A Novel Genetic Risk Score Predicts Ischemic Stroke in Patients with Cardiometabolic Disease

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TIMI Study Group

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Disclosures

- **None**

Genetic risk may contribute to risk for ischemic stroke

- **Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) that are associated with an increased risk of stroke**
- **Genetic risk scores (GRS) have garnered interest for their potential to improve risk prediction in many common diseases**
- **Early attempts at using GRS to predict ischemic stroke have shown promise**
- **Whether a GRS can independently predict risk for ischemic stroke, in patients who are older and already have established cardiometabolic disease, is still not known**

Aims

1. **Evaluate whether a GRS could identify subjects at higher risk for ischemic stroke after accounting for traditional clinical risk factors in five trials across the spectrum of cardiometabolic disease**

2. **Investigate how GRS performance differs across key subgroups**

Methods: Study Population

- **Five randomized controlled TIMI trials**

Trial Name	Brief Description of Cohort
ENGAGE AF-TIMI 48	Patients with atrial fibrillation
SOLID-TIMI 52	Patients with recent acute coronary syndrome
SAVOR-TIMI 53	Patients with T2DM
PEGASUS-TIMI 54	Patients with prior myocardial infarction
FOURIER	Patients with prior myocardial infarction, stroke, or PAD

**Subjects who consented for genetic analysis, passed quality control, and were of European ancestry*

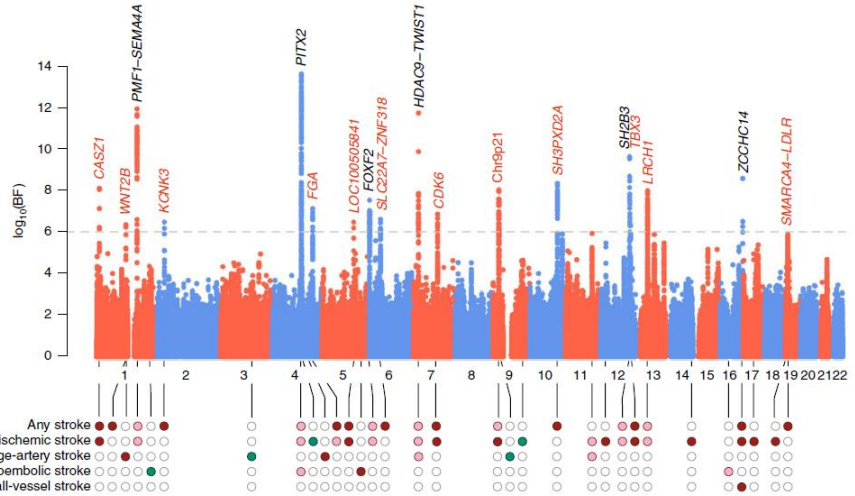
Methods: Genetic Risk Scoring

- A recently published set of 32 SNPs was used to calculate a GRS in each patient
- Score calculated using the genotype dosage for each allele, multiplied by its weight, and then summed across all variants
- Patients were divided into tertiles of genetic risk

