Barriers in Access to CVD Therapies: PCSK9 Inhibitors
A Case Study

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Bringing People Together:

The ASPC ‘Barriers to Access’
Town Hall Series

A Consortium of Societies and Clinicians

The Initiative in 2016:
Unraveling the Therapeutic Conundrum

• Two Town Hall Meetings: ASPC (assessing barriers) and AHA (creating solutions)
• Input from multiple organizations: ASPC, ACC, FHF, NLA, AACE and others
• Input from multiple disciplines/stakeholders: Cardiology, Endocrinology, Lipidology, Internal Medicine, Family Practice, Nurse Practitioners, Patients, Policymakers, and Payers
• Publication of Insights and Recommendations
The Initiative in 2017: Advancing the Conversation

- CLC Publication & Multiple Town Hall Meetings:
  - ACC Scientific Sessions
  - PCNA Annual Symposium
  - AACE Scientific and Clinical Congress
  - NLA Scientific Session
  - ASPC Annual Congress
  - FH Foundation Global Summit
  - AHA Scientific Sessions

Today’s Agenda:

- Paper in Clinical Cardiology, (CLC)
- PI Consensus Definitions, a possible road to access
- Why unprecedented barriers to access?
- Brief Overview of Valuation Modeling

Clinical Cardiology (CLC) Consensus Paper
Open Access
### Barriers in Identifying the Patient

#### Prescribing Indication

<table>
<thead>
<tr>
<th>Definition/Summary</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximally tolerated statin therapy</strong></td>
<td>The highest dose on an individual can tolerate even if that dose is zero, tested as two statin attempts with one using a low dose regimen (e.g., 5 mg rosuvastatin QOD).</td>
</tr>
<tr>
<td><strong>Familial hypercholesterolemia</strong> (HeFH &amp; HoFH)</td>
<td>*Diagnosed in the presence of a positive family history of elevated cholesterol or premature CAD and LDL-C ≥160 mg/dL (≥4 mmol/L) in a child or ≥190 mg/dL (≥5 mmol/L) in an adult confirmed on 2 occasions.*1</td>
</tr>
<tr>
<td><strong>Clinical atherosclerotic cardiovascular disease</strong></td>
<td>A history of CHD, stroke, peripheral arterial disease, carotid artery disease, and other forms of atherosclerotic vascular disease.2</td>
</tr>
<tr>
<td><strong>Who requires Additional lowering of LDL-cholesterol</strong></td>
<td>A high risk patient (FH or ASCVD) with LDL-cholesterol &gt; 70 mg/dL who otherwise meets the indication.</td>
</tr>
</tbody>
</table>

#### Sources:

#### Consensus Definitions:

1. **“Maximally Tolerated Statin Therapy”**

   **Barrier:** Inconsistent Definition for “Maximally Tolerated Statin”

   Competing definitions provide uncertainty and lack of standardization in qualifying the appropriate patient.

   **Solution:** Define “Maximally Tolerated Statin”

   Definition: “Maximally tolerated statin therapy is defined as the highest tolerated intensity and frequency of a statin, even if the dose is zero.”

2. 3. **“Familial Hypercholesterolemia”**

   **Barrier:** Differing definitions for “Familial Hypercholesterolserolemia”

   Complex requirements and competing definitions provide uncertainty and lack of standardization in qualifying the appropriate patient.

   **Solution:** Define “Familial Hypercholesterolemia”

   - **Homozygous Familial Hypercholesterolemia**
     *HeFH is defined as LDL-C ≥400 mg/dL and ≥1 parent with clinically-diagnosed FH, positive genetic testing for LDL-C‐raising gene defects (LDLR, apoB, PCSK9), or autosomal-recessive FH.

   - **Heterozygous Familial Hypercholesterolemia**
     *HoFH is defined as LDL-C ≥160 mg/dL and ≥1 parent with elevated cholesterol level and ≥1 first-degree relative with FH diagnosed by clinical criteria or positive genetic testing for LDL-C‐raising gene defects (LDLR, apoB, PCSK9), or autosomal traitor.

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Consensus Definitions:

4. “Clinical ASCVD”

**Solution: Define “Clinical Atherosclerotic Cardiovascular Disease”**

“Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke or TIA presumed atherosclerotic, or peripheral arterial disease including significant atherosclerosis of the coronary, carotid, iliofemoral circulations, and the aorta.”

