High-Density Lipoproteins: Anti-atherogenic Functions and HDL-Raising Therapies

Updates for Cardiologists
September 12, 2012
Chicago, Illinois

Educational Partners
Session 2: High-Density Lipoproteins: Anti-atherogenic Functions and HDL-Raising Therapies

Learning Objectives

1. Review data demonstrating the relationship of high-density lipoprotein cholesterol (HDL-C) levels with atheroprogression and cardiovascular events.
2. Discuss evolving concepts of HDL metabolism, reverse cholesterol transport, and the anti-atherosclerotic functions of HDL as they relate to the prevention of cardiovascular events.
3. Evaluate the role of existing and emerging pharmacotherapeutic agents for raising HDL levels, enhancing HDL function, and reducing cardiovascular disease risk.

Faculty

Peter P. Toth, MD, PhD
Director of Preventative Cardiology
CGH Medical Center
Sterling, Illinois
Professor of Clinical Family and Community Medicine
University of Illinois College of Medicine
Peoria, Illinois

Dr Peter Toth is director of preventative cardiology at CGH Medical Center in Sterling, Illinois, and a visiting professor of clinical family and community medicine at the University of Illinois College of Medicine in Peoria. Dr Toth received a BA in biochemistry from Princeton University and a PhD in biochemistry from Michigan State University. He graduated from Wayne State University School of Medicine and completed residency training in family medicine at the University of Iowa Hospitals and Clinics.

Dr Toth has authored or co-authored over 220 publications in medical and scientific journals and textbooks. He is editor-in-chief of The Year in Lipid Disorders and an associate editor of the Year Book of Endocrinology. He is co-editor, with Antonio Gotto, of the textbook, Comprehensive Management of High Risk Cardiovascular Patients; with Michael Davidson, of Therapeutic Lipidology; with Kevin Maki, of Practical Lipid Management; with Christopher Cannon, of Comprehensive Cardiovascular Care in the Primary Care Setting; and with Domenic Sica, of Current Controversies in Dyslipidemia Management and Clinical Challenges in Hypertension, Volumes I and II.

Dr Toth, who has lectured on many topics in cardiovascular medicine throughout the world, is a member of the American College of Cardiology Foundation Council on Cardiovascular Disease Prevention and the American Heart Association’s Council on Lipoproteins, Lipid Metabolism, and Thrombosis.

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. Dr Brinton attended Stanford University and the University of Utah as an undergraduate, and received his medical degree at the University of Utah in Salt Lake City. He underwent residency training in internal medicine at Duke University and completed a fellowship in metabolism, endocrinology, and nutrition at the University of Washington.

Dr Brinton currently serves as president of the Utah Atherosclerosis Society and is past president of the Pacific Lipid Association. He 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 is an editor of Lipids Online and an assistant editor of the Journal of Obesity. He 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.
Faculty Financial Disclosure Statements
The presenting faculty reports the following:
Dr. Toth is a speaker and consultant for Abbott Laboratories, AstraZeneca Pharmaceuticals LP, Kowa Company Ltd., Eli Lilly and Company, and Merck & Co., Inc.; and a consultant for Amylin Pharmaceuticals, Genzyme Corporation, and Genentech, Inc.

Dr. Brinton receives research grant support and honoraria for his roles as a steering committee member and consultant for Amarin Corporation; as a researcher, consultant, and speaker for Health Diagnostic Laboratory Inc.; and as a steering committee member, consultant, and speaker for Merck & Co., Inc. In addition, he is a speaker and consultant for Abbott Laboratories, GlaxoSmithKline, and Takeda Pharmaceutical Company Limited; and a consultant for Atherotech, Inc., and Essentialis, Inc.

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Julie Johnson, PharmD, has no financial relationships to disclose.

Acronym List

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Acronym</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>ABCA1</td>
<td>ATP-binding cassette transporter 1</td>
<td>IVUS</td>
<td>intravascular ultrasound</td>
</tr>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
<td>LDL-C</td>
<td>low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>Apo</td>
<td>apolipoprotein</td>
<td>MACE</td>
<td>major adverse cardiac events</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
<td>MAP</td>
<td>mitogen-activated protein</td>
</tr>
<tr>
<td>CETP</td>
<td>cholesteryl ester transfer protein</td>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
<td>RCT</td>
<td>reverse cholesterol transport</td>
</tr>
<tr>
<td>eNOS</td>
<td>endothelial nitric-oxide synthase</td>
<td>SR-B1</td>
<td>scavenger receptor class B member 1</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethyl alcohol</td>
<td>TC</td>
<td>total cholesterol</td>
</tr>
<tr>
<td>HDL</td>
<td>high-density lipoprotein</td>
<td>TG</td>
<td>triglyceride</td>
</tr>
<tr>
<td>HDL-C</td>
<td>high-density lipoprotein cholesterol</td>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
<td>VLDL</td>
<td>very low-density lipoprotein</td>
</tr>
</tbody>
</table>

Suggested Reading List


Otros JD, Collins D, Freedman DS, et al. Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. *Circulation*. 2006;113(12):1556-1563.


