Should PCSK9 Inhibitors be Used in Statin Intolerant Patients?

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Atlanta, GA
Should PCSK9 Inhibitors be Used in Statin Intolerant Patients?

- It depends on whom you ask:
  - FDA
  - Professional Organizations (NLA, ACC, AHA, ADA, AACE)
  - Providers (lipidologists, cardiologists, primary care providers)
  - Patients (FH, ASCVD, statin intolerant, premature family history)
  - Payers
  - Federal Stakeholders (HHS, CMS, VA, DoD, CDC)
  - Pharmaceutical Companies (Amgen, Regeneron/Sanofi, Pfizer)
  - Society (Population)
  - Media (?)
Would you use a PCSK9 inhibitor in the following patients?

- PCSK ARS Questions:
Guidelines on the Use of PCSK9 Inhibitors

Current Recommendations
• FDA (2015)
• NLA (2015)
• European Medicine Authority (2015)
• NICE (2015, 2016)
• Payers- CMS, Managed Care, PBM’s

No Recommendations
• 2013 ACC/AHA Cholesterol Guideline
• ACC (pending)
• AHA
• ADA
**FDA Approved Indications for PCSK9 Inhibitors**

<table>
<thead>
<tr>
<th>ALIROCUMAB AND EVOLOCUMAB</th>
<th>EVOLOCUMAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Indicated as an adjunct to maximally tolerated statin therapy</td>
<td>• Indicated as an adjunct to other LDL-lowering therapies (statins, ezetimibe, LDL apheresis)</td>
</tr>
<tr>
<td>For the treatment of adults</td>
<td>• For patients with homozygous FH</td>
</tr>
<tr>
<td>• With heterozygous familial hypercholesterolemia or</td>
<td>• Who require additional lowering of LDL-cholesterol (LDL-C)</td>
</tr>
<tr>
<td>• Clinical atherosclerotic cardiovascular disease,</td>
<td></td>
</tr>
<tr>
<td>• Who require additional lowering of LDL-cholesterol (LDL-C)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Alirocumab and Evolocumab Prescribing Information (accessed 2016)
Questions about the FDA Indications for PCSK9 Inhibitors

What does the following terms mean?

- Indicated as an adjunct to maximally tolerated statin therapy
  - does this include those with statin intolerance unable to tolerate any dose or any dosing frequency?

- Who require additional lowering of LDL-C
  - does this include those not at LDL-C goal, those with < 50% LDL-C reduction on high intensity statins (± ezetimibe), or those as judged by a clinician to need additional LDL-C reduction given high ASCVD risk (i.e.-recurrent events, ACS,ASCVD)?
National Lipid Association Recommendations - Part 2

National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2

Terry A. Jacobson, MD*, Kevin C. Maki, PhD, Carl E. Orringer, MD, Peter H. Jones, MD, Penny Kris-Etherton, PhD, Geeta Sikand, MA, Ralph La Forge, MSc, Stephen R. Daniels, MD, PhD, Don P. Wilson, MD, Pamela B. Morris, MD, Robert A. Wild, MD, PhD, MPH, Scott M. Grundy, MD, PhD, Martha Daviglus, MD, PhD, Keith C. Ferdinand, MD, Krishnaswami Vijayaraghavan, MD, Prakash C. Deedwania, MD, Judith A. Aberg, MD, Katherine P. Liao, MD, MPH, James M. McKenney, PharmD, Joyce L. Ross, MSN, CRNP, Lynne T. Braun, PhD, CNP, Matthew K. Ito, PharmD, Harold E. Bays, MD, W. Virgil Brown, MD,

On behalf of the NLA Expert Panel
NLA Part 2 Recommendations on PCSK9 Inhibitors

Until cardiovascular outcomes trials are completed with PCSK9 inhibitors, these drugs should be considered primarily in:

- Patients with ASCVD who have LDL-C ≥100 mg/dL (non-HDL-C ≥130 mg/dL) while on maximally-tolerated statin (± ezetimibe) therapy. (B Recommendation)

- Heterozygous FH patients without ASCVD who have LDL-C ≥130 mg/dL (non-HDL-C ≥ 160 mg/dL) while on maximally-tolerated statin (± ezetimibe) therapy. (B Recommendation)

