PCSK9 Inhibitors – Are They Worth The Money?

Michael J. Blaha MD MPH
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• **SGE for the FDA, Endocrinologic and Metabolic Drug Advisory Committee (EMDAC)**
  – Worked on the regulatory side of PCSK9 approvals
Learning Objectives

By the conclusion of this talk, you will be able to:

* Provide evidence supporting the LDL Hypothesis
* Describe basic PCSK9 biology
* Discuss the results of the GLAGOV and FOURIER randomized controlled trials with patients
* Understand the role of PCSK9 Inhibitors in the new 2017 ACC Expert Pathway Consensus Document
* Summarize the general cost **ineffectiveness** of this class of drugs – and what to do about it
Modern Humans – Higher Cholesterol Than Our Ancestors!

Genetics of LDL Lowering

Very Low Levels of LDL and the Risk of Cardiovascular Events
A Meta-Analysis of Statin Trials

“IMPROVE-IT provides us with important information on the value of lowering LDL-C levels, regardless of the agent used. These data help emphasize the primacy of LDL-C lowering as a strategy to prevent CHD”

The Science Behind PCSK9 Inhibitors

Analysis of DNA-sequence variations from the ARIC Study that reduce plasma levels of LDL-cholesterol and their impact on coronary events

Black subjects (n=3363), 2.6% prevalence of PCSK9 LOF mutations, 28% reduction in LDL-C, and 88% RR in CHD events

Cohen JC et al. NEJM 2006;354:1264-1272
Interaction of LDL-Cholesterol, the LDL-Receptor, and PCSK9

PCSK9 promotes the degradation of the LDL-receptor and prevents it from recycling to the cell membrane.

PCSK9=Proprotein convertase subtilisin/kexin type
PCSK9 inhibitors are monoclonal antibodies that bind to PCSK9 and prevent association between the LDL-receptor and PCSK9.
## Currently Available PCSK9 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approval</td>
<td>July 2015</td>
<td>August 2015</td>
</tr>
<tr>
<td>Indication</td>
<td>Adjunct to diet and max tolerated statin for adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C</td>
<td>Adjunct to diet and max tolerated statin for adults with HeFH, or clinical ASCVD, who require additional lowering of LDL-C, HoFH pts on other LTT</td>
</tr>
<tr>
<td>Dosing</td>
<td>75 – 150 mg SC Q2W</td>
<td>140 mg SC Q2W or 420 mg SC monthly</td>
</tr>
<tr>
<td>How supplied</td>
<td>Single-use pre-filled autoinjector pens and pre-filled glass syringes that deliver – 75 mg/mL or 150 mg/mL</td>
<td>Single-use pre-filled syringe or SureClick® autoinjector that deliver – 1mL of 140 mg/mL</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Check LDL-C levels 4 to 8 weeks after initiating or after titrating therapy</td>
<td>Check LDL-C levels 4 to 8 weeks after initiating</td>
</tr>
<tr>
<td>Side effects</td>
<td>Nasopharyngitis; injection site reactions; hypersensitivity reactions</td>
<td>Nasopharyngitis; injection site reactions; hypersensitivity reactions</td>
</tr>
</tbody>
</table>

HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous FH. LLT = lipid lowering therapy.

www.fda.gov.
GAUSS-2:
Evolocumab in Statin Intolerant Patients

1: Ezetimibe (N=51) + PBO Q2W
2: Evolocumab 140 mg Q2W (N=103)
3: Ezetimibe (N=51) + PBO Q4W
4: Evolocumab 420 mg QM (N=102)

Mean Change in LDL-C from Baseline (%)

Day: 1 Baseline
Study Week

Study Drug Administration Q2WK SC
Study Drug Administration Q4WK SC

Evolocumab – Extension Study

OSLER Program (OSLER-1 and OSLER-2 Studies)

4,465 patients from phase 2 and 3 studies evaluating evolocumab (140 Q2W or 420 Q4W) as compared to placebo for a median of 11.1 months

73.6% vs 3.8% achieved LDL-C < 70 mg/dL

Sabatine MS et al. NEJM 2015;372:1500-1509
From: **Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis**


