

Full Title: High incidence of arterial and venous thrombosis in ANCA-associated vasculitis

Authors

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Abstract

Objective: To determine the incidence of arterial thrombotic events (ATE) and venous thromboembolism (VTE) in ANCA-associated vasculitis (AAV).

Methods: Retrospective cohort study presenting the incidence of ATE (coronary events or ischaemic stroke) and VTE (pulmonary embolism (PE) or deep venous thrombosis (DVT)), in patients diagnosed with AAV between 2005 -2014.

Results: 204 patients with AAV were identified. Median follow-up for surviving patients was 5.8 [Range: 1-10] years, accounting for 1088 person-years. The incidence of ATE was 2.67/ 100 person-years (1.56 for coronary events and 1.10 for ischaemic stroke) and for VTE was 1.47/ 100 person-years (0.83 for DVT only and 0.64 for PE with/without DVT). On multivariate analysis, prior IHD and advancing age were the only independent predictors of ATE. Among patients without prior IHD or stroke, the incidence of ATE remained elevated at 2.32/100 person-years (1.26 for coronary events and 1.06 for ischaemic stroke). ATE, but not VTE, was an independent predictor of all-cause mortality. Event rates for both ATE and VTE were highest in the first year after diagnosis of AAV but remained above the population incidence during the 10 year follow up period. In comparison to reported rates for the UK population, the event rates in our AAV patients were 15 times higher for coronary events, 11 times higher for incident stroke and 20 times higher for VTE.

Conclusion: Patients with AAV have a high incidence of arterial and venous thrombosis, particularly in the first year after diagnosis.

Key indexing terms: Anti-neutrophil cytoplasm antibody-associated vasculitis, thrombosis, cardiovascular disease, myocardial infarction, stroke, venous thromboembolism.

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Abbreviations

Anti-glomerular basement membrane (Anti-GBM)

Anti-neutrophil cytoplasm antibody (ANCA)

ANCA-associated vasculitis (AAV)

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Arterial thrombotic events (ATE)

Birmingham Vasculitis Activity Score (BVAS)

Cardiovascular disease (CVD)

Chronic kidney disease (CKD)

Deep venous thrombosis (DVT)

Eosinophilic granulomatosis with polyangiitis (EGPA)

Granulomatosis with polyangiitis (GPA)

Incidence rate (IR)

Ischaemic heart disease (IHD)

Microscopic polyangiitis (MPA)

Mixed connective tissue disease (MCTD)

Myeloperoxidase (MPO)

Myocardial infarction (MI)

Polyarteritis Nodosa (PAN)

Proteinase 3 (PR3)

Pulmonary embolus (PE)

Randomised Controlled Trial (RCT)

Renal limited vasculitis (RLV)

Renal replacement therapy (RRT)

Thrombosis in AAV

Rheumatoid arthritis (RA)

Systemic lupus erythematosus (SLE)

Transient ischaemic attack (TIA)

United Kingdom (UK)

Venous thromboembolism (VTE)

Introduction

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a group of small-vessel vasculitides comprising three syndromes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA)(1). In addition, there are patients with renal limited vasculitis (RLV), and “double positive” disease in patients with both ANCA and anti-glomerular basement membrane (anti-GBM) antibodies(2).

AAV is not widely regarded as a disease that carries a high risk of arterial thrombotic events (ATE) or venous thromboembolism (VTE), unlike other inflammatory disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), or renal disorders such as nephrotic syndrome. The incidence of ischaemic heart disease (IHD) and VTE in AAV has more recently been described(3-11). Antiplasminogen antibody has been reported together with PR3-ANCA and MPO-ANCA, and associated with disease activity in AAV(12, 13). It may be pathogenic in AAV and contribute to arterial and venous thrombosis, although this is not yet established.

We conducted a single- centre retrospective observational study to determine the incidence rate (IR) of both ATE and VTE, and risk factors for ATE and VTE, in a UK population of patients with AAV. We are the first group to look at both ATE and VTE in a contemporary cohort.

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Materials and Methods

We identified patients with the diagnosis of AAV, as defined by the Chapel Hill Consensus Conference(1), diagnosed between 2005 and 2014 with at least one year of follow up at our centre in West London. We also included patients who died within one year of follow up. All patients were treated according to a standard protocol(14, 15).

