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Incidence of Venous Thromboembolism in a Racially Diverse Population of Oklahoma County, Oklahoma

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Abstract

Background Contemporary incidence data for venous thromboembolism (VTE) from racially diverse populations are limited. The racial distribution of Oklahoma County closely mirrors that of the United States.

Objective To evaluate VTE incidence and mortality, including demographic and racial subgroups.

Design Population-based prospective study.

Setting We conducted VTE surveillance at all relevant tertiary care facilities and outpatient clinics in Oklahoma County, Oklahoma during 2012 to 2014, using both active and passive methods. Active surveillance involved reviewing all imaging reports used to diagnose VTE. Passive surveillance entailed identifying VTE events from hospital discharge data and death certificate records.

Measurements We used Poisson regression to calculate crude, age-stratified, and age-adjusted incidence and mortality rates per 1,000 population per year and 95% confidence intervals (CIs).

Results The incidence rate of all VTE was 3.02 (2.92–3.12) for those age $\geq$18 years and 0.05 (0.04–0.08) for those $<$18 years. The age-adjusted incidence rates of all VTE, deep vein thrombosis, and pulmonary embolism were 2.47 (95% CI: 2.39–2.55), 1.47 (1.41–1.54), and 0.99 (0.93–1.04), respectively. The age-adjusted VTE incidence and the 30-day mortality rates, respectively, were 0.63 and 0.121 for Asians/Pacific Islanders, 3.25 and 0.355 for blacks, 0.67 and 0.111 for Hispanics, 1.25 and 0.195 for Native Americans, and 2.71 and 0.396 for whites.

Conclusion The age-adjusted VTE incidence and mortality rates vary substantially by race. The incidence of three per 1,000 adults per year indicates an important disease burden, and is informative of the burden in the U.S. population.

Keywords
- venous thromboembolism
- pulmonary embolism
- deep vein thrombosis
- epidemiological studies
- incidence rates

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Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism, is a potentially fatal condition. Sudden death is the first clinical presentation in many patients, and inpatient mortality rates for pulmonary embolism range from 8 to 65%, depending on the severity of clinical presentation.[1] The Agency for Healthcare Research and Quality (AHRQ) established the prevention of hospital-associated VTE as a priority as it is among the most common preventable causes of hospital-related death.[2,3] However, contemporary data on the incidence of VTE in the United States are lacking.

Current population-based incidence data on VTE are needed because the nature and distribution of risk factors for VTE may change over time, and the available data from population-based studies are outdated and based on studies among predominantly white populations which do not reflect the racial diversity of the United States.[4,5]

We performed a prospective population-based study to assess the incidence of VTE in the racially diverse population of Oklahoma County, Oklahoma, United States. We also assessed VTE recurrence, mortality, and the demographic and risk factor profile of patients with VTE. Because the distribution of race, sex, and age in Oklahoma County are very similar to the overall United States population, our results are likely more reflective of VTE in the U.S. population than previous studies.

Methods

A detailed description of our surveillance system has been published.[6] In collaboration with the Centers for Disease Control and Prevention (CDC) and the Oklahoma State Department of Health, we conducted VTE surveillance in accordance with federal statutes[7] and Title 310 Oklahoma State Department of Health, Chapter 515–1-6 for public health disease surveillance, and therefore institutional review board approval was not required. The Oklahoma Commissioner of Health authorized VTE as a reportable condition during the surveillance period and delegated disease surveillance responsibilities to the authors at the University of Oklahoma Health Sciences Center. Surveillance was conducted from April 1, 2012 to March 31, 2014 using both active and passive methods. Active surveillance consisted of regularly visiting all tertiary care facilities and relevant outpatient clinics in Oklahoma County to review the text from all imaging studies from chest computed tomography (CT) or magnetic resonance imaging (MRI), lung perfusion scans, and compression ultrasonography (CUS) of the extremities to identify patients with VTE. We identified the relevant imaging studies at each facility by using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) procedure codes, current procedural terminology (CPT) codes, and free text, depending on the facilities' medical record system. Passive surveillance comprised accessing health records from the hospital discharge dataset and death certificate records from the Oklahoma State Department of Health for 2010 through 2015. The case definition and list of ICD-9 CM diagnostic and procedure codes, ICD-10 codes, and CPT codes used in the case definition are included in the ►**Supplementary Appendix A** (available in the online version). VTE events that met the case definition criteria for definite, probable, and possible cases were included in the analysis.

