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Journal of the American Heart Association

ORIGINAL RESEARCH

Sex-, Race- and Ethnicity-Based Differences in Thromboembolic Events Among Adults Hospitalized With COVID-19

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BACKGROUND: Patients hospitalized with COVID-19 have an increased risk of thromboembolic events. Whether sex, race or ethnicity impacts these events is unknown. We studied the association between sex, race, and ethnicity and venous and arterial thromboembolic events among adults hospitalized with COVID-19.

METHODS AND RESULTS: We used the American Heart Association Cardiovascular Disease COVID-19 registry. Primary exposures were sex and race and ethnicity, as defined by the registry. Primary outcomes were venous thromboembolic events and arterial thromboembolic events. We used logistic regression for risk adjustment. We studied 21 528 adults hospitalized with COVID-19 across 107 centers (54.1% men; 38.1% non-Hispanic White, 25.4% Hispanic, 25.7% non-Hispanic Black, 0.5% Native American, 4.0% Asian, 0.4% Pacific Islander, and 5.9% other race and ethnicity). The rate of venous thromboembolic events was 3.7% and was more common in men (4.2%) than women (3.2%; $P<0.001$), and in non-Hispanic Black patients (4.9%) than other races and ethnicities (range, 1.3%–3.8%; $P<0.001$). The rate of arterial thromboembolic events was 3.9% and was more common in men (4.3%) than women (3.5%; $P=0.002$), and in non-Hispanic Black patients (5.0%) than other races and ethnicities (range, 2.3%–4.7%; $P<0.001$). Compared with men, women were less likely to experience venous thromboembolic events (adjusted odds ratio [OR], 0.71; 95% CI, 0.61–0.83) and arterial thromboembolic events (adjusted OR, 0.76; 95% CI, 0.66–0.89). Compared with non-Hispanic White patients, non-Hispanic Black patients had the highest likelihood of venous thromboembolic events (adjusted OR, 1.27; 95% CI, 1.04–1.54) and arterial thromboembolic events (adjusted OR, 1.35; 95% CI, 1.11–1.65).

CONCLUSIONS: Men and non-Hispanic Black adults hospitalized with COVID-19 are more likely to have venous and arterial thromboembolic events. These subgroups may represent at-risk patients more susceptible to thromboembolic COVID-19 complications.

Key Words: COVID-19 ■ race and ethnicity ■ thromboembolic ■ thrombosis ■ women, sex, and gender

COVID-19 is a complex infectious process that impacts nearly every organ system.[1] One aspect of patients with COVID-19 that has garnered particular interest is a proclivity for thromboembolic events.[2] Evidence of abnormal coagulation parameters in patients with COVID-19 was initially described in early reports from China.[3] Similar findings have been reported by several investigators, noting an increased rate of both venous and arterial thromboembolic events among hospitalized patients with COVID-19.[4–6] These thromboembolic complications are associated with an increased likelihood of mortality, which has led to aggressive approaches aimed at preventing these events.[7,8]

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CLINICAL PERSPECTIVE

What Is New?

- This study was an investigation of >20 000 adults hospitalized with COVID-19 and examined the association between sex, race, and ethnicity with venous and arterial thromboembolic events.
- Men and non-Hispanic Black adults who are hospitalized with COVID-19 are more likely to have thromboembolic events and may represent a subgroup of at-risk patients.

What Are the Implications?

- Patients who are hospitalized with COVID-19 remain at elevated risk for venous and arterial thromboembolic events.
- Men and non-Hispanic Black adults have an even higher likelihood of events and may benefit from targeted prophylaxis regimens.
- Future trials may consider incorporating the evaluation of different racial and ethnic groups when determining patient-specific treatment regimens for thromboprophylaxis in adults hospitalized with COVID-19.

Nonstandard Abbreviations and Acronyms

ATE	arterial thromboembolic event

However, little is known about how sex and race and ethnicity potentially impact thromboembolic events among patients with COVID-19. Sex-, race- and ethnicity-based differences in cardiovascular disease and viral response mechanisms are well-documented phenomena.[9–13] Historical studies of patients without COVID-19 suggest that men and Black individuals may be at higher risk for thromboembolic events.[14–16] As such, it is likely that sex-, race-, and ethnicity-based differences also exist in the COVID-19 patient population who are at risk of venous or arterial thromboembolic events. If so, this knowledge might encourage clinicians to target antithrombotic therapy to potentially high-risk patient subgroups and would inform ongoing trials of antithrombotic therapy in patients with COVID-19.

Our objective was to study the association between sex, race and ethnicity and venous and arterial thromboembolic events among adults hospitalized with COVID-19. We aimed to define high-risk patient subgroups who may benefit from targeted prophylaxis or screening. Our hypothesis was that differences exist between men and women, and among patients of different races and ethnicities who are hospitalized with COVID-19.

METHODS

Data Sources

We used the American Heart Association Cardiovascular Disease COVID-19 registry to study the association between sex, race and ethnicity, and thromboembolic events among adults hospitalized with COVID-19.[17] The registry is part of the Get With The Guidelines programs provided by the American Heart Association and captures demographics, clinical characteristics, treatment details, and in-hospital outcomes on patients aged >18 years who were hospitalized with COVID-19. More than 100 centers participate in the registry. Data are abstracted by centers using a prespecified data collection form, and IQVIA (Parsippany, NJ) serves as the data collection and coordination center. Data are available through the American Heart Association to both participating and nonparticipating centers.

Inclusion and Exclusion Criteria

We included all patients in the registry from March 2020 (start of data availability) to March 2021 (end of data availability). We excluded patients if their sex or race and ethnicity were missing from the registry.

Primary Exposures

Our primary exposures were sex, race, and ethnicity, which were defined by the registry. Sex was categorized as men or women. Race and ethnicity was categorized as non-Hispanic White, Hispanic, non-Hispanic Black, Native American, Asian, Pacific Islander, and other/unable to determine.

Primary Outcome

Our primary outcomes were in-hospital venous thromboembolic events (VTEs) and arterial thromboembolic events (ATEs). We defined VTE as a composite of deep vein thrombosis or pulmonary embolism (PE). We defined ATE as a composite of myocardial infarction, acute limb ischemia, ischemic stroke, or intracardiac thrombus. Events were diagnosed at the discretion of the treating clinician. No screening tests were required. Any event occurring during the hospital admission was eligible to count toward these end points.

Secondary Outcomes

Secondary outcomes included bleeding requiring transfusion, admission to an intensive care unit, hospital length of stay, and severe COVID-19. We defined severe COVID-19 as the need for invasive mechanical ventilation, extracorporeal membrane oxygenation, vasopressor support, or mechanical circulatory support.

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Table 1. Patient Characteristics Overall and by Sex

