Managing Hyperlipidemia: Update 2020

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Disclosures

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- Primary Care Provider Kentucky Racing Health Services Center
- I have not received any funding for this presentation
Objectives

• Evaluate the 2018 American College of Cardiology (ACC) and American Heart Association (AHA) Multisociety Guidelines on the Management of Blood Cholesterol
• Review clinical trials and new nonstatin medications used to treat hyperlipidemia
• Describe the Mechanism of Action of nonstatin drug therapies
• Apply ASCVD Risk Calculator to a case study and develop a treatment strategy
• Summarize 10 Take Home Messages for Management of Blood Cholesterol
So......

• The question is.... Who Meets Criteria for Statin Therapy?
Historical Perspective

- Adult Treatment Panel 3 (ATP3)
- 2013 ACC/AHA Treatment Guidelines
- 2018 ACC/AHA Multisociety Guideline on the Management of Blood Cholesterol
New Guidelines....Why?

- The 2013 ACC/ AHA Guidelines
  - Took a much narrower approach
    - Focus was on highly controlled RCTs
      - Resulted in elimination of an actual LDL goal
      - This had been a mainstay in prior guidelines
  - Minimized the use of nonstatin therapies
  - Sparse data supporting the use of nonstatin therapies
New Nonstatin Drug Data

- Long awaited clinical trial data for ezetimibe (Zetia)
  - Validated use in atherosclerotic coronary vascular disease (ASCVD) reduction as statin add on therapy in acute coronary syndromes (ACS)
- Two large clinical Trials supporting use of
  - Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors
    - alirocumab (Praluent)
    - evolocumab (Repatha)
Clinical Trials...Game Changers

- **IMPROVE-IT** Trial
- Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)
- Demonstrated a 2% absolute risk reduction of CVD events with ezetimibe added to statin therapy in patients after myocardial infarction
- Individuals receiving the combination of simvastatin and ezetimibe had lower average LDL-C levels (53.2 versus 69.9 mg/dL)
Clinical Trials...Game Changers

- Two Simultaneously Published Studies
  - **Odyssey Trial** - Long Term Study carried out in 2,342 patients at high risk of ASCVD events on maximally tolerated statin
  - **Olser Trial** - study in 4,465 patients including those at high risk of ASCVD
- Showed comparable decreases of 60% in LDL-C level from the mean of 120mg/dl for evolocumab and alirocumab. This effect was associated with halving of the rate of composite ASCVD end points in post hoc analysis
MOA of PCSK9 Inhibitors

- alirocumab (Praluent): 75mg-150mg SC Q2 Weeks
- evolocumab (Repatha): 140mg Q2 Weeks or 420mg SC Q4 weeks
- Proprotein convertase (PSCK9) is involved in the degradation of low-density lipoproteins (LDL) in the liver
- Blocking the activity of these decrease the degradation of the receptors and results in an increase clearance of the LDL in the liver
MOA of ezetimibe (Zetia)

- **10mg PO Qday**

Production in liver

Absorption from intestine

Dietary cholesterol

Bloodstream

LDL-C

VLDL

Biliary cholesterol

Chylomicrons

Fecal sterols and neutral sterols

Cholesterol synthesis
What’s Old is New Again

New Guidelines represent a comeback for LDL-C thresholds and nonstatin therapies
<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
</table>
| 2013 | - Clinical ASCVD  
      - Severe hypercholesterolemia LDL-C > 190 without secondary cause  
      - Primary Prevention in DM in 40-75 yo with LDL-C 70-189 mg/dl; 10-y ASCVD risk ≥ 7.5%  
      - Primary Prevention no DM ages 40-75 with LDL-C 70-189; ASCVD risk risk ≥ 7.5% |
| 2018 | - No Change |
Secondary Prevention

2013
• No thresholds

2018
• LDL-C > 70mg/dl as threshold for nonstatin drug consideration
Nonstatin Agents

2013
• Individuals at higher ASCVD risk with less-than-anticipated response to statin
• Those who are totally statin intolerant

