Ambulatory Care PRN Focus Session—New Developments in Hypertension and Dyslipidemia Management
Activity No. 0217-0000-11-101-L01-P (Application-Based Activity)

Tuesday, October 18
3:30 p.m.–5:30 p.m.
Convention Center: Rooms 315 & 316

Moderator: Candice Garwood, Pharm.D., BCPS
Clinical Assistant Professor, Wayne State University, Detroit, Michigan

Agenda

3:30 p.m. Updates in Management of Dyslipidemia
Joseph J. Saseen, Pharm.D., FCCP, BCPS
Professor of Clinical Pharmacy and Family Medicine, University of Colorado School of Pharmacy and School of Medicine, Aurora, Colorado

4:30 p.m. Updates in Hypertension Management
Jonathan D. Ference, Pharm.D., BCPS
Assistant Professor of Pharmacy Practice, Wilkes University School of Pharmacy, Wilkes Barre, Pennsylvania

Faculty Conflict of Interest Disclosures
Jonathan D. Ference: no conflicts to disclose.
Joseph J. Saseen: board member for the Board of Pharmacy Specialties and the National Lipid Association.

Learning Objectives

1. Review clinical trials with clinically relevant endpoints and discuss implications on management strategies.
2. Design evidence-based treatment plans for hyperlipidemia.
3. Discuss recent developments in advanced lipid testing (such as Lp(a), CRP, etc.) and possible implications on practice.
4. Identify clinical trials with cardiovascular endpoints and discuss implications on management strategies.
5. Design evidence-based treatment plans for hypertension.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Updates in Management of Dyslipidemia

Joseph Saseen, Pharm.D., BCPS, FCCP, FASHP
Professor
University of Colorado

Learning Objectives

- Review clinical trials with clinically relevant endpoints and discuss implications on management strategies.
- Design evidence-based treatment plans for hyperlipidemia.
- Discuss recent developments in advanced lipid testing (such as Lp(a), CRP, etc.) and possible implications on practice.

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

Cardiovascular Risk Reduction Guidelines in Adults: Cholesterol Guideline Update (ATP IV)
Hypertension Guideline Update (JNC 8)
Obesity Guideline Update (Obesity 2)
Integrated Cardiovascular Risk Reduction Guideline

http://www.nhlbi.nih.gov/guidelines/cvd_adult/background.html#timeline

NCEP ATP III: LDL-C Goals


Conflicts of Interest

Joseph Saseen is a Board Member of the National Lipid Association

Lipid-Lowering Therapies

<table>
<thead>
<tr>
<th>Therapies</th>
<th>LDL-C Effect</th>
<th>HDL-C Effect</th>
<th>TG Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>↓ 18-63%</td>
<td>↑ 5-15%</td>
<td>↓ 7-30%</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>↓ 15-30%</td>
<td>↑ 5-15%</td>
<td>0 or ↑</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↓ 5-25%</td>
<td>↑ 15-35%</td>
<td>↓ 20-50%</td>
</tr>
<tr>
<td>Fibric acid derivatives</td>
<td>↓ 5-20% or ↑</td>
<td>↑ 10-20%</td>
<td>↓ 20-50%</td>
</tr>
<tr>
<td>Cholesterol absorption</td>
<td>↓ 18%</td>
<td>↑ 1%</td>
<td>↓ 7%</td>
</tr>
<tr>
<td>Omega-3 fatty acids</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>Baseline 122 Placebo 28.0 Statin 19.4</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pravastatin 40 mg</td>
<td>150</td>
<td>Baseline 112 Placebo 15.0 Statin 12.3</td>
</tr>
<tr>
<td>CARE</td>
<td>Pravastatin 40 mg</td>
<td>139</td>
<td>Baseline 98 Placebo 13.2 Statin 10.2</td>
</tr>
<tr>
<td>NPS</td>
<td>Simvastatin 40 mg</td>
<td>132</td>
<td>Baseline 93 Placebo 24.4 Statin 19.9</td>
</tr>
<tr>
<td>PROSPE</td>
<td>Pravastatin 40 mg</td>
<td>147</td>
<td>Baseline 97 Placebo 16.2 Statin 14.1</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin 40 mg</td>
<td>152</td>
<td>Baseline 109 Placebo 7.5 Statin 6.3</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>Lovastatin 20-40 mg</td>
<td>150</td>
<td>Baseline 115 Placebo 5.5 Statin 3.5</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Atorvastatin 10 mg</td>
<td>113</td>
<td>Baseline 90 Placebo 3.0 Statin 1.9</td>
</tr>
<tr>
<td>CARDS</td>
<td>Atorvastatin 10 mg</td>
<td>118</td>
<td>Baseline 77 Placebo 9.0 Statin 5.8</td>
</tr>
<tr>
<td>JUPITER</td>
<td>Rosuvastatin 20 mg</td>
<td>108</td>
<td>Baseline 55 Placebo 2.6 Statin 1.6</td>
</tr>
</tbody>
</table>