Variable	All patients (n=21 528)	Men (n=11 644)	Women (n=9884)	*P* value
Race and ethnicity				
Non-Hispanic White	8202 (38.1)	4482 (38.5)	3720 (37.6)	0.203
Hispanic	5478 (25.4)	3117 (26.8)	2361 (23.9)	<0.001
Non-Hispanic Black	5531 (25.7)	2733 (23.5)	2798 (28.3)	<0.001
Native American	106 (0.5)	52 (0.4)	54 (0.5)	0.345
Asian	857 (4.0)	478 (4.1)	379 (3.8)	0.328
Pacific Islander	78 (0.4)	34 (0.3)	44 (0.4)	0.080
Other	1276 (5.9)	748 (6.4)	528 (5.3)	0.001
Age, mean (SD), y	61.2 (17.9)	61.0 (16.8)	61.5 (19.1)	0.023
Deep vein thrombosis	725 (3.4)	366 (3.1)	359 (3.6)	0.052
Pulmonary embolism	487 (2.3)	228 (2.0)	259 (2.6)	0.001
Cerebrovascular disease	2608 (12.1)	1447 (12.4)	1161 (11.7)	0.132
Stroke	2060 (9.6)	1164 (10.0)	896 (9.1)	0.022
Transient ischemic attack	625 (2.9)	311 (2.7)	314 (3.2)	0.031
Coronary artery disease				
Prior CABG	627 (2.9)	459 (3.9)	168 (1.7)	<0.001
Prior PCI	986 (4.6)	652 (5.6)	334 (3.4)	<0.001
Prior myocardial infarction	1199 (5.6)	726 (6.2)	473 (4.8)	<0.001
Peripheral arterial disease	584 (2.7)	351 (3.0)	233 (2.4)	0.004
Smoking history	1406 (6.5)	876 (7.5)	530 (5.4)	<0.001
Hypertension	12673 (58.9)	6703 (57.6)	5970 (60.4)	<0.001
Diabetes	7614 (35.4)	4075 (35.0)	3539 (35.8)	0.222
Dyslipidemia	7423 (34.5)	4102 (35.2)	3321 (33.6)	0.013
Heart failure	2500 (11.6)	1305 (11.2)	1195 (12.1)	0.046
Atrial fibrillation/flutter	2089 (9.7)	1231 (10.6)	858 (8.7)	<0.001
Chronic kidney disease	2784 (12.9)	1626 (14.0)	1158 (11.7)	<0.001
Hemodialysis	741 (3.4)	442 (3.8)	299 (3.0)	0.002
Cancer	2680 (12.4)	1439 (12.4)	1241 (12.6)	0.677
Pulmonary disease	4015 (18.7)	1843 (15.8)	2172 (22.0)	<0.001
Body mass index, mean (SD), kg/m^2	30.8 (8.5)	29.9 (7.7)	31.8 (9.2)	<0.001
Missing, n	2422	1355	1067	

Data are given as number (percentage), unless otherwise indicated. Missing values are noted where relevant. Race and ethnicity and sex are defined as determined by the registry during data collection. CABG indicates coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

Statistical Analysis

We report continuous variables as means with SDs and compared them using robust Welch-Student *t*-test. We report categorical variables as percentages and counts and compared them using χ^2 analysis. The number of missing values is described in each table, and in Figure S1. There were no missing values for the primary exposures or outcomes. There were 2422 of 21 528 (11.2%) patients with missing values for body mass index, 446 of 21 528 (2.1%) with missing values for prehospital antiplatelet or anticoagulation medications, and 7863 of 21 528 (36.5%) with missing values for in-hospital anticoagulation medications.

We used odds ratios (ORs) and 95% CIs as relative likelihood measures. To compute the ORs, we first created unadjusted logistic regression models for the exposure of sex and the outcomes of VTE and ATE. We used the largest group (men) as the reference group. We repeated this for the exposure of race and ethnicity, using the largest category (non-Hispanic White) as the reference group. We then created adjusted regression models including all baseline covariates in Table 1, except for body mass index because of the number of missing values (sensitivity analysis including body mass index showed no meaningful change in point estimates). We adjusted for prehospital antiplatelet and anticoagulation regimen and the effect of center. Patients

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with missing information on prehospital antiplatelet or anticoagulation medications were excluded from the adjusted model (n=446/21 528 patients [2.1%]).

We performed a sensitivity analysis in which we adjusted for in-hospital anticoagulation regimen, including only patients for whom this information was known (13 665/21 528 patients [63.5%]). In this model, we adjusted for any anticoagulant that was administered during the hospitalization (see Table 2 and Table S2 for medications adjusted for). For patients who experienced a thromboembolic event, we adjusted for medications that were started before that event. We did not adjust for medications started after (ie, in response to) an event.

This study was approved by the Dartmouth-Hitchcock Institutional Review Board. Because of the retrospective and registry-based nature of the study, the need for patient consent was waived. The American Heart Association Precision Medicine Platform (https://precision.heart.org/) was used for data analysis from February to April 2021. Authors J.A.C. and P.M.C. had full access to the data and attest to the integrity of the analyses.

RESULTS

Patients

We studied 21 528 adults who were hospitalized with COVID-19 across 107 centers with a mean age of 61.2±17.9 years (Table 1 and Table S1). Men made up 54.1% (11 644/21 528) of the cohort. Intensive care was required by 30.7% of patients, and 20.3% of patients had severe COVID-19. The distribution of race and ethnicity was 38.1% (8202/21 528) non-Hispanic White, 25.4% (5478/21 528) Hispanic, 25.7% (5531/21 528) non-Hispanic Black, 0.5% (106/21 528) Native American, 4.0% (857/21 528) Asian, 0.4% (78/21 528) Pacific Islander, and 5.9% (1276/21 528) other. The mean hospital length of stay was 10.0±11.4 days for all patients, and was longer among men (10.7 days, versus 9.0 days for women; $P<0.001$), and longest among Native American patients (11.5 days, versus 9.6–10.3 days for other races and ethnicities; $P<0.001$). Comorbidities were common: 12.1% (2608/21 528) of the cohort had a history of cerebrovascular disease, 5.6% (1199/21 528) had a history of myocardial infarction, and 6.5% (1406/21 528) had a history of smoking. More than half (58.9%, 12 673/21 528) of patients had a history of hypertension, and approximately one third (35.4%, 7614/21 528) had diabetes.

The use of antiplatelet and anticoagulant medications was relatively common among the cohort (Table 2 and Table S2). Antiplatelet use at the time of admission was 27.1% (5819/21 458), and was more common in men (28.3%, 3285/11 605) than in women (25.7%, 2534/9853; $P<0.001$), and non-Hispanic White patients (33.7%, 2754/8183) than in other races and ethnicities (range, 9.0%–29.9%; $P<0.001$). Anticoagulant therapy at the time of admission was present in 14.1% (2964/21 086) of patients and again was more common in men (14.7%, 1677/11 423) than in women (13.3%, 1287/9863; $P=0.005$), and non-Hispanic White patients (18.7%, 1503/8039) than in other races and ethnicities (range, 6.4%–13.3%; $P<0.001$). Among patients for whom in-hospital anticoagulant information was available, most were either on subcutaneous heparin injections (25.0%, 3468/13 847) or low-molecular-weight heparin at a low dose (47.4%, 6547/13 822). Characteristics and outcomes stratified by sex are found in Tables 1 and 2. Characteristics and outcomes stratified by race and ethnicity are found in Table S1 and S2.

Venous Thromboembolic Events

VTEs occurred in 3.7% (805/21 528) of patients (Table 2 and Table S2). Patients who required intensive care had an event rate of 8.3% (553/6604) versus 1.7% (251/14 823; $P<0.001$) for patients treated solely on the wards. Deep vein thrombosis was more common than PE and occurred in 2.4% (508/21 528) of patients, versus PE in 1.8% (385/21 528). VTEs were more common in men (4.2%, 487/11 644) than in women (3.2%, 318/21 528; $P<0.001$). VTEs were also more common in non-Hispanic Black patients (4.9%, 271/5531) than among other races and ethnicities (range, 1.3%–3.8%; $P<0.001$).

The unadjusted OR of VTE for women compared with men was 0.76 (95% CI, 0.66–0.88; Figure S2). This protective association persisted after adjustment for clinical characteristics, with an adjusted OR of 0.71 (95% CI, 0.61–0.83; Figure 1). Sensitivity analysis including only patients for whom in-hospital anticoagulant medication data were available also demonstrated a protective association against VTE for women, with an adjusted OR of 0.43 (95% CI, 0.34–0.55; Figure S3).

Non-Hispanic Black patients had the highest likelihood of VTE when compared with non-Hispanic White patients, with an unadjusted OR of 1.32 (95% CI, 1.11–1.55; Figure S2). This association persisted after risk adjustment, with an adjusted OR of 1.27 (95% CI, 1.04–1.54; Figure 1), and on sensitivity analysis with an adjusted OR of 1.75 (95% CI, 1.26–2.44; Figure S3). Hispanic ethnicity demonstrated a protective association for VTE in the unadjusted model (unadjusted OR, 0.74; 95% CI, 0.61–0.90), but not in the adjusted model (adjusted OR, 0.87; 95% CI, 0.68–1.10). The interaction between sex and race and ethnicity was not statistically significant.

