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Prevention and Treatment of Atherosclerosis: A Practitioner's Guide for 2008

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ABSTRACT

Atherosclerosis causes nearly 75% of cardiovascular-related deaths and is found in 80% to 90% of adults ≥30 years old in the United States. Successful treatment minimizes lifetime chances of cardiovascular events, morbidity, and mortality. Risk factors for atherosclerosis should be monitored, beginning in childhood, even in asymptomatic patients. Modifiable factors (e.g., blood pressure, smoking, serum lipids) and nonmodifiable factors (e.g., age, family history) are important in the overall assessment. Clinicians and patients can partner to produce an individualized treatment plan by choosing from a variety of standard approaches. In some patients, improved dietary choices, increased exercise, and smoking cessation will reduce risk to an acceptable degree. To lower risk further, lipid-lowering pharmacotherapy and antihypertensive medication may be combined with these lifestyle improvements. For most of these patients, reducing low-density lipoprotein cholesterol is the most important lipid-lowering goal, and it is best achieved with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin). Some patients may benefit from adjunctive therapies that have proven effects (e.g., niacin, fibrates, plant stanols/sterols, omega-3 fatty acids). Antihypertensive regimens may involve stepwise adjustments of multiple medications. Good clinical judgment and communication of expectations and goals are critical for effective management of atherosclerosis.

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KEYWORDS: Atherosclerosis; Hypercholesterolemia; Risk factor; Statin; Treatment

Atherosclerosis is implicated in 75% of all cardiovascular (CV)-related deaths in the United States.[1] Factors that influence the risk of developing atherosclerosis occur throughout one's lifetime; the disease or its precursors begin in childhood with asymptomatic but identifiable pathology (see Figure 1 in the article by Insull[2] in this supplement) and then progress slowly into adulthood.[3] By the time young adults reach their 30s, some degree of atherosclerosis has developed in 80% to 90% of young men and women in the United States.[3]

Both sexes and all ethnic groups are at risk for development of atherosclerosis. Abnormal lipid profiles appear to be predictive of atherosclerotic CV disease (CVD), and nearly 50% of the US population, regardless of sex or ethnicity, has elevated low-density lipoprotein (LDL) cholesterol (Figure 1).[4] (See also Figure 1 in the article by Bays[5] in this supplement.)

Atherosclerosis is the natural outcome of a lifetime of atherogenic risk, including high cholesterol levels, defined as total cholesterol levels >200 mg/dL (1 mg/dL = 0.02586 mmol/L).[6] In populations with LDL cholesterol levels <70 mg/dL, virtually no atherosclerosis occurs.[7] About 46% of Americans have higher-than-optimal levels of LDL cholesterol, the primary lipid component of risk factor modification targeted by guidelines.[1] Obesity, hypertension, diabetes mellitus, physical inactivity, and smoking all are contributors to the development of atherosclerotic CVD.[6]

WHAT CAN PRACTITIONERS DO?

Back to Basics

Practitioners face an increasing complexity of patient healthcare needs that must be met within the time con-

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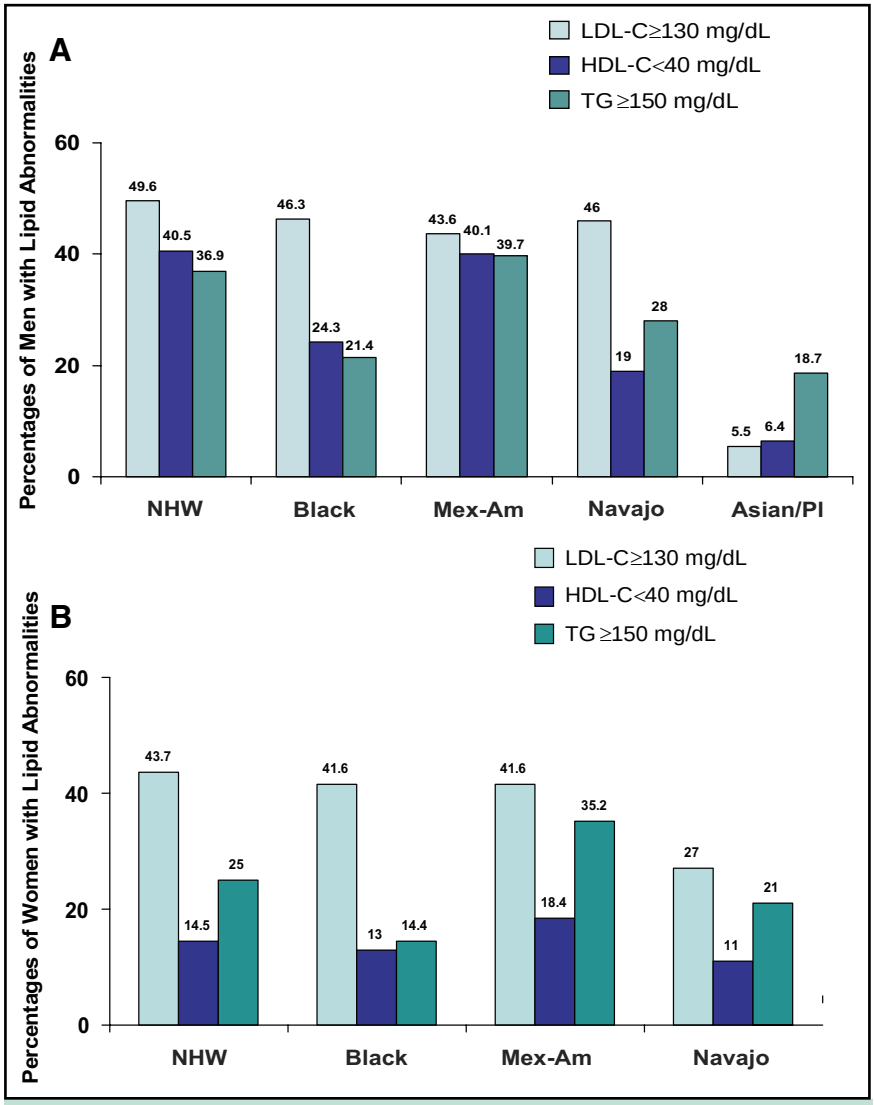

