The Moving LDL Target: Getting Your Patients to Goal

Tampa, Florida
December 4, 2008
Session 4: The Moving LDL Target: Getting Your Patients to Goal

Learning Objectives

• Describe at least 2 challenges in treating dyslipidemia to NCEP-ATP III goals and getting patients to goal.
• Define the patients at increased risk for cardiovascular events and identify at least 2 lipid-lowering strategies that will help these patients reach goal taking into consideration current lifestyle and pharmacologic treatment options available for lipid management.

Faculty

Emma A. Meagher, MD
Associate Professor, Medicine and Pharmacology Executive Chair
Associate Director, Cardiac Risk Program
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Dr Meagher received the MB (MD) degree from the Royal College of Surgeons in Dublin, Ireland. Since 1995, she has been associate professor of medicine, Division of Experimental Therapeutics at the University of Pennsylvania School of Medicine.

Dr Meagher’s area of research interest includes mechanisms of vascular dysfunction in cardiovascular disease and alcohol-induced vascular disease. Her clinical practice is in the area of cardiovascular risk modification. She is associate director of the Center for Assessment and Treatment of Complex Hypertension and associate director of the Cardiovascular Risk Intervention Program at the University of Pennsylvania School of Medicine.

Dr Meagher is program director of the Patient Oriented Research Training Program at the University of Pennsylvania. This training program in research methodology includes a course for medical students, residents, fellows, and junior faculty. In addition, she is the director of a master’s degree program in experimental medicine and translational research, and she is the course director for pharmacology education in the school of medicine.

Dr Meagher is a member of the American Heart Association’s Council on Atherosclerosis, Thrombosis, and Vascular Biology, the American Society of Hypertension, the American Federation for Medical Research, and the American Gastroenterological Association. She has written extensively on lipid lowering drug therapy in primary prevention, antioxidant therapy and atherosclerosis, the safety and effectiveness of niacin in combination with lovastatin, lipid peroxidation, and balancing cardioprotection and gastroprotection with selective COX-2 inhibitors.

Barry L. Hainer, MD
Professor, Department of Family Medicine
Medical University of South Carolina
Charleston, South Carolina

Dr Barry Hainer writes for and speaks to primary care physician audiences on a variety of clinical topics. He is a reviewer for American Family Physician and is a member of the Society of Teachers of Family Medicine, among other professional societies. He is a Diplomate of the National Board of Medical Examiners and the American Board of Family Medicine and was awarded the Certificate of Added Qualifications in Geriatrics by the American Board of Family Practice and American Board of Internal Medicine. Dr Hainer is included in the 2007-2008 edition of Guide to America’s Top Physicians.

Dr Hainer received his MD degree from Georgetown University, Washington, DC. He completed a residency in the Department of Family Medicine at the Medical University of South Carolina, Charleston.

Faculty Financial Disclosure Statements

The presenting faculty reported the following:
Dr Meagher is a consultant for Abbott Laboratories.
Dr Hainer is on the speakers bureau of Merck & Co, Inc. and Sanofi Pasteur Inc.

Education Partner Financial Disclosure Statements

The content collaborators at Turnkey Solutions, LLC have reported the following:
Emily A. Bakerman, RN, MS, APN-C, executive vice president, has nothing to disclose.

Drug List

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin</td>
<td>Lipitor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>colesevelam</td>
<td>Welchol</td>
</tr>
</tbody>
</table>
Generic | Trade
--- | ---
ezetimibe | Zetia
ezetimibe/simvastatin | Vytorin
fenofibrate | Tricor
gemfibrozil | Lopid
glipizide | Glucotrol
losartan | Cozaar
lovastatin | Altoprev, Mevacor
metformin | Glucophage

Generic | Trade
--- | ---
niacin (nicotinic acid) | Niacor, Niaspan
omega-3 fatty acids | Lovaza (formerly Omacor)
pravastatin | Pravachol
rosuvastatin | Crestor
simvastatin | Zocor
stanol esters | Benecol margarine
sterol esters | Take Control margarine
valsartan/HCTZ | Diovan HCT