Arterial Thromboembolic Events

ATEs occurred in 3.9% (847/21 528) of patients (Table 2 and Table S2). Patients who required intensive

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Table 2. Thromboembolic Events and Antithrombotic Treatment of Patients, Overall and by Sex

Variable	All patients (n=21 528)	Men (n=11 644)	Women (n=9884)	*P* value
Venous thromboembolic events				
DVT (+/–PE)	508 (2.4)	317 (2.7)	191 (1.9)	<0.001
PE (+/–DVT)	385 (1.8)	223 (1.9)	162 (1.6)	0.141
Arterial thromboembolic events				
Acute limb ischemia	44 (0.2)	29 (0.2)	15 (0.2)	0.155
Myocardial infarction	655 (3.0)	377 (3.2)	278 (2.8)	0.077
Ischemic stroke	168 (0.8)	106 (0.9)	62 (0.6)	0.023
Left ventricular thrombus	168 (0.8)	106 (0.9)	62 (0.6)	0.023
Bleeding requiring transfusion	747 (3.5)	436 (3.7)	311 (3.1)	0.018
Required ICU care	6604 (30.7)	4008 (34.4)	2596 (26.3)	<0.001
Missing, n	101	56	45	
Severe COVID-19	4347 (20.3)	2699 (23.3)	1648 (16.7)	<0.001
Missing, n	104	56	48	
Hospital length of stay, days				
Mean (SD)	10.0 (11.4)	10.7 (12.4)	9.0 (10.2)	<0.001
Median (IQR)	6.5 (3.6–11.7)	6.7 (3.7–12.6)	5.8 (3.5–10.8)	<0.001
Death	3326 (15.4)	2021 (17.4)	1305 (13.2)	<0.001
Prehospital antithrombotics				
Antiplatelet	5819 (27.1)	3285 (28.3)	2534 (25.7)	<0.001
Missing, n	70	39	31	
Aspirin	5327 (24.8)	3001 (25.9)	2326 (23.6)	0.611
P2y12 inhibitor	968 (4.5)	577 (5.0)	391 (4.0)	0.033
Other antiplatelet	150 (0.7)	90 (0.8)	60 (0.6)	0.420
Dual antiplatelet	621 (2.9)	382 (3.3)	239 (2.4)	0.008
Anticoagulant	2964 (14.1)	1677 (14.7)	1287 (13.3)	0.005
Missing, n	442	221	221	
Direct thrombin inhibitor	109 (0.5)	58 (0.5)	51 (0.5)	0.526
Factor Xa inhibitor	1429 (0.7)	779 (0.7)	650 (0.7)	0.028
Warfarin	519 (2.5)	297 (2.6)	222 (2.3)	0.797
Other anticoagulant	937 (4.4)	561 (4.9)	376 (3.9)	0.017
In-hospital anticoagulants				
Prophylactic dose anticoagulant				
Subcutaneous heparin	3468 (25.0)	1966 (26.6)	1502 (23.3)	<0.001
Missing, n	7681	4254	3427	
LMWH, low dose	6547 (47.4)	3460 (46.9)	3087 (47.8)	0.307
Missing, n	7706	4275	3431	
Therapeutic dose anticoagulant				
Intravenous heparin	1381 (10.0)	877 (11.9)	504 (7.8)	<0.001
Missing, n	7695	4268	3427	
LMWH, intermediate dose	1717 (12.4)	913 (12.4)	804 (12.4)	0.909
Missing, n	7679	4258	3421	
LMWH, full dose	1623 (11.7)	994 (13.5)	629 (9.7)	<0.001
Missing, n	7673	4256	3417	
Argatroban	78 (0.6)	51 (0.7)	27 (0.4)	0.041
Missing, n	7493	4173	3320	
Bivalirudin	26 (0.2)	17 (0.2)	9 (0.1)	0.295

(*Continued*)

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Table 2. Continued

Variable	All patients (n=21 528)	Men (n=11 644)	Women (n=9884)	*P* value
Missing, n	7493	4173	3320	
DOAC	1460 (10.4)	863 (11.5)	597 (9.1)	<0.001
Missing, n	7500	4173	3327	
Apixaban	1108 (7.9)	658 (8.8)	450 (6.8)	<0.001
Dabigatran	22 (0.1)	17 (0.2)	5 (<0.1)	0.041
Edoxaban	1 (<0.1)	1 (<0.1)	0	…
Rivaroxaban	319 (2.3)	182 (2.4)	137 (2.1)	0.188
Warfarin	330 (2.4)	198 (2.7)	132 (2.0)	0.015
Missing, n	7510	4181	3329	

Data are given as number (percentage), unless otherwise indicated. Percentages are calculated out of the number of nonmissing values for that variable. The number of missing values for each variable is noted in the table where necessary. Sex is defined as determined by the registry. Severe COVID-19 is defined as the need for invasive mechanical ventilation, extracorporeal circulatory or pulmonary support, or vasopressor or inotropes. DOAC indicates direct oral anticoagulant; DVT, deep vein thrombosis; ICU, intensive care unit; IQR, interquartile range; LMWH, low-molecular-weight heparin; and PE, pulmonary embolism.

care had an event rate of 8.6% (568/6604) versus 1.9% (279/14 823; *P*<0.001) for patients treated solely on the wards. Myocardial infarction was the most common event and occurred in 3.0% (655/21 528) of patients. Acute limb ischemia was the least common event, occurring in 0.2% (44/21 528) of patients. Arterial events were more common in men (4.3%, 502/11 644) than in women (3.5%, 345/9884; *P*=0.002). Arterial events were also more common in non-Hispanic Black patients (5.0%, 278/5531) than among other races and ethnicities (range, 2.3%–4.7%; *P*<0.001).

The unadjusted OR of ATE for women compared with men was 0.80 (95% CI, 0.70–0.92; Figure S4). This protective association persisted after adjustment for clinical characteristics, with an adjusted OR of 0.76 (95% CI, 0.66–0.89; Figure 2). Sensitivity analysis

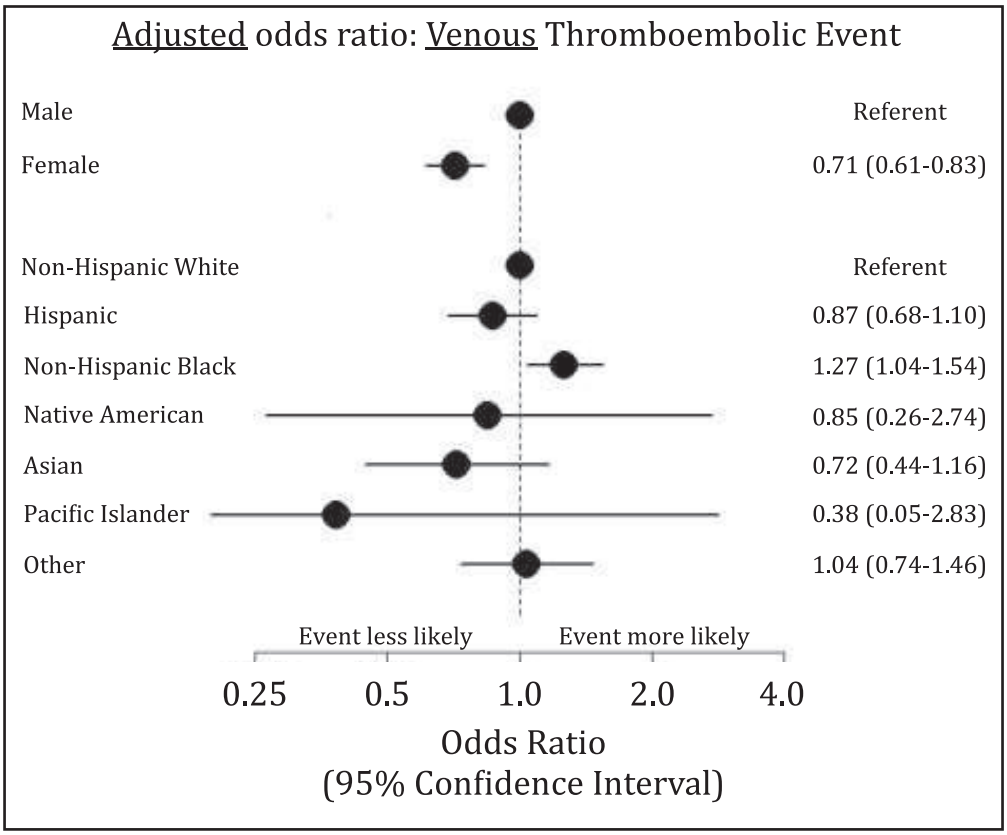


Figure 1. Likelihood of venous thromboembolic events by sex and race and ethnicity.