Learning Objectives

- Review data demonstrating the relationship of HDL-C levels with atheroprogression and CVD events
- Discuss evolving concepts of HDL metabolism, reverse cholesterol transport, and the anti-atherosclerotic functions of HDL as they relate to the prevention of cardiovascular events
- Evaluate the role of existing and emerging pharmacotherapeutic agents for raising HDL levels, enhancing HDL function, and reducing CVD risk

Relative to Dyslipidemia: please indicate the approximate number of patients that you see each week for this condition.

1. None
2. 1-10
3. 11-30
4. 31-60
5. 61+

How confident are you in appropriately identifying and treating patients with high residual cardiovascular risk?

1. Very confident
2. Moderately confident
3. Somewhat confident
4. Not at all confident

In my practice, I always use strategies to elevate HDL-C in my management of patients with low HDL-C and high cardiovascular risk.

1. Strongly agree
2. Somewhat agree
3. Undecided
4. Somewhat disagree
5. Strongly disagree
How confident are you in your ability to prioritize and improve anti-atherosclerotic functions of HDL in your high CV risk patients?

1. Very confident
2. Moderately confident
3. Somewhat confident
4. Not at all confident

Case Study # 1

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Director of Preventive Cardiology
Sterling Rock Falls Clinic
Sterling, Illinois
Professor of Clinical Family and Community Medicine
University of Illinois School of Medicine
Peoria, Illinois

Case Study # 1

A 45-year-old Asian-Indian male
Family history: father, paternal grandfather, and great grandfather all had MIs in their late 40s and died in their early to mid 50s
Patient is worried that history will repeat itself
Successful architect, married, 3 children
Strict vegetarian
Physical exam:
- Asymptomatic, no complaints
- Height 65", Weight 137 lbs, BMI 22.5 kg/m²
- Physical exam unremarkable, no signs or symptoms of CVD, EKG: WNL, BP: 100/50 mmHg, past medical history: normal
- Runs 5 miles 3x/wk, practices yoga, plays golf at least 1x/wk
- Does not smoke or drink alcohol
- No prescription meds, takes multivitamin

Case 1: Fasting Lab Results (Initial)

- Chemistry profile: WNL, with glucose 80 mg/dL
- LFTs: WNL
- Lipid Profile
  - TC: 155 mg/dL
  - HDL-C: 21 mg/dL
  - LDL-C: 120 mg/dL
  - TG: 70 mg/dL

What follow-up is needed?

Case 1: Hypoalphalipoproteinemia

Recommendations:
- Counsel regarding: low HDL-C with + fam hx of premature CHD
- Recent meta-analysis in Asians (Asia Pacific Cohort Studies Collaboration and the Obesity in Asia Collaboration) showed that isolated low levels of HDL-C were as strongly associated with coronary heart disease risk as low levels of HDL-C combined with other lipid abnormalities (hazard ratio, 1.67 [95% CI, 1.27–2.19] vs 1.63 [95% CI, 1.24–2.15], respectively).¹
- Inform patient regarding: AFCAPS/TexCAPS trial results
  - Primary prevention study which showed 3-fold benefit of statin therapy for patients with baseline HDL-C < 40 mg/dL compared to > 40 mg/dL.
- Pharmacotherapy
  - Begin statin (lovastatin 40 mg)
  - Repeat lipid profile in 6 weeks

Case 1: Fasting Lab Results (Follow-up)

- LFTs: WNL
- Lipid Profile:
  - TC: 117 mg/dL
  - HDL-C: 24 mg/dL
  - LDL-C: 83 mg/dL
  - TG: 50 mg/dL

- What follow-up is needed?

Attempt to Further Increase HDL-C

- Consider adding extended-release niacin
  - Counsel patient regarding: no data in primary prevention; however, patient wants everything possible done to adjust lipids
  - Flushing expectations and tips to help reduce flushing
  - Instruct to take 325 mg aspirin prior to taking intermediate-release niacin
  - Start intermediate-release niacin at 500 mg at bedtime, titrate gradually to 1500 mg

- After 6 months:
  - HDL-C rose to 38 mg/dL
  - Tolerated combination therapy without complications
  - Patient insisted on titration to 2000 mg

- After 1 year:
  - HDL-C rose to 41 mg/dL
  - Tolerating lovastatin 40 mg + 2000 mg extended-release niacin without flushing, myalgias, or hepatotoxicity

High-Density Lipoproteins: Epidemiology and Antiatherogenic Functions

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Sterling, Illinois
Professor of Clinical Family and Community Medicine
University of Illinois School of Medicine
Peoria, Illinois

Residual Risk

Which of the following statements most accurately reflects current evidence regarding HDL-C?

1. Raising HDL-C reduces CV risk
2. Lowering HDL-C only reduces CV risk in certain patient populations
3. HDL-C has no effect on CV risk
4. There is not enough data to determine the effect of HDL-C on CV risk

AFCAPS/TexCAPS: Risk Reduction by HDL-C Tertile at Baseline


Downs et al.
MIRACL and PROVE-IT: Benefit of Statins Post ACS, But Considerable Residual Risk

Death, non-fatal MI, recurrent unstable AP (%)

Death, MI, ACS, stroke, revascularization (%)

Residual risk with Atorvastatin 80


Where Are HDL Particles Produced?

HDL Biogenesis

Adipose Inflammation

Because adipose inflammation is a hallmark of central obesity and type 2 diabetes mellitus, loss of adipocyte lipolysis of HDL may contribute directly to lower HDL-C levels in these inflammatory, insulin-resistant states.

