Beyond Statins: Persistent Myths & Current Controversies in Managing Dyslipidemia

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Beyond Statins: Persistent Myths & Current Controversies in Managing Dyslipidemia

Program Overview

Coronary heart disease (CHD) is a major public health problem. It was responsible for one of five deaths in the United States in 2004. The estimated direct and indirect cost of CHD for 2007 is $151 billion. Dyslipidemia is a major risk factor for CHD. More than 79 million American adults have high low-density lipoprotein (LDL) cholesterol levels (130 mg/dL or higher), and 44 million adults have low levels of the protective type of cholesterol, high-density lipoprotein (HDL) cholesterol (<40 mg/dL). Many patients with dyslipidemia also have the metabolic syndrome, a cluster of risk factors for CHD: low HDL cholesterol levels, high triglyceride levels, increased numbers of small, dense LDL particles, high blood pressure, elevated fasting glucose levels, and a large waist circumference. An estimated 47 million Americans have the metabolic syndrome.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel updated its evidence-based guidelines with therapeutic goals for reducing LDL cholesterol concentrations based on CHD risk in 2004. A target HDL cholesterol level was not specified in the NCEP guidelines because of a lack of evidence on which to base such a recommendation, however the NHLBI guidelines for metabolic syndrome have identified target HDL cholesterol values. Recent research suggests that raising HDL cholesterol levels by more than 7.5% and substantially reducing LDL cholesterol is associated with regression of coronary atherosclerosis. These findings suggest the need to focus on HDL cholesterol as well as LDL cholesterol, triglycerides, and non-HDL cholesterol when treating patients with dyslipidemia.

Statins are considered first-line therapy for most patients with dyslipidemia because they are the most effective drugs for reducing LDL cholesterol and reducing risk of CHD. However, many patients fail to achieve their LDL cholesterol goal with statins alone, and some patients require additional dyslipidemia therapy to address hypertriglyceridemia and low HDL cholesterol levels. Niacin and fibrates produce greater increases in HDL cholesterol, reductions in triglycerides, as well as increases in LDL particle size than do statins, so adding niacin or a fibrate to statin-based therapy is a rational approach for a patient with an inadequate response to statin monotherapy. Niacin and fibrates have beneficial effects in patients with the metabolic syndrome.

The treatment of dyslipidemia remains complex despite the availability of NCEP guidelines and increasing knowledge from epidemiologic and clinical trials because of various persistent myths and unresolved controversies (e.g., the risk for drug interactions when certain combinations of antilipemic agents are used, the best approach to treating mixed dyslipidemia or dyslipidemia in patients with type 2 diabetes or the metabolic syndrome). Research is underway to dispel many of these myths and clarify these controversies. However, clinicians must balance these myths and controversies with scientific evidence to provide appropriate patient care in the management of dyslipidemia.

This program will provide a brief review of the relationship between dyslipidemia, the metabolic syndrome, and CHD and current NCEP guidelines for treating dyslipidemia. The importance of HDL cholesterol in determining CHD risk and the impact of raising levels on risk for CHD will be described. The role of statins, niacin, fibrates, and other agents in the treatment of dyslipidemia, including effects of the drugs on patients with mixed dyslipidemia, type 2 diabetes, and the metabolic syndrome, also will be presented. Persistent myths and unresolved controversies in dyslipidemia management that are not addressed in the NCEP guidelines will be discussed.
Learning Objectives

At the conclusion of this program, participants should be able to:

- Explain the relationship between dyslipidemia, the metabolic syndrome, and CHD, and discuss the prevalence of and morbidity and mortality from these conditions.

- Summarize the current NCEP guidelines for treating dyslipidemia, and identify a persistent myth or an unresolved controversy in dyslipidemia treatment that is not adequately addressed by the guidelines.

- Explain the importance of HDL cholesterol in determining CHD risk and the impact of raising levels on CHD risk.

- Describe the role of statins, niacin, fibrates, and other agents in the treatment of dyslipidemia, including effects of the drugs on patients with mixed dyslipidemia, type 2 diabetes, or the metabolic syndrome.

- Describe the clinical significance of drug interactions that may occur during combination therapy for the management of dyslipidemia.

Program Faculty

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**Matthew K. Ito, Pharm.D., FCCP**
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**Joseph Saseen, Pharm.D., FCCP**
Dr. Saseen declares that he has served as a speaker for Daiichi-Sankyo.

**Cathy C. Bowles, R.Ph.**
Ms. Bowles declares that she has no relationships pertinent to this activity.

**Susan R. Dombrowski, M.S., R.Ph.**
Ms. Dombrowski declares that she has no relationships pertinent to this activity.
Challenges in Managing Dyslipidemia in Patients with Mixed Dyslipidemia, Type 2 Diabetes, or the Metabolic Syndrome

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Joseph J. Saseen, Pharm.D., FCCP, is Associate Professor of Clinical Pharmacy and Family Medicine at the University of Colorado. He is board-certified as a pharmacotherapy specialist (BCPS) with added qualifications in cardiology. Dr. Saseen is also certified as a Clinical Lipid Specialist, and is recognized as a Fellow of the American College of Clinical Pharmacy.

Dr. Saseen received both his B.S. pharmacy and Pharm.D. from the State University of New York at Buffalo. He then completed an ambulatory care research fellowship at the University of Illinois. In his current position, Dr. Saseen practices as a clinical pharmacy specialist at the University of Colorado’s Family Medicine Center, while educating pharmacy and medical students. His research and other scholarly endeavors focus on cardiovascular pharmacotherapy.

