

# Outpatient Treatment of Deep Vein Thrombosis in the United States: The Reasons for Geographic and Racial Differences in Stroke Study

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**BACKGROUND:** Outpatient versus inpatient treatment of deep vein thrombosis (DVT) is believed to result in equivalent outcomes with decreased costs. Little is known about the adoption of outpatient DVT treatment in the United States.

**OBJECTIVE:** To describe the uptake of outpatient DVT treatment in the United States and understand how comorbidities and socioeconomic conditions impact the decision to treat as an outpatient.

**DESIGN AND SETTING:** The Reasons for Geographic and Racial Differences in Stroke cohort study recruited 30,329 participants between 2003 and 2007. DVT events were ascertained through 2011.

**MEASUREMENTS:** Multivariable logistic regression was used to determine the correlates of outpatient treatment of DVT accounting for age, sex, race, education, income, urban or rural residence, and region of residence.

**RESULTS:** Of 379 venous thromboembolism events, 141

participants had a DVT without diagnosed pulmonary embolism and that did not occur during hospitalization. Overall, 28% (39 of 141) of participants with DVT were treated as outpatients. In a multivariable model, the odds ratio for outpatient versus inpatient DVT treatment was 4.16 (95% confidence interval [CI], 1.25-13.79) for urban versus rural dwellers, 3.29 (95% CI, 1.30-8.30) for white versus black patients, 2.41 (95% CI, 1.06-5.47) for women versus men, and 1.90 (95% CI, 1.19-3.02) for every 10 years younger in age. Living outside the southeastern United States and having higher education and income were not statistically significantly associated with outpatient treatment.

**CONCLUSIONS:** Despite known safety and efficacy, only 28% of participants with DVT received outpatient treatment. This study highlights populations in which efforts could be made to reduce hospital admissions. *Journal of Hospital Medicine* 2017;12:826-830. Published online first September 6, 2017. © 2017 Society of Hospital Medicine

Venous thromboembolism (VTE) is a common medical condition comprising deep vein thrombosis (DVT) and pulmonary embolism (PE). Estimates of the incidence of DVT in the United States vary between 0.5 and 1.5 cases per 1000 person-years.<sup>1</sup> Left untreated, roughly 50% of DVT patients progress to a PE, of whom 10% to 25% die within 3 months.<sup>2</sup>

Since the 1990s, multiple randomized controlled studies<sup>3-5</sup> demonstrated the safety and efficacy of outpatient treatment for selected DVT patients with low molecular weight heparin and warfarin. The United States Food and Drug Administration approved enoxaparin, a low molecular weight heparin for outpatient use in 1998,<sup>6</sup> and by the end of the decade, multiple treatment guidelines for VTE acknowledged the safety of outpatient treatment of DVT with low molecular weight heparin in selected patients.<sup>7-9</sup> Recently,

the approval of direct oral anticoagulants (DOACs) by the Food and Drug Administration allows an all-oral treatment regimen for VTE, which could further facilitate outpatient treatment of DVT.

Costs associated with treatment of VTE are enormous. For outpatient treatment, researchers differ on individual estimates of cost savings associated with outpatient DVT management, but most report a cost savings of several thousand dollars per patient treated as an outpatient compared with as an inpatient.<sup>6,10</sup> Given the incidence of DVT, reducing costs while maintaining a high quality of care in even a small percentage of DVT patients would result in significant healthcare cost savings as well as increased convenience for patients.

Despite high-quality evidence supporting the efficacy and safety of outpatient DVT treatment, little is known about the adoption of outpatient DVT treatment in the United States. Several studies that have been published were limited to single hospitals and were small in size<sup>11,12</sup> or limited to a cohort of patients already diagnosed with DVT.<sup>13</sup>

The purpose of this study was to report the frequency of outpatient treatment of DVT in the United States and describe patient characteristics associated with outpatient treatment. Information was gathered from The Reasons for

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Geographic and Racial Differences in Stroke (REGARDS) study, a contemporary cohort study of more than 30,000 patients residing in the contiguous United States with racial and geographic diversity. We hypothesized that an individual's age, sex, race, region of residence, urban or rural residence, education level, and personal income would be associated with outpatient treatment. Results would allow the implementation of interventions to promote the appropriate use of outpatient treatment in order to reduce healthcare costs and increase patient convenience without compromising safety or efficacy of care.

