Risk of Pulmonary Embolism After Cerebral Venous Thrombosis

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Background and Purpose—Cerebral vein thrombosis (CVT) is a type of venous thromboembolism. Whether the risk of pulmonary embolism (PE) after CVT is similar to the risk after deep venous thrombosis (DVT) is unknown.

Methods—We performed a retrospective cohort study using administrative data from all emergency department visits and hospitalizations in California, New York, and Florida from 2005 to 2013. We identified patients with CVT or DVT and the outcome of PE using previously validated *International Classification of Diseases, Ninth Revision, Clinical Modification* codes. Kaplan–Meier survival statistics and Cox proportional hazards models were used to compare the risk of PE after CVT versus PE after DVT.

Results—We identified 4754 patients with CVT and 241 276 with DVT. During a mean follow-up of 3.4 (±2.4) years, 138 patients with CVT and 23 063 with DVT developed PE. CVT patients were younger, more often female, and had fewer risk factors for thromboembolism than patients with DVT. During the index hospitalization, the rate of PE was 1.4% (95% confidence interval [CI], 1.1%–1.8%) in patients with CVT and 6.6% (95% CI, 6.5%–6.7%) in patients with DVT. By 5 years, the cumulative rate of PE after CVT was 3.4% (95% CI, 2.9%–4.0%) compared with 10.9% (95% CI, 10.8%–11.0%; $P<0.001$) after DVT. CVT was associated with a lower adjusted hazard of PE than DVT (hazard ratio, 0.26; 95% CI, 0.22–0.31).

Conclusion—The risk of PE after CVT was significantly lower than the risk after DVT. Among patients with CVT, the greatest risk for PE was during the index hospitalization. **(*Stroke*. 2017;48:563-567. DOI: 10.1161/STROKEAHA.116.016316.)**

Key Words: cerebral venous thrombosis ■ deep vein thrombosis ■ pulmonary embolism ■ thrombosis ■ venous thromboembolism

Cerebral venous thrombosis (CVT) often affects young patients and can result in substantial disability and death.[1–4] Though mortality rates among patients with CVT have declined, new epidemiological data suggests a higher annual incidence of CVT than previously reported.[5–7] A diagnosis of CVT is associated with subsequent risk of venous thromboembolism, including deep vein thrombosis (DVT), pulmonary embolism (PE), and recurrent CVT, contributing to the adverse clinical outcomes of some CVT patients.[4,8–12] However, whether the risk of recurrent venous thromboembolism after CVT is similar to that after a diagnosis of DVT has not been carefully explored. To help quantify the disease burden of CVT, we used a large heterogeneous group of patients to evaluate the risk of incident PE, a particularly dangerous form of venous thromboembolism, among patients with CVT as compared with those with DVT.[13,14]

Methods

Study Design

We performed a retrospective cohort study using administrative claims data from all emergency department visits and nonfederal hospitalizations in California from 2005 to 2011, in New York from 2006 to 2013, and in Florida from 2005 to 2013. These data were collected by the California Office of Statewide Health Planning and Development, the New York Statewide Planning and Research Cooperative System, and the Florida Agency for Healthcare Administration. These agencies provide data to the Agency for Healthcare Research and Quality for its Healthcare Cost and Utilization Project.[15] Each patient is assigned a personal linkage number that allows for anonymous tracking through all subsequent hospitalizations.[16] Up to 25 discharge diagnoses are coded at each encounter using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) system. The institutional review board at Weill Cornell Medicine approved this study and waived the requirement for written informed consent.

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Subjects

We identified all adult patients with an emergency department visit or hospitalization with a first-recorded discharge diagnosis of CVT or DVT. CVT was defined using *ICD-9-CM* codes 325.0, 437.6, and 671.5 in any discharge diagnosis code position. These codes have been previously validated via detailed medical record review and have a positive predictive value of 76%, sensitivity of 78%, and specificity of 93%.[17] DVT was defined using *ICD-9-CM* codes 451.19, 451.2, 451.81, 451.9, 453.1, 453.2, 453.8, or 453.9 in any emergency department visit or hospital discharge diagnosis code position. These codes have been shown to have a positive predictive value of 96% when compared with detailed medical record review.[18] To assess incident cases of PE, patients with diagnoses of PE before the index visit for CVT or DVT were excluded. To minimize misclassification error, patients with both CVT and DVT during the same index hospitalization were excluded. Finally, we excluded nonresidents from California, New York, and Florida to maximize the completeness of follow-up.