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

MEGASTROKE
Malik et al, *Nat Genetics* 2018



Methods: Statistical Analysis

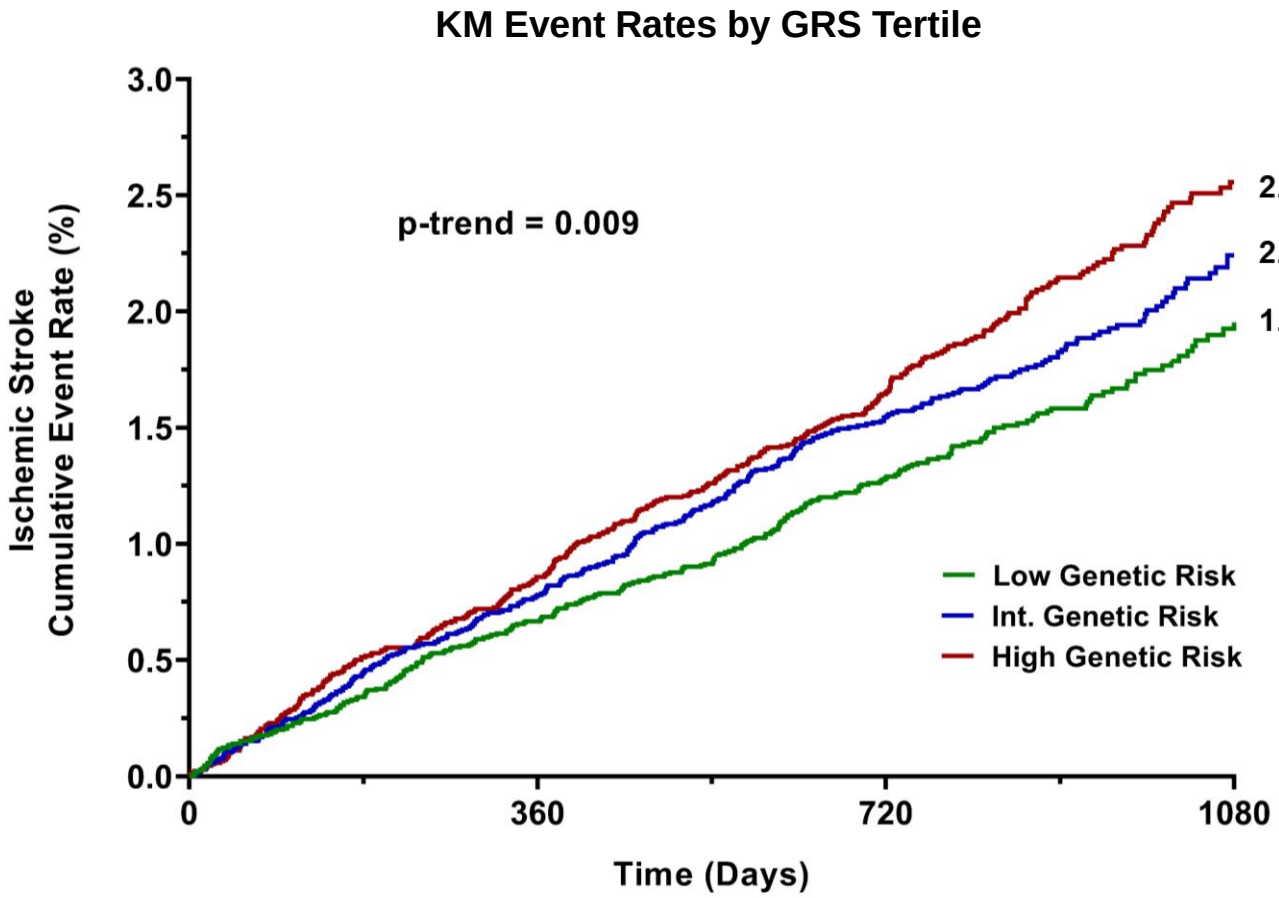
- **Endpoint: ischemic stroke adjudicated by clinical endpoint committee**
- **Analysis plan: Cox proportional hazards model**
- **Adjustments:**
  - **Age, sex, ancestry**
  - **HTN, HLD, smoking, DM, AF, vascular disease, and CHF**
- **Analyses were performed in:**
  - **Overall genetic cohort**
  - **Primary vs secondary prevention**
  - **ENGAGE AF-TIMI 48 trial (Atrial Fibrillation)**
  - **Across CHA_2DS_2-VASc ranges**

Results: Baseline Characteristics

- **51,288 subjects were eligible for inclusion in this analysis**

	Low Genetic Risk	Intermediate Genetic Risk	High Genetic Risk	P-Value
Participants	17096	17096	17096	
Demographics				
Age, years (SD)	66.1 (9.2)	65.9 (9.3)	65.6 (9.2)	<0.001
Female Sex (%)	28	28	29	0.005
Medical History (%)				
Hypertension	80	83	84	<0.001
Hyperlipidemia	61	60	60	0.09
Diabetes	43	41	42	<0.001
Smoking	18	18	19	0.33
Atrial Fibrillation	25	28	32	<0.001
Vascular Disease	83	82	80	<0.001
Congestive Heart Failure	26	29	33	<0.001
Stroke/TIA	12	14	15	<0.001

