Translational Science of the LDL Receptor

AN NLA CORE CURRICULUM INTENSIVE PROGRAM
Therapy of LDL-Receptor Disorders

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Washington University School of Medicine
Outline

- Treatment considerations
  - Adults
  - Children
  - Pregnancy
  - Considerations for homozygous FH
- Lifestyle
- Statins
- Ezetimibe
- Bile acid sequestrants
- Niacin
- Fibrates
- Mipomersen
- Lomitapide
- LDL apheresis
Evidence for Treating All FH Patients

• Untreated FH
  • Mean onset CVD
    • Men early 40’s
    • Women in early 50’s
  • 24 times higher risk of MI before age 40

• Long-term statin treatment largely ameliorates excess CVD risk due to FH

• Risk of long-term statin treated FH patients = Risk of general population


Robinson JG, Goldberg A. J Clinical Lipidol 2011 5:S18-29
Rationale for Treatment of FH in Adults

• No outcomes trials specifically in FH patients
• West of Scotland (mostly primary prevention) and 4S (secondary prevention) enriched with FH patients
• Very high lifetime risk of CHD
• Very high risk of premature onset CHD.
• Early treatment is highly beneficial.
• FH requires lifelong treatment and regular follow-up.
Risk Stratification Algorithms Should Not be Used in FH Patients

• Individuals with FH are at high short and long-term CHD risk.
  • 10-year CHD risk in the FH patient is not adequately predicted by any conventional risk assessment tools
• 10-year assessment of risk is NOT recommended.
• All FH patients require treatment regardless of 10-year CHD risk
  • Lifestyle management
  • Most will require lipid-lowering drug therapy.

Robinson JG, Goldberg A. J Clinical Lipidol 2011 5:S18-29
Drug Therapy Required for Almost All* FH Patients

• Drug therapy required for children and adults if (after lifestyle changes):
  • LDL-C ≥190 mg/dL OR
  • Non-HDL-C ≥220 mg/dL

• For adult FH patients (≥20 years of age), drug treatment to lower LDL-C by at least 50%

• Statins should be the initial treatment for all adults with FH.

* Special considerations in women in child-bearing years: No statins, ezetimibe, or niacin during conception, pregnancy, or lactation

Highest Risk FH Patients = Intensify Drug Treatment

- Consider more aggressive treatment goals for highest risk FH patients
  - LDL cholesterol <100 mg/dL
  - Non-HDL cholesterol <130 mg/dL
- FH patients at highest risk
  - (very high risk compared to patients without FH)
  - Clinically evident CHD or other atherosclerotic CVD
  - Diabetes
  - Family history of very early CHD
    - Men <45 years of age or women <55 years of age
- Current smoking
- >2 CVD risk factors

Integrated guidance on the care of familial hypercholesterolemia from the International FH Foundation

• All adult patients with FH must receive advice on lifestyle modifications and advice to correct all non-cholesterol risk factors should be provided according to expert recommendations. [2A]

• Therapy should ideally aim for at least a 50% reduction in plasma LDL-cholesterol, followed by an LDL-cholesterol < 2.5 mmol/L (absence of CHD or other major risk factors) and < 1.8 mmol/L (presence of CHD or other major risk factors). [2C]

• Achieving these targets will require a fat-modified, heart-healthy diet and statin therapy with or without ezetimibe. [1A]

• Drug combinations including bile acid sequestrants, niacin, probucol or fibrates, may be required with more intensive strategies to further reduce LDL-cholesterol. [1B]

Treatment of FH: Adults

- **Lifestyle changes**
  - Decrease saturated fatty acids to ≤7% of total energy intake; limit dietary cholesterol <200 mg/day; add plant stanol/sterols (2 g daily); soluble fiber (10-20 g daily)
  - Physical activity and weight control
  - **Smoking cessation**
- **Medications:** Moderate to high doses of high-potency statins (atorvastatin, rosvastatin)
  - Increase statin dose to maximum available or tolerable dose to achieve a LDL-C reduction ≥50% from baseline
  - If not achieved, consider adding ezetimibe, bile acid sequestrant, and/or niacin
- LDL apheresis
- Homozygous patients: medications, apheresis
Traditional Sequence in Approach to Familial Hypercholesterolemia

• Diet and exercise do help—up to 20% decrease of LDL-cholesterol
  • Decrease saturated fat, utilize plant sterol/stanols, soluble fiber
• Potent statin (rosuvastatin, atorvastatin, simvastatin) at moderate to high dosage
• Ezetimibe and/or bile acid sequestrant
• Niacin up to 2000 mg/day when added to statin
• Mipomersen or lomitapide for homozygous FH
• LDL-apheresis: if inadequate response to maximally tolerated therapy
Lifestyle Recommendations Include:

Advise Adults Who Would Benefit from LDL-Cholesterol Lowering to:

- Consume a dietary pattern that emphasizes
  - Intake of vegetables, fruits, and whole grains
  - Includes low-fat dairy products, poultry, fish, legumes
  - Non-tropical vegetable oils and nuts

And limits intake of:

- sweets, sugar-sweetened beverages & red meats.

