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Risk of Cardiovascular Disease and Venous Thromboembolism Among Patients With Incident ANCA-Associated Vasculitis: A 20 year Population-Based Cohort Study

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Abstract

Objectives—To assess the cardiovascular disease (CVD) and venous thromboembolism (VTE) risks among patients with newly diagnosed ANCA-associated vasculitis (AAV).

Patients and Methods—A population-based incident AAV cohort of 58 patients diagnosed between 1996 and 2015 in Olmsted County (Minnesota, USA) was identified by medical record review. For each patient, 3 age- and sex-matched non-AAV comparators were randomly selected from the same population and assigned an index date corresponding to the AAV incidence date. Medical records of cases and comparators were reviewed for CVD events, which included cardiac events (coronary artery disease, heart failure and atrial fibrillation), cerebrovascular accidents

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(CVA), peripheral vascular disease (PVD) and VTE, which included deep vein thrombosis (DVT) and pulmonary embolism (PE).

Results—Baseline total cholesterol, high-density lipoprotein and current smoking rate were lower in AAV than comparators ($P=.03$, $P=.01$ and $P=.04$, respectively), while other CVD risk factors and Framingham risk score were not significantly different between the 2 groups. CVD events developed in 13 patients and 17 comparators, corresponding to a >3 fold increased risk (hazard ratio [HR] 3.15; 95% confidence interval [CI]:1.51-6.57). By subtypes, risks were increased for cardiac events (HR 2.96, 95%CI:1.42-6.15) and CVA (HR 8.16, 95%CI:2.45-27.15), but not for PVD. The HR for VTE was 3.26 (95%CI: 0.84-12.60), significantly increased for DVT (HR 6.25, 95%CI:1.16-33.60), but not for PE (HR 1.33, 95%CI:0.23-7.54).

Conclusions—Despite a similar prevalence of CVD risk factors at baseline, the risk of CVD is >3 fold higher and for CVA 8-fold higher in patients with incident AAV than matched comparator subjects.

Keywords

ANCA-associated vasculitis; cardiovascular risk; stroke; myocardial infarction; granulomatosis with polyangiitis

INTRODUCTION

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are a heterogeneous group of systemic diseases characterized by inflammation of small- and medium-sized vessels (1–3), variably associated with ANCAs directed against proteinase 3 (PR3) or myeloperoxidase (MPO) (3–5). Among AAV, granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) and microscopic polyangiitis (MPA) are the two most common subtypes, and with eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) account for an estimated combined prevalence of 42.1 per 100,000 adult population in the United States (U.S.) (6). Modern treatments have greatly improved survival in AAV (7–10), but many patients suffer cardiovascular and thrombotic complications during long-term follow up (11, 12).

Overall, patients with AAV appear at greater risk of CVD (13) and have an increased CVD-related mortality due to accelerated atherosclerosis (14). Significantly increased risks of myocardial infarction (MI) and ischemic stroke have been reported in GPA (12, 14, 15). However, other studies reported a non-statistically significant trend toward an increased risk of ischemic stroke (12, 13, 15), or an identical risk of stroke and even lower risk of acute coronary syndrome compared to matched controls (13). Different study designs, different comparator populations and case ascertainment strategies may explain the heterogeneity of findings among these different studies and hamper direct comparisons among them. Only a few population based investigations of CVD risk have been performed in all forms of AAV including MPA and EGPA.

An increase in the risk of venous thromboembolism (VTE) has been observed in AAV with a close temporal relationship to active disease (16–20), although the risk of developing VTE also remains increased during inactive AAV (21). Population-based studies specifically

addressing the risks of heart failure (HF), atrial fibrillation (AF), and peripheral vascular disease (PVD) in patients with AAV have not yet been conducted, although cardiac involvement has been reported to be twice as common in patients with GPA, and three times as common in EGPA than in comparators from the general population (22).

The current study aimed to better characterize the risk of CVD and thrombotic events among newly diagnosed patients with GPA, MPA and EGPA in the Olmsted County (Minnesota, USA) adult population, from 1996 to 2015. The incidence of CVD and VTE in patients with AAV was compared to that in sex- and age-matched comparator subjects without AAV, randomly selected from the same population.

METHODS

Data sources

All patients with AAV and comparators were residents of Olmsted County, Minnesota, where the Rochester Epidemiology project (REP) systematically collects the clinical records of all residents seeking medical care. Due to the availability of this comprehensive medical data, the population of Olmsted County is particularly suitable for the investigation of AAV epidemiology,

This record linkage system allows direct access to the medical records of both inpatients and outpatients, from all healthcare providers in Olmsted County, including Olmsted Medical Center and Mayo Clinic and their affiliated hospitals, local nursing homes and the few private general practitioners.

The utility of this data system in population-based studies has previously been described (23, 24) (25). The REP facilitates complete ascertainment of the outcomes of interest (i.e., any CVD and VTE) for AAV cases and comparators among Olmsted County residents.

