Clinical Feature:
HDL—Quality Trumps Quantity

DANIEL E. SOFFER, MD
University of Pennsylvania
Preventive Cardiology
Philadelphia, PA
Diplomate, American Board of Clinical Lipidology

nla community
connect • collaborate • contribute

Discuss this article at **www.lipid.org**
Go to *"Topics/Lipid Spin Spring 2011"* and look for *"Clinical Feature."*

MLS is a 64-year-old Caucasian vital former smoker who had a recent acute myocardial infarction (MI) requiring deployment of two sequential drug-eluting stents in the right coronary artery. She has had very high levels of high-density lipoprotein cholesterol (HDL-C) as long as she can remember and had never taken any cholesterol-lowering therapy prior to the MI. Her clinical features and metabolic/lipid profile before starting medication follow:

- *Former smoker (30-pack years; quit 20 years ago)*
- *Hypertension, diabetes mellitus, metabolic syndrome: neg*
- *Family history premature coronary heart disease (CHD): neg*
- *Early surgical menopause (age 40); on ERT x 20 years*

There is an inverse relationship between high-density lipoprotein cholesterol (HDL-C) levels and cardiovascular risk noted in clinical and epidemiologic trials including the Framingham Heart Study.[1] A number of epidemiologic studies have demonstrated that the low levels of HDL-C are predictive of high cardiovascular (CV) risk, while the highest HDL-C levels exhibit the lowest risk for coronary artery disease (CAD). Similarly, it has been demonstrated that a 2% to 3% reduction in risk results from every 1 mg/dL increase in HDL-C.[2]

There is significant residual cardiovascular risk in treated people and raising HDL-C levels is an important goal in targeting CAD risk reduction after low-density lipoprotein cholesterol (LDL-C) and non-HDL-C goals are met. However, clinical trial evidence for achieving risk reduction with HDL-raising therapy is lacking and certainly less robust than that for LDL-C levels. As monotherapy, nicotinic and fibric acid derivatives have documented value, but tolerability of niacin and inconsistent benefit from fibrates limit their clinical utility. Results of the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) and Atherothrombosis Intervention in Metabolic Syndrome with low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) are eagerly awaited.

HDL is atheroprotective because of its combined ability to limit oxidation, inflammation and thrombosis and because of its role in reverse cholesterol transport (RCT). However, there are exceptional conditions and functional assays that have documented that HDL is not always atheroprotective in the ability to limit oxidation and inflammation.[3] In the wake of the torcetrapib failure,[4] more robust surrogate markers of atherosclerosis and protection are surely needed. Recent work by Khera, et al. presented a novel assay for evaluating the ability of HDL to promote cholesterol efflux from cultured macrophage cells. Their finding that cholesterol efflux capacitance has a strong inverse relationship with atherosclerosis strongly supports the concept that HDL is the main player in reverse cholesterol

Component *Latest Ref Rng*		7/7/2010	1/11/2011
Apolipoprotein A1	*101-198 mg/dL*	255 mg/dL	288 mg/dL (H)
Apolipoprotein B	*High: 49-103*	105 mg/dL	
Glucose	*65-99 mg/dL*		87 mg/dL
Creatinine	*0.63-1.22 mg/dL*		0.94 mg/dL
eGFR, Non-AA	*Low: > OR = 60 mL/min/1.73m²*		59 mL/ min/1.73m² (L)
AST	*6-40 U/L*		66 U/L
ALT	*6-40 U/L*		30 U/L
Total Cholesterol	*125-200 mg/dL*	270 mg/dL	282 mg/dL (H)
HDL Cholesterol	*Low: > OR = 46 mg/dL*	115 mg/dL	153 mg/dL
Triglycerides	*Low: <150 mg/dL*	92 mg/dL	81 mg/dL
LDL Cholesterol	*Low: <130 mg/dL (calc)*	137 mg/dL	113 mg/dL
Lipoprotein (a)	*< 75*	33 nmol/L	
Uric Acid	*2.5-7.0*	9.6 mg/dL	
TSH	*mIU/L*	0.42 mIU/L	

Table 1.

transport (RCT) and it is this role that provides the protective property of HDL.[5] Targeting this aspect of HDL functionality may prove to be the most important goal in HDL therapeutics.

CV disease remains the primary cause of death and disease in industrialized nations, despite terrific advances in public health, individual pharmacotherapy and revascularization procedures over the past several decades. Blood pressure control and anti-platelet pharmacotherapy are part of the foundation of therapy for prevention and management of coronary and peripheral arterial disease, but no regimen is complete without therapy for the reduction of apolipoprotein B-containing (apoB-containing) particles, especially LDL-C levels.

While management of apoB-containing particles is well validated and is the cornerstone of therapy, there remains significant residual cardiovascular risk in treated people, especially when there is inadequate LDL-C lowering and/or elevated triglyceride (TG) and suppressed HDL-C levels. This problem strongly suggests the need for better pharmacotherapy for combined dyslipidemia.

Pharmacologic interventions for HDL-C raising are presently limited to nicotinic (primarily) and fibric (secondarily) acid derivatives, though the data documenting the clinical value are, thus far, underwhelming. Ongoing clinical trials will attempt to answer the question about the real value of the addition of niacin and fibrates to statin therapy.[6,7] As of now, the "measuring stick" for assessing functional response to pharmacotherapy is the lipid profile, which is a quantitative focus on lipoprotein-cholesterol levels. LP particle size and number is an alternative and emerging measure of CV risk, as well. These newer assays, along with apolipoprotein levels, predict CV risk with better accuracy than LP-cholesterol levels[8] and are helpful but not yet widely accepted in clinical management. Similarly, atherosclerosis imaging with carotid intima-medial thickness (CIMT) and coronary artery calcification are potentially attractive tools for assessing atherosclerosis progression, but confirmatory studies are still forthcoming as a tool for monitoring therapy.

