Advances in Dyslipidemia Diagnosis & Management:

A Short-course for Registered Dietitians & Nutritionists

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U.S. Indian Health Service, Albuquerque NM
Three part series

I. 7:45 – 10:00 a.m. Friday
II. 1:15 – 3:15 p.m. Friday
III. 10:45 – 12:45 a.m. Saturday
Course Curriculum

Lipids, Lipoproteins and Atherosclerosis

Diagnosis of dyslipidemia: essential diagnostic categories

Clinical Trials Overview

NCEP Guidelines overview

Nutrition and dietary management of dyslipidemia

Pharmacologic therapy

Physical activity intervention and dyslipidemia

Laboratory assessment of dyslipidemia

The Identification and Management of Cardiometabolic Risk
SCAN LIPID PROGRAM AGENDA

Introduction 15 min

The ACCL and BCCL certifications and competencies
Opportunities for RD’s and nutritionists
Important Resources

Atherosclerosis, lipids and lipoproteins 30 min I

Diagnostic categories of dyslipidemia 30 min

Clinical Trials Overview 45 min

NCEP (ATP III/IV) Guidelines overview 15 min

NCEP dietary recommendations/nutrition and dyslipidemia 90 min II

Nutrient-drug interactions 15 min

Exercise and Dyslipidemia 20 min

Pharmacologic Therapies and Treatment Targets 40 min

Laboratory assessment of lipids and lipoproteins 30 min III

Cardiometabolic Risk Assessment 15 min

Q & A and Wrap-Up 15 min

Total contact teaching hours for: 6.0 hours (three 2 hour segments)
The National Lipid Association defines “clinical lipidology” as a multidisciplinary branch of medicine focusing on lipid and lipoprotein metabolism and their associated disorders.
There are two professional boards involved with credentialing those in clinical lipidology:

- **American Board of Clinical Lipidology (ABCL)** *physicians*
- **Accreditation Council for Clinical Lipidology (ACCL)** *nonphysicians*
Certification and Competency Exams

www.lipid.org

**ABCL**
American Board of Clinical Lipidology

**ACCL**
Accreditation Council for Clinical Lipidology

*CLS*
Clinical Lipid Specialist

**BCCL**
Basic Competency in Clinical Lipidology

- Lipid Academy (lipid mgmt train. Course)
- Four-volume SAP manuals
RDs Strive for Excellence

Demonstrate Your Expertise by Achieving Certification as a Clinical Lipid Specialist

The ACCL Offers Two Pathways to Recognition:

I. The Clinical Lipid Specialist (CLS) Certification Program is open to licensed RDs with advanced knowledge, experience and/or interest in specializing in lipid management.

II. The Basic Competency in Clinical Lipidology (BCCL) Exam is a competency assessment and credentialing pathway open to any healthcare professional with basic involvement in the lipid field.

Select a pathway that matches your professional goals. ACCL exams will evaluate and validate the specialized knowledge and training required to practice in the dynamic and multifaceted field of lipid management.

Demonstrate your professional commitment to the prevention of cardiovascular disease and document your expertise for patients, colleagues and employers.

"I was asked to join a multidisciplinary team focused on chronic disease management as the lipid specialist. Through this I gained a new level of respect from my teammates. Clinicians now consult me for the best lipid management tactics for their patients through which I have increased job security as I am the only registered dietitian certified as a Clinical Lipid Specialist in my state."

Julie Bolick, RD, MS, CD, CLS
Salt Lake City, Utah

Learn more at
www.lipidspecialist.org
Phone: 904.309.6250
NLA SAP
Edition III
2012

Volume I: BASIC LIPOPROTEIN METABOLISM, DIAGNOSIS AND TREATMENT OF DYSLIPIDEMIAS
Volume II: MANAGEMENT OF CARDIOMETABOLIC RISK, BIOMARKERS OF ATHEROSCLEROSIS, EPIDEMIOLOGY AND STATISTICS, AND CLINICAL TRIALS
Volume III: COMPLEX CASE MANAGEMENT AND ADVANCED PHARMACOLOGY
Volume IV: VASCULAR BIOLOGY, ADVANCED LIPID METABOLISM AND LIPOPROTEIN BIOCHEMISTRY

Order at: (904) 998-0854 or e-mail CME@lipid.org.
This 1.5-day (12 hour) course provides a comprehensive indoctrination to lipid science and essential information for the systematic management of dyslipidemia and the metabolic syndrome. The curriculum covers basic competencies in Lipidology and sets the stage for effectively working in a lipid clinic setting. Elevate your knowledge of the fundamentals while preparing for more advanced training and/or a certification pathway such as the Certified Lipid Specialist or Basic Competency in Clinical Lipidology program.

**Course Curriculum**
- Lipids, Lipoproteins and Atherosclerosis
- Clinical Trials Overview
- Diagnosis, Clinical Appraisal and Treatment Targets
- Nonpharmacologic Therapies
- Pharmacologic Therapies and Treatment Guidelines
- Advanced Risk Assessment and Management of Residual Risk
- The Identification and Management of Cardiometabolic Risk
Introduction

Lipid Academy Online is a user-friendly, tech-savvy adaptation of the NLA's live training course. This series of 7 interactive modules provides a comprehensive introduction to lipid science and essential information for the systematic management of dyslipidemia and the metabolic syndrome. The one-of-a-kind course covers the core competencies in Lipidology, while preparing you to work more effectively in clinical practice.

The Lipid Academy online learning platform allows you to learn at your own pace, without travel expenses. The program features slide-audio presentations recorded by our expert faculty, along with evidence-based lecture notes and references, embedded assessment questions to reinforce your learning, and a robust collection of resource materials for further study.