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including only patients for whom in-hospital anticoagulant medication data were available also demonstrated a protective association against ATE for women, with an adjusted OR of 0.61 (95% CI, 0.47–0.78; Figure S5).

Non-Hispanic Black patients had the highest likelihood of ATE when compared with non-Hispanic White patients, with an unadjusted OR of 1.18 (95% CI, 1.01–1.39; Figure S4). This persisted after risk adjustment, with an adjusted OR of 1.35 (95% CI, 1.11–1.65; Figure 2), and on sensitivity analysis with an adjusted OR of 1.56 (95% CI, 1.12–2.18; Figure S5). Hispanic ethnicity again demonstrated a protective association for ATE in the unadjusted model (unadjusted OR, 0.53; 95% CI, 0.43–0.65), but not in the adjusted model (adjusted OR, 0.93; 95% CI, 0.72–1.20). The interaction between sex and race and ethnicity was not statistically significant.

DISCUSSION

In this retrospective observational study of >20 000 adults hospitalized with COVID-19 across >100 centers in the United States, we found significant sex-, race- and ethnicity-based differences in the incidence of both VTE and ATE. Specifically, when compared with men, women were ≈30% less likely to experience a VTE, and 25% less likely to experience an ATE, a finding that persisted after adjustment for baseline comorbidities and antithrombotic use. In addition, when compared with non-Hispanic White patients, non-Hispanic Black patients were ≈25% more likely to experience a VTE, and 35% more likely to experience an ATE, a finding that again persisted after risk adjustment. Although many unknowns remain surrounding the most appropriate treatment strategies for adults with COVID-19, men and non-Hispanic Black patients may represent at-risk subgroups more susceptible to thromboembolic COVID-19 complications. Understanding the underlying mechanisms that play a role in sex-, race- and ethnicity-based differences in COVID-19–related venous and arterial events is critical to develop strategies to decrease these adverse outcomes.

During the pandemic, many investigators have sought to generate and diffuse new knowledge of the presentation, clinical course, and treatment modalities for patients with COVID-19. It has now been recognized that the COVID-19 virus appears to confer an increased risk of venous and arterial thromboembolic events. A recent meta-analysis, including 48 studies assessing venous thromboembolism among patients

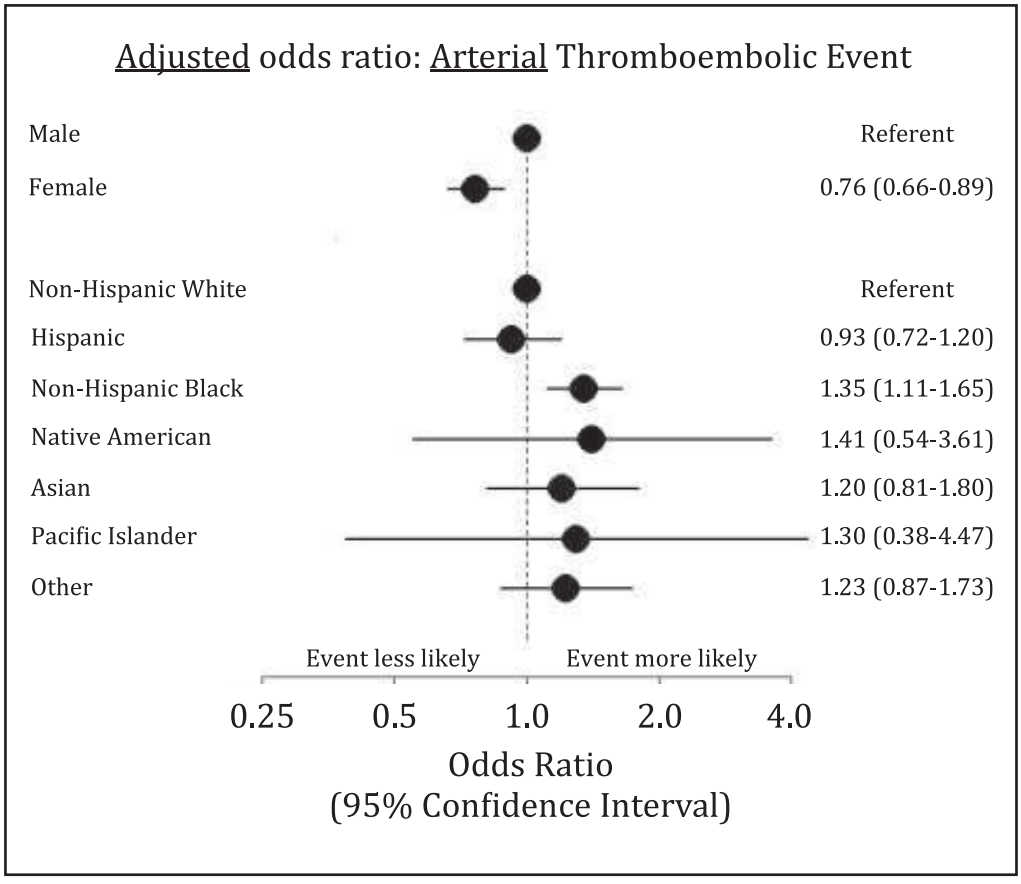


Figure 2. Likelihood of arterial thromboembolic events by sex and race and ethnicity.

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with COVID-19, found that the pooled incidence was 17.0%, ranging from 0% to 85.4%.[2] Although this was a comprehensive meta-analysis, most included studies were from individual centers with <500 patients.[2] The 3 largest studies included in this meta-analysis reported much lower rates of venous thromboembolism, ranging from <1%, to 3.6%.[18–20] Most events in these studies were identified clinically, rather than through widespread screening, and were more prevalent in patients who required intensive care. This is further supported by results of the recent (INSPIRATION) Intermediate-dose Versus Standard Prophylactic Anticoagulation In cRitically-ill pATIents With COVID-19 trial of thromboprophylaxis among adults with COVID-19, where the rate of VTE was 3.4%.[21] Our results demonstrate similar rates of venous thromboembolism to these reports but include >5-fold the number of hospitalized patients across >100 centers. These findings in aggregate may indicate that the true rate of clinically relevant venous thromboembolism among patients with COVID-19 is in the <5% range.

The mechanisms underlying the impact of sex on the likelihood of thromboembolic events in patients with COVID-19 remain unclear. COVID-19–associated thrombosis is thought to occur because of an activation of coagulation-related factors, which may be the result of a cytokine storm (eg, increased CRP [C-reactive protein] and interleukin-6) combined with patient-specific factors (eg, underlying comorbidities that increase the risk of thromboembolic events).[7,22,23] This coagulopathy may be expressed as increased D-dimer levels, fibrinogen degradation products, elevated prothrombin time, and activated partial thromboplastin time.[24] The prevalence and intensity of viral infection appear to be lower for women than men, which could be attributable to a more robust immune response in women. with quicker clearance of the virus.[13,25] This is suggested by lower levels of CRP, D-dimer, interleukin-6, interleukin-8, and interleukin-18 in women compared with men with COVID-19.[25,26] There may also be an inherent difference in the risk associated with baseline cardiovascular disease between women and men.[27] In our study, men were more likely to have a history of coronary and peripheral artery disease. Still, after controlling for baseline characteristics, men were significantly more likely to have an arterial thromboembolic event during hospitalization. Furthermore, although women were more likely to have had a prior venous thromboembolic event, they were significantly less likely to have a VTE while hospitalized when compared with men. These findings suggest that the strategies for venous thromboembolism prevention may need to be different between men and women who are hospitalized with COVID-19.