Figure 1 (*A*) Prevalence of lipid abnormalities in various populations of men in the United States. (*B*) Prevalence of lipid abnormalities in various populations of women in the United States. For cholesterol, 1 mg/dL = 0.02586 mmol/L; for triglyceride, 1 mg/dL = 0.01129 mmol/L. Asian/PI = Asian/Pacific Islander; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Mex-Am = Mexican American; NHW = non–Hispanic white. Data were not available for Asian/Pacific Islander women. (Reprinted with permission from *Am J Med.*[4])

straints of practice. The aim of this article is to provide short, practical advice to help physicians quickly identify patients at risk for atherosclerosis and offer guidance for their treatment. A glossary of terms used in this article is provided in Table 1.

Risk assessment for CVD should begin during childhood.[8,9] Because the atherosclerotic process begins in childhood, one should be alert for the presence of risk factors in children and adolescents. Screening for dyslipidemia should begin in childhood for children with a family history of premature CVD or dyslipidemia. For those without familial or historical high-risk indicators, careful clinical and laboratory assessment of CV risk beginning in young adulthood is recommended. Inherent in assessment of smoking, physical activity level, obesity, and stress behaviors in children and adults[3] is an opportunity for the clinician to encourage entire families to adopt health-promoting diet/lifestyle/exercise (Table 2).

Risk Assessment

Risk Factors. ***Nonmodifiable Risk Factors.*** Family history and age are associated with nonmodifiable higher risk for atherosclerotic CVD. Studies such as the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based, multiethnic survey of a cohort of asymptomatic individuals, found that a family history of premature CVD in a

parent or sibling was highly predictive of the presence of asymptomatic atherosclerosis.[10] The risk conferred by family history was independent of the presence of other CV risk factors.

Modifiable Risk Factors. Modifiable risk factors for atherosclerosis are the same for men and women.[11] Major risk factors include dyslipidemia, hypertension, diabetes, smoking, obesity, and physical inactivity. Although 1 major risk factor (e.g., diabetes, family history) may already represent very high risk, for most individuals, it is a combination of risk factors rather than a single risk factor that puts them at high risk for an atherosclerotic CV event.[12] Thus, modification of all risk factors is important. Although high-risk patients (10-year risk for coronary heart disease [CHD] ≥20%) tend to be identified and treated to goal by primary care physicians, moderate-risk patients (10% to 19% 10-year risk) may be misclassified or may go untreated.[13] The simple addition of a tool (Figure 2) during assessment that lists a patient's global CV risk increases the number of moderate-risk patients who receive treatment.[6,11,13] Use of such a tool also helps to reduce inappropriate therapy for low-risk patients, enhancing the efficiency of resource allocation. Such a tool can be implemented in the waiting room or by the medical assistant prior to the physician visit.

Risk Factor Assessment

Obtain a Fasting Lipid Profile. The National Cholesterol Education Program (NCEP) recommends that all adults be tested periodically for dyslipidemia, starting at age 20 (Table 3).[6] An elevated level of total cholesterol in young adults is a good predictor of a higher rate of premature CHD.[6] A lipid profile is warranted for children or adolescents who are overweight, or who have a family history of atherosclerotic CVD or dyslipidemia.[3]

LDL cholesterol and CHD risk have a continuous, nonlinear relationship. At any level of LDL cholesterol, the change in relative risk associated with a given change in LDL cholesterol concentration is the same, so that people with a low level of LDL cholesterol but with other risk factors benefit from lowering LDL cholesterol to the same extent as those starting with a higher LDL cholesterol level.[14] The Heart Protection Study suggested that reducing LDL cholesterol from any baseline level provides additional benefit to high-risk patients.[15]

When dyslipidemia is identified, secondary causes (e.g., hypothyroidism, uncontrolled diabetes, chronic renal failure, chronic liver disease, steroid use) should be evaluated before LDL cholesterol−lowering therapy is initiated.

Evaluate for Hypertension. Patients with hypertension (≥140/>90 mm Hg) are at increased risk for CVD.[16] Even moderate lowering of blood pressure (−6/−3 mm Hg) in patients with prehypertension (120 to 139/80 to 89 mm Hg)

Table 1 Glossary of terms

Term	Definition
ATP III	Treatment guidelines for high levels of blood cholesterol
Fibrates	A class of amphipathic carboxylic acids (e.g., fenofibrate) used to treat metabolic disorders such as hypercholesterolemia
Framingham Risk Score	A prediction algorithm developed from Framingham Heart Study data that estimates individual 10-yr risk on the basis of age, sex, TC, HDL-C, smoking status, and SBP; separate score sheets have been developed for men and women
LDL-C	Transports cholesterol and TGs from the liver to peripheral tissues; elevated plasma concentrations of LDL-C are associated with increased risk for CVD
Niacin (nicotinic acid)	Synonymous with vitamin B_3; niacin can be used in the treatment of dyslipidemia
Omega-3 fatty acids	A group of naturally occurring polyunsaturated fatty acids found in plants and in high levels in some fish; omega-3 fatty acids are essential nutrients in humans
Reynolds Risk Score	A risk prediction algorithm specifically designed to estimate 10-yr CV risk in women
Statin	A class of drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme involved in an early step of cholesterol biosynthesis

ATP III = Adult Treatment Panel III; CV = cardiovascular; CVD = CV disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride.

