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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:

- Describe at least one potential mechanism to explain the increased morbidity and mortality observed with use of the CETP inhibitor torcetrapib.
- Relate the importance of the continuation of statin treatment as a means to reduce the risk of future cardiovascular events and to underscore patient adherence.
- Discuss the association between total cholesterol levels and stroke mortality.

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Some of the drug treatments discussed in this issue may note uses not approved by the Food and Drug Administration. Articles containing such uses will be noted at the end of the article.

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CETP Inhibitor Torcetrapib Produces Off-Target Effects in ILLUMINATE Trial

A range of evidence supports the consideration of high-density lipoprotein cholesterol (HDL-C) as a therapeutic target—including the strong inverse association between HDL-C levels and the risk for coronary heart disease (CHD); data from experimental models and human clinical trials; and the persistence of residual risk for cardiovascular disease (CVD) following statin therapy in patients with low HDL-C levels. One means of increasing HDL-C levels and decreasing LDL-C levels is the inhibition of cholesterol ester transfer protein (CETP), which promotes the transfer of cholesteryl esters from HDL-C to other lipoproteins. As a result, the development of CETP inhibitors—including torcetrapib—has been the focus of much attention.

The antiatherosclerotic properties of torcetrapib in animal models, coupled with its ability to concomitantly and significantly increase HDL-C and reduce LDL-C levels in human studies, positioned this compound as a potential, novel agent for the management of dyslipidemia and its associated cardiovascular risks.

However, several large clinical imaging studies demonstrated that torcetrapib does not exert a significant effect on atheroma burden or carotid intima-media thickness.

The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial examined whether torcetrapib, in combination with atorvastatin, reduces major CVD events when compared to atorvastatin alone. ILLUMINATE was a prospective, randomized, multicenter, double-blind clinical trial of 15,067 patients, 45 to 75 years of age, at high cardiovascular risk (defined as a history of CHD, peripheral vascular disease, symptomatic carotid artery disease, or type 2 diabetes). The trial was prematurely terminated because of the increased risk of death and cardiac events in patients treated with torcetrapib. The results of ILLUMINATE were recently published by Barter and colleagues.

Following an initial 4- to 10-week run-in period, incorporating lifestyle counseling and atorvastatin treatment, patients were randomized to receive

either atorvastatin plus placebo (n=7534) or atorvastatin plus 60 mg of torcetrapib (n=7533). The primary outcome was the time to first occurrence of a major cardiovascular event, a composite endpoint of death from CHD, nonfatal myocardial infarction (MI), stroke, and hospitalization for unstable angina. Secondary outcomes were the time to first occurrence of each individual component of the primary endpoint, the time to death from any cause, and the change from baseline in LDL-C and HDL-C. Median follow-up was 550 days.

At one year, treatment with torcetrapib was associated with an expected substantial increase of 72% in HDL-C levels and a decrease (25%) in LDL-C levels (all $P<0.001$). In addition, torcetrapib treatment increased systolic blood pressure (+5.4 mm Hg), decreased serum potassium, and increased serum sodium, bicarbonate, and aldosterone ($P<0.001$ for each), all consistent with activation of the renin-angiotensin-aldosterone system.

An excess of major cardiovascular disease events (hazard ratio [HR] 1.25; $P=0.001$; 95% confidence interval [CI], 1.09-1.44) and deaths (cardiovascular and non-cardiovascular causes) (HR=1.58; $P=0.006$; 95% CI, 1.14-2.19) occurred in the torcetrapib group. Specifically, there were 49 deaths from cardiovascular causes in the torcetrapib with atorvastatin group versus 35 in the atorvastatin-only group; there were 40 deaths from noncardiovascular causes in the torcetrapib with atorvastatin group versus 20 in the atorvastatin-only group. Serious adverse events were reported by 16.4% and 15.0%, respectively, of subjects in the torcetrapib with atorvastatin group and atorvastatin-only group ($P=0.02$).

Based on a post-hoc analysis, the investigators suggest two potential mechanisms that could explain the increased mortality and morbidity associated with use of torcetrapib. First, torcetrapib may induce an off-target effect, unrelated to CETP inhibition. The increase in blood pressure seen with torcetrapib is one example; and this may be related to the observed increased aldosterone levels in the torcetrapib group. However, how torcetrapib might

Two potential mechanisms could explain the increased mortality and morbidity associated with use of torcetrapib.

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trigger the aldosterone increase is not clear. Additionally, there may be other as yet unknown off-target effects of torcetrapib. Second, CETP inhibition *per se* might be responsible, as there have been suggestions that this may lead to the generation and accumulation of nonfunctional or even proatherogenic forms of HDL-C. Regardless, the investigators stress these post hoc observations are only suggestions, and further investigation is warranted.

