Advanced Treatment of LDL: How Low Should You Go?

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Potential Conflicts of Interest

- The speaker has no actual or perceived conflicts germane to this presentation.
- He has not received research or speaker funding from any commercial entity for products covered in this presentation.
Objectives for Lecture

- At the conclusion of the lecture and post-lecture study, the successful learner will be able to:
  - Identify current cholesterol guidance and the reasons major guidelines have changed
  - Select a treatment goal for an individual patient and determine whether monotherapy or adjunctive therapy is sufficient
  - Select the appropriate first and adjunctive therapies for patients with differing patient profiles
  - Identify the benefits of pharmacist provided care for patients with cholesterol disorders

NCEP ATP III Guidelines 1985

- LDL Goals
  - ASCVD <100mg/dL
  - Moderate risk < 130mg/dL
  - Low risk <160mg/dL
AHA/ACC 2013 Lipid Guidelines

ASCVD

LDL >190mg/dL

Diabetes + ASCVD 10-yr risk ≥ 7.5%

ASCVD 10 yr Risk ≥7.5%

Diabetes

High Intensity Statins

>75 Years of Age

Moderate Intensity Statins

White CM. Drug Topics 2014;2:53-60

Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>High Intensity</th>
<th>Moderate Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL Reduction &gt;50%</td>
<td>LDL Reduction 30-50%</td>
</tr>
<tr>
<td>Atorvastatin 40-80mg</td>
<td>Atorvastatin 10-20mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40mg</td>
<td>Rosuvastatin 5-10mg</td>
</tr>
<tr>
<td>Simvastatin 20-40mg</td>
<td>Pravastatin 40-80mg</td>
</tr>
<tr>
<td>Pravastatin 40-80mg</td>
<td>Lovastatin 40mg</td>
</tr>
<tr>
<td>Lovastatin 40mg</td>
<td>Fluvastatin 40mg BID</td>
</tr>
<tr>
<td>Fluvastatin 40mg BID</td>
<td>Pitavastatin 2-4mg</td>
</tr>
</tbody>
</table>

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AHA/ACC Risk Calculator

http://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp then click on web based risk calculator in upper right.

AHA/ACC 2016 Update

• “May consider” LDL goal <100mg/dL in ASCVD patients when secondary causes [dietary excess, drugs, diseases, and metabolism disorders] are absent and baseline LDL <190mg/dL
• “May consider” LDL goal <70mg/dL when secondary causes are present or the LDL level is ≥190mg/dL
AHA/ACC 2016 Update

- Patients without ASCVD or secondary causes but an LDL $\geq$190mg/dL, diabetes, or a 10-year ASCVD risk $\geq$7.5% may consider an LDL goal of $<100$mg/dL
- Ezetimibe the first drug added with PCSK9 inhibitors only utilized if statin and ezetimibe therapy is insufficient, regardless of how far away the patient is from reaching the stated LDL goal on statin alone.

Question 1

- Mary Maple is an 80 year old with angina pectoris, what intensity of statin therapy should she receive and how much should her LDL be reduced?
  a) Moderate intensity, 30%
  b) High intensity, 50%
  c) Low intensity, 20%
Why Did the NCEP ATP III Guidelines Change to the AHA/ACC 2013 Guidelines?

Statin vs. Placebo: Landmark Clinical Trials

- **Primary Prevention**: WOSCOPS, AFCAPS/TexCAPS, ASCOT-LLA, JUPITER
  - Prava, lova, atorva, rosuva reduce cardiac events
    - JUPITER: LDL goal near 100mg/dL may be better than 130mg/dL
- **Secondary prevention**: CARE, LIPID, 4S, HPS, GREACE
  - Prava, simva, atorva reduce mortality and recurrent events
High vs. Low Intensity Statins:
Landmark Clinical Trials

- Secondary Prevention Trials
- PROVE-IT Trial
  - Prava 40mg vs Atora 80mg
  - LDL 90-100mg/dL vs. 60-70mg/dL
- TNT Trial
  - Atorva 10mg vs. Atorva 80mg
  - LDL 90-100mg/dL vs. 60-70mg/dL
- LOWER LDL IS BETTER
## PROVE-IT: Final Health Outcomes

<table>
<thead>
<tr>
<th>Primary end point</th>
<th>Pravastatin 40 mg (n=1973)</th>
<th>Atorvastatin 80 mg (n=2003)</th>
<th>Relative risk reduction, %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, MI, UA, PCI, CABG, Stroke</td>
<td>26.3%</td>
<td>22.4%</td>
<td>16%</td>
<td>0.005</td>
</tr>
</tbody>
</table>

