Performance of a Novel Genetic Risk Score to Identify Residual Risk of Ischemic Stroke in Patients Anticoagulated for Atrial Fibrillation

Nicholas A. Marston, MD\textsuperscript{1,2}, Francesco Nordio, PhD\textsuperscript{1}, Yared Gurmu, PhD\textsuperscript{1}, Carolina Roselli, MS\textsuperscript{3}, Steven A. Lubitz, MD, MPH\textsuperscript{4}, Robert P. Giugliano, MD, SM\textsuperscript{1,2}, Michael A. Grosso, MD\textsuperscript{5}, Michele F. Mercuri, MD\textsuperscript{5}, Hans-Joachim Lanz, MD\textsuperscript{5}, Howard Rutman, MD, Elliot M. Antman, MD\textsuperscript{1,2}, Eugene Braunwald MD\textsuperscript{1,2}, Marc S. Sabatine, MD, MPH\textsuperscript{1,2*}, Patrick T. Ellinor, MD, PhD\textsuperscript{3,4*}, Christian T. Ruff, MD, MPH\textsuperscript{1,2*}.

\textsuperscript{*}Contributed equally to this work

\textsuperscript{1}TIMI Study Group, Boston, MA, USA; \textsuperscript{2}Division of Cardiovascular Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; \textsuperscript{3}Cardiovascular Disease Initiative, Broad Institute of MIT and Harvard Cambridge, MA, USA; \textsuperscript{4}Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA; \textsuperscript{5}Daiichi Sankyo, Tokyo, Japan. \textsuperscript{6}Mount Sinai, New York, NY, USA.

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Background

• Despite anticoagulation, patients with atrial fibrillation (AF) remain at risk of ischemic stroke.

• Whether a recently developed genetic risk score (GRS) for stroke can help identify patients at increased risk beyond CHA$_2$DS$_2$VASc is not known.
Aims

1) To evaluate the prognostic value of a recently developed genetic risk score in the prediction of stroke in patients anticoagulated for atrial fibrillation.

2) To determine how genetic risk compares to components of CHA₂DS₂VASc for predicting stroke risk.
Methods

• The ENGAGE AF-TIMI 48 trial was a multinational, randomized, double-blind trial testing the non-inferiority of edoxaban compared to warfarin in patients with atrial fibrillation.

• We performed a nested cohort study of 11,164 unrelated European-ancestry patients consented for genetic analysis.

• The endpoint was ischemic stroke.

• Median follow-up was 2.8 years.
Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes

- A genetic risk score was developed using 32 SNPs from a recently published set of stroke-associated SNPs
- Some SNPs have overlap with other cardiovascular diseases
- The 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 genetic risk tertiles:

- **Low Genetic Risk** = tertile 1
- **Intermediate Genetic Risk** = tertile 2
- **High Genetic Risk** = tertile 3

Cox proportional hazards model was used to calculate hazard ratios across genetic risk categories.

Analyses were adjusted for age, sex, ancestry, and components of the CHA$_2$DS$_2$VASc score.
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-yrs (median)</td>
<td>73</td>
<td>72</td>
<td>72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>0.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical History</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA$_2$DS$_2$VASc Score</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>0.45</td>
</tr>
<tr>
<td>CrCl &lt;=50 ml/min (%)</td>
<td>16</td>
<td>15</td>
<td>16</td>
<td>0.36</td>
</tr>
<tr>
<td>Prior Stroke (%)</td>
<td>15</td>
<td>17</td>
<td>17</td>
<td>0.04</td>
</tr>
<tr>
<td>Prior heart failure (%)</td>
<td>58</td>
<td>59</td>
<td>59</td>
<td>0.44</td>
</tr>
<tr>
<td>Hx of CAD (%)</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td>0.69</td>
</tr>
<tr>
<td>Hx of PAD (%)</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>0.17</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>95</td>
<td>96</td>
<td>96</td>
<td>0.51</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>38</td>
<td>37</td>
<td>37</td>
<td>0.77</td>
</tr>
</tbody>
</table>
Comparison of a novel 32-SNP GRS to traditional CHA$_2$DS$_2$VASc risk factors for the prediction of ischemic stroke in patients anticoagulated for atrial fibrillation

**Genetic Risk Score**
- **High**
- **Intermediate**
- **Low**

**Components of CHA$_2$DS$_2$VASc**
- Stroke/TIA
- Age $\geq$ 75
- Age 65-74
- Female
- Heart Failure
- Vascular Disease
- Diabetes
- Hypertension

**Adjusted HRs**
- HR 1.31, $p = 0.037$
- HR 1.12, $p = 0.39$
- HR 2.08, $p < 0.0001$
- HR 1.84, $p < 0.0001$
- HR 1.38, $p = 0.027$
- HR 1.32, $p = 0.007$
- HR 1.31, $p = 0.02$
- HR 1.04, $p = 0.72$
- HR 1.02, $p = 0.83$
- HR 0.99, $p = 0.98$
Performance of a novel 32-SNP GRS for the prediction of ischemic stroke in patients anticoagulated for atrial fibrillation (stratified by CHA₂DS₂VASc score)

<table>
<thead>
<tr>
<th>CHA₂DS₂VASc</th>
<th>GRS</th>
<th>Adjusted HRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3</td>
<td>High</td>
<td>HR 1.76, P = 0.025</td>
</tr>
<tr>
<td></td>
<td>Low/Int</td>
<td>referent</td>
</tr>
<tr>
<td>4-5</td>
<td>High</td>
<td>HR 1.28, P = 0.079</td>
</tr>
<tr>
<td></td>
<td>Low/Int</td>
<td>referent</td>
</tr>
<tr>
<td>&gt;5</td>
<td>High</td>
<td>HR 0.93, P = 0.68</td>
</tr>
<tr>
<td></td>
<td>Low/Int</td>
<td>referent</td>
</tr>
</tbody>
</table>

^HRs adjusted for age, sex, and principal components 1-5

P-Trend = 0.041
Performance of a novel 32-SNP GRS for the prediction of ischemic stroke in patients anticoagulated for atrial fibrillation (stratified by CHA₂DS₂VASc score)

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<td>^HRs adjusted for age, sex, and principal components 1-5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHA₂DS₂VASc</th>
<th>N</th>
<th>Adj. Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2,275</td>
<td>1.57</td>
<td>0.92-2.69</td>
<td>0.10</td>
</tr>
<tr>
<td>1-2</td>
<td>796</td>
<td>3.5</td>
<td>0.94-13.3</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Limitations

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

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

• Standard cut-points for genetic risk have not been developed in the general population. Therefore, genetic risk is relative to this study cohort.
  • In this higher risk population, some patients are forced into lower risk categories than if compared to general population, which may have attenuated the gradient of risk seen.
1) A recently developed **32-SNP genetic risk score** is an independent predictor of residual risk of ischemic stroke in patients anticoagulated for atrial fibrillation.

2) This genetically-mediated risk is greater than or on par with many of the components of the CHA$_2$DS$_2$VASc score.

3) The predictive ability of this 32-SNP GRS tends to be greater in patients with lower CHA$_2$DS$_2$VASc scores.
Future Directions

1) Need to define standard genetic risk cut points in the normal population
   • Prevents genetic risk from changing based on study cohort
2) Hone in on predictive value in CHA₂DS₂VASc 0-1
   • Could high genetic risk be enough to anticoagulate a CHA₂DS₂VASc of 0-1?
3) Expand work to genome-wide polygenic risk scores and stroke subtype-specific genetic risk scores.
   • Cardioembolic
   • Large artery
   • Small artery
Thank you!