Volume 4, Issue 2 / Winter 2008

Heart Health Times

A newsletter from NewYork-Presbyterian Hospital Preventive Cardiology Program

Sponsored by **Columbia University College of Physicians & Surgeons** *in coordination with* **Weill Cornell Medical College**

HDL Raising Drugs: In Search of the Holy Grail?

Lori Mosca, MD, PhD, *Editor-in-Chief* ***(Conflict Disclosures: Pfizer: Research Support, Consultant; Merck: Consultant)***

No one disputes that low levels of high density lipoprotein (HDL) cholesterol are associated with a heightened risk of cardiovascular disease (CVD). Due to the limitations of current lipid altering drugs to significantly raise HDL and/or because of their sometimes poor tolerability, researchers have actively searched for new methods to increase HDL. One promising novel mechanism to raise HDL is inhibition of cholesteryl ester transfer protein (CETP). This protein transfers cholesterol from HDL to low density lipoprotein (LDL). Torcetrapib was developed as a potent inhibitor of CETP resulting in retention of cholesterol in the protective HDL. The drug has been shown to significantly raise the level of HDL in humans, lower LDL, and protect against atherosclerosis in rabbits.

At the recent American Heart Association Scientific Sessions in November 2007 in Orlando, Florida, the final results of the ILLUMINATE trial were presented. The double-blind randomized controlled study tested the hypothesis that inhibition of CETP with torcetrapib would protect against CVD in humans. The trial involved over 15,000 patients at high CVD risk who received either torcetrapib alone or in combination with atorvastatin. Despite an increase in HDL of 72% and a decrease in LDL of 25%, there was a significant 25% increased risk of CVD events and a 58% significant increased risk of death due to any cause including an increase in deaths from cancer and infections.

Although the mechanism of the adverse effect is not definitively established, the authors (I was one of them) documented an increase of systolic blood pressure, a decrease in serum potassium, and increases in serum bicarbonate and aldosterone, suggesting hypertension and electrolyte disturbances secondary to hyperaldosteronism. It is not known if the off-target effects of this particular CETP inhibitor accounted for the adverse effects observed in the trial or if there is a potential toxic effect related to the pharmaceutical increase in HDL (HDL, for example may bind endotoxin and increase infections and/or cancer). We do not know if other CETP inhibitors without these off target effects will yield a clinical benefit, but many experts are in favor of continuing the search (see commentary by Dr. Alan Tall, also an author). What is known is that HDL remains an important indicator of CVD risk, and lifestyle maneuvers to raise it can be recommended in practice. These include: 1) smoking cessation, 2) regular physical activity, 3) weight loss, 4) replace saturated fat with mono- and polyunsaturated fat, 5) eliminate trans fat, 6) decrease consumption of simple carbohydrates, and 7) drink alcohol in moderation if you drink at all. A patient page with information on methods to raise HDL through positive lifestyle changes is included in this issue of Heart Health Times.

> "Although the ILLUMINATE trial resulted in the death of torcetrapib, the HDL hypothesis is still alive and well. Until new HDL raising drugs are tested for benefit and risks, clinicians should encourage lifestyle and other proven therapies to manage lipids and lower CVD risk."
>
> ***Antonio M. Gotto, Jr., MD, DPhil***
> *Dean, Weill Cornell Medical College*

References:
1. Barter et al, Effects of Torcetrapib in Patients at High Risk for Coronary Events. N Engl J Med 2007;357:2109-22.

Does a High Level of HDL Protect Against Atherosclerosis: Insights from Recent Basic and Clinical Studies.

By **Alan Tall, PhD** ***(Conflict Disclosures: Pfizer: Research Support, Consultant; Merck: Research Support, Consultant, Speakers Bureau)***

A recent analysis of the ILLUMINATE study presented at the 2007 AHA scientific sessions showed that torcetrapib treatment in addition to raising HDL levels was associated with decreases in serum potassium and elevations in aldosterone levels.[1] Along with studies in animal models and cultured cells also presented at the meeting, these findings indicate that at least part of the mechanism responsible for hypertension seen in animals and humans

CONTINUED ON P. 2

INSIDE THIS ISSUE

Columbia University College of Physicians and Surgeons
Weill Cornell Medical College
NewYork-Presbyterian The University Hospital of Columbia and Cornell

