



Early View

Research letter

Risk of acute arterial and venous thromboembolic events in Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss syndrome)

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**Risk of acute arterial and venous thromboembolic events in Eosinophilic Granulomatosis
with Polyangiitis (Churg-Strauss syndrome)**

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Take-home message: Eosinophilic Granulomatosis with Polyangiitis is associated with a high risk of acute arterial and venous thromboembolic events (AVTE), particularly around the time of diagnosis and in patients with high disease activity or history of previous AVTE.

Eosinophilic Granulomatosis with Polyangiitis (EGPA, Churg-Strauss syndrome) is a rare anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) characterized by respiratory manifestations and systemic organ involvement [1]. Particularly, cardiac manifestations occur in 40-60% of patients, representing the leading cause of mortality [2]. Recent reports suggest that venous thromboembolic events might also represent a consistent burden of disease [3, 4], as already known for the other AAVs [5–7], possibly due to eosinophil-mediated vascular inflammation [5]. Nevertheless, the occurrence of arterial and venous thrombotic events (AVTE) has never been systematically explored in EGPA.

This retrospective study assessed incidence, type and timing of AVTE in the largest EGPA cohort reported thus far. Incidence estimates were compared with those from a population-based reference cohort, and baseline risk factors for AVTE occurrence after EGPA diagnosis were explored.

The study included 573 EGPA patients followed between 1988 and 2018 at 28 Italian referral centres. The study was approved by the Ethics Committee of the University Hospital Careggi, Florence. All patients fulfilled the American College of Rheumatology criteria for EGPA [8] or the MIRRA trial criteria [9].

Demographic, serological and clinical data collected at EGPA diagnosis were retrospectively retrieved from medical charts, including age, sex, previous AVTE, cardiovascular risk factors, EGPA manifestations, disease activity [assessed using the Birmingham Vasculitis Activity Score (BVAS)[10]], and laboratory parameters (see <https://doi.org/10.1101/2020.11.09.20228197>).

Ongoing cardiovascular treatment and immunosuppressive therapy started after EGPA diagnosis were also recorded.

After EGPA diagnosis, we recorded the first AVTE and the time of occurrence. Venous events included deep venous thrombosis (DVT), pulmonary embolism, superficial venous thrombosis (SVT), and thrombosis at atypical locations. Arterial events included acute myocardial infarction (AMI), stroke, transient ischemic attack (TIA), acute ischemia of the upper and lower limbs, and arterial retinal occlusion.

For each patient, the accumulated person-time was calculated from EGPA diagnosis until the first AVTE or the last follow-up. AVTE rates were compared with those from a reference population-based cohort (the Bruneck cohort from Northern Italy [11, 12]), and age-standardized event ratios (SERs) of AVTE were calculated (see <https://doi.org/10.1101/2020.11.09.20228197>).

Within the EGPA cohort, Cox regression models were fitted to derive Kaplan-Meier curves and to estimate the adjusted hazard ratios (HR) of AVTE and related 95% confidence intervals (CI) according to baseline demographic, clinical and laboratory features. p-values <0.05 were considered statistically significant.

In our cohort, most patients were female (297/573, 51.8%), with a median age at EGPA diagnosis of 55.3 years (interquartile range, IQR 44.8–64.0). Among cardiovascular risk factors, hypertension was reported in 28.5%, hypercholesterolemia in 16.6%, while 80 patients (15.4%) were smokers (active or former). Regarding cardiovascular treatment, 25.3% of patients were receiving antihypertensive agents, 10.4% antiplatelets, 8.6% statins and 5.4% anticoagulants. Most patients had active disease at EGPA diagnosis, the median BVAS being 12 (IQR 7-18), and mainly presented with lower respiratory tract (96.3%), ear-nose-throat (79.4%), or peripheral neurological involvement (63.2%). Out of 485 patients with ANCA test results, 50.1% tested positive, mostly for p-ANCA/anti-myeloperoxidase. Additional clinical and laboratory parameters are reported in <https://doi.org/10.1101/2020.11.09.20228197>. In the two months after

EGPA diagnosis, most patients (301, 52.5%) received traditional or biologic immunosuppressants, 44.4% systemic glucocorticoids alone, while sixteen (2.8%) did not receive immunosuppressive therapy.