Race and ethnicity also appear to have an important impact on patients with COVID-19. We found that non-Hispanic Black patients were significantly more likely to develop both VTE and ATE, even after controlling for baseline comorbidities and antithrombotic therapy. The interplay between race and ethnicity and cardiovascular outcomes among patients without COVID-19 is complex and based on the relationship between social (ie, inequality of treatments and differences in access to care), environmental (ie, salt consumption, physical activity, and tobacco use), and genetic (ie, salt sensitivity and lipid metabolism) determinants of health, with higher rates of cardiovascular disease in non-Hispanic Black individuals.[12,28] Incidence of venous thromboembolism in patients without COVID-19 seems to be the highest in non-Hispanic Black individuals and lowest in Asian individuals and Pacific Islanders.[9] This finding may relate to higher factor VIII levels,[11] higher frequency of endothelial cell nitric oxide synthase allele,[10] or prothrombin gene mutations.[29] More important than these biologic factors may be social determinants of health, including undiagnosed comorbid conditions attributable to decreased access to care,[30] failure to accurately capture the racial identity of each patient,[31] or other complex social factors that are difficult to account for in large registries.[32] Future studies understanding the reason for these differences among races and ethnicities will be of paramount importance to decrease the risk of adverse outcomes in patients with COVID-19.

The risk of both VTE and ATE appears to remain elevated despite the use of prophylactic anticoagulant therapy.[33,34] Retrospective studies suggest that antithrombotic therapy may be associated with improved outcomes.[35–37] However, the most appropriate antithrombotic regimen to treat patients hospitalized with COVID-19 remains poorly defined. Most patients in our study were treated with some form of prophylactic or therapeutic dose anticoagulant agent; despite this, the rate of clinical VTE and ATE remained elevated, with rates at, or slightly above, those seen in prior randomized trials of patients without COVID-19. In the APEX (Acute Medically Ill VTE Prevention With Extended Duration Betrixaban Study) trial, the rate of deep vein thrombosis/PE was 5.3% in patients receiving extended prophylaxis with betrixaban, an oral Xa inhibitor. However, most VTE cases were asymptomatic and found on screening, in contrast to our study, where screening was not required and events were diagnosed at the discretion of the treating clinician.[38] The rate of ATE (cardiovascular death, myocardial infarction, or stroke) in APEX was 2.4% in betrixaban group.[39] In the MARNIER (Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolism Risk) trial, the 45-day rate of VTE was 0.83% in patients receiving extended thromboprophylaxis with rivaroxaban and 1.1% in patients not receiving extended thromboprophylaxis.[40] Importantly, only symptomatic

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VTE events were included.[40] The rate of ATE (myocardial infarction or stroke) was 0.52% in rivaroxaban arm and 0.65% in the placebo arm.[41] Our findings among COVID-19 demonstrate thromboembolic event rates that are similar to, or slightly higher than, these trials. However, our findings remain much lower than other published smaller studies of patients with COVID-19, which likely means that the real risk of thromboembolism among patients with COVID-19 may not be as high as once previously thought.[2] In addition, rates of VTE were similar across races and ethnicities in both trials, which may indicate a difference between medically ill cohorts in the trials and patients with COVID-19.

Patients included in our study were diagnosed at the discretion of the treating clinician, which likely indicates that events detected were more clinically relevant and may be more severe. This notion is supported by the fact that >40% of VTEs occurring in our study were PE, whereas in trials of low-molecular-weight heparin, PE made up just 10% of the events.[42] Furthermore, similar to our results, the recent INSPIRATION trial documented that 7 of 19 (37%) VTE events occurring among included patients were PE.[21] At the time of writing this article, there are >70 ongoing randomized controlled trials evaluating antithrombotic regimens for inpatients and outpatients with COVID-19.[8] Although these results are awaited, guidelines from the International Society of Thrombosis and Haemostasis suggest a prophylactic-dose regimen of low-molecular-weight heparin in patients hospitalized with COVID-19.[43] Our findings suggest that these ongoing randomized studies should consider incorporating the assessment of sex- and race- and ethnicity-based differences into their analyses to better individualize treatment regimens.

Our study has limitations. It is a retrospective analysis of in-hospital outcomes and is subject to selection and reporting bias. Race and ethnicity were defined by the registry and may not be as accurate as patient self-reporting. The registry does not capture in-hospital antiplatelet medications. The population of patients affected by COVID-19 may have changed over the course of the pandemic; we adjusted for this by including calendar time in the regression model, but residual confounding may remain. Some myocardial infarction events represented non–ST-segment–elevation infarctions, and as such may not represent true plaque rupture and coronary thrombosis. The inpatient anticoagulant regimen was missing in approximately one third of patients in the cohort, which limits our ability to better define the impact of the anticoagulant regimen on outcomes among patients with COVID-19. In addition, the registry captures only inpatient thromboembolic events. Patients with COVID-19 may remain at risk for thromboembolic events post-discharge, but we are unable to comment on this with the data available.

CONCLUSIONS

In this retrospective observational study of >20 000 adults hospitalized with COVID-19 across >100 centers in the United States, we found that compared with men, women were 30% less likely to experience a VTE, and 25% less likely to experience an ATE. Furthermore, when compared with non-Hispanic White patients, non-Hispanic Black patients were 25% more likely to experience a VTE, and 35% more likely to experience an ATE. Although many unknowns remain surrounding the most appropriate treatment strategies for adults with COVID-19, men and non-Hispanic Black patients may represent at-risk subgroups more susceptible to thromboembolic COVID-19 complications.

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Disclosures

None.

Supplementary Material

Table S1–S2
Figure S1–S2

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Supplemental Material

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Table S1. Patient characteristics overall and by race/ethnicity.

Variable	*All patients* n=21528 (%)	*Non-Hispanic White* n=8202 (%)	*Hispanic* n=5478 (%)	*Non-Hispanic Black* n=5531 (%)	*Native American* n=106 (%)	*Asian* n=857 (%)	*Pacific Islander* n=78 (%)	*Other* n=1276 (%)	*p-value*
Sex									
Male	11644 (54.1)	4482 (54.6)	3117 (56.9)	2733 (49.4)	52 (49.1)	478 (55.8)	34 (43.6)	748 (58.6)	<.001
Female	9884 (45.9)	3720 (45.4)	2361 (43.1)	2798 (50.6)	54 (50.9)	379 (44.2)	44 (56.4)	528 (41.4)	<.001
Age, year (SD)	61.2 (17.9)	67.0 (17.3)	55.2 (17.6)	59.0 (16.6)	58.7 (17.4)	62.4 (17.1)	48.4 (16.9)	60.2 (17.9)	<.001
Deep vein thrombosis	725 (3.4)	368 (4.5)	91 (1.7)	217 (3.9)	1 (0.9)	10 (1.2)	0	38 (3.0)	<.001
Pulmonary embolism	487 (2.3)	241 (2.9)	40 (0.7)	172 (3.1)	2 (1.9)	8 (0.9)	0	24 (1.9)	<.001
Cerebrovascular disease	2608 (12.1)	1054 (12.9)	551 (10.1)	809 (14.6)	13 (12.3)	77 (9.0)	5 (6.4)	99 (7.8)	<.001
Stroke	2060 (9.6)	796 (9.7)	436 (8.0)	667 (12.1)	11 (10.4)	64 (7.5)	5 (6.4)	81 (6.3)	<.001
Transient ischemic attack	625 (2.9)	327 (4.0)	90 (1.6)	178 (3.2)	2 (1.9)	13 (1.5)	0	15 (1.2)	<.001
Coronary artery disease									
Prior CABG	627 (2.9)	401 (4.9)	72 (1.3)	98 (1.8)	2 (1.9)	17 (2.0)	3 (3.8)	34 (2.7)	<.001
Prior PCI	986 (4.6)	568 (6.9)	138 (2.5)	187 (3.4)	1 (0.9)	39 (4.6)	1 (1.3)	52 (4.1)	<.001
Prior myocardial infarction	1199 (5.6)	639 (7.8)	174 (3.2)	286 (5.2)	8 (7.5)	33 (3.9)	4 (5.1)	55 (4.3)	<.001
Peripheral arterial disease	584 (2.7)	285 (3.5)	82 (1.5)	178 (3.2)	2 (1.9)	12 (1.4)	0	25 (2.0)	<.001
Smoking history	1406 (6.5)	603 (7.4)	246 (4.5)	418 (7.6)	14 (13.2)	42 (4.9)	2 (2.6)	81 (6.3)	<.001
Hypertension	12673 (58.9)	5173 (63.1)	2419 (44.2)	3838 (69.4)	62 (58.5)	471 (55.0)	35 (44.9)	675 (52.9)	<.001
Diabetes	7614 (35.4)	2600 (31.7)	1844 (33.7)	2355 (42.6)	46 (43.4)	308 (35.9)	33 (42.3)	428 (33.5)	<.001
Dyslipidemia	7423 (34.5)	3480 (42.4)	1286 (23.5)	1914 (34.6)	34 (32.1)	310 (36.2)	19 (24.4)	380 (29.8)	<.001
Heart failure	2500 (11.6)	1244 (15.2)	314 (5.7)	771 (13.9)	13 (12.3)	54 (6.3)	7 (9.0)	97 (7.6)	<.001
Atrial fibrillation / flutter	2089 (9.7)	1342 (16.4)	242 (4.4)	357 (6.5)	5 (4.7)	58 (6.8)	4 (5.1)	81 (6.3)	<.001
Chronic kidney disease	2784 (12.9)	1131 (13.8)	450 (8.2)	974 (17.6)	9 (8.5)	79 (9.2)	7 (9.0)	134 (10.5)	<.001
Hemodialysis	741 (3.4)	155 (1.9)	203 (3.7)	318 (5.7)	2 (1.9)	29 (3.4)	2 (2.6)	32 (2.5)	<.001
Cancer	2680 (12.4)	1340 (16.3)	477 (8.7)	647 (11.7)	12 (11.3)	80 (9.4)	6 (7.7)	118 (9.2)	<.001
Pulmonary disease	4015 (18.7)	1994 (24.3)	580 (10.6)	1076 (19.5)	23 (21.7)	126 (14.7)	14 (17.9)	202 (15.8)	<.001
Body mass index, mean (SD)	30.8 (8.5)	30.3 (8.5)	30.6 (7.5)	32.5 (9.3)	30.8 (8.5)	26.1 (5.6)	35.4 (10.2)	29.7 (7.3)	<.001
Missing	2,422	677	903	510	10	101	4	217	