Table 2 10-minute evaluation

- Obtain patient's history. Ask about the following:
  - — Age
  - — Smoking
  - — Physical activity level
  - — Diet
  - — Family history of premature CV events
  - — Disease history: diabetes mellitus, hypertension, metabolic syndrome
- Measure height and weight and calculate BMI
- Measure blood pressure
- Perform physical examination of heart, lungs, aorta, and major arteries
- Encourage family healthy eating and exercise

BMI = body mass index; CV = cardiovascular.

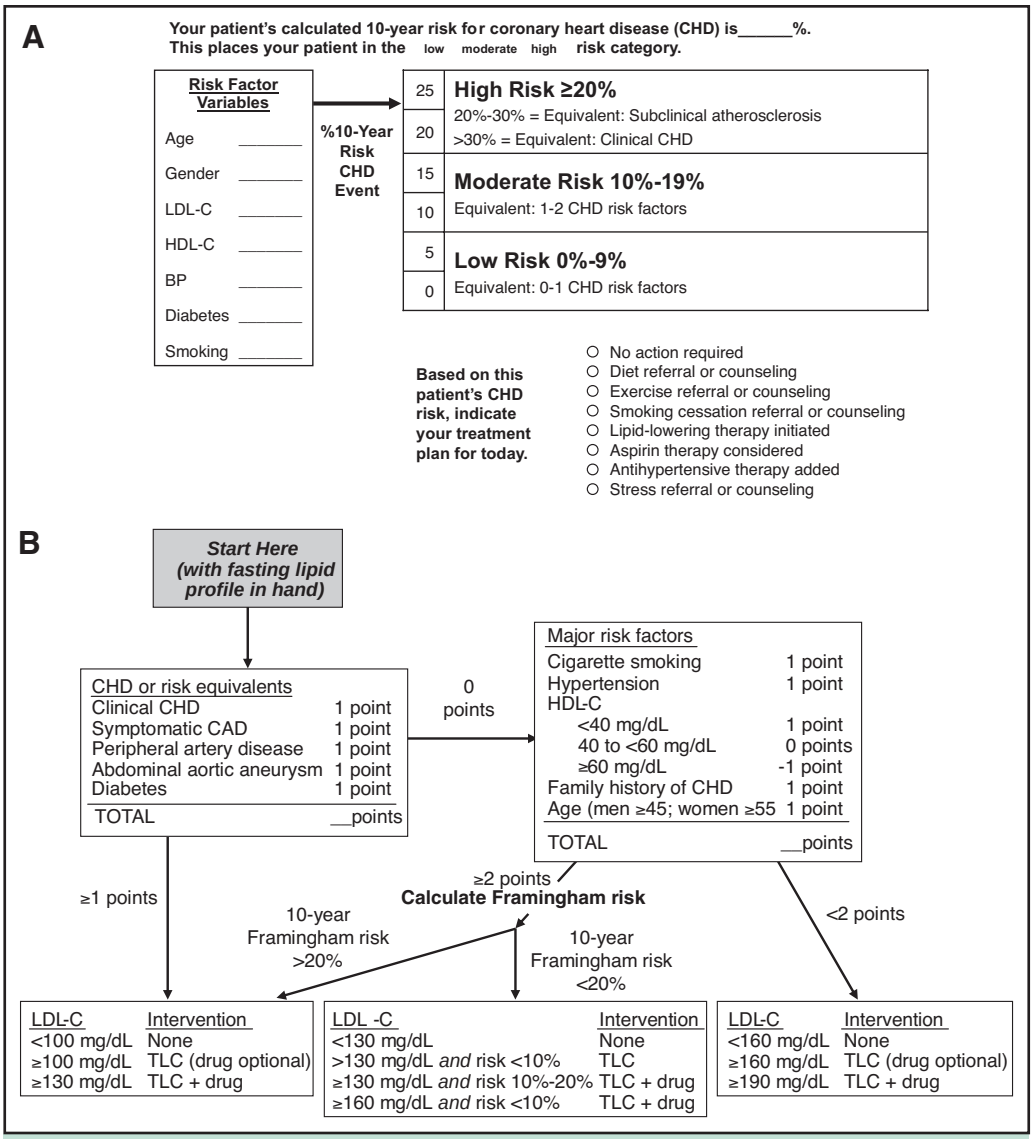

Figure 2 (*A*) One type of global risk educational tool adapted from the American Heart Association (AHA). (*B*) Suggested approach for risk assessment and treatment of patients, based on National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines. For cholesterol, 1 mg/dL = 0.02586 mmol/L; for triglyceride, 1 mg/dL = 0.01129 mmol/L. BP = blood pressure; CAD = coronary artery disease; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TLCs = therapeutic lifestyle changes. (Adapted from *Circulation*,[6] *JAMA*,[11] and *Curr Med Res Opin.*[13])

reduces risk for stroke, heart failure, and myocardial infarction.[6,17,18] Lower blood pressures reduce the relative risk for major CV events, regardless of the treatment used to achieve reduction in blood pressure.[19] The presence of hypertension or treatment for hypertension increases global risk and may intensify lipid therapy goals.[6]

Screen for Diabetes. Diabetes confers a high risk that a patient may have a CV event. An asymptomatic, otherwise healthy patient with diabetes has a CV risk equivalent to that of a patient who has already had a myocardial infarction.[6] Type 2 diabetes, by far the more common form, increases the risk of CV events >3-fold.[19]

Screening for diabetes with a fasting glucose test should be considered in all individuals who are ≥45 years old and for younger patients who have risk factors such as being overweight. A fasting plasma glucose concentration >100 mg/dL (1 mg/dL = 0.05551 mmol/L) is considered abnormal, and a fasting plasma glucose concentration ≥126 mg/dL provides a provisional diagnosis of diabetes.[20] For patients with an abnormal fasting glucose, a 2-hour glucose tolerance test should be performed. Emphasis on recognition of abnormal glucose levels may help patients modify their behavior and may slow the progression to type 2 diabetes. For patients who already have received a diagnosis

Table 3 The fasting lipid profile*

- Typical components and values associated with low risk of CVD:
  - TC <200 mg/dL
  - LDL-C <100 mg/dL
  - HDL-C ≥40 mg/dL
  - TG <150 mg/dL
  - Non–HDL-C <130 mg/dL (useful when TG >200 mg/dL)
  - Ratio of TC/HDL-C <3.0
- Typical methods of determination:
  - Direct: TC, HDL-C, and TG
  - Calculated:
    - LDL-C = TC − HDL-C − TG/5†
    - Non–HDL-C = TC − HDL-C

CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

*For conversion to SI units 1 mg/dL cholesterol = 0.02586 mmol/L; 1 mg/dL TG = 0.01129 mmol/L.

