Lipid Therapy: Statins and Beyond

Ivan Anderson, MD
RIHVH Cardiology
Outline

• The cholesterol hypothesis and lipid metabolism

• The Guidelines
  – 4 Groups that Benefit from Lipid therapy
  – Initiation and monitoring of therapy

• Other therapies
Outline

• The cholesterol hypothesis and lipid metabolism

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  – 4 Groups that Benefit from Lipid therapy
  – Initiation and monitoring of therapy

• Other therapies
Atheroma Formation
Background

\[
\text{acetyl CoA + acetoacetyl CoA} \rightarrow \text{HMG CoA synthase} \rightarrow \text{HMG CoA} \rightarrow \text{HMG CoA reductase} \rightarrow \text{mevalonate} \rightarrow \text{mevalonate PP} \rightarrow \text{farnesyl PP} \rightarrow \text{farnesylated proteins} \rightarrow \text{squalene} \rightarrow \text{lanosterol} \rightarrow \text{cholesterol} \rightarrow \text{steroid hormones, vitamin D, bile acids}
\]
Outcomes Data for Secondary Prevention with Statins

NEJM 2005; 352:1425-35
Lipoprotein Structure
Outline

• The cholesterol hypothesis and lipid metabolism

• The Guidelines
  – 4 Groups that Benefit from Lipid therapy
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• The cholesterol hypothesis and lipid metabolism

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  – Initiation and monitoring of therapy

• Other therapies
### Before Initiation, Reversible Causes of Elevated Lipids

<table>
<thead>
<tr>
<th>Secondary Cause</th>
<th>Elevated LDL–C</th>
<th>Elevated Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Saturated or <em>trans</em> fats, weight gain, anorexia</td>
<td>Weight gain, very low-fat diets, high intake of refined carbohydrates, excessive alcohol intake</td>
</tr>
<tr>
<td>Drugs</td>
<td>Diuretics, cyclosporine, glucocorticoids, amiodarone</td>
<td>Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides</td>
</tr>
<tr>
<td>Diseases</td>
<td>Biliary obstruction, nephrotic syndrome</td>
<td>Nephrotic syndrome, chronic renal failure, lipodystrophies</td>
</tr>
<tr>
<td>Disorders and altered states of metabolism</td>
<td>Hypothyroidism, obesity, pregnancy*</td>
<td>Diabetes (poorly controlled), hypothyroidism, obesity; pregnancy*</td>
</tr>
</tbody>
</table>
4 Groups Benefiting From Statin Therapy

1. Diagnosed atherosclerotic cardiovascular disease (ASCVD, i.e. MI, CVA, PAD)

1. LDL > 190 mg/dL

1. Diabetes I or II, age 40-75

1. >7.5% estimated 10-year risk of ASCVD by the ACC risk calculator
ASCVD Statin Benefit Groups

Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL–C 70-189 mg/dL.

- Adults age >21 y and a candidate for statin therapy
  - Clinical ASCVD
    - Yes: Estimated 10-y ASCVD risk ≥7.5%
      - High-intensity statin
    - Yes: LDL–C ≥190 mg/dL
      - High-intensity statin
    - Yes: Diabetes Type 1 or 2 Age 40-75 y
      - High-intensity statin
    - Yes: Age ≤75 y
      - High-intensity statin
    - Yes: Age >75 y OR if not candidate for high-intensity statin
      - Moderate-intensity statin
  - No: Moderate-intensity statin
  - No: Estimated 10-y ASCVD risk ≥7.5%
    - Yes: Moderate-to-high intensity statin
    - No: High-intensity statin

Definitions of High- and Moderate-Intensity Statin Therapy

(See Table 5)
- High: Daily dose lowers LDL–C by approx. ≥50%
- Moderate: Daily dose lowers LDL–C by approx. 30% to <50%

ASCVD prevention benefit of statin therapy may be less clear in other groups

In selected individuals, consider additional factors influencing ASCVD risk and potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment.
7.5% 10-Year risk ASCVD: NNT > NNH

NNH = 33
Harm and Benefit of Statins in Primary Prevention

- **Number needed to treat (NNT)**
  - 35% relative risk reduction with moderate-intensity statin (NNT = 38-44)
  - 45% relative risk reduction with a high-intensity statin (NNT = 30)

- **Number needed to harm (NNH)**
  - Driven mostly by development of diabetes
  - ~1/10,000 risk of myopathy
  - ~1/10,000 risk of hemorrhagic stroke
  - NNH = 100 for moderate-intensity statin
  - NNH = 33 for high-intensity statin

- **Secondary prevention:** 20% reduction in ASCVD events for every 39 mg/dL reduction in LDL
Estimate 10-y ASCVD Risk with Pooled Cohort Equations*

ASCVD prevention benefit of statin therapy may be less clear in other groups.