Models of apoA-I Containing HDL Particles

HDL Epidemiology

Because adipose inflammation is a hallmark of central obesity and type 2 diabetes mellitus, loss of adipocyte lipolysis of HDL may contribute directly to lower HDL-C levels in these inflammatory, insulin-resistant states.
National Health And Nutrition Examination Survey (NHANES) III: Distribution of Low HDL-C Bottom Tertile of Population

- < 40/50 mg/dL men/women are the bottom tertile of population
- < 20 mg/dL occurs in 1/200 men & 1/400 women
- < 10 mg/dL occurs in <1/20,000

Risk for CHD Based on Lipid Fractions: Lipid Research Clinics Program Study

Comparison of lipids in predicting CVD mortality in men and women

<table>
<thead>
<tr>
<th>Lipid Fraction</th>
<th>Relative Risk (95% CI)</th>
<th>( \chi^2 ) for addition to model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL-C</td>
<td>1.19 (1.13 to 1.26)</td>
<td>24.3</td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.11 (1.02 to 1.22)</td>
<td>5.0</td>
</tr>
<tr>
<td>TC</td>
<td>1.10 (1.04 to 1.22)</td>
<td>14.6</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.77 (0.69 to 0.88)</td>
<td>23.2</td>
</tr>
</tbody>
</table>

Risk of coronary heart disease in men aged 50-70 by LDL and HDL cholesterol levels

Framingham Heart Study

Comparison of lipid levels in predicting CVD mortality in men and women

<table>
<thead>
<tr>
<th>Lipid Fraction</th>
<th>Risk of CHD Per 1000 Subjects Over a 6-year Period According to HDL-C Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td>Incidence per 1000 (in 6 years)</td>
</tr>
<tr>
<td>&lt;35</td>
<td>110</td>
</tr>
<tr>
<td>35-55</td>
<td>30</td>
</tr>
<tr>
<td>&gt;55</td>
<td>21</td>
</tr>
</tbody>
</table>

PROCAM* Results at 6 Years of Follow-up Levels of LDL-C and Percent Change in HDL-C

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Percent Change in HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>0%</td>
</tr>
<tr>
<td>35-55</td>
<td>30%</td>
</tr>
<tr>
<td>&gt;55</td>
<td>70%</td>
</tr>
</tbody>
</table>

*PROCAM: Prospective Cardiovascular Münster study.

The independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.
Relative risk of CHD for sex-specific lipid factor quintiles with adjustment for age and race in ARIC women and men \( N=12,339 \), 10-year follow-up, 725 events


Women Men

<table>
<thead>
<tr>
<th>HDL-C Cholesterol (mmol/L)</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>65</th>
<th>81</th>
<th>31</th>
<th>38</th>
<th>43</th>
<th>49</th>
<th>62</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C Cholesterol (mg/dL)</td>
<td>39</td>
<td>48</td>
<td>56</td>
<td>65</td>
<td>81</td>
<td>31</td>
<td>38</td>
<td>43</td>
<td>49</td>
<td>62</td>
</tr>
</tbody>
</table>

Relative Risk

HDL-C Provides Substantial CHD Prediction: ARIC Study

Coronary Heart Disease Incidence Is Related to HDL-C Levels in Various Clinical Trials

Coronary Heart Disease Incidence Is Related to HDL-C Levels in Various Clinical Trials

% Change in Risk per Increments (1 mg/dL) in HDL-C*

FHS LRC F HCP MRFIT FHS LRC

CHD Incidence

Men Women

Angiographic Effects of Lipid Drug Classes Meta-Analysis, 12 Trials

\[
\begin{align*}
\Delta \% &= 3.0 - 0.078 (\% \text{HDL-C}) + 0.06 (\% \text{LDL-C}) \\
R^2 &= 0.99, P<0.004
\end{align*}
\]

Impact of Low HDL-C on Clinical Outcomes

Post Drug-Eluting Stent Implantation

Event-Free Survival

Death

% of Patients

Days

N = 1032

*98% of patients were discharged on 40 mg atorvastatin with mean LDL-C of 105 mg/dL.


Insulin Resistance and the Relationship of Dyslipidemia to Coronary Heart Disease: the Framingham Heart Study

Unadjusted Kaplan-Meier curves showing the cumulative incidence of CHD events in the entire study sample \( N=2915 \) with and without IR and with lower or higher values of fasting plasma HDL-C (A) and with lower or higher values of plasma triglycerides (B)


Coronary Heart Disease Incidence Is Related to HDL-C Levels in Various Clinical Trials

% Change in Risk per Increments (1 mg/dL) in HDL-C*

FHS LRC F HCP MRFIT FHS LRC

CHD Incidence

Men Women

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Post Drug-Eluting Stent Implantation

Event-Free Survival

Death

% of Patients

Days

N = 1032

*98% of patients were discharged on 40 mg atorvastatin with mean LDL-C of 105 mg/dL.

