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ORIGINAL ARTICLE

Genetic Risk Score to Identify Risk of Venous Thromboembolism in Patients With Cardiometabolic Disease

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BACKGROUND: Venous thromboembolism (VTE) is a major cause of cardiovascular morbidity and mortality and has a known genetic contribution. We tested the performance of a genetic risk score for its ability to predict VTE in 3 cohorts of patients with cardiometabolic disease.

METHODS: We included patients from the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk), PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin), and SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) trials (history of a major atherosclerotic cardiovascular event, myocardial infarction, and diabetes, respectively) who consented for genetic testing and were not on baseline anticoagulation. We calculated a VTE genetic risk score based on 297 single nucleotide polymorphisms with established genome-wide significance. Patients were divided into tertiles of genetic risk. Cox proportional hazards models were used to calculate hazard ratios for VTE across genetic risk groups. The polygenic risk score was compared with available clinical risk factors (age, obesity, smoking, history of heart failure, and diabetes) and common monogenic mutations.

RESULTS: A total of 29 663 patients were included in the analysis with a median follow-up of 2.4 years, of whom 174 had a VTE event. There was a significantly increased gradient of risk across VTE genetic risk tertiles (P-trend <0.0001). After adjustment for clinical risk factors, patients in the intermediate and high genetic risk groups had a 1.88-fold (95% CI, 1.23–2.89; P=0.004) and 2.70-fold (95% CI, 1.81–4.06; P<0.0001) higher risk of VTE compared with patients with low genetic risk. In a continuous model adjusted for clinical risk factors, each standard deviation increase in the genetic risk score was associated with a 47% (95% CI, 29–68) increased risk of VTE (P<0.0001).

CONCLUSIONS: In a broad spectrum of patients with cardiometabolic disease, a polygenic risk score is a strong, independent predictor of VTE after accounting for available clinical risk factors, identifying 1/3 of patients who have a risk of VTE comparable to that seen with established monogenic thrombophilia.

Key Words: genetics ■ genomics ■ myocardial infarction ■ pulmonary embolism ■ venous thromboembolism

Venous thromboembolism (VTE) is a major cause of cardiovascular morbidity and mortality. In the United States, there are ≈900 000 VTEs annually, resulting in up to 100 000 deaths.[1,2] While acute precipitants and clinical risk factors are often the focus of determining the cause of VTE, a small minority of patients have a

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Nonstandard Abbreviations and Acronyms

GRS	genetic risk score
HR	hazard ratio
VTE	venous thromboembolism
TIMI	Thrombolysis in Myocardial Infarction

mutation in a limited number of genes leading to an inherited thrombophilia.[3] To that end, hypercoagulability and/or genetic testing can identify some uncommon genetic mutations such as factor V Leiden, antithrombin deficiency, protein C or S deficiency, or a prothrombin gene mutation.[3] However, standard testing is usually unrevealing, with mutations present in only about 5% of the general population.[1,2] Thus, for many patients with VTE, no clear precipitant or risk factor is ever identified.

In contrast to uncommon thrombophilias, recent work has used genome-wide association studies to identify 297 independent single nucleotide polymorphisms associated with VTE, from which a polygenic risk score was developed.[4] Application of the genetic risk score (GRS) in the general population led to the identification of many more individuals with a genetic predisposition for VTE than previously recognized. In this study, we tested the performance of this polygenic risk score in 3 TIMI (Thrombolysis in Myocardial Infarction) trials to evaluate whether a polygenic risk score predicts VTE in patients across the spectrum of cardiometabolic disease. In addition, we contrast the magnitude of risk compared with established clinical risk factors for VTE and classic monogenic thrombophilias.

METHODS

This study was approved by the local institutional review committees at each study site. Complete methods outlining the study design, study population, genotyping, imputation, GRS, clinical end points, and statistical analysis are included in Appendix in the Data Supplement. Although data and study material will not be made universally available, we encourage parties interested in collaboration to contact the corresponding author directly.

RESULTS

A total of 29 663 patients from the 3 trials were included in these analyses including 12 981 from FOURIER, 10 607 from PEGASUS-TIMI 54, and 6075 from SAVOR-TIMI 53. The baseline characteristics by tertile of genetic risk are included in Table 1; there were no clinically significant differences across genetic risk groups. The median follow-up across the study cohort was 2.4 years. There were 174 VTE events (95 deep vein thrombosis and 79 pulmonary embolism), 1232 myocardial infarctions, and 387 ischemic strokes.

