

**The American Association of Clinical Endocrinologists
Medical Guidelines for Clinical Practice for the
Diagnosis and Treatment of Dyslipidemia
and Prevention of Atherogenesis
2002 Amended Version**

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2002 Amended Version

On August 8, 2001, the Food and Drug Administration removed Baycol (cerivastatin sodium) from the market. This amended version of these guidelines reflects this action and removes references to this medication.

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INTRODUCTION

Paul S. Jellinger, MD, FACE

Chairman, Task Force

*Medical Guidelines for Clinical Practice for the Diagnosis and Treatment
of Dyslipidemia and Prevention of Atherogenesis*

Atherosclerosis is the accumulation of lipid, inflammatory cells, and fibrous tissue in the intima, which causes intimal thickening of large and mid-sized arteries. The clinical manifestations differ depending on the circulatory bed affected. The coronary arteries are particularly susceptible to atherogenesis; atherosclerosis of the coronary arteries may lead to angina pectoris and myocardial infarction (1). Dyslipidemia is a primary, major risk factor for coronary artery disease (CAD) and may even be a prerequisite for CAD, occurring before other major risk factors come into play (2).

CAD is the single largest killer and cause of disability in both women and men in the United States (3). From 13 to 14 million adult Americans have a history of CAD, and this year, approximately 1.1 million people will suffer a coronary event in the United States (3). Although men have traditionally been the focus of clinical study, mortality from CAD is high in women (3,4). CAD accounts for 46% of mortality in women, and twice as many women as men die within the first few weeks after occurrence of a myocardial infarction (MI) (5). In 1999, CAD and stroke accounted for approximately \$150 billion in direct and indirect health-care costs in the United States (3).

Recent epidemiologic data also suggest that hypercholesterolemia and perhaps coronary atherosclerosis itself are risk factors for ischemic stroke (6). As a result, advocacy for aggressive lipid-lowering therapy for prevention of stroke is increasing (6). Mounting evidence also points to insulin resistance—which results in increased levels of plasma triglyceride and low-density lipoprotein cholesterol (LDL-C) and a decreased concentration of high-density lipoprotein cholesterol (HDL-C)—as an important risk factor for peripheral vascular disease (7).

Our understanding of the pathogenesis of atherogenesis and the role of treatment of lipid disorders in preventing and modifying this process has dramatically advanced during the past decade. For prevention of atherogenesis and CAD, all identifiable risk factors must be managed. Treatment of dyslipidemia—through nutrition therapy and physical activity, with or without drug therapy—is one essential component of both primary and secondary prevention. Compelling and abundant scientific, epidemiologic, and clinical evidence shows that treatment of lipid disorders not only lowers the risk of primary and

secondary coronary events but also can slow, prevent, or even reverse the progression of atherosclerosis (8). Angiographic studies have demonstrated plaque regression in many treated patients. Recently, the importance and value of treating the dyslipidemia of persons with diabetes even more aggressively than persons without diabetes have been elucidated.

The important concept of plaque stability rather than plaque size has implications in our daily practice, as do the emerging roles of inflammation, hypercoagulable state, insulin resistance, and LDL phenotypes. The polycystic ovary syndrome (PCOS) with associated insulin resistance and dyslipidemia is likely the most common endocrine disorder among young women.

We have been guided in our approach to the patient with dyslipidemia by the familiar National Cholesterol Education Program (NCEP) guidelines. A document written by clinical endocrinologists was considered necessary to emphasize areas recognized by clinical endocrinologists as important, such as the age of patients at screening, treatment of elderly patients, diabetes-associated dyslipidemia, role of triglycerides, and PCOS. Lipoprotein metabolism and the relationship of atherogenesis and dyslipidemia to insulin action and insulin resistance, the importance of hypertriglyceridemia, and aggressive treatment of risk factors in patients with type 2 diabetes are familiar concepts to most endocrinologists. The American Association of Clinical Endocrinologists (AACE) accepted this challenge and in 1999 formed a Task Force for the creation of *Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Dyslipidemia and Prevention of Atherogenesis*.

This document, prepared by clinical endocrinologist members of AACE, is designed to review and sort out our current understanding of the diagnosis of dyslipidemia and provide a guideline for the treatment of lipid disorders and the relationship of these disorders to atherogenesis. These guidelines also analyze the growing body of evidence that suggests atherogenesis is not simply a manifestation of the total cholesterol burden. In these guidelines, we consider the small, dense LDL (pattern B) and the effect of clustered metabolic disorders on the process of atherogenesis—factors that add both complexity and opportunity to lipid management (8).

Case studies presented throughout the text illustrate treatment options and other concepts. Special sections address the cardiovascular dysmetabolic syndrome, dyslipidemia of diabetes, dyslipidemia in pediatric patients, PCOS, estrogen therapy, cost-to-benefit considerations, and non-lipid-associated risk factors. An introductory Clinical Summary is provided, reviewing the main points of the document.

With these guidelines, we hope to help reverse the current patterns of underevaluation and undertreatment of dyslipidemia (9). Currently, only one in four persons who need lipid-lowering therapy receives it, and only 4% of those identified as requiring treatment actually reach target cholesterol levels (10).

Only with a clearer understanding of the pathogenesis, familiarity with the emerging developments, and review of the available treatment options can we make further progress against America's number one killer. We hope that this document is found to be a useful adjunct in clinical practice and is read in full by all those who treat patients with lipid disorders.

I wish to thank the lipid guidelines committee members—Richard A. Dickey, MD, FACP, FACE, Om P.

Ganda, MD, Adi E. Mehta, MD, FRCP(C), FACE, Tu T. Nguyen, MD, FACE, Helena W. Rodbard, MD, FACE, John A. Seibel, MD, FACE, Mark D. Shepherd, MD, FACE, and Donald A. Smith, MD—for their outstanding contributions to these guidelines. Although all committee members made very significant contributions, Donald Smith and Adi Mehta deserve special recognition for their particularly comprehensive efforts. Appreciation is also extended to the AACE Publications Committee for their review and to Alan Garber, MD, PhD, Ronald Goldberg, MD, and Robert Kreisberg, MD, who offered their time as special reviewers of this document.

Periodically, these guidelines will be updated to reflect the latest advances in the prevention and treatment of dyslipidemia. They will be available on the AACE home page on the Internet. Please visit our web site at www.aace.com for the most recent version of these guidelines.

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CLINICAL SUMMARY

The purpose of this summary is to present an overview of the diagnosis, evaluation, and management of various lipid disorders. Special considerations in patients with diabetes and pediatric patients who have dyslipidemia are also outlined. After this prefatory summary, a more in-depth scientific analysis of these issues is presented.

Risk Factors

The lipid-associated and non-lipid-associated risk factors for CAD are summarized in Table S-1.

Patients with the common *lipid triad*—hypertriglyceridemia, high LDL-C, and low HDL-C—have a high risk for CAD (34). This risk is even greater when the lipid triad is accompanied by insulin resistance, a procoagulant state, and hypertension—a condition known as the *cardiovascular dysmetabolic syndrome* (34).

Epidemiologic evidence also suggests that high HDL-C is a negative risk factor in that it confers cardio-protection in many (but not all) persons (18,22,47).

Diagnosis and Risk Assessment

Step 1: Screen

Screening for dyslipidemia is warranted for all adults up to 75 years of age regardless of CAD risk status and for adults more than 75 years old who have multiple CAD

risk factors. The recommended screening schedules for dyslipidemia in various adult populations are as follows:

For young adults ≥ 20 years of age

- Every 5 years when no CAD risk factors are present
- More often if family history of premature CAD exists (that is, definite MI or sudden death before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative)

For middle-aged adults

- Every 5 years when no CAD risk factors are present
- More often if CAD risk factors exist

For elderly patients to 75 years of age

- Every 5 years when no CAD risk factors are present
- More often if CAD risk factors exist

For elderly patients >75 years of age

- Evaluate if patient has multiple CAD risk factors, established CAD, or a history of revascularization procedures and good quality of life with no other major life-limiting diseases

The recommended screening tests for cholesterol and triglyceride levels are outlined in Table S-2.

Step 2: Assess Lipid-Related Risk

Serum lipid concentrations that are considered borderline or high risk are shown in Table S-3.

When dyslipidemia exists, secondary causes must be excluded, inasmuch as treatment of an underlying contributing disease may alleviate the lipid abnormality. Once secondary causes have been ruled out, a thorough family history and physical evaluation are needed to determine the presence of additional risk factors or any genetic factors causing or contributing to the dyslipidemia. Genetic factors are particularly valuable prognostic indicators (27,34,50,51). The findings on the patient history, physical examination, and basic lipid profile will dictate any need for additional diagnostic tests. For example, the following additional lipid tests may be useful in special circumstances:

Postprandial triglycerides

- Direct measurement may be useful when fasting triglyceride levels are marginally elevated (150 to 200 mg/dL) (52-57).

LDL subfraction B

- Direct measurement of LDL subfraction B may be useful when fasting triglyceride levels are marginally elevated (150 to 200 mg/dL).

Step 3: Determine the Basic Treatment Approach

An isolated focus on LDL-C is not always sufficient to prevent heart disease in at-risk persons or to treat existing atherosclerosis. In patients with hypertriglyceridemia

Table S-1
Risk Factors for Coronary Artery Disease*

Lipid risk factors

High total cholesterol or LDL-C (11-13)
Small, dense LDL (14-17)
Low HDL-C (18-22)
Hypertriglyceridemia (11,16,23-26)

Other risk factors

Advancing age (27)
Type 2 diabetes mellitus (28,29)
Hypertension (30)
Obesity (31,32)
Cigarette smoking (33)
Family history of CAD (34)
Increased levels of Lp(a) lipoprotein (35-37)
Factors related to blood clotting, including increased levels of fibrinogen and PAI-1 (38-42)
Hyperhomocysteinemia (43)
Certain markers of inflammation, including C-reactive protein (44-46)

*CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; PAI-1 = plasminogen activator inhibitor-1.

Table S-2
Recommended Screening Tests for Various Lipids*

Evaluation	Recommended testing
Total cholesterol, triglyceride, and HDL-C profile	The 12- to 14-hour fasting profile is preferable to the nonfasting profile whenever possible The 12- to 14-hour fasting profile is essential when: A nonfasting profile reveals total cholesterol ≥ 200 mg/dL or HDL-C < 35 mg/dL (or both) The patient smokes The patient has CAD or peripheral vascular disease The patient has diabetes or glucose intolerance The patient has central obesity The patient has hypertension The patient has chronic renal disease The patient has a family history of CAD
LDL-C	Calculate LDL-C by using the Friedewald equation. Average two LDL-C calculations when drug therapy is being considered (8) When fasting triglyceride levels exceed 250-300 mg/dL, use the direct LDL-C assay or non-HDL-C calculation (8,48)

*CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

who have increased LDL-C or decreased HDL-C, those with triglyceride levels of 150 to 250 mg/dL can be treated with nutrition management and physical activity, whereas those with triglyceride levels that exceed 250 mg/dL should receive drug therapy; the goal should be a triglyceride level < 200 mg/dL (27,58). The recommended treatment approaches for patients with dyslipidemia based on the number of CAD risk factors, the LDL-C level, and the HDL-C level are outlined in Tables S-4 and S-5.

Management

The approach to prevention of atherogenesis requires management of all known risk factors. The program should include smoking cessation, regular physical activity, weight management, antiplatelet or anticoagulant therapy, management of associated metabolic conditions, and control of blood pressure in addition to treatment of the dyslipidemia.

Table S-3
Borderline and High-Risk
Serum Lipid Concentrations (16,23,24,27,49)*

Lipid	Borderline serum concentration (mg/dL)	High-risk serum concentration (mg/dL)
Cholesterol	200-239	≥ 240
HDL-C	35-45	< 35
LDL-C	130-159	≥ 160
Triglycerides [†]	150-200	> 200

*HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

[†]Both borderline and high-risk values may signify familial combined dyslipidemia or dyslipidemia of diabetes; values $> 1,000$ indicate high risk for pancreatitis.

Table S-4
Recommended Treatment Approach
Based on Coronary Artery Disease Risk and LDL-C Level (27)*

Setting	Nutrition therapy, physical activity	Drug therapy	Goal
CAD risk factors†			
<2	≥160	≥190	<160
≥2	≥130	≥160	<130
With atherosclerotic disease	≥100	≥130	<100
With type 2 diabetes mellitus	≥100	≥130	<100

*CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; data are shown as mg/dL.
†Subtract one risk factor when HDL-C ≥60 mg/dL.

Physical Activity and Nutrition Therapy

A sound rationale exists for prescribing some type of nutrition therapy plus physical activity for all patients with dyslipidemia (8,25,28,34,65-72). The American Heart Association (AHA)-NCEP Step I and Step II diets reflect a beneficial nutritional pattern that encourages limited intake of salt, calories, saturated and *trans* fatty acids, and cholesterol (Table S-6) (27,73,74). The Step I diet is recommended for the healthy US population older than the age of 2 years; the Step II diet is recommended for patients with established CAD (73). Patients with hypercholesterolemia should adhere to the Step II diet if the Step I diet fails to lower LDL-C values to the goal level.

Several other dietary approaches may also be appropriate for individual patients, including low-fat diets high in soluble fiber (75), diets with plant stanol ester-containing margarines (76-79), moderate consumption of alcoholic beverages (80-82), and diets containing 2 to 4 g of fish oils (omega-3 fatty acids) per day (primarily for hypertriglyceridemia) (83,84).

Nutrition therapy should be prescribed for at least 3 months and up to 6 months before drug therapy is

initiated, unless the patient is at very high risk (27). In such cases, a Step II diet and lipid-lowering drug therapy are usually indicated concomitantly.

Lipid-Lowering Drug Therapy

Current lipid-lowering drugs include nicotinic acid (niacin), bile acid sequestrants (resins), hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins), and fibric acid derivatives (fibrates). When drug therapy is prescribed, the physician and patient should establish each patient's lipid goal together, and treatment should be tailored to achieve that goal. Pharmacotherapy may consist of one, two, or, in cases of extreme dyslipidemia, three agents (that is, a statin, fibrate, and niacin). The recommended pharmacologic approaches, which should be prescribed in conjunction with nutrition therapy and physical activity, are summarized in Table S-7.

Additional Treatment Considerations

Age.—In *young adult patients* with dyslipidemia, lifestyle modifications (nutrition therapy, weight control,

Table S-5
Recommended Treatment Approach for Patients With Isolated Low HDL-C (18,22,59-64)*

Gender	Weight loss, physical activity, smoking cessation	Drug therapy	Goal
Male	<35 mg/dL	<35 mg/dL with strong risk factors†	>35 mg/dL‡ or >45 mg/dL§
Female	<45 mg/dL	<45 mg/dL with strong risk factors†	>45 mg/dL‡ or >55 mg/dL§

*CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
†Borderline LDL-C, a family history of premature CAD, overt CAD, or any combination of these factors.
‡In the presence of a strong family history of CAD.
§In the presence of overt CAD.

Table S-6
Dietary Recommendations
From the American Heart Association and the
National Cholesterol Education Program (27,74)

Component	Step I diet*	Step II diet†
Total fat‡	<30%	<30%
Saturated	<10%	<7%
Monounsaturated	5-15%	5-15%
Polyunsaturated	<10%	<10%
Carbohydrate‡	50-70%	50-70%
Protein‡	10-20%	10-20%
Cholesterol	<300 mg/day	<200 mg/day

*For healthy US population >2 yr old.
†For patients with established coronary artery disease.
‡As percentage of total calories.
From Schaefer (73). With permission.

and physical activity) are essential. Drug therapy should be considered for otherwise healthy men <45 years old who have LDL-C levels >190 mg/dL that do not respond to a maximum of 6 months of conservative therapy. For other young men at risk for CAD, especially those with a family history of premature CAD, drug therapy should be considered if the LDL-C level is ≥160 mg/dL after 6 months of conservative therapy (8).

In *elderly patients*, as in other patient populations, global risk management is important (33). Drug therapy for

either primary or secondary prevention is justified for high-risk patients between 65 and 75 years of age (33,98-108).

Patients >75 years old who are already receiving treatment should continue any therapy that was prescribed at an earlier age (33). The decision to initiate therapy in this patient population should be based on the degree of risk and on individual circumstances, such as physiologic age (27).

Female Gender.—In women with dyslipidemia, special consideration should be given to the following factors:

Table S-7
Recommended Pharmacologic Therapy for Patients With Various Lipid Abnormalities*

Primary lipid abnormality	Recommended approach
Hypercholesterolemia	Statin monotherapy (85)
Hypercholesterolemia resistant to statin monotherapy	Statin + resin combination therapy (85-94). May consider adding niacin when needed to achieve lipid goal (86,95,96)
Hypertriglyceridemia;† may also have low HDL-C or increased small, dense LDL (or both)	Fibrate monotherapy (8,28,64,85,92). Niacin monotherapy is a second choice but may be preferred for patients with concomitantly increased Lp(a)
The lipid triad‡	Statin + fibrate combination therapy or statin + niacin combination therapy (28,87)
Isolated low HDL-C	Statin monotherapy if LDL-C is borderline or increased. Niacin therapy if LDL-C is normal. Statin + niacin combination therapy if monotherapy fails to increase HDL-C to goal level (18,22,61-63)

*CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

†Patients with familial hypertriglyceridemia do not seem to have an increased risk of CAD (27,50,51). Treatment should focus on reducing the risk of pancreatitis attributable to increased triglyceride level (27,50,51,97).

‡Hypertriglyceridemia, high LDL-C, and low HDL-C.

- Polycystic ovary syndrome
- Nutrition therapy
- Drug treatment
- Estrogen replacement therapy

In the presence of *polycystic ovary syndrome* (PCOS), a triglyceride level of >150 mg/dL and an HDL-C level <45 mg/dL may be considered specific risk factors (109).

In reference to *nutrition therapy*, research has suggested that restriction of dietary fat tends to be less effective for lowering the cholesterol level in women than in men (110). Dietary therapy and weight reduction, however, are effective for lowering triglyceride levels in women (25). For at-risk women with hypertriglyceridemia, a triglyceride level of ≤200 mg/dL should be the goal (111), and pharmacotherapy should be initiated if this goal is not achieved with nutrition therapy alone.

A strong rationale exists for as aggressive *drug treatment* of dyslipidemia in postmenopausal women as in men (111-114).

Currently, *estrogen replacement therapy* (ERT) may have an important role in primary CAD prevention for women who are already receiving ERT for other reasons (115). For most postmenopausal women with dyslipidemia, however, ERT should not be prescribed as an alternative to lipid-lowering pharmacotherapy. It may be considered lipid-lowering therapy only in lower-risk women with mildly increased LDL-C levels (130 to 160 mg/dL) and normal triglyceride levels. ERT may also allow use of a lower dosage of lipid-lowering medication. In women with hypertriglyceridemia, ERT should only be used cautiously.

Dyslipidemia of Diabetes

More than half of all patients with type 2 diabetes mellitus have established CAD (116), and once atherosclerotic disease is established, diabetes worsens the prognosis. In comparison with patients who do not have diabetes, patients with type 2 diabetes mellitus have a twofold to fourfold increased risk of CAD (28,29) and a dramatically higher risk of accelerated cerebral and peripheral vascular disease (29,117). Patients with diabetes who do not have CAD have the same risk of MI as those without diabetes who have had a coronary event (29). Mortality from CAD is also extremely high in this population (29).

The same risk factors that contribute to CAD in the general population contribute to CAD in patients who have diabetes, but the overall effect of each risk factor is greater (118,119).

Identification of Risk Factors

Identifying all risk factors is important. A complete, fasting lipid panel should be measured at least yearly in adults with diabetes (29). Dyslipidemia in the patient with type 2 diabetes mellitus is characterized by moderate hypertriglyceridemia and low plasma HDL-C.

Goals of Therapy

Aggressive intervention for management of dyslipidemia is warranted for all patients with diabetes, whether or not they have established CAD (28,29,118,119). Appropriate goals for lipid levels in patients with type 2 diabetes are shown in Table S-8.

Nonpharmacologic Intervention

Management of the hyperglycemia, nutrition therapy, weight reduction in overweight patients, and increased physical activity are essential in patients with diabetes and dyslipidemia. Nutrition therapy plus physical activity alone can be pursued for 6 months in patients without established CAD in an attempt to achieve lipid goals unless the LDL-C level is increased >25 mg/dL above the goal (29). In such cases, pharmacotherapy can be started as early as 3 months after initiation of nutrition therapy and physical activity (29). In patients with *established* CAD, nutrition therapy, physical activity, and pharmacotherapy should be initiated concurrently.

Nutrition Therapy.—Enlistment of the assistance of a registered dietitian is strongly recommended. In general, the patient should initially reduce total fat intake to <30% of total calories, with <10% saturated fat (AHA Step I diet, Table S-6). Furthermore, caloric intake should be controlled to maintain weight if the patient is lean or to reduce weight if the patient is overweight. If lipid goals are not achieved in 3 months with use of the Step I diet, the Step II diet (modified as necessary, depending on the need for weight loss) is recommended (Table S-6) (117).

Physical Activity.—Physical activity should be of moderate intensity, 30 to 45 minutes in duration, and performed 3 to 5 times a week. The pulse rate should be monitored to ensure that target levels are achieved.

Table S-8
Lipid Targets for Patients
With Type 2 Diabetes Mellitus
and Dyslipidemia (29,120)*

Plasma lipid	Target (mg/dL)	
	Acceptable	Ideal
Triglyceride	<200	<150
Total cholesterol	<200	<170
LDL-C	<130	<100
Non-HDL-C†	<160	<130
HDL-C	>35	>45

*HDL-C = high-density lipoprotein cholesterol;
LDL-C = low-density lipoprotein cholesterol.
†Total serum cholesterol minus HDL-C.

Table S-9
Recommended Pharmacologic Therapy
for Patients With Type 2 Diabetes Mellitus and Dyslipidemia*

Primary lipid abnormality	Recommended approach
Hypercholesterolemia	Statin monotherapy (29,116,117,121,122). Consider a resin or a low-dose statin + resin combination for refractory patients with substantially increased LDL-C without concomitant hypertriglyceridemia (120)
Hypertriglyceridemia with or without low HDL-C	Fibrate monotherapy (29,117,120,123)
Combination of hypercholesterolemia and hypertriglyceridemia	Aggressive glycemic control and high-dose statin or fibrate therapy (29). Consider combination statin + fibrate or statin + low-dose niacin therapy for selected patients when monotherapy fails to achieve lipid goal (29,120,124)

*HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Pharmacotherapy.—Treatment with glucose-lowering agents is important and should usually be initiated before specific lipid-lowering pharmacotherapy. When control of blood glucose is not achieved or the lipid profile fails to normalize within 4 to 6 months, treatment with appropriately selected lipid-lowering agents is warranted. *Of importance, waiting any longer is inappropriate.* A borderline or normal LDL-C level should not obscure the need for pharmacotherapy, in light of the propensity for these patients to carry the small, dense LDL pattern (119). The choice of therapy should be based on the nature of the dyslipidemia and the special needs of the patient with diabetes (Table S-9).

Dyslipidemia in Pediatric Patients

There is growing consensus that primary preventive nutrition is warranted in the very young population (125-131). The AHA Step I diet (Table S-6) is recommended for all healthy children >2 years old (131).

Screening

A total cholesterol, LDL-C, and triglyceride profile should be determined for all the following:

- Children >2 years old and adolescents with a family history of premature CAD or dyslipidemia (or both) (131,132)
- Children >2 years old and adolescents who smoke, have hypertension, are overweight or obese, or have diabetes (126,133)
- All adolescents >16 years of age (126,134)

When the lipid profile is interpreted in children and adolescents, the clinician should be aware that lipid levels fluctuate during childhood and adolescence (135). In

addition, a low HDL-C level may not have the same implications in children as it does in adults (136-138). Some investigators have found that girls tend to have higher plasma cholesterol levels than do boys throughout childhood and adolescence (129).

The lipid screen should be repeated when the LDL-C level exceeds 110 mg/dL (131). Nutrition therapy, regular physical activity, and risk factor management are warranted for a verified LDL-C level of 110 to 129 mg/dL; more intensive dietary therapy and pharmacotherapy may also be warranted in some pediatric patients with LDL-C levels ≥130 mg/dL (131).

Intervention

Dyslipidemia in pediatric patients necessitates global risk factor management and lifestyle counseling. This holistic approach is essential for children and adolescents.

Nutrition Therapy.—Low-fat diets can reduce the total cholesterol level and have a significant but modest effect on the LDL-C level in pediatric populations (129,136,139,140). When a low-fat diet is prescribed for children or adolescents, the following information must be considered:

- Total cholesterol and HDL-C levels are positively correlated until the age of 20 years, and lower-fat diets that reduce total cholesterol have been associated with HDL-C reductions (141,142).
- Increased intake of carbohydrates may increase plasma triglyceride concentrations in children (143).
- Fish oil supplements have a profound effect on serum triglyceride levels in children and have been used in pediatric patients with end-stage renal insufficiency (144).

- Water-soluble fiber does not reduce the serum cholesterol level in children as it does in adults (145-148).

Use of the AHA Step II diet may be attempted when a child or adolescent fails to respond to the Step I diet. Close monitoring of all lipid levels is imperative to ensure adequate intake of nutrients and energy.

Drug Therapy.—Because the potential long-term effects of lipid-lowering drug therapy on growth, development, and biochemical variables are unclear, the prescribing decisions must be based on empiric and indirect evidence and the needs of the patient (129). When the need for lipid-lowering drug therapy is assessed in pediatric patients, the following factors must be considered:

- The effectiveness of delaying treatment until adulthood
- The nature of the pediatric dyslipidemia

Beginning treatment in adulthood can halt atherogenesis and may induce regression in some patients with polygenic and familial combined hyperlipidemia (149,150). Children and adolescents with genetic dyslipidemias should be treated with lipid-lowering drugs, when needed, to achieve LDL-C levels <130 mg/dL (151,152). A persistent increase in LDL-C coupled with a parental history of dyslipidemia may predict the presence of an underlying genetic disorder (153).

Cholestyramine and colestipol are the only approved drugs for treating hypercholesterolemia in children. They are not associated with systemic toxicity or other serious adverse or toxic effects (154-156). LDL-C reductions of 15 to 20% are possible with relatively low dosages of cholestyramine (8 g/day) or colestipol (10 g/day) (154, 157). These agents should not be used in children with hypertriglyceridemia (129,158). They should be prescribed in conjunction with multivitamin supplements, including folic acid and cholecalciferol (129,154,157).

Long-term studies are needed to assess the potential effects of statins in children. Investigators have suggested that small doses of statins may be useful for boys with severely increased cholesterol levels who are approaching the end of the maturation process, as a supplement to dietary and resin therapy (159,160).

Additional study is also needed before fibrates can be recommended. Niacin is not recommended for this population (161).

Follow-Up and Monitoring

For all patients receiving intervention of any type, the lipid status should be assessed 4 to 6 weeks after therapy

is instituted and again at 6-week intervals until the treatment goal is reached (27). At each 6-week interval, the physician should monitor the response to and side effects of therapy. Thereafter, once the lipid goal has been achieved, consultations should be scheduled at 6- to 12-month intervals. The precise interval depends on patient adherence to therapy and the consistency of the lipid profile. In addition, certain clinical circumstances warrant more frequent evaluation. *The lipid status should always be reassessed in the following situations:*

- Control of diabetes has deteriorated over time
- The patient has been prescribed a new drug known to affect lipid levels
- The patient's cardiovascular status has changed
- The patient has gained considerable weight
- A recent lipid profile has revealed an unexpected adverse change in any lipid level
- A new risk factor has been identified

Both triglyceride and HDL-C concentrations should be part of each follow-up lipid assessment, along with serum total cholesterol and LDL-C levels. These factors are especially important in patients with type 2 diabetes mellitus and in those with macrovascular disease. Some patients who have had their LDL phenotype determined may need reanalysis of the phenotype, particularly if their clinical status deteriorates or if lipid-lowering drug therapy has been altered. This reanalysis should be performed only after the patient has received lipid-lowering drug therapy for ≥ 3 months.

