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Racial differences in the prevalence of Factor V Leiden mutation among patients on chronic warfarin therapy.

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Abstract

We report the prevalence of Factor V Leiden (FVL) in European American and African American patients on warfarin therapy residing in Alabama.

Methods— Detailed history was obtained and FVL genotype was determined for 288 patients enrolled in a prospective cohort: *Pharmacogenetic Optimization of Anticoagulation Therapy*. Racial differences in genotype frequency were assessed by the Chi-square statistics and HWE assumptions by G-statistics. Race-specific analysis for the association between site of thromboembolism and the presence of FVL mutation was assessed using logistic regression.

Results—The overall heterozygote (GA genotype) frequency was 4.9%. No patient was found to be homozygous (AA) for the variant allele. The prevalence of GA was higher in European American (8.6%) compared to African American (1.4%) patients (p=0.004). The FVL genotype frequency was significantly different across race for venous thromboembolic events (p = 0.014) but not for arterial thromboembolic events (p = 0.20). Multivariable race-specific analysis highlights the contribution of FVL mutation to the risk of venous thromboembolic events in European American (p = 0.03) but not in African American patients (p = 0.95). European American patients with the GA mutation were approximately 6.3 times more likely to have experienced a venous, rather than arterial thromboembolic event.

Conclusion—In Alabama, among patients on warfarin, the GA genotype is more prevalent in European Americans compared to African Americans. In European Americans, but not in African Americans, the GA genotype was more prevalent in patients with venous compared to arterial thromboembolic events.

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Keywords

Factor V Leiden; Prevalence; European American; African American; Arterial and Venous Thrombosis

Introduction

Thromboembolism is a major cause of morbidity affecting over 2 million Americans every year. [1] Multiple complex interactions between genetic and environmental factors occur during the pathobiological course of arterial and venous thromboembolism. [2;3;4;5] Several mutations in the genes coding for coagulation cascade proteins have been associated with an increased risk of thromboembolism. [4;5] The most common inherited defect of coagulation currently recognized is due to a single adenine (A) to guanine (G) point mutation in the factor V gene. [6] This G1691A mutation results in the substitution of glutamine for arginine on factor V rendering it relatively resistant to degradation by activated protein C.[7] The resultant prothrombotic state is described as activated protein C resistance or Factor V Leiden mutation (FVL). [4;5;8]

The identification of FVL as a prevalent risk factor for thrombophilia spurred efforts to determine and quantify the strength of its association with venous and arterial thromboembolic events. Although the association of FVL with venous thromboembolic events is widely accepted, [2;9;10;11;12;13;14;15;16;17] its association with thrombosis in the arterial circulation (with resultant myocardial infraction, ischemic stroke or peripheral arterial disease) is less well established. [18;19;20;21;22;23] Herein we report the prevalence of FVL in European American and African American patients, residing in Alabama, undergoing chronic anticoagulation therapy for arterial and venous thromboembolic events.

Materials and methods

The Pharmacogenetic Optimization of Anticoagulation Therapy (POAT) is an ongoing prospective cohort study aiming at defining the influence of polymorphisms within the gene coding for cytochrome P450-2C9 (CYP2C9) on the dose of warfarin and risk of warfarin related complications during a 2-year follow-up period. [24] As part of the study protocol FVL genotype was also assessed in all participants.

Participant enrollment

Patients older than 19 years of age were identified at the initiation of chronic warfarin therapy (target INR 2–3, anticipated duration of treatment > 2 years). The study protocol was explained to all patients and informed consent was obtained. The Institutional Review Boards at the University of Alabama at Birmingham and Jefferson Clinics approved the study protocol.

Data Collection

After obtaining informed consent a structured interview form was used at the time of enrollment to obtain a detailed medical, lifestyle and concomitant medication history from each patient. Data collected included information on self-reported race, indication for therapy, demographics, height and weight, concomitant medications and co-morbid conditions. Lifestyle and socioeconomic data included smoking, alcohol use, education, annual income, medical insurance, physical activity, dietary vitamin k intake. Detailed information about previous episodes of venous and arterial thromboembolism was collected in addition to family history of thromboembolic events. The self-reported history was verified by reviewing medical records and indication for therapy was verified by diagnostic study results.

