

Cholesterol: Managing Its Effect on Cardiovascular Disease Risk



A peer-reviewed monograph component of the AAFP Video CME program



American Academy
of Family Physicians



Table of Contents

Risk Assessment: The Essential Step
Screening Recommendations
Risk Factors Beyond Elevated LDL-C Level
Upgrading Diabetes to a CHD Risk Equivalent
Assessing Risk Factors and Estimating CHD Risk
Lowering LDL-C Treatment Threshold
Metabolic Syndrome
Hypertriglyceridemia
Therapeutic Lifestyle Changes
Physical Activity
General Principles of Pharmacotherapy
Special Circumstances
Follow-Up and Maintenance
References
Patient Education
Resources

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Cholesterol: Managing Its Effect on Cardiovascular Disease Risk

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Learning Objectives

After completing this program, you should be able to:

1. Describe the impact of cholesterol on cardiovascular risk.
2. Identify typical patient profiles and risk factors for cardiovascular disease events.
3. Understand the link between cholesterol metabolism and cardiovascular risk reduction.
4. Discuss and apply NCEP ATP III guidelines in practice, including the scoring assessment system.
5. Outline treatment options.
6. Discuss common problems encountered in helping patients minimize risk.
7. Effectively encourage patients to adopt healthy lifestyle changes.

Cholesterol: Managing Its Effect on Cardiovascular Disease Risk

Cardiovascular disease (CVD) is the leading cause of death in adult men and women in the United States, resulting in 1 death every 33 seconds or approximately 2,400 deaths every day¹—the equivalent loss of life of 10 jet crashes. Evaluation of study results from more than 50 clinical trials indicates that cholesterol treatment reduces morbidity and mortality associated with coronary heart disease (CHD), the cause of more than half of all cardiovascular events in adults younger than age 75 years.¹ It is vital to assess cardiovascular risk in all adult patients and to identify which patients will most clearly benefit from cholesterol treatment.

Risk Assessment: The Essential Step

It is important to be able to identify a patient's cardiovascular disease risk to determine which patients to treat more aggressively. Risk assessment tools are now available which can provide a quick, easy method of separating patients into high- or low-risk categories for future cardiovascular disease events such as myocardial infarction or sudden cardiac death.² Consider two women with identical total cholesterol (TC) levels (See *Patient Examples*). Patient 1 is 65 years of age and has a TC of 250 mg/dL, but other than age and post-

Patient Examples

Patient 1

Woman

Age: 65 years

Postmenopausal

- HDL-C = 68 mg/dL
- LDL-C = 155 mg/dL
- TC = 250 mg/dL
- TG = 135
- BP = 118/74 mmHg

Patient 1 has no personal or family history of CHD. The patient exercises regularly, maintains a normal weight, does not smoke, and has no other associated risk factors. Age, postmenopause, and an elevated TC level are the identified risk factors, but are allayed by an elevated HDL-C level as HDL-C is a powerful predictor of reduced cardiovascular risk. Results from one study indicate that a 6% increase in HDL-C levels correlates with a reduction in first acute major coronary events in adults with average baseline LDL-C levels and below-average HDL-C levels.³ The NCEP ATP III guidelines consider HDL-C >60 mg/dL to be a negative risk factor.

Using the calculation tool recommended by the ATP III, Patient 1 has a 10-year CHD risk <10%, and pharmacotherapy is not required at this time as the LDL-C goal for a patient with a 10-year risk is <160 mg/dL.

Patient 2

Woman

Age: 65 years

Receiving pharmacotherapy for high blood pressure

- HDL-C = 38 mg/dL
- LDL-C = 181 mg/dL
- TC = 248 mg/dL
- TG = 155 mg/dL
- BP = 148/94 mmHg
- FBG = 118 mg/dL

Patient 2 smokes one-half pack of cigarettes a day. In addition to the risk factors of age and elevated TC level, a low HDL-C level, elevated blood pressure, and a high blood glucose level are further risk factors that result in a 10-year risk of >20%, which is the same 10-year risk of CHD events as a patient with prior CHD history. The NCEP ATP III guidelines refer to a 10-year risk >20% as a "CHD risk equivalent." Due to this very high risk, Patient 2 is a candidate for aggressive cholesterol treatment with a goal LDL-C of <100 mg/dL.

BP = blood pressure; FBG = fasting blood glucose; HDL-C = high-density lipoprotein; LDL-C = low-density lipoprotein; TC = total cholesterol; TG = triglycerides

menopausal state, has no other CHD risk factors. Patient 2 is also 65 years of age and also has a TC of 250 mg/dL, but has multiple CHD risk factors. How would you decide whether either patient should be started on cholesterol therapy, and what would the goals of treatment be?

The National Cholesterol Education Program's (NCEP) Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Pressure in Adults (Adult Treatment Panel III),² or ATP III, recommends a quick, easy method for calculating 10-year risk and illuminating the answer to those questions. The panel suggests using the "Risk Assessment Tool for Estimating 10-year Risk of Developing Hard Coronary Heart Disease (Myocardial Infarction and Coronary Death)," available online as part of the ATP III report at: <http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=pub>.

This 10-year risk assessment method is so simple that patients can assess their own risk while in the physician's office waiting room. The risk assessment takes only about 20 to 30 seconds to complete, is only necessary every 5 years, and can distinguish between two patients with the same cholesterol levels who have very different risks and different goals. Note that the 10-year risk provided refers to what are known as "hard" CHD endpoints (myocardial infarction or sudden cardiac death).

Figure 1 provides a summary of the point calculation for men and women found in the NCEP's ATP III Guidelines At-A-Glance Quick Desk Reference. This tool makes it easy for physicians to see how calculations are done, specifically for the two patient examples above.

Screening Recommendations

Risk assessment requires measurement of LDL-C level as well as identifying other risk determinants. The NCEP ATP III recommends obtaining a fasting lipoprotein profile (consisting of TC, LDL-C, HDL-C, and TG levels) every 5 years in adults aged 20 years and older (Table 1). The American College of Physicians⁴ and the U.S. Preventive Services Task Force (USPSTF)⁵ recommend less frequent screening, particularly in the primary prevention setting. The USPSTF recommends routine screening of men aged 35 years and older and women aged 45 years and older unless other

risk factors for CHD are present, in which case routine screening should be initiated as early as age 20 years.

THE VALUE OF NON-HDL-C

Non-HDL-C is a practical, reliable, and predictive measurement that simplifies screening and achievement of treatment goals and be used widely in clinical practice. Since non-HDL-C is derived from TC and HDL-C levels, neither of which require fasting, the test is very practical for the physician's office. Both LDL-C and TG-rich lipoprotein particles are atherogenic. Using non-HDL-C screening increases predictive value for CVD, since non-HDL-C is a good estimate of all the atherogenic lipoproteins in the serum. Based on this information, the NCEP ATP III guidelines state that non-HDL-C should be used for monitoring patients with TG levels >200 mg/dL.

Non-HDL-C treatment targets are calculated by adding 30 mg/dL to LDL-C goals. Non-HDL-C treatment goals, as recommended by ATP III when TG = 200 to 400 mg/dL, are listed in Table 2.

Non-HDL-C becomes very useful as a screening tool only if TC and HDL-C measurements are available or when monitoring long-term therapy, because non-HDL-C is as predictive as LDL-C. It is useful to know the whole lipoprotein profile to identify dyslipoproteinemias and guide therapy.

In the presence of elevated TG levels >200 mg/dL, treatment of patients with non-HDL-C levels becomes a secondary target after the primary target of lowering LDL-C is attained. If non-HDL-C is the parameter utilized and the TC level is ≥ 200 mg/dL, it may be necessary to obtain at least one fasting lipoprotein profile in order to tailor appropriate management strategies.⁶

Data from The Strong Heart Study,⁷ evaluating persons with diabetes but without evidence of CVD at baseline, indicate non-HDL-C to be a strong predictor of CVD in men and women with diabetes and is particularly indicative of coronary events. Similarly, it is reported that estimation of LDL-C levels via the traditional Friedewald formula becomes progressively less accurate as plasma TG concentrations increase and ultimately the formula becomes inapplicable.⁶

Risk Factors Beyond Elevated LDL-C Level

In addition to an elevated LDL-C level, risk factors include the presence or absence of CHD and other clinical forms of atherosclerotic disease and the following²:

- Current cigarette smoking
- Hypertension (blood pressure $\geq 140/90$ mmHg, or current treatment with an antihypertensive agent)
- HDL-C <40 mg/dL
- Family history of premature CHD (first-degree relative: man younger than 55 years or woman younger than 65 years)
- Age (man age 45 years or older; woman age 55 years or older)



Practice Recommendation: The National Cholesterol Education Program Guidelines recommend measuring nonfasting TC and HDL-C every 5 years in women beginning at age 20. The U.S. Preventive Services Task Force and American College of Physicians recommend beginning routine cholesterol screening of average-risk women at age 45, and perhaps earlier screening for high-risk women (those with multiple risk factors, diabetes, strong family history). All organizations recommend advising all patients to reduce dietary saturated fat, maintain a healthy weight, and increase physical activity (www.ahrq.gov/research/oct00/1000ra10.htm).

Level of Evidence: Clinical guidelines and evidence reports.

