PCSK9 Inhibitors

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Disclosures

I have no relevant disclosures.
Objectives

• Review the mechanism of action of PCSK9 inhibitors (PCSK9i)
• Discuss results from the PCSK9i outcome trials
• Understand the role of PCSK9i in current guidelines
**PCSK9 inhibitors**

**Overview + Approved Indications**

- **Alirocumab (Praluent)** – approved July 2015
  - FDA approved for: Heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) requiring additional LDL lowering
  - Doses: 75mg Q2 weeks, 150mg Q2 weeks, 300mg Qmonth

- **Evolocumab (Repatha)** – approved August 2015
  - FDA approvals:
    - Reduce the risk of MI, stroke, and coronary revascularization in adults with established cardiovascular disease
    - Primary hyperlipidemia (including HeFH) to reduce LDL
    - Homozygous FH (HoFH) requiring additional LDL lowering
  - Doses: 140mg Q2 weeks, 420mg Qmonth

Mechanism of Action

LDL
LDL-R
+PCSK9i

Hepatocyte

PCSK9

Outcome Trials

FOURIER, ODYSSEY OUTCOMES, SPIRE
Evolocumab

**FOURIER**

- Multinational, multicenter, randomized, double-blind, placebo controlled trial
  - Average follow up of 25 months
- Inclusion criteria
  - At least one of: MI, non-hemorrhagic stroke, symptomatic PAD
  - 1 major or 2 minor risk factors
    - Major: DM, age >65yo, MI or non-hemorrhagic stroke within 6 months, recurrent MI or non-hemorrhagic stroke, current daily smoker, h/o PAD
    - Minor: h/o non-MI related coronary revascularization, residual CAD (stenosis > 40% in ≥2 large vessels), most recent HDL <40 for men or <50 for women, most recent hs-CRP >2, most recent LDL >130 or >70 after two weeks of lipid lowering therapy, presence of metabolic syndrome, most recent TG <400
- Notable exclusion: NYHA class III or IV heart failure or LVEF <30%

Evolocumab

FOURIER

- Primary outcome: major CV events (CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization)
- \( N = 27,564 \)
  - Average age 63
  - 75.4% male
  - 85% white
- Type of atherosclerosis at study entry
  - MI 81.1%, stroke 19.4%, PAD 13.2%
- At study entry:
  - 69.3% high intensity statin and 30.4% moderate intensity statin
  - 5.2% ezetimibe

<table>
<thead>
<tr>
<th>Average Baseline Lipid Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
</tr>
<tr>
<td>TG</td>
</tr>
<tr>
<td>HDL</td>
</tr>
<tr>
<td>LDL</td>
</tr>
<tr>
<td>Lp(a)</td>
</tr>
</tbody>
</table>
# Evolocumab

## FOURIER - Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Evolocumab N = 13,784</th>
<th>Placebo N = 13,780</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>1344 (9.8%)</td>
<td>1563 (11.3%)</td>
<td>0.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death, MI, stroke</td>
<td>816 (5.9%)</td>
<td>1013 (7.4%)</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>251 (1.8%)</td>
<td>240 (1.7%)</td>
<td>1.05</td>
<td>0.62</td>
</tr>
<tr>
<td>All cause death</td>
<td>444 (3.2%)</td>
<td>426 (3.1%)</td>
<td>1.04</td>
<td>0.54</td>
</tr>
<tr>
<td>MI</td>
<td>468 (3.4%)</td>
<td>639 (4.6%)</td>
<td>0.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>207 (1.5%)</td>
<td>262 (1.9%)</td>
<td>0.79</td>
<td>0.01</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>759 (5.5%)</td>
<td>965 (7.0%)</td>
<td>0.78</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Evolocumab

FOURIER - Conclusions

- Limitations:
  - Outcomes study with median follow up of 26 months
  - Most patients on high intensity statin
  - Study population relatively young, and predominantly male and Caucasian
  - Overall low CV mortality rates (<2%)
  - Benefit driven by prevention of non-fatal events

- Conclusions:
  - Reduced primary composite and key secondary composite endpoint
  - Kaplan-Meier curves diverge at ~6 months, with difference increasing with time
  - Results consistent across subgroups and baseline LDL
  - Again demonstrated trend that lower LDL results in better outcomes
  - NNT: 74 patients for 2 years to prevent a CV death, MI, or stroke

**ODYSSEY OUTCOMES**

- Multinational, multicenter, randomized, double-blind, placebo controlled trial
  - Study period November 2012 – November 2017
  - Average follow up of 2.8 years
- Inclusion criteria
  - Age >40
  - Acute MI or unstable angina within 1-12 months prior to randomization
  - High intensity statin therapy or documented intolerance to statins
    - All patients had a 2-16 week run in period of high intensity statin
    - LDL $>$ 70mg/dL, non-HDL $>$ 100mg/dL, or apo B $>$ 80mg/dL
- Notable exclusion: NYHA class III or IV heart failure or LVEF <25%