## METHODS

### Cohort Characteristics

VTE events were ascertained in the REGARDS cohort, a prospective, longitudinal cohort study investigating the causes of racial and geographic disparities in stroke and cognitive decline.<sup>14</sup> Between 2003 and 2007, there were 30,239 participants in the contiguous United States  $\geq 45$  years old enrolled in REGARDS. By design, 55% were female, 41% were black, the mean age was 65 years, and 56% lived in the southeastern United States. Participants were recruited from a commercial list by mail and telephone contact followed by verbal consent. A telephone interview was followed by an in-home examination, including obtaining written informed consent. On study entry, many participants had comorbid conditions, including 8% with reported atrial fibrillation, 56% receiving treatment for hypertension, 22% receiving treatment for diabetes, 3.7% taking warfarin, and 14% who were actively smoking.<sup>15,16</sup> Participants were only excluded if they had active cancer, stated a self-reported race other than white or black, were unable to converse in English, had cognitive impairment as judged by the telephone interviewer, or were residing in or on the waiting list for a nursing home. Study methods were reviewed and approved by the institutional review boards at each study institution and have been published elsewhere.<sup>14</sup>

### Event Ascertainment and Definitions

DVT event ascertainment is complete through 2011, with identification by telephone interview, review of reported hospitalizations, and review of deaths.<sup>17</sup> Questionnaires in similar epidemiological studies have 98% specificity and  $>70\%$  sensitivity for ascertaining VTE events.<sup>18</sup> A research nurse reviewed the text and recorded each reported hospitalization through 2011. Any report of a blood clot in the legs, arms, or lungs was a potential case for physician review. Medical records were retrieved for 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 (to include limb ultrasounds, computed tomography scans, and magnetic resonance imaging), autopsies, and outpatient notes were retrieved using up to 3 attempts.<sup>19</sup> Using all available information, characteristics of the VTE

event and treatment were systematically recorded. For each potential VTE case, two of three physician reviewers abstracted medical records to validate and classify the event. If the physician reviewers disagreed, the third physician would review the case, and if VTE status remained uncertain, cases were discussed and resolved. Race was determined by participant self-report as black or white. Location of residence was defined by geocoding the addresses, and urban or rural status was defined by United States census tract data using rural-urban commuting area codes (RUCA; with rural areas being RUCA codes 4–10).<sup>20</sup> Other risk factors were obtained through surveys, telephone interviews, or in-home visits.<sup>14</sup>

Outpatient treatment was defined as receiving a DVT diagnosis in an emergency department or ambulatory clinic but not receiving an overnight hospitalization. Inpatient treatment was defined as at least 1 overnight stay in a hospital (but not in an emergency department). Only participants admitted with a primary diagnosis of DVT were included in the analysis. If someone was noted to have DVT but was admitted to the hospital for another cause, he or she was not included in the analysis and classified as a hospital-associated DVT. A provoked DVT was defined as occurring within 90 days of a major trauma, surgery, or marked immobility or was associated with active cancer or treatment for cancer (ie, chemotherapy, radiotherapy, or surgical therapy), while an unprovoked DVT was defined as having none of the above provoking factors. A distal DVT was defined as a DVT occurring in the posterior tibial, anterior tibial, peroneal, or soleus sinuses. The primary outcome was DVT treated as an outpatient only without concurrent diagnosis of PE or VTE as a complication of hospitalization (as these individuals were not eligible for outpatient treatment at the time).

### Statistical Analysis

Age, sex, race, region of residence (inside or outside the southeastern United States), education, income (determined as greater or less than \$20,000 per year), and urban or rural status of residence were compared between DVT patients treated as outpatients and inpatients using  $\chi^2$  analysis by inpatient or outpatient treatment. Univariable and multivariable logistic regression was then used to determine the odds ratio (OR) of receiving outpatient DVT treatment by the same variables with age per 10-year increment. ORs were adjusted for age, sex, race, year of DVT diagnosis, and region of residence as appropriate. Statistical significance was defined as  $P < 0.05$ . All statistical analyses were performed by N.A.Z. and conducted with SAS version 9.3 (SAS Institute, Cary, NC). All authors had access to the primary clinical data.