Figure 1. Estimates of 10-Year Risk for Men and Women (Framingham Point Scores*)

Men					Women						
Age	Points	Age	Points		Age	Points	Age	Points			
20-34	-9	55-59	8		20-34	-7	55-59	8			
35-39	-4	60-64	10		35-39	-3	60-64	10			
40-44	0	65-69	11		40-44	0	65-69	12			
45-49	3	70-74	12		45-49	3	70-74	14			
50-54	6	75-79	13		50-54	6	75-79	16			
Total Cholesterol					Total Cholesterol						
mg/dL	Age	Points			mg/dL	Age	Points				
	20-39	40-49	50-59	60-69	70-79	20-39	40-49	50-59	60-69	70-79	
<160	0	0	0	0	0	<160	0	0	0	0	
160-199	4	3	2	1	0	160-199	4	3	2	1	
200-239	7	5	3	1	0	200-239	8	6	4	2	
240-279	9	6	4	2	1	240-279	11	8	5	3	
≥280	11	8	5	3	1	≥280	13	10	7	4	
HDL					HDL						
	Age	Points				Age	Points				
	20-39	40-49	50-59	60-69	70-79		20-39	40-49	50-59	60-69	70-79
Nonsmoker	0	0	0	0	0	Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1	Smoker	9	7	4	2	1
Systolic BP					Systolic BP						
mmHg		If Untreated	If Treated		mmHg		If Untreated	If Treated			
<120		0	0		<120		0	0			
120-129		0	1		120-129		1	3			
130-139		1	2		130-139		2	4			
140-159		1	2		140-159		3	5			
≥160		2	3		≥160		4	6			
Point Total	10-Year Risk (%)	Point Total	10-Year Risk (%)		Point Total	10-Year Risk (%)	Point Total	10-Year Risk (%)			
<0	<1	9	5		<9	<1	17	5			
0	1	10	6		9	1	18	6			
1	1	11	8		10	1	19	8			
2	1	12	10		11	1	20	11			
3	1	13	12		12	1	21	14			
4	1	14	16		13	2	22	17			
5	2	15	20		14	2	23	22			
6	2	16	25		15	3	24	27			
7	3	≥17	≥30		16	4	≥25	≥30			
8	4										
		10-YEAR RISK ____%					10-YEAR RISK ____%				

BP = blood pressure; HDL = high-density lipoprotein.

*—The risk factors included in the Framingham calculation of 10-year risk are age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment of hypertension, and cigarette smoking. The first step is to calculate the number of points for each risk factor.

(From Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Available at: <http://www.hnlbi.nih.gov/guidelines/cholesterolatglance.pdf>)

Table 1. Screening Guidelines

Screening Risk Group	Begin Screening	Frequency	Test
CHD, CHD risk equivalent, or ≥ 2 risk factors	Age 20 years or at onset	1 to 2 years	Fasting lipid panel
Familial dyslipidemia or family history of premature CHD	Age 20 years	2 years	Fasting lipid panel
None of the above	Age 20 years	5 years	Fasting lipid panel or nonfasting total and HDL-C

Note: If nonfasting lipids are measured, obtain a fasting lipid profile if total cholesterol is >200 mg/dL or HDL-C is <40 mg/dL. For rare patients with CHD or a CHD risk equivalent but no evidence of a dyslipidemia, rescreen every 1 to 2 years depending on the presence or absence of associated risk factors. CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol.

(Information from NCEP ATP III.)

Table 2. Risk Categories With Corresponding Lipid Treatment Goals and Cutpoints

Treatment Risk Group	Primary	Secondary (if TG >200)
CHD or CHD risk equivalent	LDL-C <100	Non-HDL-C <130
No CHD, ≥ 2 risk factors, but 10-year CHD risk $<20\%$	LDL-C <130	Non-HDL-C <160
No CHD, ≤ 1 risk factor	LDL-C <160	Non-HDL-C <190

CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Non-HDL-C = total cholesterol minus HDL-C; TG = triglycerides.

(Information from NCEP ATP III.)

Based on these risk determinants, the NCEP ATP III guidelines outline three categories of risk along with their corresponding LDL-C and non-HDL-C goals (Table 2).² Patients with established CHD have a 10-year risk of having a CHD event (ie, cardiac death or myocardial infarction [MI] that is $\geq 20\%$ ($>2\%$ per year)). These persons, therefore, have the lowest LDL-C goal level (<100 mg/dL) and should be treated aggressively. Patients without known CHD, but with a CHD risk equivalent (ie, 10-year risk $>20\%$), which includes those with non-coronary atherosclerosis (cerebrovascular disease, peripheral vascular disease, abdominal aortic aneurysm), or type II diabetes mellitus, should also have an LDL-C goal of <100 mg/dL according to NCEP ATP III. Similarly, extreme lipid abnormalities from genetic abnormalities in patients (ie, LDL-C level >220 mg/dL, HDL-C level of <30 mg/dL, or TG level >800 mg/dL) indicate the need for more aggressive treatment.

Upgrading Diabetes to a CHD Risk Equivalent

Results of many studies have demonstrated that a 7- to 10-year history of diabetes mellitus is a very high risk factor for future CVD events. In fact, the risk is equivalent to prior history of CVD. Accordingly, the ATP III Panel upgraded

diabetes mellitus to a “CHD risk equivalent”—a risk equivalent that is now recognized as one of the most important CHD risk factors. This is largely because mortality in most persons with diabetes is not associated with the diabetic condition; rather, two out of three persons with diabetes die from a heart attack or stroke.⁸

Diabetes is a complex metabolic syndrome with a number of physiologic abnormalities that increase cardiovascular risk. Patients with diabetes have high rates of hypertension and obesity, hyperlipidemia, impaired vascular function, a prothrombotic state, and other abnormalities that promote atherosclerosis.^{9,10} Study data have repeatedly linked poor glycemic control to an elevated risk of cardiovascular events. The frequent association of diabetes with multiple risk factors for CHD brings with it a high risk of new-onset CHD within 10 years of diagnosis. In fact, studies indicate that at the time of diagnosis of type II diabetes, up to 50% of patients already have obstructive coronary artery lesions. The risk of CHD is at least twice as high in persons with diabetes as it is in persons without the disease,⁸ and may be up to seven times higher in women.¹¹ In addition, persons with diabetes tend to have higher levels of LDL-C and TG, and lower levels of HDL-C, in the blood.

So strong is the link between diabetes and the increased risk of CHD that the American Diabetes Association created

an award-winning program entitled, “Make the Link!” (www.diabetes.org). This program helps patients understand the association between the two diseases and offers suggestions for reducing the risk associated with CHD. Despite the fact that an overwhelming majority of persons with diabetes also have associated dyslipidemia, they do not associate their diabetic condition to unhealthy cholesterol levels. A recent American Diabetes Association/American College of Cardiology survey¹² of persons with diabetes indicates that 60% of participants did not believe they were at risk for cholesterol problems. Only 8% recognized that lowering their cholesterol level could reduce their risk of CHD. Perhaps most importantly, almost one half (45%) of the survey participants stated that their physician never discussed lowering their cholesterol level.¹²

The good news is that lipid-lowering therapy is highly efficacious. Results from various studies^{13,14} demonstrate that persons with diabetes benefit as much or more than patients without diabetes from the cardioprotective effects of lipid-lowering pharmacotherapeutic agents. For example, results of the 4S study,¹⁵ which included 202 patients with type II diabetes and average levels of TC (255 mg/dL) and TG (155 mg/dL), found that major coronary events (ie, coronary artery disease death, nonfatal myocardial infarction, coronary artery bypass grafting, and percutaneous transluminal coronary angioplasty) occurred in 63% of the placebo group versus 32% of the group receiving simvastatin, resulting in a relative risk reduction of approximately 50%.¹⁶

The Cholesterol and Recurrent Events (CARE) trial¹⁷ included 586 patients with pre-existing type II diabetes. Results calculated from this study demonstrate that major coronary events occurred in 37% of the study participants who received placebo and 29% who received pravastatin, resulting in a relative risk reduction of 22%.¹⁵ Data from the recent Heart Protection Study,¹⁸ which enrolled almost 4,000 patients with diabetes mellitus, demonstrate an approximate 25% reduction in the rate of major vascular events among the study participants who had no history of coronary disease.¹⁸

Assessing Risk Factors and Estimating CHD Risk

For primary prevention, the assessment of a patient’s CHD risk through evaluating risk factors is critical because it defines the LDL-C goal level treatment should achieve. The NCEP ATP III guidelines identified three categories of risk for assigning LDL-C goals based on 10-year risk for CHD events: >20% risk (or a CHD risk equivalent), 10% to 20% risk, or 0% to 10% ten-year risk. A different LDL-C goal is assigned for each of these levels of risk as shown in *Table 2*.²

It is already established that patients with known atherosclerosis or diabetes mellitus have a 10-year risk of CHD events >20% and have a goal LDL-C of <100 mg/dL. Determining the level of risk in other patients is

accomplished by first counting the number of risk factors. For persons with two or more risk factors, a 10-year risk assessment is determined using the modified Framingham scoring system developed for the ATP III guidelines. For those with an estimated 10-year risk of CHD that is 10% to 20%, the LDL-C goal is <130 mg/dL.²

The third category consists of persons with a 0 to 1 risk factor. Framingham scoring is unnecessary in this group because, with few exceptions, persons in this group have a 10-year risk of CHD of <10%. Because they are at very low 10-year risk, an LDL-C goal of <160 mg/dL is acceptable. One exception is the genetic condition familial hypercholesterolemia (>200 mg/dL), in which a very high LDL-C level (>160mg/dL) may still warrant consideration of medical intervention.²

Numerous other lifestyle and emerging risk factors can influence a person’s lipid profile, including obesity, physical inactivity, an atherogenic diet, lipoprotein(a), homocysteine, prothrombotic and pro-inflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease. While all of these risk factors represent the need for possible intervention, they do not alter the LDL-C goal in current guidelines.¹⁹

Persons with an elevated LDL-C level or another form of dyslipidemia should be assessed for secondary causes prior to initiation of pharmacotherapy. Such secondary causes include:

- Obesity
- Diabetes
- Medicines such as diuretics, beta-blockers, estrogens, progestins, anabolic steroids, and corticosteroids
- Chronic renal failure
- Chronic or obstructive liver disease
- Cushing’s syndrome
- Acute intermittent porphyria
- Glycogen storage disease
- Hyperparathyroidism
- Hypopituitarism
- Hypothyroidism
- Lipodystrophy
- Dysglobulinemia
- Pancreatitis
- Pregnancy
- Uremia

Lowering LDL-C Treatment Threshold

Many experts now suggest a more stringent pharmacotherapeutic treatment guideline based in part on the findings of the Heart Protection Study.¹⁸ The 5-year study involved more than 20,000 persons considered to be at high risk of coronary events because of a prior history of MI, diabetes, peripheral vessel disease, or stroke. In this study, simvastatin was shown to significantly reduce the risk of MI and stroke in all subgroups—even in those study participants who presented with LDL-C levels <116 mg/dL and in participants with TC levels <193 mg/dL. Extrapolating the

results, 5 years of treatment with simvastatin (or presumably any other statin) would prevent one major vascular event in approximately 70 to 100 persons per 1,000.¹⁸ The findings have left many experts wondering whether pharmacotherapy should be initiated at a lower LDL-C level and whether the impetus for therapy should be based on overall atherosclerosis risk rather than lipid levels.