In the end, the authors write that the ILLUMINATE study does not validate or invalidate the proposition that increasing HDL-C levels by means of CETP inhibition is cardioprotective.

Barter PJ, Caulfield M, Eriksson M, et al; for ILLUMINATE investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med.* 2007;357(21):2109-2122.

Post-Test Question 1

According to the results from the ILLUMINATE study, the increased morbidity and mortality seen with torcetrapib:

- Negates the potential cardioprotective effects of increasing HDL-C with CETP inhibition
- Supports the potential cardioprotective effects of increasing HDL-C with CETP inhibition
- Neither supports nor refutes the potential for cardioprotection by raising HDL-C with CETP inhibitors
- Demonstrates that CETP inhibition is not a viable therapeutic target

COMMENTARY

Ezra A. Amsterdam, MD, Professor of Medicine; Associate Chief, Division of Cardiology, University of California Davis, Sacramento, California. Faculty member, Committee on Cardiovascular and Metabolic Diseases™ (CCMD™).

The high hopes for early availability of a novel pharmacologic agent for raising high-density lipoprotein cholesterol (HDL-C), and thereby complementing low-density lipoprotein cholesterol (LDL-C) reduction in decreasing cardiovascular events, were soundly dashed one year ago with the news that torcetrapib was associated with an increase in adverse clinical events in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial. ILLUMINATE was the first trial to assess the effect of the drug on clinical outcomes. Earlier studies had shown that this cholesteryl ester transfer protein (CETP) inhibitor produced remarkable elevations of HDL-C, which, although also seen in the ILLUMINATE trial, did not translate into clinical benefit.

This article, published one year after the trial was terminated because of the adverse events associated with torcetrapib, presents the detailed findings and addresses possible mechanisms for the results. One year after randomization, patients receiving torcetrapib plus atorvastatin had significantly higher rates of cardiovascular events and all-cause mortality than the atorvastatin-treated group. As anticipated, HDL-C increased markedly (+72%) in the torcetrapib patients in whom LDL-C fell 25%. However, they also had evidence of a mineralocorticoid effect reflected by increased serum sodium and decreased potassium, as well as increased aldosterone. Concomitant with these findings, torcetrapib was associated with a 5 mm Hg increase in blood pressure.

*These metabolic and hemodynamic findings are referred to as “off-target” results that may have contributed to the adverse clinical outcomes. The potential role of unrecognized detrimental effects of torcetrapib must also be considered. Thus, whether the results of ILLUMINATE are attributable to the torcetrapib molecule *per se*, a result of CETP inhibition, or a combination of these mechanisms, is currently unknown. Future studies with CETP inhibitors that do not elevate blood pressure or exert mineralocorticoid-like action will help to clarify this issue.*

Despite the demise of torcetrapib, we should remain cognizant of the risk incurred by low HDL-C, the potential benefits of increasing this lipid fraction, and available methods for achieving this goal. These include weight reduction, smoking cessation, physical activity, and several of the lipid modifying drugs. Finally, experimental, epidemiologic, and clinical studies all support the concept that increases in HDL-C reduce cardiovascular risk.

Effect of Statin Withdrawal on C-Reactive Protein and LDL-C

A mple evidence demonstrates that elevated levels of the C-reactive protein (CRP) predict cardiovascular events. In addition to lowering lipid levels, statins also lower levels of CRP. However, it is not known whether discontinuation of statin therapy results in a rebound of CRP levels or whether statin treatment results in long-lasting changes.

To examine this question, van der Harst and colleagues examined the effect of withdrawal from 4 years of statin therapy on CRP. Study subjects (n=566) were patients from the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND-IT). Study participants were randomized to fosinopril 20 mg, matching placebo and

pravastatin 40 mg, or matching placebo for 4 years. At the end of the study, CRP levels nonsignificantly increased by 9% in those patients from the placebo arm as compared with their baseline measurements. In contrast, treatment with pravastatin lowered CRP levels by 12% ($P=0.001$). Similarly, LDL-C levels were unchanged in the placebo group but decreased 27% ($P<0.001$) with pravastatin treatment. Furthermore, changes in CRP levels were not associated with, or dependent upon, changes in LDL-C.

