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

prescription then goes to the physician, who can encourage adherence and monitor progress.

a) First: dietary assessment

A thorough and detailed assessment of the patient's knowledge, attitudes, and behavior regarding diet is essential for effective nutrition counseling. Assessment requires attention to dietary history, cultural influences, and current eating habits. It also includes recording the patient's weight and weight history, BMI, and waist circumference. The presence of abdominal obesity points to the metabolic syndrome. To assess current eating 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.

b) 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.

ATTACHMENT 1 (Part 6)

(ATP-III)

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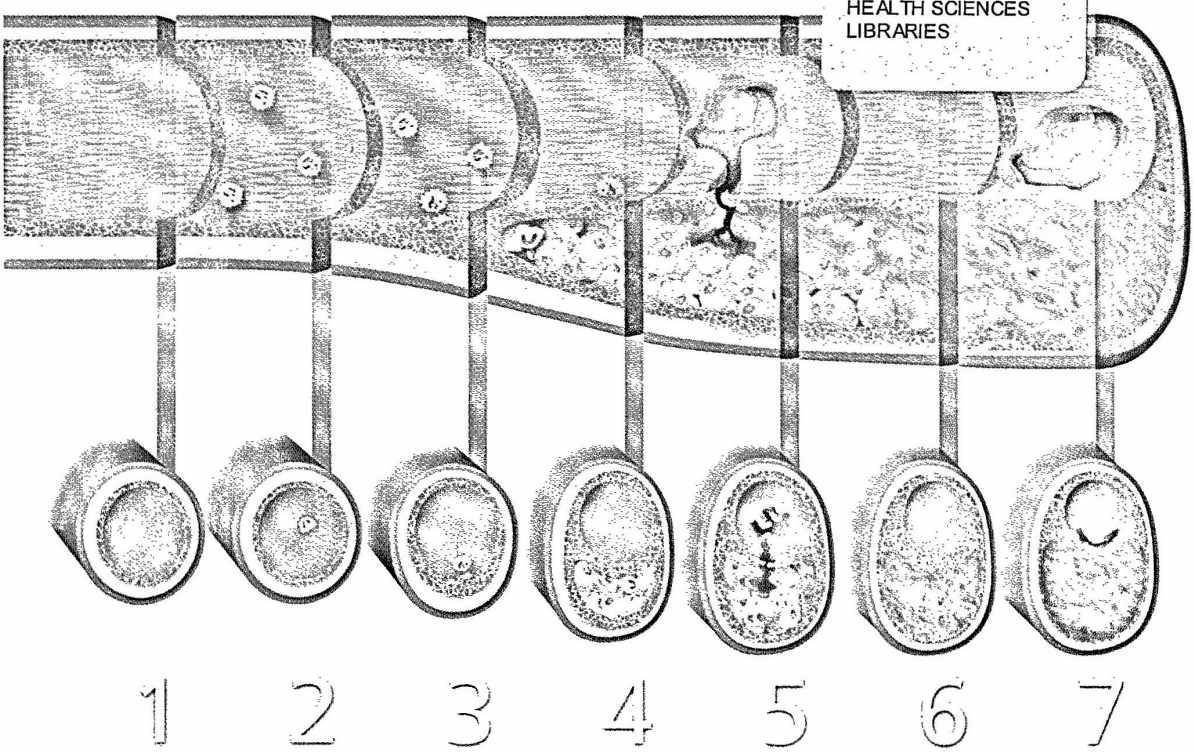

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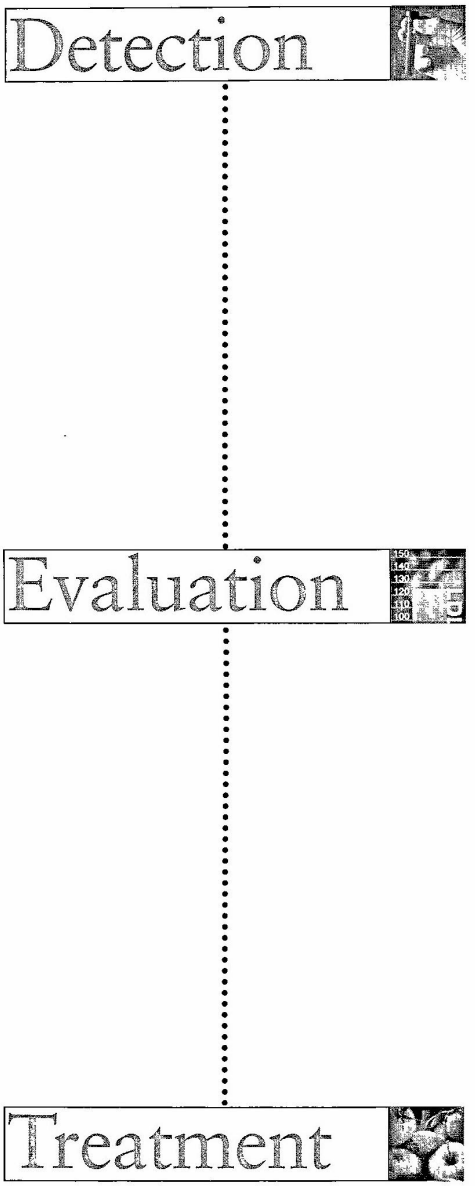