**Barrier: Inconsistent Definition for “Clinical Atherosclerotic Cardiovascular Disease”**

Competing definitions provide uncertainty and lack of standardization in qualifying the appropriate patient:

- ACC/AHA
- IAS

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Consensus Definitions:

5. “Additional Lowering of LDL-Cholesterol”

**Solution: Define “Who require Additional Lowering of LDL-Cholesterol”**

Patients with clinical ASCVD, HeFH, or HoFH who may require additional lowering of LDL-C include those with less than expected percent reduction in LDL-C or residual absolute levels of LDL-C, non-HDL-C, or apoB that exceed goals for atherogenic lipoproteins as specifically defined in any of the current guidelines for these very high-risk and ‘extreme risk’ populations.

**Barrier: Inconsistent Definition for “Who require Additional Lowering of LDL-Cholesterol”**

Competing definitions provide uncertainty and lack of standardization in qualifying the appropriate patient:

- LDL’s relationship to ASCVD, no longer a “hypothesis”
- Multiple levels of evidence: Physiology, RCTs, Mendelian Randomization studies
- Most recent NHANES shows only 20% of such patients have LDL-C < 70mg/dL

Thus there is a large unmet need in the high risk patient population.

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Clinical Cardiology (CLC) Consensus Paper
Open Access
Why the Faulty Process?

- Un-harmonized Cholesterol Guidelines?
- Un-harmonized PCSK9 mab Statements?
- Poor Utilization Review, Adjudication, and Oversight???
Un-harmonized Lipid Guidelines

- AHA/ACC
- ESC/EAS
- AACE

2013 ACC/AHA Guidelines

*STATINS are FIRST-LINE for CVD prevention*

2013 ACC/AHA Cholesterol Guideline

**NET BENEFIT APPROACH**

Strong evidence of net ASCVD risk reduction benefit

- Use statins in 4 patient groups:
  - Clinical ASCVD
  - LDL-C >190 mg/dl
  - Diabetes age 40-75 years
  - 2.5% 10-year ASCVD (hard event) risk

2016 ESC/EAS Guidelines for the Management of Dyslipidemias

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Definition</th>
<th>LDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td>Documented CVD</td>
<td>LDL-C &lt;70 mg/dL or ≥50% reduction if LDL-C 70-135 mg/dL.</td>
</tr>
<tr>
<td>High</td>
<td>Cholesterol &gt;310 mg/dl or BP ≥180/110 mmHg</td>
<td>LDL-C &lt;100 mg/dL or ≥50% reduction if LDL-C 100-200 mg/dL.</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-year risk 1%-5% for fatal CVD</td>
<td>LDL-C &lt;115 mg/dL</td>
</tr>
<tr>
<td>Low</td>
<td>10-year risk &lt;1% for fatal CVD</td>
<td>LDL-C &lt;115 mg/dL</td>
</tr>
</tbody>
</table>
**AACE: CAD Risk Categories and LDL-C Treatment Goals**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Factors</th>
<th>20-Year ASCVD Risk (30-Year PAR)</th>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
<th>Apo B (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High Risk</td>
<td>Established ASCVD or family history of CAD, hypertension, diabetes, obesity, or other risk factors</td>
<td>&gt;7.5%</td>
<td>&lt;100</td>
<td>&lt;180</td>
<td>&lt;50</td>
</tr>
<tr>
<td>High Risk</td>
<td>Diabetes or established ASCVD or family history of CAD, hypertension, obesity, or other risk factors</td>
<td>3% - 7.5%</td>
<td>100 - 180</td>
<td>180 - 250</td>
<td>50 - 70</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>Diabetes, hypertension, or established ASCVD, or family history of CAD in a relative younger than 65 years</td>
<td>1% - 3%</td>
<td>180 - 250</td>
<td>250 - 350</td>
<td>70 - 100</td>
</tr>
<tr>
<td>Low Risk</td>
<td>No major risk factors</td>
<td>&lt;1%</td>
<td>&gt;250</td>
<td>&gt;350</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

**Abbreviations:** ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CHD, coronary heart disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-ethnic Study of Atherosclerosis; NR, not recommended; UKPDS, United Kingdom Prospective Diabetes Study.

