4th and Goal To Go...

“How Low Should We Go?”:
Evaluating New Lipid Lowering Therapies

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Disclosure

The presenter has nothing to disclose concerning possible financial or personal relationships with any entities mentioned in this presentation.
My Two “Homes Away from Home”
Learning Objectives

• Summarize recommendations from clinical practice guidelines regarding lipid lowering therapy.

• Discuss clinical evidence and place in therapy for proprotein convertase subtilisin kexin type 9 (PCSK-9) inhibitors.

• Develop a therapeutic plan for a patient with complex lipid lowering needs.
Outline

Guideline overview
- Lipid lowering targets- a historical perspective

Injectable therapy- new kids on the block
- Decision pathways for non-statin agents

Patient case discussion
Clinical Significance

U.S. adults...

• ~70% report recent lipid profile

• ~55% who are indicated for lipid lowering medication are currently taking it

• ~37% have elevated low-density lipoprotein (LDL) cholesterol levels

http://www.cdc.gov/cholesterol/facts.htm
Patient Case

- 56 year old African American male
- Recently started on lipid lowering therapy after a hospitalization for MI
- PMH: Hypertension x 4 years, GERD x 2 years, STEMI 3 months ago
- Social history: quit smoking after hospitalization; no alcohol use reported; wife and patient recently met with dietitian
- Family history: mother living, age 78, with diabetes and hypertension; father deceased (stroke, age 60)
Patient Case

- Current Medications
  - HCTZ 25mg QAM
  - Amlodipine 10mg Qdaily
  - Metoprolol tartrate 50mg BID
  - Aspirin 81mg Qdaily
  - Clopidogrel 75mg Qdaily
  - Atorvastatin 80mg Qdaily
  - Lansoprazole 30mg Qdaily

- Recent Labs
  - Baseline lipid panel (October 2017): TC 225, TG 160, LDL 176, HDL 32
  - Lipid panel today: TC 205, TG 150, LDL 135, HDL 36
  - BP today: 128/72; HR 66
Guidance Statements

- NCEP Adult Treatment Panel (ATP) 2001/2004 update
- American College of Cardiology/American Heart Association (ACC/AHA) 2013
- National Lipid Association 2015
- ACC Non-Statin Decision Pathway 2016/2017 update
- American Association of Clinical Endocrinologists 2017

Grundy SM. Then and Now: ATP III vs. IV. American College of Cardiology December 2013.
ACC/AHA Guideline

• Specific lipid goals (LDL and non-HDL targets) eliminated

• New risk estimation calculator

• Treatment recommendations focus on “benefit groups”

• Primary drug therapy focus is the use of statins
ASCVD Risk Calculator [Plus]

• Provides estimation of 10 year risk for those 40-79 years of age
  – Provides lifetime risk if 20-59 years of age

• Based on risk factors (sex, age, race, total cholesterol, LDL & HDL cholesterol, SBP, treatment of HTN, diabetes, smoking status, on statin, on aspirin)
  – Based on Pooled Cohort Equations

Secondary prevention of ASCVD

LDL 70-189 mg/dL and 10 yr ASCVD risk ≥7.5% or 5 to <7.5%

Benefit Groups

Diabetes

LDL ≥190 mg/dL

High intensity statin

Moderate intensity statin if 10 year ASCVD risk $\geq 5\%$ and $<7.5\%$

Moderate to high intensity statin if 10 year ASCVD risk $\geq 7.5\%$

Benefit Groups

Moderate intensity statin

High intensity statin if 10 year ASCVD risk $\geq 7.5\%$

High intensity statin

# Statin Potency

<table>
<thead>
<tr>
<th>High-Intensity</th>
<th>Moderate-Intensity</th>
<th>Low-Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Lowers LDL-C by (~\geq 50%))</td>
<td>(Lowers LDL-C by (\sim 30% \text{ to } &lt; 50%))</td>
<td>(Lowers LDL-C by (\sim &lt; 30%))</td>
</tr>
<tr>
<td>Atorvastatin 40-80mg</td>
<td>Atorvastatin 10-20mg</td>
<td>Simvastatin 10mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40mg</td>
<td>Rosuvastatin 5-10mg</td>
<td>Pravastatin 10-20mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40mg</td>
<td>Lovastatin 20mg</td>
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<tr>
<td></td>
<td>Pravastatin 40-80mg</td>
<td>Fluvastatin 20-40mg</td>
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<tr>
<td></td>
<td>Lovastatin 40mg</td>
<td>Pitavastatin 1mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40mg BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4mg</td>
<td></td>
</tr>
</tbody>
</table>