The median follow-up after EGPA diagnosis was of 1677 days (IQR 663–3137).

Overall, 129 EGPA patients (22.5%) experienced AVTE (**figure 1a**): specifically, 70 patients experienced AVTE (47 arterial, 18 venous, five unknown) before EGPA diagnosis, and 75 following EGPA diagnosis, after a median time of 577 days (IQR 81–2100). Of them, sixteen patients experienced AVTE both before and after EGPA diagnosis. Notably, most AVTE clustered in the two years before (41/70) and after the diagnosis (42/75), peaking in the periods of highest disease activity (**figure 1a-b**). Specifically, 10 events occurred at time of EGPA diagnosis. Among AVTE after EGPA diagnosis, 32 were venous (19 DVT, five pulmonary embolism, three SVT, and five thrombosis at atypical locations, including two Budd-Chiari syndromes, two retinal vein occlusions, one intracardiac thrombosis), and 43 were arterial (23 AMI, 10 stroke, seven TIA, a retinal artery occlusion, an acute upper limb ischemia and an acute lower limb ischemia).

A significantly higher age-standardized AVTE risk was observed in the EGPA cohort compared to the reference population-based cohort [SER of 2.10 (1.67-2.63); $p < 0.001$], particularly for patients younger than 65 years (**figure 1c**). Venous events, although less frequent than arterial ones, were associated with the highest SER (3.32 (2.35-4.70) and 1.64 (1.22-2.22) for venous and arterial events, respectively). Moreover, the SER for venous events was significantly higher as compared to the reference population-based cohort in all age classes.

Within the EGPA cohort, the AVTE risk was significantly higher in patients with previous AVTE [HR 2.06 (1.15-3.67), $p = 0.015$] or with BVAS ≥ 20 at diagnosis [HR 2.02 (1.03–3.96) as

compared with patients with BVAS 0-9, $p=0.041$]. There was a tendency towards a higher risk of AVTE in patients with ear-nose-throat or cardiac involvement [HR 1.98 (0.99–3.92) and 1.65 (0.97-2.82), respectively].

No other demographic, clinical or laboratory features significantly influenced the risk of AVTE. Particularly, common cardiovascular risk factors had no impact on AVTE risk. The fact that active inflammation promotes AVTE in EGPA, was supported by the observed effects of treatment. Indeed, patients not receiving immunomodulating therapy within the first two months following EGPA diagnosis had a significantly higher risk of AVTE as compared with those receiving systemic glucocorticoids [HR 3.67 (1.37– 9.89), $p=0.010$], whereas the risk was comparable in patients treated with immunosuppressants or glucocorticoids alone. Regarding cardiovascular medications, no association was found between antiplatelet, anticoagulant or statin therapy at EGPA diagnosis and AVTE risk [HR 0.99 (0.98–1.01) for antiplatelets, 0.35 (0.09–1.57) for anticoagulants, and 0.96 (0.40–2.26) for statins].

Our study has some limitations. First, data were retrospectively captured from medical charts and referred to a broad time period, thus recall bias cannot be excluded. Second, the low number of events did not allow to conduct separate analysis on predictors of venous and arterial events. Third, heterogeneity in clinical management due to the long-term study period cannot be excluded. Finally, no information on the prognosis and outcome following AVTE was available. Despite these limitations, our study finds its strengths in its large sample size, the long follow-up, and the presence of a population-based reference cohort.

