New Drugs for Lipid Management

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Disclosure

- Site PI for the following clinical trials:
  - Odyssey Outcomes, a study of Alirocumab in the prevention of coronary events, sponsored by Sanofi Aventis.
  - Omthera Strength, sponsored by Omthera Pharmaceuticals
  - CLEAR Serenity, sponsored by Esperion Therapeutics

HMG-CoA Reductase Inhibitor: Secondary Prevention

Relationship between LDL Levels and Event Rates in Secondary Prevention Trials of Patients with Stable CHD

Residual Cardiovascular Risk in Major Statin Trials

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus: The ACCORD Study Group

- Primary outcome: P=0.32
- Expanded macrovascular outcome: P=0.30
- Death from any cause: P=0.33
- Death from cardiovascular causes: P=0.26

Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE)

- 15,000 patients on Atorvastatin with CAD or DM
- Increase of HDL cholesterol by 72.1% on torcetrapib
- Decrease of LDL cholesterol by 25% on torcetrapib
- Systolic BP increased by 6 mm Hg on torcetrapib

Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome: Dal-outcomes Trial

- 15,000 patients
- Mean HDL cholesterol level was 42 mg per deciliter
- Mean low-density lipoprotein (LDL) cholesterol level was 76 mg per deciliter
- HDL cholesterol levels increased from baseline by 4 to 11% in the placebo group and by 31 to 40% in the dalcetrapib group.
AIM-HIGH: Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy.

HPS2-THRIVE: Randomized placebo-controlled trial of ER niacin and laropiprant in 25,673 patients with pre-existing cardiovascular disease.

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

<table>
<thead>
<tr>
<th>Statin Benefit Groups</th>
<th>4 Statin Benefit Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical ASCVD</td>
<td>• ACS</td>
</tr>
<tr>
<td></td>
<td>• MI</td>
</tr>
<tr>
<td></td>
<td>• Stroke</td>
</tr>
<tr>
<td></td>
<td>• TIA</td>
</tr>
<tr>
<td></td>
<td>• Angina</td>
</tr>
<tr>
<td></td>
<td>• Renovascularization</td>
</tr>
<tr>
<td></td>
<td>• PAD</td>
</tr>
<tr>
<td>LDL 2190mg/dL</td>
<td>• History of elevated LDL, with or without therapy</td>
</tr>
<tr>
<td>Diabetic</td>
<td>• 40–75 years old</td>
</tr>
<tr>
<td></td>
<td>• LDL 70-189mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Without clinical ASCVD</td>
</tr>
<tr>
<td>Primary Prevention</td>
<td>• 10-year risk score &gt;5%</td>
</tr>
<tr>
<td></td>
<td>• Without clinical ASCVD</td>
</tr>
<tr>
<td></td>
<td>• Not diabetic</td>
</tr>
<tr>
<td></td>
<td>• LDL 70-189mg/dL</td>
</tr>
</tbody>
</table>

Intensity of Statin Therapy

<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 by &gt;50%</td>
<td>Daily dose lowers LDL-C by 30-50%</td>
<td>Daily dose lowers LDL-C by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Simvastatin 5-10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin XL 80 mg</td>
<td>Pitavastatin 2-4 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 1 mg</td>
<td></td>
</tr>
</tbody>
</table>
2014 National Lipid Association Executive Summary

- When intervention beyond public health recommendations for long-term ASCVD risk reduction is employed, levels of atherogenic cholesterol (non-HDL-C and LDL-C) should be primary targets for therapies.
- Non-HDL-C primary target (Except TG if TG ≥ 500mg/dL)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Non-HDL-C</th>
<th>LDL-C</th>
<th>Apo B*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;130</td>
<td>&lt;100</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt;130</td>
<td>&lt;100</td>
<td>&lt;90</td>
</tr>
<tr>
<td>High</td>
<td>&lt;130</td>
<td>&lt;100</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Very High</td>
<td>&lt;100</td>
<td>&lt;70</td>
<td>&lt;80</td>
</tr>
</tbody>
</table>

*Apo B is a secondary, optional target of treatment or LDL particle concentration.