H is for Higher: Diet Tips for Raising HDL-Cholesterol

By **Heidi Mochari, MPH, RD** *(Conflict disclosure: none)*

A high density lipoprotein (HDL) cholesterol level of less than 40mg/dL is a major risk factor for coronary heart disease. According to the National Cholesterol Education Program, there are simple diet changes that have been shown to have an HDL-cholesterol raising effect:

- **Replace dietary saturated fat with monounsaturated fat**
  Keeping monounsaturated fats in the diet when cutting out saturated fats may help maintain healthy HDL-cholesterol levels. Monounsaturated fats can be found in avocados, nuts, olives, and oils such as olive and canola oils.
- **Eliminate dietary trans fat**
  Trans fats may not only increase low density lipoprotein (LDL) cholesterol, but is also associated with decreased HDL-cholesterol levels. Trans fat is often found in foods processed in or cooked with partially hydrogenated oils such as cookies, crackers, donuts, and French-fries. Avoiding products that list trans fat on the label and asking restaurants to cook without trans fat may promote higher HDL-cholesterol levels.
- **Reduce total calorie consumption**
  Overweight and obesity are associated with lower HDL-cholesterol levels. Reduction of daily caloric intake through heart healthy diet habits along with increased physical activity promotes improved body weight which is associated with increases in HDL-cholesterol.
- **Only drink alcohol in moderation**
  Moderate consumption of alcohol has been shown to raise HDL-cholesterol levels, but the benefit of raising HDL-cholesterol via this mechanism to reduce coronary heart disease risk is not established. Excess alcohol consumption is associated with hypertension and can provide extra calories which may promote weight gain.

References:
1. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Final Report. Circulation. 2002; 106(25): 3143–421.
2. Goldberg IJ, Mosca L, Piano MR, Fisher EA. Wine and Your Heart: A Science Advisory for Healthcare Professionals From the Nutrition Committee, Counsel on Epidemiology and Prevention, and Counsel on Cardiovascular Nursing of the American Heart Association. Circulation 2001; 103: 472-475.
3. Nutrient composition of foods: USDA Agricultural Research Service Nutrient Data Laboratory. http://www.nal.usda.gov/fnic/foodcomp/search/; Accessed 11/13/07.

Heart Healthy Diet Changes to Promote Higher HDL-Cholesterol

Instead of:	Try:
A tablespoon of butter *(102 calories; 7.3g saturated fat; 0.0g trans fats; 3.0g monounsaturated fat)*	**1/4 of an avocado** *(80 calories; 1.1g saturated fat; 0.0g trans fats; 4.9g monounsaturated fat)*
1/4 cup diced cheddar cheese cubes in your salad *(133 calories; 7.0g saturated fat; 0g trans fats; 3.1g monounsaturated fat)*	**1/4 cup sliced unsalted almonds in your salad** *(132 calories; 0.8g saturated fat; 0.0g trans fats; 7.1g monounsaturated fat)*
Two tablespoons ranch salad dressing *(145 calories; 2.4g saturated fat; 0.1g trans fat; 3.4g monounsaturated fat)*	**Two tablespoons equal parts olive oil and balsamic vinegar** *(133 calories; 1.9g saturated fat; 0.0g trans fat; 9.9g monounsaturated fat)*
Medium size portion of commercial French fries *(387 calories; 5.1g saturated fat; 6.0g trans fat; 12.9g monounsaturated fat)*	**Sweet potato roasted in olive oil** *(234 calories; 1.9g saturated fat; 0.0g trans fat; 9.9g monounsaturated fat)*
1/2 cup premium vanilla ice cream *(270 calories; 11.0g saturated fat; 0.5g trans fat; 4.8g monounsaturated fat)*	**1/4 cup equal parts cashew nuts and raisins** *(153 calories; 1.6g saturated fat; 0.0g trans fat; 4.7g monounsaturated fat)*

Does a High Level of HDL Protect Against Atherosclerosis: Insights from Recent Basic and Clinical Studies

(CONTINUED FROM P. 1)

treated with torcetrapib likely involved increased aldosterone secretion by the adrenal gland. Aldosterone has been shown to have a variety of different vascular toxicities in cell, animal, and human studies. Interestingly, patients whose decreases in serum potassium level were greater than the median had an excess of deaths and of the primary cardiovascular end-point, compared to patients whose changes were less than the median. While the precise mechanisms are still not understood, these findings provide a strong hint that increased activity of some aspect of the renin-angiotensin-aldosterone system may have explained at least part of the adverse outcome of the ILLUMINATE study. In contrast, patients whose increases in HDL were more than the median had a smaller number of cardiovascular events than patients whose increases were below the median.