Indications for warfarin therapy were reviewed to determine whether the patient had experienced a venous or arterial thromboembolic event. Venous thromboembolism was considered established if deep vein thrombosis (DVT) was confirmed by ultrasound or venography, and pulmonary embolism (PE) ventilation/perfusion lung scanning, spiral computed tomography (CT) scanning or pulmonary angiography. Arterial thromboembolism was considered established if myocardial infarction was diagnosed according to clinical, enzymatic and electrocardiographic criteria, ischemic stroke demonstrated by CT or magnetic resonance imaging and clinical symptamatology. If a cerebral event completely resolved within 24 h without cerebral lesions at scanning, it was classified as transient ischemic attack (TIA). Patients such as those atrial fibrillation (confirmed by electrocardiography), low left ventricular ejection fraction (confirmed by echocardiography) without are prior history of arterial or venous thromboembolic events comprised the group with no thromboembolic events. Information on comorbid conditions including diabetes mellitus, hypertension, hyperlipidemia, renal failure, renal insufficiency, congestive heart failure, and coronary artery disease was collected during the initial interview and confirmed by review of medical records using ICD-9 codes.

Blood sample collection and laboratory methods

Approximately 8 ml of blood was collected in a Qiagen PAXgene tube (Qiagen Inc., Valencia, CA) at the time of patient consent. Samples were batched for weekly DNA extraction using the PAX gene blood DNA extraction kits. Purified DNA was aliquoted and stored at 2–8 °C.

The FVL mutation was assessed utilizing the polymerase chain reaction (PCR) as described by Hézard with some modifications. [25;26] Each 15 μL reaction contained 2X Thermopol Buffer II (New England Biolabs, Beverly, MA), 1.2μM of each FVL primer, 0.1μM of each Factor IX internal amplification control primer, 3.3mM $MgSO_4$, 1μM of each dNTP, 20% betaine, 0.117U/μl HotStartTaq DNA Polymerase (Qiagen Inc., Valencia, CA) and 100ng genomic DNA. Primer sequences and amplification conditions are displayed in Table 1. Amplified products were separated by electrophoresis through a 2% agarose gel and visualized by staining with ethidium bromide.

Statistical Methods

Genotypes were classified as homozygous wild type (GG), heterozygotes (GA) or homozygotes (AA) for the variant allele. The homozygous wild type was the referent group for all analyses. Student's t-tests were used to test differences for continuous variables and the $?^2$ test of independence was used to assess the differences for categorical variables between racial groups. The differences between allele frequencies by race and site of thromboembolism were assessed using the $?^2$ test of independence. The assumption of Hardy Weinberg Equilibrium (HWE) for FVL polymorphism was tested using a likelihood-ratio test (G statistic).[27]

Logistic regression (LR) was used to calculate race-specific odds ratios (ORs) and 95% confidence intervals (CIs) for the association between site of thromboembolism and the presence of FVL mutation. When considering the potential confounding influence of demographic, lifestyle and medical characteristics, two separate analyses were conducted. The first approach considered all characteristics listed in Table 2 regardless of their impact on the association between FVL mutation and site of thromboembolism or their statistical significance. The second, more parsimonious approach retained only those variables that demonstrated a statistically significant association with site of thromboembolism or seemed to confound the association between site of thromboembolism and FVL mutation. The determination of which variables should be retained as confounders was based on the change-

in-estimate criteria using a value of 10%. [28] All analyses were performed using JMP version 5.1 (SAS Institute, Cary NC) at a non-directional α level of 0.05.

Results

Participants recruited for current analysis

This report includes 317 patients newly initiated on chronic warfarin therapy. Patients were recruited between August 2003 and April 2005. The genotype was not reconfirmed for 27 patients and medical records were unavailable for one. These patients in addition to one Hispanic patient were not considered in the following analysis. Thus the results of analyses herein reported include 288 patients (149 African Americans, 139 European Americans).

Table 2 displays the demographic, lifestyle and clinical characteristics of study participants by race. The mean age was significantly higher in European American compared to African American patients (63.9 vs. 59.5 years, p=0.016). There were no significant differences in gender distribution, body mass index (BMI; kg/M^2), smoking status and family history of arterial and venous thromboembolic events by race. More European American patients were light drinkers (alcohol intake: 1–7 drinks/week) (p=0.013) and were marginally more physically active (p=0.07) compared to African American patients. European American patients were more likely to have medical insurance (p=0.0009), higher education (p<0.0001) and higher income (p<0.0001). There were no significant differences by site of thromboembolism except venous thromboembolism, which was marginally more prevalent in African American compared to European American patients (p=0.07). This finding was consistent with the higher prevalence of prior history of venous thromboembolic event in the African American patients (p=0.013). The prevalence of comorbidity was similar between the two groups with the exception of renal disease and hypertension, which were more prevalent among African American (p=0.08 and 0.009 respectively) compared to European American patients.

