Coronary heart disease (CHD), the leading cause of death in men and women in the United States, was responsible for about 1 of every 6 deaths in 2006.

The US National Health and Nutrition Examination Survey (NHANES; 2003 - 2006) estimated that 17.6 million Americans aged 20 years or older have CHD. Atherosclerosis is a lifelong disease that results from a combination of genetic and environmental factors, including oxidation, modification, and retention of apolipoprotein B (apoB)-containing lipoproteins in the arterial wall intima. The complex interaction between these modified lipoproteins and recruited inflammatory cells (eg, monocytes, T lymphocytes) in the intima leads to the formation of fatty streaks and, subsequently, fibrous plaques. Atherosclerotic plaques may progressively narrow the arterial lumen, restricting blood flow and causing clinical symptoms such as angina. Some plaques may rupture, causing sudden thrombosis of major conduit arteries and leading to myocardial infarction or stroke.

Atherosclerosis typically is asymptomatic for many years, and clinical symptoms of CHD do not arise until the disease has progressed substantially. As part of the 5-year longitudinal US population-based Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD), a cross-sectional analysis of 2006 survey data revealed that CHD was first diagnosed after symptoms developed in 50% of patients; only 19% reported that a CHD diagnosis was made during routine screening. The study highlighted the need for earlier identification of risk and intervention, which can be achieved by raising public awareness and by screening for major CHD risk factors, such as dyslipidemia, hypertension, diabetes, smoking, obesity, physical inactivity, atherogenic dietary habits, increasing age, and family history of premature CHD. Among these risk factors, dyslipidemia has an important role in the initiation and progression of atherosclerosis for middle-aged and older persons and for young adults. A recent prospective study found that nonoptimal lipid levels in otherwise healthy young adults contributed to a higher prevalence of coronary calcification 2 decades later. Treatment of dyslipidemia must be accompanied by interventions to address the modifiable risk factors for CHD, including lifestyle changes, such as smoking cessation, diet and weight control, and increased physical activity, as well as treatment of hypertension and diabetes.

ATP III GUIDELINE RECOMMENDATIONS

The 2001 National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines and the 2004 update (available at http://www.nhlbi.nih.gov/guidelines/cholesterol) recommend low-density lipoprotein cholesterol (LDL-C) as the primary target of lipid-lowering therapy for risk reduction. This recommendation is based on strong evidence from epidemiologic studies that elevated LDL-C is a major predictor of cardiovascular events and on results from large, randomized, controlled trials establishing that lowering LDL-C reduces cardiovascular risk. Specific LDL-C goals are stratified by a person’s short-term (10-year) level of risk, and patients at higher risk have a lower target value (Table 1). ATP III guidelines also introduced non–high-density lipoprotein cholesterol (non–HDL-C) as a secondary target of therapy in patients with high triglycerides (≥ 200 mg/dL) (see Table 1). The guidelines recognize that the measurement of cholesterol in the low-density lipoprotein particle fraction underestimates the burden of other lipoproteins that can contribute to atherogenesis, including intermediate-density lipoprotein, very low-density lipoprotein, and lipoprotein(a), especially in patients with hypertriglyceridemia. In addition, many studies have shown that non–HDL-C is a better predictor of cardiovascular events than LDL-C and that the magnitude of non–HDL-C lowering is associated directly and consistently with cardiovascular risk reduction. From a practical point of view, the non–HDL-C level can be determined for patients in a nonfasting state, is easy to calculate (total cholesterol minus HDL-C), and adds no additional expense beyond the standard lipid panel measurements.
GAP BETWEEN CLINICAL PRACTICE AND GUIDELINE RECOMMENDATIONS

Statin treatment in high-risk patients has been shown to alter the course of atherosclerosis and reduce the rate of cardiovascular events in clinical trials.\textsuperscript{17-22} Even healthy older persons without known atherosclerosis derive substantial cardiovascular benefit from statin therapy.\textsuperscript{23} Yet, despite the demonstrated benefit of lipid-lowering therapy, dyslipidemia is not adequately controlled in clinical practice, especially in the high-risk groups.

