



Update on Clinical Controversies in Dyslipidemia

A continuing education (CE) activity entitled *Current Controversies in the Management of Dyslipidemia: Separating Fact from Fiction* was presented as one of three CE in the Mornings topics at the 45th ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, in December 2010 (which are available at www.ashpadvantage.com/cemornings). The program was presented by Joseph Saseen, Pharm.D., FCCP, FNLA, BCPS, CLS. Attendees submitted questions about unresolved issues and controversies that were later addressed by Dr. Saseen in a live webinar conducted on February 2, 2011. Some of the highlights of the webinar pertaining to the use of combination lipid-lowering therapy in patients with dyslipidemia and the management of dyslipidemia in patients with chronic kidney disease were described in an e-Newsletter released in April. Highlights of the webinar pertaining to late-breaking clinical trials with implications for the management of dyslipidemia and progress in achieving lipid goals in patients with dyslipidemia are described in this e-Newsletter.

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Late-Breaking Clinical Trials

The results of several clinical trials with implications for the management of dyslipidemia were published in late 2010. The results of a meta-analysis of large randomized, controlled clinical trials of the effectiveness and safety of intensive low-density lipoprotein (LDL) cholesterol reduction using statins in patients with dyslipidemia were reported by the Cholesterol Treatment Trialists' (CTT) Collaboration in November 2010.¹ At least 1000 study participants and a treatment duration of at least 2 years were required for the trials included in the meta-analysis. Five trials compared more intensive statin regimens with less intensive ones after a median follow-up time of 5.1 years, and 21 trials compared statin therapy with control therapy after a median follow-up time of 4.8 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 0.51 mmol/L (roughly 19 mg/dL). Similarly, significant further reductions in major vascular events by 15%, coronary death or non-fatal myocardial infarction (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 regimens. The cardiovascular event reductions were proportionate to LDL cholesterol concentration reductions, even when the baseline LDL cholesterol



concentration was low (<2 mmol/L, or <77 mg/dL). All-cause mortality was reduced by 10% for each 1.0-mmol/L (i.e., 39-mg/dL) reduction in LDL cholesterol concentration. There was no evidence of any threshold for benefits within the cholesterol range studied. The safety analysis detected no significant effects from the use of more intensive regimens instead of less intensive ones on deaths due to cancer or other non-vascular causes or the incidence of cancer, even at low LDL cholesterol concentrations. Thus, intensive statin therapy appears safe and effective for reducing cardiovascular events, with benefits that exceed what is provided by less intensive statin therapy.

In late December 2010, the results of a meta-analysis of 20 large randomized, controlled trials of statin therapy were published.² There were at least 1000 person-years of follow up in these trials, and high-density lipoprotein (HDL) cholesterol concentrations and MI were reported in all of the trials. After adjusting for on-treatment LDL cholesterol concentrations, age, hypertension, diabetes, and tobacco use, there was a significant inverse association between HDL cholesterol concentration and the risk for MI in both statin-treated patients and control patients. The estimated number of additional MIs, cardiovascular deaths, and all-cause deaths for every 10-mg/dL decrease in HDL cholesterol concentration was not significantly different in statin-treated patients and patients not receiving statins. These findings demonstrate that statin therapy does not mitigate the cardiovascular risk associated with low HDL cholesterol concentrations, and suggest that some patients receiving statin therapy may benefit from additional treatment addressing low HDL cholesterol concentrations.

The results of a phase III, randomized, double-blind, placebo-controlled study of the efficacy and safety of anacetrapib, an investigational cholesteryl ester transfer protein (CETP) inhibitor, in patients with or at high risk for coronary heart disease (CHD) were published online in November 2010 and in print in the December 16, 2010 issue of *New England Journal of Medicine*.³ Cholesteryl ester transfer protein ordinarily transfers cholesteryl esters from HDL particles to apolipoprotein B-containing lipoproteins (e.g., very-low-density lipoprotein, LDL cholesterol) as part of the reverse cholesterol transport process that moves cholesterol from peripheral tissues to the liver. Inhibition of CETP has the potential to significantly increase HDL cholesterol concentrations and reduce LDL cholesterol concentrations and the risk of cardiovascular events.