Dr. Saseen serves on the Board of Regents for the American College of Clinical Pharmacy, is a member of the Board of Directors for the National Lipid Association’s Accreditation Council for Clinical Lipidology, and serves on the Board of Directors and Editorial Board of Pharmacotherapy. He has won several teaching awards at UCDHSC and most recently was the recipient of the 2006 President’s Excellence in Teaching Award.
HDL Cholesterol as a Therapeutic Target in Patients with Dyslipidemia

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Professor and Chair of Pharmacy Practice
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Oregon Health & Science University
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Portland Campus at Oregon Health & Science University

Matthew K. Ito, Pharm.D., FCCP, is Professor and Chair of Pharmacy Practice at Oregon State University/Oregon Health & Science University. Dr. Ito received his doctorate in Pharmacy in 1986 at the University of Southern California, where he also completed a post-doctoral residency and fellowship. Dr. Ito started his academic career at the University of the Pacific (UOP) Thomas J. Long School of Pharmacy and Health Sciences, where he was Assistant Professor and the Regional Coordinator in San Diego for the Advanced Experiential Program. Dr. Ito became Associate Professor with Tenure in 1994, and Professor in 1999. In 2002, Dr. Ito accepted a position as Vice-Chair of Pharmacy Practice. During his tenure at UOP he received numerous faculty awards for teaching and scholarship.

Dr. Ito was appointed Professor and Chair of Pharmacy Practice at Oregon State University in 2005. Dr. Ito’s research interests are the effects of lipid-modifying agents on endothelial dysfunction, pharmacokinetics, pharmacodynamics, and clinical outcomes research. Dr. Ito has received $750,000 in research grants, has published over 80 research papers, review articles, book chapters, and abstracts in both the pharmacy and medical literature. He has delivered over 300 presentations to professional audiences at the local, state, and national levels. Dr. Ito has trained research fellows since 1995. Dr. Ito is a diplomat of the American Council on Clinical Lipidology.

Dr. Ito is active in several national pharmacy and medical organizations. He is a member and fellow of the American College of Clinical Pharmacy, a member of the Council on Arteriosclerosis, Thrombosis & Vascular Biology for the American Heart Association, is an officer for the Pacific Lipid Association, and serves on the editorial board for Journal of Clinical Lipidology and Annals of Pharmacotherapy.
Top Medical Myths in Dyslipidemia

- All patients with AVD must have an LDL-C goal < 70 mg/dL.
- The NCEP has defined goals for HDL-C as > 40 mg/dL in males and > 50 mg/dL in females.
- Low HDL-C is always a risk factor for CHD.
- Raising HDL-C is not associated with a reduction in risk of CHD.
- Raising HDL-C with CETP inhibitors is no longer considered a viable therapeutic option.
- Adding a fibrate in patients with diabetes reduces CV risk.
- Gemfibrozil interacts with statins via inhibition of the CYP P450.
- Niacin is contraindicated in patients with diabetes.
- The use of niacin is limited due to cutaneous flushing.
- OTC “Fish Oils” and prescription omega-3 fatty acids are interchangeable.
- “Fish Oils” and omega-3 fatty acids can cause bleeding and contain mercury.
- “Fish Oils” can be used to lower LDL-C.
- Dyslipidemia should not be aggressively treated in older patients.
- When recommending lipid-lowering agents for older persons, low doses should empirically be used.
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Learning Objective

- Explain the relationship between dyslipidemia, the metabolic syndrome, and CHD, and discuss the prevalence of and morbidity and mortality from these conditions.

CV Disease in the United States

- #1 cause of death in the U.S. every year since 1918:
  - 1 out of every 2.8 deaths
  - Primary cause: 36%
  - Contributing cause: 58%

AHA/NHLBI Scientific Statement

<table>
<thead>
<tr>
<th>Measure</th>
<th>Metabolic Syndrome Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut Points</td>
<td></td>
</tr>
<tr>
<td>(3 of 5 constitutes diagnosis)</td>
<td></td>
</tr>
<tr>
<td>Elevated waist circumference (in)</td>
<td>≥100 (men), ≥35 (women)*</td>
</tr>
<tr>
<td>Elevated TG (mg/dL)</td>
<td>≥150 or drug therapy</td>
</tr>
<tr>
<td>Reduced HDL-C (mg/dL)</td>
<td>&lt;40 (men), &lt;50 (women) or drug therapy</td>
</tr>
<tr>
<td>Elevated BP (mm Hg)</td>
<td>≥130/85 or drug therapy</td>
</tr>
<tr>
<td>Elevated fasting glucose (mg/dL)</td>
<td>≥100 or drug therapy</td>
</tr>
</tbody>
</table>

* Lower cut points among Asian patients

Risk for CHD and Diabetes Based on Number of Metabolic Syndrome Criteria

Metabolic Syndrome and Incident CV Events and Death

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies (N)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV event</td>
<td>11</td>
<td>2.18</td>
<td>1.63-2.93</td>
</tr>
<tr>
<td>CHD event</td>
<td>18</td>
<td>1.65</td>
<td>1.37-1.99</td>
</tr>
<tr>
<td>CV death</td>
<td>10</td>
<td>1.91</td>
<td>1.47-2.40</td>
</tr>
<tr>
<td>CHD death</td>
<td>7</td>
<td>1.60</td>
<td>1.28-2.01</td>
</tr>
<tr>
<td>Death</td>
<td>12</td>
<td>1.60</td>
<td>1.37-1.92</td>
</tr>
</tbody>
</table>

Decreased risk Increased risk

HDL Cholesterol as a Therapeutic Target in Patients with Dyslipidemia

Matthew K. Ito, Pharm.D., FCCP, CLS
Professor and Chair
Department of Pharmacy Practice
Oregon State University
Oregon Health & Science University
College of Pharmacy

Learning Objectives

- Define low HDL cholesterol (HDL-C), list three possible causes of low HDL-C, and describe the impact of raising HDL-C on coronary heart disease (CHD) risk.
- Identify an authoritative study documenting the benefit from raising HDL-C in patients with low levels and explain the nature of this benefit.
- Discuss the use of niacin and fibrates to raise HDL-C.
- Name an investigational therapy for raising HDL-C and explain its mechanism of action.

