Racial and Regional Differences in Venous Thromboembolism in the United States in 3 Cohorts

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Background—Blacks are thought to have a higher risk of venous thromboembolism (VTE) than whites. However, prior studies are limited to administrative databases that lack specific information on VTE risk factors or have limited geographic scope.

Methods and Results—We ascertained VTE from 3 prospective studies: the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), and the Reasons for Geographic and Racial Differences in Stroke study (REGARDS). We tested the association of race with VTE using Cox proportional hazard models adjusted for VTE risk factors. Over 438,090 person-years, 916 incident VTE events (302 in blacks) occurred in 51,149 individuals (17,318 blacks) who were followed up. In risk factor–adjusted models, blacks had a higher rate of VTE than whites in the CHS (hazard ratio, 1.81; 95% confidence interval, 1.20–2.73) but not ARIC (hazard ratio, 1.21; 95% confidence interval, 0.96–1.54). In REGARDS, there was a significant region-by-race interaction (P=0.01): Blacks in the Southeast had a significantly higher rate of VTE than blacks in the rest of the United States (hazard ratio, 1.63; 95% confidence interval, 1.08–2.48) that was not seen in whites (hazard ratio, 0.83; 95% confidence interval, 0.61–1.14).

Conclusions—The association of race with VTE differed in each cohort, which may reflect the different time periods of the studies or different regional rates of VTE. Further studies of environmental and genetic risk factors for VTE are needed to determine which underlie racial and perhaps regional differences in VTE. (Circulation. 2014;129:1502-1509.)

Key Words: continental population groups ■ epidemiology ■ venous thrombosis

Venous thromboembolism (VTE), consisting of pulmonary embolism (PE) and deep venous thrombosis (DVT), is a common cardiovascular disease, affecting >300,000 individuals annually in the United States with 100,000 fatalities per year.1 Many studies suggest that black Americans have higher rates of VTE than white Americans.2 Reasons for these potential racial differences are unclear, with risk factors such as obesity,3 diabetes mellitus,4 and elevated factor VIII5 being more common in blacks and genetic polymorphisms such as factor V Leiden and the prothrombin gene 20210A mutation more common in whites.2

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Prior studies on race and VTE in the United States have been limited in that they examined administrative databases without validation of VTE events,5–8 had limited numbers of blacks, were from discrete geographic areas, or excluded outpatient-treated DVTs.9 Furthermore, many studies were not able to evaluate whether differences in VTE risk factors explained any race association.5–8 To determine the association of race with VTE and to evaluate whether conventional VTE risk factors might mediate any observed differences, we assessed VTE incidence in blacks and whites in 3 large cohorts: the Cardiovascular Health Study (CHS), the Atherosclerosis Risk in Communities Study (ARIC), and the Reasons for Geographic and Racial Differences in Stroke study (REGARDS).10–13 Together, these studies have followed up 51,149 individuals over 439,090 person-years and include 17,318 blacks. They offer a unique opportunity to study the association of race with VTE and, in the case of REGARDS, to evaluate the association of region of residence with VTE in the United States. Our goal was to study the association of race with VTE risk in these 3 cohorts and whether common VTE risk factors affected any race association.

Methods

Cohorts

VTE events were ascertained in 3 longitudinal cohorts designed to study the causes and consequences of vascular disease (Table 1 and Table I in the online-only Data Supplement). ARIC12 recruited 15,792 individuals (4,266 blacks) 45 to 64 years old in 1987 to 89 from 4 field centers: Forsyth County, North Carolina; Washington County, Maryland; suburban Minneapolis, MN; and Jackson, MS. CHS13 recruited 5,201 individuals 265 years of age in 1989 to 90 and an
additional 687 black men and women in 1991 to 92 from 4 field centers: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, PA (924 blacks). The study of VTE in CHS and ARIC is called the Longitudinal Investigation of Thromboembolism Etiology (LITE) study. The methods for the LITE study, including VTE case ascertainment, have been described in detail elsewhere.10

REGARDS recruited 30,239 black and white individuals ≥45 years of age between 2003 and 2007 in the contiguous United States, oversampling blacks and individuals living in the Southeast (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee).11 Exclusion criteria included self-reported race other than white or black, inability to converse in English, cognitive impairment as judged by the telephone interviewer, residence in or on the waiting list for a nursing home, or active cancer or current treatment for cancer. After enrollment, medical history (including self-reports of prior VTE events) and risk factors were assessed via computer-assisted telephone interview followed by an in-home visit, which included anthropomorphic and blood pressure measures, medication ascertainment, and phlebotomy (Examination Management Systems Inc, Irving, TX).

Participants in ARIC, CHS, and REGARDS gave written informed consent. This study was approved by the Institutional Review boards of all participating institutions.