- Aim for a dietary pattern that achieves 5%–6% of calories from saturated fat.

Women of Childbearing Age

- Women with FH should receive pre-pregnancy counseling and instructions to stop statins, ezetimibe, and niacin at least 4 weeks before discontinuing contraception and should not use them during pregnancy and lactation.

- Consultation with her healthcare practitioner regarding continuation of any other lipid medications is recommended.

- In case of unintended pregnancy, a woman with FH should discontinue statins, ezetimibe, and niacin immediately and should consult with her healthcare practitioner promptly.

Treatments Options During Pregnancy

- Statins (category X), ezetimibe (category C), and niacin (category C) should not be used during pregnancy. Use of other lipid lowering medications (e.g., colesevelam – category B) may be considered under the guidance of the healthcare practitioner.

- Consider LDL apheresis during pregnancy if there is significant atherosclerotic disease or if the patient has homozygous FH.

Treatment of FH: Children and Adolescents

• LDL > 190 mg/dl or > 160 mg/dl with multiple risk factors, after diet

• Clinical trials with medium term follow up suggest safety and efficacy of statins

• Goal: 50% reduction or LDL-C < 130 mg/dl; need for balance between increased dosing and potential for side effects vs achieving goals

• Consider more aggressive LDL targets for those with additional CVD risk factors

• Ideally, prevent the development of atherosclerosis

Age When Treatment is Considered

• Five statins approved age 10 and above and pravastatin approved starting at age 8
• Pathologic/imaging data suggest age 10 or so is a critical period for advanced atherosclerosis development
• Higher risk subsets exist (higher LDL levels, multiple risk factors, family history)
• Some experts start earlier—age 6 in HeFH
• Treat girls and boys starting at the same age
• Get in several years of therapy before discontinuing for pregnancy
Two years of pravastatin therapy induced significant regression of carotid atherosclerosis in children with familial hypercholesterolemia
Homozygous FH

- Therapy begins at diagnosis regardless of age
- Statins, ezetimibe and other agents may help but LDL apheresis often necessary
- Liver transplantation recommended by some groups if apheresis is not feasible
- Cardiovascular disease monitoring critical
- Additional drugs approved for homozygous FH patients over age 18:
  - Mipomersen
  - Lomitapide
- Evolocumab if not receptor negative
Patients with Homozygous FH can Benefit from Therapy

- Homozygotes often have untreated LDL-C >500 mg/dL
  - CAD onset in childhood and adolescence
  - Insufficient response to usual lipid lowering medication, even in combination
- South African population with few patients treated with LDL apheresis
  - Pre 1990: average age at death 18.4 years, age at first cardiac event 12.8
  - Post 1990: average age at death 32.9 years, age first event 28.3 years
  - Mean LDL cholesterol reduction 26.4%

Lipid Lowering Therapy in Homozygous FH

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Taking Modern Lipid-Lowering Therapy</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>17.3±3.8</td>
<td>13.1±3.3*</td>
<td>−24.3</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.28±0.81</td>
<td>1.18±0.63</td>
<td>−7.8</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.89±0.33</td>
<td>0.91±0.25</td>
<td>2.2</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>15.9±3.9</td>
<td>11.7±3.4*</td>
<td>−26.4</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>21.4±10.9</td>
<td>13.5±5.9*</td>
<td>−36.9</td>
</tr>
</tbody>
</table>

LDL-C 614 mg/dL 452 mg/dL

Raal et al *Circulation*. 2011;124:2202-2207
Risk of first MACE among Homozygous FH patients before and after the introduction of modern lipid lowering therapy

Benefit from modern lipid therapy (Endpoint: MACE)

Algorithm for management of HoFH

Homozygous Familial Hypercholesterolaemia

LDL-C targets:
- <2.5 mmol/L [<100 mg/dL] (adults)
- <3.5 mmol/L [<135 mg/dL] (children)
- <1.8 mmol/L [<70 mg/dL] if clinical CVD

At diagnosis
Lifestyle and Diet + Statin
(most efficacious at highest dose depending on tolerability)

Ezetimibe 10 mg + resins or other drugs*
*Fibrate, nicotinic acid, probucol (use of these additional treatments may be limited by tolerability and drug availability)

LDL-Apheresis
As early as possible if available (by 5 years, no later than 8 years)
every 1 or 2 weeks

In selected patients
Liver Transplant

Lomitapide
Approved by FDA, EMA

Mipomersen
Approved by FDA

New Therapeutic options

Future Therapeutic options

PCSK9 inhibitors
CETP inhibitors
Gene therapy

LDL Receptor: Common Pathway for Statins, Resins, Cholesterol Absorption Inhibitors and Investigational Agents
Lipid Lowering Therapies and LDL Receptor Function

