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Original article

Recurrence rate of venous thromboembolic events in granulomatosis with polyangiitis

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Abstract

Objective. The incidence of first-time venous thromboembolic events (VTEs) is high in granulomatosis with polyangiitis (GPA). The incidence of recurrent VTEs is unknown. We aimed to describe the recurrence rate of second VTEs in patients with GPA.

Methods. Retrospective chart review was performed in patients with GPA and at least one VTE at a single centre from 2002 to 2016. Inclusion criteria were 1990 ACR criteria or 2012 Revised International Chapel Hill nomenclature for GPA, at least two follow-up visits, at least one VTE during the study period, and VTE occurrence after or within 3 months before GPA diagnosis. Second VTE event-free survival rates were estimated.

Results. Out of 147 patients initially screened for GPA and with at least one VTE, 84 met inclusion criteria. Median age at first VTE was 57 years. Incidence rate for second VTE was 8.4 events per 100 patient-years (95% CI: 5.7, 12.3). Eighty-three point three per cent of first VTEs and 57.7% of second VTEs occurred when disease was active ($P < 0.001$). Renal involvement and constitutional symptoms at the time of first VTE were associated with VTE recurrence.

Conclusion. GPA has a high rate of VTE recurrence compared with the reported data in the general population with unprovoked VTE. Our results suggest that VTE in GPA is a recurrent co-morbidity, not always during active vasculitis, and more so in those with renal involvement and constitutional symptoms at the time of first VTE.

CLINICAL SCIENCE

Lay Summary

What does this mean for patients?

Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is a group of diseases that cause inflammation of small blood vessels, referred to as vasculitis. Patients with AAV are at high risk of blood clots in the lower body and lungs. Patients who develop blood clots are often treated with blood thinners. However, we do not know how long patients should remain on blood thinners after their first blood clot. This is partly because we do not know whether blood clots are likely to recur in people with AAV. We studied 84 people with granulomatosis with polyangiitis (GPA), a type of AAV, who had at least one blood clot. We found that the recurrence of blood clots was higher in GPA patients than in the general population. The second blood clot did not always occur during active vasculitis. People with GPA who have disease in their kidneys owing to vasculitis and/or fever or weight loss are at higher risk of recurring blood clots. Our findings will help to guide future research into the monitoring of these patients, in addition to the length of time they should be treated with blood thinners.

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Key words: granulomatosis with polyangiitis, thrombosis, recurrence, venous thromboembolic events

Key messages

- The recurrence rate of venous thromboembolic events is higher in granulomatosis with polyangiitis patients than in the general population.
- Recurring venous thromboembolic events do not always occur during active vasculitis.
- Patients with renal involvement and constitutional symptoms are at highest risk of a second venous thromboembolic event.

Introduction

Patients with ANCA-associated vasculitis (AAV) are at risk for venous thromboembolic events (VTEs). Endothelial injury owing to neutrophilic activation, release of tissue factor and impaired thrombolytic mechanisms owing to anti-plasminogen antibodies have all been implicated in the pathogenesis of VTE in such patients [1]. The incidence rate of first-time VTE in granulomatosis with polyangiitis (GPA) was initially described by Merkel *et al.* [2] and found to be as high as 7.0 per 100 person-years, more so during active disease. However, more than one decade after VTEs were recognized as an important co-morbidity in GPA, the adequate duration of anticoagulation treatment in these patients is unknown [3]. This is mainly attributable to the knowledge gap regarding the clinical course of VTE in GPA, particularly the incidence rate of recurrence and time to recurrence. In this study, we characterized a cohort of GPA patients with at least one VTE, described the recurrence rate of second VTEs and its temporal relationship with disease activity and explored associations between clinical characteristics and the risk of developing a second VTE.