What to Expect Before Getting Started

The Lipid Academy Online provides you with a comprehensive lipid education resource center and personalized professional development experience. Within this space, you will find:

- Multimedia slide lecture modules (with downloadable PDFs of slide-audio presentation modules with evidence-based notes and references)
- Learning Reinforcement Test Questions and Answers at the Completion of Each Module
- A Complete Pre- and Post-Test to determine your achievement of the educational objectives for the program
- A personalized My Learning Dashboard containing your assignments, transcript and assessment scores
- A Glossary of Common Terms and Common Abbreviations
- Key Clinical Studies List
- A complete list of References per Module
- Links to Additional Educational Resources
- A Program Evaluation
- A Certificate of Completion at the conclusion of the program

Features and Benefits

- Complete lectures and slides from the live course in synchronized presentations
- Participate from anywhere—on your own schedule, with no travel costs or time away from your family and patients
- Downloadable audio versions for learning on the go
- Earn CME/CE credit eligible for certification in Clinical Lipidology
- Bonus online resources and tools to enhance your learning and practice

System Requirements

To view this educational activity you will need a JavaScript enabled web browser (Google Chrome, Firefox version 3.0 or greater OR Internet Explorer version 8.0 or greater recommended) with Browser Cookies enabled and Adobe Flash™ version 9.0 or greater.

NLA Professional Development Pathway

Level 2 | CORE

Lipid Academy™ serves as an entry point to the NLA professional development track and addresses the core competencies delineated in the NLA Core Curriculum in Clinical Lipidology. This curriculum identifies and defines areas of knowledge important to the delivery of quality care and serves as a basis for the content of the certification examinations in Clinical Lipidology.

*For details on participating in a live NLA Lipid Academy course, click here.
Job Functions/Opportunities for RD Clinical Lipid Specialists

• Independent referrals from level 1 and 2 lipid clinics

• Lipid clinic staff member

• Specialization in dietary management of specialized lipid and lipoprotein disorders, e.g.,
  Familial hypercholesterolemia, PCOS, familial hypertriglyceridemia, mixed hyperlipidemia, hyperchylomicronemia, diabetic dyslipidemia

• Opportunity to incorporate anthropometric assessment and exercise recommendations into comprehensive lifestyle dyslipidemia management program
What are the key areas of lipidology that dietitians need to be familiar with?

- Lipid and lipoprotein disorder categories
- Current NIH Guidelines
- Pharmacology
- Key clinical trials
- Lifestyle specifics
- Laboratory assessment
- Resources
Clinical Lipidology

Bare Essentials
Characterized by:
- Surface apoproteins
- Density
- Chemical constituents, e.g., TG-CE content
APOLIPOPROTEINS

- Structural support
- Enzymatic triggers
- Ligand for receptor binding (apo B, E, A-1)
<table>
<thead>
<tr>
<th>Major core lipids</th>
<th>High Density</th>
<th>Low Density</th>
<th>Very Low Density</th>
<th>Chylo-microns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apolipoproteins</td>
<td>A-I, A-II E, Cs</td>
<td>B-100</td>
<td>B-100, Cs, E</td>
<td>B-48, Cs, E A-I, A-II</td>
</tr>
<tr>
<td>Relative sizes</td>
<td>HDL₂</td>
<td>Cholesteryl ester</td>
<td>Triglyceride</td>
<td>Triglyceride</td>
</tr>
<tr>
<td></td>
<td>HDL₃</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non HDL-C (apoB)
Lipolytic Cascade for Lipoproteins

Lipoproteins are quasi discrete structures. Interconversions of lipoprotein subfractions are a continuum that extends across the spectrum of intermediates that may begin for example with VLDL and end with a mature product LDL.

*Gotto A, 2002*
Atherogenesis and Lipids
Development of Human Coronary Atherosclerosis

Intimal thickening
Intimal xanthoma
Pathologic intimal thickening
Fibrous cap atheroma
Thin-cap Fibroatheroma

FC = fibrous cap
LP = lipid pool
NC = necrotic core

Ladich ER 2011
Fibrous cap atheroma
First advanced lesion atherosclerosis

Necrotic core contains cholesterol esters, free cholesterol, phospholipids, TG, necrotic debris
Fibrous cap consists of SMC in a proteoglycan collagen matrix

Ladich ER 2011
Consistency and vulnerability to rupture of coronary plaques

Braunwald 2007
Coronary Artery Calcium Progression: An Important Clinical Measurement?

McEvoy J et.al. JACC. 2010;56:1613  JHU
Calcification is a good marker for plaque burden but correlation between plaque instability and absolute calcium score has not been demonstrated.

Aggressive management of lipids and/or lifestyle has also demonstrated no significant effect on CC although several have shown a trend for slowing progression of CC.

Venkatesan S, 2011; McEvoy 2010
Lipid and Lipoprotein Targets

Important Dyslipidemias
Current Therapeutic Lipid Targets
NCEP ATP III

- LDL Cholesterol
- HDL Cholesterol *
- Triglycerides
- Non HDL-C
- LDL-P
- Apo B
- C-reactive protein
- Lp(a)
- LpPLA2
- Homocysteine
- Fibrinogen
- Oxidized LDL-C
- Calcium score, EBCT
- Apo protein isoforms
- Others

* Under scrutiny as target
Lipoprotein subclasses
Atherogenic Particle Focus

Non-HDL-C
(apo B, LDL-P)

Chylomicron Remnants

Chylomicrons

Lp(a)

LDL

IDL

VLDL

Diameter (nm)

Density (g/ml)
### FREDRICKSON, LEVY, LEES CLASSIFICATION SCHEME FOR LIPID/LIPOPROTEIN DISORDERS

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Lipid Elevation (primary)</th>
<th>Lipoprotein Elevation (primary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Triglycerides</td>
<td>Chylomicrons</td>
</tr>
<tr>
<td>Type IIA</td>
<td>Cholesterol</td>
<td>LDL</td>
</tr>
<tr>
<td>Type IIB</td>
<td>Cholesterol &amp; Triglycerides</td>
<td>LDL &amp; VLDL</td>
</tr>
<tr>
<td>Type III</td>
<td>Cholesterol &amp; Triglycerides</td>
<td>Beta-VLDL (VLDL &amp; Chylomicron remnants)</td>
</tr>
<tr>
<td>Type IV</td>
<td>Triglycerides</td>
<td>VLDL</td>
</tr>
<tr>
<td>Type V</td>
<td>Triglycerides</td>
<td>Chylomicrons &amp; VLDL</td>
</tr>
</tbody>
</table>

Chylomicrons present/predominant: Triglycerides $\geq 1500$ mg/dL
Beta VLDL present: VLDL/Triglycerides $> 0.30$
Examples of Relatively Complex Dyslipidemias