Consultation with an endocrinologist or lipid specialist is recommended when uncontrolled diabetes and dyslipidemia coexist, when unusual or refractory lipid levels persist despite treatment, or when CAD manifests despite favorable lipid levels.

Cost-to-Benefit Considerations

Economic studies have demonstrated that drug treatment of dyslipidemia is cost-effective for all patients with established CAD and for primary prevention when the patient has a moderately high or higher risk of CAD (162-165). Because of the accelerated rate of atherosclerosis in patients with type 2 diabetes mellitus, aggressive and early treatment should be cost-effective for these patients.

Although economic data are useful for guiding treatment decisions, they should not dictate treatment approach. To be clinically effective and therefore cost-effective, any lipid-lowering drug therapy (whether for primary or secondary prevention) must be tailored to the individual patient's dyslipidemia and risk profile (34).

LIPID DISORDERS AS A RISK FACTOR FOR ATHEROGENESIS

Risk Factors for CAD

Epidemiologic evidence clearly shows that many people have multiple risk factors and that these factors exponentially increase the risk for CAD (166). An assessment of the Framingham and Multiple Risk Factor Intervention Trial (MRFIT) data showed that approximately 85% of excess risk for premature CAD is due to one or more of the following major risk factors: advancing age, high serum total cholesterol level, high LDL-C concentration, type 2 diabetes mellitus, hypertension, cigarette smoking, and a family history of premature CAD (definite MI or sudden death before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative) (27,33). The following material reviews the major CAD risk factors.

Advancing Age

CAD is most commonly diagnosed after 65 years of age. Men ≥ 45 years old and women ≥ 55 years old or those who have experienced premature menopause and have not received ERT have an increased risk for CAD (27).

High Total Cholesterol and LDL-C

The association between high serum cholesterol level, especially high LDL-C, and CAD is causal and independent of other risk factors (11-13,24). In fact, hypercholesterolemia may be a prerequisite for the adverse effects of cigarette smoking or hypertension to take their toll (2). The risk attributed to cholesterol is not linear and increases sharply over the higher ranges (167). The MRFIT data, based on an epidemiologic review of 316,099 men, showed that a 20% reduction in the serum cholesterol level from 300 to 240 mg/dL reduced absolute CAD risk by approximately 14 per 10,000 men (168). When the baseline serum cholesterol concentration was 180 mg/dL and was reduced 20% (to 144 mg/dL), the absolute risk was reduced to 4 per 10,000 men (168).

Small, Dense LDL

The genetically influenced small, dense LDL-C particle is believed to be especially atherogenic (14,15), and case-control studies in men suggest that this pattern commonly precedes disease (169). The Boston Area Heart Health Project and the Stanford Five City Project showed that the small, dense LDL-C pattern was associated with a threefold increased CAD risk independent of many classic risk factors, including total cholesterol, HDL-C, body mass index, and apolipoprotein B (16,17).

Some patients may carry the small, dense LDL pattern despite normal LDL-C levels, including premenopausal women with androgen excess and chronic anovulation (PCOS) and patients with underlying insulin resistance. It can manifest clinically as moderate hypertriglyceridemia and low levels of HDL-C. Increased non-HDL-C (that is, total serum cholesterol minus HDL-C) or apolipoprotein B

levels (or both) are additional clinical markers of the small, dense LDL (8).

Low HDL-C

Numerous epidemiologic and intervention studies have shown that a low level of HDL-C (< 35 mg/dL) is an independent risk factor for CAD (18-22,170-173), although the atherogenicity of low HDL-C can depend on both genetic and environmental factors (22). In rare cases, low plasma HDL-C is due to a genetic deficiency, but low HDL-C levels are usually the secondary consequence of increased plasma levels of very-low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL) (chylomicrons and their remnants).

Like hypertriglyceridemia, low HDL-C levels can act synergistically with other lipid risk factors to increase the risk of CAD. For example, the ratio of total cholesterol or LDL-C to HDL-C is a clinically valuable and potentially more sensitive marker of CAD risk than HDL-C alone (174).

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) results support the use of a low HDL-C level to justify aggressive treatment of borderline LDL-C in older men and postmenopausal women (18,22). For more information on the therapeutic approach to the patient with low HDL-C as the primary lipid abnormality, see *Isolated Low HDL-C* (page 191).

Hypertriglyceridemia

Triglyceride levels are an important part of the risk evaluation in both men and women (27). Historically, the significance of hypertriglyceridemia as an independent risk factor weakened or disappeared when LDL-C and HDL-C concentrations were considered. Recent clinical evidence and epidemiologic studies, however, indicate that an increased triglyceride level is a strong, independent risk factor (11,16,23-26). The importance of hypertriglyceridemia as a CAD risk factor in men seems to increase with advancing age, as triglyceride levels also increase with aging (16,25,26). In addition, a meta-analysis of 17 population-based prospective studies showed that hypertriglyceridemia was associated with approximately a 30% increase in cardiovascular risk in men and a 75% increase in women (175). After adjustments were made for HDL-C and other CAD risk factors, these relative risks declined to 15% and 30%, respectively, but remained statistically significant (175). Because of the strength of this association, a triglyceride level > 200 mg/dL is considered an additional, major risk factor, especially in women.

Furthermore, studies suggest that high serum triglyceride levels may act synergistically with other lipid abnormalities to increase the risk of CAD. Hypertriglyceridemia (≥ 200 mg/dL) has been shown to increase the incidence of definite CAD by approximately 2.5-fold in men and women with LDL-C levels ≥ 155 mg/dL (24). Serum triglyceride levels may also predict coronary risk when they are associated with a high LDL-C:HDL-C ratio (> 5) or when HDL-C levels are low (11,22,24,54,176). In the primary prevention Helsinki Heart Study, patients with

the combination of triglyceride level >204 mg/dL and an LDL-C:HDL-C ratio >5 had the greatest risk of coronary events and benefited most from treatment with gemfibrozil (177). In addition, patients who have the common *lipid triad*—hypertriglyceridemia, high LDL-C, and low HDL-C—are at high risk for CAD; this pattern is found in 50% of men with CAD (34).

Although hypertriglyceridemia can be an independent genetic disorder, it is also widely accepted as a marker of insulin resistance. Insulin resistance, often related to obesity, predisposes patients to type 2 diabetes mellitus and is associated with premature CAD, even in the absence of hyperglycemia (178). Hypertriglyceridemia is also commonly associated with a procoagulant state and hypertension (28). The combination of the lipid triad, insulin resistance, a procoagulant state, and hypertension constitutes the very high-risk *cardiovascular dysmetabolic syndrome*. This syndrome increases the risk of CAD threefold, independent of other classic CAD risk factors (34).

Type 2 Diabetes Mellitus

Patients with type 2 diabetes commonly have other risk factors as well, including hypertension, low serum HDL-C level, and hypertriglyceridemia. (For a review of type 2 diabetes mellitus and dyslipidemia, see *Dyslipidemia of Diabetes*, page 194. For a more comprehensive review of the treatment of diabetes, see the *AACE Medical Guidelines for the Management of Diabetes Mellitus* at www.aace.com.)

Hypertension

Systolic blood pressure >130 mm Hg or diastolic blood pressure >85 mm Hg independently accelerates atherogenesis (30), and the risk of CAD increases as blood pressure increases. Hypertension has been identified as the chief precursor of left ventricular hypertrophy (179), and left ventricular hypertrophy was identified as a powerful cardiac risk factor in the Framingham analysis (180). Lowering of blood pressure reduces CAD risk, but hypertension remains a risk factor for CAD even when normalized with treatment (27).

Obesity

Approximately a third of the adults in the United States are overweight or obese, and the associated annual health-care costs total more than \$70 billion (32). Obesity, particularly android or abdominal obesity, increases CAD risk. Whether the presence of excess visceral fat confers an independent risk is unknown, but obesity clearly increases the risk of CAD through an increased risk of dyslipidemia, hypertension, and diabetes (31,32). Mortality from cardiovascular disease is almost 50% higher in obese patients than in those of average weight and is 90% higher in those with severe obesity (181). (For a comprehensive review of the treatment of obesity, see the *AACE/ACE Obesity Position Statement* at www.aace.com.)

Cigarette Smoking

Cigarette smoking is a powerful risk factor, especially for MI, peripheral arterial disease, and stroke. It accelerates

development of coronary plaques and may lead to rupture of plaques, and it is especially dangerous in patients with advanced coronary atherosclerosis (33).

Family History of CAD

Atherosclerosis and CAD are often the result of a complex interaction between genes and the environment. Seventy-seven percent of coronary patients and 54% of their first- and second-degree relatives express a genetically linked dyslipidemia (34).

Other Risk Factors

There are several other CAD risk factors. The Appendix (page 201) contains more information about their clinical relevance. A brief list follows:

- Increased Lp(a) lipoprotein
- Factors related to blood clotting
- Hyperhomocysteinemia
- Markers of inflammation

Lp(a) production is largely a genetic trait and is a strong marker of inherited CAD in certain populations (35-37). Increased fibrinogen and plasminogen activator inhibitor-1 (PAI-1) are both possible CAD risk factors (38-42). Homocysteine, a metabolite of methionine, is highly reactive. It is thought to damage the vessel wall in several ways and thereby may induce intimal fibrosis (182,183). Research suggests that markers of inflammation, including C-reactive protein, may predict the risk of atherosclerotic events (44-46).

High HDL-C as a Negative Risk Factor

When HDL-C exceeds 60 mg/dL, one risk factor can be subtracted from the patient's overall risk profile (27). An analysis of four of the largest epidemiologic studies adjusted for other variables suggests that for each 1 mg/dL increase in HDL-C, CAD risk decreases by 2% in men and 3% in women (18,47). This cardioprotective effect may be due to the role of HDL in reverse cholesterol transport (see *Lipoprotein Metabolism, Endogenous Pathway*, page 175) and other mechanisms such as the ability of HDL to prevent LDL-C oxidation (18,184). Of importance, these results apply to the general population, and a high HDL-C concentration may not confer cardioprotection in every individual patient (22).

LIPOPROTEIN METABOLISM

Lipid metabolism is divided into two pathways—exogenous and endogenous (1,185).

Exogenous Pathway

Dietary triglyceride and cholesterol are absorbed in the intestinal mucosa and incorporated to form the core of nascent chylomicrons, which are then transported to plasma (Fig. 1). In peripheral tissues, chylomicrons interact with lipoprotein lipase, which removes most of the core

triglyceride from the lipoprotein particle. The resulting glycerol and fatty acids are taken up by adipose and other tissues, re-formed into triglyceride, and stored. Redundant surface material (apolipoprotein C, phospholipids, and cholesteryl ester) joins the HDL particle. The remnant chylomicron particles, which are now smaller and enriched in their core with cholesteryl ester and some remaining triglyceride, are taken up by the liver. This dietary cholesterol can then be used for bile acid formation, incorporated into membranes, resecreted back into the circulation as lipoprotein cholesterol, or excreted into bile as cholesterol.

Endogenous Pathway

Triglycerides and cholesterol are also synthesized in the liver. This endogenous system, which conveys these lipids from the liver to peripheral tissues and back to the liver, is divided into two subsystems: the apo B-100 lipoprotein system (VLDL-C, IDL-C, and LDL-C) and the apo A-I lipoprotein system (HDL-C).

Apo B-100 Lipoprotein System

In the liver, triglycerides and cholesterol are packaged with apo B-100 and phospholipids to form VLDL (Fig. 2). Once released into plasma, VLDL undergoes triglyceride removal by means of lipoprotein lipase; the resulting cholesteryl ester-rich remnants are the IDL. Unlike the chylomicron remnants, IDL can be converted by further triglyceride removal to even smaller and denser LDL. During this process, the lipoprotein loses all its surface apolipoproteins except apo B-100.

Apo A-I Lipoprotein System

HDL, rich in apo A-I, transports cholesterol from peripheral tissues to the liver (Fig. 3). Cholesterol-poor HDL₃ particles first form in plasma from coalescence of phospholipid-apolipoprotein complexes. Free cholesterol then transfers from cell membranes to HDL₃, where it converts into cholesteryl ester and enters the HDL core. The HDL₃ can then accept more free cholesterol and become the larger, more cholesterol-rich HDL₂ particle. HDL₂ is then metabolized by one of two main pathways: transfer to apo B lipoproteins (which are subsequently removed by the liver) by means of cholesteryl ester transfer protein or direct hepatic metabolism with removal of the HDL₂ apoproteins from plasma.

LIPIDS AND ATHEROGENESIS

Atherosclerosis is an inflammatory disease, with lipoproteins, vascular endothelial cells, monocytes, macrophages, smooth muscle cells, activated T lymphocytes, and platelets all interacting through adhesion molecules, cytokines, chemokines, and prothrombotic factor (186, 187). Clinically, the importance of inflammation in the atherosclerotic process is demonstrated by the power of C-reactive protein to predict coronary events (45). (For more information on C-reactive protein, see the *Appendix*, page 201.)

The development of the coronary plaque—from the benign fatty streak phase 1 lesions to the slow progression of fibrosis or rapid organization of mural or occlusive thrombi into the phase 5 fibrotic and highly stenotic lesions—has been well described (187,188). Because extracellular lipids form the center of the necrotic core of

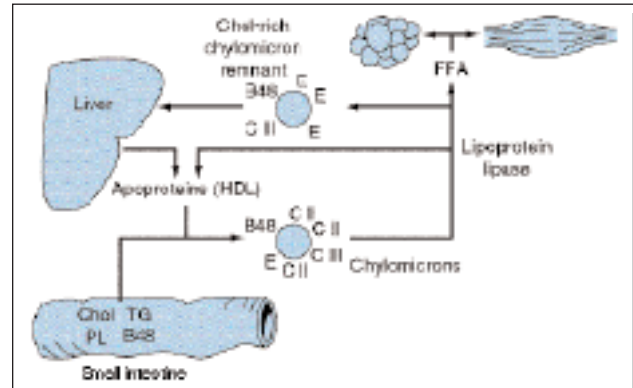


Fig. 1. Transport of exogenously derived lipids from the intestine to the peripheral tissues and liver. FFA = free fatty acids; HDL = high-density lipoproteins; PL = phospholipase; TG = triglycerides. From Ginsberg (185). With permission.

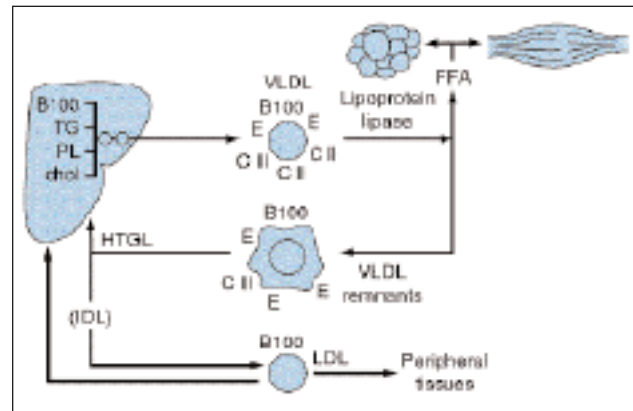


Fig. 2. Transport of endogenous hepatic lipids by means of very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and low-density lipoproteins (LDL). HTGL = hepatic triglyceride lipase. For explanations of other abbreviations, see Figure 1 legend. From Ginsberg (185). With permission.

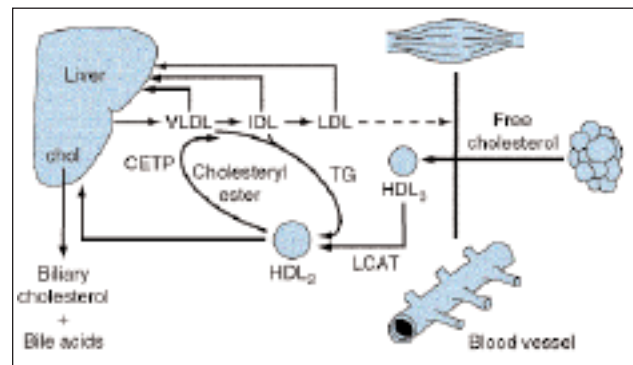


Fig. 3. High-density lipoprotein metabolism and the role of high-density lipoproteins in reverse cholesterol transport. CETP = cholesteryl ester transfer protein; LCAT = lecithin:cholesterol acyltransferase. For explanations of other abbreviations, see Figure 1 and 2 legends. From Ginsberg (185). With permission.

the atherosclerotic plaque, pathogenic dyslipidemias are central to understanding clinical CAD risk. Recent research has shown that plasma LDL-C can incite many early features of the atherosclerotic inflammatory response through oxidative modification (189). Oxidized LDL particles contribute to formation of unstable plaques by stimulating recruitment of monocytes from the circulation into the subendothelial space to form activated macrophages. Investigators have observed that the smaller, dense LDL is particularly susceptible to oxidation and may have easier access to the subendothelial space than the large, buoyant LDL particle (169,190).

The unstable plaques are susceptible to rupture or erosion, which results in hemorrhage into the plaque, thrombosis, and occlusion (unstable angina or acute MI). Emerging evidence suggests that the unstable lesions have thin, rupture-prone fibrous caps, large lipid cores, and high amounts of lipid-laden macrophages (Fig. 4) (191-193). Progression of the unstable lesion can also activate genes that induce arterial calcification, which in turn changes the mechanical characteristics of the artery wall and further predisposes to rupture (192). Overall, rupture of the plaque occurs in approximately 80% of fatal coronary thrombotic occlusions, whereas severe stenoses and underlying denuded, broken, or irregular intima occur in the other 20% (194).

LDL-C may also contribute to atherogenesis through other mechanisms, including stimulation of macrophage production of metalloproteinases, which can degrade the collagenous matrix and fibrous cap; production of cytokines capable of inducing apoptosis of smooth muscle cells, which produce collagen; and uninhibited engorgement of modified LDL by the macrophage, transforming it into a foam cell that, on cell death, adds to the cholesteryl ester liquid plaque core (195). Approximately 75% of human plasma cholesterol is contained in LDL particles, and both the LDL particles and their more triglyceride-rich precursors (IDL) can produce these cholesteryl ester-laden

macrophages in vitro. A threshold plasma cholesterol concentration is believed to exist, above which abnormal amounts of lipid accumulate in the arteries and transform macrophages into foam cells, although the precise threshold is unknown (196).

Current angiographic evidence also points to certain partially catabolized lipoproteins of chylomicrons and VLDL particles—which include small VLDL, IDL, and β -VLDL particles—as being atherogenic (14,178).

Triglycerides may also contribute to atherogenesis through a direct effect (54,197) or through their effect on other lipoproteins (25,198,199). Triglycerides are statistically and clinically correlated with low HDL-C levels and clotting factor changes that produce a procoagulant state (25,178). Furthermore, increased triglyceride levels in the core of LDL can promote aggressive lipolysis (triglyceride removal) and the formation of the small, dense LDL particles (25). High triglyceride levels may also adversely affect endothelial function, as demonstrated after consumption of a fatty meal when the level of triglyceride increase is directly proportionate to the level of arterial dysfunction (200).

CLASSIFICATION OF DYSLIPIDEMIAS

Major Lipid Disorders

Dyslipidemia can result from single-gene or polygenic disorders, other disease states, or environmental factors. The two primary classifications relevant to clinical practice are outlined in Tables 1 and 2. The Fredrickson classification (Table 1), although very familiar to physicians, is used less commonly today than the classification presented in Table 2.

Secondary Dyslipidemia

Common secondary causes of lipoprotein abnormalities are outlined in Table 3. The mechanisms by which these conditions or therapies alter lipid levels are depicted in Figure 5.

Additional causes of secondary dyslipidemia follow (60,201-203):

Hypercholesterolemia

- Acute intermittent porphyria (also associated with hypertriglyceridemia)
- High saturated fat intake in patients with hyperabsorption (increased total cholesterol and LDL-C)
- Anorexia nervosa (isolated hypercholesterolemia occurs as a result of mobilization of cholesterol from tissues)

Hypertriglyceridemia

- Cushing's syndrome (also associated with hypercholesterolemia)
- Lipodystrophy and type I glycogen storage disease
- Consumption of simple carbohydrates including fructose (increased VLDL secretion in some patients)

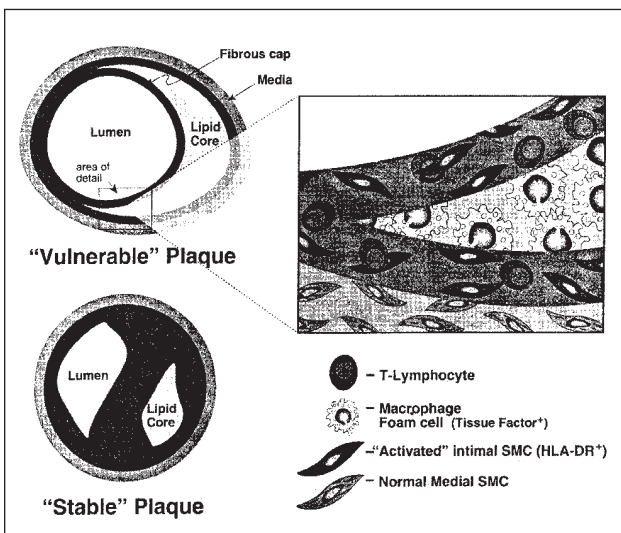


Fig. 4. Anatomy of stable and unstable (vulnerable) plaques. From Libby et al. (191). With permission.

Table 1
Fredrickson Classification of Lipid Disorders*

Type	Appearance of overnight serum	Elevated particles	Associated clinical disorders	Serum TC	Serum TG
I	Creamy top layer	Chylomicrons	Lipoprotein lipase deficiency, apolipoprotein C-II deficiency	→	↑↑
IIa	Clear	LDL	Familial hypercholesterolemia, polygenic hypercholesterolemia, nephrosis, hypothyroidism, familial combined hyperlipidemia	↑↑	→
IIb	Clear	LDL, VLDL	Familial combined hyperlipidemia	↑↑	↑
III	Turbid	IDL	Dysbetalipoproteinemia	↑	↑
IV	Turbid	VLDL	Familial hypertriglyceridemia, familial combined hyperlipidemia, sporadic hypertriglyceridemia, diabetes	→↑	↑↑
V	Creamy top, turbid bottom	Chylomicrons, VLDL	Diabetes	↑	↑↑

*IDL = intermediate-density lipoproteins; LDL = low-density lipoproteins; TC = total cholesterol; TG = triglycerides; VLDL = very-low-density lipoproteins; ↑ = increased; ↑↑ = greatly increased; → = normal; →↑ = normal or increased.

- Systemic lupus erythematosus
- Retinoid therapy (also associated with low HDL-C)
- Bile acid sequestrants (can exacerbate hypertriglyceridemia in patients with preexisting triglyceride elevation)

Low HDL-C

- Secondary to hypertriglyceridemia regardless of cause (except alcohol- and estrogen-induced hypertriglyceridemia)
- Anabolic steroids and probucol (can decrease HDL-C without increasing triglycerides)
- Cigarette smoking
- Sedentary lifestyle
- Very-low-fat diet
- MI or a major surgical procedure (can temporarily lower HDL-C)

DIAGNOSIS AND RISK ASSESSMENT

Identification of risk factors enables the physician to tailor the therapy for dyslipidemia to each patient's risk level and thereby maximize treatment effectiveness (204).

Step 1: Screen

AACE advocates screening for dyslipidemia in all adults up to 75 years of age regardless of CAD risk status and for adults older than 75 years who have multiple CAD risk factors.

Screening Considerations by Age-Group

Young Adults.—Even though the risk of CAD in young adults is very low, adults ≥ 20 years old should be evaluated for dyslipidemia every 5 years as part of a global risk assessment. *Autopsy studies have demonstrated that atherosclerosis begins in late adolescence in males and in early adulthood in both sexes (205-207), and cholesterol levels and other risk factors predict the development and severity of atherosclerotic lesions and vascular disease later in life (206,208-210).* A young man with a total cholesterol level in the highest quartile has 9 times the risk of MI during the ensuing 30 to 40 years as does a young man with a total cholesterol level in the lowest quartile (211). As a result, screening may help promote lifestyle changes that can prevent or slow atherogenesis (72,211). More frequent assessments are warranted for young persons with a family history of premature CAD (definite MI or sudden death before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative) (27).

Middle-Aged Adults.—Middle-aged persons should be assessed for dyslipidemia every 5 years when no CAD risk factors are present and more often when CAD risk factors exist. Intervention trials involving middle-aged men and women clearly show that treatment of dyslipidemia is beneficial (see *Lipid-Lowering Drug Therapy*, page 184).

Table 2
Features of Major Genetic Lipoprotein Disorders*

Disorder	Principal plasma abnormality [corresponding Fredrickson classification†]	Clinical features	Estimated frequency
Heterozygous familial hypercholesterolemia	↑ LDL only (inherited abnormality of the LDL receptor) [IIa]	Tendinous xanthomas Corneal arcus Premature CAD Family history of hypercholesterolemia	0.2% of general population 5% of MI survivors <60 yr old Autosomal codominant
Familial defective apolipoprotein B	↑ LDL (inherited abnormality of apoprotein B interferes with binding to LDL receptor) [IIa]	Same clinical features as heterozygous familial hypercholesterolemia	Same frequency as heterozygous familial hypercholesterolemia
Familial combined hyperlipidemia	1/3: ↑ LDL only [IIa] 1/3: ↑ VLDL only [IV] 1/3: ↑ LDL and VLDL [IIb] Apo-B overproduction is common	Usually >30 yr old Often overweight Usually no xanthomas Premature CAD Different generations have different lipoprotein abnormalities	0.5% of general population 15% of MI survivors <60 yr old Autosomal dominant
Polygenic hypercholesterolemia	↑ LDL [IIa]	Premature CAD No xanthomas No family history of hypercholesterolemia	Unknown
Familial hypertriglyceridemia (200-1,000 mg/dL)	↑ VLDL only (high VLDL production, decreased lipoprotein lipase activity) [IV]	Often overweight >30 yr old Often diabetic Hyperuricemic May or may not have premature CAD Determined by family history and HDL-C	1% of general population 5% of MI survivors <60 yr old Autosomal dominant
Severe hypertriglyceridemia (>1,000 mg/dL)	↑ Chylomicrons and VLDL (high VLDL production, decreased lipoprotein lipase activity) [V]	Usually middle-aged Often obese Often hyperuricemic Usually diabetic Risk for recurrent pancreatitis	Unknown
Familial hypoalpha-lipoproteinemia	↓ HDL (<30 mg/dL in males; <35 mg/dL in females) (decreased apo A-I production)	Premature CAD	1% of general population 25-30% of patients with premature CAD Autosomal dominant
Dysbetalipoproteinemia (TC: 250-500 mg/dL; TG: 250-600 mg/dL)	↑ IDL, ↑ chylomicron remnants (defective apo E2/2) [III]	Yellow palmar creases Palmar xanthomas Tuberoeruptive xanthomas Premature CAD	Uncommon 3% of MI survivors Autosomal recessive

*CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; IDL = intermediate-density lipoproteins; LDL = low-density lipoproteins; MI = myocardial infarction; TC = total cholesterol; TG = triglycerides; VLDL = very-low-density lipoproteins.