Regression of Coronary Atherosclerosis Associated with On-Treatment Levels of LDL-C and Percent Change in HDL-C

Post-hoc Analysis of TNT

Low HDL-C was Associated with Higher CV Events in Patients with LDL-C < 70 mg/dL


 Associations Between HDL-C and Cardiovascular Outcomes: Statin Treatment Does Not Alter Inverse Relationship

Primary Endpoint Incidence Rates in JUPITER According to On-Treatment HDL-C and apoA-I Quartiles


What Differentiates HDL Particles From Other Lipoproteins?
It Appears to be Primarily Antiatherogenic

The HDL Proteome
Which of the following is considered an atheroprotective effect of HDL?

1. Anti-apoptotic
2. Anti-infectious
3. Anti-inflammatory
4. Anti-thrombotic
5. All of the above

Potential Antiatherogenic Actions of HDL

Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors

Model of HDL-Induced eNOS Activation by Lysophospholipid Receptor S1P3

Vascular Tone
Inflammation
Hemostasis
Endothelium Integrity

HDL

ENDOTHELIAL PROTECTION

Atherosclerosis
Plaque erosion/rupture
Arterial thrombosis
Restenosis
Ischemia-reperfusion injury

Vasorelaxation

N
c

Cooperative Activation
PI-PLC
Ca²⁺/calmodulin
PSK

Ser177

Ser473

Akt

eNOS

NO

HDL

βγ

Ser473

Akt

SPC S1P, LBF

Direct Activation
Conclusions

- There is considerable consistency worldwide in the finding from observational cohorts that there is an inverse relationship between HDL-C and risk for cardiovascular events
- HDL particles have a complex proteome, which confers diverse functionality
- Reverse cholesterol transport has been confirmed in humans and is likely the most important function of HDL particles, though other functions such as antagonizing oxidation and inflammation and participating in immunity (among others) may also be important
- Randomized prospective trials are needed to: (1) differentiate whether HDL-C is a marker of risk or target of therapy and (2) whether or not HDL-C, HDL-P, or HDL functionality should be therapeutically targeted in patients at risk

Case Study #2

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Director of Atherometabolic Research
Utah Foundation for Biomedical Research, and
President, Utah Lipid Center
Salt Lake City, UT

Case Study #2

- 64 y/o Hispanic male
- Had acute MI 2 years ago, no chest pain since
- Presents for lipid f/u
- Past Medical Hx: no DM, HBP, or erectile dysfunction
- Meds: simvastatin 40 mg qd, clopidogrel 75 mg qd,
  ASA 81 mg qd, and carvedilol 6.25 mg bid
- Family history: father had MI at age 60, mother had T2DM age 53
- Social: landscape contractor, married, 4 children, no tobacco or
  EtOH, job is active but no other exercise
- Prior labs: Fasting glucose 112 mg/dL, A1c 5.7%, creatinine nl
- Physical exam:
  - Height 5’7”, Weight 184 lbs, BMI 28.8 kg/m²
  - BP: 130/86 mmHg
  - No retinopathy, nl CV exam, no xanthomas
Case 2: Lab Results
- 64 y/o Hispanic male w/MI 2 years ago, on post MI meds
- Chemistry profile: WNL except for FSG 108 mg/dL (ALT, creatinine, and uric acid all nl)
- Fasting Lipid Profile (on simvastatin 40 mg/day)
  - TC: 142 mg/dL
  - HDL-C: 35 mg/dL
  - LDL-C: 69 mg/dL
  - TG: 188 mg/dL
  - Non-HDL-C: 107 mg/dL

Case 2: Lab Results and Follow-up
- 64 y/o Hispanic male w/MI 2 yrs ago, on post-MI meds
- Chemistry profile: WNL except for FSG 108 mg/dL
- Fasting Lipid Profile (on simvastatin 40 mg/d)
  - TC: 142 mg/dL
  - HDL-C: 35 mg/dL
  - LDL-C: 69 mg/dL
  - TG: 188 mg/dL
  - Non-HDL-C: 107 mg/dL

- How high is his residual risk of a CVD event?
- Would any further testing be indicated/helpful?
- Should we consider changing his statin? To which?
- Should we consider adding another lipid agent?
  - If so, which one(s)?

Low HDL-C Predicts Residual CVD Risk After Optimal Statin Rx: TNT Study
- LDL-C ≤ 70 mg/dL on statin
- 5-Year Risk of Major CVD Events, %
  - Q1: <37
  - Q2: 37 to <42
  - Q3: 42 to <47
  - Q4: 47 to <52
  - Q5: ≥ 52

- Risk ratios vs Q1:
  - Hazard Ratio vs Q1: 0.85, 0.57, 0.55, 0.61

Fibrates Reduce CVD in HTG/Low HDL-C
- Fibrates vs Control in HTG/Low HDL-C
  - Reductions in major CVD events
  - HDL-C: 22%
  - TG: 18%

JELIS: Effects of EPA on MACE in High TG/Low HDL-C Subgroup
- Efficacy of EPA (4 g/day) in reducing CVD events
  - MACE HR: 0.47
  - 95% CI: 0.23 - 0.93
  - P = 0.043

Case 2 Clinical Trial Application
- Is the patient like subjects in:
  - TNT?
  - AIM-HIGH?—high risk yes, but how to Rx?
  - ACCORD?—are T2DM subject data applicable to metabolic syndrome patients?
  - JELIS?—is “TG Rx” helpful with mild to minimal TG elevations?
- Do these trials help us decide Rx?
- What should we do with patients with low HDL-C after aggressive statin mono-Rx?
Existing and Emerging Therapies for Raising HDL-C and Enhancing HDL Function

