Advances in treatment of hypercholesterolemia

Melina Braly, Pharm.D., BCPS
PGY-2 Critical Care Resident
Baptist Hospital of Miami
March 12, 2016

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Objectives

• Pharmacist Objectives:
  — Recall the Adult Treatment Panel (ATP) IV guidelines
  — Review the lipid-lowering medications
  — Develop a patient specific treatment algorithm

• Pharmacy Technician Objectives:
  — Recognize the Adult Treatment Panel (ATP) IV guidelines
  — Acknowledge the health risks of hypercholesterolemia
  — Appreciate the lipid-lowering medications

Disclosure

• I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Hypercholesterolemia in the United States

1,2

• 73.5 million adults (31.7%) have high LDL
• 31 million adults have a total cholesterol greater than 240 mg/dL
• Most prevalent among white, non-hispanic females
• 48.1% of adults with high LDL cholesterol are receiving lipid-lowering therapy
  — 29.5% with high LDL are optimized
Causes of Lipoprotein Abnormalities

- **Primary**
  - Homozygous familial hypercholesterolemia (HoFH)
  - Heterozygous familial hypercholesterolemia (HeFH)
- **Secondary**
  - Hypercholesterolemia
    - Hypothyroidism, obstructive liver disease, nephrotic syndromes, medications (thiazides, progestins, steroids)
  - Hypertriglyceridemia
    - Obesity, diabetes mellitus, sepsis, pregnancy, lipodystrophy, acute hepatitis, alcohol, medications (β-blockers, azoles)
  - Low HDL
    - Malnutrition, obesity, medications (progestins, anabolic steroids)

Risks of Hypercholesterolemia

- Acute myocardial infarction
- Heart failure
- Coronary arteriosclerosis
- Thromboembolic stroke
- Peripheral vascular disease
- Pancreatitis

Lipid Panel

- Standard lipid panel includes:
  - Total cholesterol (TC)
    - TC= LDL + HDL + (TG/5)
    - Optimal range: less than 200 mg/dL
  - Low-density lipoprotein (LDL) cholesterol
    - Optimal range: less than 130 mg/dL
  - High-density lipoprotein (HDL) cholesterol
    - Optimal range: greater than 40 mg/dL
  - Triglycerides (TGs)
    - Optimal range: less than 200 mg/dL

Lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Triglyceride (%)</th>
<th>Phospholipid (%)</th>
<th>Protein (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicron</td>
<td>80-95</td>
<td>1-9</td>
<td>1-2</td>
</tr>
<tr>
<td>VLDL</td>
<td>55-80</td>
<td>10-20</td>
<td>6-10</td>
</tr>
<tr>
<td>LDL</td>
<td>5-15</td>
<td>18-24</td>
<td>18-22</td>
</tr>
<tr>
<td>HDL</td>
<td>5-10</td>
<td>20-30</td>
<td>45-55</td>
</tr>
</tbody>
</table>
**Cholesterol Synthesis**

**Exogenous**
- Dietary fats
- Bile salts
- Cholesterol

**Endogenous**
- LDL
- VLDL

- ApoA-I
- ApoE
- Chylomicron remnants
- LPL
- FFA

- Muscles
- Adipose

---

**Atherosclerotic Cardiovascular Disease (ASCVD)**

- ASCVD includes coronary heart disease (CHD), stroke, and peripheral artery disease
- Primary prevention:
  - Prevent the onset of ASCVD
- Secondary prevention:
  - Requires identification of ASCVD at early stage and initiation of management
Evolution of the ACC/AHA Cholesterol Guidelines

ATP-I: Focus on primary prevention
- LDL target < 130 mg/dL

ATP-II: Focus on secondary prevention
- LDL target < 100 mg/dL; HDL introduced as CVD risk

ATP-III: Primary and secondary prevention
- Life-modification program (TLC); Framingham Risk Score

Revised ATP-III: LDL target < 70 mg/dL for high-risk patients

ATP-IV: Tailored treatment approach

Global Risk Assessment for Primary Prevention

- Pooled Cohort Equation
  - Replaces Framingham Risk Score
  - Enables health care providers and patients to estimate 10-year and lifetime risks for ASCVD