Statins
Inhibit HMG-CoA reductase, rate limiting step in cholesterol synthesis

Ezetimibe
Inhibits the absorption of cholesterol

Bile Acid Sequestrants
Inhibit enterohepatic reuptake of bile acids and increase fecal loss of bile salts

PCSK9 inhibitors
Inhibit degradation of LDL receptors and increase recycling

All work by increasing expression of LDL receptors
Niacin, lomitapide, mipomersen do not work by upregulating LDL receptors
(possibly some effect of high dose statins)
Cholesterol Biosynthetic Pathway

- Acetyl CoA → HMG-CoA
- HMG-CoA Reductase
- Mevalonate → Farnesyl Pyrophosphate
- Squalene Synthase
- Squalene → Cholesterol
- Dolichol
- Farnesyl Transferase
- Ras Protein
- Farnesylated Proteins
- E,E,E-Geranylgeranyl Pyrophosphate
- Geranylgeranylated Proteins
- Ubiquinones
## HMG CoA Reductase Inhibitors (Statins)

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>20-80* mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10-80 mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>5-80* mg</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20-80 mg</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10-80 mg</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5-40 mg</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>1-4 mg</td>
</tr>
</tbody>
</table>

*Simvastatin 80 mg should not be used unless already in use for over a year and no likely drug interactions*
# Typical Percent LDL-C Reduction by Statin and Dose

<table>
<thead>
<tr>
<th>Treatment (drug/dose)</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>-40</td>
<td>-46</td>
<td>-52</td>
<td>-55</td>
<td>------</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>------</td>
<td>-37</td>
<td>-43</td>
<td>-48</td>
<td>-51</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>-26</td>
<td>-30</td>
<td>-38</td>
<td>-41</td>
<td>-47*</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>------</td>
<td>-21</td>
<td>-27</td>
<td>-31</td>
<td>-40</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>------</td>
<td>-20</td>
<td>-24</td>
<td>-30</td>
<td>-36</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>------</td>
<td>------</td>
<td>-22</td>
<td>-25</td>
<td>-35</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>------</td>
<td>(1 mg) -32</td>
<td>(2 mg) -36</td>
<td>(4 mg) -43</td>
<td></td>
</tr>
</tbody>
</table>

*Simvastatin 80 mg only in patients already taking for > 1 year and no other contraindications (higher risk of rhabdomyolysis)*

Compiled from various clinical trials and package inserts
Patient Response to Statins is Variable

Percent Change in LDL-C by Individual Patients

- Simvastatin 40 mg
  n=141
- Simvastatin 80 mg
  n=144

Adapted from Davidson, M.H., et al., Am J Cardiol 1997;79:38-42
Statin Safety

• Muscle-related adverse experiences
• Liver concerns
  • FDA removed routine monitoring in 2012
  • Serious liver problems extremely rare
• Diabetes mellitus: clear benefit of statins in FH
• Neurologic concerns
  • Cognitive function—very few good data and likely very rare, most due to other problems
• NLA Statin safety update

Statins and Risk of Incident Diabetes: a Collaborative Meta-analysis of Randomized Statin Trials

13 randomized trials, 91,140 patients of whom 4,278 (2,226 assigned statins and 2,052 assigned placebo) developed diabetes during a mean FU of 4 yrs.

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Statin Events</th>
<th>Rate</th>
<th>Placebo or control Events</th>
<th>Rate</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-LA</td>
<td>7773</td>
<td>154</td>
<td>11.9</td>
<td>134</td>
<td>10.5</td>
<td>1.14 (0.89-1.46)</td>
<td>7.07%</td>
</tr>
<tr>
<td>HPS</td>
<td>14573</td>
<td>335</td>
<td>9.2</td>
<td>293</td>
<td>8.0</td>
<td>1.15 (0.98-1.35)</td>
<td>13.91%</td>
</tr>
<tr>
<td>JUPITER</td>
<td>17802</td>
<td>270</td>
<td>16.0</td>
<td>216</td>
<td>12.8</td>
<td>1.26 (1.04-1.51)</td>
<td>11.32%</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>5974</td>
<td>75</td>
<td>5.2</td>
<td>93</td>
<td>6.5</td>
<td>0.79 (0.58-1.10)</td>
<td>4.24%</td>
</tr>
<tr>
<td>LIPID</td>
<td>6997</td>
<td>126</td>
<td>6.0</td>
<td>138</td>
<td>6.6</td>
<td>0.91 (0.71-1.17)</td>
<td>6.53%</td>
</tr>
<tr>
<td>CORONA</td>
<td>3534</td>
<td>100</td>
<td>20.9</td>
<td>88</td>
<td>18.5</td>
<td>1.14 (0.84-1.55)</td>
<td>4.65%</td>
</tr>
<tr>
<td>PROSPER</td>
<td>5023</td>
<td>165</td>
<td>20.5</td>
<td>127</td>
<td>15.8</td>
<td>1.32 (1.03-1.69)</td>
<td>6.94%</td>
</tr>
<tr>
<td>MEGA</td>
<td>6086</td>
<td>172</td>
<td>10.8</td>
<td>164</td>
<td>10.1</td>
<td>1.07 (0.86-1.35)</td>
<td>8.03%</td>
</tr>
<tr>
<td>AFCAPS/TEXCAPS</td>
<td>6211</td>
<td>72</td>
<td>4.5</td>
<td>74</td>
<td>4.6</td>
<td>0.98 (0.70-1.38)</td>
<td>3.76%</td>
</tr>
<tr>
<td>4S</td>
<td>4242</td>
<td>198</td>
<td>17.3</td>
<td>193</td>
<td>16.8</td>
<td>1.03 (0.84-1.28)</td>
<td>8.88%</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>6087</td>
<td>238</td>
<td>16.4</td>
<td>212</td>
<td>14.4</td>
<td>1.15 (0.95-1.41)</td>
<td>10.33%</td>
</tr>
<tr>
<td>GISSI HF</td>
<td>3378</td>
<td>225</td>
<td>34.8</td>
<td>215</td>
<td>32.1</td>
<td>1.10 (0.89-1.35)</td>
<td>9.50%</td>
</tr>
<tr>
<td>GISSI PREV</td>
<td>3460</td>
<td>96</td>
<td>27.5</td>
<td>105</td>
<td>30.6</td>
<td>0.89 (0.67-1.20)</td>
<td>4.94%</td>
</tr>
</tbody>
</table>

