Dilemma in Dyslipidemia management
Is there a new place for PSCK9 therapy?

By

DR. YEHIA KISHK

Professor of Cardiology; Assiut University

February 2018

Agenda

• Limitations of Current Statin Therapies patients with ASCVD and hypercholesterolemia.
• The mechanism of action for PCSK9 inhibitors.
• Clinical Trials for PCSK9 inhibitors.
Benefits of Decreased LDL-C

LDL: Lower is Better

Meta-analysis of 8 Statin Trials (Moderate- to High-Intensity Dosing): Patients Who Achieved Very Low LDL Levels Had Lower Risk for Major Cardiovascular Events

Adjusted* Hazard Ratio for Major CV Events

*adjusted for sex, age, smoking, diabetes, SBP, HDL-C, and trial

** > 200 mg/dL for non-HDL-C

Cutoffs: LDL-C, ApoB, non-HDL-C

Achieved On-Trial Atherogenic Cholesterol and Lipoprotein Concentration, mg/dL

Abbreviations: apo, apolipoprotein; CV, cerebrovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Efficacy of Intensive LDL-C Lowering in Patients With Low Baseline LDL-C

Meta-analysis of randomized controlled trials of major vascular events (coronary death, myocardial infarction, coronary revascularization, and ischemic stroke) with at least 1,000 patients and ≥2 years of more vs. less intense statin dosage (N=169,138)

For each 39 mg/dL reduction in LDL-C:

- Individuals with baseline LDL-C <77 mg/dL had a 29% further reduction in major vascular events (P=0.007)
- Those with baseline LDL-C <70 mg/dL had a 37% further reduction in major vascular events (P=0.004)


Despite Statins Therapy, a Substantial Residual Risk Remains

A meta-analysis of 21 randomized clinical trials (n=129,526) revealed that Statin treatment prevented approximately 2 out of 10 major vascular events* (a 22% relative risk reduction, p<0.0001)

Statins prevent approximately 2 out of 10 events

* Coronary death, nonfatal myocardial infarction, coronary revascularisation or stroke

Limitations of Statin Therapy

- Doubling the dose of the statin decreases the LDL level further by only 6%.
- Intolerance: characterized by the inability to tolerate at least 2 statins. About 10–15% of patients are Statin Intolerant.
- Lack of Adherence: 40% to 70% of patients discontinue statin therapy within one year of initiation.
- Risk of Type II diabetes, liver damage, rhabdomyolosis.


2016 ACC Consensus Statement on Addition of non-statin drug

Non-statins may be considered in:

- High-risk patients and failure to achieve at least a 50% reduction in LDL-C on maximally tolerated statin,
- Patients who can not take a statin or an effective dose.
- Almost all patients with Ho / He FH.

Non-statins may be considered in this order:

1. Ezetimibe – first additional medication added
2. Bile acid sequenstrants – inefficacy of/intolerance to ezetimibe
3. PCSK9 inhibitors if therapy goals are not met on maximally tolerated statin/ezetimibe therapy

Proprotein convertase subtilisin/kexin type 9 (PCSK9)

LDL receptor pathways in hepatocytes

Monoclonal antibodies to PCSK9

PCSK 9 is synthetized in ER and its 1ry function is regulation of LDLR levels by its effect on receptor recycling.

PCSK 9 Inhibitors

PCSK 9 inhibitors are probably the most promising and the next wonder drug after statins that may save the lives of millions of people in the future.

- **Evolocumab (Repatha®)** marketed by Amgen
- **Alirocumab (Praluent®)** Currently marketed by Sanofi
- **Bococizumab** Expected release around 2017-2018 by Pfizer


HeFH: heterozygous familial hypercholesterolemia
HoFH: homozygous familial hypercholesterolemia
ASCVD: atherosclerotic cardiovascular disease


Images available from: https://www.repathahcp.com/
Clinical Trials For Currently Marketed Evolocumab (Repatha®) and Alirocumab (Praluent®)

- DESCARTES Trial
- ODYSSEY Long-Term Trial
- FOURIER Trial
- GLAGOV Trial
DESCARTES trial

- 2120 patients with LDL levels >75 mg/dl were included:
- Of the 901 patients who received a study drug,
  111 received background lipid-lowering therapy with diet alone,
  383 received 10 mg of atorvastatin daily,
  218 received 80 mg of atorvastatin daily, and
  189 received 80 mg of atorvastatin plus 10 mg of ezetimibe daily.