### Event Ascertainment

In CHS and ARIC, VTE (consisting of DVT and PE) events were captured by review of hospital discharge codes and verified by 2 physicians (A.R.F. and M.C.). Briefly, participants in ARIC were followed up by clinic visits every 3 years and annual telephone calls. Further hospitalizations not captured by other methods were obtained from surveillance of community hospitals. In CHS, participants were followed up by alternating telephone calls and clinic visits every 6 months. Hospitalizations were also identified through Medicare records. For all hospitalizations, hospital discharge codes were used to identify possible cases of thrombosis. By design, hospital record review was similar to that reported in REGARDS below. A detailed description of event ascertainment

### Table 1. Cohort Characteristics by Race

<table>
<thead>
<tr>
<th></th>
<th>ARIC</th>
<th>CHS</th>
<th>REGARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blacks</td>
<td>Whites</td>
<td>Blacks</td>
</tr>
<tr>
<td>Participants, n</td>
<td>4266</td>
<td>11,478</td>
<td>924</td>
</tr>
<tr>
<td>Mean (SD) follow-up, y</td>
<td>15.1 (4.4)</td>
<td>15.8 (3.7)</td>
<td>7.9 (2.8)</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>65,263</td>
<td>181,829</td>
<td>7336</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>53.6 (5.8)</td>
<td>54.4 (5.7)</td>
<td>72.9 (5.7)</td>
</tr>
<tr>
<td>Minimum, maximum age, y</td>
<td>44, 66</td>
<td>44, 66</td>
<td>64, 100</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>1831 (38)</td>
<td>54,286 (47)</td>
<td>343 (37)</td>
</tr>
<tr>
<td>BMI (SD), kg/m²</td>
<td>29.6 (6.2)</td>
<td>27.0 (4.9)</td>
<td>28.5 (5.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Obesity, n (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (BMI &lt;18.5 kg/m²)</td>
<td>45 (1)</td>
<td>97 (0.8)</td>
<td>16 (2)</td>
<td>81 (2)</td>
<td>111 (0.9)</td>
<td>199 (1)</td>
</tr>
<tr>
<td>Normal (BMI 18.5–24.9 kg/m²)</td>
<td>887 (21)</td>
<td>4,162 (36)</td>
<td>226 (25)</td>
<td>1,934 (39)</td>
<td>2,074 (17)</td>
<td>4,873 (28)</td>
</tr>
<tr>
<td>Overweight (BMI 25–29.9 kg/m²)</td>
<td>1,589 (37)</td>
<td>4,597 (40)</td>
<td>381 (41)</td>
<td>2,036 (42)</td>
<td>4,016 (33)</td>
<td>6,814 (39)</td>
</tr>
<tr>
<td>Obese (BMI ≥30 kg/m²)</td>
<td>1,730 (41)</td>
<td>2,612 (23)</td>
<td>297 (32)</td>
<td>860 (18)</td>
<td>5,823 (48)</td>
<td>5,447 (31)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>821 (20)</td>
<td>1,046 (9)</td>
<td>230 (26)</td>
<td>715 (15)</td>
<td>3,588 (31)</td>
<td>2,672 (16)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2,374 (56)</td>
<td>3,121 (27)</td>
<td>713 (77)</td>
<td>3,138 (64)</td>
<td>8,641 (71)</td>
<td>8,821 (51)</td>
</tr>
<tr>
<td>Mean (SD) eGFR, mL·min⁻¹·1.73 m⁻²</td>
<td>103 (18)</td>
<td>93 (13)</td>
<td>80 (23)</td>
<td>67 (17)</td>
<td>90 (26)</td>
<td>82 (21)</td>
</tr>
</tbody>
</table>

### Region, Race, and Venous Thrombosis in the US

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VTE events. PE was considered thrombus in the pulmonary arter-
ies and for the reasons for any hospitalizations. A research nurse
reviewed the text recorded for each reported hospitalization through
February 2010. Any report of a blood clot in the legs, arms, or lungs
was considered a potential case for physician review. Second, a tele-
phone interview was developed and administered between February
2010 and February 2011 to ascertain participant-reported VTE events
back to baseline. Similar questionnaires in epidemiological studies
have 98% specificity and >70% sensitivity for ascertaining VTE.15
Third, the reasons for all deaths were reviewed by the use of any
available data (National Death Index determination of death, exit
interview with proxy/next of kin, or records from last hospital stay). 
Fourth, VTE events discovered from a review of other events (stroke and
coronary heart disease) were abstracted. On the basis of all available
information, we retrieved medical records up to 1 year before and
1 year after potential events. Retrieved records were used to help
guide further record retrieval if they did not contain the primary VTE
event. Primary inpatient and outpatient records, including history and
physical examinations, discharge summaries, imaging reports, and
outpatient notes, were retrieved using up to 3 attempts. If after review
by a research nurse and confirmation by a physician (N.A.Z.) it was
ascertained that no VTE occurred and no workup for VTE occurred,
the record was closed as a nonevent. If separate events were judged
by the research nurse and the physician to be 1 event (ie, a DVT and
PE that occurred on the same day) or events were captured via >1
mechanism (ie, through reviewing reasons for hospitalizations and
through the telephone interview), the events were consolidated. Each
potential event was reviewed by 2 of 3 physicians (N.A.Z. reviewed
all events; M.C. and A.R.F. each reviewed 60% of events). Major dis-
agreements, defined as a disagreement in the level of evidence of a
VTE event or whether the event was provoked or unprovoked, were
adjudicated by blind review by the third reviewer. Telephone con-
ferences were used in cases when all 3 reviewers disagreed. Minor
disagreements (such as date of a VTE event) were resolved by a physi-
cian (N.A.Z.) and the research nurse.