Clinical Case…

RP is a 68 year old man who is hospitalized for an acute coronary syndrome. He is discharge on atorvastatin 80 mg daily. His provider 2 weeks later asks you if he can be treated with a lower dose of a statin since his baseline LDL was only 110 mg/dL.

How do you respond? Would you feel differently if it were simvastatin?

Cholesterol Treatment Trialists’ (CTT) Collaboration

- Meta-analysis of large (n>1000), randomized clinical trials that were ≥2 yrs duration
  - More vs. Less intensive statin therapy:
    - 5 trials (n=39,612), median 5 yr follow-up
    - Statin vs. control:
      - 21 trials (n=129,526), median 4.8 yr follow-up
  - Average CV event risk reductions per 1.0 mmol/L LDL-C reduction at 1 year after randomization were calculated

Simvastatin Label Changes (June 2011)

- Do not start new patients on 80 mg daily
- Contraindicated with:
  - Itraconazole, ketoconazole, posaconazole, erythromycin, clindamycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol
  - Do not exceed 10 mg daily with:
    - Amiodarone, diltiazem, verapamil
  - Do not exceed 20 mg daily with:
    - Amiodipine, ranolazine
  - Avoid grapefruit juice (>1 quart daily)

Statin and Risk of Incident Diabetes

- 2010 meta-analysis of 13 trials (n=91,140)
  - 4278 developed diabetes (2226 with statins vs. 2052 with control) over a mean 4 yrs
    - 9% increased risk (OR 1.09 [1.02–1.17])
    - NNH was 255 patients
- 2011 meta-analysis of 5 trials (n=32,752)
  - 2749 developed diabetes (1449 with intensive-dose statin vs. 1300 with moderate-dose statin) over a mean 1.9 yrs
    - 12% increased risk (OR 1.12 [1.04–1.22])
    - NNH was 498; but, NNT for CV events was 155

Unwanted Effects of Statins

- Prospective open cohort study in new statin users (n=225,922) and non-users (n=1,778,770)
- Extensive analysis by individual statin and sex
- Results:
  - No risk: Parkinson’s disease, RA, VTE, dementia, osteoporotic fracture, several common cancers
  - Lower risk: Esophageal cancer
  - Higher risk: Liver dysfunction, acute renal failure, myopathy, cataracts
- Overall – VERY LOW INCIDENCE RATES

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>Bile Acid Sequestrant</td>
<td>Statin + Omega-3 Fatty Acids</td>
</tr>
<tr>
<td></td>
<td>Ezetimibe</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>

Clinical Case...

