Hyperlipidemia

Intensive Review of Internal Medicine

Scott Kinlay, MBBS, PhD
Cardiovascular Division, VA Boston Healthcare System
Cardiovascular Division, Brigham & Women’s Hospital
Harvard Medical School, Boston, MA

Disclosures

• Research support to the VA Boston Cardiovascular Division
  • Novartis
  • The Medicines Company

Cholesterol Pathways
### Calculating LDL-Chol

\[
LDL = TC - HDL - VLDL
\]

\[
VLDL = 20\% \text{ of all fasting triglycerides}
\]

\[
LDL = TC - HDL - TG/5
\]

**Friedewald Equation**

Valid through TG ~ < 400 mg/dL

### Genetic Dyslipidemias

Commonly in the Boards

- LDL
  - Familial Hypercholesterolemia
- Triglycerides
  - Type III Hyperlipidemia
    - (yellow palm creases, TGs > 500mg/dL)
  - Lipoprotein Lipase Defects
- HDL
  - Tangier’s Disease
    - Low HDL
  - Defect in ABCA1

### Familial Hypercholesterolemia

- Cutaneous/tendon xanthomas, corneal arcus, strong family history
- Autosomal dominant
  - Homozygous – 1:1 million
    - Early course. drugs, apheresis, liver transplant
  - Heterozygous – 1: 500
    - Drugs, ± apheresis
  - Defect: LDL receptor mutations ( >200 known):
    - Receptor activity influences disease course
  - ↑ in certain populations (founder effect):
    - Lebanon, French Canadians, Lithuanian Jews

### Diagnosis: FH

- Clinical
- Definitive:
  - CHO > 260 in children < 16 or >290 adults OR
  - LDL > 190 adults
  - AND
  - Tendon xanthoma in patient or 1st/ 2nd degree relative
- Possible:
  - Elevated lipids plus
    - FHx MI < 50 in 2nd degree or < 60 1st degree
  - FhX CHO > 290

### Secondary Causes of HyperTriglyceridemia

- Nephrotic syndrome (Urine analysis)
- Thyroid abnormalities (TSH)
- Drugs (Thiazides, HRT, beta blockers, etc)
- Diet (Excess carbs)
- Diabetes:
  - Inadequate control - Thiazolidinedione: Actos, Avandia?
  - Undiagnosed
- Alcohol
- Obesity

### Heterozygous Familial Hypercholesterolemia is Characterized by ..

- Elevated LDL
- Palmar xanthomas
- Autosomal Recessive Inheritance
- Low HDL
- Pancreatitis
Heterozygous Familial Hypercholesterolemia is Characterized by ..

a) Elevated LDL  
b) Palmar xanthomas  
c) Autosomal Recessive Inheritance  
d) Low HDL  
e) Pancreatitis

Answer:  a. Elevated LDL

Secondary Contributors to Hypertriglyceridemia Include..

a) Nephrotic Syndrome  
b) Poorly controlled diabetes mellitus  
c) Excessive alcohol intake  
d) Hypothyroidism  
e) All of the above

Answer:  e. All of the above

Secondary Contributors to Hypertriglyceridemia Include..

a) Nephrotic Syndrome  
b) Poorly controlled diabetes mellitus  
c) Excessive alcohol intake  
d) Hypothyroidism  
e) All of the above

Answer:  e. All of the above

Cholesterol & Cardiovascular Risk

LDL Lowering Therapies

• Statins – Primary Agents (more proof)  
• Secondary Agents
  • Cholesterol GI Uptake
    • Binders (Cholestyramine, Colesevelam)  
    • Ezetimibe  
  • Plant Stanol Esters  
    • Benecol  
  • Niacin (more effect on HDL/Trigs)  
  • Fibrates (more effect on HDL/Trigs)  
  • Fish Oil (more on Trigs, platelets, arrhythmia)
Statins and Cause of Death: Meta-Analysis of 14 Trials
Cholesterol Treatment Trialists’ Collaboration

