Drug Treatment of Hyperlipidemia
The value of cholesterol values

At the population level, cholesterol values clearly predict CHD risk

Observational data from MRFIT trial (n=356,222);
Circulation 1998;97:1436
....but we’re all on different curves: *Risk Curve Concept*
CAD Treatment Gap - Community

Provider awareness does not equal successful implementation

Physician Awareness of NCEP Guideline: 95%
Patient Treated to Goal: 18%
L-TAP: % of Patients at LDL-C Goal

<table>
<thead>
<tr>
<th>Risk group—Lipid-lowering therapy</th>
<th>LDL-C goal*</th>
<th>% Success</th>
<th>% Failure</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2RF (n=282)</td>
<td></td>
<td>59</td>
<td>41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥2RF (n=361)</td>
<td></td>
<td>22</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>CHD (n=108)</td>
<td></td>
<td>7</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Total (n=751)</td>
<td></td>
<td>34</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td><strong>Drug therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;2RF (n=861)</td>
<td></td>
<td>70</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>≥2RF (n=1924)</td>
<td></td>
<td>40</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>CHD (n=1352)</td>
<td></td>
<td>18</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Total (n=4137)</td>
<td></td>
<td>39</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

*Does not include patients who were nonevaluable.
Person’s chi-square=682.91; d=2; P=0.001.
Drugs for Lipids

• Lipid-regulating drugs must be taken indefinitely (?)
  – Plasma lipid levels return to pretreatment levels within 2-3 weeks when stopped

• Should NOT be a substitute for lifestyle changes
  – Diet + Exercise + Lipid-lowering drugs optimal for treatment/prevention
## Metabolic Effects of Lipid-Lowering Agents on Lipoproteins

<table>
<thead>
<tr>
<th>Agents</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>VLDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid sequestrants</td>
<td>↑ clearance</td>
<td>(modest ↑)</td>
<td>↑ secretion</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓ synthesis</td>
<td>↓ clearance</td>
<td>↓ synthesis</td>
</tr>
<tr>
<td>Fibric acid derivatives</td>
<td>(modest ↓)</td>
<td>↑ synthesis</td>
<td>↑ clearance</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (statins)</td>
<td>↑ clearance</td>
<td>(modest ↑)</td>
<td>↑ clearance</td>
</tr>
<tr>
<td>Ezetimibe (Zetia)</td>
<td>↓ Absorption</td>
<td></td>
<td>↓ synthesis*</td>
</tr>
</tbody>
</table>
Cholesterol Biosynthetic Pathway

**HMG-CoA reductase**

Acetyl CoA → HMG-CoA → Mevalonate → Farnesyl pyrophosphate → Squalene → Cholesterol

*Ras protein* → Farnesyltransferase

Farnesylated proteins → E,E,E-Geranylgeranyl pyrophosphate

Geranylgeranylated proteins → Ubiquinones
HMG-CoA-Reductase Inhibitors:

• Inhibit first step **rate-limiting** in sterol (cholesterol) synthesis
• **Structural analogs of natural substrate**
  – 3-hydroxy-3-methyl-glutaric acid
• Block hydroxy-methyl-glutaryl-Coenzyme A reductase
  – Reduces conversion of HMG-CoA to mevalonic acid
• Most compounds are related to compounds occurring naturally in fungi
• **Lovastatin** first agent in class
• Inhibit de novo cholesterol synthesis
  – Deplete intracellular supply of cholesterol
  – Increase LDL receptors
HMG-CoA-Reductase Inhibitors:

• A dose related decrease in LDL-cholesterol
  – Occurs within 3 days
  – Peaks at one month
  – 25 to 45% reduction in cholesterol
  – Reduces Apo B

• Also causes reduction in TG (up to 25%)

• Raises HDL up to 10%

• Effective in all Hyperlipoproteinemias
  – Less effective in familial homozygous Type IIA
    • Lack LDL receptors

• Often combined with other agents to increase effect

• Administer once daily in the evening
HMG-CoA-Reductase Inhibitors:

- Lovastatin (Mevacor®) 1987
- Simvastatin (Zocor®) 1991
- Pravastatin (Pravachol®) 1991
- Fluvastatin (Lescol®) 1993
- Atorvastatin (Lipitor®) 1996
- Cerivastatin (Baycol®)
  - Withdrawn because of toxicity
- Rosuvastatin (Crestor®) 2003
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Simvastatin</th>
<th>Atorvastatin</th>
<th>Fluvastatin</th>
<th>Cerivastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal dose (mg/day)</td>
<td>80</td>
<td>40†</td>
<td>80</td>
<td>80</td>
<td>40</td>
<td>0.3</td>
</tr>
<tr>
<td>Maximal serum LDL cholesterol reduction produced (%)</td>
<td>40</td>
<td>34</td>
<td>47</td>
<td>60</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Serum LDL cholesterol reduction produced (%)†</td>
<td>34</td>
<td>34</td>
<td>41</td>
<td>50</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Serum triglyceride reduction produced (%)‡</td>
<td>16</td>
<td>24</td>
<td>18</td>
<td>29</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Serum HDL cholesterol increase produced (%)‡</td>
<td>8.6</td>
<td>12</td>
<td>12</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Plasma half-life (hr)</td>
<td>2</td>
<td>1–2</td>
<td>1–2</td>
<td>14</td>
<td>1.2</td>
<td>2–3</td>
</tr>
<tr>
<td>Effect of food on absorption of drug</td>
<td>Increased absorption</td>
<td>Decreased absorption</td>
<td>None</td>
<td>None</td>
<td>Negligible</td>
<td>None</td>
</tr>
<tr>
<td>Optimal time of administration</td>
<td>With meals (morning and evening)</td>
<td>Bedtime</td>
<td>Evening</td>
<td>Evening</td>
<td>Bedtime</td>
<td>Evening</td>
</tr>
<tr>
<td>Penetration of central nervous system</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal excretion of absorbed dose (%)</td>
<td>10</td>
<td>20</td>
<td>13</td>
<td>2</td>
<td>&lt;6</td>
<td>33</td>
</tr>
<tr>
<td>Mechanism of hepatic metabolism</td>
<td>Cytochrome P-450 3A4</td>
<td>Sulfation</td>
<td>Cytochrome P-450 3A4</td>
<td>Cytochrome P-450 3A4</td>
<td>Cytochrome P-450 2C9</td>
<td>Cytochrome P-450 3A4, 2C8</td>
</tr>
</tbody>
</table>

*The synthetic statins atorvastatin and cerivastatin contain only the active enantiomers; fluvastatin contains both active and inactive enantiomers. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.

†An 80-mg dose has also been studied, which reduces serum LDL cholesterol concentrations by 38 to 39 percent and is safe. However, the approved maximal dose is 40 mg per day.

‡This effect was elicited by a daily dose of 40 mg of lovastatin, pravastatin, simvastatin, atorvastatin, and fluvastatin and by a daily dose of 0.3 mg of cerivastatin in patients with hypercholesterolemia. Reductions in LDL cholesterol of 30 to 32 percent are more typical of once-daily treatment with lovastatin and twice-daily treatment with pravastatin.
### Relative LDL-lowering Efficacy of Statin and Statin-based Therapies

<table>
<thead>
<tr>
<th>Atorva</th>
<th>Fluva</th>
<th>Pitava</th>
<th>Lova</th>
<th>Prava</th>
<th>Rosuva</th>
<th>Vytornin*</th>
<th>Simva</th>
<th>%↓ LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>-----</td>
<td>40 mg</td>
<td>1 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>-----</td>
<td>-----</td>
<td>10 mg</td>
<td>30%</td>
</tr>
<tr>
<td>10 mg</td>
<td>80 mg</td>
<td>2 mg</td>
<td>40 or 80 mg</td>
<td>40 mg</td>
<td>-----</td>
<td>-----</td>
<td>20 mg</td>
<td>38%</td>
</tr>
<tr>
<td>20 mg</td>
<td>-----</td>
<td>4 mg</td>
<td>80 mg</td>
<td>80 mg</td>
<td>5 mg</td>
<td>10/10 mg</td>
<td>40 mg</td>
<td>41%</td>
</tr>
<tr>
<td>40 mg</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>10 mg</td>
<td>10/20 mg</td>
<td>80 mg</td>
<td>47%</td>
</tr>
<tr>
<td>80 mg</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>20 mg</td>
<td>10/40 mg</td>
<td>-----</td>
<td>55%</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>40 mg</td>
<td>10/80 mg</td>
<td>-----</td>
<td>63%</td>
</tr>
</tbody>
</table>

* No More effective than placebo compared to statins alone
Statin Evidence: Landmark Statin Trials