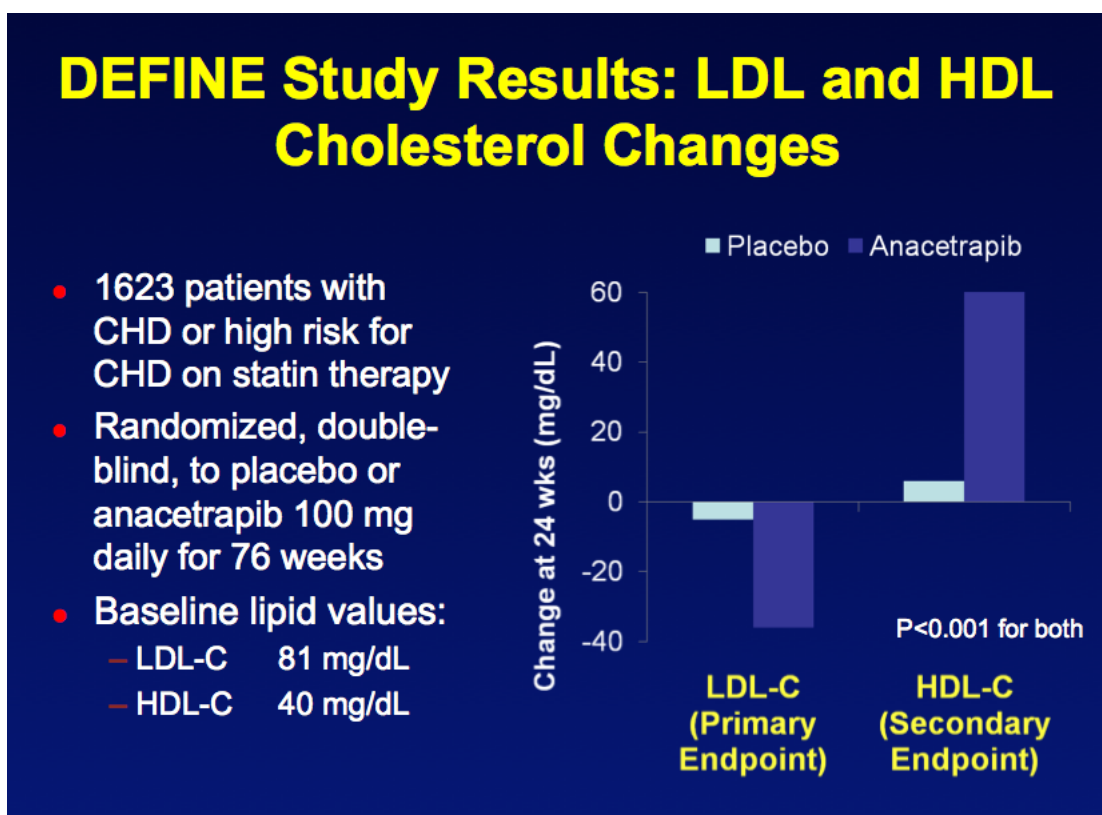
Participants in the Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) study were taking a statin and on average had an HDL cholesterol concentration of 40 mg/dL and LDL cholesterol concentration of 81 mg/dL at baseline.³ The 1623 patients were randomly assigned to receive anacetrapib 10 mg or placebo once daily in addition to statin therapy for 76 weeks. After 24 weeks of treatment, the increase from baseline in HDL cholesterol and reduction from baseline in LDL cholesterol were significantly greater in the anacetrapib group than in the placebo group (Figure 1 on next page).

The development of another CETP inhibitor, torcetrapib, was halted in 2006 because of an increased risk of death and major cardiovascular events.⁴ In the DEFINE study there was no significant difference between anacetrapib and placebo in pre-specified adjudicated cardiovascular events, suggesting a low probability of the problems associated with torcetrapib in patients receiving anacetrapib.³

The recently reported results of clinical trials of drug therapies for the management of dyslipidemia underscore the importance of lowering LDL cholesterol and raising HDL cholesterol. Achieving these goals may require intensive statin therapy and a second agent in combination with the statin. New drug therapies, such as CETP inhibitors, hold promise for improving the management of dyslipidemia.



