The Value of PCSK9 Inhibitors: A Matter of Perspective

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Learning Objectives

1. Summarize the epidemiology and pathophysiology of atherosclerotic cardiovascular disease (ASCVD)
2. Summarize recommendations for prevention of ASCVD
3. Review the PCSK9 inhibitor drug class, including relevant clinical and economic analyses
4. Identify appropriate patient population for PCSK9 inhibitor use
Cardiovascular Disease & Hyperlipidemia

1. Atherosclerotic Cardiovascular disease (ASCVD)
   a. American College of Cardiology/American Heart Association (ACC/AHA) definitions include:
      i. Myocardial infarction (MI)
      ii. Coronary heart disease (CHD)
      iii. Unstable angina
   b. Overall death rate attributable to ASCVD
      i. 230 deaths/100,000 Americans per year
      ii. More than 2,150 Americans die of ASCVD each day; 1 death every 40 seconds
      iii. 34% of ASCVD-associated deaths occur before age of 75 years
   c. Costs of ASCVD
      i. Estimated annual costs for ASCVD (2011)—$320.1 billion
      ii. Projected to increase to more than $818 billion annually by 2030
      iii. Average hospital charge (in 2012)
         1. Cardiac/vascular surgery—$78,897
         2. Cardiac revascularization—$149,480
         3. Percutaneous intervention—$70,027

<table>
<thead>
<tr>
<th>Table 1: Risk factors of ASCVD²</th>
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<tbody>
<tr>
<td>Modifiable</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30 kg/m²)</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hyperlipidemia</td>
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</tbody>
</table>

2. Hyperlipidemia (HLD)
   a. Cholesterol is an essential component of life
      i. Building block of cell membranes
      ii. Component of steroid hormone synthesis
      iii. Required for production of bile acids
   b. Role in ASCVD
      i. Circulating cholesterol penetrates and accumulates in arterial walls
         1. Initiates inflammatory response
         2. Enhances foam cell/plaque formation leading to partial or complete occlusion
      ii. Atherosclerosis increases risk of CHD, stroke, and peripheral vascular disease
   c. Lipids transported throughout body as complexes with proteins
      i. Low-density lipoproteins (LDL)
         1. Elevated levels are associated with increased risk of CVD
         2. Taken up by liver via membrane LDL-receptors
         3. LDL particle size influences atherogenic potential
      ii. High-density lipoproteins (HDL)
         1. Removes cholesterol from peripheral tissue and transports to liver for excretion
         2. Low serum concentrations associated with increased risk of CVD events
      iii. Triglycerides (TGs)
         1. Serum levels strongly influenced by recent dietary intake
         2. Unclear role in ASCVD development
Hyperlipidemia (HLD) continued

d. Familial Hypercholesterolemia (FH)
   i. Genetic defects that result in hypercholesterolemia
      1. Autosomal dominant inheritance pattern
      2. Most mutations occur in the LDL-receptor gene—on chromosome 19
      3. Mutations to Apolipoprotein B (ApoB) account for ~5% of FH cases
      4. Mutations to proprotein convertase subtilisin type-9 (PCSK9) account for ~1% of FH cases

   ii. Heterozygous FH (HeFH)
      1. Associated with LDL levels 250-350 mg/dL
      2. ~1:500 people globally; 500,000-1,300,000 cases in US
      3. Severe HeFH associated with significantly increased risk of CVD

   iii. Homozygous FH (HoFH)
      1. Associated with LDL levels >500 mg/dL
      2. ~1:1,000,000 people globally; 300-500 diagnosed cases in US
      3. High levels of plasma cholesterol often prevalent at birth
      4. Untreated patients often experience first major CV event during adolescence

iv. Clinical presentation
   1. Strong family history of elevated cholesterol levels or early cardiovascular events
   2. Cholesterol levels resistant to treatment in parent(s)
   3. Xanthomas—cholesterol deposits in skin or tendons
   4. Xanthelasmas—cholesterol deposits in the eyelids
   5. Elevated levels of inflammatory markers reflect early atherogenesis
   6. Coronary calcification significantly more prominent in adolescents with FH
Hyperlipidemia (HLD) continued

e. Supplemental predictors of CV risk \(^{6,14-16}\)