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Final Report

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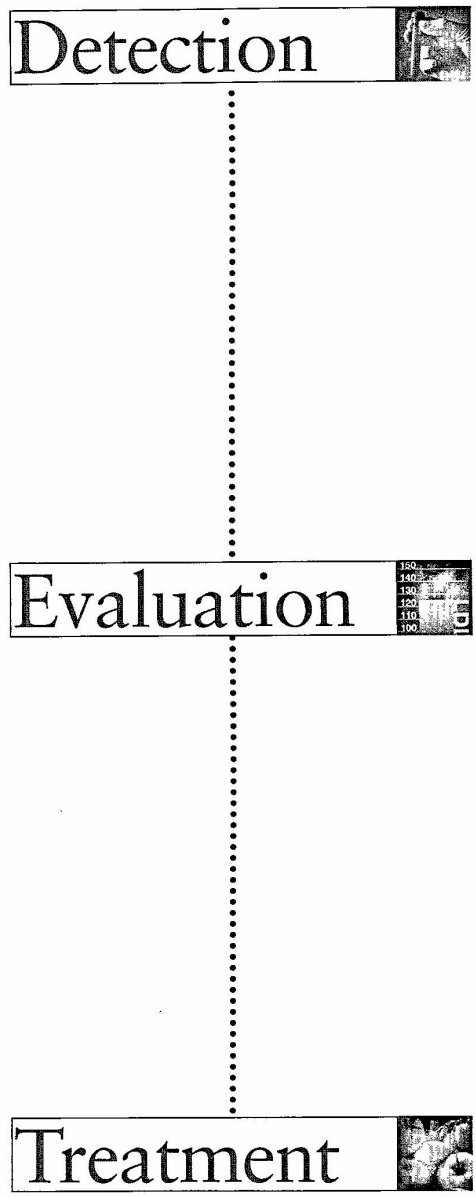
Contents



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

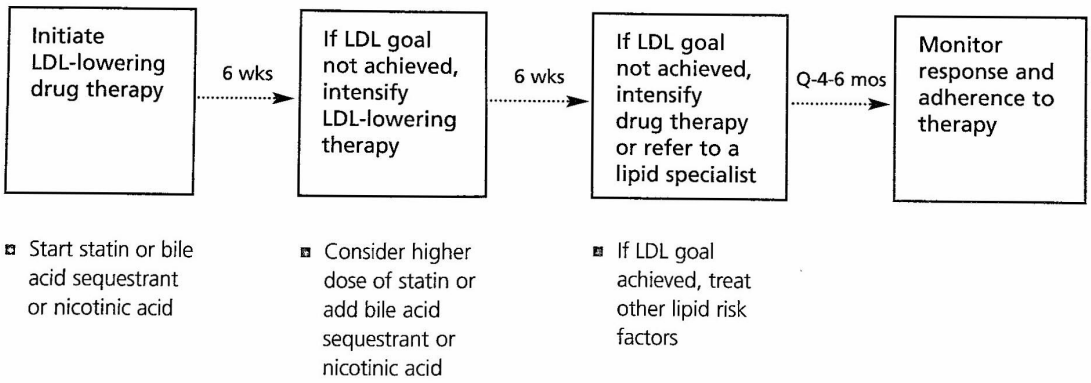
be increased to reduce both LDL and VLDL, or (b) consideration can be given to adding a triglyceride-lowering drug (fibrate or nicotinic acid) to LDL-lowering therapy, which will mainly lower VLDL (see Section VII). The latter approach has the advantage of raising HDL cholesterol in addition to lowering 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