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Target Audience

This educational activity is designed for primary care physicians, endocrinologists, cardiologists, internists, and other healthcare professionals involved in the diagnosis and management of dyslipidemia and its comorbidities.

Learning Objectives

With information from the latest evidence-based studies, participants should be able to:

- Identify the atherogenic qualities of the lipoprotein(a) molecule [Lp(a)].
- Recognize the predictive value of HDL-C levels for major CV events, even when LDL-C levels are below 70 mg/dL.
- Characterize follow-up statin safety and efficacy data after the end of a landmark lipid-lowering study.

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CLINICAL INSIGHTS® IN

LIPID Management

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HDL-C Levels Predict CV Events Even When LDL-C is Low in Statin-Treated Patients

A bundant evidence supports the beneficial impact of using statins to reduce low-density lipoprotein cholesterol (LDL-C) levels and the subsequent association with a reduction in the risk for future coronary heart disease (CHD). Nonetheless, even statin-treated individuals still demonstrate a substantial residual risk for cardiovascular (CV) events. A low baseline high-density lipoprotein cholesterol (HDL-C) level provides one potential explanation, a concept supported by data from several trials demonstrating that low HDL-C levels remain predictive of major CV events even during statin treatment.

Indeed, numerous population studies have shown HDL-C levels to strongly and independently correlate inversely with CV disease. The analysis of data from several large studies shows that each 1 mg/dL increase in HDL-C is associated with a 2% to 3% decrease in the risk of future coronary heart disease. Some hold that HDL-C should be considered as a therapeutic target independent from lowering LDL-C. Others argue that in the presence of already lowered LDL-C levels, HDL-C levels have little consequence—though, to date, no data are available to support this hypothesis.

In the Treating to New Targets (TNT) study, subjects undergoing statin therapy achieved LDL-C levels <70 mg/dL. Further, the American Heart Association and the American College of Cardiology have proposed LDL-C <70 mg/dL as a reasonable therapeutic target in those patients with coronary heart disease or other forms of atherosclerotic disease. In a posthoc analysis of the TNT trial, Barter and colleagues examined the relationship between the frequency of major CV events and HDL-C levels in a population of patients with clinically evident CHD who underwent statin treatment. In addition, the

authors examined whether the inverse relationship between HDL-C and the risk for CV events pertained even at very low (<70 mg/dL) LDL-C levels. The primary outcome measure was the time to a first major CV event, defined as death from coronary heart disease, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal/nonfatal stroke.

Analysis of these data demonstrated that, across the TNT study cohort (n=9,770), HDL-C levels in patients receiving statins predicted major CV events. This finding held regardless of whether HDL-C was considered a continuous variable or whether study subjects were stratified in quintiles according to HDL-C level. The predictive value of an HDL-C level for assessing the risk of major CV events was of borderline significance ($P=0.05$) when the analysis was stratified on the basis of an LDL-C level. The authors regarded this finding as a suggestion that higher HDL-C levels may offset the increased risk associated with higher

LDL-C levels in patients with coronary heart disease. The inverse relationship between HDL-C levels and CV events was also maintained in a subset (n=2,661) of patients with LDL-C levels <70 mg/dL. Those in the highest quintile of HDL-C had lower risk of major CV events than those in the lowest quintile ($P=0.03$).

In summary, the authors contend that HDL-C levels predict major CV events in patients even during statin treatment, and that this predictive relationship holds true—even when LDL-C levels are <70 mg/dL.

Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med.* 2007;357:1301-1310.

Numerous population studies have shown HDL-C levels to strongly and independently correlate inversely with cardiovascular disease.

^a Dr Libby has indicated relevant financial relationships as noted: consultant for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Interleukin Genetics, Kowa Research Institute, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc, sanofi-aventis, and Schering-Plough; speaker for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc, sanofi-aventis, and Schering-Plough.

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Post-Test Question 1

Which of the following correctly completes this sentence: _____ HDL-C levels may offset the increased risk associated with _____ LDL-C levels in patients with CHD.