In selected individuals, consider additional factors influencing ASCVD risk‡ and potential ASCVD risk benefits and adverse effects, drug-drug interactions.

≥7.5% estimated 10-y ASCVD risk and age 40-75 y

Coronary Calcium Score

Moderate-to-high intensity statin
## Statins by Intensity

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
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</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL–C by approximately ≥50%</td>
<td>Daily dose lowers LDL–C by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C by &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40†)–80 mg</strong>&lt;br&gt;<strong>Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg</strong>&lt;br&gt;<strong>Rosuvastatin (5) 10 mg</strong>&lt;br&gt;<strong>Simvastatin 20–40 mg‡</strong>&lt;br&gt;<strong>Pravastatin 40 (80) mg</strong>&lt;br&gt;<strong>Lovastatin 40 mg</strong>&lt;br&gt;<strong>Fluvastatin XL 80 mg</strong>&lt;br&gt;<strong>Fluvastatin 40 mg bid</strong>&lt;br&gt;<strong>Pitavastatin 2–4 mg</strong></td>
<td><strong>Simvastatin 10 mg</strong>&lt;br&gt;<strong>Pravastatin 10–20 mg</strong>&lt;br&gt;<strong>Lovastatin 20 mg</strong>&lt;br&gt;<strong>Fluvastatin 20–40 mg</strong>&lt;br&gt;<strong>Pitavastatin 1 mg</strong></td>
</tr>
</tbody>
</table>
Other therapies

- Ezetimibe
- Omega 3 Fatty acids
- Niacin
- Fibrates
- CETP Inhibitors
- PCSK-9 inhibitors
• Other therapies
  – Ezetimibe
  – Omega 3 Fatty acids
  – Niacin
  – Fibrates
  – CETP Inhibitors
  – PCSK-9 inhibitors
Mortality Reduction by LDL Level Across Statin Trials + Improve-IT

Outcome Data for Improve-IT

![Graph showing event rates over time for Simvastatin monotherapy and Simvastatin-ezetimibe. Hazard ratio, 0.936 (95% CI, 0.89–0.99) P=0.016.]

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<tr>
<th>Years since Randomization</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<td>Event Rate (%)</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
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No. at Risk

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<th>Drug</th>
<th>0</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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</thead>
<tbody>
<tr>
<td>Simvastatin-ezetimibe</td>
<td>9067</td>
<td>7371</td>
<td>6801</td>
<td>6375</td>
<td>5839</td>
<td>4284</td>
<td>3301</td>
<td>1906</td>
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<tr>
<td>Simvastatin</td>
<td>9077</td>
<td>7455</td>
<td>6799</td>
<td>6327</td>
<td>5729</td>
<td>4206</td>
<td>3284</td>
<td>1857</td>
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</table>

• Other therapies
  – Ezetimibe
  – Omega 3 Fatty acids
  – Niacin
  – Fibrates
  – CETP Inhibitors
  – PCSK-9 inhibitors
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The JELIS Trial

- In Japanese men aged 40 to 75 years and postmenopausal women ≤75 years with and without CHD and LDL–C ≥170 mg/dL, EPA 1,800 mg added to statin therapy:
  - Did not reduce LDL–C and modestly reduced triglycerides (5%), compared with statin therapy alone.
  - Reduced the risk for CHD events (including revascularization and unstable angina) by 19%, compared with statin therapy alone.
  - Caused a similar magnitude of risk reduction in primary- and secondary-prevention populations, but the study was insufficiently powered to evaluate these populations separately.
  - Increased the risk for gastrointestinal disturbance, skin abnormalities, hemorrhage, and abnormal SGOT.

Am Heart J 2003; 146:613-20
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Other therapies

- Ezetimibe
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Niacin

• If at first you don’t succeed trial, trial again
• RCT of Niacin
  – CDP
  – HATS
  – AIM-HIGH
Lipid Values at Baseline and during Follow-up

- Lowered LDL–C levels to an additional 6%
- Increased HDL–C by an additional 14%
- Reduced triglycerides by an additional 23%
- Lowered apoB by an additional 10%
- Reduced Lp(a) by an additional 19%

Kaplan–Meier Curve for the Primary End Point.