Definitions
Consistent definitions were used in REGARDS and LITE to define
VTE events. PE was considered thrombus in the pulmonary arter-
ies, and DVT was considered thrombus of the deep veins of the
legs or arms (including distal veins). Provoked VTE was defined as
a VTE event preceded within 90 days by major trauma, surgery, or
marked immobility or associated with active cancer or chemotherapy.
All other events were considered unprovoked. Definite VTE events
required an autopsy, unambiguous imaging, or a healthcare provider’s
description of positive imaging. Probable VTE events required a high
clinical suspicion but without a record of definitive radiology evi-
dence of VTE. Baseline VTE was defined as a self-reported history of
PE or DVT before enrollment.

Body mass index was defined as weight in kilograms divided
by the square of height in meters. Estimated glomerular filtration
rate was defined with the Chronic Kidney Disease Collaboration
equation.16 Diabetes mellitus was defined as fasting glucose
≥126 mg/dL, nonfasting glucose ≥200 mg/dL, or participant
report of diabetes mellitus or the use of hypoglycemic medica-
tion. Hypertension was defined as blood pressure >140/90 mm Hg
or self-report of current treatment for hypertension. Because of the
differing years of recruitment and because participants only
selected ranges for income, income was divided into cohort-spe-
cific percentiles by cohort with a category for refused (<20th,
21st–50th, 51st–75th, and >75th percentile). Race was defined from
participant self-report.

Statistical Analysis
As a result of differences in methodology, follow-up, and start date,
analyses were stratified by cohort. Differences between blacks and
whites were tested by the use of \( t \) tests, Wilcoxon rank-sum tests, and
\( \chi^2 \) tests of associations as appropriate. After the exclusion of partic-
ients with self-reported baseline VTE, Poisson regression was used to
estimate VTE incidence rates accounting for age, sex, and race. Cox
proportional hazard models tested the association of race with
VTE, excluding individuals with baseline VTE (Table 1). Interaction
terms of race with age, sex, and region (in REGARDS) were assessed,
and values of \( P<0.10\) were considered significant. Because of a sig-
nificant region-by-race interaction, analyses in REGARDS were pre-
sented stratified by race or region. Sensitivity analyses were done by
determining the probability that nonretrieved records in REGARDS
represented VTE events and including the probabilities in analyses.
The probability that a nonretrieved record would be a VTE was cal-
culated on the basis of the percent of retrieved records that were VTE
(stratified by region and race). Follow-up time for the probable events
was determined from a random uniform distribution, the distribu-
tion most closely representing the temporal distribution of validated
VTE events in REGARDS (Tables II and III in the online-only Data
Supplement). Analyses were performed with SAS version 9.3 (SAS
Institute Inc, Cary, NC).

Results
The cohort characteristics by race are reported in Table 1 and
Table I in the online-only Data Supplement. Briefly, ARIC had the
lowest mean age (54 years), CHS had the highest mean age
(73 years), and REGARDS had an intermediate mean age (65
years). The prevalence of obesity was lowest in CHS (20%) and
highest in REGARDS (38%), with the highest prevalence of
diabetes mellitus in REGARDS. In all cohorts, blacks had a
higher body mass index than whites, had greater prevalences
of diabetes mellitus in REGARDS. In all cohorts, blacks had
the lowest mean age (54 years), CHS had the highest mean age
(73 years), and REGARDS had an intermediate mean age (65
years). The prevalence of obesity was lowest in CHS (20%)
and highest in REGARDS (38%), with the highest prevalence of
diabetes mellitus in REGARDS. In all cohorts, blacks had a
higher body mass index than whites, had greater prevalences
of diabetes mellitus and hypertension, were less likely to be
in the top 25th percentile of income, and were more likely to
have lower levels of education (Table 1).