†See Table 1.

Table 3
Common Secondary Causes of Dyslipidemia (27,201,202)*

Affected lipids	Conditions
Total cholesterol and LDL-C ↑	Hypothyroidism Nephrosis Dysgammaglobulinemia (SLE, multiple myeloma) Progestin† or anabolic steroid treatment Obstructive liver diseases due to abnormal lipoproteins, as in primary biliary cirrhosis
Total triglycerides and VLDL-C ↑	Chronic renal failure Type 2 diabetes mellitus Antihypertensive medications (thiazide diuretics and β-adrenergic blocking agents) Obesity Excessive alcohol intake Corticosteroid therapy (or severe stress that increases endogenous corticosteroids) Orally administered estrogens,‡ oral contraceptives, pregnancy Hypothyroidism

*HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SLE = systemic lupus erythematosus; VLDL-C = very-low-density lipoprotein cholesterol.
 †Progestational agents, especially those with androgenic activity, can increase LDL-C and decrease HDL-C.
 ‡Transdermally administered estrogens are not associated with increased triglyceride levels.

Elderly Adults.—Regular screening for dyslipidemia every 5 years is warranted for elderly patients up to 75 years old. The prevalence of CAD is highest in persons >65 years of age (98); up to 80% of deaths from CAD occur after age 65 years in both men and women (99). Although the association between high LDL-C concentration and CAD weakens with age, increased serum cholesterol level is an important risk factor in elderly patients because it is associated with a greater number of acute coronary events in this population than in middle-aged or younger populations (98). In addition, hypertriglyceridemia and a low HDL-C level seem to be increasingly important risk factors with advancing age (99).

Patients >75 years old should undergo lipid assessment if they have multiple CAD risk factors, established CAD, or a history of revascularization procedures and have good quality of life and no other major life-limiting diseases (99).

Recommended Screening Tests

A growing body of evidence suggests that an isolated, nonfasting total cholesterol determination does not sufficiently select and identify patients at risk for vascular disease (212). The Framingham Study showed that 80% of patients with CAD had total cholesterol levels equivalent to those who did not have CAD (34,213). Furthermore, although LDL-C levels are powerfully linked to risk of atherosclerosis, reduction of LDL-C alone does not

prevent CAD. In a substantial portion of patients receiving cholesterol-lowering therapy who achieve LDL-C reductions, ischemic heart disease still develops (34). Moreover, the total cholesterol level may overestimate risk of CAD in patients with high total cholesterol values due to high serum HDL-C; this situation occurs more often in women than in men (27).

Therefore, a *fasting total cholesterol, triglyceride, and HDL-C profile* should be determined whenever possible. When the patient smokes, has CAD or peripheral vascular disease, diabetes or glucose intolerance, central obesity, hypertension, chronic renal disease, or a family history of CAD, a *fasting* lipid profile is essential (27,211). A 12- to 14-hour fast is needed to avoid the effect of food intake on chylomicron and VLDL triglycerides (8). Although a nonfasting assessment may be useful as a minimal screen, a nonfasting profile that reveals a total cholesterol level ≥200 mg/dL or an HDL-C concentration <35 mg/dL (or both) dictates the need for a *fasting* profile. This approach will improve the accuracy of the diagnosis (27).

LDL-C may then be calculated by using the Friedewald equation (27):

$$\text{LDL-C} = (\text{Total cholesterol} - \text{HDL-C}) - \frac{\text{Triglycerides}}{5}$$

Results with use of the Friedewald equation will vary by about 10%, and the combined biologic and laboratory variability of triglyceride and cholesterol levels may be

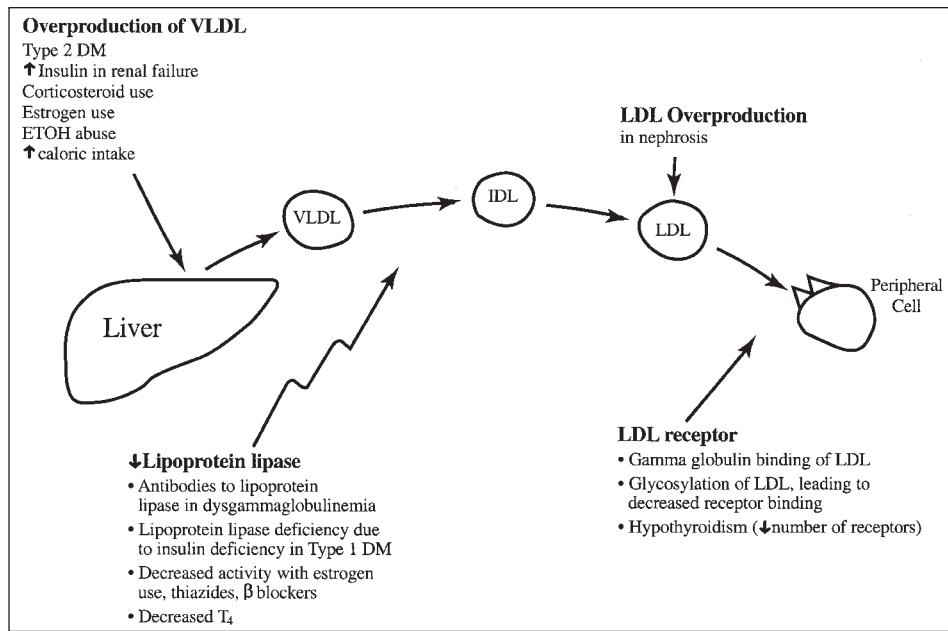


Fig. 5. Mechanisms of lipid alterations. *DM* = diabetes mellitus; *ETOH* = alcohol; *IDL* = intermediate-density lipoproteins; *LDL* = low-density lipoproteins; *T₄* = thyroxine; *VLDL* = very-low-density lipoproteins.

>50 mg/dL (8). Therefore, an average of two calculated LDL-C levels should be used when drug therapy is being considered (8). The Friedewald equation is valid only for values obtained during the fasting state, becomes increasingly inaccurate when triglyceride levels exceed 200 mg/dL, and is considered inaccurate when triglyceride values exceed 400 mg/dL (8).

When fasting triglyceride levels exceed 250 to 300 mg/dL, the direct LDL-C assay may be useful. If this is not feasible, the non-HDL-C (total serum cholesterol minus HDL-C) can be useful for determining a treatment goal. In addition, the direct assay, which also varies by about 10% (48), is especially useful for patients with diabetes and for those with known vascular disease who have fasting triglyceride levels >250 to 300 mg/dL (8). (For a complete discussion of assessment and treatment of dyslipidemia in the patient with type 2 diabetes mellitus, see *Dyslipidemia of Diabetes*, page 194.)

When fasting triglyceride levels are marginally increased (150 to 200 mg/dL), two additional lipid evaluations may be warranted. First, direct measurement of the LDL pattern B phenotype is recommended when the patient has fasting triglyceride levels in this range. Second, evaluation of the postprandial triglyceride level can be useful in such a patient. A growing body of evidence suggests that the small triglyceride-rich lipoproteins produced postprandially are particularly atherogenic (52-57). Occasionally, a patient will demonstrate an exaggerated postprandial increase in triglycerides, and this finding supports the need for treatment when fasting triglyceride levels are in the range of 150 to 200 mg/dL. The assessment of postprandial triglyceride levels has not been

standardized, however, and a normal postprandial triglyceride reference range has not been established.

Step 2: Assess Lipid-Related Risk

Abnormal serum lipid concentrations are outlined in Table 4.

Secondary causes of dyslipidemia (see *Secondary Dyslipidemia*, page 176) must be ruled out with a thorough medical and dietary history as well as laboratory testing for glucose, thyroid, liver, and renal functions. Increased plasma levels of large, triglyceride-rich VLDL particles due to alcohol consumption or estrogen use are unlikely to be atherogenic (27,50,51). Treatment of an underlying contributing disease may alleviate the lipid abnormality, although dyslipidemia in the patient with diabetes is an often overlooked indication for aggressive lipid-lowering therapy (see *Dyslipidemia of Diabetes*, page 194).

In addition to excluding secondary causes of dyslipidemia, the physician should perform a thorough family history and physical evaluation to determine additional risk factors and any genetic factors causing or contributing to the dyslipidemia. Genetic factors are particularly valuable prognostic indicators. The risk for CAD is approximately 50% in siblings of patients with premature CAD (34). Furthermore, *familial* hypertriglyceridemia does not seem to be associated with a definitively increased risk of CAD (27,50,51).

The patient history, physical examination, and basic lipid profile will reveal whether any additional diagnostic lipid tests are needed. The following are examples of patients who may require a more detailed lipid evaluation or other studies.

Patients With Hypertriglyceridemia and Low HDL-C

A patient with hypertriglyceridemia and low HDL-C should prompt clinical suspicion for the presence of the small, dense LDL pattern or the extremely high-risk cardiovascular dysmetabolic syndrome—especially when a family history of CAD or type 2 diabetes mellitus is present. Such a patient should undergo assessment for insulin resistance; a mild increase in the fasting glucose level of 100 to 125 mg/dL suggests the presence of the syndrome (28). Other methods of identifying patients susceptible to the cardiovascular dysmetabolic syndrome are outlined in the following material.

Measurement of Waist Circumference.—A waist circumference >40 inches (102 cm) in men or >36 inches (91.5 cm) in women is considered “categorical abdominal obesity.” This finding is one of the most effective approaches to detection of the cardiovascular dysmetabolic syndrome (28).

A 12- to 14-Hour Fasting Triglyceride Study.—In any patient whose fasting triglyceride concentration exceeds 150 mg/dL, the presence of the cardiovascular dysmetabolic syndrome should be considered (28).

Non-HDL-C Evaluation.—Many patients with the cardiovascular dysmetabolic syndrome have increased LDL and VLDL levels (28). A simple way to estimate risk from VLDL and LDL as well as IDL and Lp(a) in patients with moderate hypertriglyceridemia is to determine the non-HDL-C content (total cholesterol minus HDL-C) (214). Several researchers have proposed that non-HDL risk levels should be 30 mg/dL higher than established LDL-C risk levels (178,214,215). Therefore, because an LDL-C concentration of 130 mg/dL or higher is considered above normal (Table 4), a non-HDL-C concentration of 160 mg/dL or more should raise clinical suspicion of the syndrome.

Ambulatory Blood Pressure Assessment.—A careful, 24-hour or home blood pressure evaluation is important (28) because even a slight elevation can increase the risk for CAD (see *Risk Factors for CAD, Hypertension*, page 174) (11). Available evidence clearly suggests that insulin resistance predisposes patients to hypertension (28).

Apo A-I Evaluation.—A normal apo A-I level in a patient with low HDL-C suggests adequate numbers of HDL-C particles that contain less cholesterol, an indication of less risk (8).

Patients With CAD and Relatively Normal Lipid Levels

Measurement of total plasma apo B can be useful in the assessment of patients with CAD who have relatively normal levels of lipids. A high apo B level (>130 mg/dL) and LDL-C <160 mg/dL with or without hypertriglyceridemia identify hyperapobetalipoproteinemia, or hyperapo B, which is a cause of premature CAD (8). The physician should also consider measuring Lp(a), plasma homocysteine, and factors contributing to a hypercoagulant state, especially in patients with premature CAD.

Step 3: Determine the Basic Treatment Approach

For the clinical management of patients with dyslipidemia, a reasonable goal is to strive for target lipid levels in the range of normal based on population studies, and more aggressive goals can be set for higher-risk patients. The recommended treatment approaches for patients with dyslipidemia based on the number of CAD risk factors and the LDL-C level are outlined in Table 5. Because an isolated focus on LDL-C is not always sufficient to prevent CAD in at-risk persons or to treat existing atherosclerosis, control of triglycerides and HDL-C (Table 6) is also an important goal. In patients with hypertriglyceridemia who have increased LDL-C or decreased HDL-C,

Lipid	Borderline serum concentration (mg/dL)	High-risk serum concentration (mg/dL)
Cholesterol	200-239	≥240
HDL-C	35-45	<35
LDL-C	130-159	≥160
Triglycerides†	150-200	>200

*HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
 †Both borderline and high-risk values may signify familial combined dyslipidemia or dyslipidemia of diabetes; values >1,000 indicate high risk for pancreatitis.

nutrition therapy and physical activity are recommended for those with triglyceride levels from 150 to 250 mg/dL, whereas pharmacotherapy is needed for those with triglyceride levels that exceed 250 mg/dL; the goal should be a triglyceride level <200 mg/dL (27,58). Other important considerations include patient age and gender and the presence of type 2 diabetes mellitus. These treatment considerations are discussed in the next section of these guidelines (see *Management*).

MANAGEMENT

When a patient has a lipid abnormality, treatment of that abnormality is just one component of a comprehensive approach to prevention of atherogenesis. The approach requires management of all known risk factors; the program should include smoking cessation, regular physical activity, weight management, antiplatelet or anticoagulant therapy, management of associated metabolic conditions, and control of blood pressure in addition to treatment of the dyslipidemia.

Physical Activity and Nutrition Therapy

Rationale

A sound rationale exists for prescribing some type of nutrition therapy plus physical activity for all patients with dyslipidemia. The following four factors are important consequences of such intervention.

Control of Other Coronary Risk Factors.—Nutrition therapy can help control other coronary risk factors. Weight reduction leads to improved lipid and glucose levels and better control of blood pressure (66-69). Physical activity and associated fat loss can substantially reduce the small, dense LDL-C mass while increasing overall LDL-C mass, for no net change in total LDL-C (70,71).

Reduction of Progression of CAD.—Nutrition therapy plus physical activity or smoking cessation can slow the progression of CAD. Clinical trials that combined nutrition therapy with physical activity or smoking cessation have shown significant reductions in progression of angiographic lesions and cardiovascular events in patients with established disease (68,69). Furthermore, although statins can be effective without restriction of dietary fats, dietary saturated fat is associated with angiographic evidence of progression of CAD independent of LDL-C levels in patients treated with lipid-lowering drugs (8).

Decrease in Triglyceride Levels.—Hypertriglyceridemia can be highly responsive to nutrition therapy. Triglyceride levels are more likely to decrease than other lipoprotein fractions as a result of dietary management, weight reduction, and physical activity. Accordingly, weight loss and physical activity are effective first-line therapy for patients with hypertriglyceridemia (25,28).

Addition of Diagnostic Information.—Nutrition therapy has diagnostic significance. Patients who do not respond to nutrition therapy despite good adherence are more likely to have a genetic dyslipidemia (72).

General Recommendations

The Nutrition Committee of the AHA (216) and that of the American Diabetes Association (217) recommend similar diets for managing lipids and other risk factors that promote atherosclerosis (for example, hypertension and obesity). These nutritional guidelines encourage limited intake of salt, calories, saturated and *trans* fatty acids, and cholesterol (216,217). The resulting diet is rich in fruits and vegetables; whole grains and cereals; low-fat and skim dairy products; and fish, lean meats, and skinless poultry. The AHA-NCEP Step I and Step II diets,

Table 5
Recommended Treatment Approach
Based on Coronary Artery Disease Risk and LDL-C Level (27)*

Setting	Nutrition therapy, physical activity	Drug therapy	Goal
CAD risk factors†			
<2	≥160	≥190	<160
≥2	≥130	≥160	<130
With atherosclerotic disease	≥100	≥130	<100
With type 2 diabetes mellitus	≥100	≥130	<100

*CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; data are shown as mg/dL.

†Subtract one risk factor when HDL-C ≥60 mg/dL.

Table 6
Recommended Treatment Approach for Patients With Isolated Low HDL-C (18,22,59-64)*

Gender	Weight loss, physical activity, smoking cessation	Drug therapy	Goal
Male	<35 mg/dL	<35 mg/dL with strong risk factors†	>35 mg/dL‡ or >45 mg/dL§
Female	<45 mg/dL	<45 mg/dL with strong risk factors†	>45 mg/dL‡ or >55 mg/dL§

*CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

†Borderline LDL-C, a family history of premature CAD, overt CAD, or any combination of these factors.

‡In the presence of a strong family history of CAD.

§In the presence of overt CAD.

endorsed by the surgeon general and numerous medical specialty organizations (72) including AACE, reflect this beneficial dietary pattern (Table 7). The Step I diet is recommended for the entire healthy US population older than the age of 2 years, and the Step II diet is recommended for patients with established CAD (73). Furthermore, patients with hypercholesterolemia should adhere to the Step II diet if the Step I diet fails to lower LDL-C values to the goal level.

On average, the Step II diet has produced a modest decrease in LDL-C levels (4 to 5%) in outpatient clinical trials (72,73). Considerable individual variability has been noted, however, in the response to nutrition therapy. A few patients can experience remarkable lowering of LDL-C (by as much as 100 mg/dL); nevertheless, a substantial portion of patients with hypercholesterolemia have little or no response to diet (218,219). Numerous factors influence the response to diet, including adherence (73), baseline diet (for example, degree of baseline saturated fat, *trans*

fatty acid, and cholesterol consumption), gender, and a host of genetic traits (8). For example, the size of the LDL particle can determine the dietary response; men and women with large amounts of the small, dense LDL particles (pattern B) can have a 2-fold greater LDL-C and a 10-fold greater apo B reduction in response to a decrease in dietary fat than patients with larger LDL-C particles (pattern A) (220,221).

Several other nutritional approaches may also be appropriate for individual patients, preferably as a single intervention along with a low-fat diet to test for efficacy. Studies have provided information about the following dietary approaches.

Low-Fat Diets High in Soluble Fiber.—Metabolic studies have shown that the fiber in oats, barley, and pectin-rich fruits and vegetables can reduce lipids even more than a diet with reduced total and saturated fat alone (75). Diets that are both high in fiber and low in fat can

Table 7
Dietary Recommendations
From the American Heart Association and the
National Cholesterol Education Program (27,74)

Component	Step I diet*	Step II diet†
Total fat‡	<30%	<30%
Saturated	<10%	<7%
Monounsaturated	5-15%	5-15%
Polyunsaturated	<10%	<10%
Carbohydrate‡	50-70%	50-70%
Protein‡	10-20%	10-20%
Cholesterol	<300 mg/day	<200 mg/day

*For healthy US population >2 yr old.

†For patients with established coronary artery disease.

‡As percentage of total calories.

From Schaefer (73). With permission.

yield cholesterol reductions of 10 to 15% (75), and studies of fiber supplements added to the Step I diet show an additional 9% decrease in LDL-C levels over the Step I diet alone (222).

Diets Including Plant Stanol Ester-Containing Margarines.—Clinical studies ranging from 4 weeks to 1 year have demonstrated that substitution of conventional home dietary fats with a margarine containing plant stanol esters can reduce LDL-C levels by approximately 15 to 20% (76-79). Plant stanol esters, which are virtually unabsorbable, selectively inhibit dietary and biliary cholesterol absorption in the small intestine.

Moderate Consumption of Alcoholic Beverages.—Consumption of alcohol equivalent to one or two standard drinks for men and one drink for women on a daily basis has been associated with a lower incidence of heart disease (80-82).

Diets Containing 2 to 4 g of Fish Oils (Omega-3 Fatty Acids) per Day.—A critical review of 65 controlled crossover and parallel-group studies demonstrated that ingestion of 2 to 4 g of fish oils per day can decrease triglyceride levels by 25% or more while slightly increasing LDL-C levels (4% versus placebo) and producing no significant effect on HDL-C (83,84). This review also showed that a definite dose-response relationship exists, that the triglyceride-lowering effect of such supplementation seems to persist as long as the supplementation is continued, and that the slight LDL-C increase seems to diminish with time (84). In addition, two controlled trials showed that fish oils—either ingested through a high-fiber diet containing approximately 600 mg of oily fish per day or given as daily supplementation of 2 g of the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid—can lower cardiac events and associated mortality in men with CAD after 1 to 2 years (223-225). The only known side effect is eructation, which was reported with supplementation of a concentrated omega-3 fatty acid product (84).

Duration

Nutrition therapy should be prescribed for at least 3 months and up to 6 months before drug therapy is instituted, unless the patient is at very high risk (27). In such cases, a Step II diet and lipid-lowering drug therapy are usually initiated concomitantly.

Lipid-Lowering Drug Therapy

Numerous well-designed clinical trials show irrefutably that lipid-lowering drug therapy is effective for both primary and secondary prevention (72). Recent clinical evidence suggests that lipid-lowering drug therapy can both prevent CAD from developing and stabilize

early, occult lesions (226). In addition, occlusive lesions can be clinically reversed after aggressive treatment with lipid-lowering drugs (186). Such reversal takes 6 months to 2 years and probably involves hydrolysis of cholesteryl esters and increasing the proportion of insoluble cholesterol monohydrate crystals, a process that stiffens the plaque and reduces stress on the fibrous cap. Decreasing plasma LDL-C also presumably decreases the subendothelial oxidative LDL stimulus for the recruitment and activation of macrophages, ultimately allowing for production of a thicker and stronger fibrous cap. Cholesterol lowering also improves endothelial function, which promotes vasodilation rather than constriction during ischemic periods (227,228). An improved vascular endothelium could also improve fibrinolysis and decrease thrombosis in the event of rupture of a plaque.

Most intervention trials indicate that the clinical benefit of lipid-lowering drug therapy generally increases as cholesterol levels decline (10) (see Tables 9 and 10), but whether there is a threshold lipid value or percentage reduction at which therapy yields no further beneficial effect is unclear. Some data indicate the existence of a definite point of diminishing returns, but other research suggests that high-risk patients can benefit from very aggressive lipid-lowering therapy. Moreover, low HDL-C may be an indicator that the patient may benefit from aggressive reduction of the LDL-C level (229).

The Case for Aggressive Therapy

Some investigators have reported that aggressive LDL-C lowering to as low as <85 mg/dL may benefit many patients—including certain patients with average or elevated LDL-C levels, those who have the small, dense LDL pattern B, and patients who have undergone a coronary artery bypass grafting (CABG) procedure.

Patients With Average or Elevated LDL-C.—The AFCAPS/TexCAPS data demonstrated that lovastatin (20 to 40 mg daily) plus a low-saturated fat, low-cholesterol diet designed to achieve an LDL-C target of ≤ 110 mg/dL significantly reduced the risk of a first acute major coronary event in both men and women with marginally increased LDL-C levels (mean, 150 mg/dL) and below-average HDL-C values (mean, 36 mg/dL) (229). In this trial, the mean LDL-C level declined to 114 to 116 mg/dL after an average duration of 5.2 years. Triglycerides also declined 15%, and HDL-C levels increased 6%. In addition, the Scandinavian Simvastatin Survival Study (4S) (230) showed that patients with documented CAD and mean baseline LDL-C of 188 mg/dL benefited from aggressive LDL-C lowering with simvastatin (mean LDL-C reduction, 37% [118 mg/dL]). In this trial, the risk of major coronary events decreased 34% with treatment after 5.4 years (230). The authors of this study estimated that each 1% reduction in LDL-C level decreased major coronary event risk by 1.7% (230).

Patients With the Small, Dense LDL Pattern B.—SCRIP-Berkeley investigators reported that multifactorial risk reduction produced significant arteriographic benefit in patients with LDL-C levels <125 mg/dL who had LDL pattern B but did not benefit patients with LDL-C levels <125 mg/dL who had LDL pattern A (34,231).

Patients Who Have Undergone CABG.—In the Post CABG Clinical Trial, which was prospectively designed to compare the efficacy of aggressive versus moderate cholesterol lowering, aggressive statin plus as-needed cholestyramine therapy (LDL-C goal, <85 mg/dL) significantly reduced the incidence of total obstruction, the percentage of grafts showing substantial progression of disease, and the unwanted changes in saphenous vein graft luminal dimensions in comparison with moderate statin plus as-needed cholestyramine therapy (LDL-C goal, 130 to 140 mg/dL) irrespective of age, gender, or certain CAD risk factors (232,233). On the basis of angiography performed 4 to 5 years after enrollment, the rate of progression of disease was 31% lower in aggressively treated patients (with the LDL-C goal of <85 mg/dL) than in patients treated in this same study with a higher LDL-C goal of 130 to 140 mg/dL (234).

The Threshold Theory

Other data from two major clinical studies suggest that an LDL-C threshold may exist, beyond which lipid-lowering drug therapy benefits the patient no further (235,236). In the West of Scotland Coronary Prevention Study (WOSCOPS) (mean baseline LDL-C, 186 mg/dL), patients with a mean LDL-C reduction of 24% after treatment with pravastatin (40 mg/day) had the greatest CAD risk reduction (45% risk reduction), and patients with additional LDL-C reductions up to 39% had no further decrease in CAD risk (236). The second study, a post hoc subgroup analysis from the Cholesterol and Recurrent Events (CARE) Trial of post-MI patients with average cholesterol levels (<240 mg/dL), suggested that LDL-C lowering reduced coronary deaths or recurrent MI by 24% but had no further benefit when LDL-C concentrations declined below 125 mg/dL (235). Contrary to the WOSCOPS analysis, this analysis showed that the percentage reduction in LDL-C level had little relationship to coronary events (235); rather, 125 mg/dL was the threshold value.

Lipid-Lowering Drugs

Current lipid-lowering drugs include nicotinic acid (niacin), bile acid sequestrants (resins), hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins), and fibric acid derivatives (fibrates). The primary metabolic effects and main drawbacks of these four drug classes are summarized in Table 8.

The clinical efficacy of these pharmacologic agents for both primary and secondary prevention of coronary events and mortality, based on recent, large-scale controlled trials, is outlined in Tables 9 and 10. Most of the studies summarized in Tables 9 and 10 were not designed to demonstrate an overall reduction in mortality (72), but

some follow-up research has revealed a long-term overall decrease in mortality. The 4S investigation, a secondary prevention trial designed to test the effect of therapy on mortality, revealed a 30% decrease in total mortality risk and a 42% decrease in coronary mortality risk after 5.4 years (251).

Monotherapy Versus Combination Therapy

When drug therapy is prescribed, the physician and the patient should collaborate to establish the patient's lipid goal, and then treatment should be tailored to achieve that goal. Pharmacotherapy may consist of one, two, or, in cases of extreme dyslipidemia, three agents (that is, a statin, fibrate, and niacin).

Statin Monotherapy.—Major coronary prevention trials clearly show that statin monotherapy is beneficial for both primary and secondary prevention of acute coronary events in at-risk patients with increased cholesterol or average (<264 mg/dL with LDL-C <190 mg/dL) cholesterol levels (Tables 9 and 10). One recent 18-month, 341-patient controlled trial showed that aggressive therapy with atorvastatin (80 mg/day) was at least as effective as angioplasty plus subsequent lipid-lowering treatment in reducing the incidence of ischemic events (253).

All statins produce a similar effect on serum total cholesterol, LDL-C, HDL-C, and triglycerides (8), although some differences in the magnitude of effect may be noted. The lipid-altering effects of various statins found in the Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin (CURVES) are generally representative of those reported in the literature (Table 11) (256). This study suggested that atorvastatin had a greater LDL-C-lowering effect than other statins; however, the men and women in this study had very high LDL-C levels (192 to 244 mg/dL) (256). A separate study of patients with lower, albeit still elevated, LDL-C levels (baseline range, 170 to 175 mg/dL) demonstrated that the LDL-C-lowering effect of atorvastatin was comparable with that of lovastatin and simvastatin (258). The CURVES investigation also suggested that simvastatin may have a greater HDL-C-elevating effect than other statins (Table 11) (256).