1. Familial hypercholesterolemia
2. Familial hypertriglyceridemia
3. Familial combined hyperlipidemia
4. Chylomicronemia
5. Familial hypoalphalipoproteinemia
6. Familial dysbetalipoproteinemia
7. Hypobetalipoproteinemia
8. Lipoprotein lipase deficiency
9. Therapeutically resistant dyslipidemias

Diagnostic methods:
- Blood labs
- Cutaneous & ophthalmologic expressions
- Genotype
Estimated Prevalence of Dyslipoproteinemias

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial heterozygous hypercholesterolemia</td>
<td>1/300-500</td>
</tr>
<tr>
<td>Familial homozygous hypercholesterolemia</td>
<td>1/1,000,000</td>
</tr>
<tr>
<td>Familial defective apolipoprotein B-100</td>
<td>1/500</td>
</tr>
<tr>
<td>Polygenic hypercholesterolemia</td>
<td>1/10 - 1/20</td>
</tr>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>1/150</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia</td>
<td>1/100 - 1/300</td>
</tr>
<tr>
<td>Familial hypobetalipoproteinemia</td>
<td>1/500 heterozygotes</td>
</tr>
<tr>
<td>Familial lipoprotein lipase deficiency (type I, CmS)</td>
<td>1/100,000</td>
</tr>
<tr>
<td>Familial dysbetalipoproteinemia (type III)</td>
<td>1/5,000</td>
</tr>
<tr>
<td>Familial hypoalphalipoproteinemia</td>
<td>1/50</td>
</tr>
<tr>
<td>Excess lipoprotein (a)</td>
<td>1/3</td>
</tr>
<tr>
<td>Sitosterolemia</td>
<td>1/1,000,000</td>
</tr>
<tr>
<td>Homocysteinuria</td>
<td>1/100</td>
</tr>
</tbody>
</table>

Gotto A Manual of Lipid Disorders 2009
John Guyton, 2005
LaForge 2012
Polygenic vs Complex Dyslipidemia
**Polygenic hypercholesterolemia**
(nonfamilial hypercholesterolemia, ICD-9 272.0; ICD-10 E78.0)

**Susceptible genotype**
- Dietary trans and saturated fat, weight gain
- TC - 240-350 mg/dL
- LDL - >160
- TG nml
- no family history
- no xanthomases
- premature CAD

**Complex hypercholesterolemia**
ICD 9 272.2-5; ICD 10 – E78.2-5

- Genetic defects, insulin resistance, metabolic syndrome, or combination
- Very high LDL-C, or
- Very high TG, or
- Combined dyslipidemia
- Very low HDL-C
- Xanthomases and/or corneal arcus
- Premature CAD
Familial Hypercholesterolemia

Heterozygous or Homozygous
Tendonous xanthomas

*Male 40 yr FH  LDL 490 mg/dL, TG 250*
Tuberous xanthomas (LDL++)

Xanthelasma (FH)

Microscopic view: xanthelasma (lipid-laden macrophages)

Tuberous xanthomas (LDL++)

Eruptive xanthomas (TG++)
The expert panel recommends universal screening for elevated cholesterol by 20 years of age and that FH should be suspected:

- **In adults** >20 years if they have LDL cholesterol >190 mg/dL or non-HDL cholesterol >220 mg/dL.

- **All children** aged 9 – 11 years should also be screened, with FH suspected in those with LDL cholesterol or non-HDL cholesterol >160 mg/dL and >190 mg/dL, respectively.

- Even children as young as two years should be screened for FH but only if there is a family history of premature cardiovascular disease or very high cholesterol levels suggesting FH in a parent.

Pediatric Cholesterol Levels

TC: <170 mg/dL
LDL: <110 mg/dL

TC borderline high: 170 - 199 mg/dL
LDL borderline high: 110 - 129 mg/dL

* It is considered high if total cholesterol is greater than 200 mg/dL and LDL is greater than 130 mg/dL. In addition, HDL should measure 35 mg/dL or higher and triglycerides less than 150 mg/dL.

HDL: ≥35 mg/dL
TG: <150 mg/dL.
Corneal Arcus

Sometimes a feature of FH and Familial Combined Hypercholesterolemia

A ring of opacity in the peripheral part of the eye caused by a deposition of phospholipid and cholesterol in the corneal stroma
Excess central fat tends to be the most informative determinant of the expression of hypertriglyceridemia.

The data indicate that FCHL develops against a background of abdominal obesity.

Lipemia Retinalis

↑↑TG, VLDL, Chylomicrons
Hypoalphalipoproteinemia

(Isolated low HDL-C, e.g., <35 mg/dL)

- **25-35 mg/dL** Primary or familial HAL
  - Apo A-1_milano
  - Apo A-1_Iowa
  - Apo A-1 deficiency
  - ABCA1 mutation (Tangiers disease)
  - LCAT deficiency (fish eye disease)
  - LPL deficiency
  - Disappearing HDL syndrome (R, F, R+F)
- **5-20 mg/dL** Anabolic steroid use
Hypertriglyceridemia
Why Elevated Fasting Triglycerides Can Be a Clinical Issue

• Likely to be an indicator of poor lifestyle habits

• The lipoprotein company they tend to keep (apoB, IDL, LDLp#)

• Frequently associated with decreased HDL-C

• Correlated with post prandial lipemia, arterial exposure to atherogenic TGRL’s, and arterial endothelial dysfunction

• Positive relationship with the metabolic syndrome, CHD, and insulin resistance

• Effects clotting time at high levels

• Increases risk of pancreatitis
Dietary Carbohydrate Increases VLDL Production
5 Minute Lesson in TG Management

**TG 150 - 199 mg/dL**
- ↓ CHO<sub>hg</sub>, ex, wgt loss

**TG 200 - 499 mg/dL**
- ↓ CHO<sub>hg</sub>, ex, wgt loss, ↑ n3, fib, niacin, statin

**TG 500-2000 mg/dL**
- ↓ Fat (avoid with Atkins), lifestyle changes, fibrates, n3, niacin
Drugs That Cause High TG

- **Large effects:** oral contraceptives, glucocorticoids, isotretinoin (Accutane), ketoconazole, cholestyramine, colestipol

- **Small effects:** postmenopausal estrogens, diuretics, beta blockers
Critical Triglyceride Level for Pancreatitis and Other Symptoms of Chylomicronemia

2,000 mg/dl

Risk begins to significantly increase beginning at ~ 1000 mg/dL
Indicate with a true (T) or false (F) regarding which of the following nutrients or treatments usually raise serum triglyceride levels but also raise HDL Levels.

