Applying the Science Behind HDL and Cardiovascular Risk Into Primary Care

Wednesday, April 11, 2012

Anaheim, California

Educational Partner
Session 6: Applying the Science Behind HDL and Cardiovascular Risk Into Primary Care

Learning Objectives

1. Determine the most appropriate risk stratification techniques and screening procedures to identify patients thought to be at risk for chronic heart disease (CHD), including those with low high-density lipoprotein (HDL).
2. Examine the epidemiology of HDL, assess the various functions of HDL, including its metabolism and molecular dynamics, and integrate the appropriate drug therapy to modulate and manage HDL to decrease cardiovascular risk and overall atherosclerosis development.
3. Evaluate the safety and efficacy of emerging therapies thought to improve HDL quality and quantity to be knowledgeable on therapeutics that may reduce residual cardiovascular risk.

Faculty

Sergio Fazio, MD, PhD
Cornelius Vanderbilt Professor of Medicine
Chief, Section of Cardiovascular Disease Prevention
Vanderbilt University
Nashville, Tennessee

Dr Sergio Fazio is the Cornelius Vanderbilt Professor of Medicine and Pathology at Vanderbilt University School of Medicine in Nashville, where he is Section Chief of Cardiovascular Disease Prevention.

After earning a medical degree from the University of Rome in Italy, Dr Fazio remained there to complete an internship and residency in internal medicine and a clinical fellowship in metabolic diseases. In addition, he holds a doctorate in experimental medicine from the University of Siena in Siena, Italy.

Dr Fazio’s clinical interest is in the management of patients with dyslipidemia. He participates in clinical trials and is involved in the determination of new mutations that cause altered lipid levels in humans. His research interests are focused on the pathogenesis of genetic dyslipidemias, the early cellular events of atherogenesis, and gene therapy approaches to atherosclerosis. An Established Investigator of the American Heart Association, Dr Fazio is currently principal investigator or co–principal investigator of several studies sponsored by the National Institutes of Health.

Eliot A. Brinton, MD, FAHA, FNLA
Director of Atherometabolic Research
Utah Foundation for Biomedical Research
Salt Lake City, Utah

Dr Eliot Brinton is director of atherometabolic research at the Utah Foundation for Biomedical Research. He currently serves as president of the Utah Atherosclerosis Society and is past president of the Pacific Lipid Association. Dr Brinton was a founding board member and vice president of the American Board of Clinical Lipidology, and was a founding board member of the National Lipid Association.

Dr Brinton attended Stanford University and the University of Utah as an undergraduate, and received his MD from the University of Utah. He completed his residency in internal medicine at Duke University, as well as a fellowship in metabolism, endocrinology and nutrition at the University of Washington.

Dr Brinton is an editor of Lipids Online and an assistant editor of the Journal of Obesity. He also serves on the editorial boards of the Journal of Clinical Endocrinology and Metabolism, the Journal of Clinical Lipidology, the Journal of Managed Care Pharmacy, and Clinical Lipidology.
Dr Gregory Pokrywka is a board-certified internist from Baltimore and Towson, Maryland, and an assistant professor of general internal medicine at the Johns Hopkins University School of Medicine. He attended Duke University, worked as a biochemist, attended the University of Maryland Medical School, and was chief resident in internal medicine at Mercy Hospital in Baltimore.

Dr Pokrywka has been in private practice since 1987 and founded the Baltimore Lipid Center in 2001. He pursued his interest in menopausal lipidology through certification as a credentialed menopause practitioner by the North American Menopause Society. A November 2005 inaugural diplomate of the American Board of Clinical Lipidology, Dr Pokrywka is one of a handful of US physicians double-certified in menopause and lipidology.

In March 2009, Dr Pokrywka was elected fellow of the National Lipid Association (NLA) by his peers. Fellowship in the NLA recognizes the excellence, innovation, and leadership of health professionals with respect to clinical lipidology in private practice or academic settings.

**Faculty Financial Disclosure Statements**

The presenting faculty report the following:

Dr Brinton has received compensation as a speaker, consultant and/or researcher for Abbott Laboratories; Amarin Corporation; Atherotech Diagnostic Labs; Bristol-Myers Squibb; Daiichi-Sankyo, Inc.; GlaxoSmithKline; Kowa Pharmaceuticals America, Inc.; Merck & Co., Inc; and Takeda Pharmaceuticals USA, Inc.

