Disclosures

• None.
Management of Hypercholesterolemia
PCSK9 inhibitors are approved for:

1. Statin intolerant patients
2. Patients with familial hypercholesterolemia
3. Patients with atherosclerotic heart disease on maximally tolerated dose of statins with insufficient LDL-C lowering.

A. All of the above
B. 1 only
C. 2 only
D. 2 and 3
True or False

PCSK9 inhibitors lower LDL-C, apolipoprotein B, and Lp(a).

A. True
B. False
An important addition to our current armamentarium

- Diet and Exercise
- Statins
- Cholesterol Absorption Inhibitor
- Bile Acid Sequestrants
- Niacin
- Microsomal Triglyceride Transfer Protein Inhibitor
- Oligonucleotide inhibitor of apo B-100
- LDL apheresis
- PCSK9 inhibitors
Proprotein convertase subtilisin/kexin 9

• PCSK9 is an enzyme that is encoded to the PCSK9 gene.
• It binds to the LDL receptor in the liver.
• When it binds to the LDLR, the receptor is broken down and can no longer remove LDL-C from the blood.
What does PCSK9 do?
PCSK9 inhibitors are monoclonal antibodies.
PCSK9 Inhibitors

• Are monoclonal antibodies
• Target and inactivate PCSK9 (proprotein convertase subtilisin kexin 9 in the liver)
• Dramatically decrease LDL-C
PCSK9 inhibitors prohibit binding to the LDLR
PCSK9 inhibitors dramatically lower LDL-C

PCSK9 inhibitors shown to lower LDL cholesterol 2 ways:

- **Acting Alone**
  - Lower LDL up to 50%

- **Acting together with statins**
  - Lower LDL up to 70%

Statins lower LDL-C

Statins are Current Treatment of Choice for High Cholesterol

- Lower LDL by 30% to 60%*
- Up to 30% fewer heart attacks**
- Up to 20% fewer strokes#

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**LDL-C Lowering with Statins**

<table>
<thead>
<tr>
<th>Statin</th>
<th>High-Intensity</th>
<th>Moderate-Intensity</th>
<th>Low-Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowers LDL &gt;50%</td>
<td>Lowers LDL 30% to 49%</td>
<td>Lowers LDL &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40 mg – 80 mg</td>
<td>10 mg – 20 mg</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>20 mg – 40 mg</td>
<td>5 mg – 10 mg</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td></td>
<td>40 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
<td>20 mg – 40 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td>40 mg – 80 mg</td>
<td>10 mg – 20 mg</td>
</tr>
<tr>
<td>Fluvastatin (XL)</td>
<td></td>
<td>80 mg</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td></td>
<td>40 mg (twice daily)</td>
<td>20 mg – 40 mg</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td></td>
<td>2 mg – 4 mg</td>
<td>1 mg</td>
</tr>
</tbody>
</table>

LDL = low-density lipoprotein.
PCSK9 Inhibitors

• Are monoclonal antibodies
• Target and inactivate PCSK9 (proprotein convertase subtilisin kexin 9 in the liver
• Dramatically decrease LDL-C
PCSK9 decreases LDLR and increases LDL-C

Absence of PCSK9
- More LDLR
- Lower plasma LDL-cholesterol

PCSK9 secretion

Presence of PCSK9
- Less LDLR
- Higher plasma LDL-cholesterol
How did all of this come about?

- PCSK9 found to cause FH by a gain-of-function mutation, resulting in increased serum LDL-C and expression of FH phenotype
- Hypothesis: if a gain-of-function mutation leads to an increased LDL-C, then will a loss-of-function mutation lead to a decrease in LDL-C?
- Epidemiologic analysis supports this hypothesis, with rates of CHD for populations of individuals that have loss-of-function mutations in PCSK9 being lower than that observed in the general public
African-Americans without PCSK9 mutation

African Americans with PCSK9 mutation

PCSK9 Mutations: Dallas Heart Study
Distribution of Plasma LDL (panel A) and incidence of coronary artery disease (panel B) among Black Subjects, according to the presence or absence of a PCSK9 allele.
What about individuals with little or no PCSK9?

