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

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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_2DS_2VASc 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 CHA_2DS_2VASc for predicting stroke risk.

Methods

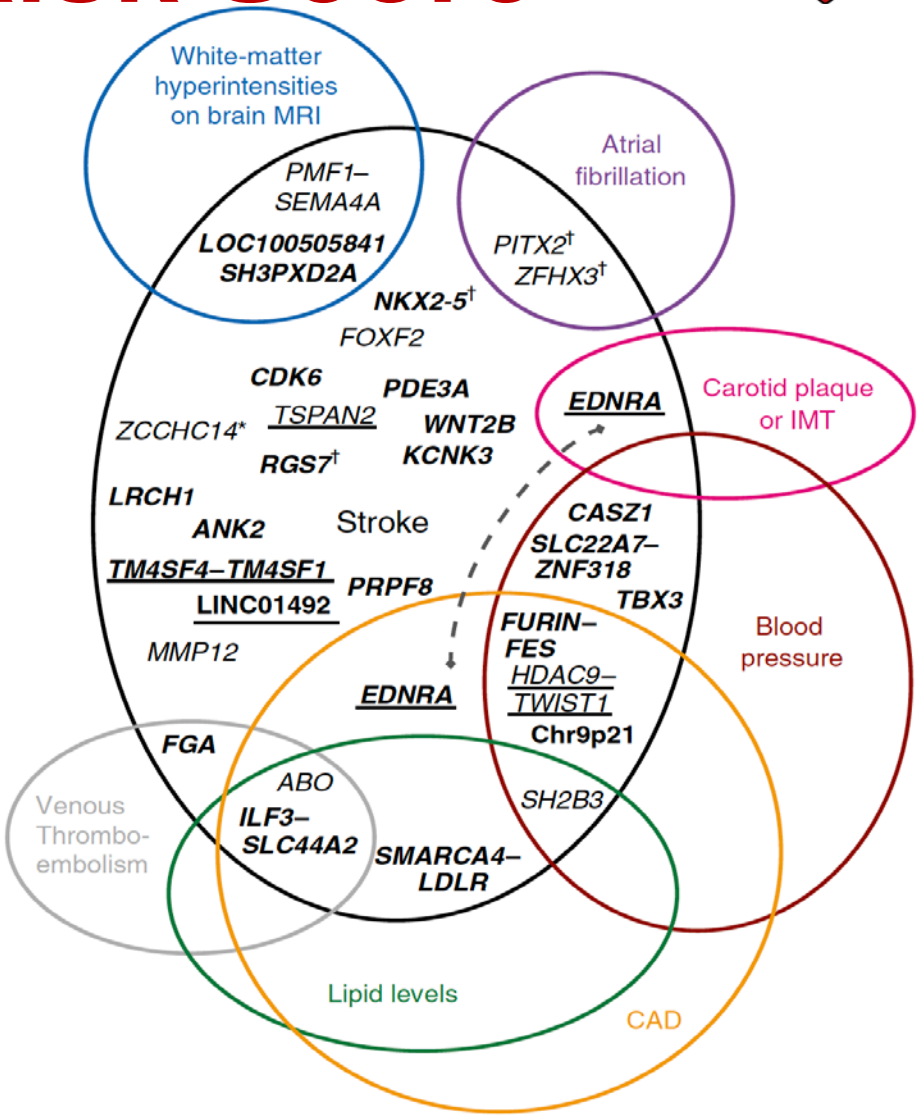
- The ENGAGE AF-TIMI 48 trial was a multinational, randomized, double-blind trial testing the non-inferiority of edoxaban compared to warfarin in patients with atrial fibrillation.
- We performed a nested cohort study of **11,164 unrelated European-ancestry patients** consented for genetic analysis.
- The endpoint was ischemic stroke.
- Median follow-up was 2.8 years.

