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ORIGINAL ARTICLE

Racial disparities in the incidence and risk factors of major bleeding during extended anticoagulant therapy for venous thromboembolism

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Abstract

Background: Guidelines recommend extended anticoagulation after a first unprovoked venous thromboembolism (VTE) for individuals at low risk of bleeding. However, racial disparities in bleeding risks during extended treatment remain understudied.

Objectives: To compare risks of anticoagulant-associated bleeding and performance of a risk assessment model by racial group during extended VTE treatment.

Methods: We analyzed 2 prospective cohorts of patients (223 Black participants and 4314 White participants) with a first unprovoked/weakly provoked VTE who continued anticoagulation after ≥3 months of initial treatment. Primary outcome was adjudicated International Society on Thrombosis and Haemostasis-defined major

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bleeding. Secondary outcomes included intracranial hemorrhage, fatal bleeding, and clinically relevant nonmajor bleeding. We determined incidence and hazard ratios (HRs) by race, then adjusted for bleeding risk factors that included the Creatinine, Hemoglobin, Age, antiPlatelet model.

Results: Black participants had higher prevalence of bleeding risk factors and a 1.9-fold higher risk of major bleeding (HR, 1.87; 95% CI, 1.04-3.36) compared with White participants. Adjustment attenuated racial difference for major bleeding but not intracranial hemorrhage (adjusted HR, 2.35; 95% CI, 1.23-4.48). Among those classified as low risk by Creatinine, Hemoglobin, Age, antiPlatelet model, Black participants had numerically higher major bleeding incidence than White participants (2.5 vs 1.1 per 100 person-years). We did not observe racial disparities in fatal bleeding or clinically relevant nonmajor bleeding.

Conclusion: Black individuals on extended anticoagulation have higher risk of major bleeding compared with White individuals. This effect appears to persist in those classified as *low risk* for bleeding. Risk assessment models for anticoagulant-associated bleeding that are generalizable to racialized populations are needed.

KEYWORDS
ethnic and racial minorities, hemorrhage, venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third leading cause of cardiovascular mortality after myocardial infarction and stroke [1–3]. VTE accounts for >500 000 hospital admissions in North America each year, and is one of the leading preventable causes of hospital-acquired morbidity globally [4,5]. Half of all VTE events are not attributable to a strong risk factor, thus classifying them as unprovoked or weakly provoked [6]. After 3 to 6 months of primary anticoagulant treatment, decision-making about anticoagulant duration in VTE requires consideration of net clinical benefit by assessing the trade-off between incidence and case fatality rates of both recurrent VTE and major bleeding with treatment continuation vs cessation. While major society guidelines recommend extended anticoagulation in patients with a first unprovoked VTE with low risk of bleeding [7,8], the risk of anticoagulant-associated major bleeding that forms the basis of this recommendation ranges from 1.1% to 1.7% [9]. It is often underrecognized that the case fatality rate of major bleeding is 3 times that of recurrent VTE [10], such that extended anticoagulation becomes unfavorable if the predicted risk of treatment-associated major bleeding >3% per year [11]. Crucially, data that inform net clinical benefit of extended anticoagulation in VTE are predominantly represented by individuals of European ancestry or the White racial group [12].

Despite a 3-fold increase in the risk of anticoagulant-associated major bleeding observed in Black participants enrolled in the EINSTEIN-DVT/PE trial compared with White participants [13], evaluation of racial disparities in anticoagulant-associated major bleeding in the setting of VTE remains sparse. Specifically, no data exist on disparities in bleeding risks that focus on the extended treatment phase of VTE. Furthermore, the accuracy of existing risk assessment models used to predict anticoagulant-associated major bleeding requires critical evaluation of racialized populations, given known variations in clinical, social, and structural determinants of cardiovascular health across racial groups [14]. Therefore, we performed a combined analysis of 2 large prospective cohort studies to determine disparities in major bleeding risk factors and incidence associated with extended anticoagulant therapy for VTE between self-reported Black and White participants, and to assess the performance of an existing bleeding risk assessment model in both groups.

2 | METHODS

2.1 | Study design and population

We performed a post hoc analysis of 2 international, multicenter prospective cohorts (BLEEDRISK and REVERSE-II studies, see Figure 1 for flow diagram) [15,16].