Methods

This retrospective chart review study included patients with GPA and at least one VTE at a single vasculitis centre from 2002 to 2016. The inclusion criteria were as follows: 1990 ACR criteria [4] or 2012 Revised International Chapel Hill nomenclature for GPA [5]; at least two follow-up visits at the study centre; at least one VTE documented during the study period; and VTE occurrence after diagnosis of GPA or within 3 months before GPA diagnosis. Patients who had their first VTE $\geq$3 months before their GPA diagnosis or were wheelchair bound before GPA diagnosis were excluded. This was in an effort to limit the likelihood that the first VTE was related to non-GPA factors. The institutional review board at the Cleveland Clinic approved the study. The institutional review board waived the requirements for written informed consent considering the nature of the study (retrospective chart review).

Data collection

Data were extracted from electronic medical records and paper charts when needed; data were stored in a secure Web database [Research Electronic Data Capture (REDCap)].

Demographic characteristics, GPA manifestations and treatment were collected. Active disease was defined as a BVAS for Wegener's granulomatosis (BVAS/WG) [6] score of at least one. The BVAS/WG score was extracted retrospectively from the electronic medical records 3 months pre- and post-VTE, and the highest score was chosen as the peri-VTE period score. Transient risk factors at the time of first and second VTEs were obtained; these included: major surgery (within 3 months of events), hospitalization (if VTE diagnosed after 48 h), central or peripherally inserted central catheters (at the time of VTE diagnosis), severe infection, medical intensive care unit admission (at the time of VTE diagnosis), active malignancy, prolonged travel ($\geq$6 h), heparin-induced thrombocytopenia and obesity (BMI $\geq$ 30 kg/m^2). Lastly, the presence of aPL and aspirin exposure at the time of first and second VTEs were also obtained.

VTE was defined as deep vein thrombosis or pulmonary embolism. Deep vein thrombosis was considered present if reported as acute through venous Doppler US. Pulmonary embolism was considered present if documented by CT angiography or if ventilation–perfusion scan showed high probability, or if the clinician decided to treat for pulmonary embolism when ventilation–perfusion scan reported intermediate probability. Deep vein thrombosis recurrence was defined as follows: thrombosis of a different extremity, thrombosis of other deep vein within the affected limb or proximal propagation of the known thrombus upon re-imaging as part of surveillance or upon the development of new symptoms. Recurrent pulmonary embolism was defined as a new symptom of dyspnoea, chest pain and/or hypoxaemia along with new filling defect on CT angiography or at least intermediate probability on ventilation–perfusion scan. Duration of anticoagulation and presence of inferior vena cava (IVC) filters at the time of second VTE was also collected.

For the incidence rate calculation, the initial date was the date of the initial VTE event, and the end date was

the last date of follow-up at the study centre or the date of the second VTE, whichever occurred first.

Analysis

Demographics, GPA characteristics and VTE type were reported as the mean or median, as appropriate. Kaplan–Meier survival analysis was used to estimate second VTE event-free survival rates. Factors associated with second VTE occurrence were assessed using univariate Cox proportional hazards models (when feasible) and log-rank tests, otherwise. Given the low number of recurrences, for age- and sex-adjusted results we used Firth's penalized estimates in the Cox model [7]. *P*-values of $\leq$5% were considered of statistical significance. GPA disease activity and transient risk factors for VTE were described as the frequency and percentage during the first and second VTE, and a *z*-test for partly overlapping proportions was used to assess statistically meaningful differences between both groups [8]. Statistical analysis was conducted through SAS software (v.9.4; Cary, NC, USA).

Results

Patients

Out of 147 patients initially screened for GPA and at least one VTE, 84 patients met inclusion criteria, with 63 patients excluded for the following reasons: 9 had incomplete data, 28 did not have GPA, 10 had VTE $\geq$3 months before GPA diagnosis, 4 had a first VTE that was chronic (or of indeterminate age), and in 12 the VTE documentation was not found. The median age at the time of GPA diagnosis and first VTE was 56 and 57 years, respectively. The majority of patients were Caucasian and male sex (Table 1). The median follow-up after the first VTE was 2.4 years (interquartile range: 0.6–5.5 years). There were 11 deaths during the study period: 3 owing to infection, 2 from interstitial lung disease, 1 from chronic obstructive pulmonary disease, 1 owing to failure to thrive associated with depression, 1 owing to metastatic renal carcinoma and 3 owing to an unknown reason.