# National Lipid Association (NLA)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal Non-HDL-C (mg/dL) LDL-C (mg/dL)</th>
<th>Consider Drug Therapy Non-HDL-C (mg/dL) LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1 major ASCVD risk factors; consider other risk indicators</td>
<td>&lt;130; &lt;100</td>
<td>≥ 190; ≥ 160</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 major ASCVD risk factors; consider risk scoring and other indicators</td>
<td>&lt;130; &lt;100</td>
<td>≥ 160; ≥ 130</td>
</tr>
</tbody>
</table>
| High          | ≥ 3 major ASCVD risk factors  
|               | Diabetes (0-1 major ASCVD risk factors)  
|               | Chronic kidney disease stage 3b or 4  
|               | LDL-C ≥ 190 mg/dL  
|               | Quantitative risk score indicating high risk | <130; <100 | ≥ 130; ≥ 100 |
| Very High     | ASCVD  
|               | Diabetes (≥ 2 other major ASCVD risk factors OR evidence of end-organ damage) | <100; <70 | ≥ 100; ≥ 70 |
### American Association of Clinical Endocrinologists (AACE)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C (mg/dL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-HDL (mg/dL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apo B (mg/dL)</td>
</tr>
<tr>
<td>Low</td>
<td>• 0 risk factors</td>
<td>&lt;130; &lt;160; not recommended</td>
</tr>
<tr>
<td>Moderate</td>
<td>• ≤ 2 risk factors and 10 year risk &lt; 10%</td>
<td>&lt;100; &lt;130; &lt;90</td>
</tr>
</tbody>
</table>
| High          | • ≥ 2 risk factors and 10 year risk 10-20%  
    • Diabetes or CKD stage 3 or 4 | <100; <130; <90 |
| Very High     | • Recent hospitalization for acute coronary syndrome, ASCVD, 10 year risk > 20%  
    • Diabetes or CKD stage 3 or 4, with 1 or more risk factors  
    • Heterozygous familial hypercholesterolemia (HeFH) | <70; <100; <80 |
| Extreme       | • Progressive ASCVD including unstable angina even after achieving LDL < 70mg/dL  
    • ASCVD + Diabetes, CKD stage 3 or 4, or HeFH  
    • Premature ASCVD (<55 male, <65 female) | <55; <80; <70 |
# How Low Should We Go?

## How Low is too Low?

<table>
<thead>
<tr>
<th>ACC/AHA</th>
<th>The Lower the Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider decreasing statin dose if two consecutive LDL levels are &lt;40 mg/dL</td>
<td><strong>Meta-analyses data</strong></td>
</tr>
</tbody>
</table>

## The Lower the Better

- LDL <50 mg/dL resulted in significantly lower risk for major cardiovascular events, even compared with LDL between 75 and 100 mg/dL [adjusted HR 0.81; 95% CI: 0.70-0.95]¹

- Individuals with a low baseline LDL (<70 mg/dL) experienced further benefit (decreased event rate) with additional lowering²

- No significant evidence that further lowering of LDL [evaluating trials of more versus less intensive therapy] produced adverse effects²

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• Current lipid lowering guidelines recommend:
  • Assessment of cardiovascular risk
  • LDL-lowering based on risk and lipid parameters
  • Adjunctive therapy with lifestyle modifications

• Statins have been the cornerstone of LDL-lowering therapy for decades

• In high risk patients, the question remains...
  • Which therapies, either as monotherapy or in addition to statins, lower LDL and reduce cardiovascular event rate?
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK-9)