In brief, the BLEEDRISK study (NCT00788736) prospectively enrolled adults ≥18 years with an objectively proven, symptomatic, proximal DVT or PE that was weakly provoked or unprovoked between September 2008 and September 2016 [15]. Eligible patients must have completed ≥3 months of treatment with a vitamin K

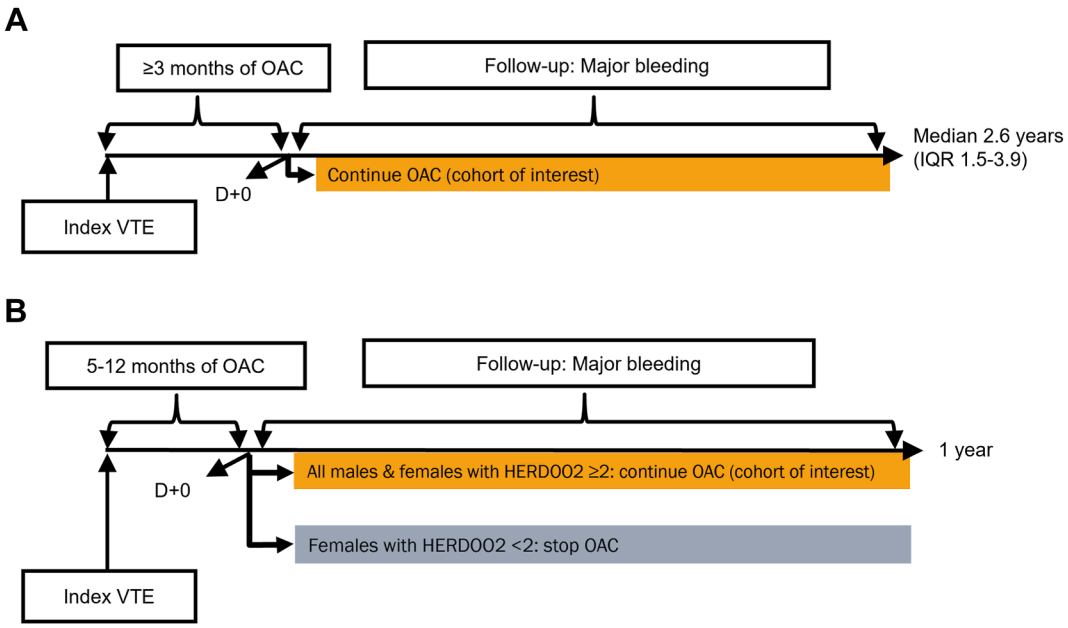

FIGURE 1 Flow diagram of BLEEDRISK (A) and REVERSE-II (B) studies included in the analysis. HERDOO2, **h**yperpigmentation, **e**dema, or **r**edness in leg, **D**-dimer ≥ 250 μg/L, **o**besity [body mass index ≥30], or **o**lder age [≥65 years]); OAC, oral anticoagulants; VTE, venous thromboembolism.

antagonist (VKA) with a target international normalized ratio of 2.0 to 3.0 or a direct oral anticoagulant (DOAC) at therapeutic dosing and were planned to receive extended anticoagulation for secondary prevention as indicated by the treating clinician. Weakly provoked VTE was defined as VTE associated with minor persistent risk factors (eg, lower extremity paralysis or paresis) or minor transient risk factors (eg, hospitalization for medical illness, travel >8 hours, pregnancy, exogenous estrogen, or puerperium) [15]. Unprovoked VTE was defined as VTE occurring in the absence of major risk factors (eg, major surgery or active cancer) or the aforementioned minor risk factors [17].

In the REVERSE-II study (NCT00967304), individuals with a first objectively confirmed, symptomatic, unprovoked or weakly provoked VTE who had completed 5 to 12 months of anticoagulant treatment were enrolled between November 2008 and February 2015, and all men and women who fulfilled ≥2 of HERDOO2 criteria (**h**yperpigmentation, **e**dema, or **r**edness in leg, **D**-dimer ≥ 250 μg/L, **o**besity [body mass index ≥30], or **o**lder age [≥65 years]) continued anticoagulation [16]. Unprovoked or weakly provoked VTE consisted of proximal DVT or PE not associated with lower extremity fracture or plaster cast, immobilization for ≥3 days, major surgery in the 3 months before the index event, and no diagnosis of a malignancy in the past 5 years (except for localized skin cancer) [16].

2.2 | Data collection and follow-up

Baseline demographic and clinical data were collected at enrollment. Race was collected at time of enrollment as a self-reported measure within a list of categories based on adaptation of categories used in the 1997 revised U.S. Office of Management and Budget standards [18]. For both cohorts, demographic and clinical variables included age, sex (as biological characteristic), index VTE location, weight, body mass index, prior provoked VTE, presence of postthrombotic syndrome, exogenous estrogen use, and anticoagulant agent. All patients in REVERSE-II had VIDAS D-dimer (bioMérieux) collected, whereas this was not mandated in the BLEEDRISK study. On the other hand, the BLEEDRISK study collected baseline hemoglobin, concurrent antiplatelet agents, renal function, as well as presence of hypertension and diabetes. Furthermore, 90% of BLEEDRISK participants had DNA collection for factor (F)V Leiden and prothrombin gene G20210A genotyping, whereas testing for these thrombophilias in the REVERSE-II study was not mandated.