A. Alcohol    T
B. Polyunsaturated fats    T
C. Bile acid sequestrants    T
D. Oral conjugated estrogens    T
E. Carbohydrates
LDL-C

The most important therapeutic lipoprotein target
LDL-C Levels Correlate with Angiographic Progression of CAD

However, ≥10-15% reduction in LDL-C can significantly reduce clinical events, e.g., MI and stroke

**LDL-C “thresholds” for atherosclerotic plaque volume changes**

(projected from IVUS studies)

<table>
<thead>
<tr>
<th>LDL-C Level (mg/dL)</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 – 130</td>
<td>Slow progression</td>
</tr>
<tr>
<td>65 – 80</td>
<td>? Stop progression?</td>
</tr>
<tr>
<td>&lt;65</td>
<td>Regression</td>
</tr>
</tbody>
</table>

Nissen S 2010
HDL-C

High Density Lipoprotein
POTENTIAL ANTIATHEROGENIC ACTIONS OF HDL

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

HDL inhibits oxidation of LDL-C

HDL promotes efflux of cholesterol from foam cells

MCP-1 = monocyte chemoattractant protein-1

FUNCTIONAL AND COMPOSITIONAL ASSESSMENT OF HDL

Cholesterol efflux
Antioxidant activity
Anti-inflammatory activity
Proteomics/lipidomics

Note: these are research tools w/o known clinical relevance of application

HDL-C RISK FACTOR VS RISK MARKER?

Low HDL-C predicts high CVD Risk
High HDL-C predicts anti-atherogenic effects:

- Anti-inflammatory
- Antioxidant
- Antithrombotic
- Pro-endothelial

But clinical trials have not yet proven that:

HDL is a causative factor vs biomarker of risk, or
Raising HDL-C reduces CVD risk
LIFESTYLE MODIFICATIONS TO RAISE HDL-C LEVELS

• **Smoking Cessation**
  - HDL-C levels are 7-20% lower in smokers, but return to normal 1-2 months after smoking cessation

• **Whole Food Plant Based Diet**

• **Weight Reduction**
  - For every 3 kg (7 lb) of weight loss, HDL-C levels increase about 1 mg/dL (~2-4% increase)

• **Exercise**
  - Aerobic exercise (40 min, 3-4 times weekly) increases HDL-C by about 2.5 mg/dL (~5-10% increase)


Key Clinical Trials
Landmark Clinical Event Trials: Relevance to Clinical Practice

Continuum of Risk

- **High-risk CHD patients**
  - 4S (Simva)
  - CARE LIPID (Prava)
  - IDEAL (Atv vs Sim)
- **Majority of CHD patients at risk**
  - TNT & PROVE-IT (Atorva)
  - HPS (Simva)
- **Patients at high risk for CHD**
  - WOSCOPS (Pravastatin)
  - ASCOT (Atorvastatin)
- **Patients at low risk for CHD**
  - AFCAPS/TexCAPS (Lovastatin)
  - VA-HIT, JUPITER (Gemfibrozil, Rosuvastatin)
Multiple Studies Showed a Relationship Between LDL-C Reduction and CHD Relative Risk

Nonfatal MI and CHD death relative risk reduction, %

LDL-C reduction, %

MI = myocardial infarction.

Lipid Research Clinics
Coronary Primary Prevention Trial

- 3806 men aged <60 yr with total cholesterol ≥265 mg/dL and high LDL-C, initially free of coronary disease
- Followed 7.4 yr
- Cholestyramine 24 g/day vs. placebo
- LDL-C -20.3%
  HDL-C +1.6%
- 19% reduction in CHD death and/or nonfatal MI

Cumulative MI + CV Deaths (%)

Years

Placebo
Cholestyramine

Statins & LDL-C
SCANDINAVIAN SIMVASTATIN SURVIVAL STUDY (4S)
Randomized trial of cholesterol lowering in 4,444 patients with CAD: The Scandinavian Simvastatin Survival Study.

To investigate whether long-term simvastatin therapy reduces total mortality and coronary events in post-MI and or angina patients with total cholesterol between 212-309 mg/dL. \textit{Mean LDL-C = 188 mg/dL}
4S Treatment Schedule

Simvastatin 20 mg/day or matching placebo

Increased to 40 mg/day if TC exceeded 200 mg/dL

Study Goal:
TC 116-200 mg/dL

The Lancet, Vol 344, November 19, 1994
4S DOSAGE TITRATION

4,444 randomized patients

2,221 simvastatin 20 mg/day

20 mg/day 63%

2,223 placebo patients

40 mg/day 37%

The Lancet, Vol 344, November 19, 1994
# BASELINE CHARACTERISTICS 4S

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=2223)</th>
<th>Simvastatin (n=2221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)-men</td>
<td>58.1</td>
<td>58.2</td>
</tr>
<tr>
<td>Mean age (years)-women</td>
<td>60.5</td>
<td>60.5</td>
</tr>
<tr>
<td>Angina only</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>MI only</td>
<td>62%</td>
<td>63%</td>
</tr>
<tr>
<td>Both angina and MI</td>
<td>17%</td>
<td>16%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Smoker</td>
<td>27%</td>
<td>24%</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>260</td>
<td>260</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>180</td>
<td>180</td>
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</tbody>
</table>

*The Lancet, Vol 344, November 19, 1994*
The Lancet, Vol 344, November 19, 1994
Coronary Mortality 4S

The Lancet, Vol 344, November 19, 1994
# All-Cause Mortality 4S

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Placebo (n=2223)</th>
<th>Simvastatin (n=2221)</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary</td>
<td>189</td>
<td>111</td>
<td>42%</td>
</tr>
<tr>
<td>Noncoronary vascular</td>
<td>18</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>49</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>-Cancer</td>
<td>35</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>-Suicide</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>-Trauma</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>-Other</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>All Deaths</strong></td>
<td><strong>256</strong></td>
<td><strong>182</strong></td>
<td><strong>30%</strong></td>
</tr>
</tbody>
</table>

