Impact of PCSK9-Inhibitors

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Specialty Therapies: A Forum For Payers
2017
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Objectives

• Review PCSK9-inhibitors and their use
• Analyze pricing pressures of PCSK9-inhibitors
• Work through a cost-effectiveness analysis to determine value
• Examine patient adherence to PCSK9-inhibitors
• Explore the pipeline and how it may affect current drugs on the market
Cholesterol Homeostasis

• Cholesterol is used in the body to:
  – Maintain cell membranes
  – Help synthesize vitamin D
  – Produce hormones, steroids, bile acids

• Too much cholesterol alters the balance:
  – Lipoproteins metabolism, transporting lipids to and from tissues
  – Extra LDL deposits in arterial wall
  – High LDL areas cause inflammation, then plaques

Familial Hypercholesterolemia (FH)

• Autosomal: 2 genes for all proteins
• Complex and numerous mutations, all adding at least a little to the equation
• Heterozygous (1 in 200-500 people)
  – vs. homozygous (1 in 1,000,000 births)
• High LDL values impact ASCVD risk
• Prognosis: untreated pts can have up to 3x risk of ASCVD
• Treatment: statins, then others

Atherosclerotic Cardiovascular Disease

• Multifactorial etiology
  – Family history genetics; smoking, hypertensives, diabetes, hyperlipidemia, metabolic syndrome, etc.

• Three main dimensions (not mutually exclusive)
  – Coronary Heart Disease\(^1\)
    • Most common cause of death in the US, about 1 in 4
    • At age 40y, incidence is 49% in men and 32% in women
  – Cerebrovascular\(^2\)
    • Global incidence ischemic stroke is 68%; “stroke belt”
  – Peripheral vascular\(^3\)
    • Prevalence increases greatly with age, 0.9% for 40-49yo and 23.2% 80+yo

• Sanofi/Regeneron provided 16 pages of ICD-10s to assist with billing PCSK9 medications\(^4\)

• Treatments based on etiology and comorbidities; often polypharmacy

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Heart Attack Death Rates, 2011-2013
Adults, Ages 35+, by County

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Source:
National Vital Statistics System
National Center for Health Statistics

https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/images/fs_heart_attack.jpg
PCSK9 and Inhibition

• LDL-receptors ‘grab’ LDL from the blood for processing in the cell
• PCSK9 binds to LDL-receptors, causing degradation once brought into the cell
  – Doesn’t prevent from working, just decreases recycling
• Blocking PCSK9 activity increase LDL-receptor recycling

http://www.nature.com/nrcardio/journal/v11/n10/images_article/nrcardio.2014.84-f1.jpg
# Current PCSK9 Products

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab (Praluent)</th>
<th>Evolocumab (Repatha)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Sanofi/Regeneron</td>
<td>Amgen</td>
</tr>
<tr>
<td><strong>FDA Approval Date</strong></td>
<td>July 24th, 2015</td>
<td>August 27th, 2015</td>
</tr>
<tr>
<td><strong>FDA Approved Indications</strong></td>
<td>Adjunct to diet and maximally tolerated statin for HeFH or clinical ASCVD</td>
<td>Adjunct to diet and • maximally tolerated statin for HeFH or clinical ASCVD • Other LDL-lowering in HoFH</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>75mg SC Q 2 weeks, can increase to 150mg</td>
<td>140mg SC Q 2 weeks, or 420mg Q 1 month</td>
</tr>
<tr>
<td><strong>Administration Concerns</strong></td>
<td>Must be refrigerated at all times, 24 hour window</td>
<td>420mg: 9 min infusion vs. 3 injections Room temp, but must use w/in 30 days</td>
</tr>
<tr>
<td><strong>Efficacy (LDL decrease)</strong></td>
<td>- 58% in LDL-C (wk 24)</td>
<td>-56% to -62% in LDL-C (wk 12)</td>
</tr>
<tr>
<td><strong>Safety (Common Adverse Events)</strong></td>
<td>Local injection site reactions, URI, nasopharyngitis</td>
<td>Rare: severe allergic reactions, neurocognitive events</td>
</tr>
<tr>
<td><strong>AWP (2015)</strong></td>
<td>$14,240/year</td>
<td>$14,100/year</td>
</tr>
</tbody>
</table>
What is “Maximally Tolerated Statin”? 

