Lipids: Translating Studies into Practice

WD04: Cortney Joneikis, MD, MS
Bob Gleeson, MD
Jeff Whittle, MD, MPH
Discussants:

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  Assistant Professor of Medicine, General Internal Medicine
  Medical College of Wisconsin

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  Assistant Professor of Medicine, General Internal Medicine
  Medical College of Wisconsin

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  Associate Professor of Medicine, General Internal Medicine
  Medical College of Wisconsin
Format of the Lipid Workshop – 3 cases, 12 questions

• Intro – 5 minutes
• Break into 3 groups to each discuss one case and specific questions – 30 minutes
• Reconvene and one person from each group will give their group’s suggested answer to the questions, and we will give what we believe to be the best answer with references – 55 minutes or 18 minutes per case
• The cases contain all pertinent information with no red herrings.
• The cases are all slightly controversial to better stimulate discussion.
• Ending evaluation – 5 minutes
Case 1: 62 yo nonsmoker female with new dyspnea on exertion.
FH: negative  PMH: Pre-eclampsia with second child, BP 128/78 on Rx, no other meds, ROS and PE otherwise negative. Her treadmill shows questionable ST changes. A CT angio shows moderate calcium and luminal irregularities.
TC 155  TG 90  HDL 45  LDL 95  Non-HDL 110

Q: What is your target LDL?
Q: How common is CAD in people with an LDL-C that is low enough it would not require treatment by ATP III?
Q: What other medications should she be on?
Q: Given the history above, what factors increased her risk of CAD?
Q: Was the CT angio indicated?
Case 2: 56 yo male new patient annual exam. No complaints. PMH: sleep apnea controlled with CPAP and BP 128/82 on lisinopril. 5’10” 240 lbs BMI 34 Waist 42 TC 195 TG 216 HDL 37 LDL 115 non-HDL 158 FBS 115

Q: Does this person have the metabolic syndrome?
Q: How does metabolic syndrome impact his CV risk?
Q: Do you need additional lipid test(s) to adequately assess his risk? And what do they measure?
Q: If treat lipids, how and what are the goals?
Case 3: A 62-yo male nonsmoker with hyperlipidemia. He previously developed myalgias to simva 40 and both atorva 20 and 40. He was on no medications when he developed a non-STEMI. He was started on optimal medical therapy (ACEi, beta blockers, aspirin), and referred to you for statin management.

TC 264  TG 150  HDL 44  LDL 190  non-HDL 224

Q: What is his LDL-C target?
Q: How can we get him to goal?
Q: Which statins have the highest and lowest myalgia rates?
Q: What alternative statin and/or statin regimen can we try?
Q: What laboratory tests should be considered in patients with statin myalgia?
Q: How far can diet take him toward his lipid goals?
Stop here if you plan to attend this workshop.

Cases and answers follow.
Case 1: Heart disease in a woman with a low Framingham Risk Score
Case 1: 62 yo nonsmoker female with new dyspnea on exertion. FH: negative  PMH: Pre-eclampsia with second child, BP 128/78 on Rx, no other meds, ROS and PE otherwise negative. Her treadmill shows questionable ST changes. A CT angio shows moderate calcium and luminal irregularities.

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Q: What is her 10-year risk of CAD/CVD?

A: 1. Her FRS score gives her a 3% ten-year risk of CAD and an 8% risk of CVD

2011 AHA Women’s Consensus recommends using CVD rather than CAD risk in women

2. Her CAC score is at the 84th percentile*, placing her at higher risk

*http://www.mesa-nhlbi.org/CACReference.aspx
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TC 155  TG 90  HDL 45  LDL 95  Non-HDL 110

Q: What is her target LDL?