Log-Linear Relationship Between LDL-C Levels and Relative Risk for CHD

- This relationship is consistent with a large body of epidemiologic data and data available from clinical trials of LDL-C-lowering therapy.
- These data suggest that for every 30-mg/dL change in LDL-C, the relative risk for CHD is changed by about 30%.
- The relative risk is set at 1.0 for LDL-C = 40 mg/dL.

LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease.


CHD Risk According to HDL-C Levels

Framingham Study

Kannel WB. Am J Cardiol 1983;52:9B–12B.

In ARIC, Reductions in Women’s CHD Risk Were Observed With HDL-C Levels up to 80 mg/dL (2.1 mmol/L)

Potential Antiatherogenic Actions of HDL-C

Monocyte

Adhesion molecule

Cytokines

Macrophage

LDL-C inhibits expression of endothelial cell adhesion molecules and MCP-1

HDL-C inhibits oxidation of LDL-C

Oxidized LDL-C

Fom cell

HDL-C promotes efflux of cholesterol from foam cells

MCP-1=monocyte chemoattractant protein-1.


Monocyte

Macrophage

Foam cell

Vessel lumen

Endothelium

Cytokines

Adhesion molecule

Oxidized LDL-C

HDL-C inhibits expression of endothelial cell adhesion molecules and MCP-1

HDL-C inhibits oxidation of LDL-C

MCP-1=monocyte chemoattractant protein-1.


Causes of Low HDL-C

Common causes of low HDL-C:

- Causes associated with insulin resistance
  - Hypertriglyceridemia
  - Overweight/obesity
  - Physical inactivity
  - Type 2 diabetes
- Other causes
  - Cigarette smoking
  - Very high carbohydrate intake (> 60% of calories)
  - Drugs (anabolic steroids, progestational agents)
- Familial Hypoalphalipoproteinemia (<40 mg/dL)
- Severe HDL deficiency (<10 mg/dL)
  - Tangiers disease
  - Fish eye disease
  - Lecithin-Cholesterol Acyltransferase (LCAT) deficiency

Myth

The NCEP has defined goals for HDL-C as > 40 mg/dL in males and > 50 mg/dL in females.

NCEP ATP III

- Low HDL-C is a strong independent predictor of CHD.
- Low HDL-C is defined as a level < 40 mg/dL.
- In the present guidelines, low HDL-C both modifies the goal for LDL-C therapy and is used as a risk factor to estimate 10-year risk for CHD.
- ATP III does not specify a goal for HDL-C raising.
- Although clinical trials suggest that raising HDL will reduce risk, the evidence is insufficient to specify a goal.


NCEP ATP III

- Nonetheless, low HDL should receive clinical attention and management according to the following sequence:
  - Primary goal is LDL-C
  - Reduce non-HDL-C if metabolic syndrome is present.
  - For isolated low HDL-C, drugs for raising HDL can be considered in high-risk patients (CHD or CHD equivalent).


Effects of Drug Classes on Serum Lipids

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>TC</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resins</td>
<td>↓20%</td>
<td>↓10%–20%</td>
<td>↑3%–5%</td>
<td>Variable</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↓25%</td>
<td>↓10%–15%</td>
<td>↑15%–35%</td>
<td>↓20%–50%</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓15%</td>
<td>Variable</td>
<td>↑6%–15%</td>
<td>↓20%–50%</td>
</tr>
<tr>
<td>Statins</td>
<td>↓15%–60%</td>
<td>↓20%–60%</td>
<td>↑3%–15%</td>
<td>10%–40%</td>
</tr>
</tbody>
</table>


Myth
Raising HDL-C is not associated with a reduction in risk of CHD.

VA HIT: Favorable Effects of Gemfibrozil on CVD Events in CHD Patients With Isolated Low HDL-C

Subjects: 2,531 men
Age: ≤74 yr (avg 64 yr)
Mean baseline LDL-C: 111 mg/dL
Mean baseline HDL-C: 32 mg/dL
Mean baseline TG: 161 mg/dL
Duration: 7 yr
Intervention: Gemfibrozil 600 mg twice daily

*P<0.01; †P=0.006; ‡P=0.05
P=placebo group; Rx=treated group.

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Age: ≤74 yr (avg 64 yr)
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Duration: 7 yr
Intervention: Gemfibrozil 600 mg twice daily

*P<0.01; †P=0.006; ‡P=0.05
P=placebo group; Rx=treated group.

HDL-Atherosclerosis Treatment Study (HATS)

• Study design
  – 3-year double-blind trial with 160 patients with coronary disease, low HDL cholesterol levels and normal LDL cholesterol levels
  – Mean baseline HDL: 35 mg/dL (men); 40 mg/dL (women)
  – Mean baseline LDL: 145 mg/dL
  – Mean baseline TG: 213 mg/dL
  – 48% (n=77) had the metabolic syndrome
• Study intervention
  – Simvastatin plus niacin; antioxidants; simvastatin-niacin plus antioxidants; or placebo
• Primary endpoints
  – Arteriographic evidence of change in coronary stenosis
  – Occurrence of a first cardiovascular event (death, MI, stroke, or revascularization)


HATS: Lipid Outcomes

% Change
LDL-C HDL-C TG
Placebo -8.6 -42* 26*
Simvastatin / niacin 6.2 -36*

*P<0.001 vs placebo.