*Extrapolated to 5 years

% with CHD event vs. LDL-C, mmol/L (mg/dL)

*Extrapolated to 5 years
Clinical Benefits of Cholesterol Reduction

- A recent meta-analysis of 38 trials demonstrated that for every 10% reduction in TC
  - CHD mortality decreased by 15% ($P<0.001$)
  - Total mortality decreased by 11% ($P<0.001$)

- Decreases were similar for all treatment modalities

- Cholesterol reduction did not increase non-CHD mortality
Potential Mechanisms of Benefit of Statins

- **LDL-C reduction**
  - Reduction in chylomicron and VLDL remnants, IDL, LDL-C
  - Restore endothelial function
  - Maintain SMC function
  - Anti-inflammatory effects
  - Decreased thrombosis

Macrophages

Lumen

Lipid core

Smooth muscle cells
Beneficial Effects of Statins:

• Reduction in plasma viscosity
• Decrease in platelet aggregation and thrombin formation
• Reduction in inflammation
  – Decrease in CRP
• Reduction in fractures
Magnitude of LDL and Reduction in Cardiac Event Rate (Cardiac Death and Nonfatal Myocardial Infarction) in the ALERT Study and Other Major Statin Outcome Trials in Other Populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (n)</th>
<th>Follow up (years)</th>
<th>Baseline LDL (mg/dL)</th>
<th>LDL-C net change (mg/dL)</th>
<th>CHD event rate/year</th>
<th>CHD risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>4444</td>
<td>5.4</td>
<td>191</td>
<td>66</td>
<td>5.2?</td>
<td>34</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>6595</td>
<td>4.9</td>
<td>195</td>
<td>50.7</td>
<td>1.5</td>
<td>32</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>6605</td>
<td>5.2</td>
<td>152</td>
<td>39</td>
<td>1.0</td>
<td>37</td>
</tr>
<tr>
<td>CARE</td>
<td>4159</td>
<td>5.0</td>
<td>140</td>
<td>39</td>
<td>2.6</td>
<td>24</td>
</tr>
<tr>
<td>HPS</td>
<td>20536</td>
<td>5.0</td>
<td>133</td>
<td>39</td>
<td>2.3</td>
<td>27</td>
</tr>
<tr>
<td>PROSPER</td>
<td>5804</td>
<td>3.2</td>
<td>148</td>
<td>39</td>
<td>3.8</td>
<td>19</td>
</tr>
<tr>
<td>ASCOT</td>
<td>10305</td>
<td>3.3</td>
<td>133</td>
<td>39</td>
<td>0.9</td>
<td>36</td>
</tr>
<tr>
<td>ALERT</td>
<td>2102</td>
<td>4.1</td>
<td>160</td>
<td>39</td>
<td>2.0</td>
<td>35</td>
</tr>
<tr>
<td>LIPID</td>
<td>9014</td>
<td>3.9</td>
<td>152</td>
<td>35</td>
<td>2.6</td>
<td>24</td>
</tr>
<tr>
<td>LIPS</td>
<td>1677</td>
<td>3.4</td>
<td>133</td>
<td>35</td>
<td>1.8</td>
<td>31</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>10355</td>
<td>3.8</td>
<td>148</td>
<td>35</td>
<td>1.7</td>
<td>9</td>
</tr>
</tbody>
</table>
HMG-CoA-Reductase Inhibitors: Adverse Effects

• Generally well tolerated; few adverse effects
• Patients who don’t tolerate one statin may tolerate another
• Hepatic dysfunction
  – Elevation in transaminase levels
  – >3x ULN increase occurs in 1-2%
  – Symptomatic hepatitis rare
• Contraindicated in pregnancy
Common, Clinically Significant Drug Interactions: Statins

• Most HMG Co A Reductase Inhibitors are significantly metabolized by the CP450 3A4 isoenzyme and most interactions are related to 3A4 enzyme inhibition

• In addition to metabolism interactions with statins, monitor also for myopathy “synergy” and LFT elevations
## Drug interactions with simvastatin

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Prescribing advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potent CYP3A4 inhibitors:</td>
<td>Avoid simvastatin</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Azole antifungals</td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td>Danazol</td>
<td></td>
</tr>
<tr>
<td>Verapamil, Diltiazem</td>
<td>Do not exceed <strong>10mg simvastatin</strong></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Do not exceed <strong>20mg simvastatin</strong></td>
</tr>
<tr>
<td>ranolazine</td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Effect of anticoagulant (warfarin) increased, monitor INR and adjust accordingly</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Reduces plasma levels of simvastatin so may need to increase dose</td>
</tr>
</tbody>
</table>
# Lovastatin

