Targeting HDL to Reduce Cardiovascular Disease Risk

A CALL TO ACTION
Session 4: Targeting HDL to Reduce Cardiovascular Disease Risk: A Call to Action

Learning Objectives

• Identify barriers to achieving optimal lipid profiles, review national guidelines, and evaluate clinical studies, applying intensive lipid-lowering therapy to meet these optimal lipid goals
• Define the importance of high-density lipoprotein cholesterol (HDL-C) in coronary risk and discuss treatment strategies to improve HDL-C within the overall lipid profile

Faculty

Sergio Fazio, MD, PhD  
Professor of Medicine and Pathology  
Co-Director, Atherosclerosis Research Unit  
Vanderbilt University Medical Center  
Nashville, Tennessee

Dr Fazio is professor of medicine and pathology at Vanderbilt University in Nashville, Tennessee. He is director of the Lipid Laboratory and co-director of the Lipid Clinic and the Atherosclerosis Research Unit.

A graduate of the medical school of the University of Rome, Italy, Dr Fazio completed his residency in internal medicine and was then a fellow in metabolic diseases at the same institution. In 1985, he undertook a PhD program in experimental medicine at the University of Siena, Italy, and completed it at the University of California, San Francisco (UCSF). Between 1988 and 1993, Dr Fazio worked at UCSF as a postdoctoral scientist first and then as an instructor in medicine. He has been a member of the medical faculty at Vanderbilt University since 1993. His clinical interest is in the management of dyslipidemic patients, and his research focuses on the pathogenesis of genetic dyslipidemias, the early cellular events of atherogenesis, and gene therapy approaches to atherosclerosis. Dr Fazio is a fellow of the councils on Atherosclerosis and on Nutrition, Physical Activity, and Metabolism of the American Heart Association (AHA). He is a member of the American Society for Clinical Investigation, and is the recipient of several National Institutes of Health (NIH) grants. He serves as a member of the NIH study section “Atherosclerosis and Inflammation in Cardiovascular Sciences” (National Heart, Lung, and Blood Institute) and is a consultant to the pharmaceutical industry in the area of lipid modulation and anti-atherosclerosis therapy. He has published more than 130 original papers, review articles, and book chapters on the subjects of dyslipidemia, atherosclerosis, and cardiovascular risk management.

Keith C. Ferdinand, MD, FACC  
Clinical Professor, Cardiology Division of Emory University  
Chief Science Officer Association of Black Cardiologists, Inc.  
Atlanta, Georgia

Keith C. Ferdinand, MD, was a clinical cardiologist prior to Hurricane Katrina serving as medical director of Heartbeats Life Center and professor of clinical pharmacology at Xavier University, in New Orleans, Louisiana. He currently serves as clinical professor of medicine, Emory University; and chief science
officer at the Association of Black Cardiologists, Inc (ABC), where he directs the Health Outreach
Prevention and Empowerment (HOPE) project.

Dr Ferdinand is past vice-president of the American Society of Hypertension, past-president and member of
the Louisiana State Board of Medical Examiners, past-president of the Orleans Division of the AHA
Louisiana Affiliate, and past-chairman of the ABC. He serves on the editorial board of *Journal of Clinical
Hypertension* and *Journal of the Cardiometabolic Syndrome* and has authored or coauthored over 90
articles and book chapters.

A Telluride Scholar at Cornell University, Dr Ferdinand received his BA in biology from the University of
New Orleans and an MD from Howard University College of Medicine. He completed an internship at the
New Orleans US Public Health Hospital and a residency and fellowship at LSU Medical Center of New
Orleans; He completed his cardiology training at Howard University Hospital. He is board certified in
cardiocvascular diseases, ASH-specialist in hypertension, and a diplomate, nuclear cardiology.

**Faculty Financial Disclosure Statements**
The presenting faculty reported the following:

Dr Fazio gives lectures for Merck & Co., Inc.; Schering-Plough Corporation; Abbott; and
GlaxoSmithKline; he does receive honoraria for these lectures.

Dr Ferdinand is on the speakers bureau for AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb; Merck
& Co., Inc.; Novartis Pharmaceuticals Corporation; Forest, Pfizer, Inc.; and sanofi aventis U.S. Dr
Ferdinand receives grant/research support from Bristol-Myers Squibb and Novartis Pharmaceuticals
Corporation.