- An enzyme (a serine protease) synthesized and secreted by the liver
- LDL receptor: binds circulating LDL and internalizes this complex into the hepatocyte...results in elimination, allowing for recycling of the LDL receptor to the hepatocyte surface
  - Binding of PCSK-9 to LDL receptor prevents recycling
  - Cell surface receptor expression reduced
  - Reduces capacity for LDL particles to be removed from circulation
PCSK-9 Inhibitors
Alirocumab (Praluent®)

• Approved July 2015

• Indications
  • As adjunct to diet and maximally tolerated statin therapy, for the treatment of adults with: HeFH OR clinical ASCVD, who require additional LDL lowering

• Dosing
  • Initial: 75mg subcutaneously Q2 weeks (can be increased to 150mg)
  • Alternative starting dose: 300mg Q4 weeks

• How Supplied

75 mg/1 mL pen

150 mg/1 mL pen
Evolocumab (Repatha®)

- Approved August 2015

- Indications
  - Reduce risk of MI, stroke, and coronary revascularization in adults with established ASCVD
  - As adjunct to diet, alone or in combination with other therapies, for the treatment of adults with: primary hyperlipidemia, HeFH, or HoFH who require additional LDL lowering

- Dosing
  - 140mg subcutaneously Q 2 weeks OR 420mg monthly
  - *HoFH: monthly dosing

- How Supplied
# PCSK-9 Inhibitors: Clinical Outcomes

- Meta-analysis of 35 phase 2/3 randomized controlled trials

## Cardiovascular & efficacy endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause and CV mortality</td>
</tr>
<tr>
<td>MI*</td>
</tr>
<tr>
<td>Unstable angina requiring hospitalization</td>
</tr>
<tr>
<td>CHF exacerbation requiring hospitalization</td>
</tr>
<tr>
<td>Stroke*</td>
</tr>
<tr>
<td><strong>Coronary revascularization</strong>*</td>
</tr>
<tr>
<td>% change from baseline in LDL, HDL, total cholesterol, apo-B, lipoprotein(a)</td>
</tr>
</tbody>
</table>

## Safety endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
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<tbody>
<tr>
<td>Neurocognitive adverse events</td>
</tr>
<tr>
<td>New onset or worsening of pre-existing diabetes</td>
</tr>
<tr>
<td>Increase in CK (&gt;3x ULN)</td>
</tr>
<tr>
<td>Increase in LFTs (&gt;3x ULN)</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Treatment-emergent serious adverse events</td>
</tr>
</tbody>
</table>

*Significant difference between groups
PCSK-9 Inhibitors: Lipid Endpoints

Mean Percentage Change

- LDL Reduction (vs ezetimibe)
- LDL Reduction (vs placebo)
- Change in HDL (vs placebo)
- Reduction in Total Cholesterol (vs placebo)

Percentage Change

Figure 1. Timeline of randomized controlled trials of alirocumab and evolocumab. FDA indicates US Food and Drug Administration; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia.
## Cardiovascular Outcomes: OSLER 1 & 2

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>n= 4465; mean age 58 years; ~80% with 1+ CV risk factor; ~70% on statin; median baseline LDL ~120mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Combination of 2 open-label randomized trials (vs. standard therapy) Patients had completed one “parent trial”</td>
</tr>
</tbody>
</table>
| Outcome Measures  | • Incidence of adverse events  
• Percent change in LDL level & other lipid parameters  
• Adjudicated cardiovascular events (pre-specified, exploratory, composite outcome) |
| Results           | • Similar rates of CK and LFT elevation; neurocognitive events < 1%  
• LDL reduction ~61% (week 12)  
• Patients in evolocumab group had significantly lower rate of CV events (at 1 year, 0.95% vs 2.18%; HR 0.47; 95% CI 0.28-0.78; p=0.003) |
| Conclusions       | Evolocumab + standard therapy, compared with standard therapy alone, significantly reduced LDL, and the incidence of CV events. |
## Cardiovascular Outcomes: ODYSSEY LONG TERM