- PCSK9 inhibitors may be considered for selected high risk patients with ASCVD (i.e.- recurrent ASCVD events) who have LDL-C ≥ 70 mg/dl (non-HDL-C ≥100 mg/dL) while on maximally-tolerated statin (± ezetimibe) therapy.** (C Recommendation)

- PCSK9 inhibitors may be considered in selected high or very high risk patients with statin intolerance who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid lowering therapies.** (C Recommendation)

**Such use would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy.

European Medicines Agency Labeling for PCSK9 Inhibitors

- Is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin; or

- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contra-indicated;

- Is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies. (Evolocumab only)

Important Considerations in Using PCSK9 Inhibitors

- Efficacy (LDL-C reduction)
- Outcomes (ASCVD reduction)
- Safety (Long term)
- Cost ($14,000/year)
- Value (Cost-effectiveness)
- Clinical Judgment
- ASCVD Risk
- LDL-C response on maximally tolerated statins
- Shared Decision Making between Patient and Provider
- Patient Preferences
Statin intolerance: A major limitation in the use of statins

• Statin intolerance broadly defined as the inability to tolerate statin therapy due to muscle-related side-effects

• Many patients in clinical practice (approximately 10–25%) report intolerance to statins

Large, well-controlled randomized trials of cholesterol-lowering drugs in statin intolerant patients are lacking

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NLA Definition of Statin Intolerance

Statin intolerance is a clinical syndrome:

- characterized by the inability to tolerate at least 2 statins: one statin at the lowest starting daily dose AND another statin at any daily dose
- due to either objectionable symptoms (real or perceived) or abnormal lab determinations,
- which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge
- with other known determinants being excluded (such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, and underlying muscle disease).

Statin Associated Muscle Symptoms

- Statin associated muscle symptoms (SAMS) is one of the main reasons for statin non-adherence and discontinuation

- Poor statin adherence results in increased cardiovascular morbidity and mortality

- There is a discrepancy in reported SAMS in RCT’s (3-5%) versus “real world” Observational Studies (10-29%).

- There is no “gold standard” diagnostic test for evaluating SAMS.

### PRIMO: Risk of Muscular Symptoms with Individual Statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dosage</th>
<th>Percentage of patients with muscular symptoms*</th>
<th>Odds Ratio† [95% CI]</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>40 mg/day</td>
<td>10.9%</td>
<td>1.421 [1.171–1.723]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40–80 mg/day</td>
<td>14.9%</td>
<td>1.812 [1.463–2.245]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40–80 mg/day</td>
<td>18.2%</td>
<td>0.437 [0.352–0.542]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>80 mg/day</td>
<td>5.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*% values relative to the total number of patients with or without muscular symptoms.
† Odds ratios were calculated using pravastatin as the reference.
‡ P values were determined by Pearson’s Chi-squared test.

Timing of Myalgia in PRIMO

Statin Intolerance as a Barrier to Risk Reduction

- How frequent are SAMS?
- How do we diagnose SAMS?
- How should we manage SAMS?
The STOMP Study: The Effect of Statins on Skeletal Muscle Performance

Effect of Statins on Skeletal Muscle Function
Beth A. Parker, Jeffrey A. Capizzi, Adam S. Grimaldi, Priscilla M. Clarkson, Stephanie M. Cole, Justin Keadle, Stuart Chipkin, Linda S. Pescatello, Kathleen Simpson, C. Michael White and Paul D. Thompson

Circulation. 2013;127:96-103; originally published online November 26, 2012;
STOMP

Subjects (n=440)
- Men and women
- >20 years
- No prior statin use

Design
- Randomised, double blind
- 80 mg atorvastatin vs. placebo for 6 months

Muscle function
- Handgrip strength
- Elbow flexor/extensor
- Knee flexor/extensor

Aerobic performance (VO₂ Max)
Physical activity (accelerometer)
Muscle symptoms - called twice monthly
STOMP: Muscle Symptoms at 6 Months

Assessment made before and after atorvastatin 80 mg or placebo, administered for 6 months to 420 healthy, statin-naive subjects.
What is the probability that the following patient is statin intolerant?