**Acronym List**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CAI</td>
<td>cholesterol absorption inhibitors</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>CPK</td>
<td>creatine phosphokinase</td>
</tr>
<tr>
<td>HbA1c</td>
<td>hemoglobin A1c</td>
</tr>
<tr>
<td>HDL-C</td>
<td>high-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>HTN</td>
<td>hypertension</td>
</tr>
<tr>
<td>IDL</td>
<td>intermediate-density lipoprotein</td>
</tr>
<tr>
<td>IGT</td>
<td>impaired glucose tolerance</td>
</tr>
<tr>
<td>IMT</td>
<td>intima media thickness</td>
</tr>
<tr>
<td>LDL-C</td>
<td>low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>total cholesterol minus HDL-C</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>non–ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>TC</td>
<td>total cholesterol</td>
</tr>
<tr>
<td>TG</td>
<td>triglyceride</td>
</tr>
<tr>
<td>TFT</td>
<td>thyroid function test</td>
</tr>
<tr>
<td>TLC</td>
<td>therapeutic lifestyle changes</td>
</tr>
<tr>
<td>VLDL</td>
<td>very low-density lipoprotein</td>
</tr>
</tbody>
</table>

**Suggested Reading List**


The Moving LDL Target: Getting Your Patients to Goal

EMMA A. MEAGHER, MD
Associate Professor, Medicine and Pharmacology
Executive Chair, Associate Director, Cardiac Risk Program
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

### Key Lessons From Lipid Trials (>90,000 pts)

**LOWERING LDL REDUCES CV EVENTS**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment Events (%)</th>
<th>Control Events (%)</th>
<th>Relative Risk (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>2001 (4·4) 2769 (6·2)</td>
<td></td>
<td>0·74 (0·70 – 0·79)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1548 (3·4) 1960 (4·4)</td>
<td></td>
<td>0·81 (0·75 – 0·87)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>3337 (7·4) 4420 (9·8)</td>
<td></td>
<td>0·77 (0·74 – 0·80)</td>
</tr>
<tr>
<td>Any coronary revascularisation</td>
<td>2620 (5·6) 3434 (7·6)</td>
<td></td>
<td>0·76 (0·71 – 0·82)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>194 (0·2) 99 (0·2)</td>
<td></td>
<td>0·95 (0·79 – 1·14)</td>
</tr>
<tr>
<td>Presumed ischemic stroke</td>
<td>1235 (2·8) 1518 (3·4)</td>
<td></td>
<td>0·81 (0·74 – 0·89)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1340 (3·0) 1617 (3·7)</td>
<td></td>
<td>0·83 (0·78 – 0·88)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>6354 (14·1) 7994 (17·8)</td>
<td></td>
<td>0·73 (0·77 – 0·81)</td>
</tr>
</tbody>
</table>


### ATP III Update 2004: LDL-C Goals and Cutoffs for Therapy in Different Risk Categories

<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>Very High risk:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS, CHD w/DM, mult CRF</td>
<td>&lt;70 mg/dL</td>
<td>≥70 mg/dL</td>
<td>≥70 mg/dL</td>
</tr>
<tr>
<td>High risk:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD or CHD risk equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL</td>
<td>≥100 mg/dL</td>
<td>≥100 mg/dL (&lt;100 mg/dL: consider drug Rx)</td>
</tr>
<tr>
<td>Moderately high risk:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+ risk factors (10-year risk 10% to 20%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥130 mg/dL (&lt;130 mg/dL: consider drug Rx)</td>
</tr>
<tr>
<td>Moderate risk:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+ risk factors (risk &lt;10%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥160 mg/dL (&lt;160 mg/dL: consider drug Rx)</td>
</tr>
<tr>
<td>Lower risk:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL (&lt;190 mg/dL: consider drug Rx)</td>
</tr>
</tbody>
</table>

Adapted from Grundy, S. et al., *Circulation* 2004;110:227-239.


**KEY CHANGES**

Lower LDL < 70 goal in very high-risk groups:
- Diabetes
- Other clinical forms of atherosclerotic disease (with multiple risk factors, recent ACS, CAD, PAD, Carotid disease)
- Multiple risk factors and increased 10-y CHD risk