2. She needs to have her LDL ↓ of 30% (ATP III*)

ÅCCF/AHA comments on Coronary Artery Calcium

- CAC is an independent risk factor for CVD
- The higher the CAC score, the greater the risk
- CAC predicts events better than FRS
- ACCF/AHA supports use of CAC in patients at *intermediate* risk of CAD (IIa level B) to reclassify risks

AHA statement on CAC Circ 2006; 114 1761-1791
Higher CAC Score Predicts Higher Mortality

10,377 consecutive scans followed for 5 years

Budoff, JACC 2007;49:1860-1870
Case 1: 62 yo nonsmoker female with new dyspnea on exertion. FH: negative PMH: Pre-eclampsia with second child, BP 128/78 on Rx, no other meds, ROS and PE otherwise negative. Her treadmill shows questionable ST changes. A CT angio shows moderate calcium and luminal irregularities. TC 155 TG 90 HDL 45 LDL 95 Non-HDL 110

Q How common is low LDL-C in people with CAD?
LDL-C Levels in 136,905 Patients Hospitalized With CAD between 2000 and 2006 – only 25% were on statins

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TC 155  TG 90  HDL 45  LDL 95  Non-HDL 110

Q: Given the history above, what might have contributed to her risk of CAD?

A: Pre-eclampsia doubles risk future CVD
Meta-analysis of 3,488,160 women, of which 198,252 had pre-eclampsia.

Bellamy BMJ 2007;335:974
Mosca et al 2011;123:1243-1262
Case 1: 62 yo nonsmoker female with new dyspnea on exertion. FH: negative PMH: Pre-eclampsia with second child, BP 128/78 on Rx, no other meds, ROS and PE otherwise negative. Her treadmill shows questionable ST changes. A CT angio shows moderate calcium and luminal irregularities. TC 155  TG 90  HDL 45  LDL 95  Non-HDL 110

Q: Was the CT angio indicated?

A: CT angio indicated CP syndrome in those with intermediate pretest probability of CAD and uninterpretable EKG or stress test or inability to exercise

• In acute CP in those with intermediate pretest probability of CAD and no ECG changes and serial enzymes negative

• Evaluation of coronary arteries in patients with new-onset heart failure to assess etiology

Bluemke DA Circ 2008;118:586-606
Case 1  Take home lessons

1. The majority of CAD events happen in patients with an LDL-C that would not require treatment by ATP III.
2. All patients with CAD should receive statins to lower their LDL-C, even those whose LDL is already below treatment guidelines.
3. Pre-eclampsia and other complications of pregnancy increase a woman’s future risk of cardiac disease.
Case 2: The most common patient in your waiting room has borderline lipids
Case 2: 56 yo male new patient annual exam. No complaints. PMH: sleep apnea controlled with CPAP and BP 128/82 on lisinopril. 5’10” 240 lbs BMI 34 Waist 42 TC 195 TG 216 HDL 37 LDL 115 non-HDL 158 FBS 115
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PMH: sleep apnea controlled with CPAP and BP 128/82 on lisinopril. 5’10” 240 lbs  BMI 34  Waist 42
TC 195  TG 216  HDL 37  LDL 115  non-HDL 158  FBS 115

Q: What syndrome does he have?
Criteria of the Metabolic Syndrome from NCEP ATP III

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Our patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist</td>
<td>≥ 40 inches</td>
<td>≥ 35 inches</td>
<td>42</td>
</tr>
<tr>
<td>BP</td>
<td>&gt; 130/&gt;85 or RX</td>
<td>&gt; 130/&gt;85 or RX</td>
<td>on Rx</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥ 150 mg/dl</td>
<td>≥ 150 mg/dl</td>
<td>216</td>
</tr>
<tr>
<td>HDL</td>
<td>&lt; 40</td>
<td>&lt; 50</td>
<td>37</td>
</tr>
<tr>
<td>FBS</td>
<td>&gt; 100</td>
<td>&gt; 100</td>
<td>115</td>
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</table>
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PMH: sleep apnea controlled with CPAP and BP 128/82 on lisinopril. 5’10” 240 lbs BMI 34 Waist 42
TC 195 TG 216 HDL 37 LDL 115 non-HDL 158 FBS 115

Q: Does Metabolic syndrome impact his CV risk?

Metabolic Syndrome increases risk—even in the absence of diabetes

Meta-analysis of 900,000 people*:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative risk</th>
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<tbody>
<tr>
<td>Cardiovascular mortality</td>
<td>2.40</td>
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<tr>
<td>Cardiovascular disease</td>
<td>2.35</td>
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<tr>
<td>MI</td>
<td>1.99</td>
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<tr>
<td>Stroke</td>
<td>2.27</td>
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</table>

Case 2: 56 yo male new patient annual exam. No complaints. PMH: sleep apnea controlled with CPAP and BP 128/82 on lisinopril. 5’10” 240 lbs BMI 34 Waist 42 TC 195 TG 216 HDL 37 LDL 115 non-HDL 158 FBS 115

Q: Do you need additional lipid test(s) to adequately assess his risk?

