Therapeutic Strategies to Reduce Residual Cardiovascular Risk With Combination Lipid-Modifying Therapy

Faculty
Ralph M. Vicari, MD
Michael H. Davidson, MD

Friday, November 21, 2008
10:00 am - 11:15 am
Chicago, Illinois
Session 3: Therapeutic Strategies to Reduce Residual Cardiovascular Risk With Combination Lipid-Modifying Therapy

Learning Objectives

- Explain the rationale for high-density lipoprotein cholesterol (HDL-C) and triglycerides as independent lipid risk factors and evidence-based therapeutic targets for cardiovascular risk reduction.
- Compare and contrast currently available treatment options for raising HDL-C and lowering triglycerides, in combination with LDL-C–lowering therapy, to optimize cardiovascular outcomes in high-risk patients with atherogenic dyslipidemia.

Faculty

**Ralph M. Vicari, MD**
Staff Cardiologist
Holmes Regional Medical Center
Director-Chairman
Melbourne Internal Medicine Associates
Melbourne, Florida

Dr Ralph M. Vicari is staff cardiologist at the Holmes Regional Medical Center and director-chairman of Melbourne Internal Medicine Associates, both in Melbourne, Florida. In addition, he is a member of the board of directors of Florida Lipid Associates. The author or coauthor of several publications and abstracts, and a frequent lecturer, Dr Vicari has been a principal investigator in more than 80 clinical trials.

Dr Michael H. Davidson is clinical professor of medicine and director of preventive cardiology and atherosclerosis research at the University of Chicago, and founder, president, and chief executive officer of the Chicago Center for Clinical Research, currently part of Radiant Research. Dr Davidson earned his medical degree from Ohio State University College of Medicine in Columbus, after which he completed a residency in internal medicine and a fellowship in cardiology at Rush-Presbyterian–St Luke’s Medical Center in Chicago.

**Michael H. Davidson, MD**
Clinical Professor and Director of Preventive Care
The University of Chicago Pritzker School of Medicine
Executive Medical Director
Radiant Research
Chicago, Illinois

Dr Davidson’s clinical research background encompasses both pharmaceutical and nutritional clinical trials, as well as extensive work with food additives, drug supplements, and health claim petitions to the US Food and Drug Administration. He has also done extensive research on statins, lipid-lowering drugs, and nonpharmacologic risk factor reduction. Dr Davidson is a frequently invited lecturer on lipid disorders, nutrition, and atherosclerosis, having coordinated more than 700 preventive cardiology clinical trials and published more than 130 journal articles.

A fellow of the American College of Cardiology and the American College of Chest Physicians, Dr Davidson also serves as president of the Midwest Lipid Association and is a board member of the National Lipid Association. He was listed in the 2004-2005 edition of Guide to America’s Top Physicians and designated 3 times as one of The Best Doctors in America.

Faculty Financial Disclosure Statements

The presenting faculty report the following:

Dr Vicari is a speaker for Abbott, AstraZeneca Pharmaceuticals LP, and Merck & Co., Inc.

Dr Davidson receives grant/research support from and is a speaker and consultant for Abbott; AstraZeneca Pharmaceuticals LP; Daiichi Sankyo, Inc.; diaDexus, Inc.; Merck & Co., Inc.; Merck/Schering-Plough Pharmaceuticals; Pfizer Inc.; Roche; and Takeda Pharmaceuticals North America, Inc.; is a speaker for Oscent Pharmaceuticals; and is a consultant for sanofi-
aventis U.S. and Synarc Inc. In addition, he is an advisor to Abbott; AstraZeneca Pharmaceuticals LP; AtheroGenics, Inc.; Daiichi Sankyo, Inc.; KineMed, Inc.; Merck & Co., Inc.; Merck/Schering-Plough Pharmaceuticals; Oc- sient Pharmaceuticals; Pfizer Inc.; PreEmptive Meds, Inc.; Roche; Takeda Pharmaceuticals North America, Inc.; and Xinthria Pharmaceuticals; and serves on the board of directors of Angiogen Pharmaceuticals, Sonogene LLC, and Professional Evaluation, Inc.

Education Partner Financial Disclosure Statement
The content collaborators at ACHL have nothing to disclose.