32-SNP Genetic Risk Score

ARTICLES
https://doi.org/10.1038/s41588-018-0058-3
nature genetics

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



Malik, R, et al. *Nature Genetics*. 2018.

Statistical Analysis

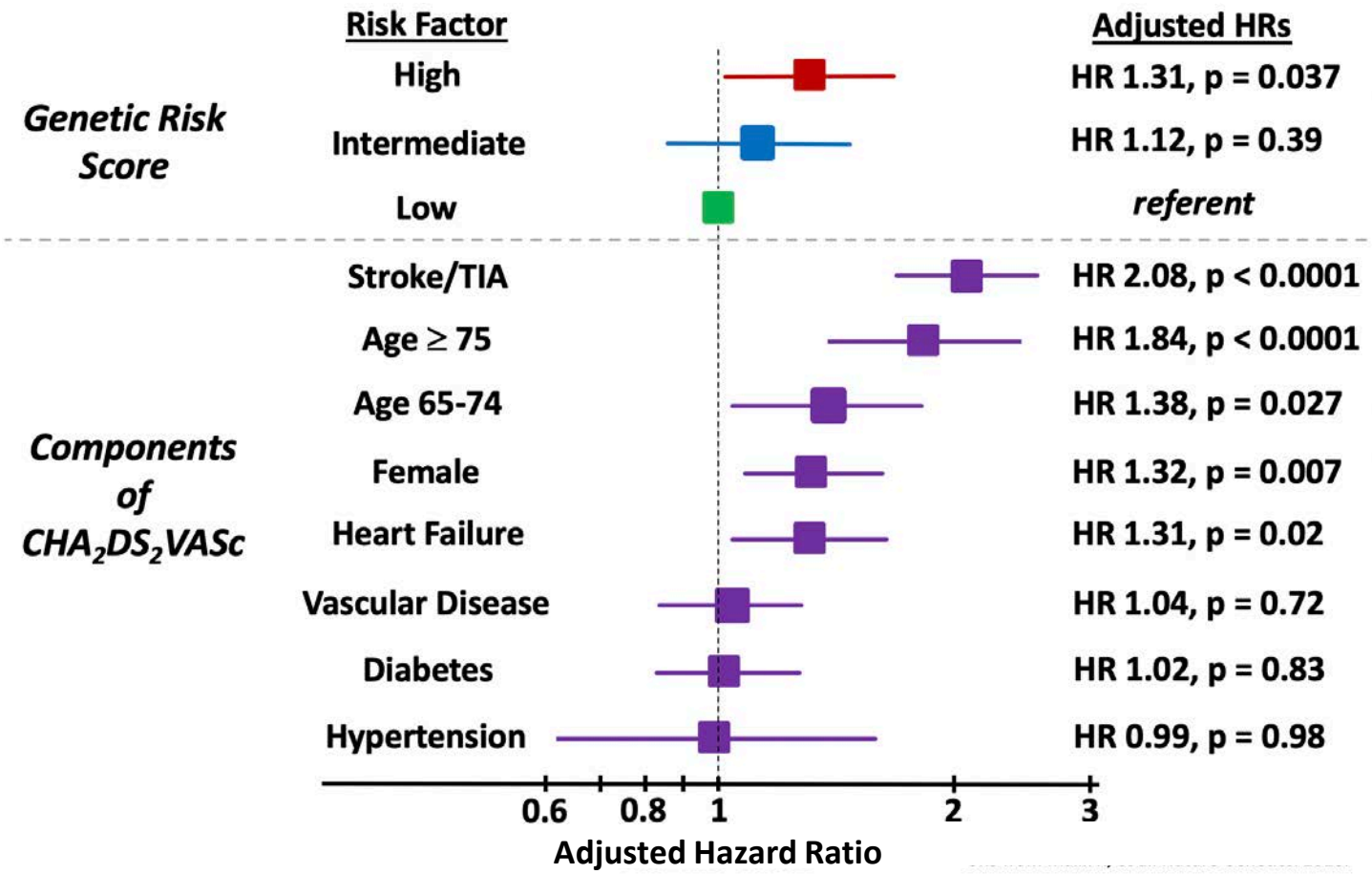
- Patients were stratified into genetic risk categories based on genetic risk tertiles:
  - **Low Genetic Risk = tertile 1**
  - **Intermediate Genetic Risk = tertile 2**
  - **High Genetic Risk = tertile 3**
- Cox proportional hazards model was used to calculate hazard ratios across genetic risk categories.
- Analyses were adjusted for age, sex, ancestry, and components of the CHA_2DS_2VASc score.

