Managing Dyslipidemia in Special Patient Populations

Initiative Faculty

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The management of dyslipidemia was the subject of 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. In a live webinar conducted on March 22, 2012, 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 in patients with dyslipidemia expected in ATP IV were described in an **e-newsletter released earlier** (PDF). 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 [CKD]) and unresolved controversies in the management of dyslipidemia are described in this e-newsletter.

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.**

Faculty Podcast Interviews

Visit the CE in the Mornings **web portal** to listen to podcast interviews with the faculty. Four interviews, each lasting approximately 5 to 14 minutes, are available.

Question: What progress has been achieved in improving the management of dyslipidemia?

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in the United States, and dyslipidemia is a major risk factor for CVD.[3] Low-density lipoprotein (LDL) cholesterol has been and should continue to be the primary target of efforts to reduce the risk for CVD.[1] Success in achieving goal LDL cholesterol concentrations was poor in the past and has improved in recent years. In the Lipid Assessment Treatment Project (L-TAP), a study of 4888 Americans with or at risk for CVD conducted in the late 1990s, the goal LDL cholesterol concentration was achieved in 38% of patients receiving lipid-lowering therapy.[4] In a subset of patients at very high risk for cardiovascular events because of established coronary heart disease (CHD), the success rate in achieving the LDL cholesterol goal was only 18%.

In L-TAP 2, a follow-up survey of patients with dyslipidemia conducted in 2006 and 2007, the overall rate of success in achieving the goal LDL cholesterol concentration was 73% in 9955 patients who were receiving stable lipid-lowering therapy (statins for most patients).[5] Participants lived in one of several countries, including the United States. The percentage of patients at low, moderate, high, and very high risk for CVD who achieved their goal LDL cholesterol concentration (<160 mg/dL, <130 mg/dL, <100 mg/dL, and <70 mg/dL, respectively) was 86%, 74%, 67%, and 30%, respectively. Although the success rates in achieving goal LDL cholesterol concentrations in patients treated for dyslipidemia have improved in recent years, there is room for further improvement, especially in patients at very high risk for CVD.

Question: Is lowering LDL cholesterol to very low levels dangerous, especially for the elderly? What recommendations pertaining to this practice are made in ATP III, and how might these recommendations change in ATP IV?

Target LDL cholesterol levels recommended for primary prevention of cardiovascular events in patients with dyslipidemia in ATP III are less than 160 mg/dL, 130 mg/dL, or 100 mg/dL, depending on cardiovascular risk.[2] According to ATP III, an optional LDL cholesterol goal of less than 70 mg/dL applies only to secondary prevention in individuals with CHD and multiple major risk factors who are at very high risk for cardiovascular events.[2] Concerns about the potential for increased mortality from lowering LDL cholesterol to much lower levels have been raised in the past. In 2001, ATP III stated that the decision to achieve very low LDL levels in patients at very high risk for CVD should be based on the evidence of benefit, recognizing that there appears to be only a remote possibility of side effects from LDL lowering per se.[1,2]

The impact of statin therapy on cardiovascular events in apparently healthy patients with elevated levels of high-sensitivity C-reactive protein (hsCRP), a biomarker for inflammation, was evaluated in a randomized, double-blind, placebo-controlled primary prevention trial known as JUPITER because statins have been shown to reduce hsCRP.[6] More than 17,000 men 50 years of age or older and women 60 years of age or older with LDL cholesterol levels less than 130 mg/dL and hsCRP levels of 2.0 mg/L or higher were randomly assigned to receive rosuvastatin 20 mg daily or placebo. The primary endpoint was myocardial infarction (MI), stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. Treatment was planned for 3.5 years but the study was terminated early after a mean of 1.9 years because rosuvastatin significantly reduced the incidence of the primary end point by 44% from 1.36 per 100 person-years in the placebo group to 0.77 per 100 person-years in the rosuvastatin group. The median LDL cholesterol concentration after 12 months was 110 mg/dL and 55 mg/dL, respectively. One in four patients had an LDL cholesterol value less than 44 mg/dL, with no increased risk for death, myopathy, or hepatotoxicity. In subgroup analyses, the benefit from statin therapy was similar in men and women, elderly (age >65 years) and nonelderly patients, and whites and non-whites. In a secondary analysis of 5695 JUPITER participants who were 70 years of age or older, rosuvastatin was associated with a significant 39% reduction in the primary endpoint compared with placebo.[7] The new ATP IV recommendations should incorporate these findings that statin therapy for primary prevention in apparently healthy patients with elevated hsCRP (including very

elderly persons) reduces the risk of cardiovascular events, and treating to a very low LDL cholesterol goal with statin therapy does not incur an increased risk for death, myopathy, or hepatotoxicity.

