New Clinical Guidelines for Aggressive Cholesterol Management: Strategies for Meeting the Challenge

Podcast of a Symposium held during the 39th ASHP Midyear Clinical Meeting
New Clinical Guidelines for Aggressive Cholesterol Management: Strategies for Meeting the Challenge

PROGRAM AGENDA

Welcome and Introductory Remarks
Matthew K. Ito, Pharm.D., Program Moderator

NCEP Clinical Guidelines: Evaluating New Evidence for Aggressive Management
Ori Ben-Yehuda, M.D.

Meeting the Challenge in Clinical Practice: Combining Efforts to Reduce Cholesterol and Cardiovascular Risk
Matthew K. Ito, Pharm.D.

Questions and Answers

PROGRAM FACULTY

Matthew K. Ito, Pharm.D., FCCP, BCPS
Professor and Vice Chair of Pharmacy Practice
Director, Cardiac Rehabilitation Cholesterol Clinic
University of the Pacific, Stockton
VA San Diego Healthcare System
San Diego, California

Ori Ben-Yehuda, M.D., FACC
Associate Professor of Medicine
Director, Coronary Care Unit
University of California, San Diego
New Clinical Guidelines for Aggressive Cholesterol Management: Strategies for Meeting the Challenge

PROGRAM OBJECTIVES

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

• Discuss recent clinical research for the management of dyslipidemia, including modifications to National Cholesterol Education Program and American Diabetes Association guidelines.

• Identify patient risk factors for diabetes, hypertension, and the metabolic syndrome, and discuss the challenges for achieving target LDL-C goals and lifestyle changes.

• Explain the pathophysiology of the metabolic syndrome and the resulting cardiovascular risk factors.

• Summarize the benefits of lowering LDL-C and raising HDL-C with appropriate dosing of statins, fibrates, niacin, and combination regimens in high-risk patients.

• Explain data from recent clinical trials that compared standard cholesterol-lowering therapy with dual inhibition combination therapy to achieve target LDL.

• Describe the role of the pharmacist in providing cost-effective interventions for the management of patients with hypercholesterolemia.
New Clinical Guidelines for Aggressive Cholesterol Management: Strategies for Meeting the Challenge

Ori Ben-Yehuda, M.D., FACC
Associate Professor of Medicine
Director, Coronary Care Unit
University of California, San Diego

Dr. Ori Ben-Yehuda is Associate Professor of Medicine at the University of California, San Diego (UCSD), and Director of the Coronary Care Unit at UCSD Medical Center. He also serves as Deputy Editor of the Journal of the American College of Cardiology (JACC).

After attending Harvard College, Dr. Ben-Yehuda received his M.D., magna cum laude, from the Sackler School of Medicine at Tel Aviv University in 1985. Following his internship at the Rabin Medical Center he served as a physician in Infantry and Special Forces in the Israeli Army. He was a Resident in internal medicine at the Soroka Medical Center at Ben-Gurion University in Beer-Sheba, Israel, and also a Resident and Chief Resident in internal medicine at Bellevue Hospital/New York University Medical Center, in New York City. Dr. Ben-Yehuda was a Fellow and subsequently a Chief Fellow in cardiovascular medicine at the University of California, San Diego. He was a Merck/ACC and AHA Postdoctoral Fellow in the Specialized Center for Research in Atherosclerosis, also at the University of California, San Diego.

Dr. Ben-Yehuda’s research includes studies in hyperlipidemia, coronary disease, hypertension, sleep apnea, the effects of amphetamines on the heart, and pulmonary thromboembolic disease. He has published numerous articles and book chapters in cardiovascular medicine.
Low density lipoprotein-cholesterol (LDL-C) is a key target in prevention and treatment of atherosclerosis. While earlier landmark studies such as the 4S study demonstrated the value of LDL lowering in coronary patients with high levels of LDL-C, there was uncertainty regarding the efficacy in patients with low LDL-C levels. Similarly there was uncertainty regarding LDL target levels. Recent trials such as the Heart Protection Study and Prove-It (TIMI 22) have demonstrated the benefit of LDL-C lowering in a broad range of high-risk patients irrespective of baseline LDL-C levels. Additionally, the data from these studies as well as epidemiologic studies supports the concept of "lower is better" particularly in high risk patients. These new data have led to a revision of national guidelines for cholesterol management with an alternative LDL-C goal of <70 mg/dl in very high risk patients. Despite the efficacy of statin therapy for LDL-C lowering, significant treatment gaps remain. These are likely to increase given newer, more aggressive LDL-C targets, which have been lowered. This presentation will explore improved options for achieving LDL-C targets using dual inhibition combination therapy with a statin and a selective cholesterol-absorption inhibitor.
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Lifetime Risk of Developing CHD Is High