Overall (I²=11.2% [95% CI 0.0-50.2%])

9% increase in risk of incident diabetes:
1 additional case of DM per 255 pts taking statins for 4 yrs

The association between statins and risk of diabetes mellitus was stronger in trials with older participants, but baseline BMI and percentage change in LDL concentration did not seem to be important factors.

Sattar et al. Lancet 2010; 375:735-742
Statins and Risk of Incident Diabetes: Intensive vs Moderate Statin Therapy

Meta-analysis of 5 randomized trials; 32,752 non diabetic patients followed for a mean duration of 4.9 yrs.

2 additional cases of DM per 1,000 pts treated with high dose statins

Number need to harm = 498 per year

The risk of new-onset diabetes was small compared to the benefit in cardiovascular risk reduction

Preiss et al. JAMA 2011; 305:2556-2564
Incidence of Muscle Adverse Effects

(180,000 Patients in 21 Major Statin Trials for avg of 3 yrs)

<table>
<thead>
<tr>
<th>Muscle AE</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias</td>
<td>1.5% to 3%</td>
</tr>
<tr>
<td>Myopathy (Sx + ↑CK)</td>
<td>5/100,000</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1.6/100,000</td>
</tr>
</tbody>
</table>

Law M et al. Am J Cardiol. 2006; 97 (suppl 8A): 52C-61C.
Prédiction du Risque Musculaire en Observationnel (PRIMO): Risk of Muscular Symptoms with Individual Higher Statin Doses

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dosage</th>
<th>Percentage of patients with muscular symptoms*</th>
<th>Odds Ratio† [95% CI]</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>40 mg/day</td>
<td>10.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40–80 mg/day</td>
<td>14.9%</td>
<td>1.28 [1.02–1.60]</td>
<td>0.035</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40–80 mg/day</td>
<td>18.2%</td>
<td>1.78 [1.39–2.29]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>80 mg/day</td>
<td>5.1%</td>
<td>0.33 [0.26–0.42]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*% values relative to the total number of patients with or without muscular symptoms.
† Odds ratios were calculated using pravastatin as the reference.
‡ P values were determined by Pearson’s Chi-squared test.

Factors That Increase the Risk of Statin-Induced Myopathy

### Patient Characteristics
- Increasing age
- Female sex
- Renal insufficiency
- Hepatic dysfunction
- Hypothyroidism
- Diet (e.g., grapefruit juice with statins metabolized by 3A4)
- Polypharmacy and multiple chronic diseases

### Statin Properties
- High systemic exposure (higher doses, high bioavailability, limited protein binding)
- Potential for drug-drug interactions metabolized by CYP pathways (and common conjugation and transporter pathways)

Managing lipid therapy in patients with muscle problems on statins

- Diagnose and treat hypothyroidism, vitamin D deficiency (controversial), depression, rheumatic diseases
- Use a different statin—consider pharmacology
  - CYP3A4 issues: less with fluvastatin, pravastatin, rosuvastatin, pitavastatin
  - CYP3A4 issues: more with simvastatin, lovastatin, atorvastatin
  - Minimal renal excretion: fluvastatin, atorvastatin
- Run drug interaction programs
- Question patients about all medications and supplements—red yeast rice may contain low dose lovastatin
Managing Lipid Therapy in Patients with Muscle Problems on Statins

- Dose adjustments: very low doses, every other day dosing (cut pills in half)
- Combination of low-dose statin and resin or ezetimibe
- Non-statin therapies: resin, niacin, ezetimibe
- Add plant sterols/stanols—up to 10% LDL-C reduction (Benecol, Take Control)
- Psyllium: 5 grams twice a day about 5% decrease in LDL-C
Use of Every-Other-Day Rosuvastatin

