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Preparing for New Dyslipidemia Management Guidelines

Initiative Faculty

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A continuing education (CE) activity entitled *Reducing Cardiovascular Risk: Current Approaches to Clinical Decision Making in the Management of Dyslipidemia* was presented as one of four CE in the Mornings topics at the 46th ASHP Midyear Clinical Meeting and Exhibition in New Orleans, Louisiana, in December 2011. The program was presented by Joseph Saseen, Pharm.D., FASHP, FCCP, BCPS. Attendees submitted questions about unresolved issues and controversies that were later addressed by Dr. Saseen in a live webinar. Dr. Saseen discussed anticipated changes to evidence-based guidelines from the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III for the detection, evaluation, and treatment of dyslipidemia.[1,2] The release of new NCEP guidelines (ATP IV) is expected sometime this year. Some of the highlights of the webinar pertaining to new recommendations for lipid goals and therapeutic strategies expected in ATP IV are described in this e-newsletter. Highlights of the webinar pertaining to new more specific recommendations anticipated in ATP IV for special patient populations (e.g., patients who are very elderly or have chronic kidney disease) and unresolved controversies in the management of dyslipidemia are described in an e-newsletter to be released in May.

Expand Your Knowledge

On-demand CPE Activities

If you were unable to attend the live symposium, *Reducing Cardiovascular Risk: Current Approaches to Clinical Decision Making in the Management of Dyslipidemia*, conducted at the 2011 ASHP Midyear Clinical Meeting, a **1-hour CPE activity is available on demand.**

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Cardiovascular disease (CVD) and its cardiometabolic risk factors (hypertension, obesity, smoking, dyslipidemia, and diabetes mellitus) are common in the United States. More than 82 million Americans have CVD, including 16.3 million who have coronary heart disease (CHD), 7.9 million with myocardial infarction (MI), 7.0 million with stroke, and 5.7 million with heart failure.[3] More than 33 million Americans have hyperlipidemia as defined by the American Heart Association (AHA) as a total cholesterol concentration of 240 mg/dL or higher. However, many other people have

dyslipidemia (an umbrella term that encompasses a variety of lipid disorders in addition to elevated total cholesterol levels) that increases their risk for CVD without meeting the AHA criterion. Analysis of epidemiologic data revealed that 71 million Americans had elevated levels of low-density lipoprotein (LDL) cholesterol between 2005 and 2008.[4] The percentage of patients with dyslipidemia who received treatment (48%) and achieved control (33%) had increased since 1999-2002, but room for improvement remains. Managing dyslipidemia can minimize the burden of CVD.

The pace of new research findings in patients with dyslipidemia is rapid, and evidence-based guidelines for the management of dyslipidemia quickly become out of date. The ATP III guidelines were published in 2001 and updated in 2004.[1,2] An updated guideline for secondary prevention and risk reduction in patients with CHD and other atherosclerotic vascular disease from AHA and the American College of Cardiology (ACC) was released in November 2011.[5] A 2012 version of the American Diabetes Association (ADA) standards of medical care in diabetes that addresses dyslipidemia in this patient population also is available.[6] The release of new NCEP guidelines (ATP IV) has been delayed several times since 2009 and is now expected sometime this year.

Question: What are likely to be some of the main differences between the recommendations in ATP IV and those in ATP III, and what evidence is the basis for these changes?

The primary target in treating dyslipidemia has been and will likely continue to be LDL cholesterol because it is the most atherogenic lipoprotein and it correlates more closely than other lipids with CHD.[2] Statin therapy will likely continue to be emphasized because statins are the most effective lipid-lowering agents for reducing LDL cholesterol concentrations, and their efficacy for lowering the risk for cardiovascular events has been proven.[1]

The goal LDL cholesterol levels in ATP III (Table 1) depend on the presence of atherosclerotic vascular disease (e.g., CHD, ischemic stroke, peripheral arterial disease, abdominal aortic aneurysm), diabetes, and major cardiovascular risk factors (age ≥45 years for men or ≥55 years for women, hypertension, smoking, family history of premature CHD, and high-density lipoprotein [HDL] cholesterol <40 mg/dL). In ATP III, an optional LDL cholesterol goal of less than 70 mg/dL applies only to individuals who are at very high risk for cardiovascular events.[2] Very high risk is defined as the presence of established CVD plus multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), multiple metabolic syndrome risk factors (especially triglycerides ≥200 mg/dL plus non-HDL-cholesterol ≥130 mg/dL with HDL cholesterol <40 mg/dL), or acute coronary syndrome (ACS).[2]

The ATP IV recommendations should reflect the results of recent clinical trials evaluating the impact of aggressive LDL cholesterol reduction on cardiovascular events. The benefit of intensive LDL cholesterol reduction using atorvastatin 80 mg/day instead of atorvastatin 10 mg/day (the control group) for 5 years was demonstrated in a subgroup analysis of 1501 patients with CHD and diabetes participating in the randomized, double-blind Treating to

Table 1.