The NEPTUNE II survey evaluated lipid target attainment in the United States under the updated ATP III guidelines. Overall, 67% of patients (n = 4885) achieved their LDL-C targets. LDL-C goal attainment was associated inversely with cardiovascular risk category: higher-risk patients had lower success rates.\textsuperscript{24} Among very high-risk patients (see Table 1), only 18% met the optional LDL-C goal of < 70 mg/dL.\textsuperscript{24} Among patients with high triglycerides, only 39% achieved combined LDL-C and non–HDL-C goals.\textsuperscript{24} The L-TAP 2 survey conducted a few years later (between 2006 and 2007) showed some improvement in lipid goal attainment in the United States: 76% and 72% of all patients (n = 3049) achieved ATP III–recommended LDL-C and non–HDL-C target levels, respectively; 35% of very high-risk patients (n = 511) attained the optional LDL-C target of < 70 mg/dL.\textsuperscript{25}

Although dyslipidemia management has improved since the updated ATP III guidelines were issued, about one-third of patients are not at their lipid goals; even fewer very high–risk patients attain the optional goal. More attention to the identification of at-risk candidates for therapy and initiation of appropriate lipid-lowering drug treatment is needed to improve clinical outcomes.

INDIVIDUALIZED RISK ASSESSMENT

Ideally, the clinical decision about appropriateness of lipid treatment begins with a comprehensive assessment of a patient’s global risk of CHD. The higher the short-term (10-year) risk of CHD, the greater the absolute benefits from a targeted treatment plan.

Guideline-based risk assessment and modification. As detailed in ATP III guidelines, current CHD risk assessment focuses on counting the number of traditional risk factors and estimating 10-year CHD risk using the Framingham risk score (FRS) (Figure).\textsuperscript{4} (A 10-year risk calculator is available at http://www.nhlbi.nih.gov/guidelines/cholesterol; a primary care model for general cardiovascular risk is available at http://www.framinghamheartstudy.org/risk/gencardio.html.) The LDL-C primary and non–HDL-C secondary goals depend on a person’s baseline LDL-C level and absolute risk of CHD (ie, the person’s risk category; see Table 1).\textsuperscript{4,7} Therapeutic lifestyle change is a core requirement for achieving both LDL-C and non–HDL-C goals\textsuperscript{4,26}; drug therapy should be considered for all high-risk patients in addition to changes in lifestyle (see Figure, Table 2). Along with traditional risk factors, life-habit risk factors, such as obesity, physical inactivity, atherogenic diet, and other emerging risk factors (discussed in the following section), also influence the risk of CHD.\textsuperscript{4}

The importance of lifestyle intervention in improving overall health and well-being recently prompted the development of Lifestyle Medicine Competencies for Primary Care Physicians.\textsuperscript{26} Metabolic syndrome (Table 3) is a specific combination of factors (abdominal obesity, mixed dyslipidemia [high triglycerides, small LDL-C particles, low HDL-C], high blood pressure, and impaired glucose handling) that is associated consistently with an increased risk of CHD and diabetes.\textsuperscript{4,27} According to ATP III guidelines, management of metabolic syndrome is a secondary target for risk reduction, and therapeutic lifestyle change has a more prominent role in treatment.

Role of emerging risk factors. ATP III guidelines–based risk prediction for cardiovascular events relies solely on the traditional FRS. However, evidence from studies conducted since the 2004 update of ATP III guidelines suggests that the FRS alone may underestimate total CHD risk,\textsuperscript{28,29} especially in asymptomatic persons with evidence of subclinical atherosclerosis. 30 Biomarkers, such as apoB and high-sensitivity C-reactive protein (hsCRP), and imaging evidence of subclinical atherosclerotic disease have been shown to have additional predictive value (Table 4).\textsuperscript{28,30-34} ApoB is present in each particle of chylomicrons, very low-density lipoprotein, intermediate-density lipoprotein, low-density lipoprotein, and lipoprotein(a), all of which are considered atherogenic.\textsuperscript{35} As with non–HDL-C, apoB is superior to LDL-C in predicting cardiovascular events, particularly for patients with high triglycerides and those receiving lipidlowering therapy.\textsuperscript{35} An American Diabetes Association/American College of Cardiology consensus conference on lipid management in patients with cardiometabolic risk (eg, metabolic syndrome or diabetes) included LDL-C, non–HDL-C, and apoB as treatment targets for lipid-lowering therapy: apoB < 90 mg/dL, LDL-C < 100 mg/dL, and non–HDL-C < 130 mg/dL for high-risk patients; and apoB < 80 mg/dL, LDL-C < 70 mg/dL, and non–HDL-C < 100 mg/dL for very high–risk patients.\textsuperscript{5} Standardized apoB assays are not widely available. However, because non–HDL-C is highly correlated with apoB in patients with or without lipidlowering therapy,\textsuperscript{36-38} non–HDL-C may be used as a surrogate marker for apoB to assess cardiovascular risk in these patients.
Measurement of hsCRP independently predicts future cardiovascular events. Adding hsCRP to the standard FRS can change classification of risk of CHD, especially for patients with a 10-year risk of 10% to 20%. These results are consistent with the 2003 CDC/American Heart Association consensus statement that recommended the use of hsCRP when evaluating asymptomatic patients at intermediate risk of CHD to potentially alter a treatment plan. Results from largescale clinical trials have further confirmed that hsCRP is useful in identifying risk of incident CHD in men older than 50 years and women older than 60 years; patients without elevated LDL-C (< 130 mg/dL) but with elevated hsCRP (≥ 2 mg/L) received significant cardiovascular benefit from statin therapy compared with placebo.