Dr Fazio has received compensation for advisory work with Amarin Corporation; Kowa Pharmaceuticals America, Inc.; Merck & Co., Inc.; Pfizer Inc.; and Roche USA.

Dr Pokrywka has received compensation as a speaker for AstraZeneca; Genentech; Health Diagnostic Laboratory, Inc.; Kowa Pharmaceuticals America, Inc.; Liposcience Inc.; Metagenics, Inc.; and Daiichi Sankyo, Inc.

**Education Partner Financial Disclosure Statement**

The content collaborators at Vindico Medical Education report the following:

Dr Ronald Codario, Medical Director, and Chris Rosenberg, Director of Medical Education, have no financial relationships to disclose.

**Suggested Reading List**


Pre/Post Question #1

Which statement is true?

1. Residual risk in major statin trials is 20-30%
2. Residual risk in the CARDS trial was 38%
3. Residual risk in major statin trials is 60-70%
4. Residual risk for patients with diabetes in the HPS trial was 48%

Pre/Post Question #2

Which of the following is not a cause of low HDL-C?

1. Viral Hepatitis
2. LCAT Deficiency
3. Renal Disease
4. Impaired CETP Activity

Pre/Post Question #3

Which of the following statements is true?

1. Dalcetrapib decreases LDL-C and increases HDL-C
2. Anacetrapib increases HDL-C and has no effect on LDL-C
3. Anacetrapib lowers LDL-C and lowers HDL-C
4. Dalcetrapib increases HDL-C and has no effect on LDL-C

HDL and Residual Cardiovascular Risk

Sergio Fazio, MD, PhD
Cornelius Vanderbilt Professor of Medicine and Professor of Pathology, Immunology, and Microbiology
Chief, Section of Cardiovascular Disease Prevention
Vanderbilt University Medical Center
Nashville, Tennessee

Many Ways to Get in Trouble

Abnormal Lipid Metabolism
- LDL C
- ApoB
- HDL C
- Triglycerides

Cardiovascular Risk
- Age
- Race
- Gender
- Family History
- Inflammation
- Hypercoagulation

Arterial Wall Plaque
- Age
- Race
- Gender
- Family History
- Inflammation
- Hypercoagulation

Many Ways to Get in Trouble

Genetics
Overweight/Obesity
Abnormal Lipid Metabolism
- LDL
- ApoB
- HDL
- Triglycerides

Age
Inflammation
Hypercoagulation

Abnormal Lipid Metabolism
- LDL
- ApoB
- HDL
- Triglycerides
Definition of Residual Risk

- Exposure to loss remaining after other known risks have been countered, factored in, or eliminated (Business/Investing)
- Any element of risk that remains once the risk assessment as been made and responses implemented (Project Management)
- Residual risk of vascular events persisting in patients at treatment goals [...] including risk related to dyslipidemia…. (R3i)

Macrophages and Inflammation in the Artery Wall

CVD Prevention Is Based Only on Systemic Maneuvers

- Lifestyle changes
- Blood pressure control
- Diabetes treatment
- Inhibition of platelet aggregation
- Lipid management

Future Therapies Must Target the Plaque!
- Activation of cholesterol efflux
- Regulation of cell death, egress
- Control of oxidation and inflammation

ADA and ACC Consensus Statement on Lipoprotein Management in High-Risk Patients

<table>
<thead>
<tr>
<th>Treatment Goals</th>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
<th>ApoB (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high-risk patients:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Known CVD</td>
<td>&lt; 70</td>
<td>&lt; 100</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>2. Diabetes + CVD risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk patients:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Two or more CVD risk factors</td>
<td>&lt; 100</td>
<td>&lt; 130</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>2. Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statin-Induced LDL Lowering and CVD Risk Reduction in Secondary Prevention Trials

- CARE = Cholesterol and Recurrent Events Trial
- 4S = Scandinavian Simvastatin Survival Study
- HPS = Heart Protection Study
- TNT = Treating to New Targets

LDL-C (mg/dL)

0 70 90 110 130 150 170 190 210

Event (%)
Mortality Risk Reduction per 1 mmol/L (38.7 mg/dL) LDL-C Reduction in Statin Trials

- CHD (-20%)
- Stroke (-4%)
- Vascular Events (-14%)
- Non-Vascular Events (-3%)
- Any Death (-10%)

