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Reasons for Differences in the Incidence of Venous Thromboembolism in Black Versus White Americans

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Abstract

INTRODUCTION: Venous thromboembolism incidence rates are 30–100% higher in American blacks than whites. We examined (a) the degree to which differences in the frequencies of socioeconomic, lifestyle, and medical risk factors, and genetic variants explain the excess venous thromboembolism risk in blacks and (b) whether some risk factors are more strongly associated with venous thromboembolism in blacks compared with whites.

METHODS: We measured venous thromboembolism risk factors in black or white participants of the Atherosclerosis Risk in Communities study in 1987–89 and followed them prospectively through 2015 for venous thromboembolism incidence.

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RESULTS: Over a mean of 22 years, we identified 332 venous thromboembolisms in blacks and 578 in whites, yielding 65% higher crude incidence rates per 1,000 person-years in blacks. The age and sex-adjusted hazard ratio (95% CI) of venous thromboembolism for blacks, compared with whites, was 2.04 (1.76, 2.37) for follow-up >10 years, and was attenuated to 1.14 (0.89, 1.46), when adjusted for baseline confounders or mediators of the race association, which tended to be more common in blacks. For example, adjustment for just baseline weight, family income, and plasma factor VIII concentration reduced the regression coefficient for race by 75%. There were no significant ($p<0.05$) two-way multiplicative interactions of race with any risk factor, except with a 5-SNP genetic risk score (a weaker venous thromboembolism risk factor in blacks) and with heart failure hospitalization (a stronger venous thromboembolism risk factor in blacks).

CONCLUSIONS: The higher incidence rate of venous thromboembolism in blacks than whites was mostly explained by blacks having higher frequencies of venous thromboembolism risk factors.

Keywords

Ethnicity; Prospective study; Pulmonary embolism; Race; Venous thrombosis

INTRODUCTION

Incidence rates of venous thromboembolism, comprising deep vein thrombosis and pulmonary embolism, are 30–100% higher in black Americans than white Americans.[1–11] In the Atherosclerosis Risk in Communities (ARIC) Study, the lifetime risk of venous thromboembolism from ages 45 to 85 was 11.5% in blacks compared with 6.9% in whites.[12] The racial disparity in hospitalized venous thrombosis rates in Medicare recipients has grown over time, and was double in blacks than whites in 2010.[11]

The reasons for higher venous thromboembolism rates in black Americans are unclear.[2,3] Race is mainly a sociocultural construct in the US,[13] and therefore social disadvantage and culturally influenced lifestyle risk factors (e.g., obesity) may be root causes. Yet, there are some differences in frequencies of venous thromboembolism-related gene variants among race groups (e.g., sickle trait), reflecting a potential contribution of biology as well. Furthermore, compared with whites, blacks generally have higher levels of many plasma biomarkers associated with venous thromboembolism (e.g., D-dimer, factor VIII, factor XI), and a higher prevalence of many medical conditions leading to provoked venous thromboembolism.[2,3] In contrast, blacks have lower frequencies than do whites of several of the strongest thrombophilic genetic variants related to venous thromboembolism (e.g., Factor V Leiden and non-O blood group), and these variants may have different impacts in blacks than whites. We recently reported that a 5-SNP genetic risk score, comprising 5 single nucleotide polymorphisms consistently associated with venous thromboembolism in whites, was less strongly associated in blacks.[14]

We used ARIC data to examine (a) the degree to which differences in the frequencies of socioeconomic status, lifestyle, and medical risk factors, and genetic variants explain the excess venous thromboembolism risk in blacks versus whites and (b) whether some risk

factors are more strongly associated with venous thromboembolism in blacks compared with whites.

METHODS

Study Sample

Previous publications described the ARIC study design, methods, and venous thromboembolism incidence rates in detail.[15,16] In brief, 15,792 predominantly self-designated black or white men and women aged 45 to 64 years enrolled in the ARIC study baseline in 1987–1989. ARIC performed subsequent examinations in 1990–92, 1993–95 (Visit 3), 1996–98, 2011–13, 2016–2017, as well as annual or semi-annual telephone contact. The institutional review committees at each ARIC study center approved the methods, and ARIC staff obtained informed participant written consent.