**Content Collaborator Financial Disclosure Statements**
The content collaborators at Vindico Medical Education have reported that they have no relevant
relationships to disclose.

**Drug List**

<table>
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<th>Generic</th>
<th>Trade</th>
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</thead>
<tbody>
<tr>
<td>ezetimibe</td>
<td>Zetia</td>
</tr>
<tr>
<td>simvastatin</td>
<td>Zocor</td>
</tr>
<tr>
<td>extended-release niacin (ERN)</td>
<td>Niaspan</td>
</tr>
<tr>
<td>gemfibrozil</td>
<td>Lopid</td>
</tr>
</tbody>
</table>

**Investigational**

laropiprant
extended-release niacin + laropiprant (Cordaptive)

**Suggested Reading List**

Toth P, Maki K. *Practical Lipid Management: Concepts and Controversies*. Malden, MA: Wiley-
Blackwell; 2008.

Guyton JR, Bays HE. Safety considerations with niacin. *Am J Cardiol*. 2007;99:22C-31C.

Paolini JF, Mitchel YB, Reyes R, et al. Effects of laropiprant on nicotinic acid-induced flushing in patients

Brown BG, Stukovsky KH, Zhao XQ. Simultaneous low-density lipoprotein-C lowering and high-density
lipoprotein-C elevation for optimum cardiovascular disease prevention with various drug classes, and their
Targeting HDL to Reduce Cardiovascular Disease Risk:

A Call to Action

Case Study 1

- JC is 35-year-old male computer technician who comes in for a routine exam. He is a nonsmoker and exercises 3x/week. He denies illicit drug use and drinks alcohol socially (3–5 drinks/week).
- Medications: None
- Family History: Father had a stent placement at 52, mother 55 and is healthy
- Vital Statistics: Blood pressure 120/78 mmHg, Height 5’9”, weight 170 pounds, BMI 25 kg/m², waist circumference 36”
- Labs (mg/dL):
  - Total cholesterol 190; HDL-C 25; TG 160; LDL-C 133
  - Fasting glucose 90

All of the Following are Associated with Low HDL-C except: ?

1. Sedentary lifestyle
2. Smoking
3. Alcohol excess
4. Obesity
5. Anabolic steroids

Secondary Causes of Low HDL-C

- Obesity
- Physical inactivity
- Type 2 diabetes
- Cigarette smoking
- End-stage renal disease
- Hypertriglyceridemia
- Probucol
- Androgens
- Proteinuria
- Insulin resistance
- Progestins
- High-dose thiazide diuretics
- High-dose beta-blockers
- Very low-fat diet
- Dysglobulinemia
- Severe liver disease
- Malabsorption
- Malnutrition
- Severe inflammatory disease

Would you treat this patient’s lipids? ?

1. Yes
2. No

In YOUR Practice, What is Your LDL-C Goal for this Patient? ?

1. < 70 mg/dL
2. < 100 mg/dL
3. < 130 mg/dL
4. < 160 mg/dL
5. I would not treat this patient
Based on 2004 ATP-III Guideline Update, What is the LDL-C Goal for this Patient?

1. < 70 mg/dL
2. < 100 mg/dL
3. < 130 mg/dL
4. < 160 mg/dL
5. < 190 mg/dL

Intensive LDL-C Goals for High-Risk Patients

**ATP III Update 2004**

- **<100 mg/dL:** Patients with CHD or CHD risk equivalents (10-year risk >20%).
- **<70 mg/dL:** Therapeutic option for very high-risk patients.

**AHA/ACC guidelines for patients with CHD:**

- **<100 mg/dL:** Goal for all patients with CHD.
- **<70 mg/dL:** A reasonable goal for all patients with CHD.