Certain metabolic differences between statins, however, may have clinical significance. Some research has shown that pravastatin and fluvastatin are both relatively safe for patients needing cyclosporine, but lovastatin therapy has been shown to result in rhabdomyolysis (8). The different statins also have variable effects on smooth muscle cell migration and proliferation independent of their hypocholesterolemic properties as well as platelet reactivity and function, although the clinical relevance of these differences is not clear (8).

Statins do not seem to alter LDL-C subfraction diameter (259-261). One small, retrospective study of patients with LDL pattern A (mean LDL-C, 240 mg/dL) suggested that atorvastatin may reduce the number of small, dense LDL particles (262), but additional prospective studies in patients with LDL pattern B are clearly needed.

Table 8
Primary Lipid-Lowering Drug Classes (8,72,92,178,218,237-240)*

Drug class	Metabolic effect†	Main drawbacks‡
Niacin (nicotinic acid)	↓ LDL-C 10-25%, ↓ TG 20-30%, ↑ HDL-C 10-35% by decreasing hepatic synthesis of LDL-C and VLDL-C ↓ Lp(a) Transforms LDL-C to less atherogenic form	Deleterious effect on serum glucose at higher doses Increases uric acid levels Potential for hyperuricemia, hepatotoxicity (rare but may be severe), peptic ulcer, frequent skin flushing, pruritus, nausea, abdominal discomfort Only 50-60% of patients can tolerate nicotinic acid in effective doses for a prolonged time
Bile acid sequestrants (cholestyramine, colestipol)	Primarily ↓ LDL-C 10-30% by binding bile acids at the intestinal level	May ↑ serum TG Frequent non-life-threatening GI events, which can reduce patient adherence Many potential drug interactions (see product labeling) May reduce absorption of folic acid and fat-soluble vitamins such as vitamins K, A, and D
HMG-CoA reductase inhibitors (statins§)	Primarily ↓ LDL-C 15-40% by competitively inhibiting rate-limiting step of cholesterol synthesis in the liver Effect on HDL-C is less pronounced (↑ 2-12%)	Monitoring of liver function required Muscle aches and fatigue in a small proportion of patients
Fibric acid derivatives (gemfibrozil, fenofibrate)¶	Primarily ↓ TG 30-55%, ↑ HDL-C 15-25% by stimulating lipoprotein lipase activity¶ Fenofibrate may ↓ TC and LDL-C 20-25% Both lower VLDL and LDL, causing reciprocal rise in LDL-C; transform LDL-C into less atherogenic form Fenofibrate ↓ fibrinogen level	Gemfibrozil may ↑ LDL-C 10-15% GI symptoms, possible cholelithiasis, # myopathy when used with other agents May potentiate effects of orally administered anticoagulants Gemfibrozil may ↑ fibrinogen level** Gemfibrozil and fenofibrate can ↑ homocysteine independent of vitamin concentrations Rhabdomyolysis when used with statin (rare)

*GI = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; HMG-CoA = hydroxymethylglutaryl-coenzyme A; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; VLDL-C = very-low-density lipoprotein cholesterol.

†Percentage change varies depending on baseline lipid variables and dosages. Potency and therefore dosages of statins vary.

‡Most frequent. Does not include rare occurrences. See prescribing information for complete contraindications, warnings, precautions, and side effects.

§Lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin.

¶Cofibrate is also available and approved for type II hyperlipidemia that is unresponsive to nutrition therapy (241).

Currently, however, this agent is used infrequently because of a possibly increased risk of malignant tumor and cholelithiasis (241).

¶Specific mechanisms differ among fibrates.

#Cholelithiasis not seen in major clinical trials with gemfibrozil or fenofibrate.

**Results vary. Gemfibrozil has been shown to decrease, have no effect on, or increase fibrinogen depending on the study (242-247).

Table 9
Summary of Major Randomized Controlled Drug Trials for Primary Prevention*

Trial	Treatment	Patients		FU (yr)	Starting level†		Reduction (%)				Cor death	
		M	F		LDL-C	TG	LDL-C	TG	PTCA	MI		
<i>Statins:</i>												
WOSCOPS (236)	Pravastatin	6,595	...	4.9	188	154	26	14	12	31	33	
AFCAPS/ TexCAPS (229)‡	Lovastatin	5,608	997	5.2	146	161	25§	15§	33//	40	¶	
<i>Fibrates:</i>												
WHO (248)	Clofibrate	3,806	...	5.3	188	...	9 (TC)	19	19	
HHS (58)	Gemfibrozil	4,081	...	5.0	201	182	11	35	...	34	37	
<i>Resin:</i>												
LRC (249)	Cholestyramine	10,627	...	7.4	199	154	8	+3	...	25	20	

*AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; Cor = coronary; FU = follow-up; HDL-C = high-density lipoprotein cholesterol; HHS = Helsinki Heart Study; LDL-C = low-density lipoprotein cholesterol; LRC = Lipid Research Clinics Coronary Primary Prevention Trial; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; TC = total cholesterol; TG = triglycerides; WHO = World Health Organization; WOSCOPS = West of Scotland Coronary Prevention Study.

†Mean values, expressed in mg/dL.

‡Participants had below-average baseline HDL-C (45 to 47 mg/dL). Treatment increased HDL-C by 6%.

§At 1 year.

//All revascularizations.

¶Too few events to perform survival analyses.

Modified from Wierzbicki (250).

Fibrate Monotherapy.—Both gemfibrozil and fenofibrate are effective for treating patients with severe hypertriglyceridemia and for patients at risk for CAD who have an increased triglyceride level or low HDL-C level (or both) as the primary lipid abnormality (27,50,51,263). The recent Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (64) and the Helsinki Heart Study (58) both demonstrated that fibrate monotherapy reduced triglyceride levels, increased HDL-C levels, and decreased cardiovascular events in men with or without CAD. Two recent angiographic trials supported these metabolic findings and revealed an independent effect of fibrate therapy on progression of lesions (264,265). In patients with the small, dense LDL pattern B, fibrate treatment can also significantly reduce small LDL and increase large LDL concentrations without altering the overall LDL-C concentration (266). Unlike gemfibrozil, fenofibrate can also reduce total cholesterol and LDL-C in patients with type IIb hyperlipidemia (263). Fibrate monotherapy is preferable to niacin therapy in patients with type 2 diabetes mellitus because it does not seem to worsen glycemic control (267).

Niacin Monotherapy.—Niacin is a powerful LDL-C and triglyceride-lowering drug that also substantially increases HDL-C. It produces a more favorable lipid response than a fibrate (Table 8), has been associated with angiographic evidence of regression of CAD, and has been

associated with reduced mortality 9 years after discontinuation of use (268-270). Generally, however, niacin is considered a second choice after fibrates for lowering triglyceride levels and raising HDL-C levels because of its side effect profile (Table 8). Flushing occurs in approximately 75% of patients; this adverse effect can be ameliorated with use of aspirin (Table 8). Side effects can be considerably reduced by slowly titrating the dosage upward. Recent studies suggest that a new formulation of extended-release niacin administered once nightly may be better tolerated (271,272), with the incidence of flushing reduced to 20%, but additional study is needed. Because it decreases Lp(a), niacin may be preferable for patients with associated Lp(a) elevations.

Combination Therapy.—Certain clinical situations warrant use of a combination of lipid-lowering agents. The side effects of two or more drugs may be additive, and clinical judgment is needed to balance the risks and benefits of combination therapy. Combination therapy should be considered in the following circumstances:

- The cholesterol level is severely increased, and monotherapy does not achieve the therapeutic goal (86,87,95) (see *Therapeutic Considerations for Specific Phenotypes, Hypercholesterolemia*, page 188). In addition, statins yield only incremental, additional LDL-C reductions when the dose is doubled; therefore,

Table 10
Summary of Major Randomized Controlled Drug Trials for Secondary Prevention*

Trial	Treatment	Patients		FU (yr)	Starting level†		Reduction (%)				Cor death
		M	F		LDL-C	TG	LDL-C	TG	PTCA	MI	
<i>Statins:</i>											
4S (251)‡	Simvastatin	3,617	827	5.4	188	131	35	10	37	37	42
CARE (114)	Pravastatin	3,583	576	5.0	135	91	28	14	27	27	24
LIPID (252)	Pravastatin	7,498	1,516	6.1	146§	145§	25	11	19	29	24
AVERT (253)	Atorvastatin	341	...	1.5	146//	170//	46	11	¶	¶	¶
<i>Fibrates:</i>											
BECAIT (254)	Bezafibrate	47	...	5.0	175§	221§	1.9	31.4	#	#	#
BIP (237,255)**	Bezafibrate	2,856	266	6.25	148	149	6.5	20.6	NR	NR	NR
VA-HIT (64)††	Gemfibrozil	2,531	...	5.1	<140	<300	NC	31	‡‡	22§§	22§§
<i>Combination:</i>											
Stockholm (107)	Clofibrate + niacin	442	113	5.0	157	213	13 (TC)	19	NR	30	36

*AVERT = Atorvastatin Versus Revascularization Treatment Study; BECAIT = Bezafibrate Coronary Atherosclerosis Intervention Trial; BIP = Bezafibrate Infarction Prevention Study; CARE = Cholesterol and Recurrent Events Trial; Cor = coronary; FU = follow-up; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LIPID = Long-Term Intervention With Pravastatin in Ischemic Disease; MI = myocardial infarction; NC = no change; NR = not reported; PTCA = percutaneous transluminal coronary angioplasty; 4S = Scandinavian Simvastatin Survival Study; Stockholm = Stockholm Ischaemic Heart Disease Secondary Prevention Study; TC = total cholesterol; TG = triglycerides; VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

†Mean values (unless otherwise noted), expressed in mg/dL.

‡HDL-C increased 8%.

§Median.

//Estimated.

¶Ischemic events reduced 36% versus the comparator patients, who underwent angioplasty (not statistically significant).

#All coronary events reduced 21% versus placebo group.

**HDL-C increased 17.9%.

††HDL-C increased 6%; total cholesterol decreased 4%.

‡‡Carotid endarterectomy reduced 65%. No statistically significant reductions in rates of coronary revascularization or hospitalization for unstable angina.

§§Nonfatal MI and coronary death reduced 22%.

Modified from Wierzbicki (250).

adding a drug with a complementary mode of action may be more cost-effective than increasing the statin dosage.

- Lower dosages of two or more drugs may avoid or minimize toxicity associated with higher dosages of a single drug (86,95).
- The patient has increased cholesterol and triglyceride levels. If high-dose monotherapy does not achieve the lipid goal, a combination regimen may be warranted to lower both cholesterol and triglyceride levels and to raise the HDL-C level (87,95) (see *Therapeutic Considerations for Specific Phenotypes, The Lipid Triad*, page 189).

Therapeutic Considerations for Specific Phenotypes

Hypercholesterolemia (Type IIa)

Clear evidence indicates that a statin plus physical activity and nutrition therapy is appropriate for patients with increased LDL-C levels who require drug therapy (85). When needed, however, a resin can be added to the

statin regimen to achieve the cholesterol target and contain costs (86-91). In relatively small doses, the bile acid sequestrants are generally better tolerated than large doses of nicotinic acid, and they are safe (85). In separate clinical trials, cholestyramine plus pravastatin or lovastatin produced decreases in LDL-C levels of 39% and 49%, respectively, and slight increases (6%) in triglyceride levels (93,94). In other independent trials, lovastatin plus a bile acid sequestrant decreased LDL-C levels by 18% more and lovastatin plus nicotinic acid decreased LDL-C levels by 14% more than lovastatin alone (92).

For patients with severe familial hypercholesterolemia, three drugs with complementary effects may be needed to achieve the cholesterol target (86,95). One 15-month study (96) showed that colestipol (30 g/day), niacin (5.5 g/day, mean dose), and lovastatin (60 mg/day) reduced total cholesterol levels by 58% and LDL-C levels by 69% in comparison with baseline in this patient population. Case 1 is an example in which multiple lipid-lowering drugs were needed to achieve the lipid goals (Table 12).

Table 11
Comparison of Statin Effects on Lipids After 8 Weeks of Treatment
in Men and Women With LDL-C From 192 to 244 mg/dL (N = 534) (256)*

Statin	Dosage range (mg)	Change (%)			
		TC	LDL-C	HDL-C	TG
Lovastatin	20-80	↓ 21 to ↓ 36	↓ 29 to ↓ 48	↑ 4.6 to ↑ 8.0	↓ 12 to ↓ 13
Pravastatin	10-40	↓ 13 to ↓ 24	↓ 19 to ↓ 34	↑ 3.0 to ↑ 6.2	↑ 3 to ↓ 10
Simvastatin	10-40	↓ 21 to ↓ 30	↓ 28 to ↓ 41	↑ 6.8 to ↑ 9.6	↓ 12 to ↓ 15
Fluvastatin	20-40	↓ 13 to ↓ 19	↓ 17 to ↓ 23	↑ 0.9 to ↓ 3.0	↓ 5 to ↓ 13
Atorvastatin	10-80	↓ 28 to ↓ 42	↓ 38 to ↓ 54	↑ 5.5 to ↓ 0.1	↓ 13 to ↓ 25

*HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.

Note: The lipid-lowering effect of the various statins in this study are representative of those seen in other controlled trials, with one exception. In the CARE (114), WOSCOPS (236), and LIPID (252) trials, pravastatin had a slightly greater triglyceride-lowering effect (11-14%; see Tables 9 and 10).

Fibrates are inappropriate for patients with isolated hypercholesterolemia; in the only study of fibrates in which a subgroup analysis of patients with type IIa versus type IIb hyperlipoproteinemia was conducted, the relative decrease in incidence of CAD was substantially less in the type IIa phenotype (85,273).

The Lipid Triad (Types IIa, IIb, and IV)

In this high-risk patient group, aggressive intervention is warranted, when needed, to meet the lipid goals. Nutrition therapy and physical activity designed to decrease or control body weight and favorably alter the LDL subfraction profile are essential (28,34,71,220,221). In patients with the cardiovascular dysmetabolic syndrome, the insulin-resistant state should be directly treated with weight control and physical activity (28).

Because hypertriglyceridemia increases the absolute risk of CAD above that conferred by the hypercholesterolemia alone (85), many patients with this phenotype will also benefit from a combined regimen of a fibrate or niacin plus a statin (28,87).

Statin-Fibrate Combinations.—Because they target different lipid variables, statins and fibrates can favorably alter the entire lipid profile when used together. In addition, gemfibrozil (1,200 mg/day) has been shown to reduce significantly the risk of major cardiovascular events in men with features of the cardiovascular dysmetabolic syndrome (64).

In the past, use of statin-fibrate combinations was limited because of reports of increased risk of a myopathy

(87). Increasing evidence indicates, however, that statin-fibrate combinations can be used safely for prolonged periods in most patients (87,274-276). In addition, two long-term investigations (one 3-year and one 4-year study) designed to assess the safety of this combination showed that statin-fibrate treatment did not cause myopathy and was not associated with any significantly abnormal biochemical markers of muscle malfunction (creatinine kinase) (274,275). In one of these studies, five patients (1.3% of the cohort) were withdrawn from the study because transaminase levels increased more than 3 times the upper limit of normal (274); the other study revealed no biochemical marker of liver malfunction (275). With use of this combination, careful monitoring for liver toxicity is essential for all patients, and patients should be informed to alert their physician if they experience “flu-like” symptoms of myalgias and malaise or severe muscle pain (28).

In order to decrease the risk of myopathy, the statin dosage should be kept low and statin-fibrate combinations should be avoided in patients who are elderly, have acute or serious chronic illness (especially chronic renal disease), are undergoing a surgical procedure, or are taking multiple medications (drug interactions increase the risk of occurrence of myopathy) (28). In addition, an alternate-day administration regimen may be considered. One recent study showed that simvastatin (10 mg) administered on alternate days with fenofibrate (250 mg) for combined hyperlipidemia was as effective as the every-day combination of the same drugs but was associated with better tolerance and safety (277).

Table 12
Case 1: 51-Year-Old Man After Coronary Artery Bypass Grafting Procedure*

Lipid value (mg/dL)					Management
TC	TG	HDL-C	LDL-C	TC/HDL-C ratio	
457	204	41	375	11.1	Diet ↓ Statin A 40 mg qd Bile acid binder 2 packets q pm 2 packets bid 3 packets bid Niacin 1,500 mg 3,000 mg
388	174	34	319	11.4	
296	159	37	227	8.0	
291	173	46	210	6.3	
263	206	50	172	5.3	
228	214	41	144	5.6	
219	104	47	151	4.7	
155	102	56	79	2.8	

*bid = twice a day; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; qd = each day; q pm = each evening; TC = total cholesterol; TG = triglycerides.

Comment: This man, with familial heterozygous hypercholesterolemia and coronary artery disease, was given multiple drugs to achieve LDL-C <100 mg/dL while concomitantly lowering triglycerides and raising HDL-C. More powerful and higher-dose statin regimens have made such combinations less necessary in some cases.

Case 2 provides an example of application of statin-fibrate combination therapy (Table 13).

Statin-Niacin Combinations.—Clinical evidence supporting combination statin-niacin therapy is limited. The sample sizes of clinical trials of this combination therapy have been relatively small—no more than 44 subjects per study (278). In addition, this combination is often avoided because of the risk of muscle and liver toxicity (278). Although clinical trials of combination statin-niacin therapy have not revealed any cases of myopathy or discontinuation of treatment because of hepatic toxicity, one study designed to assess the safety and effectiveness of this therapeutic combination showed a 53% mean increase in alanine aminotransferase and a 42% mean increase in aspartate aminotransferase related to the use of sustained-release niacin at a target dosage of 1 g twice a day (279).

Case 3 illustrates the strategy of using increasing dosages of niacin plus a low-dose statin to achieve lipid goals, including a dramatic increase in HDL-C, in a man with type IIb hyperlipidemia (Table 14). Alternatively, a higher statin dose could be administered in conjunction with a relatively low niacin dosage of ≤2 g/day, depending on the clinical circumstance. This combination can yield a moderate reduction in triglyceride level and increase in HDL-C level while minimizing hepatotoxicity, hyperglycemia, and hyperuricemia (178).

Bile Acid Sequestrants.—Bile acid sequestrants may be used, but only after triglyceride levels have been reduced and controlled.

Moderate Hypertriglyceridemia (Type III)

When moderate hypertriglyceridemia is the primary disorder (in association with increased serum cholesterol or low HDL-C levels), physical activity and weight control are important. When drug therapy is needed to achieve the target triglyceride level, fibrate or niacin monotherapy is most effective (8,64,85). Although statins may enhance IDL clearance, they are generally not as effective for this disorder (85). Bile acid sequestrants are not indicated in this setting because they may increase serum triglyceride levels (85,92).

Familial Hypertriglyceridemia

Not all patients with elevated triglyceride levels have an increased risk of CAD, and patients with familial hypertriglyceridemia do not seem to have an increased risk (27,50,51). Treatment should focus on reducing the risk of pancreatitis as a result of an increased triglyceride level (27,50,51,97).

Severe Hypertriglyceridemia (Type V)

Most patients with severe hypertriglyceridemia have type V hyperlipoproteinemia, signifying an increase in

Table 13
Case 2: 66-Year-Old Man Who Had Had a Myocardial Infarction*

Lipid value (mg/dL)					Management
TC	TG	HDL-C	LDL-C	TC/HDL-C ratio	
283	318	26	193	10.9	<p>Gemfibrozil 600 mg bid</p> <p>Bile acid binder 2 packets bid</p> <p>2 packets bid q pm</p> <p>Statin A 10 mg 20 mg 40 mg</p>
218	78	42	160	5.2	
252	112	42	188	6.0	
157	170	38	85	4.1	
190	56	31	148	6.1	
196	56	28	157	7.0	
199	117	32	144	6.2	
192	223	33	114	5.8	
170	123	44	101	3.9	
180	132	42	112	4.3	
171	140	40	103	4.3	

*For explanations of abbreviations, see Table 12.

Comment: This man, with familial combined hyperlipidemia, was first treated to lower triglycerides and raise HDL-C. LDL-C reduction was then achieved with bile acid binders and finally a statin. Today, one might simply add a low-dose statin to fibrate therapy and then lower the fibrate dosage while increasing the statin dosage to prevent myositis. Because the increase in triglyceride level was mild, some physicians would prescribe a statin alone to reduce triglycerides to <200 mg/dL and LDL-C to <100 mg/dL.

both chylomicrons and VLDL (28). The need to lower triglyceride levels in this population is urgent, in order to prevent acute pancreatitis and the chylomicronemia syndrome. These patients often respond to fibrates or nicotinic acid (28,92), and although serum triglyceride levels rarely return to normal, they usually decline enough (to <1,000 mg/dL) to reduce the risk of these disorders substantially.

In addition, ingestion of 2 to 4 g of fish oils (omega-3 fatty acids) every day can decrease triglycerides by 25% or more (see *Physical Activity and Nutrition Therapy*, page 182). Case 4 illustrates how low-dose fish oil capsules in combination with a fibrate helped achieve lipid goals in a 70-year-old woman with type V hyperlipoproteinemia after low-dose niacin therapy had failed (Table 15).

Isolated Low HDL-C

Isolated low HDL-C has been defined as HDL-C levels <35 mg/dL, LDL-C levels <160 mg/dL, and triglyceride levels <250 mg/dL (61). Because no intervention targets only HDL-C, it has been difficult to determine from clinical trials whether increasing the HDL-C level alone is clinically beneficial (22,47,64). The VA-HIT study, however, showed that increasing HDL-C and lowering

triglyceride levels in patients with CAD whose primary lipid abnormality was low HDL-C (≤ 40 mg/dL in conjunction with triglycerides ≤ 300 mg/dL and LDL-C ≤ 140 mg/dL) significantly reduced the rate of coronary events by 24% (64). Moreover, the AFCAPS/TexCAPS results (229) (Table 9) have also been suggested as support for using low HDL-C as justification for more aggressive treatment of borderline LDL-C levels in older men and postmenopausal women without CAD (22). In light of these results and the epidemiologic evidence supporting a cardioprotective role of HDL-C in the general population, intervention is appropriate when the HDL-C level is low, other risk factors exist (including borderline LDL-C levels from 130 to 159 mg/dL, family history of premature CAD, or existing CAD), and secondary causes of low HDL-C have been excluded (see *Secondary Dyslipidemia*, page 176) (18,22,47,59,64). The recommended HDL-C goals are outlined in Table 6.

Physical activity, weight loss in overweight or obese patients, and cessation of smoking should be prescribed because they can all raise HDL-C levels (71,280,281). Nutrition therapy should be prescribed cautiously, however, because a very low-fat, high-carbohydrate diet may further reduce HDL-C in some patients (13).

Table 14
Case 3: 62-Year-Old Man With Hypertension,
Atypical Chest Pain, Positive Thallium Stress Test, and Mild Claudication*

Weight (lb)	Lipid value (mg/dL)				TC/HDL-C ratio	Management
	TC	TG	HDL-C	LDL-C		
179	294	282	30	208	9.8	
174	238	221	40	154	6.0	Diet
169	253	91	64	171	4.0	Niacin 1,500 mg qd
165	238	139	58	152	4.1	3,000 mg qd
172	208	146	62	117	3.4	Statin 10 mg qd
170	186	135	62	97	3.0	

*For explanations of abbreviations, see Table 12.

Comment: This man, with a type IIb hyperlipidemia (most likely, familial combined hyperlipidemia), has been well managed with weight loss, increasing doses of niacin, and the addition of a low-dose statin. Although a high-dose statin may have achieved equally good TG and LDL-C levels, a remarkable increase in HDL-C was achieved with niacin.

When drug therapy is needed to raise HDL-C to goal levels in the high-risk patient, a statin or low-dose niacin (or both) may be effective (18,22,61-63). A statin is appropriate if the LDL-C level is borderline (22), and adjunctive niacin can further increase HDL-C if clinically appropriate (22,63). Of the statins, simvastatin may yield the greatest HDL-C increase (Table 11). For the patient who has normal LDL-C, low-dose niacin monotherapy can effectively increase HDL-C. In one study of 55 patients with cardiovascular disease (62), niacin (1 g/day) increased the HDL-C level 31% and reduced the total cholesterol:HDL-C ratio by 27%. At this low dose, however, unpleasant side effects were still an issue; a 40% dropout rate reflected poor tolerance.

Additional Treatment Considerations

Age

AACE believes that the lipid values outlined in Table 4 should apply to all adults regardless of age, for the reasons outlined under *Screening Considerations by Age-Group*, page 177.

Young Adults.—For young patients with dyslipidemia, lifestyle modifications (that is, diet, weight control, and physical activity) are essential. Drug therapy should be considered for otherwise healthy men <45 years old who have LDL-C levels >190 mg/dL that do not respond to a maximum of 6 months of conservative therapy. For other young men at risk for CAD, especially those with a family history of premature CAD, drug therapy should be

considered if the LDL-C level is ≥160 mg/dL after 6 months of conservative therapy (8).

Elderly Patients.—As with other populations, global risk management in elderly patients is important. Smoking cessation and treatment of systolic hypertension reduce the risk of CAD and stroke in all age-groups (33), and nutrition therapy is as efficacious in elderly patients as it is in younger patients (99).

Clinical trial data supporting lipid-lowering drug therapy in the elderly population are limited, although subgroup analyses of the >65-year-old population in the 4S, CARE, and Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) trials showed that these patients benefited from cholesterol-lowering drug therapy as much as younger patients (98,107,108). Angiographic studies have also shown that even advanced coronary atherosclerosis responds to cholesterol-lowering therapy (99). In addition, statin therapy does not seem to pose an increased safety risk for older patients with hypercholesterolemia or established cardiovascular disease (99-106). For these reasons, and because of the clear association between hypercholesterolemia and risk of CAD in elderly persons (99), drug therapy for either primary or secondary prevention is warranted for high-risk patients between ages 65 and 75 years (33).

The use of lipid-lowering drugs in patients >75 years of age is controversial because no data are available for this population. Patients >75 years old who are already receiving treatment should continue any therapy that was prescribed at an earlier age (33). The decision to initiate

Table 15
Case 4: 70-Year-Old Woman With Dyslipidemia and Crohn's Disease
Who Had a History of Smoking and a Family History of Premature CAD*†

Weight (lb)	Lipid value (mg/dL)					Non-HDL-C	Management
	TC	TG	HDL-C	LDL-C	TC/HDL-C ratio		
...	518	1,732	41	...	12.6	477	Niacin 1,400 mg qd
118	449	1,567	37	54	12.1	412	Gemfibrozil 600 mg bid
120	217	302	29	128	7.5	188	Fish oil capsules 4 bid
113	203	132	40	137	5.1	163	

*CAD = coronary artery disease; ERT = estrogen replacement therapy; MI = myocardial infarction. For explanations of other abbreviations, see Table 12.

†No ERT; ileostomy, radical colectomy, and ex-smoker (2 packs/day). Father had an MI at age 51 yr; mother had an MI in her 60s. No diabetes; no hypertension.

Comment: This woman, with a type V hyperlipidemia and two non-lipid CAD risk factors (estrogen loss with no ERT, family history of early CAD), should ideally have LDL-C <130 mg/dL and TG <200 mg/dL or a non-HDL-C <160 mg/dL. When low-dose niacin failed, a fibrate plus low-dose fish oil capsules, plus some weight loss, produced the desired results.

therapy in this population should be based, in part, on the degree of risk. Surgical coronary bypass is often performed in patients >75 years old, and the universal acceptance of this aggressive treatment justifies the use of aggressive preventive therapy as well. The decision to initiate therapy in this age-group should also be predicated on individual circumstances such as “physiologic” age. Elderly patients with advanced physiologic or chronological age or severe illnesses may not be candidates for drug therapy (27).