VTE reports from each data source were linked by name, birthdate, social security number, and ZIP code, which enabled the identification of unique patients meeting the case definition. Population denominator data for 2013 (surveillance midpoint) were obtained from the U.S. Census Bureau[8] and the Surveillance, Epidemiology, and End Results (SEER) Program.[9] Incident VTE events were defined as the first VTE event detected during the 2-year surveillance period. A recurrent event was defined as a new VTE occurring $\geq$72 hours after the incident VTE but detected within the surveillance period. All-cause case fatality rates were calculated at 30 days, 90 days, and 180 days after the diagnosis date of the incident VTE event.

We categorized VTE events as persistent provoked, transient provoked, or unprovoked according to the recommendations of the International Society on Thrombosis and Haemostasis (ISTH).[10] Persistent provoking factors included active cancer (either metastatic or diagnosed within 6 months prior to VTE diagnosis), inflammatory bowel disease, antiphospholipid syndrome, and systemic lupus erythematosus. Transient provoking factors included a history of hospitalization (past 2 months); immobilization, surgery, trauma, central venous catheterization, congestive heart failure, myocardial infarction, or stroke, all within the past 3 months; pregnancy (past 2 months, or past 3 months if cesarean delivery); and select medications (past 2 months). The medications included estrogen- and progesterone-containing drugs, raloxifene, tamoxifen, erythropoietin, romiplostim, oprelvekin, eltrombopag, thalidomide, and lenalidomide. Patients held in observation at a tertiary care facility but not admitted were categorized as treated in an outpatient setting.

Statistical Analysis

Crude incidence rates and all-cause case fatality rates and corresponding 95% confidence intervals (CIs) were calculated using Poisson regression in SAS 9.4 (Cary, North Carolina, United States). Pulmonary embolism cases were categorized as with or without deep vein thrombosis. Deep vein thrombosis cases were categorized as either (1) proximal deep vein thrombosis (involving the popliteal, femoral, internal/external iliac veins, or inferior vena cava, with or without associated calf vein thrombosis), (2) isolated calf deep vein thrombosis (confined to the posterior or anterior tibial, peroneal, gastrocnemius, or soleal veins), or (3) upper extremity deep vein thrombosis (involving the brachial, axillary, subclavian, innominate, jugular veins, or superior vena cava, without associated thrombosis of the leg). For patients identified from death certificates, age at death was imputed for age at time of VTE event and those with ICD-10 codes I26 and I80 were classified as pulmonary embolism and those with I73, I81, and I82 were classified as VTE only.

Age-stratified incidence rates and mortality rates were calculated for persons $<$18 years and $\geq$18 years, and then further divided into 18–39, 40–49, 50–59, 60–69, 70–79, and

≥80 years. Age-adjusted incidence rates and mortality rates were calculated overall and stratified by sex and race by using PROC STDRATE in SAS 9.4 (Cary, North Carolina), using the direct standardization method with the 2013 U.S. population as the reference using the age group 0 to 1 year and subsequent 5 year age groups until age 85+ years. All incidence rates and mortality rates are given per 1,000 population per year.

Race was categorized by non-Hispanic Asian/Pacific Islander, non-Hispanic black, Hispanic, non-Hispanic Native American, and non-Hispanic white. Persons of multiple and unknown race were excluded from the race-stratified analyses.

Results

The age and race distribution of Oklahoma County is provided in ►**Table 1**. We screened 56,967 imaging reports from 14 inpatient facilities and seven outpatient facilities. We identified 2,596 VTE events (2,385 inpatient events and 211 outpatient events) from active surveillance and 1,219 events from passive surveillance (1,052 events from hospital discharge data and 167 from mortality records), for a total of 3,815 VTE events among 3,422 unique patients. Of the 3,815 VTE events, 2,347 (61.5%) presented as deep vein thrombosis only, 844 (22.1%) as pulmonary embolism only, 457 (12.0%) as pulmonary embolism with associated deep vein thrombosis, and 167 (4.4%) were identified from mortality records. Of the 3,422 unique patients, 2,934 (85.7%) met the criteria for definite VTE, 485 (14.2%) were categorized as probable VTE, and three (0.01%) were possible VTE.

Excluding the 167 patients identified via mortality records, 1,125 (34.6%) of the remaining 3,255 unique patients were diagnosed ≥1 day after being admitted to the hospital, 1,346 (41.3%) were diagnosed before or at the time of admission to the hospital, and 784 (24.1%) patients were not admitted to the hospital.

