PRACTICAL MANAGEMENT OF LIPID DISORDERS

Edited by
John C. LaRosa, M.D.

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Introduction

The relationships between circulating lipids, lipoproteins and coronary atherosclerosis have become clearer in the last decade. There is now widespread consensus that lowering of low-density lipoprotein cholesterol (LDL-C) can provide significant health benefits.

The value of changes in other circulating blood lipid levels, including high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) is less certain. Epidemiologic and clinical data strongly suggest that increases in HDL-C are of value but less consistently demonstrate benefits in triglyceride-lowering. Therapy of abnormal blood lipids may require diet or drug therapy, or both.

This book is meant to be a practical guide to the use of both diet and drug therapy in clinical practice. Chapters on the selections of patients for therapy, the use of both diet and drug therapies and the effects of commonly used drugs, including lipid-lowering agents, antihypertensive agents and gonadal hormones, are presented. The book is intended to be a text for practitioners to be used in their daily patient encounters. A large number of adult Americans are potentially affected with hypercholesterolemia and related lipid abnormalities. Proper clinical use of the guidelines provided in this book can provide an effective tool for the successful treatment of an important coronary risk factor.

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Guidelines for the Diagnosis and Treatment of Lipid Abnormalities

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INTRODUCTION

In the last decade the value of lowering elevated blood cholesterol for the prevention of clinical coronary artery disease has become well established. The transfer of that concept to clinical practice, however, involves several discrete steps and a fund of knowledge that may not yet be readily available to all physicians.

In this chapter, the currently recommended approach to identifying and selecting patients who require cholesterol lowering will be reviewed.

SCREENING FOR HIGH BLOOD CHOLESTEROL

Overall Guidelines

As the relationship between high blood cholesterol and coronary heart disease (CHD) has gained widespread public recognition, various screening projects of one kind or another have appeared. These projects range from formal programs sponsored by hospitals and other medical facilities with strong physician support to more commercial enterprises in shopping malls and other public places. The National Cholesterol Education Program (NCEP), in its initial report describing guidelines for identifying and treating adults with hypercholesterolemia,[1] did not endorse such mass screening. Rather, the report emphasized that cholesterol testing should be part of a physician-patient encounter.

Subsequent to the issuance of that report, however, it became clear that mass screenings were going to go on, with or without the endorsement of the NCEP. Therefore, a set of screening guidelines was issued in 1989 by the NCEP.[2] These recent guidelines do not endorse the notion of widespread mass screenings, but suggest that, if such screenings were performed, they be done with:

- properly calibrated instruments;
- trained medical personnel on site to obtain proper specimens and advise individuals about their cholesterol results; and
- the local medical community prepared to accept patients referred with hypercholesterolemia for further evaluation and treatment.

There are now several studies in progress to evaluate the efficacy of such widespread screening and to determine the conditions under which it is most likely to be productive. It is already established that accurate

mass screening can be accomplished with newer fingerstick methodologies only as long as careful attention is paid both to the proper training of technical personnel and to the careful maintenance and calibration of the devices used to make measurements.[3] Until requirements for reliable public screening are better defined, the ideal setting for cholesterol "screening" remains the doctor's office, where the results can be discussed and a proper plan designed to deal with the findings.

Adults

Of note, the first report of the NCEP, outlining guidelines for the detection and treatment of hypercholesterolemia in adults, recommended that every adult know his or her cholesterol level. Adults were defined as individuals over 20 years old and included both men and women. Left unresolved were questions about cholesterol screening at the extremes of age, i.e., below age 20 and above age 65.

Children

A separate panel of the NCEP is now considering the issues surrounding cholesterol screening and treatment in children and adolescents. Current screening recommendations, endorsed by both the American Academy of Pediatrics and the American Heart Association, suggest that children from "high-risk" families (defined as those children with a first degree relative with coronary artery disease or dyslipidemia) be screened, but that screening in children not be extended beyond such individuals.[4] Unfortunately, it has been repeatedly demonstrated that no more than half of the children with hypercholesterolemia (defined as total cholesterol above about 200 mg/dl) will be detected by such a strategy.[5] This underdetection is accounted for by a variety of reasons, particularly the fact that many children will not have parents old enough themselves to have manifested overt evidence of coronary disease. Whatever recommendations are finally made by the NCEP, anything short of measuring the cholesterol level of all children at the time of the physician visit may be made functionally irrelevant because of the ease, accuracy and widespread availability of fingerstick methods.