All participants were interviewed by telephone or in person every 6 months ±3 weeks for as long as they received anticoagulation, death, withdrawal of consent, or termination of the study. Over 98% of participants in both studies completed follow-up.

2.3 | Outcome

The primary outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) [19]. During conduct of both studies, all suspected bleeding events and deaths were independently adjudicated by evaluators who were blinded to potential predictor data used. Secondary outcomes were intracranial hemorrhage (ICH) and fatal bleeding (captured in both studies), as well as clinically relevant nonmajor bleeding (CRNMB, captured in the BLEEDRISK study only).

2.4 | Statistical analysis

First, we determined the annualized incidence of major bleeding in patients on extended anticoagulant therapy by racial group from enrollment and reported them as events per person-years. We then calculated the hazard ratios (HRs) of major bleeding between Black and White participants using the Cox proportional hazards model. Both unadjusted and adjusted HRs were derived, with latter accounting for racial differences in the distribution of known risk factors for anticoagulant-associated bleeding. In the combined cohort, these covariates included age, sex, and anticoagulant type (VKA vs DOAC). In the BLEEDRISK cohort, we adjusted for additional items captured in the Creatinine, Hemoglobin, Age, antiPlatelet (CHAP) model, which included presence of renal function (as absolute creatinine), hemoglobin, and use of concurrent antiplatelet therapy (model 1). We then incorporated 3 additional risk factors associated with anticoagulant-associated major bleeding in atrial fibrillation with known racial disparities: hypertension, prior strokes, and prior gastrointestinal bleeds (model 2) [20–22].

Finally, we compared the calibration (predicted vs actual risk of major bleeding) of the CHAP model according to racial group. Calibration in this study refers to the ratio of observed vs expected incidence of major bleeding (in low- vs high-risk categories) by racial group. The CHAP model is an externally validated clinical prediction tool that identifies individuals at high risk of major bleeding using a combination of creatinine, hemoglobin, age, and use of antiplatelet agents [15]. Missing data were handled with pairwise deletion, and imputation was not used. A 2-sided P value of $\leq .05$ was considered statistically significant. All analyses were performed using SAS software version 9.4 (SAS Institute Inc).

2.5 | Sample size

Based on the number of participants enrolled in the 2 studies and their respective follow-up duration, we assumed a follow-up duration ratio of 1:18 for Black and White participants enrolled in the 2 cohorts. Assuming a 1.2% risk per year of major bleeding in participants observed in the REVERSE-II study [16], we expected to require a minimum of 429 person-years of follow-up for Black participants and 7722 person-years of follow-up for White participants to achieve 80% power to detect a 1.8% absolute risk increase in major bleeding incidence (corresponding to an annualized bleeding risk $\geq$3% per year at which net clinical benefit of extended anticoagulation becomes unfavorable).

3 | RESULTS

Between 2008 and 2016, the BLEEDRISK and REVERSE-II studies enrolled a total of 4952 patients with first unprovoked VTE who continued anticoagulation after at least 3 months of acute VTE treatment [15,16]. The combined cohort included 4314 White participants and 223 Black participants (Figure 2). Total duration of follow-up was 8926.6 person-years, including 8460.4 person-years for White participants and 466.2 person-years for Black participants. Median follow-up in the combined cohort was 1 year and did not differ between racial groups (Table 1); median duration of VTE treatment prior to enrollment was 9.1 and 6.6 months for Black and White participants, respectively.

3.1 | Baseline characteristics

Mean age of the combined cohort was 57.1 years, and 41.2% (n = 2042) were female. Distribution of index VTE sites was comparable between Black and White participants, while a higher proportion of Black participants (14.3%) had a history of provoked VTE prior to the qualifying index event compared with White participants (7.7%; Table 1).

Among participants who underwent FV Leiden (n = 3272) and prothrombin G20210A mutation (n = 3484) testing, we observed FV Leiden and prothrombin gene mutation carriership in 448 (13.7%) and 149 (4.3%) of White participants, respectively, proportions that were higher than Black participants (0.1% and 0.2%, respectively; Table 1). While >80% of participants were treated with a VKA, higher DOAC use was observed in White participants compared with Black participants (14.7% vs 8.1%). Among 3722 VKA-treated patients (n = 3713 warfarin; n = 9 acenocoumarol), median time in therapeutic range was 70.3% for Black participants and 74.7% for White participants. During follow-up, anticoagulant rotation occurred in 17.7% of Black participants and 18.7% of White participants. Proportion of censoring events (eg, death and permanent anticoagulant discontinuation) among Black and White participants was similar (Supplementary Table S1).