Risk for First CHD Event for 40-Year-Old Men and Women
Patients With Diabetes Are at Even Greater Risk for CHD

Patients With Diabetes Without History of CHD Have Incidence of MI Comparable to Patients Without Diabetes With CHD History

7-Year MI Incidence, %

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>No diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>40%</td>
<td>5.5%</td>
</tr>
<tr>
<td>No CHD</td>
<td>18.8%</td>
<td>20.2%</td>
</tr>
</tbody>
</table>

N=2,412

Most Myocardial Infarctions Are Caused by Low-Grade Stenoses

Coronary stenosis severity prior to MI

- >70% Stenosis: 14%
- 50%-70% Stenosis: 68%
- <50% Stenosis: 18%


Characteristics of Plaques Prone to Rupture

CAD: A Changing Paradigm

Old Paradigm:
- Focal disease
- High grade stenoses account for morbidity and mortality

Rx: PCI and CABG

New Paradigm:
- Diffuse Disease of the entire artery
- High grade stenoses cause angina-
- Vulnerable plaques cause MI's

Rx: Lipid lowering rx,
ASÁ, ACE Inhibitors
CABG/PCI for angina,
ischemic cardiomyopathy
CHD = coronary heart disease; MRFIT = Multiple Risk Factor Intervention Trial.

Early Primary-Prevention Trials: Overview

Early Secondary-Prevention Trials: Overview

CHD Risk Increases as Plasma Cholesterol Increases


* Net difference between treatment and control groups (P values are for events).
N=number enrolled.
 ns=not significant.

Inclusion Criteria

- Men and women
- Age 35 – 70 years
- History of angina pectoris or acute myocardial infarction
- Serum total cholesterol level 5.5–8.0 mmol/L (213 – 310 mg/dL)
- Serum triglyceride level ≤ 2.5 mmol/L (< 220 mg/dL)


### 4S Main Results

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Simvastatin better</th>
<th>Placebo better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>256</td>
<td>182</td>
</tr>
<tr>
<td>CHD mortality</td>
<td>189</td>
<td>111</td>
</tr>
<tr>
<td>Major CHD event</td>
<td>622</td>
<td>431</td>
</tr>
<tr>
<td>Any CHD event</td>
<td>927</td>
<td>708</td>
</tr>
<tr>
<td>Any atheroscl. event</td>
<td>1,023</td>
<td>796</td>
</tr>
<tr>
<td>CABG or PTCA</td>
<td>383</td>
<td>252</td>
</tr>
</tbody>
</table>

Relative Risk (95% Confidence Intervals)

5
**Survival**

Survival analysis showing the proportion of patients alive over time with Simvastatin and Placebo treatments. Log-rank test statistic is $P = 0.0003$.

Patients at Risk at the beginning of each year:

**Simvastatin Survival Study**

Risk of Coronary Mortality

- Placebo (n = 2223)
- Simvastatin (n = 2221)

Cumulative Coronary Deaths over years since randomization.

Years since randomization:
- $P < 0.0001$

Risk of coronary mortality (secondary endpoint) was reduced by 42%.

Data on file, Merck & Co., Inc.