- PCSK9 ARS Part 2 (Statin Intolerance Questions):
Statin Myalgia Clinical Index Score

Regional distribution/pattern

- Symmetric hip flexors/thigh aches 3
- Symmetric calf aches 2
- Symmetric upper proximal aches 2
- Non-specific asymmetric, intermittent 1

Temporal pattern

- Symptoms onset < 4 weeks 3
- Symptoms onset 4–12 weeks 2
- Symptoms onset >12 weeks 1

Dechallenge

- Improves upon withdrawal (2–4 weeks) 1
- Does not improve upon withdrawal 0
- (>4 weeks)

Rechallenge

- Same symptoms reoccur upon rechallenge (< 4 weeks ) 3
- Same symptoms reoccur upon rechallenge (4–12 weeks ) 1

Statin Myalgia Clinical Score

- Probable 9–11
- Possible 7–8
- Unlikely <7

Adapted from Rosenson et al. Journal of Clinical Lipidology (2014) 8: S58–S71
Features of Statin Associated Muscle Symptoms (SAMS)

- Affect large muscle groups (thighs, buttocks, calves and back muscles)
- Usually occur early (within 4–6 weeks) of starting statin; but can occur after many years of treatment.
- May occur with an increase in statin dose, initiation of an interacting drug, or increase in physical activity.
- May appear more rapidly if patient is re-challenged with a statin.
Use of PCSK 9 Inhibitors in Statin Intolerant Patients

Clinical Trials:

- Odyssey Alternative Study (alirocumab)
- Gauss 2 (evolocumab)
- Gauss 3 (evolocumab) (results ACC April 2016)
Unable to tolerate at least 2 different statins, including 1 at the lowest dose, due to muscle-related symptoms

**ODYSSEY ALTERNATIVE Study Design**

Statin intolerant patients* with LDL-C ≥70 mg/dL (very-high CV risk) or ≥100 mg/dL (moderate/high risk)

Double-Blind Treatment Period (24 Weeks)

N=100

**Alirocumab 75/150 mg SC Q2W + placebo PO QD**
administered via single 1-mL injection using prefilled pen for self-administration

N=100

**Ezetimibe 10 mg PO QD + placebo SC Q2W**

N=50

**Atorvastatin 20 mg PO QD + placebo SC Q2W**

Assessments

W -4  W0  W4  W8  W12  W16  W24

Patients discontinued if muscle-related AEs reported with placebos during run-in

Per-protocol dose increase if W8 LDL-C ≥70 or ≥100 mg/dL (depending on CV risk)

Primary endpoint
(LDL-C % change from baseline, ALI and EZE only)
Safety analysis (all groups)

*Unable to tolerate at least 2 different statins, including 1 at the lowest dose, due to muscle-related symptoms

†4-week single-blind placebo run-in follows 2 week washout of statins, ezetimibe and red yeast rice. Patients randomized [R] before entering run-in.

OLTP: Open-label treatment period, W, Week. olume

Patient disposition

Entered placebo run-in (N=361)

Excluded (N=47)
- 25 due to muscle-related AE during placebo run-in (6.9% of those entering run-in)
- 22 due to other inclusion/exclusion criteria

Randomized (N=314)

Alirocumab (N=126) (all patients treated)
- Completed 24 Weeks (N=96)
  - Discontinued: 23.8% (N=30)
    - Due to AE (N=23)
- Primary analysis (N=126)
  - Safety analysis (N=126)

Ezetimibe (N=125) (1 patient not treated)
- Completed 24 Weeks (N=82)
  - Discontinued: 33.6% (N=42)
    - Due to AE (N=31)
- Primary analysis (N=122)
  - Safety analysis (N=124)

Atorvastatin (N=63) (all patients treated)
- Completed 24 Weeks (N=42)
  - Discontinued: 33.3% (N=21)
    - Due to AE (N=16)
- Safety analysis only (N=63)

Entered OLTP – all patients receiving alirocumab* (N=281, 89.5%)
- Discontinued (N=9), Ongoing (N=272)

*Dose ↑ from 75 mg to 150 mg Q2W at W36 based on the LDL-C level at W32 and the judgment of the investigator
Alirocumab Significantly Reduced LDL-C from Baseline to Week 24 versus Ezetimibe

Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C

-45.0% vs. -14.6%

LS mean difference (SE) vs. ezetimibe: -30.4 (3.1); P < 0.0001

Intent-to-treat (ITT) analysis.
*49.5% of 109 patients who received at least one injection after W12 had dose increase.
### Safety Analysis

