

Venous Thromboembolism Risk Factors in AAV.

Clinical Associations with Venous Thromboembolism in ANCA-Associated Vasculitides.

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Abstract

Objective. To assess potential associations for the development of venous thromboembolic events in patients with anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV).

Methods. 417 patients enrolled to participate in randomised controlled trials conducted by the European Vasculitis Society (EUVAS) were identified. Univariate and multivariate analyses were performed to validate previously proposed and identify novel risks associated with VTE in AAV.

Results. Venous thromboembolism (VTE) occurred in 41 of 417 (9.8%) patients. Uncorrected univariate analysis retained Birmingham Vasculitis Activity Score (BVAS) (OR 1.05, CI 1.01-1.10, $p=0.013$), subsequent development of malignancy (OR 2.6, CI 1.19-5.71, $p=0.017$), mucous membrane / eye involvement (OR 2.13, CI 1.10-4.11, $p=0.024$) and baseline creatinine (OR ..., $p=0.037$) to be associated with the development of VTE. Multivariate analysis highlighted C-reactive protein (CRP, per 10 mg/l increase, OR 1.05, CI 1.01-1.09, $p=0.025$), cutaneous (OR 4.83, CI 1.63-14.38, $p=0.005$) and gastrointestinal involvement (OR 6.27, CI 1.34-29.37, $p=0.02$) among the BVAS items as well as baseline creatinine (per 100 $\mu\text{mol/l}$ increase, OR 1.17, CI 1.02-1.35, $p=0.029$) to be associated with VTEs.

Conclusions. Our results highlight a role of CRP, baseline creatinine, cutaneous and gastrointestinal involvement in the risk stratification to be associated with thromboembolic events. Moreover, there might be an association between VTEs and subsequent development of malignancy and disease activity in general.

Key words:

ANCA, vasculitis, venous thromboembolism, deep venous thrombosis, pulmonary embolism, malignancy.

Key messages:

An increased risk of venous thromboembolic events in ANCA-associated vasculitis is confirmed by our study.

There is an association between C-reactive protein, creatinine at diagnosis, cutaneous and gastrointestinal involvement and thrombotic events.

Identification of patients at risk will foster our way towards tailored anticoagulation.

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1. Introduction

A hallmark of autoimmune disorders is an increased risk of venous thromboembolism (VTE) with a standardised incidence rate of 6.38 in the first year of diagnosis [1]. During the prospective follow-up of the WGET trial, 8.9% of the patients with granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) presented with VTE, yielding an incidence of 7.0 per 100 patient years. In contrast, healthy age-matched individuals had an incidence rate of 0.3 per 100 patient years. Older age was associated with VTE and the majority of GPA patients had active disease or activity within 2 months before the thromboembolic event [2], although an elevated prothrombotic risk still persists during remission of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) [3]. Retrospective analyses have reported VTE associations with older age, male gender, previous VTE and stroke with motor deficit in patients with GPA, microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) and polyarteritis nodosa (PAN) [4]. A lower frequency of VTE was found in GPA patients with proteinase 3 (PR3) positivity [5]. We sought to determine novel and validate proposed associations with VTE in patients with GPA and MPA/renal limited vasculitis (RLV) in a large dataset derived from patients enrolled in European Vasculitis Society (EUVAS) trials.

2. Material and methods

2.1. Patients

EUVAS conducted four randomised controlled trials enrolling patients from 70 hospitals in 15 countries between 1995 and 2002 [6-9]. All trials were conducted according to the 1964 Declaration of Helsinki and subsequent amendments. Patients were diagnosed with GPA, MPA or RLV. These randomised controlled trials recruited patients according to disease severity and extent subgroupings; 'early systemic vasculitis', one study [6], 'generalised vasculitis', two studies, [7, 8] and 'severe disease', one study [9] (for more information see Supplemental Table 1).

2.2. Data collection

Data were collected in accordance with the respective trial protocol. Long-term follow-up data were retrieved from participating physicians to determine survival. Respective ethical approval was obtained by national and local ethics committees as has been described before [10]. Disease activity was recorded with the Birmingham Vasculitis Activity Score (BVAS) [11] and the Disease Extent Index (DEI) [12]. Damage was recorded using the Vasculitis Damage Index (VDI) [13]. In general, the BVAS score reflects disease severity with life-threatening manifestations yielding a higher score which may allow a more robust prediction of disease severity, whereas the DEI score is a simplified tool with an uniform scoring system (all manifestations yielding two points, except of constitutional symptoms which yields one point). Baseline demographics (including age, sex and weight), renal function

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expressed as baseline creatinine and creatinine clearance (estimated glomerular filtration rate was calculated using the MDRD formula), ANCA subtype, GPA or MPA/RLV and co-morbidities such as malignancy, diabetes, chronic heart failure, stroke as well as death and smoking status (never, current, previous) were recorded.