**Drug List**

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<thead>
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<th>Generic</th>
<th>Trade</th>
<th>Investigational</th>
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<tr>
<td>atorvastatin</td>
<td>Lipitor</td>
<td>fenofibric acid</td>
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<tr>
<td>cerivastatin</td>
<td>Baycol</td>
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<td>fixed-dose niacin ER + simvastatin</td>
<td>Simcor</td>
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<tr>
<td>fluvastatin</td>
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<td>lovastatin</td>
<td>Mevacor, Altoprev</td>
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<tr>
<td></td>
<td></td>
<td>Niaspan</td>
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<tr>
<td></td>
<td></td>
<td>omega-3 fatty acids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Omacor, Lovaza</td>
</tr>
</tbody>
</table>

**Suggested Reading List**


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


What Lipid Risk Factors Contribute to Residual CVD Risk After Statin Therapy?

Ralph M. Vicari, MD  
Staff Cardiologist  
Holmes Regional Medical Center  
Director  
MIMA Century Research  
Melbourne, Florida

Case Study: Visit 1
- Caucasian female, 63 years old (not on HRT), diabetes
- Blood pressure, 116/78 mm Hg (on ACE-Inhibitor)
- Fasting plasma glucose, 91 mg/dL (on metformin)
- Dyslipidemia, mg/dL
  - TC 240
  - LDL-C 141 (directly measured)
  - HDL-C 45
  - Triglycerides 271
  - Non-HDL-C 195 (TC – HDL-C)
- Diagnosed with diabetic retinopathy 11 months ago

High-Risk Patient Populations:  
Metabolic Syndrome and Diabetes

The American Diet
- Americans account for 7% of the world’s population
- Americans consume 40% of the world’s food production
- Only 3% of American adults meet 4 of the 5 recommendations for the intake of grains, fruits, vegetables, dairy products, and meat

America’s Getting Fat
- 66% of U.S. adults were overweight (BMI 25 - 29.9 kg/m²) or obese (BMI ≥ 30 kg/m²) (NHANES 2003-2004)¹  
  - In a direct survey, only 44% of American adults admit to being overweight
- 17% of American children were overweight or obese (NHANES 2003-2004)²  
  - That’s 3x as many as there were in 1980

Disclaimer/Exposure
- Light travels faster than sound
- That is why some people appear bright until you hear them speak
We Are What We Eat

The famous “hamdog” from Mulligan’s in Atlanta—
Hot dog wrapped in a beef patty deep fried and covered with chile and cheese and served on a large hoagie roll.

Coronary Heart Disease
Likely the cause of your demise

Fast Food in the United States

- Americans spent over 105 billion dollars on fast foods in 2001
- Over 50% of the population lives within 3 minutes of a fast food restaurant
- One of five Americans visits a fast food restaurant every day, four of five every month

Obesity Trends* Among US Adults

Risk Factors of the Metabolic Syndrome and Defining Levels

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist Circumference</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Men: &lt;40 mg/dL, Women: &lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>≥130/≥85 mmHg</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>≥110 mg/dL*</td>
</tr>
</tbody>
</table>

*ADA cutpoint for IFG is ≥100 mg/dL

Abdominal Adiposity: The Critical Adipose Depot

Is this where you measure?
Elevated and Earlier Risk of CAD in Patients With Hypertriglyceridemic Waist Phenotype

Experienced first CAD symptoms 5 years earlier than those without phenotype

Among 592 men and women with glucose intolerance or type 2 diabetes

1.0
1.2
1.5
2.0

Pr = 0.02

<table>
<thead>
<tr>
<th>TG, mg/dL</th>
<th>Waist, in</th>
<th>Relative CAD Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;177</td>
<td>&lt;35.4</td>
<td>1.0</td>
</tr>
<tr>
<td>≥177</td>
<td>≥35.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>


Metabolic Syndrome and Atherosclerotic Burden Predict Cardiovascular Risk

Follow-Up, Weeks

Patients, %

Diabetes: US Trends

- 23.6 million Americans (7.8%)1
  - Diagnosed: 17.9 million
  - Undiagnosed: 5.7 million

- 1.6 million new adult cases/year1

- Rapid growth of high-risk populations
  - 25.9% of adults have IFG2
  - 32.9% of adults are obese3

