

Venous Thrombotic Events in ANCA-Associated Vasculitis: Incidence and Risk Factors

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Abstract

Background The incidence of venous thromboembolism (VTE) is increased in ANCA-associated vasculitis (AAV). We assessed the frequency of VTE observed among patients with AAV evaluated at our center and identified risk factors.

Methods Patients from the Johns Hopkins Vasculitis Center cohort who were evaluated between 1998 and 2018 and had a diagnosis of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) were eligible for analysis. Baseline demographics and clinical and serologic data were extracted. Univariate and multivariate analyses were performed to identify factors associated with VTE in AAV.

Results A total of 162 patients with AAV were identified, 105 (65%) with GPA; 22 (14%) of these patients had a recorded VTE with a median time to VTE of 1 month. The mean (SD) age in the VTE versus non-VTE groups was 54±20 versus 55±17 years ($P=0.99$), 64% versus 60% female ($P=0.93$), 82% versus 49% PR3-ANCA positive ($P=0.01$), with a total mean BMI of 33.3±5.7 versus 28.3±6.1 kg/m², ($P<0.001$) respectively. The median Birmingham Vasculitis Activity Score (BVAS version 3) was 19 versus 14 ($P=0.02$). Univariate analyses identified PR3-ANCA, rapidly progressive GN (RPGN), and hypoalbuminemia. In multivariate analysis, the significant associations with VTE included PR3-ANCA (OR, 4.77; $P=0.02$), hypoalbuminemia (OR, 4.84; $P=0.004$), and BMI (OR, 1.18; $P<0.001$).

Conclusions VTE is a surprisingly common complication of AAV. PR3-ANCA and hypoalbuminemia are risk factors for developing VTEs. Further studies are needed to confirm these findings.

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Introduction

Recent studies have noted an increased incidence of venous thromboembolisms (VTEs) during active flares of ANCA-associated vasculitis (AAV) (1). A landmark analysis of 33 autoimmune disorders in a Swedish cohort found a standardized incidence rate of 6.57 within the first year of diagnosis in patients with granulomatosis with polyangiitis (GPA) (2). The Wegener's Clinical Occurrence of Thrombosis (WECLLOT) study showed an incidence rate of 7.0 for first VTE per 100 person-years, whereas a healthy, demographically matched Swedish population had a VTE incidence rate of 0.31 per 100 person-years (3). In patients without active vasculitis, there is evidence of hypercoagulability with increased thrombin formation (4) and risk of VTE remains elevated (1).

A large retrospective cohort study of AAV subtypes found VTE incidences of 8.2% among patients with eosinophilic GPA, 8% among patients with GPA, and 7.6% among patients with microscopic polyangiitis (MPA) (5). A recent study of trial data from the European Vasculitis Study Group found C-reactive protein (CRP), cutaneous involvement, gastrointestinal involvement, and worsening renal function to be associated with

increased risk of VTE among patients with GPA and MPA (6). Patients with AAV also have a greater risk of cardiovascular events, such as acute coronary syndrome, new onset angina, peripheral vascular disease, and transient ischemic attacks, which can be seen in patients with prothrombotic states (7).

The pathophysiology of thrombotic events in AAV is not well understood. Several studies have sought to uncover molecular determinants of active vasculitis. There is increased recognition that antibodies against proteinase-3 (PR3) correlates well with the incidence of VTE (6,8). A slightly older study, however, did note a protective effect of PR3-ANCA (1). More recent studies have identified plasminogen as a potential target antigen in patients with PR3 vasculitis and demonstrated its interaction with autoantibodies directed toward complementary PR3, leading to decreased plasmin levels and fibrinolysis with a subsequent hypercoagulable state (9,10). Additionally, it is increasingly appreciated that neutrophil α -defensins—antimicrobial particles released from activated neutrophils—and neutrophilic-endothelial interactions play a significant role in thrombosis among patients with AAV (11,12). In this study, we aimed to determine the incidence of

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VTE in a well characterized, single center cohort and uncover new factors that may be associated with increased risk of thrombosis.