2.3. Statistical analysis

Characteristics of patients are presented as mean \pm standard deviation or %. To identify factors associated with VTE logistic regression analyses were performed and corrected for multiple testing. All factors having a p-value <0.0013 in univariate logistic regression models and clinically significant factors were considered for a multivariate logistic regression analysis adjusted for age, gender, weight, baseline creatinine and C-reactive protein (CRP). The strength of associations of each variable with VTE is shown as odds ratio (OR) with 95 % confidence interval (CI). All statistical analyses were performed with SPSS® Version 21.0 software.

3. Results

3.1. Demography

Four hundred and seventeen patients were enclosed in the analysis with a median age of 60 (IQR 48-68), 54.4% of whom were male. Diagnosis was GPA in 55% and MPA or RLV in 45%, with PR3 and MPO-ANCA present in 56% and 34%, respectively. At baseline, the median creatinine was 181.0 (IQR 92.5-448.0) $\mu\text{mol/l}$. Disease activity as assessed by BVAS was 18.0 (IQR 12.5-23.0) and 5.0 (IQR 3.0-7.0) using the DEI. Concomitant co-morbidities consisted of diabetes in 5.5%, chronic heart disease in 7.4% and stroke before enrolment in 4.1% of patients. A majority of patients enrolled were never (54.0%) or former smoker (36.1%). There was no significant difference in follow-up period for patients with VTE compared to those without VTE ($p=0.445$). A detailed distribution is shown in Supplemental Table 2.

3.2. Frequency of VTEs and Univariate Analyses Identifying Risk Factors

Among the 417 patients, forty-one had at least one episode of VTE during follow-up (9.8%, CI 7.0-12.7). Median age of patients with VTE at inclusion was 63.0 (IQR 51.0-71.0). Patients with VTE had higher baseline creatinine (OR 1.08, CI 0.99-1.18, $p=0.037$) compared to those without VTE. No significant difference in the occurrence of VTEs was found between the four studies, although the highest odds ratio was observed in patients with severe renal disease (MEPEX, OR 1.75, CI 0.86-3.53, $p=0.120$) and the lowest in patients with early systemic disease (NORAM, OR 0.46, CI 0.16-1.32, $p=0.148$). In accordance with these findings, there was a trend towards a higher VTE risk in patients undergoing plasma exchange (OR 2.00, CI 0.74-5.41, $p=0.173$). After correcting for multiple testing, an increased risk of VTEs could be found for two BVAS items, namely for cutaneous involvement (OR 3.09, CI 1.59-6.01, $p=0.001$) and for gastrointestinal involvement (OR 5.69, CI 1.98-16.31, $p=0.001$). At the uncorrected level, a further BVAS item, namely mucous membrane / eye involvement (OR 2.13, CI

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1.10-4.41, $p=0.024$), was associated with VTE. Univariate analysis demonstrated no significant difference in CRP in patients having VTE or not (OR 1.02, CI 0.99-1.05, $p=0.184$). In accordance, no significant difference was found for erythrocyte sedimentation rate (data not shown). Furthermore, subsequent development of malignancy during follow-up (OR 2.61, CI 1.19-5.71, $p=0.017$) was associated with the risk for an onset of VTEs (specific entities are highlighted in Supplemental Table 3). Importantly, a significant association between total BVAS and the development of VTEs was found (OR 1.05, CI 1.01-1.10, $p=0.013$), whereas disease activity as assessed by DEI was not associated with VTEs (OR 1.04, CI 0.96-1.12, $p=0.363$). Treatment with cyclophosphamide had an odds ratio of 1.04 and association with VTEs was not significant (CI 0.35-3.08, $p=0.944$). In general, treatment was protocolised. Cumulative glucocorticoid treatment was non significantly higher in patients having VTE (39.8 (18.8), median 48 months) compared to those without (37.4 (18.5), median 36 months) ($p=0.369$) (Table 1). There was no association between VTEs and development of stroke before and during follow-up as well as diabetes before enrolment, since none of the patients had a thromboembolic event. Other factors analysed did not show an association with the onset of VTE.