VTE event ascertainment has previously been reported in
detail for ARIC and CHS.10 In REGARDS, 936 potential VTE
events were identified (Figure). Among the 785 events for
which records were requested (after consolidation of duplicate
events), 624 records (79.5%) were successfully retrieved, and
471 (75.5%) were reviewed by physicians. Among blacks, 231
of 321 records (72%) were reviewed, and among whites, 393
of 464 records (85%) were reviewed. Among the 471 records
reviewed, there were 379 VTE events in 332 individuals; 268
were first-time VTE events in those not reporting VTE at
baseline (123 in blacks). Retrieval rates by race and region in
REGARDS and the percent of retrieved records that became
cases are presented in Tables II and III in the online-only Data
Supplement. Blacks had lower record retrieval than whites,
although there were no differences by region. In CHS, there
were 172 validated incident VTE events (37 in blacks), and in
ARIC, there were 476 validated incident VTE events (163 in
blacks; Table 2). In all cohorts, blacks had a higher percentage
of VTEs that were DVTs than whites but a similar percentage
of VTEs that were PEs, except in ARIC in which blacks had a
lower percent of PEs than whites (26% versus 41%). The
percent of VTEs that were provoked was similar in blacks and
whites in each cohort (Table 2).

Table 3 presents VTE rates for ARIC, CHS, and REGARDS
in blacks and whites normalizing to the mean age and sex
distribution of each cohort. Overall, blacks had a higher
incidence of VTE than whites in ARIC, in CHS, and in the Southeast in REGARDS but not in REGARDS outside the Southeast. These differences were statistically significant in CHS and ARIC but not in REGARDS. These patterns were similar for DVT. In contrast, PE incidence was not higher in blacks than whites in ARIC, CHS, or REGARDS. The rate of provoked VTE was higher in blacks than whites in CHS but not in ARIC or REGARDS.

Table 4 presents a series of sequentially adjusted Cox proportional hazard models demonstrating the association of black versus white race with incident VTE in each of the cohorts. In a model adjusted for age and sex, blacks had a greater risk of VTE than whites in ARIC and CHS. In REGARDS, blacks had a nonsignificantly increased hazard of VTE compared with whites in the Southeast (hazard ratio [HR], 1.33; 95% confidence interval [CI], 0.94–1.87) and a nonsignificantly decreased hazard of VTE than whites in the rest of the nation (HR, 0.78; 95% CI, 0.54–1.12; P for interaction=0.03). Adjusting for body mass index reduced the HR for race by >10% in ARIC, in CHS, and in participants living in the Southeast in REGARDS. Adjusting for body mass index, hypertension, diabetes mellitus, kidney disease, and baseline warfarin use decreased the association of race with VTE in ARIC (HR from 1.61 to 1.25) but had little effect on the HR in CHS (HR from 1.82 to 1.72) or REGARDS in the Southeast (HR from 1.33–1.34). Adjustment for socioeconomic factors had little effect on the association of race with VTE in ARIC but decreased the black versus white HR in CHS and in participants in the Southeast in REGARDS. In a final model including all risk factors, the association of race with VTE was

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**Table 2. Number and Distribution of Incident Venous Thrombosis Events by Cohort**

<table>
<thead>
<tr>
<th></th>
<th>ARIC</th>
<th>CHS</th>
<th>REGARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td>VTE, n</td>
<td>476</td>
<td>163</td>
<td>313</td>
</tr>
<tr>
<td>DVT, n (%)*</td>
<td>373 (78)</td>
<td>140 (88)</td>
<td>233 (74)</td>
</tr>
<tr>
<td>PE, n (%)†</td>
<td>171 (36)</td>
<td>43 (26)</td>
<td>128 (41)</td>
</tr>
<tr>
<td>Unprovoked VTE, n (%)</td>
<td>174 (37)</td>
<td>58 (36)</td>
<td>116 (37)</td>
</tr>
<tr>
<td>Provoked VTE, n (%)</td>
<td>302 (63)</td>
<td>105 (64)</td>
<td>197 (63)</td>
</tr>
</tbody>
</table>

ARIC indicates Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; DVT, deep venous thrombosis; PE, pulmonary embolism; REGARDS, Reasons for Geographical and Racial Differences in Stroke; and VTE, venous thrombosis.

* DVT=DVT±PE.
† PE=PE±DVT.
no longer significant in ARIC (HR, 1.21; 95% CI, 0.96–1.54) and was little changed in CHS (HR, 1.81; 95% CI, 1.20–2.73) and REGARDS (outside the Southeast: HR, 0.68; 95% CI, 0.46–1.02; in the Southeast: HR, 1.34; 95% CI, 0.93–1.94). In REGARDS, a significant regional difference in the association of race with VTE was found in all models (all $P$ for interactions $\leq 0.03$). Among blacks in REGARDS, the HR of VTE for living in the Southeast versus elsewhere was 1.63 (95% CI, 1.08–2.48), but among whites, living in the Southeast was not associated with increased risk (Table 5).