What is the Relationship between LDL-C and CHD Risk?
Total Cholesterol Distribution: CHD vs Non-CHD Population

Framingham Heart Study—26-Year Follow-up

35% of CHD Occurs in People with TC <200 mg/dL

Total Cholesterol (mg/dL)

CHD vs Non-CHD Population

Cholesterol Levels and CHD Risk

Possible Relationship between LDL-C Levels and CHD Risk (2001)
ELIGIBILITY: MRC/BHF Heart Protection Study

- Increased risk of CHD death due to prior disease:
  - Myocardial infarction or other coronary heart disease;
  - Occlusive disease of non-coronary arteries; or
  - Diabetes mellitus or treated hypertension
- Age 40-80 years
- Total cholesterol $\geq 3.5$ mmol/l ($\geq 135$mg/dl)
- Statin or vitamins not considered clearly indicated or contraindicated by patient’s own doctors

PRIOR DISEASE at BASELINE

<table>
<thead>
<tr>
<th>Prior disease</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any MI</td>
<td>8510</td>
<td>41%</td>
</tr>
<tr>
<td>Other CHD</td>
<td>4876</td>
<td>24%</td>
</tr>
<tr>
<td>No CHD*</td>
<td>7150</td>
<td>35%</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>1820</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>2701</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3982</td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>20,536</td>
<td>100%</td>
</tr>
</tbody>
</table>

* Overlap between categories within "No CHD" group.
Heart Protection Study (HPS)
Range of LDL-C Levels at Entry

HPS: Reduction in Major Vascular Events
According to Baseline LDL-C (mg/dL)

HPS: Major Vascular Events in Upper and Lower Thirds of Baseline LDL
Prove-It (TIMI - 22)

- Statin therapy is highly effective vs. placebo in long-term treatment of CHD
  - Are statins effective in reducing events in patients with an acute coronary syndrome (ACS)?
  - Does “intensive” LDL-C lowering to an average of 65 mg/dL achieve a greater reduction in clinical events than “standard” LDL-C lowering to an average of 95 mg/dL?

PROVE IT - TIMI 22:
Study Design

4162 patients with an Acute Coronary Syndrome < 10 days
- Double-blind:
  - ASA + Standard Medical Therapy
  - Intensive Therapy: Atorvastatin 80 mg
  - Standard Therapy: Pravastatin 40 mg
- 2x2 Factorial: Gatifloxacin vs. placebo
- Duration: Mean 2 year follow-up (>925 events)
- Primary Endpoint: Death, MI, Documented UA requiring hospitalization, revascularization (> 30 days after randomization), or Stroke

Patient Population

- Inclusion Criteria:
  - Hospitalization for acute MI or high-risk unstable angina < 10 d
  - Total cholesterol ≤ 240 mg/dL (< 200 mg/dL if on Lipid ↓ Rx)
  - Stabilized (i.e., without ischemia, CHF, post PCI if performed)

- Major Exclusion Criteria:
  - Co-morbidity: patient survival < 2 years
  - Current therapy with simvastatin or atorvastatin 80 mg
  - Need for, or anticipated use of fibrates or niacin
  - CABG for treatment of qualifying ACS
  - Liver disease or unexplained CK elevations
  - Strong inhibitors of CYP450 3A4 (2’atorvastatin metabolism)
Changes from (Post-ACS) Baseline in Median LDL-C

<table>
<thead>
<tr>
<th></th>
<th>LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin 40mg</td>
<td>21% ↓</td>
</tr>
<tr>
<td>Atorvastatin 80mg</td>
<td>49% ↓</td>
</tr>
</tbody>
</table>

P < 0.001

All-Cause Death or Major CV Events in All Randomized Subjects

% with Event

Heart Protection Study (5-Year Trial)

26% Reduction in CVD

22% Reduction in CVD

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

- This relationship is consistent with a large body of epidemiologic 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 in proportion by about 30%.
- The relative risk is set at 1.0 for LDL-C = 40 mg/dL.


