PCSK9 inhibition and aortic stenosis
An analysis from the FOURIER trial

American College of Cardiology 2020 Scientific Sessions


TIMI Study Group
Brigham and Women’s Hospital
Harvard Medical School
Disclosures

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Calcific Aortic Valve Stenosis

- **Common** (~5% prevalence in older adults)

- **Morbid** (25-50% 1-yr mortality for untreated symptomatic severe AS)

- Despite rapid evolution in valve replacement technique, there is **no disease-modifying pharmacotherapy**
Pathobiology similar to atherosclerosis?

Table 3. Clinical Factors Associated With Aortic Stenosis or Sclerosis by Stepwise Multiple Logistic Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
<th>Odds Ratio</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>2.18*</td>
<td>2.15, 2.20</td>
</tr>
<tr>
<td>Male gender</td>
<td>&lt;0.001</td>
<td>2.03</td>
<td>1.7, 2.5</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>&lt;0.001</td>
<td>1.23†</td>
<td>1.14, 1.32</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.001</td>
<td>0.84‡</td>
<td>0.75, 0.93</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>0.002</td>
<td>1.23</td>
<td>1.1, 1.4</td>
</tr>
<tr>
<td>Present smoking</td>
<td>0.006</td>
<td>1.35</td>
<td>1.1, 1.7</td>
</tr>
<tr>
<td>LDLc (mg/dl)</td>
<td>0.008</td>
<td>1.12†</td>
<td>1.03, 1.23</td>
</tr>
</tbody>
</table>

*± 75th vs. 25th percentile. †± 10-year increase. ‡± 10-unit increase. LDLc = low density lipoprotein cholesterol; Lp(a) = lipoprotein(a).

Stewart BF. JACC. 1997;29:630-4
Three RCTs of LDL-C-lowering with statins

**SALTIRE**
N=155
Atorvastatin 80 mg vs PBO

**SEAS**
N=1873
Simva 40/Eze 10 mg vs PBO

**ASTRONOMER**
N=269
Rosuvastatin 40 mg vs PBO

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Cowell SJ. NEJM. 2005;3522:2389-97

Rossebo AB. NEJM. 2008;359:1343-56

Chan KL. Circulation. 2010;121:306-14
GWAS for aortic valve calcification

Adjusted HR (95%CI) per risk allele

Aortic stenosis 1.68 (1.32-2.15)
AVR 1.54 (1.05-2.27)
Lp(a) is a circulating lipoprotein that consists of an “LDL-like” molecule covalently bound to apo(a)

Gencer B. Eur Heart J. 2017;38:1553-60
Lp(a) and aortic stenosis progression

Echocardiographic progression

Cardiac death or AVR

A

Progression Rate of \( V_{\text{peak}} \) (m/s/yr)

- Tertiles 1 & 2
  - Lp(a) \( \leq 58.5 \text{mg/dL} \)
  - Progression Rate: 0.17 ± 0.02
    (n = 147)
- Tertile 3
  - Lp(a) > 58.5 mg/dL
  - Progression Rate: 0.26 ± 0.03
    (n = 73)

\( p = 0.005 \)

B

Adjusted Event-Free Survival (%)

Follow-Up (Years)

- Tertiles 1 & 2 of Lp(a)
- Tertile 3 of Lp(a)

*HR = 2.0 (1.1-3.7); p = 0.02
PCSK9 genetics and Lp(a)

PCSK9 sequence variant R46L

↓ Lp(a) concentration

↓ AS incidence

Aortic valve stenosis

N = 103,083
Events = 1437
Log-rank p = 0.06

PCSK9 R46L non-carrier
PCSK9 R46L carrier

Trend p=0.02

N= 48,324
1284
9

Years of age
PCSK9 inhibition lowers Lp(a)