• Question answered:
  • 32-year-old women with LDL-C of 14 mg/dl and complete loss-of-function of PCSK9
    – Healthy college graduate
    – Normal fertility and development
    – No history of cancer or neurocognitive issues
ODYSSEY LONG
TERM Design

- HeFH or High CV-risk patients
  On max-tolerated statin ± other lipid-lowering therapy
  LDL-C ≥1.81 mmol/L [70 mg/dL]

Assessments

- Double-blind treatment (18 months)
- Follow-up (3 weeks)
- Alirocumab 150 mg Q2W SC (single 1-mL injection using prefilled syringe for self-administration)
- Placebo Q2W SC

Primary efficacy endpoint
Pre-specified analysis
  Efficacy: All Patients To W52
  Safety: Baseline-W78 (all patients at least W52)
1° Efficacy Endpoint: LDL-C
## Cardiovascular Outcomes

<table>
<thead>
<tr>
<th>Cardiovascular adverse events of interest</th>
<th>no. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from coronary heart disease, including death from unknown cause</td>
<td>4 (0.3) 7 (0.9) 0.26</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>14 (0.9) 18 (2.3) 0.01</td>
</tr>
<tr>
<td>Fatal or nonfatal ischemic stroke</td>
<td>9 (0.6) 2 (0.3) 0.35</td>
</tr>
<tr>
<td>Unstable angina requiring hospitalization</td>
<td>0 1 (0.1) 0.34</td>
</tr>
<tr>
<td>Congestive heart failure requiring hospitalization</td>
<td>9 (0.6) 3 (0.4) 0.76</td>
</tr>
<tr>
<td>Ischemia-driven coronary revascularization procedure</td>
<td>48 (3.1) 24 (3.0) 1</td>
</tr>
<tr>
<td>Positively adjudicated cardiovascular events, including all cardiovascular adverse events listed above</td>
<td>72 (4.6) 40 (5.1) 0.68</td>
</tr>
<tr>
<td>Adjudicated major adverse cardiovascular events in post hoc analysis</td>
<td>27 (1.7) 26 (3.3) 0.02</td>
</tr>
<tr>
<td>Event</td>
<td>Alirocumab (N = 1559)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Summary of adverse events — no. of patients (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>1255 (81.0)</td>
</tr>
<tr>
<td><strong>Serious adverse event</strong></td>
<td>290 (18.7)</td>
</tr>
<tr>
<td>Adverse event leading to study-drug discontinuation</td>
<td>111 (7.2)</td>
</tr>
<tr>
<td>Adverse event leading to death</td>
<td>8 (0.5)</td>
</tr>
<tr>
<td><strong>Other adverse events of interest</strong></td>
<td></td>
</tr>
<tr>
<td>General allergic reaction — no. of patients (%)</td>
<td>156 (10.1)</td>
</tr>
<tr>
<td>Local injection-site reaction — no. of patients (%)</td>
<td>91 (5.9)</td>
</tr>
<tr>
<td><strong>Myalgia — no. of patients (%)</strong></td>
<td>84 (5.4)</td>
</tr>
<tr>
<td>Neurologic event — no. of patients (%)</td>
<td>65 (4.2)</td>
</tr>
<tr>
<td><strong>Neurocognitive disorder — no. of patients (%)¶</strong></td>
<td>18 (1.2)</td>
</tr>
<tr>
<td>Amnesia</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>4 (0.3)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>4 (0.3)</td>
</tr>
<tr>
<td>Ophthalmologic event — no. of patients (%)¶</td>
<td>45 (2.9)</td>
</tr>
<tr>
<td>Hemolytic anemia — no. of patients</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes in patients with no history of diabetes — no. of patients/total no. (%)**</td>
<td>18/994 (1.8)</td>
</tr>
<tr>
<td>Worsening of diabetes in patients with history of diabetes — no. of patients/total no. (%)**</td>
<td>72/556 (12.9)</td>
</tr>
<tr>
<td><strong>Laboratory values of interest — no. of patients/total no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase &gt;3× ULN</td>
<td>28/1533 (1.8)</td>
</tr>
<tr>
<td>Aspartate aminotransferase &gt;3× ULN</td>
<td>22/1533 (1.4)</td>
</tr>
<tr>
<td>Creatine kinase &gt;3× ULN</td>
<td>56/1507 (3.7)</td>
</tr>
</tbody>
</table>
ODYSSEY – Long Term Adverse Effects

- Serious adverse events balanced between active and placebo arms of this double blind study
- Fewer nonfatal MIs and CV events in those treated alirocumab
- Incidence of myalgias and local injection site reactions were higher in alirocumab versus the placebo arm.
- Lab abnormalities relative to liver or renal were balanced between the two arms.
Summary

• **ODYSSEY LONG TERM Study of Alirocumab:**
  - Enrolled high-risk participants in a double-blind, RCT
  - Essentially all participants were on statin therapy at baseline

• **Conclusions:**
  - **Exciting**
    - Robust reductions in LDL-C and other lipids like Lp(a) out to 18 months
    - Signal for reduced cardiovascular events
  - **Concerning**
    - Signal for adverse neurocognitive effects (though not associated with LDL-C levels)
ODYSSEY – Long Term Adverse Effects

- Serious adverse events balanced between active and placebo arms of this double blind study
- Fewer nonfatal MIs and CV events in those treated alirocumab
- Incidence of myalgias and local injection site reactions were higher in alirocumab versus the placebo arm.
- Lab abnormalities relative to liver or renal were balanced between the two arms.
OSLER program- Longer term effects of evolocumab

