Marked LDL-C Reduction with Pharmacologic Agents:
Potential Benefits and Safety Concerns

Peter W. F. Wilson, MD
Atlanta VA Medical Center
Emory Clinical Cardiovascular Research Institute
Atlanta, GA
Outline

• Safety
  Older LDL Lowering Medications
  Safety Realms
  FDA Lipid Medication Advisory
  Newer LDL Lowering Medications

• Efficacy
  LDL-C vs CVD Risk
  Subclinical Outcomes
  Clinical Trial Outcomes
Cardiometabolic Safety Background

• Statins
  Lovastatin
  Cerivastatin
  Simvastatin
• Fibrates
• Bile Acid Resins
• Niacin
• Cholesterol Absorption Inhibitors
Low LDL-C
Safety and Experience

- Liver
- Muscle
- Kidney
- Glycemia
- Skin (injected meds)
- Immunologic
- Vitamin Deficiency
- Cognition
- Lab Accuracy
- Genetic low beta lipoprotein
- Others
# Muscle Adverse Events with Statin Therapy

<table>
<thead>
<tr>
<th>Muscle Adverse Events</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias</td>
<td>0 to 10%</td>
</tr>
<tr>
<td>Myopathy (Symptoms + CK elevation)</td>
<td>~1%</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Less than 1/500</td>
</tr>
</tbody>
</table>
Statin Benefit: Risk - Liver Effects

Persistent ALT* >3× ULN: Frequency by LDL-C Reduction

- Fluvastatin (20–80 mg)
- Lovastatin (20–80 mg)
- Simvastatin (40–80 mg)
- Atorvastatin (10–80 mg)
- Rosuvastatin (5–40 mg)

*Elevation to >3 × ULN on 2 successive occasions

Brewer HB, Am J Cardiol 2003;92(Suppl):23K–29K;
Rosuvastatin Tolerability and Safety – Muscle Effects

CK >10x ULN: Frequency by LDL-C Reduction

Brewer HB. Am J Cardiol 2003;92(Suppl):23K–29K;
Simvastatin Warnings

• Do not use Simvastatin 80 mg/day
  – Unless > 12 months without side effects
• Do not exceed 10 mg simvastatin daily
  Verapamil
  Diltiazem
• Do not exceed 20 mg simvastatin daily
  Amlodipine
  Ranolazine
  Amlodipine
• Caution Simva + Niacin (> 1gm/d) in Chinese
Statins and Incident Diabetes
Meta-Analysis

Figure 2: Association between statin therapy and incident diabetes in 13 major cardiovascular trials†

Sattar Lancet 2011; 375: 735
Incident Diabetes and CVD Relative Risk According to Statin Potency

<table>
<thead>
<tr>
<th>Incident Diabetes</th>
<th>Intensive Dose</th>
<th>Moderate Dose</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT-TIMI 22, 2004</td>
<td>101/1707 (5.9)</td>
<td>99/1688 (5.9)</td>
<td>1.01 (0.76-1.34)</td>
</tr>
<tr>
<td>A to Z, 2004</td>
<td>65/1768 (3.7)</td>
<td>47/1736 (2.7)</td>
<td>1.37 (0.94-2.01)</td>
</tr>
<tr>
<td>TNT, 2005</td>
<td>418/3798 (11.0)</td>
<td>358/3797 (9.4)</td>
<td>1.19 (1.02-1.38)</td>
</tr>
<tr>
<td>IDEAL, 2005</td>
<td>240/3737 (6.4)</td>
<td>209/3724 (5.6)</td>
<td>1.15 (0.95-1.40)</td>
</tr>
<tr>
<td>SEARCH, 2010</td>
<td>625/5398 (11.6)</td>
<td>587/5399 (10.9)</td>
<td>1.07 (0.95-1.21)</td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td>1449/16408 (8.8)</td>
<td>1300/16344 (8.0)</td>
<td>1.12 (1.04-1.22)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incident CVD</th>
<th>Intensive Dose</th>
<th>Moderate Dose</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>PROVE IT-TIMI 22, 2004</td>
<td>315/1707 (18.4)</td>
<td>355/1688 (21.0)</td>
<td>0.85 (0.72-1.01)</td>
</tr>
<tr>
<td>A to Z, 2004</td>
<td>212/1768 (12.0)</td>
<td>234/1736 (13.5)</td>
<td>0.87 (0.72-1.07)</td>
</tr>
<tr>
<td>TNT, 2005</td>
<td>647/3798 (17.0)</td>
<td>830/3797 (21.9)</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>IDEAL, 2005</td>
<td>776/3737 (20.8)</td>
<td>917/3724 (24.6)</td>
<td>0.80 (0.72-0.89)</td>
</tr>
<tr>
<td>SEARCH, 2010</td>
<td>1184/5398 (21.9)</td>
<td>1214/5399 (22.5)</td>
<td>0.97 (0.88-1.06)</td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td>3134/16408 (19.1)</td>
<td>3550/16344 (21.7)</td>
<td>0.84 (0.75-0.94)</td>
</tr>
</tbody>
</table>