Relative risk reduction per 1-mmol/L (38.7-mg/dL) reduction in LDL-C: 23% (relative risk, 0.77 [95% CI, 0.75-0.79]; *P*<.001)

- Squares – Upregulation of LDL receptor
- Circles – Other mechanisms
INTERVENTIONS  Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420 mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks, in addition to statins.
GLAGOV – Percent Change in LDL-C During Treatment

Study Week

Mean LDL-C 93.0 mg/dL
Change from baseline 3.9%

Mean LDL-C 36.6 mg/dL
Change from baseline -59.8%

90 mg/dL
29 mg/dL
GLAGOV Primary Endpoint: Percent Atheroma Volume

<table>
<thead>
<tr>
<th>Change in Percent Atheroma Volume (%)</th>
<th>Statin monotherapy</th>
<th>Statin-evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>-0.2</td>
<td>-0.95</td>
</tr>
<tr>
<td>P = NS</td>
<td>P &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td></td>
<td></td>
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</tbody>
</table>

0.05 - 0.95

-0.2 - 0.6

-0.8 - 0.4
GLAGOV:
Mean On-Treatment LDL-C vs. Change in PAV

Locally Weighted Polynomial Regression (LOESS) Plot with 95% confidence limits
FOURIER
Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

MS Sabatine, RP Giugliano, AC Keech, N Honarpour, SM Wasserman, PS Sever, and TR Pedersen, for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017
 Trial Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

RANDOMIZED DOUBLE BLIND

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

Follow-up Q 12 weeks

LDL Cholesterol

Placebo

59% mean reduction (95%CI 58-60), P<0.00001

Absolute reduction: 56 mg/dl (95%CI 55-57)

Evolocumab

(median 30 mg/dl, IQR 19-46 mg/dl)
## Safety

<table>
<thead>
<tr>
<th>Adverse events (%)</th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>77.4</td>
<td>77.4</td>
</tr>
<tr>
<td>Serious</td>
<td>24.8</td>
<td>24.7</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Treatment-related and led to d/c of study drug</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Cataract</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Diabetes (new-onset)</td>
<td>8.1</td>
<td>7.7</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>1.6</td>
<td>1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory results (%)</th>
<th>Evolocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding Ab</td>
<td>0.3</td>
<td>n/a</td>
</tr>
<tr>
<td>Neutralizing Ab</td>
<td>none</td>
<td>n/a</td>
</tr>
</tbody>
</table>

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC
Primary Endpoint

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001

Placebo

14.6%

Evolocumab

12.6%
# Types of CV Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Evolocumab (N=13,784)</th>
<th>Placebo (N=13,780)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-yr Kaplan-Meier rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD, MI, stroke, UA, or revasc</td>
<td>12.6</td>
<td>14.6</td>
<td>0.85 (0.79-0.92)</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>7.9</td>
<td>9.9</td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>MI</td>
<td>4.4</td>
<td>6.3</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
<tr>
<td>Hosp for unstable angina</td>
<td>2.2</td>
<td>2.3</td>
<td>0.99 (0.82-1.18)</td>
</tr>
<tr>
<td>Coronary revasc</td>
<td>7.0</td>
<td>9.2</td>
<td>0.78 (0.71-0.86)</td>
</tr>
<tr>
<td>Urgent</td>
<td>3.7</td>
<td>5.4</td>
<td>0.73 (0.64-0.83)</td>
</tr>
<tr>
<td>Elective</td>
<td>3.9</td>
<td>4.6</td>
<td>0.83 (0.73-0.95)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4.8</td>
<td>4.3</td>
<td>1.04 (0.91-1.19)</td>
</tr>
</tbody>
</table>
Comorbidities include age >65, diabetes, recent (<3 months) acute ASCVD event, ASCVD event while on a statin, substantial residual coronary disease, PAD, baseline LDL-C >190 mg/dL, poorly controlled major ASCVD risk factors, smoking, elevated Lp(a), and chronic kidney disease.

ACC Expert Consensus Pathway on Non-Statin Therapies

Stable ASCVD with comorbidities on statin for 2º prevention

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin. Consider referral to lipid specialist if statin intolerant.
5. Control other risk factors.