Incidence of VTE

The annual crude incidence per 1,000 population of all VTE identified during the surveillance period was 2.26 (95% CI: 2.19–2.34); incidence rates were 3.02 (2.92–3.12) for those age ≥18 years and 0.05 (0.04–0.08) for those <18 years (►**Table 2**). The age-adjusted incidence rate of all VTE was 2.47 (95% CI: 2.39–2.55). The incidence rate was highest among non-Hispanic blacks (3.25, 95% CI: 3.02–3.49) and lowest among Asians/Pacific Islanders (0.63, 95% CI: 0.43–0.91) and Hispanics (0.67, 95% CI: 0.54–0.82).

Of the 3,422 unique patients, 658 had a history of VTE prior to initiating surveillance, leaving 2,764 (80.8%) patients with first-lifetime VTE during the surveillance period. The annual crude incidence rate of first-lifetime VTE among all ages was 1.83 (95% CI: 1.76–1.90). The incidence among those age ≥18 years was 2.44 (95% CI: 2.35–2.53) and among those age ≥65 years was 8.62 (95% CI: 8.21–9.05). Among

Table 1 Distribution of age and race in the United States and Oklahoma County: 2013 American Community Survey

Demographic characteristic	United States		Oklahoma County	
	N	%	*N*	%
Total	316,128,839	100.0	755,639	100.0
Age (y)				
<18	73,585,872	23.3	192,960	25.5
18–39	93,906,010	29.7	241,263	31.9
40–49	42,057,226	13.3	90,239	11.9
50–59	43,753,656	13.8	97,987	13.0
60–69	32,730,718	10.4	70,674	9.4
70–79	18,285,930	5.8	37,633	5.0
≥80	11,809,427	3.7	24,883	3.3
Race/ethnicity				
Non-Hispanic white	230,592,579	72.9	501,213	66.3
Non-Hispanic black	39,167,010	12.4	109,245	14.5
Native American	2,540,309	0.8	22,738	3.0
Asian	15,231,962	4.8	22,536	3.0
Pacific Islander	526,347	0.2	500	0.1
Other race	14,746,054	4.7	27,886	3.7
Two or more races	8,732,333	2.8	48,000	6.4
Missing	4,592,545	1.5	23,521	3.1
Hispanic[a]	54,203,686	17.1	121,309	16.0

[a]Not a mutually exclusive category with the race categories.

Table 2 Annual crude, age-adjusted, and age-, sex-, and race-stratified incidence rate (per 1,000 population) estimates of venous thromboembolism (VTE), stratified by disease presentation, detected in Oklahoma County, Oklahoma, April 1, 2012–March 31, 2014

Measure	VTE[a]		DVT only		PE ± DVT	
	IR	95% CI	IR	95% CI	IR	95% CI
Crude overall	2.26	(2.19–2.34)	1.35	(1.29–1.41)	0.91	(0.87–0.96)
Age-adjusted[b]	2.47	(2.39–2.55)	1.47	(1.41–1.54)	0.99	(0.93–1.04)
Age-stratified						
< 18	0.05	(0.04–0.08)	0.04	(0.02–0.06)	0.02	(0.01–0.03)
≥ 18	3.02	(2.92–3.12)	1.80	(1.73–1.88)	1.21	(1.15–1.28)
18–39	0.81	(0.74–0.90)	0.47	(0.42–0.54)	0.34	(0.29–0.40)
40–49	2.16	(1.96–2.39)	1.32	(1.16–1.50)	0.84	(0.71–0.98)
50–59	3.35	(3.11–3.62)	2.10	(1.91–2.31)	1.25	(1.11–1.42)
60–69	5.10	(4.74–5.48)	2.96	(2.69–3.26)	2.13	(1.90–2.38)
70–79	7.76	(7.15–8.41)	4.42	(3.97–4.93)	3.31	(2.92–3.75)
≥ 80	13.16	(12.19–14.20)	8.01	(7.27–8.84)	5.12	(4.53–5.79)
Sex[b]						
Male	2.45	(2.33–2.57)	1.52	(1.43–1.62)	0.92	(0.85–1.00)
Female	2.50	(2.38–2.61)	1.43	(1.35–1.53)	1.06	(0.98–1.14)
Race/ethnicity[b]						
Asian/Pacific Islander	0.63	(0.43–0.91)	0.41	(0.26–0.65)	0.22	(0.11–0.41)
Non-Hispanic black	3.25	(3.02–3.49)	1.97	(1.80–2.16)	1.27	(1.13–1.43)
Hispanic	0.67	(0.54–0.82)	0.39	(0.30–0.51)	0.27	(0.19–0.37)
Native American	1.25	(0.98–1.58)	0.69	(0.50–0.95)	0.56	(0.39–0.80)
Non-Hispanic white	2.71	(2.61–2.83)	1.59	(1.50–1.67)	1.12	(1.06–1.20)

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; IR, incidence rate; PE, pulmonary embolism; VTE, venous thromboembolism.
[a]VTE category includes 6 patients identified from mortality records that were not classified as PE or DVT. Data on race were unknown in 99 (2.9%) of the 3,422 unique patients and these patients were excluded from the race analysis.
[b]Adjusted using direct standardization to the U.S. 2013 population.