Special pharmacotherapy considerations in the elderly population include the potential for drug interactions and constipation from bile acid sequestrants. Resins bind nonspecifically to other drugs; thus, absorption is usually reduced and serum levels are affected (99). Statins are associated with potential for myonecrosis if used in combination with cyclosporine, fibrates, or erythromycin (99).

Female Gender

The incidence of CAD is lower in premenopausal women than in men of similar age, potentially attributable to a cardioprotective effect of estrogen. After menopause and estrogen loss, the risk of CAD increases substantially in all women (99). Generally, plasma LDL-C levels increase and HDL-C levels decrease (both by approximately 10 to 20%) after menopause.

The link between endogenous estrogen and cardiac protection for women should not obscure the clinical significance of classic risk factors in premenopausal women or postmenopausal women receiving ERT. CAD-related mortality is exceedingly high in women; twice as many women as men die within the first few weeks after MI. As

with men, serum cholesterol level is a strong predictor of risk of CAD in women until after 80 years of age (111,211), although the link between LDL-C levels and CAD risk is weaker in women. Importantly, both HDL-C and triglyceride levels seem to be independently associated with CAD risk in women, and as stated earlier, a triglyceride level >200 mg/dL should be considered an additional, strong risk factor in women (27).

Special considerations in women with dyslipidemia include the following factors:

- Polycystic ovary syndrome
- Nutrition therapy
- Drug therapy
- Estrogen replacement therapy

PCOS, which occurs in as many as 10 to 15% of premenopausal women and is characterized by hyperandrogenism and anovulatory cycles, is another important indicator of CAD (109,282-284). PCOS is associated with high triglyceride levels, low HDL-C, a trend toward insulin resistance, and high testosterone (282), with no significant change in total cholesterol or LDL-C levels. In patients with PCOS, a triglyceride level of >150 mg/dL and an HDL-C level <45 mg/dL may be considered specific risk factors (109). Emerging literature demonstrates the benefits of insulin sensitizer therapy (thiazolidinediones or biguanides) in women with PCOS (285-287), but whether this therapy will help protect against diabetes or prevent the development or progression of CAD is unclear.

Studies of *nutrition therapy* suggest that restriction of dietary fat tends to be less effective for lowering the

cholesterol level in women than in men (110). In contrast, however, nutrition management and weight reduction are effective for lowering triglyceride levels in women and are considered first-line therapy for hypertriglyceridemia in this population (25). For at-risk women with hypertriglyceridemia, a triglyceride level of ≤ 200 mg/dL should be the goal (111), and pharmacotherapy should be initiated if this goal is not achieved with nutrition therapy.

A strong rationale exists for treating dyslipidemia as aggressively in postmenopausal women as in men (111). Lipid-lowering *drug therapy* can benefit women as much as it benefits men, according to subgroup analyses of major lipid-lowering trials (111-114). In addition, two recent lipid-lowering trials performed in postmenopausal women (288,289) demonstrated that statin therapy produced significant reductions in LDL-C levels. In the Women's Atorvastatin Trial on Cholesterol, up to 87% of postmenopausal women with hypercholesterolemia reached target LDL-C levels by week 16 of atorvastatin therapy (10 mg/day) (288). In a separate statin trial of 58 postmenopausal women with hypercholesterolemia, 8 weeks of therapy reduced total cholesterol and LDL-C levels by 26% and 36%, respectively, while increasing HDL-C and decreasing triglycerides (289). Case 5 illustrates use of statin monotherapy to help achieve an LDL-C level < 100 mg/dL in a woman with hypercholesterolemia and multiple CAD risk factors (Table 16).

ERT, with or without progestin, has been shown to reduce LDL-C levels by 10 to 24% in postmenopausal women (289,290). ERT may be prescribed as lipid-lowering therapy in lower-risk postmenopausal women with mildly increased LDL-C levels (130 to 160 mg/dL) and normal triglyceride levels. ERT, however, should not be prescribed as an alternative to lipid-lowering pharmacotherapy for most postmenopausal women with dyslipidemia. The only large-scale, controlled clinical trial to assess the effect of ERT on CAD risk found no benefit when the therapy was prescribed for women with CAD (291). The recent Heart and Estrogen/Progestin Replacement Study (HERS) specifically showed that a standard daily conjugated equine estrogen-progestin regimen administered for 4.1 years did not reduce the overall risk of any cardiovascular event in postmenopausal women < 80 years old (mean age, 66.7 years) who had *significant CAD* (291). The therapy was associated with more cardiovascular events during the first year of treatment and fewer events in years 4 and 5; whether continued therapy would have produced a late benefit is unclear. Perhaps more aggressive adjunctive treatment may have yielded greater benefit. Most of these women did not achieve universally accepted LDL-C goals despite treatment with lipid-lowering agents; 37% achieved ≤ 130 mg/dL, and 9% achieved ≤ 100 mg/dL. In this trial, hormone therapy was also associated with an overall increased risk of venous thromboembolic events and gallbladder disease (291). It is not clear whether these results apply to younger, healthy postmenopausal women. In addition, ERT is associated with triglyceride increases up to 25% (289,290); therefore,

it should only be used cautiously in women with hypertriglyceridemia.

ERT may have an important role in primary CAD prevention for women who are already receiving ERT for other reasons (such as menopausal symptoms or prevention of osteoporosis). In epidemiologic studies, ERT is almost universally linked with reduction of CAD risk. For this reason, and because of the potential for a late benefit, most authorities agree that women who are already receiving hormone replacement therapy may benefit from its continued use (115).

DYSLIPIDEMIA OF DIABETES

In comparison with patients who do not have diabetes, patients with type 2 diabetes mellitus have a twofold to fourfold increased risk of CAD (28,29) and a dramatically higher risk of accelerated cerebral and peripheral vascular disease (29,117). Patients with diabetes without known CAD have the same risk of MI as those without diabetes who have had a coronary event (29). In addition, more than half of all patients with type 2 diabetes mellitus have established CAD (116), and once atherosclerotic disease is established, the presence of diabetes worsens the prognosis. Mortality from CAD is also extremely high in this population: the case fatality rate from onset of clinical symptoms of CAD through 1 year is 45% in men and 38% in women with diabetes (29).

Diabetes negates the cardioprotective effect of estrogen, and as a result, women with type 2 diabetes mellitus are particularly predisposed to early CAD (117). The rate of CAD in premenopausal women with type 2 diabetes mellitus is equal to that in men of the same age who do not have diabetes (117).

The same risk factors that contribute to CAD in the general population contribute to CAD in patients with diabetes (118); however, the overall effect of each risk factor is greater (119), and diabetes itself confers an independent risk. Most likely, the diabetic state causes added atherogenic insult through enhanced lipoprotein glycation and oxidation as well as accumulation of advanced glycation end products in the arterial wall (29,116). Furthermore, the VLDL particles in patients with diabetes are readily bound to macrophages and contribute more cholesteryl ester to macrophages than do those in patients without diabetes (29).

Identification of Risk Factors

Identification of all risk factors is important (119), inasmuch as the benefit of treatment may be even greater in the patients with diabetes than in the general population. A *complete, fasting* lipid panel should be measured at least yearly in adults with diabetes because changes in glycemic control will affect lipid values (29).

Dyslipidemia in the patient with type 2 diabetes mellitus is characterized by moderate hypertriglyceridemia and low plasma HDL-C level. The weight of evidence

Table 16
Case 5: 62-Year-Old Woman With Multiple Risk Factors*†

Lipid value (mg/dL)					TC/HDL-C ratio	Management
TC	TG	HDL-C	LDL-C			
307	269	51	202	6.0		
256	163	50	173	5.1		
263	209	48	173	5.5		
214	174	47	132	4.6		
208	145	57	122	3.6		
2 years later: Ultrafast CT of heart for coronary calcium deposition Her score: 551 (Normal: 97; CAD: 469) Repeated thallium: Positive reversible defect consistent with obstructive CAD						
158	135	55	76	2.9		

*CAD = coronary artery disease; CT = computed tomography; ECG = electrocardiography; ERT = estrogen replacement therapy; MI = myocardial infarction. For explanations of other abbreviations, see Table 12.

†Father had an MI at age 50 yr. Brother diagnosed with angina at age 67 yr. Mother died of breast cancer. Patient was postmenopausal without ERT. Smoked 2-3 cigarettes/day. Stress test-ECG: 1.5 →1.9 mm ST depressions inferior leads—equivocal. Thallium study: normal findings except breast diminution over septum.

Comment: This woman, with 3 non-lipid risk factors (family history of early CAD, postmenopausal but no ERT, and cigarette smoking), successively received 2 statins with increasing potency to reduce LDL-C to approximately 130 mg/dL. When a diagnosis of significant CAD was finally suggested with an electron-beam CT scan and confirmed by repeated thallium study, one could either raise the dose of the current statin or, as in this case, prescribe another more powerful statin at the same dose to achieve LDL-C <100 mg/dL. She also stopped smoking.

shows that hypertriglyceridemia may be the best lipid predictor of CAD in patients with type 2 diabetes mellitus (119), likely because increased triglycerides are correlated with other components of the insulin resistance syndrome (29). Recent studies of patients with diabetes have demonstrated the triglyceride level to be a risk factor for ischemic heart disease independent of HDL-C level, despite glycemic control (23,119). In most patients with diabetes, the plasma triglyceride level is <250 mg/dL; patients with levels >400 mg/dL likely have a genetic disorder of lipoprotein metabolism (292). In addition, total cholesterol and LDL-C levels may appear relatively normal, but the non-HDL-C profile (LDL-C, IDL-C, and VLDL-C combined) is often elevated (29,119). Patients with diabetes often have a higher proportion of the atherogenic small, dense LDL-C pattern B (119).

Goals of Therapy

Because available data show that intervention benefits these patients, and because of the high CAD risk and mortality in this population, aggressive intervention is warranted for all patients with diabetes and dyslipidemia,

whether or not they have established CAD (28,29, 118,119). The goals of therapy for all patients with diabetes should reflect the strictest goals previously outlined for patients with established CAD. The lipid targets for all patients with type 2 diabetes mellitus and dyslipidemia are presented in Table 17.

Nonpharmacologic Intervention

For achievement of the recommended lipid targets, management of the hyperglycemia, nutrition therapy, weight reduction in overweight patients, and increased physical activity are essential. Nutrition therapy, weight loss, and daily physical activity for 30 minutes or more will often decrease insulin resistance, decrease plasma triglyceride and VLDL levels, increase HDL-C, and lower LDL-C 15 to 25 mg/dL (29).

Nutrition Therapy

Enlistment of the assistance of a registered dietitian is strongly recommended. In general, the patient must initially reduce total fat intake to <30% of total calories, with <10% saturated fat (AHA Step I diet; see Table 7), and

control caloric intake to maintain weight if lean or reduce weight if overweight. The patient should increase the intake of soluble fiber and, to compensate for the reduction in saturated fat, increase complex carbohydrates or monounsaturated fats (29). If weight loss is a goal, a high-carbohydrate diet may be effective, although control of energy intake seems more important. One review suggests that a moderate-carbohydrate + moderate-fat diet may be more effective for both weight loss and lipid control than a high-carbohydrate + low-fat diet in patients with diabetes (293). In addition, because a high-carbohydrate intake can increase plasma triglycerides, the patient should select foods containing complex carbohydrates with a low glycemic index (that is, with low glucose-raising potency) (29,117). If weight loss is not needed, a diet higher in monounsaturated fats with a lower carbohydrate content of 50 to 55% of total calories may produce better metabolic effects (117). If lipid goals are not achieved in 3 months with use of the Step I diet, implementation of the Step II diet (modified as needed, depending on the importance of weight loss) is recommended (Table 7) (117).

Physical Activity

Physical activity should be of moderate intensity, 30 to 45 minutes in duration, and performed 3 to 5 times a week while the pulse rate is monitored to ensure target levels are achieved. It is important to use caution and to supervise physical activity programs for patients who have complications that place them at risk while exercising. At the physician’s discretion, patients at risk may be tested for “silent” ischemia or myocardial disease or for labile hypertension exacerbated by physical activity. Extremity ulceration, peripheral neuropathy, or deformity may limit or result from a physical activity program.

Duration of Nonpharmacologic Intervention

Physical activity and nutrition therapy can be pursued for 6 months in an attempt to achieve lipid goals in patients without established CAD, unless the LDL-C level is >25 mg/dL above the goal. In such a case, pharmacotherapy can be instituted as early as 3 months after initiation of physical activity and nutrition therapy because diet and exercise are not expected to lower the LDL-C level by more than 15 to 25 mg/dL (29). In patients with established disease, physical activity, nutrition therapy, and pharmacotherapy should be initiated concurrently.

Pharmacotherapy

Therapy with glucose-lowering agents is an important element of management of type 2 diabetes and, in most cases, should be initiated before specific lipid-lowering pharmacotherapy. Triglyceride levels usually decline with better glucose control, and optimal glycemic control may decrease LDL-C levels by 10 to 15% (29). Metformin has a small but favorable effect on triglyceride and HDL-C levels. The United Kingdom Prospective Diabetes Study

(UKPDS) (294) demonstrated that agents used to control blood glucose (including sulfonylureas, metformin, and insulin) did not increase the risk of cardiovascular events. In fact, metformin has been associated with a reduced rate of cardiac events in obese patients with diabetes (294). The thiazolidinediones, or “glitazones,” have a variable effect on lipid factors, depending on the baseline triglyceride level and the particular agent (295,296). The glitazones generally increase the LDL-C level but not the LDL-C/HDL-C ratio, and evidence indicates that they may increase the proportion of the large, less atherogenic LDL-C subfractions (297). Case 6 illustrates use of a combined weight loss and glucose control program for successful management of hypertriglyceridemia in a young patient with type 2 diabetes mellitus (Table 18).

Nevertheless, lipid levels rarely normalize with glucose-lowering therapy because the magnitude of plasma glucose control is not directly proportionate with that of the lipid control (117,119). When glucose control is not achieved or the lipid profile fails to normalize within 4 to 6 months, treatment with appropriately selected lipid-lowering agents is warranted. *Any further delay is inappropriate.* Because of the propensity for these patients to carry the small, dense LDL, a borderline or normal LDL-C level should not obscure the need for pharmacotherapy (119). The choice of therapy should be based on the nature of the dyslipidemia and the special needs of the patient with diabetes.

Hypercholesterolemia


For the patient with hypercholesterolemia as the primary lipid disorder, statins are recommended (29,116, 117). Statins are generally well tolerated, do not affect glycemic control, and have been shown to have equivalent lipid-lowering properties in patients with and those without diabetes. In a limited trial of patients with type 2 diabetes mellitus, lovastatin lowered total cholesterol levels by up to 26%, LDL-C levels by 28%, and triglyceride

Table 17
Lipid Targets for Patients
With Type 2 Diabetes Mellitus
and Dyslipidemia (29,120)*

Plasma lipid	Target (mg/dL)	
	Acceptable	Ideal
Triglyceride	<200	<150
Total cholesterol	<200	<170
LDL-C	<130	<100
Non-HDL-C†	<160	<130
HDL-C	>35	>45

*HDL-C = high-density lipoprotein cholesterol;
LDL-C = low-density lipoprotein cholesterol.
†Total serum cholesterol minus HDL-C.

Table 18
Case 6: 31-Year-Old Man With Type 2 Diabetes Mellitus and Hypertriglyceridemia†**

Weight (lb)	Lipid value (mg/dL)				TC/HDL-C ratio	Non- HDL-C	HbA _{1c} (%)	Management
	TC	TG	HDL-C	LDL-C				
283	 Glipizide XL 10 mg
263	260	682	31	...	8.4	229	7.5	
243	159	131	43	90	3.7	116	6.1	

*CAD = coronary artery disease; HbA_{1c} = glycosylated hemoglobin; IW = ideal weight; PE = physical examination. For explanations of other abbreviations, see Table 12.

†Patient, who was an ex-smoker, also had dry mouth and polyuria. No hypertension. No family history of early CAD. PE: 74 inches tall, 263 lb (IW = 195 lb).

Comment: This young man, with type 2 diabetes mellitus, was able to manage his hypertriglyceridemia through weight loss and glucose control by using a sulfonylurea. Currently, an orally administered antidiabetic agent such as metformin would be preferable to a sulfonylurea because of its superior ability to lower triglyceride levels and its beneficial effect on weight maintenance or weight loss.

levels by 31% without affecting glycemic control and with no significant change in HDL-C levels (298). Subgroup analyses of patients with type 2 diabetes mellitus from the CARE and 4S intervention trials have clearly shown that statin therapy reduced CAD events in patients with diabetes and existing CAD to a degree equal to or greater than that in patients without diabetes regardless of baseline LDL-C level (121,122).

Patients with substantially increased LDL-C levels without concomitant hypertriglyceridemia who have failed to reach the LDL-C goal with use of maximal statin dosages may respond to a bile acid sequestrant or a combination of a low-dose statin and a bile acid sequestrant. In addition to lowering LDL-C, bile acid sequestrants may modestly improve glycemic control (120). Because these agents can increase triglyceride levels, they should be used cautiously in this population. In one limited study of patients with type 2 diabetes mellitus with triglyceride levels <300 mg/dL, cholestyramine decreased LDL-C levels by 28% but increased triglyceride levels 13.5% (299).

Niacin monotherapy has been “relatively contraindicated” in patients with type 2 diabetes mellitus (29). This recommendation, however, is based on a study of patients with type 2 diabetes mellitus, in which mean plasma glucose levels increased 16% (from 7.8 to 9.1 mmol/L) and glycosylated hemoglobin concentrations increased 21% during therapy with a high daily dosage (4.5 g) of short-acting niacin (300). Lower dosages may possibly have a lesser effect on glycemia while still producing a beneficial effect on lipid levels (301). Therefore, lower-dose niacin can be used cautiously in some patients with type 2 diabetes mellitus. The physician must carefully monitor glucose levels and decide whether the lipid-lowering benefits outweigh any glucose-raising effect.

Hypertriglyceridemia With or Without Low HDL-C

Fibrates are the agents of choice for treating primary or isolated hypertriglyceridemia when efforts to control plasma glucose fail to lower triglyceride levels (117, 120,123). Both gemfibrozil and fenofibrate can decrease plasma triglyceride levels and increase HDL-C levels in patients with type 2 diabetes mellitus without affecting glycemic control (120,123); fenofibrate can also reduce total cholesterol and LDL-C levels in these patients (123). In a subgroup analysis of 135 men with diabetes who participated in the Helsinki Heart Study for primary prevention, treatment with gemfibrozil decreased coronary events 68% in the study population with diabetes versus 34% in the total population (267). Although this difference was not statistically significant because of the small numbers of events, these results suggest a trend. Glycemic control was unchanged (267). In addition, gemfibrozil has been associated with a statistically significant 24% reduction in cardiovascular events in patients with diabetes and CAD (64).

Combined Hypercholesterolemia and Hypertriglyceridemia

For patients with diabetes and increased levels of both cholesterol and triglycerides, aggressive glycemic control plus high-dose statin or fibrate therapy should be considered (29). If this approach fails to achieve the lipid goals, a combination of a statin plus fibrate or a statin plus low-dose niacin may be considered for selected patients with type 2 diabetes mellitus and severe hypertriglyceridemia (29,120). These combinations can achieve notable reductions in non-HDL-C and increases in HDL-C levels (120). This combination of statin and fibrate increases the risk of myopathy (>5%), although the myopathy is rarely severe. The presence of renal disease may considerably increase

the risk of myopathy (28,178). It should be avoided in patients with increased creatinine levels. Careful monitoring is essential.

DYSLIPIDEMIA IN PEDIATRIC PATIENTS

Because of the mounting evidence that atherosclerosis begins early in life (205-207) and that the severity of early lesions is related to serum lipid levels (206,208-210), there is growing consensus that primary preventive nutrition is warranted in very young subjects (125-131). Nevertheless, the most effective approaches to screening for and treatment of dyslipidemia in the pediatric population are far from clear and remain controversial. This section of the guidelines reviews recent evidence that is beginning to illuminate these areas of controversy and provides recommendations based on this evidence.

Primary Preventive Nutrition

A decade ago, experts almost universally agreed that low-fat diets were inappropriate for whole populations of children because of a concern that fat restriction could limit growth and intake of important vitamins and minerals (127,302). Low-fat diets were generally reserved for the occasional, very-high-risk pediatric patient (127). Since then, however, clinical studies have firmly demonstrated that normal growth and adequate or improved micronutrient intake can occur in children and adolescents who consume low-fat diets, provided energy needs are met with a variety of alternative, nutritious foods (126,128, 142,303-311). As a result, and because it is commonly believed that children need to be "imprinted" early with healthy lifestyle habits (130), the AHA Step I diet is recommended for all healthy children >2 years old (see Table 7) (131).

Universal Versus Targeted Screening

Currently, consensus groups emphasize targeted screening for children and adolescents (131-133,312). AACE agrees that physicians should screen plasma total cholesterol, LDL-C, and triglyceride levels of children >2 years old who have a family history of premature CAD or dyslipidemia (or both) (131,132). AACE also believes that children >2 years old and adolescents should be screened for dyslipidemia when they smoke, have hypertension, are overweight or obese, or have diabetes (126,133). The Bogalusa Heart Study showed that the severity of asymptomatic coronary and aortic atherosclerosis in young people increases with the number of these coexisting risk factors (313). Furthermore, AACE recommends screening for dyslipidemia in *all adolescents >16 years of age* (126, 134). Targeted screening misses many children with high plasma cholesterol levels (129,134); this more comprehensive approach will disclose a greater proportion of young adults with increased cholesterol or LDL-C levels (134).

Several important points must be considered when the lipid profile is interpreted in children and adolescents:

- *Lipid levels fluctuate during childhood and adolescence.* In Caucasian boys, plasma cholesterol normally peaks before puberty, between the ages of 8 and 11 years, and often declines profoundly along with HDL-C during puberty (314).
- *Low HDL-C may not have the same implications in children as it does in adults.* More than half of the children with low HDL-C levels have normal HDL-C levels when they become adults (136,137). In addition, low HDL-C level is not a hallmark of insulin resistance syndrome in children; rather, obesity and hypertriglyceridemia are the best predictors of this syndrome (136,138).
- *Lipid levels naturally vary by gender.* Girls tend to have higher plasma cholesterol levels than do boys throughout childhood and adolescence (129).

Generally, an LDL-C level <110 mg/dL is acceptable in pediatric patients (131). Therefore, the lipid screen should be repeated and verified when the LDL-C level exceeds 110 mg/dL (131). Nutrition therapy, physical activity, and risk factor management are warranted for a verified LDL-C of 110 to 129 mg/dL; more intensive nutrition therapy and pharmacotherapy may also be warranted in some pediatric patients when LDL-C is \geq 130 mg/dL (131).

Intervention

As with dyslipidemia in adult patients, dyslipidemia in pediatric patients necessitates global risk factor management and lifestyle counseling. This holistic approach is essential for children and adolescents, for several reasons. First, in pediatric patients with dyslipidemia, drug therapy should be avoided when possible and is usually reserved for those with genetic or severe dyslipidemias. Second, adverse habits such as smoking and physical inactivity synergistically degrade serum lipoprotein profiles in young adults (315). A 6-year study of adolescents showed that those who maintained a high level of physical activity during transition into adulthood had higher HDL-to-total cholesterol ratios, lower serum triglyceride and serum insulin concentrations, and thinner skinfolds than those who remained physically inactive (316). Finally, as mentioned earlier, many authorities believe that lifestyle intervention is most effective early in life, when behavioral habits are being established (151,317).

Nutrition Therapy

Clinical studies have shown that low-fat diets can reduce total cholesterol level and have a significant but modest effect on LDL-C level in pediatric populations (129,136,139,140,318). The effect on LDL-C is only mod-

erate, likely because LDL-C concentrations in children with hyperlipidemia are primarily a reflection of severity of disease (136,139). Of these dietary studies, two were major prospective controlled trials (141,142). One showed a modest reduction in LDL-C after 3 years in pubertal children 8 to 10 years of age who received 28% of calories from fat, in comparison with children who consumed 33 to 34% of calories from fat (141). The other study showed a significant reduction of total cholesterol level in boys but not in girls (142).

The following factors should be considered when a low-fat diet is prescribed for children or adolescents:

- *Total cholesterol and HDL-C levels are positively correlated until the age of 20 years, and low-fat diets that decrease total cholesterol levels have been associated with HDL-C reductions* (141,142). This finding, considered with the fact that low-fat diets do not usually yield substantial LDL-C reductions, may be clinically important because a reduction in HDL-C that is not associated with a similar LDL-C reduction may be atherogenic (310). Data from a cross-sectional study of 67 children with hypercholesterolemia suggest, however, that HDL-C reductions can be avoided in children consuming low-fat diets by limiting the intake of simple sugars but not necessarily of complex carbohydrates (136,143).
- *Increased intake of carbohydrates may increase plasma triglyceride concentrations in children* (143). For children with hypertriglyceridemia, high intake of carbohydrate is not recommended.
- *Fish oil supplements have a profound effect on serum triglyceride levels in children* and have been used in pediatric patients with end-stage renal insufficiency (144).
- *Studies consistently show that water-soluble fiber does not reduce serum cholesterol levels in children as it does in adults* (145-148).

More aggressive nutrition therapy (AHA Step II diet) may be attempted when a child or adolescent with dyslipidemia fails to respond to the Step I diet. Close monitoring of all lipid levels and nutritional intake is imperative, however, to ensure that changes in the lipid profile are beneficial and that intake of both energy and nutrients is adequate. Children and young adults with low fat intake may be at risk for low intake of fat-soluble vitamins or minerals (151).

Drug Therapy

Evidence-based pharmacotherapeutic options for pediatric patients are limited because few lipid management trials have been conducted in this population. The potential long-term effects of lipid-lowering drug therapy on growth, development, and biochemical variables are unclear. For this reason, the prescribing decisions must be

based on empiric and indirect evidence (129) and the needs of the patient. When the need for lipid-lowering drug therapy is assessed in pediatric patients, the following factors must be considered:

- The effectiveness of delaying treatment until adulthood
- The nature of the pediatric dyslipidemia

Beginning treatment in adulthood can halt atherogenesis and may induce regression in some patients with polygenic and familial combined hyperlipidemia (149,150). There is general consensus that children and adolescents who have genetic dyslipidemias associated with CAD (familial hypercholesterolemia and familial combined hyperlipidemia) should be treated with lipid-lowering drugs, when needed, to achieve LDL-C levels <130 mg/dL (151,152). Clinical evidence shows that these children often experience a premature cardiovascular event as early as the third decade of life and that delaying treatment into adulthood may not reverse the major atherogenic effects of the childhood dyslipidemia (152,319-322). Although accurate detection of genetic dyslipidemia is difficult, a recent study designed to assess this diagnostic problem revealed that a persistent increase in LDL-C coupled with a parental history of dyslipidemia is a good predictor of the presence of an underlying genetic disorder (153).

Bile Acid Sequestrants.—Cholestyramine and colestipol are the only approved drugs for treating hypercholesterolemia in children. They are not absorbed from the gastrointestinal tract and are therefore not associated with systemic toxicity or other serious adverse or toxic effects (154-156). Pediatric studies have generally demonstrated LDL-C reductions of 15 to 20% with bile acid sequestrant therapy, and recent evidence shows that these reductions are possible with relatively low dosages of cholestyramine (8 g/day) or colestipol (10 g/day) (154, 157). For this reason, lower dosages are recommended for pediatric patients regardless of body weight, and the physician should consider initiating therapy with <8 g/day of cholestyramine or <10 g/day of colestipol to maximize tolerability (154,157,323).