Recurrence rate of second VTE

Out of the 84 patients with at least one VTE, 26 patients had a second VTE during the observation period (30.9%), yielding an incidence rate for second VTE of 8.4 events per 100 patient-years (95% CI 5.7, 12.3). Within the first 6 months, the incidence rate of second VTE was the highest at 31 events per 100 patient-years. The rate for the 0- to 3-year period was 11.9 per 100 patient-years. The median time to the second event was 10.6 years (Fig. 1). The cumulative recurrence rates at 3, 6 and 12 months, 3 and 5 years were 9.7, 13.8, 15.1, 27.1 and 27.1%, respectively. As a sensitivity analysis, death as a competing risk was evaluated, and the results were very similar to the primary analysis and are not presented.

Out of 26 patients with second VTEs: 5 had only IVC filters, 2 had IVC filters and anticoagulation (one was therapeutic on warfarin and the other on i.v. heparin), 3 were on anticoagulation alone (1 sub-therapeutic), 13 were off any treatment, and for 3 data were unknown.

Factors associated with VTE recurrence

Constitutional symptoms at the time of GPA diagnosis were associated with second VTE occurrence [hazard ratio (HR): 2.5 (95% CI: 1.1, 5.8)]. The same was true for renal involvement [HR: 3.4 (95% CI: 1.26, 9.2)] and constitutional symptoms [HR: 2.5 (95% CI: 1.08, 5.7)] at the time of the first VTE. Diffuse alveolar haemorrhage at the time of the first VTE was associated with increased risk of a second VTE, but the CI argued against statistical significance [HR: 2.2 (95% CI: 0.98, 4.9)]. Skin involvement at the time of GPA diagnosis and the first VTE was associated with a second VTE, but results adjusted for age and sex were not statistically significant (Table 1). Remission induction treatment with rituximab was used in 8 patients, MTX in 11 patients, CYC (either i.v. or oral) in 52 patients; the remaining patients were treated with CSs alone at the time of GPA diagnosis, and for 1 patient data were unknown. There was no statistically significant difference in the risk of a second VTE between those treated with CYC compared with rituximab [HR: 0.43 (95% CI: 0.12, 1.62), $P = 0.22$, adjusted for age and sex].

Among the types of VTEs, upper extremity deep vein thrombosis was associated with increased risk of a second VTE. The duration of anticoagulation after the first VTE was not associated with increased risk of a second VTE (Table 2). Use of aspirin was noted to be infrequent at the time of first and second VTEs, with five and three patients, respectively. aPL were tested infrequently at the time of the first VTE: 16 patients were tested for aCL, 11 patients were tested for B2-glycoprotein antibodies, and lupus anticoagulant was tested in 9 patients, with positive results only for aCL in 2 patients.

Disease activity and VTE

Regarding disease activity at the time of the first and second VTE, 89.3% of first VTEs and 57.7% of second VTEs occurred when disease was active ($P < 0.001$; Fig. 2). The median BVAS at first VTE was 8.5 *vs* 4.0 at the time of second VTE ($P = 0.030$).

Transient risk factors and VTE

First VTEs were more often associated with transient risk factors than second VTEs, and this difference was significant (Fig. 2). Transient risk factors were distributed equally among first and second VTEs, except for line-related VTEs, which were more common during first VTEs ($P = 0.037$ for *z*-test for paired overlapping proportions; Table 3).