The Elderly

Cholesterol screening in individuals over age 65 is more problematic. As cohorts in Framingham and Honolulu have aged in sufficient numbers to provide reliable data, it has become clear that total cholesterol, as well as lipoprotein cholesterol subfractions, including low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), are predictive of coronary morbidity and mortality, even in older individuals.[6,7] In fact, the case can be made that since coronary morbidity and mortality

are more prevalent in older individuals, the potential benefits of cholesterol lowering are likely to be even greater in this age group. On the other hand, it seems likely that there is an age beyond which attempts to prevent atherosclerosis collide with the law of diminishing returns. There is simply insufficient data to know where to draw the line. However, because older patients are often more concerned with health issues, the physician may be under increased pressure to provide cholesterol measurements and follow-up for these individuals.

Until these issues are clarified it is prudent to treat hypercholesterolemia in older individuals with caution, reassurance and tolerable dietary change. Cholesterol-lowering drugs should probably be reserved for those who already have established atherosclerosis.

Women

Critics of the NCEP have tried to make the case that cholesterol is a less important risk factor in women than in men. It is certainly true that manifestations of coronary morbidity and mortality in women lag about 10 years behind their appearance in men.[8] Nevertheless, it should be remembered that more women die of cardiovascular disease than from all forms of cancer combined, and that even among premenopausal women, the rate of death from myocardial infarction almost equals that of the rate of death of breast cancer.[9] Since total cholesterol, as well as lipoprotein subfractions, are potent predicators of risk in women as well as in men, it is entirely proper and indeed essential that adult women, as well as adult men, be evaluated and treated for hypercholesterolemia.

THE NCEP GUIDELINES FOR DETECTION AND TREATMENT OF HYPERCHOLESTEROLEMIA IN ADULTS

The first major report of the NCEP addressed the issue of the detection and treatment of hypercholesterolemia in adults.[1] These guidelines are anchored on two principles. First, screening for hypercholesterolemia should be accomplished by measuring circulating levels of total cholesterol — remembering that the blood cholesterol level is composed of the sum of cholesterol carried in all lipoprotein fractions, including LDL, HDL, very low-density lipoprotein (VLDL), and in the nonfasting state, chylomicrons. Since the cholesterol in chylomicrons (which are present only 6-8 hours after a meal) accounts for such a very small amount of the total cholesterol, screening for total cholesterol need not be done on a fasting sample. Thus, total cholesterol can be measured during any patient-physician encounter, and indeed, could be done in the context of a mass screening, provided that the previously discussed conditions for successful screening[2] have been met.

TABLE I. Total cholesterol level: relationship to classification of individuals and recommended action (modified from reference 1)

Total Cholesterol Level	Classification	Action
< 200 mg/dl	Desirable	Repeat in 5 years
200-239 mg/dl	Borderline high	IF NO RISK FACTORS* Diet instruction Repeat in 1 year WITH RISK FACTORS* obtain triglycerides, HDL-C and estimated LDL-C
> 240 mg/dl	High	Obtain triglycerides, HDL-C and estimated LDL-C

*See Table II for risk factors.

The guidelines provide specific, numerical cutpoints, which allow individuals to be placed into one of three categories (Table I). Those with cholesterol over 240 mg/dl are said to have a "high" cholesterol level; those with cholesterol less than 200 mg/dl are said to have a "desirable" blood cholesterol level; and those in the 200 mg/dl to 239 mg/dl range are said to have a "borderline high" level. In the U.S. population a cholesterol level of 240 mg/dl defines roughly the 75th percentile for adults. These guidelines were applied to a representative sample of the U.S. population identified in the Health and Nutrition Survey conducted by the Department of Health and Human Services.[10] Approximately 27 percent of the sample (and, by inference, of the population) had a total cholesterol level above 240 mg/dl. Since the mean cholesterol in the United States is about 210 mg/dl, it can be expected that roughly half of the population will have a total cholesterol level in the "borderline high" or "high" range.