*And other forms of atherosclerotic disease.*

Factors that place a patient at very high risk: established cardiovascular disease (CVD) plus:

- Metabolic syndrome (triglycerides >150 mg/dL, HDL-C < 40 mg/dL, and key cardiovascular risk factors including those with:
  - Hyperglycemia
  - Hypertension
  - Hyperlipidemia
  - Cigarette smoking
  - Family history of premature CHD
  - Chronic kidney disease
  - Hypertrophic cardiomyopathy

Intensive LDL-C Goals for High-Risk Patients

**LDL-C: NCEP / ATP III Goals and Cutpoints**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal (mg/dL)</th>
<th>LDL-C Level at Which to Initiate Therapeutic Lifestyle Changes (TLC) (mg/dL)</th>
<th>LDL-C Level at Which to Consider Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD Risk Equivalents (10-year risk &gt;20%)</td>
<td>&lt;100</td>
<td>&gt;100</td>
<td>≥130 (100–129 drug options)</td>
</tr>
<tr>
<td>2+ Risk Factors (10-year risk ≥20%)</td>
<td>&lt;130</td>
<td>≥130</td>
<td>≥130 (100–129 drug options)</td>
</tr>
<tr>
<td>0–1 Risk Factor</td>
<td>&lt;160</td>
<td>≥160</td>
<td>≥190 (160–189 LDL-C-lowering drug optional)</td>
</tr>
</tbody>
</table>

**ADA and ACC Consensus Statement on Lipoprotein Management**

**Adverse Lipid Metabolism**

1. Lipids
2. Blood Pressure
3. Glucose
4. Hypertriglyceridemia
5. Inflammation
6. Hypercoagulation
7. Smoking
8. Physical Inactivity
9. Unhealthy Eating
10. Hypertension
11. Family History
12. Age, Race, Gender

**TREATMENT GOALS**

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
<th>ApoB (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 70</td>
<td>&lt; 100</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>&lt; 130</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>&lt; 130</td>
<td></td>
<td></td>
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</tbody>
</table>

**ADA and ACC Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk**

**Particle Quantification**

- Measurement of apoB is warranted in patients with cardiometabolic risk on pharmacologic treatment
- In particular apoB should be used to guide adjustments to therapy
- LDL-P as measured by NMR appears equally informative as apoB
- The panel recommends that the apoB goal be reached

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<td>&lt; 80</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>&lt; 130</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>&lt; 130</td>
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</tbody>
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**TREATMENT GOALS**

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<th>ApoB (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 70</td>
<td>&lt; 100</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>&lt; 130</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>&lt; 130</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Would You use Framingham Risk Scoring to Assess this Patient’s CVD Risk?

1. Yes
2. No

What is his Risk* for any Cardiovascular Event in the Next 10 Years?

1. 0–5%
2. 5–10%
3. 10–20%
4. 20–30%
5. > 30%

*Based on Framingham Risk Scoring

Framingham Risk Scoring (Men)

Step 1: Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-34</td>
<td>-9</td>
</tr>
<tr>
<td>35-39</td>
<td>-4</td>
</tr>
<tr>
<td>40-44</td>
<td>0</td>
</tr>
<tr>
<td>45-49</td>
<td>3</td>
</tr>
<tr>
<td>50-54</td>
<td>6</td>
</tr>
<tr>
<td>55-59</td>
<td>8</td>
</tr>
<tr>
<td>60-64</td>
<td>10</td>
</tr>
<tr>
<td>65-69</td>
<td>11</td>
</tr>
<tr>
<td>70-74</td>
<td>12</td>
</tr>
<tr>
<td>75-79</td>
<td>13</td>
</tr>
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</table>

Step 2: Total Cholesterol

<table>
<thead>
<tr>
<th>Total Cholesterol (mg/dL)</th>
<th>Age</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 160</td>
<td>20-39</td>
<td>0</td>
</tr>
<tr>
<td>160-189</td>
<td>35-39</td>
<td>-3</td>
</tr>
<tr>
<td>200-239</td>
<td>40-44</td>
<td>-1</td>
</tr>
<tr>
<td>240-279</td>
<td>45-49</td>
<td>0</td>
</tr>
<tr>
<td>≥ 280</td>
<td>50-54</td>
<td>-1</td>
</tr>
</tbody>
</table>

Step 3: HDL Cholesterol

<table>
<thead>
<tr>
<th>HDL-C (mg/dL)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>-1</td>
</tr>
<tr>
<td>50-59</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>2</td>
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</table>

Step 4: Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Systolic BP (mm Hg)</th>
<th>Points (Untreated)</th>
<th>Points (Treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>120-129</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>130-139</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>140-159</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>≥ 160</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Step 5: Smoking Status

<table>
<thead>
<tr>
<th>Age</th>
<th>Nonsmoker</th>
<th>Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50-59</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60-64</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>70-74</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>75-79</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Step 6: Add up the Points