Optimal Low-Density Lipoprotein Is 50 to 70 mg/dl

Lowery Is Better and Physiologically Normal

James H. O’Keefe, Jr, MD; Lona Cecelia, PA-C; William H. Harris, MD*; Ralph L. Moore, MD; Robert Vogel, MD

Kansas City, Missouri; Fort Collins, Colorado, and Baltimore, Maryland

The current lipoprotein (LDL) cholesterol range is 70 to 100 mg/dL for active healthy patients, patients under stress, for young persons, and for well-controlled diabetic patients. For all other persons, LDL cholesterol less than 100 mg/dL should be achieved in the total range of 70 to 100 mg/dL. The most effective way to reduce LDL cholesterol is to achieve a target LDL cholesterol level of less than 100 mg/dL with a combination of diet, exercise, and medications.

What’s New for High-Risk Patients?

- ATP III LDL-C goal: <100 mg/dL
  - For very high risk: optional goal <70 mg/dL
  - For LDL-C ≥100 mg/dL, start LDL-lowering drug simultaneously with lifestyle changes
  - For LDL-C <100 mg/dL, LDL-lowering drug is a therapeutic option
  - For high TG/low HDL-C, consider fibrate or nicotinic acid in combination with LDL-lowering drug

Candidates for Very Low LDL-C Goal of <70 mg/dL

- Very high risk patients
  - Established atherosclerotic CVD
    - + multiple risk factors (esp. diabetes)
    - + severe and poorly controlled risk factors (e.g., cigarette smoking)
    - + metabolic syndrome (high TG, low HDL-C)
    - + acute coronary syndromes (PROVE IT)

What’s New for Moderately High Risk Patients?

- ATP III LDL-C goal: <130 mg/dL
- LDL-C level ≥130 mg/dL: start drug with diet Rx
- New therapeutic option: LDL-C goal <100 mg/dL
- LDL-C level 100–129 mg/dL: drug therapy optional
Lifestyle-Related Risk Factors (High or Moderately High Risk)

- Treat lifestyle-related risk factors, regardless of LDL-C level
  - Obesity
  - Physical inactivity
  - Elevated triglyceride
  - Low HDL-C
  - Metabolic syndrome

For people in lower-risk categories, recent clinical trials do not modify the treatment goals and cutpoints of therapy

Many Patients Have LDL-C in Excess of Optimal Levels

- NCEP ATP III considers LDL-C <100 mg/dL as optimal for all patients.\(^1\)
- Less than one quarter of people in the United States have LDL-C <100 mg/dL.\(^2,3\)

NCEP ATP = National Cholesterol Education Program Adult Treatment Panel.
In a Process of Care Study, Many Patients Did Not Achieve LDL-C Goal

- 2829 high-risk patients with CHD and/or diabetes
- Baseline LDL-C = 150 mg/dL
- 6-month follow-up
- Most patients not at goal were titrated once
- More patients may have achieved goal with additional titrations


Pharmacologic Therapy: Statins—Dose Response

<table>
<thead>
<tr>
<th>Statin</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
<th>% Reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin 20/80 mg</td>
<td>19</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin 20/80 mg</td>
<td>31</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Simvastatin 20/80 mg</td>
<td>27</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Pravastatin 20/80 mg</td>
<td>35</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 10/80 mg</td>
<td>37</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 10/40 mg</td>
<td>46</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>

*Pravachol® (pravastatin) PI.

Lipid Lowering Therapy

Quantitative Cholesterol Balance

- Intake of cholesterol (300 mg/day)
- Intake of dietary fat (1500 mg/day)
- Synthesis of cholesterol (100 mg/day)
- Cholesterol synthesis from Acyl CoA
- HDL, LDL, VLDL, Chol, Acyl CoA

Liver

[Diagram showing cholesterol balance and pathways]
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Professor and Vice Chair of Pharmacy Practice
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University of the Pacific, Stockton
VA San Diego Healthcare System
San Diego, California

Matthew K. Ito is Professor and Vice Chair of Pharmacy Practice and Director of the Southern California Clinical Experience Program at the University of the Pacific. Dr. Ito practices and conducts his research at the VA Medical Center in San Diego where he is Director of the Cardiac Rehabilitation Cholesterol Clinic and the Cardiovascular Pharmacodynamics Laboratory. Dr. Ito has trained research fellows since 1995. Dr. Ito received his Doctorate in Pharmacy degree in 1986 at the University of Southern California, where he also completed a post-doctoral residency and fellowship.