### Secondary end points

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin 40 mg (n=1973)</th>
<th>Atorvastatin 80 mg (n=2003)</th>
<th>Relative risk reduction, %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>3.2%</td>
<td>2.2%</td>
<td>28%</td>
<td>0.07</td>
</tr>
<tr>
<td>Revascularization</td>
<td>18.8%</td>
<td>16.3%</td>
<td>14%</td>
<td>0.04</td>
</tr>
</tbody>
</table>


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## Statin + HDL Increasing Adjunctive Therapy

- Adjunctive therapies improve lipid effects over statins alone
- Therapy to raise HDL
  - Niacin + Simva vs. Simva alone (AIM-HIGH, HPS-THRIVE)
  - Fenofibrate + Statin vs. Statin alone (ACCORD)
  - CETP Inhibitors + Statin vs. Statin Alone (ILLUMINATE)
  - Combo does not impact final cardiovascular health outcomes (death, MI, ACS, stroke, revascularization)
  - These drugs had little to no LDL lowering and niacin trials had high withdrawal rates
Statin + Niacin

- AIM-HIGH – Secondary Prevention Trial
- 3414 participants in US and Canada with a history of cardiovascular disease, low HDL cholesterol, and high triglycerides
- Simvastatin + Placebo vs. Simvastatin + Niacin ER (doses up to 2000mg/day)
- Additional LDL lowering, 25% high HDL, lower triglycerides
  - LDL-cholesterol levels maintained at the target range between 40 and 80 mg/dL

Statin + Niacin

- AIM-HIGH Results
  - Simva + niacin ER did not reduce the five-component end point [MI, stroke, hospitalizations for ACS, or revascularization]
    - 5.8% in the high-dose-niacin group vs 5.6% in placebo group (p=NS)
  - 28 strokes (1.6%) reported with simva + niacin ER vs. 12 strokes (0.7%) in the control group (p=NS)
Question 2

• What did clinical trials adding adjunctive therapy that attempted to raise HDL above a statin alone do to cardiovascular events?

a) Events went way down when adjunctive therapy was used
b) Events went modestly down when adjunctive therapy was used
c) Events were unchanged or went up slightly when adjunctive therapy was used

Why Did the AHA/ACC Update their Guidelines in 2016?
Statin + Ezetimibe: IMPROVE-IT Trial

1. Pts enrolled <10d from ACS event
2. LDL reduced from 95mg/dL to 70mg/dL (Simva 40mg) or 53mg/dL (Simva 40mg + Ezetimibe 10mg)
3. Follow-up 2.5-7y

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Simva 40 mg n=9077 (%)</th>
<th>Ezet 10mg/Simva 40mg, n=9067 (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point (CV death, MI, UA, PCI/CABG, or stroke)</td>
<td>34.7%</td>
<td>32.7%</td>
<td>0.016</td>
</tr>
<tr>
<td>All-cause death</td>
<td>15.3%</td>
<td>15.4%</td>
<td>0.782</td>
</tr>
<tr>
<td>MI</td>
<td>14.8%</td>
<td>13.1%</td>
<td>0.002</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.8%</td>
<td>4.2%</td>
<td>0.052</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>4.1%</td>
<td>3.4%</td>
<td>0.008</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.9%</td>
<td>2.1%</td>
<td>0.618</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>23.4%</td>
<td>21.8%</td>
<td>0.107</td>
</tr>
</tbody>
</table>

Cannon C. AHA November 2014

PCSK9 Inhibitors + Statin

- Meta-analysis of preliminary trials found reductions in overall mortality [OR 0.45 (95%CI: 0.23 to 0.86)] and MI [OR 0.49 (95%CI: 0.26 to 0.93)]
- Since none of these trials had this as a primary endpoint, this was promising but not proven

What Information was the AHA/ACC Lacking When Updating their Guidelines?

PCSK9 Inhibitor + Statin: FOURNIER Trial

- 27,564 patients randomized to evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or placebo
- Patients had hx of MI, nonhemorrhagic stroke or peripheral artery disease + 1 or more CV risk factors
- The trial only included those with a LDL $\geq 70$ mg/dL despite a statin at least as potent as atorvastatin 20mg

PCSK9 Inhibitor + Statin: Fournier Trial

- Median LDLs went from baseline 92 mg/dL to 30 mg/dL (p<0.001)
- Evolocumab patients had fewer coronary revascularizations (5.5% vs. 7.0%, p<0.001), MIs (3.4% vs 4.6%, p<0.001), and strokes (1.5% vs. 1.9%, p=0.01) vs. placebo
- More injection site reactions with evolocumab but similar neurocognitive events vs. placebo


LDL-CV Event Reduction Relationship

- Cholesterol Treatment Trialists (CTT) assessment of all major statin vs. placebo, statin vs. statin, and statin + adjunct ezetimibe or PCSK9 inhibitor vs. statin trial
- For every 39mg/dL reduction in LDL, the 5-year risk of cardiovascular events is reduced by 22%
  - Holds for LDL’s as low as 30mg/dL
Question 3