Case ascertainment

Incident cases of AAV from January 1, 1996 to December 31, 2015 this geographically defined region of the U.S. were previously identified by medical record review (6). AAV cases were included if they fulfilled the criteria of at least one of the following classification schemes: American College of Rheumatology (ACR) classification criteria or the modified ACR criteria for GPA (26) (27), ACR criteria for EGPA (28), Chapel Hill Consensus Conference (CHCC) definition (29), or European Medical Agency (EMA) algorithm (30). Organ involvement and disease activity at disease incidence were described using items and domains of the Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS-WG) (31). Renal insufficiency was defined as an estimated glomerular filtration rate <60 ml/min/1.73m². For each patient with incident AAV, 3 age (± 3 years) and sex-matched comparators without AAV were randomly selected from the Olmsted County population, and assigned an index date corresponding to the incidence date of AAV.

Cardiovascular and thrombotic diseases ascertainment

Data on CVD risk factors at baseline, that included hypertension, diabetes mellitus, dyslipidemia, body mass index, and smoking status, were collected. Medical records of all

cases and comparators were reviewed for the events of interest, i.e. CVD and VTE. The former included coronary artery disease (CAD), atrial fibrillation (AF), heart failure (HF), cerebrovascular accident (CVA) and peripheral vascular disease (PVD). VTE events included deep vein thrombosis (DVT) and pulmonary embolism (PE).

CAD included both fatal and nonfatal MI. Classification of CAD was based on physician diagnosis as entered in the medical record, and was supported by coronary angiography, when performed. Coronary revascularization procedures (percutaneous transluminal coronary angioplasty and coronary artery bypass grafting) were also defined as CAD. Classification of HF was based on the Framingham criteria for HF (32). AF was classified based on electrocardiography reports. CVA was defined as ischemic stroke, hemorrhagic stroke, subarachnoid hemorrhage, transient ischemic attack, amaurosis fugax or death from CVA. CVA was classified by physician diagnosis, and was verified by cerebrospinal fluid analysis or imaging. Transient ischemic attack was defined by physician diagnosis and negative brain imaging studies. PVD included peripheral arterial disease, abdominal aortic aneurysm, renal artery stenosis or arterial thromboembolism. Peripheral arterial disease was defined by a resting ankle-brachial systolic pressure index of ≤ 0.9 (33). Classification of abdominal aortic aneurysm required imaging showing the diameter of the abdominal aorta more than 1.5 times normal diameter (34). Renal artery stenosis was verified by ultrasound/renal scintigraphy/angiography, and arterial thromboembolism was based on clinical diagnosis supported by angiography. DVT were verified by ultrasound or phlebography/venography and PE by computed tomography angiography, arteriography or scintigraphy.

The 10-year general Framingham risk score for CVD was calculated. When lipid values were not available, the office-based 10-year Framingham risk score, which does not include laboratory values, was used (35). All patients with active disease were treated with an induction therapy (glucocorticoid plus methotrexate, mycophenolate mofetil, cyclophosphamide or rituximab) followed by a maintenance treatment of variable duration (glucocorticoids, rituximab, methotrexate, azathioprine, mycophenolate mofetil, trimethoprim/sulfamethoxazole, alone or in combination). Follow-up was continued until death, migration or January 1, 2017. The study was approved by the Institutional Review Boards of Mayo Clinic and Olmsted Medical Center.

Statistical analysis

Descriptive statistics (percentages, mean, etc.) were used to summarize the characteristics of each cohort. Chi-square and rank sum tests were used for comparisons between the cohorts. Fisher's exact test was used to examine whether there were increases in prevalence of any CVD and VTE overall and by subtype prior to development of AAV between the cohorts. The CVD and VTE cumulative incidence overall and by subtype adjusted for the competing risk of death was estimated (36). These methods are similar to the Kaplan-Meier method with censoring of patients who are still alive at last follow-up. However, patients who died before the occurrence of CVD or VTE events are appropriately accounted for to avoid overestimation of the rate of occurrence of these events, which is possible if such subjects are simply censored at death. For each type of CVD and VTE, cases in which first

occurrence was prior to the diagnosis of AAV, or prior to the index date for subjects in the non-AAV comparison cohort, were excluded from the analysis of cumulative incidence.

For the estimation of the overall CVD and VTE cumulative incidence, the date of occurrence was the earliest date of occurrence of any of the individual CVD or VTE events. Cox proportional hazard ratios were used to compare the rate of development of CVD and VTE, individually and in combination, between patients with AAV and the non-AAV comparison cohort. These models were also used to examine the association between AAV-related features and development of CVD. First relapse was modeled as a time-dependent covariate. Person-year methods were used to examine the rates of CVD/VTE events according to time since AAV incidence/index date. Rate ratios comparing the AAV and non-AAV cohorts were computed. Ninety-five percent confidence intervals (CI) were obtained by assuming the rates followed the Poisson distribution. A *P*-value of $<.05$ was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics of AAV cases and comparators

Baseline demographic and clinical characteristics of AAV cases and comparators are described in Table 1. Median (interquartile range) length of follow-up was 6.5 (2.8, 11.3) years for AAV and 6.7 (4.1, 8.9) years for comparators. Among the 58 incident AAV cases identified, 48% were women and 98% Caucasian, with a mean $\pm$ SD age of 61.1 $\pm$ 16.5 years. Of the 174 non-AAV comparators, 48% were women and 95% were Caucasian, with a mean $\pm$ SD age of 61.2 $\pm$ 16.3 years. AAV cases included 23 (40%) GPA, 28 (48%) MPA and 7 (12%) EGPA. ANCA antibody testing was performed in 56 (97%) patients at diagnosis, with positive result for MPO-AAV in 34 (61%) patients, for PR3-AAV in 17 (30%) patients, and a negative ANCA result in 5 (9%) patients.