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
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<tr>
<td>LDL-C</td>
<td>A calculated estimate of the mass of cholesterol in apoB lipoproteins</td>
</tr>
<tr>
<td>non-HDL-C</td>
<td>A measure of the cholesterol in all of the potentially atherogenic apoB lipoproteins</td>
</tr>
<tr>
<td>apoB</td>
<td>A measure of all the potentially atherogenic lipoproteins</td>
</tr>
<tr>
<td>LDL-P</td>
<td>A measure of the number of LDL particles</td>
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</table>
Lipoproteins

Apo B

B-48
Chylomicron → Chylo remnants

B-100
VLDL → IDL → LDL

Atherogenic
The cholesterol in these B-100 lipoproteins may cause CVD

Lp(a)

Apo A-I

HDL

Anti-atherogenic
Normal apoB 100 metabolism

Liver

- FFA
- CE

VLDL → LPL → IDL → LDL-P → Artery

Artery
Metabolic Syndrome: FFA $\rightarrow$ HyperTG $\rightarrow$ ↑ CETP $\rightarrow$ more TG in LDL-P $\rightarrow$ continued LPL activity $\rightarrow$ smaller LDL-P

Liver

FFA
FFA
FFA
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CE
CE

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CETP exchanges TG and CE between lipoproteins to balance internal composition
Metabolic discord

- Primary target of therapy is LDL-C (evidence level A)
- When Trigs > 200, Secondary target of therapy is non-HDL-C (evidence level A)
- ADA, ACC/AHA, AACC, AACE, CCS: recommend treating apoB in patients with Metabolic Syndrome
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PMH: sleep apnea controlled with CPAP and BP 128/82 on lisinopril. 5’10” 240 lbs BMI 34 Waist 42
TC 195 TG 216 HDL 37 LDL 115 non-HDL 158 FBS 115

Q: What are the lipid goals?
A: ACE/AACE Consensus statement says lipid goals same for both prediabetes as diabetes*:

   LDL < 100 and
   non-HDL < 130
   and/ or apoB < 90

*ACE/AACE Consensus Statement on Prediabetes Endo Pract 2008;933-945
Case 2: Take home lessons

1. Metabolic syndrome doubles the risk of cardiovascular disease even in patients with a normal appearing LDL-C
2. The LDL-C in patients with metabolic syndrome is artificially lower than their non-HDL, apoB, or LDL-P
3. Non-HDL, apoB, and LDL-P all predict the risk of CAD better than LDL-C in patients with metabolic syndrome
Case 3: CAD in a patient with hyperlipidemia and statin myalgias
Case 3: A 62- yo male nonsmoker with hyperlipidemia. He previously developed myalgias to simva 40 and both atorva 20 and 40. He was on no medications when he developed a non-STEMI. He was started on optimal medical therapy (ACEi, beta blockers, aspirin), and referred to you for statin management. TC 264 TG 150 HDL 44 LDL 190 non-HDL 224
Case 3: A 62- yo male nonsmoker with hyperlipidemia. He previously developed myalgias to simva 40 and both atorva 20 and 40. He was on no medications when he developed a non-STEMI. He was started on optimal medical therapy (ACEi, beta blockers, aspirin), and referred to you for statin management. TC 264  TG 150  HDL 44  LDL 190  non-HDL 224

Q: What is his LDL-C target?
A: By ATP III Update 2004, his LDL target is $< 100$ with an option of $< 70$
Case 3: A 62-yo male nonsmoker with hyperlipidemia. He previously developed myalgias to simva 40 and both atorva 20 and 40. He was on no medications when he developed a non-STEMI. He was started on optimal medical therapy (ACEi, beta blockers, aspirin), and referred to you for statin management.

TC 264  TG 150  HDL 44  LDL 190  non-HDL 224

Q: How can we get him to goal?

