Results of the GLAGOV Trial

Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound

Steven E. Nissen MD
Stephen J. Nicholls MBBS PhD

Disclosure

Consulting: Many companies

Companies are directed to pay any honoraria directly to charity. No personal reimbursement is accepted for directing or participating in clinical trials.
• Prior intravascular ultrasound (IVUS) trials have shown that statins slow progression or induce regression of coronary disease in proportion to the magnitude of LDL-C reduction.

• No other LDL-lowering therapy has shown regression in an IVUS trial.

• The lowest LDL-C achieved in prior trials was approximately 60 mg/dL. Effects of lower levels remain unknown.

• PCSK9 inhibitors incrementally lower LDL-C when added to statins, allowing achievement of very low LDL-C levels, however, no data exist describing effects on progression.
Trial Leadership

Steven E. Nissen MD
Study Chair

Stephen J. Nicholls MBBS PhD
Principal Investigator

Executive Committee

Todd Anderson MD (Canada)
Christie Ballantyne MD (Texas)
Leslie Cho MD (USA)
John Kastelein MD PhD (Netherlands)
Wolfgang Koenig MD (Germany)
Scott Wasserman MD (USA)*

* Sponsor representative
968 patients at 197 global centers with symptomatic CAD and other high risk features. Coronary angiography showing 20-50% stenosis in a target vessel.

- Stable, optimized statin dose for 4 weeks with LDL-C >80 mg/dL or 60-80 mg with additional high risk features.
- Intravascular ultrasound via motorized pullback at 0.5 mm/sec through >40 mm segment.

- Statin monotherapy
  - 61 patients did not complete
  - 423 statin completers

- Statin plus monthly SC evolocumab 420 mg
  - 18 months treatment
  - 61 patients did not complete
  - 423 evolocumab completers

Follow-up IVUS of originally imaged “target” vessel (n=846)
### Baseline Demographics and Statin Usage

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=484)</th>
<th>Evolocumab (N=484)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.8</td>
<td>59.8</td>
</tr>
<tr>
<td>Male Gender</td>
<td>72.3%</td>
<td>72.1%</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>29.5</td>
<td>29.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21.5%</td>
<td>20.2%</td>
</tr>
<tr>
<td>Smoking</td>
<td>23.3%</td>
<td>25.6%</td>
</tr>
<tr>
<td>Baseline statin use</td>
<td>98.3%</td>
<td>98.8%</td>
</tr>
<tr>
<td>High intensity</td>
<td>59.9%</td>
<td>57.9%</td>
</tr>
<tr>
<td>Moderate intensity</td>
<td>38.2%</td>
<td>40.5%</td>
</tr>
<tr>
<td>Low intensity</td>
<td>0.2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Baseline LDL-C</td>
<td>92.4 mg/dL</td>
<td>92.6 mg/dL</td>
</tr>
</tbody>
</table>
Percent Change in LDL-C During Treatment

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

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

Study Week

LDL-C Change from Baseline (mg/dL)

90 mg/dL
29 mg/dL

0 8 16 24 32 40 48 56 64 72 80 88
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>0.05</td>
<td>-0.95</td>
</tr>
<tr>
<td>P = NS</td>
<td>P &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>P &lt; 0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Secondary Endpoint: Total Atheroma Volume

Change in Total Atheroma Volume (mm³)

<table>
<thead>
<tr>
<th>Change in Volume (mm³)</th>
<th>Statin monotherapy</th>
<th>Statin-evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.9</td>
<td>P = NS</td>
<td></td>
</tr>
<tr>
<td>-5.8</td>
<td>P &lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

P = NS
P < 0.0001
Percent of Patients Showing Regression in PAV

**Statin Monotherapy**

- Regressors: 47.3%
- Progressors: 52.7%

**Statin plus Evolocumab**

- Regressors: 64.3%
- Progressors: 35.7%

*P < 0.0001 for comparison to statin monotherapy group*
Exploratory Subgroup: Baseline LDL-C <70 mg/dL

- Mean LDL-C 70.6 mg/dL
  - Change from baseline 16.4%
  - Mean LDL-C 24.0 mg/dL
  - Change from baseline -58.3%

LDL-C Change from Baseline (mg/dL)