i. Apolipoprotein-B (ApoB)
   1. Primary protein component of non-HDL
   2. Necessary for lipid transport and LDL uptake
   3. Elevated levels associated with increased risk of ASCVD

ii. High-sensitivity C-reactive protein (hs-CRP)
   1. Acute phase reactant used to measure inflammation
   2. Elevated levels considered predictive of future CVD event risk

iii. Lipoprotein(a)
   1. Lipoprotein(a) transports lipids and reduces fibrinolysis
   2. Has structural similarities to plasminogen
   3. Levels are genetically determined and remain relatively constant

iv. Lipoprotein-associated phospholipase A\(_2\)
   1. An inflammatory enzyme associated with atherosclerosis
   2. Elevated levels shown to double risk of CV events
   3. Higher predictive value when elevated in concert with hs-CRP

v. Coronary calcium score
   1. Calcium deposits in arterial walls as response to inflammation
   2. Calcification stiffens arterial walls and reduces elasticity
   3. Significantly more prominent in adolescents with FH than those without

Fig. 2—AHA FH Diagnosis

<table>
<thead>
<tr>
<th>HeFH</th>
<th>HoFH</th>
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<tbody>
<tr>
<td>Children:</td>
<td>All:</td>
</tr>
<tr>
<td>- [LDL] &gt;160 mg/dL</td>
<td>- [LDL] &gt;400 mg/dL</td>
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<tr>
<td>Adults</td>
<td></td>
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<tr>
<td>- [LDL] &gt;190 mg/dL (adult)</td>
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<tr>
<td>Plus one of:</td>
<td></td>
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<tr>
<td>- 1st degree relative with early CHD</td>
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<tr>
<td>- 1st degree relative &quot;similarly affected&quot;</td>
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<tr>
<td>- Positive finding of genetic defect</td>
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</tbody>
</table>

Fig. 3—Treatment options for HLD

<table>
<thead>
<tr>
<th>Statins</th>
<th>Niemann-Pick Inhibitor</th>
<th>PCSK9 Inhibitors</th>
<th>Fibric Acids</th>
</tr>
</thead>
</table>
| • Atorvastatin  
• Fluvastatin  
• Lovastatin  
• Pravastatin  
• Rosuvastatin  
• Simvastatin | • Ezetimibe | • Alirocumab  
• Evolocumab | • Fenofibrate  
• Gemfibrozil |
3. Controversies surrounding lipid goals
   a. ACC/AHA—treatment-driven guidelines$^{18,19}$
      i. 4S—simvastatin reduces all-cause mortality in patients with prior MI and hyperlipidemia
      ii. WOSCOPS—pravastatin reduced incidence of MI and death in patients with moderate hyperlipidemia and no history of CVD
   b. NLA—LDL goal-driven guidelines$^{20}$
      i. PROVE IT-TIMI 22—Higher dose statin resulted in LDL <70 mg/dL and better outcomes
   c. Dearth of studies comparing treatment and goal-driven approaches

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Fig. 4—American College of Cardiology/American Heart Association guidelines for the use of statin therapy in at-risk patients$^{17}$

Fig. 5—National Lipid Association guidelines for management of hyperlipidemia$^{2}$

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Criteria</th>
<th>Treatment goal</th>
<th>Consider drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0–1 major ASCVD risk factors</td>
<td>&lt;130</td>
<td>≥190</td>
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<tr>
<td></td>
<td>Consider other risk indicators, if known</td>
<td>&lt;100</td>
<td>≥160</td>
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<tr>
<td>Moderate</td>
<td>2 major ASCVD risk factors</td>
<td>&lt;130</td>
<td>≥160</td>
</tr>
<tr>
<td></td>
<td>Consider quantitative risk scoring</td>
<td>&lt;100</td>
<td>≥130</td>
</tr>
<tr>
<td></td>
<td>Consider other risk indicators$^*$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>≥3 major ASCVD risk factors</td>
<td>&lt;130</td>
<td>≥130</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus (type 1 or 2)$^1$</td>
<td>&lt;100</td>
<td>≥100</td>
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<tr>
<td></td>
<td>o 0–1 other major ASCVD risk factors and</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>o No evidence of end-organ damage</td>
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<tr>
<td></td>
<td>Chronic kidney disease stage 3B or 4$^2$</td>
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<td></td>
<td>LDL-C of ≥190 mg/dL (severe hypercholesterolemia)$^6$</td>
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<tr>
<td></td>
<td>Quantitative risk score reaching the high-risk threshold$^5$</td>
<td></td>
<td></td>
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<tr>
<td>Very high</td>
<td>ASCVD</td>
<td>&lt;100</td>
<td>≥100</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus (type 1 or 2)$^1$</td>
<td>&lt;70</td>
<td>≥70</td>
</tr>
<tr>
<td></td>
<td>o ≥2 other major ASCVD risk factors or</td>
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<tr>
<td></td>
<td>o Evidence of end-organ damage$^8$</td>
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</tbody>
</table>