SATURN Trial: Maximum Dose Atorvastatin or Rosuvastatin

- Subjects with CAD, on Atorvastatin 80 mg or Rosuvastatin 40 mg for 104 weeks
- IVUS at baseline and end of study
- Treatment LDL 70 mg/dL (A) and 62 mg/dL (R), HDL 48 mg/dL (A) and 50 mg/dL (R), TG<130 mg/dL in both
- PAV -0.99% (A) and -1.22% (R)
- Two thirds of subjects showed regression
- Authors conclude that this is "evidence that atherosclerotic plaques can regress"

Lowering LDL-C Is Not Enough

- Major statin trials show 25%–40% CVD risk reduction regardless of baseline LDL-C
- Despite LDL-C lowering, two thirds of expected CHD recurrences not avoided
- Many patients experience plaque progression under therapy, and those who don’t have minimal regression

Aggressive LDL-C Reduction Eliminates One Third of the Expected CVD Events

Residual CVD Risk in Diabetic Patients on Statin Treatment

- Includes stroke
- Includes diabetes
- HPS: Heart Protection Study; Collaborators. Lancet. 2002;360:1261-70
- CARDS*: Includes stroke

Residual CVD Risk in Diabetic Patients on Statin Treatment

<table>
<thead>
<tr>
<th>Event Rate (No Diabetes)</th>
<th>Event Rate (Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Statin</td>
<td>On Placebo</td>
</tr>
<tr>
<td>HPS* (CHD patients)</td>
<td>19.8%</td>
</tr>
<tr>
<td>CARE†</td>
<td>19.4%</td>
</tr>
<tr>
<td>LIPID‡</td>
<td>11.7%</td>
</tr>
<tr>
<td>PROSPEER§</td>
<td>13.1%</td>
</tr>
<tr>
<td>ASCOT-LLA‡</td>
<td>4.9%</td>
</tr>
<tr>
<td>TNT</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

Event Rate (Diabetes) | On Statin | On Placebo |
----------------------|-----------|------------|
HPS* (CHD patients)   | 25.7%     | 33.4%      |
CARE†                 | 24.6%     | 28.7%      |
LIPID‡                | 15.2%     | 19.2%      |
PROSPEER§             | 16.0%     | 23.1%      |
ASCOT-LLA‡            | 8.7%      | 9.6%       |
TNT                   | 9.7%      | 13.8%      |

* CHD death, nonfatal MI, stroke, revascularizations
† CHD death, nonfatal MI, CABG, PTCA
‡ CHD death and nonfatal MI
§ CHD death, nonfatal MI, stroke
║ CHD death, nonfatal MI, resuscitated cardiac arrest, stroke


Comparison of Lipid Subgroup Analyses in Fibrate Trials

<table>
<thead>
<tr>
<th>Study (Drug)</th>
<th>CVD Reduction (%)</th>
<th>Lipid Subgroup Criteria</th>
<th>CVD Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helsinki Heart Study (gemfibrozil)†,‡</td>
<td>-34% (0.02)</td>
<td>TG ≥ 204 mg/dL; HDL-C ≥ 42 mg/dL</td>
<td>-76% (0.002)</td>
</tr>
<tr>
<td>VA-HIT (Gemfibrozil)†,‡</td>
<td>-22% (0.006)</td>
<td>TG ≥ 180 mg/dL</td>
<td>-28% (0.006)</td>
</tr>
<tr>
<td>IF (Fenofibrate)§</td>
<td>-7.3% (0.24)</td>
<td>TG ≥ 204 mg/dL; HDL-C &lt; 40 mg/dL</td>
<td>-39.3% (0.02)</td>
</tr>
<tr>
<td>FIELD (Fenofibrate)†,‡</td>
<td>-13% (0.14)</td>
<td>TG ≥ 204 mg/dL; HDL-C &lt; 40 mg/dL</td>
<td>-27% (0.005)</td>
</tr>
<tr>
<td>ACCORD (Fenofibrate)§</td>
<td>-4% (0.32)</td>
<td>TG ≥ 204 mg/dL; HDL-C &lt; 40 mg/dL</td>
<td>-31% (0.03)</td>
</tr>
</tbody>
</table>


Current Options for Management of Low HDL Cholesterol

- Lifestyle modification
- Statin
- Niacin
- Fibrate
- Thiazolidinediones (TZDs)*
- Combination therapy