The observed overall FVL GA genotype frequency was 4.9% and the observed allele frequency of the A allele was 2.43% (Table 3). Of the 288 patients evaluated, none were homozygous for the A allele. Of 149 African American patients evaluated two were found to be GA and 147 were GG (Table 3). Thus the observed genotype frequency for GA was 1.3%. The observed frequency of the A allele was 0.67%. Among the 139 European American patients evaluated 12 (8.6%) were found to be GA. The frequency of the A allele for this group was 4.32%. The prevalence of GA is significantly higher in European American compared to African American patients (p= 0.004, table 3). The distribution of genotype differed by race but not by gender (p = 0.86, data not shown). The allele frequencies were found to be in Hardy Weinberg equilibrium in both African Americans (G statistic= 0.01, p = 0.91). and European Americans (G statistic= 0.54, p = 0.46).

Since the FVL genotype frequencies differed significantly by race all further analyses were conducted after stratification by race. Table 4 presents FVL genotype frequencies by site of thromboembolism stratified by race. The FVL genotype frequency did not differ across race for arterial thromboembolic events. However, for venous thromboembolic events the frequency of variant genotype was significantly higher in European Americans (p = 0.014). The GA genotype frequency in did not differ by indication arterial (1.8%) versus venous (2.0%) thromboembolism among African American patients. However among European American patients the GA genotype was more common in patients with venous thromboembolism (18.2%) compared to patients with arterial thromboembolism (8.9%). This two-fold difference did not achieve statistical significance. There were no racial differences in the frequency of FVL mutation for patients (13 African Americans) who had experienced both arterial and venous thromboembolic events (n = 26, p = 0.31).

Logistic regression (LR) was used to calculate race-specific odds ratios (ORs) and 95% confidence intervals (CIs) for the association between site of thromboembolism and the presence of FVL mutation. However meaningful comparison of patients with 'none versus any (arterial or venous)', 'none versus arterial' and 'none versus venous' was hindered by the small sample size in the group of patients with no thromboembolic events (none) and the absence of FVL mutation with resultant unstable estimates and extremely large standard errors. Multiple education categories also resulted in unstable estimates. Therefore, education was re-categorized into two groups; less than high school and more than high school education for regression analyses.

Table 5 displays the race-specific odds for patients with arterial (n = 105, 56 events in European Americans) compared to those with venous (n = 89, 33 events in European Americans) thromboembolic events. The race-specific ORs highlight the significant contribution of FVL mutation to the risk of venous thromboembolic events in European American ($p = 0.03$) but not in African American patients ($p = 0.95$). This indicates that European American patients with the GA mutation were approximately 6.3 times more likely to have experienced a venous, rather than arterial thromboembolic event. If high cholesterol level is excluded from the model the association, although marginally diminished (OR = 5.5) remains significant ($p = 0.043$).

Discussion

The frequency of FVL mutation in healthy European Caucasian populations ranges from 2.5% to 13.3% (pooled prevalence 4.7%), with Greece [29] and Sweden [30] showing the highest prevalence and Italy [31] and Netherlands [14] the lowest. The epidemiology of FVL has been presented in several reviews. [10;29;32;33;34] In a cohort of 4,047 U.S men and women the prevalence of FVL was found to be the highest in European Americans (5.27%) compared to other racial/ethnic groups; 2.21% in Hispanic Americans, 1.23% in African Americans, 0.45% in Asian Americans, and 1.25% in Native Americans ($p < 0.001$). [35] The frequency of FVL in persons of African descent is estimated to range from 0% to 1.3%. [9;35;36;37;38]

FVL has been well established as a risk factor for venous thromboembolism. The overall prevalence of FVL in patients with venous thromboembolism is 18.3%; being lower in African Americans (1.2–2.9%) [33;36;38] and higher for Swedes.[30] Among participants of the Physicians' Health Study [35] the frequency of FVL was significantly higher in men with thromboembolism (11.6%) compared to those that did not experience a thromboembolic event (6%). This higher frequency was associated with a 2.7 fold risk [95% CI 1.3, 5.6] of venous thromboembolism ($p=0.0008$). Homozygosity for the FVL mutation further increases this risk [14] as do factors such as smoking, OCP use, surgery, immobility etc. [2;39;40;41]

