Combination Therapy for Familial Hypercholesterolemia

Anne Carol Goldberg, MD
Associate Professor of Medicine
Washington University School of Medicine
May 3, 2014
Anne Carol Goldberg, MD

Disclosures

Board Member/Advisory Panel: Foundation of the National Lipid Association; ACC/AHA Cholesterol Guideline Panel (NHLBI ATP4 panel)

Employee: Washington University School of Medicine

Research Support: Research contracts to institution—Merck, Genzyme/ISIS/Sanofi-Aventis, Glaxo-Smith-Kline, Amgen, Amarin, Regeneron/Sanofi-Aventis, Roche/Genentech

Consulting: Tekmira, Astra-Zeneca, uniQure

Editorial: Merck Manual
Outline

- Why combination therapy is needed
- Comparative FH guidelines
- Rationale for treatment
- Possible combinations
- Summary
Why Combination Therapy is needed in Familial Hypercholesterolemia

- Patients with FH are at risk of premature atherosclerotic disease
- Many patients with heterozygous FH do not get adequate LDL cholesterol reduction on high dose statins
- Addition of other risk factors put patients at even higher risk making much greater LDL cholesterol reduction desirable
- Even in homozygous FH aggressive medication therapy can help
- Some patients do not tolerate high dose statin therapy
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

Familial Hypercholesterolemia: guidelines and recommendations

- Australasia Model of Care 2011
- National Lipid Association Expert Panel on Familial Hypercholesterolemia 2011
- Consensus Statement of the European Atherosclerosis Society 2013
- International FH Foundation 2014

Treatment of familial hypercholesterolemia

2011 NLA Statement on Familial Hypercholesterolemia

- Drug therapy required for children and adults if (after lifestyle changes)
  - LDL-C ≥190 mg/dL OR
  - Non-HDL-C ≥220 mg/dL (FCH)
- For adult FH patients (≥20 years of age), drug treatment to lower LDL-C ≥50%
- Statins should be the initial treatment for all adults with FH.

Robinson JG, Goldberg A. J Clinical Lipidol 2011 5:S18-29
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
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, rosuvastatin)
  - 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
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

EAS/ESC Guidelines

DRUGS FOR TREATMENT OF HYPERCHOLESTEROLAEMIA

- If drug treatment is indicated to decrease LDL-C, a statin is recommended, up to the highest tolerable dose, to reach the target level.
- If the target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.
- A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid may also be considered in case of statin intolerance.

MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLAEMIA

- In FH patients the treatment is aiming at reaching the LDL-C goals for high risk subjects <2.5 mmol/L (<~100mg/dL) or in the presence of CVD for very high risk subjects <1.8 mmol/L (<~70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations in tolerated doses.
ACC/AHA Cholesterol Guideline

Primary prevention--LDL–C ≥190 mg/dL

Secondary causes should be ruled out

• Evidence supports high-intensity statin therapy
• LDL–C levels may still remain very high, even after the intensity of statin therapy (reduction >50%) has been achieved
• Addition of a non-statin drug may be considered to further lower LDL–C (or of LDL-C reduction is less than 50% on maximally tolerated statin)

• Do not need ASCVD risk calculation
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]

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.
  • Long-term statin treatment largely ameliorates excess CVD risk due to FH
  • Risk of long-term statin-treated FH patients = Risk of general population
• FH requires lifelong treatment and regular follow-up.

Robinson JG, Goldberg AC. *J Clinical Lipidol* 2011 5:S18-29
Kaplan–Meier curve estimates of cumulative CHD-free survival among individuals with FH according to statin treatment (P < 0.001 for difference).

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273

© The Author 2013. Published by Oxford University Press on behalf of the European Society of Cardiology.
Combination therapy to lower LDL-cholesterol

- No randomized outcomes trials of a statin alone compared with statin plus second drug to lower LDL cholesterol
  - SHARP: simvastatin/ezetimibe vs placebo in patients with renal failure
  - SANDS: carotid IMT benefit

- No randomized outcomes trials of non-statin combination therapy to lower LDL cholesterol
  - Single drug outcomes trials with bile acid sequestrant and niacin

- No outcomes trials with titration to LDL cholesterol goal
Combination therapy and coronary atherosclerosis in FH

- SCOR study, Kane et al. 1990
- Randomized controlled trial 72 FH patients
- Baseline LDL cholesterol 283 mg/dL
- Treated group (n=40) initially on colestipol up to 30 grams per day and niacin up to 7.5 grams/day; lovastatin added when available
  - 36 on niacin, 25 >1.5 g/day
  - 28 colestipol 30 g/day; 4 on 15 g/day
  - 16 on 40 to 60 mg lovastatin in 2 or 3 drug combination

Control group diet alone but some on colestipol 15 g/day

On-trial LDL C
- Decreased 10.6% in control group
- Decreased 38.1% in treated group (283 to 172)