Case notes, clinic letters, electronic records, laboratory results and medical imaging were used to obtain data. We obtained patients' demographics at presentation (age, sex, ethnicity and pathology results), evolution of the illness (diagnosis (GPA, MPA, EGPA, RLV, double positive disease or overlap syndrome), organ involvement and the number of relapses), traditional risk factors for ATE (prior ischaemic heart disease (IHD) or stroke, hypertension at presentation, history of smoking, diabetes mellitus, atrial fibrillation/ flutter and requirement for dialysis), risk factors for VTE (whether they were admitted to hospital at the time of presentation, history of smoking, cancer and prior VTE) and treatment with blood thinners (warfarin, antiplatelet agents or heparins) in the first year after diagnosis or at the time of thrombotic event. As this was a retrospective analysis, ethical approval was not required in accordance with the policy of our institution.

ATE was defined as acute coronary events (myocardial infarction or need for coronary artery intervention) and ischaemic stroke (confirmed on cerebral imaging). Haemorrhagic strokes were excluded as we were specifically interested in thrombotic events. We separately recorded episodes of peripheral vascular disease requiring amputation. We excluded angina and transient ischaemic attacks, as these diagnoses are difficult to confirm objectively in a retrospective analysis. Venous thromboembolism was defined as pulmonary embolus (PE) and/or deep vein thrombosis (DVT), with supportive imaging studies. Disease relapse was defined as clinical diagnosis of relapse leading to increase in immunosuppression. We recorded events of ATE, VTE, AAV relapse, pulmonary haemorrhage and death. We then calculated the incidence rate for ATE and VTE in our population of patients with AAV.

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Statistics

The IR was calculated per 100 person-years. All statistical analyses were performed using SPSS (IBM. Version 22). All data were regarded as non-parametric due to the relatively small sample sizes. Continuous variables are presented as median (interquartile range). Continuous data were compared using the Mann Whitney U test for comparison between 2 groups. Categorical data was analysed using chi-squared test. Logistic regression was used to perform multivariate analysis to ascertain risk factors for ATE and VTE following AAV diagnosis. Data were presented as odds ratio (OR (confidence interval); p-value). Log-rank test was used to ascertain unadjusted survival differences between patients with and without ATE/ VTE events and plotted as Kaplan–Meier curves. Cox proportional regression analysis was used to ascertain risk factors associated with mortality. Data were presented as hazards ratio (HR (confidence interval); p-value). A p-value <0.05 was considered to be statistically significant.

Results

204 patients were identified. Median follow up for surviving patients was 5.8 [range 1-10] years with a total of 1088 person-years. The baseline characteristics of our patient group are presented in Tables 1 and 2. The median age was 55 years (41-67), and 46% of patients were male. 71% of patients had renal involvement (defined as abnormal urinary sediment with or without elevated creatinine, confirmed on biopsy in 84% of cases) and the median creatinine at presentation was 117 (73–268)µmol/l. The majority of patients had GPA (54%), whilst 19% had MPA, 7% had EGPA, 13% had RLV, 4% had double positive (anti-GBM and ANCA) disease and 3% had an overlap syndrome with features of both AAV and another autoimmune disease such as SLE or MCTD. 25 patients (12.3%) died during the follow-up period.

Arterial Thrombosis

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There were 29 ATE following AAV diagnosis in 24 (11.8%) patients. This included 15 non-fatal and 2 fatal acute coronary events and 12 non-fatal ischaemic strokes, resulting in an IR of 2.67 per 100 person-years (1.56 for coronary events and 1.10 for ischaemic stroke). The incidence of ATE was highest early in the disease course with 9 events (31%) occurring in the first year, giving an incidence of 4.9 per 100 person-years. The IR from years 2 to 10 was 2.22 per 100 person-years. There were 2 events of peripheral vascular disease requiring amputation in the same patient. Due to the very low frequency of events of amputation we did not calculate an IR.