Dr. Ito has been a faculty member at the University of the Pacific for 16 years and is responsible for the student clerkship program in San Diego and supervises 7 full and part-time off-campus faculty members in the Southern California area and Hawaii. Dr. Ito’s research interests are the effects of lipid modifying agents on endothelial dysfunction, pharmacokinetics, pharmacodynamics, and clinical outcomes research. Much of Dr. Ito’s efforts have focused on designing various programs to narrow the cholesterol treatment in the veteran population. Dr. Ito has attracted close to $600,000 in research grants, has published over 60 research papers, review articles, and abstracts in both the pharmacy and medical literature and has given over 200 presentations to professional audiences at the local, state, and national levels.

Dr. Ito is active in national medical and pharmacy organizations. He is a member and fellow of the American College of Clinical Pharmacy and the Southern California College of Clinical Pharmacy. He is also a member of the Council on Arteriosclerosis, Thrombosis & Vascular Biology for the American Heart Association and the Northeast Lipid Association.
Meeting the Challenge in Clinical Practice: Combining Efforts to Reduce Cholesterol and Cardiovascular Risk

In the time since the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) was published in 2001, the results of five major clinical trials of statin therapy with clinical endpoints have been released. These trials addressed issues that were not examined in previous clinical trials of cholesterol-lowering therapy. Modifications to the ATP III treatment recommendations and goals based on the findings of these trials were published in 2004 and will be highlighted in this educational symposium. The findings of clinical trials evaluating the efficacy of combination therapy involving a statin plus another cholesterol-lowering agent (niacin, a fibrate, or ezetimibe) in patients who fail to achieve LDL cholesterol goals with a single agent also are presented. The symposium will provide a comprehensive update for pharmacists managing cholesterol-lowering therapy in patients who do not achieve recommended LDL cholesterol goals using monotherapy.
Meeting the Challenge in Clinical Practice: Combining Efforts to Reduce Cholesterol and Cardiovascular Risk

**ATP III: Updated LDL-C Goals and Treatment Cutpoints**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: CHD or CHD risk equivalents* (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL (optional: &lt;70 mg/dL)†</td>
<td>≥100 mg/dL‡</td>
<td>≥100 mg/dL (consider drug options)</td>
</tr>
<tr>
<td>Moderately high risk: ≥2 risk factors (10-year risk 10%–20%)</td>
<td>&lt;130 mg/dL (optional: &lt;100 mg/dL)</td>
<td>≥130 mg/dL‡</td>
<td>≥130 mg/dL (100–129 mg/dL: consider drug options)</td>
</tr>
</tbody>
</table>

*CHD risk equivalents: clinical manifestations of noncoronary forms of atherosclerotic disease (brachial ischemic attacks or occlusion of cardiac origin >50% obstruction in 1 carotid artery or >50% obstruction in both carotid arteries), diabetes, and ≥2 risk factors with 10-year risk >20% for hard CHD.
†The optional LDL-C goal of <70 mg/dL is favored in those at very high risk (eg, people with diabetes, smokers) as well as those with metabolic syndrome, acute coronary syndrome, high TG, and/or non–HDL-C <100 mg/dL.
‡Any person at high or moderately high risk with lifestyle-related risk factors is a candidate for TLC to modify these risk factors regardless of LDL-C level.

### Distribution of Type of Therapy in Patients with an LDL-C Goal of < 100 or 70 mg/dL (33%)

Data derived from patients seen at the Cardiac Rehabilitation Cholesterol Clinic at the VA San Diego Medical Center since publication of NCEP III Update (67% at goal)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Monotherapy</th>
<th>2 drugs</th>
<th>3 drugs</th>
<th>4 drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>20</td>
<td>33</td>
<td>40</td>
<td>7</td>
</tr>
</tbody>
</table>