Note: Missing values are noted where relevant. Race/ethnicity and sex are defined as determined by the registry during data collection. SD, standard deviation; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

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Table S2. Thromboembolic events and antithrombotic treatment of patients, overall and by race/ethnicity.

Variable	*All patients* n=21528 (%)	*Non-Hispanic White* n=8202 (%)	*Hispanic* n=5478 (%)	*Non-Hispanic Black* n=5531 (%)	*Native American* n=106 (%)	*Asian* n=857 (%)	*Pacific Islander* n=78 (%)	*Other* n=1276 (%)
Venous thromboembolic events								
DVT (+/- PE)	508 (2.4)	176 (2.1)	110 (2.0)	171 (3.1)	2 (1.9)	15 (1.8)	1 (1.3)	33 (2.6)
PE (+/-DVT)	385 (1.8)	168 (2.0)	57 (1.0)	131 (2.4)	1 (0.9)	8 (0.9)	0	20 (1.6)
Arterial thromboembolic events								
Acute limb ischemia	44 (0.2)	12 (0.1)	6 (0.1)	23 (0.4)	0	2 (0.2)	0	1 (0.1)
Myocardial infarction	655 (3.0)	289 (3.5)	91 (1.7)	205 (3.7)	5 (4.7)	26 (3.0)	3 (3.8)	36 (2.8)
Ischemic stroke	168 (0.8)	61 (0.7)	28 (0.5)	57 (1.0)	0	11 (1.3)	0	11 (0.9)
Left ventricular thrombus	168 (0.8)	5 (0.1)	6 (0.1)	9 (0.2)	0	0	0	1 (0.1)
Bleeding requiring transfusion	747 (3.5)	246 (3.0)	148 (2.7)	255 (4.6)	7 (6.6)	28 (3.3)	3 (3.8)	40 (3.1)
Required ICU care	6604 (30.7)	2732 (33.3)	1430 (26.1)	1741 (31.5)	41 (38.7)	277 (32.3)	18 (23.1)	365 (28.6)
Missing	101							
Severe COVID-19*	4347 (20.3)	1553 (19.1)	1067 (19.6)	1217 (22.1)	26 (24.7)	199 (23.3)	7 (9.1)	278 (21.9)
Missing	104	32	39	18	1	2	1	11
Hospital Length of Stay								
Mean (SD)	10.0 (11.4)	9.9 (11.1)	9.9 (11.9)	10.3 (11.3)	11.5 (11.7)	9.7 (11.2)	9.6 (11.4)	10.0 (12.2)
Median (IQR)	6.5 (3.6-11.7)	6.6 (3.6-11.8)	5.9 (3.6-7.9)	6.6 (3.6-12.5)	7.6 (4.6-3.7)	6.4 (3.6-11.6)	5.6 (3.6- 9.9)	6.0 (3.5- 11.5)
Death	3326 (15.4)	1404 (17.1)	733 (13.4)	792 (14.3)	19 (17.9)	145 (16.9)	4 (5.1)	229 (17.9)
Prehospital antithrombotics								
Antiplatelet	5819 (27.1)	2754 (33.7)	913 (16.7)	1649 (29.9)	32 (30.2)	188 (22.0)	7 (9.0)	276 (21.8)
Missing	70	19	23	16	0	1	0	11
Aspirin	5327 (24.8)	2495 (30.5)	850 (15.6)	1523 (27.6)	30 (28.3)	172 (20.1)	7 (9.0)	250 (19.8)
P2y12 inhibitor	968 (4.5)	512 (6.3)	132 (2.4)	244 (4.4)	4 (3.8)	25 (2.9)	1 (1.3)	50 (4.0)

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Other antiplatelet	150 (0.7)	65 (0.8)	14 (0.3)	60 (1.1)	2 (1.9)	4 (0.5)	0	5 (0.4)
Dual antiplatelet	621 (2.9)	314 (3.8)	83 (1.5)	177 (3.2)	4 (3.8)	13 (1.5)	1 (1.3)	29 (2.3)
Anticoagulant	2964 (14.1)	1503 (18.7)	548 (10.2)	720 (13.3)	9 (8.5)	62 (7.4)	5 (6.4)	117 (9.3)
Missing	442	163	102	135	0	18	0	24
Direct thrombin inhibitor	109 (0.5)	75 (0.9)	15 (0.3)	14 (0.3)	0	0	0	5 (0.4)
Factor Xa inhibitor	1429 (0.7)	825 (10.3)	160 (3.0)	340 (6.3)	3 (2.8)	31 (3.7)	3 (3.8)	67 (5.4)
Warfarin	519 (2.5)	315 (3.9)	59 (1.1)	119 (2.2)	2 (1.9)	5 (0.6)	1 (1.3)	18 (1.4)
Other anticoagulant	937 (4.4)	297 (3.7)	319 (5.9)	261 (4.8)	4 (3.1)	26 (3.1)	2 (2.6)	28 (2.2)
In hospital anticoagulants								
Prophylactic dose anticoagulant								
Subcutaneous heparin	3468 (25.0)	1328 (23.0)	629 (20.0)	1174 (32.2)	21 (25.9)	109 (23.6)	11 (19.3)	196 (28.5)
Missing	7681	2431	2332	1889	25	395	21	588
LMWH - low dose	6547 (47.4)	2612 (45.3)	1665 (53.1)	1553 (42.7)	45 (55.6)	290 (63.3)	34 (59.6)	348 (50.7)
Missing	7706	2440	2340	1891	25	399	21	590
Therapeutic dose anticoagulant								
Intravenous heparin	1381 (10.0)	576 (10.0)	218 (7.0)	444 (12.2)	7 (8.6)	37 (8.0)	4 (7.0)	95 (14.0)
Missing	7695	2422	2356	1881	25	393	21	597
LMWH - intermediate dose	1717 (12.4)	613 (10.6)	477 (15.2)	467 (12.8)	9 (11.1)	55 (11.8)	8 (14.0)	88 (12.8)
Missing	7679	2430	2338	1883	25	392	21	590
LMWH - full dose	1623 (11.7)	634 (11.0)	447 (14.2)	395 (10.8)	4 (4.9)	41 (8.8)	4 (7.0)	98 (14.3)
Missing	7673	2425	2336	1885	25	392	21	589
Argatroban	78 (0.6)	25 (0.4)	15 (0.5)	23 (0.6)	0	7 (1.5)	0	8 (1.2)
Missing	7493	2318	2330	1825	25	390	21	584
Bivalirudin	26 (0.2)	8 (0.1)	7 (0.2)	10 (0.3)	0	0	0	1 (0.1)
Missing	7493	2319	2328	1825	25	390	21	585
DOAC	1460 (10.4)	770 (5.8)	183 (5.8)	404 (10.9)	6 (7.4)	27 (5.8)	4 (7.0)	66 (9.6)
Missing	7500	2326	2329	1824	25	390	21	585