* TZDs not FDA-approved for raising HDL

TNT Study: Low HDL-C predicts CVD Risk in High-risk Subjects with LDL-C at Goal

<table>
<thead>
<tr>
<th>Patients with on treatment LDL-C ≤ 70 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-treatment level (3 months statin therapy): n = 2661</td>
</tr>
<tr>
<td>Mean LDL-C, 58 mg/dL; mean TG, 126 mg/dL</td>
</tr>
</tbody>
</table>

Change in Stenosis, %

<table>
<thead>
<tr>
<th>CVD Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 38</td>
</tr>
<tr>
<td>n = 38</td>
</tr>
<tr>
<td>n = 42</td>
</tr>
</tbody>
</table>

Quantitative Coronary Angiography

HATS (HDL-C Atherosclerosis Treatment Study) Clinical End Points

Adapted from Castelli WP. Can J Cardiol. 1998;4(suppl):5A-10A.
AIM HIGH: No Measurable Effects of Niacin Added to Simvastatin

- 3414 Subjects with CAD
- Simvastatin alone or with ezetimibe ± ER niacin
- On niacin TG 120 mg/dL, HDL 44 mg/dL, LDL 65 mg/dL
- Controls TG 152 mg/dL, HDL 38 mg/dL, LDL 67 mg/dL
- 282 subjects on niacin had primary endpoint (16.4%)
- 274 controls had primary endpoint (16.2%)
- Niacin did not reduce residual risk in the context of this study design


HDL-Based Therapies in Development

- Niacin + flush-blocker
- CETP Inhibitors
- HDL delipidation (extracorporeal)
- HDL mimetics (IV infusion)
- A-I synthesis-inducers
- Others
  - Enhancers of ABCA1 and other chol-efflux factors?
  - Lipase modulation?
  - PPAR agonists?
  - LXR/FXR/RXR agents?
  - SR-B1 inhibitors

Does HDL Become Dysfunctional in CAD or Does Dysfunctional HDL Cause CAD?

- Lack of association between function and HDL-C levels suggests that atherosclerosis may modify HDL
- Dysfunctional HDL may be hiding in either the low or high HDL-C range
- Dysfunctional HDL may be present in unique patient types

Does HDL Become Dysfunctional in CAD or Does Dysfunctional HDL Cause CAD?

Non-fatal MI Risk Reduction with LDL Lowering in ESRD Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D (atorva)</td>
<td>33 (1.91%)</td>
<td>35 (2.02%)</td>
</tr>
<tr>
<td>AURORA (rosuva)</td>
<td>91 (1.97%)</td>
<td>107 (2.33%)</td>
</tr>
<tr>
<td>SHARP (simva/eze)</td>
<td>134 (0.71%)</td>
<td>159 (0.85%)</td>
</tr>
</tbody>
</table>


Uremia Inhibits Atherosclerosis Regression

HDL of Patients on Renal Dialysis Have Impaired Cholesterol Efflux Capacity

Non-fatal MI Risk Reduction with LDL Lowering in ESRD Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D (atorva)</td>
<td>33 (1.91%)</td>
<td>35 (2.02%)</td>
</tr>
<tr>
<td>AURORA (rosuva)</td>
<td>91 (1.97%)</td>
<td>107 (2.33%)</td>
</tr>
<tr>
<td>SHARP (simva/eze)</td>
<td>134 (0.71%)</td>
<td>159 (0.85%)</td>
</tr>
</tbody>
</table>
Conclusions

- Lifestyle and pharmacologic interventions reduce short-term risk, but the majority of expected events cannot be prevented.
- Aggressive LDL reduction halts progression but only induces minimal regression.
- Residual risk reduction may derive from "appropriate" HDL maneuvers.