A: We need a 50% ↓ LDL

We need either a powerful statin or a moderate statin + ezetimibe + lifestyle or statin + a bile acid sequestrant
LDL lowering effects of different statins and doses
Case 3: A 62-yo male nonsmoker with hyperlipidemia. He previously developed myalgias to simva 40 and both atorva 20 and 40. He was on no medications when he developed a non-STEMI. He was started on optimal medical therapy (ACEi, beta blockers, aspirin), and referred to you for statin management. TC 264  TG 150  HDL 44  LDL 190  non-HDL 224

Q: Which statins have the highest and lowest myalgia rates?
LDL Decrease and CK Elevation by Different Statins and Doses

Adopted from Fernandez, Clev Clin 2011; 78:393-403
## Incidence of Myalgias in PRIMO Study

<table>
<thead>
<tr>
<th></th>
<th>Incidence of myalgias %</th>
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<tbody>
<tr>
<td>Fluva XL 80</td>
<td>5.1</td>
</tr>
<tr>
<td>Prava</td>
<td>10.9</td>
</tr>
<tr>
<td>Atorva 40 to 80</td>
<td>14.9</td>
</tr>
<tr>
<td>Simva 40 to 80</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Case 3: A 62-yo male nonsmoker with hyperlipidemia. He previously developed myalgias to simva 40 and both atorva 20 and 40. He was on no medications when he developed a non-STEMI. He was started on optimal medical therapy (ACEi, beta blockers, aspirin), and referred to you for statin management.

TC 264  TG 150  HDL 44  LDL 190  non-HDL 224

Q: What alternative statin and/or statin regimen can we try?

• Rosuvastatin every other day
  51 patients placed on QOD rosuva because of myalgias to other statins. They tolerated the rosuva QOD. Mean dose was 5.6 mg, which lowered LDL by 34.5%

• Pitavastain
  In the LIVES study, 19,900 patients treated with pitavastatin reported a myalgia rate of 1.04%

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TC 264  TG 150  HDL 44  LDL 190  non-HDL 224

Q: What else should we check or do in patients with statin myalgia?

A: Vitamin D deficiency

TSH

CoEnzyme Q 10 at 200 mg helps about a third of patients
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TC 264  TG 150  HDL 44  LDL 190  non-HDL 224

Q: Will diet make a difference? And which diet?

A: A Portfolio diet can lower LDL by 20%
A portfolio diet lowers LDL better than therapeutic low-fat diet

- Portfolio diet combines the AHA-type diet with foods recognized for their cholesterol-lowering properties
  - plant sterols and stanols (e.g., Benechol margarine)
  - soluble fiber (e.g., oats, barley, or psyllium)
  - soy protein (e.g., tofu, soy milk),
  - nuts, especially almonds

- Portfolio diet lowers LDL by 14% while control (AHA similar diet) lowered LDL by 3%

Jenkins  JAMA 2011: 306-839
### AHA low-fat diet versus Portfolio diet

<table>
<thead>
<tr>
<th>AHA low-fat</th>
<th>Portfolio</th>
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</thead>
<tbody>
<tr>
<td>• low-saturated, -unsaturated, and no trans fats</td>
<td>• same as above plus</td>
</tr>
<tr>
<td>• Fruits and veggies</td>
<td>• soluble fiber (oatmeal, psyllium, eggplant, ogra) 2 or 3 servings/day</td>
</tr>
<tr>
<td>• Whole grains</td>
<td>• plant stanols and sterols (Benechol margarine)</td>
</tr>
<tr>
<td>• Fish twice a week</td>
<td>• &lt; 3 servings of meat/week. Instead substitute soy products (tofu, soy milk, soy burger)</td>
</tr>
<tr>
<td>• &lt; 300 mg cholesterol/day</td>
<td>• nuts, handful daily</td>
</tr>
</tbody>
</table>
Case 3: Take home lessons

1. Fluvastatin, pitavastatin, pravastatin and rosuvastatin have lower myalgia profiles than atorvastatin, lovastatin, and simvastatin

2. Good options to try in patients with myalgia
   - pitavastatin 1 or 2
   - pravastatin 20 or 40
   - rosuvastatin 2.5 every other day

3. AHA + portfolio diet (adding foods that we know lower LDL) can lower LDL-C by 20%
Lower lipids, live longer