

# Increased Risk of Venous Thromboembolism in Patients With Amyotrophic Lateral Sclerosis

## Results From a US Insurance Claims Database Study

Varant Kupelian, PhD, Emma Viscidi, PhD, Susan Hall, PhD, Li Li, MS, Susan Eaton, MSPH, Anne Dilley, PhD, Nicolas Currier, MD, Toby Ferguson, MD, PhD, and Laura Fanning, MD

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### Correspondence

Dr. Kupelian  
varant.kupelian@biogen.com

## Abstract

### Background and Objectives

Reduced mobility in patients with amyotrophic lateral sclerosis (ALS) is hypothesized to increase the risk of venous thromboembolism (VTE). A few small, single-center studies have investigated the risk of VTE in patients with ALS. Given the high morbidity and mortality associated with VTE, further understanding of the risk in patients with ALS may inform clinical care. The objective of this study was to investigate the incidence of VTE in patients with ALS compared with controls without ALS.

### Methods

Patients were identified from a US health insurance claims database, Optum's deidentified Clinformatics Data Mart Database, between 2004 and 2019. ALS cases were defined as patients aged 18 years or older with (1) 2 or more ALS claims at least 27 days apart including at least 1 claim from a neurologist visit or (2) 1 or more ALS claims and a prescription for riluzole or edaravone. Each ALS case was matched on age and sex to 5 controls without ALS. VTE was defined as at least 1 claim for VTE and at least 1 anticoagulant prescription or VTE-related procedure within 7 days before and 30 days after a VTE claim date. Incidence rates were reported per 1,000 person-years. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model.

### Results

Among 4,205 ALS cases and 21,025 controls, incident VTE occurred in 132 ALS cases (3.1%) and 244 controls (1.2%). Incidence rates of VTE were 19.9 per 1,000 person-years (95% CI 16.7–23.6) in ALS cases compared with 6.0 per 1,000 person-years (95% CI 5.0–7.1) in controls. ALS cases were about 3 times more likely to develop VTE (HR 3.3, 95% CI 2.6–4.0), with similar results among men and women. The median time to first VTE was 10 months from the initial ALS claim in ALS cases.

### Discussion

Consistent with previous smaller studies, a higher incidence rate of VTE was observed in a large sample of patients with ALS from across the United States, as compared to matched controls. The markedly increased risk underscores the importance of preventive efforts and careful monitoring for VTE in patients with ALS and may have implications for the management of ALS.

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Amyotrophic lateral sclerosis (ALS) is a rare neurologic disorder characterized by a progressive loss of motor neurons resulting in muscle weakness and atrophy and ultimately immobility.<sup>1</sup> Neurologic conditions that affect lower limb function have been associated

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Biogen, Cambridge, MA.

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with an increased risk of venous thromboembolism (VTE) consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE).<sup>2</sup> Reduced lower extremity mobility in patients with ALS is hypothesized to increase the risk of VTE. However, the few studies investigating the risk of VTE in patients with ALS have been small, clinic based, and not necessarily representative of patients with ALS in general.

Two retrospective single-center studies based on chart review have shown an increased incidence of both DVT and PE in patients with ALS.<sup>3,4</sup> Secondary analyses of pooled data from 2 clinical trials have shown comparable results for DVTs.<sup>5</sup> A prospective study of 50 patients with ALS followed up over a 1-year period reported similar results with an increased incidence of both symptomatic and asymptomatic VTE.<sup>6</sup>

The objective of this study was to investigate the incidence of VTE in patients with ALS compared with non-ALS controls in a large, US health insurance claims database.

## Methods

Patients with ALS and controls without ALS were identified from Optum's deidentified Clinformatics Data Mart Database, a large insurance claims database in the United States covering over 100 million people between January 1, 2004, and September 30, 2019. The database consists of administrative health claims, including medical service and prescription drug claims, from commercial health insurance plans and Medicare Advantage plans across the United States.

### ALS Case Definition

ALS cases were defined as (1) having 2 or more claims for ALS (*International Classification of Diseases, Ninth Revision [ICD-9]* code 335.20 or *International Classification of Diseases, 10th Revision [ICD-10]* code G12.21) at least 27 days apart with at least 1 claim from a neurologist visit or (2) having 1 or more claims for ALS and a prescription for riluzole or edaravone (2 medications approved for the treatment of ALS in the United States).