Bile acid sequestrants should not be used in children with hypertriglyceridemia (129,158). These agents should be prescribed in conjunction with multivitamin supplements, including folic acid and cholecalciferol, because these nutrients may decrease when bile acid sequestrants are given to children (129,154,157).

Other Agents.—Several recent studies of statin therapy in children demonstrated significant LDL-C reductions (324-329). A recent controlled, 1-year study of 132 adolescent boys with heterozygous familial hypercholesterolemia (329) showed that lovastatin, in dosages from 10 to 40 mg/day, decreased LDL-C levels by 17 to 27% over placebo. Clinical and biochemical assessments indicated that therapy did not significantly alter growth, hormonal, or nutritional status (329). Nevertheless, longer-term studies are needed to assess the potential effects of statins

on these variables before universal recommendations can be made for this population. Some investigators have suggested that small doses of statins may be useful for boys with severely increased cholesterol levels who are approaching the end of the maturation process, as a supplement to nutrition and resin therapy (159,160).

Additional study is also needed before fibrates can be recommended for pediatric patients. Niacin is not recommended for this population because of a lack of tolerability data and the potential for adverse effects (161).

FOLLOW-UP AND MONITORING

For all patients receiving intervention of any type, the lipid status should be assessed 4 to 6 weeks after initiation of therapy and again at 6-week intervals until the treatment goal is reached (27). At each 6-week interval, the physician should monitor the response to and side effects of therapy. Thereafter, once the lipid goal has been achieved, the patient should be seen in consultation at 6- to 12-month intervals. The precise interval depends on patient adherence to therapy and the consistency of the lipid profile. If adherence is a concern or if the lipid profile is unstable, the patient will likely benefit from a visit every 6 months. In addition, certain clinical circumstances warrant more frequent evaluation. *The lipid status should always be reassessed in the following situations:*

- Control of diabetes has deteriorated over time
- The patient has been prescribed a new drug known to affect lipid levels
- The patient's cardiovascular status has changed
- The patient has gained considerable weight
- A recent lipid profile has revealed an unexpected adverse change in any lipid level
- A new risk factor has been identified

Because of the growing recognition of triglycerides and HDL-C as important lipid factors, both triglyceride and HDL-C levels should be part of each follow-up lipid assessment, along with serum total cholesterol and LDL-C levels. These analyses are especially important in patients with type 2 diabetes mellitus and in those with macrovascular disease. Some patients who have had their LDL phenotype determined may need reanalysis of the phenotype, particularly if their clinical status deteriorates or if lipid-lowering drug therapy has been altered. This reanalysis should be performed only after the patient has received lipid-lowering drug therapy for 3 months or longer.

Consultation with an endocrinologist or lipid specialist is recommended when uncontrolled diabetes and dyslipidemia coexist, when abnormal lipid levels persist despite treatment, or when CAD manifests despite favorable lipid levels. The treating physician must always keep in mind the considerably accelerated risk of coronary and vascular disease that diabetes confers, even when the patient has normal lipid levels. New therapies for type 2 diabetes mellitus can contribute to reduction of CAD risk by reversing insulin resistance and favorably affecting the lipid profile.

COST-TO-BENEFIT CONSIDERATIONS

Although clinical trials demonstrate that aggressive lipid-lowering therapy is efficacious, the cost of this aggressive approach has been a major concern. Sufficient evidence is now available, however, to show that drug treatment of dyslipidemia is cost-effective for all men and women with established CAD and for primary prevention when the patient has dyslipidemia and other risk factors (Fig. 6) (162-165). Because of the accelerated rate of atherosclerosis in patients with type 2 diabetes mellitus, aggressive and early treatment appears to be cost-effective in these patients.

Overall Cost-Effectiveness

Usually, economic researchers evaluate CAD interventions on the basis of the *cost per year of life saved*, a benchmark that considers the cost difference between the new therapy and any medical treatment avoided because of the new therapy, as well as any increased survival resulting from the new therapy (165). Generally, any intervention that costs \leq \$40,000 to \$50,000 per year of life saved is considered acceptable (164,165). This is a universally accepted benchmark for interventions such as long-term hemodialysis, breast cancer screening, percutaneous transluminal coronary angioplasty, and CABG procedure (165). As shown in Figure 6, statin therapy compares very favorably with other well-accepted medical interventions for CAD and is well within the acceptable range for patients who, according to these AACE guidelines, qualify for drug treatment. Cost-effectiveness has also been demonstrated for drugs in all other major lipid-lowering drug classes (165).

As shown in Figure 6, the cost-effectiveness of statin therapy for primary prevention is more variable than that for secondary prevention and depends on age, gender, and risk level. As would be expected, the younger the patient and the fewer the risk factors, the less cost-effective the primary prevention therapy. For example, one economic study demonstrated that the cost-effectiveness of primary prevention with lovastatin (20 mg/day) for men from 55 to 64 years old with cholesterol levels \geq 300 mg/dL ranged from \$20,200 per year of life saved for three risk factors to \$78,300 per year of life saved for no risk factors (1993 dollars) (164,330). In this same study, primary prevention was more expensive for women than for men but was still within the acceptable range (\$40,000 per year of life saved) for women with cholesterol levels \geq 300 mg/dL and multiple risk factors (164,330).

Clinical Application of Cost-Effectiveness Data

Although these economic data are useful for guiding treatment decisions, they should not dictate the treatment approach. Prescribing statin monotherapy and relying on an isolated cholesterol goal for all patients with dyslipidemia may ignore the heterogeneity of certain patients

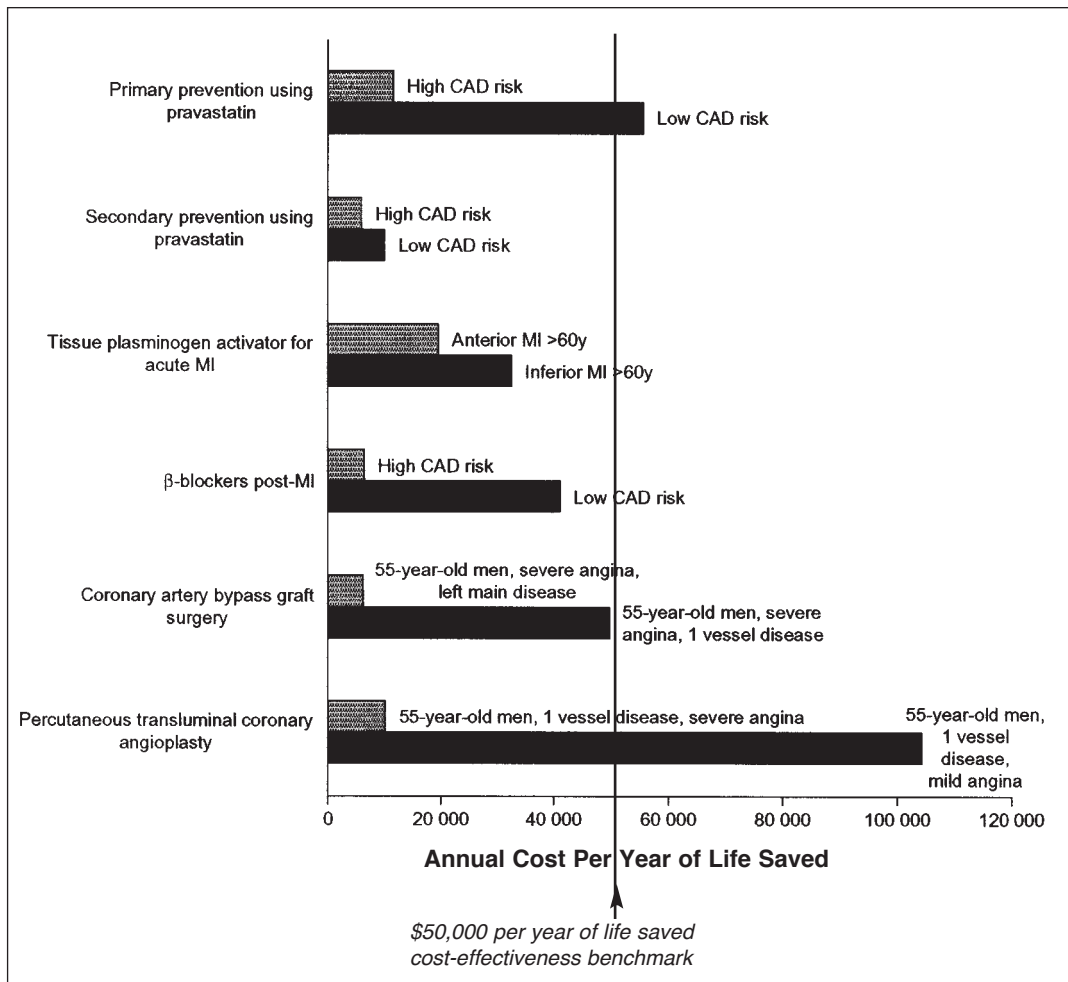


Fig. 6. Comparative cost-effectiveness of different medical strategies for management of coronary artery disease (CAD). MI = myocardial infarction. Modified from Hay et al. (165). With permission.

with CAD (34,165). To be clinically effective and therefore cost-effective, any lipid-lowering drug therapy (whether for primary or secondary prevention) must be tailored to each patient’s dyslipidemia and risk profile (34).

APPENDIX: OTHER ATHEROGENIC FACTORS

Several non-lipid-associated factors may have an important role in atherogenesis. An overview of the relative risk for future MI among healthy middle-aged men in the Physicians’ Health Study, based on Lp(a), homocysteine, and fibrinogen levels, is presented in Figure 7. Fibrinogen, in particular, was found to be a strong marker of CAD risk (44).

Increased Levels of Lp(a)

Production of Lp(a), an LDL variant, is largely a genetic trait and is a strong marker of inherited CAD in Caucasians (35-37). It has been called the “enigmatic particle,” however, because its pathogenic mechanism is

unclear and its concentrations and atherogenicity vary among ethnic groups (331). For example, no correlation has been found between Lp(a) and CAD in African Americans, even though this population generally has Lp(a) levels twice as high as those in Caucasians (332-334).

Lp(a) screening of the *general population* is not recommended because available prospective data demonstrating that Lp(a) levels improve the predictive value of total and HDL-C levels are inconsistent (44,331). Lp(a) measurement may be useful, however, for ascribing risk in Caucasians with CAD, a family history of CAD, or known metabolic disorders (44,331), as well as in adopted persons with an unknown family history. These patients who have Lp(a) values above the 80th percentile should be considered at increased risk for CAD (331).

Lp(a) is not influenced by diet or physical activity, but established therapies, including niacin and estrogen, can lower Lp(a) levels (331,335). No published prospective studies, however, have shown that Lp(a) reductions independently decrease coronary events. In addition, substantial lowering of LDL-C levels neutralizes the risk

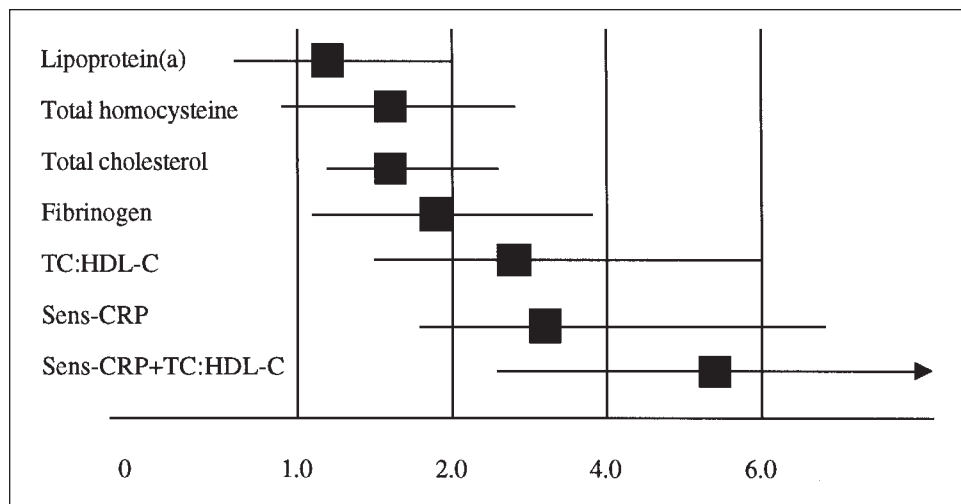


Fig. 7. Relative risk for future myocardial infarction in healthy middle-aged men in the Physicians' Health Study. Risks were computed for men in the top quartile compared with those in the bottom quartile for each marker. *HDL-C* = high-density lipoprotein cholesterol; *Sens-CRP* = sensitive C-reactive protein; *TC* = total cholesterol. Modified from Ridker (44). With permission.

conferred by increased Lp(a) in men with CAD and elevated LDL-C levels (336-338). Therefore, aggressive management of all other risk factors should take priority, and targeted Lp(a) lowering should be reserved for the following special situations:

- *Postmenopausal women with high Lp(a).* The Lp(a) level increases in menopausal women by about 20% (35). Estrogen therapy should be considered for postmenopausal women with high Lp(a) because ERT has been shown to reduce Lp(a) levels (331).
- *Patients with very high Lp(a) levels and a definite family history of CAD.* The physician should strongly consider targeting an increased Lp(a) level in this situation but should also bear in mind that Lp(a) reduction in patients with isolated Lp(a) elevations has not been assessed in clinical trials. Before niacin or estrogen is prescribed, secondary causes of high Lp(a) should be evaluated and addressed. These factors include hypothyroidism, renal disease, consumption of *trans* fatty acids, and growth hormone treatment in some patients (339).

Factors Related to Blood Clotting

Fibrinogen

An increased fibrinogen level is a strong, established marker of CAD risk in men and women (38-41), and it seems to increase the risk synergistically in patients with elevated LDL-C levels and hypertension (38). Prospective studies consistently show that adding fibrinogen to the lipid evaluation can significantly improve the prediction of CAD risk over the lipid evaluation alone (44). As with other novel CAD markers, however, fibrinogen evaluation should be reserved for patients with known metabolic disorders or

for those with a personal or family history of premature CAD (44). Routine fibrinogen screening of the general population is not recommended for several reasons:

- *Nonstandardized assays.* Currently, no universally accepted assay is available for measuring fibrinogen levels (40).
- *Lack of a universally accepted predictive value.* As with Lp(a), fibrinogen levels vary among ethnic groups, and some groups with high fibrinogen levels have a low incidence of cardiovascular disease (41).
- *Increased fibrinogen levels can result from many factors that may or may not relate to CAD,* including chronic infection, stress, smoking, insulin levels, oral contraceptive use, and season of the year (38,39,41).
- *Lowering of fibrinogen levels has not been shown effective in reversing or preventing CAD.* Reduction of fibrinogen levels with anicrod, an experimental fibrinogen-lowering drug derived from the venom of the pit viper snake, has not reversed or prevented CAD (41). In addition, although bezafibrate can reduce progression of coronary atherosclerosis, this outcome has not been independently linked with fibrinogen reductions.

Plasminogen Activator Inhibitor-1

Available data suggest that PAI-1, the principal inhibitor of the plasminogen activators, may be a risk factor for CAD (42). Studies of patients with diabetes suggest that a disproportionate PAI-1 elevation may result from hyperinsulinemia and hyperproinsulinemia (340). Studies also suggest that glycemic control and insulin sensitizers may help attenuate vascular damage induced by increased PAI-1 levels, through their PAI-1-lowering effects (340).

To date, however, not enough prospective data in healthy people are available to determine whether a reduced fibrinolytic potential increases CAD risk (42,44). In addition, assay conditions for PAI-1 are not fully standardized. For these reasons, general PAI-1 screening is not currently recommended.

Hyperhomocysteinemia

Homocysteine, a metabolite of methionine, is highly reactive and may damage the vessel wall in several ways and thereby induce intimal fibrosis (182,183). In general, prospective clinical studies of patients with CAD or risk factors for CAD have consistently associated increased levels of serum homocysteine (>15 $\mu\text{mol/L}$) with cardiovascular events (182,341). One large, controlled, prospective study in patients with CAD showed hyperhomocysteinemia to be a strong and independent predictor of coronary mortality (43). Total plasma homocysteine levels, however, may increase *after* acute MI (342-345), and results of prospective studies of healthy subjects are less consistent (44,182,341). Two recent studies, in particular, did not show an association between hyperhomocysteinemia and *subsequent* disease in healthy subjects (346, 347).

On the basis of current evidence, then, a comprehensive risk evaluation *in patients with ischemia*—especially those with unremarkable lipid levels—should include determination of total homocysteine levels (182). These patients with hyperhomocysteinemia may benefit from nutrition therapy and vitamin B tablet supplementation (348-350).

Markers of Inflammation

C-reactive protein is a sensitive marker of inflammation, and prospective data from epidemiologic studies of healthy men indicate that it improves the predictive value of lipid variables when the risk of occurrence of a first MI is being determined (44,45). One recent study showed that patients with unstable angina and increased C-reactive protein levels at dismissal from the hospital had a greater risk of refractory angina, MI, and death during the subsequent 90 days than did patients with normal levels at dismissal (46). The elevation in C-reactive protein is thought to reflect evolving inflammation at the coronary plaque or myocardial necrosis.

No available therapies specifically reduce C-reactive protein levels, but one controlled trial suggests that patients with underlying inflammation (as evidenced by the C-reactive protein level) may be responsive to preventive therapy with pravastatin (351). For this reason, a sensitive C-reactive protein screening may be considered for patients with dyslipidemia, unstable angina, CAD, a family or personal history of CAD, or any combination of these factors. The Food and Drug Administration recently approved a highly sensitive assay for C-reactive protein.

REFERENCES

1. **Ginsberg HN, Goldberg IJ.** Disorders of lipoprotein metabolism. In: Fauci AS, Braunwald E, Isselbacher KJ, et al., eds. *Harrison's Principles of Internal Medicine*. 14th ed. New York: McGraw-Hill, 1998; 2138-2149.
2. **Steinberg D, Witztum JL.** Lipoproteins and atherogenesis: current concepts. *JAMA*. 1990;264:3047-3052.
3. **American Heart Association.** 1999 heart and stroke statistical update. Available at: <http://www.americanheart.org/>.
4. **Rosamond WD, Chambless LE, Folsom AR, et al.** Trends in the incidence of myocardial infarction and in mortality due to coronary artery disease, 1987 to 1994. *N Engl J Med*. 1998;339:861-867.
5. **American Heart Association.** *Heart and Stroke Facts, 1995 Statistical Supplement*. Dallas, TX: American Heart Association, 1995.
6. **Gorelick PB, Schneck M, Berglund LF, Feinberg W, Goldstone J.** Status of lipids as a risk factor for stroke. *Neuroepidemiology*. 1997;16:107-115.
7. **Vigna GB, Fellin R.** Dyslipidemia in peripheral vascular disease. *Curr Opin Lipidol*. 1996;7:254-259.
8. **Rubinfeld M, Coletti AT, Mosca L.** Treatment strategies for management of serum lipids: lessons learned from lipid metabolism, recent clinical trials, and experience with the HMG CoA reductase inhibitors. *Prog Cardiovasc Dis*. 1998;41:95-116.
9. **Danias PG, O'Mahony S, Radford MJ, Korman L, Silverman DI.** Serum cholesterol levels are undervalued and undertreated. *Am J Cardiol*. 1998;81:1353-1356.
10. **Eisenberg DA.** Cholesterol lowering in the management of coronary artery disease: the clinical implications of recent trials. *Am J Med*. 1998;104(2A):2S-5S.
11. **Assmann G, Schulte H, Cullen P.** New and classical risk factors—the Münster Heart Study (PROCAM). *Eur J Med Res*. 1997;2:237-242.
12. **Betteridge DJ.** Lipid management: past, present, and future. *Br J Clin Pract Suppl*. 1996;77A:1-10.
13. **Van Horn L, Kavey RE.** Diet and cardiovascular disease prevention: what works? *Ann Behav Med*. 1997;19:197-212.
14. **Krauss RM.** Triglycerides and atherogenic lipoproteins: rationale for lipid management. *Am J Med*. 1998;105(1A):58S-62S.
15. **Ballantyne CM.** Low-density lipoproteins and risk for coronary artery disease. *Am J Cardiol*. 1998;82:3Q-12Q.
16. **Stampfer MJ, Krauss RM, Ma J, et al.** A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA*. 1996;276:882-888.
17. **Gardner CD, Fortmann SP, Krauss RM.** Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA*. 1996;276:875-881.
18. **Harper CR, Jacobson TA.** New perspectives on the management of low levels of high-density lipoprotein cholesterol. *Arch Intern Med*. 1999;159:1049-1057.
19. **Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB.** Incidence of coronary artery disease and lipoprotein cholesterol levels: the Framingham Study. *JAMA*. 1986;256:2835-2838.

20. **Jacobs DR Jr, Mebane IL, Bangdiwala SI, Criqui MH, Tyroler HA.** High density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: the follow-up study of the Lipid Research Clinics Prevalence Study. *Am J Epidemiol.* 1990;131:32-47.
21. **Kannel WB, Castelli WP, Gordon T.** Cholesterol in the prediction of atherosclerotic diseases: new perspectives on the Framingham Study. *Ann Intern Med.* 1979;90:85-91.
22. **Gotto AM Jr.** Prognostic and therapeutic significance of low levels of high-density lipoprotein cholesterol: current perspectives. *Arch Intern Med.* 1999;159:1038-1040.
23. **Jeppesen J, Hein HO, Suadicani P, Gyntelberg F.** Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study [published erratum appears in *Circulation.* 1998;97:1995]. *Circulation.* 1998;97:1029-1036.
24. **Assmann G, Cullen P, Schulte H.** The Münster Heart Study (PROCAM): results of follow-up at 8 years. *Eur Heart J.* 1998;19(Suppl A):A2-A11.
25. **LaRosa JC.** Triglycerides and coronary risk in women and the elderly. *Arch Intern Med.* 1997;157:961-968.
26. **Castelli WP.** The triglyceride issue: a view from Framingham. *Am Heart J.* 1986;112:432-437.
27. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA.* 1993;269:3015-3023.
28. **Grundey SM.** Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. *Am J Cardiol.* 1999;83:25F-29F.
29. **Haffner SM.** Management of dyslipidemia in adults with diabetes [American Diabetes Association position statement]. *Diabetes Care.* 1998;21:160-178.
30. **Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB.** Prediction of coronary disease using risk factor categories. *Circulation.* 1998;97:1837-1847.
31. **Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB.** Clustering of metabolic factors and coronary artery disease. *Arch Intern Med.* 1999;159:1104-1109.
32. **Shape Up America! and the American Obesity Association.** *Guidance for Treatment of Adult Obesity.* Bethesda, MD: Shape Up America!, November 1996.
33. **Grundey SM, Balady GJ, Criqui MH, et al. (American Heart Association).** Primary prevention of coronary heart disease: guidance from Framingham; a statement for healthcare professionals from the AHA Task Force on Risk Reduction. *Circulation.* 1998; 97:1876-1887.
34. **Superko HR.** Did grandma give you heart disease? The new battle against coronary artery disease. *Am J Cardiol.* 1998;82(9A):34Q-46Q.
35. **Austin MA, Hokanson JE.** Epidemiology of triglycerides, small dense low-density lipoprotein, and lipoprotein(a) as risk factors for coronary heart disease. *Med Clin North Am.* 1994;78:99-115.
36. **Seman LJ, McNamara JR, Schaefer EJ.** Lipoprotein(a), homocysteine, and remnantlike particles: emerging risk factors. *Curr Opin Cardiol.* 1999;14:186-191.
37. **Gazzaruso C, Garzaniti A, Geroldi D, Finardi G.** Genetics and cardiovascular risk: a role for apolipoprotein(a) polymorphism. *Cardiologia.* 1999;44:347-354.
38. **Montalescot G, Collet JP, Choussat R, Thomas D.** Fibrinogen as a risk factor for coronary heart disease. *Eur Heart J.* 1998;19(Suppl H):H11-H17.
39. **Folsom AR.** Fibrinogen and cardiovascular risk markers. *Blood Coagul Fibrinolysis.* 1999;10(Suppl 1):S13-S16.
40. **Lowe G, Rumley A.** Clinical benefit of fibrinogen evaluation. *Blood Coagul Fibrinolysis.* 1999;10(Suppl 1):S87-S89.
41. **Mehta P, Mehta JL.** Should fibrinogen be measured routinely in patients with unstable coronary heart disease? *Blood Coagul Fibrinolysis.* 1999;10(Suppl 1): S29-S33.
42. **Wiman B.** Plasminogen activator inhibitor 1 in thrombotic disease. *Curr Opin Hematol.* 1996;3:372-378.
43. **Nygard O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE.** Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med.* 1997;337:230-236.
44. **Ridker PM.** Evaluating novel cardiovascular risk factors: can we better predict heart attacks? *Ann Intern Med.* 1999;130:933-937.
45. **Ridker PM, Glynn RJ, Hennekens CH.** C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation.* 1998;97:2007-2011.
46. **Ferreiros ER, Boissonnet CP, Pizarro R, et al.** Independent prognostic value of elevated C-reactive protein in unstable angina. *Circulation.* 1999;100: 1958-1963.
47. **Gordon DJ, Probstfield JL, Garrison RJ, et al.** High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation.* 1989;79:8-15.
48. **Schechtman G, Patsches M, Sasse EA.** Variability in cholesterol measurements: comparison of calculated and direct LDL cholesterol determinations. *Clin Chem.* 1996;42:732-737.
49. **Superko HR.** Inclusion of lipoprotein subfractions among efficacy parameters. *Am J Cardiol.* 1998;81 (8A):52F-55F.
50. **Rader DJ, Haffner SM.** Role of fibrates in the management of hypertriglyceridemia. *Am J Cardiol.* 1999;83: 30F-35F.
51. **Hulley SB, Rosenman RH, Bawol RD, Brand RJ.** Epidemiology as a guide to clinical decisions: the association between triglyceride and coronary heart disease. *N Engl J Med.* 1980;302:1383-1389.
52. **Ooi TC, Ooi DS.** The atherogenic significance of an elevated plasma triglyceride level. *Crit Rev Clin Lab Sci.* 1998;35:489-516.
53. **Lefebvre PJ, Scheen AJ.** The postprandial state and risk of cardiovascular disease. *Diabet Med.* 1998;15(Suppl 4):S63-S68.
54. **Gotto AM Jr.** Triglyceride as a risk factor for coronary artery disease. *Am J Cardiol.* 1998;82:22Q-25Q.
55. **Boquist S, Ruotolo G, Tang R, et al.** Alimentary lipemia, postprandial triglyceride-rich lipoproteins, and common carotid intima-media thickness in healthy, middle-aged men. *Circulation.* 1999;100:723-728.
56. **Karpe F, Hellenius ML, Hamsten A.** Differences in postprandial concentrations of very-low-density lipoprotein and chylomicron remnants between normotriglyceridemic and hypertriglyceridemic men with and without coronary heart disease. *Metabolism.* 1999;48:301-307.
57. **Patsch JR, Miesenbock G, Hopferwieser T, et al.** Relation of triglyceride metabolism and coronary artery disease: studies in the postprandial state. *Arterioscler Thromb.* 1992;12:1336-1345.