12/17 high-risk patients achieved LDL<100

Muscle Problem Pointers

• Get as much detail about the previous meds, doses, and reactions as possible

• Look for vitamin D deficiency, hypothyroidism, depression, rheumatologic problems

• Consider age, size, and co-morbidities

• Ask about family members’ use of and response to cholesterol medications

• Some medication may be better than none at all

• Discontinue statin and wait for symptoms to resolve before trying the next one
Advantages/Disadvantages of Combination Therapy

• Statins, ezetimibe, niacin, and bile acid sequestrants reduce LDL cholesterol through different mechanisms and sites of action
• Thus they can be more effective in combination that when used alone
• Advantages of using combinations: greater efficacy, lower doses of individual drugs, possible amelioration of tolerance problems experienced with high doses of single agents
• Disadvantages: increased drug interactions, large number of pills, increased costs, additive side effect
• Lack of outcomes data for most combinations and multiple combinations

## Treatment Effects on LDL Cholesterol

<table>
<thead>
<tr>
<th>Modality</th>
<th>%LDL cholesterol reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle</td>
<td></td>
</tr>
<tr>
<td>--diet, exercise</td>
<td>Up to 20%</td>
</tr>
<tr>
<td>--plant stanols</td>
<td>Up to 10%</td>
</tr>
<tr>
<td>Statins</td>
<td>20 to 60%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>15 to 20%</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>5 to 35%</td>
</tr>
<tr>
<td>Niacin</td>
<td>0 to 25%</td>
</tr>
<tr>
<td>Fibrates (normal triglycerides)</td>
<td>10 to 20%</td>
</tr>
<tr>
<td>LDL apheresis</td>
<td>Up to 70% (single treatment)</td>
</tr>
<tr>
<td>PCSK9 monoclonal antibodies</td>
<td>35 to 65%</td>
</tr>
</tbody>
</table>
Components of Cholesterol Homeostasis

DIETARY CHOLESTEROL

BILIARY SECRETION

INTESTINE

Absorption

Excretion

Synthesis

19%

50%

31%

50%

50%
Intestinal Absorption of Dietary and Biliary Cholesterol

Diet

Luminal cholesterol

Micellar cholesterol

Bile salts
Unabsorbed cholesterol

Bile salts

Fecal sterols

Liver

Duodenal/jejunal enterocyte

Bile

Chol

Bile salts

Duodenal/jejunal enterocyte

Lymph

Chylomicron

Hepatic portal circulation

NPC1L1

ABCG5/G8

IBAT

Fecal sterols

Hepatic portal circulation
Ezetimibe: Mechanism of Action

- Blocks uptake of dietary/biliary cholesterol and structurally related phytosterols by intestinal enterocytes\(^1\)
- Inhibits absorption through a mechanism dependent on NPC 1L1 protein\(^2\)
- Does not reduce absorption of lipid-soluble vitamins or steroid hormones\(^3\)
- Reduces cholesterol content of chylomicrons\(^4\)

Ezetimibe: Pharmacology

- Glucuronidated in the intestine by UGT1A1, 1A3, 2B7, 2B15.
  - Glucuronidated metabolite retains activity
  - Possible contributing mechanism of interaction with CysA
- Glucuronidate and parent compound are excreted in the bile and circulate enterohepatically
  - Repeated delivery to the intestinal brush border
  - Minimized systemic exposure and potential for adverse effects
- Long half-life (22 hours) allows for once-daily dosing

Ezetimibe

• Lowers LDL-C by 15 to 20%
• Additive with statins
• Minimal side effects: GI; ?muscle; very rarely angioedema
• Dosing: 10 mg per day
• Some outcomes data—IMPROVE-IT
• Familial hypercholesterolemia—main choice for second drug
Ezetimibe Added to Statin Therapy: Effect on LDL

Mean % Change in LDL-C From Treated Baseline

<table>
<thead>
<tr>
<th></th>
<th>Statin + Placebo (n=390)</th>
<th>Statin + Ezetimibe (n=379)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LDL-C</td>
<td>139 mg/dL</td>
<td>138 mg/dL</td>
</tr>
<tr>
<td>After Adding</td>
<td>133 mg/dL</td>
<td>102 mg/dL</td>
</tr>
<tr>
<td>Placebo or Ezeti-</td>
<td>–4%</td>
<td>–25%*</td>
</tr>
<tr>
<td>mibe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001 for ezetimibe + statin vs placebo + statin.

