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## Using Torcetrapib to Raise HDL-C in Patients at High CV Risk

Studies support the consideration of therapy to raise low levels of high-density lipoprotein cholesterol (HDL-C) in patients at risk for cardiovascular (CV) disease. One method to increase HDL-C levels is to inhibit cholesteryl ester transfer protein (CETP), which promotes the transfer of cholesteryl esters from HDL to other lipoproteins. CETP inhibition has been shown to raise HDL levels and lower low-density lipoprotein cholesterol (LDL-C) levels.

Torcetrapib, a CETP-inhibitor, has been shown to raise HDL-C and lower LDL-C in early-phase patient studies; 3 large trials using ultrasonography and other imaging techniques, however, found no significant effect from torcetrapib therapy on carotid intima-media thickness or coronary atheroma burden. Barter and colleagues in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial examined the premise that torcetrapib therapy would lower the risk of CV events. The study sponsor ended the trial prematurely in December 2006 because of an increased risk of cardiac events and death in the torcetrapib group. The following are results from the abbreviated study.

ILLUMINATE was a prospective, randomized, multicenter, double-blind clinical trial of patients aged between 45 and 75 years, predominantly white males, with a history of CV disease or type 2 diabetes, which is a CV disease risk equivalent. Patients received lifestyle counseling and atorvastatin during a 4- to 10-week run-in period to achieve an LDL-C level <100 mg/dL. The 15,067 patients whose LDL-C met the target level were randomized to receive either atorvastatin at a dose established during the run-in period plus 60 mg of torcetrapib, or a combination of atorvastatin and placebo. Median follow-up was 550 days.

Primary outcome was time to first occurrence of a major CV event, a composite of death from coronary heart disease (CHD), stroke, nonfatal myocardial infarction, and hospitalization for unstable angina. Secondary outcomes included time to first occurrence of any of the individual primary outcomes, time to death from any cause, and change from baseline in HDL-C and LDL-C levels.

At 1 year, there were significant differences ($P$<0.001) in lipid levels between the torcetrapib and placebo (atorvastatin-only) groups. The placebo group showed minimal lipid changes during the study, whereas the torcetrapib group showed a 72.1% increase in HDL-C, a 24.9% decrease in LDL-C, and a 9% decrease in triglycerides.

At month 12, systolic blood pressure (BP) had increased a mean 5.4 mm Hg in the torcetrapib group vs 0.9 mm Hg in the placebo group ($P$<0.001). In the same period, the torcetrapib group also showed a mean decrease in serum potassium of 0.08 mmol/L vs an increase of 0.06 mmol/L in the placebo group ($P$<0.001). The torcetrapib group also had 2.3% of patients with serum potassium levels of <3.5 mmol/L vs 0.6% in the placebo group, and greater increases in serum levels of bicarbonate (2.28 mmol/L vs 1.93 mmol/L, respectively) and serum sodium (1.39 mmol/L vs 0.78 mmol/L, respectively); $P$<0.001 for all comparisons.

Compared with the placebo group, the hazard ratio for primary outcome of CV events in the torcetrapib group was 1.25 (95% confidence interval [CI], 1.09 to 1.44; $P$=0.001). Hazard ratios for the torcetrapib group for individual components ranged from 1.08 for stroke ($P$=0.74) to 1.35 for hospitalization for unstable angina ($P$=0.001).

There were 59 deaths in the placebo group and 93 deaths in the torcetrapib group at study termination, for a hazard ratio of 1.58 in the latter group (95% CI, 1.14 to 2.19; $P$=0.006). There was an increased risk of death from both CV (49 vs 35) and non-CV (40 vs 20) causes in the torcetrapib group. After termination of the trial, however, major reported CV events and deaths were similar in the 2 groups, with 38 major CV events in both groups and 14 deaths in the torcetrapib group and 20 deaths in the placebo group.

For major CV events, post hoc analysis showed lower rates in participants with greater increases in HDL-C and apolipoprotein A-1 and those who had smaller increases in bicarbonate and decreases in potassium. For deaths from any cause, post hoc

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# Using Torcetrapib to Raise HDL-C

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analysis associated greater decreases in potassium and greater increases in bicarbonate with higher death rates. An increase in systolic BP less than the median was unexpectedly associated with an increased risk of major CV events and death.