**Intensified therapeutic lifestyle changes (TLC) for metabolic syndrome**

**More aggressive targets (LDL, non-HDL)**


### Recent Data Since ATP III: Lower LDL Goals

**Recent Trials of Intensive LDL Lowering in Patients with ACS or Stable CAD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>LDL Cholesterol (mg/dL)</th>
<th>HPS</th>
<th>PROSPER</th>
<th>ASCOT-LLA</th>
<th>CORDIA</th>
<th>CORONA</th>
<th>IDEAL</th>
<th>METEOR</th>
<th>ASTEROID</th>
<th>CORONA</th>
<th>REVERSAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>PROVE IT</td>
<td>ACS</td>
<td>62</td>
<td>95</td>
<td>62</td>
<td>95</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>A to Z</td>
<td>ACS</td>
<td>63</td>
<td>77</td>
<td>63</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>TNT</td>
<td>Stable CAD</td>
<td>77</td>
<td>101</td>
<td>77</td>
<td>101</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>IDEAL</td>
<td>Stable CAD</td>
<td>81</td>
<td>104</td>
<td>81</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Meta-analysis of Intensive Statin Therapy: Coronary Death or MI

<table>
<thead>
<tr>
<th>Study</th>
<th>Event Rates No./Total (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>Odds Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT</td>
<td>1470/2099 (7.0)</td>
<td>0.84 (0.77-0.91)</td>
<td>-17%</td>
</tr>
<tr>
<td>A-to-Z</td>
<td>205/2266 (9.1)</td>
<td>0.84 (0.76-0.94)</td>
<td>-15%</td>
</tr>
<tr>
<td>TNT</td>
<td>334/4996 (6.7)</td>
<td>0.86 (0.78-0.95)</td>
<td>-21%</td>
</tr>
<tr>
<td>IDEAL</td>
<td>411/4439 (9.3)</td>
<td>0.84 (0.77-0.91)</td>
<td>-12%</td>
</tr>
<tr>
<td>Total</td>
<td>1097/13798 (8.0)</td>
<td>0.84 (0.77-0.91)</td>
<td>-16%</td>
</tr>
</tbody>
</table>

Odds Ratio (95% CI) 0.84, 95% CI, 0.77-0.91, p = 0.00003


### Safety of Lower LDL Goals: PROVE IT

<table>
<thead>
<tr>
<th>Event</th>
<th>PROVE IT</th>
<th>TNT</th>
<th>IDEAL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>&lt;0.001</td>
<td>0.29</td>
<td>0.48</td>
<td>0.75</td>
</tr>
<tr>
<td>CH&gt;3x ULN</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.12</td>
<td>0.18</td>
</tr>
<tr>
<td>ALT&gt;3x ULN</td>
<td>0.69</td>
<td>0.84</td>
<td>0.48</td>
<td>0.96</td>
</tr>
<tr>
<td>Retinal bleed</td>
<td>0.12</td>
<td>0.12</td>
<td>0.48</td>
<td>0.48</td>
</tr>
<tr>
<td>Hem Strokes</td>
<td>0.12</td>
<td>0.12</td>
<td>0.48</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Wiviott SD et al. JACC. 2005;46:1411-1415.

### How Low Should LDL-C Go?

- **Hazard Ratio for Primary Endpoint**
  - >80-100: 0.82 (Referent)
  - >60-80: 0.87
  - >40-60: 0.87
  - ≤40: 0.61


### Current LDL Treatment Rates: NEPTUNE II

<table>
<thead>
<tr>
<th>Achieved LDL (mg/dL)</th>
<th>% Achieving LDL Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80-100</td>
<td>0.61</td>
</tr>
<tr>
<td>&gt;60-80</td>
<td>0.67</td>
</tr>
<tr>
<td>&gt;40-60</td>
<td>0.67</td>
</tr>
<tr>
<td>≤40</td>
<td>0.61</td>
</tr>
</tbody>
</table>


### Why Aren’t Patients Getting to Goal?

- Patient non-compliance
- Lipid lowering therapies not initiated
- Low doses started with lack of further titration
- Lack of comfort in prescribing higher doses or combinations of medications
- Concerns about safety of low LDL-C levels


### ATP III 2004 Update: Stepwise Approach

1. Measure fasting lipid profile
2. Determine Risk:
   - CHD or CHD equivalents
   - Total # non-LDL risks
   - Framingham risk score
3. Determine target LDL
4. Assessment beyond LDL

**NCEP: Additional Steps**

- Target LDL-C and stay with it until it is at goal
- Use statin doses that reduce LDL-C by 30%-40%
  - Potential combinations include bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols
- Identify the metabolic syndrome and treat with more aggressive lifestyle interventions
- Consider adding fibrate or niacin to statin if non-HDL cholesterol (TC – HDL) is >30 mg/dL above LDL-C goal