These findings are reminiscent of earlier studies of genetic CETP deficiency in the Honolulu Heart Program, where a decreased incidence of cardiovascular disease was suggested in men with HDL cholesterol >60 md/dL but not at lower levels of HDL.[2] In a parallel imaging study presented at the AHA meetings in patients treated with torcetrapib/atorvastatin (T/A), the amount of coronary atherosclerosis was determined by intravascular ultrasound (IVUS) analysis. Comparing treatment with T/A to atorvastatin alone, there was no significant change in the primary end-point (% atheroma volume). However, a post-hoc analysis of IVUS results was reported to show a significant inverse correlation between changes in HDL levels and percent atheroma volume in subjects treated with T/A, and subjects whose increases in HDL levels were in the top two quartiles actually showed regression of coronary atherosclerosis.[3] These findings tend to parallel the clinical events in ILLUMINATE and suggest that subjects with marked HDL increases may have had regression of coronary atherosclerosis.

While there could still be an underlying adverse effect of CETP inhibition, together the findings are inconsistent with the notion that increased levels of dysfunctional or toxic HDL caused an adverse clinical outcome in ILLUMINATE by increasing the amount of coronary atherosclerosis. They also suggest that further trials of HDL raising therapies by CETP inhibitors that do not share the off-target effects of torcetrapib may be warranted.

References:
1. Barter P, et al. Effects of Torcetrapib in Patients at High Risk for Coronary Events. NEJM 2007;357:2109-2122.
2. Zhong S, et al. Increased Coronary Heart Disease in Japanese-American Men with mutation in the cholesteryl Ester Transfer Protein Gene Despite Increased HDL Levels. J Clin Invest 1996;97:2917-2923
3. Nicholls SJ, et al. Baseline and Changes in Atheroma Volume Predict clinical Outcome in Patients with Coronary Artery Disease: Insights from ILLUSTRATE. Circulation 2007;116:II_750.

Heart to Heart Patient Profile: Raising HDL and Lowering Heart Disease Risk – *JB of New York City*

Interview By **Allison Christian, EdD** *(Conflict disclosure: none)*

JB is a 53 year-old man with coronary heart disease who learned he had low HDL-cholesterol in 2000 and has been working to increase it ever since. The following interview provides insight into how he became one of our "Heart to Heart" success stories.

Q: What was your HDL level the first time you had it assessed and, at that time, were you aware that it was a major risk factor for heart disease?

A: In 2000 I had a regular check-up with my primary care physician who notified me that a low HDL ("good")-cholesterol level was a major risk factor for heart disease and that my current HDL level could potentially increase my risk of a cardiac-related event or death. I began seeing a preventive cardiologist to help me monitor and raise my HDL and lower my overall cardiac risk.

Q: What actions did you take to raise your HDL, which of these was the most effective, and what impact did these changes have on your overall cardiac risk?

A: My primary objective was to adhere to a new, healthy way of life. In working with a multidisciplinary health care team, I realized this could be accomplished by obtaining regular physical activity, consistently following a healthy diet which, for me, included eating 5-6 small meals each day and losing excess weight. Shortly after making these changes, I noticed that my HDL level was highest when my body mass index was in the normal range (18.5-24.9 kg/m^2) and my waist circumference was <40 inches. So, keeping the weight off was critical to my success. I also began taking prescription niacin to work in combination with diet and exercise to raise my HDL and lower my LDL. Not only did I feel better after making several lifestyle changes, but they resulted in improvements in other major risk factors for heart disease (i.e., cholesterol, glucose, blood pressure).

Q: What are your current goals?

A: My short-term goal is to lose approximately 20 lbs. This will be challenging but I am confident that by maintaining a healthy lifestyle, medication adherence, and regular follow-up with my health care team I can succeed at doing so. My long-term goal is to practice healthy, lifelong habits so that I can maintain an HDL level of 40 mg/dL or more while also keeping my LDL-cholesterol to <100 mg/dL and even lower if possible. I now know what I need to do to slow the progression, and perhaps even contribute to the regression, of heart disease. Raising my HDL is an important part of my plan to succeed.