3.2 | Additional bleeding risk factors at baseline

Hemoglobin and creatinine clearance, history of hypertension, and diabetes status were captured at baseline visit for 2474 participants enrolled in the BLEEDRISK study. Black participants in the study had lower median creatinine clearance (97.7 mL/min vs 107.0 mL/min) and higher baseline prevalence of concurrent antiplatelet use (14.4% vs 5.3%) and anemia (35.0% vs 11.0%) compared with White participants (Table 1). Consequently, the proportion of individuals classified as high risk by the CHAP tool was higher among Black participants (46.0%) compared with White participants (24.9%). Furthermore, Black participants had higher baseline prevalence of hypertension and prior strokes (Table 1).

3.3 | Risk of major bleeds by racial group

In the combined cohort, we observed 141 ISTH-defined major bleeding events >8926.6 person-years of follow-up. The incidence

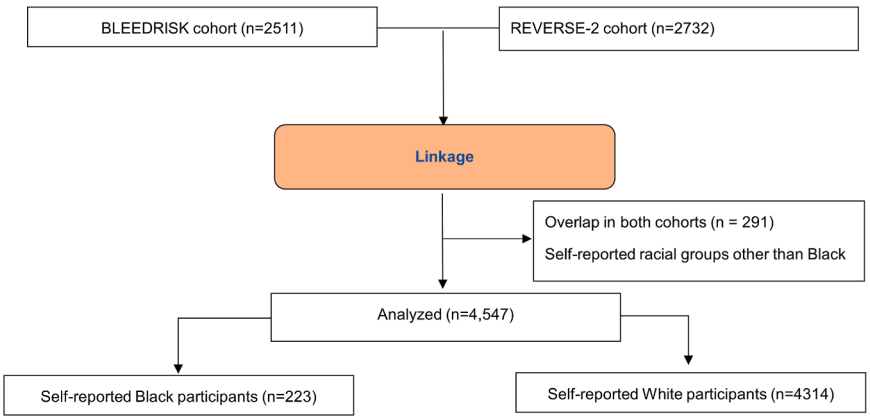

FIGURE 2 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram.

rate of major bleeding was 1.6 events per 100 person-years (95% CI, 1.3-1.8) in the overall cohort. Race-specific incidence rates of major bleeding were 2.8 (95% CI, 1.5-4.8) and 1.5 (95% CI, 1.3-1.8) per 100 person-years for Black and White participants, respectively (Figure 3).

Black participants in the combined cohort had a 1.9-fold higher risk of anticoagulant-associated major bleeding than White participants (crude HR, 1.87; 95% CI, 1.04-3.36; P = .04), which remained consistent after adjustment for age, sex, and anticoagulant type (Table 2). However, this association was attenuated after adjustment for all CHAP model parameters and anticoagulant type (DOAC vs VKA) in the BLEEDRISK subgroup (adjusted HR, 1.39; 95% CI, 0.75-2.58; P = .30; Table 3).

3.4 | Risks of ICH and fatal bleeds by racial group

In the combined cohort, incidence of anticoagulant-associated ICH and fatal bleeds was 0.3 (95% CI, 0.2-0.4) and 0.1 (95% CI, 0.1-0.2) per 100 person-years, respectively. Risk of ICH was 3-fold higher in Black participants compared with White participants (adjusted HR, 2.99; 95% CI, 1.31-6.80; P = .009; Table 2). The impact of Black race on risk of ICH remained consistent after adjustment for CHAP model parameters, anticoagulant type, hypertension, prior bleeding, and prior strokes (adjusted HR, 2.35; 95% CI, 1.23-4.48; P = .010; Table 3). There was no difference in the risk of fatal bleeding among Black participants compared with their White counterparts (Tables 2 and 3).

3.5 | Risk of CRNMB by racial group

In the BLEEDRISK cohort, we observed 298 ISTH-defined CRNMBs over 6578.1 person-years of follow-up, with an incidence rate of 4.5 events per 100 person-years (95% CI, 4.0-5.0). Contrary to major bleeding events, we did not observe differences in incidence rates of CRNMB by racial group (Table 2).