<table>
<thead>
<tr>
<th>10-Yr Risk</th>
<th>Points</th>
<th>10-Yr Risk</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0</td>
<td>&lt;1%</td>
<td>5</td>
<td>2%</td>
</tr>
<tr>
<td>0-1%</td>
<td>6</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>1-2%</td>
<td>7</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>2-3%</td>
<td>8</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>3-4%</td>
<td>9</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>4-5%</td>
<td>10</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>≥6%</td>
<td>≥17</td>
<td>≥30%</td>
<td>≥30%</td>
</tr>
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</table>

Step 7: Calculate Risk of CHD

<table>
<thead>
<tr>
<th>Systolic BP (mm Hg)</th>
<th>Points (Untreated)</th>
<th>Points (Treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>120-129</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>130-139</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>140-159</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>≥ 160</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Which of the following therapies would you initiate?

1. Lifestyle only
2. Statin only
3. Statin + niacin
4. Statin + fenofibrate
5. Statin + ezetimibe
6. Statin + omega-3 fatty acids

Case Study 1: Follow-up

- The patient and physician agree to modify his diet and begin simvastatin 20 mg
- At his 6-month followup, the patient’s overall lipid profile had improved to normal levels
Which Lipid Profile Confers the Highest Risk?

1. Total: 190; HDL-C 25; TG 160; LDL-C 133
2. Total: 250; HDL-C 51; TG 100; LDL-C 185
3. Total: 275; HDL-C 58; TG 100; LDL-C 195
4. They are the same

Values are mg/dL.

Aggressive LDL-C Reduction Does Not Eliminate Coronary Disease Events

Current Options for Management of Low HDL Cholesterol

- Lifestyle modification
- Statin
- Niacin
- Fibrate
- TZD
- Combination therapy

Potential New Therapies to Raise HDL-C

- CETP Inhibitors
- Nicotinic Acid Receptor Agonists
- PPAR-alpha agonists
- LXR agonists
- ABCA1 upregulators
- Apo A1 peptides and mimetics
- Apo A1 gene therapy
- Infusions of phospholipid/Apo A1 complexes

The Role of HDL-C in CVD Risk
There can be from one to four molecules of apoA-I per HDL particle, this apoA-I is only an approximation of the number (concentration) of HDL particles. ApoA-II is also present, predominantly on the smaller species LpA-I are apoA-I containing HDLs: LpA-I,A-II are apoA-I & apoA-II containing HDLs: Unlipidated apoA-I or phospholipidated prebeta-1 & 2 HDLs: Prebeta HDLs primarily reflect cholesterol levels within large, cholesterol-rich particles and lacks sensitivity to detect small, cholesterol-poor particles.

Low HDL-C is an independent predictor of CAD risk when LDL-C is <100 mg/dL.

Cardiovascular events in TNT according to on-treatment HDL-C.

Coronary Drug Project (CDP) Niacin Only.

Treating to New Targets (TNT) Study: Low HDL-C increases CVD risk even when LDL-C is well controlled.


275/219
-30
-25
-20
-15
-10
-5
0
Nonfatal MI/CHD death CHD death Stroke* All-cause mortality

Risk Reduction (%)

Placebo/Treated: 275/219 118/93 88/64 220/198
*Investigator-designated †P = 0.006; **P = 0.04

VA-HIT: Veterans Affairs HDL-C Intervention Trial

Effects of Fibrates on CVD Events in CHD Patients With Isolated Low HDL-C

Residual CVD Risk With Monotherapy Versus Combination Therapy

 Patients Experiencing Major CVD Events, %

Effects of Insulin on Lipoprotein Metabolism

Case Study 2

- TH is a 54-year-old male with an 8-year history of well-controlled type 2 diabetes mellitus. He also has a 4-year history of hypertension, treated with HCTZ, and has recently been diagnosed with CHD.
- Medications: Simvastatin 20 mg daily, metformin 1000 mg b.i.d.
- Family History: Father with CHD
- Vital Statistics: Blood pressure 135/88 mmHg, Height 5’10”, weight 202 pounds, BMI 29 kg/m², waist circumference 38”
- Labs:
  - Total cholesterol 220; HDL-C 28 mg/dL; TG 190; LDL-C 154 mg/dL
  - A1c 7.8%

Which of the Following Would You Consider as the First Choice to Add to this Patient’s Regimen?