Risk Stratification in the Patient with Low HDL Cholesterol

Gregory Pokrywka, MD, FACP, FNLA, NCMP
Director, Baltimore Lipid Center
Assistant Professor, Medicine, Johns Hopkins University
School of Medicine

Meta-Analysis: Predictive Value of HDL-C

- Coronary Primary Prevention Trial (CPPT)
- Multiple Risk Factor Intervention Trial (MRFIT)
- Lipid Research Clinics Prevalence Mortality Follow-up Study (LRCS)
- Framingham Heart Study (FHS)

Measures of HDL (High-density Lipoprotein)

- HDL-C: Concentration of cholesterol contained in HDL Particles
- HDL-P: Concentration of HDL particles that carry cholesterol
- Apo-A1: Concentration of Apo-A1 (building block of HDL); number of molecules of Apo-A1 can vary per HDL particle
- Why is this important?
Evaluation of Low HDL-C

- Low HDL-C has many etiologies
- While population data suggests that low HDL is associated with increased risk of CHD events, examples exist of patients with low HDL-C levels and no CHD and of patients with increased HDL-C levels who present with CHD

HDL-C Levels Often Do Not Predict ASHD

- Torcetrapib
- ApoA-1 Milano
- WHI Estrogen
- SRB1 rodent data
- LCAT deficiency
- Tangier Disease

High HDL-C Decreases Cardiovascular Risk at Low LDL-C (<70 mg/dL) – TNT Study

![Bar Chart](image)


HDL Functionality and Vascular Protection

- Macrophage Reverse Cholesterol Transport
  - A-I
- Antioxidant
- Anti-inflammatory
- Pro-fibrinolytic
- + Nitric Oxide

None of these effects has a direct relationship to HDL-C or HDL particle size

Dysfunctional HDL-C

Factors that can make the “good” cholesterol better – or worse

- Proven to promote the anti-inflammatory effect of high-density lipoprotein (HDL)
  - Apolipoprotein (apo) A-I mimetics
  - Exercise, low-fat diet
  - Polyunsaturated fat diet
  - Statins
- May promote HDL’s anti-inflammatory effect
  - Anti-rheumatic biologics
  - Apo A-I Milano
  - Delipidated HDL

- Promote proinflammatory HDL
  - Coronary atherosclerosis
  - Diabetes mellitus
  - Hemodialysis
  - Diet high in saturated fat
  - Infection
  - Rheumatoid arthritis
  - Surgery
  - Systemic lupus erythematosus

Differential Dx of Low HDL-C

- Often imparts risk or lack thereof
- Helps to understand need for treatment
- Helps to understand how aggressive treatment should be
- Helps guide the management of other secondary causes of low HDL-C

*Currently in development
Causes of Low HDL-C

• Lifestyle
• Diet
• Smoking
• Medications
• Secondary disease states
• Genetic disorders

Common Causes of HDL-C Deficiency

• Obesity, especially visceral obesity
• Insulin resistance
• Hypertriglyceridemia
• Metabolic syndrome
• Type 2 diabetes
• HIV disease
• Low fat intake or diets enriched with polyunsaturated fat
• Cigarette smoking
• Severe stress states, e.g., sepsis, burns
• Liver disease
• Renal insufficiency
• Drugs
  - Itraconazole
  - Sirolimus (rapamycin)
  - Protease inhibitors
  - Androgenic steroids
  - Non-selective β-blockers
  - Protacal
  - Recombinant interferon-2

Low HDL-C is Associated with Increased LDL-Particle #, Apo B and Non-HDL-C

Causes of Severe HDL-C Deficiency

• Moderate to severe hypertriglyceridemia
• Critical illness, including sepsis, burns, small bowel exclusion
• Anabolic steroids
• Acquired LCAT deficiency, possibly decreased ApoA-I synthesis
  - Severe cholestasis
  - Cholestatic liver disease with liver failure
  - Alcoholic hepatitis
  - Acute viral hepatitis
  - Acute cholestasis
  - Partial hepatectomy (temporary)
  - Recombinant interferon-2 therapy

Severe HDL-C Deficiency Syndromes

Characteristics of homozygotes in kindreds with severe high-density lipoprotein deficiency

<table>
<thead>
<tr>
<th>Total Cholesterol (mg/dL)</th>
<th>ApoA-I Deficiency</th>
<th>Tangier Disease</th>
<th>LCAT Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>90</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>60</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>4</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Findings