Baseline characteristics of patients with ATE and without ATE were compared (Table 1). Older age ($p=0.001$), VTE events ($p=0.004$), renal involvement ($p=0.020$), MPO-ANCA type ($p=0.011$), lower albumin level ($p=0.004$), higher CRP level ($p=0.001$) and prior IHD ($p<0.001$) at the time of AAV diagnosis were associated with subsequent ATE. Underlying AAV diagnosis, age, prior IHD and requirement for renal replacement therapy (RRT) at presentation were factors entered into the multivariate analysis for subsequent ATE. Predictors of ATE included prior IHD (10.9; (2.3-52.0); $p=0.003$) and advancing age (1.044; (1.022-1.077); $p=0.007$). There was no significant difference in frequency of relapses of AAV ($p=0.197$) or use of blood thinners ($p=0.703$), between patients with and without ATE.

Sensitivity analyses

As prior IHD was a strong predictor of ATE, we analysed the data excluding patients with prior IHD or stroke, and found that the IR of ATE was still elevated at 2.32 per 100 person-years (1.26 for coronary events and 1.06 for ischaemic stroke).

Venous Thrombosis

There were 16 VTE events in 14 (6.9%) patients, with an IR of 1.47 per 100 person-years. Of the 16 events, 9 were DVTs only, 3 were PEs only and 4 events were simultaneous DVT and PE. The incidence

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of VTE was highest early in the disease course, with 5 (31%) events within one month of the diagnosis of AAV. Almost half, 7 (44%) events occurred in the first year after diagnosis (IR 3.8 per 100 person-years). In years 2 to 10 after diagnosis the IR was 1.00 event per 100 person-years.

There was no statistically significant difference in baseline characteristics between patients with and without VTE on univariate analysis (Table 2). 11 (69%) VTE events occurred during active disease (within 3 months from a flare of disease).

10 (63%) VTE events occurred following a recent hospital admission. Hospitalisation may be considered a surrogate marker of disease severity and activity, but not all admissions appeared to be related to AAV, and hospitalisation is a known independent risk factor for VTE(16). Furthermore, 2 (13%) events were thought to be line-related thromboses and 1 patient had a newly diagnosed malignancy at the time of the event. There was no difference in relapse rate ($p=0.918$) or use of blood thinners ($p=0.985$) between patients with and without VTE.

Mortality

Patients with ATE following AAV diagnosis had a higher mortality rate compared to patients without ATE ($p=0.007$) (Figure 1). Unadjusted risk factors for mortality included ATE following diagnosis of AAV ($p=0.007$), atrial fibrillation/ flutter ($p=0.006$), prior IHD ($p=0.026$), prior stroke ($p=0.001$), AAV specific diagnosis (with GPA having a significantly better survival compared to other diagnoses) ($p=0.01$), advancing age ($p<0.001$), and requirement for RRT at presentation ($p=0.007$). Age, ATE following diagnosis of AAV, and requirement for RRT at presentation were factors entered into the Cox proportional hazards model for mortality. The only predictor of mortality on multivariate analysis was age (1.076; (1.041-1.112); $p<0.001$) (Figure 2).

Discussion

Arterial Thrombosis

The incidence of ATE in our study group was 2.67/ 100 person-years (1.56 for acute coronary events and 1.10 for ischaemic stroke). On multivariate analysis, only prior IHD and age were associated with future ATE. Among patients without prior IHD, the incidence of ATE was still raised compared to the general population at 2.32/ 100 person-years (1.26 for coronary events and 1.06 for ischaemic stroke). The median age for our cohort was 55 years.

We compared our rate of ATE in AAV to reported rates of ATE for the UK population (Table 3). Smolina et al reported the age-standardised incidence rate of acute coronary events as 0.154 per 100 person-years for men and 0.06 per 100 person-years for women among the general population in England in 2010(17). The rate of incident stroke (excluding persons with prior cardiovascular disease) was 0.10 per 100 person-years in the UK in 2008(18). Our event rate for coronary events and incident stroke in AAV was 15 and 11 times higher than in the general population respectively. Among the general population, the incidence of acute coronary events was highest in people with prior MI at 1.85 per 100 person-years(19). In people without prior MI, the IR of coronary events was 0.69 per 100 person-years in people with chronic kidney disease (CKD) and 0.54 per 100 person-years in people with diabetes. When we compared our results with this study, our rate of coronary events was similar to that in those with prior MI. In our cohort without prior IHD or stroke, the IR is double that reported by Tonelli et al(19) for people with CKD or diabetes. Therefore, it is unlikely that our event rate could be explained by these other risk factors alone. Power et al(20) reported the incidence rate of stroke in haemodialysis patients at our centre, over a similar time period, and found an incidence rate for first

thrombotic stroke of 1.12 per 100 person-years. Our event rate is similar in patients with vasculitis, most of whom did not require RRT (median Cr 117 (73–268) $\mu\text{mol/l}$; 19 percent required RRT).

