Combination Therapy for Dyslipidemia: 1 + 1 ≠ 2

Objectives

- Recite the lipid goals according to NCEP ATP III.
- Compare and contrast current data with ATP III recommendations in the treatment of specific dyslipemias.
- Determine when it is appropriate to use combination therapy to treat dyslipidemia.

Status of ATP IV
Patient Case #1

BL is a 55 year old female with Type 2 diabetes. She tries hard to control her blood glucose and currently has an A1C of 7.3%. She is concerned about her cardiovascular health. She is currently taking rosuvastatin 20mg daily and has a total cholesterol of 169, Triglycerides of 190, and LDL of 95 and a HDL of 36. She is asking for your advice about her lipids and how to further reduce her risk.

ATP III Lipid Goals

- Total Cholesterol
- Triglycerides
- HDL-C
- LDL-C
- Non-HDL-C

ATP III Lipid Classification

<table>
<thead>
<tr>
<th>Total Cholesterol (mg/dL)</th>
</tr>
</thead>
</table>
| <200                      | Desirable  
| 200–239                   | Borderline high  
| ≥240                      | High  

### ATP III Lipid Classification

**HDL Cholesterol (mg/dL)**
- <40 Low
- ≥50 High

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**LDL Cholesterol (mg/dL)**
- <100 Optimal
- 100–129 Near optimal/above optimal
- 130–159 Borderline high
- 160–189 High
- ≥190 Very high

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### Three Categories of Risk that Modify LDL-Cholesterol Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD risk equivalents or CHD plus uncontrolled risk factors</td>
<td>&lt;70</td>
</tr>
<tr>
<td>CHD or CHD risk equivalents</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Multiple (≥2) risk factors</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Zero to one risk factor</td>
<td>&lt;160</td>
</tr>
</tbody>
</table>
Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)
- Family history of premature CHD
  - CHD in male first degree relative <55 years
  - CHD in female first degree relative <65 years
- Age (men ≥45 years; women ≥55 years)


ATP III Lipid Goals

- Non-HDL Cholesterol
  - Goal is 30 points above the LDL goal


Lipid Medication Therapy

- Statins –
  - LDL by 21-63%, TG by 10-33%, HDL 5-10%
- Fibrates –
  - LDL by 6-20%, TG by 35-53%, HDL 5-20%
- Niacin –
  - LDL by 10-28%, TG by 25-30%, HDL 15-35%
- Omega 3 Fatty Acids –
  - LDL by 4-49%, TG by 23-45%, HDL 5-9%
- Cholesterol Absorption Inhibitors –
  - LDL by 17%, TG by 7-8%, HDL 1%
- Bile Acid Sequestrants –
  - LDL by 15-30%, No noticeable change in TG or HDL
Treating Dyslipidemias ATP III

- **General Rules**
  - **Target LDL first**
    - When LDL is at goal, target the Non-HDL
    - After the LDL is at goal and the Non-HDL is at goal, target either HDL or Triglycerides
    - If Triglycerides are over 500mg/dl, they become the primary goal of therapy

Specific Dyslipidemias: Elevated Triglycerides

**Non-HDL Cholesterol: Secondary Target**

- Primary target of therapy: LDL cholesterol
- Achieve LDL goal before treating non-HDL cholesterol
- Therapeutic approaches to elevated non-HDL cholesterol
  - Intensify therapeutic lifestyle changes
  - Intensify LDL-lowering drug therapy
  - Nicotinic acid or fibrate therapy to lower VLDL

Specific Dyslipidemias: Elevated Triglycerides

**Management of Very High Triglycerides (≥500 mg/dL)**

- Goal of therapy: prevent acute pancreatitis
- Very low fat diets (≤15% of caloric intake)
- Triglyceride-lowering drug usually required (fibrate or nicotinic acid)
- Reduce triglycerides before LDL lowering
Specific Dyslipidemias: Elevated Triglycerides (≥150 mg/dL)

Causes of Elevated Triglycerides
- Obesity and overweight
- Physical inactivity
- Cigarette smoking
- Excess alcohol intake

Causes of Elevated Triglycerides (continued)
- High carbohydrate diets (>60% of energy intake)
- Several diseases (type 2 diabetes, chronic renal failure, nephrotic syndrome)
- Certain drugs (corticosteroids, estrogens, retinoids, higher doses of beta-blockers)
- Various genetic dyslipidemias

Specific Dyslipidemias: Low HDL Cholesterol

Management of Low HDL Cholesterol
- LDL cholesterol is primary target of therapy
- Weight reduction and increased physical activity (if the metabolic syndrome is present)
- Non-HDL cholesterol is secondary target of therapy (if triglycerides ≥200 mg/dL)
- Consider nicotinic acid or fibrates (for patients with CHD or CHD risk equivalents)
Specific Dyslipidemias:
Low HDL Cholesterol

**Causes of Low HDL Cholesterol (<40 mg/dL)**
- Elevated triglycerides
- Overweight and obesity
- Physical inactivity
- Type 2 diabetes
- Cigarette smoking
- Very high carbohydrate intakes (>60% energy)
- Certain drugs (beta-blockers, anabolic steroids, progestational agents)

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**Patient Case #1**

BL is a 55 year old female with Type 2 diabetes. She tries hard to control her blood glucose and currently has an A1C of 7.3%. She is concerned about her cardiovascular health. She is currently taking rosvustatin 20mg daily and has a total cholesterol of 169, Triglycerides of 190, and LDL of 95 and a HDL of 36. She is asking for your advice about her lipids and how to further reduce her risk.