Metabolic Syndrome

Metabolic syndrome is essentially a constellation of health, lifestyle, and emerging risk factors, including:

- Central (abdominal) obesity
- Hyperinsulinemia (+/- glucose intolerance)
- Hypertension
- Atherogenic lipoprotein phenotype (low HDL-C, hypertriglyceridemia, small dense LDL particles)
- Prothrombotic state

More than 20% of participants in the Third National Health and Nutrition Examination Survey (NHANES III) had been diagnosed with metabolic syndrome (42% older than age 65 years), with prevalence similar among women and men.²⁰ Using year 2000 United States census data, this percentage correlates to approximately 47 million adults in the United States with metabolic syndrome. Perhaps even more disconcerting is that approximately 4% of adolescents and nearly 30% of adolescents who are overweight in the United States meet the diagnostic criteria for metabolic syndrome.²¹

The prevalence rate of metabolic syndrome varies with age, sex, ethnicity, and body mass index (BMI) and increases rapidly with advancing age and increased weight in men and women.²² Less than 10% of persons who maintain a healthy body weight (BMI <25) meet the diagnostic criteria for metabolic syndrome compared with 40% to 50% of persons with a BMI of >35.²² Persons with central obesity are more likely to develop metabolic syndrome than those who store fat peripherally, underscoring the importance and validity of measuring waist circumference. Older age and other factors that increase the odds of metabolic syndrome include: postmenopausal status, current smoking, low household income, high carbohydrate intake, no alcohol consumption, and physical inactivity.²²

The incidence of cardiovascular disease, diabetes, and all-cause mortality is increased in persons with metabolic syndrome, even in the absence of baseline CVD and diabetes, largely because these persons tend to also have associated atherosclerosis and impaired fibrinolysis.^{23,24} As such, treatment of risk factors with metabolic syndrome is an important target of risk reduction in addition to cholesterol treatment.

Perhaps the easiest method to detect the possible presence of metabolic syndrome is by measuring a person's waist circumference (Figure 2). This should be performed with a tape measure placed parallel to the floor, at the level of the superior iliac crest and at the end of a relaxed expiration. Men

with a waist circumference in excess of 40 inches and women with a waist circumference in excess of 35 inches should be assessed for the presence of other indicators. Incorporating this measure as part of usual clinical practice is the first step in addressing the syndrome. For some persons, weighing and measuring can be stressful; therefore, these measurements should be recorded privately, discreetly, and with respect and sensitivity to weight and other personal issues.

Diagnosis of metabolic syndrome depends on the presence of three or more of the following²:

- Waist circumference of >40 inches for men and >35 inches for women
- TG level \geq 150 mg/dL
- Blood pressure \geq 130/85 mmHg, or under current treatment with an antihypertensive agent
- Fasting plasma glucose \geq 110 mg/dL
- HDL-C level of <40 mg/dL in men and <50 mg/dL in women

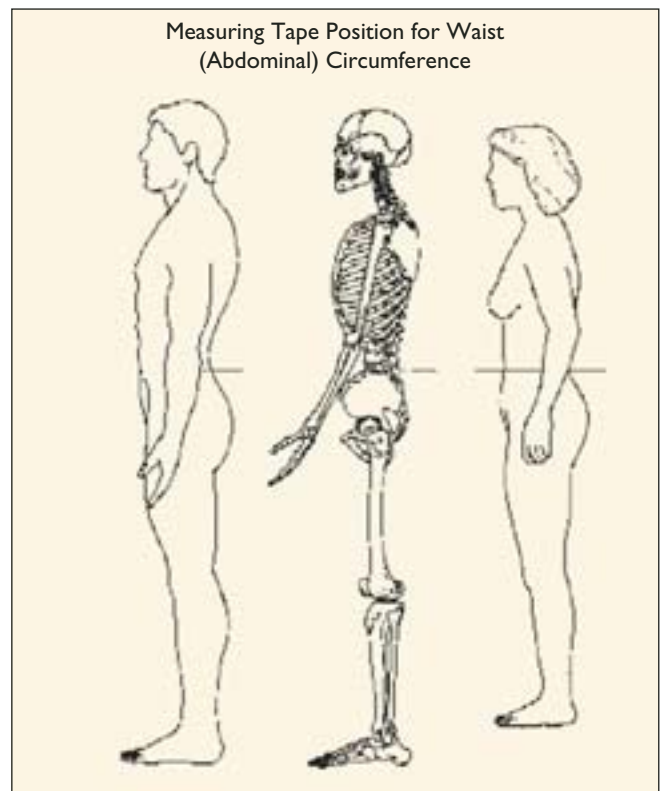


Figure 2. Waist Circumference Measurement. To measure waist circumference, locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug but does not compress the skin, and is parallel to the floor. The measurement is made at the end of a normal expiration. Abnormal waist circumference measurements: men >40 inches; women >35 inches. (From National Heart, Lung, and Blood Institute. Department of Health and Human Services. National Institutes of Health. Guidelines on overweight and obesity: electronic textbook. Available at: http://www.nhlbi.nih.gov/guidelines/obesity/e_txtbk/txgd/4142.htm. Accessed November 2003.)

Data from a recent study indicates that the accuracy of the above diagnostic criteria in predicting CHD events and new-onset diabetes could be enhanced by utilizing a BMI and a C-reactive protein measurement, and/or by lowering the glucose cutoff value to 99 mg/dL.²⁵ These criteria were utilized in a study in which the results indicate that the presence of metabolic syndrome increased the risk of a CHD event 1.76 times and increased the risk of diabetes 3.5 times. Men with four or five features of the syndrome had a 3.7-fold increased risk for CHD and a 24.5-fold increased risk for diabetes compared to men with none of the features.²⁵

Hypertriglyceridemia

Another important change to the NCEP ATP III guidelines is the greater emphasis placed on hypertriglyceridemia. This is due to the increasing number of study data demonstrating that elevated levels of TG and TG-rich lipoproteins (ie, very low-density lipoprotein [VLDL]), are considered independent risk factors for coronary artery disease.²⁶

A meta-analysis of data from population-based prospective studies demonstrated that increased plasma TG is associated with a 32% increase in risk of cardiovascular disease in men and a 76% increase in women.²⁷ After adjusting for HDL-C levels and other risk factors, the risks were decreased to 14% and 37% in men and women, respectively. As a consequence of the interaction of TG with other cardiovascular risk factors, this risk remained statistically significant.

Part of what makes hypertriglyceridemia so troubling is that an elevated TG level is often a component of a lipid triad consisting of elevated serum TG, small LDL particles and low HDL-C.²⁸ This triad, referred to by some as the “atherogenic lipoprotein phenotype,” is an important component of metabolic syndrome. The NCEP ATP III guidelines recommend the following classification of serum TG levels:

- Normal = ≤ 150 mg/dL
- Borderline-high = 150 to 199 mg/dL
- High = 200 to 499 mg/dL
- Very high = ≥ 500 mg/dL

Additionally, the NCEP ATP III guidelines identify the sum of LDL plus VLDL cholesterol (non-HDL-C) as a secondary target for therapy in persons with high serum TG (≥ 200 mg/dL). The goal for non-HDL-C as a secondary target for therapy in persons with high serum TG levels can be set at 30 mg/dL higher than that for LDL-C on the premise that a VLDL-C level of ≤ 30 mg/dL is considered normal.²

A more aggressive, broad-based approach to the management of persons with hypertriglyceridemia through diet, weight control, and exercise as the primary modes of treatment is encouraged. Pharmacotherapy should be considered for persons at high risk with TG levels of ≥ 200 mg/dL.² The non-HDL-C goal can be achieved through intensifying therapy with a statin or by adding nicotinic acid or a fibrate.

In rare cases when TG levels are ≥ 1000 mg/dL, the initial goal of therapeutic intervention is the prevention of pancreatitis. Severe hypertriglyceridemia requires an extremely low-fat diet (fat intake of 15% or less of total caloric intake), weight reduction, increased physical activity, and usually a TG-lowering medication (either nicotinic acid or a fibrate). Only after TG levels have been decreased to < 500 mg/dL should attention be turned to lowering the LDL-C level to reduce the risk of cardiovascular disease.²

Therapeutic Lifestyle Changes

The management of persons with LDL-C levels above goal includes institution of therapeutic lifestyle changes, including: (1) reduced intake of saturated fat and cholesterol, (2) increased physical activity, (3) weight control, and (4) avoidance or cessation of cigarette smoking.² These changes should be attempted in most persons for approximately 12 weeks before considering the initiation of pharmacotherapeutic intervention to lower LDL-C level (Figure 3).²

During the first 3 months of clinical assessment, priority should be given to lowering the patient's LDL-C level. During visit 1, CHD risk factors should be assessed, lipid profile obtained, as well as discussion focusing on appropriate diet, physical activity, weight loss, and cessation of cigarette smoking. Dietary CAGE questions can be useful in assessing a patient's intake of saturated fat and cholesterol (<http://circ.ahajournals.org/cgi/content/full/106/25/3253/TBL7>).

During visit 2, approximately 6 weeks later, the lipoprotein analysis should be repeated to determine progress. If the LDL-C goal is attained or at least decreased, the patient should be praised and instructed to continue the therapeutic lifestyle changes regimen. At this time, emphasis should be shifted to management of the metabolic syndrome and the associated lipid-related risk factors of elevated TG and low HDL-C levels. Because most persons with metabolic syndrome are overweight, obese and sedentary, it is important to strongly convey weight reduction parameters and physical activity guidelines in order to further reduce CHD risk.