Statin-Ezetimibe Combination

- About 20% further decrease in LDL cholesterol
- Tolerance usually good—GI, muscle
- Lack of outcomes data in FH patients
- Cost—still an issue; off patent December 2016
- Effect of ezetimibe plus statin in patients with FH
  - **Wide inter-individual variability** -39.2% to -4.7% further decrease in LDL cholesterol (Pisciotta et al *Atherosclerosis* 2007 194 e116-e122)
IMPROVE-IT

• A large scale (18,144 participants), multi-center randomized controlled trial of high risk post Acute Coronary Syndrome (ACS) patients

• Intervention: ezetimibe 10 mg added to simvastatin 40*

• Comparator: simvastatin 40*
  Both groups achieved a mean LDL-C < 70 mg/dl

• Study took 9 years; follow up was 7 years

• No increase in side effects with the intervention

• 40% dropout rate both groups
  *some uptitration allowed.
LDL-C and Lipid Changes

<table>
<thead>
<tr>
<th></th>
<th>Simva</th>
<th>EZ/Simva</th>
<th>Δ in mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>69.9</td>
<td>53.2</td>
<td>-16.7</td>
</tr>
<tr>
<td>TC</td>
<td>145.1</td>
<td>125.8</td>
<td>-19.3</td>
</tr>
<tr>
<td>TG</td>
<td>137.1</td>
<td>120.4</td>
<td>-16.7</td>
</tr>
<tr>
<td>HDL</td>
<td>48.1</td>
<td>48.7</td>
<td>+0.6</td>
</tr>
<tr>
<td>hsCRP</td>
<td>3.8</td>
<td>3.3</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

Median Time avg
69.5 vs. 53.2 mg/dL

IMPROVE-IT: Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

- Simva — 34.7%
  - 2742 events
  - HR 0.936 CI (0.887, 0.988)
  - p=0.016

- EZ/Simva — 32.7%
  - 2572 events

NNT = 50


7-year event rates
IMPROVE-IT

- MI HR 0.87
- Ischemic stroke HR 0.79
- CVD/MI/stroke HR 0.90
- No difference total mortality, CVD, Unstable angina
- No difference in cancer incidence, muscle problems
Lipid Research Clinics
Coronary Primary Prevention Trial

- 3,806 men aged <60 years with cholesterol ≥265 mg/dl and high LDL-C, initially free of coronary disease.
- 19% reduction in CHD death and/or nonfatal MI.

JAMA 1984; 251:351
Resins—Mechanism of Action

• Bind bile salts and bile acids in lumen of intestine
• Decrease enterohepatic circulation of bile
• Liver must convert more cholesterol into bile salts and bile acids
  • Intracellular cholesterol decreases
• Leading to up-regulation of LDL receptors
Bile Acid Resins: Efficacy

• In patients with hypercholesterolemia, bile acid resins:
  • Decrease LDL-C 12%-25%
  • Increase HDL-C 4%-5%
  • Increase triglyceride levels in some patients
• Colesevelam also indicated as adjunct to diet and exercise to improve glycemic control in Type II DM
Response in LDL-c in Patients With Severe Heterozygous Familial Hypercholesterolemia*

* Ten patients

Bile Acid Resins: Formulation Differences

- Tablet form (colesevelam hydrochloride, colestipol hydrochloride)
  - Colesevelam 0.625 g/tablet, 6-7 tablets/day
  - Colestipol 1.0 g/tablet, up to 16 tablets/day
- Colesevelam oral suspension- 3.75 g/day in 4-8 oz (1/2 to 1 cup) water or 1.875 grams BID with meals
- Powder form (cholestyramine) that must be mixed with water before use; 4 g/dose

# Bile Acid Sequestrants: Colesevelam and Statins

<table>
<thead>
<tr>
<th>Colesevelam</th>
<th>Statin</th>
<th>TC (%)</th>
<th>LDL-C (%)</th>
<th>HDL-C (%)</th>
<th>TG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mg (no tablets)</td>
<td>Atorvastatin 80 mg</td>
<td>-43</td>
<td>-56</td>
<td>+2</td>
<td>-43</td>
</tr>
<tr>
<td>3750 mg (6 tablets)</td>
<td>Atorvastatin 10 mg</td>
<td>-35</td>
<td>-51</td>
<td>+7</td>
<td>-11</td>
</tr>
</tbody>
</table>

Bile Acid Binding Resins

• Advantages--no systemic absorption
• Side effects: constipation, hard stools, bloating, flatulence
• Can interfere with absorption of other drugs—less with colesevelam but still need care with levothyroxine
• Special care with warfarin
Niacin (Nicotinic Acid)

- Lowers triglycerides, raises HDL cholesterol
- Higher doses reduce LDL cholesterol
- Niacinamide (nicotinamide) has no effect
- Older clinical trial data show benefit
- Recent studies show no benefit of adding niacin when the LDL cholesterol is low on a statin or statin/ezetimibe
- Niacin is not included in ACC non-statin white paper
Niacin: Adverse Effects

- Flushing is reported by as many as 88% of patients taking extended-release niacin
- Hepatotoxicity can occur at higher doses, particularly with certain types of dosage forms
- Glucose homeostasis/insulin resistance
- Blurry vision: cystoid macular edema with doses greater than 2000 mg/day
- Gout
- Gastrointestinal side effects
- Increased infection seen in HPS-THRIVE
Niacin and Flushing