Measurements

The primary outcome was PE defined by *ICD-9-CM* codes 415.1 or 415.11 in any hospital discharge diagnosis code position. This definition has been shown to have a positive predictive value of 96% when compared with detailed medical record review.[18,19] To account for factors that may explain differences in rates of PE after CVT or DVT, we used *ICD-9-CM* codes to identify the following comorbidities that have been reported as risk factors for venous thromboembolic events: hypertension, diabetes mellitus, coronary artery disease, peripheral vascular disease, congestive heart failure, chronic kidney disease, tobacco use, chronic obstructive pulmonary disease, pregnancy, alcohol abuse, atrial fibrillation, trauma, a primary hypercoagulable state, and any history of cancer.[20–31] We used the Elixhauser comorbidity index to account for disease severity.[32]

Statistical Analysis

We used standard descriptive statistics with exact confidence intervals (CI) to report crude rates. Patients were censored at the time of death or at the end of the follow-up period. Additionally, patients with CVT were censored if they had a subsequent encounter for DVT before the primary outcome of interest. Likewise, patients with DVT were censored if they had a subsequent encounter for CVT before the primary outcome of interest. Kaplan–Meier survival statistics were used to calculate cumulative rates of PE. The log-rank test was used to compare cumulative rates of outcomes between patients with CVT and DVT. We used multivariate Cox proportional hazards modeling to assess the relationship between the index diagnosis (CVT or DVT) and subsequent PE, while adjusting for demographics and comorbidities. We performed a sensitivity analysis excluding pregnant patients with CVT because this subgroup may have a unique risk of recurrent venous thromboembolism as compared with other CVT patients.[30,33] We also performed a sensitivity analysis excluding all patients with any history of cancer according to a previously reported *ICD-9-CM* diagnostic code algorithm.[34] The proportional hazard assumption was confirmed by inspection of log–log plots. All analyses were performed using Stata/MP, version 13 (StataCorp, TX). The threshold for statistical significance allowed for an alpha error of 0.05.

Results

We identified a total of 6181 patients with CVT and 286 470 patients with DVT. After excluding patients who had a prior history of PE, a concomitant CVT and DVT during the same hospitalization, or who were nonresidents from California, New York, and Florida, our final cohort consisted of 4754 patients with CVT and 241 276 patients with DVT. The mean age of patients with CVT was 43.6 (±18.4) years, and 73.3% were female; in comparison, the mean age of patients with DVT was 62.5 (±17.9) years, and 52.9% were female. Patients with CVT were more often non-white and had fewer risk factors for venous thromboembolism than patients with DVT (Table 1).

Table 1. Patient Characteristics, Stratified by Index Diagnosis

Characteristic*	DVT (N=241 276)	CVT (N=4754)
Age, mean (SD), y	62.5 (17.9)	43.6 (18.4)
Female	127 661 (52.9)	3483 (73.3)
Race†		
White	154 389 (65.3)	2568 (55.3)
Black	38 130 (16.1)	722 (15.5)
Hispanic	30 651 (13.0)	889 (19.1)
Asian	5901 (2.4)	213 (4.6)
Other	7545 (3.2)	255 (5.4)
Payment source‡		
Medicare	130 776 (54.2)	853 (18.0)
Medicaid	28 390 (11.8)	1104 (23.2)
Private	62 631 (26.0)	2301 (48.4)
Self-pay	10 107 (4.2)	265 (5.6)
Other	9331 (3.9)	231 (4.9)
Hypertension	124 299 (51.5)	1326 (27.9)
Diabetes mellitus	63 064 (26.1)	653 (13.7)
Coronary heart disease	52 191 (21.6)	243 (5.1)
Congestive heart failure	41 281 (17.1)	149 (3.1)
Peripheral vascular disease	16 393 (6.8)	76 (1.6)
Chronic obstructive pulmonary disease	33 174 (13.8)	133 (2.8)
Chronic kidney disease	44 541 (18.5)	127 (2.7)
Primary hypercoagulable state	4204 (1.7)	309 (6.5)
Cancer	44 835 (18.6)	326 (6.9)
Trauma	4793 (2.0)	127 (2.7)
Atrial fibrillation	34 717 (14.4)	171 (3.6)
Pregnancy§	44 276 (34.7)	1237 (35.6)
Tobacco use	19 022 (7.9)	223 (4.7)
Alcohol use	24 950 (10.3)	430 (9.1)
Elixhauser comorbidities,‖ mean (SD)	3.3 (2.1)	1.7 (1.6)

CVT indicates cerebral vein thrombosis; DVT, deep vein thrombosis; and SD, standard deviation.