No. at Risk
Placebo plus statin 1696 1581 1381 910 436
Niacin plus statin 1718 1606 1366 903 428
Niacin Other Trials

• CDP: Clofibrate and niacin in coronary heart disease
  – JAMA 1975;231:360–81
  – Decreased total cholesterol by 10% and triglycerides by 27%
  – Regimens were stopped before trial completion 2/2 adverse events (atrial fibrillation, skin flushing, GI side effects, gout and transammonitis)

• HATS: Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease
  – Decreased LDL, Increased HDL
  – Improved angiographic atheromas slightly
  – Not powered to detect clinical events
• Other therapies
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• Other therapies
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Fibrates – Use with Caution

- Gemfibrozil should not be used with statins related to increased risk of rhabdomyolysis
- Fenofibrate should not be used if GFR < 30 mL/min/1.73m²
  - If GFR is 30-59 mL/min/1.73m² then, do not exceed 54 mg/day of fenofibrate
  - (Typical dose of Tricor (fenofibrate) is 145 mg PO QD, alternative dose is 48 mg PO QD)
FIELD Study

- In adults aged 50 to 75 with diabetes—with total cholesterol <250 mg/dL, and total cholesterol/HDL ratio ≥4.0 or triglycerides <450 mg/dL—fenofibrate, compared with placebo:
  - Modestly reduced LDL–C, minimally increased HDL–C, and substantially reduced triglycerides.
  - In those without clinical CVD, reduced the risk for CHD/CVD events.
  - In those with clinical CVD, did not reduce the risk for CHD/CVD events.
  - Was no different than placebo for myositis or rhabdomyolysis, CK or ALT elevations, renal disease requiring hemodialysis, or cancer.
  - Had higher rates of pancreatitis, pulmonary embolism, and increased creatinine levels on average by 0.113 to 0.136 mg/dL.
Percentage Changes in Lipid Values – Helsinki Heart Study

Helsinki Heart Study – Gemfibrozil vs Placebo

VA-HIT: Gemfibrozil vs Placebo

LOPID®
(Gemfibrozil Tablets, USP)

DESCRIPTION
LOPID® (gemfibrozil tablets, USP) is a lipid regulating agent. It is available as tablets for oral administration. Each tablet contains 600 mg gemfibrozil. Each tablet also contains calcium stearate, NF; candelilla wax, FCC; microcrystalline cellulose, NF; hydroxypropyl cellulose, NF; hypromellose, USP; methylparaben, NF; Opaspray white; polyethylene glycol, NF; polysorbate 80, NF; propylparaben, NF; colloidal silicon dioxide, NF; pregelatinized starch, NF. The chemical name is 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid, with the following structural formula:

\[
\begin{align*}
\text{CH}_3 & \quad \text{O-CH}_2\text{-CH}_2\text{-CH}_2\text{-C-CH}_3 \\
\text{CH}_3 & \quad \text{O-CH}_2\text{-CH}_2\text{-CH}_2\text{-C-COOH} \\
\end{align*}
\]

5. Concomitant therapy with LOPID and an HMG-CoA reductase inhibitor is associated with an increased risk of skeletal muscle toxicity manifested as rhabdomyolysis, markedly elevated creatine kinase (CPK) levels, and myoglobinuria, leading in a high proportion of cases to acute renal failure and death. IN PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, THE BENEFIT OF COMBINED THERAPY WITH LOPID AND an HMG-CoA REDUCTASE INHIBITOR DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, Rhabdomyolysis, AND ACUTE RENAL FAILURE (see PRECAUTIONS, Drug Interactions). The use of fibrate tablets, including LOPID,
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Cholesteryl Ester Transfer Protein (CETP) Inhibitors

• Elevate HDL and lower LDL
• Mediates transfer of cholesterol between HDL and atherogenic lipoproteins containing apolipoprotein B (e.g. LDL)
• Torcetrapib
  – first CETP inhibitor used in clinical trial
  – ↑ HDL by > 70%  ↓ LDL by > 25%
  – Increased mortality 2/2 elevated aldosterone levels
More on CETP Inhibitors

• Dalcetrapib
  – In dal-OUTCOMES trial didn’t affect apoB, LDL and triglycerides much, but ↑ HDL
  – No affect on mortality

• Anacetrapib
  – Modest improvement in cardiovascular events on top of statin in the REVEAL trial

• Evacetrapib
  – No improvement on top of placebo in reducing cardiovascular outcomes in the ACCELERATE study
First Major Coronary Event during Follow-up

A First Major Coronary Event

No. at Risk
Placebo 15,224 14,649 14,088 13,293 8993
Anacetrapib 15,225 14,636 14,104 13,359 9193
Benefit per 1000 patients in anacetrapib group 1±2 2±3 6±3 9±4