2,597 patients with documentation regarding VTE prophylaxis prior to their event, 257 (9.9%) received anticoagulant prophylaxis, 86 (3.3%) were using mechanical prophylaxis, 52 (2.0%) were using both, and 2,202 (84.8%) were not receiving prophylaxis at the time of their event.

Among the 2,477 incident events of deep vein thrombosis, 1,542 (62.3%) had proximal deep vein thromboses of the leg, 344 (13.9%) had isolated calf deep vein thromboses, 551 (22.2%) had upper extremity deep vein thromboses, and 40 (1.6%) had deep vein thromboses at an unknown location. Of the upper extremity thromboses, 243 (44.1%) had a central venous catheter within the past 6 months.

Recurrent VTE

We identified 324 (9.5%) patients who had ≥2 unique VTE events during our 2-year surveillance period, of which 272 patients had two events, 36 patients had three events, 15 patients had four events, and one patient had five events. The median time between the first and second episodes was 63 days (range: 3–677 days). The cumulative incidence of the first recurrent VTE according to provoking status is summarized in ►**Fig. 1**. At the time of the first recurrent VTE event, the proportions of patients receiving anticoagulant medication were 35/136 (25.7%), 14/51 (27.5%), and 25/137 (18.2%) for those with transient provoked, persistent provoked, and unprovoked VTE, respectively.

Mortality

The age-stratified and age-standardized all-cause mortality rates for sex and race are provided in ►**Table 3**. The all-cause case fatality rates stratified by age, sex, and race are provided in ►**Table 4**. For patients age ≥65 years, the 30-day all-cause case fatality rate was 19.6% (95% CI: 17.6–21.9%).

Risk Factors

The distribution of persistent and transient risk factors for incident VTE events, excluding the 167 patients identified via mortality records ($n = 3{,}255$), are summarized in ►**Table 5**. Hospitalization (36.2%), central venous catheterization (11.2%), immobilization (10.2%), and active cancer (9.6%) were the most common risk factors. There were 163 (5.0%) patients with an identified thrombophilic or prothrombotic condition (defined in ►**Supplementary Appendix A** [available in the online version]).