HATS: Efficacy

Primary End Point: Angiographic Outcomes
% Change in stenosis
Baseline 3.9
Placebo -0.4
Simvastatin/niacin +4.0%

Secondary End Point: Clinical Outcomes
% Change in MACE
Coronary death, MI, stroke, or revascularization
Baseline 23.7
Placebo 2.6
Simvastatin/niacin +200%


ARBITER 2: Primary Endpoint – CIMT Change

Baseline
Statin + Placebo 0.868 ±0.207 mm
Statin + ERN 0.893 ±0.259 mm

Δ CIMT After 1 Year
Statin + Placebo 0.044 ±0.014 mm
Statin + ERN 0.009 ±0.011 mm

CIMT = carotid intima media thickness
ERN = extended-release niacin

Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes

- Study Design: Prevention, Randomized, Double-Blind
- Intervention: Niacin Plus Statin versus Statin to Prevent Vascular Events
- Primary Outcome Measures:
  - Composite end point of CHD death, nonfatal MI, ischemic stroke, or hospitalization for high-risk non-ST segment elevation acute coronary syndrome (measured at time to first occurrence of one of these events)
- Total Enrollment: 3300 men and women aged 45 and older with established vascular disease and atherogenic dyslipidemia
  - Atherogenic dyslipidemia defined as: (1) LDL-C ≤ 160 mg/dL; (2) HDL-C ≤ 40 mg/dL for men or ≤ 50 mg/dL for women; (3) TG ≥ 150 mg/dL and ≤ 400 mg/dL
- Study start: September 2005
- Study end: The trial will follow all living patients to a common termination date (approximately December 2010)

Myth

The use of niacin is limited due to cutaneous flushing.

Adjusted Hazard Ratios from Cox Regression for Discontinuation of Lipid-Modifying Drug

<table>
<thead>
<tr>
<th>LMD</th>
<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAS</td>
<td>3.43</td>
<td>3.35-3.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ER niacin</td>
<td>2.24</td>
<td>2.18-2.30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrates</td>
<td>1.46</td>
<td>1.43-1.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>1.11</td>
<td>1.06-1.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Statins</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*adjusted for age, gender, medical history, admissions and physician visits, #Rx, ite of other LMD, copays, insurance plan, mail order prescription, plan location, and year of index prescription


Niacin Receptor (GPR109A): Locations and Effects


Aspirin Inhibits the Nicotinic Acid-induced Increase in PGD2 Levels

Cheng K et al. Proc Natl Acad Sci U S A 2006;103:6682-6687.

Laropiprant Prostaglandin D2 Receptor Subtype 1 Antagonist

- 
  - [(3R)-4-(4-Chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopentaindol-3-yl] acetic acid (MK-0524)
  - Rapidly absorbed
  - Cmax 1 to 1.5 hours
  - 66% of dose excreted in feces
  - 22% of dose excreted in urine
  - Major metabolite glucuronic acid conjugate

ERN-LPT
(extended-release niacin/laropiprant)

- Phase III, double-blind, randomized trial enrolling 1,613 patients with primary hypercholesterolemia or mixed dyslipidemia.

**Effects of Laropiprant (LPT)**

![Graph showing flushing symptoms](image)

**Overall flushing symptoms**

**Effects of Laropiprant (LPT)**

- ERN-LPT 1g
- ER niacin 1g
- ER niacin 2g
- Placebo

Week 0

Week 4

20 weeks

65% taking statins

- ERN-LPT 1g
- ER niacin 1g
- ER niacin 2g
- Placebo

- ERN-LPT 2g
- ER niacin 2g
- Placebo

Presented at 2007 European Society of Cardiology Annual Congress.

**ERN-LPT**

(ER niacin/laropiprant)

- ERN-LPT 2 g:
  - ↓ LDL-C by 19%
  - ↓ TG by 22%
  - ↑ HDL-C by 19%

- Global Flushing Severity Score (GFSS)
  - No or mild
    - 69% ERN-LPT
    - 44% ER niacin
  - Moderate or greater
    - 27% ERN-LPT
    - 49% ER niacin

Presented at 2007 European Society of Cardiology Annual Congress.

**Myth**

Raising HDL-C with CETP inhibitors, such as torcetrapib, is no longer considered a viable therapeutic option.

CETP = cholesteryl ester transfer protein

Presented at 2007 European Society of Cardiology Annual Congress.

**Cholesterol Metabolism**

![Diagram of cholesterol metabolism](image)

**Reverse Cholesterol Transport Pathway**

![Diagram of reverse cholesterol transport pathway](image)
Complementary Activity of Torcetrapib With Atorvastatin

**Mechanism of Action**
- ↓ CETP activity
- ↓ CE transfer from HDL to Apo B particles

**Major Lipid Effects**
- ↓ HDL-C
- ↑ LDL size
- ↓ Small LDL

**Phase 3 Major Goals**
- Superior lipid Profile
- Torcetrapib/atorvastatin
- Atherosclerosis improvement compared with atorvastatin alone
- ↓ LDL-C
- ↓ Apo B-100
- ↓ Triglycerides

Vascular Imaging Trials

- **Basic premises**
  - Vessel wall thickness correlates with cardiovascular events
  - Atherosclerosis is a systemic disorder

- **Use ultrasound as lead technology**
  - Carotid IMT (change in mm/year)
  - Coronary IVUS (change in percent atheroma volume)

Torcetrapib Clinical Trial Results

- December 2, 2006, Pfizer halted the development of torcetrapib.
- Phase III trial (ILLUMINATE) comparing atorvastatin alone with atorvastatin/torcetrapib showed no difference in coronary atheroma volume between treatments and a significant increase in SBP by 4.6 mm Hg in patients receiving torcetrapib.