A high incidence of arterial thrombosis in inflammatory disorders has previously been described. Hinojosa-Azaola et al studied the incidence of thrombosis in SLE in Canada and found the incidence of arterial thrombosis (defined as myocardial infarction, cerebrovascular disease, peripheral vascular disease and visceral infarction) of 0.7/ 100 person-years among patients with SLE(21). Similarly del Ricon et al found an incidence of arterial thrombosis (defined as CVD hospitalisation including MI, stroke, other arterial occlusive events or arterial revascularisation procedures or CVD death) of 3.43 per 100 person-years in people with rheumatoid arthritis in the USA(22). Allowing for differences in the definition of arterial thrombosis, our event rate in AAV appears similar to that reported in these studies of SLE and RA. Others have previously described an elevated incidence of ATE in patients with AAV(9-11). Similar to Faurshou et al (median population age 54.5 years), we found the incidence of arterial thrombosis was highest early in the disease course but remained elevated for at least 10 years. We are the first group to describe an elevated IR for stroke; Faurshou et al did not find a difference in event rates of stroke(5). Morgan et al(9) (median population age 63 years) found a higher event rate for TIA but similar event rate for stroke, when compared to CKD matched controls. We are the first to report an incidence rate for ATE in AAV. As these previous studies did not report incidence in person-years, we were unable to compare our IR to these studies.

On univariate analysis, age, prior IHD, VTE, admission at time of diagnosis, renal involvement, lack of ENT or eye involvement, ANCA type (MPO positive), high CRP, high creatinine and low albumin were all independent predictors of ATE. However on multivariate analysis, only prior IHD and age appeared to predict ATE. The lack of statistical significance of other factors found to be significant on univariate analysis could be due to a small event number and the disproportionate size of the groups.

Venous Thrombosis

The incidence of VTE was 1.47 events per 100 person-years in the first 10 years after diagnosis. This is approximately 20 times higher than the rate of VTE in the general population of the UK, reported by Huerta et al as 0.075 events per 100 person-years(23). In our cohort, almost half, (44%) events occurred in the first year after diagnosis (IR 3.8 per 100 person-years). In years 2 to 10 the IR was 1.00 per 100 person-years which is lower than the first year, but still elevated compared to the reported incidence in the general population.

The high incidence of VTE in various inflammatory disorders has previously been described (Table 3). In systemic lupus erythematosus (SLE), studies have found an incidence of VTE between 0.5 to 3.6 events per 100 person-years(21, 24-26). Similarly, the IR of VTE in rheumatoid arthritis (RA) is elevated at approximately 0.5 per 100 person-years(27, 28). Our event rate in AAV appears similar to event rates in SLE and higher than that in RA. It has recently been reported that people with AAV have an increased risk of VTE. The Wegener's Granulomatosis Etanercept Trial (WGET)(3) was a multicentre RCT in GPA performed in the USA. Merkel et al performed a sub-study of this trial (WeCLOT) of 180 patients and found an IR of VTE of 7 per 100 person-years (median population age 50 years). Weidner et al(8) performed a retrospective cohort study of 105 patients with AAV in Germany and found an incidence of 4.3 per 100 person-years. Stassen et al conducted a retrospective cohort study of 198 patients with AAV (excluding EGPA) in the Netherlands and found an IR of 1.8 per 100 person-years, increasing to 6.7 per 100 person-years during active disease(4). Allenbach et al performed a retrospective analysis of 1130 patients with AAV and Polyarteritis Nodosa (PAN) in France and found a higher incidence of VTE in AAV than PAN (1.84 versus 0.58 per 100 person-years respectively)(7). A Danish study of 180 patients with GPA matched to population controls, performed by Faurshou et al(5), found an increased incidence of VTE in the first 2 years after diagnosis and increased incidence of DVT in the following years. 70% of events in the GPA cohort occurred during active vasculitis. The study did not report absolute incidence per person-years. The European Vasculitis Society (EUVAS)(29)

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combined four randomised controlled trials to report VTE in 9.8% of their population (median population age 60 years). The incidence rate was not reported.