Table 1 Demographic and clinical characteristics

Characteristic	Total ($n = 84$)	No recurrence ($n = 58$)	Recurrence ($n = 26$)	Unadjusted hazard ratio (95% CI)	Unadjusted *P*-value	Age-/sex-adjusted hazard ratio (95% CI)	Adjusted *P*-value
Age, years							
At GPA diagnosis	56 (43.0, 64.0)	57 (43.0, 64.0)	53 (43.0, 62.0)	1.00 (0.97, 1.03)	0.96[a]	1.00 (0.98, 1.03)	0.91[a]1
At first VTE	56.5 (45.5, 66.0)	57.5 (44.0, 67.0)	55.5 (46.0, 63.0)	1.00 (0.97, 1.02)	0.82[a]	1.00 (0.97, 1.03)	0.94[a]1
GPA duration, years	0.0 (0.0,1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.96 (0.85, 1.08)	0.51[a]	0.96 (0.85, 1.08)	0.48[a]
Sex							
Female	37 (44.0)	30 (51.7)	7 (26.9)	Reference	0.054[a]	Reference	0.054[a]2
Male	47 (56.0)	28 (48.3)	19 (73.1)	2.4 (0.98, 5.6)		2.4 (0.99, 5.6)	
Ethnicity							
Caucasian	82 (97.6)	56 (96.6)	26	Reference	0.54[b]	Reference	NA
African American	2 (2.4)	2 (3.4)	0	NA		NA	
Clinical characteristics at diagnosis							
DAH							
No	63 (75.0)	46 (79.3)	17 (65.4)	Reference	0.13[a]	Reference	0.18[a]
Yes	21 (25.0)	12 (20.7)	9 (34.6)	1.87 (0.83, 4.2)		1.75 (0.77, 4.0)	
Renal involvement							
No	31 (36.9)	20 (34.5)	11 (42.3)	Reference	0.83[a]	Reference	0.92[a]
Yes	53 (63.1)	38 (65.5)	15 (57.7)	1.09 (0.49, 2.5)		1.04 (0.46, 2.4)	
Peak creatinine*, mg/dl	2.1 (1.2,4.4)	1.8 (1.2,3.7)	3 (1.2,4.5)	0.99 (0.82, 1.21)	0.94[a]	0.99 (0.81, 1.20)	0.90[a]
ENT							
No	8 (9.5)	4 (6.9)	4 (15.4)	Reference	0.51[a]	Reference	0.38[a]
Yes	76 (90.5)	54 (93.1)	22 (84.6)	0.70 (0.24, 2.0)		0.62 (0.21, 1.81)	
Constitutional symptoms							
No	47 (56.0)	36 (62.1)	11 (42.3)	**Reference**	**0.027**[a]	**Reference**	**0.028**[a]
Yes	37 (44.0)	22 (37.9)	15 (57.7)	**2.5 (1.11, 5.6)**		**2.5 (1.1, 5.8)**	
Nervous system							
No	66 (78.6)	45 (77.6)	21 (80.8)	Reference	0.65[a]	Reference	0.60[a]
Yes	18 (21.4)	13 (22.4)	5 (19.2)	0.80 (0.30, 2.1)		0.77 (0.29, 2.1)	
Skin							
No	64 (76.2)	46 (79.3)	18 (69.2)	**Reference**	**0.048**[a]	Reference	0.074[a]
Yes	20 (23.8)	12 (20.7)	8 (30.8)	**2.5 (1.01, 6.0)**		2.3 (0.92, 6.0)	
Clinical characteristics at first VTE							
DAH*							
No	61 (74.4)	45 (80.4)	16 (61.5)	Reference	0.069[a]	Reference	0.054[a]
Yes	21 (25.6)	11 (19.6)	10 (38.5)	2.1 (0.94, 4.6)		2.2 (0.98, 4.9)	