**Non-HDL Cholesterol as the Second Goal of Therapy: NCEP ATP III**

- LDL-C lowering is the primary goal of lipid lowering therapy
- When Triglycerides are ≥ 200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal


**Interventions to Lower LDL-C**

- Dietary Interventions
  - Saturated fat <7% of calories
  - <200mg/d of dietary cholesterol
  - Plant stanol esters
- Statin Therapy at appropriate doses
- Combination Therapies


**Lipid Modifying Drugs**

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>18-55%</td>
<td>5-15%</td>
<td>7-30%</td>
<td>+++</td>
</tr>
<tr>
<td>Bile acid resins</td>
<td>15-30%</td>
<td>3-5%</td>
<td>0-15%</td>
<td>++</td>
</tr>
<tr>
<td>Absorption inhibitors (CAI)</td>
<td>18-20%</td>
<td>3%</td>
<td>8%</td>
<td>++</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>5-25%</td>
<td>15-35%</td>
<td>20-50%</td>
<td>++</td>
</tr>
<tr>
<td>Stanol Esters</td>
<td>5-14%</td>
<td>No change</td>
<td>No change</td>
<td>++</td>
</tr>
<tr>
<td>Fibrates</td>
<td>5-20%</td>
<td>10-20%</td>
<td>25-50%</td>
<td>+++</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>2-5%</td>
<td>No change</td>
<td>30-40%</td>
<td>+</td>
</tr>
</tbody>
</table>

**Change in LDL Values with Different Statin Doses**

- Pravastatin
  - 10 mg: -20
  - 20 mg: -30
  - 40 mg: -40

- Simvastatin
  - 10 mg: -25
  - 20 mg: -35
  - 40 mg: -45

- Atorvastatin
  - 10 mg: -15
  - 20 mg: -25
  - 40 mg: -35
  - 80 mg: -55

- Rosuvastatin
  - 10 mg: -25
  - 20 mg: -35
  - 40 mg: -52

% Change in LDL-C

- Pravastatin: 10 mg, 20 mg, 40 mg
- Simvastatin: 10 mg, 20 mg, 40 mg, 80 mg
- Atorvastatin: 10 mg, 20 mg, 40 mg, 80 mg
- Rosuvastatin: 10 mg, 20 mg

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**If Statins Are So Effective, Why Is Combination Therapy Often Necessary?**

- Despite overwhelming success of the statins, coronary event rates remain unacceptably high.
- The majority of patients do not reach LDL-C goals.
- If LDL is not managed on an appropriate dose of statin monotherapy then combination therapy may be warranted and more efficacious and tolerable than high-dose monotherapy.
- There's more to the story than LDL-C!

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**Therapeutic Combinations**

- Statins + niacin
- Statins + fibrates
- Statins + bile acid sequestrants
- Statins + ezetimibe
- Ezetimibe + fibrate
- Statins + omega-3 fatty acids

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**Niacin ER 1000 mg/Lovastatin 40 mg: Comparison With Atorvastatin 10 mg and 20 mg in an Open-Label Trial**

- Week 8:
  - LDL-C: Lovastatin ER/Niacin 1000 mg/40 mg: -50 vs Atorvastatin 10 mg: -42 vs 20 mg: -45
  - HDL-C: Lovastatin ER/Niacin 1000 mg/40 mg: +20 vs Atorvastatin 10 mg: +19 vs 20 mg: +4
  - TG: Lovastatin ER/Niacin 1000 mg/40 mg: -30 vs Atorvastatin 10 mg: -36 vs 20 mg: -30

- Week 12:
  - LDL-C: Lovastatin ER/Niacin 1000 mg/40 mg: -60 vs Atorvastatin 10 mg: -60 vs 20 mg: -60
  - HDL-C: Lovastatin ER/Niacin 1000 mg/40 mg: +19 vs Atorvastatin 10 mg: +13 vs 20 mg: +13
  - TG: Lovastatin ER/Niacin 1000 mg/40 mg: -30 vs Atorvastatin 10 mg: -30 vs 20 mg: -30

---

**ARBITER 2: HDL-C ↑ 18% (p=0.002); TG ↓ 10% (p=0.03); No change in LDL-C**

Baseline Carotid IMT

- 0.87
- 0.89

Carotid IMT After 1 Year

- 0.87
- 0.89

Δ Carotid IMT

- 0.044 (p=0.001)
- 0.014 (p=0.23)