3.6 | Calibration of CHAP model by racial group

Among Black and White participants enrolled in the BLEEDRISK cohort, risks of ICH were more than 3-fold higher in Black participants classified as high risk for bleeding (HR, 3.64; 95% CI, 1.69-7.87; Table 4). Among individuals not classified as high risk, annualized risk of anticoagulant-associated major bleeding remained numerically higher in Black participants compared with White participants (2.5 vs 1.1 per 100 person-years; HR, 2.49; 95% CI, 0.98-6.35; Table 4).

Using the derivation group from the BLEEDRISK cohort as reference, the observed vs expected incidence ratio for major bleeding in Black participants was 1.08 in the CHAP high-risk subgroup (95% CI, 0.382-2.49; P = .82), and 2.24 in the CHAP low-risk subgroup (95% CI, 0.70-5.55; P = .11). Calibration curves are presented in Supplementary Figure.

3.7 | Subgroup analyses

Given higher prevalence of VKA use, prior VTE, and previous bleeding events among Black participants enrolled in the combined cohort compared with White participants (Table 1), we performed subgroup analyses to examine the consistency of racial differences in bleeding risk among participants on VKA only, those without prior bleeding, and those without a history of VTE. These results were consistent with our primary findings (Supplementary Table S2).

4 | DISCUSSION

In a post hoc analysis of 2 large cohort studies with >4500 participants on extended anticoagulation for VTE treatment, we demonstrated an approximately 2-fold increase in the risk of major bleeds in Black participants compared with White participants. While this association was attenuated after adjustment for major bleeding risk factors, racial disparities in ICH risk remained. Among individuals

TABLE 1 Baseline characteristics.

Variable	Black participants (*n* = 223)	White participants (*n* = 4314)	Combined (*N* = 4537)
Demographic factors			
Age (y), mean ± SD	55.4 ± 15.8	58.0 ± 16.0	57.8 ± 16.0
Female sex, *n* (%)	105 (45)	1827 (42)	1932 (42.6)
Weight (kg), mean ± SD	93.9 ± 23.7	90.3 ± 23.2	90.4 ± 23.3
Body mass index (kg/m^2), mean ± SD	32.1 ± 7.9	30.6 ± 9.8	30.7 ± 9.7
Follow-up (y), median (IQR)	1.6 (1-3.3)	1 (1-3)	1 (1-3)
Characteristics of index VTE, *n/N* (%)			
Index VTE			
DVT	91/222 (41.0)	1820/4307 (42.2)	1911/4529 (42.2)
PE	91/222 (41.0)	1583/4307 (36.8)	1674/4529 (37.0)
PE + DVT	40/222 (18.0)	904/4307 (21.0)	944/4529 (20.8)
Prior provoked VTE	32/223 (14.3)	380/4312 (8.8)	412 /4535 (9.1)
Exogenous estrogen use	17/105 (16.2)	408/1827 (22.3)	425/1932 (30.0)
Postthrombotic syndrome	23/193 (11.9)	722/3321 (21.7)	745/3514 (21.2)
Any D-dimer, median (IQR)[a]	275.8 (143.5-611.9)	239.0 (149.0-445.8)	256.4 (150-502)
VIDAS D-dimer, median (IQR)[a]	210.4 (126.0-444.7)	230.0 (140-390.6)	230 (140-391)
Thrombophilia investigations, *n/N* (%)			
Heterozygous FVL	4/103 (3.9)	448/2784 (16.1)	452/2887 (15.7)
Heterozygous PGT	2/108 (1.9)	149/2986 (5.0)	151/3094 (4.9)
Heterozygous FVL or PGT	6/100 (6.0)	579/2783 (20.8)	585/2883 (20.3)
Anticoagulant type, *n/N* (%)			
VKA	197/223 (88.3)	3523/4314 (81.7)	3722/4537 (82.0)
Rivaroxaban	16/223 (7.1)	569/4314 (13.2)	585/4537 (12.9)
Edoxaban	2/223 (0.9)	31/4314 (0.7)	33/4537 (0.7)
Apixaban	0 (0.0)	11/4314 (0.3)	11/4537 (0.2)
Dabigatran	0 (0.0)	25/4314 (0.6)	25/4537 (0.6)
Other	8/223 (3.6)	155/4314 (4.6)	163/4537 (3.6)
BLEEDRISK cohort only, *n/N* (%)			
Hypertension	106/167 (64.6)	829/2305 (36.0)	935/2472 (37.8)
Prior gastrointestinal bleeding	8/167 (4.8)	75/2305 (3.3)	83/2472 (3.4)
Prior strokes	12/167 (7.2)	67/2305 (2.9)	79/2472 (3.2)
Creatinine clearance, median (IQR)	97.7 (67.4-130.5)	107.0 (78.5-137.0)	105.9 (77.6-136.7)
Anemia	57/163 (35.0)	251/2272 (11.0)	308/2435 (12.7)
Concurrent antiplatelet use	24/167 (14.4)	121/2305 (5.3)	145/2472 (5.9)
CHAP high risk	64/139 (46.0)	532/2135 (25.0)	596/1817 (32.8)