*The Lancet, Vol 344, November 19, 1994*
Simvastatin 20 mg, week 6

-38
-28
8
-50
-40
-30
-20
-10
0
10
20

Mean % change

LDL
TC
HDL

p<0.0001

The Lancet, Vol 344, November 19, 1994
# Safety Profile 4S

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n=2223)</th>
<th>Simvastatin (n=2221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal cancer</td>
<td>61</td>
<td>57</td>
</tr>
<tr>
<td>AST 3x ULN</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>ALT 3x ULN</td>
<td>33</td>
<td>49</td>
</tr>
<tr>
<td>CPK 10x ULN</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Rhabdomyolisis</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*The Lancet, Vol 344, November 19, 1994*
4S Summary

Compared with Placebo, Simvastatin:

- Improved survival
- Reduced coronary mortality
- Reduced major coronary events
- Reduced need for PTCA and CABG
- Improved event-free survival
- Substantially reduced TC and LDL

The Lancet, Vol 344, November 19, 1994
Collaborative Atorvastatin Diabetes Study (CARDS)


Lancet, August 21, 2004

Double-blind, randomized, placebo controlled trial (Diabetes UK) of primary prevention of CVD in 2838 men and women with T2D with no previous CHD who do not have LDL-C > 160 mg/dL. 4-year F/U

**Intervention**: Fixed dose of atorvastatin (10 mg)

**Primary end-points:**

- Major CV events (fatal and nonfatal MI)
- CV procedures (CABG, PTCA..)
- Cerebrovascular disease death and nonfatal stroke
CARDS: Effect of Atorvastatin on the Primary Endpoint: Major CV Events Including Stroke

Relative Risk Reduction 37% (95% CI, 17–52)  
$P = 0.001$

<table>
<thead>
<tr>
<th>Years</th>
<th>Placebo</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1410</td>
<td>1428</td>
</tr>
<tr>
<td>1</td>
<td>1351</td>
<td>1392</td>
</tr>
<tr>
<td>2</td>
<td>1306</td>
<td>1361</td>
</tr>
<tr>
<td>3</td>
<td>1022</td>
<td>1074</td>
</tr>
<tr>
<td>4</td>
<td>651</td>
<td>694</td>
</tr>
<tr>
<td>4.75</td>
<td>305</td>
<td>328</td>
</tr>
</tbody>
</table>

### CARDS: ADVERSE AND SERIOUS ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Placebo (n = 1410)</th>
<th>Atorvastatin 10 mg (n = 1428)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event possibly associated with study drug</td>
<td>20 (1.1%)</td>
<td>19 (1.1%)</td>
</tr>
<tr>
<td>Discontinued for AE</td>
<td>145 (10%)</td>
<td>122 (9%)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myopathy AE report</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>CPK $\geq 10 \times$ ULN</td>
<td>10 (0.7%)</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>ALT $\geq 3 \times$ ULN</td>
<td>14 (1%)</td>
<td>17 (1%)</td>
</tr>
<tr>
<td>AST $\geq 3 \times$ ULN</td>
<td>4 (0.3%)</td>
<td>6 (0.4%)</td>
</tr>
</tbody>
</table>

TNT: Effect of Lowering LDL Cholesterol Substantially Below Currently Recommended Levels in Patients With Coronary Heart Disease and Diabetes

The Treating to New Targets study
Shepherd J, Haffner, S et.al. Diabetes Care 2006;29:1220-1226

- **Atorva 80 vs 10 mg** in 1201 T2D+CHD pts with LDL <130 mg/dl

- Patients were followed for a median of 4.9 years.

- Primary end point was the time to first major cardiovascular event

RESULTS—5 yr follow-up. **Atorva 80: 77 mg/dL vs Atorva 10: 99 mg/dL**

- A primary event occurred in 135 patients (17.9%) receiving atorvastatin 10 mg, compared with 103 patients (13.8%) receiving atorvastatin 80 mg (**hazard ratio 0.75**, P = 0.026).

- Significant differences between the groups in favor of atorvastatin 80 mg were also observed for time to CBV event (0.69, P = 0.037) and any CV event (0.85, P = 0.044).
HR = 0.78 (95% CI 0.69, 0.89)
P = .0002

Relative risk reduction = 22%

CHD death, nonfatal, nonprocedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke
TNT - Diabetes

HR = 0.75 (95% CI 0.58, 0.97)
P = .026

- Atorvastatin 10 mg
- Atorvastatin 80 mg

25% decrease in patients with major cardiovascular event (%)

Patients with major cardiovascular event (%)

Time (yrs)
TNT – Metabolic Syndrome

HR = 0.71 (95% CI 0.61, 0.84)
P < .0001

Metabolic Syndrome
- Atorvastatin 10 mg (n = 2820)
- Atorvastatin 80 mg (n = 2764)

$\downarrow$ 29%
507 pts with at least single vessel disease
IVUS in non PTCA coronary artery
Rosuvastatin (Crestor) 40 for 24 months
LDL 130 → 61 mg/dL
HDL 43 → 49 mg/dL

Nissen SE et.al. JAMA 2006;295
Example of Regression of Atherosclerosis in a Patient in the Trial

Nissen, S. E. et al. JAMA 2006;0:295-10. jpc60002-10.
DUAL PRIMARY IVUS EFFICACY PARAMETERS

Median Change in Percent Atheroma Volume

-0.79

Regression p<0.001*

Median Change in Most Diseased Subsegment

-5.6

Regression p<0.001*

*Wilcoxon signed rank test for comparison with baseline
Nissen SE et al. JAMA 2006;295:1556-1565.
Progression-Regression “threshold”

It appears that an LDL-C value of 76 mg/dL was the cutoff at which the linear regression analysis predicted no plaque increase: the transition from progression to regression. (Asteroid data)

This is in agreement with our finding in patients with documented coronary artery disease treated by usual care who underwent serial ultrasonic examinations of the left main coronary artery during at least 12 months of follow-up.