- Redness, heat, flush, itch
- Usually occurs 15 – 30 minutes after administration
- May last from 5 to 60 minutes
- Patient can be red but not feel subjectively warm
- Generally not accompanied by diaphoresis
- Hypotension is a rare side effect
- May be exacerbated by spicy food, hot beverages, hot shower, alcohol
- Take ASA 325 mg 30 min prior
- Whole or half aspirin dissolved in water to abort a long lasting severe flush
Practical Advice for Multiple Drug Therapy

• Bile acid sequestrants should be given with meals and separated from other medications
• It is not necessary to give statins at bedtime
• Educate patients about the medications
• Run drug interaction programs
• Remind patient and other physicians of baseline
Fibric Acids

• Major actions
  • Lower LDL-C 5–20% (with normal TG)
  • May raise LDL-C (with high TG)
  • Lower TG 20–50%
  • Raise HDL-C 10–20%
  • PPAR alpha agonists
• Side effects: dyspepsia, gallstones, myopathy
• Contraindications: Severe renal or hepatic disease
Effect of Simvastatin plus fenofibrate or cholestyramine on LDL-C in Patients with Heterozygous FH

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Simvastatin plus Cholestyramine</th>
<th>Simvastatin plus Fenofibrate (resin vs. fibrate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>8.23±2.7 (318±102)</td>
<td>4.98±0.93 (192±36)</td>
<td>4.59±0.96 (177±37)</td>
</tr>
<tr>
<td>% reduction</td>
<td>37.1±21.9</td>
<td>40.6±20.5</td>
<td></td>
</tr>
</tbody>
</table>

Adding colesevelam to statin plus ezetimibe

- Patients with FH on statin plus ezetimibe
- Colesevelam added to statin plus ezetimibe
- 11.4% further drop of LDL cholesterol

Antisense oligonucleotide

Mechanism of Action

DNA → mRNA

Transcription → No Translation

Antisense Drug

No Disease-Associated Proteins Produced

Traditional Drug

Antisense oligonucleotides: ApoB-100 (mipomersen)

• Second generation antisense oligonucleotide
• Apo B 100 production inhibited
• Decreased secretion of apo B containing lipoproteins from the liver
• Lowers apo B, LDL-cholesterol and lipoprotein (a) in humans
Mipomersen, for Lowering of LDL-C in HoFH Patients

Mean percentage change from baseline (week 0) to primary efficacy timepoint for LDL cholesterol (A), apolipoprotein B (B), and lipoprotein(a) (C) Error bars indicate 95% CI.

### Major Reasons for Discontinuation Among Mipomersen Treated Patients

<table>
<thead>
<tr>
<th>Reason</th>
<th>Phase 3 HoFH (N=34) %</th>
<th>Phase 3 All (N=261) %</th>
<th>Open-Label Extension HoFH (N=38) %</th>
<th>Open-Label Extension All (N=141) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Reason</td>
<td>17.6</td>
<td>28.0</td>
<td>60.5</td>
<td>56.0</td>
</tr>
<tr>
<td>ALT or AST elevations</td>
<td>2.9</td>
<td>6.1</td>
<td>13.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>5.9</td>
<td>5.0</td>
<td>10.5</td>
<td>9.2</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>0.0</td>
<td>2.7</td>
<td>23.7</td>
<td>24.8</td>
</tr>
<tr>
<td>Non-AE</td>
<td>5.9</td>
<td>10.0</td>
<td>13.2</td>
<td>12.8</td>
</tr>
</tbody>
</table>
Microsomal Triglyceride Transfer Protein Inhibitors

• MTP is a lipid transfer protein
• Localized in the endoplasmic reticulum of hepatocytes and enterocytes
• Critical role in lipoprotein lipidation of apoB
• Necessary for formation of chylomicrons, VLDL and downstream remnants
• MTP deficiency--abetalipoproteinemia

Lomitapide for Patients with HoFH

Mean % Change in LDL-C

Intent to Treat (ITT) n=29
Completer Analysis (CA) n=23

Baseline: 352mg/dL
Week 26: 50.2% reduction
Week 56: 44.0% reduction
Week 78: 38.4% reduction

Adapted from Cuchel M et al. Lancet 2013; 381:40-46
### HoFH Phase 3 Study
#### Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event Category</th>
<th>n of subjects (%) weeks 0-26 N=29</th>
<th>n of subjects (%) weeks 26-78 N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>27 (93.1)</td>
<td>21 (91.3)</td>
</tr>
<tr>
<td>GI Disorders</td>
<td>27 (93.1)</td>
<td>17 (73.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (79)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (62)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Lab abnormalities</td>
<td>15 (51.7)</td>
<td>10 (43.5)</td>
</tr>
<tr>
<td>ALT elevation &gt;5 x ULN</td>
<td>4 (13.8)</td>
<td>1 (4.3)</td>
</tr>
</tbody>
</table>