## RESULTS

Over a mean of 4.7 years follow-up, 379 VTE events occurred (incident and recurrent); 185 were diagnosed with a PE, and 53 occurred as a complication of hospitalization (and were not eligible for outpatient treatment), leaving 141 DVT events potentially eligible for outpatient treatment out

**TABLE 1.** Characteristics of Participants with DVT by Treatment Location

Characteristics	Treated as Outpatient, Total = 39	Treated as Inpatient, Total = 102	P
Median age (interquartile range)	67 years (60-73)	70 years (63-76)	.02
DVT year (median)	2009	2008	.02
Female	23 (59%)	43 (42%)	.03
White	30 (77%)	62 (61%)	.04
Living outside the Southeast	21 (54%)	50 (49%)	.13
High school graduate	38 (97%)	90 (88%)	.07
Yearly income >\$20,000	12 (82%)	58 (57%)	.02
Living in an urban area	35 (90%)	71 (70%)	.01
Provoked event	10 (26%)	42 (41%)	.09
Body mass index $\geq$ 30	20 (51%)	47 (47%)	.55
Current or former smoker	17 (44%)	53 (52%)	.45
Proximal DVT	28 (72%)	92 (90%)	<.01
Treated with full dose anticoagulation	34 (87%)	89 (87%)	.99
History of cancer	6 (25%)	14 (18%)	.43
Chronic kidney disease (eGFR <60)	5 (13%)	19 (19%)	.46
History of coronary artery disease	8 (21%)	23 (23%)	.77
History of hypertension	21 (54%)	70 (69%)	.10
History of diabetes*	4 (11%)	21 (22%)	.15
History of hyperlipidemia*	22 (56%)	53 (54%)	.80

\*Data were missing for 38 participants with cancer, 1 participant with coronary artery disease, 7 participants with diabetes, and 4 participants with hyperlipidemia.

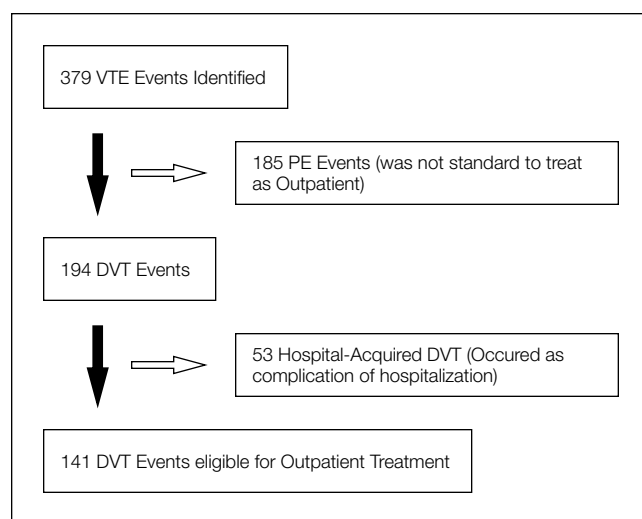
NOTE: Abbreviations: DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate.

of a population of 29,556 participants with available records and follow-up in the cohort (Figure).

Of 141 DVT events, 39 (28%) were treated as outpatients. Table 1 presents the characteristics of participants treated as inpatients and as outpatients. Factors significantly associated with outpatient DVT treatment were younger age, female sex, white race, residing in an urban area, having a distal DVT only, and having a higher income. In the study, DVT events were recorded between 2003 and 2011; the median year of a diagnosed DVT and treated as an outpatient was 2009, while the median year of inpatient treatment was 2008. Living in the Southeast versus the rest of the country ( $P = 0.13$ ) and having a high school education or greater ( $P = 0.07$ ) were marginally associated with receiving outpatient treatment. In absolute terms, 11% of people living in rural areas and 19% of black patients had outpatient DVT treatment while 33% of the urban dwellers and 32% of white patients received outpatient treatment (Table 1). At the time of cohort enrollment, 92% of participants claimed to have insurance; however, this did not differentiate between Medicare, Medicaid, and private insurance. Only 1 participant diagnosed with DVT had an estimated glomerular filtration

rate <30, and this individual was admitted for treatment.

Table 2 reports the multivariable adjusted OR for outpa-

**FIG.** VTE Events in REGARDS

NOTE: Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

**TABLE 2.** Likelihood of Receiving Outpatient Treatment for DVT

Variable	Adjusted Odds Ratio (95% CI) <sup>a</sup>
Age (per 10 years younger)	1.90 (1.19-3.02)
Year of DVT diagnosis (per 1 year later)	1.35 (1.03-1.77)
Sex (female versus male)	2.41 (1.06-5.47)
Race (white versus black)	3.29 (1.30-8.30)
Region (outside Southeast versus in Southeast)	2.00 (0.87-4.63)
Education (high school graduate versus not)	4.51 (0.52-38.82)
Income >\$20,000 (yes versus no)	2.63 (0.87-7.94)
Living in an urban area (yes versus no)	4.16 (1.25-13.79)

