Performance of a Genetic Risk Score to Identify Risk of Venous Thromboembolism and Benefit from Evolocumab Therapy

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Venous thromboembolism (VTE) is a major cause of cardiovascular morbidity and mortality with a known genetic contribution.

Recently, a 297-SNP genetic risk score was developed for risk of VTE in a general population.

However, how this genetic risk score for VTE applies to a population with cardiometabolic disease is unclear.

Background (2)

- Additionally, statin therapy has been shown to reduce the risk of VTE.

**A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism**


*The New England Journal of Medicine*

**HR 0.57**

(0.37-0.86)

p=0.007
Aims

1) To evaluate the prognostic value of a genetic risk score for VTE in cardiometabolic disease

2) To determine whether PCSK9 inhibition significantly reduces the risk of VTE

3) To assess whether patients with higher genetic risk for VTE derive the greatest treatment benefit from PCSK9 inhibition
Methods: 3 Analyses

1) Genetic Risk Score and VTE Risk Prediction
   • We performed a patient-level meta-analysis of 31,669 patients from the FOURIER, PEGASUS-TIMI 54, and SAVOR-TIMI 53 trials to assess the prognostic value of the genetic risk score to predict VTE in a cardiometabolic population

2) Effect of Evolocumab on VTE
   • We analyzed the effect of evolocumab in the FOURIER trial alone, and then as a summary level meta-analysis in combination with ODYSSEY OUTCOMES data

3) Gene x Treatment Interaction
   • We tested whether those patients at high genetic risk for VTE derived greater benefit from the PCSK9 inhibitor evolocumab
297-SNP Genetic Risk Score

Our Approach

• We calculated this genetic risk score for each patient using the genotype dosage for each allele, multiplied by its weight, and then summed across all variants.

Genome-wide association analysis of venous thromboembolism identifies new risk loci and genetic overlap with arterial vascular disease

• The 297-SNP genetic risk score was derived from the UK Biobank and was published in 2019.

• Identifies the top 5% of patients as being at a 2.9-fold increased risk of VTE.

Distribution of VTE GRS

1) Genetic Risk Score and VTE Risk Prediction
   • Patients were stratified into genetic risk categories based on tertiles
   • Cox model was used to calculate hazard ratios across genetic risk categories
   • Analyses were adjusted for age, sex, ancestry, and VTE clinical risk factors

2) Effect of Evolocumab on VTE
   • Cox model was used to assess the difference in VTE incidence between evolocumab and placebo
   • A fixed-effects meta-analysis was performed on summary-level data from FOURIER and ODYSSEY OUTCOMES

3) Gene x Treatment Interaction
   • Absolute and relative risk reductions with evolocumab therapy were calculated across genetic risk categories
   • Significance testing for gene-treatment interaction was performed
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Statistical Analyses

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## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Low Genetic Risk</th>
<th>Intermediate Genetic Risk</th>
<th>High Genetic Risk</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (n)</td>
<td>10,557</td>
<td>10,556</td>
<td>10,556</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65</td>
<td>65</td>
<td>64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male Sex (%)</td>
<td>74</td>
<td>76</td>
<td>74</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Medical History (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>79</td>
<td>79</td>
<td>79</td>
<td>0.36</td>
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<tr>
<td>Stroke</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>0.02</td>
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<tr>
<td>Peripheral Artery Disease</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td>0.006</td>
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<tr>
<td>Hypertension</td>
<td>79</td>
<td>80</td>
<td>80</td>
<td>0.26</td>
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<tr>
<td>Heart Failure</td>
<td>20</td>
<td>21</td>
<td>22</td>
<td>0.004</td>
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<tr>
<td>Diabetes</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>0.88</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>22</td>
<td>21</td>
<td>23</td>
<td>0.03</td>
</tr>
</tbody>
</table>
3-yr Incidence of VTE by GRS

Venous Thromboembolism (%)