No. MK. Data on file 10/22/04

### Major Endpoint Lipid Lowering Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>LDL-c Δ</th>
<th>CHD Risk</th>
<th>CHD Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>Lova</td>
<td>-3%</td>
<td>156-115</td>
<td>25%</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>Prav</td>
<td>14.9%</td>
<td>192-142</td>
<td>26%</td>
</tr>
<tr>
<td>FDAP/PRGCAPS</td>
<td>Lova</td>
<td>3.2%</td>
<td>196-115</td>
<td>45%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Pravastatin</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to death (yr)</td>
<td>5,170</td>
<td>5,185</td>
</tr>
<tr>
<td>Cumulative rate (%)</td>
<td>5,086</td>
<td>5,194</td>
</tr>
<tr>
<td>No. at Risk</td>
<td>Pravastatin</td>
<td>Usual Care</td>
</tr>
<tr>
<td>Time to death (yr)</td>
<td>4,809</td>
<td>4,845</td>
</tr>
<tr>
<td>Cumulative rate (%)</td>
<td>4,845</td>
<td>4,854</td>
</tr>
</tbody>
</table>

-26% -27%

*NIAID*: Total cholesterol; *Nonfatal MI or CHD death

### ALLHAT-LLT: All-Cause Mortality

9.6% difference in total cholesterol

RR, 0.99; 95% CI, 0.89-1.11; P<0.88

Reduction in CHD Risk with Lipid Lowering Therapy

![Graph showing reduction in CHD risk with lipid lowering therapy.]

- Larger LDL-C reductions
- Other lipid parameters
- Non-lipid parameters (e.g., Homocysteine)
- Statin non-responders
- Plant sterols

LDL-C Efficacy of Different Treatment Strategies

<table>
<thead>
<tr>
<th></th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>EZE 10 /SIMVA¹</td>
<td>-47%</td>
<td>-52%</td>
<td>-55%</td>
<td>-60%</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin²</td>
<td>-37%</td>
<td>-43%</td>
<td>-48%</td>
<td>-51%</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin²</td>
<td>-42%³</td>
<td>-46%</td>
<td>-52%</td>
<td>-55%</td>
<td></td>
</tr>
</tbody>
</table>

³ Am J Cardiol 2003;91:33-41.

Ezetimibe: Mechanism of Action

- Selectively blocks uptake of dietary/biliary cholesterol and structurally-related phytosterols by intestinal enterocytes
- Inhibits absorption through a mechanism dependent on NPC 1L1 protein
- Does not reduce absorption of lipid-soluble vitamins or steroid hormones
- Reduces cholesterol content of chylomicrons
Ezetimibe: Pharmacology

- Glucuronidated in the intestine
  - Glucuronidated metabolite retains activity
- Glucuronidate and parent compound are excreted in the bile and circulate enterohepatically
  - Repeated delivery to the intestinal brush border
  - Minimized systemic exposure and potential for adverse effects
- Long half-life (22 hours)


Ezetimibe Add-on to Statin for Effectiveness Trial (EASE)

Entry Criteria
- LDL-C level above NCEP-ATP III guidelines after ≥5 weeks of statin therapy
- TG ≤350 mg/dL

Original statin treatment + ezetimibe 10 mg (n=2020)  
Original statin treatment + placebo (n=1010)

Primary end point: percent reduction in LDL-C and percent of patients reaching their NCEP-ATP III LDL-C goal after 6 weeks


Ezetimibe Add-On to Statin for Effectiveness Trial (EASE): LDL-C Reduction

% Change at 6 weeks

<table>
<thead>
<tr>
<th>CHD/CHD risk equivalent</th>
<th>Total</th>
<th>≥2 RFs</th>
<th>&lt;2 RFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin + placebo (n=1010)</td>
<td>-25.8</td>
<td>-25.1</td>
<td>-23.8</td>
</tr>
<tr>
<td>Statin + ezetimibe 10 mg (n=2020)</td>
<td>-25.1</td>
<td>-4.1</td>
<td>-5.8</td>
</tr>
</tbody>
</table>

* * * *

P<0.001 vs placebo.