Baseline Characteristics

	Low	Intermediate	High	P-value
Demographics				
Age-yrs (median)	73	72	72	<0.001
Female sex (%)	61	61	61	0.99
Medical History				
CHA_2DS_2VASc Score	4	4	4	0.45
CrCl <=50 ml/min (%)	16	15	16	0.36
Prior Stroke (%)	15	17	17	0.04
Prior heart failure (%)	58	59	59	0.44
Hx of CAD (%)	38	38	38	0.69
Hx of PAD (%)	4	5	5	0.17
Hypertension (%)	95	96	96	0.51
Diabetes (%)	38	37	37	0.77

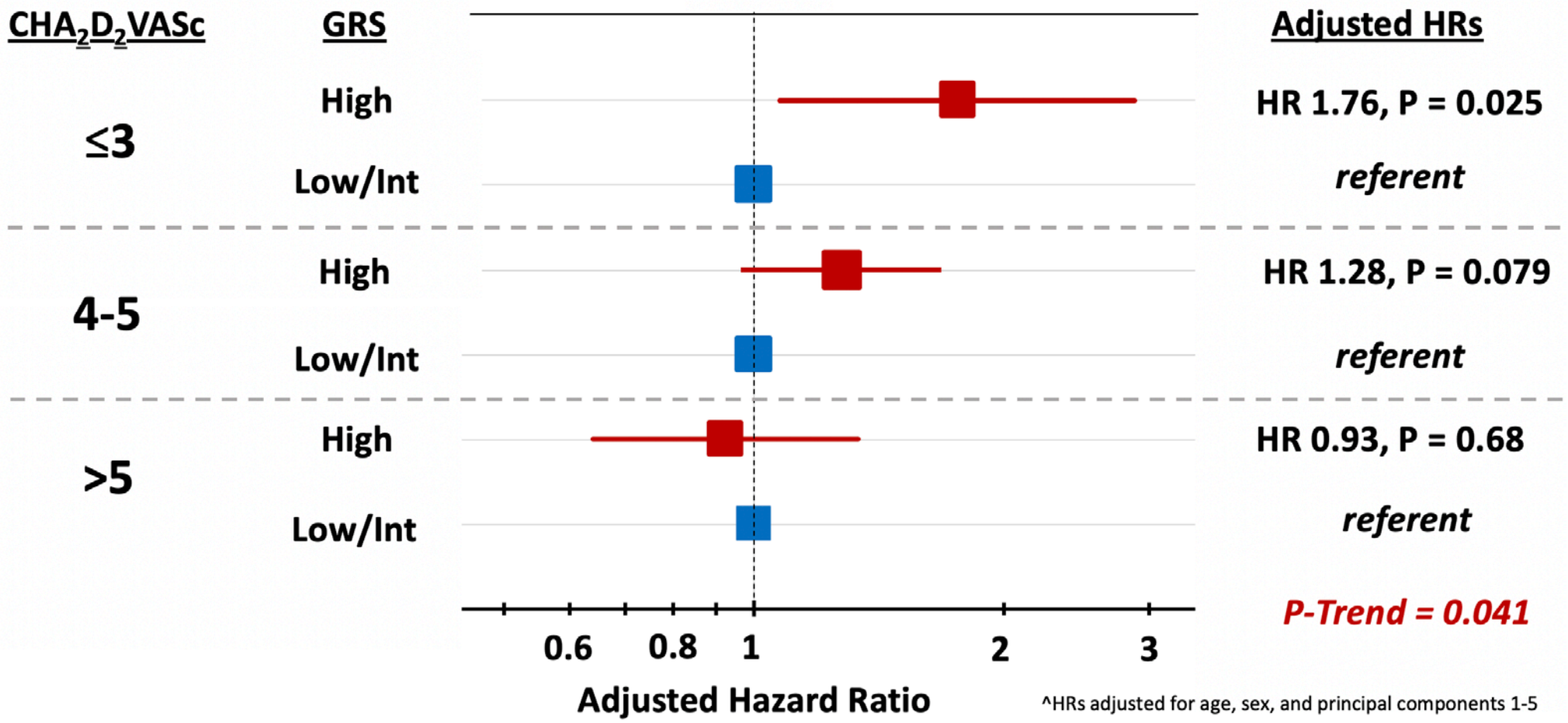
RESULTS

Comparison of a novel 32-SNP GRS to traditional CHA_2DS_2VASc risk factors for the prediction of ischemic stroke in patients anticoagulated for atrial fibrillation



32-SNP GRS by CHA_2DS_2VASc

Performance of a novel 32-SNP GRS for the prediction of ischemic stroke in patients anticoagulated for atrial fibrillation (stratified by CHA_2DS_2VASc score)