Case 1

- 52 yo accountant presented with a non ST elevation MI. Cath revealed a 90% RCA stenosis. PCI with a drug eluting stent was performed.
- Lipid levels at the time of the event were:
  - Cholesterol 220
  - LDL 178
  - HDL 38
  - TG 70
- He is discharged on high dose statin therapy with Atorvastatin 80 mg once daily.

In 3 months, repeat lipid levels reveal:

- Cholesterol 149
- LDL 99
- HDL 39
- TG 60

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

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≤30 days), or stroke
IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)
Effect of the Addition of Ezetimibe to Simvastatin Compared to Simvastatin Monotherapy.

Simvastatin (Mean LDL 70) — 34.7% 2742 events
Ezetimibe/Simvastatin (Mean LDL 53) — 32.7% 2572 events

HR 0.936 CI (0.887, 0.988) p=0.015

NNT=50

**Case 1**
Proprotein Convertase Subtilisin-Kexin Type 9 (PCSK9)

- In 2006, it was reported that a loss of function mutation in the gene encoding PCSK9 was associated with significantly lower long-term plasma levels of LDL cholesterol (1).
- A substantial (47 to 88%) lower risk of coronary heart disease was observed over a period of 15 years in middle-aged persons with such genetic polymorphisms.
- Additional genetic studies indicated that PCSK9 activity was a major determinant of plasma levels of LDL cholesterol in humans (2).
- Opened the door for drug development to synthesize inhibitors against PCSK9.


PCSK9 inhibitors

- Monoclonal antibodies directed against PCSK9
- Alirocumab and Evolocumab are clinically available
- Many others are in varying stages of development
- Injectable agents
- Early clinical trials using in a variety of patient groups show an ~60% decrease in LDL cholesterol in the treatment groups, even those treated with statin therapy.
Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events


Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events


Major adverse cardiovascular events were lower with alirocumab plus statin (1.7%) versus placebo plus statin (3.3%) in pre-specified post hoc analysis (HR 0.52; 95% confidence interval, 0.31 to 0.90; nominal P = 0.02).

Calculated LDL Cholesterol Level

Days Since Randomization

P = 0.003
**Low-Density Lipoprotein (LDL) Cholesterol Levels over Time**

- **Placebo**
- **Evolocumab**

**Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease**

Cumulative Incidence of Cardiovascular Events

- **Placebo**
- **Evolocumab**

**Odyssey Outcomes:**

- Randomized controlled double blinded clinical trial comparing alirocumab versus placebo in patients treated with statin therapy whose LDL levels remains above 70.
- 5 year outcome trial
- Results expected to be presented/published in March of 2018.

**PCSK9 inhibitors**

- Alirocumab and Evolocumab are FDA approved for clinical use, indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).
- Evolocumab also indicated for homozygous familial hypercholesterolemia
Case 1

- Decision made to add a PCSK9 inhibitor to the Atorvastatin
- 3 months later:
  - Chol 102
  - LDL 46
  - HDL 40
  - TG 64

Summary

- Diet, physical activity and for those at increased risk of cardiovascular events, statin therapy, remain the mainstay of lipid management
- For those patients who have LDL levels above NLA goal for non HDL cholesterol, secondary therapy may be considered
- Ezetimibe and the 2 PCSK9 inhibitors, Alirocumab and Evolocumab are clinically available
- Anacetrapib is a CETP inhibitor that may become available in the future
- New advances in lipid lowering improve the ability to reduce risk for cardiovascular events

Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease
The HPS3/TIMI55-REVEAL Collaborative Group