Anacetrapib (MK-0859)

- Double-blind, randomized, parallel-group dose-ranging study comparing single daily doses of anacetrapib 10 mg, 40 mg, 150 mg, and 300 mg plus placebo OR atorvastatin 20 mg.
- 589 patients with primary hypercholesterolemia or mixed dyslipidemia studied for 8 weeks.
- Primary end point: LDL-C reductions.
- Secondary end points: HDL-C increase, change in lipoproteins and apolipoproteins, and blood pressure.

Anacetrapib (MK-0859)

- Anacetrapib monotherapy at doses of 10 mg, 40 mg, 150 mg, and 300 mg reduced LDL-C by 16, 27, 40, and 39% and increased HDL-C by 44, 86, 139, and 133% compared with placebo.
- Anacetrapib co-administered with atorvastatin, across all doses, also produced significant incremental reductions in LDL-C and increases in HDL-C compared with atorvastatin alone.
- No demonstrable increases in blood pressure were seen.
- There were no reports of hepatitis, myopathy or rhabdomyolysis.

Myth

Low HDL-C is always a risk factor for CHD.
**What is ApoA-1 Milano?**

- ApoA-1 variant (arg173 → cys)
- Origin of variant gene located in Limone sul Garda, Italy
- ~1000 individuals
- All carriers coming from a single mating couple, living in the 18th century.
- Transmitted as an autosomal dominant trait.
- Low HDL-C, but no signs of atherosclerosis.


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**ApoA-1 Milano Trial Design**

Randomized, double-blind, controlled, parallel-group, multicenter trial of ETC-216 in reducing atheroma volume in ACS patients

Primary objective
- Assess effect of ETC-216 on coronary atheroma burden measured by IVUS

Therapeutic interventions and targets
- 123 patients aged 30-75 years with ACS (57 patients randomized)
- Angiography <14 days after ACS (UA, non-ST MI, or ST-elevation MI)
- ETC-216 15 mg/kg (n = 33), ETC-216 45 mg/kg (n = 22), or placebo (n = 12), given in 5 weekly infusions

Primary endpoint
- % change in atheroma volume after treatment


---

**ApoA-1 Milano Results: Atheroma Volume in Target Coronary Segment**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Patients</th>
<th>Change From Baseline, mm^2</th>
<th>Mean (SD)</th>
<th>Median (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11</td>
<td>-2.9 (23.3)</td>
<td>-0.2 (-8.6 to 8.2)</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>ETC-216 15 mg/kg</td>
<td>21</td>
<td>-15.1 (50.6)</td>
<td>-15.0 (-29.6 to -4.9)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>ETC-216 45 mg/kg</td>
<td>15</td>
<td>-12.6 (15.5)</td>
<td>-12.0 (-20.6 to -2.9)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>ETC-216 Groups Combined</td>
<td>35</td>
<td>-14.1 (39.5)</td>
<td>-13.3 (-20.7 to -7.2)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>


---

**ApoA-1 Milano Results: Atheroma Volume in Most Severely Diseased Subsegment**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Patients</th>
<th>Change From Baseline, mm^2</th>
<th>Mean (SD)</th>
<th>Median (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11</td>
<td>-0.7 (15)</td>
<td>-0.2 (-3.7 to 1.5)</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>ETC-216 15 mg/kg</td>
<td>20</td>
<td>-8.6 (15.5)</td>
<td>-4.7 (-16.8 to -2.6)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>ETC-216 45 mg/kg</td>
<td>16</td>
<td>-5.3 (7.1)</td>
<td>-2.9 (-9.8 to -0.8)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>ETC-216 Groups Combined</td>
<td>35</td>
<td>-7.2 (12.6)</td>
<td>-4.1 (-19.8 to -3.2)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>


---

**An Example of Atheroma Regression in a Patient who received ETC-216**

---

**Summary**

- Atherosclerosis is a complex, multifactorial disease process.
- Numerous lipoproteins, including LDL-C, HDL-C, and very low-density lipoprotein affect the development and progression of atherosclerosis.
- HDL particles reduce atherosclerosis through a variety of mechanisms including reverse cholesterol transport and inhibiting oxidation of LDL particles.
- Studies have shown that raising HDL-C reduces CHD risk; however, currently available drugs are only moderately effective or are associated with significant side effects.
Summary

- Niacin-induced cutaneous vasodilation and flushing caused by PGD₂ binding to the prostaglandin D₂ receptor-1 limits the use of niacin.
- Laropiprant effectively blocks nicotinic acid-induced vasodilation and flushing compared with placebo and aspirin.
- Initial trials with ApoA-1 Milano in humans and animals appear promising.
- Further evaluation of CETP inhibitor efficacy and safety (especially effect on blood pressure) is needed.

Challenges in Managing Dyslipidemia in Patients with Mixed Dyslipidemia, Type 2 Diabetes, or the Metabolic Syndrome

Joseph Saseen, Pharm.D., FCCP, BCPS, CLS
Associate Professor
University of Colorado Denver
School of Pharmacy and Medicine

Learning Objectives

- Summarize the current NCEP guidelines for treating dyslipidemia, and identify a persistent myth or an unresolved controversy in dyslipidemia treatment that is not adequately addressed by the guidelines.
- Describe the role of statins, fibrates, and other agents in the treatment of dyslipidemia, including effects of the drugs on patients with mixed dyslipidemia, type 2 diabetes, or the metabolic syndrome.
- Describe the clinical significance of drug interactions that may occur during combination therapy for the management of dyslipidemia.