Materials and Methods

Patients

Our cohort was derived from patients enrolled in an institutional review board–approved database at the Johns Hopkins Vasculitis Center. Patients with a diagnosis of AAV between 1998 and 2018 were included in this study. They were classified as GPA, MPA, or eosinophilic GPA, based on the 2012 Chapel Hill Consensus Nomenclature (13). Patients were further stratified by ANCA type. Information related to patient demographics, serum albumin, CRP, renal function, proteinuria assessed on a spot urine sample, comorbidities, newly diagnosed/relapsing disease, specific organ involvement, and details of remission induction therapy and concomitant medications were obtained by review of electronic medical records. Disease activity at diagnosis and at the time of VTE was quantified

retrospectively with the Birmingham Vasculitis Activity Score version 3 (BVAS 3) (14). Damage was quantified with the Vasculitis Damage Index (VDI) (15). GFR was estimated using the CKD Epidemiology Collaboration formula (16). Obesity was defined as body mass index (BMI) >30 kg/m². Rapidly progressive GN (RPGN) was defined as at least a 20% decrease in eGFR over a 2-week period along with hematuria and proteinuria. VTE was defined as the presence of either deep venous thrombosis (DVT), pulmonary embolism (PE), or both.

Statistical Analysis

Baseline characteristics of patients are displayed as mean \pm SD or quantity (%) for continuous and categorical variables, respectively. Characteristics between patients with and without VTE were assessed with the Wilcoxon rank sum test for continuous and the chi-squared test for categorical data. To elucidate factors associated with VTE, univariate logistic regression models were performed with $P < 0.05$ considered significant. For every significant parameter in univariate analyses, multivariate logistic models

Table 1. Demographics and baseline characteristics of patients with ANCA-associated vasculitis

Characteristic	VTE	No VTE	<i>P</i> Value
Subjects	22	140	
Age of onset, yr	54.2 \pm 19.7	55.1 \pm 16.9	0.99
Female sex	14 (64)	84 (60)	0.93
Length of follow-up, mo	57.3 \pm 72.2	72.9 \pm 61.6	0.04 ^a
Diagnosis			0.68
GPA	16 (73)	89 (64)	
MPA	6 (27)	50 (36)	
ANCA associations			0.01 ^a
PR3-ANCA	18 (82)	68 (49)	
MPO-ANCA	4 (18)	67 (48)	
None	0 (0)	5 (4)	
Smoking status			0.41
Never	13 (59)	94 (67)	
Prior	9 (41)	41 (29)	
Current	0	5 (4)	
Weight, kg	96.3 \pm 22.9	81.3 \pm 20.8	0.005 ^a
Height, m	1.68 \pm 0.14	1.68 \pm 0.11	0.56
BMI, kg/m ²	33.3 \pm 5.7	28.3 \pm 6.1	$<0.001^a$
Obesity (BMI ≥ 30 kg/m ²)	15 (68)	48 (34)	0.01 ^a
Baseline creatinine, μ mol/ml, mean (SD)	3.0 \pm 1.9	3.0 \pm 2.9	0.29
Baseline GFR, ml/min, mean (SD)	35.7 \pm 29.6	46.3 \pm 38.8	0.48
Alveolar hemorrhage, <i>n</i> (%)	5 (23)	11 (8)	0.08
Rapidly progressive GN, <i>n</i> (%)	12 (55)	36 (26)	0.01 ^a
Treated hypertension, <i>n</i> (%)	13 (59)	77 (55)	0.89
Statin treatment, <i>n</i> (%)	8 (36)	47 (34)	0.98
C-reactive protein (0–0.5 mg/L), mean (SD)	14.0 \pm 21.8	9.4 \pm 23.2	0.14
Proteinuria (grams/d), mean (SD), mean (SD)	2.95 \pm 0.66 (20)	3.69 \pm 0.70 (115)	$<0.001^a$
Hypoalbuminemia (<3.0 g/dl), <i>n</i> (%)	12 (55)	24 (17)	$<0.001^a$
Proteinuria (>3500 mg), <i>n</i> (%)	0/20	14/115 (12)	0.21
Rituximab induction, <i>n</i> (%)	17 (77)	83 (59)	0.16
Cyclophosphamide induction, <i>n</i> (%)	8 (36)	66 (47)	0.48
History of malignancy, <i>n</i> (%)	0	6 (4)	0.61
Use of aspirin/clopidogrel/warfarin			0.59
Aspirin	4 (18)	18 (13)	
Clopidogrel	0	0	
Warfarin	0	4 (3)	
BVAS at diagnosis, median (range)	19 (5–26)	14 (2–28)	0.01 ^a

VTE, venous thromboembolism; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; PR3, proteinase-3; MPO, myeloperoxidase; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score.