- Several years later, RP is treated with pravastatin 40 mg daily. He will not consider a higher dose or another statin due to cost and perceived risks. His LDL-C is 80 mg/dL, non-HDL-C is 130 mg/dL. Which of the following would you recommend?
  1. Add ezetimibe
  2. Add fenofibrate
  3. Add niacin
  4. Continue current therapy unchanged

Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE)

- Double-blind trial in 720 patients with heterozygous familial hypercholesterolemia randomized to ezetimibe/simvastatin 10/80 mg daily or simvastatin 80 mg daily for 2 yr
  - Significant differences in LDL-C reduction:
    - Baseline LDL-C: 319 and 318 mg/dL
    - LDL-C reductions: 58% and 41% (p<0.01)
  - Change in mean carotid IMT after 2 years
    - Ezetimibe/Simvastatin: 0.0111 mm
    - Simvastatin: 0.0058 mm (p=0.29)

Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness (ARBITER-6)

- Open-label trial in 208 patients with existing CHD or a CHD risk equivalent condition (e.g., diabetes, carotid or peripheral artery disease) who were receiving long-term statin therapy
  - Desirable LDL-C < 100 mg/dL and undesirable or low HDL-C < 50 mg/dL for men and < 55 mg/dL for women
  - Randomized to addition of:
    - Extended-release niacin up to 2000 mg daily or
    - Ezetimibe 10 mg daily
Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH)

- Sponsored by NHLBI
- Double-blind trial in 3114 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 (dosed up to 2000 mg daily)
- Stopped 18 months earlier than planned

AIM-HIGH... Stopped Early

- NHLBI of the National Institutes of Health stopped the trial earlier than planned: Lack of efficacy in reducing cardiovascular events prompts decision
- Adding high dose, extended-release niacin to statin treatment in people with CVD, did not reduce the risk of CV events, including heart attacks and stroke.
**Lipid-Lowering Therapy in Patients with End-Stage Renal Disease (ESRD) Requiring Hemo dialysis**

<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, fatal/nonfatal stroke, stroke,</td>
<td>0.96 (0.84–1.11)</td>
</tr>
</tbody>
</table>

**SHARP: Results**

- 68% were adherent at the end of study
- LDL-C reductions with ezetimibe/simvastatin:
  - 43 mg/dL at 1 yr, 33 mg/dL at 2.5 yr
- No difference in major adverse events:
  - Muscle pain, hepatic transaminase elevations, hepatitis, gall stones, cancer
- Myopathy (CK > 10 x ULN)
  - 9 with ezetimibe/simvastatin, 5 with placebo (p=ns)

**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)
Lipoprotein Subclasses

<table>
<thead>
<tr>
<th>Density (g/mL)</th>
<th>1.02</th>
<th>1.005</th>
<th>0.95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (nm)</td>
<td>LDL</td>
<td>IDL</td>
<td>VLDL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>LDL C</td>
<td>Non-HDL-C</td>
<td>Apo B</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>LDL Cholesterol</td>
<td>HDL cholesterol</td>
<td></td>
</tr>
</tbody>
</table>

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>Highest Risk:</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>DM with ≥1 major risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk:</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
</tr>
<tr>
<td>No CVD, no DM with ≥2 major risk factors</td>
<td></td>
<td></td>
<td></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.

Advanced Lipid Testing

- Several commercially available laboratory packages (e.g., NMR Lipoprofile, VAP, Berkley Labs)
- Measure several lipoprotein types and components, including several "biomarkers"
  - Direct LDL, LDL particle size and density, HDL subtypes, IDL, VLDL, Apo A1, Apo B
  - Lp(a), Lipoprotein Phospholipase A2 (Lp-PLA2)
  - hsCRP, homocysteine, fibrinogen,

Polling Question...

Should you consider advanced lipid testing in your high CV risk patient population to further refine their lipid-lowering therapy?