An individual with a cholesterol level below 200 mg/dl on the screening sample need only be advised to have it re-measured within the next five years. In the opinion of this author, since the American Heart Association has recommended, for almost 30 years, that all Americans be on lower saturated, lower cholesterol diets, it is prudent to provide dietary information and advice, even to individuals with cholesterol of less than 200 mg/dl. Such individuals do not, however, require intense dietary instruction and follow-up.

Individuals with cholesterol over 240 mg/dl, i.e., in the "high-risk" range, should be asked to return for a fasting blood sample for a second measurement of total cholesterol, as well as measurements of HDL-C and triglycerides (TG). As long as the TG level is below 400 mg/dl, these values can be used to estimate the level of LDL-C by the following formula:

$$\text{LDL-C} = \text{total cholesterol} - (\text{HDL-C} + \text{TG}/5)^{11}$$

The term "TG/5" is roughly equal to the level of VLDL-C. Thus, LDL-C, by this formula, is defined as the total cholesterol minus the sum of cholesterol in the other fasting lipoprotein fractions, i.e., in HDL and VLDL. Further treatment of patients with cholesterol over 240 mg/dl will depend on the level of LDL, a concept that is discussed in detail in this chapter.

For those individuals in the "borderline high" range, i.e., with cholesterol between 200 mg/dl and 239 mg/dl, the decision to go further with evaluation of their cholesterol level will depend on the presence or absence of other risk factors. All individuals who already have manifestations of coronary atherosclerosis should have the same measurement of LDL as outlined for those with cholesterol over 240 mg/dl. In addition, those who have two or more risk factors listed in Table II should also have an LDL-C determination made.

TABLE II. Factors modifying approach to borderline high risk groups* (modified from reference 1)

Documented coronary heart disease (CHD) or two of the following:

- Male sex
- Family history of premature CHD (definite myocardial infarction or sudden death before age 55 in parent or sibling)
- Cigarette smoking (currently more than 10 cigarettes/day)
- Hypertension
- Low HDL-C level (below 35 mg/dl)
- Diabetes mellitus
- History of cerebrovascular or occlusive peripheral vascular disease
- Severe obesity (≥ 30 percent overweight)

*Total cholesterol 200 mg/dl to 239 mg/dl or LDL-C 130 mg/dl to 159 mg/dl

It is important to note that one of the risk factors to be considered is male gender, so that any man with another coronary risk factor is a candidate for an LDL determination if his total cholesterol is in the 200 mg/dl to 239 mg/dl range.

The requirement of two other risk factors for women reflects the lower risk of coronary disease in females, and therefore the higher threshold for the initiation of cholesterol-lowering therapy.

In practice, about 46 percent of adult Americans in the borderline high range will have two or more of these risk factors, and therefore will be candidates for LDL-C determinations. Moreover, when these guidelines are applied to the sample of the U.S. population, about 41 percent of individuals screened will require LDL-C analysis.[10] This includes about 64 million Americans, so the potential burden on the U.S. medical system is substantial.

SELECTING PATIENTS FOR THERAPY

The Use of the LDL-C Level

Measurements of LDL, like total cholesterol measurements, may be used to classify individuals in one of three categories. Those with LDL-C over 160 mg/dl are designated as having a "high risk" LDL-C. Those with LDL-C below 130 mg/dl are classified as being "desirable." Those with LDL-C between 130 mg/dl and 159 mg/dl are in a "borderline high-risk" range (Table III). Those with an LDL-C level below 130 mg/dl are in the same "desirable" category as individuals who had total cholesterol under 200 mg/dl on initial screening. In fact, in population studies, an average cholesterol of 200 mg/dl is almost equivalent to an LDL-C of 130 mg/dl,[12] although this relationship may vary considerably from one individual to another. Individuals with LDL-C below this cutpoint need only repeat measurements within a five-year period of time and should be provided with general diet information. Individuals with LDL-C over 160 mg/dl require therapy to lower the level to at least below 160 mg/dl and preferably below 130 mg/dl (Table IV). In the absence of coronary disease or other coronary artery disease risk factors (outlined in Table II), treatment should consist only of low-saturated, low-cholesterol diets.