<table>
<thead>
<tr>
<th>Previous lovastatin label</th>
<th>New lovastatin label</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Avoid lovastatin with:</strong></td>
<td><strong>Contraindicated with lovastatin:</strong></td>
</tr>
<tr>
<td>• Itraconazole</td>
<td>• Itraconazole</td>
</tr>
<tr>
<td>• Ketoconazole</td>
<td>• Ketoconazole</td>
</tr>
<tr>
<td>• Erythromycin</td>
<td>• Posaconazole</td>
</tr>
<tr>
<td>• Clarithromycin</td>
<td>• Erythromycin</td>
</tr>
<tr>
<td>• Telithromycin</td>
<td>• Clarithromycin</td>
</tr>
<tr>
<td>• HIV protease inhibitors</td>
<td>• Telithromycin</td>
</tr>
<tr>
<td>• Nefazodone</td>
<td>• HIV protease inhibitors</td>
</tr>
</tbody>
</table>

Do not exceed 20 mg lovastatin daily with:
- • Gemfibrozil
- • Other fibrates
- • Lipid-lowering doses (≥1 g/day) of niacin
- • Cyclosporine
- • Danazol

Avoid with lovastatin:
- • Cyclosporine
- • Gemfibrozil

Do not exceed 20 mg lovastatin daily with:
- • Danazol
- • Diltiazem
- • Verapamil

Do not exceed 40 mg lovastatin daily with:
- • Amiodarone
- • Verapamil

Avoid large quantities of grapefruit juice (>1 quart daily)
Number of Cases of Rhabdomyolysis with Combination Fibrate Plus Statin*

15-Fold Increase

*Excludes cases involving cerivastatin.


Cases Reported per Million Prescriptions
Statin Advisory: Definitions of Muscle Toxicity

- **Myopathy** — a general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life
- **Myalgia** — muscle ache or weakness without creatine kinase (CK) elevation
  - Consider dose reduction or changing agent
- **Myositis** — muscle symptoms with increased CK levels
  - Stop Statins
- **Rhabdomyolysis** — muscle symptoms with marked CK elevation (>10x the upper limit of normal [ULN]) and creatinine elevation (usually with brown urine and urinary myoglobin)
  - Stop Statins
Risk Factors for Myopathy

• Age
  – < 65 yr 0.2% (2/1200)
  – ≥ 65 yr 2.3% (9/383)

• Renal insufficiency
  – CrCl ≤ 80 mL/min 1.2% (9/760)
  – CrCl > 80 mL/min 0.2% (2/823)

• OA/RA?

• Hypothyroidism
  – 2 patients with myopathy at 80-mg dose had an elevated TSH
<table>
<thead>
<tr>
<th>Statin</th>
<th>Myopathy*</th>
<th>ALT/AST ↑</th>
<th>Symptoms with the Drug (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Myalgia</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>0% (implied)</td>
<td>0.7%</td>
<td>3.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One jaundice</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Rare</td>
<td>1.1%</td>
<td>5.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minority symptomatic</td>
<td>(4.5%)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>0.06%</td>
<td>1.9%</td>
<td>2.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No liver disease</td>
<td>(1.7%)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>&lt; 0.1%</td>
<td>1.2%</td>
<td>2.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No liver disease</td>
<td>(1.0%)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>&lt; 0.03%</td>
<td>&lt; 0.1%</td>
<td>2.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 jaundice</td>
<td>(1.3%)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>0.05%</td>
<td>1.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No liver disease</td>
<td>(1.3%)</td>
</tr>
</tbody>
</table>

SEARCH Trial

- Double-blind randomized trial
- 12,064 men and women aged 18-80 years
- Patients had history of MI
- Patients either on or had indication for statin therapy
- Total Cholesterol of at least 3.5 mmol/L (135 mg/dL) if already on statin or 4.5 mmol/L (174 mg/dL) if not
- Patients with clear contraindication to study treatment were excluded
- Randomization to either 80 mg or 20 mg simvastatin daily done centrally using a minimization algorithm
- Patients assessed at 2, 4, 8, and 12 months after randomization and then every 6 months until final follow-up
- Primary endpoint was major vascular events, defined as coronary death, MI, stroke, or arterial revascularization
- Analysis was by intention to treat