Median change in Lp(a) concentration at 48 weeks in the FOURIER trial

Change from Baseline (%)
Lp(a), LDL-C, and aortic stenosis

- **Pathology** findings suggesting similarity to vascular atherosclerosis
- **Epidemiological associations** between elevated Lp(a), LDL-C, and AS
- **Genetic associations** between:
  - LPA variants, ↑ Lp(a), ↑ AS incidence
  - PSCK9 variants, ↓ Lp(a), ↓ AS incidence
- **Monoclonal antibodies** against PCSK9
  - 20-30% ↓ in Lp(a)
  - 50-60% ↓ in LDL-C

**DOES PCSK9 INHIBITION REDUCE AORTIC STENOSIS EVENTS?**
FOURIER 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

Questions

• Does evolocumab reduce AS events in patients with prior ASCVD on statin therapy?

• What are the associations between lipid concentrations [Lp(a) and LDL-C] and AS events?
Aortic stenosis events in FOURIER

- **Safety database** searched for events related to:
  - New or worsening AS; or
  - Aortic valve replacement (TAVR or SAVR)

- Search performed **blinded** to lipid levels, randomized treatment arm, clinical variables

- **63 events**
  - 26 AVR (18 surgical, 7 transcatheter, 1 unspecified)
Statistical analysis

- **Kaplan-Meier event rates** for AS events by 1-SD increase in week 12 Lp(a) and LDL-C\textsubscript{corr} [defined as LDL-C\textsubscript{corr} = LDL-C\textsubscript{meas} – 0.3 X Lp(a)]

- **Adjusted risk of AS events**
  - Model: Lp(a), LDL-C\textsubscript{corr}, age, sex, diabetes, hypertension, current smoking, eGFR

- **Evolocumab vs placebo** using Cox proportional hazards model

- **Sensitivity analysis** removing 9 patients with MACE prior to AS event
AS events per 1-SD increase in achieved lipid concentrations

Variables in model:
Lp(a), LDL-C_{corr}, age, sex, DM, HTN, current smoking, and eGFR

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR_{adj}</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)</td>
<td>1.55</td>
<td>(1.17-2.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL-C_{corr}</td>
<td>1.23</td>
<td>(0.93-1.61)</td>
<td>0.14</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>2.22</td>
<td>(1.38-3.58)</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-C_{corr}</td>
<td>1.39</td>
<td>(0.92-2.11)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

0.2 Lower risk of AS events 1.0 Higher risk of AS events 8.0
An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School

\[ \text{Evolocumab vs Placebo} \]

\[ \text{HR 1.09 (0.48-2.47)} \]
\[ P=0.84 \]

\[ \text{Evolocumab vs Placebo} \]

\[ \text{HR 0.48 (0.25-0.93)} \]
\[ P=0.026 \]

Overall HR

\[ \text{0.66 (0.40-1.09)} \]

Aortic Stenosis Events

Days

Number at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>At 0</th>
<th>At 180</th>
<th>At 360</th>
<th>At 540</th>
<th>At 720</th>
<th>At 900</th>
<th>At 1080</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>13780</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVO</td>
<td>13784</td>
<td></td>
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</tr>
</tbody>
</table>
Results

- **All AS events beyond 12 months**
  - n=40
  - HR (95% CI): 0.48 (0.25-0.93)

- **Sensitivity Analysis**
  - (AS events >12 mo removing pts w/ MACE prior to AS event)
  - n=34
  - HR (95% CI): 0.35 (0.17-0.77)

- **AVR beyond 12 months**
  - n=15
  - HR (95% CI): 0.49 (0.17-1.45)
Limitations

• *Post hoc* analysis of a randomized trial without adjustment for multiple comparisons

• Few events and not adjudicated

• Presence/severity of baseline AS not known

• Detection bias a consideration, as evolocumab reduces other CV events
  – Mitigated by sensitivity analysis

• Landmark analyses subject to non-random drop-out and censoring
Conclusions

• Achieved Lp(a) concentration associated with future AS events
• Beneficial effect of evolocumab appeared to emerge after 1 year of treatment with 52% lower rate of AS events
• These exploratory findings require validation in a dedicated RCT
Thank you

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