TABLE III. LDL-C level: relationship to classification of individuals and recommended action (modified from reference 1)

LDL-C Level	Classification	Action
< 130 mg/dl	Desirable	Repeat in 5 years
130-159 mg/dl	Borderline high risk	IF NO RISK FACTORS* Repeat in 1 year
		WITH RISK FACTORS* Begin diet therapy
> 160 mg/dl	High risk	See text and Tables IV,V

*See Table II for risk factors.

If other risk factors are present and if diet therapy, after a 3 to 6 month trial period, has failed to lower LDL-C below 160 mg/dl, drug therapy may be considered.

Individuals with LDL-C between 130 mg/dl and 159 mg/dl, but without other risk factors, should be provided diet information and instructed to return in a year for repeat sampling. Those who have other risk factors are candidates for more intensive dietary counseling, with the goal to lower the LDL-C below 130 mg/dl. Whether or not such individuals are ever candidates for drug therapy is a matter of physician judgment. However, drug therapy should not be routinely initiated in those individuals without CHD or other risk factors unless LDL-C cannot be lowered below 160 mg/dl with diet alone.

TABLE IV. Factors warranting initiation of diet therapy (modified from reference 1)

LDL-C Level (Total Cholesterol Level)*	Risk Factors	Action
≥ 160 mg/dl (≥ 270 mg/dl)	No CHD or risk factors (See Table II)	Initiate diet therapy
≥ 130 mg/dl (≥ 240 mg/dl)	CHD or 2 risk factors (See Table II)	Initiate diet therapy

* LDL-C, rather than total cholesterol, should be used to select patients for therapy. Once the relationship of total cholesterol to LDL-C is established in the patient, total cholesterol may be used to *follow* patients.

Individuals with LDL-C above 160 mg/dl, but with no other risk factors, are not considered candidates for drug therapy unless their LDL-C level cannot be lowered below 190 mg/dl on diet alone (Table V). Thus, by making the thresholds for institution of drug therapy 30 mg/dl higher than they are for diet therapy, these guidelines build in a barrier to the initiation of drug therapy. The committee that put together these guidelines provided this barrier to emphasize that drug therapy should be carefully considered and applied sparingly. In the application of all portions of these guidelines, but most particularly here, medical judgment cannot be suspended. Clearly, in some patients who have multiple risk factors or those with documented coronary disease, LDL-C lowering may be considered desirable, even to points below those outlined.

TABLE V. Factors warranting initiation of drug therapy (modified from reference 1)

LDL-C Level (Total Cholesterol Level)*	Risk Factors	Action
≥ 190 mg/dl (≥ 270 mg/dl)	No CHD or risk factors (See Table II)	Initiate drug therapy
≥ 160 mg/dl (≥ 240 mg/dl)	CHD or 2 risk factors (See Table II)	Initiate drug therapy

* LDL-C, rather than total cholesterol, should be used to select patients for therapy. Once the relationship of total cholesterol to LDL-C is established in the patient, total cholesterol may be used to *follow* patients.

In the opinion of this author, an LDL-C level below 130 mg/dl corresponding to a total cholesterol level below 200 mg/dl, is desirable for all patients, with or without risk factors, who can achieve these levels with diet alone. Since the institution of drug therapy introduces potential risk associated with the drug itself, LDL-C lowering to 160 mg/dl or below is sufficient for patients without other coronary risk factors.

When the relationship between total cholesterol and LDL-C has been well established in an individual patient, a total cholesterol level may be used as a surrogate of LDL-C. Since total cholesterol measurements are less expensive, this approach provides some potential savings. LDL-C, however, should still be measured on a yearly basis to be sure that the relationship to total cholesterol has remained constant.