- 38.1% of adults with diabetes reported being diagnosed with CVD4


Diabetes Is a CHD Risk Equivalent

- Heart disease and stroke account for ~68% of deaths in people with diabetes1

- Adults with diabetes have heart disease death rates about 2 to 4 times higher than adults without diabetes1

- NCEP ATP III Guidelines2
  - Diabetes is a major, independent risk factor for CHD and other forms of CVD
  - Patients with diabetes should be managed as a CHD risk equivalent


Microvascular Disease Significantly Contributes to Burden of Chronic Diabetes Complications

- Diabetic Retinopathy
  - Most frequent cause of new cases of blindness among adults aged 20-74 years1,2
  - Causes up to 34 000 new cases of blindness each year1,2
  - Laser treatment slows progression of disease but does not restore lost vision1,3

Major Diabetes Complications Are Associated With Substantial Reduction in Quality of Life

Reduction in QWB-SA
Health Utility Score
-0.052
-0.072
-0.078
-0.099
-0.105
-0.170
CHF
Stroke
Dialysis
Foot Ulcers
Amputation
Blindness

Microvascular
Macrovascular

Recall Case Study: Visit 1
• Caucasian female, 63 years old (not on HRT), diabetes
• Blood pressure, 116/78 mm Hg (on ACE-Inhibitor)
• Fasting plasma glucose, 91 mg/dL (on metformin)
• Dyslipidemia, mg/dL
  – TC 240
  – LDL-C 141 (directly measured)
  – HDL-C 45
  – Triglycerides 271
  – Non–HDL-C 195 (TC – HDL-C)
• Diagnosed with diabetic retinopathy 11 months ago

Given this patient’s profile, which of the following is the best first step of lipid-lowering therapy in this patient?
1. Lower LDL-C
2. Raise HDL-C
3. Lower TG
4. Reduce Non–HDL-C
5. Other

Visit 2: At 3 Months
• During visit 1, the physician prescribed therapeutic lifestyle changes (diet and exercise) and 20 mg atorvastatin to lower LDL-C
• Lipid parameters (mg/dL) 3 months later
  – TC 185 (23% reduction)
  – LDL-C 92 (35% reduction)
  – HDL-C 47 (4% increase)
  – Triglycerides 230 (15% reduction)
  – Non–HDL-C 138 (29% reduction)
• Fasting plasma glucose, 91 mg/dL (on metformin)
• No progression of diabetic retinopathy

After statin therapy in this patient, what lipid(s) do you believe contribute to increased CVD risk?
1. This patient’s lipids are well-controlled
2. Elevated LDL-C
3. Low HDL-C
4. Elevated TG and non–HDL-C
5. LDL-C, HDL-C, TG, and non–HDL-C

Residual CVD Risk After Statin Therapy
Residual Cardiovascular Risk in Major Statin Trials

CHD events occur in patients treated with statins

<table>
<thead>
<tr>
<th>Study</th>
<th>Secondary</th>
<th>High Risk</th>
<th>Primary</th>
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<tr>
<td>4S</td>
<td>4444</td>
<td>9717</td>
<td>2130</td>
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<tr>
<td>LIPID</td>
<td>1258</td>
<td>2564</td>
<td>272</td>
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<tr>
<td>CARE</td>
<td>6039</td>
<td>1256</td>
<td>916</td>
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<td>HPS2</td>
<td>20 536</td>
<td>4169</td>
<td>980</td>
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<tr>
<td>WOSCOPS</td>
<td>6595</td>
<td>13,055</td>
<td>1837</td>
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<tr>
<td>AFCAPS/TexCAPS</td>
<td>8629</td>
<td>17,276</td>
<td>1314</td>
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</tbody>
</table>

