe hypertriglyceridemia[867] and eliminate chylomicrons from plasma. Fenofibrate appears to be similarly effective in persons with severe hypertriglyceridemia.[975] The n-3 fatty acids likewise can lower triglycerides and may be used as adjunctive therapy.[969,970] Nicotinic acid also is effective, but high doses (>2 g/day) generally should be used cautiously in persons with elevated serum glucose; in these persons, nicotinic acid may worsen hyperglycemia. If the latter occurs, triglyceride levels may actually rise. For most persons with extremely high triglycerides, therapy can be considered successful if it reduces serum triglycerides to <500 mg/dL; often it is not possible to normalize triglycerides in these persons. The first priority for persons with severe hypertriglyceridemia is to prevent acute pancreatitis; a secondary goal is to reduce risk for CHD.

In very rare circumstances, triglyceride and chylomicron levels are extremely elevated from birth. Affected persons usually have a genetic form of complete absence of either lipoprotein lipase or apo C-II, an activator of lipoprotein lipase.[960] These persons run a high risk for pancreatitis throughout life. They are unresponsive to triglyceride-lowering drugs. Treatment consists of very low-fat diets, although the diet can be supplemented with medium-chain triglyceride, which does not form chylomicrons when absorbed.

3. Low HDL cholesterol (without hypertriglyceridemia)

a. Definition, causes and relationship to CHD

A low level of HDL cholesterol is associated with increased risk for CHD and is classified as a major risk factor for CHD. ATP III sets HDL-cholesterol level of <40 mg/dL as a categorical risk factor and designates it a factor that modifies the LDL goal. The causes of low HDL-cholesterol levels and postulated mechanisms for its relationship to CHD are presented in Table VII.3–1.

The causes of low HDL cholesterol also were presented in Section II.3. When serum triglycerides become

Table VII.3–1. Low Serum HDL Cholesterol: Causes and Associations with CHD

Causes of Low HDL	Postulated Factors Associating Low HDL with CHD
Elevated serum triglycerides	■ Direct atherogenic effect of low HDL Postulated mechanisms: – Decreased reverse cholesterol transport – Increased LDL oxidation – Increased LDL aggregation – Increased arterial inflammation
Overweight and obesity*	■ Marker for atherogenic dyslipidemia ("lipid triad"): – Higher VLDL triglycerides and remnant lipoproteins – Small, dense LDL – Low HDL cholesterol
Physical inactivity*	■ Marker for metabolic syndrome – Abdominal obesity – Atherogenic dyslipidemia – Elevated blood pressure – Insulin resistance and elevated plasma glucose – Prothrombotic state – Proinflammatory state
Cigarette smoking	■ Cigarette smoking – Smoking lowers HDL cholesterol
Very high carbohydrate intake (>60% of total energy)	
Type 2 diabetes*	
Certain drugs†	
Genetic factors*	

* Overweight, obesity, physical inactivity, type 2 diabetes, and certain genetic factors may exert their effects on HDL cholesterol levels in part through insulin resistance and commonly through higher triglyceride levels.

† Drugs include beta-blockers, anabolic steroids, progestational agents.

borderline high (150–199 mg/dL), HDL-cholesterol levels begin to fall. When triglyceride levels are greater than 150 mg/dL, HDL-cholesterol concentrations frequently are <40 mg/dL in men (or <50 mg/dL in women).[124,976] Thus, the term *isolated low HDL* can be reserved for HDL-cholesterol levels <40 mg/dL in the presence of serum triglycerides <150 mg/dL. Causes other than elevated triglycerides listed in Table VII.3–1 account for most cases of isolated low HDL. In the United States population, obesity and physical inactivity are major factors; genetic factors undoubtedly play an important role as well in many persons.[130] In rare cases, genetic defects in metabolism of HDL alone can cause isolated low HDL.