Secondary Dyslipoproteinemia

Often overlooked in evaluations of patients with hypercholesterolemia are other diseases that may themselves result in or aggravate high levels of LDL-C. These include diabetes, chronic renal failure, nephrosis, hypothyroidism and less commonly, dysgammaglobulinemias, various forms of obstructive liver disease, porphyria and other rare causes.[13] Therefore, every patient with an LDL-C over 160 mg/dl should have one set of measurements of renal, hepatic and thyroid function, as well as a fasting blood sugar, to rule out the possibility of secondary causes. A reasonable screening battery includes a complete blood count, urinalysis, circulating total globulin and albumin, T-4, TSH and creatinine.

On occasion hypercholesterolemia may be the first manifestation of one of these secondary disorders. In older individuals, for example, hypothyroidism may not yet be clinically apparent when cholesterol is elevated. Similarly, hypercholesterolemia may precede other clinical signs of nephrosis.

Confirmation of the LDL-C Level

Before any decisions about the institution of therapy are made, an elevated LDL-C should be confirmed by at least one additional measurement performed 1 to 2 weeks after the initial measurement. This repeat testing allows both the patient and physician to take into account normal biological variation, as well as potential error in the measurement. Multiple measurements are particularly important in LDL-C determinations, since LDL-C is a formula-derived measurement,[11] not one directly determined in the laboratory.

In summary, these guidelines provide an approach to the detection of elevations of total cholesterol and LDL-C in adults and for the initiation of diet and drug therapy for individuals in whom the LDL-C level is deemed too high and of potential risk to the patient.

CRITICISMS OF THE ADULT TREATMENT PANEL GUIDELINES

Since the release of the NCEP guidelines, there has been considerable reaction to them, and not all favorable. The emphasis on LDL-C as the major determinant of therapy has been criticized by some as downplaying the importance of HDL-C determinations, as well as the potential importance of TG levels.[14]

The focus of the guidelines on the LDL-C level is based on data from clinical trials that strongly demonstrate the importance of lowering LDL-C in preventing coronary disease.[15-17] Moreover, a strong case has been made that, without an elevated LDL-C level, coronary atherosclerosis is uncommon, even in the presence of other risk factors.[18] Also, it should be noted that HDL-C is taken into account in these guidelines, both as part of the formula used to estimate the LDL-C level and, separately, as a risk factor that determines how vigorously the LDL-C level should be treated.

With publication of the Helsinki study results,[19] it has become apparent that raising the HDL-C level may, indeed, have a separate and additional beneficial effect on coronary risk. While future iterations of these guidelines may place more emphasis on raising the HDL-C level, such emphasis should not be at the expense of the importance of LDL-C lowering, which remains paramount.

Of note, the guidelines did not make detailed recommendations about the treatment of patients with an elevated TG level. Triglycerides have been a risk factor, the importance of which has not been easy to pin down. From the epidemiologist's point of view, the TG level provides little additional information about coronary risk beyond that which is provided by LDL-C and HDL-C determinations.[20] Nevertheless, a patient with a high TG level often has a low HDL-C level and a higher than normal LDL-C level,[21] so that in an individual patient, high TG may, in fact, identify the patient at increased risk of developing coronary and other forms of atherosclerosis. It is likely that some patients with elevated TG are carrying atherogenic lipoproteins. Unfortunately, a simple total TG does not tell which patients are, and which patients are not, carriers of such lipoproteins.

The report of a consensus conference on hypertriglyceridemia in 1984[22] recommended that individuals with TG over 500 mg/dl be considered candidates for both diet and, if necessary, drug therapy to lower those levels, particularly if they had a personal or family history of coronary disease (Table VI). Certainly individuals with TG over 1000 mg/dl, who are candidates for acute pancreatitis,[23] require diet and, if necessary, drug therapy to lower the TG level. On the other hand, individuals with TG between 250 mg/dl and 500 mg/dl, but without elevations of LDL-C or decreases of HDL-C, should be treated with TG-lowering drugs.

TABLE VI. Categorization of TG level (modified from reference 22)

TG Level	Category
< 250 mg/dl	Normal
250 mg/dl to 499 mg/dl	Borderline high
> 500 mg/dl	High*

* Patients with TG > 1000 mg/dl are at especially high risk to develop acute pancreatitis.