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>n= 2341; mean age 60 years; ~70% with CVD, ~35% with diabetes, ~17% HeFH; &gt;99% on statin; mean baseline LDL ~122mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Patients randomized (2:1) to alirocumab 150mg q2weeks or placebo</td>
</tr>
</tbody>
</table>
| Outcome Measures   | • Incidence of adverse events  
• Percent change in LDL level from baseline to week 24  
• Adjudicated cardiovascular events (post hoc, composite outcome) |
| Results            | • Higher rates of myalgia (p < 0.05), neurocognitive events, and ophthalmologic events with alirocumab  
• LDL reduction ~61% (week 24, consistent through week 78)  
• Rate of major adverse CV events lower with alirocumab (1.7% vs 3.3%; HR 0.52; 95% CI 0.31-0.90; p=0.02) |
| Conclusions        | Alirocumab + statin therapy significantly reduced LDL, and in a post hoc analysis, showed evidence of CV event rate reduction. |
## Cardiovascular Outcomes: GLAGOV

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>n= 968; mean age 60 years; ~35% previous MI, 39% previous PCI, ~21% with diabetes; ~98% on statin; mean baseline LDL ~93mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Patients randomized (1:1) to evolocumab 420mg q4weeks or placebo Intravascular ultrasonography (single artery), baseline and week 78</td>
</tr>
</tbody>
</table>
| Outcome Measures   | • Nominal change in percent atheroma volume (PAV)  
• Nominal change in total atheroma volume and percentage of patients demonstrating plaque regression  
• Safety and tolerability |
| Results            | • Between group differences; LS means (95% CI)  
  PAV (%): -1.0 (-1.8 to -0.64); TAV (mm³): -4.9 (-7.3 to -2.5)  
• Patients with regression: 17% PAV, 12.% TAV; p <0.001 respectively  
• Rates of myalgia and neurocognitive events not significantly different |
| Conclusions        | After 76 weeks of treatment, addition of evolocumab to statin therapy resulted in a greater decrease in PAV compared to placebo. |
# Cardiovascular Outcomes: FOURIER

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>n= 27,564; mean age 62.5 years; ~81% previous MI, 19% previous stroke, ~13% with PAD; ~99% on statin; mean baseline LDL ~92mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Patients randomized (1:1) to evolocumab (either 140mg q2weeks or 420mg q4weeks) or placebo</td>
</tr>
</tbody>
</table>
| Outcome Measures  | • Primary: major CV events (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)  
                     • Secondary: major CV events (CV death, MI, or stroke)                                                      
                     • Safety (adverse events)                                                                                                                                 |
| Results           | • Primary: 9.8% vs. 11.3%; HR 0.85 [95% CI 0.79-0.92]                                                               
                     • Secondary: 5.9% vs. 7.4%; HR 0.80 [95% CI 0.73-0.88]                                                        
                     • No significant between group differences, with the exception of injection-site reactions (2.6% vs 1.6%) |
| Conclusions       | Adding evolocumab to statin therapy reduced the risk of CV events, and patients with ASCVD benefit from LDL lowering below current targets. |
Non-Statin Decision Pathway

**Figure 2A** Patients ≥21 Years of Age with Stable Clinical ASCVD without Comorbidities, on Statin for Secondary Prevention

- Patients with stable clinical ASCVD without comorbidities,* on statin for secondary prevention
  - Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†
    - YES
    - NO
      - Address statin adherence.
      - Intensity lifestyle (may consider phytosterols).
      - Increase to high-intensity statin if not already taking.
      - Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.¶ Consider referral to lipid specialist if statin intolerant.
      - 5. Control other risk factors.
    - Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†
      - YES
      - NO
        - CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
          1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
          2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
          3. Patient preferences (see Table 5)
        - Optional non-statin medications to consider
          - Consider ezetimibe first§
            - NO
              - Consider adding or replacing with PCSK9 inhibitor second¶¶
            - YES
              - Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
  - Decision for no additional medication

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* LDL-C is low-density lipoprotein cholesterol.
† LDL-C goal for secondary prevention of ASCVD.
¶ Additional treatment options may include ezetimibe, bile acid sequestrants, or fibrate.
§ Ezetimibe may be considered first.
¶¶ PCSK9 inhibitors may be considered next.