<table>
<thead>
<tr>
<th>Rate Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Death</td>
<td>0.92</td>
</tr>
<tr>
<td>MI</td>
<td>0.87</td>
</tr>
<tr>
<td>Coronary Death or MI</td>
<td>0.89</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>0.90</td>
</tr>
<tr>
<td>Major Coronary Event</td>
<td>0.91</td>
</tr>
<tr>
<td>Presumed Ischemic Stroke</td>
<td>0.99</td>
</tr>
<tr>
<td>Major Atherosclerotic Event</td>
<td>0.93</td>
</tr>
<tr>
<td>Major Vascular Event</td>
<td>0.93</td>
</tr>
</tbody>
</table>

0.6 0.8 1.0 1.2
Anacetrapib Better Placebo Better

N Engl J Med 2017; 377:1217-1227
New Drugs for Lipid Management

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The Ohio State University Wexner Medical Center
Clinical Assistant Professor,
The OSU College of Pharmacy

2017 ACC Focused Update of LDL Expert Consensus Decision Pathway

Adding ezetimibe to reduce LDL-C by 20%, NNT:
- 50 for very high-risk patients with LDL-C >130 mg/dL
- 30 for very high-risk patients with LDL-C >160 mg/dL
- 50 for high-risk primary prevention patients with LDL-C >190 mg/dL

Adding PCSK9 inh to reduce LDL-C by 50%, NNT:
- 50 for very high-risk and for high-risk patients with LDL-C >70 mg/dL
- 30 for very high-risk and for high-risk patients with an LDL-C >130 mg/dL
Clinical ASCVD w/ comorbidities
- Ezetimibe
  - Factors with potential greater benefit:
    - CHF, HTN, age >75, DM, CVA, CABG, PAD, eGFR <60, smoking
  - Other specific considerations:
    - >25% additional LDL lowering needed
    - Recent ACS
    - Low cost burden
    - Ease of use preferred
    - PCSK9 inhibitor
    - Consider when >25% lowering of LDL is needed
    - Should NOT be considered for patients with a primary indication of diabetes or elevated 10 year risk

Familial Hypercholesterolemia (FH) is a common genetic cause of premature coronary heart disease (CHD) due to lifelong elevated plasma low-density lipoprotein cholesterol (LDL-C) levels

- Prevalence
  - Heterozygous FH ~1:300-1:500
  - Homozygous FH ~1:1,000,000
  - ~620,000 FH patients in US
  - Most common congenital metabolic disorder

- Group of genetic defects resulting in severe elevations of blood cholesterol levels
  - LDL receptor (LDLR)
  - Apolipoprotein B (Apo B)
  - Proprotein convertase subtilisin/kexin type 9 (PCSK9)
Heterozygous FH (HeFH)

- If not treated:
  - 50% risk of CHD in men by age 50
  - 30% risk of CHD in women by age 60
- National Lipid Association Screening Recommendations¹
  - FH should be suspected when untreated fasting LDL-C or non-HDL-c levels are at or above the following

<table>
<thead>
<tr>
<th>Age</th>
<th>LDL (mg/dL)</th>
<th>Non-HDL (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20 years</td>
<td>≥ 190</td>
<td>≥ 220</td>
</tr>
<tr>
<td>&lt; 20 years</td>
<td>≥ 160</td>
<td>≥ 190</td>
</tr>
</tbody>
</table>

- For individuals with these levels, a family history of high cholesterol and heart disease should be collected


Diagnostic criteria

- Clinical diagnosis
  - Three validated sets of diagnostic criteria
  - All take into consideration a combination of the following:
    - Elevated, untreated LDL-C levels (cut points vary with age)
    - Family history (↑LDL-C; premature CHD)
    - Clinical history (premature CHD)
    - Physical examination (tendon xanthomas; corneal arcus <45y)
    - Functional mutation in LDLR, APOB, or PCSK9
- Genetic testing
  - ~$100 out of pocket for pt
  - Negative results do not rule out FH


2015 AHA Scientific Statement on FH

Initial drug monotherapy

- High-Intensity Statin Therapy (>50% LDL-C reduction)
- Resezuvastatin or alirovastatin