Results: Ischemic Stroke Event Rates by GRS Tertile

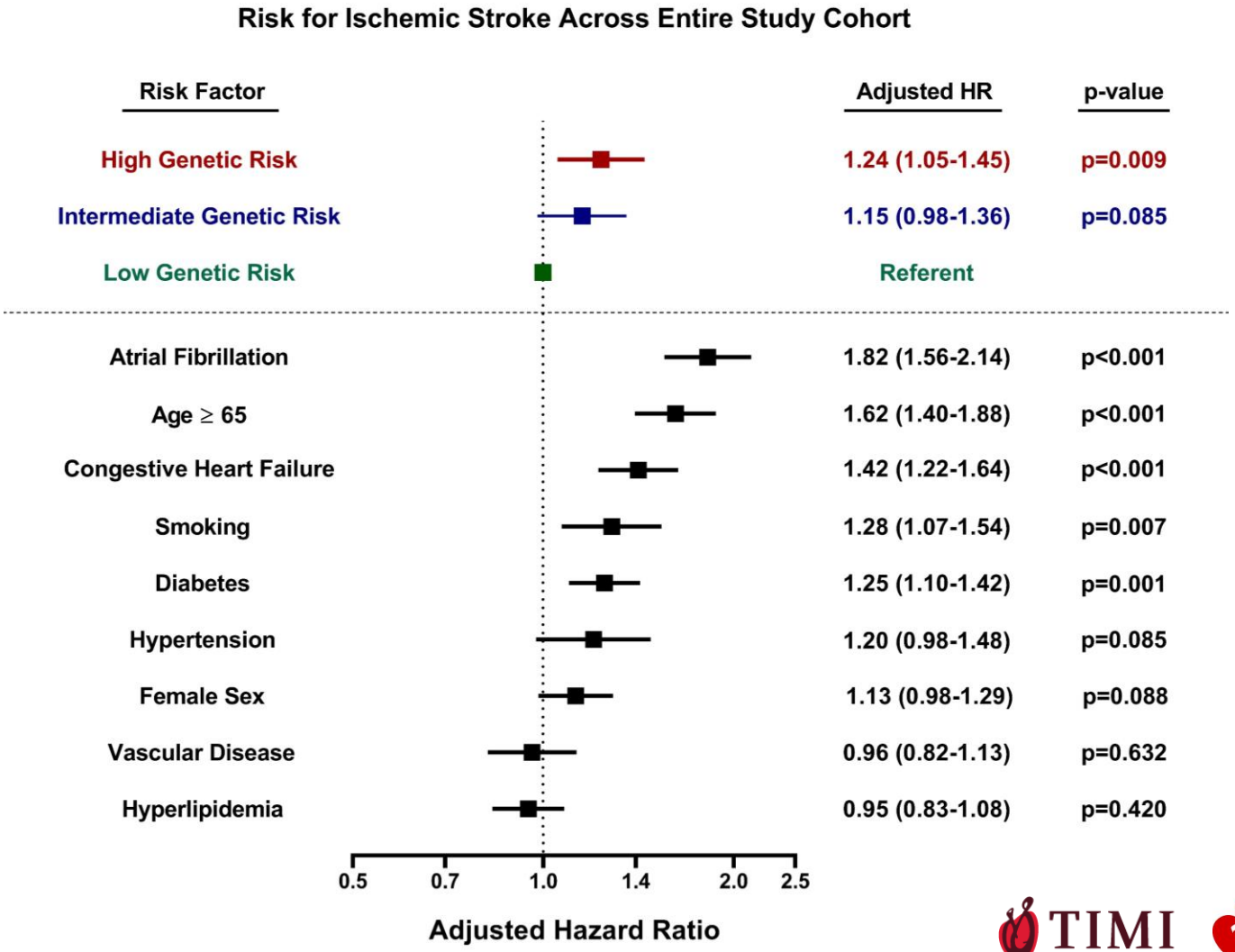


Adjusted HR vs. Low GRS	
2.56%	HR 1.24 (95% CI 1.05-1.45)
2.24%	HR 1.15 (95% CI 0.98-1.36)
1.95%	Referent

Median follow up time 2.5 years

*HR adjusted for age, sex, ancestry, HTN, HLD, smoking, DM, AF, vascular disease, and CHF