✔ We found that a mean LDL-C value of 75 mg/dL was the cutoff at which regression analysis predicted no plaque progression. (Clemens von Birgelen; Marc Hartmann 2007)
PROVE IT—TIMI 22
(2-YEAR TRIAL)

N = 4,162 with acute coronary syndrome

Log CHD Risk

LDL-C Level

Pravastatin 40 mg

Atorvastatin 80 mg

16% Reduction in CVD

Lowering LDL-C with statins appears to reduce CVD risk in both Secondary prevention and Primary prevention studies.
# SECONDARY PREVENTION TRIALS OF LIPID-ALTERING THERAPY INCLUDING PATIENTS WITH DIABETES

<table>
<thead>
<tr>
<th>Trial</th>
<th>Diabetic, n</th>
<th>Total N in Study</th>
<th>Lipid-Altering Drug, mg/d</th>
<th>CHD* Risk vs Placebo in Diabetic Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4S Reanalysis</strong></td>
<td>202†</td>
<td>4,444</td>
<td>Simvastatin 20–40</td>
<td>-55 (p=.002) -42 (p=.001)</td>
</tr>
<tr>
<td><strong>CARE</strong></td>
<td>586†</td>
<td>4,159</td>
<td>Pravastatin 40</td>
<td>-25 (p=.05)</td>
</tr>
<tr>
<td><strong>LIPID</strong></td>
<td>1,077‡</td>
<td>9,014</td>
<td>Pravastatin 40</td>
<td>-19 (NS)</td>
</tr>
<tr>
<td><strong>LIPS §</strong></td>
<td>202†</td>
<td>1,677</td>
<td>Fluvastatin 80</td>
<td>-47 (p=.04)</td>
</tr>
<tr>
<td><strong>HPS §</strong></td>
<td>3,051†</td>
<td>13,386</td>
<td>Simvastatin 40</td>
<td>-18 (p=.002)</td>
</tr>
<tr>
<td><strong>4D ¶</strong></td>
<td>1,255†</td>
<td>1,255</td>
<td>Atorvastatin 20</td>
<td>-8 (NS)</td>
</tr>
<tr>
<td><strong>VA-HIT</strong></td>
<td>769‡</td>
<td>2,351</td>
<td>Gemfibrozil 1,200</td>
<td>-32 (p=.004)</td>
</tr>
<tr>
<td>**DAIS ¶</td>
<td></td>
<td></td>
<td>418†</td>
<td>418</td>
</tr>
</tbody>
</table>

*Includes stroke in 4D and VA-HIT  
†By history  
‡By history or glucose ≥126 mg/dL  
§ Type 1 or 2 diabetes  
¶ Prospective trial in diabetic subjects; others are subgroup analyses  
|| Angiographic study

### PRIMARY PREVENTION TRIALS OF LIPID-ALTERING THERAPY INCLUDING PATIENTS WITH DIABETES

<table>
<thead>
<tr>
<th>Trial</th>
<th>Diabetic, n</th>
<th>Total N in Study</th>
<th>Lipid-Altering Drug, mg/d</th>
<th>CHD* Risk vs Placebo in Diabetic Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDS †</td>
<td>2,838</td>
<td>2,838</td>
<td>Atorvastatin 10</td>
<td>−37 (p=.001)</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>155</td>
<td>6,605</td>
<td>Lovastatin 20–40 ‡</td>
<td>−44 (NS)</td>
</tr>
<tr>
<td>HPS §</td>
<td>2,912</td>
<td>7,150</td>
<td>Simvastatin 40</td>
<td>−33 (p=.0003)</td>
</tr>
<tr>
<td>ASCOT</td>
<td>2,532</td>
<td>10,305</td>
<td>Atorvastatin 10</td>
<td>−16 (NS)</td>
</tr>
<tr>
<td>PROSPER</td>
<td>623</td>
<td>5,804</td>
<td>Pravastatin 40</td>
<td>+27 (NS)</td>
</tr>
<tr>
<td>HHS</td>
<td>135</td>
<td>4,081</td>
<td>Gemfibrozil 1200</td>
<td>−68 (NS)</td>
</tr>
</tbody>
</table>

* By history
† Prospective trial in diabetic subjects; others are subgroup analyses
‡ Mean 30 mg/d
§ Type 1 or 2 diabetes

JUPITER

Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP

No Prior CVD or DM
Men >50, Women >60
LDL <130 mg/dL
hsCRP ≥2 mg/L

4-week run-in

Rosuvastatin 20 mg (N=8901)

Placebo (N=8901)

MI
Stroke
Unstable Angina
CVD Death
CABG/PTCA

Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

## JUPITER

Baseline Blood Levels (median, interquartile range)  

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin (N = 8901)</th>
<th>Placebo (n = 8901)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP, mg/L</td>
<td>4.2 (2.8 - 7.1)</td>
<td>4.3 (2.8 - 7.2)</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>108 (94 - 119)</td>
<td>108 (94 - 119)</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>49 (40 – 60)</td>
<td>49 (40 – 60)</td>
</tr>
<tr>
<td>Triglycerides, mg/L</td>
<td>118 (85 - 169)</td>
<td>118 (86 - 169)</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>186 (168 - 200)</td>
<td>185 (169 - 199)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>94 (87 – 102)</td>
<td>94 (88 – 102)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.7 (5.4 – 5.9)</td>
<td>5.7 (5.5 – 5.9)</td>
</tr>
</tbody>
</table>

All values are median (interquartile range).  

[ Mean LDL = 104 mg/dL ]
JUPITER
Effects of rosuvastatin 20 mg on LDL, HDL, TG, and hsCRP

LDL decrease 50 percent at 12 months

HDL increase 4 percent at 12 months

hsCRP decrease 37 percent at 12 months

TG decrease 17 percent at 12 months

Ridker et al NEJM 2008
JUPITER

Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

Placebo 251 / 8901
- 44 %

Rosuvastatin 142 / 8901

Cumulative Incidence

Number at Risk
Rosuvastatin 8,901 8,901 8,412 6,540 3,893 1,958 1,353 983 544 157
Placebo 8,901 8,621 8,353 6,508 3,872 1,963 1,333 955 534 174

Follow-up (years)
Cardiovascular Event Reduction and Adverse Events Among Subjects Attaining Low-Density Lipoprotein Cholesterol <50 mg/dl With Rosuvastatin: The JUPITER Trial

In a post-hoc analysis, participants allocated to rosuvastatin were categorized as to whether or not they had a follow-up LDL-C level <50 mg/dl.