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Events (%)</th>
<th>RR CHD</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Causes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>3.4/4.4</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.9/1.1</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Other vascular</td>
<td>0.9/1.3</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Any non-CHD vascular</td>
<td>1.2/1.3</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Any vascular</td>
<td>4.7/5.7</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Any nonvascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-vascular causes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>3.4/3.4</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>0.6/0.5</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>0.1/0.1</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>1.1/1.2</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Any nonvascular</td>
<td>3.8/4.0</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Any Death</td>
<td>8.5/9.7</td>
<td>0.88</td>
<td></td>
</tr>
</tbody>
</table>


Relative Risk reduction = 12%

Statins Are Indicated For High Absolute Risk of Atherosclerosis Events

Absolute Risk

PROVE-IT: Primary Endpoint

HPS: Vascular Event By Prior Disease

*CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke
ASCOT: MI & Fatal CHD

- Atorvastatin 10 mg
- Placebo
- n = 10,305
- LDL = 125mg/dL
- LDL = 90mg/dL
- HR = 0.64 (0.50-0.83)
- p = 0.0005

36% Reduction


How to Use Statins

35% Relative Reduction Yields a Higher Absolute Risk Reduction For Higher Risk Patients

Absolute LDL Change at 1 Year and Percentage Reduction in Events

Controversy in Statin Therapy

- People at higher ABSOLUTE risk obtain more benefit from lower LDL levels
- People at low absolute risk probably get less benefit (at the same relative risk reduction)
- The controversy of statin therapy in primary prevention is economic – are statins a cost-effective use of resources in low risk patients
- Think about absolute risk to determine statin therapy and intensity

Green LA. Arch Intern Med 2010; 170: 1007
Where Statins May Not Work

Statins and Aortic Stenosis
No effect on progression of aortic stenosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>AVA % Bicuspid</th>
<th>AVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saltire</td>
<td>Atorva 80</td>
<td>~1.0 cm² ~ 5%</td>
<td>11% vs 19%</td>
</tr>
<tr>
<td>SEAS</td>
<td>Simva 40 + Ezetimibe 10</td>
<td>~ 1.3 cm² ~ 5%</td>
<td>28% vs 30%</td>
</tr>
<tr>
<td>Astronomer</td>
<td>Rosuva 40</td>
<td>~ 1.5 cm² ~ 50%</td>
<td>28% vs 27%</td>
</tr>
</tbody>
</table>

Side Effects of Statins

- Fairly low in clinical trials
- Risk of myopathy is low
- Rhabdo (↑ CK, pain, ill) 1:10,000
- Myositis (↑ CK > 10 x ULN, ache) ~ 1%
- Myalgia (normal CK, ache) 1 - 5%?
- LFT abnormalities (> 3 x ULN)
- Low risk 1-3%
- Reversible

Increased Risk of Statin Intolerance: Rhabdomyolysis

- Erythromycin
- Cyclosporin
- HIV retroviral inhibitors
- Grapefruit juice
- Combination lipid therapy: Fibrates (gemfibrozil)
- Niacin

FDA: High dose simva

Other Potential Causes of CK↑

- Hypothyroid (also increases lipids)
- Other Inflammatory Myopathies
  - Polymyositis, Dermatomyositis (heliotrope)
  - Weakness, dysphagia, ±Connective Tissue symptoms (Raynauds)
  - Also present with ↑CK and Myopathic EMG
- Polymyalgia Rheumatica (age > 50 yrs)
- Diffuse stiffness, mild fever,
- Temporal Arteritis 25% (Ocular emergency)
- Normal CK, ↑ESR
**Statin Myalgias**

- 5% in clinical trials, but higher in clinical practice? Happen with all statins
- Aches and pains without CK rise
- No clear cause
- Consider other causes of muscle aches
- No adjunctive therapy consistently works

**Management**

- Trial of stopping and starting statin
- Move to another statin/low dose statin

**Non-Statin Therapies**

**Second Agent for LDL-Lowering**

- Plant stanol ester (5-10% ↓ LDL)
- Margarines: (Benecol, Take Control) - Modest effect
- Pill: Health food store – (Basikol)
- Cholesterol uptake
  - Bile Acid Sequestrants (10-15% ↓ LDL)
  - Colesevelam (Wellchol): 3 tabs po BID
  - Cholestyramine/Not with elevated Tg’s
  - Ezetimibe (Zetia) (10-20% ↓ LDL)