- According to the CTT relationship, whether the intensity of statin was increased or adjunctive therapy with ezetimibe or evolocumab was used, the relationship between LDL lowering and cardiovascular event reduction had the same relationship

  a) True
  b) False

What Should We Be Recommending To Clinicians and Why?
Everyone Should not have an LDL of 30mg/dL

- If 50 of 100 of people over 5 years will have an ASCVD event, reducing that risk by 50% prevents 25 events
- If 10 of 100 people over 5 years will have an ASCVD event, reducing it by 50% prevents 10 events
- $1/\text{ARR} = \text{NNT}$
- NNT = number needed to treat to prevent one event

NNTs for Different Patients

LDL Goals

- LDL goals should be created for each patient as specified by AHA/ACC 2016
- Statins are drugs of first choice in all patients who tolerate starting with high or moderate intensity via AHA/ACC 2013
- If unable to achieve those goals on statins alone, intensify statin therapy (to max FDA doses) or adjunctive therapy

AHA/ACC 2016

- LDL goal <70mg/dL when ASCVD and either secondary causes or the LDL level is >190mg/dL
  - Secondary causes = dietary excess, drugs, diseases, and metabolism disorders
    - Treat the secondary cause and aggressively treat the LDL
    - Diseases: hypothyroid, genetic lipid degradation or storage, and mitochondrial
    - Drugs: corticosteroids, cyclosporine, protease inhibitors, progestin
AHA/ACC 2016

• LDL goal $<100\text{mg/dL}$
  – ASCVD patients when secondary causes [dietary excess, drugs, diseases, and metabolism disorders] are absent and baseline LDL $<190\text{mg/dL}$
  – Patients without ASCVD but an LDL $\geq 190\text{mg/dL}$, diabetes, or a 10-year ASCVD risk $\geq 7.5\%$

AHA/ACC 2016 Update

• Regardless of the LDL goal, everyone should get at least a 30% to 50% reduction in their LDL from baseline
• For example someone with an LDL of 100mg/dL before their MI without secondary causes should get at least a 50% reduction even though he/she is close to the goal of 100mg/dL
**Recommended Adjunctive Therapies**

<table>
<thead>
<tr>
<th>Reduction to Goal</th>
<th>Ezetimibe</th>
<th>Ezet + BAS</th>
<th>PCSK9 Inh</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% Reduction to Goal</td>
<td>++++ Effective, safe, well tolerated, low cost, proof of event reductions</td>
<td></td>
<td>Impossible to have cost/QALY &lt;$150,000/year</td>
</tr>
<tr>
<td>35% Reduction to Goal</td>
<td>++ Effective, safe, well tolerated, low cost BUT no proof of benefits over ezet alone</td>
<td>++ Effective, safe, well tolerated, proof of event reduction BUT very high cost</td>
<td></td>
</tr>
<tr>
<td>50% Reduction to Goal</td>
<td></td>
<td>Lower NNTs Help with Cost-Effectiveness</td>
<td>+++ Effective, safe, well tolerated, proof of event reduction BUT very high cost</td>
</tr>
</tbody>
</table>

**Question 4**

- Aliki Vishalli is a 65 year old patient without ASCVD but with diabetes mellitus type 2, what is the recommended LDL goal?
  - a) <30mg/dL
  - b) <70mg/dL
  - c) <100mg/dL
Question 5

- If Mr Vishalli in the previous question was on atorvastatin 10mg orally and needs a 20% reduction to achieve his LDL goal, what is the best therapeutic option?
  a) Substitute atorvastatin 80mg orally
  b) Add ezetimibe 10mg orally
  c) Add evolocumab 140mg Q2weeks

PCSK9 Cost Effectiveness

- In an analysis, the cost-effectiveness of the PCSK9 inhibitors was estimated
- If the NNT on PCSK9 inhibitor therapy is 30 to 50, 15 to 29, or 10 to 14, therapy would cost $300 000, $280 000, or $150 000 per quality adjusted life year (QALY) at $14 000 per year
  - With 50% discount, PCSK9 with an NNT of 30-50 would be reasonably cost effective (~75,000)
### Lipid Impact