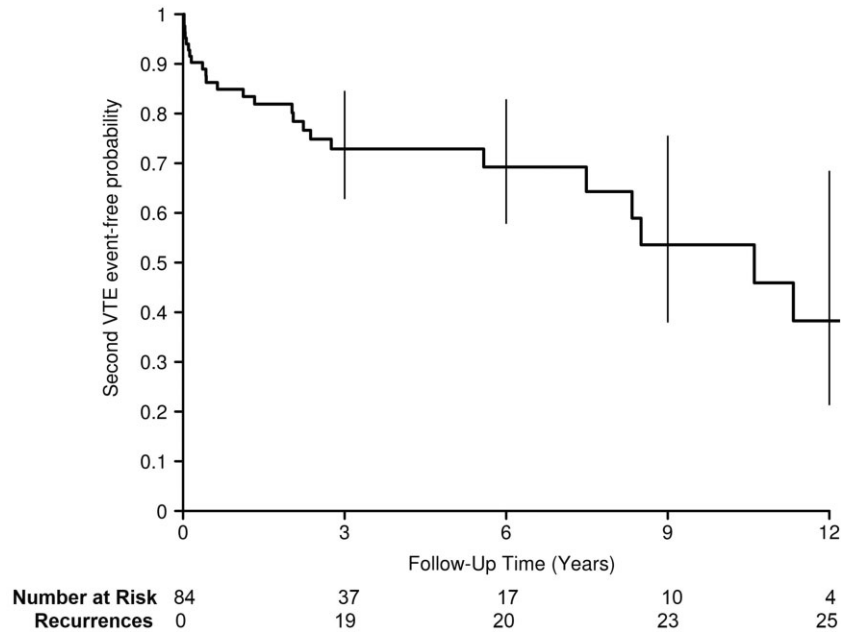
(continued)

Table 1 Continued

Characteristic	Total ($n = 84$)	No recurrence ($n = 58$)	Recurrence ($n = 26$)	Unadjusted hazard ratio (95% CI)	Unadjusted *P*-value	Age-/sex-adjusted hazard ratio (95% CI)	Adjusted *P*-value
Renal involvement*							
No	33 (40.2)	26 (46.4)	7 (26.9)	**Reference**	**0.043**[a]	**Reference**	**0.016**[a]
Yes	49 (59.8)	30 (53.6)	19 (73.1)	**2.5 (1.03, 6.3)**		**3.4 (1.26, 9.2)**	
ENT							
No	21 (52.6)	13 (23.2)	8 (30.8)	Reference	0.69[a]	Reference	0.62[a]
Yes	61 (74.4)	43 (76.8)	18 (69.2)	1.2 (0.50, 2.9)		1.26 (0.51, 3.1)	
Constitutional symptoms							
No	49 (59.8)	36 (64.3)	13 (50)	**Reference**	**0.034**[a]	**Reference**	**0.031**[a]
Yes	33 (40.2)	20 (35.7)	13 (50)	**2.4 (1.07, 5.4)**		**2.5 (1.08, 5.7)**	
Nervous system							
No	68 (82.9)	46 (82.1)	22 (84.6)	Reference	0.51[a]	Reference	0.43[a]
Yes	14 (17.1)	10 (17.9)	4 (15.4)	0.70 (0.24, 2.0)		0.65 (0.22, 1.90)	
Skin							
No	66(80.5)	48(85.7)	18 (69.2)	**Reference**	**0.021**[a]	Reference	0.055[a]
Yes	16(19.5)	8(14.3)	8 (30.8)	**2.8 (1.16, 6.5)**		2.4 (0.98, 6.1)	
Historical ANCA Positive ANCA, indirect immunofluorescence*							
No	8 (9.8)	7 (12.5)	1 (3.8)	Reference	0.21[a]	Reference	0.078
Yes	74 (90.2)	49 (87.5)	25 (96.2)	3.57 (0.49, 25.0)		6.8 (0.81, 57.6)	
iANCA type, by enzyme linked immunoassay *							
PR3	62 (92.5)	38 (88.4)	24 (100.0)	Reference	0.13[b]	Reference	NA
MPO	5 (7.5)	5 (11.6)	0 (0.0)	NA		NA	

Statistics are presented as the mean (S.D.), median [percentile 25, percentile 75] or *n* (column percentage). *P*-values: [a]Cox model Wald test; [b]log-rank test. *Data not available for all subjects: missing peak creatinine at diagnosis: 33; missing DAH at first event: 2; missing renal involvement at first event: 2; missing ANCA IFF results: 2; missing ANCA ELISA: 4. Notes: 1 = sex adjusted only, 2 = age at diagnosis adjusted only. DAH: Diffuse alveolar haemorrhage; GPA: granulomatosis with polyangiitis; NA: not applicable; VTE: venous thromboembolic events. Bold text highlights statistically significant results.