The Finnish Diabetes Prevention Trial²⁹ and the Diabetes Prevention Program³⁰ demonstrate the benefit of even modest weight loss, moderate dietary adjustments, and increased physical activity in preventing the onset of diabetes in patients who are overweight and have impaired glucose tolerance. Data also demonstrate metformin to be effective in preventing the development of diabetes in persons diagnosed with impaired glucose tolerance (a 31% decrease in diabetes incidence), but less so than lifestyle modifications.^{29,30} Results of both trials found the incidence of diabetes decreased by 58% in patients with high blood sugar when counseled about exercise and healthy eating.^{29,30} Results from another clinical trial investigating the effects of exercise and weight loss on cardiac risk factors associated with metabolic syndrome demonstrate that exercise

training, when combined with a structured weight loss program, is an effective treatment modality for persons with hyperinsulinemia and in lowering diastolic blood pressure in patients with metabolic syndrome.³¹

If the LDL-C goal has not been attained by visit 3 (approximately 6 weeks later) a decision as to whether to initiate lipid-lowering pharmacotherapy should be made based on the progress made toward the LDL-C goal. Therapeutic lifestyle changes should continue to be encouraged. Results of a recent study found that intensive nutrition management, with the addition of nuts, soy protein, soluble (viscous) fiber, and plant sterols/stanols (eg, Benecol or Take Control Margarine) to a low-saturated-fat, low trans-fatty acid, low-cholesterol diet, can be as effective as initiating a statin medication in decreasing serum TC and LDL-C levels by approximately 30%.³²

Long-term follow-up visits consist mostly of monitoring patient adherence to lifestyle changes and pharma-

cotherapy. When no lipoprotein abnormalities other than an elevated LDL-C level are present, follow-up at 6-month intervals is appropriate.

At all stages of dietary therapy, referral to registered dietitians and other qualified nutritionists for additional professional, specialized assistance in meeting dietary goals may be indicated. The addition of plant sterols/stanols to the diet and/or increased fiber through intake of cereal grains, fruits, vegetables, and dried beans, peas, and legumes can also be considered. If it appears that the LDL-C goal may not be attained through dietary modifications alone, pharmacotherapeutic intervention should be considered.²

THE THERAPEUTIC LIFESTYLE CHANGES DIET

This intervention focuses on reducing saturated fats in the diet to <7% of total caloric intake and reducing cholesterol intake to <200 mg per day. Additional nutritional elements and goals of this diet are listed in Table 3.²

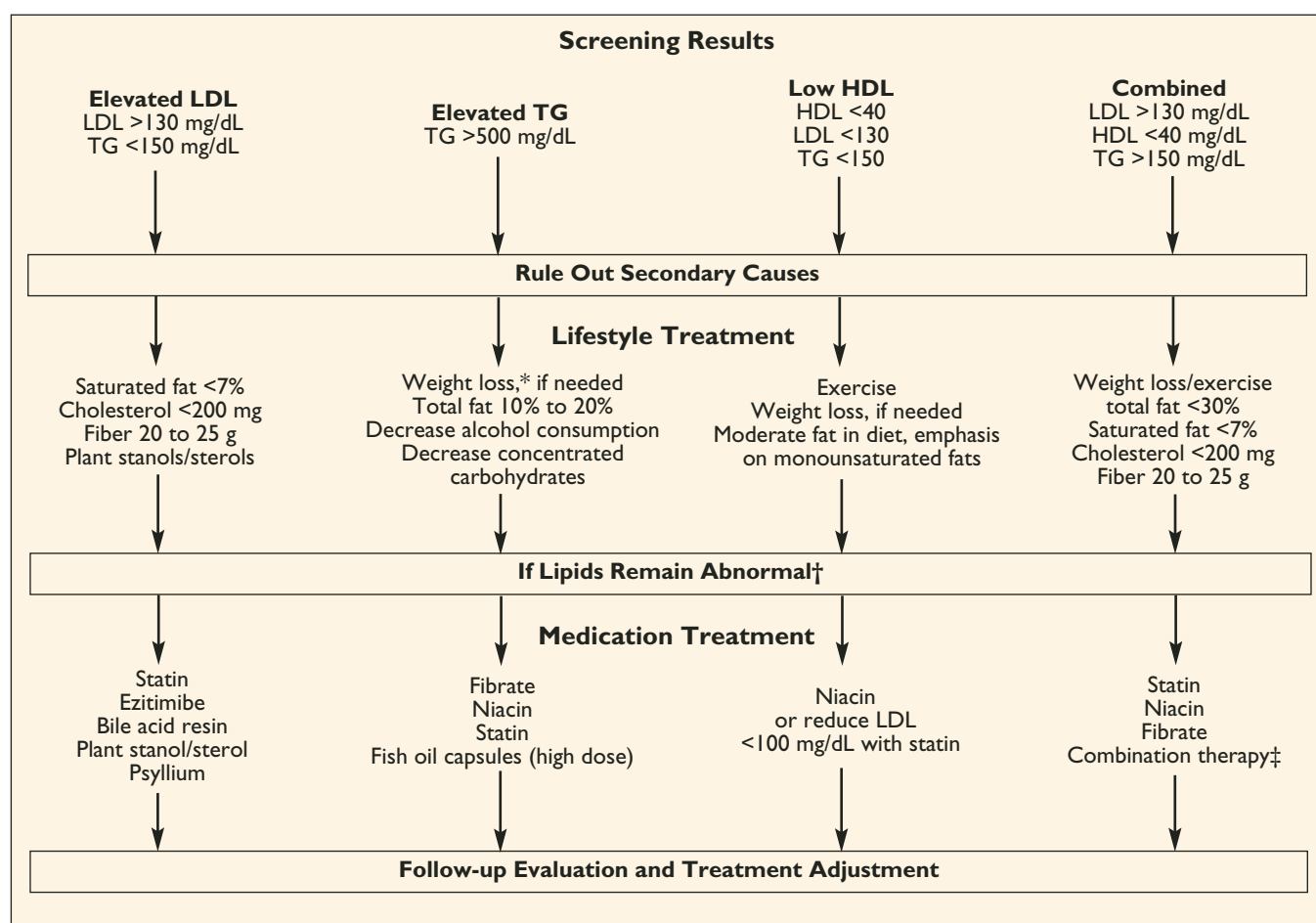


Figure 3. Dyslipidemia Treatment Summary.

*—Exception: immediate medication (gemfibrozil or niacin) for patients with TG >1,000 mg/dL due to high risk of pancreatitis or LDL-C >220 mg/dL due to genetic disorders and resistance to nonpharmacologic treatment after ruling out secondary causes.

†—Notes: (1) goal LDL-C <100 mg/dL with coronary heart disease (CHD)/noncoronary atherosclerosis, diabetes mellitus, or 10-year CHD risk >20%; (2) goal LDL-C <130 mg/dL if no known CHD or noncoronary atherosclerosis but high risk (LDL-C >160 mg/dL with two or more risk factors or LDL-C >190 mg/dL in isolation).

‡—Statins and fibrates and/or niacin may be used in combination with close monitoring for hepatitis or myositis (risk of interaction 1% to 5%).

LDL = low-density lipoprotein; TG = triglycerides; HDL = high-density lipoprotein.

Saturated fatty acids have been identified as the most deleterious source of fat in the American diet. Study data indicate that for every 1% increase in calories derived from saturated fatty acids as a percent of total energy, the serum LDL-C level increases approximately 2%.^{1,2}

Of the total caloric intake in the typical American diet an average of 11% is derived from saturated fatty acids with the major sources being high-fat dairy products (eg, whole milk, cheese, butter, ice cream, cream), high-fat meats, tropical oils (eg, palm, coconut, palm kernel) and baked products and mixed dishes containing dairy fats, shortening, and tropical oils.

Trans-fatty acids represent another dietary issue. Formed during hydrogenation, which solidifies liquid vegetable oils, these fatty acids are found in products such as shortenings, fried foods, and commercially manufactured food items such as crackers, cookies, and donuts. Some trans-fatty acids occur naturally in animal fats. Of total caloric intake, the mean intake of trans-fatty acids in the typical American diet is 2.6%.

Compared with unsaturated fatty acids, trans-fatty acids raise TC and LDL-C levels and lower HDL-C levels. Liquid vegetable oil or semiliquid margarine produces the most favorable change in TC and LDL-C levels and ratios of TC to HDL-C compared with butter and stick margarines.

For many years, monounsaturated fatty acids were considered to produce a neutral effect on lipid levels when compared with carbohydrates. Polyunsaturated fatty acids were the replacement of choice. Researchers have determined, however, that monounsaturated fatty acids (when substituted for dietary saturated fat) exhibit similar chole-

sterol lowering properties as polyunsaturated fatty acids but can raise HDL-C levels in some patients.

High dietary cholesterol intake increases LDL-C levels and raises the ratio of TC to HDL-C, adversely affecting the serum cholesterol profile. On average, the response of serum cholesterol to dietary cholesterol is 10 mg/dL per 100 mg dietary cholesterol per 1,000 kcal. At present, the average U.S. daily consumption of cholesterol is 256 mg. Intake of eggs represents approximately one third of this figure. Other sources of cholesterol include animal products, dairy, meats, poultry, and shellfish. While some study data suggest that dietary cholesterol increases the risk of heart disease independent of its effects on serum LDL-C levels, an analysis of two prospective cohort studies, the Nurses Health Study and the Health Professionals Study, indicate no significant association between the frequency of reported egg consumption and CHD except among women with diabetes.³³

Research suggests that for some persons, the type of dietary fat is more important than the amount of total fat consumed. Among the fatty acids that comprise the intake of total fat in the diet, only saturated and trans-fatty acids raise LDL-C levels. While it may be wise to keep total fat intake to a minimum for other health reasons (eg, to reduce body weight and the risk of certain forms of cancer), overly restricting all fat intake is unnecessary and can cause more harm if simple carbohydrates replace the fats. Substitution of simple carbohydrates for saturated fatty acids frequently causes a decrease in HDL-C levels and an increase in TG levels, unless consumed as part of a high-fiber diet, in which case the effects are moderate.