Question: What recommendations might appear in ATP IV for the use of statins in patients with CKD or end-stage renal disease (ESRD)?

Significant reductions in LDL cholesterol concentrations are achieved with the use of statin therapy in patients with ESRD requiring hemodialysis, but whether these reductions translate into reductions in cardiovascular events in this patient population is unclear.[8] In a 3.8-year, randomized, double-blind, placebo-controlled study of 2776 patients requiring long-term hemodialysis (the AURORA study) and a 4-year, randomized, double-blind, placebo-controlled study of 1255 patients with diabetes who required long-term hemodialysis (the 4D study), a reduction in cardiovascular events was not demonstrated from the use of statin therapy.[9,10]

The impact of statin-based therapy on major atherosclerotic events in 9270 adults at least 40 years of age with CKD (a serum or plasma creatinine of at least 1.7 mg/dL in men or 1.5 mg/dL in women) but no history of MI was evaluated in the Study of Heart and Renal Protection, a randomized, double-blind, placebo-controlled study referred to as SHARP.[11] Roughly one third of the study participants were receiving hemodialysis and 5% were receiving peritoneal dialysis at the time of randomization. Study participants were randomly assigned to receive placebo, simvastatin 20 mg/day alone, or simvastatin 20 mg/day plus ezetimibe 10 mg/day. Patients in the simvastatin monotherapy group were randomized again after 1 year to receive simvastatin plus ezetimibe or placebo alone because of the availability of 1-year data demonstrating the safety of ezetimibe in combination with simvastatin. The median follow-up time was 4.9 years. Only two thirds of patients were adherent to therapy at the end of the study. The average placebo-corrected LDL cholesterol reductions from baseline in the simvastatin-ezetimibe group (43 mg/dL after 1 year and 33 mg/dL after 2.5 years) were less robust than those observed in separate studies of patients without CKD who were receiving similar therapy.

The incidence of major atherosclerotic events (non-fatal MI or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure) was 13.4% with placebo and 11.3% with simvastatin-ezetimibe, reflecting a significant 17% reduction from the use of statin-based therapy. Most of the benefit was observed in patients with CKD not yet requiring dialysis; the incidence of major atherosclerotic events was 9.5% with statin-based therapy versus 11.9% with placebo in these patients. However, in the subset of patients requiring dialysis, the incidence of major atherosclerotic events was 16.5% and 15.0% with placebo and simvastatin-ezetimibe, respectively, a difference that is not significant.

> **“The new ATP IV guidelines probably will address the management of dyslipidemia in special populations, including patients who are very elderly and patients with chronic kidney disease, with more specific recommendations than those that appear in ATP III.”**
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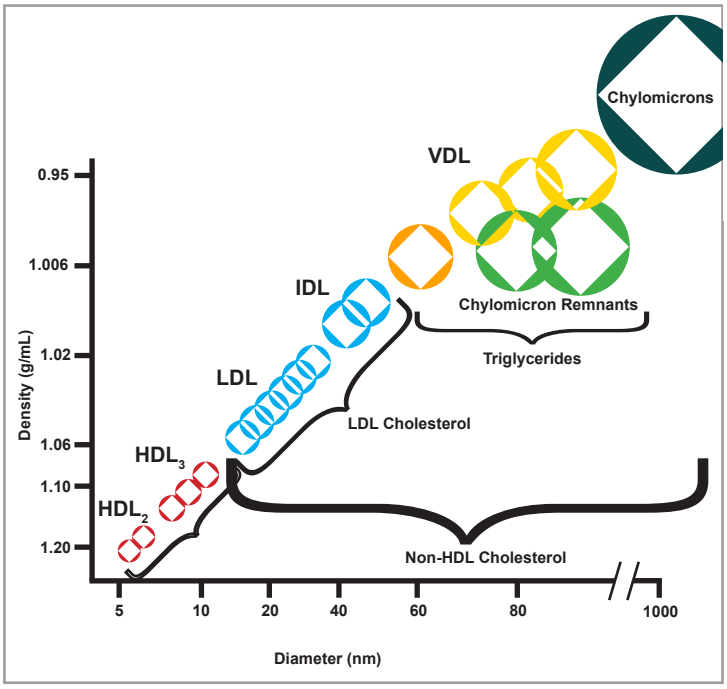
> — Joseph Saseen, Pharm.D., FASHP, FCCP, BCPS

The recommendations in ATP IV should reflect the SHARP data, which were published in 2011. Statin-based therapy will likely be recommended for patients with CKD despite the fact that cardiovascular event lowering has been demonstrated only in the portion of the CKD population that does not require long-term dialysis.

