Lipids & Hypertension Update

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Learning objectives

1. Apply updated guidelines for lipid management to the primary and secondary prevention of heart disease.
2. Identify hypertension treatment targets for patients with and at high risk for heart disease.

Outline

• Lipid management
  Indications for statins
  Selecting and dosing statins
  Statin intolerance
  Non-statin medications
• Hypertension
  Risks and benefits of intensive control
  Treatment targets

Case #1

• 59 year old male
• No diabetes
• Never smoker
• No family history

- Hypertension
  Lisinopril 10 mg/day
  BP 110/70 mmHg
- Attempted lifestyle modification

Total cholesterol 187 mg/dL
Triglycerides 150 mg/dL
HDL-C 41 mg/dL
LDL-C 116 mg/dL

Who requires statin therapy?

- 2° prevention
  Coronary disease (MI or angina)
  Cerebrovascular disease
  Peripheral arterial disease
  Coronary or arterial revascularization

- Other risk factors
  Strong family history
  LDL-C 160 – 189 mg/dL
  hs-CRP ≥2.0 mg/dL
  Cor cal ≥300 Agatston units (≥75° percentile)
  ABI ≤0.9

- LDL-C ≥190 mg/dL
- 10-year risk
  ≥7.5%
  5 – 7.5%

- Diabetes mellitus
- Age 40-75 years
- AND
- LDL-C ≥70 mg/dL

How should you select & dose statins?

2° prevention

- Age ≤75 years
  - High intensity
- Age >75 years
  - Moderate intensity

10-year risk

- ≥7.5%
  - Moderate or high intensity
- 5-7.5%
  - Moderate intensity
- <5.5%
  - Low intensity

Intensity LDL lowering Examples

High

≥50%
- Atorvastatin 40-80 mg
- Rosuvastatin 20-40 mg

Moderate*

30-50%
- Rosuvastatin 5-10 mg
- Simvastatin 20-40 mg
- Pravastatin 40-80 mg

Low*

<30%
- Simvastatin 10 mg
- Pravastatin 10-20 mg

*Fluvastatin, lovastatin, & pitavastatin also have low- and moderate-intensity dose options.

How should you assess cardiovascular risk?

Pooled Cohort Risk Assessment Calculator

http://tools.acc.org/ASCVD-Risk-Estimator/

- Stroke as endpoint
- Diabetes mellitus as predictor variable
- Gender & race specific equations

Our patient’s risk

10-YEAR RISK = 7.7%

- 59 year old male
- No diabetes
- Never smoker
- No family history

Hypertension
- Lisinopril 10 mg/day
- BP 110/70 mmHg

Attempted lifestyle modification

- Total cholesterol
- 187 mg/dL
- Triglycerides
- 150 mg/dL
- HDL-C
- 41 mg/dL
- LDL-C
- 116 mg/dL

Patient returns 6 months later...

- 59 year old male
- Treated hypertension
- Simvastatin 20 mg/day

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>187 mg/dL</td>
<td>150 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>150 mg/dL</td>
<td>145 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>41 mg/dL</td>
<td>39 mg/dL</td>
</tr>
<tr>
<td>LDL-C</td>
<td>116 mg/dL</td>
<td>82 mg/dL</td>
</tr>
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</table>

What happened to LDL-C goals?

“The Expert Panel did not find evidence to support titrating cholesterol-lowering drug therapy to achieve optimal LDL-C or non–HDL-C levels...”

- 10-year risk
  - ≥10% <70 mg/dL
  - 5-10% <100 mg/dL
  - <5% <115 mg/dL


How low should we go?
Pros and cons of an LDL-C goal

**Pros**
- Motivation
- Lower is better
- Concordant with other guidelines
- Encourages surveillance
- Reduction from baseline difficult to determine

**Cons**
- Simpler
- Emphasis on risk
- No data on titrating to goals
- Accuracy of goals
- Inappropriate use of medications

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The patient returns 6 months later...

- 60 year old male with treated hypertension and hyperlipidemia
- “Doc, my legs are killin’ me…”
- “…and...I’ve seen the news reports about those statin medications…”

Statin-associated muscular effects

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Definition</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Myalgias</td>
<td>Aches, Soreness, Stiffness, Tenderness, Cramps with exercise</td>
<td>5 – 30%</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Weakness</td>
<td>1%</td>
</tr>
<tr>
<td>Myositis</td>
<td>Inflammation</td>
<td>--</td>
</tr>
<tr>
<td>Myonecrosis</td>
<td>≥3x elevation of CK</td>
<td>~1-2%</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>≥3x elevation of CK AND Acute renal failure OR myoglobinuria</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>

Myalgia scoring index

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
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<tbody>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Bilateral hips and thighs</td>
<td>3</td>
</tr>
<tr>
<td>Bilateral calves</td>
<td>2</td>
</tr>
<tr>
<td>Bilateral proximal arms</td>
<td>2</td>
</tr>
<tr>
<td>Non-specific, asymmetric, intermittent</td>
<td>1</td>
</tr>
</tbody>
</table>

Onset since exposure to statin
- <4 weeks: 3
- 4-12 weeks: 2
- >12 weeks: 1

Improvement after stopping statin
- <2 weeks: 2
- 2-4 weeks: 1
- >4 weeks: 0

Recurrence upon re-challenge
- Same symptoms <4 weeks: 3
- Same symptoms 4-12 weeks: 1
- Different symptoms, any time: 0

Interpretation
- Probable statin intolerance: 9-11 points
- Possible statin intolerance: 7-8 points
- Unlikely statin intolerance: <7 points