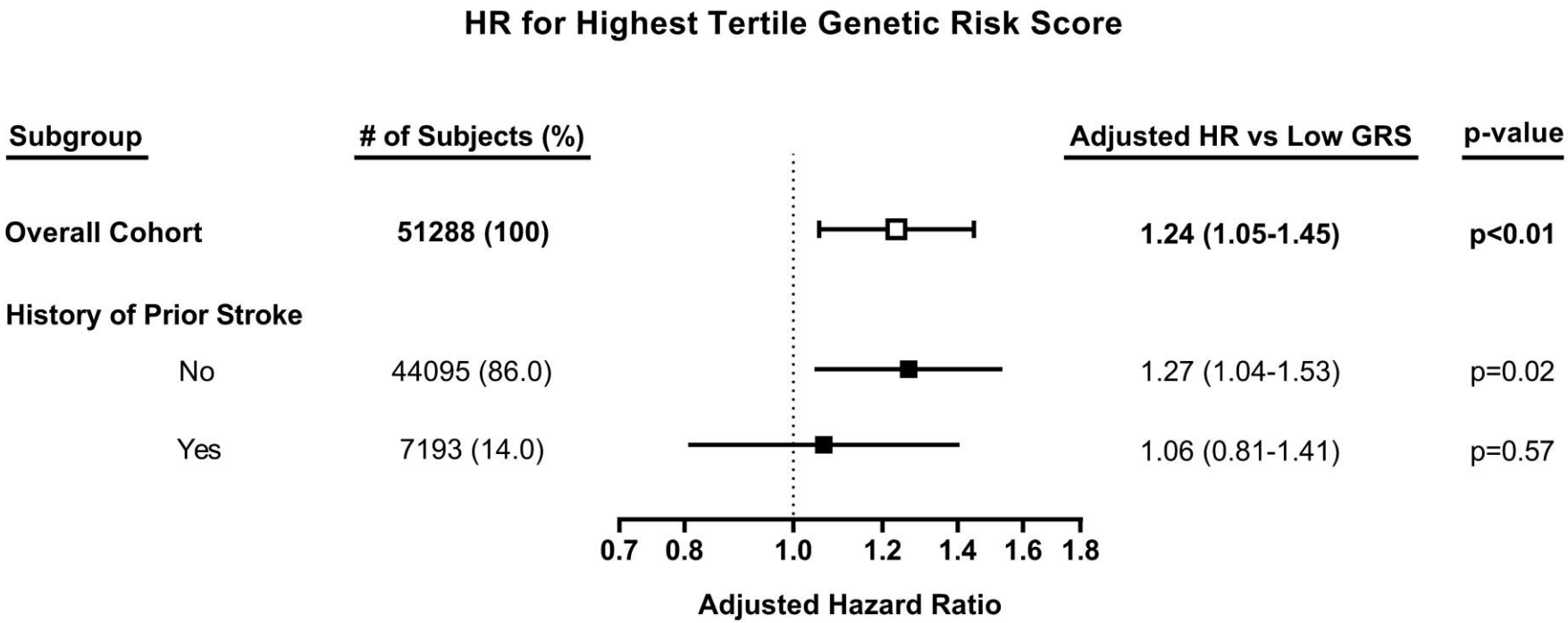
Results: GRS Comparison vs Traditional Risk Factors



Median follow up time 2.5 years

*HR adjusted for age, sex, ancestry, HTN, HLD, smoking, DM, AF, vascular disease, and CHF