Treatment with torcetrapib was associated with increased risk of major CV events and increased mortality in this group of patients. The reasons, however, are unclear. The study offers 2 possible causes for these results: an off-target effect of torcetrapib unrelated to CETP inhibition, possibly related to the increase in BP and higher aldosterone levels in the torcetrapib group, or an adverse effect of CETP inhibition, possibly by the generation of dysfunctional or proatherogenic HDL-C. *Ed. note: Use of torcetrapib in this study was experimental.*

Barter PJ et al; for ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357:2109-2122.

## COMMENTARY

**BURTON E. SOBEL, MD. Professor of Medicine and Director, Cardiovascular Research Institute, University of Vermont, Burlington, Vermont. Co-chairman, NDEI.**

*We have observed that "optimal public policy related to drug development…requires that those responsible make the essential distinction between dependent variables in mechanistic studies and clinical outcomes such as mortality[1]." Recently, hopes regarding the promise of torcetrapib were dashed when Barter et al[2] terminated the ILLUMINATE study of 15,067 patients at high cardiovascular risk (CV) randomized to treatment with either atorvastatin alone or atorvastatin plus torcetrapib. It had been anticipated that the latter, an inhibitor of cholesteryl ester transfer protein (CETP), would increase the concentration of high-density lipoprotein cholesterol (HDL-C) and therefore reduce the incidence of CV events.*

*However, despite the successful and marked elevation of HDL-C achieved, the study had to be terminated prematurely with early discontinuation of treatment of 6,695 and 6,520 patients in the 2 groups, respectively, because of an unexpected, statistically significant increased hazard ratio for overall death, and an increased risk of death from both CV and non-CV in patients treated with torcetrapib. Thus, one lesson learned is that elevation of HDL-C per se may not confer protection unless the mechanism by which the elevation induced is a beneficial one.*

*Inhibition of CETP is an attractive target for elevation of HDL-C and prevention of atherosclerosis, as judged from the longevity of people with a genetic deficiency of CETP and compelling epidemiologic evidence that a high HDL-C phenotype is protective with respect to CV disease. Why, then, were the results in ILLUMINATE adverse? One possibility is that elevation of concentrations of HDL-C in blood induced by inhibition of CETP was a "good" thing, but that the drug used impacted on lipid metabolism through other mechanisms that constituted a "bad" thing. In fact, the mechanism(s) by which HDL-C is elevated are undoubtedly pivotal in terms of consequences. Torcetrapib may have interfered with reverse cholesterol transport at a site entirely different from CETP, such as the ABCA1 (ATP-binding cassette subfamily A1 protein), known to control efflux of cholesterol from nascent atheroma and potentially giving rise to a proatherogenic form of HDL-C.[3-7] Alternatively, the adverse effects in ILLUMINATE may have been attributable to the unforeseen significant increase in systolic blood pressure (5.4 mm Hg in the torcetrapib group vs 0.9 mm Hg in the placebo group), likely due to increased aldosterone, reflected as well by a diminution of serum potassium (potentially arrhythmogenic) and by increases in serum sodium and bicarbonate (all of which were significant).*

*Of particular importance with respect to future drug development is the question of whether the deleterious effects that led to premature termination of ILLUMINATE are a class effect of all inhibitors of CETP or if they reflect off-target consequences of this particular drug that can be avoided with other CETP inhibitors. Torcetrapib retards atherosclerosis in experimental animals and increases concentrations of HDL-C in patients while lowering low-density lipoprotein cholesterol. Thus, despite the failure of torcetrapib in ILLUMINATE, CETP inhibition certainly merits further exploration.*

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2. 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;357:2109-2122.

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# Overweight in Childhood Increases CHD Risk as Adults

Obesity has become a worldwide public health issue for children and adolescents. In the United States, the prevalence of overweight in the population of children and adolescents aged 6 to 19 years has increased 3 times since 1970, and more than 9 million children and adolescents are currently considered to be overweight. Furthermore, children are becoming overweight at progressively younger ages. Approximately 19% of children aged 6 to 11 years are overweight, with a body mass index (BMI) greater than the 95th percentile for their age and sex, according to the Centers for Disease Control and Prevention (CDC) growth charts.

An increased BMI has been associated with several risk factors for coronary heart disease (CHD), such as hypertension, dyslipidemia, diabetes, and vascular abnormalities. These risk factors are also identifiable in overweight children. The high prevalence of overweight children and adolescents is predicted to result in an increased risk of CHD in adults; however, the severity of the long-term effects of overweight during childhood and adolescence on future CHD in adulthood is still not clear. Two reports recently published in the *New England Journal of Medicine* by Baker et al[1] and Bibbins-Domingo et al[2] have demonstrated the association of overweight in children and adolescents with CHD events in adults.