Measurement of Venous Thromboembolism Risk Factors

Except where noted, this analysis included venous thromboembolism risk factors measured at the ARIC baseline or Visit 3 examination using methods previously reported.[1,12,15,17–20] These included socioeconomic, lifestyle, medical, hemostatic, and genetic risk factors. ARIC isolated genomic DNA and measured six key variants important for venous thromboembolism: *F5* Leiden rs6025, *F2* rs1799963, *ABO* rs8176719, *FGG* rs2066865, *F11* rs2036914, and created a genetic risk score, as previously reported.[14] ARIC also identified incident hospitalized heart failure, hospitalized stroke, and cancer during participant follow-up, using published methods and criteria.[21–23]

Venous Thromboembolism Occurrence

ARIC staff contacted participants annually or semi-annually and retrieved hospital records with possible venous thromboembolism discharge codes through 2015. To validate venous thromboembolism events, two physicians reviewed the hospital records using standardized criteria.[16] The reviewers sub-classified venous thromboembolisms as unprovoked (no obvious cause) or provoked (associated with cancer, major trauma, surgery, marked immobility). For this report, we restricted deep vein thromboses to those in the lower extremity or vena cava, because upper extremity deep vein thromboses were relatively few and almost always the result of indwelling venous catheters.

Statistical Methods

From the ARIC baseline cohort (n = 15,792), we successively excluded 48 who were not black or white; 276 who reported a history of venous thromboembolism at baseline, and 87 who were taking anticoagulants at baseline, leaving 15,397 participants.

Using SAS, we computed crude incidence rates of venous thromboembolism for blacks and whites; follow-up began at ARIC baseline and went until the first date of venous thromboembolism, loss to follow-up, death, or December 31, 2015. We performed proportional hazards regression to estimate the hazard ratio (HR) of venous thromboembolism for race (black versus white). We tested the proportional hazards assumption by testing interactions of race with follow-up time, by race-specific plots of the

survival function over time, and by correlating Schoenfeld residuals and the ranking of individual failure times. Each method showed that the proportional hazards assumption for race was violated, in that that blacks had an increasingly greater risk of venous thromboembolism, compared with whites, as follow-up lengthened (Figure 1). To overcome this problem, we stratified follow-up into the first 10 years and >10 years, whereupon the proportional hazard assumption was not violated for either period.

Proportional hazard Model 1 estimated the race HR adjusted for baseline age and sex. Then, to test our first hypothesis, we assessed in Model 2 the degree of attenuation of the HR of race with venous thromboembolism after introducing other risk factors (i.e., potential confounders or "mediators" of the race association, as shown in the footnote of Table 3). Model 3 added baseline plasma hemostatic factors and the genetic risk score. Model 4 added ARIC visit 3 hemostatic factors (factor XI and D-dimer). Model 5 added to Model 1 time-dependent variables for prevalent or incident heart failure, stroke, or cancer.

To explore our second aim regarding whether some risk factors may be more strongly associated with venous thromboembolism in blacks compared with whites, we tested multiplicative two-way interactions of race with each potential risk factor, using the likelihood ratio in proportional hazards regression models, with venous thromboembolism after 10 years as the outcome.

Data Sharing Statement

For original data, please contact folso001@umn.edu

RESULTS

Differences in Venous Thromboembolism Risk Factors and Rates Between Blacks and Whites

At baseline in 1987–89, this population-based cohort initially free of venous thromboembolism included 15,397 men and women aged 45–64 years; 4,171 (27%) self-identified as black and 11,226 (73%) as white. Compared with whites, blacks had higher means or prevalences of most potential or known non-genetic venous thromboembolism risk factors (Table 1), other than blacks having less current use of post-menopausal HRT, higher estimated glomerular filtration rate, and equivalent activated partial thromboplastin time (aPTT). In the subset of participants who completed ARIC visit 3 (n=12,217), mean values were also higher for blacks than whites for plasma factor XI (116% vs. 112%) and D-dimer (0.60 μg/mL vs. 0.47 μ/mL).