- Statins
  - Very potent LDL-lowering effects
  - Proven outcomes trials
  - Cornerstone of ASCVD primary and secondary prevention
  - Adverse events common: myopathies and GI issues
- “The highest dose associated with an acceptable side-effect profile” – ODYSSEY study w/ alirocumab
- Adds a subjective variable to the process
Pricing Pressures/Issues

• Less expensive alternatives with greater evidence
• New generics on the market soon for newer generation alternatives
• Market access via PBM and payer contracts
• Pfizer pulled bococizumab on November 1st, no other PCSK9i soon

• Ongoing litigation for Amgen’s patents
  – As of 1/7, Amgen won lawsuit and federal judge banned sale of Regeneron’s product, still can appeal or settle.¹

• Large discrepancy between ICER-reported value and WAC
• Outcomes ever more important in healthcare

“The Next Big Thing”

• Many articles trumpeting approval and impact:
  – Specialty Pharmacy Times, August 11, 2015¹
    • 2.3 million eligible, could cost $23 billion annually
    • PRIME estimates for Medicare of $15.66 PMPM
    • ~240k Americans who do not tolerate statins, possibly adding $2.1 billion
  – USA TODAY, August 16, 2016²
    • $120 billion added to costs if all eligible took PCSK9s, according to JAMA

Why Pay for Something Unproven?

• Ezetimibe story:
  – FDA approved in 2002 to lower LDL
  – Article in 2008 showed lack of effect on carotid intima-media thickness in familial hypercholesterolemia, even though it lowered LDL levels greater than simvastatin alone (-39.1% vs -55.6%)\(^1\)
  – Article in 2015 showed a 2 percentage-point absolute risk reduction for composite death from CVD, major coronary event, or nonfatal stroke. (24% additional lowering of LDL-C w/ ezetimibe)\(^2\)

• Guidelines:\(^3\)
  – Maximize lifestyle changes and statin adherence before considering a nonstatin drug
  – Add nonstatin drug that have been shown risk-reduction in RCTs

Stone NJ et al. 2013 ACC/AHA Blood Cholesterol Guidelines. [http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a](http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a)
PCSK9i PA Criteria

- CVS/Caremark as an example:
- Complex compared to non-specialty PA criteria

### III. CRITERIA FOR INITIAL APPROVAL

#### A. Clinical atherosclerotic cardiovascular disease (ASCVD)

Authorization of 12 months may be granted for members who meet ALL of the criteria listed below [1, 2, 3 and 4]:

1. Member is 18 years of age or older
2. Member has a history of ASCVD or cardiovascular event (See Appendix A)
3. Member meets at least ONE of the following requirements [a, b or c]:
   a. Member has a current LDL-C level ≥ 70 mg/dL after at least three months of an adherent treatment with a high-intensity statin (i.e., atorvastatin ≥ 40 mg or rosuvastatin ≥ 20 mg daily) plus ezetimibe 10 mg daily.
   b. Member has a current LDL-C level ≥ 70 mg/dL with contraindication or intolerance to statin (See Appendices B and C) and is taking ezetimibe with or without other lipid lowering medications at maximally tolerated doses or at the maximum doses approved by the FDA.
   c. Member has a current LDL-C level ≥ 70 mg/dL and contraindication to both statin and ezetimibe (See Appendix C)
4. Member’s current triglyceride is less than or equal to 400 mg/dL
CONTINUATION OF THERAPY

A. ASCVD

1. Authorization of 12 months may be granted for members who have received at least a three-month supply of the requested medication within the previous 120 days through a prior authorization process for a pharmacy or medical benefit and achieve or maintain an LDL-C reduction, as defined below [a, b or c]:
   a. LDL-C reduction $\geq$ 35%
   b. Absolute reduction in LDL-C $\geq$ 40 mg/dL
   c. Reduction below an LDL-C level of 70 mg/dL

2. Authorization of 12 months may be granted for members who have received at least a three-month supply of another PCSK9 inhibitor within the previous 120 days through a prior authorization process for a pharmacy or medical benefit.
APPENDIX B. Statin-associated muscle symptoms (SAMS) and statin re-challenge

