ATP IV: Predicting Guideline Updates

Disclosures

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  – Speaker’s Bureau
  - Merck
  - Janssen
  - Boehringer-Ingelheim

Learning Objectives

- Describe at least two evidence-based recommendations for dyslipidemia treatment that are different than what is currently recommended in the NCEP ATP III.
- Explain the proven patient demonstrated benefits of specific drug therapy options for the treatment of dyslipidemia.

American Heart Association (AHA)
Heart Disease and Stroke Statistics—2012 Update
82.6 Million Americans have Cardiovascular Disease

**Prevalence, Treatment, and Control of High Levels of LDL-Cholesterol**

- CDC analysis based on NHANES data
- 71 million Americans with high LDL-C from 2005-2008

**Lipid Treatment Assessment Project 2 (L-TAP2)**

- 9955 patients on stable lipid-lowering therapy from 9 different countries

**Consensus Recommendations for Dyslipidemia Management**

- 2001 - National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)
- 2004 - NCEP ATP III implications
- 2011 - ACC guidelines
- 2013 - ADA Standards of Medical Care in Diabetes.

*NCEP ATP IV (expected in 2013)*

**Targets of Treatment in Dyslipidemia**

Primary Target: LDL-C

Secondary Target: Non-HDL-C

- EXCEPTION: Triglyceride lowering is an immediate target of therapy if ≥500 mg/dL
- Raising HDL-C is a tertiary target in certain patients
**NCEP ATP III: LDL-C Goal Values**

- **CVD or Diabetes**: Yes/No
  - Yes: >2 major CV risk factors
    - Yes: 10-year CHD risk: Framingham Score
      - >20%: High Risk <100 mg/dL
      - 10-20%: Moderately High Risk <130 mg/dL
      - <10%: Lower Risk <100 mg/dL
    - No: High Risk <100 mg/dL
  - No: Lower Risk <100 mg/dL

- **Very High Risk**: Is optional if >2 major CV risk factors

**ATP III: Very High Risk Definition**

- Presence of established CVD plus:
  1. multiple major risk factors (esp. diabetes)
  2. severe and poorly controlled risk factors (esp. continued cigarette smoking),
  3. multiple metabolic syndrome risk factors (esp. triglycerides ≥ 200 mg/dL plus non-HDL-C ≥ 130 mg/dL with HDL-C < 40 mg/dL), and
  4. patients with acute coronary syndromes

Optional goal of <70 mg/dL does not apply to individuals who are not high risk

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**ATP III: 30-40% Recommendation**

When LDL-lowering drug therapy is employed in high-risk or moderately high-risk intensity of therapy should be sufficient to achieve at least a 30-40% LDL-C reduction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/day)</th>
<th>LDL-C reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10</td>
<td>39</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>40-80</td>
<td>25-35</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5-10</td>
<td>39-45</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20-40</td>
<td>35-41</td>
</tr>
</tbody>
</table>

Pitavastatin (not available in 2004) 1-2 mg/day attains 30-40% LDL-C reductions.

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**Lipid-Lowering Therapies**

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Pitavastatin, Rosuvastatin</td>
<td>↓18-63%</td>
<td>↑5-15%</td>
<td>↓7-30%</td>
</tr>
<tr>
<td><strong>Bile acid sequestrants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colesevelam, Cholestyramine, Colestipol</td>
<td>↓15-30%</td>
<td>↑3-5%</td>
<td>0 or ↑</td>
</tr>
<tr>
<td><strong>Nicotinic acid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓5-25%</td>
<td>↑15-35%</td>
<td>↓20-50%</td>
<td></td>
</tr>
<tr>
<td><strong>Fibric acid derivatives</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil, Fenofibrate</td>
<td>↓5-20% or ↑</td>
<td>↑10-20%</td>
<td>↓20-50%</td>
</tr>
<tr>
<td><strong>Cholesterol absorption inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>↓18%</td>
<td>↑1%</td>
<td>↓7%</td>
</tr>
<tr>
<td><strong>Omega-3 fatty acids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Rx strength)</td>
<td></td>
<td>↑9%</td>
<td>↓45%</td>
</tr>
</tbody>
</table>