Baseline total cholesterol (median 179 mg/dL for AAV; 191 mg/dL for comparators; $P=.03$), high density lipoprotein (median 47 versus 53 mg/dL, $p=.013$) and current smoking (5% versus 19%; $P=.04$) were lower in AAV than comparators. The other CVD risk factors were not significantly different between the 2 groups.

At disease incidence, patients with MPA were older than patients with GPA or EGPA (mean $\pm$ SD, 67.6 $\pm$ 16.2 versus 56.1 $\pm$ 15.1 versus 51.5 $\pm$ 13.4 years, respectively). Systolic blood pressure and Framingham risk score were consistently higher in MPA versus GPA or EGPA ($P=.02$ and $P=.03$, respectively), but statistically non-significant after correction for age and sex (Supplemental Table). After age- and sex-adjustment, hypertension was more frequent in patients with MPA than GPA at AAV diagnosis (79% versus 43%, $P=.04$), as well as the use of anti-hypertensive medication (78% versus 36%, $P=.01$) (Supplemental Table). None of the patients had clinical or serologic evidence of antiphospholipid antibody syndrome or other thrombophilic disorders.

Association between AAV and incident CVD and VTE

Overall CVD and VTE prevalence prior to date of diagnosis/index date was not significantly different between patients with AAV and the non-AAV comparison cohort (27% and 28%, respectively; $p=.93$). Table 2 shows CVD and VTE cumulative incidence after diagnosis/index date for cases and comparators.

CVD events developed in 13 patients with AAV and 17 comparators. The risk of incident CVD adjusted for age, sex and calendar year was significantly higher among patients with AAV (hazard ratio [HR] 3.15, 95% CI:1.51-6.57) (Figure 1A). After adjusting for smoking status, presence of diabetes mellitus, presence of hypertension, use of anti-hypertensives, presence of dyslipidemia, and use of lipid-lowering medications, the risk of CVD was even higher (HR 4.62, 95% CI:1.87-11.42; $P<.001$).

By subtypes, age- and sex-adjusted risks were increased for cardiac events (CAD, HF or AF) (HR 2.96, 95% CI:1.42-6.15; $P=.004$) (Figure 1B), CVA (HR 8.49, 95% CI:2.54-28.30; $P<.001$) with all cases reported having an ischemic stroke (Figure 1C), but not for PVD (HR 0.70, 95% CI:0.08-6.40, $P=.75$). The HR for VTE was 3.26 (95% CI:0.84-12.60), significantly increased for DVT (HR 6.25, 95% CI:1.16-33.60) but not for PE (HR 1.33, 95% CI:0.23-7.54) (Table 2).

The factors associated with CVD events in the AAV cohort were age (HR per 10 year increase: 2.03; 95% CI:1.26-3.25), obesity (BMI ≥ 30 kg/m²; age-adjusted HR: 4.32; 95% CI: 1.30-14.31), dyslipidemia (age-adjusted HR:7.07; 95% CI:1.88-26.54), and diabetes mellitus type II (age-adjusted HR 7.42; 95% CI:1.59-34.64). The other demographic (sex, calendar year of AAV diagnosis), cardiovascular (previous or current smoking habit, hypertension) and AAV-related features tested (BVAS-WG at diagnosis, renal insufficiency, C-reactive protein, clinical diagnosis of GPA versus MPA, ANCA-specificity, relapse) were not associated with CVD risk.

The incidence rate of overall CVD events during follow-up was calculated according to time after AAV incidence/index date (Table 3, Figure 2). In the AAV cohort, this rate was greatest in the first 2 years after diagnosis (6.89 per 100 person-years, 95% CI:2.24-16.06), and gradually declined in subsequent years. In contrast, this rate was stable over time during the first 10 years of follow-up in the comparator cohort at about 2 events per 100 person-years (95% CI:1.2-3.2). Consequently, when compared to non-AAV comparators, the rate ratio was highest for the first 2 years after diagnosis (rate ratio: 3.43; 95% CI:0.99-11.90) and decreased thereafter.

At disease incidence, patients with MPA were older than patients with GPA or EGPA (mean $\pm$ SD; 67.6 $\pm$ 16.2, 56.1 $\pm$ 15.1 and 51.5 $\pm$ 13.4, respectively) (Supplemental Table). After age- and sex-adjustment, hypertension was more frequent in patients with MPA than GPA at AAV diagnosis (79% versus 43%, $P=.04$), as well as the use of anti-hypertensive medication (78% versus 36%, $P=.01$).