FVL mutation has been hypothesized as an important risk factor for arterial thromboembolic events (predominantly myocardial infarction and stroke), which are the leading causes of illness and death in the United States. However the overall prevalence of 5.4% among patients is very similar to that in healthy population controls. [10;38] FVL mutation was not found to be associated with myocardial infarction (6.1%; $p >0.2$) or cerebrovascular disease (4.3% percent; $p >0.2$). [35] Furthermore, most population-based, case-control studies and pooled analyses confirm that FVL mutation is not a risk factor for myocardial infarction or cerebrovascular disease. [19;20;35;42;43] The association of FVL mutation with thrombosis in the arterial circulation is at best modest (OR=1.21, 95% CI [0.99–1.49]) and remains equivocal. [10;20]

Our patient population was comprised of individuals requiring chronic anticoagulation and did not have significant predisposing conditions for DVT (e.g. surgery, etc.). As expected the prevalence of FVL was lower in African American (1.3%) compared to European American

patients (8.6%, Table 3). Surprisingly, no patient was found to be homozygous for the mutation and we did not encounter the presence of FVL mutation in patients with conditions such as atrial fibrillation or low ejection fraction. The latter finding may be due to small sample size in this subgroup (n=68), 45.6% of which was constituted by African Americans patients (n = 31), or perhaps chance.

In our study the frequency of FVL mutation among African American patients with venous thromboembolism was 2.0%, similar to that reported by Dowling and Hooper. [36;38] We observed a similar frequency for African American patients with arterial thromboembolism (1.8%). This lack of difference in the frequency of FVL by site of thromboembolism could be due to the rarity of the mutation or due to its relative lack of contribution to the thromboembolic disease in this racial group (table 4).

The GA genotype frequency among European Americans in our study was similar to that reported by Ridker and Rosendaal. [2;13;33;35] Results of univariate analysis, although statistically non-significant, indicate an approximate two-fold difference in frequency of the GA genotype among European-American subjects being treated for venous (18.2%) versus arterial (8.9%) thromboembolism (Table 4). However after statistical adjustments for other variables, the odds ratio exceeds 6.

To understand reasons for this change in effect size in European American patients further analysis was conducted. The significant difference in the age (mean ± SD) between patients with arterial thromboembolism (67.7 ± 12.3) and venous thromboembolism (55.6 ± 17.3) partly explains the change in effect size. This difference in age was even more pronounced among European American patients with the GA genotype and arterial thromboembolism (75.2 ± 8.4) and patients with the GA genotype and venous thromboembolism (57.3 ± 17.0). These substantial age differences result in a dramatic increase in the odds ratio for the GA mutation in European Americans when age is included in the logistic regression model.

Our results indicate that European American patients with the GA genotype were approximately six times more likely to suffer from a venous, rather than arterial thromboembolism after controlling comorbidities and demographic variables (Table 5). As reported by Dilley et al [37], the GA genotype was not found to be associated with an increased risk of arterial versus venous thromboembolism in African American patients. This could be due to the low power of the study to detect allelic effects in African Americans. Given the low frequency of the ‘A’ allele among the African Americans in this study (0.67%), there would need to be a sample size of 1154 African Americans to detect an Odds Ratio of 2 with 80% power at $\alpha = 0.05$.

The influence of FVL mutation in European American but not in African American patients raises the concern of confounding due to population stratification. When comparing the frequency of the FVL mutation, among various racial and ethnic groups one has to consider the contribution of racial admixture. The difference in the reported frequencies of FVL mutation could be due to racial differences or to the various degree of racial admixture within a given racial/ethnic group. Although several ethnic groups are represented in the Alabama European American population, there is a large constituency of those with Scotch/Irish and English ancestry. [44;45] The degree of racial admixture among African Americans is known to vary considerably among those living in different geographic regions of the US. [46;47; 48] Thus, if one is attempting to determine whether a mutation varies between any groups that are being compared it is important that the two groups are recruited from the same geographic region. [49] Although the small sample size and the evaluation of only one gene did not allow us to conduct admixture studies the patients recruited all resided in a relatively defined area which is the third least migratory region of the US. [50]

Conclusion

In Alabama European American and African American patients undergoing chronic anticoagulation therapy the observed overall FVL GA genotype frequency was 4.9% and the observed allele frequency of the A allele was 2.43%. The prevalence of the FVL mutation was significantly higher among European American (8.6%) compared to African American patients (1.3%). In European Americans, but not in African Americans, the GA genotype was significantly more prevalent in patients with venous compared to arterial thromboembolic events. A larger sample size would provide additional power to determine if the frequency of the FVL mutation differs significantly in patients by site of the thromboembolic event, both arterial and venous by race. Evaluation of more genes would also afford consideration of the contribution of racial admixture.