### Adverse Effects Comparison

<table>
<thead>
<tr>
<th></th>
<th>80 mg simvastatin daily (n=6031)</th>
<th>20 mg simvastatin daily (n=6033)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alanine aminotransferase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 to ≤4 times ULN</td>
<td>197 (3.3%)</td>
<td>119 (2.0%)</td>
</tr>
<tr>
<td>&gt;4 times ULN</td>
<td>51 (0.8%)</td>
<td>40 (0.7%)</td>
</tr>
<tr>
<td>&gt;4 times ULN on repeat visits</td>
<td>14 (0.2%)</td>
<td>10 (0.2%)</td>
</tr>
<tr>
<td><strong>Creatine kinase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 to ≤10 times ULN</td>
<td>77 (1.3%)</td>
<td>31 (0.5%)</td>
</tr>
<tr>
<td>&gt;10 to ≤40 times ULN *</td>
<td>45 (0.7%)</td>
<td>12 (0.2%)</td>
</tr>
<tr>
<td>&gt;40 times ULN *</td>
<td>23 (0.4%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Myopathy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incipient</td>
<td>82 (1.4%)</td>
<td>12 (0.2%)</td>
</tr>
<tr>
<td>Definite†</td>
<td>53 (0.9%)</td>
<td>2 (0.0%)</td>
</tr>
<tr>
<td>No rhabdomyolysis</td>
<td>46 (0.8%)</td>
<td>2 (0.0%)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>7 (0.1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are number of patients (%). ULN = upper limit of normal for laboratory.

*20 (vs 11) patients with creatine kinase more than ten times ULN were asymptomatic (and so not classified as myopathy). †Five (vs one) of the patients with definite myopathy did not have a recorded measurement of creatine kinase more than ten times ULN, but presented with clinical myopathy.

Table 4: Myopathy and raised alanine aminotransferase and creatine kinase concentrations
Primo Study

• Study Design: Observational study of muscular symptoms in a population of 7,924 hyperlipidemic patients aged 18-75 years receiving high dosage statin therapy in a usual care, outpatient setting in France.

• Results: Muscular symptoms were reported by 10.49% of patients receiving high dose statin therapy. The highest rate of muscular symptoms was observed among patients receiving treatment with 80 mg simvastatin, at 18.2%.

• Risk factor analysis found that a personal or family history of muscular symptoms, cramps, hypothyroidism, and elevated CK levels are major risk factors for muscular symptoms during high dosage statin therapy.
Risks

High intensity statins:

• 3 excess cases of diabetes per 1000 statin-treated individuals per year

• 1 excess case of myopathy per 10,000

• 1 excess case Hemorrhagic stroke per 10,000

• Nausea/abdominal pain

• measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.
study patterns of use in a cohort of 34,501 elderly (65 years or more) patients using statins. 1990-1999

<table>
<thead>
<tr>
<th>Duration of treatment (months)</th>
<th>Adherent (%)</th>
<th>Partially adherent (%)</th>
<th>Non-adherent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>60</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>60</td>
<td>26</td>
<td>18</td>
<td>56</td>
</tr>
<tr>
<td>120</td>
<td>32</td>
<td>18</td>
<td>50</td>
</tr>
</tbody>
</table>

Benner JS et al. JAMA 2002;288:455
HMG-CoA-Reductase Inhibitors:

• Pravastatin and atorvastatin indicated for children
Possible Atherogenic Changes Accompanying Hypertriglyceridemia

- Increased VLDL cholesterol-rich remnants
- Low HDL
- Small, dense LDL
- Increased chylomicron remnants
- Coagulation changes

Risk of CHD by Triglyceride Level
(The Framingham Heart Study)

N=5127

Castelli WP. Am J Cardiol. 1992;70: 3H-9H.
Fibrates

Fenofibrate

![Fenofibrate structure](image)

Gemfibrozil

![Gemfibrozil structure](image)
# Pharmacokinetic Properties of Gemfibrozil and Fenofibrate