Question: What other new recommendations do you expect to see in ATP IV? What controversies in the management of dyslipidemia currently remain unresolved?

Lipoprotein particles vary in density and diameter from the smallest high-density lipoprotein (HDL) particles to the largest chylomicrons (Figure 1).

Figure 1. Lipoprotein Subclasses



According to ATP III, non-HDL cholesterol is a secondary therapeutic target once the LDL cholesterol goal is met if the triglyceride level is 200 mg/dL or higher.[2] Non-HDL cholesterol can be determined from a standard lipid profile, and it does not require patients to fast before measurement as do typical fasting lipid panels. Non-HDL cholesterol provides an estimate of apolipoprotein B (Apo B), which is the most accurate reflection of all of the atherogenic lipoproteins in the circulation. Tests are available to measure Apo B and provide a more refined assessment of the atherogenicity of circulating lipids. ATP IV will likely continue to emphasize LDL cholesterol as

Practice Changes Related to Managing Dyslipidemia

In a survey conducted approximately 8 weeks after the December 2011 CE in the Mornings program on the management of dyslipidemia, program attendees were asked what practices they had implemented or improved (or intend to implement or improve) based on the knowledge acquired by participating in the program. Many attendees had already made improvements or implemented practices to promote antimicrobial stewardship in their institutions. These practice changes include:

- Discussing the predicted prevalence and the clinical and economic impact of coronary heart disease (CHD) and dyslipidemia as they apply to the practice setting,
- Outlining current recommendations for managing dyslipidemia (specifically targeted LDL-cholesterol reduction), the limitations of statin-based therapy, and recent developments related to the efficacy and safety of these therapies and combination approaches,
- Identifying new lipid-lowering drug therapies in development and explaining their mechanisms of action and possible benefits, and
- Recommending an appropriate therapeutic strategy to reduce CHD risk in a patient with dyslipidemia.

Barriers to implementation of or improvement in practices included a lack of time, lack of personnel, lack of financial resources, lack of administrative support, lack of experience, and resistance from others on the health care team. Information on managing dyslipidemia provided in the CE in the Mornings educational initiative should help overcome these barriers and improve patient care and outcomes.

the primary target of therapy for patients with dyslipidemia, but there may be an increased emphasis on addressing non-HDL cholesterol and Apo B as other important therapeutic targets. Whether non-HDL cholesterol and Apo B will be secondary targets or primary targets along with LDL cholesterol is controversial.

The size and atherogenicity of LDL particles varies, with greater atherogenicity from small, dense LDL particles than larger, fluffy LDL particles. Advanced lipid tests have been developed to differentiate LDL particle sizes, but the role of advanced lipid testing in differentiating small, dense LDL particles from larger, fluffy, less atherogenic LDL particles is controversial. These advanced lipid tests are available through several different vendors, but the costs are much higher than those of the standard of care fasting lipid panels. Universal standards defining the normal ranges for several of the advanced lipoprotein components are lacking. The largest barrier to the routine use of advanced lipid tests is the absence of clear proof of benefit from using these types of tests in place of standard fasting lipid panels.

The role of targeting a specific LDL cholesterol concentration as a therapeutic goal in patients with dyslipidemia has been debated. Some clinicians advocate reducing LDL cholesterol levels by a fixed percentage instead of using a specific concentration as the therapeutic goal. An intensity of LDL-lowering therapy that results in a reduction in LDL cholesterol by 30% to 40% is already recommended in ATP III because that magnitude of reduction is what was associated with the cardiovascular benefits demonstrated in landmark studies of statin-based therapy.[2] Other clinicians have suggested abandoning the LDL cholesterol concentration as a therapeutic target and instead focusing on reducing the overall 5- or 10-year cardiovascular risk.[12]

Recommendations for statin therapy in ATP IV should be revised to reflect current knowledge about the safety of this class of drugs. The FDA recently approved changes to statin labeling related to liver enzyme monitoring, reversible cognitive effects, increases in blood glucose and A1c levels, and drug interactions.[13] Liver function testing is no longer recommended because of evidence that it is unnecessary.[14] Increased blood glucose and A1c levels occur during statin therapy, but the changes are small and the benefits of statin therapy outweigh the risks in patients at increased risk for cardiovascular events.[15,16]

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