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.
**Objective**
- To identify whether additional LDL-lowering adding ezetimibe to statin therapy is clinically beneficial

**Design**
- Multicenter, double-blind, randomized controlled trial
- n=18,144
- Median follow-up: 6 years

**Inclusion Criteria**
- Age ≥50 years
- Recent hospitalization for ACS
- LDL-C ≥50 mg/dL

**Exclusion Criteria**
- Stroke or TIA
- Use of statin more potent than simvastatin 40 mg
- Untreated LDL ≥125 mg/dL, treated LDL ≥100 mg/dL
- Planned CABG for ACS event

**Primary Outcome**
- Composite of: CV mortality, major CV event, or nonfatal stroke

**Interventions**
- Simvastatin 40 mg + ezetimibe 10 mg daily, or
- Simvastatin 40 mg + placebo daily

**Results**

**Primary outcome:**
- Composite of CV mortality, major CV event, or nonfatal stroke: 32.7% vs. 34.7% [HR 0.94; CI 0.89-0.99; p=0.016]

**Secondary outcomes:**
- Composite of all-cause mortality, major CV event, or nonfatal stroke: 38.7% vs. 40.3% [HR 0.95; CI 0.9-1.0; p=0.03]
- Composite of CV mortality, nonfatal MI, urgent revascularization: 17.5% vs. 18.9% [HR 0.91; CI 0.85-0.98; p=0.02]
- All-cause mortality: 15.3% vs. 15.4% [HR 0.99; CI 0.91-1.07; p=0.78]
- Mortality from CV causes, MI, or stroke: 20.4% vs. 22.2% [HR 0.84; CI 0.8-0.96; p=0.003]
- Stroke: 4.2% vs. 4.8% [HR 0.86; CI 0.73-1.0; p=0.05]
- MI: 13.1% vs. 14.8% [HR 0.87; CI 0.8-0.95; p=0.002]
- LDL at 1-year follow-up: 53.2 vs. 69.9 mg/dL (p<0.001)

**Safety**
- No difference in pre-specified safety endpoints

**Author’s Conclusion(s)**
- Lipid-lowering therapy with ezetimibe plus simvastatin improved clinical outcomes, supporting intensive lipid-lowering therapy after an initial CV event.

**Reviewer Critique**
- Use of moderate-intensity statin in high-risk population is not standard of care
- Lower serum LDL associated with significant decreases in MI, stroke, and CV-related mortality
- Establishes a role for addition of non-statin therapy in high-risk patients
Proprotein Convertase Subtilisin/Kexin Type-9 (PCSK9)

4. Physiologic function of PCSK9
   a. Degrades hepatic LDL receptors
   b. Fewer LDL receptors results in higher serum LDL concentrations
   c. Sterol receptor element binding proteins (SREBP-2s) regulate PCSK9 and LDL-receptor production
   d. Statins induce production of PCSK9
   e. PCSK9 function can be inhibited with monoclonal antibodies (mAbs)
      i. Bind the epidermal growth factor-like A (EGF-A) domain
      ii. EGF-A is the catalytic domain where PCSK9 binds and initiates LDL-R degradation

   Fig. 6—The role of PCSK9 in lipid metabolism

5. PCSK9 role in CVD
   a. Gain-of-function (GOF) mutations to PCSK9 promote LDL-receptor degradation and result in high serum LDL concentrations, early stroke and MI
   i. Three generations of French family with GOF mutation had serum LDL concentrations of 466 mg/dL
   b. Loss-of-function (LOF) mutations to PCSK9 inhibit LDL-receptor breakdown and result in low serum LDL concentrations
   i. Two women with LOF mutations resulted in serum LDL concentrations measured ~15 mg/dL
   ii. Increased rates of LOF mutations in blacks found to result in 28% lower serum LDL concentrations and nearly 90% lower risk of CAD