Adapted from Cuchel M et al. Lancet 2013; 381:40-46
LDL Apheresis

- LDL apheresis is an FDA-approved process of selectively removing Apo B-containing particles from the circulation through extracorporeal precipitation with either dextran sulphate cellulose or heparin.
- The procedure must be repeated every 1 to 2 weeks.
- In a single procedure, LDL apheresis typically removes at least 60% of the Apo B-containing lipoproteins.
LDL-Apheresis

• LDL-apheresis—the setting: inadequate response to maximally tolerated therapy in patients with familial hypercholesterolemia

• Requires good vascular access (2 vein sites or A-V fistula)

• Usually done weekly for homozygous patients and every two weeks for heterozygous patients

• Over time 50% reduction of LDL-C
Pre-Apheresis
- Total Cholesterol: 611 mg/dL
- LDL-C: 507 mg/dL
- Fibrinogen: 446 mg/dL
- CRP: 2.0 mg/dL

Post-Apheresis
- Total Cholesterol: 216 mg/dL
- LDL-C: 134 mg/dL
- Fibrinogen: 193 mg/dL
- CRP: 0.5 mg/dL

Slide courtesy Dr. Patrick Moriarty
# Mean Percentage Reduction of Plasma Proteins with Different Methods of Lipoprotein-apheresis

<table>
<thead>
<tr>
<th>mg/dL</th>
<th>MDF</th>
<th>Lipid Filtration</th>
<th>HELP</th>
<th>DALI</th>
<th>DSA</th>
<th>IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>56-62%</td>
<td>61%</td>
<td>55-61%</td>
<td>53-76%</td>
<td>49-75%</td>
<td>62-69%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>25-42%</td>
<td>6%</td>
<td>5-17%</td>
<td>5-29%</td>
<td>4-17%</td>
<td>9-27%</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>53-59%</td>
<td>61%</td>
<td>55-68%</td>
<td>28-74%</td>
<td>19-70%</td>
<td>51-71%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>37-49%</td>
<td>56%</td>
<td>20-53%</td>
<td>29-40%</td>
<td>26-60%</td>
<td>34-49%</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>52-59%</td>
<td>42%</td>
<td>51-58%</td>
<td>13-16%</td>
<td>17-40%</td>
<td>15-21%</td>
</tr>
</tbody>
</table>

High variation of values are partially due to differences in treated plasma and blood volumes.


Moriarty PM. Clinical Lipidology, Ballantyne: A Companion to Braunwald’s Heart Disease; 363-74. 2009
LDL-Apheresis (CMS rules)

• LDL-apheresis: inadequate response to maximally tolerated therapy in patients with familial hypercholesterolemia
  • Functional homozygotes with LDL-C > 500 mg/dl
  • Functional heterozygotes with LDL-C > 300 mg/dl and no evidence of vascular disease
  • Functional heterozygotes with LDL-C > 200 mg/dl and evidence of vascular disease
Candidates for LDL Apheresis: NLA FH Recommendations

In patients who, after six months, do not have an adequate response to maximum tolerated drug therapy, LDL apheresis is indicated according to these guidelines:

• Functional homozygous FH patients with LDL-C $\geq$ 300 mg/dL (or non-HDL-C $\geq$ 330 mg/dL).

• Functional heterozygous FH patients with LDL-C $\geq$ 300 mg/dL (or non-HDL-C $\geq$ 330 mg/dL) and 0-1 risk factors.

• Functional heterozygous FH patients with LDL-C $\geq$ 200 mg/dL (or non-HDL-C $\geq$ 230 mg/dL) and high risk characteristics such as $\geq$ 2 risk factors or high lipoprotein (a) $\geq$ 50 mg/dL using an isoform insensitive assay.

• Functional heterozygous FH patients with LDL-C $\geq$ 160 mg/dL (or non-HDL-C $\geq$ 190 mg/dL) and very high risk characteristics (established CHD, other cardiovascular disease, or diabetes).

Lipoprotein-Apheresis (LA) and the reduction of CV Events

Proportion of Patients Without Any Event

Years

Medication and LA

Medication

p = 0.0088

RRR = 72%
NNT = 4
There’s no such thing as a sudden heart attack. It requires years of preparation.

The number of years involved depends on LDL level, other risk factors, and treatment.
LDL Cholesterol Burden in Individuals with or without FH as a Function of the Age of Initiation of Statin Therapy
Conclusions

• FH is treatable
• Earlier recognition and appropriate treatment can decrease the risk of developing CHD
• Screen early and screen family members
• Statins have changed the natural history of FH and more can be done with combination therapy
• LDL apheresis for patients with inadequate response to therapy
• Mipomersen and lomitapide: HoFH indication
• PCSK9 Mab and other treatments in the pipeline
Take Home Messages

• Aggressive therapy is often needed in patients with FH
• Therapies using different mechanisms of action are additive
• Ezetimibe preferred second drug in a number of international guidelines
• Mipomersen and lomitapide for homozygous FH
• LDL apheresis and new therapies build on current medications and combinations
Thank you!

agoldber@dom.wustl.edu