Residual CVD Risk in Patients Treated With Intensive Statin Therapy

Secondary High Risk Primary

 Patients Experiencing Major CHD Events, %

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>LDL-C mg/dL</th>
<th>Placebo</th>
<th>Statin</th>
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<tbody>
<tr>
<td>4S</td>
<td>4444</td>
<td>95</td>
<td>28.0</td>
<td>19.2</td>
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<tr>
<td>LIPID</td>
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<td>62</td>
<td>15.9</td>
<td>13.1</td>
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<td>6039</td>
<td>104</td>
<td>12.6</td>
<td>10.2</td>
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<tr>
<td>HPS2</td>
<td>20 536</td>
<td>81</td>
<td>11.8</td>
<td>9.7</td>
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<tr>
<td>WOSCOPS</td>
<td>6595</td>
<td>536</td>
<td>7.9</td>
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<tr>
<td>AFCAPS/TexCAPS</td>
<td>8629</td>
<td>690</td>
<td>5.5</td>
<td>4.3</td>
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Residual CVD Risk Is Particularly High in Patients With Diabetes Treated With Statins

Meta-Analysis of CHD Patients in 14 Statin Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>LDL-C mg/dL</th>
<th>Control</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>PROVE IT-TIMI 22</td>
<td>4162</td>
<td>96</td>
<td>26.3</td>
<td>22.4</td>
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<tr>
<td>IDEAL</td>
<td>10 001</td>
<td>104</td>
<td>13.7</td>
<td>12.8</td>
</tr>
<tr>
<td>TNT</td>
<td>8888</td>
<td>101</td>
<td>10.9</td>
<td>10.9</td>
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</table>

What Lipid Risk Factors Contribute to Residual CVD Risk After Statin Therapy?

Elevated TG and Low HDL-C Predict Heart Disease in Men With High and Low LDL-C

- High triglyceride levels
  - TG-rich remnant lipoproteins (VLDL)
  - Altered metabolism of LDL and HDL particles
- Although LDL-C may not be increased, LDL particle number may be significantly increased
  - Predominantly small, dense LDL particles
- Low levels of HDL-C (may reduce RCT)


Low HDL-C Increases CVD Risk Even if LDL-C Levels Are Well-Controlled

Treating to New Targets (TNT) Study
Patients With LDL-C ≤70 mg/dL on Statin

<table>
<thead>
<tr>
<th>HDL-C Quintiles</th>
<th>5-Year Risk of Major CVD Events (%)</th>
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</thead>
<tbody>
<tr>
<td>Q1 &lt;37</td>
<td>10.0</td>
</tr>
<tr>
<td>Q2 37 to &lt;42</td>
<td>9.8</td>
</tr>
<tr>
<td>Q3 42 to &lt;47</td>
<td>9.6</td>
</tr>
<tr>
<td>Q4 47 to &lt;55</td>
<td>9.2</td>
</tr>
<tr>
<td>Q5 ≥55</td>
<td>8.8</td>
</tr>
</tbody>
</table>

HDL-C Quintiles, mg/dL: Q1 <37, Q2 37 to <42, Q3 42 to <47, Q4 47 to <55, Q5 ≥55

Impact of Low HDL-C on Clinical Outcomes
Post Drug-Eluting Stent Implantation

- High HDL-C
- Low HDL-C

Event-Free Survival

N = 1032
98% of patients were discharged on 40 mg atorvastatin with mean LDL-C of 105 mg/dL
Mean HDL-C of 55 mg/dL (>40 mg/dL in men and >45 mg/dL in women)
Mean HDL-C of 32 mg/dL (<40 mg/dL in men and <45 mg/dL in women)

Cumulative Effect of Elevated Triglycerides on Incidence of CHD

MELANY Study

N = 13,953

Time 1 TG Levels
- Low (<53 mg/dL)
- Intermediate (54-147 mg/dL)
- High (≥148 mg/dL)

Time 2 TG Levels
- Low (<53 mg/dL)
- Intermediate (54-147 mg/dL)
- High (≥148 mg/dL)

TG >150 mg/dL Increases CHD Events
In Patients With ACS on Statins

PROVE IT-TIMI 22 Trial

N = 4,162

LDL-C
- ≤70
- <70

TG
- >150
- ≤150

CHD Event Rate, %

Days After Month 1 Visit

LDL-C

HR: 0.84
P = .192

HR: 0.73
P = .017

HR: 0.85
P = .180

Referent

In patients with hypertriglyceridemia, which lipid parameter do you believe gives you the most accurate assessment of their CVD risk?