ATP III LDL Cholesterol Goals in Patients with Dyslipidemia[2]

Risk Category	LDL Cholesterol Goal (mg/dL)
High risk: CHD or CHD risk equivalents[a] (10-year risk >20%)	<100 (optional <70)
Moderately high risk: ≥2 risk factors[b] (10-year risk 10% to 20%)	<130 (optional <100)
Moderate risk: ≥2 risk factors[b] (10-year risk <10%)	<130
Lower risk: 0 or 1 risk factor[b]	<160

ATP = adult treatment panel; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein

[a]CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic vascular disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and ≥2 risk factors with 10-year risk for hard CHD >20%.

[b]Risk factors include cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol, (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age or female first-degree relative <65 years of age), and age (men ≥45 years; women ≥55 years).

New Targets trial.[7] A significant 25% lower incidence of major cardiovascular events was observed in the intensive therapy group compared with the control group. The mean LDL cholesterol at the end of the study was 77 mg/dL with intensive therapy and 99 mg/dL with less intensive therapy.

The benefit of intensive LDL cholesterol reduction using statins in patients with CHD, dyslipidemia, and relatively low baseline LDL cholesterol levels (<77 mg/dL) was demonstrated in the Cholesterol Treatment Trialists' Collaboration.[8] In this meta-analysis of five randomized, controlled clinical trials involving 39,612 study participants with CHD and a median follow-up time of 5.1 years, the use of more intensive regimens instead of less intensive ones was associated with a weighted mean further reduction in LDL cholesterol concentration after 1 year of approximately 19 mg/dL. Significant further reductions in major vascular events by 15%, coronary death or non-fatal MI by 13%, coronary revascularization by 19%, and ischemic stroke by 16% were realized from the use of more intensive regimens instead of less intensive ones. The cardiovascular event reductions were proportionate to LDL cholesterol concentration reductions, even when the baseline LDL cholesterol concentration was low. Thus, the ATP IV guidelines are likely to recommend an LDL cholesterol goal less than 70 mg/dL for all patients with CHD, regardless of the presence of other comorbidities.

Question: What LDL cholesterol goals and treatment strategies are likely to be recommended in ATP IV for patients with diabetes?

The ATP IV recommendations for patients with diabetes and dyslipidemia probably will reflect the results of several noteworthy clinical trials. The effectiveness of aggressive LDL cholesterol reduction using atorvastatin 10 mg/day for primary prevention of major cardiovascular events in patients with type 2 diabetes without high baseline concentrations of LDL cholesterol was demonstrated in a randomized, double-blind, placebo-controlled study.[9] After a median follow up of 3.9 years, there was a 37% lower incidence of major cardiovascular events in the atorvastatin group compared with the placebo group, a difference that is significant. At the end of the study the mean LDL cholesterol concentration was unchanged from baseline (118 mg/dL) in the placebo group and 77 mg/dL in the atorvastatin group.

In a 2003 subgroup analysis of 5963 patients with diabetes who participated in the Heart Protection Study, a randomized, double-blind, placebo-controlled study of simvastatin 40 mg/day for 5 years in more than 20,000 adults (40-80 years of age) at high risk for major cardiovascular events, a significant reduction by 22% in major vascular events was observed.[10] The average LDL cholesterol concentration in the simvastatin group decreased from 123 mg/dL at baseline to 89 mg/dL over the course of the study. The reduction in major cardiovascular events in the 2426 diabetic participants whose baseline LDL cholesterol concentration was less than 116 mg/dL (27%) also was significant.