- Intolerable SAMS persisting at least two weeks confirmed with at least two attempts of statin re-challenge.
  NOTE: Re-challenges must include two different statins. One of the statins must be atorvastatin or rosuvastatin.
- Statin-associated elevation in CK level ≥ 10 times upper limit of normal (ULN)
  NOTE: Statin re-challenge is NOT required for members who have experienced an elevation of CK level greater than or equal to 10 times ULN after receiving lipid-lowering therapy (LLT) with a statin.
- Statin-associated rhabdomyolysis (i.e., statin-associated elevation in CK level > 10,000 IU/L or significant elevation in creatinine level)
  NOTE: Statin re-challenge is NOT required for members who have experienced rhabdomyolysis after receiving LLT with a statin.
APPENDIX C. Contraindications to statin and ezetimibe

- Contraindications to statins
  - Active liver disease, including unexplained persistent elevations in hepatic transaminase levels (e.g., alanine transaminase (ALT) level ≥ 3 times ULN)
  - Women who are pregnant or may become pregnant
  - Nursing mothers
- Contraindication to ezetimibe
  - Hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash and urticaria)

APPENDIX D: Diagnosis of familial hypercholesterolemia (FH)

A definite diagnosis of FH is made when one of the following diagnostic criteria is met:

- Genetic confirmation
  - An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation
- Simon-Broome Diagnostic Criteria for definite FH
  - Total cholesterol > 290 mg/dL or LDL-C > 190 mg/dL, plus tendon xanthomas in the patient, first (parent, sibling or child) or second degree relative (grandparent, uncle or aunt)
- Dutch Lipid Clinic Network Criteria for definite FH
  - Total score > 8 points
• Cost-effectiveness models are variable
• Each estimate compounds itself
• Slight adjustments in estimates can mean above or below an end threshold
• Something to occupy the industry as we wait for real outcomes data
## High Level Summary of Literature

<table>
<thead>
<tr>
<th>Cost-Effectiveness Article</th>
<th>Statin-Benefit Group</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kazi et al, JAMA 2016¹</td>
<td>ASCVD</td>
<td>$414,000/QALY</td>
</tr>
<tr>
<td></td>
<td>HeFH</td>
<td>$316,300/QALY</td>
</tr>
<tr>
<td>Tice et al, JAMA Int Med 2016²</td>
<td>ASCVD (statin intolerant)</td>
<td>$274,000/QALY</td>
</tr>
<tr>
<td></td>
<td>ASCVD (LDL&gt;70)</td>
<td>$302,000/QALY</td>
</tr>
<tr>
<td></td>
<td>HeFH</td>
<td>$290,000/QALY</td>
</tr>
<tr>
<td>Gandra et al, Clinical Cardiology 2016³</td>
<td>ASCVD (statin intolerant)</td>
<td>$100,309/QALY</td>
</tr>
<tr>
<td></td>
<td>ASCVD (LDL&gt;70)</td>
<td>$141,699/QALY</td>
</tr>
<tr>
<td></td>
<td>HeFH</td>
<td>$141,699/QALY</td>
</tr>
</tbody>
</table>

Kazi et al Data Sources

- Example for costs:

<table>
<thead>
<tr>
<th>Cardiovascular Costs</th>
<th>Costs of CHD care, 2015 US $f</th>
<th>Log normal</th>
<th>California OSHPD, 200827,28; US Census Bureau29; Bureau of Labor Statistics30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute fatal MI hospitalization</td>
<td>53 565 (44 638-64 278)</td>
<td>Log normal</td>
<td>California OSHPD, 200827,28; US Census Bureau29; Bureau of Labor Statistics30</td>
</tr>
<tr>
<td>Acute nonfatal MI hospitalization</td>
<td>38 766 (32 305-46 519)</td>
<td>Log normal</td>
<td>California OSHPD, 200827,28; US Census Bureau29; Bureau of Labor Statistics30</td>
</tr>
<tr>
<td>Acute nonfatal MI and CABG</td>
<td>99 092 (82 577-118 910)</td>
<td>Log normal</td>
<td>California OSHPD, 200827,28; US Census Bureau29; Bureau of Labor Statistics30</td>
</tr>
<tr>
<td>Acute MI posthospitalization year 1 costs</td>
<td>12 338 (10 282-14 806)</td>
<td>Log normal</td>
<td>California OSHPD, 200827,28; US Census Bureau29; Bureau of Labor Statistics30</td>
</tr>
<tr>
<td>CHD costs, subsequent years</td>
<td>2520 (2100-3024)</td>
<td>Log normal</td>
<td>AHRQ31; Bureau of Labor Statistics30</td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
<td>19 512 (16 260-23 414)</td>
<td>Log normal</td>
<td>California OSHPD, 200827,28; US Census Bureau29; Bureau of Labor Statistics30</td>
</tr>
<tr>
<td>Fatal stroke hospitalization</td>
<td>26 699 (22 249-32 039)</td>
<td>Log normal</td>
<td>California OSHPD, 200827,28; US Census Bureau29; Bureau of Labor Statistics30</td>
</tr>
<tr>
<td>Nonfatal stroke hospitalization</td>
<td>19 732 (16 443-23 678)</td>
<td>Log normal</td>
<td>California OSHPD, 200827,28; US Census Bureau29; Bureau of Labor Statistics30</td>
</tr>
<tr>
<td>Poststroke cost, months 2-11</td>
<td>34 712 (28 927-41 654)</td>
<td>Log normal</td>
<td>California OSHPD, 200827,28; US Census Bureau29; Bureau of Labor Statistics30</td>
</tr>
<tr>
<td>Poststroke cost, annual, subsequent years</td>
<td>5305 (4421-6366)</td>
<td>Log normal</td>
<td>AHRQ31; Bureau of Labor Statistics30</td>
</tr>
</tbody>
</table>
Sensitivity Analysis from Kazi et al 2016 JAMA Article

• Throw in odd values or changes to the system
• Sensitivity analyses performed include:
  – Higher LDL-C thresholds to define HeFH
  – Assume higher ASCVD risk than predicted
  – Used outcomes effects from clinical trials
  – Adding PCSK9i only after MI event
  – Adding PCSK9i for all eligible patients
  – Varying statin-intolerance from 3-20%
  – Adding 0.5% mild neuro issues w/ PCSK9i
  – Treating all statin-eligible/tolerant with statins
• The annual PCSK9i cost to line up with a $100,000 QALY: $4536

• Some scenarios that favored a higher cost (but still not AWP cost):
  – Higher LDL for dx of HeFH
  – Assuming higher ASCVD risk (2x) associated with LDL levels
  – Restricting to only statin-intolerant
  – Restricting to only MI pts
  – Reducing rate of statin-intolerance from 10% to 3%
# Payer Coverage

<table>
<thead>
<tr>
<th>Payer</th>
<th>Alirocumab (Praluent)</th>
<th>Evolocumab (Repatha)</th>
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<tbody>
<tr>
<td>United/OptumRx</td>
<td>Covered, PA</td>
<td></td>
</tr>
<tr>
<td>CVS/Caremark</td>
<td></td>
<td>Covered, PA</td>
</tr>
<tr>
<td>Express Scripts</td>
<td>Covered, PA</td>
<td>Covered, PA</td>
</tr>
<tr>
<td>Aetna</td>
<td>Covered, PA</td>
<td>Covered, PA</td>
</tr>
<tr>
<td>Prime</td>
<td>Covered, PA</td>
<td>Covered, PA</td>
</tr>
<tr>
<td>Humana</td>
<td>Covered, PA</td>
<td></td>
</tr>
<tr>
<td>Cigna</td>
<td>Covered, PA</td>
<td>Covered, PA</td>
</tr>
</tbody>
</table>
At-Risk/Value-Based Contracts

• Standard discounts (access, tier, PA criteria, etc.)
• Additional discounts if medication does not meet LDL-C values in RCTs
• Soft spots:
  – Specific contract definitions for specific populations
  – Defining adherence criteria
  – Collection/housing of labs and outcome data

Personal Opinion

• It appears that WAC is so arbitrary that it’s a number used only for investors and shareholders, at the true cost of the uninsured.

• This appears to drive “cash price” up, but do payers or manufacturer’s care about cash-paying patients?