**Results:** During a median follow-up of 2 years (range up to 5 years), rates of the primary trial endpoint (MI, Stroke, UA/Revascularization, CV Death) were:

- **Placebo RRR:** +18%
- **LDL >50 mg/dL:** -14% (N=4,000)
- **LDL <50 mg/dL:** -56% (N=4,154)

*1.18, 0.86, and 0.44 per 100 person-years*
Rates of myalgia, muscle weakness, neuropsychiatric conditions, cancer, and diabetes mellitus were not significantly different among rosuvastatin-allocated participants with and without LDL-C <50 mg/dl.

**Conclusions:** Among adults with LDL-C <130 mg/dl and high-sensitivity C-reactive protein 2 mg/l, rosuvastatin-allocated participants attaining LDL-C <50 mg/dl had a lower risk of cardiovascular events without a systematic increase in reported adverse events.
LDL-C AND DISEASE PROGRESSION

Median Change Percent Atheroma Volume

LDL-C AND DISEASE PROGRESSION

REVERSAL Pravastatin
CAMELOT Placebo
STRADIVARIUS Placebo
A-PLUS Placebo
REVERSAL Atorvastatin
ILLUSTRATE Atorvastatin +Placebo
ASTEROID Rosuvastatin
SATURN Rosuvastatin
SATURN Atorvastatin

Mean LDL-C (mg/dL)
LOOK AHEAD: STUDY DESIGN

Look Action for Health in Diabetes

N = 5145
45(55)-74 years with T2DM, BMI ≥25 kg/m² (≥27 kg/m² if taking insulin)

Usual medical care + diabetes support and education for 4 years

Total follow-up 11.5 years

Usual medical care + lifestyle intervention*
4 years; maintenance counseling thereafter

Primary endpoint: CV death, nonfatal MI, nonfatal stroke

*≥7% mean weight loss with hypocaloric diet ± pharmacologic therapy + ≥175 min/week moderate physical activity

Diet = 1200-1500 kcal/day (<250 lbs) or 1500-1800 kcal/day (≥250 lbs)

Physical activity goal: 175 minutes/wk of moderate intensity exercise
e.g., brisk walking and similar aerobic activity*
* ≥10 minutes duration

Plus, *Lifestyle Activity*
e.g., stairs, pedometer activity, etc.
The ILI group experienced significantly greater average improvements in all risk factors except LDL-C levels.

Weight loss: Year 1: 8.6% Year 11: 4.9%

- TG 179 to 155 mg/dL
- HDL 43 to 46 mg/dL
- LDL 112 to 100 mg/dL

Statistical significance criteria: Five thousand participants will provide a minimum of 80% power to detect an 18% relative decrease in the rate of the primary outcome in participants assigned to the Lifestyle Intervention.

✔ PRIMARY OUTCOME: rate of nonfat MI, nonfat stroke, death, or hosp. for angina
Meta-analysis of Statin Trials for New-Onset Type 2 Diabetes During Follow-up

All statins (n = 39,791) 1.03 (0.89, 1.19)
Pravastatin (n = 13,911) 0.84 (0.86, 1.49)
Rosuvastatin (n = 3534) 1.13 (0.86, 1.49)
Simvastatin (n = 14,573) 1.14 (0.98, 1.33)
Atorvastatin (n = 7773) 1.14 (0.91, 1.42)
Excluding pravastatin (n = 25,880) 1.14 (1.02, 1.28)
Do Statins Alter Glucose/Insulin Metabolism?

Possible Mechanisms
- Improvement in pancreatic islet vasculature?
- Increase or decrease in insulin secretion?
- Decrease or increase in insulin sensitivity?
  - IRS-1/GLUT4 effects
  - Lipid-mediated effects
  - Adipokine effects
  - Anti-inflammatory effects
  - Other?
- Differential effects on diabetes vs pre-diabetes?

Class Effects vs Agent-Specific Effects
- Basic data mixed and very confusing
- Clinical trial data emerging

IRS-1 = insulin receptor substrate-1
Niacin
(nicotinic acid)
&
HDL-C
**Niacin** raises HDL-C up to 30%
but also lowers LDL, LDL-P, and VLDL

**Fibrates** raise HDL-C 5-20%

**Statins** raise HDL-C 3-15%

*CETP inhibitors (investigational)
raise HDL-C 40-90%*
ARBITER* 2: Effect of ER-Niacin 1000 mg hs Added to Statin on Carotid IMT in CAD Patients

- 167 patients with known CAD, mean age 67 yr
- Extended-release niacin 1000 mg hs (at bedtime) vs. placebo added to background statin Rx (all participants on statin at baseline, average duration 4.8 ± 4.3 y, most on simvastatin ≥20 mg)
- Primary endpoint: change in CIMT at 1 year
- HDL-C 40 mg/dL → 47 mg/dL
- Baseline CIMT: 0.868 mm (placebo), 0.893 mm (niacin)

* Arterial Biology for Investigation of Treatment Effects of Reducing Cholesterol

Statin vs Statin + Niasin

Coronary heart disease death, myocardial infarction, stroke, or high-risk acute coronary syndrome hospitalization

N=3400, Metsyn
Study Design

Open-Label Run-In: Up-Titrate Niacin from 500mg to 2,000mg/day 4-8 weeks

ER Niacin + 40-80 mg/day simvastatin

Placebo + 40-80 mg/day simvastatin

Adjust simva to LDL 40 – 80 mg/dL

Follow to end of study

Months Relative to Randomization

AIM-HIGH: Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Niacin</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>75.8</td>
<td>65.2</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>35.3</td>
<td>44.1</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>162</td>
<td>120</td>
</tr>
</tbody>
</table>

- Incidence of Primary Endpoint
  - Statin plus placebo: 16.2%
  - Statin plus niacin: 16.4%  p=0.80

New Study Looks at Niacin and Statin Combination Therapy for Atherosclerosis Regression, CVD Prevention: AIM-HIGH
Michos ED Am Coll Cardiol 2012; DOI:10.1016/j.jacc.2012 (April)

The reasons for the increase in HDL cholesterol in the placebo arm are unclear, but:

• more patients in the placebo arm were taking higher doses of statins, and this might have contributed to the increase.

• In addition, to ensure blinding, placebo patients received a very low dose of niacin to induce flushing, and even though the 200-mg extended-release niacin dose was well below the therapeutic dose of 1500 mg/day, it is impossible to know whether this was responsible for the increase in HDL cholesterol in the placebo arm.