CHAP, Creatinine, Hemoglobin, Age and antiPlatelet model; DVT, deep vein thrombosis; FVL, factor V Leiden; PE, pulmonary embolism; PGT, prothrombin gene mutation; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a] A total of 3337 participants had D-dimer values available for analysis. Of these, 2949 were VIDAS D-dimer assays.

identified as *low risk* by the CHAP risk assessment model for anticoagulant-associated major bleeding, we observed a numerically higher incidence of major bleeds in Black participants compared with their White counterparts. We did not observe a statistically significant difference in risks of CRNMB or fatal bleeding between the 2 racial groups.

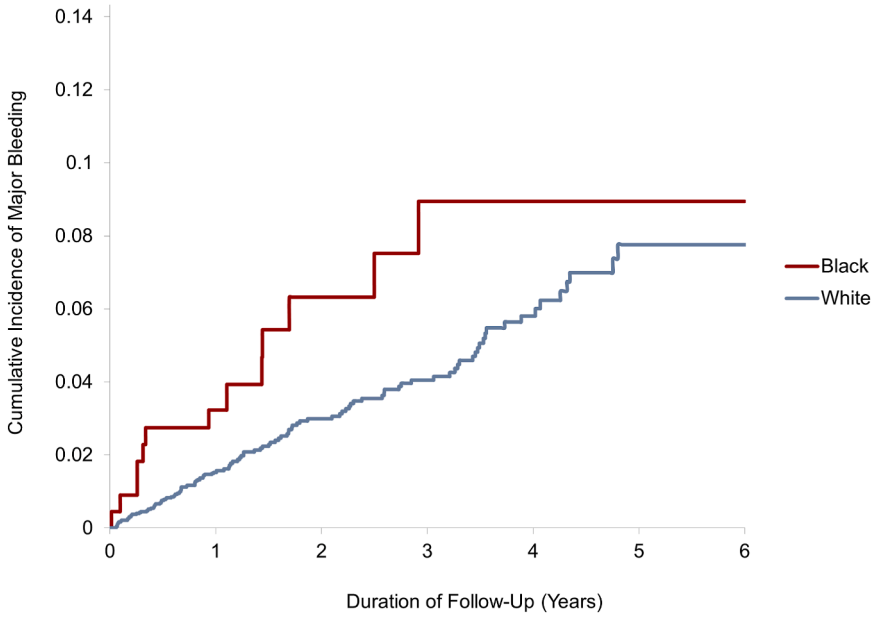

FIGURE 3 Cumulative incidence of major bleeding by racial group during extended treatment for first unprovoked venous thromboembolism.

Our findings are in line with existing literature that demonstrates racial disparities in anticoagulant-associated bleeding risks in VTE during the acute phase of treatment. For example, Di Nisio et al. [13] retrospectively evaluated 8246 patients with acute VTE enrolled in the EINSTEIN-DVT and -PE studies, demonstrating a 3.3-fold increased risk of major bleeding in Black participants during the initial 3 weeks of anticoagulant treatment compared with White participants after accounting for treatment arm and bleeding risk factors. In the same study, the effect of race on anticoagulant-associated bleeding was similar to the impact of active malignancy (HR, 3.47) or concurrent use of antiplatelet drugs (HR, 2.07) [13]. Our results are also supported by retrospective studies in patients undergoing long-term anticoagulation for atrial fibrillation, suggesting a 2- to 4-fold higher risk of warfarin-associated ICH in Black individuals compared with White individuals [23].

The clinical and research implications of our results require careful consideration. Optimal treatment duration after a first episode of unprovoked or weakly provoked VTE requires consideration of the risks (incidence) and consequences (case fatality rates) of recurrent VTE and major bleeding with extended vs time-limited anticoagulant treatment [11]. The absolute incidence of major bleeding among Black participants in our combined cohort was 2.8% per year, with upper limit of 95% CI at 4.8 events per 100 person-years, which exceeds the 3% per year threshold of major bleeding above which extended anticoagulation is deemed unfavorable due to case fatality rates associated with such events [11]. Risk of major bleeding was numerically higher in Black participants categorized as *low risk* in the CHAP risk assessment model, and their annualized major bleeding risk (2.5 events per 100 person-years) approaches this 3% per year threshold as well, with upper bound of 95% CI exceeding it. If replicated in future studies, our analysis suggests that existing risk assessment models require validation in racially diverse populations to ensure consistent predictive accuracy. Given higher risks of ICH in Black participants, our findings also emphasize the need to ensure equitable access to DOACs in the treatment of VTE among eligible patients. While DOACs have been consistently demonstrated to confer lower risks of ICH compared with warfarin, they are underprescribed in Black patients in several retrospective analyses in the U.S. for both VTE and atrial fibrillation, even when socioeconomic factors are accounted for [24,25]. A pharmacoequity approach is therefore needed to reduce racial disparities in anticoagulant-associated bleeding outcomes [26]. Furthermore, our