1. LDL-C
2. Non–HDL-C
3. Apo B or LDL particle number
4. HDL-C
5. All of the above
NCEP ATP III: Triglyceride-Rich Remnant Lipoproteins Are Atherogenic

- Elevated triglyceride levels are a marker for elevated levels of atherogenic remnant lipoproteins
- VLDL-C is the most readily available measure of atherogenic remnant lipoproteins for clinical practice
- When triglyceride levels are elevated, non–HDL-C (LDL-C + VLDL-C) better represents the concentrations of all atherogenic lipoproteins than does LDL-C alone
- Non–HDL-C should be a secondary target of therapy when triglyceride levels are ≥200 mg/dL

Non–HDL-C Is Superior to LDL-C in Predicting CHD Risk

The Framingham Study

- Within non–HDL-C levels, no association was found between LDL-C and the risk for CHD
- In contrast, a strong positive and graded association between non–HDL-C and risk for CHD occurred within every level of LDL-C
- Non–HDL-C is a stronger predictor of CHD risk than LDL-C

Elevated Triglycerides Are Associated With Increased Small, Dense LDL Particles

Correlates with:
- TC: 198 mg/dL
- LDL-C: 130 mg/dL
- TG: 90 mg/dL
- HDL-C: 50 mg/dL
- Non–HDL-C: 148 mg/dL

Correlates with:
- TC: 210 mg/dL
- LDL-C: 110 mg/dL
- TG: 250 mg/dL
- HDL-C: 30 mg/dL
- Non–HDL-C: 180 mg/dL

Non–HDL-C calculation:\n- Non–HDL-C = TC – HDL-C
- Non–HDL-C = LDL-C + VLDL-C + IDL-C + Lp(a)
- Non–HDL-C goal:\n  - Normal VLDL-C defined as value when TG <150 mg/dL
  - Non–HDL-C goal is 30 mg/dL above goal for LDL-C

Elevated Triglycerides Are Associated With Altered Metabolism of LDL and HDL Particles

Summary

- CVD and microvascular disease confer substantial morbidity and mortality and adversely affect quality of life in patients with diabetes
- Residual CVD risk is especially high in diabetic patients treated with statins, likely due to the atherogenic dyslipidemia characteristic of this patient population (elevated TG and low HDL-C)
- Elevated TG and non-HDL-C and low levels of HDL-C contribute to residual risk for atherosclerosis and CVD even after LDL-C is well-controlled
- Non-HDL-C is a stronger predictor of CVD than LDL-C, especially in patients with elevated TG

Using Combination Lipid-Modifying Therapy to Reduce Residual CVD Risk

Michael H. Davidson, MD, FACC, FACP
Clinical Professor and Director of Preventive Cardiology
The University of Chicago Pritzker School of Medicine
Executive Medical Director, Radiant Research
Chicago, IL

Recall Visit 2: At 3 Months

- During visit 1, the physician prescribed therapeutic lifestyle changes (diet and exercise) and 20 mg atorvastatin to lower LDL-C
- Lipid parameters (mg/dL) 3 months later
  - TC 185 (23% reduction)
  - LDL-C 92 (35% reduction)
  - HDL-C 47 (4% increase)
  - Triglycerides 230 (15% reduction)
  - Non-HDL-C 138 (29% reduction)
- Fasting plasma glucose, 91 mg/dL (on metformin)
- No progression of diabetic retinopathy

What is the best next step in treating this patient to reduce residual CVD risk remaining despite statin monotherapy?

1. This patient does not have residual CVD risk that can/should be reduced with additional lipid-modifying therapy
2. Increase statin dose
3. Add adjunct therapy (fibrate, niacin, omega-3 fatty acids)
4. Other

Visit 3: At 6 Months

- During visit 2 (at 3 months), physician re-emphasized lifestyle changes and prescribed fenofibrate (145 mg) as an add-on to atorvastatin therapy
- Lipid profile (mg/dL) after 3 months of combination therapy
  - TC 162 (12% reduction)
  - LDL-C 82 (10% reduction)
  - HDL-C 54 (16% increase)
  - Triglycerides 124 (46% reduction)
  - Non-HDL-C 107 (22% reduction)
- Fasting plasma glucose, 90 mg/dL (on metformin)
- No progression of diabetic retinopathy
- No adverse muscle, liver, or kidney events

