Risk of acute arterial and venous thromboembolic events in eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)

To the Editor:

Eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg–Strauss syndrome) is a rare anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) characterised 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 (AVTEs) 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 (as previously described [11]). 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 ischaemic attack (TIA), acute ischaemia 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 [12, 13]), and age-standardised event ratios (SERs) of AVTE were calculated [11].

Within the EGPA cohort, Cox regression models were fitted to derive Kaplan–Meier curves and to estimate the adjusted hazard ratios (HRs) of AVTE and related 95% confidence intervals 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 years). Among cardiovascular risk factors, hypertension

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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 http://bit.ly/3sKnvzQ

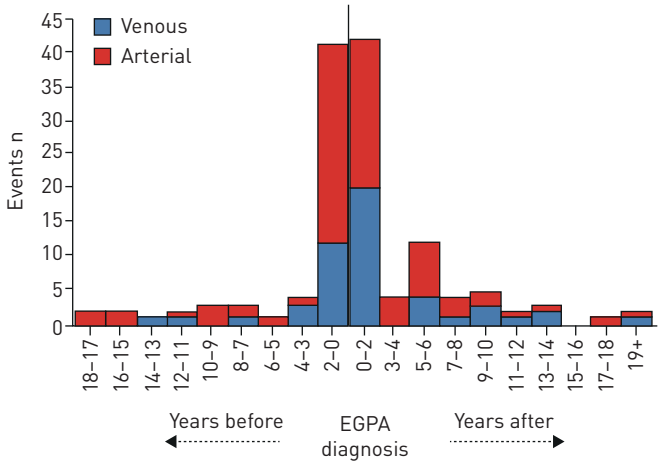
Cite this article as: Bettiol A, Sinico RA, Schiavon F, *et al.* Risk of acute arterial and venous thromboembolic events in eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome). *Eur Respir J* 2021; 57: 2004158 [https://doi.org/10.1183/13993003.04158-2020].

was reported in 28.5%, hypercholesterolaemia 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 have been previously reported [11]. In the 2 months after EGPA diagnosis, most patients (301, 52.5%) received traditional or biologic immunosuppressants, 44.4% systemic glucocorticoids alone, while 16 (2.8%) did not receive immunosuppressive therapy.

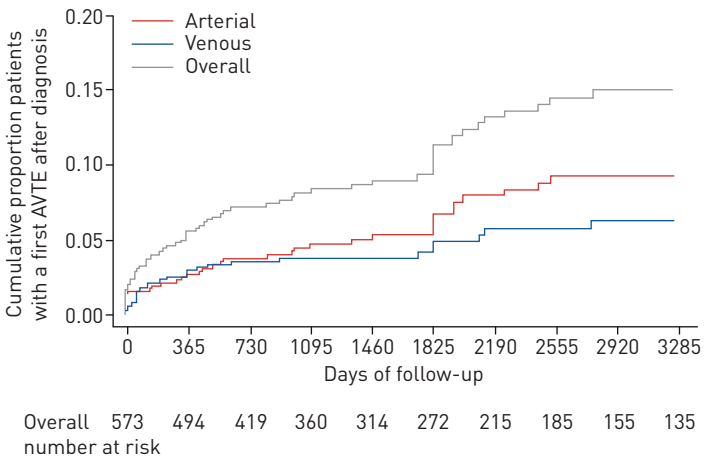
The median follow-up after EGPA diagnosis was of 1677 days (IQR 663–3137 days).

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,

a) Occurrence of AVTE before and after EGPA diagnosis



b) Time to occurrence of AVTE



Overall number at risk	573	494	419	360	314	272	215	185	155	135

c) Rates of AVTE standardised to the Bruneck cohort

	Bruneck cohort, rate per 1000 person-years	EGPA cohort, observed events n	EGPA cohort, expected events n	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

FIGURE 1 a) Time of occurrence of acute arterial and venous thromboembolic events (AVTEs) before and after the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA). b) Kaplan–Meier curves of the occurrence of overall AVTEs in the study cohort after EGPA diagnosis. c) Rates of acute AVTEs standardised to the Bruneck cohort (reference cohort). SER: standardised event ratio.

after a median time of 577 days (IQR 81–2100 days). Of them, 16 patients experienced AVTE both before and after EGPA diagnosis. Notably, most AVTE clustered in the 2 years before (41/70) and after the diagnosis (42/75), peaking in the periods of highest disease activity (figure 1a and 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 ischaemia and an acute lower limb ischaemia).