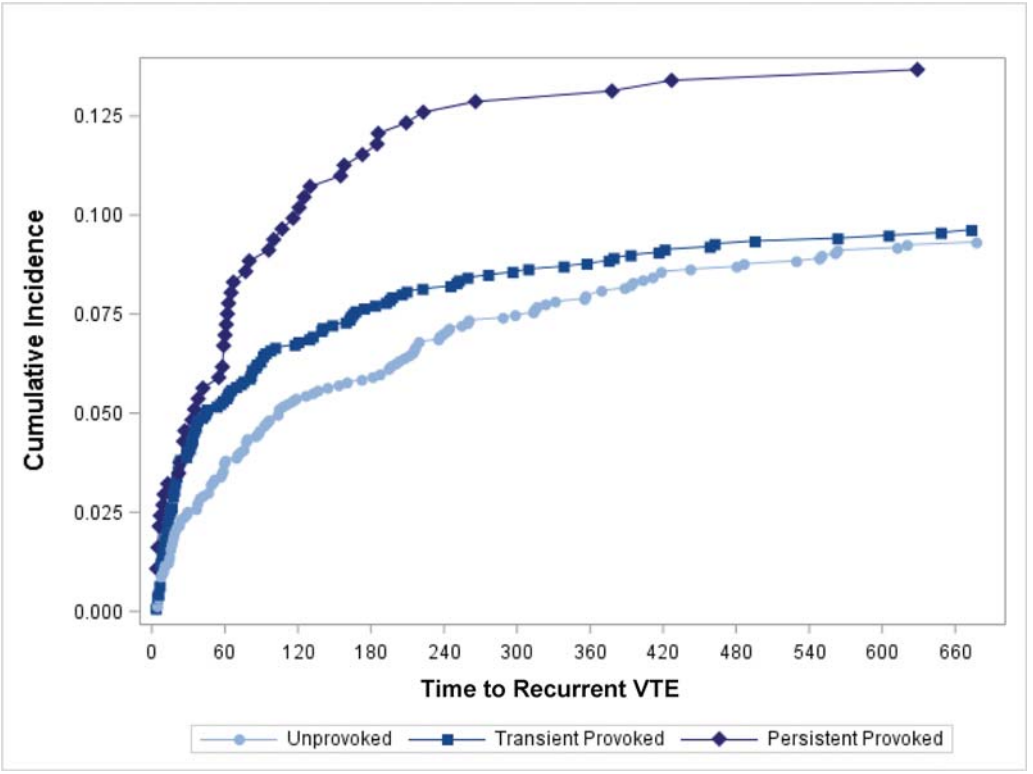

Fig. 1 Cumulative incidence of the first recurrent venous thromboembolic event ($n = 324$) detected during the surveillance period (April 1, 2012–March 31, 2014) among all incident events ($n = 3,251$[a]), stratified by provoked status[b]. [a]Among the 3,255 incident VTE events, four were excluded because of insufficient information to calculate time to recurrence between first and second observed episodes during the surveillance window. [b]Unprovoked: 137 (9.3%) recurrent events of 1,469; transient provoked: 136 (9.6%) recurrent events of 1,411; persistent provoked: 51 (13.7%) recurrent events of 371.

Discussion

Our results suggest several inferences. First, VTE is a common disorder, as shown by the age-adjusted annual incidences of 2.47 per 1,000 population and of 3.02 per 1,000 adults (►**Table 2**). Second, the population-based incidence and mortality rates vary substantially by race. Third, VTE is associated with an important disease burden, as shown by the incidence and significant morbidity from recurrent VTE events. Fourth, hospital-associated VTE continues to comprise a significant proportion (36.2%) of the total VTE burden. We expand on these aspects in turn below.

The annual age-adjusted incidence of 2.47 per 1,000 (95% CI: 2.39–2.55) found in our study is higher than estimates from most other published studies assessing VTE incidence or hospitalization rates.[4,5,11–18] Our study design is most comparable to the cohort data from Olmsted County, Minnesota, which during 1966 to 1990, calculated the incidence of VTE to be 1.17 per 1,000 (95% CI: 1.12–1.22),[4] and the Worcester VTE study in 1999, which calculated the incidence of VTE to be 1.04 per 1,000 (95% CI: 0.95–1.14).[5] A more recent study from the CDC using hospital discharge data during 2007 to 2009[11] reported an annual rate of hospitalized VTE events to be 2.39 per 1,000 (95% CI: 1.99–2.79) among those age ≥18 years. Incidence estimates from studies in the United States, Canada, and Western Europe using cohort data[5,12,14,16] and administrative data[13,15,17,18] range from 0.90 per 1,000 to 1.57 per 1,000. Factors which likely contributed to the higher age-adjusted incidence observed in our study include conducting active surveillance, including upper extremity deep vein thrombosis events, including potentially incidental pulmonary embolism events picked up by high-resolution multidetector row CT imaging,[19] and including patients presenting to outpatient clinics.

Applying our incidence rate for those age ≥18 years to the U.S. population at the time of surveillance (2013), we estimate 591,805 (95% CI: 569,976–613,634) first-episode events and at least 732,480 (95% CI: 708,226–759,160) any-episode VTE events occurring in adults in the United States each year. If these rates are applied to the most current U.S. population estimates (2018), the estimated annual number of VTE occurrences among adults nationally is 766,522.

The observed difference in VTE incidence by race is substantial among blacks, whites, and Native Americans. Asians/Pacific Islanders and Hispanics had the lowest rates, but not significantly different from each other. The relative rank order of VTE incidence by race is similar to estimates reported by White et al for unprovoked VTE from hospital discharge data.[13] To our knowledge, this is the first study to estimate the population incidence of VTE among Native Americans in the general population (►**Table 2**).

The age-standardized all-cause mortality rates after the incident VTE diagnosis were highest among black individuals and among white individuals, both of which were higher than those of the other races (►**Table 3**). The relative rank order of these mortality rates by race paralleled the order of

Table 3 Number of deaths (*n*) and age-standardized[a] all-cause mortality rates per 1,000 population during intervals of 30, 90, and 180 days after incident VTE diagnosis and cumulatively during the surveillance period April 1, 2012 through March 31, 2014