†For typical TG <200-400 mg/dL; other methods are required for patients with hypertriglyceridemia. Adapted from *JAMA*.[11]

Table 4 Clinical identification of metabolic syndrome*

Risk Factor	Defining Level†	Patient's Level
Elevated waist circumference	Men: ≥40 in (102 cm); women: ≥35 in (88 cm)	
Elevated TG level	≥150 mg/dL	
Reduced HDL-C level	Men: <40 mg/dL; women: <50 mg/dL	
Elevated blood pressure	≥130/85 mm Hg	
High fasting blood glucose level	≥100 mg/dL	

HDL-C = high-density lipoprotein cholesterol; TG = triglyceride.

*The American Heart Association and the National Heart, Lung, and Blood Institute recommend that the metabolic syndrome should be identified as the presence of ≥3 of these components.

†For cholesterol, 1 mg/dL = 0.02586 mmol/L; for TG, 1 mg/dL = 0.01129 mmol/L; for glucose, 1 mg/dL = 0.05551 mmol/L.

Adapted from *Circulation*.[21]

of diabetes, glycosylated hemoglobin (HbA_{1c}) should be followed at 3-month intervals. The goal for patients in general is HbA_{1c} <7%.[20]

Screen for Metabolic Syndrome. Metabolic syndrome is characterized by abdominal obesity, atherogenic dyslipidemia (high triglyceride [TG] levels, low levels of high-density lipoprotein [HDL] cholesterol, small LDL cholesterol particles), high blood pressure, insulin resistance (±glucose intolerance), and inflammatory or prothrombotic states (Table 4).[21] Taken together, these risk factors increase CHD risk independent of LDL cholesterol level.[11] Persons with CHD and metabolic syndrome are more likely than those with CHD alone to experience a major CV event.[22] Weight reduction and increased physical activity are first-line approaches to management of metabolic syndrome and can help to mitigate other risk factors.[11] (See the article by Bays[5] in this supplement for additional information.) A guide to new and evolving risk-identification tests is presented in Table 5.

Table 5 New and evolving risk identifiers

The following tests may be helpful for determining the appropriate intensity of treatment for the intermediate-risk patient:

- Imaging
  - CAC score
    - Measured via computed tomography
    - Correlates with quantity of plaque
    - May be predictive of CVD in asymptomatic patients
    - Expensive and not widely available
    - Does not change with treatment
  - IMT measurement
    - Ultrasound measurement of carotid wall thickness
    - Used in research trials as surrogate for progression of atherosclerosis
    - Not generalizable to common clinically available measurements
    - Helpful in assessment of intermediate-risk patient
    - Widely available carotid ultrasound (e.g., at shopping malls) may not involve patient–physician interaction; however, may serve as means of engaging patient in primary prevention
- Clinical biomarkers
  - hs-CRP measurement
    - Measurable biomarker of inflammation
    - Accepted as independent risk factor for atherosclerosis/CV risk
    - Lowered by statin therapy
    - The JUPITER trial in men aged ≥50 and women aged ≥60 with LDL-C <130 mg/dL and hs-CRP ≥2 mg/L showed significant event reduction in primary prevention with a statin.[23]

CAC = coronary artery calcium; CV = cardiovascular; CVD = CV disease; hs-CRP = high-sensitivity C-reactive protein; IMT = intima-media thickness; JUPITER = Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol.

Essential Physician–Patient Communication

One of the most challenging aspects of managing CV risk is to engage the well patient (primary prevention) in acknowledgment and intervention for risk factors (Table 6). To overcome skepticism about preventive strategies, it is important for the clinician to emphasize that lifestyle changes and medications have been shown to reduce or eliminate risk factors and slow the progression of atherosclerosis. It is sometimes helpful in establishing a therapeutic partnership for long-term health[19] to define goals and stratify their importance (Table 7). Allowing patients to choose priorities and to pick goals can help break down barriers. This may

Table 6 Motivating your patients

- Measure fasting lipids, glucose, and chemistries before the visit for more effective use of time
  - — Give lab slips to patients for 6- and 12-month tests to emphasize the need for ongoing interactions
- Offer dietary counseling
- Provide a list of community exercise facilities/programs
- Encourage enrollment in a smoking cessation program
- Have the patient set goals for lifestyle changes
- Have the nursing staff make regular patient follow-up calls
- Provide information on health action plans available from insurance providers
- Provide information on community and Web-based resources for weight loss, smoking cessation, and exercise
- Schedule regular follow-up visits that match timelines set up by the patient
- Consider a contract

Table 7 Setting goals and priorities: a contract for partnership

- 3 Months of a therapeutic diet
  - — Assess lipid changes, blood pressure, and weight
  - — Add exercise if needed
- 6 Months of diet ± exercise
  - — Assess lipids, blood pressure, and overall risk level
  - — If necessary, adjust diet and exercise and/or initiate drug therapy
  - — Review goals and set plan for long-term maintenance of progress
- Annually
  - — Review lipids and other indicators of risk
  - — Monitor adherence to diet, exercise, weight control, and drug therapy, adjusting as needed
  - — Discuss any updates to treatment guidelines and goals

restore control to the patient for self-directed care and may reduce some of the frustration physicians feel when dealing with multiple risk factors simultaneously.