6. PCSK9 Inhibitors
   a. Alirocumab (Praluent®) [Regeneron/Sanofi]—fully human mAb approved July 24th, 2015
      i. 75 mg, 150 mg sq injection every 2 weeks
      ii. AWP ~$14,600/year
   b. Evolocumab (Repatha™) [Amgen]—fully human mAb approved August 27th, 2015
      i. 140 mg sq injection every 2 weeks, or 420 mg sq injection every 4 weeks
      ii. AWP ~$14,100/year
   c. Investigational
      i. RN316 (bococizumab) [Pfizer]—humanized mAb
      ii. LY3015014 [Eli Lilly]—fully human mAb
Fig. 7—Timeline of PCSK9 inhibitor discovery and development

Gearing ME. A potential new weapon against heart disease: PCSK9 inhibitors. Harvard University. 2015.

7. Current litigation
   a. Amgen contends Regeneron/Sanofi infringed on evolocumab patents
   b. Regeneron/Sanofi argue the patents were invalid
   c. US courts ruled in favor of Amgen in March
   d. Praluent™ may be taken off the market

8. FDA approved indications
   a. Additional lowering of LDL in patients unable to control serum levels with current treatment options
   b. As an adjunct to diet and maximally-tolerated statin therapy in select patient groups

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adjunctive therapy for HeFH</th>
<th>Adjunctive therapy for HoFH</th>
<th>Adjunctive therapy in patients w/ clinical ASCVD requiring additional LDL-lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>√</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

9. Safety
   a. Adverse effects:
      i. Diarrhea, increased serum transaminases, injection-site reactions, hypersensitivity reactions, infection, myalgia
      ii. Neurocognitive impairment
         1. 2nd most common patient-reported adverse effect of statins
         2. Mechanism of development is unclear, or even related to cholesterol levels
            a. Decreased rates of neuronal re-myelination due to decreased cholesterol
            b. Decreased cholesterol delivery to neurons causing impaired synaptic firing
         3. FDA has mandated further assessment in phase IV studies
### Preliminary Outcomes