Prevention Practice Tools: A Motivational Tool to Help Patients Improve Risk Factors

By **Allison Christian, EdD** *(Conflict disclosure: none)*

More than half of all Americans with chronic diseases do not follow their physician's medication and lifestyle guidance. Thus, it is critical to identify methods to help physicians improve their patient's level of compliance.

Practitioners can become effective agents of change by modifying their traditional roles as authoritative figures and using motivational interviewing techniques. Motivational interviewing is patient-oriented and geared to enhancing intrinsic motivation by exploring and resolving the patient's ambivalence about lifestyle change. A key goal of motivational interviewing is to help a patient reframe the change in positive terms (i.e., what is gained versus what is lost) and to identify a source or motivation that can sustain these behavior changes.

EXAMPLE CLINIC FLOW SHEET

Date	10/1/07	11/12/07	12/24/07
Blood Pressure	145/95	130/82	
Weight	213	206	
Body Mass Index	29	28	
Waist Circumference	42	40	
Total Cholesterol	226	209	
LDL-Cholesterol	154	142	
Triglycerides	195	145	
HDL-Cholesterol	35	38	
Glucose	108	97	
Medications	None	None	
>80% Exercise Adherence (min. 4 days/wk, 30 mins/day)	No	Yes	
>80% Adherence to TLC diet	No	Yes	
Smoking (#cigarettes/day)	5	0	
ETOH (#alcohol equivalents/day)	0	0	

A clinic flow sheet, similar to the one provided above, can be used along with motivational interviewing at each visit to monitor a patient's progress, modify the treatment plan as needed, and provide encouragement. Often, when patients see how lifestyle changes can impact risk factors, they are more motivated to make and sustain healthy lifestyle changes. In this example, the increased exercise, decreased smoking, increased adherence to the TLC diet, and weight loss resulted in a 9% increase in HDL which is what would be projected based on aggregate data summarized in the National Cholesterol Education Program ATP III Guidelines: 1) weight reduction: 5–20% increase in HDL, 2) physical activity: 5–30% increase in HDL, and 3) smoking cessation: 5% increase in HDL.

CME

COURSE DESCRIPTION: To continue our mission to improve the quality of preventive cardiovascular care through a newsletter that provides late-breaking science and information on cardiovascular prevention.

TARGET AUDIENCE: Cardiologists, endocrinologists, ob/gyn's, internal medicine physicians, family practitioners, and other health care providers.

OBJECTIVE: Participant will learn about torcetrapib and its effect on cardiovascular disease in a recent major clinical trail. Participants will also gain knowledge about lifestyle methods to raise HDL-cholesterol.

NewYork-Presbyterian Hospital

Columbia University College of Physicians & Surgeons

Weill Cornell Medical College

Preventive Cardiology

This newsletter is partially supported by an educational gift from Pfizer, Inc.

Email Newsletter inquiries to:
Lisa Rehm, *Publication Coordinator*
lmr2@columbia.edu

Disclaimer: This resource provides brief, general information about heart health. It does not take the place of the instructions you receive from your health care providers. For answers to other questions, talk to your physician or other health care provider. NewYork-Presbyterian Hospital does not endorse specifically any test, treatment, or procedure mentioned in this newsletter.

CME Questions:

1. The ILLUMINATE trial showed that torecetrapib was associated with:
   - A. An increased risk of cardiovascular events
   - B. An increased risk of death due to all causes
   - C. Both
   - D. Neither

2. All of the following are seen with the CETP inhibitor torcetrapib except:
   - A. Increased HDL
   - B. Increased LDL
   - C. Increased aldosterone
   - D. Decreased potassium

3. Which of the following is associated with increased HDL levels:
   - A. Cigarette smoking
   - B. Trans fat
   - C. Weight gain
   - D. Physical activity

4. Diet maneuvers to increase HDL includes which of the following:
   - A. Replace saturated fat with mono- and polyunsaturated fats
   - B. Eliminate trans fat
   - C. Moderate alcohol consumption if one drinks
   - D. All of the above

5. Increased physical activity can improve HDL levels between 5 to 30%.
   True or False

The College of Physicians and Surgeons of Columbia University is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The College of Physicians and Surgeons designates this educational activity for a maximum of 1 credit *AMA PRA Category 1 Credit(s).*™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

Visit our website www.hearthealthtimes.com

Columbia University in the City of New York
College of Physicians & Surgeons
601 West 168th Street, #43
New York, NY 10032