TAILORING LIPID TREATMENT TO THE TOTAL PATIENT

The purpose of primary prevention for atherosclerosis is to avoid a CV event in the asymptomatic patient. Treatment must be individualized, and success must begin with an accurate assessment of an individual's global and lifetime risk for atherosclerotic CVD.

Primary prevention includes both population strategies and clinical strategies, with the primary care physician serving as the link between large-scale public health measures (e.g., no-smoking campaigns, weight-loss guidelines) and identification of individual patients who could benefit from risk factor modification on the basis of their unique profiles.

Table 8 Lifestyle changes to recommend to your patients

- Stop smoking
- Limit cholesterol intake to <200 mg/day
- Maintain a healthy weight
- Increase physical activity

Lowering of LDL cholesterol levels is a primary goal of both long-term (lifetime) and short-term (<10 years) primary prevention of atherosclerotic CV events.[6]

Therapeutic Lifestyle Changes

Therapeutic lifestyle changes constitute first-line therapy for reducing LDL cholesterol levels in persons at risk for atherosclerotic CV events.[6] All persons, regardless of their short- or long-term risks, should be counseled to adopt positive changes, including a low-cholesterol diet, increased physical activity, and cessation of smoking (Table 8). Diets should include limits for saturated fats, polyunsaturated fats, monounsaturated fats, total fat, carbohydrates, and protein. Total cholesterol intake should be kept to <200 mg/day.[11] Physical activity guidelines continue to change but should include at least 30 minutes of aerobic activity 5 to 6 days a week. If this is beyond a patient's initial capability, stepwise modest goal setting will promote adherence.

Unfortunately, many patients cannot achieve target goals with therapeutic lifestyle changes alone. Counseling provided by a dietitian may help some to adhere to dietary restrictions. For those who still cannot achieve goals, lipid-lowering therapy should be considered.[11] Steps should be taken to treat components of the metabolic syndrome and to intensify weight management and physical activity.[11] In those patients whose risk factors put them at risk for a CV event (Framingham Risk Score >10%[11]), action should be taken immediately to control blood pressure, hyperglycemia, and elevated LDL cholesterol.[14]

Lipid-lowering therapy should be instituted for those patients who do not reach their primary prevention goals through therapeutic lifestyle changes, for higher-risk patients, and for secondary prevention. Studies confirm that for patients at highest risk and for some who require secondary prevention, an LDL cholesterol goal <70 mg/dL is warranted. Factors that favor intensifying therapy to achieve these levels include established CV disease plus ≥1 of the following: diabetes, multiple major risk factors, severe or poorly controlled risk factors, metabolic syndrome or its components, and acute coronary syndromes.[14] The first step is to identify appropriate treatment regimens that are based on needed intensity for assessed risk factors (Tables 9 and 10; Figure 2).[6,11,13,14] One should target therapy first toward LDL cholesterol goals and secondarily to TG and HDL cholesterol levels, unless very high TGs put the patient at immediate risk. Older adults benefit from and should re-

Table 9 Major risk factors that modify low-density lipoprotein cholesterol goals

- Age (>45 yr for men; ≥55 yr for women)
- Family history of premature CHD (<65 yr in female first-degree relative; <55 yr in male first-degree relative)
- Cigarette smoking
- Diabetes mellitus
- Low HDL-C (<40 mg/dL [1 mg/dL = 0.02586 mmol/L])
- Hypertension (BP ≥140/90 mm Hg or current treatment for hypertension)

BP = blood pressure; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol.
Reprinted with permission from *JAMA*.[11]

Table 11 Are women different?

- Modification of risk factors provides benefit for women and for men
- In general, women present with cardiac events about 10 yr later than men[11]; however, individual risk requires evaluation without a population timeline
- Framingham Risk Assessment may underestimate risk in women because family history is not included
- The Reynolds Risk Score is tailored to women[24]
- National campaigns such as "Go Red for Women" (goredforwomen.org) provide tools that can be used to support women in risk evaluation and treatment

Table 10 Proposed modifications to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) low-density lipoprotein cholesterol (LDL-C) goals based on recent clinical trials

Risk Category	LDL-C Goal*	Initiate TLC	Consider Drug Therapy†
High risk (CHD or CHD risk equivalent; 10-yr risk >20%)	<100 mg/dL Optional: <70 mg/dL	≥100 mg/dL	≥100 mg/dL <100 mg/dL: consider drug options
Moderately high risk (≥2 risk factors; 10-yr risk 10% to 20%)	<130 mg/dL Optional: <100 mg/dL	≥130 mg/dL	≥130 mg/dL 100-129 mg/dL: consider drug options
Moderate risk (≥2 risk factors; 10-yr risk <10%)	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk (≤1 risk factor)	<160 mg/dL	≥160 mg/dL	≥190 mg/dL 160-189 mg/dL: LDL-C–lowering drug optional

CHD = coronary heart disease; TLC = therapeutic lifestyle changes.
*For cholesterol, 1 mg/dL = 0.02586 mmol/L; for triglyceride, 1 mg/dL = 0.01129 mmol/L.
†When use of drugs is considered, intensity of therapy should be sufficient to lower LDL-C by 30% to 40%.
Reprinted with permission from *Circulation*.[14]

ceive the same LDL cholesterol–lowering therapy that is given to other age groups. Considerations for risk evaluation and treatment of women are given in Table 11.[11,24]