Landmark Statin-based Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Statin Treatment (mg/day)</th>
<th>LDL-C (mg/dL)</th>
<th>Primary Endpoint/CV Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>Simvastatin 20-40 mg</td>
<td>188</td>
<td>28.0</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pravastatin 40 mg</td>
<td>156</td>
<td>15.0</td>
</tr>
<tr>
<td>CARE</td>
<td>Pravastatin 40 mg</td>
<td>139</td>
<td>13.2</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin 40 mg</td>
<td>132</td>
<td>24.4</td>
</tr>
<tr>
<td>PROSPER</td>
<td>Pravastatin 40 mg</td>
<td>147</td>
<td>16.2</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin 40 mg</td>
<td>192</td>
<td>7.5</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>Lovastatin 20-40 mg</td>
<td>150</td>
<td>5.5</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Atorvastatin 10 mg</td>
<td>133</td>
<td>3.0</td>
</tr>
<tr>
<td>CARDS</td>
<td>Atorvastatin 10 mg</td>
<td>118</td>
<td>9.0</td>
</tr>
<tr>
<td>JUPITER</td>
<td>Rosuvastatin 20 mg</td>
<td>108</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Critical Analysis of Evidence that Questions ATP III Recommendations

Audience Question 1

- A 72 year old woman who was hospitalized for acute coronary syndrome 6 weeks ago has been treated with atorvastatin 20 mg daily. Her LDL-C is 90 mg/dL, HDL-C is 40 mg/dL, TG are 200 mg/dL, non-HDL is 130 mg/dL. Which of the following would you recommend?
  1. Continue atorvastatin 20 mg daily
  2. Increase atorvastatin to 80 mg daily
  3. Change atorvastatin to simvastatin 40 mg daily
  4. Change atorvastatin to rosuvastatin 10 mg daily

Treat to New Targets (TNT) Trial

- Sub-analysis of 1,501 patients with CHD and diabetes
- Randomized to atorvastatin 10 mg or 80 mg daily for 5 yrs

![Graph showing LDL-C reduction with atorvastatin 10 mg and 80 mg daily.](image)
**Cholesterol Treatment Trialists’ (CTT) Collaboration**

- Meta-analysis of large (n>1000), randomized trials of ≥ 2 yrs duration
  - More vs. Less intensive statin therapy:
    - 5 trials (n=39,612), median 5 yr follow-up
    - Trials were in patients with coronary heart disease
  - Statin vs. control:
    - 21 trials (n=129,526), median 4.8 yr follow-up
- CV event risk reductions per 1.0 mmol/L LDL-C reduction at 1 year were estimated

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**CTT Collaboration: More vs. Less Statin Therapy**

- Weighted mean further reduction in LDL-C was 0.51 mmol/L (~19 mg/dL)
- CV event reductions proportionate to LDL-C reductions, even when baseline LDL-C was <2 mmol/L (77 mg/dL)

<table>
<thead>
<tr>
<th>Event</th>
<th>Reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Vascular Events</td>
<td>15%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHD Death or Non-Fatal MI</td>
<td>13%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>19%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>16%</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

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**LDL Goals of < 70 mg/dL**

- **ATP III recommendation:**
  - Therapeutic option for patients with established CV disease and additional risk factors or high risk comorbidities
- **Evidence-based recommendation:**
  - Appropriate for all patients with coronary heart disease regardless of the presence of other comorbidities

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**American Diabetes Association: Standards of Medical Care in Diabetes**

**Dyslipidemia:**

- Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients with overt CVD, or without CVD if >40 yrs with ≥ 1 other CVD risk factors
- If drug-treated patients do not reach targets on maximal tolerated statin therapy, a reduction in LDL-C of 30-40% from baseline is an alternative therapeutic goal
- Triglycerides <150 mg/dL and HDL-C >40 mg/dL in men and >50 mg/dL in women, are desirable. However, LDL-C–targeted statin therapy remains the preferred strategy.
- If targets not reached on maximally tolerated doses of statins, combination therapy using statins and other lipid-lowering agents may be considered but has not been evaluated in outcome studies for either CVD outcomes or safety
Collaborative Atorvastatin Diabetes Study (CARDS)
- Double-blind, randomized trial in 2838 primary prevention patients with type 2 diabetes randomized to placebo or atorvastatin 10 mg daily for 3.9 years

Primary Endpoint: Major CV Event (%)
- Placebo (LDL-C ~ 118 mg/dL)
- Atorvastatin 10 mg/day (LDL-C ~ 77 mg/dL)

37% reduction
p=0.001

The Heart Protection Study (HPS)
- High-risk patients, age 40-80 yr, randomized, double-blind, to placebo or simvastatin 40 mg daily for 5 yr
- Subgroup of 5963 had diabetes
- LDL-C decreased from 123 mg/dL to 89 mg/dL

Reductions even when baseline was LDL-C < 116 mg/dL

ADA and ACC Consensus Statement: Lipoprotein Management in Patients With Cardiometabolic Risk

<table>
<thead>
<tr>
<th>Goal Values (mg/dL)</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highest Risk:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD or DM with ≥1 major risk factor</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td><strong>High Risk:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CVD, no DM with ≥2 major risk factors</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
</tr>
<tr>
<td>DM with no major risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other major risk factors (beyond dyslipidemia) include cigarette smoking, hypertension, and family history of premature coronary artery disease.

