Polygenic Risk Stratification for Risk of Venous Thromboembolism: Analysis of >31K Individuals from the Women's Genome Health Study and JUPITER Trials

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BACKGROUND/AIM

- Venous thromboembolism (VTE) carries **high morbidity and mortality**
- **Early risk identification** could guide preventive strategies that decrease the burden of VTE
- There is limited data in clinical trial populations on whether **polygenic risk scoring (PRS)** is an independent risk factor for VTE
- We aim to determine whether a recent PRS is an **independent predictor of VTE risk** in a cardiovascular disease primary prevention population

Methods and Materials

- Applied the **2023 VTE genetic risk score derived by PRS-continuous shrinkage by Ghouse et al[1]**, which includes Factor V Leiden and prothrombin gene variants, to imputed genetic data from two trial populations without history of cardiovascular disease, **JUPITER and WGHS[2,3]**
- **Calculated adjusted hazard ratios (aHR) of VTE** for each trial by risk categories of low (bottom 20%), intermediate (middle 60%) and high (top 20%) risk PRS
- Covariables included diabetes status, age (>=65), sex (only JUPITER), BMI (>=30), smoking status, history of CHF (only JUPITER), and hs-CRP (>=5 in JUPITER and >=2 in WGHS)
- Created **Kaplan Meier curves for VTE cumulative events over time by PRS risk category** for JUPITER and WGHS

Results – Baseline Characteristics

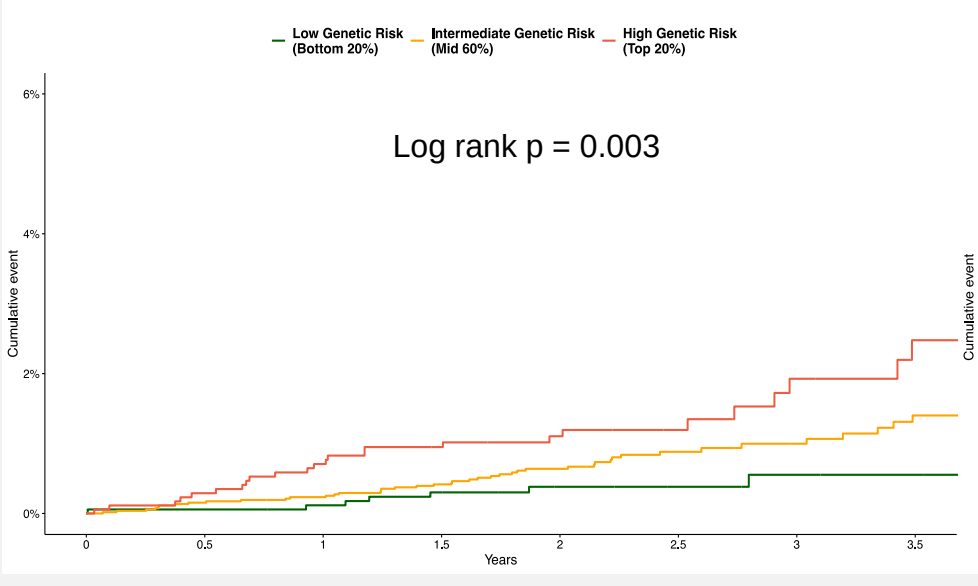
JUPITER			
	Low-Risk PRS (n=1,750)	Moderate-Risk PRS (n=5,249)	High-Risk PRS (n=1,750)
Age, years	66	66	66
Sex, % male	68%	68%	66%
BMI, kg/m^2	28.3	28.7	29.0
Current smoker	14%	13%	13%
Diabetes	0.6%	0.4%	0.3%
CHF	0.2%	0.3%	0.2%
LDL, mg/dL	110	110	110
hs-CRP, mg/L	4.0	4.1	4.1

WGHS			
	Low-Risk PRS (n=4,659)	Moderate-Risk PRS (n=13,976)	High-Risk PRS (n=4,659)
Age, years	53	53	53
Sex, % male	0%	0%	0%
BMI, kg/m^2	24.6	24.9	25.0
Current smoker	11%	12%	12%
Diabetes	2.3%	2.5%	2.9%
CHF	0.2%	0.1%	0.1%
LDL, mg/dL	121	121	122
hs-CRP, mg/L	2.0	2.0	2.0