Special Considerations for Patients with Diabetes and the Metabolic Syndrome

Patients with diabetes frequently exhibit the pattern of low HDL cholesterol plus high TG levels—an atherogenesis-promoting pattern that is often part of a conglomerate of signs and symptoms referred to as the metabolic syndrome.[6] Most measures of LDL cholesterol are calculated; however, in the presence of high TGs, this calculation may be inaccurate. Non–HDL cholesterol (calculated as total cholesterol minus HDL cholesterol) is a more accurate assessment of risk in the patient with high TGs. According to NCEP guidelines, the non–HDL cholesterol goal is 30 mg/dL higher than that for LDL cholesterol (Table 12). Lowering LDL cholesterol in patients with diabetes can significantly decrease the overall rate of vascular events by as much as 22%, as was shown in a previous study.[15] Type 2 diabetes is a CV risk equivalent; therefore, consideration of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) treatment for all patients with diabetes is reasonable.[25]

LDL Cholesterol–Lowering Therapies

A summary of medications currently approved in the United States for treatment of atherosclerosis is given in Table 13.[26-32]

Statins. Statins are the best tolerated and most effective way to reduce LDL cholesterol levels and are considered the first-line medication choice toward this end.[6] Depending on the statin and dose used, decreases in LDL cholesterol of up to 55% and in TG levels of up to 30%, along with increases in HDL cholesterol of up to 15%, can be expected (Figure 3).[11] Statins differ in terms of their efficacy in improving lipid profiles[33,34] (Figure 4 and Table 14). TGs are lowered and HDL cholesterol values are raised by statins to various degrees, again depending on the dose and the specific statin used (Table 14).

Statins provide a greater absolute benefit for persons at higher risk, but relative risk reduction is similar across all

Table 12 Non–high-density lipoprotein cholesterol (non–HDL-C): a better target in diabetes

Example	Lipid Values*
Example 1: Acceptable TC, low HDL-C, high TG	Measured: TC = 150 mg/dL; HDL-C = 35 mg/dL; TG = 250 mg/dL Calculated: LDL-C = TC−HDL-C − TG/5 = 65 mg/dL (desirable) Calculated: Non–HDL-C = TC−HDL-C = 115 mg/dL (desirable)
Example 2: High TC, borderline HDL-C, high TG	Measured: TC = 220 mg/dL; HDL-C = 40 mg/dL; TG = 250 mg/dL Calculated: LDL-C = 130 mg/dL (too high) Calculated: Non–HDL-C = 180 mg/dL (too high)
Example 3: Very high TC, high HDL-C, high TG	Measured: TC = 250 mg/dL; HDL-C = 55 mg/dL; TG = 250 mg/dL Calculated: LDL-C = 145 mg/dL (too high) Calculated: Non–HDL-C = 195 mg/dL (too high)

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

*To calculate values in SI units 1 mg/dL = 0.02586 mmol/L for cholesterol; 1 mg/dL = 0.01129 mmol/L for TG.

Table 13 Medications with US-approved indications for atherosclerosis*

Drug	Indication
Rosuvastatin[30]	As adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy designed to lower TC and LDL-C to target levels
Fluvastatin[26]	To slow the progression of coronary atherosclerosis in patients with CHD as part of a treatment strategy intended to lower TC and LDL-C to target levels
Lovastatin[27]	To slow the progression of coronary atherosclerosis in patients with CHD as part of a treatment strategy used to lower TC and LDL-C to target levels
Pravastatin[29]	In patients with clinically evident CHD, indicated to slow the progression of coronary atherosclerosis
Niacin[28]	In combination with a bile acid–binding resin to slow progression or promote regression of atherosclerotic disease in patients with a history of CHD and hypercholesterolemia

CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.

*Consult the Product Information for each agent to confirm its complete indications, adverse effects, drug interactions, and contraindications.[26-32]

levels of risk.[35] The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) established that lowering LDL cholesterol, even in people with only borderline high levels, produces a significant reduction in risk of CV events.[36]

Statins have been shown to be safe and well tolerated.[6] Issues of liver safety remain a major concern for both practitioners and patients who hear repeated warnings in direct-to-consumer statin advertising. The National Lipid Association (NLA) reviewed liver safety and the use of statins and concluded that the most important issue related to statins and the liver was not whether increases in liver function tests (aspartate aminotransferase or alanine aminotransferase >3 times upper limit of normal [ULN]) were seen in <1% of patients on starting or intermediate doses and in 2% to 3% of those on 80 mg[37]), but whether they cause serious liver dysfunction or failure. They report that these events are extremely rare and may occur in patients on statins and in the general public at similar rates, offering alternative conclusions: (1) that no relation exists between statins and liver failure, or (2) that liver failure may be a very rare idiosyncratic reaction. Table 15 offers a summary of this group's recommendations.[37,38]

At present, assessment of liver function before beginning a statin and reassessment at intervals as recommended on the package insert are advised, and instructions should be provided to patients regarding signs of serious liver dysfunction. Liver function tests performed twice a year with fasting lipid measurements will not identify the idiosyncratic case of liver failure but may be helpful in encouraging adherence to the medication regimen by reminding the patient of the goals for lipid lowering.

Not only are statins well tolerated by older adults, but they also provide risk reduction benefits similar to those seen in younger patients.[14,39-41] Clinical judgment must be used to weigh efficacy or treatment effects against safety, tolerability, and patient preference.

When prescribing a statin, physicians should use doses high enough to achieve appropriate target levels; this may require a 30% to 40% reduction in LDL cholesterol from baseline or selection of a dose that should help a patient get to goal (Table 14).[14] Depending on the usual starting dose of the chosen statin, achievement of a specific goal may require uptitration. In such a case, let the patient know that the goal may not be achieved on the first dose, and that uptitration may be needed. With anticipation of this possible outcome by the patient, adherence may be improved by removing the feeling of failure when the "goal" is not achieved. Choosing the statin that can be anticipated to enable the patient to reach goal will help with adherence as well. An effect should be seen within 6 weeks of initiation of therapy; it rarely becomes more robust after that time.[42] Measurement of lipid levels and liver function on a regular basis (e.g., every 6 months) solidifies the patient's understanding of the importance of this intervention.