The sample having complete data for the 5-SNP genetic risk score included 3,099 blacks and 9,520 whites. Blacks and whites had different frequencies of individual risk alleles in the 5-SNP genetic risk score, but a fairly similar distribution of the overall unweighted score (Table 2).

Over a mean of 22 years of follow-up (maximum, 29 years), we identified 910 participants as having incident venous thromboembolisms: 332 occurred in blacks (55% deep vein thrombosis only, 45% pulmonary embolism; 39% unprovoked, 61% provoked) and 578 in

whites (47% deep vein thrombosis only, 53% pulmonary embolism; 39% unprovoked, 61% provoked). The crude incidence rates of venous thromboembolism per 1,000 person years of 3.8 (95% confidence interval (CI) = 3.5, 4.2) in blacks and 2.3 (2.1, 2.5) in whites. Thus, the crude incidence rate over the entire follow-up was 65% higher in blacks than whites. However, as explained in the statistical methods, the proportional hazards assumption for race and venous thromboembolism was violated, such that the age and sex-adjusted HR (95% CI) for blacks, compared with whites, was a nonsignificant 1.13 (0.79, 1.62) for the first 10 years of follow-up, whereas it was 2.04 (1.76, 2.37) for >10 years (Table 3).

Explaining the Higher Risk of Venous Thromboembolism After 10 Years of Follow-Up in Blacks than Whites

As shown in Table 3, the 2.04-fold higher incidence of venous thromboembolism after 10 years of follow-up for blacks versus whites in Model 1 was substantially attenuated to 1.45 (1.18, 1.80), when adjusted for baseline values of potential non-genetic or non-hemostatic confounders or mediators of the race association (Model 2). This suggests that the Model 2 risk factors measured at ARIC baseline explained a substantial part of the higher risk in blacks than whites. Additional adjustment for measured baseline hemostatic factors and the genetic risk score (Model 3) largely eliminated the remaining higher venous thromboembolism risk of blacks compared with whites [race HR = 1.14 (0.89, 1.46)], or an 82% reduction in the regression coefficient for race from Model 1 to Model 3. Further adjustment for factor XI and D-dimer in Model 4 had no additional impact [race HR = 1.15 (0.88, 1.51)].

Among all of the explanatory risk factors in Models 2–4 of Table 3, those whose individual adjustment affected the Model 1 regression coefficient for black versus white race the most were body weight (21% reduction in the race coefficient), family income (26% reduction), factor VIII (23% reduction), and von Willebrand factor (19% reduction). Adjustment for the genetic risk score only reduced the race coefficient by 9%. Simultaneous adjustment for just three factors -- weight, family income, and factor VIII -- reduced the Model 1 regression coefficient for race by 75%, and it was no longer statistically significant (p=0.10).

Model 5 evaluated whether the racial difference in venous thromboembolism rates between blacks and whites might be explained by racial differences in incidence of three major diseases. Adjustment for prevalent or incident heart failure (24% occurrence in ARIC through 2015) reduced the age- and sex-adjusted venous thromboembolism regression coefficient for black race by 9%, suggesting greater heart failure incidence contributed somewhat to the higher venous thromboembolism rate in blacks. Adjustment for prevalent or incident stroke (10% occurrence through 2015) reduced the regression coefficient for race by 5%. In contrast, adjustment for prevalent or incident cancer (32% incidence through 2012) increased the regression coefficient for black versus white race by 7%.

Evaluation of Whether Some Risk Factors are More Strongly Associated with Venous Thromboembolism in Blacks Compared with Whites

In models for the outcome of venous thromboembolism after 10 years of follow-up, adjusted for sex and age, there were no significant ($p<0.05$) two-way multiplicative interactions of

race with education, income, weight, height, HRT, smoking status, diabetes, systolic blood pressure, antihypertensive medication, sport index, eGFR, factor VIII, von Willebrand factor, aPTT, protein C, factor XI, or D-dimer, nor were there any with time-dependent cancer or stroke diagnoses. The race by genetic risk score interaction was statistically significant, in that the genetic risk score was associated more weakly with venous thromboembolism in blacks than whites, as reported previously.[14] In addition, the race by time-dependent heart failure interaction was statistically significant, indicating that heart failure hospitalization was more strongly related with later venous thromboembolism in blacks than whites.