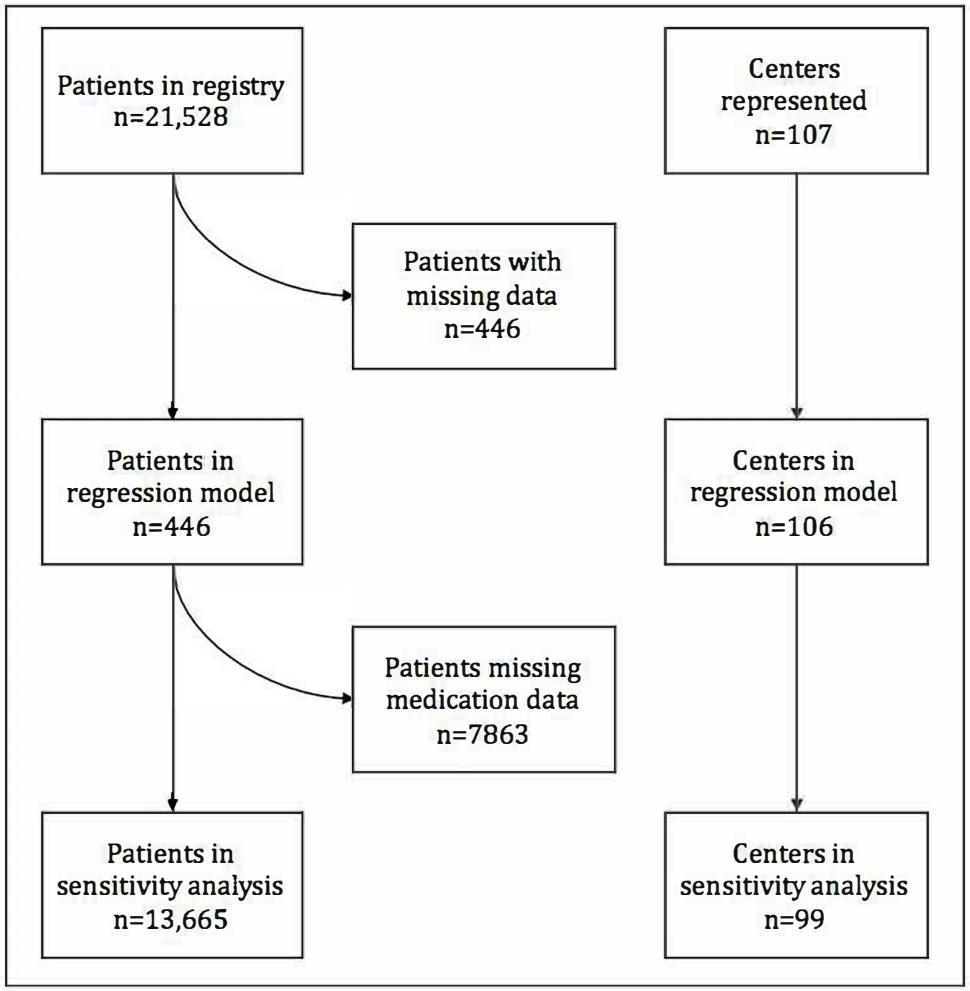
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Apixaban	1108 (7.9)	561 (9.5)	145 (4.6)	317 (8.6)	6 (7.4)	22 (4.7)	3 (5.3)	54 (7.8)
Dabigatran	22 (0.1)	18 (0.3)	1 (<0.1)	2. (0.1)	0	0	0	1 (0.1)
Edoxaban	1 (<0.1)	0	0	0	0	0	0	1 (0.1)
Rivaroxaban	319 (2.3)	187 (3.2)	35 (1.1)	82 (2.2)	0	4 (0.9)	1 (1.8)	10 (1.4)
Warfarin	330 (2.4)	196 (3.3)	45 (1.4)	73 (2.0)	1 (1.2)	3 (0.6)	1 (1.8)	11 (1.6)
Missing	7510	2331	2331	1825	25	390	21	587

Note: Percentages are calculated out of the number of non-missing values for that variable. The number of missings for each variable is noted in the table where necessary. Race/ethnicity is defined as determined by the registry. Severe COVID-19 is defined as the need for invasive mechanical ventilation, extracorporeal circulatory or pulmonary support, or vasopressor or inotropes. DVT, deep vein thrombosis; PE, pulmonary embolism; ICU, intensive care unit; LMWH, low molecular weight heparin; DOAC, direct ora anticoagulant.

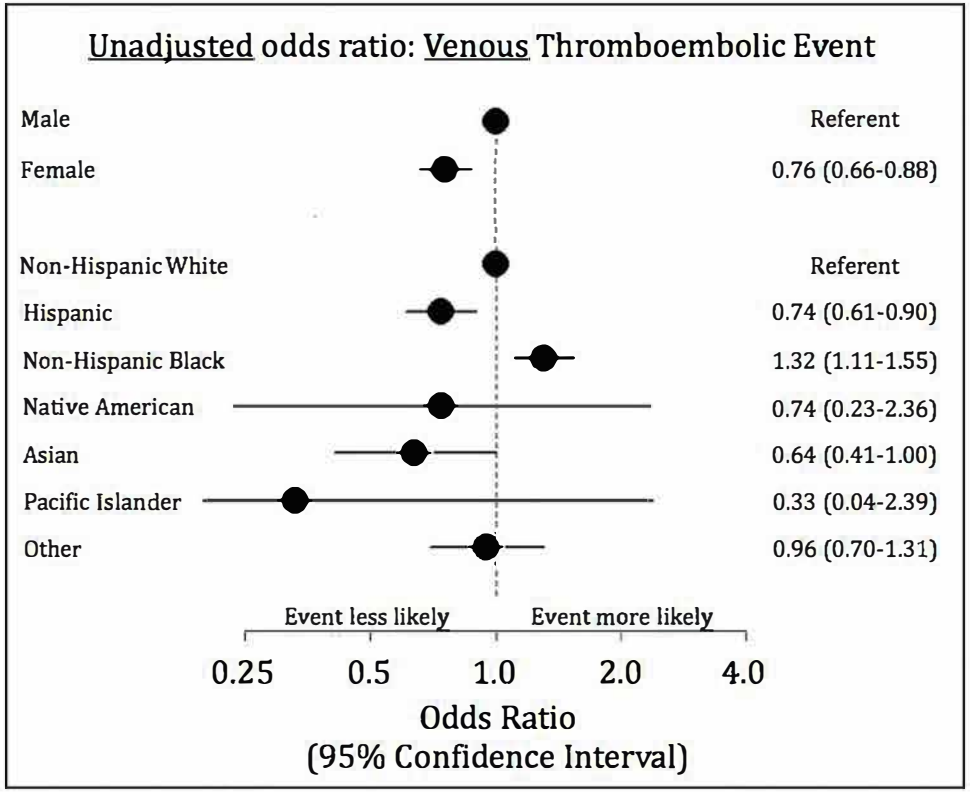
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Figure S1. Creation of the analytic cohort and missing data.