Table 1. Baseline Characteristics by Tertile of Genetic Risk

	Tertile 1	Tertile 2	Tertile 3	*P*-value
Participants, n	9888	9887	9888	
FOURIER, %	42	44	45	
PEGASUS, %	37	36	35	
SAVOR, %	21	20	20	
Demographics				
Age, y ±SD	64.5±8.7	64.2±8.6	64.0±8.5	<0.001
Male sex, (%)	7365 (74)	7442 (75)	7319 (74)	0.12
BMI ±SD	29.9±5.1	30.0±5.2	29.9±5.1	0.33
Medical history, n (%)				
Myocardial infarction	7896 (80)	7954 (80)	7905 (80)	0.53
Stroke	872 (9)	906 (9)	942 (10)	0.23
Peripheral artery disease	1037 (11)	979 (10)	1093 (11)	0.03
Hypertension	7833 (79)	7913 (80)	7892 (80)	0.33
Heart failure	1900 (19)	1982 (20)	2043 (21)	0.04
Diabetes	4487 (45)	4536 (46)	4463 (45)	0.56
Current smoker	2164 (22)	2150 (22)	2302 (23)	0.16

BMI indicates body mass index.

Performance of GRS

There was a significantly increased gradient of risk across VTE genetic risk tertiles (*P*-trend <0.0001; Figure 1). After adjustment for clinical risk factors, patients in the intermediate genetic risk group had a 1.88-fold increased risk of VTE (95% CI, 1.23–2.89; *P*=0.004) and patients in the high-risk group had a 2.70-fold higher risk of VTE (95% CI, 1.81–4.06; *P*<0.0001; Figure 2) compared with the low genetic risk group. The risk of VTE increased linearly throughout the spectrum of genetic risk (Figure I in the Data Supplement), such that each standard deviation increase in the GRS carried a 47% increased risk of VTE (Adj. hazard ratio [HR], 1.47 [1.29–1.68]; *P*<0.0001). The GRS for VTE was not associated with an increase in arterial events such as myocardial infarction or ischemic stroke (Table I in the Data Supplement). There was no heterogeneity in the performance of the VTE GRS across multiple clinical subgroups (Figure 3).

Comparison to Clinical Risk Factors

Of the available clinical risk factors, only age ≥65 (HR, 1.87 [1.35–2.59]; *P*=0.0002) was a significant predictor of VTE, with risk similar to that conferred by an intermediate GRS. Obesity (HR, 1.34 [0.98–1.83]; *P*=0.07) was a weaker predictor of VTE, and there was no appreciable risk associated with diabetes (HR, 1.18 [0.86–1.61]; *P*=0.30), heart failure (HR, 1.1 [0.75–1.61]; *P*=0.64), or active smoking (HR, 1.09 [0.73–1.63]; *P*=0.67; Figure 2). The *c*-index for VTE for all the clinical factors was 0.63 (0.59–0.67), whereas for the GRS alone, it was 0.67 (0.63–0.71). The addition of

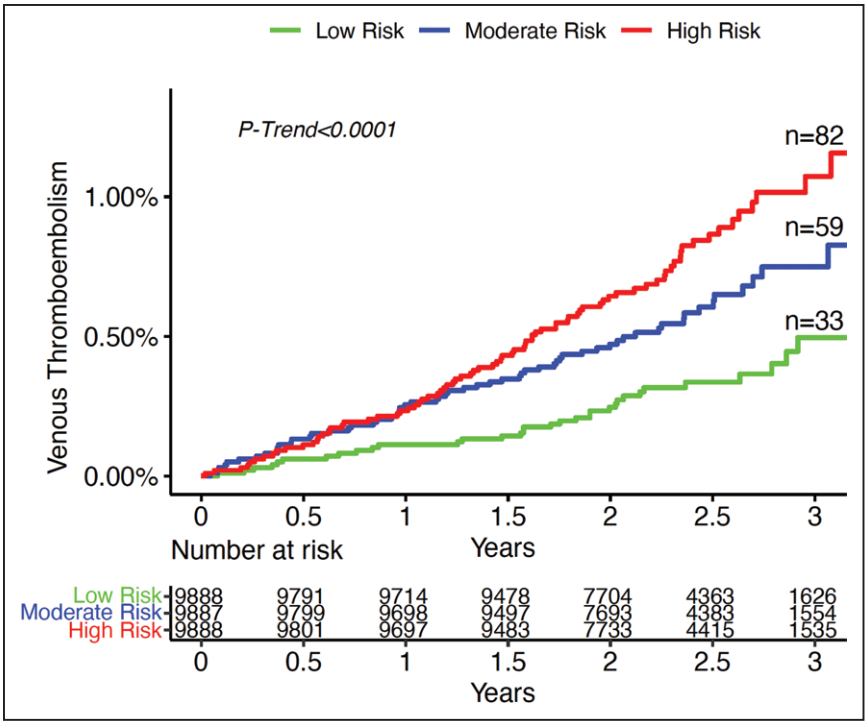

Figure 1. Three-year incidence of venous thromboembolism by tertile of genetic risk.