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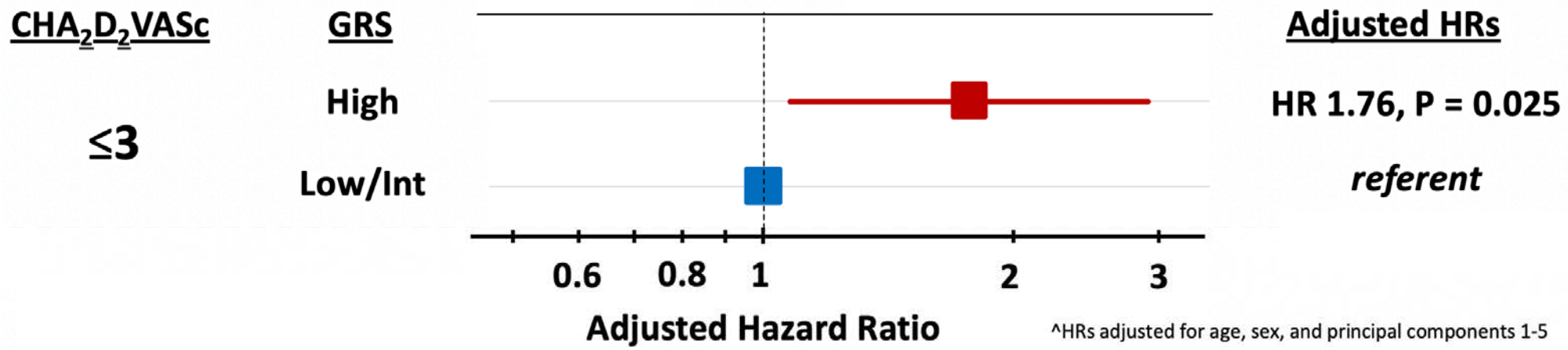

CHA_2DS_2VASc	N	Adj. Hazard Ratio	95% CI	P-value
3	2,275	1.57	0.92-2.69	0.10
1-2	**796**	**3.5**	**0.94-13.3**	**0.06**

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.

Summary

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_2DS_2VASc score.

3) The predictive ability of this 32-SNP GRS tends to be greater in patients with lower CHA_2DS_2VASc 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 CHA_2DS_2VASc 0-1
   - Could high genetic risk be enough to anticoagulate a CHA_2DS_2VASc 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!

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Scientific Sessions