^aStatistically significant ($P < 0.05$).

were constructed, adjusting for age, gender, and weight. The strength of each variable's association with VTE is presented as an odds ratio (OR) with 95% confidence intervals (95% CIs) and *P* values. All statistical analyses were performed with RStudio version 1.2.5001 (RStudio, Inc., Boston, MA).

Results

Patient Characteristics

This retrospective cohort study included 162 patients with AAV. We stratified all analyses by VTE and non-VTE subgroups (see Table 1). A total of 22 subjects (14%) had recorded VTEs, 13 of which were DVTs, four PEs, and five had both. Of the 22 patients, 20 experienced VTE during active disease whereas the remaining two were in disease remission at the time of VTE. There was no preceding history of trauma or surgery in patients who developed VTE. There was no prior history of DVT or PE in the VTE group. The median time to VTE was 1 month (range 1–239 months). Overall, a significantly higher BVAS at diagnosis was seen in patients with VTE: 19 (5–24) versus 14 (2–28), *P*=0.01. Of the 86 patients who were PR3-ANCA positive, 18 were found to have VTE, whereas four of 71 who were positive for myeloperoxidase (MPO)-ANCA had VTE (*P*=0.01). Looking at classic comorbidities and risk factors for VTE, there were significant differences in weight (96.3 kg versus 81.3 kg, *P*=0.005) and BMI (*P*<0.001) between the two groups. Notably, there were no significant differences between other characteristics, including gender, age, smoking status (never, prior, current), eGFR, nephrotic range proteinuria, hypertension, statin use, anticoagulation/antiplatelet therapy, use of rituximab or cyclophosphamide for induction therapy, or presence of alveolar hemorrhage.

Logistic Regressions

Univariate logistic regressions were performed to identify variables that might be significantly associated with the development of VTEs. Classic risk factors such as BMI (OR, 1.1; 95% CI, 1.0 to 1.2; *P*=0.002) and the presence of obesity (OR, 3.3; 95% CI, 1.3 to 9.4; *P*=0.02) significantly increased risk of VTE (Supplemental Table 1). The presence of RPGN also significantly increased risk of VTE (OR, 3.47; 95% CI, 1.38 to 8.89; *P*=0.008). Hypoalbuminemia (<3.0 g/dl) also increased VTE risk (OR, 5.70; 95% CI, 2.22 to 15.03; *P*<0.001). BVAS scores were separated into low (<8),

medium (<16), high (<24), and extreme (≥24) categories. For each subsequent level of activity, the odds of developing VTE increased significantly (OR, 1.82; 95% CI, 1.06 to 3.30; *P*=0.04). Higher BVAS cutaneous (OR, 3.32; 95% CI, 1.19 to 8.92; *P*=0.02) and BVAS chest (OR, 4.01; 95% CI, 1.41 to 14.43; *P*=0.02) scores were also associated with VTE, whereas other BVAS and VDI subtypes were not. There was also no evidence of a relationship between the development of VTE and age, gender, CRP, or presence of alveolar hemorrhage. Additional BVAS and VDI analyses are included in Supplemental Tables 1 and 2.

A multivariate regression model was constructed and used to confirm associations demonstrated by univariate analyses (Table 2). The presence of PR3-ANCA versus MPO-ANCA increased the odds of developing VTE significantly (OR, 4.77; 95% CI, 1.32 to 20.77; *P*=0.02). Hypoalbuminemia (OR, 5.84; 95% CI, 1.78 to 20.69; *P*=0.004) and the classic risk factor of BMI (OR, 1.16; 95% CI, 1.05 to 1.27; *P*=0.002) were both significant factors in the development of VTE in the data set. BVAS activity level, RPGN, age of onset, and gender were not determined to be significant.