Computer-based coronary angiography
Progression in control group
Regression in treated group, also seen when women analyzed separately

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%

# Typical 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>(1 mg) -32</td>
<td>(2 mg) -36</td>
<td>(4 mg) -43</td>
<td></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
Components of Cholesterol Homeostasis

- Dietary Cholesterol: 31%
- Absorption: 50%
- Synthesis: 19%
- Biliary Secretion: 50%
- Excretion: 50%
Bile Acid Binding Resins

- Cholestyramine and colestipol powders
- Colestipol tablets - one gram
- Give 4 to 30 grams daily, divided, with meals
- Colesevelam: 625 mg tablets or suspension
- LDL lowered by 10 to 25%
- Additive with statins
- Can raise triglycerides
- Monotherapy outcomes trial (CPPT) with cholestyramine
Response in LDL-c in Patients With Severe Heterozygous Familial Hypercholesterolemia*

* Ten patients

Bile Acid Binding Resins

- Advantages: no systemic absorption
- Can be used alone but can be combined with statins for greater LDL reduction
- Side effects: constipation, hard stools, bloating, flatulence
- Can interfere with absorption of other drugs
- Special care with warfarin
Bile Acid Binding Resins: Colesevelam

- Polymer with greater binding activity than cholestyramine and colestipol
- 625 mg tablets or suspension
- 6 to 7 tablets per day with one or two meals
- 18% reduction of LDL-C at maximum dose (also additive with statins)
- Fewer drug interactions than older resins (thyroxine)
- Usually less constipating (but not always)
- BAS may lower blood sugar: decrease HgbA1c by 0.5% \((\text{Zieve et al Clinic Ther 29:74, 2007})\)
# 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>

Combination therapy to lower LDL-cholesterol

- Statin plus bile acid sequestrant
  - All three of the available BAS studied in combination with different statins
  - 10 to 25% further LDL C reductions
  - Constipation, GI side effects
  - Drug interaction issues with older resins, but less with colesevelam
  - Large number of pills versus suspensions
Ezetimibe

- Cholesterol absorption inhibitor
- Works at the enterocyte brush border
- Inhibits cholesterol absorption through a mechanism dependent on NPC 1L1 protein
- Glucuronidated in the intestine and cleared by liver, extensive enterohepatic recirculation
- Minimal levels in systemic circulation
- Half-life about 22 hours
- FDA approval 2002
Ezetimibe

- Lowers LDL-C by 15% to 18%
- Additive with statins
- Side effects – muscle, GI
- Dosing: 10 mg per day (can be taken any time)
- Transaminases may increase when used in combination with statins – usually return to normal on medication
Combination therapy to lower LDL-cholesterol

- Statin plus ezetimibe
  - About 20% further decrease in LDL cholesterol
  - Tolerance usually good
  - Lack of outcomes data in FH patients
  - Cost
  - SHARP trial as combination therapy

- 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)
Ezetimibe Added to Statin Therapy: Effect on LDL

<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 Placebo or Ezetimibe</td>
<td>133 mg/dL</td>
<td>102 mg/dL</td>
</tr>
</tbody>
</table>

Mean % Change in LDL-C From Treated Baseline

- Statin Monotherapy: 0%
- After Adding Placebo or Ezetimibe: -4%
- Statin + Ezetimibe: -25%*

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

Combination therapy to lower LDL-cholesterol

- Statin plus niacin
  - LDL-C lowering dose-dependent: 10 to 20%
  - Maximum dose with statin 2000 mg daily
  - Lower doses in elderly patients
  - Toxicity and side effect issues—blood sugar concern
  - Coronary drug project: decreased non-fatal MI during 6 year study
COMPELL: Niacin ER/Statin Combination

McKenney JM, et al. *Atherosclerosis.* 2007;192:432-437

N = 292; 12 weeks
*P<.05 versus atorva + niacin ER
Three or four drug combinations are sometimes needed in FH

- Statin/resin/niacin
- Statin/ezetimibe/niacin
- Statin/ezetimibe/BAS/niacin
- Benefits: substantial LDL cholesterol reduction
- Disadvantages: number of pills, side effects, cost
Further additive therapies for Familial Hypercholesterolemia

- Lomitapide and mipomersen for homozygous FH
  - Studied on background of combination therapy
- LDL apheresis also in addition to combination therapy
- PCSK9 inhibitors on background statin or combination therapy
- Combinations of therapies for patients with severe heterozygous FH, homozygous FH or statin intolerance offer possibility of substantial LDL cholesterol reduction and decreased risk of atherosclerotic cardiovascular disease
LDL cholesterol burden in individuals with or without FH as a function of the age of initiation of statin therapy.

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
Take Home Messages

- Combination therapy is often needed in patients with FH
- Therapies using different mechanisms of action are additive
- There is evidence of benefit
- Ezetimibe preferred second drug in a number of international guidelines
- Pheresis and new therapies build on current combinations
Thank you!