<table>
<thead>
<tr>
<th>Title</th>
<th>OLYSSEY LONG TERM&lt;sup&gt;27&lt;/sup&gt;</th>
<th>OSLER&lt;sup&gt;28&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>• To obtain longer-term data on alirocumab’s safety and LDL cholesterol reduction</td>
<td>• To obtain longer-term data on evolocumab’s safety, side-effect profile, and LDL cholesterol reduction</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>• Multicenter, double-blind, parallel-group, randomized, controlled trial</td>
<td>• Two open-label, randomized, controlled trials</td>
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<tr>
<td></td>
<td>• n=2,310</td>
<td>o OSLER-1: Phase II</td>
</tr>
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<td></td>
<td>• ITT analysis</td>
<td>o OSLER-2: Phase III</td>
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<td></td>
<td></td>
<td>• Each trial composed of 5-7 smaller trials</td>
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<tr>
<td></td>
<td></td>
<td>• n=4,465</td>
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<tr>
<td><strong>Inclusion Criteria</strong></td>
<td>• ≥ 18 years</td>
<td>• 18-80 years</td>
</tr>
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<td></td>
<td>• High risk for cardiovascular event:</td>
<td>• High risk of cardiovascular event</td>
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<tr>
<td></td>
<td>o HeFH</td>
<td>• LDL 75-189 mg/dL</td>
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<td></td>
<td>o CHD or risk equivalent</td>
<td>• Stable on statin therapy ≥4 weeks</td>
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<td>• LDL-C ≥70 mg/dL</td>
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<td>• Receiving high-dose statin therapy or max tolerated ≥4 weeks</td>
<td></td>
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<tr>
<td><strong>Exclusion Criteria</strong></td>
<td>• LDL &lt;70 mg/dL or TG &gt;400 mg/dL</td>
<td>• Clinical diagnosis of HoFH</td>
</tr>
<tr>
<td></td>
<td>• Recent or future plasma exchange</td>
<td>• Liproprotein apheresis in preceding 4 months</td>
</tr>
<tr>
<td></td>
<td>• ACS, stroke, or PVD intervention in previous 3 mos.</td>
<td>• Malignancy</td>
</tr>
<tr>
<td></td>
<td>• NYHA class III or IV</td>
<td>• Recent MI or stroke</td>
</tr>
<tr>
<td></td>
<td>• HoFH</td>
<td>• 10-Year Framingham risk score &gt;10%</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>• Statin + alirocumab 150 mg sq Q2W</td>
<td>• Standard therapy + evolocumab</td>
</tr>
<tr>
<td></td>
<td>• Statin + placebo sq Q2W</td>
<td>o Evolocumab 140 mg Q2W, or</td>
</tr>
<tr>
<td></td>
<td>• Randomized 2:1</td>
<td>o Evolocumab 420 mg Q4W, or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Standard therapy + placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Randomized 2:1</td>
</tr>
<tr>
<td><strong>Mean Age</strong></td>
<td>60.4 vs. 60.6 years</td>
<td>57.8 vs. 58.2 years</td>
</tr>
<tr>
<td><strong>Hx of CHD</strong></td>
<td>68% vs. 70%</td>
<td>19.8% vs. 20.6%</td>
</tr>
<tr>
<td><strong>Median TC level</strong></td>
<td>153 vs. 152 mg/dL</td>
<td>202 vs. 205 mg/dL</td>
</tr>
<tr>
<td><strong>Median LDL level</strong></td>
<td>123 vs. 122 mg/dL</td>
<td>120 vs. 121 mg/dL</td>
</tr>
<tr>
<td><strong>Primary Outcomes</strong></td>
<td>• Change in LDL-C from baseline to week 24: -74.2 vs. -3.6 mg/dL (p&lt;0.001)</td>
<td>• Incidence of adverse events: 69.2% vs. 64.8% (p=NR)</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td>• LDL-C &lt;70 mg/dL: 79.3% vs. 8.0% (p&lt;0.001)</td>
<td>• % change in LDL-C from baseline: 61% (CI 59-63%, p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>• LDL-C Δ from baseline-week 78: -52.4 mg/dL vs. +3.6 mg/dL (p&lt;0.001)</td>
<td>• LDL &lt;70 mg/dl at 12 weeks: 73.6% vs. 3.8%</td>
</tr>
<tr>
<td></td>
<td>• Post-hoc major CV events: 1.7% vs. 3.3% (p=0.02)</td>
<td>• Cardiovascular event rates: 0.95% vs. 2.18% [HR 0.47, CI 0.28-0.78 (p=0.003)]</td>
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<tr>
<td></td>
<td>• Nonfatal MI: 0.9% vs. 2.3% (p=0.01)</td>
<td></td>
</tr>
<tr>
<td><strong>Any AE</strong></td>
<td>81% vs 82.5% (p=0.4)</td>
<td>69.2% vs. 64.8% (p=NR)</td>
</tr>
<tr>
<td><strong>Serious AE</strong></td>
<td>18.7% vs. 19.5% (p=0.66)</td>
<td>7.5% vs. 7.5% (p=NR)</td>
</tr>
<tr>
<td><strong>Myalgia</strong></td>
<td>5.4% vs. 2.9% (p=0.006)</td>
<td>6.4% vs. 6.0% (p=NR)</td>
</tr>
<tr>
<td><strong>Neurocognitive AE</strong></td>
<td>1.2% vs. 0.5% (p=0.17)</td>
<td>0.9% vs. 0.3% (p=NR)</td>
</tr>
</tbody>
</table>
Pharmacoeconomics

10. So what?30-32
   a. Americans spent ~$310 billion on all medications in 2015
      i. $18.7 billion spent on cholesterol-lowering medications
   b. PCSK9 inhibitors projected to be the costliest drug class ever
      i. Estimated $16B-$150 billion additional spend annually in the US
   c. An estimated 3 in 5 bankruptcies are due to medical bills
   d. Hospital and health-system pharmacies traditionally viewed as cost-centers