National Guidelines Recommend Treating Beyond LDL-C to Reduce Residual CVD Risk

Treating Beyond LDL-C: Other Targets of Lipid-Lowering Therapy

NCEP ATP III

- Lipoprotein species other than LDL are involved in atherogenesis (ie, VLDL, IDL, HDL)1
- NCEP ATP III concluded on the basis of several types of data that elevated non–HDL-C in patients with hypertriglyceridemia will impart increased risk even after the goal of LDL-C has been reached1
  - Non–HDL-C should be a secondary target of therapy when triglyceride levels are ≥200 mg/dL2
  - Non–HDL-C goal is 30 mg/dL above the LDL-C goal2

NCEP ATP III 2004 update2: “For those high-risk patients who have elevated triglycerides or low HDL-C levels, addition of a fibrate or nicotinic acid to LDL-lowering therapy can be considered.”

ADA/AHA 2007 Scientific Statement: Primary Prevention of CVD in Patients With Diabetes

- Elevated LDL-C is primary target of lipid-lowering therapy – LDL-C goal <100 mg/dL
- TG-rich lipoproteins, especially VLDL, are often elevated in patients with diabetes, appear to be atherogenic, and represent a secondary target of lipid-lowering therapy
- ADA – TG goal <150 mg/dL; HDL-C goal >40 mg/dL
- AHA – If TG are 200-499 mg/dL, non–HDL-C goal ≤130 mg/dL
  - If TG are ≥500 mg/dL, lowering TG is primary target
  - Combination therapy of LDL-C-lowering drugs (statins) with fibrates or niacin may be necessary to achieve lipid targets

ADA/ACC 2008 Consensus Statement: Treatment Goals in Patients With Cardiometabolic Risk and Lipoprotein Abnormalities

Goals

<table>
<thead>
<tr>
<th>Highest-Risk Patients</th>
<th>LDL-C</th>
<th>Non–HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known CVD</td>
<td>&lt;70 mg/dL</td>
<td>&lt;100 mg/dL</td>
<td>&lt;80 mg/dL</td>
</tr>
<tr>
<td>Diabetes plus ≥2 additional major CVD risk factor*</td>
<td>&lt;100 mg/dL</td>
<td>&lt;130 mg/dL</td>
<td>&lt;90 mg/dL</td>
</tr>
</tbody>
</table>

*In individuals on statin therapy who continue to have low HDL-C or elevated non–HDL-C, especially if Apo B levels remain elevated, combination therapy is recommended.”

Do you agree with the 2008 ADA/ACC panel recommendation for an Apo B goal in patients with cardiometabolic risk and lipoprotein abnormalities?

1. Yes
2. No
3. Not Sure
Patients With CHD Risk Equivalents Not Achieving Potential Lipid Goals


Patients Not Achieving Goal, %

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>HDL-C</th>
<th>Non-HDL-C (LDL+C)</th>
<th>Non–HDL-Cb</th>
<th>21 LipidGoal</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>67</td>
<td>59</td>
<td>66</td>
<td>81</td>
</tr>
<tr>
<td>71</td>
<td>84</td>
<td>88</td>
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</tr>
</tbody>
</table>

*96% had diabetes
*40 patients with TG ≥200 mg/dL

Clinical Trial Evidence Supports Treating Beyond LDL-C to Reduce CVD Risk

Addition of Eicosapentaenoic Acid (EPA) to Statin Therapy in Japanese Patients


Major CHD Events

- Statin (n = 9319)
- Statin + EPA 1.8 g (n = 9326)

4.6-year mean follow-up

-19% Reduction P = .011

Lipid Effects

-40 -30 -20 -10 0 10 20 Change From Baseline, %

HDL-CLDL-C TG

P <.001

Coronary Drug Project: Macrovascular Outcomes

CDP Research Group. JAMA. 1975;231:360-381.

Placebo (n = 2789)
Niacin (n = 1119)

Nonfatal CHD Death/Nonfatal MI

Event Rate, %

15% Reduction P <.05

24% Reduction P <.05

Stroke/TIA CV Surgery

47% Reduction P <.05

Significant Inverse Correlation Between Increase in HDL-C and Regression of CIMT


HDL-C ↑ 0.2 mg/dL

-0.027 -0.041 -0.046

CIMT Progression

CIMT Regression

r = -0.23 P <.001
**HHS: Marked Reduction of CHD Events in Patients With High Triglyceride Levels and LDL/HDL Ratio**

- Placebo
- Gemfibrozil

71% Reduction P<.005

![Graph showing reduction in CHD events](image)

- TG ≤204
- TG >204
- LDL/HDL ≤5
- LDL/HDL >5

Triglyceride values are in mg/dL.