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

HDL Composition & Function in Clinical Practice

- HDL Function
  - HDL appears to have many anti-atherogenic functions, but
  - The relative importance of these functions is not yet clear
  - HDL function assays are not yet clinically practical
  - Clinical recommendations re: HDL function are premature

- HDL Levels and Composition
  - HDL composition determines & reflects HDL function, but
  - The nature of this interrelationship is not yet clear
  - Standard assays of HDL levels (HDL-C and apo A-I) are well-established predictors of CVD risk
  - Advanced assays of HDL levels (2-D Gel, HDL-P, etc) provide additional information, but their clinical use is controversial

AFCAPS/TexCAPS: Statin CHD Benefits Are Best With Baseline HDL-C <40

CVD Risk Prediction in HPS: HDL-P ≈ HDL-C & Apo A-I

HDL Particles vs Recurrent CHD in VA-HIT

Existing Treatments for Low HDL-C
Effects of Diet and Lifestyle on HDL-C Levels

- Caloric restriction/weight loss
  - ↓ HDL-C w/ acute decrease in weight loss, but ↑ HDL-C after weight stabilization (~1 mg/dL/3 kg weight)
- Total fat/carb intake
  - ↓ HDL-C 5%-20% w/ ↓ sat fat/carb, but ↑ HDL-C after weight stabiliz. (~↑1 mg/dL/3 kg weight)
- Smoking cessation
  - ↓ HDL-C 7%-20% ~1-2 months after quitting
- Exercise
  - ↑ HDL-C 5%-10%, dose-dependent
- Alcohol
  - ↓ HDL-C 5%-15% w/ regular EtOH use (dose-dependent), not clinically useful (AEs, lack of control)

Bottom-Line: Diet & lifestyle → modest ↑ HDL-C (any ↑ HDL function of uncertain importance)


LOOK AHEAD

- Attenuation of CV risk factor benefits from year 1 to 4
- What will happen to event rate at 10 years?
- How powerful will metabolic memory be – if it occurs at all?

We will have to wait 14 years to find out!

Available Agents for HDL-C Raising

<table>
<thead>
<tr>
<th>Agent</th>
<th>Primary Use</th>
<th>HDL-C ↑</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinic acid</td>
<td></td>
<td>15%-35%</td>
</tr>
<tr>
<td>Fibrates</td>
<td></td>
<td>5%-20%</td>
</tr>
<tr>
<td>Statins</td>
<td></td>
<td>5%-15%</td>
</tr>
<tr>
<td>Prescr. Om-3*</td>
<td></td>
<td>2%-10%</td>
</tr>
<tr>
<td>Bile-acid resins</td>
<td></td>
<td>2%-5%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td></td>
<td>1%-3%</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td></td>
<td>5%-20%</td>
</tr>
<tr>
<td>Estrogens</td>
<td></td>
<td>10%-25%</td>
</tr>
<tr>
<td>α-blockers</td>
<td></td>
<td>10%-20%</td>
</tr>
<tr>
<td>Alcohol*</td>
<td></td>
<td>5%-15%</td>
</tr>
</tbody>
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* Lacking FDA-approved indication for HDL-C raising

Niacin Reduces CVD: Pre-AIM-HIGH Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds OR</th>
<th>95% CI 66% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABRIER-6 HIGHT</td>
<td>2/137</td>
<td>2/137</td>
<td>0.50 (0.99, 0.94)</td>
<td></td>
</tr>
<tr>
<td>Ovulhini et al</td>
<td>1/176</td>
<td>1/176</td>
<td>0.16 (0.99, 1.99)</td>
<td></td>
</tr>
<tr>
<td>ARESOS</td>
<td>1/171</td>
<td>1/171</td>
<td>0.10 (0.99, 1.01)</td>
<td></td>
</tr>
<tr>
<td>ARSPORT</td>
<td>1/29</td>
<td>1/29</td>
<td>0.30 (0.14, 0.65)</td>
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<tr>
<td>HATS</td>
<td>1/29</td>
<td>1/29</td>
<td>0.13 (0.04, 0.44)</td>
<td></td>
</tr>
<tr>
<td>LECH B3</td>
<td>1/18</td>
<td>1/18</td>
<td>0.14 (0.05, 0.45)</td>
<td></td>
</tr>
<tr>
<td>PACE</td>
<td>1/26</td>
<td>1/26</td>
<td>0.30 (0.14, 0.65)</td>
<td></td>
</tr>
<tr>
<td>STROKES</td>
<td>7/26</td>
<td>7/26</td>
<td>0.30 (0.14, 0.65)</td>
<td></td>
</tr>
<tr>
<td>CLAS</td>
<td>15/94</td>
<td>15/94</td>
<td>0.24 (0.09, 0.65)</td>
<td></td>
</tr>
<tr>
<td>COP</td>
<td>514/1139</td>
<td>514/1139</td>
<td>0.30 (0.14, 0.65)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>125/182</td>
<td>125/182</td>
<td>0.30 (0.14, 0.65)</td>
<td></td>
</tr>
</tbody>
</table>

Data for heterogeneity: $P = 0.08$, $I^2 = 50.3$

Subtotal-excluding COP

<table>
<thead>
<tr>
<th>Odds OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.49</td>
<td>(0.97, 0.91)</td>
</tr>
</tbody>
</table>


Treating the Patient With Low HDL-C: Why HDL-C Raising?

