When Should You Start Statin Therapy and/or Consider Other Lipid Lowering Medications?

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Disclosures

None
Objectives

• Using the “new” 2018 Guideline on the Management of Blood Cholesterol:
  – Identify higher risk patients who can benefit from LDL-cholesterol lowering with statins
  – Review the recommendations on risk assessment and treatment in primary prevention of ASCVD.
  – Discuss the management of the secondary prevention patient.
  – Describe the role of non-statin therapies in the management of elevated cholesterol
Case 1:

64 y/o woman presents for routine care. Besides being a little overweight and fairly sedentary she is otherwise healthy. She does not take any medications. She went through menopause at age 50 and was on HRT for just a year or two. She is concerned about her family history of early CVD. She tries to eat a healthy diet, but she does not exercise much. She is former remote smoker. She drinks wine occasionally. Her ROS is otherwise essentially negative.

Exam: BP 134/80  Wt-188  BMI 27  WC 36”
otherwise normal exam

Should we screen her for hyperlipidemia? If so, what test(s) should we order?
Determine Lipoprotein Levels

• Adults 20 y/o and older should have lipid panel done at least every 4-6 years
• Obtain *complete lipid profile* after 8-12 hr fast (if possible)
  – Can be done non-fasting if no high fat intake within 8 hours
  – Repeat in fasted state if TG’s are elevated (esp if >400 mg/dl)
• LDL is still the primary lipoprotein of “interest”
• Newer “Modified Calculation” is more accurate
• Direct LDL-C can be considered when the LDL is very low or with hypertriglyceridemia
• Caveats:
  – Biologic and seasonal variation 4-12%
  – Lab variability 5 – 7%
Case 1:

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Exam: BP 134/80  Wt-188  BMI 27  WC 36”
otherwise normal exam

Labs: Tchol 221  TG 238  HDL 39  LDL 134
Glu-102  A1c 5.9%  AST-12  ALT-16

What now, start a statin?
### “Pre-2013”: NCEP ATP III

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 RF</td>
<td>&lt;160</td>
</tr>
<tr>
<td>≥2 RFs</td>
<td>&lt;130 optional: &lt;100</td>
</tr>
<tr>
<td>(CAD risk ≤20%)</td>
<td></td>
</tr>
<tr>
<td>CAD or CAD risk equivalent</td>
<td>&lt;100 optional: &lt;70*</td>
</tr>
<tr>
<td>(CAD risk &gt;20%)</td>
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</tbody>
</table>

*consider in “very high-risk” patients

2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults

4 Major Statin Benefit Groups:

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Individuals with <strong>known</strong> clinical ASCVD</td>
</tr>
<tr>
<td>2</td>
<td>Individuals with LDL ≥ 190 mg/dl</td>
</tr>
<tr>
<td>3</td>
<td>Individuals with diabetes (&gt;40 yo and LDL&gt;70)</td>
</tr>
<tr>
<td>4</td>
<td>Individuals (&gt;40 yo, LDL&gt;70) without ASCVD or diabetes who have an estimated 10-year ASCVD risk ≥ 7.5%</td>
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</tbody>
</table>
2018 ACC/AHA Guideline on the Management of Blood Cholesterol

Statin Benefit Groups:

1. Individuals with known clinical ASCVD
2. Individuals with LDL ≥ 190 mg/dl
3. Individuals with diabetes (>40 yo and LDL>70)
4. Individuals (>40 yo, LDL>70) without ASCVD or diabetes who have an estimated 10-year ASCVD risk ≥ 7.5%

Consider those at “very high risk” and LDL ≥70 mg/dl for more aggressive therapy

Assess 10-yr ASCVD risk if LDL>70

Expand list of “Risk Enhancing” Factors

Consider different levels of risk from low to high

Special populations:
Younger (<40)
Older (>75)
Women
Ethnicity/Race

Grundy et al. Circulation 2018
Primary Prevention of ASCVD
2018 ACC/AHA Guideline on the Management of Blood Cholesterol

4 Major Statin Benefit Groups:

1. Individuals with **known** clinical ASCVD

2. Individuals with LDL ≥ 190 mg/dl

3. Individuals with diabetes (>40 yo)

4. Individuals (>40 yo, LDL>70) without ASCVD or diabetes who have an elevated 10-year ASCVD risk

Grundy et al. *Circulation* 2018
Severe Hypercholesterolemia

• Guideline recommendations for patients 20-75 yrs with an LDL ≥190:
  – High-Intensity (maximally-tolerated) statin therapy
  – If achieve less than a 50% reduction in LDL and/or LDL ≥100, consider adding:
    • Ezetimibe
    • Bile Acid Sequestrant (if TGs <300)
    • PCSK9 inhibitor
    • Bempedoic acid

• Screen family members
• Screen for elevated Lipoprotein(a)
Recommendations for Patients with Diabetes Mellitus (aged ≥ 40)

