Cardiovascular Outcomes in Patients with Established Atherosclerosis and LDLR Loss of Function: Results from the FOURIER Trial

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**Disclosures**

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Approximately 1:500 (0.2%) individuals carry a loss of function (LoF) mutation in the LDL receptor (LDLR) gene.

These individuals have lifelong elevations in LDL-C, putting them at greater risk of cardiovascular disease.

The importance of such mutations in patients with established atherosclerosis, and their interaction with polygenic risk is not clear.

We aimed to:

1. Determine the risk of coronary events in patients with LDLR LoF compared with those with intact LDLR function.

2. Evaluate whether polygenic risk for CAD adds to monogenic risk in this secondary prevention clinical trial cohort.
Methods

• We performed a prospective genetic cohort analysis from the FOURIER trial, including all 14,297 patients who consented for genetic testing, passed QC, and were of European ancestry.

• All patients had established ASCVD and were on moderate or high intensity statin therapy.

• The primary endpoint was major coronary events, a composite of:
  • CHD death
  • Myocardial infarction
  • Coronary revascularization
Methods: Defining Monogenic and Polygenic Risk

- Whole exome sequencing was performed and LoF mutations in LDLR were identified using LOFTEE, a tool for detecting protein-truncating variants.

- Polygenic risk for CAD was calculated for each patient using a previously validated 27-SNP genetic risk score*.
  - high genetic risk \( \geq \) the median
  - low genetic risk \(<\) the median

## Results: Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>LDLR LoF N = 111 (0.8%)</th>
<th>Wild Type N = 14186</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 10</td>
<td>63 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>76%</td>
<td>76%</td>
<td>0.44</td>
</tr>
<tr>
<td>Baseline BMI (kg/m²)</td>
<td>29 ± 6</td>
<td>30 ± 5</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Myocardial Infarction</td>
<td>86%</td>
<td>82%</td>
<td>0.35</td>
</tr>
<tr>
<td>History of Coronary Revascularization</td>
<td>82%</td>
<td>69%</td>
<td>0.003</td>
</tr>
<tr>
<td>History of Cerebrovascular Disease</td>
<td>22%</td>
<td>22%</td>
<td>0.96</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24%</td>
<td>24%</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Baseline Laboratory Value (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>160 ± 45</td>
<td>98 ± 27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>233 ± 51</td>
<td>175 ± 32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>45 ± 13</td>
<td>47 ± 13</td>
<td>0.20</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>140 ± 75</td>
<td>151 ± 70</td>
<td>0.14</td>
</tr>
</tbody>
</table>
Results: Major Coronary Events stratified by LDLR Loss of Function Mutation Status

HR adjusted for age + sex

HR 1.71
(1.04, 2.81)
p=0.03
Results: Major Coronary Events stratified by LDLR Loss of Function Mutation Status and Polygenic Risk for CAD

2.5-year follow up
Limitations

• LDLR mutations are rare, and therefore the number of patients identified in this study is limited

• Since all patients in FOURIER have established atherosclerosis and are on intensive lipid-lowering therapy, the effects of LDLR LoF may be more attenuated than they would be in a primary prevention population
Conclusions

• The FOURIER trial was enriched for individuals with LDLR LoF mutations, with a 4-fold greater prevalence than the general population.

• Among patients with ASCVD, those with LDLR LoF mutations were 7 years younger than those with normal LDLR function.

• Patients with LDLR LoF mutations had persistently elevated LDL-C and increased CV risk despite intensive statin therapy.

• The combination of a monogenic LDLR mutation with high polygenic risk for CAD appeared additive in this secondary prevention cohort.