- Required information to estimate ASCVD risk includes age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking status

2013 ACC/AHA Cholesterol Guidelines: ATP IV

- Updates in the guidelines
  - A new perspective on LDL/HDL treatment goals
    - Giving up the goal to treat paradigm
    - No RCTs support achieving a certain target LDL improve ASCVD outcomes
    - Use of LDL targets may lead to:
      - Suboptimal dose of statins
      - Overtreatment with non-statin drugs that have not shown a ASCVD risk reduction
    - Focus on ASCVD risk reduction
      - 4 statin benefit groups

Pooled Cohort Equation

https://www.americanheart.org/professional/statements/guidelines/prevention-guidelines ACC/AHA Cholesterol Guidelines
Treatment Approach

Lifestyle Modifications

- Diet:
  - Saturated and trans fat restriction
  - Dietary salt restriction
  - Achieve with the USDA dietary pattern, DASH, or ADA diet
- Exercise (aerobic and resistance training)
  - Moderate intensity: 150 minutes/week
  - Vigorous intensity: 75 minutes/week

Lipid Lowering Therapy

- Current Therapies
  - Fibric Acid Derivatives (Fibrates)
  - Nicotinic Acid (Niacin)
  - Omega-3 Fatty Acids (FAs)
  - Bile Acid Sequestrants (BAS)
  - Cholesterol Absorption Inhibitor (CAI)
  - HMG-CoA Reductase Inhibitors (Statins)
  - PCSK9 Monoclonal Antibody (mAB)
- Future Therapy
  - Cholesteryl Ester Transfer Protein (CETP) Inhibitors

Lipid Lowering Therapy

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrates</td>
<td>Inhibit lipolysis, decreases hepatic fatty acid uptake and inhibit hepatic secretion of VLDL</td>
<td>Dyspepsia, upper GI distress, cholesterol gallstones, myopathy</td>
<td>Major effects are to decrease triglycerides and increase HDL</td>
</tr>
<tr>
<td>BAS</td>
<td>Bind bile acids in the intestine that is eliminated in feces which results in lowering of cholesterol</td>
<td>Upper and lower GI distress, constipation</td>
<td>Typically used as adjunctive therapies</td>
</tr>
</tbody>
</table>

PCSK9: proprotein convertase subtilisin kexin type 9
### Lipid Lowering Therapy

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinic Acid</td>
<td>Inhibits mobilization of free fatty acids from peripheral adipose tissue to the liver and reduces VLDL synthesis</td>
<td>Flushing, hyperglycemia, hyperuricemia, GI distress, hepatotoxicity</td>
<td>• Can reduce triglyceride levels (less than fibrates)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• May worsen glucose tolerance, caution in diabetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Combination with statins may have harmful effects</td>
</tr>
<tr>
<td>Omega-3 FAs</td>
<td>Unknown</td>
<td>Bleeding complications</td>
<td>• Increase HDL and decrease triglycerides</td>
</tr>
<tr>
<td></td>
<td>Possible modulation VLDL and chylomicron metabolism</td>
<td></td>
<td>• Important as a supplement in patients with CHD</td>
</tr>
<tr>
<td>Statin: Mechanism</td>
<td></td>
<td></td>
<td>• Drug of choice for high LDL or CHD/CHD risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Inhibit HMG-CoA reductase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Reduce hepatic cholesterol content</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Increase expression of LDL receptors</td>
</tr>
</tbody>
</table>

### Cholesterol Absorption Inhibitor

- Ezetimibe (ZETIA®), 10 mg tablet
- Outcomes Data:
  - IMPROVE-IT
    - Ezetimibe 10 mg + simvastatin 40 mg PO daily vs simvastatin 40 mg PO daily
    - LDL reduction: 53.7 mg/dL vs 69.5 mg/dL (P < 0.001)
    - Event rate at 7 years: 32.7% vs 34.7% (P = 0.016)
    - Total events: 4,562 vs. 4,983 (P = 0.007)

Event: cardiovascular (CV) death, myocardial infarction, stroke, unstable angina leading to hospitalization, coronary revascularization > 30 days post-randomization.