Our results show a higher risk of AVTE in patients with EGPA as compared to a population-based reference cohort, particularly around the time of EGPA diagnosis. Most events were arterial, not yet convincingly reported in literature for EGPA. Indeed, to date most studies

focused on the association between AAVs and venous thromboembolism [3, 5, 13], while limited evidence supports an association with arterial manifestations [6, 7, 14]. According to our results, EGPA seems to represent a cardiovascular risk factor *per se*, aside from known cardiovascular risk factors, and AVTE risk was particularly increased in patients with previous AVTE and high disease activity. Our findings also suggest that immunosuppressants might exert a protective effect, while the role of anticoagulant and antiplatelet agents was unclear; however, further studies are needed to corroborate these findings. Overall, our data support the current view that AVTE are directly determined by active EGPA vascular involvement [13, 15], and seem to suggest that AVTE might be prevented by adequate and timely immunosuppression.

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Alessandra Bettiol and Peter Willeit performed the statistical analysis.

Giacomo Emmi, Augusto Vaglio, and Domenico Prisco interpreted the results.

Alessandra Bettiol wrote the manuscript, assisted by Giacomo Emmi and Augusto Vaglio.

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REFERENCES

1. Vaglio A, Buzio C, Zwerina J. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. *Allergy* 2013; 68: 261–273
2. Dennert RM, van Paassen P, Schalla S, Kuznetsova T, Alzand BS, Staessen JA, Velthuis S, Crijns HJ, Tervaert JWC, Heymans S. Cardiac involvement in Churg-Strauss syndrome. *Arthritis Rheum.* 2010; 62: 627–634
3. Allenbach Y, Seror R, Pagnoux C, Teixeira L, Guilpain P, Guillevin L, French Vasculitis Study Group. High frequency of venous thromboembolic events in Churg-Strauss syndrome, Wegener's granulomatosis and microscopic polyangiitis but not polyarteritis nodosa: a systematic retrospective study on 1130 patients. *Ann. Rheum. Dis.* 2009; 68: 564–567
4. Novikov P, Makarov E, Moiseev S, Meshkov A, Strizhakov L. Venous thromboembolic events in systemic vasculitis: Table 1. *Ann. Rheum. Dis.* 2015; 74: e27–e27
5. Ames PRJ, Margaglione M, Mackie S, Alves JD. Eosinophilia and thrombophilia in churg strauss syndrome: a clinical and pathogenetic overview. *Clin. Appl. Thromb. Hemost.* 2010; 16: 628–636
6. Morgan MD, Turnbull J, Selamet U, Kaur-Hayer M, Nightingale P, Ferro CJ, Savage COS, Harper L. Increased incidence of cardiovascular events in patients with antineutrophil cytoplasmic antibody-associated vasculitides: a matched-pair cohort study. *Arthritis Rheum.* 2009; 60: 3493–3500
7. Faurschou M, Mellemkjaer L, Sorensen IJ, Svalgaard Thomsen B, Dreyer L, Baslund B. Increased morbidity from ischemic heart disease in patients with Wegener's granulomatosis. *Arthritis Rheum.* 2009; 60: 1187–1192

8. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum.* 1990; 33: 1094–1100
9. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, Merkel PA, Moosig F, Specks U, Cid MC, Luqmani R, Brown J, Mallett S, Philipson R, Yancey SW, Steinfeld J, Weller PF, Gleich GJ, EGPA Mepolizumab Study Team. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N. Engl. J. Med.* 2017; 376: 1921–1932
10. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, Flossmann O, Hall C, Hollywood J, Jayne D, Jones R, Lanyon P, Muir A, Scott D, Young L, Luqmani RA. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann. Rheum. Dis.* 2009; 68: 1827–1832
11. Kiechl S, Willeit J. In a Nutshell: Findings from the Bruneck Study. *Gerontology* 2019; 65: 9–19
12. Willeit P, Kiechl S, Kronenberg F, Witztum JL, Santer P, Mayr M, Xu Q, Mayr A, Willeit J, Tsimikas S. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. *J. Am. Coll. Cardiol.* 2014; 64: 851–860
13. Emmi G, Silvestri E, Squatrito D, Amedei A, Niccolai E, D’Elios MM, Della Bella C, Grassi A, Becatti M, Fiorillo C, Emmi L, Vaglio A, Prisco D. Thrombosis in vasculitis: from pathogenesis to treatment. *Thromb. J.* 2015; 13: 15
14. Kang A, Antonelou M, Wong NL, Tanna A, Arulkumaran N, Tam FWK, Pusey CD. High Incidence of Arterial and Venous Thrombosis in Antineutrophil Cytoplasmic Antibody–

