Predicting Benefit from Evolocumab Therapy in Patients with Atherosclerotic Disease Using a Genetic Risk Score: Results from the FOURIER Trial

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Background

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

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Background

Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials


Coronary Events

Comparison of hazard ratios across genetic risk score categories: p=0.0277

Aims

1) To evaluate the prognostic value of a genetic risk score in patients with established cardiovascular disease

2) To determine if a genetic risk score could identify patients who have a greater benefit from PCSK9 inhibition
The FOURIER trial was a multinational, randomized, double-blind, placebo-controlled trial of the efficacy of evolocumab in patients with clinically evident atherosclerotic cardiovascular disease.

We performed a nested cohort study of 14,298 unrelated European-ancestry patients enrolled in the FOURIER trial.

We examined two centrally adjudicated outcomes:

- Major coronary events (CHD death, MI, coronary revascularization)
- Major vascular events (CHD death, MI, coronary revascularization, stroke)

Patients in the genetic cohort were followed for a median of 2.3 years.
Genetic risk score was calculated using the genotype dosage for each allele, multiplied by its weight, and then summed across all variants. Patients were stratified into genetic risk categories based on their genetic risk quintiles:

- **Low Genetic Risk** = quintile 1
- **Intermediate Genetic Risk** = quintiles 2-4
- **High Genetic Risk** = quintile 5

Cox proportional hazards regression was used to calculate adjusted hazard ratios (HR) across genetic risk categories, using the low genetic risk category as a reference.

For comparison, **we also categorized patients by burden of major atherosclerotic clinical risk factors** including diabetes, hypertension, baseline LDL-C >= 100 mg/dl, and smoking; the presence of **multiple (>=2) risk factors was considered high clinical risk**.

Absolute and relative risk reductions with evolocumab therapy were calculated across each genetic + clinical risk category for major vascular and coronary events.

Significance testing for gene-treatment interaction was performed for ARR and RRR.
# Baseline Characteristics

Base*

*Baseline Characteristics by Genetic Risk Category based on the GRS-27.*

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Low N=2859</th>
<th>Intermediate N=8580</th>
<th>High N=2859</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63</td>
<td>63</td>
<td>62</td>
<td>&lt;0.0001</td>
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<tr>
<td>Male (%)</td>
<td>77</td>
<td>77</td>
<td>74</td>
<td>0.01</td>
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<tr>
<td>Medical History</td>
<td></td>
<td></td>
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<tr>
<td>Myocardial infarction (%)</td>
<td>78</td>
<td>82</td>
<td>85</td>
<td>&lt;0.0001</td>
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<tr>
<td>Ischemic stroke (%)</td>
<td>21</td>
<td>18</td>
<td>14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral artery disease (%)</td>
<td>14</td>
<td>15</td>
<td>15</td>
<td>0.16</td>
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<tr>
<td>Hypertension (%)</td>
<td>81</td>
<td>81</td>
<td>80</td>
<td>0.55</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>35</td>
<td>33</td>
<td>31</td>
<td>0.001</td>
</tr>
<tr>
<td>Current cigarette use (%)</td>
<td>30</td>
<td>30</td>
<td>27</td>
<td>0.009</td>
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<tr>
<td>Median Lipid Measures</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>91</td>
<td>92</td>
<td>94</td>
<td>&lt;0.0001</td>
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<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>0.68</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>138</td>
<td>135</td>
<td>131</td>
<td>0.02</td>
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</tbody>
</table>
Risk Prediction in Placebo Arm

- Major Vascular Events:
  - Adjusted Hazard Ratio: 1.37 (1.10-1.71)
  - P-Trend = 0.005

- Major Coronary Events:
  - Adjusted Hazard Ratio: 1.65 (1.30-2.1)
  - P-Trend < 0.0001

Legend:
- Red = high genetic risk
- Blue = intermediate genetic risk
- Green = low genetic risk

Adjusted for age, sex, hypertension, diabetes, smoking, eGFR, and ancestry
Risk Prediction in Placebo Arm

Major Coronary Events
(MI, CHD Death, Coronary Revascularization)

Adjusted HR vs. Low GRS
High GRS: 1.65 (1.30-2.1)
Int GRS: 1.23 (0.99-1.52)
P-Trend <0.0001

Event Rate (%)

Low Genetic Risk (N=2859)
Intermediate Genetic Risk (N=8580)
High Genetic Risk (N=2859)

Years

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Treatment Effect of Evolocumab

<table>
<thead>
<tr>
<th>Genetic Risk Category</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>HR 0.92 (0.72-1.18)</td>
<td>HR 0.91 (0.79-1.03)</td>
</tr>
<tr>
<td></td>
<td>ARR 0.7%</td>
<td>ARR 0.9%</td>
</tr>
</tbody>
</table>

P-Trend (HR) = 0.07
P-Trend (ARR) = 0.04

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Treatment Effect of Evolocumab on Major Vascular Events

a) Without multiple clinical risk factors or high genetic risk
   \( N=4269 \)
   HR 1.02
   \( 0.83-1.25, p=0.86 \)
   ARR -0.2%

b) Multiple clinical risk factors but without high genetic risk
   \( N=7170 \)
   HR 0.87
   \( 0.75-0.998, p=0.047 \)
   ARR 1.4%
   NNT = 71

c) High genetic risk (irrespective of clinical risk)
   \( N=2858 \)
   HR 0.69
   \( 0.55-0.86, p=0.0012 \)
   ARR 4.0%
   NNT = 25
Limitations

• This was a subgroup analysis of a clinical trial population and therefore the results may not be generalizable to all populations.

• Specifically, this study focused on patients of European ancestry because this is where the majority of GWAS data is derived.

• Additionally, patients were divided into categories based on percentile relative to the study population, not a healthy reference population.
  • This likely resulted in higher genetic risk patients being forced into lower risk categories than would otherwise be expected.
  • This may have weakened the signal for risk prediction.
Summary

1. This is the first study to demonstrate an interaction between a genetic risk score and treatment benefit from a PCSK9 inhibitor.
2. Patients without multiple clinical risk factors or high genetic risk had a low event rate and did not appear to derive benefit from evolocumab over 2 yrs.
3. Conversely, patients with multiple clinical risk factors but without high genetic risk had intermediate risk and intermediate risk reduction.
4. Patients in the top 20% of genetic risk, regardless of clinical risk, had a high event rate and derived the greatest relative and absolute benefit from evolocumab, which completely mitigated this risk.
Predicting Benefit From Evolocumab Therapy in Patients With Atherosclerotic Disease Using a Genetic Risk Score
Results From the FOURIER Trial

Thank you!