<table>
<thead>
<tr>
<th></th>
<th>LDL</th>
<th>TG</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Apheresis</td>
<td>-50 to -68%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Statins</td>
<td>-35 to -58%</td>
<td>-10 to -25%</td>
<td>+7 to +12%</td>
</tr>
<tr>
<td>PCSK9 Inhibitors</td>
<td>-35 to -58%</td>
<td>-5 to -15%</td>
<td>+4 to +6%</td>
</tr>
<tr>
<td>Lomitapide</td>
<td>-30 to -40%</td>
<td>-40 to -50%</td>
<td>-7%</td>
</tr>
<tr>
<td>Mipomerson</td>
<td>-25%</td>
<td>-18%</td>
<td>+15%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>-15 to -20%</td>
<td>-5 to -8%</td>
<td>+3 to +5%</td>
</tr>
<tr>
<td>BAS</td>
<td>-15 to -20%</td>
<td>0 to -10%</td>
<td>+3 to +5%</td>
</tr>
<tr>
<td>Niacin</td>
<td>-15 to -20%</td>
<td>-20 to -50%</td>
<td>+15 to +35%</td>
</tr>
<tr>
<td>Fibric Acid Deriv</td>
<td>-10 to +10%</td>
<td>-30 to -60%</td>
<td>+9 to +20%</td>
</tr>
<tr>
<td>Omega-3 FAs</td>
<td>-5 to -44%</td>
<td>-30 to -60%</td>
<td>+5 to +10%</td>
</tr>
</tbody>
</table>

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**Use in Renal Dx**

<table>
<thead>
<tr>
<th>Statin</th>
<th>Yes</th>
<th>Pregnancy: Cat X Breastfeed: Unsafe</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAS</td>
<td>Yes</td>
<td>Pregnancy: Cat B Breastfeed: Safe</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Yes</td>
<td>Pregnancy: Cat C Breastfeed: Possible Use</td>
</tr>
<tr>
<td>PCSK9 Inh</td>
<td>Yes, No Data in Severe Dx</td>
<td>Pregnancy: No Data Breastfeed: No Data</td>
</tr>
</tbody>
</table>

**Drug Intx**

- Simva/Lova + CYP3A4 inh = ⊲ Myopathy
- Statin + Fibrate = ⊲ Myopathy and Liver Damage
- Pitavastatin + UGT inh = ⊳ Myopathy
- Ezet + Feno = ⊳ Increased Gallbladder Risk
- Ezet ⊳ Cyclosporin

**GI ADEs**

- + Dyspepsia
- + Constipation, Bloating
- +++ Constipation, Bloating
- + Diarrhea

**Notes**

- Prava and Fluva – take at bedtime
- Atora and Fluva – higher liver risk
- Simva and Lova – higher muscle damage risk
- Pravater and Fluva – take at bedtime
- Atorvastatin and Fluvastatin – higher liver risk
- Simvastatin and Lovastatin – higher muscle damage risk
- Colesvelam < Drug Intx Risk and Less Vitamin A, D, E, K Absorption Blocking
- No use in Gastroparesis
- Use Colesevelam Suspension in Dysphagia
- Only one dose (10mg)
- Not Recommended in ⊳ LFTs but not Contraind
- SQ dosing (q2 or 4 weeks)
- Injection site irritation
- Immunogenicity potential
- Possible neurocognitive ADEs

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Question 6

- Which therapy is NOT linked to a contraindication or strong precaution for the use of that drug?
  a) BAS – gastroparesis
  b) Statin – pregnancy
  c) PCSK9 inhibitor - myopathy

Can Pharmacist Provided Cognitive Services Enhance LDL Attainment?
Pharmacist Care Enhances Efficacy

- Pharmacist dyslipidemia programs versus usual care in VA medical centers showed greater LDL goals attainment than usual care
  - Study 1: 64.3% vs 15.7%, $P < 0.001$
  - Study 2: 80.3% vs 65.3%, OR = 2.6, 95% CI = 1.6-4.3)

- 91.4% and 87.8% of VA patients and providers reporting feeling strongly or somewhat satisfied with pharmacist care

Pharmacist Care Enhances Efficacy

- Pharmacist and physician team to manage LDL assessed in two non-VA medical settings

- 2- to 4-fold increases in the percentage of patients reaching their goals versus teams without such collaboration (  
  - Study 1: 43% vs 21%, $P < 0.05$
  - Study 2: 72% vs 18%, $P < 0.001$)
Factors that Pharmacists Use to Impact LDL Goal Attainment

• Better adherence
  – Patient education
  – Shared decision-making
  – Motivational interviewing
• More aggressive follow-up
• Different mixes of drugs that maximize benefits and minimizes adverse effects

Conclusions

• Guidelines abandoned LDL goals in 2013 but are coming back to them now
  – Driven by evolving clinical trial evidence
• LDL reduction reduces cardiovascular events (39mg/dL decreases CV events 22%)
• The greater the baseline CV risk, the baseline LDL concentration, and the % LDL reduction; the lower the NNT to decrease events (more cost-effective)
Conclusions

• PCSK9 inhibitors are new, expensive, potent LDL reducers with strong cardiac event reductions when combined with statins
• Ezetimibe has strong cardiac event reductions when combined with statins
• Pharmacists are well trained and positioned to help patients achieve their LDL goals