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin

Yes

Monitor adherence to meds & lifestyle, & LDL-C response

No

Monitor adherence to meds & lifestyle, & LDL-C response

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin

Yes

No

Lloyd-Jones DM, et al. JACC. 2017
ACC Expert Consensus Pathway on Non-Statin Therapies

Stable ASCVD with comorbidities on statin for 2\(^{o}\) prevention

Clinician-patient discussion factors to consider
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy.
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy.
3. Patient preferences.

Optional non-statin meds to consider
- Ezetimibe

No

Patient has \(\geq 50\%\) LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin/other medications

Yes

Decision for no additional medication

Monitor adherence to meds & lifestyle, & LDL-C response

* Factors favoring ezetimibe include need for <25% LDL lowering, age >75, cost, desire for oral therapy, recent ACS

* Factors favoring PCSK9i include need for >25% LDL lowering

With Trial Results, Should Amgen Reconsider Its Pricing For Repatha?

Harlan Krumholz, CONTRIBUTOR

So now we have evidence of the size of the benefit, should the pricing be adjusted accordingly? The trial indicated that for every $10,000 a year—then it would cost about $1.4 million for every event averted.

The cost of Repatha is about $14,000/year. Is it worth it?
Updated Cost-effectiveness Analysis of PCSK9 Inhibitors Based on the Results of the FOURIER Trial

Cost-effectiveness of Evolocumab Therapy for Reducing Cardiovascular Events in Patients With Atherosclerotic Cardiovascular Disease

Gregg C. Fonarow, MD; Anthony C. Keech, MD; Terje R. Pedersen, MD; Robert P. Giugliano, MD, SM; Peter S. Sever, PhD, FRCP; Peter Lindgren, PhD; Ben van Hout, PhD; Guillermo Villa, PhD; Yi Qian, PhD; Ransi Somaratne, MD; Marc S. Sabatine, MD, MPH

Updated Cost-effectiveness Assessments of PCSK9 Inhibitors From the Perspectives of the Health System and Private Payers Insights Derived From the FOURIER Trial

Alejandro Arrieta, PhD; Jonathan C. Hong, MD, MHS; Rohan Khera, MD; Salim S. Virani, MD, PhD; Harlan M. Krumholz, MD, SM; Khurram Nasir, MD, MPH
Cost-effectiveness of PCSK9 Inhibitors
Proof in the Modeling

Robert O. Bonow, MD, MS; Robert A. Harrington, MD; Clyde W. Yancy, MD, MSc

In the 3 analyses,¹⁻³ a variety of scenarios and sensitivity analyses resulted in variations of these estimates, but all indicated that a substantial reduction in annual drug costs (a 62%-71% reduction in the projected price of more than $14 000 per person per year) would be required to achieve what is considered a societally acceptable ICER of $100 000 per QALY gained.
“Current pricing of PCSK9 inhibitors abjectly fails every analysis of cost-effectiveness.....As currently offered, PCSK9 inhibitor therapy restricts access to care & likely accentuates disparities.”

“....the path forward currently requires only 1 intervention: lower the cost.”
“Painful as it is, draconian restrictions on access to drugs that are priced for profit maximization out of proportion to any value proposition.....may continue to be the only way medicine can send a strong signal to innovators that their future rewards are tied not just to scientific advancement but also to affordability.”
Association of Prior Authorization and Out-of-pocket Costs With Patient Access to PCSK9 Inhibitor Therapy

Ann Marie Navar, MD, PhD; Benjamin Taylor, PhD; Hillary Mulder, MS; Eugene Fievitz, MSc; Keri L. Monda, PhD; Anna Fievitz, BS; Juan F. Maya, MD, MS; J. Antonio G. López, MD; Eric D. Peterson, MD, MPH

Key Points

**Question**  What is the association of prior authorization and copay with patient access to PCSK9 inhibitors among those who are prescribed therapy?

**Findings**  In this observational analysis, in the first year of PCSK9 inhibitors availability, only 47.2% of patients prescribed PCSK9 inhibitors received insurance approval for therapy, and of those, 34.7% never filled the prescription from the pharmacy. Prescription abandonment was largely explained by out-of-pocket cost.

**Meaning**  Less than one-third of patients prescribed PSCK9 inhibitors therapy never received therapy owing to a combination of lack of insurance approval and cost sharing.
What Determines NNT with Lipid-Lowering Therapy?