Demographic	0–30 d			31–90 d			91–180 d			>180 d			Cumulative		
	n	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95% CI	*N*	Rate	95% CI
Overall	460	0.339	0.309–0.371	198	0.146	0.127–0.168	149	0.110	0.94–0.129	279	0.207	0.184–0.232	1,086	0.801	0.755–0.850
Age															
<18	1	0.003	0.000–0.018	2	0.005	0.001–0.021	0	0	–	0	0	–	3	0.008	0.003–0.024
≥18	459	0.408	0.371–0.447	196	0.174	0.151–0.200	149	0.132	0.113–0.155	279	0.248	0.220–0.279	1,083	0.962	0.906–1.021
18–39	21	0.044	0.028–0.067	6	0.012	0.006–0.028	4	0.008	0.003–0.022	6	0.012	0.006–0.028	37	0.077	0.056–0.106
40–49	24	0.133	0.089–0.198	13	0.072	0.042–0.124	5	0.028	0.012–0.225	17	0.094	0.059–0.152	59	0.327	0.253–0.422
50–59	65	0.331	0.260–0.422	23	0.117	0.078–0.176	31	0.158	0.111–0.225	44	0.224	0.167–0.301	163	0.831	0.712–0.968
60–69	103	0.728	0.600–0.883	39	0.276	0.201–0.377	25	0.177	0.119–0.262	58	0.410	0.317–0.530	225	1.590	1.396–1.812
70–79	93	1.236	1.008–1.514	58	0.771	0.596–0.997	34	0.452	0.323–0.632	56	0.744	0.573–0.967	241	3.202	2.822–3.632
≥80	153	3.073	2.623–3.601	57	1.145	0.883–1.484	50	1.004	0.761–1.325	98	1.969	1.615–2.400	358	7.191	6.483–7.976
Sex															
Male	218	0.334	0.292–0.381	94	0.145	0.118–0.177	81	0.123	0.010–0.153	130	0.200	0.168–0.238	523	0.082	0.736–0.873
Female	242	0.345	0.304–0.391	104	0.148	0.122–0.180	68	0.098	0.077–0.125	149	0.214	0.182–0.251	563	0.805	0.741–0.874
Race/ethnicity															
Asian/Pacific Islander	5	0.121	0.049–0.296	4	0.080	0.030–0.213	0	0	–	2	0.048	0.012–0.194	11	0.248	0.136–0.453
Non-Hispanic black	77	0.355	0.284–0.445	47	0.215	0.161–0.286	31	0.145	0.102–0.206	50	0.224	0.169–0.295	205	0.938	0.818–1.077
Hispanic	15	0.111	0.065–0.190	4	0.023	0.008–0.065	4	0.034	0.012–0.096	8	0.061	0.029–0.125	31	0.229	0.158–0.332
Native American	10	0.195	0.105–0.363	4	0.072	0.027–0.194	2	0.036	0.009–0.145	7	0.133	0.063–0.279	23	0.437	0.290–0.658
Non-Hispanic white	346	0.396	0.357–0.441	135	0.156	0.132–0.185	107	0.123	0.102–0.149	203	0.235	0.204–0.269	791	0.910	0.849–0.976

Abbreviations: CI, Confidence interval; VTE, venous thromboembolism.
[a]Overall, sex-stratified, and race/ethnicity-stratified results are standardized to the 2013 U.S. population.

Table 4 Number of deaths (*n*) and all-cause case fatality (%) during intervals of 30, 90, and 180 days after incident VTE diagnosis, and cumulatively during the surveillance period April 1, 2012 through March 31, 2014