Variables	Univariate logistic regression		
	OR	(95% CI)	p-value
Age (per 10 yrs. increase)	1.17	(0.92-1.50)	0.199
Gender (Ref.=female)	1.20	(0.63-2.31)	0.579
Baseline creatinine (per 100 $\mu\text{mol/l}$ increase)	1.08	(0.99-1.18)	0.037
Weight	1.02	(1.00-1.04)	0.069
C-reactive protein (per 10 mg/l increase)	1.02	(0.99-1.05)	0.184
BVAS	1.05	(1.01-1.10)	0.013
Cutaneous*	3.09	(1.59-6.01)	0.001
GI*	5.69	(1.98-16.31)	0.001
Mucous Membranes / Eyes*	2.13	(1.10-4.11)	0.024
Subsequent Cancer	2.61	(1.19-5.71)	0.017

Table 1. Univariate logistic regression results: Significant associations between different factors and the development of VTEs. Abbreviations used: BVAS (Birmingham Vasculitis Activity Score), GI (gastrointestinal); * (refers to the respective BVAS item). Level of significance after correcting for multiple testing is 0.0013.

3.3. Associating Factors with VTE Occurrence: Multivariate Analysis

In a multivariate model, an increased risk for the development of VTEs was found for cutaneous involvement (OR 4.83, CI 1.63-14.38, $p=0.005$), gastrointestinal manifestation (OR 6.27, CI 1.34-29.37, $p=0.020$) as assessed as BVAS items, baseline creatinine (per 100 $\mu\text{mol/litre}$ increase, OR 1.17, CI 1.02-1.35, $p=0.029$) and CRP (OR 1.05, CI 1.01-1.09, $p=0.025$) after adjustment was made for age, gender and weight (Table 2).

	Multivariate logistic regression
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Variables	OR	(95% CI)	p-value
Age (per 10 yrs. increase)	1.21	(0.81-1.81)	0.353
Gender (Ref.=female)	0.69	(0.24-1.97)	0.489
Baseline creatinine (per 100 µmol/l increase)	1.17	(1.02-1.35)	0.029
Weight	1.02	(1.00-1.04)	0.095
C-reactive protein (per 10 mg/l increase)	1.05	(1.01-1.09)	0.025
Cutaneous*	4.83	(1.63-14.38)	0.005
GI*	6.27	(1.34-29.37)	0.020

Table 2. Multivariate logistic regression results: Association between different factors and the development of VTEs. Abbreviations used: VTEs (venous thromboembolisms), GI (gastrointestinal); * (refers to the respective BVAS item).

4. Discussion

Among the co-morbidities associated with AAV, VTEs have emerged as a frequent finding. The frequency of VTEs in the context of AAV ranged from a standardised incidence ratio of 6.57 (as assessed in a Swedish registry) to a frequency of 12% in a Dutch cohort of patients with severe disease [1, 5]. In our analysis, the frequency of thromboembolic events was 9.8%, which is within the range of previous observations. Analysis of the WGET study reported higher age as a risk to develop a thromboembolic event in GPA [2] which has previously been described in the general population [14] as well and was corroborated by a retrospective analysis of the French Vasculitis Study Group (FVSG) including patients with GPA, MPA, EGPA and PAN [4]. In contrast, we found no significant association of age with VTEs in AAV. Stassen and co-workers found a lower frequency of VTEs in patients with GPA and those with PR3-ANCA positivity [5]. This protective effect could not be replicated in our analysis. Retrospective analysis of data collected from the FVSG revealed a higher occurrence rate of VTEs in AAV compared to PAN. In addition to age, they identified male sex, previous VTE, stroke with motor deficit as being associated with a higher VTE risk and lower limb motor neuropathy to be associated with a lower VTE risk [4]. Again, we could not find an association of male gender with risk of VTE in our analysis, moreover none of the patients with stroke before enrolment or during follow-up had a VTE.