1. Niacin
2. Fenofibrates
3. Prescription Omega-3 Fatty Acid (P-OM3)
4. Bile acid sequestrants
5. Ezetimibe
6. Up-titrate Statin

ADA and ACC Consensus Statement on Lipoprotein Management

- When both non-HDL-C and apoB are measured, the two are highly correlated, but only moderately concordant
- At any given level of non-HDL-C there will be wide variations of apoB levels and vice versa indicating the correlation is of limited value for assessing individual risk
  - This lack of concordance is particularly marked in patients with elevated triglyceride levels
- The panel concludes that routine use of non-HDL-C constitute a better index than LDL-C for identifying high risk patients

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ADA and ACC Consensus Statement on Lipoprotein Management

Particle Quantification

- Measurement of apoB is warranted in patients with cardiometabolic risk on pharmacologic treatment
- In particular, apoB should be used to guide adjustments to therapy
- LDL-P as measured by NMR appears equally informative as apoB
- The panel recommends that the apoB goal be reached

Brunzell JD, Davidson M, Furberg CD et al. Diabetes Care 2008;31:811-822

The Role of Combination Therapies in Lipid Management

Lipid Effects of Adding Niacin ER to Baseline Statin Therapy

SAFARI: Combination Therapy in Patients With Combined Hyperlipidemia

COMBOS: Primary and Secondary Efficacy Results

Statin/Fibrate Combination Therapy: Pharmacokinetic Interactions
HATS (HDL-C-Atherosclerosis Treatment Study) Clinical End Points

Quantitative Coronary Angiography

Change in Stenosis, %

CVD Events

%50 Reduction


Change in Stenosis, %

CVD Event Rate, %*

90% Reduction

P = .03*

CVD Events

n = 38

n = 38

n = 42

n = 34

n = 33

n = 40

Placebo

Niacin + Simvastatin

Niacin + Simvastatin + AO

*P ≤ .005 versus placebo

Mean dose of simvastatin was 13 mg/day

Mean dose of niacin was 2400 mg/day

COMPELL: Niacin ER/Statin Combination Therapy

Change From Baselines, %

ARBITER 2
Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol

Objective

To compare the effect of prescription, extended-release niacin 1000 mg/d vs. placebo in the mean change in carotid intima-media thickness (CIMT) after one year

Study Design

Double-blind, randomized, placebo-controlled, single-center; 167 patients with stable CHD on statin therapy; LDL-C <130 mg/dL and HDL-C <45 mg/dL

Randomization to Treatment

ERN 1000 mg (+ statin) OR Matching placebo (+ statin)

Study Measurements

CIMT – baseline and 12 months

Labs and lipid panel – baseline, 3, 6, and 12 months

Endpoints

Primary: Change in CIMT at 12 months

Secondary: Change in serum lipids, composite clinical cardiovascular events, adverse events


ARBITER 2 Conclusions

• Statin monotherapy: significant progression of IMT

• Combination therapy with statin + niacin ER 1000 mg/d
  - Slowed IMT progression among individuals with
    Known CHD
    Well-controlled LDL-C (<100 mg/dL)
    Moderately low HDL-C (40 mg/dL)

• First clinical trial to show:
  - Superiority of combination therapy over monotherapy for a validated surrogate endpoint
  - Incremental benefit of adding niacin ER to existing statin therapy
  - Greater increases in HDL-C independently associated with superior effects on CIMT

CIMT between groups at baseline and 12 months was P = 0.52 and 0.89, respectively


ARBITER 2 Diabetes/Metabolic Syndrome Subgroup Analysis

DM = Diabetes Mellitus

MS = Metabolic Syndrome


Which of the Following are Barriers to Successful Treatment with Niacin?