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Abbreviations

FVL

Factor V Leiden

POAT

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Table 1

Primer sequence, PCR conditions, primer mix and reaction mixture specifications

	Specifications
Primers	Primer FVL(G1961A)-C 5'-tgt tat cac act ggt gct taa-3' Primer FVL(G1961A)-N 5'-cag atc cct gga cag acg-3' Primer FVL(G1961A)-M 5'- cag atc cct gga cag aca-3' Primer Factor IX-F 5'-ctc ctg cag cat tga ggg aga tgg aca tt-3' Primer Factor IX-R 5'-ctc gaa ttc ggc aag cat atc aat gta t-3'
Primer Mix	Factor IX-F@10μM (0.10μM) Factor IX-R@10μM (0.10μM) FVLM (G1961A)-C@10μM (1.20μM), FVL (G1961A)-N@10μM (1.20μM) FVL (G1961A)-M@10μM (1.20μM) sterile water (qs)
Reaction mixture	10X Thermopol Buffer II (2X), 100mM $MgSO_4$ (3.3mM) 10mM dNTP solution* (100μM) Betaine (20%) Taq Polymerase (0.117U/μl) Sterile water
PCR conditions	94ºC x 5' / (94ºC x 30"; 55ºC x 30"; 72ºC x 15") x 10 / (94ºC x 30"; 50ºC x 30"; 72ºC x 15") x 20 / 72ºC x 5' / 4ºC Pause. Heated lid at 98ºC.

* 10mM dNTP solution is composed of 2.5mM each of dATP, dCTP, dGTP and dTTP

Table 2

Demographic, lifestyle and clinical characteristics of study participants

Characteristic		African American (n=149)	European American (n=139)	p-value
Age, mean (SD)		59.5 (15.95)	63.9 (14.9)	**0.016**
Body Mass Index, mean (SD)		29.7 (7.56)	28.9 (7.3)	0.38
Gender				
	Female	70 (47.7)	68 (48.9)	0.83
	Male	78 (52.3)	71 (51.1)	
Smoking Status				
	Current	30 (20.1)	20 (14.4)	0.28
	Never	48 (32.2)	55 (39.6)	
	Past	48 (32.2)	42 (30.2)	
Alcohol (drinks per week)				
	0	110 (73.8)	87 (62.6)	**0.013**
	1–7	22 (14.8)	40 (28.8)	
	>8	13 (8.7)	8 (5.7)	
No Medical Insurance		33 (22.1)	11 (7.9)	**0.0009**
Education				
	< High School	53 (35.6)	14 (10.0)	
	High School	70 (47.0)	58 (41.7)	**<0.0001**
	College	23 (15.4)	48 (34.5)	
	Graduate School	1 (0.7)	17 (12.2)	
Yearly Income				
	<15,000	51 (34.2)	19 (13.7)	
	15,000–25,000	61 (40.9)	30 (21.6)	**<0.0001**
	25,000–50,000	33 (22.1)	40 (28.8)	
	50,000–100,000	2 (1.3)	38 (27.3)	
	>100,000	1 (0.7)	10 (7.2)	
Level of Physical Activity				
	Wheelchair bound	8 (5.4)	7 (5.0)	
	Uses Walker/Cane	25 (16.8)	12 (8.6)	0.07
	Ambulates without assistance	37 (24.8)	28 (20.1)	
	Physically active	78 (52.3)	87 (62.5)	
	Consistent/Intensive exercise	1 (0.7)	5 (3.6)	
Site of thromboembolism*				
	Arterial	55 (36.9)	56 (40.3)	0.55
	Venous	50 (33.6)	33 (23.7)	0.07
	Both	13 (8.7)	13 (9.3)	0.85
	None	31 (20.8)	37 (26.7)	0.24
Comorbidity				
	Hypertension	84 (56.4)	57 (41.0)	**0.009**
	Hypercholesterolemia	48 (32.2)	50 (36.0)	0.50
	Heart disease	67 (45.0)	64 (46.0)	0.85
	Diabetes Mellitus	49 (32.9)	42 (30.2)	0.62
	Renal Disease	32 (21.5)	19 (13.7)	*0.08*
	OCP/HRT	7 (4.7)	7 (5.0)	0.89
Prior Thromboembolic event				
	Venous thromboembolism	59 (39.6)	36 (25.9)	**0.013**
	Stroke	41 (27.5)	34 (24.5)	0.55
	CAD/MI	49 (32.9)	51 (36.7)	0.49
Family history of:				
	Venous Thrombosis	19 (12.7)	12 (8.6)	0.34
	Arterial thrombosis	110 (73.8)	109 (78.4)	0.36