NCEP ATP III (2004)
Primary Target: LDL-C Goal

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>&lt; 100 (Optional &lt;70)</td>
</tr>
<tr>
<td>CHD or equivalents (10-yr risk &gt; 20%)</td>
<td></td>
</tr>
<tr>
<td>Moderately High Risk</td>
<td>&lt; 130 (Optional &lt; 100)</td>
</tr>
<tr>
<td>2+ risk factors (10-yr risk 10 to 20%)</td>
<td></td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>2+ risk factors (10-yr risk &lt; 10%)</td>
<td></td>
</tr>
<tr>
<td>Lower Risk</td>
<td>&lt; 160</td>
</tr>
<tr>
<td>0 to 1 risk factor</td>
<td></td>
</tr>
</tbody>
</table>


Myth

All patients with CHD must have an LDL-C goal < 70 mg/dL.

AHA/ACC Guidelines:
Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease (AVD)

- LDL-C Goal Values:
  - 100 mg/dL
  - Further reduction to 70 mg/dL is reasonable
  - 70 mg/dL if baseline LDL-C is 70-100 mg/dL
- If < LDL-C 70 mg/dL is not possible because of a high baseline LDL-C:
  - Achieve LDL-C reduction of 50% with statins or combination regimens.

**Lipid-Lowering Therapies**

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)</td>
<td>↓ 18-63%</td>
<td>↑ 5-15%</td>
<td>↓ 7-30%</td>
</tr>
<tr>
<td><strong>Bile Acid Sequestrants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(colesevelam, cholestyramine, colestipol)</td>
<td>↓ 15-30%</td>
<td>↑ 3-5%</td>
<td>0 or ↑</td>
</tr>
<tr>
<td><strong>Nicotinic Acid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(gemfibrozil, fenofibrate)</td>
<td>↓ 5-20 or ↑</td>
<td>↑ 10-20%</td>
<td>↓ 20-50%</td>
</tr>
<tr>
<td><strong>Fibric Acid Derivatives</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(gemfibrozil, fenofibrate)</td>
<td>↓ 5-20 or ↑</td>
<td>↑ 10-20%</td>
<td>↓ 20-50%</td>
</tr>
<tr>
<td><strong>Cholesterol Absorption Inhibitor</strong> (ezetimibe)</td>
<td>↓ 18%</td>
<td>↑ 1%</td>
<td>↓ 7%</td>
</tr>
<tr>
<td><strong>Omega-3 fatty acids</strong> (prescription strength only)</td>
<td>?</td>
<td>↑ 9%</td>
<td>↓ 45%</td>
</tr>
</tbody>
</table>

**Attain LDL-C Goal Values**

- Multiple studies consistently demonstrate that LDL-C goal attainment rate is poor
  - Most patients with LDL-C goals of <100 mg/dL or <70 mg/dL are not at goal
- Statin-based pharmacotherapy (optimal):
  - Monotherapy
  - Plus ezetimibe therapy
  - Plus bile acid sequestrant therapy

**STELLAR Trial**

![STELLAR Trial chart](Am J Cardiol 2003;93:152-160).

**Ezetimibe Added to a Statin**

- Double-blind, controlled trial
- 769 patients not at LDL goal while on statin monotherapy
- Randomized to placebo or ezetimibe 10 mg daily

![Ezetimibe Added to a Statin chart](Am J Cardiol 2002;90:1084-91).

*P < 0.001 for differences

**Ezetimibe/Simvastatin vs Atorvastatin**

![Ezetimibe/Simvastatin vs Atorvastatin chart](Am J Cardiol 2004;93:1487-1494).

**Ezetimibe/Simvastatin vs Rosuvastatin**

![Ezetimibe/Simvastatin vs Rosuvastatin chart](Current Med Res Opin 2006;22(10):2041-2053).
Colestervelam added to Simvastatin

Mean LDL-C Change (%)

-26*
-34*
-42*
-50
-40
-30
-20
-10
0

* p< 0.05 vs placebo
# p< 0.05 vs individual agents alone


Treatment Goals After LDL-C

<table>
<thead>
<tr>
<th>NCEP/AHA</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary Target</strong></td>
<td><strong>TERTIARY TARGET</strong>***</td>
</tr>
<tr>
<td>• Non-HDL-C</td>
<td>• HDL-C</td>
</tr>
<tr>
<td>&lt; LDL-C goal + 30</td>
<td>&gt; 40 mg/dL, men</td>
</tr>
<tr>
<td>TERTIARY TARGET**</td>
<td>&gt; 50 mg/dL, women</td>
</tr>
<tr>
<td>• HDL-C</td>
<td>• Triglycerides:</td>
</tr>
<tr>
<td>&gt; 40 mg/dL</td>
<td>&lt; 150 mg/dL</td>
</tr>
<tr>
<td>&gt; 50 mg/dL</td>
<td>&gt; 40 mg/dL, men</td>
</tr>
<tr>
<td>&gt; 50 mg/dL</td>
<td>&gt; 50 mg/dL, women</td>
</tr>
</tbody>
</table>

*Only if LDL-C goal is achieved and if TG are 200 to 499 mg/dL.
**Only if LDL-C and non-HDL-C goals are achieved (based on definition of metabolic syndrome).