**FIELD: Primary and Secondary End Points in Patients With Diabetes**

- Placebo (n = 4900)
- Fenofibrate (n = 4895)

11% Reduction P=.005

![Graph showing primary diabetes endpoints](image)

**FIELD: Microvascular Disease**

- Nontraumatic Amputations

38% Reduction P=.01

![Graph showing amputations reduction](image)

**FIELD: Summary of Significant CVD and Microvascular End Points**

- Macrovacular
- Microvascular

![Graph showing CVD and microvascular endpoints](image)

**FIELD 2007 Ophthalmology Substudy**

Primary Outcome: Progression of Retinopathy

- Placebo (n = 500)
- Fenofibrate (n = 512)

11% Reduction P=.004

![Graph showing retinopathy progression](image)
FIELD 2007 Ophthalmology Substudy: Other Significant Outcomes

- Laser Treatment:
  - Placebo (n = 500)
  - Fenofibrate (n = 512)

- Significant Retinal Pathology:
  - 79% Reduction
  - P = .0004
  - 34% Reduction
  - P = .022


WHAT IS YOUR SCIENTIFIC/ClinICAL OPINION ABOUT THE MICROVASCULAR BENEFITS OBSERVED WITH FENOFIBRATE?

1. The data are strong, and I am convinced that there are added microvascular benefits with fenofibrate.
2. The data are strong, but I need more evidence to be convinced.
3. The data are weak, and I am not convinced there are any added microvascular benefits with fenofibrate.
4. I am not sure.

Efficacy and Safety of Combination Lipid-Modifying Therapy

COMBOS: Omega-3 Fatty Acid/Statin Combination Therapy in Patients With Hypertriglyceridemia

All Patients Were on Simvastatin 40 mg

- Add Placebo (n = 122)
- Add Omega-3 FA 4 g (n = 132)

Median Change From Statin Monotherapy Baseline, %

- LDL-C
- Non-HDL-C
- TG
- HDL-C

* p < .001 versus adding placebo

2007 NLA Safety Task Force: Omega-3 FA Therapy

- Clinical trial evidence does not support an increased bleeding risk with omega-3 FA, even when used in combination with agents such as aspirin or warfarin, although it is reasonable to monitor such patients.
- Rigorous purification processes reduce risk of FA oxidation, hypervitaminosis, and exposure to environmental toxins.
- Clinicians and patients should be aware of the variance in fish oil therapy purification processes; fish oil supplements are not subject to FDA approval.
- Not all fish oil therapies are equivalent; EPA and DHA concentrations (not total amount of fish oil concentrate) determine necessary dosage, efficacy, and tolerability.


Bays HE. Am J Cardiol. 2007;99(suppl):35C-43C.
Efficacy of Fixed-Dose Niacin ER/Simvastatin Combination Therapy

**SEACOAST I**

- Simvastatin 20 mg (n = 90)
- Niacin ER/Simvastatin 1000/20 mg (n = 78)
- Niacin ER/Simvastatin 2000/20 mg (n = 40)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Simvastatin 20 mg</th>
<th>Niacin ER/Simvastatin 1000/20 mg</th>
<th>Niacin ER/Simvastatin 2000/20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL-C</td>
<td>-7.4</td>
<td>-7.1</td>
<td>-6.7</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-7.6</td>
<td>-15.3</td>
<td>-13.9</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-13.1</td>
<td>-26.5</td>
<td>-16.7</td>
</tr>
<tr>
<td>TG</td>
<td>-14.2</td>
<td>-38.0</td>
<td>-25.0</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>-22.5</td>
<td>-40</td>
<td>-30</td>
</tr>
</tbody>
</table>
| Median % Change From Baseline

*P < .05; **P < .01; ***P < .001 versus simvastatin 20 mg


2007 NLA Safety Task Force: Niacin/Statin Combination Therapy

- "2 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.