Safety analysis from double-blind treatment period

<table>
<thead>
<tr>
<th>% of patients</th>
<th>Alirocumab (N=126)</th>
<th>Ezetimibe (N=124)</th>
<th>Atorvastatin (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs</td>
<td>82.5%</td>
<td>80.6%</td>
<td>85.7%</td>
</tr>
<tr>
<td>Treatment-emergent SAEs</td>
<td>9.5%</td>
<td>8.1%</td>
<td>11.1%</td>
</tr>
<tr>
<td>TEAEs leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs leading to discontinuation</td>
<td>18.3%</td>
<td>25.0%</td>
<td>25.4%</td>
</tr>
<tr>
<td>Any skeletal-muscle related TEAE*</td>
<td>32.5%</td>
<td>41.1%</td>
<td>46.0%</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>15.9%</td>
<td>20.2%</td>
<td>22.2%</td>
</tr>
</tbody>
</table>

TEAE = treatment emergent adverse event. TEAE period = time from first to last injection of study treatment + 70 days.

*Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.

Significantly Fewer Skeletal Muscle AEs with Alirocumab than with Atorvastatin

Kaplan-Meier Estimates for Time to First Skeletal Muscle Event*

Cox model analysis:
HR ATV vs. ALI = 1.63 (95% CI: 1.01 to 2.62), p = 0.042
HR EZE vs. ALI = 1.41 (95% CI: 0.94 to 2.13), p = 0.096

*Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.

Interim Safety Results from the Ongoing 3-Year Open-Label Treatment Period (OLTP)

Safety analysis from start of OLTP up to 52 weeks

- 89.5% of randomized patients entered the OLTP.
- All patients in OLTP receive alirocumab 75 mg Q2W (with dose increase possible to 150 mg Q2W after 12 weeks OLTP treatment).

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) exposure during OLE</td>
<td>13.9 (6.8) weeks</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>55.9% (n=157)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4.3% (n=12)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>1.8% (n=5)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>0.7% (n=2)</td>
</tr>
<tr>
<td>TEAE leading to discontinuation</td>
<td>2.8% (n=8)</td>
</tr>
<tr>
<td>Myalgia (leading to discontinuation)</td>
<td>0.7% (n=2)</td>
</tr>
</tbody>
</table>

A Phase 3 Double-blind, Randomized Study to Assess Safety and Efficacy of Evolocumab (AMG 145) in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of Statin

Erik Stroes\(^1\), David Colquhoun\(^2\), David Sullivan\(^3\), Fernando Civeira\(^4\), Robert S. Rosenson\(^5\), Gerald F Watts\(^6\), Eric Bruckert\(^7\), Leslie Cho\(^8\), Ricardo Dent\(^9\), Beat Knusel\(^9\), Allen Xue\(^9\), Rob Scott\(^9\), Scott M Wasserman\(^9\), and Michael Rocco\(^8\) for the GAUSS-2 Investigators

\(^1\)Academic Medical Center, Amsterdam, Netherlands; \(^2\)Wesley Medical Centre, Auchenflower, Australia; \(^3\)Royal Prince Alfred Hospital, Camperdown, Australia; \(^4\)Hospital Universitario Miguel Servet, Zaragoza, Spain; \(^5\)Icahn School of Medicine at Mount Sinai, NY, USA; \(^6\)Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Australia; \(^7\)Hopital Pitié-Salpêtrière, Paris, France; \(^8\)Cleveland Clinic, Cleveland, OH, USA; \(^9\)Amgen, CA, USA

March 30, 2014, Joint ACC/JAMA Late-breaking Clinical Trials Session 402
American College of Cardiology, Washington DC
GAUSS-2 Study Design

Screening period
Fasting LDL-C 5–10 days before randomization
Subcutaneous injection of placebo

End of Study

Randomization 2:2:1:1

- Evolocumab 140 mg SC Q2W + Placebo PO QD
  - N = 103

- Evolocumab 420 mg SC QM + Placebo PO QD
  - N = 102

- Placebo SC Q2W + Ezetimibe 10 mg PO QD
  - N = 51

- Placebo SC QM + Ezetimibe 10 mg PO QD
  - N = 51

Maximum 6 weeks

Time point
- Day 1
- Week 2
- Week 4
- Week 6
- Week 8
- Week 10
- Week 12
- Week 14