2018 On Max Statin Therapy
• ezetimide (Zetia) for clinical ASCVD and LDL-C > 70mg/dl (IIb, Level C)
• ezetimide (Zetia) and PCSK9 Inhibitor as add-on therapy for very high-risk ASCVD and LDL-C > 70mg/dl
Value Statement

2013
• None

2018
• PCSK9 Inhibitor low value based or value was undetermined
## Good RX - Praluent

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<th>Pharmacy</th>
<th>Retail Price</th>
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<th>Get Coupon</th>
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*Set your location for drug prices near you.*
Good RX-Zetia

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<thead>
<tr>
<th>Free Coupons</th>
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<td>Prices as low as $5.81</td>
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Set your location for drug prices near you

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## ASCVD Risk Assessment

<table>
<thead>
<tr>
<th>2013</th>
<th>2018</th>
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</thead>
<tbody>
<tr>
<td>Pooled Cohort Equations</td>
<td>&lt;5% low risk</td>
</tr>
<tr>
<td></td>
<td>5-7.5% borderline risk</td>
</tr>
<tr>
<td></td>
<td>&gt;7.5%-&lt;20% intermediate risk</td>
</tr>
<tr>
<td></td>
<td>&gt;20% high risk</td>
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</tbody>
</table>
## Additional Risk Factors

<table>
<thead>
<tr>
<th>2013</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be considered if treatment uncertain</td>
<td>Risk-Enhancing factors favor statin initiation/intensification</td>
</tr>
<tr>
<td>• LDL-C &gt; 160mg/dl</td>
<td>• Metabolic Syndrome</td>
</tr>
<tr>
<td>• Fam hx of premature ASCVD</td>
<td>• CKD</td>
</tr>
<tr>
<td>• hs-CRP &gt; 2mg/L</td>
<td>• Chronic Inflammatory Conditions</td>
</tr>
<tr>
<td>• CAC &gt; 300</td>
<td>• Premature Menopause</td>
</tr>
<tr>
<td>• ABI &lt; 0.9</td>
<td>• High Risk Race/Ethnicity</td>
</tr>
<tr>
<td></td>
<td>• Elevated Trigs &gt; 175mg/dl</td>
</tr>
</tbody>
</table>
Coronary Artery Calcification (CAC)

2013
- In select individuals when statin decision uncertain
- Upgrade risk if CAC $>300$ or 75\textsuperscript{th} percentile for age/sex/ethnicity

2018
- CAC=0; No statin
- CAC 1-99 and age $\geq 55$; reasonable to initiate statin
- CAC$>100$ or 75\textsuperscript{th} Percentile; reasonable to initiate statin
Primary Prevention Treatment According to Risk

Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia → statin

Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

Age 40-75 y and
LDL-C ≥70 – <100 mg/dL (≥1.8 –<4.9 mmol/L)
without diabetes mellitus
30-year ASCVD risk percent begins risk discussion

Age >75 y
Clinical assessment, Risk discussion

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/dL, ≥2.0 mmol/L)
In selected individuals if measured:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- apoB ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy
Secondary Prevention

Clinical ASCVD

Healthy Lifestyle

ASCVD not at very high-risk*

Age ≤75 y

High-intensity statin (Goal: ↓ LDL-C ≥50%) (Class I)
- If high-intensity statin not tolerated, use moderate-intensity statin (Class I)
- If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (Class IIb)

Age >75 y

Initiation of moderate- or high-intensity statin is reasonable (Class IIa)

Continuation of high-intensity statin is reasonable (Class IIa)

Very high-risk* ASCVD

High-intensity or maximal statin (Class I)
- If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)
- If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)
- Dashed arrow indicates RCT-supported efficacy, but is less cost effective

If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable (Class IIa)

*ASCVD indicates atherosclerotic cardiovascular disease.
Too Fast or Not to Fast?

2013
• Fasting Preferred

2018
• Fasting or nonfasting appropriate unless known TGs >400mg/dl
What about Triglycerides?