The relationship between HDL and CHD risk is complex (see Table VII.3–1). First, a low HDL per se may directly promote the development of coronary atherosclerosis and predispose to CHD. Several mechanisms have been implicated: impaired reverse cholesterol transport, loss of protection against atherogenicity of LDL, and reduction in HDL-carried, anti-atherogenic factors.[110-116] Some persons with severe deficiency of HDL do not manifest premature CHD;[119,120] this suggests that HDL is not uniquely involved in atherogenesis, as is LDL. But this finding does not rule out the possibility that HDL provides some protection against development of CHD. Second, a low HDL commonly is a *marker* for atherogenic dyslipidemia (lipid triad)—raised triglycerides and remnant lipoproteins, small LDL particles, and low HDL.[123,124] Both remnants and small LDL may have independent atherogenic properties (see Section II.3). Finally, a low HDL cholesterol can be a *marker* for the metabolic syndrome; many persons with isolated low HDL have the other risk factors characteristic of this syndrome.[122] Besides atherogenic dyslipidemia, these persons often have hypertension and insulin resistance, the latter being indicated by the presence of abdominal obesity. Prothrombotic and proinflammatory states typically are noted in persons with the metabolic syndrome (see Section II.6). Finally, cigarette smoking reduces HDL-cholesterol concentrations and represents another factor contributing to the HDL-CHD relationship in smokers.

b. Therapeutic considerations in persons with low HDL cholesterol

1) *Clinical trial evidence*

Several clinical trials suggest that raising HDL-cholesterol levels contributes to decreased risk for CHD (see Section II.3.c). Nonetheless, in these trials, changes in other lipoproteins also have occurred. For this reason, the benefit of raising HDL per se is not known with certainty. Several clinical trials have recruited persons with low HDL-cholesterol levels and no significant elevations of triglycerides (Table VII.3–2). These trials thus provide information on the benefit of lipoprotein modification in persons with low HDL-cholesterol levels. For example, the AFCAPS/TexCAPS[207] trial recruited men and women without cardiovascular disease who had relatively low HDL levels; in this study, LDL lowering with lovastatin reduced risk for CHD. Similar results were observed in persons with CHD treated with statins (see Table II.2–3). Furthermore, angiographic trials have documented reductions in progression of atherosclerosis in persons with low levels of HDL cholesterol treated with fluvastatin in the Lipoprotein and Coronary Atherosclerosis Study (LCAS)[977] or with lovastatin in the Post Coronary Artery Bypass Graft Trial.[434] In the latter trial, LDL-cholesterol levels were reduced moderately and markedly in two arms of therapy. For those subjects with low HDL-cholesterol levels, there was a marked reduction in risk in the group with LDL-cholesterol levels of 95 mg/dL as compared to 135 mg/dL. Finally, meta-analyses of statin trials showed no difference in benefit of LDL lowering between high HDL and low HDL strata (Table II.2–3). These studies taken together document that lowering LDL cholesterol in persons with isolated low HDL significantly reduces risk for CHD.

The VA-HIT study[48] specifically targeted persons with isolated low HDL for gemfibrozil therapy. Persons in this trial had low levels of HDL cholesterol (mean 32 mg/dL), only modestly elevated triglycerides (mean 161 mg/dL), and LDL-cholesterol concentrations <140 mg/dL (mean 111 mg/dL). The reduction in major cardiovascular events in this trial observed with gemfibrozil therapy was attributed in part to raising HDL-cholesterol levels. Likewise, the decrease in major coronary events during gemfibrozil therapy in the Helsinki Heart Study[139] was estimated to be due partly to an increase in HDL-cholesterol levels.

Table VII.3–2. Low HDL-C: Clinical Trial Evidence and HDL Response to Therapy

Clinical Trial Evidence of Benefit of Therapy for Persons with Low HDL	Aggregate Evidence from Literature Review on HDL Response to Therapy
■ Statin trials*: LDL-lowering therapy reduces CHD risk in persons with low HDL – 4S – CARE – LIPID – WOSCOPS – AFCAPS/TexCAPS – LCAS – Post-CABG ■ Nicotinic acid trials: – Nicotinic acid effectively raises HDL – Coronary Drug Project indicated that nicotinic acid reduces major coronary events ■ Fibric acid trials: – Fibrates favorably modify atherogenic dyslipidemia – Multiple fibrate trials in aggregate produce favorable trend for reduction of CHD events (see Section II.3)	■ Weight reduction – 5–20% increase in HDL ■ Physical activity – 5–30% increase in HDL ■ Smoking cessation – 5% increase in HDL ■ Statin therapy – 5–10% increase in HDL ■ Fibrate therapy – 5–15% increase in HDL ■ Nicotinic acid therapy – 15–30% increase in HDL