Demographic	0–30 d			31–90 d			91–180 d			>180 d			Cumulative		
	N	%	95% CI	*n*	%	95% CI	*N*	%	95% CI	*n*	%	95% CI	*N*	%	95% CI
Overall	460	13.4	(12.3–14.7)	198	6.7	(5.8–7.7)	149	5.4	(4.6–6.3)	279	10.7	(9.5–12.0)	1,086	31.7	(29.9–33.7)
Age															
<18	1	4.8	(0.7–33.8)	2	10.0	(2.5–40.0)	0	0.0	(0.0–0.0)	0	0.0	(0.0–0.0)	3	14.3	(4.6–44.3)
≥18	459	13.5	(12.3–14.8)	196	6.7	(5.8–7.7)	149	5.4	(4.6–6.4)	279	10.7	(9.6–12.1)	1,083	31.8	(30.0–33.8)
18–39	21	5.3	(3.5–8.2)	6	1.6	(0.7–3.6)	4	1.1	(0.4–2.9)	6	1.7	(0.74–3.7)	37	9.4	(6.8–13.0)
40–49	24	6.2	(4.1–9.2)	13	3.6	(2.1–6.1)	5	1.4	(0.6–3.4)	17	4.9	(3.0–7.9)	59	15.1	(11.7–19.5)
50–59	65	9.9	(7.7–12.6)	23	3.9	(2.6–5.8)	31	5.4	(3.8–7.7)	44	8.2	(6.1–11.0)	163	24.8	(21.2–28.9)
60–69	103	14.3	(11.8–17.3)	39	6.3	(4.6–8.6)	25	4.3	(2.9–6.4)	58	10.5	(8.1–13.5)	225	31.2	(27.4–35.6)
70–79	93	15.9	(13.0–19.5)	58	11.8	(9.1–15.3)	34	7.9	(5.6–11.0)	56	14.0	(10.8–18.2)	241	41.3	(36.4–46.8)
≥80	153	23.4	(20.0–27.4)	57	11.4	(8.8–14.7)	50	11.2	(8.5–14.8)	98	24.8	(20.4–30.2)	358	54.7	(49.3–60.6)
Sex															
Male	218	13.3	(11.7–15.2)	94	6.6	(5.4–8.1)	81	6.1	(4.9–7.6)	130	10.4	(8.8–12.4)	523	31.9	(29.3–34.8)
Female	242	13.6	(12.0–15.4)	104	6.7	(5.6–8.2)	68	4.7	(3.7–6.0)	149	10.9	(9.3–12.8)	563	31.6	(29.1–34.3)
Race/ethnicity															
Asian/Pacific Islander	5	17.2	(7.2–41.4)	4	16.7	(6.3–44.4)	0	0.0	(0.0–0.0)	2	10.0	(2.5–40.0)	11	37.9	(21.0–68.5)
Non-Hispanic black	77	10.4	(8.3–13.0)	47	7.1	(5.3–9.4)	31	5.0	(3.5–7.2)	50	8.6	(6.5–11.3)	205	27.7	(24.2–31.8)
Hispanic	15	14.2	(8.5–23.5)	4	4.4	(1.6–11.7)	4	4.6	(1.7–12.3)	8	9.6	(4.8–19.3)	31	29.2	(20.6–41.6)
Native American	10	14.9	(8.0–27.7)	4	7.0	(2.6–18.7)	2	3.8	(0.9–15.1)	7	13.7	(6.5–28.8)	23	34.3	(22.8–51.7)
Non-Hispanic white	346	14.5	(13.1–16.1)	135	6.6	(5.6–7.8)	107	5.6	(4.7–6.8)	203	11.3	(9.9–13.0)	791	33.2	(31.0–35.6)

Abbreviations: CI: Confidence interval; VTE, venous thromboembolism.

Table 5 Distribution of risk factors prior to the first VTE episode ($n = 3,255$, excluding 167 patients identified from mortality records) in Oklahoma County, Oklahoma, April 1, 2012–March 31, 2014, using the timeframes indicated in the ISTH risk factor guidance[10]

Risk factors	First episode VTE	
	n	%
Provoking risk factors		
Cancer, active[a]	308	9.6
Hospitalization[b]	1,177	36.2
Immobilization[c]	331	10.2
Surgery	105	3.2
Trauma	251	7.7
Central venous catheterization	363	11.2
Congestive heart failure	58	1.9
Myocardial infarction	25	0.8
Stroke	55	1.7
Pregnancy	17	0.5
Medications[d]	118	3.6
Persistent provoked[e]	373	11.5
Transient provoked[e]	1,411	43.3
Unprovoked[e]	1,471	45.2

Abbreviations: ISTH, International Society on Thrombosis and Haemostasis; VTE, venous thromboembolism.
[a]Metastatic or cancer diagnosed ≤180 days of VTE diagnosis.
[b]VTE event diagnosed ≥1 day after hospital admission or hospitalization within 60 days prior to diagnosis.
[c]Immobilized for ≥3 days in bed.
[d]Medications include estrogen- and progesterone-containing drugs, tamoxifen, raloxifene, erythropoietin, romiplostim, oprelvekin, eltrombopag, thalidomide, and lenalidomide.
[e]Provoked status: persistent provoked = cancer, antiphospholipid syndrome, systemic lupus erythematosus, or inflammatory bowel disease; transient provoked = central venous catheterization, congestive heart failure, hospitalization, immobilization, medications, myocardial infarction, stroke, surgery, pregnancy, or trauma; unprovoked = none of the above.

VTE incidence by race. Barco and colleagues have recently reported that black individuals had higher pulmonary-embolism-related mortality than white individuals and those of other races.[20] Our results for blacks are consistent with those of Barco et al.[20] The reason for the similar mortality for blacks and whites in our study is unknown and requires further investigation.