- HDL appears to be the most powerful anti-atherosclerosis factor
- HDL-C is the best-established HDL metric
- Low HDL-C is the single most common lipid phenotype in CHD, especially after statin-based LDL-C lowering

HDL-C raising in general and niacin treatment in particular sounded so good until AIM-HIGH...

In your patients at high cardiovascular risk, how often do you prescribe niacin to increase HDL-C and/or reduce their cardiovascular risk?

1. Frequently
2. Sometimes
3. Rarely
4. Never
Could 60 Years of Niacin Studies Be Wrong?

The “Low-Down” on AIM-HIGH

AIM-HIGH: No True “Placebo” or “Monotherapy” Arm—Instead an Active Comparator Control Arm

Control (“placebo”) arm
- Extra ↓ LDL-C (and apo B/non-HDL-C) via:
  - ↑ Simvastatin dose (vs extended-release niacin [ERNA] arm)
  - ↑ Ezetimibe use (>2x more vs ERNA)
- Immediate-release niacin (IRNA) 50mg in each 500 or 1000 mg tab up to 1500-2000 mg/d:
  - 10% ↑ HDL-C (from baseline)
  - Beneficial vascular effects?

Does AIM-HIGH Tend to Mislead Us? If So, Why/How?

- AIM-HIGH design: test of HDL Hypothesis
- Comparator arm issues
  - Niacin in both arms
  - Non-niacin treatment
- Study duration—early stopping → loss of information
- Subject characteristics
  - Baseline and on-Rx LDL-C
  - Baseline and on-Rx HDL-C
  - Prior statin and niacin use

Gemfibrozil Reduced CVD at ~3½+ Years in Low HDL-C Patients in VA-HIT, But...

...If Terminated at 3 years, VA-HIT Might Not Have Shown Benefit

Gemfibrozil Reduced CVD at ~3½+ Years in Low HDL-C Patients in VA-HIT, But...
AIM-HIGH Subject Characteristics

- Few women (15%)
- Few non-Caucasians (8%)
- High prior statin Rx (94%) skews data, but:
  - Most niacin is with a statin
  - Did not prevent events—CVD in 5.6%/year!
- Very aggressive on-study LDL-C Rx (avg ~65 mg/dL) atypical, but:
  - CVD in 5.4%/year
- Therefore:
  - Residual low HDL-C carries huge risk!
- Prior niacin Rx (~20%) might confound data


AIM-HIGH vs HPS2-THRIVE Design Comparison

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Niaspan - AIM HIGH</th>
<th>HPS2-THRIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Size</td>
<td>3300</td>
<td>25,000</td>
</tr>
<tr>
<td>Patient Population</td>
<td>High Risk; HDL-C &lt;42 (on statin)</td>
<td>High Risk; No Lipid Criteria</td>
</tr>
<tr>
<td>Study Design – Niacin ERNA (Niaspan) 1.5-2g/d (up-titrated in 500mg increm. x4 wks — Placebo arm given IRNA 100-150 mg/d</td>
<td>ERNA + laropiprant (Tredaptive) 4 wks at 1 g/d, then 2g thereafter</td>
<td></td>
</tr>
<tr>
<td>Study Design – Statin</td>
<td>Simva 40 w/ active titration ↑↓, +/- ezetimibe to LDL-C 40-80 mg/dL</td>
<td>Simva 40 no titration, +/- ezetimibe to LDL-C &lt;80 mg/dL</td>
</tr>
<tr>
<td>Powered for % Risk Reduction</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>Duration Planned/Actual</td>
<td>3.5 y / 2.5 y</td>
<td>4 y / TBD—no early stop</td>
</tr>
<tr>
<td>Estimated Completion</td>
<td>May 2011 (original plan 9/12)</td>
<td>June 2012?</td>
</tr>
<tr>
<td>Patent Expiration</td>
<td>3Q2013</td>
<td>2023</td>
</tr>
</tbody>
</table>


CVD Events per Study

AIM-HIGH Is Small Relative to Earlier & Later Niacin Clinical Trials

- HPS2 addresses well:
  - Niacin as statin add-on
  - Niacin in low (vs high) HDL-C

AIM-HIGH Summary and Conclusions

AIM-HIGH Design and Execution Issues

- NOT (well) designed to test CVD effects of niacin (+/- test of HDL-C-raising via niacin)
- NO "mono-Rx"/"placebo" arm (↑ simva, ↑ ezet, +niacin)
- Stopped at 3 years—too early for benefit?
- Small vs prior/future niacin trials
- Additional unresolved issues
  - Niacin dose, formulation
  - Is the low HDL-C patient best or worst for niacin?