Drugs potentially interacting with statins

<table>
<thead>
<tr>
<th>Anti-microbials</th>
<th>Calcium channel blockers</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV protease inhibitors</td>
<td>Verapamil</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Diltiazem</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Amiodipine</td>
<td>Danazol</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Ranolazine</td>
<td></td>
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<tr>
<td>Erythromycin</td>
<td>Nefazodone</td>
<td></td>
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<tr>
<td>Clarithromycin</td>
<td>Gemfibrozil</td>
<td></td>
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<tr>
<td>Telithromycin</td>
<td>Grapefruit juice (&gt;1 quart daily)</td>
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What about ezetimibe?
- Decreases intestinal cholesterol absorption
- Lowers LDL-C when added to statin therapy

↓ LDL ~15% when adding ezetimibe to statin
Never been shown to improve outcomes

IMPROVE-IT Trial
Ezetimibe + statin vs. statin alone

Post-ACS patients
LDL-C ≤125 mg/dL
LDL-C ≤100 mg/dL if on statin

Primary outcome
CV death, myocardial infarction, unstable angina, revascularization, stroke


What is the role of ezetimibe?
One cardiologist’s opinion...
- Generally well tolerated
- Add to patients who need additional LDL-C lowering...
  Despite max dose statin therapy
  Who can’t tolerate higher dose statin therapy
- May provide small benefit when added to a statin after acute coronary syndrome
- Supports hypothesis that “lower is better”

IMPROVE-IT Trial
Results
Median LDL-C
70 mg/dL in simvastatin group
54 mg/dL in simvastatin + ezetimibe group

Event rate = 34.7%
P = 0.016
NNT = 50

What is the role of ezetimibe?
One cardiologist’s opinion...
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Evolocu... what?
PCSK-9 inhibitors
- Evolocumab (Repatha)
- Alirocumab (Praluent)
- FDA approval July-August, 2015
- Monoclonal antibodies against PCSK-9 protein
- Block degradation of LDL receptor
- Reduce circulating LDL-C levels

LDL-C lowering with evolocumab

Mean LDL-C values


Evolocumab
Repatha
Alirocumab
Praluent
PCSK-9 inhibitors
LDL-C lowering with evolocumab

Mean LDL-C values

**Indications**

**PCSK-9 inhibitors**
- Homozygous familial hypercholesterolemia
- In addition to diet and max statin therapy, if further LDL-C lowering is necessary
  - Heterozygous familial hypercholesterolemia
  - Clinical atherosclerotic cardiovascular disease

**When to consider**
- High risk patients unable to achieve adequate LDL-C levels despite trials of 3 different statins, ezetimibe, and lifestyle

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm460082.htm
Accessed October 12, 2016

**So what’s the downside?**
- Evolocumab (Repatha) \(~\$14,500 / year!\)
- Alirocumab (Praluent)
- Myalgias (~5%)
- Injection site reactions (~5%)
- Neurocognitive side effects (~1%)
- No prospective outcomes data

http://www.reuters.com/article/2015/09/01/us-health-heart-amgen-europe-idUSKCN0R13VI20150901
Accessed October 12, 2016

Robinson JG, et al. 

**PCSK-9 inhibitors**

**Bottom line**
- Promising LDL-C lowering data
- Use limited by price and access
- Need outcomes data

**What about the other non-statin meds?**
- Niacin
- Bile acid sequestrants \(\rightarrow\) Frequent side effects
- Fibrates \(\rightarrow\) Limited efficacy data
- Isolated hypertriglyceridemia

**Recap**

**Lipid management**
- Lipid management
  - Indications for statins
  - Selecting and dosing statins
  - Statin intolerance
  - Non-statin medications
- Hypertension
  - Risks and benefits of intensive control
  - Treatment targets

**Case #2**
- 55 year old male
- Unstable angina 3 years ago
- Stent to right coronary artery
- Normal left ventricular function
- No diabetes or angina
- Creatinine = 0.9 mg/dL
What is a good blood pressure?

2967 men without hypertension in Framingham Heart Study

Increased events with “high-normal” vs. “optimal” blood pressure

120-129 / 85-89 mmHg

120-129 / 80-84 mmHg

<120 / 80 mmHg

Summary Curve Model

Review of 13 hypertensive treatment studies

Diastolic BP <85 mmHg may increase events

How low is too low?

What is a clinician to do?

J-shaped curve

Diastolic BP <85 mmHg may increase events

So what do the guidelines say?

Blood pressure goals

JNC-8

Age ≥60 years

SBP ≤150 mmHg

DBP ≤90 mmHg

Age <60 years

Diabetes mellitus

Chronic kidney disease

SBP ≤140 mmHg

DBP ≤90 mmHg

ACC/AHA/ASH

Coronary disease

Heart failure

SBP ≤140 mmHg

DBP ≤90 mmHg

Coronary disease

Stroke, TIA, PAD, AAA

Carotid disease

SBP ≤130 mmHg

DBP ≤90 mmHg

So what is a clinician to do?

Diastolic BP <85 mmHg may increase events

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Diastolic BP <85 mmHg may increase events
Recap

Hypertension

- Lipid management
  - Indications for statins
  - Selecting and dosing statins
  - Statin intolerance
  - Non-statin medications

- Hypertension
  - Risks and benefits of intensive control
  - Treatment targets

Take home points

1. Consider an LDL-C goal of <100 mg/dL in primary prevention and <70-80 mg/dL in secondary prevention.
2. In statin-intolerant patients, first try a low dose of an alternative statin.
3. PCSK-9 inhibitors offer promising LDL-C lowering potential but may see limited initial use.
4. A blood pressure goal of <130/80 mmHg is reasonable in patients with coronary disease.

Thank you!

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