1. Yes
2. No

2010 ACCF/AHA Guideline:
Assessment of CV Risk in Asymptomatic Adults

- Advanced lipid testing:
  - Not recommended
- Lipoprotein Phospholipase A2 (Lp-PLA2)
  - Reasonable in intermediate risk patients
- hsCRP
  - Reasonable in men ≥50 yrs or women ≥60 yrs with LDL<130 mg/dL not on lipid-lowering therapy
  - Reasonable in men <50 yrs or women <60 yrs if intermediate risk (not if low risk)
  - Not recommended in any high risk patients

Lipoprotein Phospholipase A2 (Lp-PLA2)

- An enzyme bound primarily to atherogenic lipoproteins
- Secreted by inflammatory cells within atherosclerotic plaques
- Expression is significantly increased in advanced atherosclerotic lesions
- Changes in Lp-PLA2 levels have been associated with reduced CV events in subgroup analyses of the PROVE-IT trial

2011 ACCP Annual Meeting

New Developments in Hypertension and Dyslipidemia Management

7
C-Reactive Protein (CRP) and Atherosclerosis

- Localizes in atherosclerotic, but not normal, intima
- Induces complement activation
- Recruits monocytes into arterial wall
- Attenuates NO production
- Induces production of tissue factor in monocytes
- Blunts endothelial vasoreactivity
- Mediates LDL uptake by macrophages
- Triggers LDL oxidation
- Mediates PAI-1 expression

hsCRP as a CV Risk Marker

  - Endorsement of hsCRP as the analyte of choice to associate inflammation with CV risk
    - Low risk: <1 mg/L
    - Average risk: 1 to 3 mg/L
    - High risk: >3 mg/L
  - Meta-Analysis of 160,309 subjects in 54 long-term prospective studies
    - Elevated CRP continuously associated with the risk of CHD, ischemic stroke, vascular death, and non-vascular death

JUPITER Trial

- Primary objective:
  - First major CV event
- Patients randomized to rosuvastatin 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

JUPITER: Median Baseline Values

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin (n=8901)</th>
<th>Placebo (n=8901)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Female (%)</td>
<td>38.5</td>
<td>37.9</td>
</tr>
<tr>
<td>White/Black/Hispanic (%)</td>
<td>71.4/12.4/12.6</td>
<td>71.1/12.6/12.8</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>28.3</td>
<td>28.4</td>
</tr>
<tr>
<td>Blood Pressure (mm Hg)</td>
<td>134/80</td>
<td>134/80</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>15.7</td>
<td>16.0</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>4.2 (2.8-7.1)</td>
<td>4.3 (2.8-7.2)</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>108 (94-119)</td>
<td>108 (94-119)</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>49 (40-60)</td>
<td>49 (40-60)</td>
</tr>
</tbody>
</table>

All comparisons, p>0.05

JUPITER: Results

- Stopped early after a mean of 1.9 years
- Median (interquartile range) LDL-C at 12 mo:
  - Placebo 110 mg/dL (94-125)
  - Rosuvastatin 55 mg/dL (44-72) P<0.001
JUPITER Results: Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th># of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11,001</td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>Female</td>
<td>6,801</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65 yr</td>
<td>8,541</td>
<td>0.80</td>
<td>0.32</td>
</tr>
<tr>
<td>&gt;65 yr</td>
<td>9,261</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race or Ethnic Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12,683</td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Non-white</td>
<td>5,117</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


JUPITER Results in Older Patients: 5695 Patients Age ≥ 70 yrs

Lipid Treatment Assessment Project 2 (L-TAP2)

<table>
<thead>
<tr>
<th>LDL-C Level</th>
<th>% Patients at LDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (&lt;160)</td>
<td>86</td>
</tr>
<tr>
<td>Moderate risk (+130)</td>
<td>74</td>
</tr>
<tr>
<td>High risk (&lt;100)</td>
<td>67</td>
</tr>
<tr>
<td>Very high risk (+70)</td>
<td>30</td>
</tr>
</tbody>
</table>


Conclusions

- Several clinical trials have been published that impact patient care since that are not reflected in the current NCEP guidelines
- Evidence-based treatment plans for hyperlipidemia consist of statin-based therapy
- Advanced lipid testing have little impact in patient care for most patients based on current standards