Table 3. Nutrient Composition of the Therapeutic Lifestyle Changes (TLC) Diet

Nutrient	Recommended Intake
Saturated fat (<i>trans</i> fatty acids should also be kept to a minimum)	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25% to 35% of total calories
Carbohydrates (Derive carbohydrates predominantly from foods rich in complex carbohydrates, such as grains, especially whole grains, fruits, and vegetables.)	50% to 60% of total calories
Fiber	20 to 30 g/day
Protein	Approximately 15% of total calories
Cholesterol	<200 mg/day
Total calories	Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain. Include at least moderate physical activity, contributing at least 200 kcal/day.

Note: One of the reasons total fat is allowed to range from 25% to 35% is that a higher intake of fat, mostly in the form of unsaturated fat, can help reduce triglycerides and raise high-density lipoprotein cholesterol in persons with metabolic syndrome.

(Information from NCEP ATP III.)

Plant Sterols/Stanol

Patients may wish to add plant stanols/sterols to their diet. These substances are isolated from soy and tall pine-tree oils. More than 40 plant sterols (or phytosterols) have been identified, but sitosterol, campesterol, and stigmasterol are the most common. The major plant stanols are sitostanol and campestanol, which are much less abundant in nature than sterols.

Approximately 50% of cholesterol intake is absorbed in the intestinal tract, whereas plant stanols and sterols are absorbed at a decreased level. Absorption is approximately 10% to 15% for campesterol and campestanol, respectively, 4% to 7% for sitosterol, and 1% for sitostanol.³⁴ Thus, foods enriched with these substances lower serum cholesterol levels through reducing intestinal absorption of cholesterol without affecting HDL-C or TG levels and, often, in as little time as 1 to 2 weeks.³⁵

Because lipids are necessary to solubilize stanol/sterol esters, they are usually found in commercial margarines. Benecol and Take Control Margarines, in quantities of approximately 1 tablespoon with meals (or approximately 2 to 3 grams per day), have been shown to reduce LDL-C levels from 8% to 14% with little or no change in HDL-C or TG levels.^{36,37} A recent meta-analysis of 41 trials revealed that intake of stanols or sterols of 2 grams per day reduced LDL-C levels by 10%, with higher intakes adding little benefit. Combining intake of stanols/sterols with a diet low in saturated fat and cholesterol and high in fiber could raise the reduction benefit to 20%.³¹

Plant stanol ester has been shown to significantly augment the cholesterol-lowering effect of statins.³⁴ Adding sterols or stanols to lipid-lowering therapy with a statin may be as effective as doubling the statin dose. Addition of plant sterols or stanols to the diet resulted in a reduction in blood cholesterol levels of approximately 15% in children with familial hypercholesterolemia and in persons with diabetes.³¹ No clinically significant adverse effects have been detected to date, though long-term clinical trials have not been conducted.^{36,37}

Products such as fortified orange juice, yogurt, cream cheese spreads, and cereal bars containing stanols or sterols have been introduced in some countries, and cereals and fruit juice containing free (ie, unesterified) plant sterols and stanols are being test marketed in the United States.

Other Dietary Elements

A meta-analysis of 67 controlled trials indicates that incorporating 3 to 6 grams per day of soluble fiber derived from oat products or psyllium may decrease the LDL-C level by approximately 7% without affecting HDL-C or TG levels.³⁸ Similarly, results from a number of studies suggest that inclusion of almonds (68 to 100 grams per day)—in the context of a heart-healthy diet—can lower serum LDL-C levels from 7% to 29%.³⁹⁻⁴¹ Data from one study demonstrates that intake of almonds produced changes similar to those changes associated with intake of high monounsaturated fat oils in

patients with diabetes.⁴¹ Total cholesterol and LDL-C concentrations declined with progressively higher intakes of almonds, indicating a dose-response relationship.⁴⁰

While fish oil (omega-3 fatty acids) supplements (3 to 12 grams per day with meals) produce no effect on LDL-C levels, lower serum TG and VLDL levels have been reported, often with a moderate elevation in HDL-C levels. In addition, omega-3 fatty acids are believed to reduce platelet aggregation, increase resistance to cardiac arrhythmias, and improve endothelial function, further contributing to a reduced risk of sudden cardiac death and cardiovascular disease. One prospective cohort study involving data from The U.S. Physicians Health Study⁴² indicates that fish consumption 1 time per week decreases the risk of sudden cardiac death in men by half.

Soy protein (25 to 40 grams per day) in a diet low in saturated fatty acids and cholesterol can lower LDL-C levels by approximately 5%.⁴³ In fact, soy protein appears to have some of the broadest ranges of benefit on serum lipoproteins and cardiovascular risks. It decreases serum TC, LDL-C and TG levels; slightly increases HDL-C levels; and may selectively decrease the amount of atherogenic small, dense LDL particles.⁴⁴

Moderate alcohol consumption is linked to cardioprotective mechanisms, with benefits attributable to reduction of platelet aggregation, elevation of HDL-C levels, and inhibition of LDL oxidation. More than two drinks per day, however, increases the risk of all-cause mortality. Because alcohol consumption is associated with numerous risks it is not recommended as a sole means to lower lipid levels.^{1,2}

Physical Activity

The importance of physical activity cannot be overstated, particularly for persons with metabolic syndrome. Physical inactivity is considered a major risk factor for CHD. Regular physical activity reduces VLDL levels, raises HDL-C levels, and, in some persons, lowers LDL-C levels. Physical activity also lowers blood pressure and reduces insulin resistance. For persons who struggle with weight control, walking has been found to be one of the most important factors in maintaining a healthy weight.

Data from one study demonstrates that in the absence of regular aerobic exercise in men and postmenopausal women with an LDL-C level between 125 and 210 mg/dL and an HDL-C of <59 mg/dL, even a fat- and cholesterol-restricted diet was ineffective in improving lipid profiles.⁴⁵

Exercise plus weight loss is an effective treatment for hyperinsulinemia and lowering diastolic blood pressure in persons with metabolic syndrome.³¹ In a study of 522 overweight, glucose-tolerance-impaired subjects, evidence suggested that combined with a low-fat, high-fiber diet, exercise plus weight loss reduced the risk of type II diabetes by 58%.²⁹

Even a small amount of physical activity can make a big difference in cardiovascular and overall health. Patients who are inactive should be encouraged to begin walking for

10 minutes 3 times daily. Other forms of exercise include taking the stairs rather than the elevator. Patients who are somewhat active may join a gym, find an exercise partner, or find other ways of varying and energizing their exercise routine to prevent burnout. Exploration of a new sports activity or other active interests may also keep patients focused on a healthy lifestyle. The initial activity goal should include an aerobic form of exercise that involves the use of large muscle groups (eg, walking, swimming) a minimum of 30 minutes per day most days of the week.⁴⁶

General Principles of Pharmacotherapy

Lowering LDL-C levels is the primary goal of clinical lipid management. In many persons, therapeutic lifestyle changes will achieve the goal. However, some persons will require pharmacotherapeutic intervention. Available options include statins, bile acid resins (cholestyramine, colestipol, colesevelam), niacin/nicotinic acid (crystalline, timed-release preparations, niaspan), fibric acid derivatives (fibrates: gemfibrozil, fenofibrate), a niacin/statin combination product, and a new cholesterol absorption inhibitor, ezetimibe (*Table 4*).

The NCEP ATP III guidelines recommend that pharmacotherapy be considered if LDL-C or non-HDL-C levels are ≥ 30 mg/dL above target values. For persons with CHD, CHD risk equivalents, or a 10-year risk of 10% to 20%, pharmacotherapy may be considered in combination with therapeutic lifestyle changes at any time. Persons with LDL-C levels ≥ 130 mg/dL are often started on an LDL-C lowering medication and therapeutic lifestyle changes simultaneously because the LDL-C goal of < 100 mg/dL may not be attainable through therapeutic lifestyle changes alone.

In general, statin therapy is initiated first. The initial dose depends on the baseline LDL-C level. Generally, therapy is initiated at the lowest dose and then titrated to the level of effect. Six-week follow-up is recommended. If the treatment goal is attained, the current dose can be maintained. If not, increasing the statin dose or combining a statin with a bile acid resin or ezetimibe can intensify therapy. The LDL-C goal of < 100 mg/dL is attained in fewer than half of persons with CHD on a standard dose of statins.⁴⁷ In the presence of atherogenic dyslipidemia, nicotinic acid or a fibric acid may be added to the regimen.

The largest LDL-C lowering effect is a result of the initial dose of the statin. Further, doubling the dose may decrease the LDL-C level by an additional 5% to 7%, which is an important pharmacologic principle to remember when making pharmacologic treatment decisions for cholesterol.

If the LDL-C goal remains below goal, therapy should be intensified and the patient reassessed in 6 weeks. An increase in the dose of the LDL-lowering medication or the addition of a TG-lowering medication (eg, a fibrate or nicotinic acid) to the regimen may be necessary to reduce LDL and VLDL levels. This approach usually has the added benefit of raising the HDL-C level.

While LDL-C level is the primary target of therapy, other lipid factors affect CHD risk, including low HDL-C, an elevated TG level (especially VLDL remnants), and possibly, small LDL particles. This lipid triad, or atherogenic dyslipidemia, commonly occurs as one component of the metabolic syndrome. Weight reduction and increased physical activity constitute first-line therapy followed by pharmacotherapy with statins, nicotinic acid, or fibrates. When the TG level is elevated, non-HDL-C becomes a secondary target of therapy. If a statin alone is insufficient to attain the non-HDL-C goal, a combination of a statin and nicotinic acid may be indicated.⁴⁸ This combination is now available in a combination tablet.

LDL-lowering pharmacotherapy should initially be monitored at 6-week intervals. Once LDL-C levels are within normal range, the lipoprotein profile can be monitored every 6 to 12 months.