DISCUSSION

The prospective population-based ARIC study of initially 45–64 year old US adults corroborated evidence that blacks have higher venous thromboembolism incidence rates than whites do. Overall, the rate was about 65% higher in blacks, which is similar to 30–100% reported by previous studies.[1–11] However, upon deeper exploration, the venous thromboembolism rates for blacks were quite similar to whites during early ARIC follow-up but rose more steeply during later follow-up, when participants became elderly. The observed two-fold higher venous thromboembolism incidence in blacks than whites after >10 years is consistent with our previous estimate, based on four fewer years of follow-up, that lifetime risk in ARIC is 11.5% in blacks compared with 6.9% in whites.[12] Nationwide, rates of hospitalized deep vein thrombosis in Medicare recipients have increased in blacks and decreased in whites from 1999 to 2010, and simultaneously rates for pulmonary embolism have increased more in blacks than in whites.[11,24]

This higher burden of venous thromboembolism in blacks than whites motivated us to determine whether differences in risk factors could explain the race difference in incidence. Indeed, our novel finding was that the 2-fold higher venous thromboembolism rate after 10 years in ARIC blacks could be almost fully explained by blacks' more frequent lifestyle, medical, and hemostatic risk factors. ARIC has shown that blacks also have higher rates of several other major cardiovascular diseases (stroke, coronary artery disease, heart failure) than do ARIC whites, and much of these disparities is similarly explained by higher arterial risk factor prevalences in blacks.[25,26] We also demonstrated here that greater incidence rates of heart failure and stroke, but not cancer, may contribute to the higher venous thromboembolism rate in blacks than whites.

The racial disparity in venous thromboembolism likely has little to do with genetics, as lifestyle and environment contribute the most to differences in risk factor levels and disease between blacks and whites.[13] Even though the rare *F5* Leiden and *F2* risk variants for venous thromboembolism are less common in blacks than whites, the mean 5-SNP genetic risk score for venous thromboembolism was similar in blacks and whites in ARIC (Table 2), and adjustment for the genetic risk score thus had little impact on the regression coefficient for race. Yet, we corroborated here that the genetic risk score is associated more strongly with venous thromboembolism in whites than blacks.[14] Nevertheless, the genetic risk score and heart failure hospitalization were the only venous thromboembolism risk factors, out of many studied, that associated with thromboembolism differently in blacks and whites. In

short, there was essentially no evidence that the higher risk of venous thromboembolism in blacks was the result of baseline demographic, environmental, or hemostatic risk factors being more strongly related to venous thromboembolism in blacks than whites.

The three risk factors that seemed to explain the higher incidence rate of venous thromboembolism in blacks than whites were blacks' greater body weight, lower family income, and a higher factor VIII concentration. In so far as these risk factors are modifiable, they or "Life's Simple 7"[27,28] could be targeted for reducing the excess risk of venous thromboembolism in blacks. The important contribution of low family income is noteworthy, suggesting that large socioeconomic disparity between blacks and whites could be a major contributor to the racial disperity in venous thromboembolism.

Rates of unprovoked and provoked venous thromboembolism were both 2-fold higher in ARIC blacks than whites. Thus, in addition to risk factor modification for prevention, aggressive prophylaxis, when indicated, would also be important for reducing venous thromboembolism disparities in blacks.