### EASE: LDL-C Goal Attainment

<table>
<thead>
<tr>
<th>% Change at 6 weeks</th>
<th>Total</th>
<th>CHD/CHD risk equivalent</th>
<th>&gt;2 RFs</th>
<th>&lt;2 RFs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>52.4</td>
<td></td>
<td></td>
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<td>90.7</td>
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</tbody>
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*<p value>0.001 vs placebo.

Statin + placebo (n=1010)
Statin + ezetimibe 10 mg (n=2020)


### Variability of Cholesterol Absorption Among Individuals

- Number of patients: N=94.

### High Cholesterol Absorption Efficiency (cholesterol to cholestane ratio) and Relative Risk of Major Coronary Events From 4S

Initial LDL-c Response to Statin Therapy Predicts Subsequent Response to the Addition of Ezetimibe

\[
\Delta \text{ezetimibe (actualLDL-predictedLDL)} = \Delta \text{statin (actualLDL-predictedLDL)}
\]


Ongoing Surrogate and Clinical End Point Trials With Ezetimibe/Statin Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>Treatment</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENHANCE(^1)</td>
<td>Heterozygous FH</td>
<td>Ezetimibe 10 mg/simvastatin 80 mg vs. simvastatin 80 mg</td>
<td>Progression of intima media thickness</td>
</tr>
<tr>
<td>SEAS(^2)</td>
<td>Aortic Stenosis (N=1400)</td>
<td>Ezetimibe 10mg/simvastatin 40 mg vs. placebo</td>
<td>Progression of aortic stenosis, Major CV events</td>
</tr>
<tr>
<td>SHARP(^3)</td>
<td>Chronic kidney disease (N=9000)</td>
<td>Ezetimibe/simvastatin vs. simvastatin</td>
<td>Major vascular events (MI, cardiac death, stroke, or revascularization)</td>
</tr>
</tbody>
</table>

3. ENHANCE=Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression
   SHARP=Study of Heart and Renal Protection
   SEAS=Simvastatin and Ezetimibe in Aortic Stenosis

HATS: Lipid Outcomes

HATS: Efficacy

Primary End Point: Angiographic Outcomes
Secondary End Point: Clinical Outcomes

Mean change in CIMT at baseline and 12 months during treatment with either placebo or extended release niacin (1 gm) added to stable statin therapy

Combination of Statin and Fibrate: Effect on Lipid Levels

All patients (N=12) received fenofibrate 200 mg monotherapy for 6 weeks, followed by atorvastatin 40 mg monotherapy for 6 weeks. Patients then received atorvastatin/fenofibrate combination therapy for 6 weeks.

* P<0.01 vs baseline; † P<0.05 vs baseline.
VA HIT: Favorable Effects of Fibrate on CVD Events in CHD Patients With Isolated Low HDL-C

Subjects: 2,531 men
Age: ≤74 (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 bid


Action to Control Cardiovascular Risk in Diabetes (ACCORD): Study Design

10,000 type II diabetes patients

Primary end point: Major CVD (MI, stroke, CVD death)


Sitosterol and CHD Risk: PROCAM

PROCAM = Prospective Cardiovascular Munster study.
Phytosterols are Poorly Esterified in Macrophages

Accelerated Phytosterol-Induced CAD Hypothesis

What can we do?

- Improve implementation of guidelines
  - Education/motivation of patients and providers
  - Palm pilots based programs
  - Global risk - scoring aids
  - Identify high - risk patients
- Help to identify patients with unmet treatment goals
  - Poor adherence
  - Dose titration
  - Combination drug therapy
  - Lack of treatment
- Educate providers on emerging drug therapies
What can we do (cont.)?

- Formulary management
  - Cost-effective agents
  - Sound formulary guidelines
- Intervention programs
  - Lipid clinics
  - Disease state management programs

Summary

- The increased use of combination drug therapy is needed to meet the current LDL-C targets especially in those patients who are at the highest risk.
- Dual inhibition of cholesterol synthesis and absorption provides significantly greater improvements in lipids and LDL-C goal attainment vs statin monotherapy and data suggest it may be particularly useful in statin hypo-responders.
- Combination of statins with niacin or fibrates provides significantly greater improvements in TG and HDL-C vs statin monotherapy and may reduce the residual risk of CHD.
- Pharmacists can effectively reduce the cardiovascular risk of hypercholesterolemia through pharmaceutical care services and education.