- Studied subjects with LDL-C <25mg/dl, <50 mg/dl, and >50 mg/dl
- No significant differences in adverse effects among the 3 groups
- Neurocognitive events – more frequent with evolocumab subjects
  - No correlation between neurocognitive events and degree of LDL-C reduction
  - Lipoproteins and monoclonal antibodies don’t cross blood-brain barrier, therefore difficult to find a mechanism to explain.
  - Open label design of the study and fact that subjects had more visits provided more opportunities to mention a neurocognitive event, particularly in the treatment group.
OSLER Program

4465 patients (74%) elected to enroll into OSLER extension study program. 1324 from Ph2 trials into OSLER-1. 3141 from Ph3 trials into OSLER-2.

Randomized 2:1

Evolocumab plus standard of care (n=2976)

Standard of care alone (n=1499)

Eligible if medically stable and on study drug
Methods

- **Intervention**
  - Open-label evolucumab via subcutaneous injections
  - Dosed either 140 mg q 2 wk or 420 mg q month

- **Endpoints**
  - Adverse events (primary)
  - LDL-cholesterol (secondary)
  - Cardiovascular (CV) clinical outcomes (prespecified, exploratory):
    - Death
    - Coronary: MI, UA requiring hospitalization, revascularization
    - Cerebrovascular: stroke or TIA
    - HF requiring hospitalization

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>58 (11)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>51</td>
</tr>
<tr>
<td>Cardiovascular risk factor (%)</td>
<td>80</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>34</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>15</td>
</tr>
<tr>
<td>Family hx of premature CAD</td>
<td>24</td>
</tr>
<tr>
<td>Known familial hyperchol.</td>
<td>10</td>
</tr>
<tr>
<td><strong>Known vascular disease (%)</strong></td>
<td><strong>25</strong></td>
</tr>
<tr>
<td>Coronary</td>
<td>20</td>
</tr>
<tr>
<td>Cerebrovascular or Peripheral</td>
<td>9</td>
</tr>
</tbody>
</table>
LDL-C

Standard of care alone

61% reduction (95%CI 59-63%), P<0.0001

Absolute reduction: 73 mg/dL (95%CI 71-76%)

Evolocumab plus standard of care

Median LDL-C (mg/dL)

Baseline (Parent study) N=465
4 weeks (OSLER) N=1258
12 weeks N=4259
24 weeks N=4204
36 weeks N=1243
48 weeks N=3727
Cardiovascular Outcomes

Composite Endpoint: Death, MI, UA → hosp, coronary revasc, stroke, TIA, or CHF → hosp

HR 0.47
95% CI 0.28-0.78
P=0.003

Standard of care alone (N=1489)

Evolocumab plus standard of care (N=2976)

Cumulative Incidence (%)
# Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events (%)</th>
<th>&lt;25 mg/dL (n=773)</th>
<th>25 to &lt;40 mg/dL (n=759)</th>
<th>&lt;40 mg/dL (n=1532)</th>
<th>≥40 mg/dL (n=1426)</th>
<th>All Evolocumab (n=2976)</th>
<th>Std of Care Alone (n=1469)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>70.0</td>
<td>68.1</td>
<td>69.1</td>
<td>70.1</td>
<td>69.2</td>
<td>64.8</td>
</tr>
<tr>
<td>Serious</td>
<td>7.6</td>
<td>6.9</td>
<td>7.2</td>
<td>7.8</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>4.9</td>
<td>7.1</td>
<td>6.0</td>
<td>6.9</td>
<td>6.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>0.5</td>
<td>1.2</td>
<td>0.8</td>
<td>1.0</td>
<td>0.9</td>
<td>0.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab results (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/AST &gt;3×ULN</td>
<td>0.9</td>
<td>0.8</td>
<td>0.8</td>
<td>1.3</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>CK &gt;5×ULN</td>
<td>0.4</td>
<td>0.9</td>
<td>0.7</td>
<td>0.5</td>
<td>0.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Neurocognitive Events

• Incidence slightly higher with alirocumab
  – Alirocumab: 1.2% vs. 0.5% (placebo)
  – Evolocumab: 0.9% vs. 0.3% (placebo)

• Good assessment of neurocognitive effects won’t happen until the very large outcome studies are completed
Fourier Study

- Fourier study to be completed in 2018, will provide the long term cardiovascular outcomes of PCSK9 inhibitors.

- 22,500 patient trial evaluating evolocumab versus statin therapy in high-risk patients.