### Statin: Clinical Efficacy

In a meta-analysis of 14 primary and secondary prevention trials with statins, all-cause death was reduced by 12%.
**Statin Safety**

- Characteristics predisposing individuals to statin adverse effects include, but are not limited to:
  - Multiple or serious comorbidities, including impaired renal or hepatic function
  - History of previous statin intolerance or muscle disorders
  - Unexplained ALT elevations ≥3 times ULN
  - Patient characteristics or concomitant use of drugs affecting statin metabolism
  - Age >75 years
- Obtain baseline CK and LFTs

**Statin Therapy**

<table>
<thead>
<tr>
<th>High-Intensity Statins</th>
<th>Moderate-Intensity Statins</th>
<th>Low-Intensity Statins</th>
</tr>
</thead>
<tbody>
<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>Rosuvastatin (5) 10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 (80) mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Fluvastatin 20-40 mg BID</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin Xl 80 mg daily</td>
<td>Fluvastatin 40 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluvastatin 2-4 mg</td>
</tr>
</tbody>
</table>

**4 Statin Benefit Groups**

- **Statin Therapy**
  - **Clinical ASCVD**
  - **Diabetes mellitus** (age 40-75) LDL 70-189
  - **LDL ≥ 190**
  - **≥ 7.5% 10 year risk** (age 40-75)

**Bold** indicates evaluated by RCTs

**Italics** indicates doses approved by FDA but not tested

* = Evidence from 1 RCT

*** = Initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy
4 Statin Benefit Groups

**Benefit Group**
- Clinical ASCVD
- Diabetes mellitus (age 40-75) LDL 70-189
- LDL ≥ 190
- ≥ 7.5% 10-year risk (age 40-75)

**Statin Therapy**
- ≤ 75 yo
  - High-intensity statin
- > 75 yo
  - Moderate-intensity statin
- ≥ 7.5% 10-year risk
  - High-intensity statin
- < 7.5% 10-year risk
  - Moderate-intensity statin
- LDL ≥ 190
  - High-intensity statin
- ≥ 7.5% 10-year risk (age 40-75)
  - Moderate-to-high intensity statin

**Biomarkers and Noninvasive Tests**

- Primary ASCVD prevention for individuals not in a statin benefit group and to initiation of statin therapy is unclear
- Additional Factors to Consider
  - Elevated lifetime risk of ASCVD
  - LDL ≥160 mg/dL*
  - hs-CRP > 2 mg/L
  - Ankle-brachial index <0.9
  - Family history of premature ASCVD
  - CAC score ≥300 Agatston units

*hs-CRP: high-sensitivity C-reactive protein
CAC: coronary artery calcium
* or other evidence of genetic dyslipidemias
Advances and New Treatment Options

PCSK9 Regulation

PCSK9 Monoclonal Antibodies

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab (Praluent™)</th>
<th>Evolocumab (Repatha™)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approval Date</strong></td>
<td>July 2015</td>
<td>August 2015</td>
</tr>
<tr>
<td><strong>Approved Indications</strong></td>
<td>Clinical atherosclerotic disease</td>
<td>Clinical atherosclerotic disease</td>
</tr>
<tr>
<td></td>
<td>• HoFM</td>
<td>• HoFM</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>75 mg – 150 mg SQ every 2 weeks</td>
<td>140 mg SQ every 2 weeks or 420 mg SQ every 4 weeks (HoFM)</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>Tmax: 3 to 7 days</td>
<td>Tmax: 3 to 4 days</td>
</tr>
<tr>
<td></td>
<td>Bioavailability: 85%</td>
<td>Bioavailability: 72%</td>
</tr>
<tr>
<td></td>
<td>Elimination: Binding to target, proteolytic pathway</td>
<td>Elimination: Binding to target, proteolytic pathway</td>
</tr>
<tr>
<td></td>
<td>T1/2: 17-20 days</td>
<td>T1/2: 11 to 17 days</td>
</tr>
</tbody>
</table>