As edaravone potentially increases the risk of VTEs,<sup>7</sup> analyses were repeated excluding ALS cases with an edaravone prescription at any point during the study period (eTable 1, [links.lww.com/CPJ/A394](https://links.lww.com/CPJ/A394)).

### Control Definition

Controls were defined as patients who did not have medical claims containing ALS or motor neuron disease ICD codes (ICD-9 codes 335.2x or ICD-10 codes G12.2x, eTable 2, [links.lww.com/CPJ/A394](https://links.lww.com/CPJ/A394)) at any time during the study period. All potential motor neuron disease cases were excluded from the control group because this condition is similar or related to ALS.

### Index Date Definition

The index date for patients with ALS was defined as the date of the first ALS medical claim from the ALS case definition

during the study period. For non-ALS controls, the index date was randomly assigned during the same year as the index date year of the matched ALS case.

### Inclusion Criteria for the Study

ALS cases and controls without ALS were included if the following inclusion criteria were met: (1) age  $\geq 18$  years at index date, (2)  $\geq 6$  months of continuous enrollment in a medical benefit plan before the index date, (3) no VTE before the index date, and (4)  $\geq 30$  days of follow-up from the index date to the end of the study period.

### Analysis Sample and Case:Control Matching

All patients with ALS who met the eligibility criteria during the study period (January 1, 2004, to September 30, 2019) were included in the analysis sample. Controls were matched to ALS cases on age, sex, and the year of the index date with a case:control ratio of 1:5.

### Identification of VTE

The VTE definition used in this study was based on a combination of ICD codes and prescription of anticoagulants or VTE-related procedures (eTables 3 and 4, [links.lww.com/CPJ/A394](https://links.lww.com/CPJ/A394)).<sup>8</sup> VTE was defined as 1 or more diagnostic codes (ICD-9 and ICD-10), inpatient or outpatient (if inpatient, VTE was the primary diagnosis at discharge), and 1 or more anticoagulant prescriptions or 1 or more VTE-related procedures within 7 days before and 30 days after the diagnostic code date. The date of incident VTE was defined as the earliest VTE diagnostic code meeting the VTE definition above. In addition, DVT and PE were considered separately as outcomes. Analyses were repeated with the VTE definition expanded to include instances of 2 or more VTE diagnostic codes where 1 or more of the diagnostic codes were the primary diagnosis at hospital discharge. ICD-9 and ICD-10 codes used to identify VTE including DVT and PE are presented in eTable 2. ICD codes used for the categorization of the DVT location as lower extremity, upper extremity, or others are also presented in eTable 2.

### Additional Covariates

A hypercoagulable state was defined as claims for the following diagnostic codes at any point in the study period: ICD-9 codes for the primary hypercoagulable state (289.81), hemoglobinuria due to hemolysis from external causes (283.2), or antiphospholipid antibody with hemorrhagic disorder (286.53); or ICD-10 codes for activated protein C resistance (D68.51), prothrombin gene mutation (D68.52), other secondary thrombocytopenia (D69.59), antiphospholipid syndrome (D68.61), or paroxysmal nocturnal hemoglobinuria (D59.5). These disorders, either inherited or acquired, are known to significantly increase the risk for VTE.<sup>9</sup>

### Statistical Analysis

The follow-up time was calculated starting on the index date through either incident VTE date or censoring date (defined

**Table 1** Characteristics of ALS Cases and Matched Controls

	ALS cases (N = 4,205)	Controls (N = 21,025)
<b>Age at index date,<sup>a</sup> y</b>		
Mean (SD)	65.4 (12.0)	65.4 (12.0)
Median (range)	67 (21–90)	67 (21–90)
<b>Age at index date,<sup>a</sup> y, category, n (%)</b>		
<30	27 (0.6)	135 (0.6)
30–39	96 (2.3)	480 (2.3)
40–49	338 (8.0)	1,690 (8.0)
50–59	732 (17.4)	3,660 (17.4)
60–69	1,260 (30.0)	6,300 (30.0)
70–79	1,327 (31.6)	6,635 (31.6)
≥80	425 (10.1)	2,125 (10.1)
<b>Sex, n (%)</b>		
Female	1,814 (43.1)	9,070 (43.1)
Male	2,391 (56.9)	11,955 (56.9)
<b>Hypercoagulable state, n (%)</b>		
No	4,175 (99.3)	20,896 (99.4)
Yes	30 (0.7)	129 (0.6)

Abbreviation: ALS = amyotrophic lateral sclerosis.