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**Monotherapy Endpoint Evidence**

- **Statins** –
  - Primary prevention – Decreases risk of CHD and mortality (Jupiter, APCAPS/TexCAPS, WOSCOPS, ASCOT-LLA)
  - Secondary Prevention – Decreases risk of second MI, revascularization and mortality (HPS, 4S, Prove-it, CARE)
- **Niacin** –
  - Secondary Prevention – Coronary Drug Project Trial
- **Fibrates** –
  - Primary prevention – Helsinki Heart Study, FIELD trial
  - Secondary prevention – VA-HIT
- **Omega 3 Fatty Acids** –
  - Secondary prevention – GISSI Trial
Combination Therapy Endpoint Evidence

- Statin with a fibrate
  - ACCORD
- Statin with niacin
  - AIM-HIGH

ACCORD

- Group of 3 studies looking at high cardiovascular risk individuals with diabetes
- The lipid trial randomized 5,518 patients to receive either simvastatin or simvastatin plus fenofibrate
- Primary outcome - the first occurrence of a major cardiovascular event
  - Nonfatal MI, nonfatal stroke, or death from CVD


ACCORD

- Baseline characteristics were similar in the 2 groups
- Average LDL was 100, HDL – 38, Triglycerides – 162
- Average follow-up time was 4.7 years
**ACCORD**

- No difference in the primary or secondary outcomes.
- A trend toward worse cardiovascular outcomes in women taking the combination and a trend toward improved cardiovascular outcomes in men taking the combination.
- In those patients with very low HDL (avg – 29.5) and high triglycerides (avg – 284), there was an improvement with the combination.


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**AIM-HIGH**

- Does the combination of niacin and a statin reduce the risk of cardiovascular events compared to a statin alone in patients with pre-existing cardiovascular disease who have low HDL levels and elevated triglyceride levels?
- 3414 patients were randomly assigned to either group.

AIM-HIGH

- **Primary outcome**
  - Composite of the first event of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization (for > 23 hours) for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.

- **Average lipid levels at initiation**
  - LDL – 74
  - HDL – 35
  - TG – 161

- **Other baseline values were similar between the groups**


AIM-HIGH

- **Results for the niacin group**
  - Decrease in LDL from 74 to 62
  - HDL increased from 35 to 42
  - TG decreased from 164 to 122
  - Trial stopped early
  - No difference seen in the primary or secondary outcomes


HPS2-THRIVE

- **25,673 patients with CHD randomized to statin therapy or statin therapy with niacin/laropiprant.**

- **Primary outcome –**
  - Major vascular events after 4 years of follow-up

- **Results –**
  - No difference in the primary outcome
  - Significant differences in infection and bleeding rates.

http://www.thrivestudy.org
Effects of ER niacin/laropiprant on lipids

<table>
<thead>
<tr>
<th>Year of FU</th>
<th>LDL-C (mg/dL)</th>
<th>HDL-C (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-12</td>
<td>6</td>
<td>-35</td>
</tr>
<tr>
<td>4</td>
<td>-7</td>
<td>6</td>
<td>-31</td>
</tr>
<tr>
<td>STUDY AVERAGE</td>
<td>-10</td>
<td>6</td>
<td>-33</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>(-0.25)</td>
<td>(0.16)</td>
<td>(-0.37)</td>
</tr>
</tbody>
</table>

“Based on previous observational studies and randomized trials, it was anticipated such lipid differences might translate into a 10-15% reduction in vascular events”  
Eur Heart Journal 2013

Effect of ERN/LRPT on SERIOUS adverse events  
(median follow-up 3.9 years)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Excess</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic complication</td>
<td>3.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>1.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infection</td>
<td>1.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>0.7%</td>
<td>0.0008</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.4%</td>
<td>0.05</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.7%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Skin</td>
<td>0.3%</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

Shotgun vs. Rifle

Legend:
- Red: ERN/LRPT
- Blue: Placebo
Topics for Further Study

- Does combination therapy improve outcomes in patients whose LDL level is not at goal.
- Does combination therapy improve outcomes in patients whose triglycerides are very high or whose HDL levels are very low.
- Does non-statin medication treatment for very-high triglycerides lower either cardiovascular risk or pancreatitis risk

Take Home Points

- Carefully evaluate the risks vs. benefit of combination therapy to treat dyslipidemia
- Treat LDL first
- Statin therapy is very effective
- Additive therapy to statins may improve lipid numbers, but may not improve outcomes

Patient Case #2

- GB is a 55 year old patient who had 2 stents placed 10 months ago. He has a history of dyslipidemia, hypertension and allergic rhinitis. He currently takes the following medications –
  - Simvastatin 40mg PO Daily
  - Lisinopril/HCTZ 20/12.5mg PO Daily
  - Clopidogrel 75mg PO Daily
  - Aspirin 81mg PO Daily
  - Metoprolol Succinate ER 50mg PO Daily
  - Loratadine 10mg PO Daily
  - Fluticasone Nasal Spray
Patient Case #2

- His most recent fasting lipid profile reveals the following:
  - TC = 180, LDL = 98, HDL = 32, TG = 250
- Now that his LDL is less than 100, the physician would like to treat his Non-HDL. Assuming his LDL goal to be less than 100, what is his Non-HDL goal? What is his Non-HDL value?
- What are the good and bad points about prescribing the following medications?
  - Fibric acid derivative
  - Niacin
  - Increasing the statin dose/changing to a more potent statin