PCSK9 Monoclonal Antibodies

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab (Praluent™)</th>
<th>Evolocumab (Repatha™)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warnings/ Precautions</strong></td>
<td>Hypersensitivity reactions</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td>Injection site reaction (7.2%)</td>
<td>Injection site reaction (5.7%)</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis (11.3%)</td>
<td>Nasopharyngitis (8.6-10.5%)</td>
</tr>
<tr>
<td></td>
<td>Influenza (5.7%)</td>
<td>Influenza (7.5-9.1%)</td>
</tr>
<tr>
<td></td>
<td>Allergic reaction (8.6%)</td>
<td>Nasopharyngitis (8.6-10.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper respiratory infection (9.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rash (1%), urticaria (0.4%)</td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
<td>75 mg/ml and 150 mg/ml single dose prefilled pen/syringe</td>
<td>140 mg/ml single dose prefilled pen/syringe</td>
</tr>
<tr>
<td><strong>Phase III trial programs</strong></td>
<td>ODYSSEY (14 trials)</td>
<td>PROFICIO (22 trials)</td>
</tr>
</tbody>
</table>
ODYSSEY COMBO I

- Population:
  - Documented CVD and LDL-C ≥ 70 mg/dL OR high risk for CVD and LDL-C ≥ 100 mg/dL
  - All patients uncontrolled on standard therapy
- Primary Endpoint:
  - Reduction of LDL-C at the end of 24 weeks
- Treatment Arms: (+ max tolerated statin)
  - Alirocumab 75 mg SQ every 2 weeks (n= 205)
    - May be increased to 150 mg SQ every 2 weeks if LDL at week 8 was > 70 mg/dL
  - Placebo SQ every 2 weeks (n= 207)
ODYSSEY OPTIONS I

- Population:
  - Documented CVD and LDL-C ≥ 70 mg/dL OR high risk for CVD and LDL-C ≥ 100 mg/dL
  - All patients uncontrolled on standard therapy
- Primary Endpoint:
  - LDL-C reduction from baseline to 24 weeks

ODYSSEY OPTIONS I: Treatment Arms

ODYSSEY OPTIONS I: Results
ODYSSEY ALTERNATIVE

- Population:
  - Moderate (LDL-C > 70 mg/dL) to high (LDL-C > 100 mg/dL) CV risk
  - Previous intolerance to ≥ 2 statins
- Primary Endpoint:
  - LDL-C reduction from baseline to 24 weeks for alirocumab vs ezetimibe
- Treatment Arms:
  - Alirocumab 75 mg SC every 2 weeks (n= 126)
  - Ezetimibe 10 mg PO daily (n= 122)
  - Atorvastatin 20 mg PO daily (n= 62)
- Results:
  - LDL-C reduction of 45.0% for alirocumab and 14.6% for ezetimibe, with a difference between groups of 30.4% (P < .0001)
  - Incidence of skeletal muscle adverse event: 32.5% (ALI), 41.1% (EZE), 46% (ATR)

Mendel-2: Results

- Largest monotherapy trial with PCSK9 inhibitors
- Population:
  - Adults with fasting LDL-C ≥ 100 and <190 mg/dl and Framingham risk scores ≤ 10%
- Primary Endpoint:
  - LDL-C reduction from baseline to 12 weeks
- Treatment Arms:
  - Placebo (n = 151)
  - Ezetimibe 10 mg PO daily (n = 149)
  - Evolocumab 140 mg SQ every 2 weeks (n = 153)
  - Evolocumab 420 mg SQ every 4 weeks (n = 153)

GAUSS-2

- Population:
  - Adults (18 to 80 yo) with uncontrolled LDL-C on no or low-dose statins
  - Previous intolerance to ≥ 2 statins
- Primary Endpoint:
  - LDL-C reduction from baseline mean of weeks 10 and 12
- Treatment Arms:
  - Evolocumab 140 mg SQ every 2 weeks (n = 103)
  - Evolocumab 420 mg SQ every 4 weeks (n = 103)
  - Ezetimibe 10 mg PO daily (n = 102)
GAUSS-2: Results