ODYSSEY OUTCOMES

- Primary outcome: occurrence of cardiovascular events (composite of CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization) in patients with ACS 4 to 52 weeks prior to entry
  - N = 18,924
  - Average age 58
  - 74.8% male
  - Average time to randomization 2.6 months
- Patient history:
  - Prior MI 19.2%
  - ACS type (NSTEMI 48.5%, STEMI 34.6%, unstable angina 16.9%)
  - Revascularization for index ACS 72.3%
- At study entry: 88.9% high intensity statin, ezetimibe 2.9%


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<td>HDL</td>
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<tr>
<td>LDL</td>
</tr>
</tbody>
</table>
### Alirocumab

**ODYSSEY OUTCOMES - Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alirocumab N = 9,462</th>
<th>Placebo N = 9,462</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>903 (9.5%)</td>
<td>1052 (11.1%)</td>
<td>0.85</td>
<td>0.0003</td>
</tr>
<tr>
<td>CHD death</td>
<td>205 (2.2%)</td>
<td>222 (2.3%)</td>
<td>0.92</td>
<td>0.38</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>626 (6.6%)</td>
<td>722 (7.6%)</td>
<td>0.86</td>
<td>0.006</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>111 (1.2%)</td>
<td>152 (1.6%)</td>
<td>0.73</td>
<td>0.01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>37 (0.4%)</td>
<td>60 (0.6%)</td>
<td>0.61</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Intent to treat

Schwartz GG, et al. ACC.18
## Alirocumab

**ODYSSEY OUTCOMES – Secondary Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alirocumab N = 9,462</th>
<th>Placebo N = 9,462</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD event</td>
<td>1199 (12.7%)</td>
<td>1349 (14.3%)</td>
<td>0.88</td>
<td>0.001</td>
</tr>
<tr>
<td>Major CHD event</td>
<td>793 (8.4%)</td>
<td>899 (9.5%)</td>
<td>0.88</td>
<td>0.006</td>
</tr>
<tr>
<td>CV event</td>
<td>1310 (13.7%)</td>
<td>1474 (15.6%)</td>
<td>0.87</td>
<td>0.0003</td>
</tr>
<tr>
<td>Death, MI, ischemic stroke</td>
<td>973 (10.3%)</td>
<td>1126 (11.9%)</td>
<td>0.86</td>
<td>0.0003</td>
</tr>
<tr>
<td>CHD death</td>
<td>205 (2.2%)</td>
<td>222 (2.3%)</td>
<td>0.92</td>
<td>0.38</td>
</tr>
<tr>
<td>CV death</td>
<td>240 (2.5%)</td>
<td>271 (2.9%)</td>
<td>0.88</td>
<td>0.15</td>
</tr>
<tr>
<td>All cause death</td>
<td>334 (3.5%)</td>
<td>392 (4.1%)</td>
<td>0.85</td>
<td>0.026*</td>
</tr>
</tbody>
</table>

*observational

Schwartz GG, et al. ACC.18
Alirocumab

**ODYSSEY OUTCOMES**

- **Limitations:**
  - Most patients on high intensity statin
  - Large proportion of men and Caucasians
  - Relatively young average age
  - Benefit driven by prevention of non-fatal events

- **Conclusions:**
  - Large portion of benefit in the group with baseline LDL >100mg/dL
  - Benefit in year one increases beyond year one
  - Results consistent across subgroups
  - NNT: 64, but for patients with LDL >100mg/dL, NNT = 29

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Bococizumab

SPIRE

• 27,438 patients in total received bococizumab
• SPIRE-1
  • Baseline LDL >70mg/dL
  • Median follow up 7 months
  • Major cardiovascular events: HR 0.99, p 0.94
• SPIRE-2
  • Baseline LDL >100mg/dL
  • Median follow up 12 months
  • Major cardiovascular events: HR 0.79, p 0.02
• Combined HR 0.88 with p 0.08
• Ultimately trials stopped due to neutralizing antibodies

Study Comparison

<table>
<thead>
<tr>
<th></th>
<th>FOURIER</th>
<th>ODYSSEY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Population</td>
<td>Established ASCVD or significant risk</td>
<td>Post- ACS</td>
</tr>
<tr>
<td>Median Follow Up</td>
<td>~ 26 months</td>
<td>~ 34 months</td>
</tr>
<tr>
<td>LDL Reduction</td>
<td>Maintained</td>
<td>Slight attenuation</td>
</tr>
<tr>
<td>NNT</td>
<td>74</td>
<td>64 (29 if LDL &gt;100mg/dL)</td>
</tr>
</tbody>
</table>

Overall (both studies):
- Younger, male, Caucasian patients
  - Are results generalizable?
- Benefit driven by reduction in nonfatal events
- No safety issues
- RRR improves with time
**PCSK9 inhibitors**

*Place in Therapy – 2017 ACC Focused Update*

- Consider addition of PCSK9 to maximally tolerated* statin therapy for patients above LDL targets with:
  - Clinical ASCVD
    - No comorbidities – after trial of ezetimibe (add or replace)
    - With comorbidities – option as second agent
  - H/o LDL >190 – option as second agent
  - Not recommended in diabetic patients or patients 40-75yo with or without high risk features
- Not approved for use in pregnancy/lactation

*maximally tolerated may be none!"
Questions?