Predictive Utility of a CAD Polygenic Risk Score in Primary Prevention Based on Age and Clinical Risk

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Session: Elizabeth Barrett-Connor Research Award for Early Career Investigators Competition
Sunday, November 14, 2021
Disclosures

• **Presenter:** grant support from the National Institutes of Health and involvement in clinical trials with Amgen, Pfizer, Ionis, Novartis, and AstraZeneca without personal fees, payments, or increase in salary.

• **Co-Authors:** JPP reports grant support from NIH grant 1K08HL159346 and has received personal fees from Maize Therapeutics. GEM reports no disclosures. SK has no disclosures. FKK reports no disclosures. CR is supported by a grant from Bayer AG to the Broad Institute focused on the development of therapeutics for cardiovascular disease. YK has no disclosures. KA has no disclosures. ASB reports funding from NIHR Blood and Transplant Research Unit in Donor Health and Genomics (NIHR BTRU-2014-10024), UK Medical Research Council (MR/L003120/1), British Heart Foundation (SP/09/002; RG/13/13/30194; RG/18/13/33946), NIHR Cambridge BRC (BRC-1215-20014) and Health Data Research UK, grants from AstraZeneca, Bayer, Biogen, BioMarin, Bioverativ, Merck, Novartis and Sanofi, and personal fees from Novartis, outside the submitted work. KI has no disclosures. SAL is supported by NIH grant 1R01HL139731 and American Heart Association 18SFRN34250007. Dr. Lubitz receives sponsored research support from Bristol Myers Squibb / Pfizer, Bayer AG, Boehringer Ingelheim, Fitbit, and IBM, and has consulted for Bristol Myers Squibb / Pfizer and Bayer AG. PTE reports grants and personal fees from Bayer AG, personal fees from Novartis, personal fees from Quest Diagnostics, outside the submitted work. MSS reports research grant support through Brigham and Women’s Hospital from Amgen; AstraZeneca; Bayer; Daiichi-Sankyo; Eisai; GlaxoSmithKline; Intarcia; IONIS; Janssen Research and Development; Medicines Company; MedImmune; Merck; Novartis; Pfizer; Poxel; Quark Pharmaceuticals; Takeda; Consulting for Amgen; Anthos Therapeutics; AstraZeneca; Bristol-Myers Squibb; CVS Caremark; DaiCor; Dyrnamix; Esperion; IFM Therapeutics; Intarcia; Ionis; Janssen Research and Development; Medicines Company; MedImmune; Merck; Moderna; Novartis and Novo Nordisk. Dr. Sabatine is a member of the TIMI Study Group, which has also received institutional research grant support through Brigham and Women’s Hospital from: Abbott, Aralez, Roche, and Zora Biosciences. CTR reports grants from Boehringer Ingelheim, grants from Daiichi Sankyo, grants from MedImmune, grants from National Institute of Health, personal fees from Bayer, personal fees from Bristol Myers Squibb, personal fees from Boehringer Ingelheim, personal fees from Daiichi Sankyo, personal fees from Janssen, personal fees from MedImmune, personal fees from Pfizer, personal fees from Portola, personal fees from Anthos, outside the submitted work; Dr. Ruff is a member of the TIMI Study Group, which has received institutional research grant support through Brigham and Women’s Hospital from: Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., BRAHMS, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, Zora Biosciences.
What is a Polygenic Risk Score?

rgare.com

#AHA21
Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants

Polygenic Prediction of primary coronary artery disease

Per-allele odds ratio for CAD

Minor Allele Frequency

Hazard Ratio

- Novel genome-wide
- Previously reported genome-wide
- Among 1% FDR set

2015 PRS

Per SD
Bottom 10%
Middle 80%
Top 10%

Conclusions

The addition of a polygenic risk score for CAD to pooled cohort equations was associated with a statistically significant, yet modest, improvement in the predictive accuracy for incident CAD and improved risk stratification for only a small proportion of individuals. The use of genetic information over the pooled cohort equations model warrants further investigation before clinical implementation.
Aims

1) Investigate the predictive power of a CAD PRS across a range of ages

2) Determine whether genetics can be used to reclassify patients’ ASCVD risk to guide initiation of statin therapy
Study Design and Population

• Prospective cohort study in the UK Biobank

• Included all individuals without a history of ASCVD and who were not on lipid-lowering therapy (statin or non-statin)

• Individuals were followed for 10 years

• Endpoints of Interest:
  • Myocardial Infarction
  • ASCVD Events (CAD diagnosis, stroke, death)
Analyses

1) **Assessing the CAD PRS risk prediction as a function of age**
   - The CAD PRS was based on all 241 genome-wide significant SNPs from the recent CAD GWAS (CARDIoGRAMplusC4D Consortium)
   - Continuous (per 1-SD) and categorical analyses
   - Low (bottom 20%), Intermediate (middle 60%), and High (top 20%)