Preiss JAMA 2011; 305: 2556
Statin Safety Summary

• **Liver Function abnormal**
  0.5 % > 3x ULN—assess patient

• **Muscle**
  Myalgia (5% -15%)—consider non statin causes
  Myositis (<1%, myalgias, CK >5X to 10 X ULN)
  Rhabdomyolysis (0.2%, CK>10 X ULN)
    Serum creatinine, urine for myoglobin, IV fluids

• **Blood glucose increase**
  Diabetes risk outweighed by CVD benefit
  Metabolic syndrome factors very important

• **Memory loss**
  Not well substantiated for statin users
FDA Guidance to Industry Developing Drugs for Diabetes Treatment and Prevention

“The objective of lipid-altering therapy is not merely to alter serum lipids but to diminish the morbidity and mortality from cardiovascular disease and/or pancreatitis that is associated with abnormal serum lipid levels”

“Lipid altering agents should be shown to have a relatively low incidence of adverse effects prior to approval for marketing.”

Psaty JAMA 2008; 299: 1474
http://www.fda.gov/cder/guidance/lipid.pdf
CETP Safety

• Torcetrapib
  – BP increase 4 mm Hg
  – Hyperaldosteronism in some patients
  – Harm in clinical trial (ILLUMINATE)

• Dalcetrapib
  – Clinical outcomes trial no benefit (DALOUTCOMES)

• Anacetrapib

Barter NEJM 2007; 357: 2109
Nissen NEJM 2007; 356: 1304
Schwartz NEJM 2012; 367: 2089
Cannon NEJM 2010; 363: 2406
Lipoprotein B Molecular Biology

- MTP inhibitor (Lomitapide)
- HMGCoA reductase inhibitor (statins)
- PCSK9 inhibition
- Apo Antisense Oligonucleotide (Mipomersen)

Key processes:
1. Microsomal transfer protein
2. Vesicle Export
3. Import
4. Lysosome
5. Cytosol
6. Exterior
Very Low Beta Lipoprotein Levels
(Abetalipoproteinemia and Hypobetalipoproteinemia)

• Causes
  • Genetic
    APOB, NGPTL, MTP, PCSK9
  • Environment
    Chronic Hepatitis C
    Vegan diet, malnutrition

• Criteria
  Cholesterol < 150 mg/dL
  LDL-C < 70 mg/dL
  Apo B < 50 mg/dL (lowest 5% of pop’n)
  No chylomicrons

Schonfeld J Lipid Research 2003; 44: 878
Low Betalipoprotein Levels
Possible Medical Complications

• Liver/Gastrointestinal
  Fat malabsorption especially pediatric
  AST/ALT often increased
  Steatosis 10% adults

• Neurologic
  Spinocerebellar ataxia risk
  Myositis possible

• Eye
  Retinal pigmentary changes
  Night blindness → blindness

• Hematologic
  Acanthocytosis, No rouleaux
  Low sed rate

• Fat Soluble Vitamin Deficiencies
  Vitamins K, A, D, E

Berriot-Varoqueaux Ann Rev Nutr 2000; 20: 663
Lomitapide Safety

- Liver Function Test Abnormalities
- Hepatic Steatosis
ALT, AST and Hepatic Fat
Lomitapide Therapy in Homozygous FH

Mipomersen Safety

- Liver Function Test Abnormalities
- Hepatic Steatosis
- Injection site reactions
- Immunity
ALT Change and Mipomersen Therapy 12 Months or Longer

Liver Fat Content and Mipomersen Therapy 12 Months or Longer

LDL-C Level and CVD Risk

- LDL-C to CVD risk relationship
- Relative Risk Reduction
- Number needed to treat (NNT)
- Cost per event prevented
Serum Cholesterol and CHD Death
MRFIT Screenees

Stamler JAMA 1986; 256: 2823
Cholesterol Level and Mortality
17,718 Whitehall Study Men 40-64 Years

Rose Lancet 1980; p523
25 Year CHD Mortality in 12,467 Men age 40-59 yr
7 Countries Study

Verschuren JAMA 1995; 275: 131
HMG-CoA Reductase Inhibitor Evidence: Primary Prevention and LDL-C on Therapy

CHD event rate (%) vs LDL cholesterol (mg/dL)

- Statin
- Placebo

WOSCOPS: West of Scotland Coronary Prevention Study
AFCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study
ASCOT: Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm
LDL-C: Low density lipoprotein cholesterol