- QM EOS
- Q2W EOS*

*Phone call for AEs, SAEs. AEs, adverse events; EOS, end of study; LDL-C, low-density lipoprotein cholesterol; SAEs, serious adverse events; SC, subcutaneous; PO, oral; Q2W, every 2 weeks (biweekly); QM, monthly

Stroes E. et al. JACC 2014;63(23):2541-2548
### GAUSS-2: Baseline Characteristics II

<table>
<thead>
<tr>
<th></th>
<th>Biweekly</th>
<th>Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO Q2W + EZE QD (N = 51)</td>
<td>Evolocumab 140 mg Q2W + PBO QD (N = 103)</td>
</tr>
<tr>
<td>Number of intolerable statins, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>≥ 3</td>
<td>51</td>
<td>55</td>
</tr>
<tr>
<td>≥ 4</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Worst muscle-related side effect*, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Myositis</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lipid lowering therapy, %</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>Statin use, %</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

*Data missing for one patient in the evolocumab Q2W arm

EZE, ezetimibe; PBO, placebo; Q2W, biweekly; QM, monthly; QD, daily

Stroes E. et al. JACC 2014;63(23):2541-2548
GAUSS-2: Evolocumab
Primary Endpoint *Biweekly* Dose

**Primary Endpoint**

<table>
<thead>
<tr>
<th>Study Week</th>
<th>BL, Day 1</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 10</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Percent Change in LDL-C from Baseline</strong></td>
<td>-18%</td>
<td>-56%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Study Drug Administration**

- **1: Ezetimibe (N = 51)**
- **2: Evolocumab 140 mg Q2W (N = 103)**

BL, baseline. Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values. *P* value is multiplicity adjusted.
GAUSS-2: Safety and Tolerability

<table>
<thead>
<tr>
<th>Adverse Events (AEs), n(%)</th>
<th>Ezetimibe (N = 102)</th>
<th>Evolocumab (N = 205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent AEs</td>
<td>74 (73)</td>
<td>135 (66)</td>
</tr>
<tr>
<td>Common treatment-emergent AEs (≥5% of patients in either treatment arm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9 (9)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>18 (18)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Extremity pain</td>
<td>1 (1)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>4 (4)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (10)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (7)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (7)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>5 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>4 (4)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>AEs leading to study drug discontinuation</td>
<td>13 (13)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Potential injection site reactions*</td>
<td>8 (8)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Muscle-related SMQ†</td>
<td>23 (23)</td>
<td>25 (12)</td>
</tr>
<tr>
<td>Neurocognitive AEs††</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anti-evolocumab antibodies‡</td>
<td>NA</td>
<td>0</td>
</tr>
</tbody>
</table>

*Reported using high-level term grouping, including IS - rash, inflammation, pruritus, reaction, urticaria. †Standard MedDRA Queries. ††Searched HLGT terms: Deliria (incl confusion); Cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders. *Binding or neutralizing; data missing for one patient. NA = not applicable
COST-EFFECTIVENESS OF PCSK9 INHIBITORS
AN ANALYSIS FROM THE CVD POLICY MODEL

Target Populations

- FH population
  - LDL-C ≥ 200mg/dL on statins or LDL-C ≥ 250mg/dL off statins

- Atherosclerotic CVD requiring additional lipid lowering
  - On statins but not at goal (LDL ≥ 70mg/dL)
  - Statin-intolerant (subset of those not using statins), LDL ≥ 70mg/dL
Costs

- Annual drug costs = average wholesale acquisition costs:
  - Statin: $812
  - PCSK9 inhibitor: $14,350 (average of two agents)
Outcomes

- Major Adverse Clinical Outcomes (MACE):
  - Nonfatal myocardial infarction, nonfatal stroke, CVD death
- Number-needed-to-treat over 5 years ($NNT_5$)
- Health care costs related to cardiovascular disease
- Quality-adjusted life years (QALYs)
- Incremental cost-effectiveness ratio: $/$QALY
Results: FH

- 605,000 patients in 2015

<table>
<thead>
<tr>
<th></th>
<th>Total MACE averted</th>
<th>NNT&lt;sub&gt;5&lt;/sub&gt;</th>
<th>QALYs gained</th>
<th>Incremental Drug Costs (million $)</th>
<th>Incremental Costs, Other CV Care (million $)</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>comparator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin + PCSK9 inhibitor</td>
<td>324,200</td>
<td>28</td>
<td>665,200</td>
<td>$210,516</td>
<td>-$17,304</td>
<td>$290,000</td>
</tr>
</tbody>
</table>