The Reynolds risk score (RRS), a newer risk assessment instrument, adds apoB, hsCRP, and additional risk factors (eg, family history of premature CHD; hemoglobin A1c if the patient has diabetes) to the traditional risk factors. Use of the RRS has been shown to significantly improve the accuracy of global cardiovascular risk prediction compared with the FRS. (The RRS calculator is available at http://www.reynoldsriskscore.org.) In addition to apoB and hsCRP, objective measures of atherosclerosis in asymptomatic people (eg, carotid intima-media thickness [CIMT] and coronary artery calcium [CAC] score) also can be used to improve risk assessment (see Table 4). CIMT measurement has been used in research trials for many years to monitor the progression of atherosclerosis; however, its use in clinical practice is relatively recent. Properly performed measures of common far wall CIMT can be compared with age- and gender-based population percentiles, and high CIMT percentiles in an individual are predictive of future CHD and stroke risk. CAC scoring measures calcification in the coronary arteries by CT scan and appears to be a better predictor of cardiac events than CIMT. Use of CIMT and CAC scoring has been recommended for additional risk assessment of persons with an intermediate FRS (ie, CIMT for patients with 6% to 20% FRS46 and CAC for those with 10% to 20% FRS47). These assessments may result in the reclassification of patients to a highrisk category.

ATTAIN LIPID GOALS WITH STATIN TREATMENT

Choose the most effective statin to achieve LDL-C target. For patients who cannot achieve their ATP III LDL-C target with therapeutic lifestyle changes alone, statins are the preferred agents, with other lipidlowering drugs as options. Statins are first-line therapy because of their well-documented efficacy in lowering LDL-C and reducing cardiovascular disease risk. An important consideration in selecting the appropriate statin is the percentage of LDL-C reduction needed for each patient from baseline level to target. Updated ATP III guidelines recommend that the intensity of therapy in highrisk or moderately high–risk persons should be sufficient to reduce LDL-C levels by at least 30% to 40%, a recommendation that is evidence based. This recommendation implies that the efficacy of the statin and adequate dosing are critical for goal achievement. A number of clinical studies have demonstrated that US FDA-recommended initial doses of statins (atorvastatin, 10 mg; pravastatin, 40 mg; rosvastatin, 5 - 10 mg; and simvastatin, 20 - 40 mg) can produce LDL-C reductions of 30% to 40%. (A more in-depth discussion of statin efficacy is provided on page S11 of this supplement.)

Individualize the initiation dose. ATP III guidelines recommend starting statins at moderate doses to attain the 30% to 40% minimum LDL-C reduction and increasing the dose if LDL-C goals are not achieved. All statins available in the United States have several starting dose options. However, starting with the lowest dose may require return visits for increased dosing, which not only increase costs (laboratory tests, office visits), but may also lead to undertreatment. Results of recent clinical efficacy trials showed that patients at high risk of cardiovascular events were more likely to reach their LDL-C goals if they were started at higher doses of statins. Moreover, a meta-analysis of 37 comparative studies of rosvastatin and atorvastatin or simvastatin, with a total of more than 32,000 participants across risk categories, revealed that statin dose was a significant predictor of lipid goal achievement.