AHA/NHLBI Scientific Statement

Metabolic Syndrome Diagnostic Criteria

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cut Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference (in)</td>
<td>≥ 40 (men), ≥ 35 (women)*</td>
</tr>
<tr>
<td>Elevated TG (mg/dL)</td>
<td>≥ 150 or drug therapy</td>
</tr>
<tr>
<td>Reduced HDL-C (mg/dL)</td>
<td>&lt; 40 (men), &lt; 50 (women) or drug therapy</td>
</tr>
<tr>
<td>Elevated BP (mm Hg)</td>
<td>≥ 130/85 or drug therapy</td>
</tr>
<tr>
<td>Elevated fasting glucose (mg/dL)</td>
<td>≥ 100 or drug therapy</td>
</tr>
</tbody>
</table>

* Lower cut points among Asian patients


Dyslipidemia in Metabolic Syndrome or Type 2 Diabetes

- At increased risk for CV events
- Mixed dyslipidemia often requires intensive and/or combination drug therapy for:
  - Modestly elevated LDL-C
  - High non-HDL-C (↑ TG and ↓ HDL-C)
- Proven CV risk reduction with statin therapy
- Unclear long-term benefits of combination regimens for mixed dyslipidemia


Targeting Non-HDL-C

Non-HDL-C = (Total Cholesterol) – (HDL-C)

- Target of therapy only after LDL-C is lowered and if triglycerides are 200 to 499 mg/dL
- Pharmacotherapy options to reduce non-HDL-C:
  - More intense LDL-C-lowering therapy
  - Niacin (after LDL-C-lowering therapy)
  - Fibrate therapy (after LDL-C-lowering therapy)
  - Omega-3 fatty acids (after LDL-C-lowering therapy)


Myth

Adding a fibrate in patients with diabetes reduces CV risk.
Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

- 9795 patients with type 2 diabetes
- Randomized, double-blind to placebo or fenofibrate 200mg daily x 5 yr
- Primary endpoint:
  - CHD death + nonfatal MI
- Statin “drop in” rate was high

Action to Control Cardiovascular Risk in Diabetes Trial

- Randomized, multicenter trial in 10,251 patients with type 2 diabetes
- Testing the effects of treatment to ↑ HDL-C and ↓ triglycerides on CV events:
  - Fenofibrate + simvastatin therapy versus placebo + simvastatin
  - Duration is 4 to 8 years (mean 5.6)
- Results expected in early 2010

National Lipid Association (NLA)

- Increased risk of myopathy and rhabdomyolysis with statin/fibrate combination therapy
- However, statin/fibrate combination therapy is NOT contraindicated

Myth

Gemfibrozil interacts with statins via inhibition of the CYP P450.

Statin/Fibrate Interaction

- Gemfibrozil
  - Reduced maximum statin dose in combination:
    - Lovastatin 20mg daily
    - Rosuvastatin 10mg daily
    - Simvastatin 10mg daily
- Fenofibrate
  - Does not have any maximum dose restrictions.
  - The preferred fibrate when used with a statin; however, using maximum statin doses with fenofibrate is still not advisable.
Coronary Drug Project: 6 year follow up

Interactive P-value = NS


<table>
<thead>
<tr>
<th>Baseline Fasting Plasma Glucose (mg/dL)</th>
<th>Nonfatal MI Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;95</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Niacin</td>
</tr>
<tr>
<td>95-104</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Niacin</td>
</tr>
<tr>
<td>105-125</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Niacin</td>
</tr>
<tr>
<td>≥126</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Niacin</td>
</tr>
</tbody>
</table>

Myth
Niacin is contraindicated in patients with diabetes.

Arterial Disease Multiple Intervention Trial (ADMIT)

- Prospective, randomized double-blind trial evaluating niacin in patients with diabetes
- Crystalline niacin 3000 mg/day (or a max tolerated dose) or placebo for 2.5 years

<table>
<thead>
<tr>
<th>Patients with Diabetes (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin  (n=64)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
</tr>
<tr>
<td>A1C (%)</td>
</tr>
<tr>
<td>Uric Acid (mg/dL)</td>
</tr>
</tbody>
</table>


Omega-3 Fatty Acids

- Active compounds are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
- Clinical uses:
  - Hypertriglyceridemia
  - CV protection in patients with AVD
- Lovaza™ is the only prescription product FDA approved to lower TG when ≥ 500 mg/dL.
- Many “fish oil” products available as nutritional supplements.

Am J Cardiol 2007;99[Suppl]:35C–43C.

Myth

OTC “Fish Oils” and prescription omega-3 fatty acids are interchangeable.

“Fish Oil” vs. Omega-3 Fatty Acids

<table>
<thead>
<tr>
<th>Nature’s Bounty (&quot;Fish Oil&quot;)</th>
<th>Carlson Super-DHA™ (&quot;Fish Oil&quot;)</th>
<th>Lovaza™ (Omega-3 Acid Ethyl Esters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>180/120</td>
<td>200/100</td>
<td>465/375</td>
</tr>
<tr>
<td>700</td>
<td>400</td>
<td>160</td>
</tr>
<tr>
<td>2 to 4 daily</td>
<td>1 to 2 daily</td>
<td>4 daily</td>
</tr>
<tr>
<td>11.2</td>
<td>5.6</td>
<td>4</td>
</tr>
</tbody>
</table>
**Myth**

“Fish Oils” and omega-3 fatty acids can cause bleeding and may contain mercury.

---

**Omega-3 Fatty Acids and “Fish Oils” Safety Concerns**

- Omega-3 fatty acids:
  - No antithrombotic effects; not proven to increase bleeding risk
  - Rigorous manufacturing purification processes reduce risk of hypervitaminosis and exposure to environmental toxins (e.g., mercury, dioxin)
- “Fish Oils”
  - USP verification not required for all products
  - Not equal to prescription omega-3 fatty acids

*Am J Cardiol 2007;99(suppl):35C–43C.*

---

**Myth**

“Fish Oils” can be used to lower LDL-C.

---

**Fenofibrate and Omega-3 Fatty Acids Relative Difference vs Placebo in Patients with Very High TG (≥ 500 mg/dL)**

![Graph showing relative differences in TG, HDL-C, and LDL-C between Omega-3 Fatty Acids and Fenofibrate compared to Placebo.]