- Higher; higher
- Lower; higher
- Higher; lower

NEW!

Slides examining the results of a recent clinical trial studying the effects of aliskiren and valsartan

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COMMENTARY

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This is a posthoc analysis from the important Treating to New Targets (TNT) trial that established the benefits of high-dose atorvastatin in comparison with low-dose atorvastatin in patients with established coronary heart disease (CHD).

The authors have shown that even when LDL-C levels are driven low with statin therapy, a low level of HDL-C remains predictive of additional CHD risk. To grasp the clinical significance, let's think about HDL-C as both a risk marker and a risk target. HDL-C is a powerful marker of risk. A low level of HDL-C is a major risk factor for CHD, is counted as one of the five components of the metabolic syndrome, is often associated with increased LDL particles (as reflected in increased non-HDL-C or apolipoprotein B) and consistently identifies the subset of patients in clinical trials who benefit most from statin therapy. Thus, it may not be surprising that low HDL-C predicts risk, even at low levels of LDL-C. Should we directly raise HDL-C? Nicotinic acid is one of several therapies that can effectively raise HDL-C; the AIM-HIGH trial, now underway, is testing whether simvastatin and niacin, as combination therapy, is more efficacious and just as safe as simvastatin monotherapy. Perhaps tackling the underlying pathophysiologic processes seen with metabolic risk factor clustering (insulin resistance, hypercoagulability, and inflammation) might also lower the residual increased risk in these patients.

Certainly, if these CHD patients with statin-induced low LDL-C and low HDL-C have the metabolic syndrome, getting them to eat less, eat smart, and move more daily is a sound byte (or bite) worth repeating at each visit!

Long-Term Risk Reduction of Coronary Events Seen With Statin Therapy

The West of Scotland Coronary Prevention Study (WOSCOPS) compared pravastatin with placebo in a randomized, double-blind, placebo-controlled trial in hypercholesterolemic, middle-aged men with no prior history of myocardial infarction (MI). The average follow-up in the WOSCOPS trial was 5 years. Treatment with pravastatin reduced both the combined outcome of death as a result of definite coronary heart disease or definite nonfatal MI, from 7.9% to 5.5% ($P < 0.001$), and also the risk of death from definite or suspected coronary MI, from 1.9% to 1.3% ($P = 0.04$). Furthermore, there was a trend toward a reduction in the risk of stroke, and no evidence of increased risk of death from non-cardiovascular causes.

In their recent report, Ford and colleagues report the results of an extended follow-up of WOSCOPS. To assess ongoing safety and efficacy, researchers monitored the use of statin therapy for 5 years following the end of the study, and collected clinical events data for 10 years after the end of the study. Five years after the trial, 38.7% of the original statin group and 35.2% of the original placebo group were taking a statin. The current follow-up study tracked all deaths, hospitalizations and deaths due to coronary events and stroke, incident cancers, and deaths from cancer in the WOSCOPS survivors.

At the end of the follow-up period, patients originally assigned to pravastatin treatment had a

rate of death from any cause of 18.7%, compared with 20.5% for the placebo group (hazard ratio [HR] 0.88, 95% CI, 0.79 to 0.99, $P = 0.03$). For all deaths from cardiovascular causes, the event rate was 7.6% for the pravastatin group as compared with 9.0% for the placebo group (HR 0.81, 95% CI, 0.68 to 0.96; $P = 0.01$). During the entire follow-up period, the rate of death as a result of coronary heart disease or nonfatal MI was 11.8% as compared with 15.5% for the pravastatin and placebo groups, respectively (HR 0.73, 95% CI, 0.63 to 0.83; $P < 0.001$).

Thus the pravastatin-treated group throughout the entire follow-up period enjoyed significant reductions in deaths from cardiovascular causes, from coronary heart disease or nonfatal MI, and from any cause. Further, there were no excess deaths from noncardiovascular causes or excess fatal or incident cancers. These data demonstrate that 5 years of treatment with pravastatin lowered the risk of coronary events for a subsequent 10 years in men with hypercholesterolemia with no history of MI.