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**ARBITER 3: ER Niacin for 12-24 mths**

- 88% (n=130) of pts in ARBITER 2 cont’d in the open-label ARBITER 3 study
- All pts rec’d ER Niacin from months 12 -> 24

Δ HDL< 5 mg/dL -> progression

Δ HDL> 12 mg/dL -> regression
Statin Plus Fibrate Combination Therapy

- Targets both LDL-C (statin) and TGs (fibrate)
- When fibrates are added to statins:
  - Decrease TG and VLDL levels by 20-50%
  - Decrease LDL-C by 5-20% (fenofibrate)
  - Increases HDL-C by 10-29%
  - Reduces small dense LDL levels
- Safety/efficacy data come from small clinical trials
- No outcomes data yet
- Increased risk of myopathy
- Only approved with low-dose statins

ACC/AHA/NHLBI Clinical Advisory on Statins.

SAFARI: Combination Therapy in Patients With Combined Hyperlipidemia


Stanol Esters: The Evidence

- Over 20 published studies support efficacy
- Cholesterol absorption is nearly halved
- Cholesterol-lowering effect of plant stanols
  - TC is lowered by up to 10%
  - LDL-C is lowered by up to 14%
  - HDL-C and TG are unaffected
- Must take 2-3 grams/day
  (OJ, chocolate, granola chews, yogurt drinks etc)
- Now incorporated as part of TLC diet


Bile Acid Sequestrants

- Major actions
  - Reduce LDL-C 15%-30%
  - Reduces LDL-C by additional 10-16% when added to statin therapy
  - May increase TG
  - Colesevelam added to sulfonylurea, metformin or insulin improves glycemic control in type 2 diabetics
- Side effects
  - GI distress/constipation
  - Decreased absorption of other drugs
- Contraindications
  - Elevated TG (especially >400 mg/dL)


Clinical Studies of Ezetimibe: Monotherapy

Pooled Results From 2 Phase III Multicenter, Double-Blind, Placebo-Controlled, 12-Wk Studies in 1719 Patients With Primary Hypercholesterolemia


Combination Therapy: Ezetimibe Plus Simvastatin vs. Rosuvastatin

**Long-Term Ezetimibe + Fibrate**

Change in Lipids From Baseline to 48 Weeks

- TC: P<0.001
- LDL-C: P<0.001
- HDL-C: P=0.02
- TG: P<0.001

Early Discontinuation

- TC: 63%
- LDL-C: 7%
- HDL-C: 1%
- TG: 35%


**Clinical Uses and Safety of Ezetimibe**

**Potential Clinical Uses**

- **Monotherapy**
  - Patients with mild to moderate LDL-C elevation in whom statin therapy fails or is contraindicated
- **Combination therapy**
  - Patients who do not reach goal with starting statin dose
  - Patients who do not reach goal with maximal statin dose

**Safety**

- Slight increase in LFTs when coadministered with statins
- Postmarketing reports of hypersensitivity reactions, including angioedema, rash, and cholelithiasis
- No increase in muscle side-effects when added to statin

**ENHANCE Trial**

- Randomized double blind comparator trial of 720 patients with heterozygous familial hypercholesterolemia (rare condition affecting 0.2% of population)
- Baseline LDL of 320 mg/dL
- 80% of patients previously treated with statins
- Surrogate endpoint
- Primary endpoint – mean change in carotid intima media thickness (IMT)
- Study duration – 24 months

**ENHANCE Trial**

<table>
<thead>
<tr>
<th></th>
<th>Ezetimibe/ Simvastatin</th>
<th>Simvastatin</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IMT Δ</td>
<td>0.0111</td>
<td>0.0058</td>
<td>0.29 (NS)</td>
</tr>
<tr>
<td>LDL Δ</td>
<td>-58%</td>
<td>-41%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CV Death</td>
<td>2/357</td>
<td>1/363</td>
<td>NS</td>
</tr>
<tr>
<td>Non Fatal MI</td>
<td>3/357</td>
<td>2/363</td>
<td>NS</td>
</tr>
<tr>
<td>Non Fatal CVA</td>
<td>1/357</td>
<td>1/363</td>
<td>NS</td>
</tr>
<tr>
<td>ALT Δ</td>
<td>2.8%</td>
<td>2.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Elevated CPK</td>
<td>1.1%</td>
<td>2.2%</td>
<td>NS</td>
</tr>
</tbody>
</table>