11. ACC/AHA economic analysis33
   a. Published formal recommendations for inclusion of cost in assessing the value of care
   b. Value is defined as a function of results (eg. safety, outcomes) and cost
   c. Summary of implementation recommendations
      i. Analyses should be undertaken from the societal perspective
      ii. Analyses should be limited to use of data relevant to the United States or North America
      iii. Thresholds for value should include an upper and lower boundary
      iv. Performance measures should consider cost analyses results

12. Pharmacoeconomic analysis34-38
   a. Subset of outcomes research intended to provide objective measures of value
   b. Value is assumed from the perspective of either society, payers, providers, or patients
   c. Four basic types of analyses compare costs inputs of a product/service with outcomes

   | Table 3: Pharmacoeconomic analyses |
   |-------------------------------|-----------------|-----------------|
   | **Methodology**              | **Cost Measurement Unit** | **Outcome Measurement Unit** |
   | Cost-minimization analysis   | $ or other monetary unit | N/A; assumed equivalent |
   | Cost-benefit analysis        | $ or other monetary unit | $ or other monetary unit |
   | Cost-effectiveness analysis  | $ or other monetary unit | A common natural unit |
   | Cost-utility analysis        | $ or other monetary unit | Quality-adjusted life year (QALY) or other utility |

   Analyses should employ one of: societal, payer, provider, or patient perspective

Adapted from: Rascati KL. Essentials of pharmacoeconomics. 2nd ed. Baltimore, MD. Lippincott Williams & Wilkins. 2014.

d. Cost-effectiveness analysis (CEA)
   i. Compares relative costs and outcomes of ≥2 products/services
   ii. Cannot compare products/services with different outcome measures
   iii. Does not account for differences in side-effect profiles

e. Cost-utility analysis (CUA)
   i. Compares relative costs and utility-weighted outcomes of ≥2 products/services
   ii. Utility weights are a 0.0 (death) to 1.0 (perfect health) measure of outcome preference
   iii. Incorporates patient or societal preferences into value measures

f. Measuring value
   i. Willingness-to-pay (WTP): How much people are willing to pay to reduce the chance of an adverse health outcome
   ii. Incremental cost-effect ratio (ICER): (Cost A – Cost B)/(Outcome A – Outcome B)
   iii. Quality-adjusted life years (QALYs): Outcomes in years of life gained, adjusted for patient preference
   iv. Budgetary impact: the estimated overall cost of adding a product to the formulary
Pharmacoeconomic analysis continued

**g. Historic value benchmarks**
- Regularly cited $50,000/QALY threshold stems from a congressional mandate that dialysis be covered for Medicare recipients
- The World Health Organization (WHO) values QALYs at 3x GDP per capita

**h. Recent value benchmarks**
- New treatment options for hepatitis C were evaluated as high-to-reasonable value at ≤$20,000/QALY
- Meta-analyses of current dialysis value reports ICERs between $65,496-$488,360 per QALY

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**Economic Literature**

**Tice JA, Ollendorf DA, Cunningham C, Pearson SD, Kazi DS, et al. PCSK9 inhibitors for treatment of high cholesterol: effectiveness, value and value based price benchmarks. ICER November 2015.**

| Purpose | To evaluate the comparative clinical effectiveness and comparative value of PCSK9 inhibitors as a class for patients with elevated LDL |
| Design | Cost-utility analysis
- Care value
- Budgetary impact |
| Scenarios Modeled | Familial hypercholesterolemia (FH)
- Clinical CVD—secondary prevention
  - Statin-intolerant (assumed 10%)
  - Statin-tolerant, not at LDL goal (<70 mg/dL)
- Willingness-to-pay thresholds
  - $50,000/QALY
  - $100,000/QALY
  - $150,000/QALY |
| Populations Modeled | Outcomes
- Cost per quality-adjusted life-year (QALY) |
| Methods | Used CVD policy model
- Entire US adult population age 35-74 years in 2015
- Assumed health system perspective for both analyses
- Defined familial hypercholesterolemia as:
  - LDL >250 mg/dL without statin use
  - LDL ≥200 mg/dL with statin use
- Stratified 10% of the population with history of CVD to model statin-intolerance
- Applied lifetime horizon of 95-years old
- Discounted future costs and benefits by 3% each successive year |
| Assumptions | Costs from the health system perspective
- Drug effects on outcomes are directly proportional to degree of LDL reduction |
• PCSK9 inhibitors have no effect on risk of stroke
• Ten percent of persons exposed to statins are intolerant
• Age and sex specific costs were extrapolated from national data
• Annual cost based on wholesale acquisition cost
  o Ezetimibe—$2,828/yr
  o PCSK9 inhibitors (class)—$14,350/yr
• ~2.6 million persons would receive a PCSK9 inhibitor in the following 5 years
• Budget impact threshold is $904 million