Dr. Brinton’s Suggested Take-Away Conclusions

- Low HDL-C = high CVD risk despite statin Rx
- Niacin is safe with statins
- Draw few/no conclusions re:
  - Niacin effects on CVD (wait for HPS2-THRIVE)
  - HDL-C raising hypothesis (wait for many more studies)

Fibrates Reduce CVD in Low HDL-C/High TG Patients (Little/No Effect if HDL-C & TG Normal)

- Fenofibrate is better than gemfibrozil in the “statin world” (statin-combo safety)
- CVD with fibrates seems to require:
  - Low HDL-C and/or high TG and/or
  - Insulin resistance and/or T2DM??
- Rx for microvascular benefit in diabetes?—reasonable evidence (FIELD, ACCORD)
- GFR effects: likely neither harm nor benefit
- Choice of statin adjunct in HTG/HDL-C:
  - fibrate vs omega-3 vs niacin vs other?

“Take-Home” Messages Regarding Fibrate Rx Post FIELD & ACCORD

- Fenofibrate is better than gemfibrozil in the “statin world” (statin-combo safety)
- CVD with fibrates seems to require:
  - Low HDL-C and/or high TG and/or
  - Insulin resistance and/or T2DM??
- Rx for microvascular benefit in diabetes?—reasonable evidence (FIELD, ACCORD)
- GFR effects: likely neither harm nor benefit
- Choice of statin adjunct in HTG/HDL-C:
  - fibrate vs omega-3 vs niacin vs other?
Relative Risk of Death In Postmenopausal Women: Nurses Health Study


<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. of cases</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Causes</td>
<td>2051</td>
<td>NEVER</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>289</td>
<td>CURRENT 1.0, 0.63 (0.56-0.70), PAST 1.03 (0.94-1.12)</td>
</tr>
<tr>
<td>Stroke</td>
<td>91</td>
<td>CURRENT 1.0, 0.47 (0.32-0.69), PAST 0.99 (0.75-1.30)</td>
</tr>
<tr>
<td>All Cancer</td>
<td>1103</td>
<td>NEVER</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>246</td>
<td>CURRENT 1.0, 0.71 (0.52-0.84), PAST 1.04 (0.90-1.17)</td>
</tr>
<tr>
<td>Stroke</td>
<td>85</td>
<td>CURRENT 1.0, 0.17 (0.05-0.56), PAST 0.83 (0.63-1.09)</td>
</tr>
</tbody>
</table>

*CI = Confidence Interval. Values are adjusted for age, age at menopause, type of menopause, BMI, DM, high BP, high cholesterol, smoking, OC use, family H/O MI or breast CA, parity

WHI: HRT Has Early Benefit and Late Harm

Pooled analysis of E and E+P arms of WHI

<table>
<thead>
<tr>
<th>Age of HRT onset (yrs)</th>
<th>AbsOLUTE Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>40</td>
</tr>
<tr>
<td>60-69</td>
<td>30</td>
</tr>
<tr>
<td>70-79</td>
<td>20</td>
</tr>
</tbody>
</table>

Endocrine Society Scientific Statement re: Menopausal Hormone Therapy (MHT), Based on WHI, etc: Selected Conclusions

Overall mortality
• MHT was associated with a 40% reduction in mortality in...participants...below 60 years or...within 10 years of menopause onset.

Coronary heart disease (CHD)
• Basic science, animal models, and observational studies support the hypothesis that MHT may prevent atherosclerosis and reduce CHD events.
• Lack of benefit or increase in CHD risk...may have...resulted from harmful effects of MHT in older women starting therapy many years after onset of menopause.

HDL-Based Therapies in Development
• Niacin-flush-blockers
• CETP inhibitors
• HDL delipidation (extracorporeal)
• HDL mimetics (IV infusion)
• Apo A-I synthesis-inducers
• Others
  – ABCA1 agonists?
  – PPAR agonists?
  – SR-BI inhibitors
  – Lipase modulation?
  – LCAT agonists?
  – LXR/FXR/RXR agents?

PERISCOPE: Effect of Pioglitazone on TG/HDL-C and Coronary Athero in T2DM

Chemical name: laropiprant (P) blocks final step in flushing pathway

Pharmacotherapy to Inhibit Niacin Flushing

Epidermal Langerhans

Dermal Blood Vessel

PGD2 Receptor 1 (DP1) Pathway

Vasodilation and Flushing
Laropiprant (LRPT)* Reduces Flushing with Extended Release Niacin (ERN)

Mean (SE) Percentage of Days During Which GFSS ≥ 4

<table>
<thead>
<tr>
<th>Study Week</th>
<th>ERN 1g</th>
<th>LRPT (pooled) + ERN</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ERN: Extended Release Niacin; LRPT: Laropiprant; GFSS: Global Flushing Severity Score

*L FDA Status: Phase III Trials

CETP Inhibition May Help HDL Function

CETP transfers CE from HDL to apo-B-containing lipoproteins (VLDL and LDL) in exchange for TG, and may hinder reverse cholesterol transport

**HDL Function

Free Cholesterol (FC) in extrahepatic tissues

**Lipid Effects of CETP-Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>HDL-C</th>
<th>Apo A-I</th>
<th>LDL-C</th>
<th>TG</th>
<th>CETP Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalcetrapib* 600 mg/d</td>
<td>↑29%</td>
<td>↑13%</td>
<td>ND</td>
<td>9%</td>
<td>Partial (~22%)</td>
</tr>
<tr>
<td>Anacetrapib** 100 mg/d</td>
<td>↑138%</td>
<td>↑45%</td>
<td>↓40%</td>
<td>↓36%</td>
<td>Very high</td>
</tr>
<tr>
<td>Evacetrapib*** 100 mg/d</td>
<td>↑79%</td>
<td>ND</td>
<td>↑1%</td>
<td>ND</td>
<td>High?</td>
</tr>
</tbody>
</table>