Mean (SD) displayed for continuous variables and frequency counts (column percent) for categorical variables Information on missing for smoking (45 patients), alcohol (8 patients), income/education/medical insurance (2 patients).

*Arterial thromboembolism includes patients with MI, Stroke & TIA. Venous thromboembolism includes patients with DVT & PE. Both include patients with venous and arterial events. None includes patients with no thromboembolic events (e.g. Atrial Fibrillation), Significant p-values **bolded**

Table 3

Distribution of variant allele "A" and heterozygote "GA" genotype in European American and African American participants

Race	FVL genotype				Allele frequency[?]	
	GG		GA			
	n	% Positive	n	% Positive	'G'	'A'
All patients	274	95.1	14	4.9	97.57 %	2.43 %
African Americans	147	98.7	2	1.3	99.33 %	0.67 %
European Americans	127	91.4	12	8.6	95.68 %	4.32 %
p-value[*]	$\chi^2 = 8.34$, $p = 0.004$				$\chi^2 = 8.13$, p =0.004	

[?] Frequency of 'G' allele calculated ($n_{GA} + 2n_{GG}$)/2 total-n for racial group. Frequency of 'A' allele calculated (1-G) No participant was homozygous for the AA genotype

[*] p-values refer to significance of differences by race

Table 4

Distribution of FVL genotype in European American and African American patients with arterial and venous thromboembolic events.

Race	Genotype	Site of Thromboembolism* None (n=68)		Arterial (n=111)		Venous (n= 89)	
		n	**%**	**n**	**%**	**n**	**%**
African American	GA	0	0.0	1	1.8	1	2.0
	GG	31	100.0	54	98.2	49	98.0
European American	GA	0	0.0	5	8.9	6	18.2
	GG	37	100.0	51	91.1	27	81.8
p-value		-		0.206		**0.014**	

No participant was homozygous for the 'AA' genotype

*Arterial thromboembolism includes patients with MI, Stroke & TIA. Venous thromboembolism includes patients with DVT & PE**.** 'None' denotes patients with no thromboembolic event. 26 patients (13 African Americans) had both arterial and venous events.

Significant p-values **bolded**

Table 5

Race specific odds of venous versus arterial thromboembolic events in study participants

Race	Predictors retained in the model	Odds Ratio [95% CI]	p-value
European American (n=89)	Age	**1.07 [1.02, 1.12]**	**0.003**
	Gender*	**3.57 [1.08, 11.85]**	**0.037**
	Income	0.69 [0.37, 1.28]	0.24
	< High School education	2.50 [0.46, 3.48]	0.28
	BMI	0.96 [0.89, 1.04]	0.36
	Hypercholesterolemia	2.40 [0.56, 10.32]	0.24
	Hypertension	0.51 [0.13, 2.01]	0.33
	Diabetes	0.93 [0.27, 3.18]	0.91
	FVL (GA) mutation	**6.35 [1.20, 33.7]**	**0.030**
African American (n=105)	Age	1.09 [1.04, 1.14]	**<0.0001**
	Gender*	3.92 [1.14, 13.49]	**0.03**
	Income	1.69 [0.87 3.29]	0.12
	< High School education	0.28 [0.09, 0.89]	**0.032**
	BMI	1.03 [0.95, 1.11]	0.48
	Hypercholesterolemia	0.47 [0.13, 1.63]	0.23
	Hypertension	0.58 [0.19, 1.80]	0.35
	Diabetes	1.05 [0.34, 3.21]	0.93
	FVL (GA) mutation	1.07 [0.05, 24.42]	0.97

Significant p-values **bolded**

*Females constitute the referent group for gender comparisons Arterial thromboembolism includes patients with MI, Stroke & TIA. Venous thromboembolism includes patients with DVT & PE.