DISCUSSION

This population-based study demonstrates that patients with AAV, despite similar baseline CV risk factors and history of prior CVD, are at more than 3 times higher risk for CVD overall compared to the general population, a risk that is more than 4-fold after baseline CVD risk factor adjustment, and at 6 times higher risk for DVT. Moreover, this is the first study to demonstrate a substantially increased incidence of CVA in patients with AAV. This CVD risk is especially increased during the first 2 years after diagnosis. The main baseline factors associated with this increased risk are older age and some traditional CV risk factors (obesity, diabetes mellitus and dyslipidemia), which need to be aggressively treated in these high-risk patients.

In contrast to the majority of the previous studies reporting an increased risk of MI in patients with AAV (12, 13, 15), the results of the current study found no increase in MI. The higher cumulative incidence of cardiac events overall was mainly driven by a higher incidence of HF. A large population-based study recently reported an approximately doubled risk of MI in patients with GPA (12). As discussed by the authors, the accuracy of that study may have been limited by its design, which used an administrative registry to identify the patients and the outcomes of interest without further verification of individual medical records, with a potential over ascertainment of cases and events.

Other authors have reported an increased risk of MI, especially during the first 5 years after the diagnosis (15, 37). However, these were not population-based studies with matched comparators. One of them identified patients using hospital registries (15), which could potentially decrease the incidence denominator by selecting only patients with more severe disease. Another study used data from patients included in clinical trials (37), who are likely at higher risk for CVD since they are older and have higher rates of renal impairment and higher disease activity scores than patients in observational cohorts (38).

The incidence of CVA in the current study was markedly higher in patients with AAV compared with the general population. Indeed, the CVA risk was more than 8 times higher than that of comparator subjects, and was driven by ischemic strokes. One of the biggest single center GPA cohorts reported neurological involvement in 33.6% of patients, but only 16 out of 324 patients had stroke (39). To the best of our knowledge, the only population-based study to assess the risk of ischemic stroke in AAV reported a moderately increased risk in patients with GPA compared with matched non-GPA comparator subjects (HR:1.50), without reaching statistical significance (12).

A possible contributor to the higher stroke prevalence in the current study is that cardiovascular risk factors could be higher in general population of USA compared to that of Canada. The only directly comparable cardiovascular risk factor in the current and the population-based Canadian study was obesity, present in about 30% of cases and comparator subjects in the current study, compared to less than 1% in Canadian study (12). Notably, no patients in the current study had a clinical diagnosis of antiphospholipid syndrome, which is rarely reported to coexist with AAV and to be the cause of thromboembolic and CVA complications (40). Ultimately, many factors could have contributed to the finding of

increased CVA risk in the current study, highlighting the importance of CVA among all other CVD complications suffered by patients with AAV.

Premature atherosclerosis associated with inflammation is likely the key driver behind the increased risk for CVD events in patients with AAV (41), related to increased local and systemic expression of several pro-inflammatory cytokines (42). This hypothesis is particularly appealing since the prevalence of CVD risk factors in this cohort was similar between patients with AAV and matched comparators at baseline, but it was strongly associated with the subsequent risk of developing CVD risk in the AAV cohort. Interestingly, baseline AAV-related factors (such as CRP, BVAS-WG, ANCA specificity or renal insufficiency due to vasculitis) did not *per se* increase this CVD risk. It is possible that inflammation due to vasculitis might trigger an acceleration of atherosclerosis in those predisposed individuals, with a higher CVD risk at diagnosis. At present, however, it is still not clear how much the systemic and vascular inflammatory process may contribute to the pathogenesis of CVD among patients with AAV.

Finally, in this study, the incidence of VTE in patients with AAV was more than 3 times higher than comparator subjects, significantly increased for DVT (> 6 times), but not for PE. This result is consistent with previous observations of an increased incidence of VTE in AAV (18–20), suggesting that some disruption of venous endothelium in AAV might create a microenvironment promoting thrombosis.

Although it is well documented that a history of previous CVD events predicts the risk of subsequent CVD and CVA in the general population and in AAV as well (13, 43, 44), unlike the current study, most of the previous AAV studies usually did not exclude patients with prior events from the risk analyses, thus potentially leading to overestimation of the risk of CVD in patients with AAV. The current study, instead, gives a clearer picture of CVD risk in patients with AAV. Its major strength is the population-based design and the utilization of the REP, a comprehensive record linkage system which allows capture of virtually all clinically recognized cases of AAV in Olmsted County, including those patients with mild/localized GPA that may be omitted from hospital-based databases. The diagnosis of AAV was verified by medical record review, minimizing the likelihood of over-diagnosis or physician-based diagnosis not fulfilling international classification criteria, a common concern in coding-based studies.