Limitations of this study warrant consideration. Firstly, in ARIC race is self-designated and confounded by community location -- blacks resided in Mississippi and North Carolina, whereas whites resided in North Carolina, Minnesota, and Maryland. Zakai et al. reported race-related regional differences in venous thromboembolism in the US,[10] so it is possible that unmeasured risk or protective factors differ by ARIC community and explain what appear to be higher venous thromboembolism rates in blacks. Yet, the venous thromboembolism risk factors for which we could adjust almost fully explained, by themselves, the difference in venous thromboembolism incidence by race. Alternatively, it is possible that there were unrecognized differences in the quality of medical documentation for venous thromboembolism among communities or by race and over time. However, our use of standardized criteria for venous thromboembolism should have mitigated such differences. Secondly, our study had a long follow-up and potentially mediating venous thromboembolism risk factors were often only measured once. Risk factors undoubtedly changed over time and perhaps differently in blacks than whites; nevertheless, baseline risk factors did largely explain the higher risk of venous thromboembolism in blacks than whites. To further address this problem, we ran supplemental analyses substituting risk factors available from later exams (not shown), and our conclusions were unchanged. Thirdly, a cohort study cannot fully address whether blacks had more acute precipitants for venous thromboembolism than whites, but it seems unlikely that this would explain blacks' higher venous thromboembolism rate, because 61% were provoked in both race groups. Fourthly, we had no information on venous thromboembolism prophylaxis, which might have differed in frequency or efficacy between blacks and whites. Finally, we identified only venous thromboembolism patients who were hospitalized, but ARIC pilot data suggest the vast majority of patients with first venous thromboembolisms in ARIC were hospitalized. If blacks were more likely than whites to be hospitalized when they had a venous thromboembolism, the HR for black race would have been overestimated.

In conclusion, the frequently reported higher incidence rate of venous thromboembolism in blacks than whites was explained in ARIC by blacks having higher frequencies of venous

thromboembolism risk factors, particularly higher body weight, lower family income, and higher factor VIII concentrations, as well as greater incidence of stroke and heart failure. Several venous thromboembolism risk factors are potentially modifiable and thus offer a potential avenue, along with medical prophylaxis when indicated, for primary prevention of venous thromboembolism in blacks and whites.

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CLINICAL SIGNIFICANCE

- Our cohort's incidence of venous thromboembolism was double in blacks than whites.
- This disparity was largely (>75%) explainable by risk factor differences.
- The most explanatory variables were weight, income, and factor VIII level.

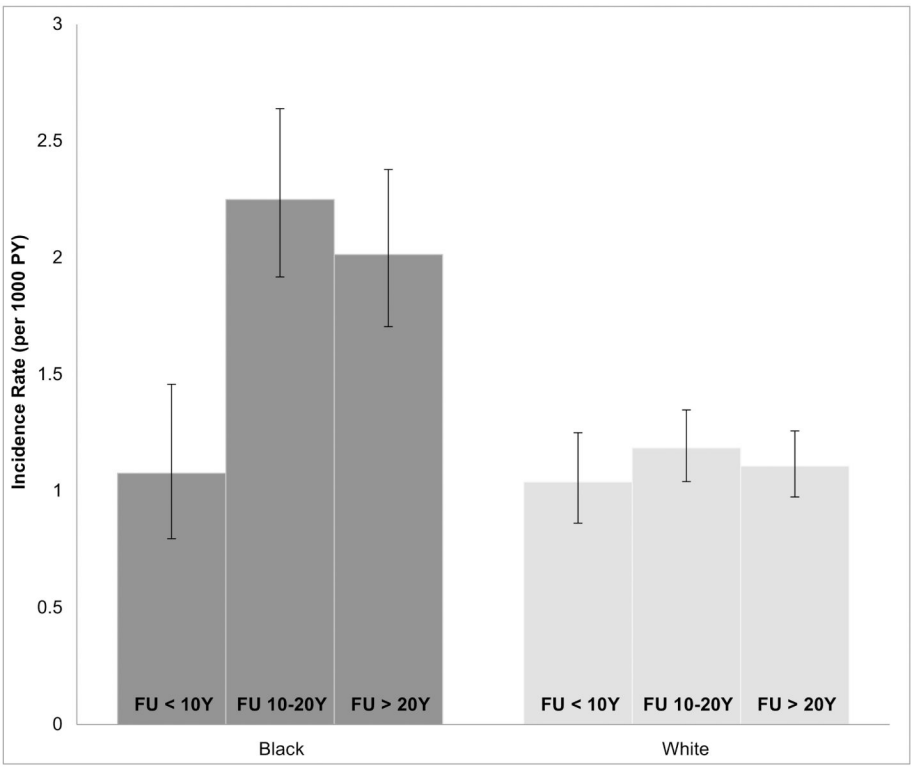

Figure 1.