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

2) Recommendations for low HDL cholesterol in persons with CHD or CHD risk equivalents, 10-year risk >20 percent

Low HDL-cholesterol levels are common in persons with CHD or CHD risk equivalents. In these persons, the primary target of therapy is LDL cholesterol. If the person with low HDL cholesterol has the metabolic syndrome, TLC should emphasize weight reduction and increased physical activity. Consideration can also be given to using a drug to modify HDL metabolism. For example, the VA-HIT trial evaluated the effects of gemfibrozil therapy in CHD patients with low HDL;[48] the significant reduction of major coronary events observed in this trial supports the efficacy of this approach. Nicotinic acid can be used instead of a fibrate; it has the advantage of raising HDL cholesterol two- to three-fold more than fibrates. Finally, the combined use of an LDL-lowering drug with either a fibrate or nicotinic acid is attractive for high risk persons with isolated low HDL to improve the whole lipoprotein profile. Using drugs in combination may increase the likelihood of side effects.

3) Considerations for persons with low HDL cholesterol in other risk categories, 10-year risk ≤20 percent

In persons *without* CHD or CHD risk equivalents, low HDL cholesterol counts as a risk factor that modifies the goal for LDL cholesterol. The first line of therapy for isolated low HDL is to maximize life habit changes. These include all components of TLC—reduction in cholesterol-raising nutrients, LDL-lowering options, weight reduction, and increased physical activity. The AFCAPS/TexCAPS trial demonstrated that LDL lowering in persons with low HDL reduces CHD risk.[207] Whether a drug to modify atherogenic dyslipidemia, i.e., fibrate or nicotinic acid, could achieve similar benefit in primary prevention is uncertain because primary prevention trials with these drugs have not targeted persons with isolated low HDL.

Persons with low HDL cholesterol and 0–1 other risk factor can present a quandary for clinical management. Apparently some forms of low HDL are atherogenic, whereas others are not. Some authorities advocate the use of emerging risk factors to assist in risk assessment in apparently low risk persons with low HDL. For example, noninvasive assessment of coronary or carotid atherosclerosis by coronary EBCT or carotid sonography, respectively, could assist in identifying which "low-risk" persons with low HDL-cholesterol levels are at higher risk.

4. Diabetic dyslipidemia

a. Definition of diabetic dyslipidemia

The term *diabetic dyslipidemia* essentially refers to *atherogenic dyslipidemia* occurring in persons with type 2 diabetes.[144] It is characterized by elevated TGRLP, small LDL particles, and low HDL-cholesterol concentrations. Diabetic dyslipidemia must be considered as one component of the metabolic syndrome, which is exceedingly common in persons with type 2 diabetes.

b. Role of elevated LDL and other risk factors in causation of CHD in persons with diabetes (Table VII.4–1)

LDL-cholesterol levels in persons with diabetes typically are not higher than those of persons without diabetes who are matched for age, sex, and body weight.[978-980] Nonetheless, since LDL levels are relatively high in populations such as the United States, it is invalid to conclude that elevated LDL cholesterol is not a significant "risk factor" in persons with type 2 diabetes.[979] Moreover, the number of LDL particles in persons with type 2 diabetes usually is greater than is reflected by LDL-cholesterol levels because LDL particles are small and partially depleted of cholesterol.[981] Moreover, the adverse atherogenic interaction between elevated LDL and other risk factors of the metabolic syndrome imparts greater pathological significance to LDL cholesterol in type 2 diabetes.

The importance of LDL cholesterol in type 2 diabetes is confirmed by reports from major clinical trials of statin therapy. The 4S, CARE, and LIPID trials[206,435,436] each contained subgroups of persons with diabetes. Subgroup analysis of each of these trials revealed a strong trend towards reduction in major coronary events with LDL lowering in persons with diabetes. In the 4S trial[203,204] and CARE study,[205] reductions in major coronary events in subgroups with diabetes were statistically significant. In the LIPID trial the apparent reduction in risk in persons with diabetes, although not

Table VII.4–1. Role of CHD Risk Factors in Persons with Diabetes: Evidence and Postulated Mechanisms of Causation