Figure 1. DEFINE Study Results: LDL and HDL Cholesterol Changes



Cannon CP et al. *N Engl J Med.* 2010; 363:2406-15.

Room for Improvement

Low-density lipoprotein cholesterol is the primary target of efforts to reduce the risk for CHD.⁵ Success in achieving goal LDL cholesterol concentrations has been poor in the past. In the Lipid Assessment Treatment Project (L-TAP), a study of 4888 Americans with or at risk for CHD conducted in the late 1990s, the goal LDL cholesterol concentration was achieved in 38% of patients receiving lipid-lowering therapy.⁶ The success rate in achieving the LDL cholesterol goal was only 18% in the subset of patients at very high risk because of established CHD.

The results of L-TAP 2, a survey conducted in 2006 and 2007 of the rate of success in achieving lipid goals in 9955 patients, were published in 2009.⁷ Participants were receiving stable lipid-lowering therapy (statin-based therapy in most patients) in one of nine countries (the United States, Canada, Mexico, Brazil, Spain, the Netherlands, France, Taiwan, or Korea). The overall success rate in achieving the goal LDL cholesterol concentration was 73%. The percentage of patients at low, moderate, high, and very high risk for CHD 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.



The improved overall success rate in achieving goal LDL cholesterol concentrations observed in L-TAP 2 compared with L-TAP is noteworthy because the goals were lowered in the time that elapsed between L-TAP and L-TAP 2 based on evidence of an added benefit from more aggressive treatment and reduction in LDL cholesterol, especially in patients at very high risk for CHD. However, the L-TAP 2 findings illustrate a need for further effort to improve success rates in reaching LDL cholesterol goals.

“Improvement has been made over the past decade in success rates in achieving LDL cholesterol goals in patients with dyslipidemia, but there is room for improvement. Continued diligence is needed to achieve lipid goals in patients with dyslipidemia, especially those with coronary heart disease.”

—Joseph Saseen, Pharm.D., FCCP, FNLA, BCPS, CLS

Practice Changes

Attendees at the CE in the Mornings program on current controversies in the management of dyslipidemia at the ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, in December 2010 were asked what changes to current practice or new services they might implement based on the knowledge acquired by participating in the program and what barriers might interfere with these plans. The program addressed the role of high-sensitivity C-reactive protein (hsCRP) as a cardiovascular risk factor, the management of dyslipidemia in patients with diabetes or end-stage renal disease, and the use of combination lipid-lowering therapy in patients with dyslipidemia.

Roughly half (48%) of the 626 respondents plan to consider current evidence-based consensus recommendations and professional guidelines when determining drug therapy options for patients with dyslipidemia. Other changes that attendees at the program might make in the future include:

- Considering patient-specific factors, such as age, ethnicity, cardiovascular risk factors, and the presence and duration of diabetes, when evaluating lipoprotein targets (42%)
- Using landmark clinical trials and recent studies to differentiate fact from fiction when making clinical decisions for patients with dyslipidemia (40%)
- Evaluating primary prevention patients (e.g., men ≥ 50 years and women ≥ 60 years who have elevated hsCRP levels and at least one cardiovascular risk factor) for consideration of statin-based therapy (29%)
- Developing a practical strategy for monitoring and counseling patients with dyslipidemia to achieve cardiovascular risk reduction and desired outcomes (24%)
- Other (e.g., recommending the use of combination lipid-lowering therapy instead of monotherapy when warranted, ensuring that therapy targets low levels of high-density lipoprotein cholesterol when needed)



Various barriers to implementing the plans were identified:

- Lack of time and personnel and financial constraints
- Lack of access to potent lipid-lowering drug therapies
- Reimbursement issues (e.g., for medications, hsCRP testing)
- Need for a simple algorithm for dyslipidemia management
- Lack of physician cooperation with evidence-based recommendations by pharmacists
- Insufficient available evidence to support some clinical decisions

Overcoming these barriers will not be easy, but information provided in the CE in the Mornings program on the management of dyslipidemia and this e-Newsletter should help clarify the controversies and improve patient care and outcomes.



References

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