Tables 5 and 6 break down the results by VTE type (PE or DVT, unprovoked or provoked). In fully adjusted models, blacks had a higher risk of DVT than whites in ARIC, in CHS, and in the Southeast in REGARDS but not outside the Southeast in REGARDS. After full multivariable adjustment, there was little evidence of an increased risk of PE for blacks versus whites in ARIC, CHS, or REGARDS. There was no association of black race with provoked or unprovoked VTE in ARIC, but the HR for blacks versus whites remained elevated in CHS for both unprovoked and provoked.
VTE. In REGARDS, again, there was evidence of a regional interaction, with blacks in the Southeast having a higher rate of both DVT and PE than whites in the Southeast but not outside the Southeast.

Sensitivity analyses excluding those on baseline warfarin or including only VTE events ascertained by the computer-assisted telephone interview in REGARDS did not materially affect the conclusions (data not shown). Table IV in the online-only Data Supplement presents one scenario of the potential effect that differential record retrieval by race or region may have had in REGARDS, which assumes that had all records been obtained, the percent validated as VTEs would have been the same for the percent actually validated among received records. From this analysis, we estimated that we missed ≈70 VTE events (44 in blacks) because of incomplete record retrieval. The region and race differences in REGARDS were preserved in a sensitivity analysis accounting for these potentially missing events, and the nearly significant inverse association of black race (versus white) with VTE outside the Southeast disappeared.

Discussion

In 3 large US cohort studies including 51,149 individuals and 916 VTE events, we found at most a modest association of race with risk of VTE, particularly once comorbid conditions and socioeconomic status were accounted for. The studied cohorts were recruited with different methods spanning 20 years (from 1987 through 2007) and revealed different results for the association of race with VTE. In ARIC, blacks had a higher risk of VTE that was attenuated by VTE risk factors; in CHS, blacks had a higher risk of VTE that was not attenuated by risk factors; and in REGARDS, there was a significant region-by-race interaction whereby blacks in the Southeast were at significantly higher risk of VTE relative to blacks outside the Southeast, whereas in the rest of the country, there was no evidence that risk of VTE varied by race. Furthermore, no study demonstrated a racial association with PE alone.

Race in the United States is as much a social construct as a marker of continental origin, with self-identified blacks having on average 20% European ancestry but with great variation both within populations and between different locations in the United States.17 There are few studies in the United States in which the risk of VTE can be directly compared between blacks and whites. In hospital discharge registries from California7,18 and the National Hospital Discharge Survey,8 blacks had a higher risk of VTE compared with whites (relative risk, 1.37 and 1.18, respectively). These analyses, although powerful, have limitations, including potential misclassification of events and race, with reliance on discharge codes for events and on census data to classify the racial characteristics of the population. International Classification of Diseases, Ninth Revision coding of VTE is challenging; in 1 report, >20% of hospitalized International Classification of Diseases, Ninth Revision–reported VTEs were miscoded.19 The assumption with administrative databases is that miscoding is consistent by race and region, which may not be the case.20 Blacks also have a 50% greater risk of death resulting from PE compared with whites in the United States, but whether this results from an increased rate of VTE or a higher case fatality rate is not known.21–24 Apart from an earlier report from the LITE,9 no other national cohorts with physician-validated VTE events have reported racial differences in VTE in the United States.

Further discussion of the differences between ARIC, CHS, and REGARDS is warranted. Our original intent was to perform a pooled analysis; however, these cohorts had different recruitment ages, geographic scopes, and enrollment years, decreasing the scientific appropriateness of a pooled analysis. Differences in the race association between CHS and ARIC could be due to age differences; however, REGARDS encompassed the entire age spectrum of ARIC and CHS. In terms of

### Table 5. Hazard Ratios (95% Confidence Intervals) of VTE for Black Versus White Race*

<table>
<thead>
<tr>
<th></th>
<th>ARIC</th>
<th>CHS</th>
<th>Rest of Country</th>
<th>Southeast</th>
<th>Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>1.39</td>
<td>(1.07–1.81)</td>
<td>2.10 (1.37–3.23)</td>
<td>0.84 (0.55–1.29)</td>
<td>1.44 (0.97–2.14)</td>
</tr>
<tr>
<td>PE</td>
<td>0.88</td>
<td>(0.57–1.35)</td>
<td>1.52 (0.69–3.35)</td>
<td>0.82 (0.49–1.38)</td>
<td>1.16 (0.70–1.93)</td>
</tr>
<tr>
<td>Unprovoked VTE</td>
<td>1.24</td>
<td>(0.84–1.84)</td>
<td>1.86 (0.92–3.77)</td>
<td>0.79 (0.47–1.34)</td>
<td>1.44 (0.89–2.34)</td>
</tr>
<tr>
<td>Provoked VTE</td>
<td>1.20</td>
<td>(0.89–1.62)</td>
<td>1.79 (1.08–2.97)</td>
<td>0.72 (0.44–1.19)</td>
<td>1.08 (0.67–1.73)</td>
</tr>
</tbody>
</table>

ARIC indicates Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; DVT, deep venous thrombosis; PE, pulmonary embolism; REGARDS, Reasons for Geographical and Racial Differences in Stroke; and VTE, venous thrombosis.