Discussion

Thrombosis is recognized as a significant consequence of AAV, particularly during active disease. Although classic risk factors for VTE were identified in our study, several disease-specific variables persisted throughout analyses. Gender and age were not significantly associated in our multivariate analyses, confirming a previous study (6). Notably, episodes of VTE occurred within 1 month of diagnosis in our data set, demonstrating the role of disease activity in determining VTE risks (1). These findings are consistent with prior studies, specifically the WECLLOT trial which found VTE occurred a median of 2.1 months after active disease (3). In our study, VTEs occurred in 14% of patients with AAV. Importantly, we were able to confirm the association of PR3-ANCA and hypoalbuminemia with VTE incidence in our data set (6,17). We were unable to confirm a previously seen association between alveolar hemorrhage and VTE in our data set, likely due to the limited number of patients with alveolar hemorrhage in our data set (8).

Our study confirms a strong relationship between PR3-ANCA and VTE risk, as seen in prior studies (6,8). In contrast, VTE incidence was higher in patients with MPO-ANCA in a retrospective study by Stassen *et al.* (1). The reason for this discrepancy is unclear. These observations, therefore, further support a pathogenic role for antiplasminogen antibodies, previously observed in patients with PR3-ANCA, and their interactions with a highly restricted motif on plasminogen resulting in decreased conversion of plasminogen to plasmin and a subsequent increase in thrombotic potential (9,10,17). These results further highlight the role of endothelial damage, likely propagated by neutrophil-endothelial interactions in a proinflammatory state in patients with AAV (11,12).

High BMI was associated with a higher risk of VTE. High BMI, being a risk factor for metabolic syndrome, induces a proinflammatory state in AAV, promoting a procoagulant state and increased VTE risk (18). We were able to confirm a relationship between disease activity, specifically

Table 2. Multivariate logistic regression

Characteristic	Odds Ratio (95% CI)	<i>P</i> Value
Age of onset, yr	1.02 (0.99 to 1.07)	0.21
Female sex	1.12 (0.36 to 3.61)	0.85
BMI, kg/m ²	1.18 (1.08 to 1.31)	<0.001 ^a
PR3-ANCA	4.77 (1.32 to 20.77)	0.02 ^a
Hypoalbuminemia	5.84 (1.78 to 20.69)	0.004 ^a
RPGN	2.60 (0.80 to 8.72)	0.11
BVAS level (low, medium, high, extreme)	1.17 (0.57 to 2.44)	0.68

BMI, body mass index; PR3, proteinase-3; RPGN, rapidly progressive GN; BVAS, Birmingham Vasculitis Activity Score.
^aStatistically significant (*P*<0.05).

hypoalbuminemia, and risk of VTE (17). Albumin has antithrombotic effects and contributes to increased VTE risk (19). In addition, in the setting of hypoalbuminemia, there is increased hepatic production of factors V and VIII and fibrinogen as a compensatory mechanism. We were unable to confirm an association between CRP levels and VTE (6). We were also unable to confirm whether increasing activity levels at diagnosis, identified by higher BVAS activity levels (low, medium, high, extreme), resulted in more VTEs.

There are several limitations to this study. First, the median time to VTE is assessed from the time of diagnosis rather than the date of disease onset, which may not be the same. Measurements for other known predisposing factors for VTE like factor VIII level, protein S, antithrombin III, factor V Leiden, and markers of endothelial function were not performed in this study. Additionally, VTEs were diagnosed clinically and not through routine screening, and the cohort did not undergo intermittent prophylactic screening.

Overall, this study found a significant association between PR3-ANCA and hypoalbuminemia with the incidence of VTE. BMI persisted in our multivariate models as a significant risk factor for VTE. We were unable to confirm previously observed relationships such as alveolar hemorrhage with VTE. Developing a metric or biomarker of PR3-plasminogen interactions, the extent of neutrophilic-endothelial damage, and neutrophil α -defensins in AAV may offer clinicians the potential to stratify patients and determine need for prophylactic anticoagulation.