<sup>a</sup>Adjusted for age, sex, race, VTE event year, and region.  
NOTE: Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; VTE, venous thromboembolism.

tient treatment of DVT adjusted for age, sex, race, region, and year of DVT diagnosis. Outpatient treatment of VTE was associated with younger age (OR 1.90; 95% confidence interval [CI], 1.19-3.02 for every 10 years younger in age), female sex (OR 2.41; 95% CI, 1.06-5.47), and white race (OR 3.29; 95% CI, 1.30-8.30). For each progressive calendar year in which the diagnosis was made, individuals had a 1.35-fold increase in their odds (95% CI, 1.03-1.77) of receiving outpatient treatment. Individuals living in urban areas were 4.16 (95% CI, 1.25-13.79) times more likely to receive outpatient treatment than those in rural areas. Living outside of the southeastern United States and having an income of more than \$20,000 per year had increased, but nonsignificant, odds of being treated as outpatient (Table 2).

## DISCUSSION

In this national, prospective, observational cohort study, only 28% of participants diagnosed with DVT were treated as outpatients versus being hospitalized. Urban area of residence, white race, female sex, and younger age were significantly associated with an increased odds of outpatient treatment. Groups that had particularly low outpatient treatment rates were rural dwellers and black participants, who had outpatient treatment rates of 11% and 19%, respectively. The odds of receiving outpatient treatment did improve over the course of the study, but in the last year of VTE assessment, outpatient treatment remained at 40%, but this was quite variable over the study years (being 8% two years prior).

The feasibility of outpatient treatment of DVTs requires a coordinated healthcare system and patient support to ensure education and appropriate anticoagulation monitoring. While not all DVTs should be treated as outpatients, differences in treatment location by sex, race, and residence point to potential healthcare disparities that increase the burden on patients and increase healthcare costs. Other studies have documented low outpatient treatment rates of

DVTs (20% in 1 United States multicenter DVT registry) but have not discussed the associations of outpatient versus inpatient treatment.<sup>13</sup> Outpatient treatment also appears to be underutilized in other developed countries; in the European Computerized Registry of Patients with Venous Thromboembolism, only 31% of DVT patients were treated on an outpatient basis between 2001 and 2011.<sup>21</sup> To our knowledge, this is the first study to document the uptake of outpatient DVT treatment in the United States across multiple states, regions, and health systems well after the safety and efficacy of outpatient treatment of DVT was established by randomized controlled trials.<sup>3-5</sup>

The strengths of this study are that these data are derived from a contemporary cohort with a large geographic and racial distribution in the United States and are well characterized with a mean of 4.6 years follow-up.<sup>19</sup> We are limited by a relatively small number of DVT events that were eligible for outpatient treatment (n = 141) and so may miss modest associations. Further, while the geographic scope of the cohort is a tremendous strength of our study, we may have missed some events and did not have complete record retrieval of reported events and could not assess access to healthcare in detail. These data were recorded before the use of DOACs became common. DOACs are an effective and safe alternative to conventional anticoagulation treatment for acute DVT.<sup>22</sup> Their use might result in increased outpatient treatment, as they are not parenteral; however, cost considerations (~\$400.00 per month), especially with high-deductible insurance plans, may limit their impact on VTE treatment location.<sup>23</sup> This study cannot account for why the racial, sex, and urban-rural differences exist, and by extension if hospitalization rates differ due to associated comorbidities or if this represents a healthcare disparity. While it is reasonable from a healthcare perspective that younger individuals would more likely be treated as outpatients, there is no data to suggest that differences in DVT by sex, race, and residential location support decreased outpatient treatment. Due to the age of the cohort, most individuals had some form of insurance and a primary care provider. However, we were unable to assess the quality of insurance and the ease of access to their primary care providers. More research is needed to determine whether patients were hospitalized on medical grounds or because of a lack of coordinated healthcare systems to care for them as outpatients.

In conclusion, only a minority of patients who were potentially eligible for outpatient DVT treatment (28%) were treated as outpatients in this study, and there were significant racial and socioeconomic differences in who received inpatient and outpatient treatment. While outpatient treatment rates were below 40% in all groups, we identified groups with especially low likelihoods of receiving outpatient treatment. While all eligible individuals should be offered outpatient DVT treatment, these data highlight the need for specific efforts to overcome barriers to outpatient treatment in the elderly, rural areas, black patients, and men. Even modest increases in the rate of outpatient DVT treatment could result

in substantial cost savings and increased patient convenience without compromising the efficacy or safety of medical care.

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