Race-specific crude incidence rates of venous thromboembolism (per 1000 person years) during three intervals since baseline, ARIC, 1987–89 through 2015. Error bars represent 95% confidence intervals. PY = person years; FU = follow up.

Table 1

Baseline Characteristics [Mean or Percent] of Black and White Participants, ARIC, 1987–1989

Characteristic	Blacks (*n* = 4,171)[†]	Whites[*] (*n* = 11,226)[†]
Age, y	53.5 (5.8)	54.3 (5.7)
Men	39%	47%
Education, <high school	42%	17%
Household income: <$25,000	93%	30%
Smoking: Current	30%	25%
Past	24%	35%
Never	46%	40%
Hormonal replacement in women	8%	11%
Diabetes	19%	9%
Antihypertensive medication	40%	20%
Systolic blood pressure, mmHg	129 (22)	119 (17)
Height, cm	168 (9)	169 (9)
Weight, kg	83 (17)	77 (16)
Body mass index, kg/m^2	29.5 (6.1)	27.0 (4.8)
Sport index, l=low to 5=high	2.2 (0.7)	2.5 (0.8)
Estimated glomerular filtration rate, ml/min/1.73 m^2	111 (20)	99 (13)
Factor VIII, %	147 (48)	126 (34)
von Willebrand factor, %	134 (57)	112 (43)
Activated partial thromboplastin time (aPTT), sec	29.1 (3.2)	29.1 (2.9)
Protein C, µg/mL	3.14 (0.65)	3.19 (0.62)

ARI = Atherosclerosis Risk in Communities.

[*] All values differed between blacks and whites at p<0.001, except aPTT.

[†] N's varied modestly among characteristics due to missing data, but most notably 10% of blacks and 4% of whites had missing household income and 3% of blacks and 2% of whites had missing hormonal replacement information.

Table 2

Race-Specific SNP Frequencies, ARIC, 1987–1989

		Risk Allele Frequency (%)*	
		Blacks	Whites
Gene	SNP	(*n* = 3,099)	(*n* = 9,520)
F5	rs6025	0.5	2.9
F2	rs1799963	0.3	1.4
ABO	rs8176719	29	37
FGG	rs2066865	30	24
F11	rs2036914	*65*	53

ARIC = Atherosclerosis Risk in Communities; SNP = single nucleotide polymorphism.

*Frequencies (%) of having 0, 1, 2, 3, 4, 5, 6, or 7 risk alleles for the 5-SNP genetic risk score were: 3, 16, 32, 29, 16, 3, 0.3, and 0 in blacks and 4, 20, 32, 27, 13, 3, 0.5, 0.05 in whites.

Table 3

Change in Hazard Ratio (HR) of Venous Thromboembolism for Blacks Versus Whites After various Adjustments, ARIC

			Venous Thromboembolism in Blacks vs Whites	
Follow-up	**Model***	**n/N†**	**HR**	**95% CI**
<10 years	1	154/15,397	1.13	0.79, 1.62
>10 years	1	756/13,756	2.04	1.76, 2.37
	2	661/12,461	1.45	1.18, 1.80
	3	538/10,413	1.14	0.89, 1.46
	4	472/9,179	1.15	0.88, 1.51

ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; HR = hazard ratio.

*Model 1 adjusted for baseline age (continuous) and sex.

Model 2 adjusted for baseline age, hormone replacement therapy-sex (women current users, women not current users, men), income (4 categories, with cutpoints at $12,500, $25,000, $50,000), education (<high school, high school graduate, >high school), height (continuous), weight (continuous), sports score (continuous), smoking status (current, former, never), diabetes (yes, no), systolic blood pressure (continuous), antihypertensive use (yes, no), and estimated glomerular filtration rate (continuous).

Model 3 also adjusted for baseline factor VIII, von Willebrand factor, activated partial thromboplastin time (linear and quadratic terms), protein C, and genetic risk score.

Model 4 also adjusted for visit 3 factor XI and D-dimer.

†Number of venous thromboembolisms/number at risk. These vary due to different start dates or different amounts of missing data.