<sup>a</sup> The index date for patients with ALS was defined as the date of the first ALS medical claim from the ALS case definition during the study period. For non-ALS controls, the index date was randomly assigned during the same year as the index date year of the matched ALS case.

as the end of the study period, disenrollment from medical benefit plan, or gap in medical benefit eligibility greater than 32 days). Descriptive statistics were used to describe the characteristics of ALS cases and controls. Means, SDs, medians, and ranges are reported for continuous variables and frequency counts and proportions for categorical variables. Incidence rates of VTE, DVT, and PE during the follow-up after the index date were reported per 1,000 person-years with Poisson 95% confidence intervals (CIs). Cox proportional hazard models were used to estimate the magnitude of the association between ALS case and control status and the occurrence of VTE during follow-up. Hazard ratios (HRs) and 95% CIs were reported. Analyses were conducted for the overall study population and stratified by sex (male, female) and by age at index date categories (18–49, 50–59, 60–69, and ≥70 years).

### Standard Protocol Approvals, Registrations, and Patient Consents

Data for these analyses were made available to the authors through a third-party license from Optum, a commercial data provider in the United States. Ethics committee approval was

not required for this study because of the use of secondary deidentified data.

### Data Availability

The datasets analyzed for the current study are not publicly available because of a licensing agreement with Optum. Data can be made available in an aggregate form on reasonable request from qualified investigators.

## Results

A total of 4,205 ALS cases were identified and matched to 21,025 controls by age and sex. Table 1 presents descriptive characteristics of the analysis sample. The mean age was 65.4 years (SD 12.0), and the median age was slightly higher at 67 years (range 21–90). Most cases were in the 60–69-year and 70–79-year age categories (30.0% and 31.6%, respectively). A higher proportion of patients with ALS were men (56.9%) than women (43.1%). Few cases and controls had ICD codes for hypercoagulable states (30 [0.7%] and 129 [0.6%], respectively).

The incidence of VTE is presented in Table 2. Overall, 132 cases (3.1%) experienced a VTE after the index date (median time to VTE 10.0 months) compared with 244 (1.2%) controls. The incidence rate among ALS cases was 19.9 per 1,000 person-years (95% CI 16.7–23.6) compared with 6.0 per 1,000 person-years among controls. ALS cases were about 3 times more likely to develop a VTE compared with controls (HR 3.30, 95% CI 2.6–4.0). Further adjustment for the hypercoagulable state did not alter the results. Results were similar by sex, with a slightly higher incidence rate in male ALS cases (21.5 per 1,000 person-years) compared with females (17.7 per 1,000 person-years).

Stratified analyses by age showed an increase in the incidence of VTE in older age among controls, whereas the incidence of VTE remained relatively constant among ALS cases. This resulted in a stronger association between ALS and VTE in younger age groups (HR 10.7 for age <50 years, 5.7 for age 50–59 years, 4.1 for age 60–69 years, and 2.1 for age ≥70 years; Figure 1).

Analyses were repeated for PE and DVT separately. The overall incidence of PE was 7.6 per 1,000 person-years in cases compared with 2.1 per 1,000 person-years in controls (HR 3.6, 95% CI 2.5–5.1; Table 3). The association of ALS and PE was stronger among men (HR 4.6, 95% CI 2.9–7.2) than in women (HR 2.5, 95% CI 1.4–4.5; Figure 2). The incidence of DVT was 14.1 per 1,000 person-years in ALS cases compared with 4.3 per 1,000 person-years among controls (HR 3.2, 95% CI 2.5–4.1). No differences were observed by sex (Table 4).

The distribution of the type of VTE was similar among ALS cases and controls with about 30% PEs and 70% DVTs