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Author Contributions

B. Antiochos, E. Gapud, D. Geetha, and B. Isaacs were responsible for methodology and resources; B. Antiochos, E. Gapud, D. Geetha, and P. Seo reviewed and edited the manuscript; E. Gapud, D. Geetha, B. Isaacs, and P. Seo were responsible for investigation; D. Geetha and B. Isaacs were responsible for data curation, project administration, validation, and visualization; D. Geetha, B. Isaacs, and P. Seo were responsible for formal analysis; D. Geetha was responsible for supervision; B. Isaacs was responsible for software; all authors conceptualized the study and wrote the original draft of the manuscript.

Disclosures

E. Gapud is a Jerome L. Greene Foundation Scholar. D. Geetha reports acting as consultant to Aurinia and ChemoCentryx. B. Antiochos, B. Isaacs, and P. Seo have nothing to disclose.

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Supplemental Material

This article contains the following supplemental material online at <http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000572019/-/DCSupplemental>.

Supplemental Table 1. Univariate logistic regression (response: VTE).

Supplemental Table 2. BVAS univariate analysis, cyclophosphamide/rituximab use.

Supplemental Table 3. VDI univariate analysis.

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Supplementary Tables

Table S1. Univariate logistic regression (Response: VTE)

Table S2. BVAS Univariate Analysis, Cyclophosphamide/Rituximab Use

Table S3. VDI Univariate Analysis

Table S1. Univariate logistic regression (Response: VTE)		
Characteristic	OR (95% CI)	p-value
Age of onset (y)	0.99 (0.97, 1.02)	0.82
Female sex	1.17 (0.5, 3.1)	0.75
Length of Follow-up (months)	0.99 (0.99, 1.00)	0.28
BMI (kg/m ²)	1.1 (1.1, 1.2)	0.001*
PR3 ANCA	4.4 (1.6, 16.0)	0.01*
Obesity (BMI ≥ 30 kg/m ²)	3.6 (1.4, 10.1)	0.009*
Weight (kg)	1.03 (1.01, 1.05)	0.004*
C-reactive Protein (mg/L)	1.01 (0.98, 1.03)	0.51
RPGN	3.47 (1.38, 8.89)	0.008*
Alveolar Hemorrhage	3.42 (0.98, 10.71)	0.04
Hypoalbuminemia (<3.0 g/dL)	5.70 (2.22, 15.03)	<0.001*
Rituximab Induction	2.33 (0.87, 7.43)	0.11
Cyclophosphamide induction	0.64 (0.24, 1.59)	0.35
History of Malignancy	∅	0.99
BVAS Level at time of diagnosis (Low, Medium, High, Extreme)	1.82 (1.06, 3.30)	0.04*

Abbreviations used: BMI (body mass index), PR3 (proteinase-3 ANCA), RPGN (Rapidly Progressive Glomerulonephritis), BVAS (Birmingham Vasculitis Activity Score)

Table S2. BVAS Univariate Analysis, Cyclophosphamide/Rituximab Use		
Characteristic	OR (95% CI)	p-value
BVAS General	0.88 (0.35, 2.16)	0.79
BVAS Cutaneous	3.32 (1.19, 8.92)	0.02*
BVAS Mucous Membranes	0.99 (0.23, 3.05)	0.99
BVAS ENT	1.36 (0.54, 3.48)	0.51
BVAS Chest	4.01 (1.41, 14.43)	0.02*
BVAS Cardiovascular	∅	0.99
BVAS Abdominal	∅	0.99
BVAS Renal	2.34 (0.74, 10.38)	0.19
BVAS Nervous System	∅	0.99
Cyclophosphamide Use	0.55 (0.20, 1.41)	0.23
Rituximab Use	2.95 (1.03, 10.68)	0.06

Table S3. VDI Univariate Analysis		
Characteristic	OR (95% CI)	p-value
VDI at 12 months	1.60 (0.85, 3.13)	0.15
VDI at 60 months	1.51 (0.66, 3.49)	0.31
VDI at end of follow-up	1.37 (0.81, 2.35)	0.23