Baker and colleagues[1] conducted a large cohort study involving 276,835 children born in Denmark from 1930 or later to investigate the association between BMI in childhood (aged 7 through 13 years) and CHD events in adulthood (aged 25 years or older). During the 46-year period of study, 10,235 CHD events occurred among men and 4,318 among women. The risk of any CHD event, a nonfatal CHD event, or a

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## ++Overweight in Childhood Increases CHD Risk as Adults

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fatal CHD event among adults were all positively associated with childhood BMI in boys aged 7 to 13 years and in girls aged 10 to 13 years. Higher BMI during childhood was associated with an increased risk of CHD in adulthood. The associations were linear for each age, and the risk of any CHD event in adulthood increased significantly for each 1-unit increase in BMI z score at each age studied in boys and girls. In general, the associations between childhood BMI and the risk of CHD in adulthood were stronger in boys than in girls.

Moreover, the risk of CHD associated with childhood BMI increased with a child's age in both boys and girls. The risk for each 1-unit increase in BMI z score in 13-year-old boys was nearly twice as high as that in those aged 7 years. Calculation of children's probability of having a future CHD event in adulthood indicated that an overweight 13-year-old boy (one weighing 11.2 kg [25 lb] more than a same-aged boy with normal weight) was predicted to have a 33% increase in the probability of having a CHD event between the ages of 25 and 60 years.

Bibbins-Domingo and colleagues[2] addressed the effect of overweight in adolescents (ie, in those aged 12 to 19 years) on future CHD in adulthood in the United States. The prevalence of adolescent overweight, defined as a weight above 95th percentile on the CDC growth charts, in 2000 was 16.7% in boys and 15.4% in girls. Overweight adolescents are likely to become obese adults. The prevalence of obese 35-year-old men and women (BMI ≥30) in 2020 is estimated to increase to a range of 30% to 37% in men (as compared with 25% now), and 34% to 44% in women (as compared with 32% now). The increase in obesity is predicted to result in a higher prevalence of high blood pressure, diabetes, and dyslipidemia among those aged 35 years.

Using the CHD Policy Model, which is a state-transition computer simulation model, the Bibbins-Domingo[2] study further estimated the excess incidence, prevalence, and mortality associated with CHD and other causes from 2020 to 2035 in US residents aged ≥35 years. It predicted that obesity-related increases in the incidence of CHD and in the total number of CHD events and deaths would occur in both young and middle-aged adults. For instance, the absolute excess events of CHD is projected to rise from 550 (an excess of 10%) in 2020 to 33,000 (an excess of 14%) in 2035, and the number of excess deaths from CHD is projected to increase from 59 in 2020 (an excess of 9%) to 3,600 in 2035 (an excess of 13%). Moreover, the higher prevalence of obesity among those aged 35 years is projected to increase the overall prevalence of CHD by 5% to 16%. More than 100,000 excess cases of CHD are expected to be attributed to adolescent overweight.

In summary, higher BMI in childhood and adolescence is associated with increased risks of future CHD events in adulthood. Children and adolescents are increasingly becoming overweight worldwide at younger ages. A greater number of this population is expected to be at high risk of having CHD events when reaching adulthood. Baker and colleagues[1] recommended that children and adolescents be advised to attain and maintain appropriate weight for prevention of future CHD events and other causes related to obesity.

1. Baker JL et al. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med.* 2007;357(23):2329-2337.

2. Bibbins-Domingo K et al. Adolescent overweight and future adult coronary heart disease. *N Engl J Med.* 2007;357(23):2371-2379.

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## Impact of Self-Monitoring of Blood Glucose on Glycemic Control in Patients with Non–Insulin Treated Diabetes

Although self-monitoring of blood glucose has been frequently recommended to non–insulin treated patients with type 2 diabetes, its effectiveness on the improvement of glycemic control is not conclusive based on currently available data. Farmer and colleagues conducted the present trial, the Diabetes Glycaemic Education and Monitoring (DiGEM) study, to assess the impact of self-monitoring of blood glucose, alone or with instruction in incorporating the results into self-care, on glycemic control in these patients.