If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to two-drug combination

- Resezuvastatin or Alirovastatin
- Exercise

If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to three-drug combination

- Resezuvastatin or Alirovastatin
- Resezuvastatin or Alirovastatin
- Exercise

If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to complex therapy combination

- Resezuvastatin or Alirovastatin
- Resezuvastatin or Alirovastatin
- Resezuvastatin or Alirovastatin
- Exercise

Complex-therapy Combination

- Consider four-drug combination² and LDL Apheresis

Gidding SS et al. Circulation 2015

Case #2
Case 2

- 24 yo white male
- Secondary prevention
- PMH:
  - Clinical HoFH diagnosed age 2 (highest TC 957)
  - Significant xanthomas on hands, elbows, achilles
  - Advanced CAD s/p mtp PCIs to LAD/Cx/RCA
  - Preserved LV systolic function
- Fam Hx:
  - Paternal GF CAD age 40. Father CAD age 46. Mother, brother, sister, father HLD
- Genetics: Compound heterozygous (both LDLR)

Case 2 Medications

- Atorvastatin 80mg daily
- Zetia 10mg daily
- Welchol 6 tabs daily
- Aspirin 81mg daily
- Plavix 75mg daily
- Metoprolol 25mg twice daily
- SL NTG prn
- Ferrous sulfate 324mg twice daily

Mipomersen (Kynamro®) – Apo B inhibitor

Lomitapide (Juxtapid®) – Microsomal TG Transfer Protein Inhibitor

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### HoFH agent comparison

<table>
<thead>
<tr>
<th>Class</th>
<th>Primary MOA</th>
<th>LDL-C HoFH</th>
<th>LDL-C HeFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Inhibition of HMG-CoA Reductase</td>
<td>Up to 28%</td>
<td>Up to 63%</td>
</tr>
<tr>
<td>Bile Acid Sequestrants</td>
<td>Bile acid re-absorption</td>
<td>&lt;10%</td>
<td>Up to 23%</td>
</tr>
<tr>
<td>Zetia</td>
<td>Intestinal Cholesterol absorption via NPC1L1</td>
<td>&lt;10%</td>
<td>~25%</td>
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</table>

### LDL Apheresis

**What is it?**

- FDA-approved process selectively removing Apo B-containing particles from bloodstream
- Extracorporeal precipitation with heparin
- Repeated every 1-2 wks
- Removes at least 60% Apo B-containing particles
- $$$$

**Candidates for Apheresis**

- Patients on 6 months of maximal therapy who have not reached goal:
  - HoFH w/ LDL ≥ 300
  - HeFH w/ LDL ≥ 300
  - + 0-1 risk factor
  - HeFH w/ LDL ≥ 200
  - + high risk (≥ 2 risk factors, Lp(a) ≥ 250mg/dL)
  - HeFH w/ LDL ≥ 160
  - + very high risk (CHD, CAD, or diabetes)

### Case 2 Current Medications

- Crestor 40mg daily
- Zetia 10mg daily
- Aspirin 81mg daily
- Plavix 75mg daily
- Metoprolol 25mg twice daily
- SL NTG prn
- Ferrous sulfate 324mg twice daily
- Weekly lipoprotein apheresis sessions

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**Case 2 Current labs**

Average pre 219mg/dL  
Average post 58mg/dL  
Time averaged 138mg/dL

**Statin intolerance**

The true frequency of statin intolerance in the population is unknown

- May approach 10%

“Intolerance” if recurrent symptoms with rechallenge of 2-3 statins

- Metabolized by different pathways, different lipophilicities, and ≥ 1 at the lowest approved dose

Real or perceived symptoms from statins may be underappreciated cause of non-adherence to therapy

- USAGE study - pt reported muscle symptoms may occur ~29%
- Effective and empathetic communication vital
  - “The secret of the care of the patient is in caring for the patient.” – Francis Peabody