### Results

<table>
<thead>
<tr>
<th>Population</th>
<th>Care Value Price: $100K/QALY</th>
<th>Care Value Price: $150K/QALY</th>
<th>Max Price at Potential Budget Impact Threshold</th>
<th>Value-Based Price Benchmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH (n=453,443)</td>
<td>$5,700/yr</td>
<td>$8,000/yr</td>
<td>$10,278/yr</td>
<td>$5,700-$8,000/yr</td>
</tr>
<tr>
<td>CVD statin-intolerant</td>
<td>$5,800/yr</td>
<td>$8,300/yr</td>
<td>$12,896/yr</td>
<td>$5,800-$8,300/yr</td>
</tr>
<tr>
<td>(n=364,948)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD not at LDL goal</td>
<td>$5,300/yr</td>
<td>$7,600/yr</td>
<td>$2,976/yr</td>
<td>$2,976/yr</td>
</tr>
<tr>
<td>(n=1,817,788)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>$5,404/yr</td>
<td>$7,735/yr</td>
<td>$2,177/yr</td>
<td>$2,177/yr</td>
</tr>
<tr>
<td>(n=2,636,179)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FH: familial hypercholesterolemia; CVD: cardiovascular disease; LDL: low-density lipoprotein; QALY: quality-adjusted life year

### Author’s discussion
• PCSK9 inhibitors may substantially reduce non-fatal MIs, non-fatal strokes, and cardiovascular death over a lifetime
• PCSK9 inhibitors generated ICERs that exceed commonly-accepted thresholds
• An 85% reduction in list price would be necessary to avoid adding excessive cost burdens to the health care system

### Reviewer’s critique
• CVD model not applicable to patients <35 years old
• FH diagnosis not in-line with current recommendations for diagnosis
• Used historic LDL treatment goal values no longer standard of care
• Ten percent statin intolerance rate is an overestimation
• Outcome event reduction does not reflect results from recent studies
• Drug effects on CVD were based on LDL reduction alone
• Sensitivity analyses of base cases consistently sensitive to lower price and longer analysis horizon
• Used arbitrary budget impact threshold that does not reflect real world policy

13. ICER report summary
   a. ICER modeled PCSK9 use in statin tolerant and intolerant patients
      i. Compared to ezetimibe use
      ii. Baseline statin use
   b. Utilized a cost-benefit analysis to compare value of ezetimibe and PCSK9 inhibitors as add-on therapies
   c. ICER finds PCSK9 inhibitors only viable as treatment options without restriction at a price of $2,177—a price less than the current AWP of ezetimibe
   d. Findings are based on questionable modeling of population and event rates
   e. Costs miss potentially significant events avoided
**Conclusion**

14. **Clinical summary**
   a. PCSK9 inhibitors significantly decrease serum LDL cholesterol
      i. Evolocumab decreased LDL by ~61% at 48-weeks
      ii. Alirocumab decreased LDL by 61% at 24 weeks, and 58% at 78 weeks
   b. LDL cholesterol levels below 70 mg/dL may result in further improved CVD outcomes
      i. Mean absolute LDL level was 48 mg/dL at 24 weeks of therapy in ODYSSEY
   c. Interim analyses indicate additional 48-53% event reduction when added to statin therapy
   d. Studies of safety conclude neither drug possesses a significant adverse effect profile
      i. Similar rates of adverse events leading to discontinuation were observed between alirocumab and placebo, respectively:
      ii. Slightly higher rates of neurocognitive events with PCSK9 inhibitors compared to placebo (not statistically significant)
   e. Interim outcomes analyses trending towards significant event reduction