B First Major Coronary Event, According to Year of Follow-up

<table>
<thead>
<tr>
<th>Year of First Event</th>
<th>Anacetrapib (N=15,225)</th>
<th>Placebo (N=15,224)</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>465 (3.1)</td>
<td>476 (3.1)</td>
<td>0.98 (0.86–1.11)</td>
<td>0.96 (0.84–1.10)</td>
</tr>
<tr>
<td>2</td>
<td>398 (2.7)</td>
<td>414 (2.8)</td>
<td>0.86 (0.75–0.99)</td>
<td>0.83 (0.73–0.94)</td>
</tr>
<tr>
<td>≥4</td>
<td>370 (2.6)</td>
<td>427 (3.0)</td>
<td>0.85 (0.76–0.95)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;1</td>
<td>1175 (8.0)</td>
<td>1327 (9.1)</td>
<td>0.81 (0.75–0.87)</td>
<td>0.004</td>
</tr>
<tr>
<td>All</td>
<td>1640 (10.8)</td>
<td>1803 (11.8)</td>
<td>0.83 (0.78–0.89)</td>
<td></td>
</tr>
</tbody>
</table>

Test for trend across years, χ²=4.87 (P=0.03)
Test for heterogeneity between ≤1 yr and >1 yr, χ²=1.82 (P=0.18)
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Proprotein Convertases

Substrates of proprotein convertases (PCs) are precursors of hormones, growth factors, receptors, enzymes, surface glycoproteins etc...

- Signal peptide
- Biologically active peptide or mature protein

Basic PCs: (R/K)-X_{n}-R
SKI-1/S1P: (R/K)-X-(hydrophobic)-Z
PCSK9: (V/I)FAQ
PCSK9, LDL Receptors, & LDL

- PCSK9 is expressed in highest levels in liver, intestine and kidney
- High PCSK9 → Increased phagocytosis of LDL Receptors (i.e. decreased liver cell surface LDL Receptors)
- Low surface LDL receptors on the liver → decreased LDL clearance
- Hence high PCSK9 levels → high LDL levels
PCSK-9 Binds the Epidermal Growth Factor-like repeat A (EGF-A) of LDL

EGF-A portion of LDL Receptor

PCSK9

Epidemiologic Studies of PCSK9

NEJM 2006; 354:1264-72
FOURIER Trial - Repatha (evolocumab)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>13,779</td>
<td>13,784</td>
<td></td>
</tr>
<tr>
<td>13,251</td>
<td>13,288</td>
<td></td>
</tr>
<tr>
<td>13,151</td>
<td>13,144</td>
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<tr>
<td>12,954</td>
<td>12,964</td>
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<td>12,311</td>
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<td>790</td>
<td>768</td>
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<tr>
<th>Weeks</th>
<th>LDL Cholesterol (mg/dl)</th>
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<tr>
<td>0</td>
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<td>4</td>
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<td>790</td>
<td>768</td>
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<table>
<thead>
<tr>
<th>Absolute difference (mg/dl)</th>
<th>54</th>
<th>58</th>
<th>57</th>
<th>56</th>
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<th>54</th>
<th>52</th>
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<td>Percentage difference</td>
<td>57</td>
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<td>61</td>
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<td>58</td>
<td>57</td>
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<td>56</td>
<td>54</td>
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<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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FOURIER Trial - Repatha (evolocumab)

A Primary Efficacy End Point

- Hazard ratio, 0.85 (95% CI, 0.79–0.92)
- P<0.001

Cumulative Incidence (%)

- Placebo
- Evolocumab

No. at Risk

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<thead>
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B Key Secondary Efficacy End Point

- Hazard ratio, 0.80 (95% CI, 0.73–0.88)
- P<0.001

Cumulative Incidence (%)

- Placebo
- Evolocumab

No. at Risk

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</table>
Safety and Efficacy – Praluent (alirocumab)


**Graph:**
- **X-axis:** Week
- **Y-axis:** Least-Squares Mean Calculated LDL Cholesterol Level (mg/dl)
- **Data Points:**
  - Placebo + statin therapy at maximum tolerated dose ± other LLT
  - Alirocumab + statin therapy at maximum tolerated dose ± other LLT

**Legend:**
- **Color Coding:**
  - Red: Placebo + statin therapy at maximum tolerated dose ± other LLT
  - Blue: Alirocumab + statin therapy at maximum tolerated dose ± other LLT

**Statistics:**
- **Placebo Group:**
  - Initial LDL: 118.9 mg/dl (3.08 mmol/liter)
  - Final LDL: 122.6 mg/dl (3.17 mmol/liter)
  - Change: -61.0%)
- **Alirocumab Group:**
  - Initial LDL: 48.3 mg/dl (1.25 mmol/liter)
  - Final LDL: 57.9 mg/dl (1.50 mmol/liter)
  - Change: -52.4%

**No. of Patients with Data Available**
- Placebo: 780, 754, 747, 746, 716, 708, 694, 676, 659, 652
- Alirocumab: 1530, 1473, 1458, 1436, 1412, 1386, 1359, 1349, 1324, 1269

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"I’m a little concerned about your cholesterol and, oh yeah, that’s not good either."