**Ezetimibe Controversy?**

- ENHANCE Study: Simva vs Simva + Ezetimibe
  - Ezetimibe no additional effect on progression of carotid intimal media thickness
- SEAS Study: Simva + Ezetimibe vs Placebo
  - No effect on progression of aortic stenosis
  - But 2ndary endpoint: Ischemic CV events
  - HR = 0.78, p = 0.02

Waiting for IMPROVE IT TIMI 39, but not a first line agent

**Agents for HDL/ Triglycerides**

- Fibrate (15% ↑ HDL/15-20% ↓ TG)
- Fenofibrate (TriCor) (48 – 145 mg/day):
  - Lowers trigs
  - Lower dose with eGFR 30-50 ml/min
- Niacin (titrate SLOWLY up to 2 grams/day)
  - (15-30% ↑ HDL/20-30% ↓ TG)
  - 15 -50% won’t tolerate; ? Worsens diabetes?
- Fish Oil (1-2 grams/day) (15-30% ↓ TG)
  - Mainly effect Trigs
  - Antiplatelet Effect
  - ?Anti-arrhythmia effect

**ACCORD: Fenofibrate in DM II**

5518 Subjects Followed for 4.7 Years

- Mean simva dose about 20mg/ d
- Fenofibrate vs placebo
  - No diff in ↓ LDL
  - ~ 2% more increase in HDL (p = 0.02)
  - ~ 15% more decrease in Trigs (p< 0.001)
- No differences in outcomes
  - Primary CV outcome (HR = 0.92, p = 0.33)
  - Major Coronary (HR = 0.92, p = 0.26)
  - Any Stroke (HR = 1.05, p = 0.80)
  - All Cause Death (HR = 0.91, p = 0.33)

The ACCORD Study Group. NEJM 2010; 362: 1563
AIM-HIGH: Niacin + Simvastatin
- RCT to assess the effect of Niacin 1.5-2g/d in addition to high dose simvastatin ± ezetimibe
- Statin and Ezetimibe to get LDL 40-80mg/dL
- CAD, PVD & atherogenic lipid profile
  - LDL < 180mg/dL, HDL < 40mg/dL, < 50mg/dL, TGs 150-400 mg/dL.
- At 2 yrs: HDL 20%↑, TG 26%↓, LDL 16%↓
- BUT Trial stopped at 3 yrs – no benefit from adding niacin to statin ± ezetimibe

AIM-HIGH Investigators. NEJM 2011; 365: 2255

NCEP ATP III: Goals for LDL

<table>
<thead>
<tr>
<th>Risk</th>
<th>LDL Goal</th>
<th>Therapeutic Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk 0-1 Risk Factor</td>
<td>≤100</td>
<td>≤160</td>
</tr>
<tr>
<td>Medium Risk 2+ Risk Factors; 10-year risk ≤20%</td>
<td>≤130</td>
<td>&lt;100</td>
</tr>
<tr>
<td>High Risk CHD and CHD Risk Equivalents; 10-year risk &gt;20%</td>
<td>≤100</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>


Summary
- Plasma Cholesterol
  - Circulates from liver, peripheral cells and gut
  - Continuous relation to cardiovascular risk
- Rare Inherited Conditions
  - Familial Hypercholesterolemia –many LDL- R defects
  - Heterozygous FH – 1:500. CHD < 40-50yrs
  - Homozygous FH - 1:10⁷. CHD < 10yrs old
  - Type III – yellow palm creases, high Trigs
  - Tangiers – Low HDL

Summary
- LDL Lowering
  - Primary focus, principally with statins
  - High dose statins for high risk patients
    - CAD, PVD, Diabetes, CVA, Hypertension
  - Non-Statin Therapies (for statin intolerant?)
    - Second line agents
    - Bile acid sequestrants – Wellchol, Colestipol
    - HDL / TG agents – Niacin, Fibrates, Fish Oil
    - Cholesterol absorption inhibitors – Ezetimibe