Considerations for Use

Place in therapy

In the pipeline
DEFINE

- Population:
  - Adults with CHD or CHD Risk-Equivalent Disease and receiving a statin, with well controlled LDL-C
- Primary Endpoint:
  - LDL-C reduction from baseline at 76 weeks
- Treatment Arms: (+ standard therapy)
  - Anacetrapib 100 mg PO daily \((n = 811)\)
  - Placebo \((n = 812)\)
- Results:
  - Anacetrapib lowered LDL by 39.8\% \((p < 0.001)\) and increased HDL by 138.1\% \((p < 0.001)\)

Overview of Agents and Developing a Treatment Plan

<table>
<thead>
<tr>
<th>Drug</th>
<th>LDL Reduction (%)</th>
<th>TC Reduction (%)</th>
<th>HDL Effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>18-55</td>
<td>14-26</td>
<td>+ 2-15</td>
</tr>
<tr>
<td>CAI</td>
<td>18</td>
<td>8</td>
<td>+ 1</td>
</tr>
<tr>
<td>Fibrates</td>
<td>5-20</td>
<td>20-50</td>
<td>+ 10-35</td>
</tr>
<tr>
<td>Bile Acid Sequestrants</td>
<td>15-30</td>
<td>No effect</td>
<td>+ 3-5</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>5-25</td>
<td>20-50</td>
<td>+ 13-35</td>
</tr>
<tr>
<td>Omega-3 FAs</td>
<td>Increase/ No change</td>
<td>20-50</td>
<td>Increase/ No change</td>
</tr>
<tr>
<td>PCSK9 Antibody</td>
<td>28-65</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>CETP inhibitor</td>
<td>7-45</td>
<td>Not reported</td>
<td>+ 30-180</td>
</tr>
</tbody>
</table>
Treatment Algorithm

1. Assess medication and chronic adherence. Failing test panel?

2. Anticipated response?
   - Yes: Management of drug therapy (Table 6, Table 7)
   - No: Anticipated response?

3. Anticipated response?
   - Yes: Management of drug therapy (Table 6, Table 7)
   - No: Intolerance to medication or drug therapy?

4. Intolerance to medication or drug therapy?
   - Yes: Management of drug therapy (Table 6, Table 7)
   - No: Reinforce adherence to intended therapy changes. Exclude secondary causes of response (Table 4).

5. Reinforce adherence to intended therapy changes. Exclude secondary causes of response (Table 4).
Summary

• Lifestyle modifications are the cornerstone of ATP IV
• Do not focus on LDL-C or non–HDL-C levels as treatment goals
• Statins are the recommended first line pharmacotherapy—reduce ASCVD risk
• Adjunctive therapies may be added in the case of statin intolerance or failure
• PCSK9 inhibitors are a promising new therapy
• CETP inhibitors shows potential as a new medication for dyslipidemias

Assessment Questions

• The newest cholesterol guidelines base cardiovascular risk solely on LDL.
  – True/False

Assessment Questions

• The newest cholesterol guidelines base cardiovascular risk solely on LDL.
  – True/False
• Statins are the first-line pharmacological treatment for hypercholesterolemia.
  – True/False
Assessment Questions

- The newest cholesterol guidelines base cardiovascular risk solely on LDL.
  - True/False
- Statins are the first-line pharmacological treatment for hypercholesterolemia.
  - True/False
- PCSK-9 inhibitors are monoclonal antibodies.
  - True/False

References

References


Advances in treatment of hypercholesterolemia

Melia Braly, Pharm.D., BCPS
PGY-2 Critical Care Resident
Baptist Hospital of Miami
melina@baptisthealth.net

www.fshp.org

References


Medication Site of Action

https://www.studyblue.com/notes/note/n/biochem-lipid-metabolism/deck/12418058

Fibrates
Nicotinic Acid
Omega-3 Fatty Acids

Dietary Lipids
Exogenous
Endogenous
LPL
HDL
LDL
VLDL
Muscle
Antiprotease
Hepatic Lipoprotein Lipase
Muscle
Antiprotease
Hepatic Lipoprotein Lipase
Muscle
Antiprotease
Hepatic Lipoprotein Lipase
Muscle
Antiprotease
Hepatic Lipoprotein Lipase
Laplace-2