Question and Answer Period

We invite your questions. Please stand and approach the nearest aisle microphone.

Please complete both sides of the evaluation form in your handout booklet. Staff will collect the evaluations as you exit quietly.

Thank you for your attendance and be sure to join us again tomorrow morning.
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**Self-Assessment Test**

**New Clinical Guidelines for Aggressive Cholesterol Management:**
**Strategies for Meeting the Challenge**

This program is located at [http://symposia.ashp.org/cemornings](http://symposia.ashp.org/cemornings)

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1. The new paradigm for treating coronary artery disease incorporates which of the following therapeutic modifications?

   a. The use of newer agents such as ezetimibe instead of statins.
   b. PCI for patients whose LDL-C levels exceed 100 mg/dl.
   c. The use of lipid-lowering agents, aspirin, and ACE inhibitors in addition to PCI and CABG.
   d. Revascularization as the primary therapeutic modification.

2. Recent updates to the NCEP/ATP III guidelines suggest which of the following LDL-C levels as an optional goal for very high-risk patients?

   a. < 50 mg/dl
   b. < 70 mg/dl
   c. < 90 mg/dl
   d. < 100 mg/dl

3. In contrast with older studies indicating that CAD risk rises more steeply with increasing LDL-C concentrations, more recent clinical evidence shows that the relationship between LDL cholesterol and CHD is:

   a. Curvilinear
   b. Exponential
   c. Log-linear
   d. There is no evidence of increased risk with diabetes.

4. What grade of coronary artery stenosis is present in the majority of patients experiencing an MI?

   a. >90%
   b. 70% - 90%
   c. 50% - 70%
   d. < 50%

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5. Many patients do not reach their LDL-C goal during their first 26 weeks of statin treatment, probably because of:
   a. The need for dual inhibition of cholesterol absorption and production.
   b. Poor compliance with statin therapy.
   c. Inadequate weight loss.
   d. Rapid escalation of statin dosing.

6. Candidates for reduction of LDL-C to a goal of less than 70 mg/dl include all of the following EXCEPT:
   a. High-risk patients with elevated triglycerides and low HDL-C.
   b. High-risk patients with established atherosclerotic CVD.
   c. Moderate-risk patients with hypertension.
   d. High-risk patients with diabetes and other risk factors.

7. Why are fibrates and niacin sometimes given in combination with statin therapy?
   a. Dose response to statins is curvilinear.
   b. Fibrates and niacin increase HDL-C and reduce triglyceride levels.
   c. Statins decrease levels of HDL-C.
   d. Statins do not affect cholesterol synthesis in the liver.

8. Statins reduce LDL-C by decreasing cholesterol synthesis. What is the mechanism of action of ezetimibe?
   a. Blocks cholesterol absorption
   b. Sequesters bile acids
   c. Increases HDL synthesis
   d. Decreases triglyceride synthesis

9. When ezetimibe was added to statin therapy during the EASE trial, patients experienced an additional LDL reduction of:
   a. 10%
   b. 15%
   c. 20%
   d. 25%
Self-Assessment Test
New Clinical Guidelines for Aggressive Cholesterol Management: Strategies for Meeting the Challenge

This program is located at http://symposia.ashp.org/cemornings

10. Which of the following statements is true?
   a. Statin hypo-responders tend to be hyper-responders to ezetimibe monotherapy.
   b. Statin hypo-responders tend to be hyper-responders to ezetimibe + statin combination therapy.
   c. Patients who are low synthesizers of cholesterol respond well to statin therapy.
   d. Statin hyper-responders do not benefit from combination therapy with agents such as ezetimibe, fibrates, and niacin.

11. Which of the following is NOT an appropriate role for pharmacists in the management of patients with hypercholesterolemia?
   a. Improve implementation of guidelines.
   b. Identify high-risk patients.
   c. Encourage statin patients to add OTC fibrate therapy.
   d. Educate providers on emerging drug therapies.