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Gemfibrozil</th>
<th>Fenofibrate (micronized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Metabolic Pathway</td>
<td>Glucuronidation</td>
<td>Glucuronidation</td>
</tr>
<tr>
<td>Effect on Oxidative Metabolism via CYP 450 Isoenzymes</td>
<td>Data inconsistent</td>
<td>Weak inhibitor of CYP 2C19, 2A6, mild to moderate inhibitor of CYP 2C9</td>
</tr>
<tr>
<td>Route of Elimination</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td>Half-Life (h)</td>
<td>1.3</td>
<td>19-27</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>98%</td>
<td>99%</td>
</tr>
<tr>
<td>Effect of Food on Absorption</td>
<td>UNK</td>
<td>Extent of absorption is increased by 35% under fed vs. fasted conditions.</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>100%</td>
<td>Nearly 100% (micronized)</td>
</tr>
<tr>
<td>Dose Reduction in Renal Impairment</td>
<td>CrCl 10-50 mL/min, reduce dose by 50%, &lt;10 mL/min, reduce dose by 75%</td>
<td>CrCl &lt;50 mL/min, reduce dose</td>
</tr>
</tbody>
</table>
Fibric Acid Derivatives

- Activate the nuclear transcription factor *peroxisome proliferator activated receptor alpha* (PPAR-alpha) which relates genes that control lipid metabolism
- Stimulates lipoprotein lipase
  - Results in hydrolysis of TG in chylomicrons and VLDL
  - Accelerates removal of VLDL and chylomicrons
- Does not alter secretion of VLDL from liver
- Also lower fibrinogen levels
Fibric Acid Derivatives

• Gemfibrozil (Lopid ®)
  – Same mechanism of action
  – More commonly used
  – Used in hypertriglyceridemia
Fibric Acid Derivatives

• Gemfibrozil
  – **Adverse effects**
    • GI effects
    • Myositis syndrome
      – Elevated CK, AST
      – Patients with renal disease at greatest risk
      – Myopathy reported in conjunction with *statins*
    • Hepatotoxicity
      – Elevated transaminase levels
      – Reversible upon discontinuation
  • Cholelithiasis
  – **Drug interactions**
    • Competes with highly bound drugs to albumin
    • Major problem with warfarin (Coumadin ®)
Fibric Acid Derivatives

• Fenofibrate (Tricor®)
  – Adjunctive therapy
  – Adult patients
  – Elevated serum triglycerides
    • At risk of pancreatitis
    • No response to dietary manipulation
  – Inhibits TG synthesis
    • Decreases VLDL
  – Stimulates catabolism of VLDL
  – Once daily administration
Presented at the American College of Cardiology conference on March 14, 2010, the ACCORD Lipid Trial, funded by the National Institutes of Health (NIH), evaluated

The occurrence of major cardiovascular events (nonfatal heart attack, nonfatal stroke, cardiovascular death) in patients receiving simvastatin plus fenofibrate, compared to simvastatin alone.

All patients in the study had a history of type 2 diabetes mellitus, were at high risk for cardiovascular disease, and were followed on average for 4.7 years. The trial found that there was no difference in cardiovascular outcomes between the two groups (Hazard Ratio = 0.92; 95% Confidence Interval: 0.79 – 1.08; p = 0.32).

The fenofibrate labeling currently states that no incremental benefit of fenofibrate on cardiovascular morbidity and mortality over and above that demonstrated for statin use alone had been established.
Niacin (Nicotinic Acid):

• Found to lower cholesterol levels in large doses as early as 1955
  – Gram doses rather than mg doses used as vitamin
  – Niacin, not niacinamide (nicotinamide)
  – Vitamin B₃
• Acts to decrease VLDL and LDL
  – Lowers cholesterol(10%) and TG (30%)
  – Maximal effects in 3 to 5 weeks
• Raises HDL
Niacin (Nicotinic Acid):

• Mechanism of Action:
  – Inhibits lipolysis in adipose tissue
    • Adipose tissue primary producer of FFA
    • FFA major precursor for TG synthesis
  – Decreases esterification of TG in liver
  – Increases lipoprotein lipase activity
  – Inhibits VLDL secretion and synthesis in liver
    • Decreases LDL production
  – Increases secretion of tPA and lowers fibrinogen
    • Reverses endothelial cell dysfunction contributing to thrombosis and atherosclerosis
  – Decreases HDL catabolism
  – Changes LDL particles from small, dense ones to ones that are large and buoyant
Niacin

- Increases HDL by up to 26%
- Decreases LDL by up to 17%
- Decreases TGs by up to 35%
- Decreases Lp(a) by up to 27%
Niacin (Nicotinic Acid):