The limitations of this study are those inherent to its retrospective nature. First, clinical information of the patients was not systematically obtained by the treating physicians following an established protocol. Consequently, some of the pertinent clinical data might not have been documented in the medical record and the BVAS/WG scoring, for instance, could have been imprecise for that reason. Because this study is based on retrospective review of data recorded in the clinical record, ascertainment bias, classification error, survivor treatment selection and other biases cannot be completely excluded. However, the results reflect a real life setting and therefore should have relevance for routine patient care.

Second, differences in CVD risk between MPA and GPA or between MPO-AAV and PR3-AAV described in other cohorts were not detected in the current study. The relatively small

base population may lack power to detect differences between these subgroups; however even with a larger cohort these differences among clinical subtypes of AAV and ANCA serology subgroups would still have been smaller than the effect of traditional CVD risk factors. Third, the results of this study may or may not reflect AAV in communities with a different racial/ethnic composition, such as those with high prevalence of African Americans or Asians. However, the findings can be carefully generalized to adult subjects with similar age, sex, race/ethnicity, living in the Midwest or Northern United States and provide a useful point of reference for the estimation of these risk factors and disease outcomes.

Conclusion

This long-term follow up study demonstrates that patients with AAV are at increased risk for any CVD and DVT, with a risk more than 3 times higher for CVD overall, and more than 8 times higher for CVA, compared to matched comparator subjects from the same population. In contrast to some previous reports, the risk of CAD in AAV is not significantly higher than the general population when patients with prior CVD events are excluded from the analysis. The risk for CVD in AAV is increased, particularly in the first two years following disease occurrence, gradually declining thereafter. For the clinician and patient, active vigilance for any CVD and VTE, and an aggressive treatment of CVD risk factors is recommended, especially in the first years after diagnosis of AAV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ANCA	anti-neutrophil cytoplasmic antibody
AAV	ANCA-associated vasculitis (AAV)
GPA	granulomatosis with polyangiitis
MPA	microscopic polyangiitis
EGPA	eosinophilic granulomatosis with polyangiitis
PR3	proteinase 3
MPO	myeloperoxidase
CVD	cardiovascular disease
VTE	venous thromboembolism

CAD	coronary artery disease
HF	heart failure
AF	atrial fibrillation
CVA	cerebrovascular accidents
PVD	peripheral vascular disease
DVT	deep vein thrombosis (DVT)
PE	pulmonary embolism
MI	myocardial infarction
HR	hazard ratio
CI	confidence interval
SD	standard deviation.

References

1. Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med*. 1997; 337(21):1512–23. Epub 1997/11/20. DOI: 10.1997/11/20 [PubMed: 9366584]
2. Cornec D, Cornec-Le Gall E, Fervenza FC, Specks U. ANCA-associated vasculitis - clinical utility of using ANCA specificity to classify patients. *Nat Rev Rheumatol*. 2016; 12(10):570–9. Epub 2016/07/29. DOI: 10.2016/07/29 [PubMed: 27464484]
3. Nolle B, Specks U, Ludemann J, Rohrbach MS, DeRemee RA, Gross WL. Anticytoplasmic autoantibodies: their immunodiagnostic value in Wegener granulomatosis. *Ann Intern Med*. 1989; 111(1):28–40. Epub 1989/07/01. [PubMed: 2660645]
4. Fussner LA, Hummel AM, Schroeder DR, Silva F, Cartin-Ceba R, Snyder MR, et al. Factors determining the clinical utility of serial measurements of antineutrophil cytoplasmic antibodies targeting proteinase 3. *Arthritis Rheumatol*. 2016; 68(7):1700–10. Epub 2016/02/18. DOI: 10.2016/02/18 [PubMed: 26882078]
5. Finkelstein JD, Merkel PA, Schroeder D, Hoffman GS, Spiera R, St Clair EW, et al. Antiproteinase 3 antineutrophil cytoplasmic antibodies and disease activity in Wegener granulomatosis. *Annals Intern Med*. 2007; 147(9):611–9. Epub 2007/11/03.
6. Berti A, Cornec D, Crowson CS, Specks U, Matteson EL. The epidemiology of ANCA associated vasculitis in Olmsted County, Minnesota (USA): a 20 year population-based study. *Arthritis Rheumatol*. 2017; Epub 2017/09/08. doi: 10.1002/art.40313
7. Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. *Am J Med*. 2003; 114(6):463–9. Epub 2003/05/03. [PubMed: 12727579]
8. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2005; 52(8):2461–9. Epub 2005/07/30. DOI: 10.2005/07/30 [PubMed: 16052573]
9. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010; 363(3):221–32. Epub 2010/07/22. DOI: 10.2010/07/22 [PubMed: 20647199]

10. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med*. 2013; 369(5):417–27. Epub 2013/08/02. DOI: 10.2013/08/02 [PubMed: 23902481]
11. Seo P, Min YI, Holbrook JT, Hoffman GS, Merkel PA, Spiera R, et al. Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET). *Arthritis Rheum*. 2005; 52(7):2168–78. Epub 2005/06/30. DOI: 10.2005/06/30 [PubMed: 15986348]
12. Avina-Zubieta JA, Mai A, Amiri N, Dehghan N, Ann Tan J, Sayre EC, et al. Risk of Myocardial Infarction and Stroke in Patients With Granulomatosis With Polyangiitis (Wegener's): A Population-Based Study. *Arthritis Rheumatol*. 2016; 68(11):2752–9. Epub 2016/10/28. DOI: 10.2016/10/28 [PubMed: 27213713]
13. Morgan MD, Turnbull J, Selamet U, Kaur-Hayer M, Nightingale P, Ferro CJ, et al. Increased incidence of cardiovascular events in patients with antineutrophil cytoplasmic antibody-associated vasculitides: a matched-pair cohort study. *Arthritis Rheum*. 2009; 60(11):3493–500. Epub 2009/10/31. DOI: 10.2009/10/31 [PubMed: 19877070]
14. Cohen Tervaert JW. Cardiovascular disease due to accelerated atherosclerosis in systemic vasculitides. *Best Practice Res Clin Rheumatol*. 2013; 27(1):33–44. Epub 2013/03/20. DOI: 10.2013/03/20
15. Faurschou M, Mellekjaer 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(4):1187–92. DOI: 10.1002/art.24386. [PubMed: 19333952]
16. Stassen PM, Derks RP, Kallenberg CG, Stegeman CA. Venous thromboembolism in ANCA-associated vasculitis—incidence and risk factors. *Rheumatology (Oxford)*. 2008; 47(4):530–4. Epub 2008/03/22. DOI: 10.2008/03/22 [PubMed: 18356178]
17. Weidner S, Hafezi-Rachti S, Rupprecht HD. Thromboembolic events as a complication of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2006; 55(1):146–9. Epub 2006/02/08. DOI: 10.2006/02/08 [PubMed: 16463427]
18. Merkel PA, Lo GH, Holbrook JT, Tibbs AK, Allen NB, Davis JC Jr, et al. Brief communication: high incidence of venous thrombotic events among patients with Wegener granulomatosis: the Wegener's Clinical Occurrence of Thrombosis (WeCLOT) Study. *Ann Intern Med*. 2005; 142(8):620–6. Epub 2005/04/20. [PubMed: 15838068]
19. Novikov P, Makarov E, Moiseev S, Meshkov A, Strizhakov L. Venous thromboembolic events in systemic vasculitis. *Ann Rheum Dis*. 2015; 74(3):e27. Epub 2014/11/09. doi: 10.2014/11/09 [PubMed: 25381230]
20. Allenbach Y, Seror R, Pagnoux C, Teixeira L, Guilpain P, Guillevin L. 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(4):564–7. Epub 2008/11/19. DOI: 10.2008/11/19 [PubMed: 19015208]
21. Hilhorst M, Winckers K, Wilde B, van Oerle R, ten Cate H, Tervaert JW. Patients with antineutrophil cytoplasmic antibodies associated vasculitis in remission are hypercoagulable. *J Rheumatol*. 2013; 40(12):2042–6. Epub 2013/10/17. DOI: 10.2013/10/17 [PubMed: 24128780]
22. Hazebroek MR, Kemna MJ, Schalla S, Sanders-van Wijk S, Gerretsen SC, Dennert R, et al. Prevalence and prognostic relevance of cardiac involvement in ANCA-associated vasculitis: eosinophilic granulomatosis with polyangiitis and granulomatosis with polyangiitis. *Intern J Cardiol*. 2015; 199:170–9. Epub 2015/07/27. DOI: 10.2015/07/27
23. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ 3rd, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. *Am J Epidemiol*. 2011; 173(9):1059–68. Epub 2011/03/25. DOI: 10.2011/03/25 [PubMed: 21430193]
24. St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ 3rd, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. *Mayo Clin Proc*. 2012; 87(2):151–60. Epub 2012/02/07. DOI: 10.2012/02/07 [PubMed: 22305027]

25. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ. History of the Rochester Epidemiology Project: Half a Century of Medical Records Linkage in a US Population. *Mayo Clin Proc.* 2012; 87(12):1202–13. DOI: 10.1016/j.mayocp.2012.08.012. [PubMed: 23199802]
26. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum.* 1990; 33(8):1101–7. Epub 1990/08/01. [PubMed: 2202308]
27. Design of the Wegener's Granulomatosis Etanercept Trial (WGET). *Control Clin Trials.* 2002; 23(4):450–68. Epub 2002/08/06. [PubMed: 12161090]
28. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum.* 1990; 33(8):1094–100. Epub 1990/08/01. [PubMed: 2202307]
29. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013; 65(1):1–11. Epub 2012/10/10. DOI: 10.2012/10/10 [PubMed: 23045170]
30. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis.* 2007; 66(2):222–7. Epub 2006/08/12. DOI: 10.2006/08/12 [PubMed: 16901958]
31. Stone JH, Hoffman GS, Merkel PA, Min YI, Uhlfelder ML, Hellmann DB, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). *Arthritis Rheum.* 2001; 44(4):912–20. Epub 2001/04/25. DOI: 10.2001/04/25 [PubMed: 11318006]
32. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation.* 1993; 88(1):107–15. Epub 1993/07/01. [PubMed: 8319323]
33. Muir RL. Peripheral arterial disease: Pathophysiology, risk factors, diagnosis, treatment, and prevention. *J Vasc Nurs.* 2009; 27(2):26–30. Epub 2009/06/03. DOI: 10.2009/06/03 [PubMed: 19486852]
34. Moxon JV, Parr A, Emoto TI, Walker P, Norman PE, Golledge J. Diagnosis and monitoring of abdominal aortic aneurysm: current status and future prospects. *Curr Probl Cardiol.* 2010; 35(10):512–48. Epub 2010/10/12. DOI: 10.2010/10/12 [PubMed: 20932435]
35. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation.* 2008; 117(6):743–53. Epub 2008/01/24. DOI: 10.2008/01/24 [PubMed: 18212285]
36. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med.* 1999; 18(6):695–706. Epub 1999/04/16. [PubMed: 10204198]
37. Suppiah R, Judge A, Batra R, Flossmann O, Harper L, Hoglund P, et al. A model to predict cardiovascular events in patients with newly diagnosed Wegener's granulomatosis and microscopic polyangiitis. *Arthritis Care Res.* 2011; 63(4):588–96. Epub 2011/04/01. DOI: 10.2011/04/01
38. Pagnoux C, Carette S, Khalidi NA, Walsh M, Hiemstra TF, Cuthbertson D, et al. Comparability of patients with ANCA-associated vasculitis enrolled in clinical trials or in observational cohorts. *Clin Exp Rheumatol.* 2015; 33(2 Suppl 89):S-77–83. Epub 2015/05/29.
39. Nishino H, Rubino FA, DeRemee RA, Swanson JW, Parisi JE. Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. *Ann Neurol.* 1993; 33(1):4–9. Epub 1993/01/01. DOI: 10.1993/01/01 [PubMed: 8388187]
40. Sebastian JK, Voetsch B, Stone JH, Romay-Penabad Z, Lo GH, Allen NB, et al. The frequency of anticardiolipin antibodies and genetic mutations associated with hypercoagulability among patients with Wegener's granulomatosis with and without history of a thrombotic event. *J Rheumatol.* 2007; 34(12):2446–50. Epub 2007/10/09. [PubMed: 17918782]
41. Pagnoux C, Chironi G, Simon A, Guillevin L. Atherosclerosis in ANCA-associated vasculitides. *Ann NY Acad Sci.* 2007; 1107:11–21. Epub 2007/09/07. DOI: 10.2007/09/07 [PubMed: 17804528]

42. Booth AD, Wallace S, McEniery CM, Yasmin Brown J, Jayne DR, et al. Inflammation and arterial stiffness in systemic vasculitis: a model of vascular inflammation. *Arthritis Rheum.* 2004; 50(2): 581–8. Epub 2004/02/12. DOI: 10.2004/02/12 [PubMed: 14872502]
43. George MG, Tong X, Bowman BA. Prevalence of Cardiovascular Risk Factors and Strokes in Younger Adults. *JAMA Neurol.* 2017; 74(6):695–703. Epub 2017/04/11. DOI: 10.2017/04/11 [PubMed: 28395017]
44. Rossouw JE, Lewis B, Rifkind BM. The Value of Lowering Cholesterol after Myocardial Infarction. *N Engl J Med.* 1990; 323(16):1112–9. DOI: 10.1056/nejm199010183231606. [PubMed: 2215579]

Figure 1. Cumulative incidence of cardiovascular events. A. Any cardiovascular disease in patients with AAV (solid line) and non-AAV comparators (dashed line); B. cardiac events; C. cerebrovascular accidents. AAV = ANCA-associated vasculitis

Figure 2. Rates of CVD according to disease duration for the AAV cohort (solid line) and non-AAV comparators (dashed line). CVD = cardiovascular disease; AAV = ANCA-associated vasculitis

Table 1

Characteristics of ANCA associated vasculitis cases and comparators at incidence/index date

Characteristics	AAV	Comparators	P value
Subjects	58	174	
Age, years	61.1±16.5	61.2±16.3	.98
Female sex	28 (48%)	84 (48%)	1.00
Race			.51
Caucasian	57 (98%)	152 (95%)	
African-American	1 (2%)	6 (4%)	
Asian	0 (0%)	2 (1%)	
Unknown	0	14	
Length of follow-up, years	7.0±4.8	6.9±3.6	–
Alive at last follow-up	38	138	–
Smoking Status			.04
Never	30 (53%)	87 (51%)	
Ex-smoker	24 (42%)	53 (31%)	
Current smoker	3 (5%)	32 (19%)	
Missing	1	2	
BMI, kg/m²	28.2±6.3	29.5±7.6	.57
Obesity (BMI ≥30 kg/m²)	17 (29%)	58 (33%)	.57
Hypertension	34±59%	85±49%	.20
Systolic BP, mmHg	133.4±21.0	130.5±21.3	.43
Diastolic BP, mmHg	73.6±11.5	75.1±11.8	.30
Hypertension drugs^a	31 (55%)	72 (41%)	.07
Dyslipidemia	28 (48%)	89 (51%)	.71
Total cholesterol, mg/dL	179 (151, 200)	191 (167, 212)	.03
Low density lipoprotein, mg/dL	100 (77, 127)	108 (84, 134)	.20
High density lipoprotein, mg/dL	47 (37, 57)	53 (43, 62)	.01
Triglycerides, mg/dL	120 (85, 179)	110 (88, 156)	.77
Dyslipidemia drugs^b	22 (38%)	73 (42%)	.59
Diabetes mellitus	9 (16%)	19 (11%)	.35
Framingham risk score, %	19.9±17.0	18.4±15.7	.65
C-reactive protein^c mg/L	12.6 (4.5, 60.0)		
eGFR, ^dmL/min/1.73m²	43.0 (21.5, 82.0)		