LDL-C Reduction in Diabetes
- **ATP III recommendation:**
  - Statin therapy if not at goal LDL value
    - < 100 mg/dL for most
    - Therapeutic option of < 70 mg/dL if established CVD
  - Evidence-based recommendation:
    - Nearly all patients (age >40 yrs) benefit from statin based therapy, regardless of LDL-C value
**Audience Question 2**

- A 60 year old man with coronary artery disease and diabetes is treated with atorvastatin 40 mg daily. He will not consider a higher dose or another statin due to cost and perceived risks. His LDL-C is 90 mg/dL, HDL-C is 35 mg/dL, TG are 250 mg/dL, non-HDL is 140 mg/dL. Which of the following would you recommend?

1. Add fenofibrate
2. Add ezetimibe
3. Add niacin
4. Continue present therapy

**Clinical Scenarios**

<table>
<thead>
<tr>
<th>Goal</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C Lowering</td>
<td>Statin</td>
<td>Statin + Bile Acid Sequestrant</td>
</tr>
<tr>
<td></td>
<td>Niacin</td>
<td>Statin + Ezetimibe</td>
</tr>
<tr>
<td></td>
<td>Bile Acid Sequestrant</td>
<td>Statin + Niacin</td>
</tr>
<tr>
<td></td>
<td>Ezetimibe</td>
<td>Others</td>
</tr>
<tr>
<td>Non-HDL-C Lowering</td>
<td>Statin (high-dose)</td>
<td>Statin + Fibrate</td>
</tr>
<tr>
<td></td>
<td>Niacin</td>
<td>Statin + Niacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statin + Omega-3 Fatty Acids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others</td>
</tr>
<tr>
<td>Triglyceride Lowering</td>
<td>Fibrate</td>
<td>Fibrate + Omega-3 Fatty Acids</td>
</tr>
<tr>
<td></td>
<td>Omega-3 Fatty Acids</td>
<td>Fibrate + Niacin</td>
</tr>
<tr>
<td></td>
<td>Niacin</td>
<td>Niacin + Omega-3 Fatty Acids</td>
</tr>
</tbody>
</table>

**ACCORD Study: Combination Lipid Therapy**

- 5518 patients with type 2 diabetes treated with open-label simvastatin randomized to fenofibrate or placebo for 4.7 years
- Primary outcome: nonfatal MI, nonfatal stroke, or CV death

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>100.6</td>
<td>81.1</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>38.1</td>
<td>41.2</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>162</td>
<td>122</td>
</tr>
</tbody>
</table>

**ACCORD Study: Results**

- Subgroup analyses:
  - Possible benefit for men and possible harm for women
  - Possible benefit in patients with both high baseline triglycerides (>204) and a low baseline HDL-C (<34)
  - P=0.057 for interaction
Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH)

- Double-blind trial in 3414 patients with a history of CVD treated with statin therapy to an LDL-C of 40-80 mg/dL
- Randomized to placebo or extended-release niacin (1500-2000 mg daily)
- Primary endpoint: Composite CV events
- Clinical trial was stopped at 3 years, 18 months earlier than planned

Audience Question 3

- A 65 year old woman has a history of hypertension, diabetes, and chronic kidney disease requiring hemodialysis. She is on no lipid lowering therapy but her LDL-C is 130 mg/dL, HDL-C is 45 mg/dL and TG are 150 mg/dL. Which of the following would you lipid lowering regimens would you recommend?
  1. Lifestyle modifications alone
  2. Lifestyle modifications + simvastatin 10 mg daily
  3. Lifestyle modifications + atorvastatin 10 mg daily
  4. Lifestyle modifications + colesevelam 3.75 g daily

AIM-HIGH: Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>75.8</td>
<td>65.2</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>35.3</td>
<td>44.1</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>162</td>
<td>120</td>
</tr>
</tbody>
</table>

- Incidence of Primary Endpoint
  - Statin plus placebo: 16.2%
  - Statin plus niacin: 16.4%  p=0.80

Combination Lipid Lowering Therapy

- ATP III recommendation:
  - If high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug

- Evidence-based recommendation:
  - The addition of a fibrate or nicotinic acid to statin-based LDL-lowering drug therapy does not reduce CV events
Lipid-Lowering Therapy in Patients with End-Stage Renal Disease (ESRD) Requiring Hemodialysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Primary Endpoint</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D Study:</td>
<td>Type 2 diabetes plus long-term hemodialysis (n=1255)</td>
<td>CV death, nonfatal MI, fatal/nonfatal stroke</td>
<td>0.92 (0.77–1.10)</td>
</tr>
<tr>
<td>AURORA Study:</td>
<td>Long-term hemodialysis (n=2776)</td>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>0.96 (0.84–1.11)</td>
</tr>
</tbody>
</table>