*Data are presented as number (%) unless otherwise specified.

†Self-reported by patients or their surrogates. Numbers do not sum to group totals because of missing race/ethnicity data in ≤2.3% of patients.

‡Numbers do not sum to group totals because of missing payment-source data in <0.01% of patients.

§The percentage of pregnant women is derived from the total number of women in the cohort.

‖Numbers represent the number of Elixhauser comorbid conditions, which comprise a comprehensive set of 28 comorbidity measures for use with large administrative data sets.

The rate of PE during the index hospitalization was 1.4% (95% CI, 1.1%–1.8%) for patients with CVT and 6.6% (95% CI, 6.5%–6.7%; $P<0.001$) for patients with DVT. During a mean follow-up of 3.4 (±2.4) years, 138 patients with CVT developed a PE and 23 063 patients with DVT developed a PE. Patients with PE were more likely to be white, more often privately insured, and had more risk factors for venous thromboembolism than those without PE (Table 2). By 5 years, the cumulative rate of PE after CVT was 3.4% (95% CI, 2.9%–4.0%) versus 10.9% (95% CI, 10.8%–11.0%; $P<0.001$) after DVT (Figure).

Table 2. Patient Characteristics, Stratified by the Diagnosis of Subsequent Pulmonary Embolism

Characteristic*	PE (N=23 201)	No PE (N=222 829)
Age, mean (SD), y	62.0 (17.2)	62.1 (18.1)
Female	12 065 (52.0)	119 079 (53.4)
Race		
White	15 852 (69.5)	141 105 (64.6)
Black	3525 (15.5)	35 237 (16.2)
Hispanic	2361 (10.4)	29 179 (13.4)
Asian	434 (1.9)	5680 (2.6)
Other	641 (2.8)	7159 (3.3)
Payment source		
Medicare	11 928 (51.4)	119 701 (53.8)
Medicaid	2636 (11.4)	26 858 (12.1)
Private	6937 (29.9)	57 995 (26.0)
Self-pay	762 (3.3)	9610 (4.3)
Other	936 (4.0)	8626 (3.9)
Hypertension	11 599 (50.0)	114 026 (51.2)
Diabetes mellitus	5192 (22.3)	58 525 (26.3)
Coronary heart disease	4444 (19.2)	47 990 (21.6)
Congestive heart failure	3535 (15.2)	37 895 (17.0)
Peripheral vascular disease	1214 (5.2)	15 255 (6.9)
Chronic obstructive pulmonary disease	3798 (16.4)	29 509 (13.3)
Chronic kidney disease	2554 (11.0)	42 114 (18.9)
Atrial fibrillation	3143 (13.6)	31 765 (14.3)
Primary hypercoagulable state	996 (4.3)	3517 (1.6)
Cancer	5945 (25.6)	39 216 (17.6)
Trauma	441 (1.9)	4479 (2.0)
Pregnancy†	3970 (32.9)	41 543 (34.9)
Tobacco use	2427 (10.5)	16 818 (7.6)
Alcohol use	2674 (11.5)	22 706 (10.2)
Elixhauser comorbidities,‡ mean (SD)	3.2 (2.0)	3.3 (2.1)

PE indicates pulmonary embolism; and SD, standard deviation.

*Data are presented as number (%) unless otherwise specified.

†The percentage of pregnant women is derived from the total number of women in the cohort.

‡Numbers represent the number of Elixhauser comorbid conditions, which comprise a comprehensive set of 28 comorbidity measures for use with large administrative data sets.

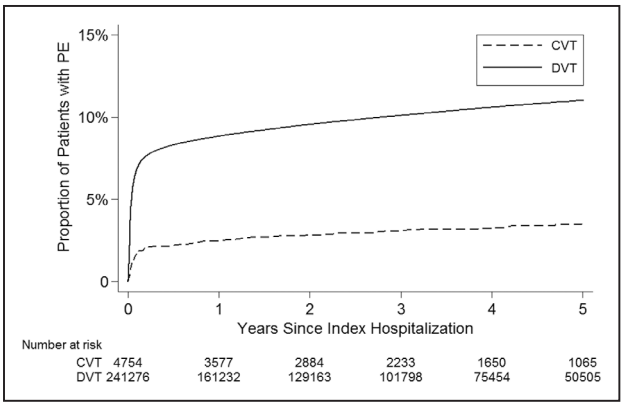

Figure. Cumulative rates of pulmonary embolism. Kaplan–Meier curves demonstrating cumulative rate of pulmonary embolism (PE) in patients with cerebral venous thrombosis (CVT) and deep venous thrombosis (DVT).