the GRS to clinical risk factors increased the *c*-index from 0.63 (0.59–0.67) to 0.67 (0.63–0.71; *P*<0.0001).

Monogenic Versus Polygenic Risk

Of the entire genetic cohort, 2474 patients (8.3%) had at least 1 of the 2 monogenic mutations (Factor V Leiden or Prothrombin) with frequency and overlap displayed in Table 2. Monogenic mutations were enriched among patients with VTE (14.9%, 26/174). Polygenic risk for VTE was balanced across patients with and without monogenic risk. In the 8.3% of patients with monogenic variants, polygenic risk did not improve risk prediction of VTE. However, the performance of the polygenic risk score strengthened when restricting the analysis to the 91.7% patients without a monogenic predisposition to VTE (HR_{adj} per 1 SD: 1.53 [1.30–1.82]; HR_{adj} for T3 versus T1: 2.88 [1.85–4.49]; Table II in the Data Supplement).

DISCUSSION

When a patient experiences a VTE event without an acute precipitant such as recent surgery, immobilization, or trauma, one often considers clinical risk factors[5] and contemplates testing for a handful of known, monogenic thrombophilia disorders. However, use of thrombophilia testing has fallen out of favor in part due to the low number of patients identified.[3] These data demonstrate that

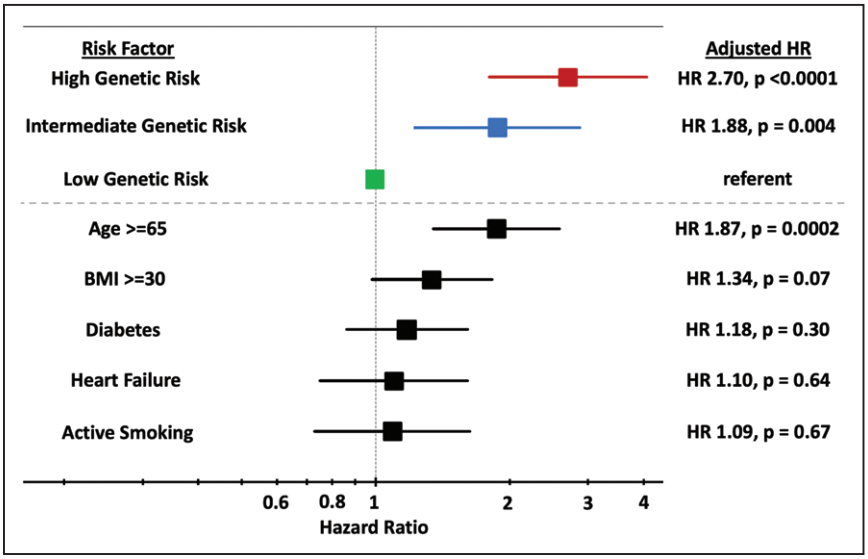

Figure 2. Forest Plot comparing high and intermediate genetic risk to clinical risk factors for venous thromboembolism.
Adjusted for age, sex, ancestry, obesity, active smoking, history of heart failure, and diabetes. BMI indicates body mass index; and HR, hazard ratio.