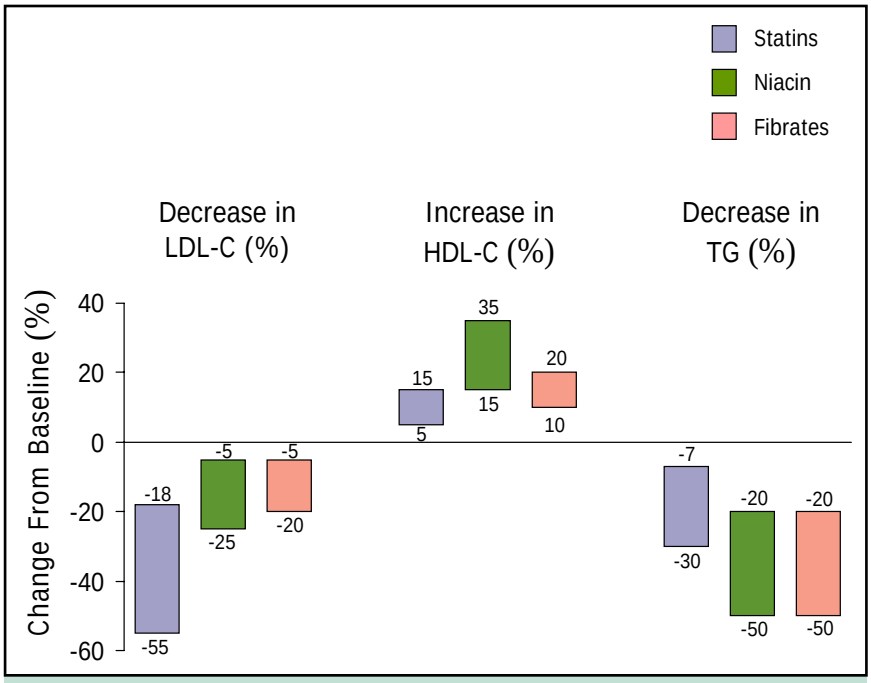

Figure 3 Range of effects on lipids of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), niacin, and fibrates. Bars represent maximum expected effect, and lines across bars indicate minimum expected effect. Magnitude of effect is dependent on the dose and type of each class of drugs. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride. (Adapted from *JAMA*.[11])

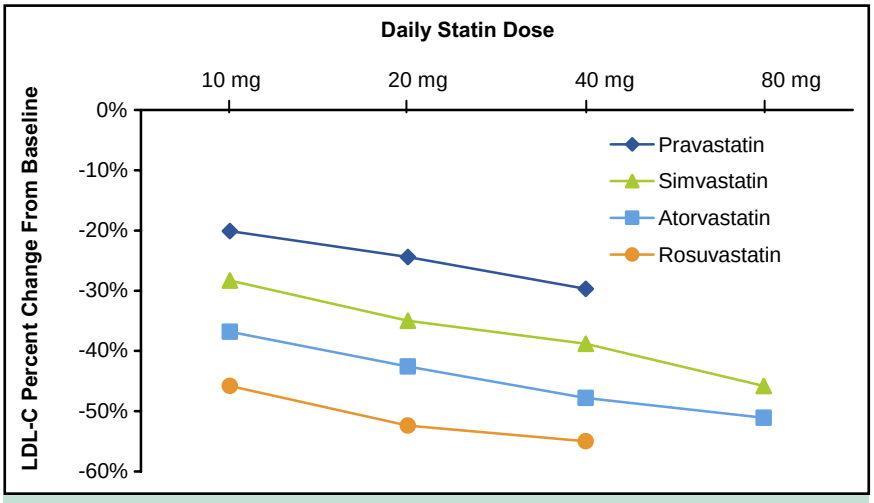

Figure 4 Least-squares mean percentage change from baseline in low-density lipoprotein cholesterol (LDL-C) with statin doses (from the STELLAR [Study to Evaluate the Safety and Efficacy of Rosuvastatin versus Atorvastatin, Pravastatin, and Simvastatin in Subjects With Hypercholesterolemia] trial). (Adapted from *Am J Cardiol*[33] and adapted with permission from *Curr Med Res Opin.*[34])

Ezetimibe. Ezetimibe can be used as weak monotherapy that is best suited for patients who cannot tolerate a statin. Ezetimibe when added to statin therapy may further decrease LDL cholesterol.[43,44] However, prospective, randomized trials to assess whether this additional reduction further improved event reduction are ongoing. Data from the first prospective study undertaken to look at a surrogate marker in patients with familial hypercholesterolemia did not show additional benefit with combination therapy.[45]

Table 14 Lipid changes with "standard" doses of currently available statins*

Statin	Dose (mg/day)	LDL-C Reduction (%)	HDL-C Increase (%)	Triglyceride Reduction (%)
Rosuvastatin[30]	5-10	45-52	13-14	10-35
Atorvastatin[31]	10	39	6	19
Simvastatin[32]	20-40	38-41	8-9	18-19
Pravastatin[29]	40	34	12	24
Lovastatin[27]	40	31	5	8
Fluvastatin[26]	40-80	25-36	4-7	14-19

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
*Based on information in US prescribing information.

Additional/Adjunctive Lipid-Lowering Therapies

Eicosapentaenoic Acid from Fish Oil. Supplements that contain the long-chain omega-3 eicosapentaenoic acid found in fish oil at doses up to 3 g/day reduce TG levels by as much as 30%.[6] Evidence supports a role for omega-3 fatty acid supplements in reducing risk factors for atherosclerosis.[6,46] The benefits of omega-3 fatty acids include reduced serum TGs, lower risk of sudden cardiac death and all-cause mortality, mildly lower blood pressure, and reduced risks of inflammation and thrombosis.[46] These can be considered for use in combination with statins for patients with elevated TGs and LDL cholesterol. When added to a statin regimen, low doses of eicosapentaenoic acid (1.8 g/day) reduced the rate of coronary events compared with that seen with statin treatment alone.[47] If patients complain of a "fishy" taste, refrigerating the pills or switching brands may help.