Risk Factor	Evidence and Mechanisms
LDL cholesterol	■ Borderline high LDL cholesterol (130–159 mg/dL) common in persons with diabetes ■ High LDL cholesterol (≥160 mg/dL) occurs at average rates in persons with diabetes ■ Statin trials show benefit from LDL-lowering therapy ■ 4S trial:[435] Simvastatin therapy reduced CHD events in persons with diabetes by 53% ■ CARE/LIPID pooled data:[47] pravastatin therapy significantly reduced CHD events in persons with diabetes
Atherogenic dyslipidemia	■ High triglycerides, low HDL, and small LDL common in type 2 diabetes ■ Elevated triglycerides appear to be an "independent" risk factor in persons with diabetes
Hyperglycemia	■ Hyperglycemia is an independent risk factor for CHD ■ Several mechanisms postulated – Glycation of arterial wall proteins – Atherogenic advanced glycation end-products (AGEs) – Induction of a proinflammatory state ■ Treatment of hyperglycemia reduces microvascular complications in both type 1 diabetes and type 2 diabetes ■ Treatment of hyperglycemia may reduce macrovascular complications (DCCT)[198] ■ Ongoing clinical trials are underway to further test efficacy for glycemic control on macrovascular clinical events
Hypertension	■ Increased frequency of hypertension in persons with diabetes ■ Commonly associated with insulin resistance ■ Diabetic renal disease may be a factor ■ Hypertension major cause of morbidity in persons with diabetes ■ Treatment of hypertension reduces cardiovascular morbidity in persons with diabetes (UKPDS)[201,202]
Cigarette smoking	■ Cigarette smoking compounds the risk for CHD accompanying diabetes
Gender considerations	■ The protective effect of female sex against CHD is reduced in persons with diabetes ■ Therefore, treatment guidelines are the same for men and women with diabetes
Prothrombotic state	■ Persons with diabetes have higher levels of prothrombotic factors than nondiabetic persons; these may contribute to higher risk for CHD in persons with diabetes
Proinflammatory state	■ Persons with diabetes have higher levels of proinflammatory factors than nondiabetic persons; these may reflect increased risk for major coronary events in persons with diabetes

statistically significant, was consistent with the benefit found in other subgroups. In a more recent pooled analysis of pravastatin studies (CARE + LIPID), patients with diabetes had a significantly reduced risk for CHD on drug therapy.[47,206] Thus, the combined results of three major clinical trials strongly suggest that LDL-lowering therapy in CHD patients with type 2 diabetes reduces risk for CHD similarly to that observed in persons without diabetes (see Table II.12–4). Unfortunately, few clinical trial data are available on the efficacy of LDL lowering in diabetic persons without CHD (primary prevention). Nonetheless, on the basis of secondary prevention trials, the ATP III panel concludes that LDL cholesterol is the primary lipid target in persons with diabetes.

Persons with diabetes often have other abnormalities in serum lipids and lipoproteins that may contribute to the increased risk for CHD accompanying diabetes. The term *diabetic dyslipidemia* is synonymous with *atherogenic dyslipidemia.*[143-145] It must be recognized, nonetheless, that abnormalities in lipids and lipoproteins represent only one factor among several that are responsible for the increased risk in persons with diabetes. Other factors include hypertension, hyperglycemia, insulin resistance, excessive glycation of cellular proteins, increased amounts of advanced glycation end-products (AGEs), increases in proinflammatory and prothrombotic factors, and cigarette smoking. The importance of controlling nonlipid risk factors is emphasized by controlled clinical trials. The UKPDS showed that treatment of hypertension improved cardiovascular outcome in persons with type 2 diabetes.[200,202] In addition, the DCCT[198] found that improved glycemic control in persons with type 1 diabetes significantly reduced microvascular complications with a trend towards reduction in macrovascular events including myocardial infarction. Thus, maximal reduction in cardiovascular risk in persons with diabetes requires a multifactorial approach in which all of the major risk factors are treated.

c. Therapeutic recommendations for lipoprotein disorders in persons with diabetes

1) Special therapeutic considerations according to LDL-cholesterol level (Table VII.4–2)