**Conclusions**

- ATP III increased the population eligible for lifestyle and pharmacologic management of lipids
- Expanded use of statins as first-line drug therapy for hypercholesterolemia
- For those who do not tolerate statins, other agents alone or in combination with intestinally active agents offer novel therapeutic approaches
- Expanded use of multiple drug therapy targeting the whole lipid profile when indicated
- Choice of therapy depends on achievement of therapeutic goals, outcomes based data, and patient safety -- especially in high-risk patients

**CASE PRESENTATIONS**

**BARRY L HAINER, MD**
Professor, Department of Family Medicine
Medical University of South Carolina
Charleston, South Carolina
**Case 1**

57-year-old overweight man with a sedentary lifestyle who has smoked one pack per day since his teens. He has medication-controlled hypertension. The patient and his father have type 2 diabetes. History of MI 4 years ago.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Physical exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan/HCTZ 100/25 mg/d</td>
<td>Wt = 220 lb, Ht = 5'11&quot; (BMI = 30)</td>
</tr>
<tr>
<td>Glipizide 10 mg OD</td>
<td>Waist = 42&quot;</td>
</tr>
<tr>
<td>Metformin 500 mg BID</td>
<td>BP = 138/94 mm Hg</td>
</tr>
<tr>
<td>Aspirin, 81 mg/d</td>
<td>No carotid bruits; good distal pulses</td>
</tr>
</tbody>
</table>

**Medication:**
- Losartan/HCTZ 100/25 mg/d
- Glipizide 10 mg OD
- Metformin 500 mg BID
- Aspirin, 81 mg/d

**Physical exam:**
- Wt = 220 lb, Ht = 5’11” (BMI = 30)
- Waist = 42”
- BP = 138/94 mm Hg

**TEST YOUR KNOWLEDGE**

**Case 1: 57M, HTN, Type 2 Diabetes**

According to the NCEP, what is the LDL-C goal?

1. <130 mg/dL
2. <100 mg/dL
3. <100 mg/dL with an option to go to <70 mg/dL
4. <70 mg/dL

**The Continuum of CV Risk in Type 2 Diabetes**

[Diagram showing the continuum of CV risk, including factors like Insulin Resistance, FFA, Apolipoprotein B, Hepatic Lipase, Hyperinsulinemia, Hyperglycemia, Hypertension, Atherosclerosis, Retinopathy, Nephropathy, Neurropathy, Blindness, Stroke, Congestive Heart Failure, Amputation.]

**Relationship Between Obesity and Insulin Resistance and Dyslipidemia**

[Diagram showing the relationship between Central Obesity, FFA, Insulin Resistance, Apolipoprotein B, Hepatic Lipase, TG, Small, Dense LDL, and HDL.]

**HDL-C and Coronary Artery Disease (CAD) Risk**

[Graph showing the relationship between HDL-C (mg/dL) and CAD Risk.]
TEST YOUR KNOWLEDGE

Case 1: 57M, HTN, Type 2 Diabetes
In addition to TLC, what medication would you use to get this patient to his LDL-C Goal:

1. Rosuvastatin 10 mg
2. Simvastatin 40 mg
3. Atorvastatin 10 mg
4. Simvastatin 40 mg + Ezetimibe 10 mg
5. Lovastatin 40 mg + Niacin ER 1000 mg
6. Simvastatin 40 mg + Fenofibrate

Current LDL-C: 152 mg/dL. Desired LDL-C: 70 mg/dL. = 54% reduction

Comparison of Statins for Surrogate Marker Reduction (Stellar Trial)
2431 Patients

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>Triglycerides</th>
<th>HDL-C</th>
<th>non HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>-46-55</td>
<td>-20-26</td>
<td>+7.7-9.6</td>
<td>-40-52</td>
</tr>
<tr>
<td>(10-40 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>-37-51</td>
<td>-20-28</td>
<td>+5.7-2.1</td>
<td>-34-46</td>
</tr>
<tr>
<td>(10-80 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>-28-46</td>
<td>-12-18</td>
<td>+5.3-6.8</td>
<td>-25-42</td>
</tr>
<tr>
<td>(10-80 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>-20-30</td>
<td>-8-13</td>
<td>+3.2-5.6</td>
<td>-19-27</td>
</tr>
<tr>
<td>(10-40 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Follow Up Data
at 6 Weeks on Rosuvastatin 10 mg