associated Vasculitis. *J. Rheumatol.* 2019; 46(3):285-293

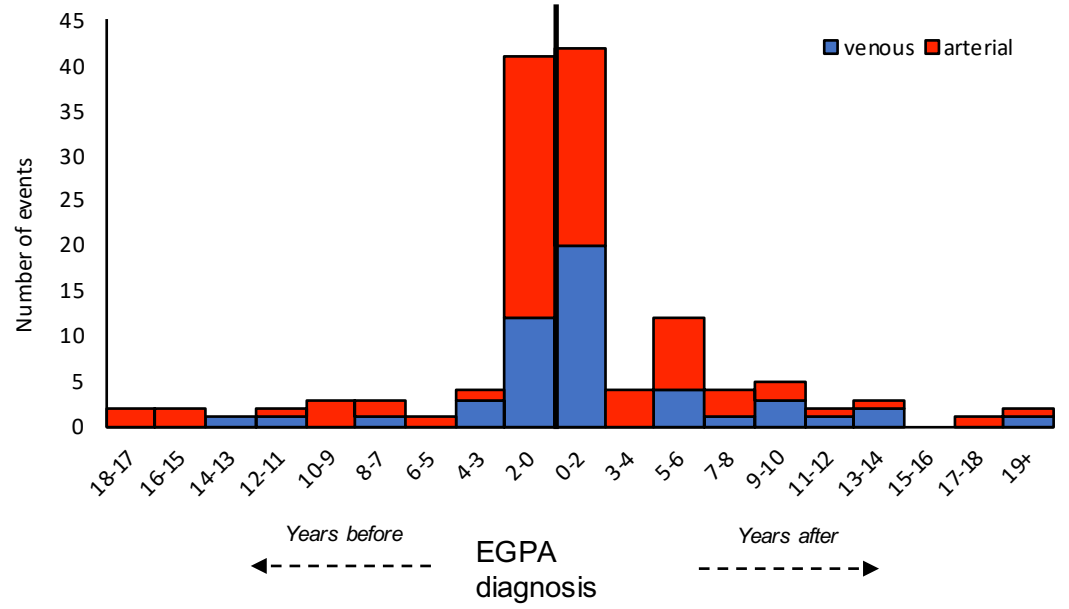
15. Emmi G, Vitale A, Silvestri E, Boddi M, Becatti M, Fiorillo C, Fabiani C, Frediani B, Emmi L, Di Scala G, Goldoni M, Bettiol A, Vaglio A, Cantarini L, Prisco D. Adalimumab-Based Treatment Versus Disease-Modifying Antirheumatic Drugs for Venous Thrombosis in Behçet's Syndrome: A Retrospective Study of Seventy Patients With Vascular Involvement. *Arthritis Rheumatol. (Hoboken, N.J.)* 2018; 70: 1500–1507