Niacin (Nicotinic Acid). Treatment with niacin at a usual dose of 1 to 2 g/day has a beneficial effect on TGs, LDL cholesterol, and HDL cholesterol. Reductions in TG levels of up to 50% and reductions in LDL cholesterol of up to 25% have been reported for both immediate-release (crystalline) and extended-release forms (Figure 3).[6,11] Long-term use of niacin may be limited by adverse effects.[6] The most common adverse effect is flushing or redness of the skin. Flushing can be mitigated by taking aspirin or a nonsteroidal anti-inflammatory drug (NSAID) with a snack (e.g., crackers) a half hour before taking niacin. Very slow uptitration may be helpful to the patient in reaching optimal doses of niacin. Gastrointestinal symptoms and other serious adverse effects have been reported.[6] High doses may worsen glucose control in patients with type 2 diabetes. Niacin given alone or in combination with statins (if LDL cholesterol level is high) is a therapeutic option for patients with atherogenic dyslipidemia.[6]

Fibrates. Fibrates are most useful as monotherapy for people with very high TGs and as adjunctive therapy to statins for people with continued high TGs (Figure 3).[6,11] Their main adverse effects include gastrointestinal problems and a possible increase in gallstones. Fenofibrate may have less impact than gemfibrozil on drug–drug interactions.

Table 15 Recommendations to healthcare professionals regarding the liver and safety of statins

1. During the routine general evaluation of patients being considered for statin and other lipid-lowering therapy, it is advisable to obtain liver transaminase levels. If these tests are found to be abnormal, further investigation should be performed to determine the etiology of the abnormal test results.
2. Until there is a change in the FDA-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.
3. The clinician should be alert to patient reports of jaundice, malaise, fatigue, lethargy, and related symptoms in patients taking statin therapy as a signal of potential hepatotoxicity. Evidence for hepatotoxicity includes jaundice, hepatomegaly, increased indirect bilirubin level, and elevated prothrombin time (rather than simple elevations in liver transaminase levels).
4. The preferred biochemical test to ascertain significant liver injury is fractionated bilirubin, which, in the absence of biliary obstruction, is a more accurate prognosticator of liver injury than are isolated aminotransferase levels.
5. Should the clinician identify objective evidence of significant liver injury in a patient receiving a statin, the statin should be discontinued. The etiology should be sought and, if indicated, the patient referred to a gastroenterologist or hepatologist.
6. If an isolated asymptomatic transaminase level is found to be elevated by 1-3 times the ULN, there is no need to discontinue the statin.
7. If an isolated asymptomatic transaminase level is found to be >3 times the ULN during a routine evaluation of a patient administered a statin, the test should be repeated and, if still elevated, other etiologies should be ruled out. Consideration should be given to continuing the statin, reducing its dose, or discontinuing it based on clinical judgment.
8. According to the Expert Liver Panel, patients with chronic liver disease, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis may safely receive statin therapy.

FDA = US Food and Drug Administration; ULN = upper limit of normal.
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Other Supplements and Therapies

Dietary supplements, herbal preparations, and alternative therapies are popular with patients who otherwise might not seek "drug" treatment, but they are of dubious benefit. The data for most such interventions are inconclusive, and at present, their routine use for prevention of atherosclerotic CV disease is not recommended.[48]

Plant stanols and sterols, when added to margarines and other food products, are effective in further reducing LDL cholesterol. A meta-analysis of 41 trials showed that intake of 2 g/day of stanols or sterols reduced LDL cholesterol by 10%.[49] Incorporation of plant stanol esters into margarine is among the first examples of a functional food with proven LDL cholesterol–lowering effectiveness.

In the Women's Health Study, no benefit of vitamin E supplements for primary prevention was seen in terms of atherosclerotic CV events.[50] In fact, a recent meta-analysis of antioxidant use for primary and secondary prevention of atherosclerotic CV events suggests that use of vitamin E supplements may increase mortality.[51]

Another food that is often used by patients for presumed CV health is garlic. A randomized clinical trial that compared raw garlic and commercial garlic supplements versus placebo found no effect for any of the garlic preparations in terms of LDL cholesterol levels or any other lipid concentrations.[52]

At this time, no data are available to support the benefit of adding coenzyme Q10 to statin therapy.[53]

PEARLS FOR CLINICAL GUIDANCE

- Atherosclerosis is a lifelong process; intervention produces significant reductions in CV morbidity and mortality.
- Risk factors for atherosclerosis are predictors of risk for a CV event.
- Primary prevention involves identification and modification of risk factors.
  - Nonmodifiable risk factors (e.g., age, family history) are part of the global assessment of risk.
  - Manage all risk factors to achieve guideline goals for blood pressure control, smoking cessation, obesity, active lifestyle, and acceptable lipid levels.
  - Initiate and reinforce therapeutic lifestyle measures such as a low-fat diet and increased physical activity.
  - Identify those patients at moderate to high risk who could benefit from intervention with medication.
- Statins are the first-choice medication for lowering LDL cholesterol in primary and secondary prevention.
- Niacin, fibrates, plant stanols and sterols, and omega-3 fatty acids may be appropriate adjunctive therapies for patients with certain lipid profiles.
- Use the global assessment of risk to identify patients with long-term risk for atherosclerosis who are candidates for primary prevention.
  - Manage their nonlipid risk factors, that is, weight, diet, and physical activity level.
  - Begin testing serum total cholesterol levels at age 20, and repeat every few years.
  - Treat patients with elevated LDL cholesterol, even in the absence of other risk factors.
  - Start with therapeutic lifestyle changes, and add medication if necessary to achieve LDL cholesterol goals.
  - Remember the additive effects of multiple risk factors.
  - Clinical judgment is essential in treating persons at intermediate risk.

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