The DiGEM study, which was an open, 4-year, randomized, 3-arm, parallel-group trial, recruited 453 patients from 48 general practices in Oxfordshire and South Yorkshire, England. Eligible patients had a mean age of 65.7 years, non–insulin treated type 2 diabetes for a median duration of 3 years, and a mean A1C level of 7.5%. Patients were randomized to 1 of 3 groups: a control group (n=152) using standardized care with measurements of A1C every 3 months; a less-intensive self-monitoring group (n=150), using a blood glucose meter for self-monitoring with advice for patients to contact their doctor for interpretation of results if glucose levels were >270 mg/dL (15 mmol/L) or <72 mg/dL (4 mmol/L); and a more intensive self-monitoring group (n=151), using a blood glucose meter for self-monitoring with additional training of patients in interpretation and application of the results to enhance motivation and maintain adherence to a healthy lifestyle such as diet, physical activity, or drug regimens. Primary outcome for the study was the measurement of A1C at 12 months.
Baseline personal and clinical features were well balanced between the groups. At 12 months, no significant differences were found in A1C levels between the groups after adjustment for baseline A1C levels ($P$=0.12). The difference in unadjusted mean change in A1C levels from baseline to 12 months between the control and less intensive self-monitoring groups was -0.14% (95% confidence interval [CI] -0.35% to 0.07%), and between the control and more intensive self-monitoring groups it was -0.17% (CI, -0.37% to 0.03%). Additionally, no differences between groups were seen in the change in A1C levels over the 12 months of follow-up.

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## Impact of Self-Monitoring of Blood Glucose

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The study noted no differences in most of the secondary outcome measures, including blood pressure, weight, and body mass index. A significant difference in the reduction in total cholesterol levels was detected among the 3 groups ($P$=0.010). However, the proportions of patients prescribed titrated or additional hypoglycemic or lipid-lowering drugs, such as statins to improve glycemic control, were not significantly different among these groups.

The DiGEM investigators concluded that, when compared to the control group, incorporation of self-monitoring of blood glucose in non–insulin treated patients with type 2 diabetes for 12 months had no significant impact on the improvement of their glycemic control. In addition, no differences in glycemic control were detected between less-intensive and more-intensive self-monitoring groups. A small but significant improvement was found in total cholesterol levels with the self-monitoring intervention, probably mediated through increased dietary adherence or regular taking of lipid-lowering drugs. The investigators recommended reviewing current guidelines that suggest the use of self-monitoring of blood glucose in patients with non–insulin treated diabetes.

Farmer A et al. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. *BMJ*. 2007;335(7611):132.

## *Clinical Insights® in Diabetes* Post-Test December 2007

1) Which of the following is NOT one of the conclusions drawn from the prematurely ended ILLUMINATE trial, in which patients with type 2 diabetes or a history of cardiovascular (CV) disease were treated with atorvastatin plus torcetrapib or placebo?
   a. Patients treated with torcetrapib showed a significant increase of HDL cholesterol levels compared with the placebo group
   b. The torcetrapib group had a significant decrease in LDL cholesterol levels vs placebo
   c. The torcetrapib group showed a decreased risk of CV events and death vs placebo
   d. The torcetrapib group showed an increased risk of CV events and death vs placebo

2) Regarding two studies of overweight children and adolescents and their risk of coronary heart disease (CHD) as adults, which of the following statements is true?
   a. Increasing numbers of children and adolescents in the United States and worldwide are overweight, and they are becoming overweight at earlier ages
   b. Increased future risk of CHD events is associated with higher body mass indices in childhood and adolescence
   c. More than 100,000 excess cases of CHD are projected in the US by 2035 attributable to overweight in today's adolescents
   d. All are true

3) In the DiGEM study, self-monitoring of blood glucose in patients with non-insulin treated type 2 diabetes showed all but one of the following results compared to the control group.
   a. No significant impact on glycemic control
   b. A small but significant improvement in total cholesterol levels
   c. A small but significant improvement in glycemic control
   d. No differences in glycemic control between less-intensive and more-intensive self-monitoring groups

### ANSWER KEY

1) c. *The torcetrapib group showed a decreased risk of CV events and death vs placebo.* The ILLUMINATE trial was ended early due to a significant increased risk of CV events and death in the torcetrapib group because of reasons that are still unclear.
2) d. *All are true.* Children and adolescents are increasingly overweight, which is projected to result in greater numbers of adults with CHD in coming decades.
3) c. *A small but significant improvement in glycemic control.* Self-monitoring of blood glucose in patients with type 2 diabetes not treated with insulin was found to have no significant impact on glycemic control.

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*Clinical Insights® in Diabetes* is co-edited by NDEI faculty members Mayer B. Davidson, MD, and Silvio E. Inzucchi, MD.

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