All results are with background statin therapy. ND=no data


Post-hoc Exploratory Analyses in the Torcetrapib/Atorvastatin Group

Similar inverse relationship seen between on-study HDL-C and coronary athero by IVUS

Dalcetrapib Phase III CVD Event Trials—Discontinued May 7, 2012

<table>
<thead>
<tr>
<th>Start Date</th>
<th>Projected End Date</th>
<th>Patient Population</th>
<th>Primary Endpoint</th>
<th>Study Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 2008</td>
<td>May 2013</td>
<td>N=15,600, acute coronary syndrome (ACS, clinically stable)</td>
<td>MACE</td>
<td>dal-OUTCOMES-I</td>
</tr>
<tr>
<td>Feb 2012</td>
<td>Oct 2016</td>
<td>N=20,000 chronic CHD (standard 2* prevention)</td>
<td>MACE</td>
<td>dal-OUTCOMES-II</td>
</tr>
</tbody>
</table>

17

Does Anacetrapib Reduce CVD Events?

DEFINE Results

Cardiovascular Events During the Treatment Phase of the Study

<table>
<thead>
<tr>
<th>Event</th>
<th>Anacetrapib (N=806)</th>
<th>Placebo (N=804)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard CVD</td>
<td>16 (2.0)</td>
<td>21 (2.6)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>6 (0.7)</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>1 (0.1)</td>
<td>6 (0.8)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>5 (0.6)</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3 (0.4)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>8 (1.0)</td>
<td>28 (3.5)</td>
</tr>
<tr>
<td>PCI</td>
<td>6 (0.7)</td>
<td>25 (3.1)</td>
</tr>
<tr>
<td>CABG</td>
<td>2 (0.2)</td>
<td>3 (0.4)</td>
</tr>
</tbody>
</table>


Which one of the following is true regarding CETP inhibitors?

1. Torcetrapib failed because it made HDL dysfunctional
2. Dalcetrapib failed because it increased CVD events
3. So far, CVD outcomes data with anacetrapib are neutral to slightly favorable
4. Evacetrapib raises HDL-C very nearly to the same degree as does anacetrapib, under comparable circumstances

SATURN: Primary IVUS Efficacy Parameter


Preß-HDL Enriched Plasma Obtained by HDL Selective Delipidation

Preß-HDL readily accepts cholesterol

SATURN: Primary IVUS Efficacy Parameter

Pravachol 40 mg
Rosuvastatin 40 mg
Atorvastatin 80 mg
Placebo


Beneficial Effect of LDL-C and HDL-C Interventions on Atheroma by IVUS

Median Change Percent Atheroma Volume

Rosuvastatin
Atorvastatin
Placebo


Preß-HDL readily accepts cholesterol

SATURN: Primary IVUS Efficacy Parameter


Preß-HDL readily accepts cholesterol

SATURN: Primary IVUS Efficacy Parameter


Preß-HDL readily accepts cholesterol

SATURN: Primary IVUS Efficacy Parameter


Preß-HDL readily accepts cholesterol
### Increasing Apo A-I Synthesis: (RVX 208 and Beyond)

- **ASSERT study**
  - Very small ↑ HDL-C and apo A-I levels
  - ↑ large HDL particles (good vs bad?):
    - effect of ↑ cholesterol efflux (good?) vs
    - cause of ↓ efflux (bad?)
- **ASSURE study**
  - 6 mos RVX 208 vs coronary athero (IVUS)
- **More effective A-I synthesis inducers likely needed** (DYB186LC, others?)

**Concept:** Apo A-I "knows" how to prevent athero so just make lots of extra apo A-I

---

### Summary and Conclusions

- **Low HDL-C** patients have high residual CVD risk, even with aggressive statin Rx → ↓ LDL-C, and
- HDL-C levels/function can be ↑ by existing/emerging Rx; however,
- Genetic studies often fail to show ↑ HDL-C → ↓ CVD (causal vs marker?), and
  - We don’t know how best to measure HDL levels/function
  - We don’t know how best to improve HDL levels/function!
- Niacin *might* help prevent CVD when added to a statin; HPS2-THRIVE data *should* answer this question
- CETP inhibition *might* be beneficial, but need to prove ↓ CVD (with anacetrapib and/or evacetrapib)
  - HDL/apo A-I mimetics & HDL delipidation → ↓ athero, but:
    - They are cumbersome to use and
    - CVD event data are lacking
- CVD-proven HDL-related meds needed (some in early devel.)

---

### How confident are you in appropriately identifying and treating patients with high residual cardiovascular risk?

1. Very confident
2. Moderately confident
3. Somewhat confident
4. Not at all confident

---

### In my practice, I will now always use strategies to elevate HDL-C in my management of patients with low HDL-C and high cardiovascular risk.

1. Strongly agree
2. Somewhat agree
3. Undecided
4. Somewhat disagree
5. Strongly disagree

---

### How confident are you in your ability to prioritize and improve the anti-atherosclerotic functions of HDL in your high CV risk patients?

1. Very confident
2. Moderately confident
3. Somewhat confident
4. Not at all confident

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