> "In the wake of the torcetrapib failure, more robust surrogate markers of atherosclerosis and protection are surely needed."

HDL is the critical component of endogenous protective measures. The particle limits the inflammatory, oxidative and prothrombotic challenges to the activated macrophage. Most importantly, however, the HDL removes oxysterols and transports them back to the liver for recycling or catabolism-completing RCT. The balance between atherogenic (apoB-containing) LP particles and HDL (apoA) can be expressed in many ways (total cholesterol: HDL-C, non-HDL; apoB:A1), but as the above case suggests, individual CV protection may not be enjoyed by all with high HDL-C levels and apparently favorable ratios do not always result in favorable outcomes. In fact, at either end of the HDL-C spectrum—both very low and very high levels—there are examples of an HDL paradox that suggests HDL function may be amplified in specific circumstances at low levels and depressed under other special circumstances at high levels. Namely, cohorts of people with the so-called ApoA1Milano genotype have a reduced CV risk,[9] while a specific subset of people from Omagari City, Japan, with a CETP gene mutation do not share the expected longevity of matched counterparts with similarly elevated HDL-C levels[10] and similar outcomes were noted

among subjects in the Honolulu Heart Program, if they had specific genetic mutations in CETP.[11]

To investigate the relationship between HDL function and CVD, an *ex vivo* method has been developed to assess the ability of HDL to promote cholesterol efflux from macrophages. The assay, which is laborious and time consuming, involves the measurement of cholesterol efflux from the macrophage by incubating apoB-depleted serum with J774 cells (a macrophage cell line) that have been preloaded with radio-labeled free cholesterol and stimulated with cyclic adenosine monophosphate (AMP) to upregulate ABCA1. The amount of radio-labeled cholesterol present in the medium after four hours of incubation with HDL represents the amount of cholesterol flux from the macrophage. Several studies were completed using this assay, but it is worth highlighting the study published recently in the *New England Journal of Medicine*. Khera, et al. evaluated 203 healthy volunteers who underwent evaluation with CIMT, 442 patients with angiographically confirmed coronary artery disease, and 351 subjects without such disease. They demonstrated that cholesterol efflux capacitance is highly inversely correlated with CIMT and atherosclerotic heart disease. This correlation was independent of the relationship to HDL-C and even apoA1 levels, supporting the hypothesis that function predicts outcome better than mass.

> "They demonstrated that cholesterol efflux capacitance is highly inversely correlated with CIMT and atherosclerotic heart disease...supporting the hypothesis that function predicts outcome better than mass."

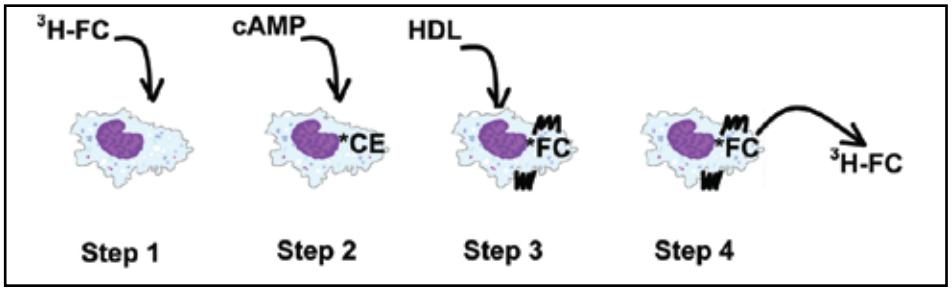

Figure 1. Cholesterol efflux assay. Step 1: Macrophages are incubated in the presence of radio-labeled free-cholesterol; this causes the accumulation of radio-labeled free cholesterol in the macrophage. Step 2: Macrophages are incubated in the presence of cyclic adenosine monophosphate (cAMP) to up-regulate ABCA1, one of the main transporter proteins involved in efflux of cholesterol. Step 3: Macrophages are incubated with HDL obtained from the subjects. Step 4: The amount of radio-labeled cholesterol effluxed from the cells is measured. Cholesterol efflux capacity is measured as percentage of radio-labeled cholesterol effluxed during the four-hour incubation (Courtesy of Dr. Cuchel).

In large populations, it is clear there is an inverse relationship between HDL and cardiovascular risk. However, clinicians regularly encounter paradoxical clinical scenarios, such as MLS. While it is an attractive concept to suggest to our patients that we think their CV risk would be lower if they could just raise their HDL-C, we presently have very few therapeutic options. Surrogate markers of HDL function, such as anti-oxidative, thrombotic and inflammatory response, and now cholesterol efflux, should provide mechanisms for guiding new pharmacotherapy development. These tools may someday be refined for the throughput required for clinical medicine but, for now, remain in the hands of our bench research colleagues.

MLS was treated with therapeutic lifestyle counseling, combination anti-platelet therapy including aspirin and clopidogrel, beta blocker and standard dose statin monotherapy. She does not require any HDL-C raising therapy, but it is reasonable to speculate that her HDL is dysfunctional to start and, hopefully, these therapies will stabilize her disease and enable longevity. ■

Disclosure Statement: Dr. Soffer has received salary support from research grants from Novartis and Pfizer Inc.

References listed on page 33.

**Questions and comments about this article may be directed to the author via e-mail at Daniel.Soffer@uphs.upenn.edu.*