1. Safety concerns in combination with statins
2. Niacin-induced flushing
3. Lack of efficacy data in combination with statins
4. Dietary supplement niacin is unregulated and can be hepatotoxic
5. 1 and 3
6. 2 and 4
7. All of the above

ARBITER 2

Langerhans' Cells Are Localized in the Epidermis

- Langerhans' cells are involved in immune responses of the skin and play a role in the flushing response.1,2
- Langerhans' cells are localized in the epidermis.1
  - Co-localization of:
    - Langerin as a specific marker of Langerhans' cells (yellow/red stain)
    - Keratin as a specific marker for the epidermis (green stain)


Nicotinic acid receptor HM74A

- Nicotinic acid receptor HM74A
- GPR109A (PUMA-G in mice)
- EP2 or EP4

2007 NLA Safety Task Force: Niacin/Statin Combination Task Force Therapy

- “Two decades of clinical evidence since the introduction of statins do not support a general myopathic effect of niacin either alone or in combination with statins.”
- No major clinical trial has suggested a potential drug interaction between statins and niacin
- There is no proposed theoretic mechanistic reason to expect a drug interaction

Guyton Jr and Bays HE. Am J Cardiol. 2007;99:22C-31C.

Hazards of Niacin as a Dietary Supplement

- 52% of patients taking sustained-release niacin developed hepatotoxic effects1
  - The sustained-release form of niacin is hepatotoxic and should be restricted from use.1
- NLA 2006 support for prescription formulations of niacin2,3
  - “If patients turn to unregulated formulations of slow-release niacin available on drugstore shelves as a lack of reimbursement for prescription extended-release niacin, many cases of severe hepatic toxicity including deaths can be expected.”2
  - Dietary supplement market lacks consistency among formulations.
    - “Timed-release niacin dietary supplements have repeatedly been shown to cause life-threatening liver toxicity.”3


Improving Compliance and Managing Flushing With Niacin

- Long term adherence with niacin is dependent on patient awareness and education
- Patients should be instructed to avoid interrupting therapy with niacin whenever possible
- Initiate therapy using small doses, taken with meals, and then slowly titrate upward over several weeks to achieve treatment goals
- Advise patients to take an adult aspirin or other NSAID 30 min prior to dose (if not contraindicated)
- Recommend that patients avoid spicy foods and hot or alcoholic beverages near dose
- Use ER instead of IR niacin to minimize adverse effects and enhance compliance


Laropiprant* + Extended Release Niacin Reduces Flushing

* FDA Status: Phase III Trials


Mean (SE) Percentage of Days During Which GFSS ≥ 4 Study Week ERN 1g ERN 2g
ERN: Extended Release Niacin; LRPT: Laropiprant; GFSS: Global Flushing Severity Score

Laropiprant + Extended Release Niacin Effects on HDL-C, LDL-C, TGs


High-Risk Patients

CDP: Reduction in Recurrence of MI* by Baseline Fasting Plasma Glucose


Diabetic Patients Have Particularly High Residual CVD Risk After Statin Treatment

* Mean 6.2 years total treatment follow-up

Residual CVD Risk in Diabetic Patients Treated With Statins


FIELD Study Design

- 5-year study against a background of usual care, including the option to add other lipid-lowering therapies

**ADA and ACC Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk**

- The exception to not targeting TG is the relatively small proportion of patients with severe hypertriglyceridemia in whom the initial treatment priority is to reduce the risk of pancreatitis by combining fat restriction with fibrate, niacin or high-dose n-3 FA therapy.
- A statin is the initial drug of choice for the vast majority of people with cardiometabolic risk who have high TG and low HDL-C.
- In patients on statins who continue to have low HDL-C or elevated non-HDL-C, especially if apoB remains elevated, combination therapy is recommended.

**FIELD: Clinically Important Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo, n</th>
<th>Fenofibrate, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed cancer</td>
<td>7.6/4900</td>
<td>8.0/4895</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0.02</td>
<td>0.06</td>
</tr>
<tr>
<td>Renal disease requiring dialysis</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>ALT &gt;3-5x ULN</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>CPK &gt;5-10x ULN</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Creatinine increase &gt;2.26 mg/dL</td>
<td>0.06</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**FIELD: Primary and Secondary End Points**

- 11% Reduction P = .035
- 11% Reduction P = .022

**Conclusions**

- Low HDL-C is a significant risk factor for CVD – Even at low levels of LDL-C
- Evidence suggests raising HDL-C using niacin and fibrates, particularly gemfibrozil, is beneficial
- Niacin/statin combination therapy improves all atherogenic lipid abnormalities, slows the progression and increases the regression of coronary atherosclerosis, and reduces residual CVD risk.