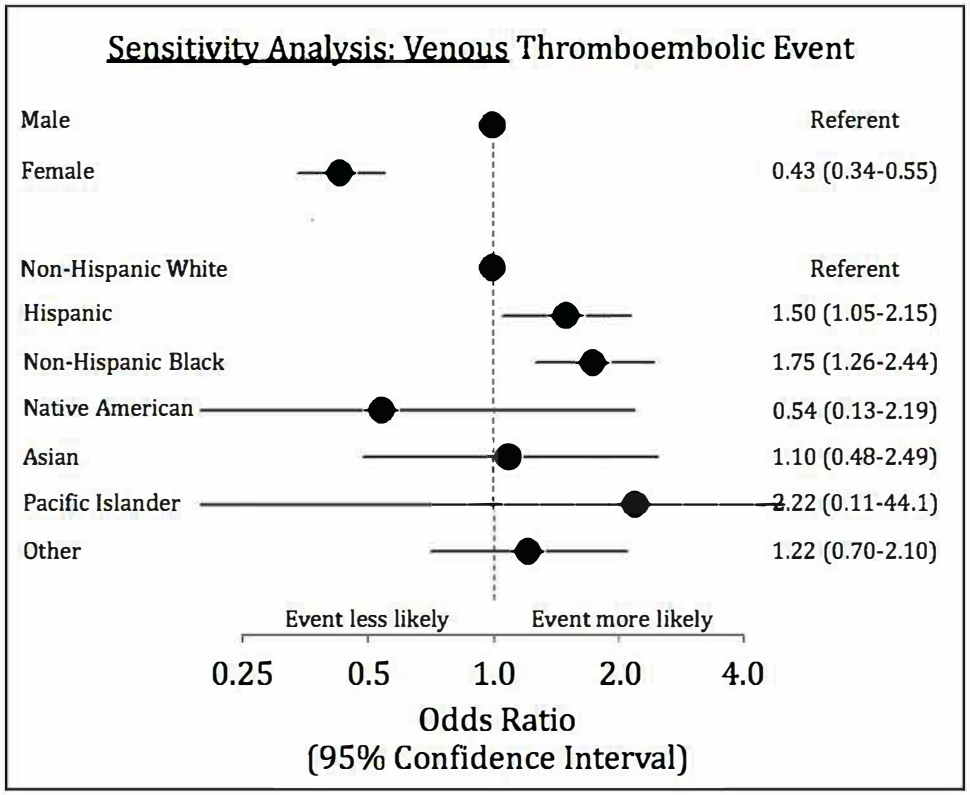
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Figure S2. Unadjusted Likelihood of Venous Thromboembolic Events by sex and race/ethnicity.



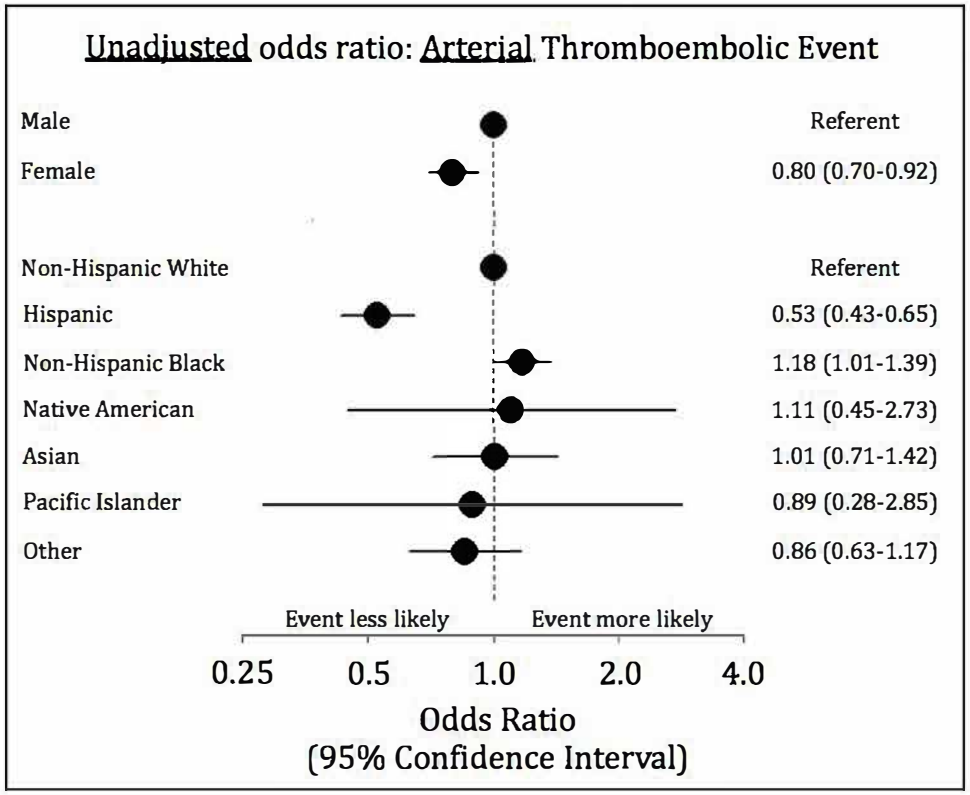
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Figure S3. Sensitivity analysis of Venous Thromboembolic Events.



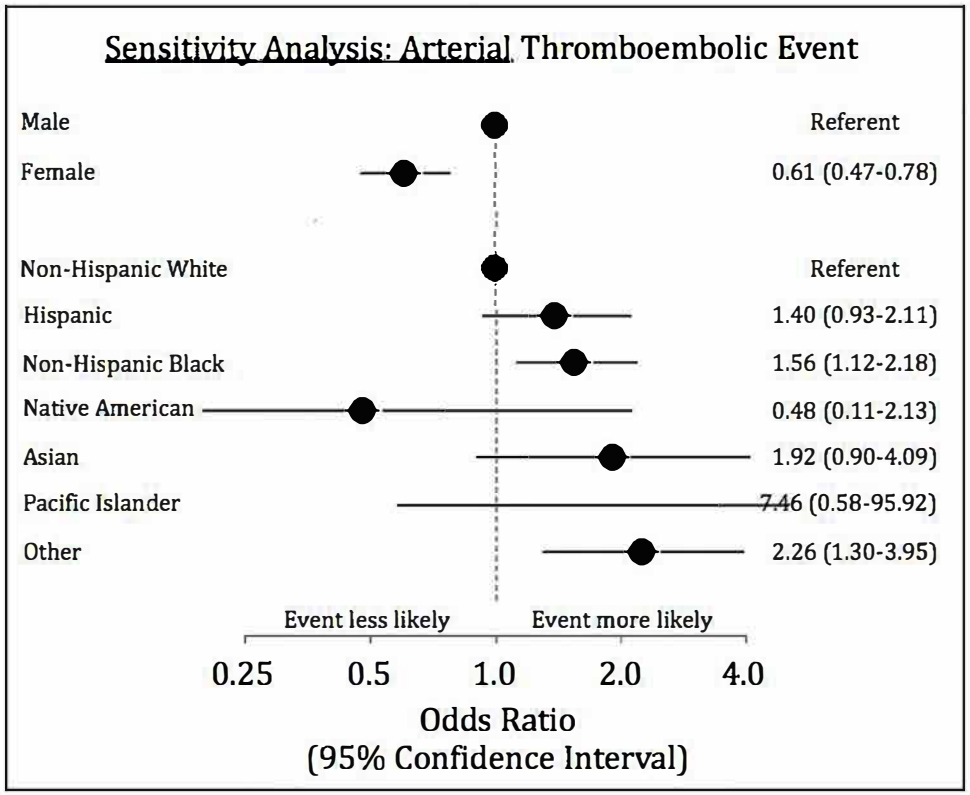
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Figure S4. Unadjusted Likelihood of Arterial Thromboembolic Events by sex and race/ethnicity.



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Figure S5. Sensitivity analysis of Arterial Thromboembolic Events.



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