The cumulative incidence of the first recurrent VTE among the patients with incident VTE during the 2-year surveillance period was 9.5% (►**Fig. 1**), underscoring the significant burden of VTE. The cumulative incidence of recurrence was highest for the persistent provoked cohort, while transient provoked and unprovoked VTE cohorts were relatively similar. Importantly, regardless of provoking status, the incidence of recurrent VTE was 9.3 to 13.7% within 2 years (►**Fig. 1**). Extended anticoagulant treatment has become safer in recent years, with an annual incidence of major bleeding for the direct oral anticoagulants of approximately 0.2 to 0.5%.[21,22] These data support the suggestion to reconsider the practice of using provoking status as a guide to selecting patients for extended anticoagulant therapy.[23] Further studies of applying extended anticoagulant treatment to a broader spectrum of the VTE population seem warranted and could have a potentially important impact on reducing the burden from recurrent VTE.

The proportion of incident VTE events identified as hospital-associated was 36.2%. Heit et al observed 52% of VTE events were hospital-related using data from 2005 to 2010.[24] Potential reasons for the observed difference include the 2-month time frame defined by the ISTH criteria compared with the traditional 3-month time frame, a change in admitting practices for procedures or conditions that are risk factors for VTE, differences in collecting hospitalization data, and earlier studies' potential inclusion of recurrent VTE events. Nevertheless, hospital-associated VTE remains an appreciable proportion of the total disease burden.

Our study has several strengths and some limitations. Strengths include the prospective, population-based design, performance of the study under federal and state public health disease surveillance statutes, conducting surveillance in both hospitals and outpatient clinics, and the use of active surveillance to supplement case finding through hospital discharge and death records data. These design features enabled us to document unique patient events, and minimized the possibility of unidentified events, as hospital refusal to participate was not applicable. The racially diverse population of Oklahoma County and its close similarity to the U.S. population indicate the results are likely to be relatively generalizable to the U.S. population. Oklahoma City was ranked as the seventh most representative city in the United States according to a poll used to determine ideal markets for companies to test their products.[25] However, the generalizability of our results to other countries is uncertain, and could be influenced by differences between the United States and other countries in the lack of universal health insurance and access to health care, and by documented health disparities according to race, socioeconomic status, and quality of care received. Additional limitations include the quality of the race data in the medical record and some incompleteness of the data on risk factors. Underreporting of Native American race,[26] particularly in the Eastern and Southern Plains,[27] and Hispanic ethnicity in medical records has been documented[28]; the true incidence of VTE may be higher in these populations. While it is possible we missed some outpatient events (for example, if a physician made a clinical diagnosis without imaging), this is likely to be minimal because objective diagnosis using imaging to confirm the diagnosis is current standard of care and we conducted surveillance in all licensed imaging facilities. The exact dates for the onset of certain risk factors were not documented in the medical record in some cases, potentially underestimating the proportion of events classified as transient provoked and overestimating the proportion with unprovoked VTE. These limitations, however, would not alter our conclusions about the overall age-adjusted incidences or case fatality.

In conclusion, our results suggest an approximate annual incidence of VTE of three per 1,000 adult population, with an

overall recurrence rate of 9.5% within 2 years, indicating that VTE results in an important disease burden. The incidence increased with each decade of age and varied substantially by race. Hospital-associated VTE comprised approximately 36% of all incident events. Strengthened efforts toward implementing effective prevention in hospitalized patients and enhanced secondary prevention through extended anticoagulant treatment for a greater proportion of patients could have an important impact on reducing the burden of disease.

What is known about this topic?

- Venous thromboembolism (VTE) contributes significantly to the global disease burden of thrombosis.
- Available data on the incidence and epidemiology of VTE are older and based mainly on studies of nonracially diverse, predominantly white populations.
- Current population-based incidence data on VTE are needed because population demographics and risk factors for VTE may change over time.

What does this paper add?

- Our study is a prospective population-based study assessing the incidence of VTE, recurrence, mortality, and the demographic and risk factor profile of patients with VTE in a racially diverse population closely mirroring that of the United States.
- Age-adjusted VTE incidence and mortality rates vary substantially by race.
- The incidence of three per 1,000 adults per year indicates a major disease burden, and is informative of the burden in the U.S. population.

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Conflict of Interest
G.E.R. discloses the receipt of consultant fees for consultant services provided to the following companies: Anthos, Bayer, BMS, Boehringer-Ingelheim, Daiichi-Sankyo, Eli Lilly, Janssen, Johnson and Johnson, Merck, Pfizer, Portola, Tetherex, and XaTek. G.E.R. and A.M.W. were recipients of research grants from the CDC. The other authors report no conflicts to disclose.

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