A significantly higher age-standardised AVTE risk was observed in the EGPA cohort compared to the reference population-based cohort (SER 2.10, 95% CI 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, 95% CI 2.35–4.70, and 1.64, 95% CI 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, 95% CI 1.15–3.67; p=0.015) or with BVAS ⩾20 at diagnosis (HR 2.02, 95% CI 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, 95% CI 0.99–3.92, and 1.65, 95% CI 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 2 months following EGPA diagnosis had a significantly higher risk of AVTE, compared with those receiving systemic glucocorticoids (HR 3.67, 95% CI 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, 95% CI 0.98–1.01 for antiplatelets, HR 0.35, 95% CI 0.09–1.57 for anticoagulants, and HR 0.96, 95% CI 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 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, 14], while limited evidence supports an association with arterial manifestations [6, 7, 15]. 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, 16], and seem to suggest that AVTE might be prevented by adequate and timely immunosuppression.

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Received: 4 Sept 2020 | Accepted: 21 Dec 2020

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Conflict of interest: A. Bettiol has nothing to disclose. R.A. Sinico has nothing to disclose. F. Schiavon has nothing to disclose. S. Monti has nothing to disclose. E.P. Bozzolo has nothing to disclose. F. Franceschini has nothing to disclose. M. Govoni has nothing to disclose. C. Lunardi has nothing to disclose. G. Guida has nothing to disclose. G. Lopalco has nothing to disclose. G. Paolazzi has nothing to disclose. A. Vacca has nothing to disclose. G. Gregorini has nothing to disclose. P. Leccese has nothing to disclose. M. Piga has nothing to disclose. F. Conti has nothing to disclose. P. Fraticelli has nothing to disclose. L. Quartuccio has nothing to disclose. F. Alberici has nothing to disclose. C. Salvarani has nothing to disclose. S. Bettio has nothing to disclose. S. Negrini has nothing to disclose. C. Selmi has nothing to disclose. S. Sciascia has nothing to disclose. G. Moroni has nothing to disclose. L. Colla has nothing to disclose. C. Manno has nothing to disclose. M.L. Urban has nothing to disclose. A. Vannacci has nothing to disclose. M.R. Pozzi has nothing to disclose. P. Fabbrini has nothing to disclose. S. Polti has nothing to disclose. M. Felicetti has nothing to disclose. M.R. Marchi has nothing to disclose. R. Padoan has nothing to disclose. P. Delvino has nothing to disclose. R. Caporali has nothing to disclose. C. Montecucco has nothing to disclose. L. Dagna has nothing to disclose. A. Cariddi has nothing to disclose. P. Toniati has nothing to disclose. S. Tamanini worked at ASST Spedali Civili Brescia, Unit of Rheumatology and Immunology during the conduct of the study, but has since been employed by GlaxoSmithKline. F. Furini has nothing to disclose. A. Bortoluzzi has nothing to disclose. E. Tinazzi has nothing to disclose. L. Delfino has nothing to disclose. I. Badiu has nothing to disclose. G. Rolla has nothing to disclose. V. Venerito has nothing to disclose. F. Iannone has nothing to disclose. A. Berti has nothing to disclose. R. Bortolotti has nothing to disclose. V. Racanelli has nothing to disclose. G. Jeannin has nothing to disclose. A. Padula has nothing to disclose. A. Cauli has nothing to disclose. R. Priori has nothing to disclose. A. Gabrielli has nothing to disclose. M. Bond has nothing to disclose. M. Tedesco has nothing to disclose. G. Pazzola has nothing to disclose. P. Tomietto has nothing to disclose. M. Pellecchio has nothing to disclose. C. Marvisi has nothing to disclose. F. Maritati has nothing to disclose. A. Palmisano has nothing to disclose. C. Dejaco has nothing to disclose. J. Willeit has nothing to disclose. S. Kiechl has nothing to disclose. I. Olivotto has nothing to disclose. P. Willeit has nothing to disclose. D. Prisco has nothing to disclose. A. Vaglio has nothing to disclose. G. Emmi has nothing to disclose.

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