15. **Cost summary**
   a. PCSK9 inhibitors projected to be costliest drug class in history at current average wholesale prices (AWPs)
      i. Praluent AWP: $14,600/year
      ii. Repatha AWP: $14,100/year
   b. ICER findings:
      i. ICERs at list price range from $274,00-$302,00 per QALY for modeled populations
      ii. Limiting use to only post-MI patients still results in costs >$150,000/QALY
      iii. Concluded class is viable at a lower price than current AWP for Zetia®
      iv. Marked flaws in modeling and cost assumptions
   c. Emerging pay-for-performance deals compensate payers for unmet clinical outcomes

16. **Clinical recommendations**
   a. Reserve as add-on agents in patients with genetically-confirmed FH after initiating statin therapy
      i. Primary prevention in patients with HoFH
      ii. Primary prevention in patients with higher-risk HeFH
      iii. Secondary prevention in most patients with HeFH
   b. Reserve as add-on agents for secondary prevention in high-risk patients without FH
   c. Keep a watchful eye on outcomes data likely to be made available by 2017
Appendix 1: Select studies assessing statin-induced LDL-lowering and CVD outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Intervention</th>
<th>Mean baseline LDL (mg/dL)</th>
<th>Mean LDL reduction</th>
<th>CVD event reduction rate</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo controlled</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S (1994)</td>
<td>4444</td>
<td>Simvastatin 20 mg</td>
<td>188</td>
<td>35%</td>
<td>34% (p&lt;0.0001)</td>
<td>15</td>
</tr>
<tr>
<td>WOSCOPS (1996)</td>
<td>6595</td>
<td>Pravastatin 40 mg</td>
<td>192</td>
<td>26%</td>
<td>31% (p&lt;0.001)</td>
<td>42</td>
</tr>
<tr>
<td>AFCAPS/TEXCAPS (1998)</td>
<td>6605</td>
<td>Lovastatin 20-40 mg</td>
<td>150</td>
<td>25%</td>
<td>37% (p&lt;0.001)</td>
<td>24</td>
</tr>
<tr>
<td>MIRACL (2001)</td>
<td>3086</td>
<td>Atorvastatin 80 mg</td>
<td>124</td>
<td>58%</td>
<td>16% (p=0.048)</td>
<td>39</td>
</tr>
<tr>
<td>ALLHAT-LLT (2002)</td>
<td>3638</td>
<td>Pravastatin 40 mg</td>
<td>146</td>
<td>28%</td>
<td>9% (p&lt;0.96)</td>
<td>43</td>
</tr>
<tr>
<td>HPS (2002)</td>
<td>20536</td>
<td>Simvastatin 40 mg</td>
<td>131</td>
<td>30%</td>
<td>23% (p&lt;0.0001)</td>
<td>19</td>
</tr>
<tr>
<td>CARDS (2004)</td>
<td>2838</td>
<td>Atorvastatin 10 mg</td>
<td>117</td>
<td>40%</td>
<td>37% (p&lt;0.001)</td>
<td>24</td>
</tr>
<tr>
<td>ASPEN (2006)</td>
<td>2410</td>
<td>Atorvastatin 10 mg</td>
<td>113</td>
<td>30%</td>
<td>10% (NS)</td>
<td>4</td>
</tr>
<tr>
<td>MEGA (2006)</td>
<td>8214</td>
<td>Pravastatin 10-20 mg</td>
<td>157</td>
<td>18%</td>
<td>33% (p=0.01)</td>
<td>6</td>
</tr>
<tr>
<td>SPARCL (2006)</td>
<td>4731</td>
<td>Atorvastatin 80 mg</td>
<td>133</td>
<td>42%</td>
<td>26% (p&lt;0.001)</td>
<td>15</td>
</tr>
<tr>
<td>JUPITER (2008)</td>
<td>17802</td>
<td>Rosuvastatin 20 mg</td>
<td>108</td>
<td>50%</td>
<td>44% (p&lt;0.00001)</td>
<td>82</td>
</tr>
<tr>
<td><strong>Statin comparative efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PROVE IT-TIMI 22 (2004)</td>
<td>4162</td>
<td>Atorvastatin 40 mg vs.</td>
<td>106 vs. 106</td>
<td></td>
<td>16% (p&lt;0.005)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pravastatin 40 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Citations


47. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT-LLT). JAMA. 2002;288(23):2998-3007.


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