*aAdjusted for age, sex, race, body mass index, hypertension, diabetes mellitus, kidney disease, baseline warfarin use, education, income (modeled as dummy variables as outlined in Table 1), and a region-by-living in the Southeast interaction term.

*bP for interaction between race and region (REGARDS).

### Table 6. Hazard Ratios (95% Confidence Intervals) of VTE for Living in the Southeast Versus Elsewhere in REGARDS in Blacks and Whites*

<table>
<thead>
<tr>
<th></th>
<th>Blacks</th>
<th>Whites</th>
<th>P for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td>1.63</td>
<td>(1.08–2.48)</td>
<td>0.83 (0.61–1.14)</td>
</tr>
<tr>
<td>DVT</td>
<td>1.71</td>
<td>(1.05–2.78)</td>
<td>0.88 (0.60–1.30)</td>
</tr>
<tr>
<td>PE</td>
<td>1.41</td>
<td>(0.77–2.58)</td>
<td>0.83 (0.52–1.34)</td>
</tr>
<tr>
<td>Unprovoked VTE</td>
<td>1.81</td>
<td>(1.00–3.29)</td>
<td>0.63 (0.40–1.01)</td>
</tr>
<tr>
<td>Provoked VTE</td>
<td>1.49</td>
<td>(0.84–2.66)</td>
<td>1.06 (0.68–1.64)</td>
</tr>
</tbody>
</table>

DVT indicates deep venous thrombosis; PE, pulmonary embolism; REGARDS, Reasons for Geographical and Racial Differences in Stroke; and VTE, venous thrombosis.

*aAdjusted for age, sex, race, living in the southeast, body mass index, hypertension, diabetes mellitus, kidney disease, baseline warfarin use, education, income (modeled as dummy variables as outlined in Table 1), and a race–by–living in the Southeast interaction term.
geographic scope, REGARDS is the only study to include a substantial number of blacks outside the Southeast. The majority of blacks in ARIC resided in Jackson, MS, and Forsyth County, North Carolina; the majority of blacks in CHS resided in Forsyth County, North Carolina, and to a lesser extent in Pittsburgh, PA. No ARIC whites came from Jackson. In ARIC and CHS, there were only 2 and 21 VTE events, respectively, in blacks outside the Southeast, precluding an analysis by region in these cohorts. Although individual-level national data on VTE in the United States do not exist, the effect of race seems modest at best in an analysis from the National Hospital Discharge Survey, with blacks having an 18% higher risk than whites. Further data from the Centers for Disease Control show that blacks were at greater risk of PE death relative to whites in the Northeast, Midwest, and South, but not the West (see Table V in the online-only Data Supplement). Reasons for these differences are unclear but may be due to true biological differences and differences in the prevalence of comorbidities that may lead to VTE, result in complications among VTE patients that predispose to death, or may relate to access to medical care, quality of medical care, and quality of medical reporting. Further confounding the observations in the current studies, differences in VTE event rates among the studies may be due to secular trends in the evaluation of suspected VTE. The diagnosis of VTE has shifted from relying on ventilation-perfusion scans for PE to computed tomography angiography and from inpatient to outpatient treatment of DVT. If these changes in medical care differed by age, race, or region, this could have contributed to the different patterns observed here. Possible limitations of our study include self-identification of race, lack of generalizability of the cohorts to the population of the United States, although the national reach of REGARDS mitigates this somewhat, and issues of underspecification or biased ascertainment for VTE. In each cohort, race was self-defined and thus represents both a social and a genetic construct. Other phenotypes such as coronary artery calcium vary by genetic origin even within racial groups, and by using self-identified race, we may have missed these associations. LITE did not capture out-of-hospital VTE deaths (there are likely few) and outpatient treatment of VTE. During the time period of LITE, the proportion of DVT events treated in the outpatient setting was small because evidence for the safety of this practice did not emerge until the late 1990s. In REGARDS, there were no discrete field centers or local hospitals to search for discharges, and case ascertainment relied predominantly on participant report. Therefore, cases were missed, but VTE events treated in the outpatient setting were sought. Despite efforts, record retrieval was not 100%, and fewer records of blacks than whites were obtained. However, although record retrieval differed by race in REGARDS, it did not differ by region. When we accounted for potential cases resulting from missing records, blacks in the Southeast remained at greater risk than whites, whereas for the rest of the country, there was no evidence of a relation (Tables II–IV in the online-only Data Supplement). Furthermore, as shown in the Centers for Disease Control data, there are clear regional and racial differences in PE mortality in the United States, demonstrating the need to define geography and race when studying racial differences in VTE (Table V in the online-only Data Supplement).