- Xanthomas
- Can have planar or tuberous xanthomas
- Negative

- Cerneal Opacification
  - Mild-Moderate
  - Very Mild
  - Staining

- Coronary Heart Disease
  - Risk

Genetic HDL Disorders

<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism</th>
<th>Δ HDL-C</th>
<th>Athero</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo A-I Mut</td>
<td>Abn A-I struct</td>
<td>-0.3 to 0</td>
<td>HDL-C</td>
</tr>
<tr>
<td>Apo A-I Milano</td>
<td>Abn A-I Arg173Cys</td>
<td>NA</td>
<td>HDL-C</td>
</tr>
<tr>
<td>Tangier Dis</td>
<td>Abn ABCA1 transporter</td>
<td>NA</td>
<td>HDL-C</td>
</tr>
<tr>
<td>LCAT DefFish Eye</td>
<td>LCAT def total or HDL only</td>
<td>NA</td>
<td>HDL-C</td>
</tr>
<tr>
<td>Niemann-Pick</td>
<td>NA</td>
<td>HDL-C</td>
<td>↓</td>
</tr>
<tr>
<td>CETP Defic</td>
<td>NA</td>
<td>HDL-C</td>
<td>↓</td>
</tr>
<tr>
<td>Fam. '86</td>
<td>HDL catabolism</td>
<td>HDL-C</td>
<td>↓</td>
</tr>
</tbody>
</table>

No clinical value: monogenic dis. rare, polygenic not understood

Hepatic Lipase

CETP

Small LDL

TG

CE

Hepatic Lipase

TG-enriched Chol-depleted

Small HDL

Take Home Pearls

- Low HDL-C has many potential causes
- HDL functionality can be impaired in insulin resistant and inflammatory conditions
- Low HDL-C is a significant independent risk factor for coronary heart disease
- Aerobic exercise, smoking cessation, and weight loss can increase HDL-C levels
- Benefits of drug therapies designed to increase HDL-C remain to be demonstrated

Case #1

44-year-old male, asymptomatic non-smoker whose father died from an MI at age 46 presents with the following data on no medications:

- HDL-C: 22 mg/dL
- LDL-C: 108 mg/dL
- Triglycerides: 135 mg/dL
- Total Cholesterol: 157 mg/dL
- Non-HDL-C: 135 mg/dL
- Fasting glucose: 88 mg/dL

What lipid lowering therapy/strategy would you institute?

1. Statin
2. Niacin-ER
3. Gemfibrozil
4. Life style changes only with no therapy
5. Fenofibrate

Case #2

61-year-old male with a myocardial infarction 3 years ago, currently on simvastatin 40 mg daily, clopidogrel 75 mg daily, aspirin 81 mg daily presents with the following data:

- LDL-C: 90 mg/dL
- HDL-C: 26 mg/dL
- Triglycerides: 177 mg/dL
- Total cholesterol: 151 mg/dL
- Non-HDL-C: 125 mg/dL
- Fasting glucose: 105 mg/dL
- A1C: 6.0%
- LDL-P: 1305 nmol/L

Lifestyle Modification on HDL-C

<table>
<thead>
<tr>
<th>Therapeutic Intervention</th>
<th>Increase in HDL-C %</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic Exercise</td>
<td>5-10</td>
<td>Increases in pre-beta HDL, RCT, LPL, TG</td>
</tr>
<tr>
<td>Tobacco Cessation</td>
<td>9-10</td>
<td>Increases LCAT and RCT, Decreases CETP</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>0.35 mg/dL per kilogram of weight lost</td>
<td>Increases LCAT, LPL, and RCT</td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td>5-15</td>
<td>Increases ABCA1, Apo-A1, paraoxonase, Decreases CETP</td>
</tr>
<tr>
<td>Dietary Factors (n-3PUFAs, n-6 PUFAs, MUFAs)</td>
<td>0-5</td>
<td>Improves LDL-C: HDL-C ratio, lower TG</td>
</tr>
</tbody>
</table>

Case #2

61-year-old male with a myocardial infarction 3 years ago, currently on simvastatin 40 mg daily, clopidogrel 75 mg daily, aspirin 81 mg daily presents with the following data:

- LDL-C: 90 mg/dL
- Fasting glucose: 105 mg/dL
- A1C: 6.0%
- Total cholesterol: 151 mg/dL
- Non-HDL-C: 125 mg/dL
- LDL-P: 1305 nmol/L

What additional lipid lowering therapy would you recommend?
1. Change to rosuvastatin 20 mg daily
2. Add ezetimibe
3. Add Niacin-ER
4. Add fenofibrate
5. Add colesevelam

Emerging HDL-Related Medications
Eliot A. Brinton, MD, FAHA, FNLA
Director of Atherometabolic Research
Utah Foundation for Biomedical Research
Salt Lake City, UT