- Composite endpoint of cardiovascular death, myocardial infarction, and hospitalization for revascularization, unstable angina, or stroke.
Additional Long Term Studies

• ODYSSEY OUTCOMES Trial with alirocumab

• The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High-Risk Subjects (SPIRE-1) and SPIRE-2 for bococizumab

• Will provide further insight into cardiovascular outcomes.
Advantages of PCSK9 Use

- Monoclonal antibodies have high specificity and affinity
- Reduce free PCSK9 to extremely low levels within hours
- Have a synergistic effect with statins
  - Statins upregulate LDLR activity, but also upregulate the production of PCSK9
  - PCSK9 inhibitors negate this effect
- Monoclonal antibodies circulate throughout the body for many days or weeks, making it possible to administer the PCSK9 inhibitor on a biweekly or monthly basis
Advantages of PCSK9 inhibitors

• Elimination of mAbs occurs via an antigen-specific targeted disposition or via the reticuloendothelial system
  – No elimination via liver or kidney
• Lowers lipoprotein (a) (Lp(a))
Apolipoprotein B and Lp(a) Lowering

Effect of PCSK9 Monoclonal Antibodies on ApoB and Lp(a)

- ApoB
  - Arilocumab
  - Evolocumab

- Lp(a)
  - Arilocumab
  - Evolocumab

Change From Baseline at week 12, %

- Placebo
- 300 mg Q4W
- 350 mg Q4W
- 150 mg Q2W
- 420 mg Q4W

P < .001 vs placebo

References:
Potential Disadvantages of Use

- Increased cost, due to complex and expensive manufacturing process
- Concerns over using parenteral vs. oral therapy
- Modest effects on HDL and triglycerides
- Long term effects on cardiovascular outcomes are yet unknown
Effects of Drug in Specific Populations

- Heterozygous familial hypercholesterolemia (HeFH)
- Homozygous familial hypercholesterolemia (HoFH)
- Statin Intolerant
Additional Issues regarding Safety and Tolerability of PCSK9 Inhibitors

• Immunogenecity
  – Direct immunogenecity does not occur as mAbs for PCSK9 are very specific and have no direct immune effects
  – Development of antidrug antibodies

• Possible adverse effects of very low LDL-C
FDA Approved Indications

Alirocumab – 7/24/15
Approved for use in addition to diet and maximally tolerated statin therapy in adult patients with HeFH or patients with clinical atherosclerotic disease, such as heart attacks or strokes, who require additional LDL lowering

Evolocumab – 8/27/15
Approved for use in addition to diet and maximally tolerated statin therapy in adult patients with HeFH, HoFH, or patients with clinical atherosclerotic disease, such as heart attacks or strokes, who require additional LDL lowering
Praluent
Repatha
Comparisons of the 2 Approved Medications

Repatha

Praluent
Repatha® (evolocumab) Pushtronex™ system
(on-body infusor with prefilled cartridge)
71 Million Americans have high cholesterol\(^1\)

11 Million Americans uncontrolled on cholesterol therapy may be targeted\(^1\)

- Statin intolerant
- Genetic disorder (FH)
- Uncontrolled on statins

1-2 Million\(^2\) Potential Targeted PCSK9 inhibitor population in U.S.
Not always an easy task!
Be certain to include in your progress notes
Preauthorization

• Provide complete documentation of:
  – Diagnoses
  – LDL-C levels after treatment with lipid-lowering therapies
  – Trial of high intensity statin therapy
  – Documentation that patient will continue to receive maximum dose of statin while taking the PCSK9 inhibitor
  – All prescribed statins and dosing levels
Preauthorization

• Statin intolerance
  – Muscle related symptoms
  – CK levels
  – Symptoms while on separate trials of atorvastatin and rosuvastatin
  – Resolution of symptoms with discontinuance of each respective statin
Expensive – explore assistance options with patients
Cost of Treatment

Average Annual Cost of Therapy
Costs could soar with widespread use of PCSK9 Inhibitors

Statins
$186

PCSK9 Inhibitors
Praluent™
$14,600
+7,700%

Utilize supports to keep patients on track
Such as...

• Refill reminders
• Text messages
• Follow up phone calls
• If possible, enlist your specialty pharmacy
A common question from patients: how low is too low?
Additional patient questions

- Duration of therapy?
- Can other lipid-lowering meds be discontinued?
- What if I forget to take my medication?
- What should I do if I leave my injector pen out of the refrigerator for a whole day?
- What about pregnancy and breastfeeding?
- May other mAbs be used?
In a Nutshell...
PCSK9 inhibitors are approved for:

1. Statin intolerant patients
2. Patients with familial hypercholesterolemia
3. Patients with atherosclerotic heart disease on maximally tolerated dose of statins with insufficient LDL-C lowering.

A. All of the above
B. 1 only
C. 2 only
D. 2 and 3
True or False

PCSK9 inhibitors lower LDL-C, apolipoprotein B, and Lp(a).

A. True
B. False