STATINS

Statins are generally recommended as first-line therapy and are currently the most widely used and most effective treatment for persons with hypercholesterolemia.² These agents are potent inhibitors of cholesterol biosynthesis and reduce morbidity and mortality associated with CHD, impede progression of atherosclerosis, contribute to regression of atherosclerotic lesions, and decrease coronary artery revascularization.² Statins stabilize plaque, improve coronary endothelial function, inhibit platelet thrombus formation, and possess anti-inflammatory activity.²

The U.S. Food and Drug Administration has approved six agents from this class of medicines for the treatment of persons with unacceptable cholesterol levels: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. These agents have been shown to lower LDL-C levels from approximately 20% to 60%, to raise HDL-C levels 5% to 15%, and to work equally effectively among men and women.^{3,16-18} However, a significant proportion of persons on statin therapy continue to have cholesterol levels above the range at which the incidence of CHD is significantly reduced.

Statins are generally administered with the evening meal or at bedtime. While well tolerated by most persons, potential side effects limit their utility when prescribed at maximal or near-maximal doses. One of the most troubling adverse events is myopathy (usually present in 1% to 5% of patients). Persons with complex medical problems and those who are taking multiple medications are at greatest risk. Nonspecific muscle aches and pains are often attributed wrongfully to statin therapy. An elevation of creatine kinase (CK) is a better indicator of statin-induced myopathy, although myalgias and arthralgias can occur without CK elevations. Nevertheless, patients should be aware that unexplained muscle pain or weakness, as well as brown urine, should be reported immediately. In the presence of these symptoms, the medication should be stopped immediately.

Table 4. Cholesterol-Lowering Medications

Medication	Dosage Range	LDL Reduction	Cost	Side Effects and Special Considerations
HMG-CoA Reductase Inhibitors (Statins)				Note: this list is for all statins
Atorvastatin	10 mg qd minimum 80 mg qd maximum	35% to 38% 50% to 60%	\$\$\$-\$\$\$\$	<ul style="list-style-type: none"> Increased hepatic transaminases and other minor GI effects (2% to 3%); 1 Continue if LFTs are elevated but <2 to 3 times normal—remonitor; 2 Myalgias/artralgias (2 to 3%); 3
Fluvastatin	20 mg qhs minimum 80 mg XL maximum	20% to 25% 35% to 38%	\$\$+	1, 2, 3
Lovastatin	10 mg qhs minimum 80 mg qhs or 40 mg bid maximum	25% to 30% 35% to 40%	\$\$-\$\$\$\$	1, 2, 3
Pravastatin (Note: Only statin not with CYP450 metabolism; less interactions)	10 mg qhs minimum 80 mg qhs maximum	25% to 32% 34% to 35%	\$\$\$-\$\$\$\$	1, 2
Simvastatin	10 mg qhs minimum 80 mg qhs maximum	35% to 40% 45% to 50%	\$\$\$-\$\$\$\$	1, 2, 3
Rosuvastatin	2 mg qhs minimum 40 mg qhs maximum	35% to 40% 55% to 60%	\$\$\$-\$\$\$\$	1, 2, 3 and may cause renal insufficiency
Bile Acids Sequestrants				
Colestipol	4 to 8 g bid to tid	10% to 25%	\$\$\$-\$\$\$\$	<ul style="list-style-type: none"> Second line for LDL-C disorders Potent combination with statins May increase TG Bloating, constipation Interferes with some medication and fat-soluble vitamin absorption Colesevelam has less GI toxicity and may interfere less with absorption of other medications
Cholestyramine	5 to 10 g bid to tid (start at a low dose)	TG may increase moderately	\$\$-\$\$\$	
Colesevelam	6 capsules (3 capsules bid or 6 qd with meal)		\$\$\$\$	
Cholesterol Absorption Inhibitors				
Ezitimibe	10 mg daily	18% to 20%	\$\$	• Slight elevation in hepatic enzymes
Plant Sources				
Stanols/Sterols (Benecol, Take Control)	3 tablespoons of margarine tid or used as salad dressing bid	8% to 15%	\$\$-\$\$	<ul style="list-style-type: none"> Minimal to no side effects Weight gain may occur due to increased calorie intake
Psyllium (fiber)	Used in 1 to 3 tablespoons qd divided bid	Reduces LDL 0% to 10%	\$	• Bloating, constipation occur frequently
Niacin				
Niacin plain (immediate release)	500 to 1,500 bid to tid (starting dose: 100 mg)	20% to 25%	\$	<ul style="list-style-type: none"> Flushing, dry skin, rash Glucose intolerance Elevated uric acid Dyspepsia or ulcer Caution with diabetes, gout, history of gastritis or peptic ulcer
Extended release (Niaspan only SR-formulation)	500 to 2,000 mg qhs	Also: 50% TG decrease, 25% HDL-C increase	\$\$-\$\$\$	
Fibrates				
Gemfibrozil	600 mg bid	TG 50% decrease	\$\$-\$\$\$	<ul style="list-style-type: none"> Nausea Myositis (2 to 6%) with statins and cyclosporine
Fenofibrate	54 to 201 mg qd	HDL-C 5% to 20% increase LDL-C 10% increase to 20% decrease		

1. All statins have moderate TG lowering (15% to 40% plus) and HDL raising (5% to 12%) effects.
 2. Increase myositis risk interaction with gemfibrozil and, possibly, fenofibrate.
 3. Cytochrome P450 metabolism with interaction with other medications that are metabolized by CYP450 enzymes may result in higher statin levels and possible myositis and/or rhabdomyolysis.
 bid = twice daily; GI = gastrointestinal; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LFTs = liver function tests; qd = every day; qhs = every night; SR = slow release; TG = triglycerides; tid = three times a day; XL = extended release.
 \$ = less than \$20 per month; \$\$ = \$20 to \$40 per month; \$\$\$ = \$40 to \$60 per month; \$\$\$\$ = \$60 to \$80 per month; \$\$\$\$\$ = \$80 or more per month.

The effects of statins in lowering TG levels are dose- and potency-dependent. As TG levels increase, higher doses of statins are required. For moderate elevations of LDL-C levels in patients with elevated TG, niaspan is a good alternative. Niaspan is the safest of the extended-release preparations with <10% of patients reporting gastrointestinal side effects. In general, statins should not be prescribed in patients with TG levels >500 mg/dL.²

BILE ACID RESINS

Bile acid resins are reported to lower LDL-C levels from approximately 10% to 25% and are an effective class of medicines in achieving this goal. Because this class of medicines remains unabsorbed in passage through the gastrointestinal tract, they do not produce systemic toxicity, lack convenience of administration, and frequently cause gastrointestinal symptoms such as constipation, abdominal pain, bloating, fullness, nausea, and flatulence. Colesevelam is more easily administered and better tolerated than other agents in this class. Colesevelam, dosed at 6 tablets daily or 3 tablets twice daily, has not been demonstrated to decrease absorption of many of the other medicines that other resins do when administered concomitantly. Cholestyramine and colestipol are administered as powders that must be mixed with water or juice and are usually taken once or twice per day with meals. Colestipol is also available as a 1-gram tablet.

Resins are particularly useful in combination with statins. Doubling the dose of a statin produces a further reduction in the LDL-C level of approximately 6%.² The addition of a resin to statin therapy can further lower LDL-C levels by 12% to 24%.^{49,50}

In women of childbearing age and in those with mild hypercholesterolemia or intolerance to statin therapy, treatment with a bile acid resin is a viable alternative. Because bile acid resin can raise TG levels, they are contraindicated in persons with TG levels >400 mg/dL and in the presence of familial dysbetalipoproteinemia.²

CHOLESTEROL ABSORPTION INHIBITORS

Ezitimibe is a new selective cholesterol absorption inhibitor. A single daily dose of 10 mg effects an average reduction of approximately 18% in plasma LDL-C levels and a 4% increase in HDL-C levels when prescribed as monotherapy, or as much as 25% LDL-C reduction in combination with a statin or fenofibrate.⁵¹⁻⁵³

Ezitimibe may be used as monotherapy for patients who require modest reductions in LDL-C levels or who cannot tolerate other lipid-lowering therapies. This agent may be most useful when prescribed in combination with a statin for patients who cannot tolerate large doses of statins or who need further reduction in LDL-C level despite statin therapeutic dose levels. Results from one study demonstrate that the addition of ezitimibe to ongoing statin therapy led to a substantial, additional reduction in LDL-C levels.⁵² The combination of the two agents reduced LDL-C levels

by approximately 25% over what had been achieved with statin therapy alone compared to an additional reduction of 3.7% when placebo was added to statin therapy.⁵²

Unlike other lipid-lowering medications that act on the gastrointestinal tract, ezitimibe does not appear to exacerbate hypertriglyceridemia (in fact, TG levels drop an average of 10% to 14%).⁵²⁻⁵⁴ Ezitimibe has an adverse event profile similar to placebo when prescribed as monotherapy or in combination with statins or fenofibrate. There is low potential for drug-drug interactions.

NICOTINIC ACID/NIACIN

Among all lipid-lowering agents, nicotinic acid appears to be the most effective for favorably modifying the lipoprotein abnormalities associated with atherogenic dyslipidemia. Niacin lowers serum TC, LDL-C (10% to 25%), and TG levels (20% to 35%), and is among the most effective lipid-lowering agents for raising HDL-C levels (a dose-dependent 10% to 30%). Doses of 2 to 3 grams per day, however, are generally necessary to produce LDL-C reductions of 15% or greater.^{55,56}

While niacin has a high success rate, its utility is limited by poor tolerability and the adverse side effects of cutaneous flushing, dyspepsia, hyperuricemia, and hyperglycemia. Flushing is significantly reduced if niacin is taken with or after meals and if 325 mg of aspirin is administered 30 to 60 minutes prior to the niacin dose. Tolerance to the flushing usually develops in 1 to 2 weeks.²

Other side effects include rash, dry skin, ichthyosis, nausea, dyspepsia, flatulence, vomiting, diarrhea, conjunctivitis, nasal stuffiness, acanthosis nigricans, retinal edema, and activation of peptic ulcer. Major adverse events can include hepatotoxicity, hyperuricemia and gout, and hyperglycemia.² Monitoring of glucose levels and liver function tests are recommended.