- TC 155 mg/dL
- HDL-C 37 mg/dL
- TG 155 mg/dL
- LDL-C 82 mg/dL
- Non-HDL-C 118 mg/dL
- FBS 108

NCEP Guidelines for Diabetics

- Get to LDL-C goal first
- When LDL-C goal is achieved, second target is non HDL-C (address low HDL-C and elevated triglycerides)


TEST YOUR KNOWLEDGE

Case 1: Take-Home Message

6 week follow up, patient is on Rosuvastatin 10 mg:
What change would you make to achieve the multiple lipid goals for this diabetic patient?

1. Add Niacin ER 500 mg
2. Add Ezetimibe 10 mg
3. Add Fenofibrate
4. Add Gemfibrozil
5. Increase Rosuvastatin to 20 mg
6. Do nothing as patient is at goal

Recognize and aggressively treat all patients with CHD or CHD risk equivalents to LDL-C goal <100 mg/dL, with the option to go as low as <70 mg/dL
- Focus on % reduction needed to get to goal
- Consider combination lipid-lowering therapies that include a statin to achieve targets safely and efficiently
Case 2
A 61-year-old female with hypertension and elevated cholesterol. Father died of a myocardial infarction at age 53.
- No known history of coronary heart disease
- On cholesterol-lowering supplement, prefers “natural” lipid lowering remedies
- Sedentary lifestyle
- Tobacco use 1 pack/day for 25 years
- Medication: Valsartan/HCTZ 80/12.5

Case 2: 61F, HTN, Elevated Cholesterol
Clinical and Laboratory Data
- BMI 30
- Waist circumference 38 inches
- BP 143/89
- TC 257 mg/dL
- HDL-C 31 mg/dL
- TG 343 mg/dL
- LDL-C 187 mg/dL
- Non-HDL-C 226 mg/dL
- FBS 101

TEST YOUR KNOWLEDGE
Case 2: 61F, HTN, Elevated Cholesterol
Does this patient have the Metabolic Syndrome?
1. Yes
2. No
3. Need more data

ATP III: The Metabolic Syndrome
Diagnosis is established when ≥3 of these risk factors are present

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Defining level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (Waist circumference*)</td>
<td>≥102 cm (≥40 in)</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;88 cm (≥35 in)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>TG†</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C †</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Men</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>BP †</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>&gt;100 mg/dL†‡</td>
</tr>
</tbody>
</table>

*Some men develop metabolic risk factors when circumference is only marginally increased. Lower waist circumference cut point (eg, 90 cm [35 inches] in men and 80 cm [31 inches] in women) appears to be appropriate for Asian Americans.
†Or drug treatment for BP, TGs or HDL-C.
‡Revised American Diabetes Association Guidelines

Metabolic Syndrome as a Predictor of CHD and Diabetes in WOSCOPS

Count Traditional CHD Risk Factors
- No history of CHD or CHD equivalents
- Age (> 45 in men, > 55 in women)
+ Medication-treated hypertension
+ Smoker

Since ≥ 2 risk factors:
- Calculate 10-y risk of CHD event to determine LDL-C level at which to start meds

Assessing CHD Risk in Women

ATP III Framingham Risk Scoring

Step 1: Age

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-34</td>
<td>-7</td>
</tr>
<tr>
<td>35-39</td>
<td>-3</td>
</tr>
<tr>
<td>40-44</td>
<td>0</td>
</tr>
<tr>
<td>45-49</td>
<td>3</td>
</tr>
<tr>
<td>50-54</td>
<td>6</td>
</tr>
<tr>
<td>55-59</td>
<td>8</td>
</tr>
<tr>
<td>60-64</td>
<td>10</td>
</tr>
<tr>
<td>65-69</td>
<td>12</td>
</tr>
<tr>
<td>70-74</td>
<td>14</td>
</tr>
<tr>
<td>75-79</td>
<td>16</td>
</tr>
</tbody>
</table>

Step 2: Total Cholesterol

<table>
<thead>
<tr>
<th>TC (mg/dL)</th>
<th>Points at Age 20-39</th>
<th>Points at Age 40-49</th>
<th>Points at Age 50-59</th>
<th>Points at Age 60-69</th>
<th>Points at Age 70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;160</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>160-199</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>200-239</td>
<td>8</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>240-279</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>≥280</td>
<td>13</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Step 3: HDL-C-Cholesterol