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Patient Population</th>
<th>Treatments * In addition to statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESCARTE S</td>
<td>Background therapy of:</td>
<td>In addition to background therapy:</td>
</tr>
<tr>
<td></td>
<td>Diet</td>
<td>1) Evolocumab</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin 10 mg</td>
<td>2) Placebo</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atorvastatin 80 +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zetia</td>
<td></td>
</tr>
</tbody>
</table>

**Primary:** % change from baseline in LDL-C at week 52

**Secondary:**
- % change from baseline in LDL-C at week 12 and 52.
- % of patients with LDL-C <70 mg/dL at wk 52
- % changes from baseline for TC, HDL-C, ApoB, VLDL-C, TG, and Lp(a) at wk 52

Percent Reduction from Baseline in LDL Levels in the Evolocumab Group, as Compared with Placebo Group, at Weeks 12 and 52, According to Background Lipid-Lowering Therapy.
A randomized trial involving 2341 patients at high risk for cardiovascular events who had LDL cholesterol levels of >70 mg/dl were receiving treatment with statins at the maximum tolerated dose with or without other lipid-lowering therapy.

Patients were randomly to receive alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks for 78 weeks.
ODYSSEY Long-Term Trial (Alirocumab)

**Post-Acute coronary syndromes age ≥40 yrs**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>780</th>
<th>754</th>
<th>747</th>
<th>746</th>
<th>716</th>
<th>708</th>
<th>694</th>
<th>676</th>
<th>659</th>
<th>652</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>1330</td>
<td>1473</td>
<td>1458</td>
<td>1436</td>
<td>1412</td>
<td>1386</td>
<td>1359</td>
<td>1349</td>
<td>1324</td>
<td>1269</td>
<td></td>
</tr>
</tbody>
</table>


Conclusions

Over a period of 78 weeks, alirocumab, when added to statin therapy at the maximum tolerated dose, significantly reduced the risk of cardiovascular events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%). In a post hoc analysis, the rate of major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal p=0.02).

The New England Journal of Medicine

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease


For the FOURIER Steering Committee and Investigators

**ABSTRACT**

Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and lowers low-density lipoprotein cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.

**METHOD**

We conducted a randomized, double-blind, placebo-controlled trial involving 22364 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization. The 3 years efficacy and safety data for the
FOURIER Trial: Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk

This randomized, double-blind, placebo-controlled trial investigated the effects of adding evolocumab to high-intensity statin therapy compared with high-intensity statins alone.

**Abbreviations:** FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol.

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; MI, myocardial infarction.


### Endpoints

**Primary Endpoint** Major cardiovascular events, defined as the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization.

**Secondary Endpoint** Composite of cardiovascular death, MI, or stroke.

---

**Cumulative event rates for the primary efficacy endpoint**

(Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)

**Cumulative rates for the key secondary efficacy endpoint**

(Composite of cardiovascular death, MI, or stroke)

---

SJ Nicholls and coauthors

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial

Published online November 15, 2016

Available at jama.com and mobile.jamanetwork.com
The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment 5/2013 to 1/2015) conducted at 197 academic and community hospitals in 6 continents, enrolling 968 patients (mean age 59.8 years, 27.8% female) with CAD.

Patients with angiographic CAD were randomized to receive monthly evolocumab (420 mg) (n=484) or placebo (n=484) SQ for 76 weeks, in addition to statins. Locally weighted polynomial regression (LOESS) plot demonstrates a linear continuous relationship between achieved LDL-C level and PAV progression/regression for levels of LDL-C ranging from 110 mg/dL to as low as 20 mg/dL.

**Abbreviations:** CAD, coronary artery disease; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody; LDL-C, low-density lipoprotein cholesterol; SQ, subcutaneous.

**With a PCSK9 Antibody as Measured by Intravascular Ultrasound**

**Trial design:** Patients with CAD and elevated LDL-C on statin therapy were randomized to SQ evolocumab (n=484) vs SQ placebo (n=486).

**Results**

- Nominal change in percent atheroma volume at 78 weeks: -0.95% in the evolocumab group vs. 0.05% in the placebo group (P<0.001 for between-group comparison)
- Patients with plaque regression: 64.3% with evolocumab vs. 47.3% with placebo (P<0.001)
- Major adverse cardiac events: 12.2% with evolocumab vs. 15.3% with placebo

**Conclusions**

- Among patients with angiographic evidence of CAD on chronic statin therapy, the PCSK9 inhibitor evolocumab resulted in a greater change in percent atheroma volume and a greater proportion of patients with plaque regression.