• **Pharmacokinetics**
  - Orally administered
    • Rapidly absorbed
    • Peak levels in under one hour
  - Converted to nicotinamide
    • Incorporated into cofactor NAD
  - Excreted in urine
    • 88% excreted unchanged

• **Therapeutic Use**
  - Raises HDL (most effective agent)
Niacin (Nicotinic Acid): Toxicity

- Many untoward effects limit usefulness
- Flushing
  - Cutaneous vasodilatation in almost all
  - Accompanied by warmth and itching
  - Tolerance within one to two weeks
  - Blunted by use of aspirin ½ hour earlier
- GI distress
- Liver dysfunction
- Hyperuricemia
  - Inhibits tubular secretion of uric acid
- Impaired glucose tolerance
  - Acanthosis appearance associated with insulin resistance
Niacin

- Immediate release, quickly-absorbed
- Extended release, absorbed over 8 hrs
- Sustained release, absorbed over 12-24 hours
- Combination of extended release niacin and immediate release lovastatin
Flushing Tips

• When beginning or increasing dose- take 400mg Ibuprofen (or equivalent Naproxen or Aspirin) 30 min before Niaspan®

• Avoid Hot drinks, Hot shower, or spicy foods 1 hr before or anytime after Niaspan® dosing

• Eat a low-fat snack with Niaspan®

• Take right before going to bed
Bile Acid Binding Resins:

- Cholestyramine, Colestipol, Colesevelam
- Anion exchange resins
  - Large polymeric cations
  - Insoluble chloride salt
  - Ion exchange sites are trimethyl-benzyl-ammonium groups
- Bind negatively charged bile acids and bile salts in small intestine
  - Prevents absorption of bile acids and cholesterol
  - Chloride exchanged for bile acids
  - Resin itself not absorbed
Cholestyramine: Bile acid effects
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dose/day</th>
<th>% Decrease LDL</th>
<th>Cost/ Month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>8-32 gm</td>
<td>20</td>
<td>$126.53</td>
</tr>
<tr>
<td>(Questran)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colestipol</td>
<td>4-30 gm</td>
<td>20</td>
<td>$115.11</td>
</tr>
<tr>
<td>(Colestid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colesevelam</td>
<td>2.6-3.8 gm</td>
<td>18</td>
<td>$141.75</td>
</tr>
<tr>
<td>(Welchol)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Bile Acid Binding Resins:

• Bile acids normally 95% reabsorbed in jejunum
• 10 fold excretion of bile acids noted
• Bile acids are metabolites of cholesterol
• Lowering bile acids causes hepatocytes to increase conversion of cholesterol to bile acids
• Intracellular cholesterol concentration decreases
  – Activates hepatic uptake of LDL and fall in serum LDL
  – Increased uptake mediated by up-regulation of cell surface LDL receptors
Bile Acid Binding Resins:

- **Drugs of choice in treating IIA and IIB**
  - For homozygous IIA, no effect since LDL receptors lacking
  - 20-25% reduction in LDL-C after 2 to 4 weeks
  - Increase in HDL-C

- **Toxicity**
  - Unpleasant texture
  - Nausea, constipation, bloating, flatulence
  - Need large amount of fluids, high bulk diet
  - Impaired absorption of fat-soluble vitamins

- **Useful also in itching associated with partial biliary obstruction**
Bile Acid Binding Resins:

• Drug Interactions
  – Interfere with intestinal absorption of anionic drugs
    • Thiazides
    • Digoxin
    • Warfarin
    • Thyroxin
    • Tetracycline
  – Drugs to be taken 2 hours before or 4 hours after cholestyramine or colestipol
• Large Doses needed
  – Cholestyramine 8 grams three times daily
  – Colesevelam 3 tablets (1875 mg) twice a day
Ezetimibe (Zetia®)

- Localizes and acts at brush border of small intestine
  - Inhibits absorption of cholesterol
  - Leads to decrease in delivery of intestinal cholesterol to the liver
- Causes reduction of hepatic cholesterol stores and increase in clearance of cholesterol from the blood
Ezetimibe (Zetia®)

- Mechanism of action is complementary to that of HMG-CoA reductase inhibitors
- Results in reductions in:
  - Total cholesterol
  - LDL-C (18%)
  - Apolipoprotein B
  - Triglycerides
- Results in increase in HDL-cholesterol
Ezetimibe (Zetia®)