• Value-based pricing vs. investment-recoup pricing
REAL WORLD DATA
• Fairview Specialty Services Pharmacy:
  – Therapy Management program to ensure purposeful and thoughtful use of PCSK9 medications

• Program Structure:
  – Five to seven days after a patient receives their medication a pharmacist screens for potential adverse events, difficulty with self-injection, and potential adherence concerns

• Cholesterol values, including LDL cholesterol, are recorded prior to therapy initiation and again 100 days post-therapy to assess treatment effectiveness
• Dispensing data and health records were reviewed for all patients who received at least 84 days of PCSK9 Inhibitor therapy
• Dispensing data was used to calculate individual Medication Possession Ratios (MPR) adherence metric
• Health records were reviewed for change in LDL and any documented barriers to medication adherence, such as adverse events
• MPR values were then compared to LDL cholesterol laboratory value change from baseline to lab values after initiation of PCSK9 therapy
Change in LDL Values

Figure 1: Baseline LDL Vs. LDL With PCSK9 Therapy
(Arranged by % LDL reduction)

<70mg/dL
Adherence Data

Figure 1: Baseline LDL Vs. LDL With PCSK9 Therapy
(Arranged by % LDL reduction)

Figure 2: MPR for Treatment Regimen (N = 25)
Results

- Thirty patients were included in our evaluation of PCSK9 Inhibitor treatment; Average duration of PCSK9 Inhibitor therapy was 179 days (range 84 to 336 days)
- Patients with recorded LDL cholesterol values after initiation of therapy (N=25) experienced an average decrease of 100 mg/dL from baseline resulting in a 6% to 80% individual reduction
- The average MPR was 0.91 with a range from 0.67 to 1
- Two adverse events were reported and deemed unrelated to PCSK9i therapy
- Due to the small patient population and high level of adherence among patients with follow-up LDL values the impact of adherence on LDL lowering could not be assessed
Most Recent Data

• Discussion

• No LDL Available?
  – LDL = total cholesterol - VLDL - HDL
  – VLDL is often approximated by TG/5
  – If TG > 400, the calculation is invalid
  – Can order a direct LDL, but doesn’t occur often
  – **All guidelines used estimated, not-direct
Prime Therapeutics PCSK9i UM Poster from AMCP 2016

• UM, cost and discontinuation rate
• 13.4 million commercial members
• Examined first 5 months post-launch
• Discontinuation defined as 28-day gap

• Results:
  – 1,608 members w/ paid or rejected claim
  – 128 members had paid claim (380 claims total)
  – 2/3 Rx’d by cardiology or endocrine specialist
  – Use trended up, ended at 1.2/100,00 members
  – 57 (28%) discontinued therapy

Hyperlipidemia Pipeline

- **Inclisiran**
  - Medicines Company
  - Inhibits PCSK9 synthesis through RNA interference
  - SC dosing, possibly 2-3x/year
  - Phase III
- **Discussion:**
  - Similar efficacy to available PCSK9-inhibitors
  - Could compete directly

- **LY3015014**
  - Eli Lily
  - PCSK9 inhibitor
  - SC dosing, Q 4-8 Weeks
  - Phase II
- **Discussion:**
  - Not as robust of response, 37.1% to 50.5% reduction (better with 4 week dose)
  - Once it hits market, it would be a possible alternative

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Hyperlipidemia Pipeline

• Anacetrapib
  – Merck
  – Cholesterol ester transfer protein (CETP) inhibitor
  – Oral, QD
  – Phase III
• Discussion:
  – 3 previously failed CETP drugs
  – Nov 13, 2015: interim analysis recommended continuation; results in 2017
  – Decreases LDL at statin-levels and increase HDL by 44-139%

• TA-8995
  – Amgen
  – Cholesterol ester transfer protein (CETP) inhibitor
  – Oral QD
  – Phase III
• Discussion:
  – 3 previously failed CETP drugs
  – Still early, last trial published January 2015
  – Decreases LDL at statin levels and increase HDL by 75-179%

Hyperlipidemia

- Bempedoic acid
  - Esperion
  - ATP-cirtrate lyase inhibition, disrupts cholesterol synthesis
    - Oral, QD
    - Phase III
- Discussion:
  - LDL lowering up to 43%
  - Outcomes far away

- Generic for ezetimibe/simvastatin
  - Possible game changer for contracting and preferred agents

http://www.esperion.com/therapies-progress/etc-1002/
Conclusions

• PSCK9i’s have a place in management of hyperlipidemia
• For now, that’s a very specific space
• PSCK9i’s are well tolerated and effective at lowering LDL-C in a small real-world cohort
• While we wait for outcomes data hopefully later this year, we can argue over cost-effectiveness models
Questions?

• Thank you for this opportunity!