In general, the association of higher disease activity with the occurrence of VTE is a plausible finding, although this could not be confirmed after correction for multiple testing. We identified novel associations with the onset of VTE: among the BVAS items, cutaneous and gastrointestinal involvement were retained as significant in multivariate analysis, whereas mucous membrane / eye involvement showed association in uncorrected univariate analysis only. The risk for VTEs was 4.83 times higher in patients with cutaneous and 6.27 times higher in individuals with gastrointestinal involvement. These associations were independent of age, gender, weight, baseline creatinine and CRP. Inflammatory markers, such as CRP, have been identified as biomarker of disease activity in AAV [15]. We have found an association of elevated CRP levels and risk of VTE in our study. This is in

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accordance with a higher risk of developing VTE in the general population having elevated CRP levels at baseline [16]. Cutaneous vasculitis may provoke local changes leading to hypercoagulability, and gastrointestinal involvement as a severe manifestation was associated with worse outcome in a recent cluster analysis of AAV [17]. Our finding is in accordance with a recent study reporting an association of cutaneous vasculitis and onset of VTE in patients with systemic lupus erythematosus [18]. Additionally, patients with inflammatory bowel disease are at an approximately 3-fold increased risk of VTE compared to healthy controls, and prophylaxis is recommended in these patients during disease flares, since the increased risk is more prominent while active disease is present [19]. Furthermore, impaired kidney function is a recognised risk factor for VTEs [20]. We found an association of higher baseline creatinine and risk for the development of VTEs. Several influences may prone patients with impaired kidney function towards thrombotic events, including abnormal flow patterns, increase in pro-coagulant and loss of anti-coagulant factors as well as impaired endothelial factors [21]. In uncorrected univariate analysis, our analysis highlighted an association of a classic risk factor, namely malignancy [22], and onset of VTE in AAV. This is in contrast with earlier reports, which stated that classic associations may play a subsidiary role when assessing the risk of AAV patients [4, 5]. We may speculate that the longer follow-up of patients included in the EUVAS trials depicted the association in our analysis.

The high incidence of VTEs in AAV may be explained by changes in the coagulation pathways. Anti-plasminogen antibodies have been identified in AAV patients (whilst non-existent or very rare in healthy controls) and were associated with presence of glomerular fibrinoid necrosis, cellular crescents and more severely impaired renal function [23]. An association of anti-plasminogen antibodies with VTE was described in PR3-positive patients before, but total numbers were low and inferences should be drawn with caution [24]. Whether or not anti-plasminogen antibodies may emerge as essential biomarker to predict VTE events in AAV needs to be clarified in future studies. More recently, it was shown that prothrombin fragments and D-dimer levels are elevated during active disease and decreased considerably in remission. However, patients exhibited elevated FVIII as well as VWF:RCo and VWF:antigen during active disease and in remission [25]. This is in line with another recent study which showed persistent elevation of FVIII and tissue factor pathway inhibitor during diverse disease states [3]. Inflammatory mediators and ANCA per se might be able to induce tissue factor and lead to expression in neutrophil extracellular traps and microparticles [26], whilst the latter also mediate enhanced thrombin generation associated with clinical thromboembolic events [27]. These findings clearly highlight disease-associated factors, which may make patients prone towards thrombosis and inflammation. Moreover, it is well established that in active AAV several cytokines, growth factors and chemokines are higher expressed than in remission (including platelet-derived growth factor-AB, circulatory endothelial cells, microparticles of endothelial and platelet origin

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and interleukin-8) and some of these are higher in remission compared to healthy controls (including platelet-derived growth factor-AB and interleukin-8) [15].

Clearly, several limitations have to be taken into consideration. Firstly, there was no generalised protocol for long-term follow-up of patients recruited into the EUVAS trials. Moreover, information regarding time to event and occurrence of previous VTE events is missing. Analysis of the WGET trial highlighted that thromboembolic events occurred early after study inclusion (median time to VTE 2.07 months) [2]. This needs to be addressed by future studies reporting on VTE risk in AAV. The impact of high cumulative glucocorticoid exposure needs to be addressed in future trials testing low or no oral steroids compared to standard dose (i.e. the PEXIVAS trial [28]). Furthermore, we could not provide data on the potential association between malignancy, VTE and cumulative CYC exposure in our work.

Overall, we found an association of VTE with subsequent development of malignancy, with higher vasculitis activity and among the BVAS items mucous membrane / eye involvement in univariate analysis. After adjustment for age, gender, weight, baseline creatinine and CRP, baseline creatinine, CRP, cutaneous and gastrointestinal involvement were associated with the onset of VTEs. These associations are novel and need to be confirmed in further follow-on studies to prove or disprove the generated hypotheses. More research in the field is necessary to establish markers, which may identify patients at risk and allow tailored, prophylactic anticoagulation for the AAV patient subsets with higher VTE risk.

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6. Disclosure Statement

All authors have declared no conflicts of interest.

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