FIGURE LEGEND

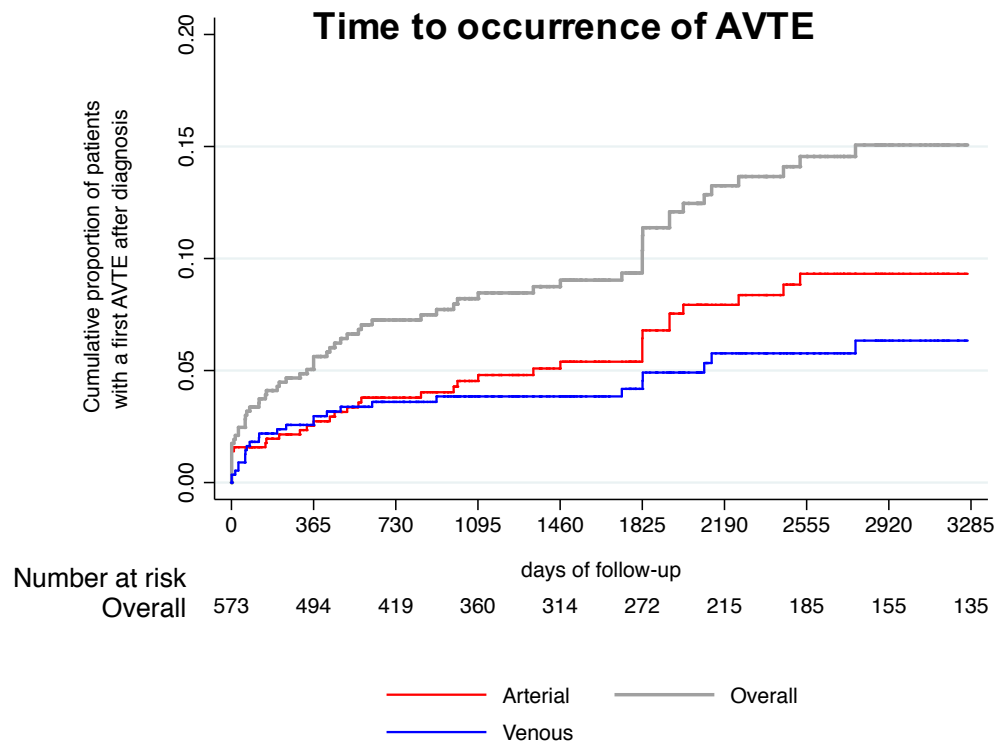
Figure 1. a) Time of occurrence of acute arterial and venous thromboembolic events before and after the diagnosis of EGPA; **b)** Kaplan-Meier curves of the occurrence of overall, arterial and venous thromboembolic events in the study cohort after EGPA diagnosis; **c)** Rates of acute arterial and venous thromboembolic events standardized to the Bruneck cohort (reference cohort).

AVTE: arterial and venous thromboembolic events; CI: confidence interval; EGPA: eosinophilic granulomatosis with polyangiitis; SER standardized event ratio.

a) Occurrence of AVTE before and after EGPA diagnosis



b)



c) Rates of AVTE standardized to the Bruneck cohort

	Bruneck cohort, rate per 1000 person- years	EGPA cohort, observed no. of events	EGPA cohort, expected no. of events	SER (95% CI)
All thromboembolic events				
Age category				
<55 years	5.7 (3.5-9.2)	25	8.0	3.12 (2.11-4.62)
55 to <65 years	7.4 (5.3-10.4)	23	7.1	3.24 (2.16-4.88)
65 to <75 years	16.5 (13.3-20.5)	13	12.5	1.04 (0.60-1.78)
≥75 years	34.4 (29.3-40.4)	14	8.2	1.72 (1.02-2.90)
Overall		75	35.8	2.10 (1.67-2.63)
P<0.001				
Arterial events				
Age category				
<55 years	2.5 (1.2-5.2)	17	3.5	4.86 (3.02-7.81)
55 to <65 years	5.8 (4.0-8.6)	13	5.6	2.33 (1.35-4.01)
65 to <75 years	13.3 (10.5-16.9)	5	10.1	0.49 (0.21-1.19)
≥75 years	29.3 (24.6-34.9)	8	6.9	1.15 (0.58-2.31)
Overall		43	26.1	1.64 (1.22-2.22)
P<0.001				
Venous events				
Age category				
<55 years	3.2 (1.7-6.1)	8	4.5	1.78 (0.89-3.55)
55 to <65 years	1.6 (0.7-3.3)	10	1.5	6.65 (3.58-12.36)
65 to <75 years	3.2 (1.9-5.2)	8	2.4	3.31 (1.65-6.62)
≥75 years	5.1 (3.4-7.8)	6	1.2	4.95 (2.23-11.03)
Overall		32	9.6	3.32 (2.35-4.70)
P<0.001				