TABLE 2 Racial differences in anticoagulant-associated bleeds in the combined cohort.

	No. of events		Person-years of follow-up		Incidence per 100 person-years (95% CI)		Crude HR (95% CI)		Adjusted HR[a] (95% CI)	
Outcome	White	Black	White	Black	White	Black	White	Black	White	Black
Major bleeding	128	13	8460.4	466.2	1.51 (1.26-1.80)	2.79 (1.48-4.77)	Ref	1.87 (1.04-3.36)	Ref	1.88 (1.22-2.89)
ICH	19	3			0.22 (0.14-0.35)	0.64 (0.13-1.88)	Ref	2.74 (0.86-8.71)	Ref	2.99 (1.31-6.80)
Fatal bleeding	8	1			0.09 (0.04-0.19)	0.21 (0.01-1.20)	Ref	2.06 (0.66-6.41)	Ref	3.47 (0.53-22.56)

HR, hazard ratio; ICH, intracranial hemorrhage; Ref, reference.

[a] Adjusted for age, sex, and anticoagulant type (vitamin K antagonist vs direct oral anticoagulant).

TABLE 3 Racial differences in anticoagulant-associated bleeds in the BLEEDRISK cohort.

Outcome	No. of events		Person-years of follow-up		Incidence per 100 person-years (95% CI)		Crude HR (95% CI)		Adjusted HR by model 1[a] (95% CI)		Adjusted HR by model 2[b] (95% CI)	
	White	Black	White	Black	White	Black	White	Black	White	Black	White	Black
Major bleeding	107	12	6517.7	411.7	1.64 (1.35-1.98)	2.91 (1.51-5.09)	Ref	1.78 (1.04-3.01)	Ref	1.39 (0.75-2.58)	Ref	1.33 (0.76-2.33)
ICH	16	3			0.25 (0.14-0.40)	0.73 (0.15-2.13)	Ref	2.87 (1.00-8.21)	Ref	2.76 (1.29-5.92)	Ref	2.35 (1.23-4.48)
CRNMB	279	19			4.28 (3.79-4.81)	4.46 (2.04-8.47)	Ref	1.09 (0.81-1.45)	Ref	1.08 (0.81-1.46)	Ref	1.03 (0.76-1.40)
Fatal bleeding	6	1			0.09 (0.03-0.20)	0.24 (0.01-1.35)	Ref	2.62 (0.83-8.32)	Ref	3.35 (0.42-26.44)	Ref	4.46 (0.51-38.9)

CRNMB, clinically relevant nonmajor bleeding; HR, hazard ratio; ICH, intracranial hemorrhage; Ref, reference.

[a] Model 1: adjusted for Creatinine, Hemoglobin, Age, antiPlatelet model components and anticoagulant type (vitamin K antagonist vs direct oral anticoagulant).

[b] Model 2: adjusted for Creatinine, Hemoglobin, Age, antiPlatelet model components, anticoagulant type (vitamin K antagonist vs direct oral anticoagulant), hypertension, prior major gastrointestinal bleeding, and prior strokes.

observation of clinically relevant racial differences in the distribution of several risk factors for DOAC-associated major bleeding (eg, renal dysfunction and concurrent antiplatelet therapy) suggests that their optimization may further reduce the racial gap in anticoagulant-associated bleeding in VTE treatment [27].

While differences in inherited risk factors and hemostatic phenotypes have been observed between ethnic groups [28,29], race is a social construct and identity [30]. Therefore, our finding of racial disparity in anticoagulant-associated bleeding risks is not intended to create race-specific recommendations for VTE treatment. Race-based clinical risk adjustment is increasingly recognized to exacerbate disparities and does not account for the complexity of sociodemographic factors, access to care gaps, and quality of care disparities experienced by racialized populations (eg, trust in healthcare providers) [31]. Instead, our findings should serve as an imperative to identify and address clinical and sociodemographic risk factors that contribute to disparities in anticoagulant-associated bleeding, to diversify the evidence base for anticoagulant treatment in VTE that forms the basis of current guideline recommendations, and to develop novel risk prediction tools that are generalizable to underrepresented populations in VTE research.