Study Week

Mean LDL-C 70.6 mg/dL
Change from baseline 16.4%

Mean LDL-C 24.0 mg/dL
Change from baseline -58.3%
Exploratory Subgroup: Baseline LDL-C < 70 mg/dL

**Percent Atheroma Volume**

- Statin monotherapy: -0.35 (P = NS)
- Statin-evolocumab: -1.97 (P < 0.0001)

**Fraction Showing Regression**

- Statin monotherapy: 48.0%
- Statin-evolocumab: 81.2%
Mean On-Treatment LDL-C vs. Change in PAV

Locally Weighted Polynomial Regression (LOESS) Plot with 95% confidence limits
### Interaction: Selected Prespecified Subgroups (PAV)

**Age**
- < median: \(-1.09 (-1.61, -0.57)\)
- ≥ median: \(-0.95 (-1.47, -0.43)\)

**Gender**
- Female: \(-1.45 (-2.15, -0.76)\)
- Male: \(-0.86 (-1.29, -0.43)\)

**Baseline non-HDL**
- < median: \(-1.32 (-1.82, -0.83)\)
- ≥ median: \(-0.67 (-1.23, -0.11)\)

**Diabetes**
- Yes: \(-1.32 (-2.10, -0.54)\)
- No: \(-0.93 (-1.34, -0.51)\)

**Statin Intensity**
- High: \(-0.86 (-1.33, -0.39)\)
- Mod/Low: \(-1.22 (-1.81, -0.62)\)

**Interaction P value**
- Age: 0.70
- Gender: 0.17
- Baseline non-HDL: 0.09
- Diabetes: 0.39
- Statin Intensity: 0.36
<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=484)</th>
<th>Evolocumab (N=484)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>2.9%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>0.6%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Hosp. for Unstable Angina</td>
<td>0.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>13.6%</td>
<td>10.3%</td>
</tr>
<tr>
<td>First Major Cardiovascular Event</td>
<td>15.3%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>0%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Anti-evolocumab binding antibody</td>
<td>NA</td>
<td>0.2%</td>
</tr>
<tr>
<td>Neutralizing antibodies</td>
<td>NA</td>
<td>0%</td>
</tr>
<tr>
<td>Neurocognitive events</td>
<td>1.2%</td>
<td>1.4%</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>3.7%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5.8%</td>
<td>7.0%</td>
</tr>
</tbody>
</table>
Limitations

• The GLAGOV trial assessed a select group of patients with coronary disease presenting for a clinically-indicated angiogram treated for only 18 months:

• Although retention was better than previous IVUS studies, 13% of patients did not have a follow up examination.

• IVUS is a useful measure of disease activity, but the critical determination of benefit and risk will require completion of large outcomes trials currently underway.
In statin-treated patients with symptomatic coronary disease, addition of evolocumab, 420 mg monthly for 18 months:

- Achieved LDL-C levels averaging 36.6 mg/dL compared with 93 mg/dL for a statin alone.

- Produced regression, mean change in PAV of -0.95% compared with +0.05% in statin-only patients, ($P<0.0001$).

- Induced regression in a greater percentage of patients, 64% vs. 47% ($P<.00001$).

Post hoc analysis showed a incremental benefit for combination therapy at LDL-C levels as low as 20 mg/dL.
Conclusions-2

• Benefits of combination therapy were observed in patients with baseline LDL-C below the lowest levels recommended by global guidelines (<70 mg/dL).

• No safety issues were identified at the mean LDL-C levels of 36.6 mg/dL achieved in the trial:
  – No excess in new onset diabetes, myalgia, or neurocognitive adverse effects.
  – However, the sample size of the trial was modest, providing limited power for safety assessments.
Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial

SJ Nicholls and coauthors

Published online November 15, 2016

Available at jama.com and mobile.jamanetwork.com
Some Final Thoughts

LDL is now universally accepted as the major driver of atherosclerosis, however, the question of how far to reduce lipid levels has remained a moving target.

In medical school, we were taught that a “normal” total cholesterol was any value <300 mg/dL.

Over 4 decades, evidence has accumulated suggesting that optimal LDL-C levels for patients with coronary disease may be much lower than commonly achieved.

While we await large outcome trials for PCSK9 inhibitors, the GLAGOV Trial provides intriguing evidence that clinical benefits may extend to LDL-C levels as low as 20 mg/dL.