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

Step 4: Systolic Blood Pressure

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>Points (if untreated)</th>
<th>Points (if treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>120-129</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>130-139</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>140-159</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>≥160</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

Step 5: Smoking Status

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Points at Age 20-39</th>
<th>Points at Age 40-49</th>
<th>Points at Age 50-59</th>
<th>Points at Age 60-69</th>
<th>Points at Age 70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmoker</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smoker</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>


Step 6: Adding Up the Points (Sum from Steps 1–5)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age = 61</td>
<td>10</td>
</tr>
<tr>
<td>TC = 257</td>
<td>3</td>
</tr>
<tr>
<td>HDL-C = 31</td>
<td>2</td>
</tr>
<tr>
<td>SBP = 143</td>
<td>5</td>
</tr>
<tr>
<td>Smoker</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>22</td>
</tr>
</tbody>
</table>

ATP III Update 2004: Pharmacologic Treatment

<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>Very High risk: ACS, CHD w/DM, mult CRF</td>
<td>&lt;70 mg/dL</td>
<td>≥70 mg/dL</td>
<td>≥70 mg/dL</td>
</tr>
<tr>
<td>High risk: CHD or CHD risk equivalents (10-year risk ≥20%)</td>
<td>&lt;100 mg/dL (optional goal: &lt;70 mg/dL)</td>
<td>≥100 mg/dL</td>
<td>≥100 mg/dL (&lt;100 mg/dL: consider drug Rx)</td>
</tr>
<tr>
<td>Moderately high risk: 2+ risk factors (10-year risk 10% to 20%)</td>
<td>&lt;100 mg/dL</td>
<td>≥100 mg/dL</td>
<td>≥150 mg/dL (100-199 mg/dL: consider Rx)</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors (risk &lt;10%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td>Lower risk: 0-1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL</td>
</tr>
</tbody>
</table>


Case 2: 61F, HTN, Elevated Cholesterol

Initial Pharmacologic Management: What LDL goal would you choose?
1. <130 mg/dL (30% reduction needed)
2. <100 mg/dL (47% reduction needed)
3. <70 mg/dL (64% reduction needed)

Case 2: 61F, HTN, Elevated Cholesterol

In addition to TLC, which medication would you choose?
1. Rosuvastatin 10 mg
2. Atorvastatin 20 mg
3. Simvastatin 40 mg
4. Simvastatin 20 mg/ Ezetimibe 10 mg
5. Lovastatin 40 mg/ Niacin ER 1000 mg
**Statin and Complementary GI-Acting Drugs vs Statin Titration**

![Diagram showing 1-step co-administration and 3-step titration of statins with GI-acting drugs.](image)


**Follow Up Visit After Six More Weeks**

Patient is on Simvastatin 20 mg and Ezetimibe 10 mg

- LDL-C 94 mg/dL
- HDL-C 34 mg/dL
- TG 280 mg/dL
- TC 164 mg/dL
- Non-HDL-C 130 mg/dL

**TEST YOUR KNOWLEDGE**

61F, HTN, Elevated Cholesterol

At this point, which further therapeutic option would you select?

1. Add Niacin
2. Add Fenofibrate
3. Add fish oils
4. Increase Simvastatin/Ezetimibe to 40/10 mg
5. No further therapy

**Case 2 Take-Home Message**

- Become familiar with calculating absolute risk (Framingham). This will allow for better risk stratification
- Think about your NCEP targets in terms of % reduction needed to get your patient to goal; in general target at least 30% reduction*
- Then choose agents based on evidence, efficacy, and patient safety
- Don’t forget to counsel on lifestyle changes


**Omega-3 AEE Improve the Lipid Profile in Patients With High TG on Simvastatin**

Simvastatin 10-40 mg/day (average 32 mg/day)

- TG -4.6%
- VLDL -3.8%
- Non-HDL-C -4.6%
- LDL-C -1.7%
- HDL-C -1.1%

*after 48 weeks (NS after 24 weeks)

AEE=Acid Ethyl Esthers

*P <0.0005


**The Moving LDL Target: Getting Your Patients to Goal**

EMMA A. MEAGHER, MD
BARRY L HAINER, MD