Ford I, Murray H, Packard CJ, et al. Long-term follow-up of West of Scotland Coronary Prevention Study. *N Engl J Med.* 2007;357:1477-1486.

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Post-Test Question 2

Which of the following statements is correct about this study?

- Patients in the pravastatin group saw significant reductions in deaths from cardiovascular causes, from coronary heart disease or nonfatal MI, and from any cause, but excessive deaths from noncardiovascular causes.
- Patients in the pravastatin group saw significant reductions in deaths from cardiovascular causes, from coronary heart disease or nonfatal MI, and from any cause, as well as no excess deaths from noncardiovascular causes.

Emerging Insights on Role of Lp(a)-Associated Phospholipase A₂ in Atherosclerosis and CVD

The atherogenic lipoprotein(a) molecule [Lp(a)] may independently predict risk of atherosclerotic cardiovascular disease (CVD). In advanced atheromata, Lp(a) mainly colocalizes with foam cells in the intima.

In addition to a low-density lipoprotein (LDL)-like particle linked to apolipoprotein(a), Lp(a) also contains an enzyme referred to as lipoprotein-associated phospholipase A₂ (Lp-PLA₂). The role of Lp-PLA₂ in atherogenesis is not well understood. While some data from animal studies suggest that Lp-PLA₂ may exert antiatherogenic actions, some but not all observational studies in humans find a correlation between LpPLA₂ levels and risk of CV events.

Substrates for Lp-PLA₂ include oxidized phospholipids (OxPLs), implicated in atherogenesis. OxPLs preferentially associate with Lp(a) and may undergo hydrolysis and hence inactivation by Lp(a)-PLA₂. The recent finding regarding sequestration of OxPLs by Lp(a) has sparked interest in Lp(a)-PLA₂ function and its role in CVD. A recent paper by Tsimikas and colleagues provides new insights on this very question.

Sequestration and potential hydrolysis of OxPLs by Lp(a)-associated Lp-PLA₂ may comprise a mechanism for detoxification of proinflammatory OxPL. Hence, under normal conditions, a basal level of Lp(a) may actually confer benefit based on its OxPL-scavenging properties. Previous studies by the authors demonstrated that Lp(a) of patients with

coronary artery disease carries less Lp-PLA₂ mass with less activity, leading to the suggestion that OxPLs could competitively inhibit enzyme activity. Thus, increased sequestration of OxPLs by Lp(a) under conditions of acute inflammation and oxidative stress may deplete Lp(a)-PLA₂ activity, causing the lipoprotein to become proatherogenic. Hence, the authors suggest that OxPLs may contribute to the atherogenicity of Lp(a) and explain in part its role as a putative risk factor for CVD. Tsimikas and colleagues suggest that impairment of Lp-PLA₂ by one or more mechanisms promotes pathways that lead to atherogenesis and plaque rupture. According to the authors, much remains to be investigated to test these hypotheses. They acknowledge the need for further studies to elucidate the relationship between Lp(a)-PLA₂ mass and activity with OxPL and Lp(a). In addition, they call for studies to delineate the role of the Lp(a)-PLA₂, and to assess its clinical and pathophysiological relevance.

Tsimikas S, Tsironis LD, Tselepis AD. New insights into the role of lipoprotein(a)-associated lipoprotein-associated phospholipase A₂ in atherosclerosis and cardiovascular disease. *Arterioscler Thromb Vasc Biol.* 2007;27:published online.

Post-Test Question 3

According to the hypothesis of Tsimikas et al, during conditions of acute inflammation, Lp(a) can become proatherogenic by which of the following mechanisms?

- OxPLs can sequester Lp(a), leading to less Lp(a) in the atherosclerotic lesion.
- OxPLs can inhibit Lp-PLA₂ activity, leading to accumulation of OxPLs and Lp(a).
- OxPLs reduce the basal level of Lp(a), reducing its beneficial effects.
- All of the above.
- None of the above.