**Table 2** Incidence Rate of VTE and Association of ALS With VTE, Overall and Stratified by Sex and Age

	ALS cases	Controls
<b>All</b>	4,205	21,025
Patients with a VTE during follow-up, n (%)	132 (3.1)	244 (1.2)
Median time to VTE, mo	10.0	17.4
Incidence rate of VTE per 1,000 person-years (95% CI)	19.9 (16.7–23.6)	6.0 (5.3–6.8)
Hazard ratio (95% CI)	3.3 (2.6–4.0)	
<b>Men</b>	2,391	11,955
Patients with a VTE during follow-up, n (%)	84 (3.5)	133 (1.1)
Median time to VTE, mo	10.8	15.6
Incidence rate of VTE per 1,000 person-years (95% CI)	21.5 (17.1–26.6)	6.0 (5.0–7.1)
Hazard ratio (95% CI)	3.5 (2.7–4.6)	
<b>Women</b>	1,814	9,070
Patients with a VTE during follow-up, n (%)	48 (2.6)	111 (1.2)
Median time to VTE, mo	9.3	19.1
Incidence rate of VTE per 1,000 person-years (95% CI)	17.7 (13.1–23.5)	6.0 (4.9–7.2)
Hazard ratio (95% CI)	2.9 (2.1–4.1)	
<b>Age at index date</b>		
<50 y	461	2,305
Patients with a VTE during follow-up, n (%)	16 (3.5)	6 (0.3)
Median time to VTE, mo	13.0	8.7
Incidence rate of VTE per 1,000 person-years (95% CI)	16.7 (9.5–27.1)	1.6 (0.6–3.5)
Hazard ratio (95% CI)	10.7 (4.2–27.4)	
50–59 y	732	3,660
Patients with a VTE during follow-up, n (%)	32 (4.4)	27 (0.7)
Median time to VTE, mo	10.6	15.2
Incidence rate of VTE per 1,000 person-years (95% CI)	26.5 (18.1–37.5)	4.6 (3.0–6.6)
Hazard ratio (95% CI)	5.7 (3.4–9.5)	
60–69 y	1,260	6,300
Patients with a VTE during follow-up, n (%)	39 (3.1)	56 (0.9)
Median time to VTE, mo	9.9	13.4
Incidence rate of VTE per 1,000 person-years (95% CI)	21.0 (14.9–28.7)	4.8 (3.6–6.3)
Hazard ratio (95% CI)	4.1 (2.7–6.3)	
≥70 y	1,752	8,760

**Table 2** Incidence Rate of VTE and Association of ALS With VTE, Overall and Stratified by Sex and Age (continued)

	ALS cases	Controls
Patients with a VTE during follow-up, n (%)	45 (2.6)	155 (1.8)
Median time to VTE, mo	8.8	19.6
Incidence rate of VTE per 1,000 person-years (95% CI)	17.3 (12.6–23.1)	8.0 (6.8–9.4)
Hazard ratio (95% CI)	2.1 (1.5–3.0)	

Abbreviations: ALS = amyotrophic lateral sclerosis; CI = confidence interval; VTE = venous thromboembolism.

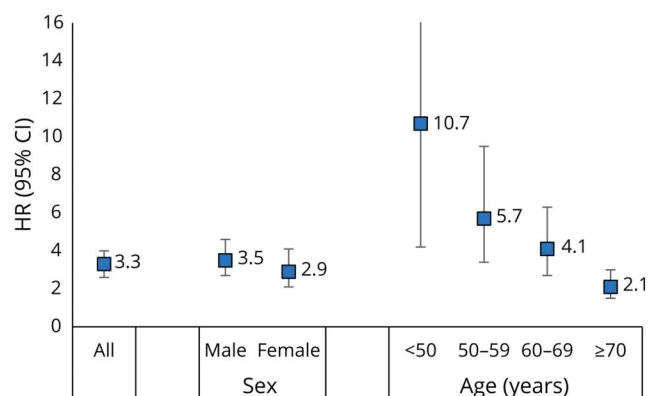
(Figure 3). Some differences were observed by sex, with a higher proportion of PEs among men (33.3% of cases vs 26.3% of controls) compared with women (22.9% of cases vs 32.4% of controls). Most DVTs affected the lower extremities (about 74%), with only about 12% in upper extremities.

Analyses repeated using the expanded VTE definition did not alter the results observed. Results are shown in eTable 5 (links.lww.com/CPJ/A394). Finally, analyses repeated excluding 60 (1.4%) ALS cases with a prescription for edaravone at any point in the study did not show substantial differences in observed results (eTable 1, links.lww.com/CPJ/A394).

## Discussion

The results of this study show that the incidence of VTE was higher in patients with ALS (19.9 per 1,000 person-years) compared with matched controls without ALS (6.0 per 1,000 person-years). Incidence rates for DVT and PE among ALS cases were 14.1 and 7.6 per 1,000 person-years, respectively. The risk of VTE was increased 3-fold in ALS compared with

**Figure 1** Association of Amyotrophic Lateral Sclerosis and Venous Thromboembolism



CI = confidence interval; HR = hazard ratio.