Results: Subgroups Stratified by Prior Ischemic Stroke

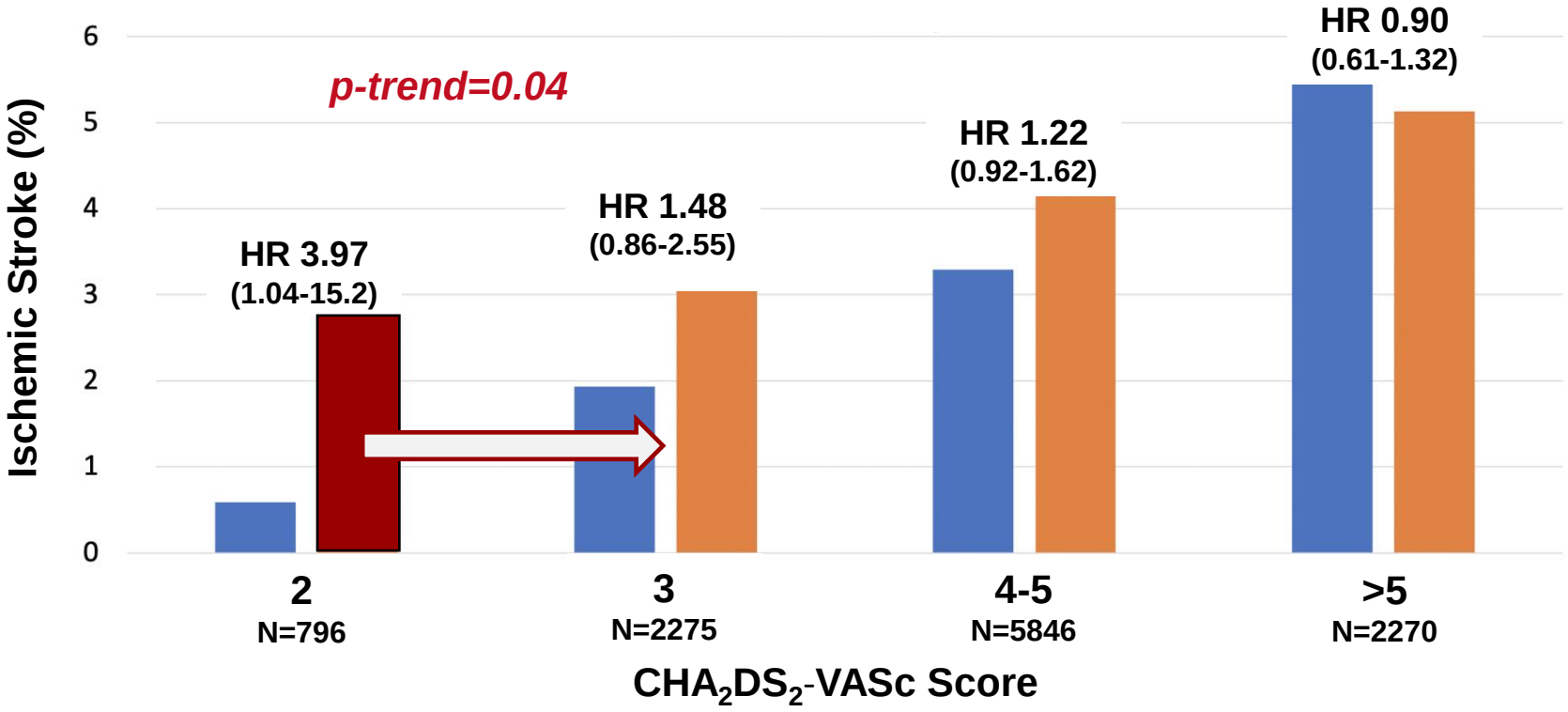


Risk For Ischemic Stroke in Patients With AF

Can genetic risk scoring refine stroke risk in ENGAGE AF-TIMI 48, a trial of patients with atrial fibrillation?

Results: GRS Performance in ENGAGE AF-TIMI 48

- GRS was stronger in patients with lower CHA_2DS_2-VASc scores
- High genetic risk reclassified one third of patients with CHA_2DS_2-VASc 2 to risk levels equivalent to CHA_2DS_2-VASc of 3



*HR adjusted for components of CHA_2DS_2VASc

Limitations

- **Our study population included subjects enrolled in five clinical trials across the spectrum of cardiometabolic disease**
- **Our analysis was limited to subjects who were of European ancestry**
- **This study does not explore the biologic heterogeneity of stroke**

Conclusions

- **Across five clinical trials of subjects with cardiometabolic disease, a 32-SNP GRS was a strong, independent predictor of ischemic stroke**
- **The predictive value of the GRS appeared strongest in subjects without prior stroke, as well as in those with atrial fibrillation and low CHA_2DS_2-VASc scores**
- **In patients with atrial fibrillation and CHA_2DS_2-VASc of 2, high genetic risk identified individuals with risk equivalent to CHA_2DS_2-VASc of 3**
- **These data suggest a potential role for genetic risk scores in therapeutic decision-making**

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Thank you!

Questions can be emailed to pnpatel@partners.org

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