> **"Although 70 mg/dL or lower is considered an optional LDL cholesterol goal that applies only to patients at very high risk for cardiovascular events in current ATP III guidelines, new ATP IV guidelines are likely to recommend this goal for all patients with coronary heart disease, regardless of the presence of other comorbidities."**
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> — Joseph Saseen, Pharm.D., FASHP, FCCP, BCPS

In a 2008 consensus statement for lipoprotein management in patients with cardiometabolic risk, ADA and ACC recommend a goal LDL cholesterol less than 70 mg/dL for patients at the highest risk for cardiovascular events, which they define as:[11]

- Patients with known CVD
- Patients with diabetes plus at least one major risk factor for CVD other than dyslipidemia (e.g., cigarette smoking, hypertension, and family history of premature coronary artery disease)

A goal LDL cholesterol less than 100 mg/dL is recommended in the ADA/ACC consensus statement for patients at high risk for cardiovascular events:[11]

- Patients without CVD or diabetes but with two or more other major risk factors
- Patients with diabetes and no other major risk factors

The most recent (2012) ADA standards of medical care in diabetes call for the addition of statin therapy to lifestyle therapy, regardless of baseline lipid levels, for patients with overt CVD.[6] This therapeutic approach also is recommended by ADA for patients without CVD if they are more than 40 years of age and have at least one other CVD risk factor. The goal LDL cholesterol is less than 70 mg/dL for patients with overt CVD and less than 100 mg/dL in patients without overt CVD, according to ADA.

The new ATP IV guidelines are likely to recommend statin-based therapy for all patients with diabetes who are more than 40 years of age, regardless of their baseline LDL cholesterol value. These patients stand to benefit based on the results of the Heart Protection Study.[10] The new ATP IV guidelines probably also will recommend a goal LDL cholesterol less than 70 mg/dL for patients with CVD (regardless of the presence of diabetes) and a goal less than 100 mg/dL for patients without CVD but with multiple major risk factors (including diabetes). These goals are optional in ATP III but evidence supports their use in patients who meet these criteria, so there is an evidence-based argument to make the formerly optional goals standard goals in ATP IV.

Question: What recommendations do you expect to see in ATP IV for the use of fibrates or nicotinic acid in combination with statins?

According to ATP III, combining a fibrate or nicotinic acid with LDL-lowering therapy should be considered for patients with high triglycerides or low HDL cholesterol values once LDL cholesterol is addressed.[2] However, the results of recent studies have raised concerns about the usefulness of this treatment approach.

In the randomized, open-label, placebo-controlled ACCORD study of 5518 patients with type 2 diabetes treated with statin therapy, adding fenofibrate did not significantly reduce the annual rate of nonfatal MI, nonfatal stroke, or cardiovascular death after a mean follow-up time of 4.7 years.[12] These findings may reflect a study population that was not an ideal one for addition of a fibrate to a statin because the mean baseline LDL cholesterol (100.6 mg/dL), HDL cholesterol (38.1 mg/dL), and triglycerides (162 mg/dL) suggest a need for further LDL cholesterol lowering and possibly HDL cholesterol raising rather than triglyceride lowering. A subgroup analysis suggested that the treatment effect differed by sex, with a possible benefit for men and possible harm to women from adding the fibrate to statin therapy. A possible benefit for patients with both a high baseline triglyceride concentration and a low baseline HDL cholesterol concentration also was identified in a subgroup analysis, but the difference between this subgroup and all other patients in the primary outcome was not significant.

Adding niacin to statin therapy was explored in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) study.[13] In this randomized, double-blind trial, 3414 patients with a history of CVD treated with statin therapy to an LDL cholesterol value of 40-80 mg/dL were randomly assigned to receive extended-release niacin (1500-2000 mg daily) or placebo. The trial was stopped early after 3 years (18 months earlier than planned) because of a lack of efficacy of combination therapy for reducing the primary endpoint (a composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary or cerebral revascularization), despite improvements in lipids. The incidence of the primary endpoint was 16.4% with statin plus niacin therapy and 16.2% with statin plus placebo therapy.

Because of the disappointing results from studies of the impact of adding a fibrate or nicotinic acid to statin-based LDL-lowering drug therapy on cardiovascular events, recommendations for the use of such combination therapies in ATP IV probably will be tempered. Reserving the use of

fibrates and nicotinic acid primarily for patients with severe hypertriglyceridemia (triglycerides ≥500 mg/dL), an undisputed role for these agents in the management of dyslipidemia, may be suggested in ATP IV.

Current ADA standards of medical care in diabetes acknowledge that if lipid goals are not achieved using the maximum tolerated statin dosage, adding other lipid-lowering agents may be considered.[6] However, the ADA standards include the caveat that the safety and impact of these combinations on cardiovascular outcomes have not been evaluated in outcome studies. This caveat is reasonable based on data from the ACCORD and AIM-HIGH studies.[12,13]

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Planned and coordinated by ASHP Advantage and supported by an educational grant from Merck.

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