**Table 3** Incidence Rates of PE and Association of ALS With PE, Overall and by Sex and Age Categories

	ALS cases	Controls
<b>All</b>	4,205	21,025
<b>Patients with a PE during follow-up, n (%)</b>	51 (1.2)	86 (0.4)
<b>Median time to PE, mo</b>	12.2	19.2
<b>Incidence rate of PE per 1,000 person-years (95% CI)</b>	7.6 (5.7–10.0)	2.1 (1.7–2.6)
<b>Hazard ratio (95% CI)</b>	3.6 (2.5–5.1)	
<b>Men</b>	2,391	11,955
<b>Patients with a PE during follow-up, n (%)</b>	35 (1.5)	43 (0.4)
<b>Median time to PE, mo</b>	12	19.6
<b>Incidence rate of PE per 1,000 person-years (95% CI)</b>	8.8 (6.1–12.2)	1.9 (1.4–2.6)
<b>Hazard ratio (95% CI)</b>	4.6 (2.9–7.2)	
<b>Women</b>	1,814	9,070
<b>Patients with a PE during follow-up, n (%)</b>	16 (0.9)	43 (0.5)
<b>Median time to PE, mo</b>	13.6	19.1
<b>Incidence rate of PE per 1,000 person-years (95% CI)</b>	5.8 (3.3–9.5)	2.3 (1.7–3.1)
<b>Hazard ratio (95% CI)</b>	2.5 (1.4–4.5)	

Abbreviations: ALS = amyotrophic lateral sclerosis; CI = confidence interval; PE = pulmonary embolism.

**Table 4** Incidence Rates of DVT and Association of ALS With DVT, Overall and by Sex and Age Categories

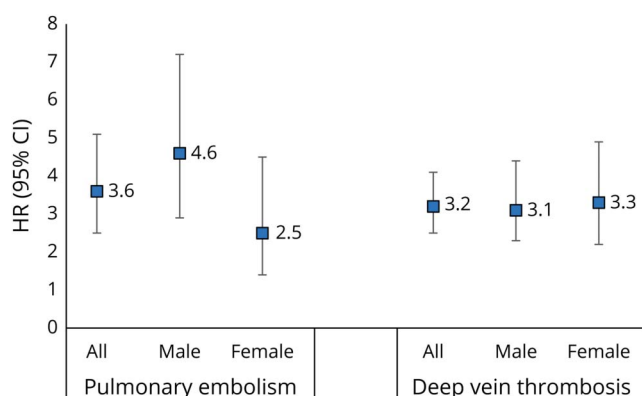
	ALS cases	Controls
<b>All</b>	4,205	21,025
<b>Patients with a DVT during follow-up, n (%)</b>	94 (2.2)	175 (0.8)
<b>Median time to DVT, mo</b>	10.1	16.7
<b>Incidence rate of DVT per 1,000 person-years (95% CI)</b>	14.1 (11.4–17.3)	4.3 (3.7–5.0)
<b>Hazard ratio (95% CI)</b>	3.2 (2.5–4.1)	
<b>Men</b>	2,391	11,955
<b>Patients with a DVT during follow-up, n (%)</b>	56 (2.3)	99 (0.8)
<b>Median time to DVT, mo</b>	11.5	14.1
<b>Incidence rate of DVT per 1,000 person-years (95% CI)</b>	14.2 (10.7–18.5)	4.5 (3.6–5.4)
<b>Hazard ratio (95% CI)</b>	3.1 (2.3–4.4)	
<b>Women</b>	1,814	9,070
<b>Patients with a DVT during follow-up, n (%)</b>	38 (2.1)	76 (0.8)
<b>Median time to DVT, mo</b>	9.3	20.7
<b>Incidence rate of DVT per 1,000 person-years (95% CI)</b>	13.9 (9.9–19.1)	4.1 (3.2–5.1)
<b>Hazard ratio (95% CI)</b>	3.3 (2.2–4.9)	

Abbreviations: ALS = amyotrophic lateral sclerosis; CI = confidence interval; DVT = deep vein thrombosis.

matched controls, with similar results observed among men and women. This association was more apparent in younger age groups, whereas the risk of VTE in the general population is lower (more than 10-fold increased risk at age <50 years

compared with a 2-fold increase in risk at age ≥70 years). Similar results were observed when examining the risk of DVT and PE separately, with the only difference being a larger magnitude of the risk of PE among men than in women.