2) **Assessing the CAD risk prediction as a function of ASCVD risk groups**
   - All patients with available baseline data had a 10-year ASCVD risk calculated using the AHA Pooled Cohort Equations
   - Low (<5%), Borderline (5-<7.5%), Intermediate (7.5-<20%) or High (≥20%)
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low PRS N=66,041</th>
<th>Intermediate PRS N=198,120</th>
<th>High PRS N=66,040</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>57 (13)</td>
<td>57 (13)</td>
<td>56 (13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>44%</td>
<td>43%</td>
<td>41%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m² (SD)</td>
<td>26.4 (5.5)</td>
<td>26.3 (5.5)</td>
<td>26.3 (5.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>10.3%</td>
<td>10.3%</td>
<td>10.2%</td>
<td>0.82</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.6%</td>
<td>0.6%</td>
<td>0.6%</td>
<td>0.54</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.3%</td>
<td>5.6%</td>
<td>5.7%</td>
<td>0.004</td>
</tr>
<tr>
<td>Lipid Parameters*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>219 (53)</td>
<td>227 (54)</td>
<td>233 (55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>136 (41)</td>
<td>142 (41)</td>
<td>148 (42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>56 (20)</td>
<td>55 (19)</td>
<td>55 (19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>161 (51)</td>
<td>169 (52)</td>
<td>176 (53)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>125 (93)</td>
<td>128 (95)</td>
<td>130 (96)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*mg/dl (+/- SD)

#AHA21
CAD PRS Risk Prediction by Age

![Graph showing the relationship between age and heart rate for MI per 1-SD of PRS with a P_interaction < 0.001.]
CAD PRS Risk Prediction by Age

- PRS Category
- High vs Low
- Intermediate vs Low

HR for MI by PRS Category

Age (Years)

1 2 3 4 5 6 7 8

20 10 0
Attributable Risk by Age
Observed ASCVD Event Rate (<50 yo)

- **All Patients**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Event Rate</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ASCVD Risk (&lt;5% Risk)</td>
<td>2.2%</td>
<td>62,807</td>
</tr>
<tr>
<td>Borderline ASCVD Risk (5-7.5% Risk)</td>
<td>6.4%</td>
<td>4,817</td>
</tr>
<tr>
<td>Intermediate ASCVD Risk (7.5-20% Risk)</td>
<td>9.1%</td>
<td>3,402</td>
</tr>
</tbody>
</table>

**AHA/ACC Guidance**

- **Initiate Statin to reduce LDL-C (Class I)**
- **Discuss Moderate-Intensity Statin (Class IIb)**
- **No Statin**
Event Rate by ASCVD and PRS

- Low PRS: 1.6% (Low ASCVD Risk: <5% Risk, N = 62,807)
- Int PRS: 4.7% (Borderline ASCVD Risk: 5-7.5% Risk, N = 4,817)
- High PRS: 9.1% (Intermediate ASCVD Risk: 7.5-20% Risk, N = 3,402)

AHA/ACC Guidance:
- Initiate Statin to reduce LDL-C (Class I)
- Discuss Moderate-Intensity Statin (Class IIb)
- No Statin
## Net Reclassification Index

<table>
<thead>
<tr>
<th></th>
<th>Borderline ASCVD Risk</th>
<th>Intermediate ASCVD Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRI</td>
<td>0.155</td>
<td>0.191</td>
</tr>
<tr>
<td></td>
<td>(0.065 - 0.300)</td>
<td>(0.076 - 0.272)</td>
</tr>
<tr>
<td>NRI+</td>
<td>0.147</td>
<td>0.036</td>
</tr>
<tr>
<td>NRI-</td>
<td>0.008</td>
<td>0.155</td>
</tr>
</tbody>
</table>

95% confidence intervals are listed in parentheses.
C-Index for MI in <50 years of age

<table>
<thead>
<tr>
<th>ASCVD Risk Category</th>
<th>C-Index for ASCVD risk alone</th>
<th>C-Index for ASCVD + PRS</th>
<th>P-value for the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.74 (0.70-0.77)</td>
<td>0.75 (0.71-0.79)</td>
<td>P=0.187</td>
</tr>
<tr>
<td>Borderline</td>
<td>0.51 (0.45-0.58)</td>
<td>0.70 (0.64-0.76)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.62 (0.54-0.66)</td>
<td>0.71 (0.66-0.76)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>
Summary

1. Polygenic risk for CAD has the greatest predictive power in younger adults and is especially strong in individuals under the age of 50.

2. Polygenic risk for CAD accounts for 30% of attributable risk of MI in younger adults, but <10% in the elderly.

3. Adding PRS testing to patients <50 years old with borderline and intermediate risk results in significant reclassification that impacts statin recommendations.

4. The addition of PRS testing to the ASCVD risk score significantly increases the C-Index among borderline and intermediate risk patients.
Conclusion

Genetic testing is not for everyone, but in patients <50 years of age with borderline or intermediate risk of ASCVD, it may help guide decision making regarding statin therapy
Thank you