HDL-Based Therapies in Development
- Niacin + flush-blocker
- CETP Inhibitors
- HDL delipidation (extracorporeal)
- HDL mimetics (IV infusion)
- A-I synthesis-inducers
- Others
  - Enhancers of ABCA1 and other chol-efflux factors?
  - Lipase modulation?
  - PPAR agonists?
  - LXR/FXR/RXR agents?
  - SR-B1 inhibitors

Mechanisms of Niacin Flushing

Laropiprant* + Extended Release Niacin Reduces Flushing

CETP Inhibitors in Development
Effect of 600 mg Dalcetrapib Administration on Plasma HDL

- Increase HDL = 32%

Progression in TVA at 24 months in the placebo arm; not seen with dalcetrapib

- Dal-PLAQUE: Dalcetrapib May Reduce Progression of Carotid Total Vessel Area by MRI

Anacetrapib and Dalcetrapib May Differ in Pre-Beta HDL Formation In Vitro

- No inhibition of Preβ-HDL formation with Dalcetrapib

Does Anacetrapib Reduce CHD events? DEFINE “Safety” Results

- Cardiovascular events during the treatment phase of the study
- Randomized evaluation of the Effects of Anacetrapib through Lipid Modification

  - 30,000 patients with occlusive arterial disease in North America, Europe and Asia
  - Background LDL-lowering with atorvastatin
  - Randomized to anacetrapib 100 mg vs. placebo
  - Scheduled follow-up: 4 years
  - Primary outcome: Coronary death, myocardial infarction or coronary revascularization

www.revealtrial.org
Evacetrapib: Percent Changes in HDL-C and LDL-C

-3.0% 53.6% 128.8% -35.9%
-20% 0% 20% 40% 60% 80% 100% 120% 140%
Placebo 30 mg 100 mg 500 mg

Preβ-HDL Enriched Plasma Obtained by HDL Selective Delipidation

HDL-C LDL-C
Placebo ■
30 mg ■
100 mg ■
500 mg ■
P<0.001 compared with placebo.

Measuring Cholesterol Efflux Capacity of Human Serum

J774 Macrophages

Loading with 3H-labeled Free Cholesterol (+ ACAT Inhibitor)

Patient Serum ➔ cAMP (upregulates ABCA1)

% Efflux Free Cholesterol

Serum Cholesterol Efflux Capacity Is Increased by HDL Delipidation Not by Statin Treatment

HDL-Raising: RVX-208 vs. Niacin (% increase, [decrease])

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measure</th>
<th>Niacin [%]</th>
<th>RVX 208 [%]</th>
<th>HMP [%]</th>
<th>Humans [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td>Chol.</td>
<td>13-35</td>
<td>74</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Apo A-I</td>
<td>Prot.</td>
<td>6-16</td>
<td>45</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pre-β</td>
<td>Prot.</td>
<td>[10]</td>
<td>56</td>
<td>No A.</td>
<td></td>
</tr>
<tr>
<td>Large alpha (spher.)</td>
<td>Chol.</td>
<td>33-37</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Niacin raises HDL levels ~1.5x to 4x more than RVX 208

Summary and Conclusions

- HDL levels and function may be enhanced by several emerging Rx approaches; however,
- We do NOT yet know which ones are best!
- Niacin might help prevent CVD when added to a statin: HPS2-THRIVE data will be critical to this question
- CETP inhibition is promising, but more CVD data are needed for dalcetrapib, anacetrapib and evacetrapib
- HDL/apo A-I Mimetics and HDL delipidation work quickly for atherosclerosis but:
  - They are cumbersome, and
  - CVD event data are lacking
- Other HDL-related treatments are in early development
Pre/Post Question #1

Which statement is true?

1. Residual risk in major statin trials is 20-30%
2. Residual risk in the CARDS trial was 38%
3. Residual risk in major statin trials is 60-70%
4. Residual risk for patients with diabetes in the HPS trial was 48%

Pre/Post Question #2

Which of the following is not a cause of a low HDL-C?

1. Viral Hepatitis
2. LCAT Deficiency
3. Renal Disease
4. Impaired CETP Activity

Pre/Post Question #3

Which of the following statements is true?

1. Dalce trapib decreases LDL-C and increases HDL-C
2. Anacetrapib increases HDL-C and has no effect on LDL-C
3. Anacetrapib lowers LDL-C and lowers HDL-C
4. Dalce trapib increases HDL-C and has no effect on LDL-C