AFCAPS= Air Force/Texas Coronary Atherosclerosis Prevention Study, ASCOT= Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm, LDL-C=Low density lipoprotein cholesterol, WOSCOPS= West of Scotland Coronary Prevention Study

LDL-C Bias and Error
College of American Pathology Survey

Vesper Clin Chem 2012; 58: 523
CTT Meta-Analysis 2010: ↓1 mmol/L LDLc and Mortality

CTT: Lancet 2010; 376: 1670
CTT Meta-Analysis 2010: ↓1 mmol/L CVD Effect by Baseline LDL-C

<table>
<thead>
<tr>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>More vs less statin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>704 (4.6%)</td>
<td>0.71 (0.52–0.98)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/L</td>
<td>1189 (4.2%)</td>
<td>0.77 (0.64–0.94)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3.0 mmol/L</td>
<td>1065 (4.5%)</td>
<td>0.81 (0.67–0.97)</td>
</tr>
<tr>
<td>≥3 to &lt;3.5 mmol/L</td>
<td>517 (4.5%)</td>
<td>0.61 (0.46–0.81)</td>
</tr>
<tr>
<td>≥3.5 mmol/L</td>
<td>303 (5.7%)</td>
<td>0.64 (0.47–0.86)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3837 (4.5%)</td>
<td>0.72 (0.66–0.78)</td>
</tr>
<tr>
<td><strong>Statin vs control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>206 (2.9%)</td>
<td>0.87 (0.60–1.28)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/L</td>
<td>339 (2.4%)</td>
<td>0.77 (0.62–0.97)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3.0 mmol/L</td>
<td>801 (2.5%)</td>
<td>0.76 (0.67–0.86)</td>
</tr>
<tr>
<td>≥3 to &lt;3.5 mmol/L</td>
<td>1490 (2.9%)</td>
<td>0.77 (0.71–0.84)</td>
</tr>
<tr>
<td>≥3.5 mmol/L</td>
<td>4205 (2.9%)</td>
<td>0.80 (0.77–0.84)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7136 (2.8%)</td>
<td>0.79 (0.77–0.81)</td>
</tr>
<tr>
<td><strong>All trials combined</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>910 (4.1%)</td>
<td>0.78 (0.61–0.99)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/L</td>
<td>1528 (3.6%)</td>
<td>0.77 (0.67–0.89)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3.0 mmol/L</td>
<td>1866 (3.3%)</td>
<td>0.77 (0.70–0.85)</td>
</tr>
<tr>
<td>≥3 to &lt;3.5 mmol/L</td>
<td>2007 (3.2%)</td>
<td>0.76 (0.70–0.82)</td>
</tr>
<tr>
<td>≥3.5 mmol/L</td>
<td>4508 (3.0%)</td>
<td>0.80 (0.76–0.83)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10973 (3.2%)</td>
<td>0.78 (0.76–0.80)</td>
</tr>
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</table>

CTT: Lancet 2010; 376: 1670
# LDL-C Lowering, NNT and CVD Prevention Costs

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>Trial Time (yrs)</th>
<th>Relative Risk</th>
<th>Absolute Risk Reduction</th>
<th>NNT</th>
<th>2015 Rx Cost/Yr ($)</th>
<th>Annual Cost Per Event Prevented ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS (1&lt;sup&gt;st&lt;/sup&gt; Prevent)</td>
<td>Pravastatin vs Placebo</td>
<td>4.8</td>
<td>0.69</td>
<td>2.4%</td>
<td>42</td>
<td>50</td>
<td>2,083</td>
</tr>
<tr>
<td>TNT (2&lt;sup&gt;nd&lt;/sup&gt; Prevent)</td>
<td>Hi Atorva vs Lo Atorva</td>
<td>5.0</td>
<td>0.78</td>
<td>2.2%</td>
<td>45</td>
<td>50</td>
<td>2,273</td>
</tr>
<tr>
<td>IMPROVE-IT (High risk)</td>
<td>Statin + Ezetimibe vs Statin</td>
<td>7.0</td>
<td>0.94</td>
<td>2.0%</td>
<td>50</td>
<td>1,000</td>
<td>50,000</td>
</tr>
<tr>
<td>ODYSSEY (HeFH)</td>
<td>Statin + Amab vs Statin</td>
<td>1.5</td>
<td>0.52</td>
<td>1.6%</td>
<td>63</td>
<td>12,000</td>
<td>756,000</td>
</tr>
<tr>
<td>OSLER (HeFH)</td>
<td>Statin + Emab vs Statin</td>
<td>1.0</td>
<td>0.47</td>
<td>1.2%</td>
<td>81</td>
<td>12,000</td>
<td>972,000</td>
</tr>
</tbody>
</table>