58. **Frick MH, Elo O, Haapa K, et al.** Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia; safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med.* 1987;317:1237-1245.
59. **Rosenson RS.** Beyond low-density lipoprotein cholesterol: a perspective on low high-density lipoprotein disorders and Lp(a) lipoprotein excess. *Arch Intern Med.* 1996;156:1278-1284.
60. **Rosenson RS.** Low levels of high-density lipoprotein cholesterol (hypoalphalipoproteinemia): an approach to management. *Arch Intern Med.* 1993;153:1528-1538.
61. **Lavie CJ, Mailander L, Milani RV.** Marked benefit with sustained-release niacin therapy in patients with "isolated" very low levels of high-density lipoprotein cholesterol and coronary artery disease. *Am J Cardiol.* 1992;69:1083-1085.
62. **Luria MH.** Effect of low-dose niacin on high-density lipoprotein cholesterol and total cholesterol/high-density lipoprotein cholesterol ratio. *Arch Intern Med.* 1988;148:2493-2495.
63. **Vega GL, Grundy SM.** Lipoprotein responses to treatment with lovastatin, gemfibrozil, and nicotinic acid in normolipidemic patients with hypoalphalipoproteinemia. *Arch Intern Med.* 1994;154:73-82.
64. **Rubins HB, Robins SJ, Collins D, et al. (Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group).** Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med.* 1999;341:410-418.
65. **Zafari AM, Wenger NK.** Secondary prevention of coronary heart disease. *Arch Phys Med Rehabil.* 1998;79:1006-1017.
66. **Deedwania PC.** Clinical perspectives on primary and secondary prevention of coronary atherosclerosis. *Med Clin North Am.* 1995;79:973-998.
67. **Schuler G, Hambrecht R, Schlierf G, et al.** Regular physical exercise and low fat diet: effects on progression of coronary artery disease. *Circulation.* 1992; 86:1-11.
68. **Hjermann I, Velve Byre K, Holme I, Leren P.** Effect of diet and smoking intervention on the incidence of coronary heart disease: report from the Oslo Study Group of a randomised trial in healthy men. *Lancet.* 1981;2:1303-1310.
69. **Hjermann I, Holme I, Leren P.** Oslo Study Diet and Antismoking Trial: results after 102 months. *Am J Med.* 1986;80(2A):7-11.
70. **Williams PT, Krauss RM, Vranizan KM, Wood PD.** Changes in lipoprotein subfractions during diet-induced and exercise-induced weight loss in moderately overweight men. *Circulation.* 1990;81:1293-1304.
71. **Wood PD, Stefanick ML, Dreon DM, et al.** Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *N Engl J Med.* 1988;319:1173-1179.
72. **Borgia MC, Medici F.** Perspectives in the treatment of dyslipidemias in the prevention of coronary heart disease. *Angiology.* 1998;49:339-348.
73. **Schaefer EJ.** New recommendations for the diagnosis and treatment of plasma lipid abnormalities. *Nutr Rev.* 1993;51:246-253.
74. **Smith SC Jr, Blair SN, Criqui MH, et al.** Preventing heart attack and death in patients with coronary artery disease [American Heart Association consensus statement]. *Circulation.* 1995;92:2-4.
75. **Van Horn L.** Fiber, lipids, and coronary artery disease: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation.* 1997;95:2701-2704.
76. **Hallikainen MA, Uusitupa MI.** Effects of 2 low-fat stanol ester-containing margarines on serum cholesterol concentrations as part of a low-fat diet in hypercholesterolemic subjects. *Am J Clin Nutr.* 1999;69:403-410.
77. **Gylling H, Miettinen TA.** Cholesterol reduction by different plant stanol mixtures and with variable fat intake. *Metabolism.* 1999;48:575-580.
78. **Gylling H, Puska P, Vartiainen E, Miettinen TA.** Serum sterols during stanol ester feeding in a mildly hypercholesterolemic population. *J Lipid Res.* 1999; 40:593-600.
79. **Miettinen TA, Gylling H.** Regulation of cholesterol metabolism by dietary plant sterols. *Curr Opin Lipidol.* 1999;10:9-14.
80. **Cottrell I, Palumbo PJ.** Wine and alcohol in moderation: ne quid nimis. *Endocr Pract.* 1998;4:65-67.
81. **Klatsky AL, Armstrong MA, Friedman GD.** Alcohol and mortality. *Ann Intern Med.* 1992;117:646-654.
82. **Friedman GD, Klatsky AL.** Is alcohol good for your health? *N Engl J Med.* 1993;329:1882-1883.
83. **Harris WS.** n-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr.* 1997;65(5 Suppl): 1645S-1654S.
84. **Harris WS.** Nonpharmacologic treatment of hypertriglyceridemia: focus on fish oils. *Clin Cardiol.* 1999; 22(6 Suppl):II40-II43.
85. **Durrington PN, Illingworth R.** Lipid-lowering drugs: who gets what? *Curr Opin Lipidol.* 1998;9:289-294.
86. **Stone NJ.** Lipid management: current diet and drug treatment options. *Am J Med.* 1996;101(4A):40S-49S.
87. **Tikkanen MJ.** Statins: within-group comparisons, statin escape and combination therapy. *Curr Opin Lipidol.* 1996;7:385-388.
88. **Mabuchi H, Sakai T, Sakai Y, et al.** Reduction of serum cholesterol in heterozygous patients with familial hypercholesterolemia: additive effects of compactin and cholestyramine. *N Engl J Med.* 1983;308:609-613.
89. **Hagen E, Istad H, Ose L, et al.** Fluvastatin efficacy and tolerability in comparison and in combination with cholestyramine. *Eur J Clin Pharmacol.* 1994;46:445-449.
90. **Jacotot B, Banga JD, Waite R, Peters TK (French-Dutch Fluvastatin Study Group).** Long-term efficacy with fluvastatin as monotherapy and combined with cholestyramine (a 156-week multicenter study). *Am J Cardiol.* 1995;76:41A-46A.
91. **Schrott HG, Stein EA, Dujovne CA, et al.** Enhanced low-density lipoprotein cholesterol reduction and cost-effectiveness by low-dose colestipol plus lovastatin combination therapy. *Am J Cardiol.* 1995;75:34-39.
92. **Dujovne CA, Moriarty PM.** Clinical pharmacologic concepts for the rational selection and use of drugs for the management of dyslipidemia. *Clin Ther.* 1996; 18:392-410.
93. **Jacob BG, Möhrle W, Richter WO, Schwandt P.** Short- and long-term effects of lovastatin and pravastatin alone and in combination with cholestyramine on serum lipids, lipoproteins and apolipoproteins in primary hypercholesterolaemia. *Eur J Clin Pharmacol.* 1992;42:353-358.
94. **Leitersdorf E, Muratti EN, Eliav O, et al.** Efficacy and safety of a combination fluvastatin-bezafibrate treatment for familial hypercholesterolemia: comparative analysis with a fluvastatin-cholestyramine combination. *Am J Med.* 1994;96:401-407.

95. **Davignon J.** Advances in drug treatment of dyslipidemia: focus on atorvastatin. *Can J Cardiol.* 1998;14(Suppl B):28B-38B.
96. **Malloy MJ, Kane JP, Kunitake ST, Tun P.** Complementarity of colestipol, niacin, and lovastatin in treatment of severe familial hypercholesterolemia. *Ann Intern Med.* 1987;107:616-623.
97. **Santamarina-Fojo S, Brewer HB Jr.** The familial hyperchylomicronemia syndrome: new insights into underlying genetic defects. *JAMA.* 1991;265:904-908.
98. **Grundy SM, Cleeman JI, Rifkind BM, Kuller LH (Coordinating Committee of the National Cholesterol Education Program).** Cholesterol lowering in the elderly population. *Arch Intern Med.* 1999;159:1670-1678.
99. **Playford DA, Watts GF.** Management of lipid disorders in the elderly. *Drugs Aging.* 1997;10:444-462.
100. **Miettinen TA, Pyorala K, Olsson AG, et al.** Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). *Circulation.* 1997;96:4211-4218.
101. **Corti MC, Barbato GM, Baggio G.** Lipoprotein alterations and atherosclerosis in the elderly. *Curr Opin Lipidol.* 1997;8:236-241.
102. **Chan P, Huang TY, Tomlinson B, Lee C, Lee YS.** Short-term safety and efficacy of low-dose simvastatin in elderly patients with hypertensive hypercholesterolemia and fasting hyperinsulinemia. *J Clin Pharmacol.* 1997;37:496-501.
103. **LaRosa JC, Applegate W, Crouse JR III, et al.** Cholesterol lowering in the elderly: results of the Cholesterol Reduction in Seniors Program (CRISP) pilot study. *Arch Intern Med.* 1994;154:529-539.
104. **Santinga JT, Rosman HS, Rubenfire M, et al.** Efficacy and safety of pravastatin in the long-term treatment of elderly patients with hypercholesterolemia. *Am J Med.* 1994;96:509-515.
105. **Lansberg PJ, Mitchel YB, Shapiro D, et al.** Long-term efficacy and tolerability of simvastatin in a large cohort of elderly hypercholesterolemic patients. *Atherosclerosis.* 1995;116:153-162.
106. **Bilheimer DW.** Clinical considerations regarding treatment of hypercholesterolemia in the elderly. *Atherosclerosis.* 1991;91(Suppl):S35-S57.
107. **Carlson LA, Rosenhamer G.** Reduction of mortality in the Stockholm Ischaemic Heart Disease Secondary Prevention Study by combined treatment with clofibrate and nicotinic acid. *Acta Med Scand.* 1988;223:405-418.
108. **Hazzard WR.** Dyslipoproteinemia in the elderly: should it be treated? *Clin Geriatr Med.* 1992;8:89-102.
109. **Wild RA, Grubb B, Hartz A, Van Nort JJ, Bachman W, Bartholomew M.** Clinical signs of androgen excess as risk factors for coronary artery disease. *Fertil Steril.* 1990;54:255-259.
110. **Clifton PM, Noakes M, Nestel PJ.** Gender and diet interactions with simvastatin treatment. *Atherosclerosis.* 1994;110:25-33.
111. **O'Brien T, Nguyen TT.** Lipids and lipoproteins in women. *Mayo Clin Proc.* 1997;72:235-244.
112. **Schrott HG, Bittner V, Vittinghoff E, Herrington DM, Hulley S (HERS Research Group).** Adherence to National Cholesterol Education Program treatment goals in postmenopausal women with heart disease: the Heart and Estrogen/Progestin Replacement Study (HERS). *JAMA.* 1997;277:1281-1286.
113. **Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ.** Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. *JAMA.* 1990;264:3007-3012.
114. **Sacks FM, Pfeffer MA, Moyé LA, et al. (Cholesterol and Recurrent Events Trial Investigators).** The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med.* 1996;335:1001-1009.
115. **Barrett-Connor E, Stuenkel C.** Hormones and heart disease in women: Heart and Estrogen/Progestin Replacement Study in perspective. *J Clin Endocrinol Metab.* 1999;84:1848-1853.
116. **Lewis GF.** Diabetic dyslipidemia: a case for aggressive intervention in the absence of clinical trial and cost effectiveness data. *Can J Cardiol.* 1995;11(Suppl C):24C-28C.
117. **Kim DK, Escalante DA, Garber AJ.** Prevention of atherosclerosis in diabetes: emphasis on treatment for the abnormal lipoprotein metabolism of diabetes. *Clin Ther.* 1993;15:766-778.
118. **O'Brien T, Nguyen TT, Zimmerman BR.** Hyperlipidemia and diabetes mellitus. *Mayo Clin Proc.* 1998;73:969-976.
119. **Taskinen MR, Smith U.** Lipid disorders in NIDDM: implications for treatment. *J Intern Med.* 1998;244:361-370.
120. **Garg A.** Treatment of diabetic dyslipidemia. *Am J Cardiol.* 1998;81(4A):47B-51B.
121. **Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G.** Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary artery disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) [published erratum appears in *Diabetes Care.* 1997;20:1048]. *Diabetes Care.* 1997;20:614-620.
122. **Goldberg RB, Mellies MJ, Sacks FM, et al. (CARE Investigators).** Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) Trial. *Circulation.* 1998;98:2513-2519.
123. **Smud R, Sermuklis B.** Bezafibrate and fenofibrate in type II diabetics with hyperlipoproteinaemia. *Curr Med Res Opin.* 1987;10:612-624.
124. **Garg A, Grundy SM.** Gemfibrozil alone and in combination with lovastatin for treatment of hypertriglyceridemia in NIDDM [published erratum appears in *Diabetes.* 1990;39:1313]. *Diabetes.* 1989;38:364-372.
125. **Strong JP, Malcom GT, McMahan CA, et al.** Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *JAMA.* 1999;281:727-735.
126. **Jacobson MS.** Heart healthy diets for all children: no longer controversial. *J Pediatr.* 1998;133:1-2.
127. **Jacobson MS, Lillienfeld DE.** The pediatrician's role in atherosclerosis prevention. *J Pediatr.* 1988;112:836-841.
128. **Jacobson MS, Tomopoulos S, Williams CL, Arden MR, Deckelbaum RJ, Stare TJ.** Normal growth in high risk hyperlipidemic children and adolescents with dietary intervention. *Prev Med.* 1998;27:775-780.
129. **Tonstad S.** A rational approach to treating hypercholesterolaemia in children: weighing the risks and benefits. *Drug Saf.* 1997;16:330-341.

130. **Deckelbaum RJ.** Preventive nutrition in childhood: a rationale. *Public Health Rev.* 1996;24:105-111.
131. **American Academy of Pediatrics.** National Cholesterol Education Program: report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics.* 1992;89(3 Pt 2):525-584.
132. **European Atherosclerosis Society International Task Force for Prevention of Coronary Artery Disease.** Prevention of coronary artery disease: scientific background and new clinical guidelines. *Nutr Metab Cardiovasc Dis.* 1992;2:113-156.
133. **Akerblom HK, Chandra RK, Franklin RA, et al.** Conclusions, guidelines and recommendations from the IUNS/WHO workshop: nutrition in the pediatric age group and later cardiovascular disease. *J Am Coll Nutr.* 1992;11(Suppl):1S-2S.
134. **Rifai N, Neufeld E, Ahlstrom P, Rimm E, D'Angelo L, Hicks JM.** Failure of current guidelines for cholesterol screening in urban African-American adolescents. *Pediatrics.* 1996;98(3 Pt 1):383-388.
135. **Kwiterovich PO Jr.** The antiatherogenic role of high-density lipoprotein cholesterol. *Am J Cardiol.* 1998;82(9A):13Q-21Q.
136. **Kasim-Karakas SE.** Dietary fat controversy: is it also applicable to children? *Am J Clin Nutr.* 1998;67:1106-1107.
137. **Webber LS, Srinivasan SR, Wattigney WA, Berenson GS.** Tracking of serum lipids and lipoproteins from childhood to adulthood: the Bogalusa Heart Study. *Am J Epidemiol.* 1991;133:884-899.
138. **Arslanian S, Suprasongsin C.** Insulin sensitivity, lipids, and body composition in childhood: is "syndrome X" present? *J Clin Endocrinol Metab.* 1996;81:1058-1062.
139. **Kwiterovich PO Jr.** Dyslipoproteinemia and other risk factors for atherosclerosis in children and adolescents. *Atherosclerosis.* 1994;108(Suppl):S55-S71.
140. **Mietus-Snyder M, Baker AL, Neufeld EJ, et al.** Effects of nutritional counseling on lipoprotein levels in a pediatric lipid clinic. *Am J Dis Child.* 1993;147:378-381.
141. **Writing Group for the DISC Collaborative Research Group.** Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol: the Dietary Intervention Study in Children (DISC). *JAMA.* 1995;273:1429-1435.
142. **Lapinleimu H, Viikari J, Jokinen E, et al.** Prospective randomised trial in 1062 infants of diet low in saturated fat and cholesterol. *Lancet.* 1995;345:471-476.
143. **Starc TJ, Shea S, Cohn LC, Mosca L, Gersony WM, Deckelbaum RJ.** Greater dietary intake of simple carbohydrate is associated with lower concentrations of high-density-lipoprotein cholesterol in hypercholesterolemic children. *Am J Clin Nutr.* 1998;67:1147-1154.
144. **Goren A, Stankiewicz H, Goldstein R, Drukker A.** Fish oil treatment of hyperlipidemia in children and adolescents receiving renal replacement therapy. *Pediatrics.* 1991;88:265-268.
145. **Zavoral JH, Hannan P, Fields DJ, et al.** The hypolipidemic effect of locust bean gum food products in familial hypercholesterolemic adults and children. *Am J Clin Nutr.* 1983;38:285-294.
146. **Gold K, Wong N, Tong A, et al.** Serum apolipoprotein and lipid profile effects of an oat-bran-supplemented, low-fat diet in children with elevated serum cholesterol. *Ann N Y Acad Sci.* 1991;623:429-431.
147. **Dennison BA, Levine DM.** Randomized, double-blind, placebo-controlled, two-period crossover clinical trial of psyllium fiber in children with hypercholesterolemia. *J Pediatr.* 1993;123:24-29.
148. **Davidson MH, Dugan LD, Burns JH, Sugimoto D, Story K, Drennan K.** A psyllium-enriched cereal for the treatment of hypercholesterolemia in children: a controlled, double-blind, crossover study. *Am J Clin Nutr.* 1996;63:96-102.
149. **Wray R, Neil H, Rees J.** Screening for hyperlipidaemia in childhood: recommendations of the British Hyperlipidaemia Association. *J R Coll Physicians Lond.* 1996;30:115-118.
150. **Wray R, Neil A, Rees A.** Hyperlipidaemia in childhood: a screening strategy; UK recommendations. In: Neil A, Rees A, Taylor C, eds. *Hyperlipidaemia in Childhood.* London: Royal College of Physicians of London, 1996: 99-105.
151. **Porkka KV, Raitakari OT.** Serum lipoproteins in children and young adults: determinants and treatment strategies. *Curr Opin Lipidol.* 1996;7:183-187.
152. **Rifkind BM, Schucker B, Gordon DJ.** When should patients with heterozygous familial hypercholesterolemia be treated? *JAMA.* 1999;281:180-181.
153. **Assouline L, Levy E, Feoli-Fonseca JC, Godbout C, Lambert M.** Familial hypercholesterolemia: molecular, biochemical, and clinical characterization of a French-Canadian pediatric population. *Pediatrics.* 1995;96(2 Pt 1):239-246.
154. **Tonstad S, Knudtson J, Sivertsen M, Refsum H, Ose L.** Efficacy and safety of cholestyramine in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr.* 1996;129:42-49.
155. **Hansen D, Michaelsen KF, Skovby F.** Growth during treatment of familial hypercholesterolemia. *Acta Paediatr.* 1992;81:1023-1025.
156. **Koletzko B, Kupke I, Wendel U.** Treatment of hypercholesterolemia in children and adolescents. *Acta Paediatr.* 1992;81:682-685.
157. **Tonstad S, Sivertsen M, Aksnes L, Ose L.** Low dose colestipol in adolescents with familial hypercholesterolemia. *Arch Dis Child.* 1996;74:157-160.
158. **Liacouras CA, Coates PM, Gallagher PR, Cortner JA.** Use of cholestyramine in the treatment of children with familial combined hyperlipidemia. *J Pediatr.* 1993;122:477-482.
159. **Ose L, Tonstad S.** The detection and management of dyslipidaemia in children and adolescents. *Acta Paediatr.* 1995;84:1213-1215.
160. **Illingworth DR.** Drug therapy for hyperlipidaemia in childhood. In: Neil A, Rees A, Taylor C, eds. *Hyperlipidaemia in Childhood.* London: Royal College of Physicians of London, 1996: 51-62.
161. **Colletti RB, Neufeld EJ, Roff NK, McAuliffe TL, Baker AL, Newburger JW.** Niacin treatment of hypercholesterolemia in children. *Pediatrics.* 1993;92:78-82.
162. **McKenney JM.** The cost of treating dyslipidaemia using National Cholesterol Education Program (NCEP) guidelines. *Pharmacoeconomics.* 1998;14 (Suppl 3):19-28.
163. **McKenney JM, Kinoshian B.** Economic benefits of aggressive lipid lowering: a managed care perspective. *Am J Manag Care.* 1998;4:65-74.
164. **Goldman L, Garber AM, Grover SA, Hlatky MA.** 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 6. Cost effectiveness of assessment and management of risk factors. *J Am Coll Cardiol.* 1996; 27:1020-1030.

165. Hay JW, Yu WM, Ashraf T. Pharmacoeconomics of lipid-lowering agents for primary and secondary prevention of coronary artery disease. *Pharmacoeconomics*. 1999;15:47-74.
166. Shepherd J. Profiling risk and new therapeutic interventions: looking ahead. *Am J Med*. 1998;104(2A):19S-22S.
167. Pfeffer MA, Sacks FM, Moyé LA, et al. Influence of baseline lipids on effectiveness of pravastatin in the Cholesterol and Recurrent Events (CARE) Trial. *J Am Coll Cardiol*. 1999;33:125-130.
168. Neaton JD, Wentworth D (Multiple Risk Factor Intervention Trial Research Group). Serum cholesterol, blood pressure, cigarette smoking, and death from coronary artery disease: overall findings and differences by age for 316,099 white men. *Arch Intern Med*. 1992;152:56-64.
169. Austin MA. Genetic epidemiology of dyslipidaemia and atherosclerosis. *Ann Med*. 1996;28:459-463.
170. Myers DE, Huang WN, Larkins RG. Lipoprotein-induced prostacyclin production in endothelial cells and effects of lipoprotein modification. *Am J Physiol*. 1996; 271(5 Pt 1):C1504-C1511.
171. Lamarche B, Despres JP, Moorjani S, Cantin B, Dagenais GR, Lupien PJ. Prevalence of dyslipidemic phenotypes in ischemic heart disease. *Am J Cardiol*. 1995;75:1189-1195.
172. Genest J Jr, McNamara JR, Ordovas JM, et al. Lipoprotein cholesterol, apolipoprotein A-1 and B and lipoprotein (a) abnormalities in men with premature coronary artery disease. *J Am Coll Cardiol*. 1992;19:792-802.
173. Goldbourt U, Yaari S, Medalie JH. Isolated low HDL cholesterol as a risk factor for coronary heart disease mortality: a 21-year follow-up of 8000 men. *Arterioscler Thromb Vasc Biol*. 1997;17:107-113.
174. Castelli WP, Anderson K, Wilson PW, Levy D. Lipids and risk of coronary heart disease: the Framingham Study. *Ann Epidemiol*. 1992;2:23-28.
175. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213-219.
176. Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease: the Prospective Cardiovascular Munster Study. *Am J Cardiol*. 1992;70: 733-737.
177. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation*. 1992;85:37-45.
178. Grundy SM. Consensus statement: role of therapy with "statins" in patients with hypertriglyceridemia. *Am J Cardiol*. 1998;81(4A):1B-6B.
179. Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure: a clinical mechanistic overview. *Arch Intern Med*. 1996;156:1789-1796.
180. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275:1557-1562.
181. Namnoum AB. Obesity: a disease worth treating. *Female Patient*. 1993;18:33-44.
182. Andreotti F, Burzotta F, Mazza A, Manzoli A, Robinson K, Maseri A. Homocysteine and arterial occlusive disease: a concise review. *Cardiologia*. 1999;44:341-345.
183. Tyagi SC. Homocyst(e)ine and heart disease: pathophysiology of extracellular matrix. *Clin Exp Hypertens*. 1999;21:181-198.
184. Mackness MI, Arrol S, Abbott C, Durrington PN. Protection of low-density lipoprotein against oxidative modification by high-density lipoprotein associated paraoxonase. *Atherosclerosis*. 1993;104:129-135.
185. Ginsberg HN. Lipoprotein physiology and its relationship to atherogenesis. *Endocrinol Metab Clin North Am*. 1990;19:211-228.
186. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115-126.
187. Fuster V, Ross R, Topol EJ, eds. *Atherosclerosis and Coronary Artery Disease*. Vol 1 and 2. Philadelphia: Lippincott-Raven, 1996.
188. Fuster V. Mechanisms leading to myocardial infarction: insights from studies of vascular biology [published erratum appears in *Circulation*. 1995;91:256]. *Circulation*. 1994;90:2126-2146.
189. Steinberg D. Oxidative modification of LDL and atherogenesis. *Circulation*. 1997;95:1062-1071.
190. Gianturco SH, Bradley WA. Atherosclerosis: cell biology and lipoproteins. *Curr Opin Lipidol*. 1994;5:313-315.
191. Libby P, Schoenbeck U, Mach F, Selwyn AP, Ganz P. Current concepts in cardiovascular pathology: the role of LDL cholesterol in plaque rupture and stabilization. *Am J Med*. 1998;104(2A):14S-18S.
192. Berliner JA, Navab M, Fogelman AM, et al. Atherosclerosis: basic mechanisms; oxidation, inflammation, and genetics. *Circulation*. 1995;91:2488-2496.
193. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature*. 1993;362:801-809.
194. Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis: characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *Br Heart J*. 1983;50:127-134.
195. Lee RT, Libby P. The unstable atheroma. *Arterioscler Thromb Vasc Biol*. 1997;17:1859-1867.
196. Stary HC, Chandler AB, Glagov S, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis: a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation*. 1994;89:2462-2478.
197. NIH Consensus Development Panel on Triglyceride, High-Density Lipoprotein, and Coronary Heart Disease. Triglyceride, high-density lipoprotein, and coronary heart disease. *JAMA*. 1993;269:505-510.
198. Assmann G, Schulte H. Role of triglycerides in coronary artery disease: lessons from the Prospective Cardiovascular Munster Study. *Am J Cardiol*. 1992;70: 10H-13H.
199. Simons LA. Triglyceride levels and the risk of coronary artery disease: a view from Australia. *Am J Cardiol*. 1992;70:14H-18H.
200. Vogel RA, Corretti MC, Plotnick GD. Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol*. 1997;79:350-354.
201. Stone NJ. Secondary causes of hyperlipidemia. *Med Clin North Am*. 1994;78:117-141.