Since diabetes falls into the category of CHD risk equivalent, the goal for LDL cholesterol in persons with diabetes, particularly type 2 diabetes, is <100 mg/dL. The rationale for identifying diabetes as a CHD risk equivalent was given in Section II.12.b. Nonetheless clinical experience and judgment are required for the management of lipids when persons have diabetes. There is widespread agreement that LDL cholesterol should be reduced to less than 130 mg/dL in almost all persons with diabetes, and the American Diabetes Association recommends an LDL-cholesterol goal of less than 100 mg/dL in most diabetic persons.[982]

TLC should be started in all persons when LDL cholesterol is ≥130 mg/dL. Most persons with diabetes will require an LDL-lowering drug to reach the LDL goal of <100 mg/dL. If the patient also has high triglycerides (≥200 mg/dL), non-HDL cholesterol will be a secondary target. Simultaneous control of other risk factors is essential.

When baseline LDL-cholesterol levels are in the range of 100–129 mg/dL, several therapeutic options are available. First, maximal changes in life habits, including reduction of saturated fat and cholesterol intakes, use of LDL-lowering dietary options (plant stanol/sterols and increased viscous fiber), weight reduction, and increased physical activity may achieve an LDL-cholesterol level <100 mg/dL in some persons without the need for LDL-lowering drugs. Second, in those who do not achieve an LDL cholesterol <100 mg/dL with TLC alone, an LDL-lowering drug can be added to the regimen. Alternatively, a drug (i.e., fibrate) that primarily targets atherogenic dyslipidemia can be used. Without question, maximal control of nonlipid risk factors, e.g., hyperglycemia and hypertension, is necessary in persons with low LDL levels. In persons with type 2 diabetes in whom LDL-cholesterol levels have been reduced into the range of 100–129 mg/dL on LDL-lowering drugs, clinical judgment is required to determine whether or how to intensify therapy. One option is to increase the dose of the LDL-lowering drugs to further reduce LDL-cholesterol levels to <100 mg/dL; along this line, two LDL-lowering drugs (e.g., statin + bile acid sequestrant) can be combined. Alternatively, intensification of LDL-lowering therapy with TLC may sufficiently lower LDL levels without changing drug therapy. Finally, a fibrate can be added to an LDL-lowering drug to improve atherogenic dyslipidemia. The advantage of combining a fibrate with an LDL-lowering drug is that the overall lipoprotein pattern is improved. The disadvantage is that it increases the risk for severe myopathy.

Table VII.4–2. Special Considerations for Lipid Management in Persons with Diabetes

Serum LDL-Cholesterol Level	Special Therapeutic Considerations
LDL ≥130 mg/dL	■ Initiate TLC in all persons ■ Many persons with type 1 or type 2 diabetes, will require LDL-lowering drugs (statins usually first choice) ■ LDL goal: <100 mg/dL ■ If triglycerides ≥200 mg/dL, non-HDL-C goal: <130 mg/dL ■ If LDL ≥130 mg/dL, LDL-lowering drug usually indicated along with TLC ■ Type 1 diabetes: clinical judgment required for how intensively to employ LDL-lowering therapy to reach an LDL of <100 mg/dL (however, consider LDL-lowering drug if LDL ≥130 mg/dL) ■ Type 2 diabetes: generally delay management of atherogenic dyslipidemia until LDL goal has been achieved ■ If triglycerides ≥200 mg/dL, consider treatment with fibrate or nicotinic acid (either as alternative to or in combination with LDL-lowering drug) to achieve goal for non-HDL-C ■ Intensively treat nonlipid risk factors (hypertension, cigarette smoking, hyperglycemia) ■ If nicotinic acid is employed, use relatively low doses (<3 g/day)
Baseline LDL 100–129 mg/dL	■ Initiate TLC in all persons ■ Intensively treat nonlipid risk factors ■ Consider therapeutic options: intensive TLC; LDL-lowering drug; drug to lower triglycerides or raise HDL; control of nonlipid risk factors ■ If triglycerides ≥200 mg/dL, non-HDL-C goal: <130 mg/dL ■ If triglycerides ≥200 mg/dL, consider treatment with fibrate or nicotinic acid (either as alternative to or in combination with LDL-lowering drug) to achieve goal for non-HDL-C ■ If nicotinic acid is employed, use relatively low doses (<3 g/day)
On-Treatment LDL 100–129 mg/dL	■ Intensify TLC in all persons ■ Intensively treat nonlipid risk factors ■ If triglycerides <200 mg/dL, consider intensifying LDL-lowering therapy (e.g., higher dose of statin or combining a statin with a bile acid sequestrant) ■ If triglycerides ≥200 mg/dL, consider adding fibrate or nicotinic acid to statin therapy to achieve non-HDL-C goal <130 mg/dL* ■ If nicotinic acid is employed, use relatively low doses (<3 g/day)
Baseline LDL <100 mg/dL	■ Initiate TLC in all persons to reduce overall risk ■ Intensively treat nonlipid risk factors ■ If triglycerides ≥200 mg/dL, consider using a fibrate or low-dose nicotinic acid to achieve non-HDL-C goal <130 mg/dL. ■ If nicotinic acid is employed, use relatively low doses (<3 g/day)