Fig. 1 Kaplan–Meier second venous thromboembolic event-free probability



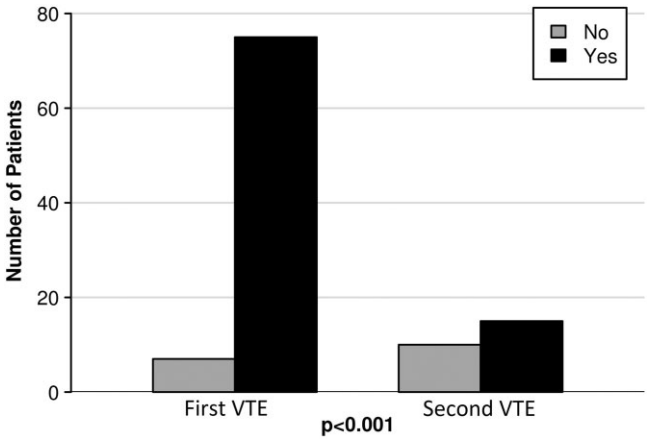
VTE: venous thromboembolic event.

Table 2 Venous thromboembolic event type and duration of treatment

VTE type	Total ($n = 84$)	No recurrence ($n = 58$)	Recurrence ($n = 26$)	Unadjusted hazard ratio (95% CI)	Unadjusted *P*-value	Age-/sex-adjusted hazard ratio (95% CI)	Adjusted *P*-value
Upper extremity							
No	72 (85.7)	54 (93.1)	18 (69.2)	**Reference**	**<0.001**[a]	**Reference**	**<0.001**[a]
Yes	12 (4.3)	4 (6.9)	8 (30.8)	**5.5 (2.2, 13.6)**		**4.8 (1.89, 12.0)**	
Lower extremity							
No	22 (26.2)	15 (25.9)	7 (26.9)	Reference	0.43[a]	Reference	0.20[a]
Yes	62 (73.8)	43 (74.1)	19 (73.1)	0.70 (0.29, 1.69)		0.53 (0.20, 1.41)	
Pulmonary embolism							
No	55 (65.5)	34 (58.6)	21 (80.8)	Reference	0.20[a]	Reference	0.36[a]
Yes	29 (34.5)	24 (41.4)	5 (19.2)	0.53 (0.20, 1.41)		0.63 (0.23, 1.71)	
Pulmonary embolism + lower extremity							
No	68 (81.0)	45 (77.6)	23 (88.5)	Reference	0.41[a]	Reference	0.42[a]
Yes	16 (19.0)	13 (22.4)	3 (11.5)	0.60 (0.18, 2.0)		0.61 (0.18, 2.1)	
Other VTE							
No	82 (97.6)	57 (98.3)	25 (96.2)	Reference	0.63[a]	Reference	0.82[a]
Yes	2 (2.4)	1 (1.7)	1 (3.8)	1.63 (0.22, 12.2)		1.28 (0.15, 11.2)	
Duration of anticoagulation, months							
≤3	7 (11.5)	6 (12.5)	1 (7.7)	Reference	0.42[a]	Reference	0.53[a]
4–6	19 (31.1)	17 (35.4)	2 (15.4)	0.39 (0.05, 9.3)		0.43 (0.03, 5.4)	
7–11	9 (14.8)	5 (10.4)	4 (30.8)	1.68 (0.18, 15.9)		1.67 (0.15, 18.4)	
≥12	26 (42.6)	20 (41.7)	6 (46.2)	0.72 (0.08, 6.2)		1.10 (0.10, 11.7)	

Statistics are presented as *n* (column percentage). *P*-values: [a]Cox model Wald test; [b]log rank test. VTE: venous thromboembolic event. Bold text highlights statistically significant results.