### Results: CVD on statins, not at goal

7,271,000 patients in 2015

<table>
<thead>
<tr>
<th></th>
<th>Total MACE averted</th>
<th>NNT&lt;sub&gt;5&lt;/sub&gt;</th>
<th>QALYs gained</th>
<th>Incremental Drug Costs (million $)</th>
<th>Incremental Costs, Other CV Care (million $)</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin comparator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin + PCSK9 inhibitor</td>
<td>5,621,800</td>
<td>21</td>
<td>10,573,800</td>
<td>$3,406,692</td>
<td>-$210,702</td>
<td>$302,000</td>
</tr>
</tbody>
</table>

### Results: CVD, statin-intolerant

- **1,460,000 patients in 2015**

<table>
<thead>
<tr>
<th></th>
<th>Total MACE averted</th>
<th>NNT&lt;sub&gt;5&lt;/sub&gt;</th>
<th>QALYs gained</th>
<th>Incremental Drug Costs (million $)</th>
<th>Incremental Costs, Other CV Care (million $)</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(no statin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment)</td>
<td>comparator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>**PCSK9 inhibitor</td>
<td>1,254,400</td>
<td>21</td>
<td>2,366,000</td>
<td>$693,450</td>
<td>-$44,627</td>
<td>$274,000</td>
</tr>
</tbody>
</table>

## Threshold Analyses

<table>
<thead>
<tr>
<th>Patient Subpopulation</th>
<th>Willingness-to-pay threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$50,000/QALY</td>
</tr>
<tr>
<td>FH - Main simulation</td>
<td>$3,400</td>
</tr>
<tr>
<td>FH - Additional Scenario Analysis (first treat all with statin)</td>
<td>$3,000</td>
</tr>
<tr>
<td>ASCVD - Statin intolerant LDL-C ≥ 70 mg/dL</td>
<td>$3,400</td>
</tr>
<tr>
<td>ASCVD on statins LDL-C ≥ 70 mg/dL</td>
<td>$3,100</td>
</tr>
<tr>
<td>ASCVD, restricting to first-ever MI</td>
<td>$4,300</td>
</tr>
<tr>
<td>ALL SUBPOPULATIONS</td>
<td>$3,166</td>
</tr>
</tbody>
</table>

# Budget Impact: Results at 5 Years

<table>
<thead>
<tr>
<th>Population</th>
<th>Number Treated (thousands)</th>
<th>Annualized Budget Impact (billions)</th>
<th>Discount to Match Annual Budget Impact Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH</td>
<td>453</td>
<td>$3.7</td>
<td>28.4%</td>
</tr>
<tr>
<td>CVD, Statin-intolerant</td>
<td>365</td>
<td>$3.0</td>
<td>10.1%</td>
</tr>
<tr>
<td>CVD, Not at goal</td>
<td>1,818</td>
<td>$14.7</td>
<td>79.3%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2,636</td>
<td>$21.4</td>
<td>84.8%</td>
</tr>
</tbody>
</table>

Important Considerations in Using PCSK9 Inhibitors

- Efficacy (LDL-C reduction)
- Outcomes (ASCVD reduction)
- Safety (Long term)
- Cost ($14,000/year)
- Value (Cost-effectiveness)
- Clinical Judgment
- ASCVD Risk
- LDL-C response on maximally tolerated statins
- Shared Decision Making between Patient and Provider
- Patient Preferences
Conclusion: Should PCSK9 Inhibitors be Used in Statin Intolerant Patients?

- It depends on whom you ask, and whether the perspective is that of the individual, the provider, the payer, or society.

- The data from the long term outcomes and safety studies will better inform the true value of PCSK9 therapy, weighing the benefits (NNT), the risks (NNH), and the cost.

- More research is needed to identify which patients are truly statin intolerant and how to best manage “statin associated muscle symptoms (SAMS).”

- A more structured approach to identifying statin intolerance is needed and a validated questionnaire may be useful to both patients and providers.

- Determining best practices for the use of PCSK9 inhibitors in statin intolerant patients is an opportunity for lipidologists and the NLA.