* The combination of statins plus fibrate is accompanied by increased risk for myopathy. Persons should be instructed to be aware of the signs and symptoms of myopathy and report these immediately to their physician.

For LDL lowering, statins are usually the drugs of choice in persons with diabetic dyslipidemia. They are highly efficacious for LDL reduction, and they are well tolerated by persons with diabetes. Post hoc analysis of major clinical trials shows that statins reduce risk for major coronary events in persons with diabetes. Moreover, statins lower VLDL remnants as well as LDL, and often can achieve the secondary goal for non-HDL cholesterol in hypertriglyceridemic persons with diabetes. Bile acid sequestrants also can be used for LDL lowering in persons with diabetes.[845] However, they do not reduce VLDL cholesterol, and in some persons, actually raise triglyceride levels.

When baseline LDL cholesterol is <100 mg/dL, the non-HDL cholesterol should be estimated to determine whether it is still a target for cholesterol-lowering therapy. TLC is indicated for treatment of atherogenic dyslipidemia and the metabolic syndrome. Other risk factors should be controlled. If the triglyceride level is ≥200 mg/dL, use of a fibrate or a low dose of nicotinic acid (<3 g/day) may assist in achieving the non-HDL-cholesterol goal of <130 mg/dL.[859]

2) Comments on specific drug classes used in management of lipid disorders in persons with diabetes

Statins are first-line therapy for reducing LDL-cholesterol levels in persons with diabetes and they are generally well tolerated. They have the advantage of lowering VLDL cholesterol as well as LDL cholesterol; thus they can assist in attaining the non-HDL-cholesterol goal when triglyceride levels are ≥200 mg/dL. Bile acid sequestrants also are effective LDL-lowering drugs in persons with diabetes.[845] Their potential utility for LDL lowering either as monotherapy or in combination with statins should not be overlooked. They generally are not contraindicated simply because of their tendency to raise triglycerides. Nonetheless, triglyceride levels should be monitored.

Fibrates favorably modify diabetic dyslipidemia. They are well tolerated, and do not worsen hyperglycemia. They probably produce some reduction in CHD risk, and could be used in persons who have low LDL-cholesterol levels and atherogenic dyslipidemia.[48] In addition, they can be combined with statins to improve the overall lipoprotein pattern.[974] For many years, fibrates were considered first-line therapy for persons with diabetes. However, the results of recent clinical trials now favor use of statins before fibrates in most persons. Still, the combination of statin + fibrate is attractive in persons with diabetes who have atherogenic dyslipidemia but in whom LDL lowering is required to achieve the LDL-cholesterol goal. Clinical trials are currently underway to test the efficacy of statin + fibrate in treatment of diabetic dyslipidemia.

Nicotinic acid also has a favorable effect on diabetic dyslipidemia. Recent clinical trials[860,861] in persons with diabetes indicated that low doses of nicotinic acid are accompanied by only modest deterioration in glucose control with no changes in HbA1C levels. Unfortunately, nicotinic acid therapy can increase insulin resistance[983,984] and clinical experience has shown that in rare instances, diabetic dyslipidemia is worsened with nicotinic acid therapy.

Treatment with hypoglycemic agents also can improve diabetic dyslipidemia. Insulin therapy, sulfonyl ureas, metformin, and glitazones can all lower triglyceride levels. Although they may not be as effective as fibrates in modifying atherogenic dyslipidemia, control of hyperglycemia should be maximized before considering a fibrate in combined lipid-lowering drug therapy. If hypertriglyceridemia can be adequately controlled by glucose-lowering therapy, a lipid-lowering drug may not be needed.