Because of niacin's side effect profile and need for higher dosing to lower LDL-C, niacin is typically not prescribed as the primary agent in lowering LDL-C levels. Niacin is also very effective in combination with statins for combined cholesterol disorders.² Niacin is used as monotherapy for elevations of non-HDL-C, triglycerides, and low HDL-C.

Among other mechanisms, niacin appears to alter lipid levels by inhibiting lipoprotein synthesis and decreasing VLDL synthesis by the liver. Many crystalline preparations of nicotinic acid are available without prescription and are inexpensive. Niaspan, an extended-release formulation of nicotinic acid, is associated with less flushing than typically occurs with crystalline preparations and has fewer gastrointestinal side effects than either crystalline niacin. Crystalline niacin is usually administered two to three times per day with or after meals. Niaspan is administered as a single dose at bedtime.²

COMBINATION NIACIN/STATIN

Advicor is the first once-daily, niacin extended-release/lovastatin combination agent. Results from one study comparing

Advicor to standard doses of atorvastatin or simvastatin demonstrate that Advicor lowered LDL-C levels 42% following 12 weeks of therapy.⁵⁷ This was comparable to reductions in the atorvastatin group and greater than reductions in the simvastatin group (34%).⁵⁷ The combination agent more effectively increased HDL-C levels than either statin alone and provided significant improvements in TG, lipoprotein(a), apolipoprotein A-1, apolipoprotein B and HDL subfractions. Only 6% of participants withdrew due to flushing. No significant differences were observed among the study group in terms of elevated liver enzymes or medicine-induced myopathy.⁵⁷

FIBRIC ACID DERIVATIVES (FIBRATES)

Fibrates (gemfibrozil and fenofibrate) are prescribed primarily to lower TG levels. The effect of fibrates in lowering LDL-C levels is generally in the range of 10% or less.² In persons with hypertriglyceridemia, LDL-C levels often rise on fibrate therapy. Fibrates typically reduce TG levels by 25% to 50%.⁵⁸

While some study data² demonstrate that fibrate therapy reduces the risk of fatal and nonfatal MIs, CHD death, and stroke, this benefit appears limited to patients with elevated TG and low HDL-C.^{58,59}

Fibrates are commonly prescribed in combination with statins for persons whose TG levels remain elevated. This combination may better achieve the secondary target for non-HDL-C than with statins alone. Fibrates are generally well tolerated, with gastrointestinal complaints being the most common adverse side effect. Because the kidney excretes fibrates, elevated serum levels occur in persons with renal failure, increasing the risk for myopathy. The combination of a fibrate with a statin also increases the risk for myopathy, which can lead to rhabdomyolysis.² This risk is more likely to occur with gemfibrozil and statins than with fenofibrate combined with a statin.⁶⁰

Special Circumstances

ACUTE MYOCARDIAL INFARCTION, STROKE, AND HOSPITALIZED PATIENTS

In these patient populations, LDL-C and HDL-C levels may be artificially low in the immediate illness phase because of inflammation or from the use of heparin. Although the NCEP ATP III guidelines endorse cholesterol screening during the first 24 hours following initial hospitalization, cholesterol levels may already be decreasing during this time period and screening may lead to underuse of appropriate therapy. Prescribing prior to discharge increases the rate of cholesterol treatment compared to prescribing through usual post-discharge care.⁶¹ For patients with acute syndromes, treatment should be based on cholesterol tests prior to the cardiac event, if available. If these values are unavailable, patients may empirically begin dietary therapy and a statin at low-to-moderate dose.¹⁵ It takes as many as

3 months for lipid levels to return to baseline after a CVD event. Later, therapy should be adjusted to LDL-C response.

Low HDL-C

Low HDL-C (≤ 40 mg/dL) is a very common lipid abnormality in persons with premature CHD, usually in association with combined hyperlipidemia or the atherogenic lipoprotein profile.⁶² The goals are to lower the LDL-C to goal level and to raise the HDL-C level by treating the associated causes (eg, hypertriglyceridemia, metabolic syndrome, physical inactivity, cigarette smoking, high carbohydrate diets). Achieving LDL-C and non-HDL-C targets and treatment of metabolic syndrome remain the dominant strategies. An isocaloric increase in dietary monounsaturated fats may help. If TG or non-HDL-C levels are significantly elevated, niacin, gemfibrozil, or fenofibrate are appropriate. Additional LDL-C lowering with a statin is also appropriate.

MEN YOUNGER THAN 35 YEARS AND PREMENOPAUSAL WOMEN

The 10-year risk of CHD events is low in these two patient populations unless risk factors such as hypercholesterolemia, heavy cigarette smoking, or diabetes mellitus are present. However, long-term risk may be very high. Although clinical CHD is uncommon in these patient populations, subclinical atherosclerosis can progress rapidly. CHD is a lifelong disease, and the presence of risk factors during youth predicts premature development of CHD.⁶³ Therapeutic lifestyle change is the dominant treatment strategy for younger persons at risk for future CHD events, with the exception of those with obvious genetic cholesterol abnormalities not responsive to lifestyle changes. These include patients with LDL-C levels of 200 to 220 mg/dL or TG levels of 800 to 1000 mg/dL.

MIDDLE-AGED WOMEN AND HORMONE REPLACEMENT THERAPY

Many women believe they are relatively safe from heart disease, spending far more time worrying about breast cancer or believing that heart disease is a man's disease. The facts are:

- In every year since 1984, CVD has killed more women than men.¹
- Cardiovascular diseases kill more women (more than half a million each year) than the next 7 causes of death combined.¹
- Approximately 1 in 29 women will die from breast cancer, while 1 in 2.4 will die from cardiovascular disease.¹
- CHD rates in women after menopause are 2 to 3 times those of same-aged women before menopause.¹

Not long ago, hormone replacement therapy (HRT) was recommended as first-line therapy for the treatment of hyperlipidemia in women. The recommendation was based on study results that demonstrated such therapy decreased

LDL-C levels and lipoprotein(a), and increased HDL-C, HDL2, apolipoprotein A-1 levels, and other proposed vascular protective effects.⁶⁴ Results of cohort studies found that women on HRT experienced less heart disease than women not taking HRT, but randomized clinical trials have demonstrated significantly greater risk of cardiovascular events, thromboembolic events, and cancer in women taking HRT.⁶⁵

The Heart and Estrogen/Progestin Replacement (HERS) study⁵⁴ evaluated estrogen/progestin replacement, finding that despite an 11% lower LDL-C level in the HRT group, there was no overall reduction in the risk of nonfatal MI or CHD mortality following over 4 years of treatment. The investigators also reported a significant increase in cardiovascular events during the first year of treatment and an increase in thromboembolic events and gall bladder disease. Data from the HERS follow-up study (HERS II) also failed to demonstrate cardiovascular benefit.⁶⁶

Similarly, results from the Estrogen Replacement and Atherosclerosis (ERA) study showed no benefit with regard to the progression of angiographically measured coronary stenosis or cardiovascular events associated with the use of either estrogen alone or estrogen plus medroxyprogesterone acetate for a mean of 3.2 years.⁶⁷

Data from the Women's Health Initiative Study,⁶⁵ indicated that the regimen of HRT most commonly prescribed for women in the United States was not only not cardioprotective, but increased the risk for adverse vascular events.

As a result of these important randomized trials, initiation or continuation of HRT is not recommended for secondary prevention of coronary heart disease.

OLDER PERSONS

Most new CHD events and coronary deaths occur in men 65 years of age or older and women 75 years of age or older. Study data have shown that older persons benefit just as much from lipid-lowering therapy as younger patients.¹⁸ Treatment recommendations are essentially the same, but are also based on the overall health and prognosis of the patient. The only complication is that risk factors, particularly LDL-C levels, decline in predictive power as people age, thus risk assessment using Framingham scoring may be less reliable. The presence of atherosclerosis or a prior atherosclerotic event is a strong predictor of future events and is an indication for aggressive cholesterol treatment. Pharmacotherapy to lower LDL levels in older persons with advanced coronary or systemic atherosclerosis is indicated even in the absence of clinical coronary symptoms.²

Follow-Up and Maintenance

A follow-up fasting lipid level and an alanine aminotransferase (ALT) should be obtained 8 to 12 weeks following

initiation or modification of pharmacotherapy. Patients started on Niacin should also have fasting glucose and uric acid levels checked. For patients at goal, lipid profiles may be obtained every 6 months as part of the maintenance regimen. Patients should be monitored for side effects from cholesterol therapy. Lipid-altering medications can infrequently cause liver enzyme elevation and myopathy. If ALT is greater than 3 times the normal range, or if the patient develops myopathy in the presence of an elevated creatinine phosphokinase (CPK)-MM fraction, the medication dose should be reduced or the therapeutic agent stopped or changed. After altering therapy, an ALT liver panel should be repeated to assess improvement or resolution. Pregnancy is an absolute contraindication to lipid-lowering agents (except in the case of the woman with severe hypertriglyceridemia).

The most common reasons for pharmacotherapeutic failure include:

- Failure of patient to alter lifestyle
- Prescribing the wrong pharmacotherapeutic agent
- Prescribing an inadequate dose
- Failing to prescribe combination therapy when appropriate
- Patient nonadherence

If an adherent patient, or patients with familial dyslipidemias or multiple risk factors, have not reached goal, consider referral to a specialty clinic.

Despite the evidence supporting the benefits of cholesterol treatment, initiation of and adherence to therapy remains less than optimal.⁶⁸ Failure to achieve goal is due to the inefficacy of the chosen pharmacotherapeutic agent for some persons; for others, failure is due to non- or poor compliance not only to the pharmacotherapeutic regimen but the therapeutic lifestyle changes as well. Results from an Australian study indicated that approximately one fourth of persons who were prescribed a lipid-lowering medication discontinued it after one month, 50% by 3 months, and 60% by the end of 1 year.⁶⁹ This is particularly troublesome in light of the fact that many of these medications require months of use before the benefits are fully realized.