- Population:
  - Adults (18-80 yo) with:
    - No previous statin with fasting LDL-C ≥ 150 mg/dL
    - Previous non-intensive statin with fasting LDL-C ≥ 100 mg/dL
    - Previous intensive statin with fasting LDL-C ≥ 80 mg/dL
- Primary Endpoint:
  - LDL-C reduction from baseline to 12 weeks and mean of weeks 10 and 12

Laplace-2: Treatment Arms

- Rosuvastatin (5 mg or 40 mg PO daily)
  - Or Simvastatin (40 mg PO daily)
- Atorvastatin (10 mg or 80 mg PO daily)
  - Evolocumab 140mg SQ Q 2wks VS placebo SQ
  - Evolocumab 420mg SQ Q 4wks VS placebo SQ
  - Evolocumab 140mg SQ Q 2wks + PO placebo
  - Evolocumab 420mg SQ Q 4wks + PO placebo
  - Ezetimibe 10 mg PO daily + SQ placebo (Q 2wks or Q 4wks)
  - PO placebo + SQ placebo (Q 2wks or Q 4wks)

Laplace-2: Results

- LDL-C reduction from baseline to 12 weeks and mean of weeks 10 and 12
ODYSSEY COMBO II

- Population:
  - Documented CVD and LDL-C ≥ 70 mg/dL OR high risk for CVD and LDL-C ≥ 100 mg/dL
  - All patients uncontrolled on standard therapy
- Primary Endpoint:
  - Reduction of LDL-C at the end of 24 weeks
- Treatment Arms: (+ standard care)
  - Alirocumab 75 mg SQ every 2 weeks (n = 467)
    - May be increased to 150 mg SQ every 2 weeks if LDL at week 8 was > 70 mg/dL
  - Ezetimibe 10 mg PO daily (n = 240)

ODYSSEY COMBO II: Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LDL-C Reduction (%)</th>
<th>Mean Difference</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab 75 mg SQ</td>
<td>-38.7 ± 1.9</td>
<td>-34 to -43</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Ezetimibe 10 mg PO</td>
<td>-31.3 ± 2.0</td>
<td>-30 to -32</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

IMPROVE-IT: Results

- First Event
- Additional Events
### Dalcetrapib Clinical Data

<table>
<thead>
<tr>
<th>Trial Title</th>
<th>dal-OUTCOMES</th>
</tr>
</thead>
</table>
| Population  | Clinically stable adult patients, ≥45 years of age  
Recently hospitalized for ACS  
Receiving evidence-based medical and dietary management of dyslipidemia |
| Endpoint    | Time to first occurrence of any component of the composite cardiovascular event (cardiovascular mortality and morbidity) |
| Methods     | Randomized, double-blind, parallel assignment, phase III treatment study  
Patients received either Dalcetrapib 600mg QD or placebo |
| Results     | N=15,871  
HDL increased by 31-40% (Dalcetrapib) vs 4-11% (placebo)  
Did not reduce the risk of recurrent cardiovascular events |

### Evacetrapib Clinical Data

<table>
<thead>
<tr>
<th>Trial Title</th>
<th>ACCELERATE (Assessment of the Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at High-Risk for Vascular Outcomes)</th>
</tr>
</thead>
</table>
| Population  | Diagnosis of high risk vascular disease  
Must be treated with a statin for at least 30 days prior to screening  
LDL-C no more than 10 mg/dL above the target chosen by the investigator (100 mg/dL or 70 mg/dL) OR if LDL-C is greater than target must be on maximally tolerated statin |
| Endpoint    | Time to first occurrence of the composite endpoint of CV death, MI, stroke,  
coronary revascularization, or hospitalization for unstable angina |
| Methods     | Randomized, double-blind, parallel allocation, safety/efficacy phase III trial  
Patients receive either Evacetrapib 130mg PO daily or placebo for up to 4 yrs |
| Results     | Discontinuation of drug development due to lack of evidence |