Lipid Efficacy of New Formulation of Fenofibrate in Combination With Rosuvastatin

Patients With Mixed Dyslipidemia

- Rosuvastatin 10 mg
- Feno-New 135 mg
- Feno-New 135 mg/Rosuvastatin 10 mg

<table>
<thead>
<tr>
<th>Metric</th>
<th>Rosuvastatin</th>
<th>Feno-New 135 mg</th>
<th>Feno-New 135 mg/Rosuvastatin 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL-C</td>
<td>152.2</td>
<td>152.7</td>
<td>155.8</td>
</tr>
<tr>
<td>LDL-C</td>
<td>38.2</td>
<td>38.5</td>
<td>38.5</td>
</tr>
<tr>
<td>HDL-C</td>
<td>295.9</td>
<td>282.8</td>
<td>267.4</td>
</tr>
<tr>
<td>TG</td>
<td>38.5</td>
<td>38.5</td>
<td>38.5</td>
</tr>
</tbody>
</table>

*P < .001 versus Feno-New; **P < .001 versus Rosuvastatin 10 mg


New Formulation of Fenofibrate Increases LDL Particle Size

Patients With Mixed Dyslipidemia

- Rosuvastatin
- Feno-New 135 mg
- Feno-New 135 mg/Rosuvastatin 10 mg

<table>
<thead>
<tr>
<th>Metric</th>
<th>Rosuvastatin</th>
<th>Feno-New 135 mg</th>
<th>Feno-New 135 mg/Rosuvastatin 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>B (Small, dense)</td>
<td>18.2%</td>
<td>51.8%</td>
<td>90.3%</td>
</tr>
<tr>
<td>A (Larger, buoyant)</td>
<td>81.8%</td>
<td>92.5%</td>
<td>22.7%</td>
</tr>
</tbody>
</table>


Other Effects of New Formulation of Fenofibrate in Combination With Statins

Patients With Mixed Dyslipidemia

- Feno-New (135 mg)/Rosuvastatin (10 mg)
  - Significantly improved the ratios of TC:HDL-C, non-HDL-C:HDL-C, Apo B:Apo A-I, and TG:HDL-C, compared with either monotherapy
  - Was well tolerated, consistent with the safety profiles of each monotherapy
- Feno-New (135 mg) in combination with 3 different statins (rosuvastatin, atorvastatin, or simvastatin) reduced glucose levels in patients with prediabetes
  - Significantly reduced mean glucose by 3.1 mg/dL from baseline compared with statin monotherapy (P < .001)


2007 NLA Safety Task Force: Fibrate/Statin Combination Therapy

- "In combination with statins, gemfibrozil generally should be avoided."
  - "The reason for the much greater propensity for gemfibrozil to increase the risk for myopathy with a statin is most likely the difference in the pharmacokinetic interactions between the 2 fibrates."
  - "The preferred option is fenofibrate, which is not associated with an inhibition of statin metabolism."

What is your scientific/clinical opinion about the safety of using fibrate/statin combination therapy?

1. I would use either fenofibrate or gemfibrozil in combination with statins
2. I prefer to use fenofibrate in combination with statins
3. I prefer to use gemfibrozil in combination with statins
4. I prefer to use another adjunct therapy (eg, niacin or omega-3-fatty acids)
5. I am not sure

Number of Cases of Rhabdomyolysis in Combination Therapy With Statins

<table>
<thead>
<tr>
<th>No. Cases Reported per Million Prescriptions</th>
<th>Fenofibrate</th>
<th>Gemfibrozil</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.58</td>
<td>0.55</td>
<td>8.6</td>
</tr>
</tbody>
</table>

15-Fold Increase


Excludes cases involving cerivastatin

Summary

- National guidelines recommend that combination therapy may be necessary to achieve all lipid targets (LDL-C, non-HDL-C, Apo B, TG, and HDL-C)
- Combination therapy with statins and niacin or fenofibrate corrects atherogenic lipid abnormalities, appears to be safe, and may be necessary to achieve all lipid goals and optimally reduce CVD in high-risk patients
- Addition of fenofibrate to statin therapy may provide additional microvascular benefits in patients with diabetes, and the mechanism(s) for these benefits remains to be elucidated