**References**

Non-Statin Decision Pathway

**Figure 2B** Patients ≥21 Years of Age with Clinical ASCVD with Comorbidities, on Statin for Secondary Prevention

- **Patients with clinical ASCVD with comorbidities,* on statin for secondary prevention**
  - **Patient has ≥50% LDL-C reduction (may consider LDL-C < 70 mg/dL or non-HDL-C < 100 mg/dL) on maximally tolerated statin therapy†**
    - **YES**
    - **NO**
      - **1. Address statin adherence.**
      - **2. Intensify lifestyle (may consider phytosterols).**
      - **3. Increase to high-intensity statin if not already taking.**
      - **4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.‡**
        - Consider referral to lipid specialist if statin intolerant.
      - **5. Control other risk factors.**

- **Patient has ≥50% LDL-C reduction (may consider LDL-C < 70 mg/dL or non-HDL-C < 100 mg/dL) on maximally tolerated statin therapy†**
  - **YES**
  - **NO**
    - **CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER**
      1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
      2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
      3. Patient preferences (see Table 5)

- **Optional non-statin medications to consider**
  - Consider either ezetimibe§ or PCSK9 inhibitor as initial non-statin agent, and addition of other agent second if needed¶

- **Patient has ≥50% LDL-C reduction (may consider LDL-C < 70 mg/dL or non-HDL-C < 100 mg/dL) on maximally tolerated statin/other medications†**
  - **YES**
  - **NO**
    - **Decision for no additional medication**
    - **Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.**
Non-Statin Decision Pathway

• Patients with ASCVD
  • Risk reduction thresholds: LDL reduction ≥ 50%; also consider LDL < 70 mg/dL or non-HDL < 100 mg/dL
  • Lower LDL levels are safe and optimal

• ASCVD + comorbidities
  • Consider either ezetimibe or a PCSK-9 inhibitor based on:
    • Additional percent LDL lowering desired, patient specific factors and preferences, cost, route of administration

• Additional high risk factors
Economic Impact

PCSK-9 Inhibitors
>$14,000 per year

Atorvastatin 80mg
<$125 per year
Economic Impact

Central Illustration: Economics of PCSK9 Inhibitors

Patient Assistance Programming

• MyPRALUENT® Copay Offer and RepathaReady®
  – Helps commercially insured patients with out-of-pocket copay costs

• Third party prior authorizations?

• Uninsured patients?

https://www.praluent.com/copay-card
https://www.repatha.com/insurance-coverage/
Patient Case

• 56 year old African American male

• Recently started on lipid lowering therapy after a hospitalization for MI

• PMH: Hypertension x 4 years, GERD x 2 years, STEMI 3 months ago

• Social history: quit smoking after hospitalization; no alcohol use reported; wife and patient recently met with dietitian

• Family history: mother living, age 78, with diabetes and hypertension; father deceased (stroke, age 60)
Patient Case

• Current Medications
  – HCTZ 25mg QAM
  – Amlodipine 10mg Qdaily
  – Metoprolol tartrate 50mg BID
  – Aspirin 81mg Qdaily
  – Clopidogrel 75mg Qdaily
  – **Atorvastatin 80mg Qdaily**
  – Lansoprazole 30mg Qdaily

Recent Labs

• Baseline lipid panel (October 2017): TC 225, TG 160, **LDL 176**, HDL 32
• Lipid panel today: TC 205, TG 150, **LDL 135**, HDL 36
• BP today: 128/72; HR 66

...What’s the next best step?
Summary

• New data and guidance statements support lowering LDL below historical targets for high risk patients.

• PCSK-9 inhibitors, although expensive, may offer an additional option to lower LDL and reduce cardiovascular events in high risk patients.

• Clinical outcomes, cost, and patient preference should be considered when choosing lipid lowering therapy.
Learning Objectives

• Summarize recommendations from clinical practice guidelines regarding lipid lowering therapy.

• Discuss clinical evidence and place in therapy for proprotein convertase subtilisin kexin type 9 (PCSK-9) inhibitors.

• Develop a therapeutic plan for a patient with complex lipid lowering needs.
Questions/Comments?