- Low Risk
- Intermediate Risk
- High Risk

P-Trend <0.0001

N = 31,669
Performance of the 297-SNP GRS

Risk of VTE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Genetic Risk</td>
<td>HR 2.36, p &lt;0.0001</td>
</tr>
<tr>
<td>Intermediate Genetic Risk</td>
<td>HR 1.73, p = 0.006</td>
</tr>
<tr>
<td>Low Genetic Risk</td>
<td>referent</td>
</tr>
<tr>
<td>Age &gt;=65</td>
<td>HR 1.77, p = 0.0002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>HR 1.32, p = 0.053</td>
</tr>
<tr>
<td>BMI &gt;=30</td>
<td>HR 1.24, p = 0.14</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>HR 1.08, p = 0.67</td>
</tr>
<tr>
<td>Active Smoking</td>
<td>HR 0.86, p = 0.40</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, ancestry, BMI, heart failure, diabetes, smoking status
1) To evaluate the prognostic value of a genetic risk score for VTE in cardiometabolic disease

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Effect of Evolocumab on VTE

HR = 0.71
(0.50-1.00)
p=0.05
Effect of Evolocumab on VTE

First Year
HR = 0.96
(0.57-1.62)
p=0.89

After 1 Year
HR = 0.54
(0.33-0.88)
p=0.014
Meta-Analysis of PCSK9i Trials

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>n</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOURIER</td>
<td>27564</td>
<td>128</td>
<td>0.71 (0.50-1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>ODYSSEY</td>
<td>18924</td>
<td>92</td>
<td>0.67 (0.44-1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Meta-Analysis</td>
<td>46488</td>
<td>220</td>
<td>0.69 (0.53-0.90)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Q-test for Heterogeneity: $p = 0.86$

Fixed Effect Model

$31\%$ RRR in VTE

Treatment Effect in Lipid Subgroups

**Baseline LDL-C**
- **Low (<Median):**
  - Placebo HR 0.68 (0.41-1.11), ARR 0.2%
  - Evolocumab ΔLDL-C -55 mg/dl, Δlp(a) -13 nmol/L
- **High (≥Median):**
  - Placebo HR 0.78 (0.46-1.33), ARR 0.2%
  - Evolocumab ΔLDL-C -67 mg/dl, Δlp(a) -14 nmol/L

**Baseline Lp(a)**
- **Low (<Median):**
  - Placebo HR 0.98 (0.59-1.62), ARR 0.0%
  - Evolocumab ΔLDL-C -61 mg/dl, Δlp(a) -7 nmol/L
- **High (≥Median):**
  - Placebo HR 0.52 (0.30-0.89), ARR 0.4%
  - Evolocumab ΔLDL-C -59 mg/dl, Δlp(a) -33 nmol/L
Aims

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Treatment Effect by Genetic Risk

<table>
<thead>
<tr>
<th>Genetic Risk Category</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not High (Bottom 2/3)</td>
<td>HR 1.20 (0.66-2.2)</td>
<td>ARR -0.1%</td>
</tr>
<tr>
<td>High (Top 1/3)</td>
<td>HR 0.45 (0.21-0.95)</td>
<td>ARR 0.7%</td>
</tr>
</tbody>
</table>

$P_{interaction} = 0.04$

$P_{heterogeneity} = 0.009$
• Collection of VTE events were not prespecified, but rather collected through physician reporting of serious adverse events throughout the trial

• This was a subgroup analysis of a cardiovascular 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
Summary

1. A genetic risk score for VTE strongly predicts VTE risk
   - Top 1/3 of genetic risk are at a 2.4-fold increased risk of VTE

2. PCSK9 inhibition significantly reduces VTE events
   - 31% relative risk reduction across FOURIER and ODYSSEY
   - Lp(a) reduction may be an important mediator

3. Patients in the top 1/3 of genetic risk appear to derive the greatest absolute & relative risk reductions for VTE
   - 55% relative risk reduction in patients with high genetic risk
For more information, please read our simultaneous publication in...

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Thank you!