### Hypertriglyceridemia

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L]) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L]), and especially fasting triglycerides ≥1000 mg/dL (11.3 mmol/L), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy.</td>
</tr>
</tbody>
</table>
**Hypertriglyceridemia**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [1.9 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides.</td>
</tr>
<tr>
<td>Ila</td>
<td>B-R</td>
<td>In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.).</td>
</tr>
</tbody>
</table>
Top 10 Take-Home Messages

2018 Cholesterol Guidelines
Top 10 Take Home Messages

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.
2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by ≥50%.
Top 10 Take Home Messages

3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.

- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L).
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid-2018 list prices.
4. In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL (≥ 4.9 mmol/L)) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

- If the LDL-C level remains ≥ 100 mg/dL (≥ 2.6 mmol/L), adding ezetimibe is reasonable.

- If the LDL-C level on statin plus ezetimibe remains ≥ 100 mg/dL (≥ 2.6 mmol/L) & the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety (>3 years) is uncertain and economic value is low at mid-2018 list prices.
5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.
6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, (LDL-C), hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);

- the presence of risk-enhancing factors (see No. 8);
- the potential benefits of lifestyle and statin therapies;
- the potential for adverse effects and drug–drug interactions;
- the consideration of costs of statin therapy; and
- the patient preferences & values in shared decision-making.
Top 10 Take Home Messages

7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

Risk-enhancing factors favor statin therapy (see No. 8).

If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.
8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include:

- family history of premature ASCVD;
- persistently elevated LDL-C levels $\geq 160$ mg/dL ($\geq 4.1$ mmol/L);
- metabolic syndrome;
- chronic kidney disease;

- history of preeclampsia or premature menopause (age $< 40$ yrs)
- chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV);
- high-risk ethnic groups (e.g., South Asian);
- persistent elevations of triglycerides $\geq 175$ mg/dL ($\geq 1.97$ mmol/L);
8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include

and, if measured in selected individuals

- apolipoprotein B ≥130 mg/dL
- high-sensitivity C-reactive protein ≥2.0 mg/L
- ankle-brachial index <0.9 and 1
- lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a).

Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk)
9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL - 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.
Top 10 Take Home Messages

10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

- Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
- In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels $\geq 70$ mg/dL ($\geq 1.8$ mmol/L) on maximal statin therapy (see No. 3).
ASCVD Risk Estimator Plus
Case Study

- 55 Year Old Male
- AA
- 160/90
- TC=220
- HDL=35
- LDL=130
- +DM
- Former Smoker (Status Unknown)
- No on HTN TX
- No on Statin
- Not on ASA Tx
- No to add information regarding a pre
Results

- 20.3% 10-year ASCVD Risk
- Lifetime = 69%
- At least moderate intensity statin
- Hi-intensity if tolerated
- LDL-C Goal is <70mg/dl
- Tap on Advice
- LDL-C Management (for this patient)
ASCVD Risk Assessment

2013
- Pooled Cohort Equations

2018
- <5% low risk
- 5-7.5% borderline risk
- >7.5%-<20% intermediate risk
- >20% high risk
Hi-Intensity Statin Choices

- At least moderate intensity for this patient
- A high intensity if reasonable to decrease LDL-C by $>50\%$
- atorvastatin (Lipitor) 40-80mg
- rosuvastatin (Crestor) 20-40mg
- Max out statin based on tolerability
- Recheck LDL-C Q4-12 Weeks
- Next Steps....ezetimide (Zetia)
- Shared Decision Making
- Still not at goal
  - (PCSK9) inhibitors
    - alirocumab (Praluent)
    - evolocumab (Repatha)
# Intensity of Statin Therapy

**Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)**

<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 approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40†)–80 mg Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg</strong></td>
<td><strong>Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg</strong></td>
</tr>
</tbody>
</table>

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.*

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (47).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.
Questions?
This slide set is adapted from the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APH A/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. Published on available at: Journal of the American College of Cardiology
https://doi.org/10.1161/CIR.0000000000000624
and Circulation. 2019;139:e1046–e1081

The full-text guidelines are also available on the following Web sites: ACC (www.acc.org) and AHA (professional.heart.org)
References