- Inhibits intestinal absorption of cholesterol by 54%
- No effect on plasma concentrations of Vitamins A, D or E
- No impairment of steroid hormone synthesis
Ezetimibe (Zetia®)

- Well-absorbed orally
- Extensively conjugated to pharmacologically active glucuronide
- Highly bound to plasma proteins
- Metabolized in liver and small bowel via glucuronide conjugation
- Biliary and renal excretion
Ezetimibe (Zetia®)

• Well tolerated
• Adverse reactions no different than placebo
• Antacids and cholestyramine decrease effect of ezetimibe
• 10 mg once daily
Effect of Ezetimibe Monotherapy on Lipids in Patients With Primary Hypercholesterolemia

- **LDL-C**: Placebo (n=226) -16.9*, Ezetimibe 10 mg (n=666) -1.6
- **TG**: Placebo (n=226) +5.7, Ezetimibe 10 mg (n=666) -5.7*
- **HDL-C**: Placebo (n=226) +1.3*, Ezetimibe 10 mg (n=666) +0.4

*P<0.01.
Effect of Ezetimibe + Lovastatin on Lipids in Primary Hypercholesterolemia

<table>
<thead>
<tr>
<th></th>
<th>LDL-C**†</th>
<th>HDL-C*</th>
<th>TG**‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe + pooled lovastatin (n=192)</td>
<td>-40</td>
<td>+9</td>
<td>-11</td>
</tr>
<tr>
<td>Pooled lovastatin groups (n=220)</td>
<td>-25</td>
<td>+4</td>
<td>-22</td>
</tr>
</tbody>
</table>

*P<0.01
†Calculated
‡Median percent change

Simvastatin With or Without Ezetimibe in Familial Hypercholesterolemia

The ENHANCE trial
ClinicalTrials.gov number: NCT00552097

Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia

John J.P. Kastelein, M.D., Ph.D., Fatima Akdim, M.D., Erik S.G. Stroes, M.D., Ph.D., Aeilko H. Zwinderman, Ph.D., Michiel L. Bots, M.D., Ph.D., Anton F.H. Stalenhoef, M.D., Ph.D., F.R.C.P., Frank L.J. Visseren, M.D., Ph.D., Eric J.G. Sijbrands, M.D., Ph.D., Mieke D. Trip, M.D., Ph.D., Evan A. Stein, M.D., Ph.D., Daniel Gaudet, M.D., Ph.D., Raphael Duivenvoorden, M.D., Enrico P. Veltri, M.D., A. David Marais, M.D., Ph.D., and Eric de Groot, M.D., Ph.D., for the ENHANCE Investigators*
Mean cIMT during 24 months of therapy
Longitudinal, repeated measures analysis

Mean IMT (mm)

- Simva
- Eze-Simva

P=0.88

Months

ENHANCE
Conclusion

The addition of Ezetimibe to Simvastatin did lead to expected changes in LDL-c and hsCRP, but did not reduce any cIMT parameter.

The reason(s) for this discrepancy currently remains unknown.
Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness

Allen J. Taylor, M.D., Todd C. Villines, M.D., Eric J. Stanek, Pharm.D., Patrick J. Devine, M.D., Len Griffen, M.D., Michael Miller, M.D., Neil J. Weissman, M.D., and Mark Turco, M.D.
Carotid intimal thickness
Results: Lipid Levels

Figure 1. Mean Percent Changes in Cholesterol and Triglyceride Levels over the 14-Month Study Period among the 208 Patients Who Completed the Study, According to Treatment Group.

P values are given for the comparison between the two treatment groups at 14 months. The vertical bars indicate the standard errors. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.
Results: Primary Endpoint
Between-group Change in CIMT

- Niacin was superior to ezetimibe for the primary endpoint of the between group difference in carotid intima-media thickness.
  - P = 0.003
Major adverse cardiovascular events occurred at a significantly lower incidence in the niacin (2/160 patients [1.2%] vs. the ezetimibe group (9/165 patients [5.5%]))

- Chi-square p=0.04; Log-rank p = 0.047
Non-statin therapies

- For hyperlipidemia, non statin therapies, alone or in combination with statins, do not provide acceptable risk reduction benefits compared to adverse effects.
- These include:
  - Zetia
  - Fibrates
  - Fish oil
  - Niacin
- For the most part, these should be avoided with few exceptions
- Why don’t non-statins play a more prominent role in the new guidelines?