5. Other secondary dyslipidemias

Hypothyroidism. A low level of thyroid hormone raises LDL-cholesterol levels. The importance of this condition is that some persons have "masked" or subclinical hypothyroidism. For this reason, any patient with LDL cholesterol >160 mg/dL should be tested for hypothyroidism.

Nephrotic syndrome. This condition is characterized by proteinuria, edema, and severe hyperlipoproteinemia. Elevation of LDL cholesterol is the major lipid abnormality, whereas hypertriglyceridemia develops in some persons. There is evidence that nephrotic dyslipidemia increases risk for CHD.[985-987] Therefore, if hyperlipidemia persists despite specific treatment for renal disease, consideration can be given to use of cholesterol-lowering drugs. Although several lipid-lowering agents appear to modify elevated lipid levels, statins are particularly effective.[988-991]

Other renal disorders. Various dyslipidemias have been reported in persons with chronic renal failure, in those on hemodialysis, and in persons following transplantation.[992] Hypertriglyceridemia and low HDL-cholesterol levels are the most frequently described lipid abnormalities with chronic renal failure and hemodialysis.[993,994] Hypercholesterolemia and hypertriglyceridemia often occur in persons following renal transplantation.[995,996] Although persons with these conditions have been reported to be predisposed to CHD, they often have other risk factors (e.g., hypertension, smoking, and diabetes) that deserve primary attention. Few studies have been carried out on treatment of dyslipidemia in these conditions, and a cautious approach should be taken since these persons are prone to drug side effects. For example, they are at increased risk for severe myopathy from both fibrates and statins.

Obstructive liver disease. Biliary obstruction can lead to severe hypercholesterolemia that is resistant to conventional cholesterol-lowering drugs. The only effective therapy is treatment of the underlying liver or biliary tract disease.

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—particularly those relating to side effects and cost.

VIII. Special Considerations for Different Population Groups

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

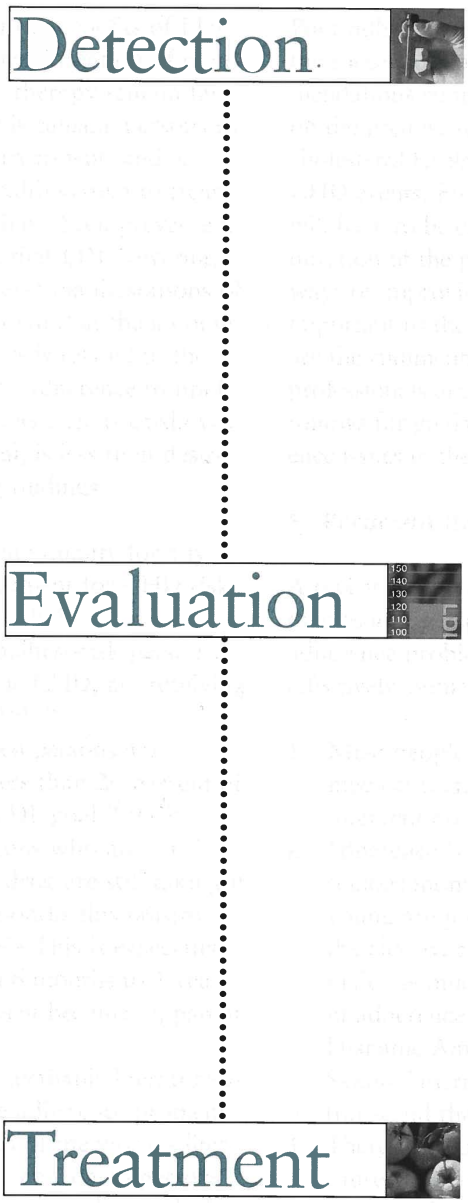
There is limited information on the risks and benefits of lipid management for reduction of CHD and CVD in this population. The Honolulu Heart Program is an ongoing prospective study of CHD and stroke in a cohort of Japanese American men living in Hawaii.[1061,1062] In this study, CHD and CVD mortality 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

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

List of Studies