When we compare our study to the previous studies, our VTE event rate was less than the WeCLOT, EUVAS and Weidner studies, but similar to the Strassen and Allenbach studies. In the WeCLOT, EUVAS and Stassen studies, patients were described as having, or received treatment for, at least early systemic disease. Disease activity was described as a risk factor for VTE in the study by Stassen, Kronbichler and Farschou. In our study, patients were not selected for disease activity or severity; we included all patients without regard for disease severity and treatment received. 18 patients were diagnosed and initially treated at another hospital and then transferred to our unit. As a result, some patients did not have any periods of active disease during the follow up period. A difference in disease activity may therefore have contributed to the difference in event rate between our study and the WeCLOT and Stassen studies. Similar to the study by Faurshou, we found that the incidence of VTE was highest earlier in the disease course.

We are the first group to specifically look at rates of relapse, rather than periods of disease activity, and did not find a difference in VTE rates when comparing patients who had more frequent episodes of relapse to those that did not relapse.

Some of the previous studies focused on one syndrome such as GPA (Faurshou et al and WeCLOT). However, other studies looked at several subgroups of AAV (Morgan et al, EUVAS, Weidner et al, Strassen et al and Allenbach et al). We did not find a statistically significant difference in the rate of arterial or venous thrombosis between subgroups of AAV and believe that all subgroups of AAV have an elevated rate of thrombosis.

Wattanakit et al has demonstrated a correlation between stage of chronic kidney disease (CKD) and increased risk of VTE (excluding patients with end-stage kidney disease)(30), with an IR of 0.15, 0.19 and 0.45 per 100 person-years for normal kidney function, mild CKD and stage III/IV CKD respectively.

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However, a large proportion of our cohort had acute kidney injury at presentation, rather than stable CKD, so direct comparison is not possible.

Strengths and Limitations

We included all patients with AAV regardless of disease severity and type of treatment received, in a large and contemporary cohort. Our study provides an understanding of the incidence of arterial and venous thrombosis in patients with AAV. To our knowledge, we are the first group to describe the incidence rate of arterial thrombosis in AAV and also the first to demonstrate a higher risk of stroke in AAV.

As with all retrospective cohort studies, we were reliant on prior documentation and cannot exclude the possibility that our event rate may be underreported if events were diagnosed outside of our unit and were not documented in case notes. Some important risk factors for arterial and venous thrombosis were not routinely tested at our clinic, such as lipid profile and body mass index, and therefore could not be included in our analysis. Similarly, the BVAS was not recorded in all patients' records so we were not able to relate disease activity scores directly to the risk of ATE and VTE. We were unable to ascertain the relative risk of ATE and VTE in comparison to an age- and eGFR- matched cohort without AAV. However, our main objective was to ascertain the risk relative to the general population.

Conclusions

People with AAV have a high rate of arterial and venous thrombosis compared to the reported rates for the general UK population, particularly in the first year after diagnosis. This early incidence may be related to disease activity or to its treatment. The role of anti-plasminogen antibodies, reported by

others in active disease, requires further investigation. Early thromboprophylaxis is not routinely given to this patient group due to bleeding risk, particularly from pulmonary haemorrhage or at the time of renal biopsy. Future studies should assess the patient benefits and risks of anticoagulation or anti-platelet agents in AAV. Our study highlights the importance of ATE and VTE as complications of AAV and suggests that its treatment should be considered in the care of these patients.

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Figure Legends

Figure 1 Kaplan Meir curves for patient unadjusted survival in patients with and without ATE

($p=0.007$ on log-rank test). Please add p value to the graph

Figure 2 Cox proportional hazards regression curves describing long-term survival in patients with and without ATE, adjusted for age, prior IHD and RRT at presentation. ($p<0.001$ for presence of ATE).

Please add p value to the graph

Figure 3 Kaplan Meir curves for unadjusted patient survival in VTE and no VTE groups. ($p = 0.926$ on log-rank test).