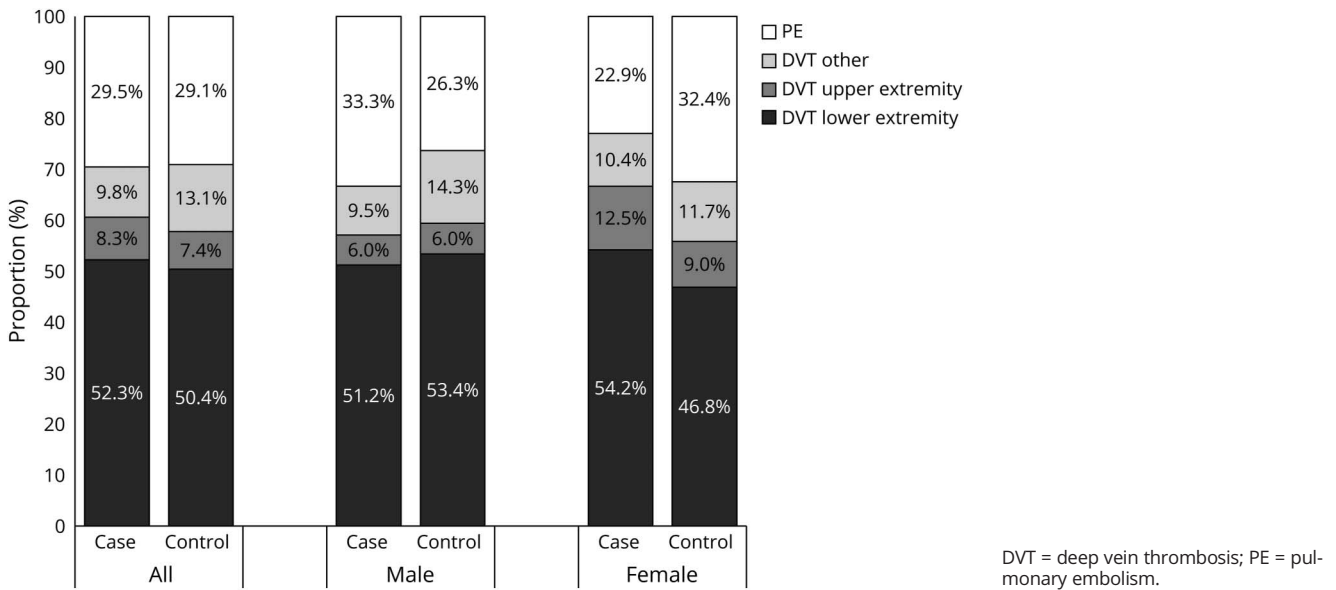
**Figure 2** Association of Amyotrophic Lateral Sclerosis With Pulmonary Embolism and Deep Vein Thrombosis



CI = confidence interval; HR = hazard ratio.

These results are consistent with previous reports of an increased incidence of VTE in ALS. Results from a retrospective study of 438 patients with ALS treated at a single US clinical center over a 4-year period (1999–2003) found that 13 patients (2.97%) had experienced VTE with an incidence rate of 33.1 per 1,000 person-years (95% CI 17.5–55.3), with the risk of VTE among nonambulatory patients 4.96 times higher (95% CI 1.39–17.78) compared with ambulatory patients. Of note, PE or PE + DVT was reported in 4 of 5 male patients who experienced VTE compared with 1 of 6 female patients.<sup>3</sup> A study of DVT among participants with ALS in 2 clinical trials reported DVT in 11 of 501 patients (2.2%) with an annual incidence rate of 2.7% (or 27 per 1,000 person-years).<sup>5</sup> A retrospective, single institution study in Australia focused on the occurrence of PE among patients with ALS over a 12 month period (2013–2014).<sup>4</sup> Four PE events were found among 130 patients with ALS, with