**Abbreviations:** CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; SQ, subcutaneous.

Lipid-Lowering Drug Therapies, Starting Dosages, and Dosage Ranges

PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCSK9 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alirocumab</td>
<td>75 mg every 2 weeks</td>
<td>75-150 mg every 2 weeks</td>
<td>SQ</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>140 mg every 2 weeks or 420 mg once monthly</td>
<td>Not applicable</td>
<td>SQ</td>
</tr>
</tbody>
</table>

**Metabolic Effects:**
- ↓LDL-C 48%-71%; ↓non-HDL-C 49%-58%, ↓TC 36%-42%, ↓Apo B 42%-55% by inhibiting PCSK9 binding with LDLRs, increasing the number of LDLRs available to clear LDL, and lowering LDL-C levels

**Main Considerations:**
- Require subcutaneous self-injection; refrigeration generally needed
- Overall levels of adverse reactions and discontinuation very low
- Adverse reactions with significantly different rates between drug and placebo were: local injection site reactions and influenza
- The most common adverse reactions with similar rates for drug vs. placebo were:
  - **Alirocumab**: nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia
  - **Evolocumab**: nasopharyngitis, back pain, and upper respiratory tract infection

Abbreviations: apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SQ, subcutaneous injection; TC, total cholesterol.


---

**Conclusions**

- Statins are as effective in reducing atherosclerotic CVD risk.
- 10 to 15% of patients are Statin Intolerant and 40% to 70% of patients/year are non-adherent.
- Monoclonal antibodies to PCSK9 added to statins, inhibit LDL-receptor degradation and ↓LDL-C by 55-60%.
- They reduce apoB, TG and TC significantly with modest increase in HDL-C.
Conclusions

- Alirocumab and evolcumarb are indicated in addition to diet and maximally tolerated statin therapy in patients with ASCVD or Homo/Heterozygous FH who require more LDL-C reduction.
- Given by S.C injections once or twice a month.
- Safety and tolerability profile have so far been excellent.
EBBINGHAUS: Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects

N=1,974 patients from FOURIER Study, followed for 96 weeks

- EBBINGHAUS is the first prospectively designed study to evaluate the relationship between PCSK9 inhibition and changes in cognition, including memory, attention, and reaction time.
- The mean change in the primary endpoint of executive function, as measured by the Spatial Working Memory strategy index (from the Cambridge Neuropsychological Test Automated Battery), was -0.29 with placebo and -0.21 with evolocumab (P<0.0001 for noninferiority).
- All secondary outcomes were similar for placebo and evolocumab, including patient self-reports and investigator-reported cognitive adverse events.

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; PCSK9, proprotein convertase subtilisin/kexin type 9.


PCSK9 Inhibitors cost nearly 100 times as much as generic atorvastatin 80 mg (2016)

ASCVD Risk Categories and LDL-C Treatment Goals

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors/10-year risk</th>
<th>Treatment goals</th>
</tr>
</thead>
</table>
| Extreme risk  | - Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL  
- Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH  
- History of premature ASCVD (<55 male, <65 female) | LDL-C (mg/dL) | Non-HDL-C (mg/dL) | Apo B (mg/dL) |
|               |                           | <55             | <80             | <70             |
| Very high risk| - Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%  
- DM or stage 3 or 4 CKD with 1 or more risk factor(s)  
- HeFH | LDL-C (mg/dL) | Non-HDL-C (mg/dL) | Apo B (mg/dL) |
|               |                           | <70             | <100            | <80             |
| High risk     | - ≥2 risk factors and 10-year risk 10%-20%  
- DM or stage 3 or 4 CKD with no other risk factors | LDL-C (mg/dL) | Non-HDL-C (mg/dL) | Apo B (mg/dL) |
|               |                           | <100            | <130            | <90             |
| Moderate risk  | ≤2 risk factors and 10-year risk <10%  
- DM or stage 3 or 4 CKD with no other risk factors | LDL-C (mg/dL) | Non-HDL-C (mg/dL) | Apo B (mg/dL) |
|               |                           | <100            | <130            | <90             |
| Low risk      |                           |                | NR              |

Genetic studies support the role of PCSK9 in affecting LDL levels

Gain in function mutation:

↑ PCSK9  ↓ LDLR  ↑ LDL-C

Causes high LDL-C levels → premature CVD.

Loss of function mutations:

PCSK9  ↑ LDLR  ↓ LDL-C

Cause low LDL-C levels → Reduced incidence of CHD.