After adjustment for demographics and comorbidities, patients with CVT had a significantly lower hazard of PE than patients with DVT (hazard ratio, 0.26; 95% CI, 0.22–0.31). Our results were similar in sensitivity analyses excluding patients who had a CVT during pregnancy (hazard ratio, 0.36; 95% CI, 0.29–0.44) and after excluding patients with any history of cancer (hazard ratio, 0.30; 95% CI, 0.24–0.37).

Discussion

In a large, heterogeneous cohort, we found that the risk of PE among patients with CVT was significantly lower than the risk of PE among patients with DVT. In addition, although absolute rates were relatively low, the highest risk period for PE after CVT was during the index CVT hospitalization.

The cumulative rate of PE among patients with CVT in our cohort is slightly higher than that of previous studies. The incidence of PE after CVT has ranged from 0.6% to 1.8% in prior studies with variable durations of follow-up.[4,8–12,33] It is possible that the lower rates of PE after CVT reported in earlier studies are related to differences in duration of follow-up and methodology of case ascertainment. In addition, because we included only cases of CVT diagnosed at an emergency department visit or hospitalization, we may have included patients with more severe disease presentations than those in previous studies thereby conferring higher PE risk.[4,35] Finally, by relying on *ICD-9-CM* codes, we may have captured several incidental, asymptomatic PEs, whereas prior research included mostly symptomatic PE.[36] The frequency of PE diagnosed during an index CVT hospitalization has to our knowledge not been previously reported, though PE is commonly thought to be a cause of early death among CVT patients.[37] The cumulative rate of PE after diagnosis of DVT in our cohort is similar to that of prior reports (range of 4.6%–19.2%).[31,38,39]

Several possible mechanisms may account for the lower risk of PE among patients with CVT than among patients with DVT. Underlying prothrombotic states or other conditions predisposing to CVT formation may be different than those associated with DVT and PE. Indeed, in our study,

patients with DVT more often had known venous thromboembolic risk factors, such as older age and male sex, as compared with patients with CVT.[20,40] Alternatively, there may be important pathophysiologic differences between systemic and intracranial venous clot formation that might at least partly underlie our central finding. For instance, in lower extremity deep veins, thrombi originate in the valve pocket, the area between a valve leaflet and the vessel wall, while cerebral venous sinuses lack valves.[41,42] Additionally, because cerebral sinuses are smaller in diameter than deep lower extremity veins, thrombi that break off from the original site in patients with CVT may be small and, therefore, less likely to cause PE.[41–43]

Our study has important limitations. First, we relied on administrative claims data using diagnosis codes to identify CVT, DVT, and PE. Though the *ICD-9-CM* codes we used to identify these 3 conditions have been previously validated through chart and imaging review, we were unable to qualify the clinical severity of thromboembolism or any imaging characteristics in our study population.[17–19] In addition, the validity of case ascertainment is further supported by the similarity in age and sex between the CVT patients in our study and those in the ISCVT cohort (International Stroke on Cerebral Vein and Dural Sinus Thrombosis).[8] Second, though we adjusted for demographics, a wide range of comorbidities, and the Elixhauser comorbidity index, we were unable to fully adjust for several venous thromboembolic risk factors, including body mass index, immobility, oral contraception use, and relevant laboratory data, such as coagulation studies.[20,22,24,44,45] Third, we lacked information regarding the use, type, duration, or intensity of anticoagulation therapy, though the currently recommended treatment algorithms for DVT and CVT are similar.[46,47]

Conclusions

In a large, heterogeneous cohort, the overall risk of PE after CVT was higher than the risk previous reports have suggested but significantly lower than the risk after DVT. Among patients with CVT, the greatest risk for PE was during the index hospitalization, suggesting that early detection of CVT and timely initiation of anticoagulation may be important. Therapeutic strategies to prevent recurrent venous thromboembolism after CVT, including the optimal duration of therapy, may require further evaluation as current guidelines rely mostly on data from studies on patients with DVT.[46,47]

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Disclosures

None.

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