---

**Myth**

Dyslipidemia should not be aggressively treated in older patients.

---

**Clinical Concerns in the Elderly**

- NLA Task Force:
  - Older patients (esp. frail elderly) at higher risk for muscle toxicity and liver function changes
  - Increased serum drug concentrations due to pharmacokinetic changes, albeit small
  - Polypharmacy - higher risk for drug interactions
- Under-represented in clinical trials (esp. very elderly)
  - CV benefits are assumed and extrapolated

*Am J Cardiol 2006;97(suppl 8A):89C–94C.*
**Cholesterol Treatment Trialists’ Collaborators**

- Statin vs placebo:
  - Patients ≥ 75 years (n>7000)
  - Risk reduction per mmol/L reduction in LDL-C
- Major coronary events:
  - 10.6% vs 12.8% (p=0.002)
- Major vascular events:
  - 16.8% vs 19.7% (p=0.001)
  - Benefits proportionate to those in younger patients
  - No association between age and increased risk of rhabdomyolysis reported


**Myth**

When using lipid-lowering drugs in older persons, low doses should be used empirically.

**Dyslipidemia Pharmacotherapy**

**Dose Adjustments in CKD**

<table>
<thead>
<tr>
<th>Agent</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60-90</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>No</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>?</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>No</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>No</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>?</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>↓ by 33%</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>No</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate

*Am J Kid Dis* 2003;41:S1-S92

*Am J Cardiol* 2007;99(supp):3C–18C.

**Conclusions**

- LDL-C is the primary target of therapy and there are many statin-based strategies.
- Non-HDL-C reduction is a secondary target of therapy and often necessitates combination pharmacotherapy.
- Common myths regarding dyslipidemia therapy may hinder appropriate CV risk reduction therapy.

**End of Presentation**

Please go to [www.ashp.org/advantage/ce/](http://www.ashp.org/advantage/ce/) to take the CE Test.
Selected References


Beyond Statins: Persistent Myths & Current Controversies in Managing Dyslipidemia
This program is located at http://esymposia.ashp.org/cemornings

This self-assessment test has been provided as a study aid only. At the conclusion of the internet-based program, click on “Take CE Test” to proceed to the ASHP CE Testing Center and take the on-line program post-test. You may print your CE statement immediately after successful completion of the post-test.

There are 11 questions associated with this self-assessment test.

1. Which of the following describes the prevalence of cardiovascular disease in the United States?
   a. One out of every 5 deaths in the U.S. results from cardiovascular disease.
   b. Cardiovascular disease is the primary cause of death in 36% of the population.
   c. Cardiovascular disease is a contributing cause of death in 36% of the population.
   d. Since 1981, cardiovascular disease has been the most common cause of death in the U.S.

2. The goal HDL-C was defined by NCEP ATP III as >40 mg/dL in men and >50 mg/dL in women.
   a. True
   b. False

3. Which of the following is a possible cause of low HDL-C?
   a. Acute viral illness.
   b. Chronic alcoholism.
   c. Immune deficiency states.
   d. Physical inactivity.

4. Which of the following outcomes was documented with the use of simvastatin plus niacin in the HDL-Atherosclerosis Treatment Study (commonly referred to as HATS)?
   a. Regression in coronary stenosis and 90% CHD risk reduction.
   b. Reduced hospitalization for acute coronary syndrome.
   c. Raising HDL-C was not associated with a reduction in risk of CHD.
   d. Lowering LDL-C was not associated with a reduction in risk of CHD.

5. The rationale for adding laropiprant to niacin is to:
   a. Avoid or minimize cutaneous flushing.
   b. Improve the HDL-C response to niacin.
   c. Improve the LDL-C response to niacin.
   d. Improve the triglyceride response to niacin.

6. Which of the following is an investigational therapy for increasing HDL-C that exerts its effect through inhibition of cholesterol ester transfer protein and the reverse cholesterol transport pathway?
   a. Anacetrapib.
   b. Ezetimibe.
   d. Laropiprant.
7. The development of torcetrapib was discontinued because adding the drug to atorvastatin caused:
   a. A decrease in carotid intima media thickness.
   b. An increase in coronary atheroma volume.
   c. A precipitous fall in systolic blood pressure.
   d. An increase in risk of death and heart failure.

8. In patients with metabolic syndrome, according to NCEP/AHA guidelines, which of the following statements is true about when to address non-HDL-C?
   a. Only after LDL-C is <120 mg/dL and HDL-C is >50 mg/dL (men and women).
   b. Only after LDL-C is lowered and if triglycerides are <150 mg/dL.
   c. Only after HDL-C is raised and if triglycerides are <150 mg/dL.
   d. Only after LDL-C goal is attained and if triglycerides are 200-499 mg/dL.

9. Use of fibrates in combination with statins increases the risk for:
   a. Cholelithiasis.
   b. Hyperglycemia.
   c. Rhabdomyolysis.
   d. Nephrotoxicity.

10. Which of the following myths pertaining to the treatment of dyslipidemia remains unresolved?
    a. The interaction between gemfibrozil and statins is mediated by CYP P-450.
    b. Niacin is contraindicated in patients with diabetes mellitus.
    c. Adding a fibrate to statin therapy in patients with type 2 diabetes reduces cardiovascular mortality.
    d. Omega-3 fatty acids can cause bleeding.

11. The Cholesterol Treatment Trialists' Collaborators concluded that the use of statins to treat dyslipidemia in elderly patients should be less aggressive than in younger patients because the reduction in major coronary events is smaller and the risk of rhabdomyolysis is higher in elderly patients compared with younger patients.
    a. True.
    b. False.