202. **Gotto AM Jr, Pownall HJ.** *Manual of Lipid Disorders.* 2nd ed. Baltimore, MD: Williams & Wilkins, 1999.
203. **Wallace RB, Hunninghake DB, Reiland S, et al.** Alterations of plasma high-density lipoprotein cholesterol levels associated with consumption of selected medications: the Lipid Research Clinics Program Prevalence Study. *Circulation.* 1980;62(4 Pt 2):IV77-IV82.
204. **Simon A, Megnien JL, Levenson J.** Coronary risk estimation and treatment of hypercholesterolemia. *Circulation.* 1997;96:2449-2452.
205. **Joseph A, Ackerman D, Talley JD, Johnstone J, Kupersmith J.** Manifestations of coronary atherosclerosis in young trauma victims—an autopsy study. *J Am Coll Cardiol.* 1993;22:459-467.
206. **McGill HC Jr, McMahan CA (Pathobiological Determinants of Atherosclerosis in Youth [PDAY] Research Group).** Determinants of atherosclerosis in the young. *Am J Cardiol.* 1998;82:30T-36T.
207. **Davies H.** Atherogenesis and the coronary arteries in childhood. *Int J Cardiol.* 1990;28:283-291.
208. **Klag MJ, Ford DE, Mead LA, et al.** Serum cholesterol in young men and subsequent cardiovascular disease. *N Engl J Med.* 1993;328:313-318.
209. **Newman WP III, Freedman DS, Voors AW, et al.** Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis: the Bogalusa Heart Study. *N Engl J Med.* 1986;314:138-144.
210. **Tracy RE, Newman WP III, Wattigney WA, Berenson GS.** Risk factors and atherosclerosis in youth autopsy findings of the Bogalusa Heart Study. *Am J Med Sci.* 1995;310(Suppl 1):S37-S41.
211. **Cleeman JL.** Detection and evaluation of dyslipoproteinaemia. *Endocrinol Metab Clin North Am.* 1998;27:597-611.
212. **Lamarche B, Lewis GF.** Atherosclerosis prevention for the next decade: risk assessment beyond low density lipoprotein cholesterol. *Can J Cardiol.* 1998;14:841-851.
213. **Schildkraut JM, Myers RH, Cupples LA, Kiely DK, Kannel WB.** Coronary risk associated with age and sex of parental heart disease in the Framingham Study. *Am J Cardiol.* 1989;64:555-559.
214. **Frost PH, Havel RJ.** Rationale for use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. *Am J Cardiol.* 1998;81(4A):26B-31B.
215. **Havel RJ, Rapaport E.** Management of primary hyperlipidemia [published erratum appears in *N Engl J Med.* 1995;333:467]. *N Engl J Med.* 1995;332:1491-1498.
216. **Krauss RM, Deckelbaum RJ, Ernst N, et al.** Dietary guidelines for healthy American adults: a statement for health professionals from the Nutrition Committee, American Heart Association. *Circulation.* 1996;94:1795-1800.
217. **American Diabetes Association.** Nutrition recommendations and principles for people with diabetes mellitus. *Diabetes Care.* 1999;22(Suppl 1):S42-S43.
218. **Marks AD.** Control of lipid disorders in patients with atherosclerotic vascular disease. *Surg Clin North Am.* 1998;78:431-446.
219. **Denke MA.** Cholesterol-lowering diets: a review of the evidence. *Arch Intern Med.* 1995;155:17-26.
220. **Dreon DM, Fernstrom HA, Miller B, Krauss RM.** Low-density lipoprotein subclass patterns and lipoprotein response to a reduced-fat diet in men. *FASEB J.* 1994;8:121-126.
221. **Dreon DM, Fernstrom HA, Williams PT, Krauss RM.** LDL subclass patterns and lipoprotein response to a low-fat, high-carbohydrate diet in women. *Arterioscler Thromb Vasc Biol.* 1997;17:707-714.
222. **Anderson JW, Zettwoch N, Feldman T, Tietzen-Clark J, Oeltgen P, Bishop CW.** Cholesterol-lowering effects of psyllium hydrophilic mucilloid for hypercholesterolemic men. *Arch Intern Med.* 1988; 148:292-296.
223. **Burr ML, Fehily AM, Gilbert JF, et al.** Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial. *Lancet.* 1989;2:757-761.
224. **Burr ML, Sweetnam PM, Fehily AM.** Diet and reinfarction [letter]. *Eur Heart J.* 1994;15:1152-1153.
225. **Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M.** Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival—4. *Cardiovasc Drugs Ther.* 1997;11:485-491.
226. **Genest J Jr, Cohn JS.** Clustering of cardiovascular risk factors: targeting high-risk individuals. *Am J Cardiol.* 1995;76:8A-20A.
227. **Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, Ganz P.** The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. *N Engl J Med.* 1995;332:488-493.
228. **Treasure CB, Klein JL, Weintraub WS, et al.** Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. *N Engl J Med.* 1995;332:481-487.
229. **Downs JR, Clearfield M, Weis S, et al.** Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/ TexCAPS). *JAMA.* 1998;279:1615-1622.
230. **Pedersen TR, Olsson AG, Faergeman O, et al.** Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation.* 1998;97:1453-1460.
231. **Superko HR, Krauss RM, et al. (SCRIP Investigators).** Arteriographic benefit of multifactorial risk reduction in patients with LDL-C <125 mg/dL is seen in LDL pattern B but not pattern A [abstract]. 4th International Symposium on Multiple Risk Factors in Cardiovascular Disease, April 1997, Washington, DC.
232. **Campeau L, Hunninghake DB, Knatterud GL, et al. (Post CABG Trial Investigators).** Aggressive cholesterol lowering delays saphenous vein graft atherosclerosis in women, the elderly, and patients with associated risk factors: NHLBI Post Coronary Artery Bypass Graft Clinical Trial. *Circulation.* 1999;99:3241-3247.
233. **White CW.** Benefit of aggressive lipid-lowering therapy: insights from the Post Coronary Artery Bypass Graft Study and other trials. *Am J Med.* 1998; 105(1A):63S-68S.
234. **Hunninghake DB.** Is aggressive cholesterol control justified? Review of the Post-Coronary Artery Bypass Graft Trial. *Am J Cardiol.* 1998;82(10B):45T-48T.
235. **Sacks FM, Moyé LA, Davis BR, et al.** Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events Trial. *Circulation.* 1998;97:1446-1452.

236. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study. *Circulation*. 1998;97:1440-1445.
237. **Behar S (BIP Study Group)**. Lowering fibrinogen levels: clinical update. *Blood Coagul Fibrinolysis*. 1999;10 (Suppl 1):S41-S43.
238. **Kornitzer M, Dramaix M, Vandenbroek MD, Everaert L, Gerlinger C**. Efficacy and tolerance of 200 mg micronised fenofibrate administered over a 6-month period in hyperlipidaemic patients: an open Belgian multicenter study. *Atherosclerosis*. 1994;119(Suppl):S49-S54.
239. **Dierkes J, Westphal S, Luley C**. Serum homocysteine increases after therapy with fenofibrate or bezafibrate [letter]. *Lancet*. 1999;354:219-220.
240. **De la Serna G, Cadarso C**. Fenofibrate decreases plasma fibrinogen, improves lipid profile, and reduces uricemia. *Clin Pharmacol Ther*. 1999;66:166-172.
241. Atromid-S (clofibrate capsules). In: *Physicians' Desk Reference*. 53rd ed. Montvale, NJ: Medical Economics Company, 1999: 3272.
242. **Durrington PN, Mackness MI, Bhatnagar D, et al**. Effects of two different fibric acid derivatives on lipoproteins, cholesteryl ester transfer, fibrinogen, plasminogen activator inhibitor and paraoxonase activity in type IIb hyperlipoproteinaemia. *Atherosclerosis*. 1998;138:217-225.
243. **Kockx M, de Maat MP, Knipscheer HC, et al**. Effects of gemfibrozil and ciprofibrate on plasma levels of tissue-type plasminogen activator, plasminogen activator inhibitor-1 and fibrinogen in hyperlipidaemic patients. *Thromb Haemost*. 1997;78:1167-1172.
244. **Broijerssen A, Hamsten A, Sileveira A, et al**. Gemfibrozil reduces thrombin generation in patients with combined hyperlipidaemia, without influencing plasma fibrinogen, fibrin gel structure or coagulation factor VII. *Thromb Haemost*. 1996;76:171-176.
245. **Athyros VG, Papageorgiou AA, Avramidis MJ, Kontopoulos AG**. Long-term effect of gemfibrozil on coronary heart disease risk profile of patients with primary combined hyperlipidaemia. *Coron Artery Dis*. 1995;6:251-256.
246. **Avellone G, Di Garbo V, Cordova R, et al**. Improvement of fibrinolysis and plasma lipoprotein levels induced by gemfibrozil in hypertriglyceridemia. *Blood Coagul Fibrinolysis*. 1995;6:543-548.
247. **Broijerssen A, Eriksson M, Wiman B, Angelin B, Hjendahl P**. Gemfibrozil treatment of combined hyperlipoproteinemia: no improvement of fibrinolysis despite marked reduction of plasma triglyceride levels. *Arterioscler Thromb Vasc Biol*. 1996;16:511-516.
248. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate: report from the Committee of Principal Investigators. *Br Heart J*. 1978;40:1069-1118.
249. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984;251:351-364.
250. **Wierzbicki AS**. Diagnosis and management of hyperlipidaemia. *Int J Clin Pract*. 1997;51:378-383.
251. **Pedersen TR**. Coronary artery disease: the Scandinavian Simvastatin Survival Study experience. *Am J Cardiol*. 1998;82(10B):53T-56T.
252. **Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Study Group**. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349-1357.
253. **Pitt B, Waters D, Brown WV, et al. (Atorvastatin Versus Revascularization Treatment Investigators)**. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. *N Engl J Med*. 1999;341:70-76.
254. **de Faire U, Ericsson CG, Grip L, Nilsson J, Svane B, Hamsten A**. Secondary preventive potential of lipid-lowering drugs: the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT). *Eur Heart J*. 1996;17(Suppl F):37-42.
255. **Goldbourt U, Brunner D, Behar S, Reicher-Reiss H**. Baseline characteristics of patients participating in the Bezafibrate Infarction Prevention (BIP) Study. *Eur Heart J*. 1998;19(Suppl H):H42-H47.
256. **Jones P, Kafonek S, Laurora I, Hunninghake D**. Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in patients with hypercholesterolemia [published erratum appears in *Am J Cardiol*. 1998;82:128]. *Am J Cardiol*. 1998;81:582-587.
257. Reference no longer applicable with the removal of Baycol (Cerivastatin Sodium) from the market.
258. **Brown AS, Bakker-Arkema RG, Yellen L, et al**. Treating patients with documented atherosclerosis to National Cholesterol Education Program-recommended low-density-lipoprotein cholesterol goals with atorvastatin, fluvastatin, lovastatin and simvastatin. *J Am Coll Cardiol*. 1998;32:665-672.
259. **Superko HR, Krauss RM, DiRicco C**. Effect of fluvastatin on low-density lipoprotein peak particle diameter. *Am J Cardiol*. 1997;80:78-81.
260. **Gaw A, Packard CJ, Murray EF, et al**. Effects of simvastatin on apoB metabolism and LDL subfraction distribution. *Arterioscler Thromb*. 1993;13:170-189.
261. **Franceschini G, Cassinotti M, Vecchio G, et al**. Pravastatin effectively lowers LDL cholesterol in familial combined hyperlipidemia without changing LDL subclass pattern. *Arterioscler Thromb*. 1994;14:1569-1575.
262. **Landray MJ, Hartland A, Hubscher D, Kendall MJ, Cramb R**. Effect of atorvastatin on low-density lipoprotein subfraction profile. *Ann Clin Biochem*. 1999;36(Pt 2):240-241.
263. **Jen SL, Chen JW, Lee WL, Wang SP**. Efficacy and safety of fenofibrate or gemfibrozil on serum lipid profiles in Chinese patients with type IIb hyperlipidemia: a single-blind, randomized, and cross-over study. *Chung Hua I Hsueh Tsa Chih (Taipei)*. 1997;59:217-224.
264. **Ericsson CG, Hamsten A, Nilsson J, Grip L, Svane B, de Faire U**. Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. *Lancet*. 1996;347:849-853.
265. **Frick MH, Syv anne M, Nieminen MS, et al. (Lipid Coronary Angiography Trial [LOCAT] Study Group)**. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. *Circulation*. 1997;96:2137-2143.
266. **Superko HR, Krauss RM**. Reduction of small, dense LDL by gemfibrozil in LDL subclass pattern B [abstract]. *Circulation*. 1995;92:1-250.

267. **Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, Frick MH.** Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care.* 1992;15:820-825.
268. **Blankenhorn DH, Johnson RL, Nessim SA, Azen SP, Sanmarco ME, Selzer RH.** The Cholesterol Lowering Atherosclerosis Study (CLAS): design, methods, and baseline results. *Control Clin Trials.* 1987;8:356-387.
269. **Canner PL, Berge KG, Wenger NK, et al.** Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol.* 1986;8:1245-1255.
270. **Brown BG, Hillger L, Zhao XQ, Poulin D, Albers JJ.** Types of change in coronary stenosis severity and their relative importance in overall progression and regression of coronary disease: observations from the FATS Trial; Familial Atherosclerosis Treatment Study. *Ann N Y Acad Sci.* 1995;748:407-417.
271. **Knopp RH, Alagona P, Davidson M, et al.** Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. *Metabolism.* 1998;47:1097-1104.
272. **Capuzzi DM, Guyton JR, Morgan JM, et al.** Efficacy and safety of an extended-release niacin (Niaspan): a long-term study. *Am J Cardiol.* 1998;82(12A):74U-81U.
273. **Huttunen JK, Manninen V, Tenkanen L, et al.** Drug-induced changes of high-density lipoprotein cholesterol and coronary heart disease: experience from the Helsinki Heart Study. In: Miller NE, ed. *High-Density Lipoproteins, Reverse Cholesterol Transport, and Coronary Heart Disease.* Amsterdam: Elsevier Science Publishers, 1989: 85-92.
274. **Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, et al.** Safety and efficacy of long-term statin-fibrate combinations in patients with refractory familial combined hyperlipidemia. *Am J Cardiol.* 1997;80:608-613.
275. **Fehér MD, Foxton J, Banks D, Lant AF, Wray R.** Long-term safety of statin-fibrate combination treatment in the management of hypercholesterolaemia in patients with coronary artery disease. *Br Heart J.* 1995;74:14-17.
276. **Smit JW, Jansen GH, de Bruin TW, Erkelens DW.** Treatment of combined hyperlipidemia with fluvastatin and gemfibrozil, alone or in combination, does not induce muscle damage. *Am J Cardiol.* 1995;76:126A-128A.
277. **Kayikçioğlu M, Özerkan F, Soydan I.** Effectiveness and safety of alternate-day simvastatin and fenofibrate on mixed hyperlipidemia. *Am J Cardiol.* 1999;83:1135-1137.
278. **Guyton JR, Capuzzi DM.** Treatment of hyperlipidemia with combined niacin-statin regimens. *Am J Cardiol.* 1998;82(12A):82U-84U.
279. **Davignon J, Roederer G, Montigny M, et al.** Comparative efficacy and safety of pravastatin, nicotinic acid and the two combined in patients with hypercholesterolemia. *Am J Cardiol.* 1994;73:339-345.
280. **Wood PD, Stefanick ML, Williams PT, Haskell WL.** The effects on plasma lipoproteins of a prudent weight-reducing diet, with or without exercise, in overweight men and women. *N Engl J Med.* 1991;325:461-466.
281. **Moffatt RJ.** Effects of cessation of smoking on serum lipids and high density lipoprotein-cholesterol. *Atherosclerosis.* 1988;74:85-89.
282. **Birdsall MA, Farquhar CM, White HD.** Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. *Ann Intern Med.* 1997;126:32-35.
283. **Dahlgren E, Janson PO, Johansson S, Lapidus L, Oden A.** Polycystic ovary syndrome and risk of myocardial infarction: evaluated from a risk factor model based on a prospective population study of women. *Acta Obstet Gynecol Scand.* 1992;71:599-604.
284. **Guzick DS, Talbott EO, Sutton-Tyrrell K, Herzog HC, Kuller LH, Wolfson SK Jr.** Carotid atherosclerosis in women with polycystic ovary syndrome: initial results from a case-control study. *Am J Obstet Gynecol.* 1996; 174:1224-1232.
285. **Nestler JE, Jakubowicz DJ.** Decrease in ovarian cytochrome P450c17(alpha) activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med.* 1996;335:617-623.
286. **Ehrmann DA, Schneider DJ, Sobel BE, et al.** Troglitazone improves defects in insulin action, insulin secretion, ovarian steroidogenesis, and fibrinolysis in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 1997;82:2108-2116.
287. **Dunaif A, Scott D, Finegood D, Quintana B, Whitcomb R.** The insulin-sensitizing agent troglitazone improves metabolic and reproductive abnormalities in the polycystic ovary syndrome. *J Clin Endocrinol Metab.* 1996;81:3299-3306.
288. **Heinonen TM, et al.** Data presented at the 66th Congress of the European Atherosclerosis Society. July 13-17, 1996.
289. **Darling GM, Johns JA, McCloud PI, Davis SR.** Estrogen and progestin compared with simvastatin for hypercholesterolemia in postmenopausal women. *N Engl J Med.* 1997;337:595-601.
290. **Writing Group for the PEPI Trial.** Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial [published erratum appears in *JAMA.* 1995;274:1676]. *JAMA.* 1995; 273:199-208.
291. **Hulley S, Grady D, Bush T, et al. (Heart and Estrogen/Progestin Replacement Study [HERS] Research Group).** Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA.* 1998;280:605-613.
292. **Brown WV.** Lipoprotein disorders in diabetes mellitus. *Med Clin North Am.* 1994;78:143-161.
293. **Shah M, Garg A.** High-fat and high-carbohydrate diets and energy balance. *Diabetes Care.* 1996;19:1142-1152.
294. **Bretzel RG, Voigt K, Schatz H.** The United Kingdom Prospective Diabetes Study (UKPDS) implications for the pharmacotherapy of type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes.* 1998;106:369-372.
295. **Actos (pioglitazone hydrochloride) prescribing information.** Lincolnshire, IL: Takeda Pharmaceuticals America, Inc; July 1999.
296. **Avandia (rosiglitazone maleate) prescribing information.** Philadelphia, PA: SmithKline Beecham Pharmaceuticals; May 1999.
297. **Tack CJ, Smits P, Demacker PN, Stalenhoef AF.** Troglitazone decreases the proportion of small, dense LDL and increases the resistance to LDL to oxidation in obese subjects. *Diabetes Care.* 1998;21:796-799.
298. **Garg A, Grundy SM.** Lovastatin for lowering cholesterol levels in non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1988;318:81-86.

299. **Garg A, Grundy SM.** Cholestyramine therapy for dyslipidemia in non-insulin-dependent diabetes mellitus: a short-term, double-blind, crossover trial. *Ann Intern Med.* 1994;121:416-422.
300. **Garg A, Grundy SM.** Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. *JAMA.* 1990;264:723-726.
301. **Henkin Y, Segrest JP.** Nicotinic acid in NIDDM [letter] [published erratum appears in *JAMA.* 1991;265:2672]. *JAMA.* 1990;264:2994-2996.
302. **Newman TB, Browner WS, Hulley SB.** The case against childhood cholesterol screening. *JAMA.* 1990;264:3039-3043.
303. **Tereshakovec AM, Jawad AF, Stallings VA, et al.** Growth of hypercholesterolemic children completing physician-initiated low-fat dietary intervention. *J Pediatr.* 1998;133:28-34.
304. **Copperman N, Schebendach J, Arden MR, Jacobson MS.** Nutrient quality of fat- and cholesterol-modified diets of children with hyperlipidemia. *Arch Pediatr Adolesc Med.* 1995;149:333-336.
305. **Obarzanek E, Hunsberger SA, Van Horn L, et al.** Safety of a fat-reduced diet: the Dietary Intervention Study in Children (DISC). *Pediatrics.* 1997;100:51-59.
306. **O'Connell JM, Dibley MJ, Sierra J, Wallace B, Marks JS, Yip R.** Growth of vegetarian children: the Farm Study. *Pediatrics.* 1989;84:475-481.
307. **Shea S, Basch CE, Stein AD, Contento IR, Irigoyen M, Zybert P.** Is there a relationship between dietary fat and stature or growth in children three to five years of age? *Pediatrics.* 1993;92:579-586.
308. **Boulton TJ, Magarey AM.** Effects of differences in dietary fat on growth, energy and nutrient intake from infancy to eight years of age. *Acta Paediatr.* 1995;84:146-150.
309. **Niimikoski H, Viikari J, Ronnema T, et al.** Regulation of growth of 7- to 36-month-old children by energy and fat intake in the prospective, randomized STRIP baby trial. *Pediatrics.* 1997;100:810-816.
310. **Niimikoski H, Viikari J, Ronnema T, et al.** Prospective randomized trial of low-saturated-fat, low-cholesterol diet during the first 3 years of life: the STRIP baby project. *Circulation.* 1996;94:1386-1393.
311. **Budow L, Beseler L, Arden M, et al.** The effect of dietary therapy on growth in hyperlipidemic children and adolescents: a prospective clinical trial [abstract]. *Pediatr Res.* 1989;25:22A.
312. **American Academy of Pediatrics Committee on Nutrition.** Cholesterol in childhood. *Pediatrics.* 1998;101:141-147.
313. **Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA.** Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults: the Bogalusa Heart Study. *N Engl J Med.* 1998;338:1650-1656.
314. **Kwiterovich PO Jr.** Biochemical, clinical, epidemiologic, genetic, and pathologic data in the pediatric age group relevant to the cholesterol hypothesis. *Pediatrics.* 1986;78:349-362.
315. **Raitakari OT, Leino M, Rakkonen K, et al.** Clustering of risk habits in young adults: the Cardiovascular Risk in Young Finns Study. *Am J Epidemiol.* 1995;142:36-44.
316. **Raitakari OT, Porkka KV, Taimela S, Telama R, Rasanen L, Viikari JS.** Effects of persistent physical activity and inactivity on coronary risk factors in children and young adults: the Cardiovascular Risk in Young Finns Study. *Am J Epidemiol.* 1994;140:195-205.
317. **Thompson GR.** Lipid lowering in the young [editorial]. *Heart.* 1996;76:1-2.
318. **Hennermann JB, Herwig J, März W, Asskali F, Bohles HJ.** Lipid and lipoprotein profiles in children with familial hypercholesterolaemia: effects of therapy. *Eur J Pediatr.* 1998;157:912-918.
319. **Goldstein JL, Hobbs HH, Brown MS.** Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease.* 7th ed. New York: McGraw-Hill, 1995: 1981-2030.
320. **Tonstad S, Joakimsen O, Stensland-Bugge E, et al.** Risk factors related to carotid intima-media thickness and plaque in children with familial hypercholesterolemia and control subjects. *Arterioscler Thromb Vasc Biol.* 1996;16:984-991.
321. **Sorensen KE, Celermajer DS, Georgakopoulos D, Hatcher G, Betteridge DJ, Deanfield JE.** Impairment of endothelium-dependent dilation is an early event in children with familial hypercholesterolemia and is related to the lipoprotein(a) level. *J Clin Invest.* 1994;93:50-55.
322. **Hegele RA.** Small genetic effects in complex diseases: a review of regulatory sequence variants in dyslipoproteinemia and atherosclerosis. *Clin Biochem.* 1997;30:183-188.
323. **Farah JR, Kwiterovich PO Jr, Neill CA.** Dose-effect relation of cholestyramine in children and young adults with familial hypercholesterolaemia. *Lancet.* 1977;1:59-63.
324. **Ducobu J, Brasseur D, Chaudron JM, et al.** Simvastatin use in children [letter]. *Lancet.* 1992;339:1488.
325. **Sinzinger H, Schmid P, Pirich C, et al.** Treatment of hypercholesterolaemia in children [letter]. *Lancet.* 1992;340:548-549.
326. **Sinzinger H, Mayr F, Schmid P, Granegger S, O'Grady J, Peskar BA.** Sleep disturbance and appetite loss after lovastatin [letter]. *Lancet.* 1994;343:973.
327. **Knipscheer HC, Boelen CC, Kastelein JJ, et al.** Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia [published erratum appears in *Pediatr Res.* 1996;40:866]. *Pediatr Res.* 1996;39:867-871.
328. **Lambert M, Lupien PJ, Gagne C, et al. (Canadian Lovastatin in Children Study Group).** Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. *Pediatrics.* 1996;97:619-628.
329. **Stein EA, Illingworth DR, Kwiterovich PO Jr, et al.** Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA.* 1999;281:137-144.
330. **Goldman L, Weinstein MC, Goldman PA, Williams LW.** Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. *JAMA.* 1991;265:1145-1151.
331. **Marcovina SM, Koschinsky ML.** Lipoprotein(a) as a risk factor for coronary artery disease. *Am J Cardiol.* 1998;82(12A):57U-66U.
332. **Guyton JR, Dahlen GH, Patsch W, Kautz JA, Gotto AM Jr.** Relationship of plasma lipoprotein Lp(a) levels to race and to apolipoprotein B. *Arteriosclerosis.* 1985;5:265-272.

333. **Sorrentino MJ, Vielhauer C, Eisenbart JD, Fless GM, Scanu AM, Feldman T.** Plasma lipoprotein (a) protein concentration and coronary artery disease in black patients compared with white patients. *Am J Med.* 1992;93:658-662.
334. **Srinivasan SR, Dahlen GH, Jarpa RA, Webber LS, Berenson GS.** Racial (black-white) differences in serum lipoprotein (a) distribution and its relation to parental myocardial infarction in children: Bogalusa Heart Study. *Circulation.* 1991;84:160-167.
335. **Scanu AM.** Atherothrombogenicity of lipoprotein(a): the debate. *Am J Cardiol.* 1998;82:26Q-33Q.
336. **Maher VM, Brown BG, Marcovina SM, Hillger LA, Zhao XQ, Albers JJ.** Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). *JAMA.* 1995;274:1771-1774.
337. **Thompson GR, Maher VM, Matthews S, et al.** Familial Hypercholesterolaemia Regression Study: a randomised trial of low-density-lipoprotein apheresis. *Lancet.* 1995; 345:811-816.
338. **Kroon AA, Aengevaeren WR, van der Werf T, et al.** LDL-Apheresis Atherosclerosis Regression Study (LAARS): effect of aggressive versus conventional lipid lowering treatment on coronary atherosclerosis. *Circulation.* 1996;93:1826-1835.
339. **Kronenberg F.** Homocysteine, lipoprotein(a) and fibrinogen: metabolic risk factors for cardiovascular complications of chronic renal disease. *Curr Opin Nephrol Hypertens.* 1998;7:271-278.
340. **Sobel BE, Woodcock-Mitchell J, Schneider DJ, Holt RE, Marutsuka K, Gold H.** Increased plasminogen activator inhibitor type 1 in coronary artery atherectomy specimens from type 2 diabetic compared with nondiabetic patients: a potential factor predisposing to thrombosis and its persistence. *Circulation.* 1998;97:2213-2221.
341. **Cattaneo M.** Hyperhomocysteinemia, atherosclerosis and thrombosis. *Thromb Haemost.* 1999;81:165-176.
342. **Maeda S, Abe A, Seishima M, Makino K, Noma A, Kawade M.** Transient changes of serum lipoprotein(a) as an acute phase protein. *Atherosclerosis.* 1989;78:145-150.
343. **Slunga L, Johnson O, Dahlen GH, Eriksson S.** Lipoprotein(a) and acute-phase proteins in acute myocardial infarction. *Scand J Clin Lab Invest.* 1992;52:95-101.
344. **Egerton W, Silberberg J, Crooks R, Ray C, Xie L, Dudman N.** Serial measures of plasma homocyst(e)ine after acute myocardial infarction. *Am J Cardiol.* 1996;77:759-761.
345. **Lindgren A, Brattstrom L, Norrving B, Hultberg B, Andersson A, Johansson BB.** Plasma homocysteine in the acute and convalescent phases after stroke. *Stroke.* 1995;26:795-800.
346. **Evans RW, Shaten BJ, Hempel JD, Cutler JA, Kuller LH.** Homocyst(e)ine and risk of cardiovascular disease in the Multiple Risk Factor Intervention Trial. *Arterioscler Thromb Vasc Biol.* 1997;17:1947-1953.
347. **Folsom AR, Nieto FJ, McGovern PG, et al.** Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphisms, and B vitamins: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* 1998;98:204-210.
348. **Malinow MR, Duell PB, Hess DL, et al.** Reduction of plasma homocyst(e)ine levels by breakfast cereal fortified with folic acid in patients with coronary heart disease. *N Engl J Med.* 1998;338:1009-1015.
349. **Stein JH, McBride PE.** Hyperhomocysteinemia and atherosclerotic vascular disease: pathophysiology, screening, and treatment. *Arch Intern Med.* 1998;158:1301-1306.
350. **Woodside JV, Yarnell JW, McMaster D, et al.** Effect of B-group vitamins and antioxidant vitamins on hyperhomocysteinemia: a double-blind, randomized, factorial-design, controlled trial [published erratum appears in *Am J Clin Nutr.* 1998;68:758]. *Am J Clin Nutr.* 1998;67:858-866.
351. **Ridker PM, Rifai N, Pfeffer MA, et al. (Cholesterol and Recurrent Events [CARE] Investigators).** Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation.* 1998;98:839-844.