**Figure 3** Type of Incident Venous Thromboembolism Among Amyotrophic Lateral Sclerosis Cases and Controls



a 1-year cumulative incidence of 3.75% for PE. All patients with PE had a lower limb onset of ALS and lower functional scores. Finally, a prospective study following 50 patients with ALS from a single Canadian institution over a period of 1 year evaluated patients with bilateral venous duplex ultrasonography at enrollment and at 6 and 12 months. VTE was detected in 4 patients (1 symptomatic DVT, 1 symptomatic PE, and 2 asymptomatic DVT), with an 11.2% 1-year incidence rate.<sup>4</sup> Of note, 2 of the 4 VTE cases identified in this study were asymptomatic and may account for the higher incidence rate observed compared with rates from other studies and the present study where it is likely that only symptomatic cases were detected. Findings from these studies, indicating the higher incidence of VTE among nonambulatory patients with ALS and with lower limb onset and functional scores, are supportive of the hypothesis that an increased risk of VTE in ALS is associated with reduced lower extremity mobility. In addition, emerging evidence suggests that abnormalities in erythrocyte morphology in patients with ALS may contribute to the risk of aggregation and thrombosis.<sup>10</sup>

The strengths of this study include the use of a large sample of patients with ALS identified from a US claims database including over 100 million individuals. This real-world sample of patients with ALS from across diverse medical settings in the United States likely represents a more representative sample of patients with ALS than previous smaller and single-institution-based studies. In addition, ALS cases in this study were matched by age and sex to a large group of controls.

Limitations of this study are those of insurance claims data that include limited information on clinical characteristics of

ALS such as site of onset, functional scores, and immobility status. There is the possibility of misclassification with both ALS and VTE case definitions relying on diagnostic codes to identify both ALS and VTE cases. However, the use of diagnostic codes in combination with medication and procedure codes reduces the likelihood of misclassification. Another potential source of bias is surveillance bias among ALS cases whereby increased health care utilization may lead to an increased likelihood of VTE detection compared with non-ALS controls. Finally, the present analysis did not control for additional risk factors for VTE such as history of cardiovascular disease, cancer, recent surgery, or oral contraceptive and hormone therapy use. Although the history of malignancy and some cardiovascular conditions such as heart failure has been associated with an increased risk of VTE,<sup>11,12</sup> studies of the increase in the risk of ALS have shown modest effects with a history of cardiovascular disease overall and no association with traditional vascular risk factors such as hypertension, body mass index, and lipid levels.<sup>13,14</sup> Similarly, no relationship was observed between previous diagnosis of cancer and the subsequent risk of ALS.<sup>15-17</sup>

The findings of this study show an increased risk of VTE among patients with ALS compared with age- and sex-matched controls without ALS in a large sample obtained from a US claims database. The increased risk was consistent among both men and women, as well as for DVT and PE considered separately. These findings confirm results from previous smaller studies. Although current clinical guidelines for the management of ALS do not recommend prophylaxis for VTE,<sup>18,19</sup> the need for increased awareness and monitoring or screening for VTE risk in patients with ALS has been suggested.<sup>4,20</sup> This information may also be relevant in

## TAKE-HOME POINTS

- Results of this study conducted in a large US claims database show a higher incidence of VTE in 4,205 patients with ALS compared with 21,025 age- and sex-matched controls with no motor neuron disease.
- The risk of VTE was increased 3-fold in ALS compared with matched controls, with similar results observed among men and women and also when examining the risk of deep vein thrombosis and pulmonary embolism separately.
- These results are consistent with previously published data from smaller studies and suggest a need for increased awareness and monitoring for venous thromboembolism risk in patients with ALS.

the evaluation of the safety and efficacy of new therapies being developed for ALS.

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## Disclosure

V. Kupelian, L. Li, S. Eaton, T. Ferguson, and L. Fanning are employees of and hold stock/stock options at Biogen. E. Viscidi, S. Hall, A. Dilley, and N. Currier were employees of Biogen at the time the research was conducted. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/cp](https://www.neurology.org/cp).

## Publication History

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## Appendix Authors

Name	Location	Contribution
<b>Varant Kupelian, PhD</b>	Biogen, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
<b>Emma Viscidi, PhD</b>	Biogen, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
<b>Susan Hall, PhD</b>	Biogen, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content

## Appendix (continued)

Name	Location	Contribution
<b>Li Li, MS</b>	Biogen, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
<b>Susan Eaton, MSPH</b>	Biogen, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
<b>Anne Dilley, PhD</b>	Biogen, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
<b>Nicolas Currier, MD</b>	Biogen, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content
<b>Toby Ferguson, MD, PhD</b>	Biogen, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content
<b>Laura Fanning, MD</b>	Biogen, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data

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