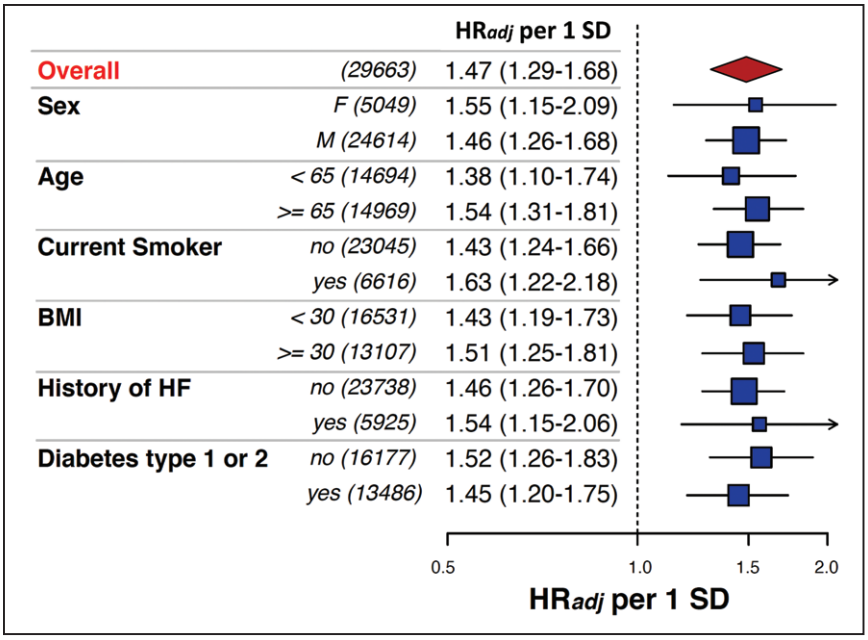

Figure 3. Subgroup analysis of venous thromboembolism risk per 1-SD increase in genetic risk score. There were no significant interactions across subgroups. BMI indicates body mass index; and HR, hazard ratio.

consideration of broader polygenic risk can identify a much larger proportion of patients at risk for VTE and is a stronger predictor than many chronic clinical risk factors.

These findings are consistent with, and build upon, recent work done by Klarin et al, who derived and validated this polygenic risk score for VTE in a general population. We now test the same score in a population with higher baseline risk and found the top one-third of patients had >2-fold increased risk of VTE, suggesting that polygenic risk offers important insight into VTE risk among those with cardiometabolic disease. Also unique to this analysis is the comparison of the GRS to both established clinical risk factors and monogenic thrombophilias.

Importantly, this GRS was specific to venous thrombotic events and did not predict arterial thrombotic events such as myocardial infarction or ischemic stroke. This is not unexpected as the score is distinct from a previously published 27-single nucleotide polymorphism score for coronary artery disease that we and others have studied.[6,7] Although there is some overlap, there is growing appreciation that risk factors and mechanisms differ between arterial and venous thrombosis. The ability of VTE GRS to strongly predict venous thromboembolic events but not arterial, such as myocardial infarction, supports this premise.

Physicians sometimes pursue hypercoagulability testing to identify uncommon but impactful etiologies for their patients with VTE. For example, Factor V Leiden (p.R506Q) is a monogenic mutation that is present in <5%[3] of the population but carries a 2.3-fold increased risk of incident VTE.[4] Similarly, prothrombin mutation carries an ≈2.8-fold increased risk.[8] This degree of VTE risk is similar to that observed in one-third of cardiometabolic patients with high polygenic risk. These data suggest that this VTE polygenic risk score would identify far more patients with genetic risk compared with standard hypercoagulability testing. Whether this increased identification of genetic risk would improve the clinical utility of hypercoagulability testing is an area requiring further investigation.

Limitations

The study was made up of patients from 3 clinical trial populations that spanned the spectrum of cardiometabolic disease; however, the results may not be generalizable to other disease domains. In particular, malignancies and pregnancies were excluded, which are major predisposing factors for VTE, and acute precipitants such as surgery and prolonged immobility were not captured. Thus, this analysis focuses on chronic risk factors for

Table 2. Prevalence of Monogenic Mutations

		Factor V Leiden			
		Wild type	Heterozygote	Homozygote	Total
Prothrombin	Wild type	27 189	1583	37	28 809
	Heterozygote	802	42	1	845
	Homozygote	9	0	0	9
	Total	28 000	1625	38	29 663

VTE. Moreover, not all trials collected use of hormonal therapies. Additionally, this analysis only included patients of European ancestry, as this is the population for which the GRS was developed, and it is unclear how well it translates to other ethnicities. Finally, VTE events were collected as investigator reported adverse events, rather than predefined Clinical Endpoints Comittee adjudicated events. A total of 174 VTE events led to wide CIs, which limited statistical power and precision. Nonetheless, in a model with clinical risk factors and GRS, the latter remained statistically significantly associated with VTE.

Conclusions

In a broad spectrum of patients with cardiometabolic disease, a polygenic risk score is a strong predictor of VTE, identifying one-third of patients with a risk of VTE similar to patients with monogenic inherited thrombophilia.

ARTICLE INFORMATION

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