Fig. 2 Active disease during first and second venous thromboembolic events



P-value from *z*-test for partly overlapping proportions. VTE: venous thromboembolic event.

Table 3 Transient risk factors for venous thromboembolic events

Factor	Total ($n = 110$)	First ($n = 84$)	Second ($n = 26$)	*P*-value
Major surgery (within 3 months of events)				0.88[a]
Yes	18 (16.4)	14 (16.7)	4 (15.4)	
No	92 (83.6)	70 (83.3)	22 (84.6)	
Current hospitalization (if diagnosed after 48 h)				0.45[a]
Yes	33 (32.0)	27 (33.8)	6 (26.1)	
No	70 (68.0)	53 (66.3)	17 (73.9)	
Central, PICC and midlines (at the time of VTE diagnosis)*				***0.037***[a]
Yes	12 (11.8)	12 (15.4)	0 (0.0)	
No	90 (88.2)	66 (84.6)	24 (100.0)	
Severe infection				0.60[a]
Yes	18 (16.4)	13 (15.5)	5 (19.2)	
No	92 (83.6)	71 (84.5)	21 (80.8)	
MICU admission among hospitalized*				0.10[a]
Yes	17 (53.1)	12 (46.2)	5 (83.3)	
No	15 (46.9)	14 (53.8)	1 (16.7)	
Active malignancy				0.27[a]
Yes	3 (2.7)	3 (3.6)	0 (0.0)	
No	107 (97.3)	81 (96.4)	26 (100.0)	
Prolonged travel (>6 h)				0.76[a]
No	100 (90.9)	76 (90.5)	24 (92.3)	
Yes	10 (9.1)	8 (9.5)	2 (7.7)	
Thrombophilia (HIT only)				0.62[a]
No	107 (97.3)	82 (97.6)	25 (96.2)	
Yes	3 (2.7)	2 (2.4)	1 (3.8)	
Obesity (BMI ≥ 30 kg/m^2)*				0.23[a]
<30 kg/m^2	46 (52.3)	32 (49.2)	14 (60.9)	
≥ 30 kg/m^2	42 (47.7)	33 (50.8)	9 (39.1)	

Statistics are presented as the mean (S.D.), median [P25, P75], median (minimum, maximum) or *n* (column percentage). *P*-values: [a]*z*-test for paired overlapping proportions. *Data not available for all subjects. Missing values: current hospitalization (if diagnosed after 48 h): 7; central, PICC and midlines (at the time of VTE diagnosis): 8; MICU admission among hospitalized: 1; obesity (BMI ≥ 30 kg/m^2): 22. HIT: heparin-induced thrombocytopenia. MICU: Medical intensive care unit; PICC: peripherally inserted central catheters. Bold text highlights statistically significant results.

Discussion

The main finding of our study is a high recurrence rate of second VTEs in patients with GPA, which was 8.4 per 100 patient-years, highest within the first 6 months (31 events per 100 patient-years). These results are higher than the overall and 6-month recurrence rate of VTE among the general population (4.9 and 11.1 per 100 person-years, respectively) [9]. Our results are comparable to those of patients with cancer (9.6 per 100 patient-years total recurrence and 22.1 per 100 patient-years within the first 6 months) [10], which reflects the magnitude of this co-morbidity in GPA.

Male sex was associated with increased risk of a second VTE (HR: 2.4); however, the 95% CI was not statistically significant, and a firm association cannot be inferred from our data. The association of male sex with a higher recurrence rate of second VTE has been reported previously in the general population with unprovoked VTE [11, 12], and it is possible that the sample size influenced our results.