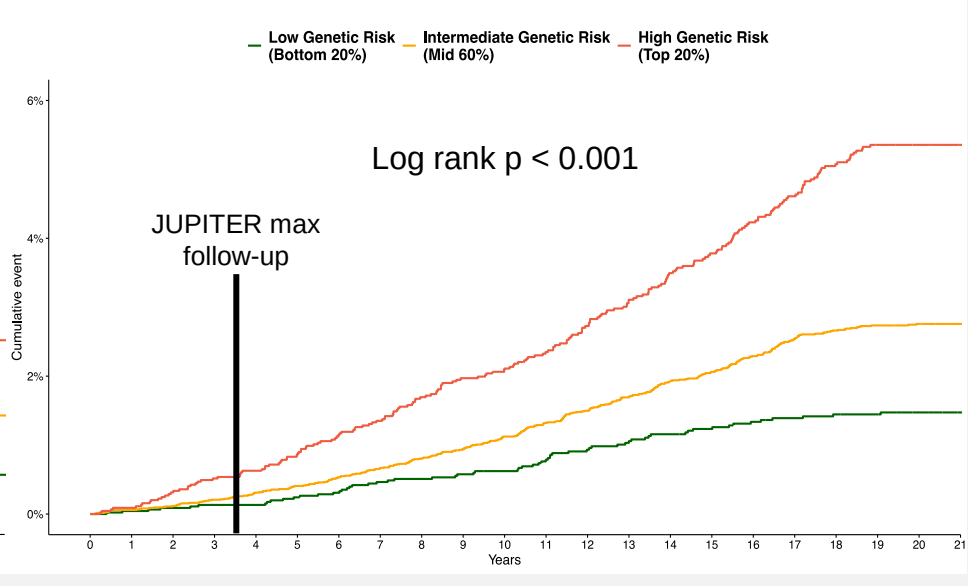
RESULTS – KM VISUALIZATION OF VTE CUMULATIVE EVENTS

- Annualized VTE event rate (per person per year) of 0.38% in JUPITER and 0.13% in WGHS
- Detected VTE events in JUPITER: Low Risk PRS – 7 (0.4%), Intermediate – 45 (0.9%), High – 25 (1.4%)
- Detected VTE events in WGHS: Low Risk PRS – 62 (1.3%), Intermediate – 339 (2.4%), High – 217 (4.7%)

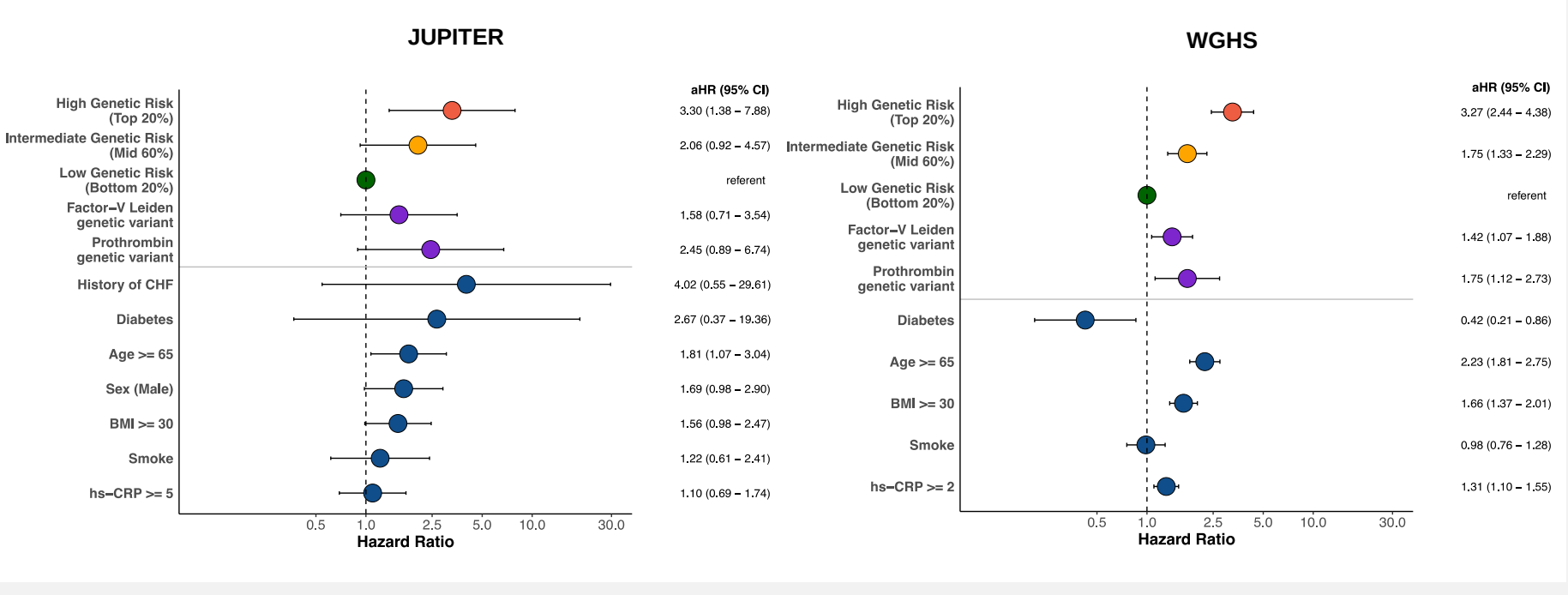
JUPITER



WGHS



Results – Adjusted Hazard Ratio by PRS and Covariable



CONCLUSIONS

- The 2023 VTE PRS, when applied to primary prevention data from JUPITER and WGHS, was a strong and non-redundant predictor of VTE risk

- Individuals with high-risk PRS had comparable VTE risk to those with monogenic thrombophilia, despite the fact that only approximately 5% of the population carries at least one copy of a pathogenic variant in the prothrombin or Factor V Leiden genes

- These findings suggest that PRS could change patient risk stratification and guide management, including consideration for longer duration of anticoagulant therapy after VTE or for familial genetic counseling

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