Conclusions
We present the most detailed examination yet of the association of race with VTE in the United States. In contrast to prior studies, we were able to study the association of race with VTE using validated VTE events and individual-level data over a long time period. The differences seen by cohort may represent secular trends in the diagnosis or incidence of VTE, may reflect an unrecognized race-by-region interaction in which blacks in the Southeast have higher rates of VTE than whites and blacks outside the Southeast, or may be an artifact of bias. Whether differences in VTE by race are compared on a regional, national, or global scale will greatly influence associations of race on VTE. Study limitations necessitate caution in the interpretation of the results, but these results highlight the need for further studies of VTE in the United States in diverse geographic and racial populations.

Acknowledgments
We thank the staff and participants of ARIC, CHS, and REGARDS for their important contributions. The Executive Committee or Publications Committee of ARIC, CHS, and REGARDS reviewed and approved this manuscript for publication.

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Disclosures
None.

References
5. Lutesky PL, Cushman M, Steffen LM, Green D, Barr RG, Herrington D, Ouyang P, Folsum AR. Plasma hemostatic factors and endothelial...

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**CLINICAL PERSPECTIVE**

Venous thromboembolism (VTE) is the third-leading cause of vascular disease in the United States with >100,000 deaths annually. Prior studies have suggested that blacks have higher rates of VTE than whites in the United States, but these studies are limited in geographic or racial scope or rely on administrative databases. We studied the association of race (black versus white) with VTE in 3 large cohort studies to assess whether race and geography are associated with VTE in the United States. In the Cardiovascular Health Study (individuals ≥65 years of age recruited between 1989 and 1991 from 4 field centers), blacks had an increased risk of VTE not explained by conventional risk factors. In the Atherosclerosis Risk in Communities Study (individuals 45–64 years of age recruited between 1989 and 1991 from 4 field centers), blacks had a higher risk of VTE explained by conventional risk factors. In the Reasons for Geographic and Racial Differences in Stroke study (individuals ≥45 years of age recruited between 2003 and 2007 from throughout the contiguous United States), overall there was no association of race with VTE; however, blacks in the Southeast had a higher risk of VTE than blacks in the rest of the nation that was not explained by VTE risk factors, with no geographic differences apparent in whites. These data highlight that there are no unquestioned differences in VTE risk in blacks compared with whites and that geographic differences may be as important as race.
Racial and Regional Differences in Venous Thromboembolism in the United States in 3 Cohorts

Neil A. Zakai, Leslie A. McClure, Suzanne E. Judd, Monika M. Safford, Aaron R. Folsom, Pamela L. Lutsey and Mary Cushman

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http://circ.ahajournals.org/content/suppl/2014/02/07/CIRCULATIONAHA.113.006472.DC1

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Supplemental Material
### Supplemental Table 1: Characteristics of the Cardiovascular Health Study, the Atherosclerosis Risk in Communities study, and the REasons for Geographic and Racial Differences in Stroke Study

<table>
<thead>
<tr>
<th></th>
<th>Atherosclerosis Risk in Communities</th>
<th>Cardiovascular Health Study</th>
<th>REasons for Geographic and Racial Differences in Stroke</th>
</tr>
</thead>
</table>
| **Primary Objectives**         | 1. Investigate the etiology and natural history of atherosclerosis  
2. Investigate the etiology of clinical atherosclerotic diseases  
3. Measure variation in cardiovascular risk factors, medical care, and disease by race, sex, place, and time | 1. To quantify associations of conventional and hypothesized risk factors with CHD and stroke  
2. To assess the association of indicators of subclinical disease, identified by noninvasive measures such as carotid ultrasonography and echocardiography, with the incidence of CHD and stroke  
3. To quantify the association of conventional and hypothesized risk factors with subclinical disease  
4. To characterize the natural history of CHD and stroke, and identify factors associated with clinical course  
5. To describe the prevalence and distributions of risk factors, subclinical disease, and clinically diagnosed CHD and stroke | 1. To provide national data on stroke incidence and case fatality and assess geographic variations and racial differences in these measures  
2. To provide national data on prevalence and levels of stroke risk factors and assess geographic and racial variation in these prevalences  
3. To assess the degree to which geographic and racial variations in stroke incidence, case fatality and mortality are attributable to variations in risk factor prevalence  
4. To assess geographic and racial variations in the magnitude of the impact of prevalent stroke risk factors  
5. To assess the impact of migration on stroke incidence, case fatality and mortality  
6. To create a blood, urine and DNA repository as a resource for future studies |
<p>| <strong>VTE Follow-up Date</strong>         | 12/31/2005                         | 12/31/2001                    | 2/1/2010                                                  |
| <strong>Number of Participants</strong>     | 15,792                             | 5,888                        | 30,239                                                    |</p>
<table>
<thead>
<tr>
<th></th>
<th>4,266</th>
<th>924</th>
<th>12,128</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Blacks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruitment Age</td>
<td>45-64</td>
<td>≥65</td>
<td>≥45</td>
</tr>
<tr>
<td>Geographic Location</td>
<td>Forsyth County, North Carolina</td>
<td>Forsyth County, North Carolina</td>
<td>Contiguous 48 United States</td>
</tr>
<tr>
<td></td>
<td>Washington County, Maryland</td>
<td>Washington County, Maryland</td>
<td>Half of individuals from the following states:</td>
</tr>
<tr>
<td></td>
<td>Suburban Minneapolis, Minnesota</td>
<td>Sacramento County, California</td>
<td>Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee.</td>
</tr>
<tr>
<td></td>
<td>Jackson, Mississippi</td>
<td>Pittsburgh, Pennsylvania</td>
<td></td>
</tr>
</tbody>
</table>