Regarding clinical manifestations of GPA and a second VTE, patients with renal involvement at the time of first VTE had a higher risk of developing a second VTE. Diffuse alveolar haemorrhage at the time of the first VTE was associated with a higher risk of a second VTE, but the results were not statistically significant, perhaps owing to the sample size. Factors associated with the recurrence of VTEs in GPA have not been explored previously. However, the association of severe forms of GPA and VTE (in general) was described by Kronbichler *et al.* [13], who reported that features such as pulmonary haemorrhage, presence of red blood cell casts and cardiovascular involvement were associated with VTE. Most recently, Moiseev *et al.* [14] showed an association between renal and pulmonary involvement and a higher incidence of VTE in AAV. Another clinical manifestation that has been associated with VTE in AAV is skin involvement, but our adjusted results did not parallel such findings [13, 14]. The association between second VTE and the presence of constitutional symptoms at the time of GPA diagnosis and first VTE in this cohort is not surprising, because constitutional symptoms might be indirect markers of the systemic inflammatory response and endothelial activation.

When assessing disease activity during VTE, patients had active vasculitis in 89% of first events, similar to results reported by Merkel *et al.* [2]. However, about half of second VTE occurred while the disease was in clinical remission, suggesting that GPA patients might be procoagulable even while in clinical remission. The latter could potentially be explained by subclinical active vasculitis, leading to a pro-coagulable milieu in a subgroup of patients, or by other pro-coagulable factors unrelated to the vasculitis (i.e. factor V Leiden mutation, protein C/S deficiency and aPL) that were not documented, or by a pro-coagulable state inherent to GPA even when in remission, such as suggested by Mendoza *et al.* [15], who reported that AAV patients who developed VTE had higher microparticle tissue factor activity and antiplasminogen antibodies than AAV patients without VTE, even during remission. Hilhorst *et al.* [16], also suggested that AAV patients in remission are hypercoagulable, as supported by their finding that patients in remission had higher endogenous thrombin potential when compared with healthy controls, in addition to elevated factor VIII, suggesting persistent endothelial activation/dysfunction that might translate into clinical procoagulability. It is important to highlight that 5 of 26 VTEs occurred in patients with IVC filters (without anticoagulation), raising the question of whether such events might be related directly to IVC filters.

The first VTE was more often associated with transient risk factors than the second VTE. VTEs related to i.v. lines were more common for first VTE than the second VTE, perhaps because these patients were severely ill at the time of the first VTE, as evidenced by a significantly higher median BVAS/WG than the median BVAS during the second VTE.

This study has some key strengths. It is the first study specifically investigating the rate of VTE recurrence in GPA. It is also the largest group of patients with GPA and at least one VTE described to date. Lastly, the study was performed at a vasculitis centre, where detailed review of systems and disease activity is assessed at each visit.

We acknowledge the limitations of the study. For the first VTE episode, only symptomatic patients were included, because tests were ordered based on clinical manifestations; therefore, it is possible that the first asymptomatic VTE was not captured and that the incidence rate of second VTEs was underestimated. The recurrence rate of second VTE in non-severe GPA might be lower than seen in this cohort, which had particularly high BVAS/WG scores at diagnosis and at the time of the first VTE, limiting the generalizability of results. Lastly, although transient risk factors were documented uniformly, pro-coagulable states, such as the presence of aPL, were not obtained uniformly by the multidisciplinary treating team. This might reflect the fact that VTE in GPA patients is often considered to be a provoked event; therefore, other aetiologies might not always be explored. However, aPL have been implicated in the pathogenesis of VTE in AAV [17], and we cannot exclude the possibility that the patients with recurring VTE had this or other pro-coagulable factors that were not captured.

In conclusion, the recurrence rate of second VTE was higher in GPA than in the general population with unprovoked VTE and closer to the rates reported in the cancer population. Second VTEs do not always occur during clinically apparent active vasculitis. VTEs in GPA patients, rather than a single event occurring merely during clinically apparent active disease, might be a recurring process that requires longer surveillance and therapy, particularly in those with renal involvement and constitutional symptoms. There is a great need for prospective studies that can explore the pathophysiology of recurrent VTE further and estimate the risks and benefits

of prolonged anticoagulation therapy in this unique patient population.

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Data availability statement

The data that support the findings of this study could be available from the leading author (Alexandra Villa Forte, MD, MPH) upon reasonable request. The data are not publicly available due to restrictions, e.g. their containing information that could compromise the privacy of the study population.

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