• The vast majority of patients were treated with simvastatin in order to reduce LDL-cholesterol levels to less than 80 mg/dL, and these low LDL-cholesterol levels might have altered the composition of the atherosclerotic plaque.
One argument why niacin did not significantly impact primary outcome of AIM HIGH:

- Niacin alters the composition of HDL not the total number of HDL-P (NMR).
- Niacin reduces the numbers of small HDL particles and increases the number of large HDL particles thus no net effect on HDL-P

Otvos J, JCL 2011
HPS2-THRIVE involved over 25,000 volunteers aged between 50 and 80 with a history of heart disease, stroke or other circulatory disease recruited from almost 250 hospitals in 6 countries (China, Denmark, Finland, Norway, Sweden and the United Kingdom).

Statin or Statin + Niacin/Lrp

Armitage J, et al ACC Mtg 2013
HPS-2 THRIVE Misses Primary End Point: **No Benefit of Niacin/Laropiprant**

12/20/12

✓ After nearly four years of follow-up, the combination of niacin with the antiflushing agent laropiprant **did not** significantly reduce the risk of the combination of *coronary deaths, nonfatal MI, strokes, or coronary revascularizations* compared with statin therapy.

✓ On average, baseline LDL-C was 63 mg/dL and non-HDL-C about 84 mg/dL, such that subjects were not in need of niacin for lowering these levels.

✓ Among the subjects from Europe there was a clinically significant ~10% decrease in vascular events with ERNL, while among the 43% of subjects from China, there was a towards a ~3% increase in MVE (heterogeneity p=06). Thus, ERNL has a net harm in Chinese patients when added to simvastatin.
Comparison of CETP Inhibitors to raise HDL-C

**Dalcetrapib**
- **Dose:** 600 mg/day
- **HDL-C:** \( \uparrow \) \( \sim \) 31%
- **LDL-C:** \( \downarrow \) \( \sim \) 2%

**Anacetrapib**
- **Dose:** 100 mg/day
- **HDL-C:** \( \uparrow \) \( \sim \) 138%
- **LDL-C:** \( \downarrow \) \( \sim \) 40%

**Torcetrapib**
- **Dose:** 60 mg/day
- **HDL-C:** \( \uparrow \) \( \sim \) 61%
- **LDL-C:** \( \downarrow \) \( \sim \) 24%

**Evacetrapib**
- **Dose:** 500 mg/day
- **HDL-C:** \( \uparrow \) \( \sim \) 129%
- **LDL-C:** \( \downarrow \) \( \sim \) 36%
Percent Change HDL-C: Evacetrapib 100 mg Combined with Statin Therapy

- Simvastatin 40 mg: 7.3% change
- Atorvastatin 20 mg: 1.4% change
- Rosuvastatin 10 mg: 5.5% change

- Evacetrapib 100 mg: 86.6% change
- Evacetrapib 100 mg: 79.9% change
- Evacetrapib 100 mg: 94.0% change

P values: <0.001 for all comparisons

12 weeks, N=393

Nicholls S, Nissen S, et.al. 2011
Cholesterol Transport Inhibitor

Ezetimibe
(Zetia)

Slows intestinal absorption of cholesterol

15-18% dec. in LDL-C
Rx: add to statin
Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE)

- 720 patients with familial hypercholesterolemia – most (81%) previously treated with statins randomly assigned to simvastatin 80 mg vs. simvastatin 80 mg + ezetimibe 10 mg for 2 years
- No difference in mean cIMT at the end of 2 years ($P = 0.64$)
**Primary endpoint**

<table>
<thead>
<tr>
<th>End point</th>
<th>Ezetimibe plus simvastatin</th>
<th>Simvastatin alone</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in mean carotid IMT after 2-y treatment (mm)</td>
<td>0.0111</td>
<td>0.0058</td>
<td>0.29</td>
</tr>
</tbody>
</table>

**Lipids**

<table>
<thead>
<tr>
<th>End point</th>
<th>Ezetimibe plus simvastatin</th>
<th>Simvastatin alone</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LDL (mg/dL)</td>
<td>319</td>
<td>318</td>
<td>NS</td>
</tr>
<tr>
<td>Reduction after 2-y treatment (%)</td>
<td>58</td>
<td>41</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
**IMPROVE IT**

**IMProved Reduction of Outcomes: Vytorin (Simva+Ez) Efficacy International Trial**

Patients stabilized post Acute Coronary Syndrome < 10 days
LDL ≤ 125 mg/dL (or ≤ 100 mg/dL if prior statin)

**Double-blind**

ASA + Standard Medical Therapy

**Simvastatin 40 mg**

**Eze / Simva 10/40 mg**

Follow-Up Visit Day 30, Every 4 Months

Duration: Minimum 2 1/2 year follow-up (>2955 events)

**Primary Endpoint: CV Death, MI, Hospital Admission for UA, revascularization (> 30 days after randomization), or Stroke**

n~18,000
Is LDL-C Passed Its Prime?
The Emerging Role of Non-HDL, LDL-P, and ApoB in CHD Risk Assessment

Michael H. Davidson

✓ An LDL-C focus has worked well in the past, but to address residual CV risk on statin therapy, the recent trials support a more significant role for non-HDL, apoB, and LDL-P

Association of LDL Cholesterol, Non–HDL Cholesterol, and Apolipoprotein B Levels With Risk of Cardiovascular Events Among Patients Treated With Statins: A Meta-analysis

Among statin-treated patients, levels of LDL-C, non–HDL-C, and apoB were each strongly associated with the risk of major cardiovascular events, but non-HDL-C was more strongly associated than LDL-C and apoB.

Boekholdt SM et.al. JAMA. 2012;307(12):1302-1309
Key Take-Away Messages: Clinical Trials

- CV event reduction (e.g., MI, stroke) is bottom line with LDL-C therapy with or without plaque regression

- Over time, lowering LDL-C reaps great benefits in terms of reduction of cardiovascular events.

- When LDL-C is lowered to optimal levels raising HDL-C probably does not matter in terms of further risk reduction

- Non-HDL-C is looming to be a slightly better CV risk predictor than LDL-C

- Clinical trials provide hope that novel therapies may provide additional benefits beyond LDL-C lowering.