The Journal of Rheumatology 2023;xx:xxxx
doi:10.3899/jrheum.220851
First Release June 2 2023

The Journal of Rheumatology

Traditional and Disease-Specific Risk Factors for Cardiovascular Events in ANCA-Associated Vasculitis: A Multinational Retrospective Study

Sergey Moiseev[1], Nikolay Bulanov[2], Matija Crnogorac[3], Haner Direskeneli[4], Kresimir Galesic[3], Ummugulsum Gazel[4], Duvuru Geetha[5], Loic Guillevin[6], Zdenka Hrušková[7], Mark A. Little[8], Liam O'Neill[9], Egor Makarov[10], Stephen P. McAdoo[11], Aladdin J. Mohammad[12], Sarah Moran[13], Pavel Novikov[2], Charles D. Pusey[11], Chinar Rahmattulla[14], Veronika Satrapová[7], Joana Silva[11], Alexander Suvorov[15], Vladimír Tesar[7], Benjamin Terrier[6], Peter Willeit[16], Ming-Hui Zhao[17], Andreas Kronbichler[18], and David R.W. Jayne[18]

ABSTRACT. ***Objective.*** To investigate the occurrence of cardiovascular events (CVEs) in a large cohort of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) across the European Union, China, Turkey, Russia, the United Kingdom, and the USA.

Methods. Patients with a definite diagnosis of AAV who were followed for ≥ 3 months and had sufficient documentation were included. Data on myocardial infarction (MI) and stroke were collected retrospectively from tertiary vasculitis centers. Univariate and multivariate Cox regression models were used to estimate hazard ratios (HRs) and 95% CIs.

Results. Over a median follow-up of 62.0 months (IQR 22.6-100.0), CVEs (mostly MIs) occurred in 245 (10.7%) of 2286 patients with AAV, with a higher frequency in China and the UK. On multivariate regression analysis, older age (55-64.9 yrs, HR 2.93, 95% CI 1.99-4.31), smoking (HR 1.98, 95% CI 1.48-2.64), Chinese origin (HR 4.24, 95% CI 3.07-5.85), and pulmonary (HR 1.50, 95% CI 1.09-2.06) and kidney (HR 3.02, 95% CI 2.08-4.37) involvement were independent variables associated with a higher occurrence of CVEs.

Conclusion. We showed that geographic region and both traditional and disease-specific (kidney involvement in particular) factors were independently associated with CVEs. Proper assessment and management of modifiable cardiovascular (CV) risk factors are essential for prevention of CV morbidity in patients with AAV.

Key Indexing Terms: ANCA-associated vasculitis, cardiovascular events, myocardial infarction, risk factors, stroke

The Irish cohort of this study was supported by the Meath Foundation (grant no. 208591). The Czech cohort was supported by the research project of the Ministry of Health (RVO 64615).

[1]S. Moiseev, MD, Professor, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, and Faculty of Medicine, Lomonosov Moscow State University, Moscow, Russia; [2]N. Bulanov, MD, P. Novikov, MD, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia; [3]M. Crnogorac, MD, K. Galesic, MD, Professor, Department of Nephrology and Dialysis, Dubrava University Hospital, Zagreb, Croatia; [4]H. Direskeneli, MD, Professor, U. Gazel, MD, Department of Internal Medicine, Division of Rheumatology, Marmara University, School of Medicine, Istanbul, Turkey; [5]D. Geetha, MD, Division of Nephrology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA; [6]L. Guillevin, MD, Professor, B. Terrier, PhD, Professor, Department of Internal Medicine, National Referral Center for Rare Systemic and Autoimmune Diseases, Hôpital Cochin, Paris, France; [7]Z. Hrušková, MD, V. Satrapová, MD, V. Tesar, MD, Professor, Department of Nephrology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; [8]M.A. Little, MD, Professor, Trinity Health Kidney Centre, Trinity Translational Medicine Institute, and Irish Centre for Vascular Biology, Tallaght University Hospital, Dublin, Ireland; [9]L. O'Neill, MD, University Hospital Galway, Dublin, Ireland; [10]E. Makarov, MD, Faculty of Medicine, Lomonosov Moscow State University, Moscow, Russia; [11]S.P. McAdoo, PhD, C.D. Pusey, MD, Professor, J. Silva, MD, Department of Immunology and Inflammation, Centre for Inflammatory Disease, Imperial College London, London, UK; [12]A.J. Mohammad, MD, Department of Rheumatology, Clinical Sciences-Lund, Lund University, Lund, Sweden, and Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, UK; [13]S. Moran, MD, Trinity Health Kidney Centre, Trinity Translational Medicine Institute, Dublin, Ireland; [14]C. Rahmattulla, PhD, Department of Pathology, Leiden University Medical Center, Leiden, the Netherlands; [15]A. Suvorov, MD, Centre for Analysis of Complex Systems, Sechenov First Moscow State Medical University, Moscow, Russia; [16]P. Willeit, PhD, Professor, Clinical Epidemiology Team, Medical University of Innsbruck, Innsbruck, Austria, and Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; [17]M.H. Zhao, MD, Professor, Renal Division, Peking University First Hospital, Key Laboratory of Renal Disease, Ministry of Health of China, Key Laboratory of CKD Prevention and Treatment, Ministry of Education of China, Beijing, China; [18]A. Kronbichler, PhD, D.R.W. Jayne, MD, Professor, Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge University Hospitals, and Department of Medicine, University of Cambridge, Cambridge, UK.