Optimal results will be attained if you choose the optimal therapy for the patients at highest risk and follow up routinely to ensure adherence to a healthy lifestyle and their medication. This can be accomplished through good physician-patient communication, efficient office systems, and access to resources for lifestyle counseling. This type of management is critical to the future as so many patients in the United States present to family physicians with complications of atherosclerosis, cardiovascular disease, and cholesterol disorders.

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Patient Education

Living Healthy and Lowering Your Cholesterol

What is Cholesterol?

Simply stated, cholesterol (pronounced: ko-less-ter-all) is one of two major fats found in your blood. The other fat is called triglyceride (pronounced: try-gliss-er-ide). Fats are an important part of your diet and serve many purposes.

Where Does Cholesterol Come From?

Cholesterol mainly gets into your blood through the foods you eat. Foods that have high levels of cholesterol, or fat, mostly come from animal fats. Examples of some of these foods are red meats, milk, cheese, ice cream, some cooking oils, butter, shellfish, and egg yolks.

How Does My Body Use Cholesterol?

Fats are a major source of “fuel” or energy for your body. They insulate your body from cold. Fats are also an important part of your cells. Fats may be stored in your cells for future use.

There are “good” and “bad” fats, or cholesterol. Let’s briefly explain the difference. First, cholesterol flows through your blood and attaches itself to proteins also found in your blood. When the cholesterol and the proteins combine, they are called lipoproteins (pronounced: lie-po-pro-teens). Like fats by themselves, these lipoproteins serve several purposes in your body. One important purpose is to carry the cholesterol through your bloodstream to where it can leave the body. In medical terms, the “good” cholesterol is called High Density Lipoprotein cholesterol, or simply HDL cholesterol. It is good because it helps take fat from the body, and is made up of more protein than fat.

The “bad” cholesterol is called Low Density Lipoprotein cholesterol, or LDL cholesterol. It is considered bad cholesterol because it is made up of more fat than protein.

Sometimes there is too much fat flowing through the blood. This can increase the level of cholesterol in your blood. High cholesterol levels can increase your risk of having heart disease, a heart attack or stroke because the fat clings to vessel walls and clogs the flow of blood.

How Do I know if My Cholesterol is Too High?

You probably will not know if your cholesterol level is too high. That is why it is important to have a routine physical examination and blood tests to make sure your cholesterol is in a normal range. You can have a good idea, however, if you are at risk of high cholesterol by looking at yourself and your lifestyle. Generally, you are at a greater risk of having a high cholesterol level if:

- You are overweight
- You are inactive
- You smoke
- You eat foods that contain high amounts of animal fats

Your doctor can order a blood test to determine the amount of cholesterol in your blood. It is a simple test that is done in your doctor’s office. Your doctor can then tell you what your total cholesterol level is, and can also tell you how much good and bad cholesterol is in your blood.

After your blood has been tested, the laboratory will send a report to your doctor. Below are the categories of cholesterol levels.

LDL or “Bad” Cholesterol

<i>If your test result is:</i>	<i>Then your bad cholesterol is:</i>
<100	Considered to be “normal”
100 to 129	Considered to be “near normal”
130 to 159	Considered to be “somewhat high”
160 to 189	Considered to be “high”
>190	Considered to be “very high”

HDL or “Good” Cholesterol

<40	Considered to be “normal”
>60	Considered to be “high”

Total Cholesterol in the Blood

<200	Considered to be “normal”
200 to 239	Considered to be “somewhat high”
>240	Considered to be “high”

What if My Cholesterol is Too High?

There are several ways to reduce your total cholesterol level, lower your bad cholesterol and raise your good cholesterol. The good news is: it is in your hands! If you are overweight, eat foods high in fat, and do not exercise, the lifestyle changes recommended below will make a difference. Remember, you don’t have to make all the changes at the same time and every small change you make reduces your risk for heart disease. The best way to approach lifestyle changes is to take one step at a time.

Eat Well and Lose Weight

Where do you begin? Let’s start with food. Americans consume high amounts of fats. Remember, you don’t have to change your entire eating style overnight. The most important thing to remember is to make a small change, incorporate this change into your life and then make another change to your eating habits. These changes are not temporary “diet” changes, but should be approached as life-long lifestyle changes.

Below are the recommended servings from the five food groups. To begin, make a small adjustment to your eating style by choosing an item from below and incorporating that into your meals. For example, if you consume more eggs than you should, decrease the number of eggs you eat to the recommended level. Try this for a couple of weeks. Then, rather than always eating red meat, you might begin substituting poultry or fish twice a week. Begin each day with breakfast—have a bowl of bran cereal and a banana. Breakfast is

This patient education handout provides an overview of this topic and does not apply to all patients. It is not a substitute for medical advice. Your family doctor can provide further information on this topic. Copyright © 2003 American Academy of Family Physicians.

Living Healthy and Lowering Your Cholesterol (continued)

‘breaking the fast’ from a night without food. Your body needs the fuel that food provides. It is very important to eat a good breakfast. Remember, simple changes add up. You will soon be proud of what you have accomplished and how much “in control” you will feel.

- Three to five servings per day of fresh, frozen or canned vegetables without added fat, sauce or salt
- Two to four servings per day of fresh, frozen, dried, or canned fruits
- Two to three servings (or about 5 ounces per day) of lean meat, skinless poultry or seafood (one serving is about the size of a deck of cards)
- Two to three servings per day of skim or low-fat milk and low-fat or fat-free dairy products, such as cheeses and yogurt
- No more than two egg yolks per week—you can switch to egg whites or egg substitutes
- Six servings of whole grain breads, cereals, pasta, beans, low-fat crackers, or starchy vegetables

Eat fats, oils, and sweets sparingly. Olive oil, cashews, peanuts and almonds are good for you, but only in small amounts. Use soft or liquid margarines instead of butter and stick margarines, and look for one that contains plant sterols/stanols. Choose spreads or salad dressings made from vegetable oil and that are low-fat or fat-free.

Eat more fiber. Fruit is an easy addition – take a banana, an apple and an orange to work for snacks. Cook a pot of refried beans in the crock-pot and enjoy a burrito when you arrive home. The following foods are rich in fiber:

- Cereal grains (barley, oatmeal, oat bran, seeds)
- Fruit (apples, bananas, blackberries, citrus fruits, nectarines, peaches, pears, plums, prunes)
- Legumes (all types of beans, lentils, chick peas, black-eyed peas)
- Vegetables (broccoli, brussel sprouts, carrots)—an easy reminder is “green is good”
- Fish, once or twice per week, that is rich in omega-3 fatty acids (like salmon)—remember, shellfish are high in fat

Alcohol has been mentioned as being beneficial for your heart. A small amount of alcohol, such as one glass of wine per day, may be beneficial, but more than this amount may also have the opposite effect. It is best to always seek your doctor’s advice before choosing alcohol as a means to lowering your cholesterol level.

If you do not currently exercise at all, research shows that even a small amount of exercise can do wonders for your health. Regular exercise is truly a miracle treatment! Regular exercise decreases the bad cholesterol and increases the good cholesterol, lowers triglycerides, and lowers blood pressure and body weight. Like changing your eating habits, you don’t have to make all the changes at once. Start slow. The important thing to remember is to continue on a regular basis.

Remember to check with your doctor before starting an exercise program, especially if you have had previous heart or blood pressure problems, or are taking any medicines.

Once you have your doctor’s approval to exercise, begin by simply walking. Walking is considered one of the best exercises. Begin walking 15 or 20 minutes per day. Increase by 5 minutes every other week. You should try to work up to a schedule of walking a minimum of 30 minutes no fewer than three days a week. A target schedule may be 30 minutes five times a week. Walk outdoors or form a walking group in your neighborhood. Check with your doctor about the best walking schedule for you.

With busy schedules, it is sometimes difficult to find the time to exercise. Other ways to work physical activity into your daily life include:

- Take the stairs instead of an elevator or escalator whenever you can
- Get off the bus or subway a few stops early and walk the rest of the way to work
- Mow the lawn with a push mower
- Rake leaves or garden
- Exercise on a stationary machine or do calisthenics while watching television
- Play *actively* with your children: basketball or baseball, rollerblade, bike, swim, ski, or hike as a family
- Walk the golf course rather than riding in a cart
- Take ballroom or another type of dance class
- Exercise should be fun. Explore a new sport that interests you. If you already walk, try rollerblading. If you swim, try water aerobics. Whatever you choose, make some physical activity part of your daily routine, especially if you work at a desk all day.

Smoking

Without question, smoking increases the risk of heart disease and negatively affects your cholesterol. The best thing you can do is to quit smoking immediately. Your doctor can suggest ways to help you kick this habit.

What if I Need Medicine for My High Cholesterol?

Sometimes you may need to take medicine to keep your cholesterol level in control.

If you need medicine to control your cholesterol level, your doctor will discuss all the details and options with you. These medicines are proven to be safe and very effective in reducing your risk of heart disease.

REMEMBER THIS FORMULA:

Lose Weight + Eat Well + Lower Cholesterol + Exercise + Stop Smoking = a Healthy Heart!

Resources

American Diabetes Association

www.diabetes.org

- Information: 1-800-DIABETES (800-342-2383)
- Nutrition Guidelines: http://care.diabetesjournals.org/cgi/content/full/25/suppl_1/s50

American Dietetic Association

www.eatright.org

- Information: 800-877-1600

American Heart Association

<http://www.americanheart.org>

- Information: 800-AHA-USA1 (800-242-8721)

American Lung Association

www2.lungusa.org

- Information: 800-LUNG-USA (800-586-4872)

Centers for Disease Control and Prevention

Health Topic: Cardiovascular Disease

<http://www.cdc.gov/health/cardiov.htm>

- Information: 800-311-3435

National Cholesterol Education Program (NCEP)

<http://www.nhlbi.nih.gov/guidelines/cholesterol/>

- NCEP Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Pressure in Adults (Adult Treatment Panel III) Full Report:
http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm
- NCEP “Live Healthier, Live Longer:”
www.nhlbi.nih.gov/chd

National Diabetes Education Program

<http://ndep.nih.gov/>

- Information: 800-438-5383

National Heart, Lung, and Blood Institute

<http://www.nhlbi.nih.gov/>

- Information: 800-575-WELL (9355)

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