2014 NLA Statin safety task force

**GAUSS 3: Evolocumab in statin intolerance**

Two double-blind phases

- Phase A: 511 patients with a history of intolerance to multiple statins due to muscle-related adverse effects
- 10 weeks:
  - Atorvastatin 20 mg
  - Placebo
- 10 weeks:
  - Atorvastatin 20 mg
  - Placebo

- Phase B: Participants entered Phase B only if they had muscle symptoms on atorvastatin, but not placebo, or CK ≥ 10 x ULN during statin treatment
- 24 weeks:
  - Monthly SC evolocumab 420 mg
  - Daily oral ezetimibe 10 mg

**Phase A: Study Drug Discontinuation Events**

<table>
<thead>
<tr>
<th>Intolerable Muscle Symptoms</th>
<th>N=491</th>
</tr>
</thead>
<tbody>
<tr>
<td>On atorvastatin, but not placebo</td>
<td>209 (42.6%)*</td>
</tr>
<tr>
<td>On placebo, but not atorvastatin</td>
<td>130 (26.5%)</td>
</tr>
<tr>
<td>On both placebo and atorvastatin</td>
<td>48 (9.8%)</td>
</tr>
<tr>
<td>No symptoms on either treatment</td>
<td>85 (17.3%)</td>
</tr>
<tr>
<td>Did not complete Phase A</td>
<td>20/511</td>
</tr>
</tbody>
</table>

Bypassed Phase A due to CK elevation ≥ 10 x ULN 19 (3.9%)*  
Nissen SE, Stroes E, et al. JAMA 2016;315:1580-90
**Statin Intolerance**

- **Drug Interactions**
  - Risk of myopathy when statins coadministered with medications that inhibit their metabolism
  - Choosing a noninteracting medication or switching to a non-interacting statin may be the safest option
- **Muscle safety**
  - Algorithm exists for the evaluation and treatment of patients who may be intolerant to statins as the result of adverse muscle events
  - Use ACC Statin intolerance app!

**Statin intolerance: Assess labs**

- Muscle symptom severity
- CK
- Rhabdomyolysis
- Creatinine & Urinalysis
- Risk factors / secondary causes
  - Thyroid panel
  - Electrolyte panel
  - Renal panel
  - Vitamin D 25-OH

**Statin intolerance clinical pearls**

- **Treat secondary causes**
  - Vit D
  - Hypothyroid
- **Re-challenge and/or Reduce**
  - Ultra-low dose statin
  - High potency, long half-life
- **Change**
  - Hydrophilic statin
  - Non-statin

**Summary**

- Patient-centered, individualized clinical judgement is best
  - Lifestyle paramount to risk reduction
- Statins as first line pharmacotherapy,
  - Strongly consider non-statin add-on therapy for patients on max-tolerated statin with residual risk
- Familial hypercholesterolemia awareness is important and requires lifelong therapy
  - Response to lipid lowering therapies may vary
- Statin intolerance, while truly uncommon, can be overcome with various clinical strategies
  - Education, monitoring, and partnership with patients is vital

**Internal data:**

- 75.9% of statin intolerant pts were able to tolerate statin therapy
- 43% achieved LDL-C goals
# OSUWMC Lipid Clinic

## What we offer
- Comprehensive, personalized, high-quality health care and patient education
- Ongoing assessment and therapeutic optimization for CAD risk reduction
- Application of current EBM and guidelines
- Quality monitoring and clinical outcomes

## Staff
- Lipid specialists (ABCL & ACCL)
- Training in statin intolerance, complex drug regimens, ADE monitoring, and management, various presentations of HLD

## Partners
- Genetics Clinic
- Specialty pharmacy
- Smoking Cessation Clinic
- Apheresis Unit

## Who to refer
- High risk ASCVD or FH with atherogenic cholesterol levels above treatment goals, on max tolerated statin
- Patient with multiple intolerance to recommended therapy
- Any patient seeking comprehensive cardiovascular risk reduction

## How to refer
- Call for appointments: 614-293-0949
- Fax referral to 614-293-8260