In the current study, individuals who were randomly assigned to receive either pravastatin or placebo were followed for an additional 3 months, with the main goal of analyzing the change in CRP and

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Effect of Statin Withdrawal on C-Reactive Protein and LDL-C

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LDL-C after discontinuation of treatment. Even after only 3 months of withdrawal from treatment with pravastatin, both LDL-C and CRP significantly increased ($P < 0.001$ and $P < 0.05$, respectively) to levels that were essentially equivalent to pretreatment. Linear regression analysis demonstrated that the changes in CRP are not predicted by the changes in LDL-C. The changes in CRP between the pravastatin and placebo groups following withdrawal were consistent and persisted in analyses that were sequentially corrected for body mass index, smoking status, blood pressure, and baseline total cholesterol, HDL-C, LDL-C, and triglycerides.

The study by van der Harst and colleagues on the effect of statin discontinuation on CRP levels in a large population clearly show the consequences of ceasing statin therapy. The findings of this study underscore the importance of continuing statin therapy once initiated and support the belief that cessation of therapy leads to reversal of their anti-inflammatory effect.

van der Harst P, Asselbergs FW, Hillege HL, et al; for the PREVEND-IT investigators. Effect of withdrawal of pravastatin therapy on C-reactive protein and low-density lipoprotein cholesterol. *Am J Cardiol.* 2007;100:1548-1551.

Post-Test Question 2

Based on the findings of van der Harst et al, which of the following is true at 3 months following discontinuation of statin treatment?

- a. LDL-C and CRP levels continued to decrease
- b. LDL-C and CRP levels returned to near pretreatment levels
- c. There was no change in LDL-C and CRP levels
- d. LDL-C increased but there was a decrease in CRP levels

Study Investigates Relationship Between Total Cholesterol and Stroke

Although the relationship between high serum total cholesterol (TC) and coronary heart disease (CHD) is well established, there is controversy surrounding the relationship between TC and stroke or stroke subtypes. Some studies indicate a positive association between TC and risk of ischemic stroke, others suggest an inverse relationship between TC and the risk for intraparenchymal hemorrhage, and still other studies find no relationship at all.

Using a nested case-control study, Cui and colleagues examined the relationship between cholesterol levels and mortality from total stroke, stroke subtypes, and CHD among 38,158 Japanese men and women 40 to 79 years of age. The odds ratios (OR) of total stroke, stroke subtype, and CHD were estimated according to 7 categories of TC (<160 mg/dL, 160-179 mg/dL, 180-199 mg/dL, 200-219 mg/dL, 220-239 mg/dL, 240-259 mg/dL, and ≥ 260 mg/dL). Multivariate analysis was adjusted for systolic blood pressure, high-density lipoprotein cholesterol, ethanol intake, smoking status, and diabetes.

Over the 10-year follow-up, 150 deaths which occurred as a result of CHD and 345 as a result of stroke (including 76 from intraparenchymal hemorrhage) were recorded. Examination of risk characteristics demonstrated an average age of 67 years for patients experiencing either a stroke or CHD. Males accounted for 53% and 54% of patients experiencing stroke and CHD, respectively. However, it should be noted that the proportion of men varied from 38% in the subarachnoid hemorrhage group,

to 68% in the ischemic stroke group. Systolic and diastolic blood pressure levels and the prevalence of hypertension and current smokers were higher in the stroke group as compared with that of the control group, whereas the prevalence of diabetes was higher in the CHD group as compared with the controls. Mean values of TC were 0.2 and 0.36 mmol/L lower for total stroke and intraparenchymal hemorrhage than for control subjects, but not different for any other stroke subtype or CHD group.

Individuals with TC levels <160 mg/dL demonstrated a higher risk of mortality from intraparenchymal hemorrhage than did those with higher TC levels. Study participants with TC ≥ 260 mg/dL had a significantly lower risk of mortality for intraparenchymal hemorrhage but not for ischemic stroke (odds ratio [OR] 0.12 [95% confidence interval (CI), 0.02-0.88]; P for trend=0.02 and OR 0.87 [95% CI, 0.18-4.24]; P for trend=0.31, respectively). In contrast, the risk of mortality from CHD was elevated in persons with TC ≥ 260 mg/dL when compared with that of individuals with TC <160 mg/dL (OR 3.74 [95% CI, 1.11-12.6]; $P=0.03$).

The findings of this study suggest that, among the Japanese, low TC levels are associated with increased mortality from intraparenchymal hemorrhage, whereas high TC levels are associated with ischemic stroke and increased mortality from CHD.

Cui R, Iso H, Toyoshima H, et al; and the JACC study group. Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: the JACC study. *Atherosclerosis.* 2007;194:415-420.

Post-Test Question 3

According to the data from the study by Cui et al, low TC levels were associated with mortality from which of the following?

- a. Intraparenchymal hemorrhage
- b. Ischemic stroke
- c. Coronary heart disease
- d. Myocardial infarction