ATP III recommendation:
- Patients with chronic kidney disease
  - SCr ≥1.7 mg/dL in men, or ≥1.5 mg/dL in women
  - Age ≥40 yrs., without prior MI
  - Primary endpoint was major atherosclerotic events
  - 4.9 yr. median follow-up

Evidence-based recommendation:
- Treating patients that have chronic kidney disease with statin-based therapy results in CV event lowering, but not in patients that require hemodialysis

\[ \text{Lancet. 2011; 377: 2181-92} \]

SHARP: Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Ezetimibe/Simvastatin (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td></td>
</tr>
<tr>
<td>Non-dialysis (n=6247)</td>
<td>296 (9.5%)</td>
<td>373 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>Dialysis (n=3023)</td>
<td>230 (15.0%)</td>
<td>246 (16.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Note: No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)

\[ \text{Lancet. 2011; 377: 2181-92} \]
**JUPITER Trial**

- Primary objective:
  - First major CV event
- Patients randomized to rosvastatin 20 mg daily or placebo (planned for 3.5 yr)
- Patient profile (n=17,802)
  - Primary prevention
  - Men ≥ 50 yr, women ≥ 60 yr
  - LDL-C <130 mg/dL with hsCRP >2 mg/L

*hsCRP = high-sensitivity C-reactive protein*

**JUPITER Results**

Stopped early after a mean of 1.9 years

- Median LDL (interquartile range) at 12 mo:
  - Placebo 110 mg/dL (94-125)
  - Rosuvastatin 55 mg/dL (44-72) P<0.001
- 25% (> 4000 patients) had LDL-C values < 44 mg/dL, with no undue harm demonstrated
- Primary Endpoint (events per 100 pt-years):
  - Placebo 1.36
  - Rosuvastatin 0.77 HR=0.56 (0.46-0.69) P<0.00001

**JUPITER Results: Subgroups**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Race or Ethnic Group</td>
<td>0.57</td>
<td></td>
</tr>
</tbody>
</table>

**JUPITER Results in Older Patients:**

5695 Patients Age ≥ 70 yrs

Lower Risk Patients and Very Low LDL-C

- **ATP III recommendation:**
  - Primary prevention patients: treat to LDL goals of <160, <130, or <100 mg/dL based on CV risk
  - "very low LDL levels…remote possibility of side effects from LDL lowering per se" 

- **Evidence-based recommendation:**
  - Statin therapy reduces CV events if hs-CRP is elevated in some primary prevention patients
  - No harm seen in statin treated patients with very low LDL-C levels

Predictions for the ATP IV

- Conversion of "optional" LDL goal of < 70 to a standard for patients with CVD
- Conversion of "optional" LDL goal of <100 to a standard for patients without CVD but with multiple CV risk factors
- Support for LDL-C targeted therapy, but further emphasis on non-HDL and apoB
- Continued emphasis on statin based therapy

Predictions for the ATP IV

- Tempered recommendations for combination lipid-lowering drug therapy
- Specific recommendations on certain subpopulations (CKD)
- Support of treatment in the very elderly
- Revised monitoring recommendations for statin therapy

http://www.nhlbi.nih.gov/guidelines/indevelop.htm#status
Controversial Topics

- Role of advanced lipid testing in the management of dyslipidemia
- Replacement of specific lipid targets with percent reduction targets
- Reserved use of nicotinic acid and fibrates for patients with hypertriglyceridemia (triglycerides ≥ 500 mg/dL)
- Others....

New Drugs

- **Anacetrapib**
  - CETP inhibitor (stops HDL from transferring into VLDL or LDL)
  - 100 mg/day
  - **DEFINE**
    - LDL ↓ 36%
    - lipoprotein(a) ↓ 36.4%
    - HDL ↑ 138%
    - No ↑ SBP or CVD (unlike torcetrapib)
  - **REVEAL ongoing (2017)**

- **Homozygous Familial Hypercholesterolemia**
  - *Kynamro ( mipomersin)*
    - Once weekly injection
    - apolipoprotein B-100 synthesis inhibitor
    - Cost: $176,000 per year

  - *Juxtaposed ( lomitapide)*
    - 5-60 mg PO daily
    - microsomal triglyceride transfer protein inhibitor
    - Cost: $235,000-295,000 per year

Questions

"That's all Folks!"