To ensure time-efficient lipid goal achievement, algorithms have been developed and tested in which the appropriate dosing level is determined based on patient characteristics such as cardiovascular risk, baseline LDL-C level, and history of statin use. An evidence-based dosing table (Table 7) allows for convenient matching of the percentage of LDL-C reduction with the dose for each statin. The use of such tables has proven to be an effective approach for optimal achievement of lipid goals, which also may improve patient adherence.

Combining lipid-modifying drugs. For high-risk patients, achieving the optional LDL-C goal of < 70 mg/dL can be challenging and may require adding other lipid-modifying drugs to statins. Ezetimibe, a cholesterol absorption inhibitor, has been shown to improve LDL-C goal achievement when combined with statins. Whether the combination of a statin and ezetimibe can improve clinical outcomes...
over statins alone is being evaluated in randomized, controlled trials (SHARP and IMPROVE-IT).\textsuperscript{60} The addition of bile acid sequestrants, such as cholestyramine and colesvelem, to statins provides significant additional LDL-C-lowering efficacy.\textsuperscript{61–64} Colestipol with lovastatin has been shown to decrease atherosclerosis progression and increase regression, as assessed by quantitative arteriography, in men with documented coronary artery disease.\textsuperscript{65}

For high-risk patients with mixed dyslipidemia (eg, elevated LDL-C and high triglycerides and/or low HDL-C), the combination of a statin with nicotinic acid (niacin) or a fibrate is recommended by ATP III guidelines.\textsuperscript{4} Niacin plus statin therapy, compared with a statin alone, has been shown to induce regression of CIMT in patients with CHD or CHD risk equivalents,\textsuperscript{66} and ongoing studies (AIM-HIGH and HPS2-THRIVE) are evaluating clinical outcomes of this drug combination.\textsuperscript{67} Combination therapy with fenofibrate and a statin is effective in reducing triglyceride levels and raising HDL-C levels in patients with mixed dyslipidemia.\textsuperscript{68–70} However, recent results of the ACCORD Lipid study showed that fenofibrate plus simvastatin, compared with simvastatin alone, did not significantly reduce the risk of cardiovascular outcomes (8% risk reduction, \textit{P} = .32) in patients with type 2 diabetes.\textsuperscript{71} However, it is worth noting that a prespecified subgroup analysis of the ACCORD Lipid study suggested that diabetic patients with baseline triglycerides of ≥ 204 mg/dL and HDL-C ≤ 34 mg/dL had a 31% lower risk of CVD events with the combination than with simvastatin alone.\textsuperscript{71}

When considering niacin or fibrate in combination with statins, be aware of the possible adverse effects of each agent. Niacin can have a number of adverse effects, including hepatic transaminase elevations, increased glucose levels in susceptible persons, and a drug interaction with statins that may cause rare cases of myositis or rhabdomyolysis.\textsuperscript{72} Flushing is also a common adverse effect that may compromise adherence.\textsuperscript{73} Fibrates infrequently cause GI upset and rarely cause gallstones, and fenofibrate can cause small increases in creatinine levels.\textsuperscript{4} In addition, the combination of statins and gemfibrozil appears to increase the risk of myopathy and rhabdomyolysis; coadministration of gemfibrozil with statins is not recommended.\textsuperscript{74–76}

Prescription doses of omega-3 fatty acids are 1 option available to treat persistent severe hypertriglyceridemia (triglycerides ≥ 500 mg/dL).\textsuperscript{77} Results of a large, open-label, blinded, end point outcomes study in 18,645 Japanese patients with hypercholesterolemia suggest that adding a purified form of marine omega-3 fatty acid (eicosapentaenoic acid) to statin therapy significantly reduces the risk of major cardiovascular events (19% risk reduction) compared with statin therapy alone.\textsuperscript{78}

References: REFERENCES:
11. Genser B, Marz W. Low density lipoprotein cholesterol, statins and cardiovascular events: a


younger individuals with a family history of premature coronary heart disease and low Framingham risk score. *Clin Cardiol.* 2008;31:542-545.


75. Wu J, Song Y, Li H, Chen J. Rhabdomyolysis associated with fibrate therapy: review of 76


**Links:**