**Exclusion Criteria**

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>4,266</th>
<th>924</th>
<th>12,128</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Cancer</td>
<td>Not Excluded</td>
<td>Excluded</td>
<td>Excluded</td>
</tr>
<tr>
<td>Resident / waiting list for nursing home or hospice</td>
<td>Not Excluded</td>
<td>Excluded</td>
<td>Excluded</td>
</tr>
<tr>
<td>Wheelchair bound at Baseline</td>
<td>Not Excluded</td>
<td>Excluded</td>
<td>Not Excluded</td>
</tr>
<tr>
<td>Cognitive Impairment</td>
<td>Not Excluded</td>
<td>Not Excluded</td>
<td>Excluded</td>
</tr>
<tr>
<td>Unable to get to field center</td>
<td>Excluded</td>
<td>Excluded</td>
<td>NA</td>
</tr>
</tbody>
</table>
Supplemental Table 2: Record Retrieval by Race and Region in REGARDS in those without Baseline VTE

<table>
<thead>
<tr>
<th>Race</th>
<th>Outside of the Southeast</th>
<th>Southeast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td>85% (106/124)</td>
<td>88% (175/198)</td>
</tr>
<tr>
<td>Blacks</td>
<td>69% (72/105)</td>
<td>72% (88/123)</td>
</tr>
</tbody>
</table>
Supplemental Table 3: Percent of Retrieved Records Resulting in a Confirmed VTE in those without Baseline VTE in REGARDS

<table>
<thead>
<tr>
<th></th>
<th>Outside of the Southeast</th>
<th>Southeast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td>74% (78/106)</td>
<td>50% (87/175)</td>
</tr>
<tr>
<td>Blacks</td>
<td>65% (47/72)</td>
<td>65% (56/88)</td>
</tr>
</tbody>
</table>
**Supplemental Table 4: Association of Race or Region with VTE in REGARDS adjusting for record non-retrieval**

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blacks (n = 146)</td>
</tr>
<tr>
<td>Southeast vs. Rest of Country</td>
<td>1.48 (1.10, 1.99)</td>
</tr>
<tr>
<td>Blacks vs. Whites</td>
<td>1.33 (0.98, 1.81)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race, body mass index, hypertension, diabetes, kidney disease, baseline warfarin, education, income and race or living in the southeast as appropriate. The probability of being a case was calculated by race and region in the 106 potential events where no records were obtained. These potential “cases” were weighted by the probability of being a case and the timing of the VTE was randomly assigned using a uniform distribution for the duration of follow-up.
**Supplemental Table 5: Age-Adjusted Rate of Pulmonary Embolism Mortality per 10,000 population in Blacks and Whites in the United States**

<table>
<thead>
<tr>
<th>Region</th>
<th>Deaths Black</th>
<th>Deaths White</th>
<th>Rate Black (95% CI)</th>
<th>Rate White (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>1,124</td>
<td>7,635</td>
<td>0.8 (0.7, 0.8)</td>
<td>0.5 (0.5, 0.5)</td>
</tr>
<tr>
<td>Midwest</td>
<td>1,761</td>
<td>12,089</td>
<td>1.2 (1.2, 1.3)</td>
<td>0.7 (0.6, 0.7)</td>
</tr>
<tr>
<td>South</td>
<td>5,235</td>
<td>17,491</td>
<td>1.2 (1.2, 1.2)</td>
<td>0.7 (0.7, 0.7)</td>
</tr>
<tr>
<td>West</td>
<td>401</td>
<td>6,281</td>
<td>0.5 (0.4, 0.5)</td>
<td>0.5 (0.5, 0.5)</td>
</tr>
<tr>
<td>Total</td>
<td>8,521</td>
<td>43,496</td>
<td>1.1 (1.1, 1.1)</td>
<td>0.6 (0.6, 0.6)</td>
</tr>
</tbody>
</table>

*Including black and white individuals 45 years and over and excluding residents of Hawaii and Alaska. Standardized to population in 2000.*