- Consider moderate-intensity statin therapy regardless of 10-year ASCVD risk.
- If LDL ≥70, assess 10-year ASCVD risk and consider high-intensity statin therapy if elevated and/or multiple ASCVD risk factors present.
- If 10-year ASCVD risk ≥20% and if achieve less than a 50% reduction in LDL with maximally tolerated statin, then consider adding ezetimibe.
- Reasonable to initiate statin therapy in those <40 yo and with diabetes of long duration (T2D ≥10 yrs, T1D ≥20 yrs) and/or microvascular disease.
Risk Calculator: Pooled Cohort Equations for ASCVD

- Risk factors used in calculation
  - Sex
  - Age
  - Race (White, African American, other)
  - Total Cholesterol (untreated)
  - HDL
  - Systolic BP (current)
  - Treatment for HTN (Y/N)
  - Diabetes (Y/N)
  - Smoker (Y/N)
Primary Prevention: Assess ASCVD Risk and Emphasize Adherence to Healthy Lifestyle

Age 40-75 y and LDL 70-189 mg/dl and without diabetes: perform 10-yr ACVD risk assessment and risk discussion

- <5% “Low Risk”
  - Risk discussion: emphasize lifestyle to reduce risk factors

- 5% - <7.5% “Borderline Risk”
  - Risk discussion: if "Risk Enhancers" present then risk discussion regarding moderate-intensity statin therapy

- ≥7.5% - <20% “Intermediate Risk”
  - Risk discussion: if risk estimate + "Risk Enhancers" favor statin initiate moderate-intensity statin therapy

- ≥20% "High Risk"
  - Risk discussion: initiate statin to reduce LDL ≥50%
“Risk Enhancing Factors”

**Historical Factors**

- Family history of premature ASCVD
- Metabolic syndrome
- CKD (no dialysis or transplant)
- Chronic inflammatory disorders (RA, SLE, HIV,...)
- History of premature menopause or pregnancy-related conditions (eclampsia)
- High-risk race/ethnicities (e.g., South Asian ancestry)
"Risk Enhancing Factors"

Biomarkers

• Primary hypercholesterolemia: LDL > 160
• Hypertriglyceridemia: TG ≥ 175
• Elevated hsCRP: ≥ 2.0 mg/L
• Elevated Lp(a): ≥ 50 mg/dL or ≥ 125 nmol/L
• Elevated apoB: ≥ 130 mg/dL
• Ankle-Brachial Index < 0.8
• Coronary Artery Calcium (CAC):
  – CAC score is ≥ 100 or ≥ 75th percentile
  – CAC score is 1-99 in patients ≥ 55 y
  – Reasonable to withhold statin therapy if CAC is zero

If it potentially changes your management then consider further risk assessments?

Most useful in “moderate risk” patients

Grundy et al. Circulation 2018
Case 1: Assessment and Plan

1. **Mixed Hyperlipidemia**: with moderately elevated TG, low HDL, and a “normalish” LDL
   - Assess 10-yr ASCVD Risk
     - 9.8% = Intermediate Risk
   - Assess for Risk Enhancers:
     - Family history of premature ASCVD
     - Metabolic Syndrome
     - Hypertriglyceridemia
   - Should we consider checking an apo B level in light of her hypertriglyceridemia?
   - Should we consider checking an Lp(a) level especially in light of her family history of premature ASCVD?
Lifestyle modification

- Heart Healthy Dietary Pattern
  - Mediterranean or DASH Diet patterns
  - Emphasize fresh vegetables/fruits, whole grains, low-fat dairy, poultry, fish, legumes, nuts, vegetable oils
- Regular exercise
- Avoidance of tobacco
- Maintenance of a healthy weight

Grundy et al. Circulation 2018
### 2018 ACC/AHA Guideline on the Management of Blood Cholesterol

#### Statin Therapy by Intensity

<table>
<thead>
<tr>
<th>*High-Intensity Statin Therapy</th>
<th>*Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average by ≥ 50%</td>
<td>Daily dose lowers LDL-C on average by 30-50%</td>
<td>Daily dose lowers LDL-C on average by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg, Rosuvastatin 20-40 mg</td>
<td>Atorvastatin 10-20 mg, Rosuvastatin 5-10 mg, Simvastatin 20-40 mg, Pravastatin 40-80 mg, Lovastatin 40 mg, Fluvastatin 40 mg BID, Pitavastatin* 2-4 mg</td>
<td>Simvastatin 10 mg, Pravastatin 10-20 mg, Lovastatin 20 mg, Fluvastatin 20-40 mg, Pitavastatin* 1 mg</td>
</tr>
</tbody>
</table>

Grundy et al. *Circulation* 2018
Case 1: Assessment and Plan

1. Mixed Hyperlipidemia:
   - “intermediate risk” + multiple “Risk Enhancing Factors”
   - Check Apo B and Lp(a)
   - r/o secondary causes of dyslipidemia: TSH, UA, CMP
   - Recommend healthy lifestyle and weight loss
   - Recommend starting “moderate-intensity” statin
     - In light of family history and multiple risk enhancing factors, I would consider high-intensity statin
     - Discuss potential side/adverse effects
     - Don’t start a new exercise regimen at the same time!
Case 2:

- 66 y/o woman with h/o of ASCVD (NSTEMI with stent at age 64, TIA at age 65) and hypertension. Doing well.
- Medications: atorvastatin 80 mg, lisinopril, aspirin, levothyroxine, omeprazole
- Family Hx: no clear premature ASCVD
- Social: heart healthy diet, walks 45 min/d, non-smoker

Exam: BP 130/80  BMI 26  otherwise normal exam
Labs: TChol 171  TG 125  HDL 48  LDL 98

Is this adequate?

Is “goal therapy” ever indicated?

What do the guidelines recommend?
Atherosclerosis and Plaque Pathogenesis
Relationship Between On-Treatment LDL-C and Risk for CV Events: Meta-Analysis

Meta-Analysis of Statin Trials

Major CVD

Adjusted HR

LDL-C (mg/dL)

>175 150-175 125-150 100-125 75-100 50-75 <50

1 0.71 0.64 0.58 0.56 0.51 0.51 0.44

**IMPROVE-IT: Primary Endpoint**

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

**HR 0.936 CI (0.887, 0.988)**

\[ p=0.016 \]

\[ \text{NNT}= 50 \]

**Simva 40: LDL 70 mg/dL**

- 2742 events - 34.7%

**EZ/Simva 10/40: LDL 53 mg/dL**

- 2572 events - 32.7%

PCSK9 Inhibitors – CV Outcome Trials

**FOURIER:**
- 27,564 patients with h/o ASCVD and LDL-C ≥70
- LDL-C 92 vs 30 mg/dl with Evolocumab

**ODYSSEY OUTCOME:**
- 18,924 patients with h/o ACS and LDL-C ≥70
- LDL-C 103 vs 66 mg/dl with Alirocumab


Secondary Prevention in Patients with Clinical ASCVD

Assess for “Very High-Risk”:
- History of multiple major ASCVD events
  or
- Multiple high-risk conditions:
  - Age ≥ 65y
  - History of CABG or coronary interventions
  - Diabetes
  - Hypertension
  - CKD
  - Smoking
  - CHF
  - Persistently elevated LDL (≥100 mg/dL)
Secondary Prevention in Patients with Clinical ASCVD

ASCVD “not” at very high-risk

High-Intensity Statin (goal: ↓LDL ≥50%)

If high-intensity statin not tolerated, use moderate-intensity statin

If on maximal statin therapy and LDL ≥70 mg/dL, consider adding ezetimibe

*Age >75 y: initiation and/or continuation of statin is reasonable

Grundy et al. Circulation 2018
ASCVD at very high-risk*

High-Intensity or Maximal Statin

- If on maximal statin therapy and LDL ≥70, consider adding ezetimibe
- If PSCK9-I is considered, add ezetimibe first before adding PCSK9-I

If on clinically judged maximal LDL lowering therapy and LDL ≥70 or non-HDL-C ≥100, consider adding PCSK9-I

Grundy et al. Circulation 2018
PCSK9 Inhibitors: Where do they fit in?

• Increase LDL-C clearance by upregulating LDL-Receptors
• $\downarrow$ LDL-C by 50-70%
• Reduce ASCVD events
• Well tolerated and safe even with very low LDL-C levels
• Indicated when “more” LDL-C lowering is needed despite maximally tolerated statin therapy in patients with:
  – “known” clinical ASCVD (high risk patients)
  – “Primary” or Familial Hypercholesterolemia
  – Elevated Lp(a)?

• Dosing:
  – Alirocumab (*Praluent*): 75-150 mg SC every 2 weeks
    300 mg SC every 4 weeks
  – Evolocumab (*Repatha*): 140 mg SC every 2 weeks
    420 mg SC every 4 weeks
Case 2:

• ASCVD and Hypercholesterolemia:
  – Why did she have premature and recurrent ASCVD?
    • Consider checking an Lp(a)
  – Per the new guidelines she is at “very high risk”:
    • multiple major ASCVD events and multiple high risk conditions
  – While she is on high intensity statin therapy, her LDL is >70 so consider more aggressive therapy.
  – Options include:
    • Intensify statin therapy: switch to rosuvastatin 40mg
    • Consider adding ezetimibe first and then consider adding a PCSK9 inhibitor if LDL still >70
    • Go straight to adding a PCSK9 inhibitor
  – Guidelines are meant to be exactly that: “guidelines”
Summary

• Assess ASCVD risk and start appropriate statin dose in high risk patients
• Start with high-intensity statin therapy in the highest risk patients and those with ASCVD
• If cannot tolerate higher dose statins go to maximally tolerated dose
• Consider non-statin lipid lowering therapies in those not at goal on maximally tolerated statin
Thank You!