To our knowledge, this is the largest evaluation of racial disparities in risks of anticoagulant-associated major bleeding during the extended treatment phase of VTE. In addition to its large sample size, the use of prospectively collected, centrally adjudicated outcome data provides additional validity to our findings. However, the study is subject to several limitations. First, the post hoc nature of our analysis suggests that our findings are intended to be hypothesis-generating and require replication in other studies. Second, patients included in the 2 cohorts who were non-White accounted for only 11% of the overall study population, and median duration of follow-up was 1 year in both groups. The number of events observed among Black participants was, therefore, limited and may have impacted the precision of our risk estimates in subgroup analyses. Nonetheless, the absolute number of Black participants included in this analysis exceeds the combined enrollment of 3 practice-changing randomized controlled trials of extended anticoagulation in unprovoked VTE (RE-MEDY, RE-SONATE, and EINSTEIN-DVT) [12]. Given the underrepresentation of racialized populations in VTE-related research [12], the need to generate accurate data that are reflective of the ethnoracial diversity of individuals living with VTE cannot be overstated. Third, we did not account for unmeasured confounding and mediating factors such as access to healthcare services, quality of care, and sociodemographic barriers, which can influence the risks and sequelae of anticoagulant-associated major bleeding between racial groups. In addition, some predictors of bleeding (eg, renal function or presence of anemia) were not captured in the REVERSE-II study, as its primary aim was to evaluate recurrent VTE. Detailed data on these variables in future investigations with longer follow-up will allow targeted interventions to address the racial disparities observed in our study. Fourth, most patients were on a VKA due to enrollment period of the 2 cohort studies. While including anticoagulant type in the model did not impact our findings,

TABLE 4 Incidence rate of anticoagulant-associated bleeds by race and Creatinine, Hemoglobin, Age, antiPlatelet model stratification (BLEEDRISK study only).

Bleeding risk classification by CHAP	Bleeding type	Race	No. of events	Person-years of follow-up	Incidence per 100 person-years (95% CI)	HR (95% CI)
High risk	Major bleeding	Black	6	141.1	4.25 (1.56-9.26)	1.08 (0.63-1.85)
		White	53	1424.1	3.72 (2.79-4.87)	Ref
	ICH	Black	3	141.1	2.13 (0.44-6.21)	3.64 (1.69-7.87)
		White	8	1424.1	0.56 (0.24-1.11)	Ref
Low risk	Major bleeding	Black	5	201.7	2.48 (0.8-5.78)	2.49 (0.98-6.35)
		White	49	4636.2	1.06 (0.78-1.40)	Ref
	ICH	Black	0	201.7	0	1.41 (0.07-29.32)
		White	8	4636.2	0.71 (0.02-3.95)	Ref

CHAP, Creatinine, Hemoglobin, Age, antiPlatelet; HR, hazard ratio; ICH, intracranial hemorrhage; Ref, reference.

the number of Black participants on DOACs was low. While our results remain relevant given the inequity in access to DOACs and racial differences in the prevalence of DOAC-associated bleeding risk factors observed in our study [24,27,32,33], further data on racial disparities in bleeding outcomes of DOAC-treated patients are needed to inform the generalizability of our findings. This is especially pertinent given recent data that indicate a lower incidence of clinically relevant bleeding in individuals randomized to low-dose DOACs in the extended phase of VTE treatment [34]. Finally, racial categories captured by the 2 cohorts included in this post hoc analysis preceded the 2024 update of the U.S. Office of Management and Budget standards, which created Middle Eastern or North African as a new minimum reporting category (previously included as White individuals) [35]. Given dynamic nature of racial categorization as a social concept, evaluation of health outcome disparities needs to incorporate evolving changes in racial groups to inform additional disaggregated analyses.

In conclusion, we observed clinically relevant racial disparities in the incidence of major bleeding during extended anticoagulant therapy for VTE. These findings emphasize the importance of understanding causative factors that contribute to racial differences in anticoagulant-associated bleeding risks and highlight the need to refine current bleeding prediction models in ethnic and racially diverse populations.

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AUTHOR CONTRIBUTIONS

Y.X. affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted. Y.X. conceived the study. All authors contributed to the study design and the proposed statistical approach. Y.X. and R.M. performed statistical analysis. D.O. and Y.X. drafted the initial manuscript, to which all authors provided key revisions to the analysis plan and the final manuscript. All authors read and approve the final version of the manuscript.

DECLARATION OF COMPETING INTERESTS

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SUPPLEMENTARY MATERIAL

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