**Un-Harmonized and Complex PCSK9i Statements**

- ACC
- NLA
- ASPC/AACE consensus paper

**2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway: Non-statin Therapies for ASCVD**
**2017 RECOMMENDATIONS**

**NLA Expert Panel on Treatment with PCSK9 inhibitors**

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients</th>
<th>Strength</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atherosclerotic cardiovascular disease (ASCVD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Stable ASCVD, with additional ASCVD risk factors LDL-C ≥70mg/dL</td>
<td>High</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>2 Progressive ASCVD LDL-C ≥70mg/dL</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>3a Age 40–79 years, uncontrolled high risk factors or markers for ASCVD LDL-C ≥100 mg/dL</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>3b Age 40–79 years, presence of uncontrolled high risk factors or markers for ASCVD or genetic confirmation of FH LDL-C ≥70 mg/dL</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>3c Age 18–39 years, presence of uncontrolled high risk factors or markers for ASCVD or genetic confirmation of FH LDL-C ≥100 mg/dL</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>3d Homozygous FH, of unknown genotype, or defective LDL receptor LDL-C ≥70 mg/dL</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>

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**Very high risk/statin intolerance**

- Who require substantial atherogenic cholesterol lowering despite use of other lipid-lowering therapies

**FH Foundation's Findings:**

Access to Non-Statin Lipid Lowering Therapies in Patients at High-Risk of Atherosclerotic Cardiovascular Disease or with ASCVD

| Characteristics of Patients Approved and Denied Access to PCSK9 Therapy By Payor |
|--------------------------------------|--------|--------|--------|
| Age                                  | Race    | Gender | Payor  |
|                                     |        |        |        |
|                                    |        |        |        |
|                                    |        |        |        |

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MTD = maximum tolerated dose; PCSK9 = proprotein convertase subtilisin/kexin 9.

Drug Valuation Models: Key Points

- Two Key Metrics: QALY & ICER
- Quality of Adjusted Life Years (QALY)
  - Not a dollar value
  - Expresses 2 variables, Quality and Quantity of life
  - Hinges on 'Utility', the quality of life: 0=Death; 1=Perfect Health
  - Average US citizen has a Utility of 0.825
  - QALY provided by a medicine = Extra time x Utility during that time
    - In valuation analyses 1 QALY = 1 year added with perfect health

Access barrier through PA and high co-pays
Drug Valuation Models: Key Points

- **ICER:** Incremental Cost Effectiveness Ratio
  - A monetary value
  - Relationship between cost and benefit of two different Rx
  - \( \frac{c_1 - c_2}{q_1 - q_2} \)
  - \( c_1 \) = cost of treatment on new drug and \( c_2 \) on SOC
  - \( q_1 \) = new drug’s QALY and \( q_2 \) is QALY with SOC
  - “Acceptable” ICER in 1st world countries is typically 3 times GDP, in US $150,000. Can range from $50,000 to $200,000
  - Choice of ICER Influences “Value” of an Intervention

Why such differences in Model outputs?
Inputs determine outputs and inputs are subjective

- Two Inputs carry most weight:
  - Baseline Event Rate
    - 3.7% vs. 6.2% (Kazi vs. Fonarow) 1, 2
  - Hinges on one’s choice of events: CVA, MI, Death. But don’t hospitalizations for revascularization also matter?
  - Treatment Effect: How the intervention impacts events
  - The importance of their impact can be distorted through the assignment of different Utility Values
    - Kazi Model used 0.96 and 0.88 for MI and CVA respectively 1
    - N.B. the average US citizen has a Utility of 0.825

- Other Important Inputs:
  - Model itself
  - Choice of LDL-C in Base Case
  - Age of patients

Important Caveat

- The Affordable Care Act prohibits the use of QALYs “as a threshold to establish what type of health care is cost effective or recommended.” 1
- Also under the ACA: “The Secretary shall not utilize such an adjusted life year (or such a similar measure) as a threshold to determine coverage, reimbursement, or incentive programs under title XVIII.” 2
Pragmatic Tools to gain PCSK9 mab access for appropriate patients

• Use the CLC paper’s 5 key definitions
• Use the CLC paper’s single page PA and Appeal letters
• Engage the patient: The patient must call the payer. Send your patients to the FH’s on-line patient groups.
• Use The FH Foundation’s Powerful Tool Kit
• Go to Peer-to-Peer and document the doctor’s name in the patient’s chart.
• If all else fails, contact your state insurance commissioner and file a complaint. An investigation will follow. Also contact your state insurance commissioner’s office patient advocacy team.
• Contact the ASPC & join our efforts to improve PCSK9i access
• Do not give up!

For Our Consideration

Why did it become medical societies’ responsibility to further refine drug indications beyond the FDA’s recommendations in drugs’ PIs?