Performance of a Polygenic Risk Score for CAD Across the Spectrum of ASCVD: An Analysis of 60k Patients from 6 TIMI Randomized Trials

BACKGROUND

Genetics can be used to refine risk prediction

Relative utility in primary vs. secondary prevention is unclear

Purpose: To compare the ability of a CAD PRS to predict coronary events according to presence and spectrum of ASCVD
METHODS

59,905 pts from 6 TIMI RCTs* stratified into low (Q1), intermediate (Q2-4), or high (Q5) genetic risk using an external genome-wide CAD polygenic risk score\(^1\)

Pts were then categorized by ASCVD status at baseline:
- ASCVD with event: prior MI or ischemic stroke (N=40,877)
- ASCVD without event: prior revasc, CAD, PAD (N=6,579)
- No overt ASCVD: none of the above (N=12,449)

*ENGAGE AF, SOLID, SAVOR, PEGASUS, DECLARE, and FOURIER

\(^1\)Aragam KG et al., Nature Genetics 2022
METHODS

Adjudicated **coronary endpoint**: CHD death, MI, or coronary revasc

Cox models were adjusted for age, sex, ancestry, trial, and ASCVD risk factors (diabetes, eGFR, smoking, use of LLT, SBP)
# Baseline Characteristics by Genetic Risk

<table>
<thead>
<tr>
<th></th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=11,981 (Q1)</td>
<td>N=35,943 (Q2-4)</td>
<td>N=11,981 (Q5)</td>
</tr>
<tr>
<td><strong>Age, yrs (mean)</strong></td>
<td>68</td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td><strong>Male sex (%)</strong></td>
<td>71</td>
<td>72</td>
<td>69</td>
</tr>
<tr>
<td><strong>Smoking (%)</strong></td>
<td>14</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td><strong>Diabetes (%)</strong></td>
<td>51</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>85</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td><strong>ASCVD status (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ASCVD</td>
<td>38</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>ASCVD w/o event</td>
<td>10</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>ASCVD w/ event</td>
<td>52</td>
<td>70</td>
<td>80</td>
</tr>
</tbody>
</table>

All p<0.001
CORONARY EVENTS BY CAD PRS IN THE OVERALL POPULATION

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>HR$_{adj}$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>1.59</td>
<td>1.47–1.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.59</td>
<td>1.47–1.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High risk</td>
<td>2.08</td>
<td>1.91–2.27</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Reference group
CORONARY EVENTS FOR HIGH VS. LOW CAD PRS, STRATIFIED BY ASCVD CATEGORY

**Performance of a PRS for CAD Across the Spectrum of ASCVD: An Analysis of 60k Patients from 6 TIMI Randomized Trials**

- **ASCVD w/ Event** (N=15,792)
  - Adjusted HR (95% CI): 1.63 (1.47–1.79)
- **ASCVD w/o Event** (N=2,633)
  - Adjusted HR (95% CI): 1.73 (1.35–2.23)
- **No ASCVD** (N=5,537)
  - Adjusted HR (95% CI): 4.63 (3.46–6.21)

*P* interaction <0.001
ABSOLUTE RATES OF CORONARY EVENTS BY CAD PRS AND ASCVD CATEGORY

Coronary death, MI, or revasc at 3 years (%)

- High CAD PRS (N=11,981):
  - ASCVD with event (N=40,877): 14.4%
  - ASCVD without event (N=6,579): 11.1%
  - No ASCVD (N=12,449): 8.5%

- Intermediate CAD PRS (N=35,943):
  - ASCVD with event (N=40,877): 4.1%
  - ASCVD without event (N=6,579): 7.4%
  - No ASCVD (N=12,449): 1.6%

- Low CAD PRS (N=11,981):
  - ASCVD with event (N=40,877): 10.7%
  - ASCVD without event (N=6,579): 13.8%
  - No ASCVD (N=12,449): 16.0%

P-trend <0.001 for all rows
CONCLUSIONS

CAD PRS refined the prediction of coronary events across the spectrum of ASCVD, and the risk gradient was strongest in patients without established ASCVD

Application of CAD PRS may be most useful in patients without ASCVD to help focus preventive measures