1. Pre-Treatment LDL-C
Simulation of Lipid-Lowering Therapy Intensification in a Population With Atherosclerotic Cardiovascular Disease

Christopher P. Cannon, MD; Irfan Khan, PhD; Alexa C. Klimchak, MS; Matthew R. Reynolds, MD, MSc; Robert J. Sanchez, PhD; William J. Sasiela, PhD

RESULTS  Inclusion criteria were met by 105,269 individuals in the database cohort (57.2% male and 42.8% female; mean [SD] age, 65.1 [12.1] years). In the simulation cohort (1 million patients; 54.8% male and 45.2% female; mean [SD] age, 66.4 [12.2] years), before treatment intensification, 51.5% used statin monotherapy and 1.7% used statins plus ezetimibe. Only 25.2% achieved an LDL-C level of less than 70 mg/dL. After treatment intensification, 99.3% could achieve an LDL-C level of less than 70 mg/dL, including 67.3% with statin monotherapy, 18.7% with statins plus ezetimibe, and 14% with add-on PCSK9 inhibitor.

CONCLUSIONS AND RELEVANCE  Large gaps exist between recommendations and current practice regarding LLT in the population with ASCVD. In our model that assumes no LLT intolerance and full adherence, intensification of oral LLT could achieve an LDL-C level of less than 70 mg/dL in most patients, with only a modest percentage requiring a PCSK9 inhibitor.
Estimation of Eligibility for Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors and Associated Costs Based on the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)

Insights From the Department of Veterans Affairs

**Figure.** Cost implications of titrating FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk)-eligible patients to high-intensity statin and ezetimibe. LDL-C indicates low-density lipoprotein cholesterol.
What Determines NNT with Lipid-Lowering Therapy?

1. Pre-Treatment LDL-C
2. Absolute Risk of the Patient
FOURIER – Increased Evolocumab Benefit with High Risk Features

Qualifying MI <2 yrs ago
- 24% RRR
- HR 0.76 (95% CI 0.64-0.89)
- Δ 2.9%
- NNT 35
- P<0.001

≥2 Prior MIs
- 21% RRR
- HR 0.79 (95% CI 0.67-0.94)
- Δ 2.6%
- NNT 38
- P=0.006

Multivessel Disease
- 30% RRR
- HR 0.70 (95% CI 0.58-0.84)
- Δ 3.4%
- NNT 29
- P<0.001

Qualifying MI ≥2 yrs ago
- 13% RRR
- Δ 1.0%
- NNT 101

1 Prior MI
- 16% RRR
- Δ 1.7%
- NNT 60

No Multivessel Disease
- 11% RRR
- Δ 1.3%
- NNT 78

Sabatine MS et al. AHA 2017
Figure 3 Clinical decision algorithm for the use of a PCSK9 inhibitor in patients with atherosclerotic cardiovascular disease (ASCVD) and with sub-

Patients with clinical ASCVD
(CAD, symptomatic PAD, ischaemic stroke)
On maximally tolerated statin therapy

± Ezetimibe*  
* According to clinical judgement
and local guidance

- LDL-C >3.6 mmol/L
  (>140 mg/dL)

- LDL-C >2.6 mmol/L (>100 mg/dL) and with additional
  indices of risk severity*

  § Including
  - Familial hypercholesterolaemia
  - Diabetes mellitus with target organ damage
    (e.g. proteinuria), or with a major risk factor such as
    marked hypertension
  - Severe and/or extensive ASCV (e.g. severe polyvascular
    disease, extensive coronary disease - refer to Box 3)
  - Rapid progression of ASCVD, i.e. repeated ACS,
    unplanned coronary revascularizations, or ischaemic
    strokes within 5 years of the index event
Summary

- Achieving very low LDL (<50-70 mg/dL) appears both safe and effective in multiple studies.

- PCSK9i, as add-on to statins, have been shown to produce coronary plaque regression and modestly reduce cardiovascular events (evolocumab).

- PCSK9i are not cost effective for most patients.

- PCSK9i are reasonable to consider as second to third line therapy in highest risk secondary prevention with inadequately treated LDL (>100-140 mg/dL).
THANK YOU!