PCSK9 inhibitor evolocumab in patients with and without PAD – even better than statins?

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Disclosure

Speaker name: Thomas Stadlbauer

I have the following potential conflicts of interest to report:

Study-Investigator: Bayer
Lecturer: Bayer, Daiichi Sankyo, Bristol Myer Squibb, Pfizer
Travel grant: Bristol Myers Squibb, Pfizer, Daiichi Sankyo
Patients with peripheral artery disease are at high risk for major cardiovascular and limb events.
AHA Guidelines 2017
Lipid-lowering therapy in patients with PAD

• Statins are recommended \textbf{for everyone} with PAD

• No LDL-C target set

“fire an forget”
ESC Guidelines 2017
Lipid-lowering therapy in patients with PAD

• Statins are recommended for everyone with PAD (1C)

Target LDL-C
↓ by ≥ 50% in patients with LDL-C 70–135 mg/dL
↓ to < 70 mg/dL

„hit the target“

Many physicians in vascular medicine go with the AHA
Most cardiologists belief: The lower the better
Lipid-lowering therapy in patients with PAD

Medical Therapy

1. Statin
   - Reduces MACE
   - YES

2. Ezetimibe
   - No/Yes in Combination

3. PCSK9-Inhibition
   - ?

Department of Vascular and Endovascular Surgery
Statins

Inhibition of matrix metalloproteinases

Endothelial dysfunction
- Decrease in EPCs
- Increase in miR-221/-222
- Telomere shortening of EPCs
- Endothelial senescence
- Increase in SIRT-1 related microRNA (miR-34a)

Senescence and apoptosis of endothelial cells

Chronic inflammation
- Activation of TLR4
- Downregulation of TLR4-responsive microRNA (let 7i)
- Activation of NLRP3 inflammasome

Progression of coronary plaque
Ezetimibe

Ezetimibe: Mode of action
PCSK9 = Proprotein Convertase Subtilisin / Kexin type 9

Evolocumab is a fully human monoclonal antibody that inhibits PCSK9

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*
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 (1.8 mmol/L) or
non-HDL-C ≥100 mg/dL (2.6 mmol/L)

Evolocumab SC
140 mg Q2W or 420 mg QM
RANDOMIZED DOUBLE BLIND

Placebo SC
Q2W or QM

Follow-up Q 12 weeks
Median f/up 2.2 yrs

PEP: CVD, MI, Stroke, UA, Coronary Revascularization
Key Secondary EP: CVD, MI, Stroke

## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Evolocumab (N = 13,784)</th>
<th>Placebo (N = 13,780)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>62.5±9.1</td>
<td>62.5±8.9</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>10,397 (75.4)</td>
<td>10,398 (75.5)</td>
</tr>
<tr>
<td>White race — no. (%) †</td>
<td>11,748 (85.2)</td>
<td>11,710 (85.0)</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>85.0±17.3</td>
<td>85.5±17.4</td>
</tr>
<tr>
<td>Type of atherosclerosis ‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction — no. (%)</td>
<td>11,145 (80.9)</td>
<td>11,206 (81.3)</td>
</tr>
<tr>
<td>Median time from most recent previous myocardial infarction (IQR) — yr</td>
<td>3.4 (1.0–7.4)</td>
<td>3.3 (0.9–7.7)</td>
</tr>
<tr>
<td>Nonhemorrhagic stroke</td>
<td>2686 (19.5)</td>
<td>2651 (19.2)</td>
</tr>
<tr>
<td>Median time from most recent previous stroke (IQR) — yr</td>
<td>3.2 (1.1–7.1)</td>
<td>3.3 (1.1–7.3)</td>
</tr>
<tr>
<td>Peripheral artery disease — no. (%)</td>
<td>1,858 (13.5)</td>
<td>1,784 (12.9)</td>
</tr>
<tr>
<td>LDL cholesterol — mg/dl</td>
<td>92 (80–109)</td>
<td>92 (80–109)</td>
</tr>
</tbody>
</table>
A Primary Efficacy End Point

Hazard ratio, 0.85 (95% CI, 0.79–0.92)  
P<0.001

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>18 Months</th>
<th>24 Months</th>
<th>30 Months</th>
<th>36 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>13,780</td>
<td>13,278</td>
<td>12,825</td>
<td>11,871</td>
<td>7610</td>
<td>3690</td>
<td>686</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>13,784</td>
<td>13,351</td>
<td>12,939</td>
<td>12,070</td>
<td>7771</td>
<td>3746</td>
<td>689</td>
</tr>
</tbody>
</table>
Fourier PAD

Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease

Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)


3642 pts with PAD
- 42% PAD / no MI or stroke
- 57% prior peripheral revascularization
- 4% limb amputation for vascular cause
Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease

Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)


A Primary Endpoint in Patients with and without PAD

- **Placebo**
  - N=3,642
  - HR 0.79
  - 95% CI (0.66 – 0.94)
  - P=0.0098
  - 16.8%

- **Evolocumab**
  - 3.5% ARR
  - NNT 29

No PAD

- N=23,922
- HR 0.86
- 95% CI (0.80 – 0.93)
- P<0.001
- 10.5%

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo PAD</th>
<th>Evolocumab PAD</th>
<th>Placebo no PAD</th>
<th>Evolocumab no PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk</td>
<td>1784</td>
<td>1858</td>
<td>11966</td>
<td>11926</td>
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MALE:
- acute limb ischemia
- Major amputation
- Urgent revascularisation

B

Major Adverse Limb Events – Patients with PAD

HR 0.63
95% CI (0.39 – 1.03)
P=0.063

MALE:
- acute limb ischemia
- Major amputation
- Urgent revascularisation

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<tr>
<th>Number at risk</th>
<th>Placebo</th>
<th>Evolocumab</th>
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</thead>
<tbody>
<tr>
<td>0.0%</td>
<td>1784</td>
<td>1858</td>
</tr>
<tr>
<td>0.5%</td>
<td>1770</td>
<td>1845</td>
</tr>
<tr>
<td>1.0%</td>
<td>1748</td>
<td>1829</td>
</tr>
<tr>
<td>1.5%</td>
<td>1721</td>
<td>1810</td>
</tr>
<tr>
<td>2.0%</td>
<td>1699</td>
<td>1795</td>
</tr>
<tr>
<td>2.5%</td>
<td>1684</td>
<td>1781</td>
</tr>
<tr>
<td></td>
<td>1648</td>
<td>1737</td>
</tr>
<tr>
<td></td>
<td>1398</td>
<td>1477</td>
</tr>
<tr>
<td></td>
<td>1072</td>
<td>1133</td>
</tr>
<tr>
<td></td>
<td>776</td>
<td>815</td>
</tr>
<tr>
<td></td>
<td>482</td>
<td>503</td>
</tr>
</tbody>
</table>

Days from Randomization

0  90  180  270  360  450  540  630  720  810  900

2.4%
1.5%
Conclusions

• PAD = high risk group (MACE + MALE)

• Evolocumab + statin (+/- ezetimibe) reduced LDL-C levels in CVD pts dramatically (92 => 32 mg/dl)

• LDL-C lowering with evolocumab in PAD pts:
  – Reduces major adverse CV events significantly
  – Reduces major adverse limb events

• No relevant side effects

• Plaque regression possible !?

Nicholls 2016
**Summery**

LDL-C reduction to very low levels should be considered in patients with PAD to reduce the risk of MACE and MALE

**Consequences**

- Physicians in vascular medicine should pay more attention to the lipid profiles.
- “Fire an forget” might not be the best strategy.
- “Go for the targets” (LDL 70 mg/dl or 1.8 mmol/l).
- Therefore, we need a more differentiated approach to „lipid-modifying therapy“. 
Thank you very much!
# Fourier PAD

Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease

*Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)*


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<th>Peripheral artery disease history</th>
<th>No PAD N=23 922</th>
<th>PAD N=3642</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic peripheral artery disease and no prior MI or stroke</td>
<td>0</td>
<td>1505 (41.3)</td>
</tr>
<tr>
<td>Current intermittent claudication and ABI &lt;0.85, n (%)</td>
<td>0</td>
<td>2518 (69.3)</td>
</tr>
<tr>
<td>Prior peripheral revascularization, n (%)</td>
<td>0</td>
<td>2067 (56.8)</td>
</tr>
<tr>
<td>Time from peripheral revascularization, y, median (IQR)</td>
<td>0</td>
<td>3.7 (1.3–7.8)</td>
</tr>
<tr>
<td>Limb amputation for vascular cause, n (%)</td>
<td>0</td>
<td>126 (3.5)</td>
</tr>
</tbody>
</table>
Nicholls SJ et al; Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. JAMA 2016; 316:2373-2384.