All variables were collected between the week prior to the index date and index date, except for lipid values, collected ± 3 years from index date (n=53 AAV and n=147 comparators). Data are presented as n, mean±SD or n (%). AAV = ANCA associated vasculitides; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate

Hypertension, dyslipidemia, diabetes mellitus were defined as physician diagnosis, based on systemic blood pressure values, lipid values and glycaemia values, respectively.

^aHypertension drugs: diuretics, beta-blockers, calcium channel antagonists, ACE inhibitors, angiotensin II receptor blockers.

^bDyslipidemia drugs: statins, fibrates and/or ezetimibe

^cData available for 38 patients; ^{\$} Data available for 56 patients

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Cumulative incidence rate of cardiovascular outcomes in ANCA associated vasculitis and comparators, 1996-2015

Table 2

	Events after index date for cases/comparators	Cumulative incidence (95% CI) at 10 years ^a		HR (95% CI) ^b	P value
		AAV (n=58)	Comparators (n=174)		
Any CVD (Cardiac events, CVA, PVD)	13/17	39.6 (18.7, 55.1)	14.0 (7.0, 20.4)	3.15 (1.51, 6.57)	.002
Cardiac events	13/18	35.4 (16.7, 49.9)	16.2 (7.3, 24.3)	2.96 (1.42, 6.15)	.004
Coronary artery disease	4/16	11.6 (0.0, 22.0)	12.2 (6.0, 18.0)	0.87 (0.29, 2.60)	.80
Congestive heart failure	8/14	14.4 (3.7, 23.9)	11.6 (5.2, 17.6)	2.62 (1.05, 6.51)	.04
Atrial fibrillation	11/20	20.0 (7.1, 31.1)	16.6 (7.7, 24.6)	1.65 (0.78, 3.48)	.19
Cerebrovascular accident	9/4	21.5 (7.3, 33.6)	2.6 (0.1, 5.1)	8.49 (2.54, 28.30)	<.001
Stroke	7/6	15.6 (3.8, 26.0)	5.8 (0.0, 11.4)	4.36 (1.42, 13.42)	.01
Transient Ischemic Attack	2/0	—	—	—	—
Peripheral vascular disease	2/4	2.2 (0.0, 6.4)	5.1 (0.0, 10.1)	0.70 (0.08, 6.40)	.75
Abdominal aortic aneurysm	0/1	—	—	—	—
Peripheral arterial disease	2/3	—	—	—	—
Venous thromboembolism	6/4	10.0 (1.2, 18.1)	2.4 (0.0, 5.9)	3.26 (0.84, 12.60)	.09
Pulmonary embolism	2/4	4.8 (0.0, 11.1)	2.9 (0.0, 6.6)	1.33 (0.23, 7.54)	.75
Deep vein thromboses	6/2	9.8 (1.2, 17.8)	0.0 (0.0, 0.0)	6.25 (1.16, 33.60)	.03

Patients with a specific previous event were excluded from that individual category. Data are presented as n/n, unless otherwise stated; CVD: cardiovascular diseases; CVA = cerebrovascular accident; PVD = peripheral vascular disease; VTE = venous thromboembolism; AAV = ANCA associated vasculitis; HR = hazard ratio; CI = confidence intervals.

^a adjusted for the competing risk of death.

^b for all events after index date, adjusted for age, sex and calendar year

Table 3

Rates of any cardiovascular disease events according to follow-up time for the aggregate ANCA associated vasculitis cohort (all AAV patients)

Time after diagnosis	Cases		Comparators	
	CVD events	Rate (95% CI) ^a	CVD events	Rate (95% CI) ^a
<2 years	5	6.9 (2.2, 16.1)	5	2.0 (0.6, 4.79)
2-5 years	4	5.2 (1.4, 13.2)	7	2.2 (0.9, 4.6)
> 5 years	4	6 (1.0, 9.4)	5	1.7 (0.6, 3.9)
Total Follow-up	13	5.0 (2.7, 8.6)	17	2.0 (1.2, 3.2)

^aRates reported per 100 person-years. Any CVD = cardiovascular diseases (cardiac events, cerebrovascular accidents, and peripheral vascular disease). AAV = ANCA associated vasculitides; CI = confidence intervals.