S. Moiseev and N. Bulanov contributed equally as first authors.
A. Kronbichler and D.R.W. Jayne contributed equally as senior authors.

The authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. A. Kronbichler, Addenbrooke's Hospital, Hills Rd, Cambridge CB2 0QQ, UK. Email: ak2283@cam.ac.uk.

Accepted for publication November 25, 2022.

In 1858, the German pathologist Rudolph Virchow proposed in his lecture on cellular pathology that "an inflammation of the inner arterial coat to be the starting point of the so-called atheromatous degeneration."[1] Virchow's theory has been revived in recent decades when the role of inflammatory mechanisms in the pathophysiology of atherosclerosis was demonstrated in multiple experimental studies.[2] Moreover, the Canakinumab Antiinflammatory Thrombosis Outcome Study showed a direct benefit of targeting inflammation on outcomes in patients with established atherosclerotic disease who had survived a myocardial infarction (MI).[3] Large-scale human genetic and biomarker data also suggest a causal association between interleukin (IL)-1α/β and IL-6R-related pathways and coronary artery disease (CAD).[4,5] These works provided the basis for the current understanding of atherosclerosis that can be defined as a lipid-driven disease characterized by low-grade, chronic inflammation of the arterial wall.[6]

Not surprisingly, various immune-mediated inflammatory diseases have been shown to be associated with premature and accelerated atherosclerosis leading to an increased risk of cardiovascular events (CVEs).[7] Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs), including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA), are not an exception, given the high occurrence of a relapsing/remitting or refractory disease with persisting inflammation.[8-10] In the European Vasculitis Study Group (EUVAS) trials, 14% of 535 patients with GPA or MPA had at least 1 CVE within 5 years of diagnosis.[11]

According to a previous metaanalysis, patients with AAV have a 1.65-fold increased risk of CVEs compared to the general population.[12] Most of this risk is driven by an increase in CAD, with a trend only for cerebrovascular accidents. Cardiovascular (CV) morbidity in AAV contributes to overall mortality, which has decreased over the last few decades as a result of improvement in immunosuppressive regimens,[13-15] but remains 2.7-times higher than in the general population.[16] An increased CV risk in AAV can be attributed to disease and treatment-related accumulation of traditional risk factors and various disease-specific mechanisms.[7,17] The latter may include endothelial dysfunction, which causes a procoagulant state and precedes atherosclerotic plaque formation.[18] Several other factors are implicated in diffuse endothelial dysfunction, including elevated levels of circulating proinflammatory cytokines[19]; accumulation of macrophages and increased secretion of growth factors and matrix metalloproteinases[20]; excess production of reactive oxygen species[20]; the formation of neutrophil extracellular traps; activation of the complement system; release of tissue factor initiating the extrinsic pathway of coagulation[21,22]; activation of circulating platelets,[23] circulating ANCA, and other autoantibodies[7]; and defective T-cell regulation resulting in acceleration of the atherosclerotic process.[24] Previous research suggests that myeloperoxidase (MPO), an enzyme that is mainly found in neutrophils and has the ability to modify low-density lipoprotein (LDL) in the intima, may also contribute to atherogenesis in patients with AAV because of enhanced MPO-mediated LDL oxidation.[25]

The objective of this multinational retrospective study is to compare the incidence rates of MI and stroke in a large cohort of patients with AAV from various countries, including the European Union (EU), China, Turkey, Russia, the United Kingdom, and the USA, and to define factors associated with higher risk of CVEs in AAV.

METHODS

Design and patients. Data on CVEs, including fatal and nonfatal MI, stroke, or both, were collected retrospectively from tertiary vasculitis centers located in Belgium, China, Croatia, Czech Republic, Denmark, Finland, France, Germany, Italy, Ireland, the Netherlands, Poland, Russia, Spain, Sweden, Switzerland, Turkey, the UK, and the USA. We enrolled patients with a definite diagnosis of GPA, MPA, or EGPA who were followed for at least 3 months from diagnosis and had sufficient data on disease activity, complications, and comorbidities. Ethics approval was obtained in all centers involved (ie, at Sechenov University, Moscow, on September 12, 2017, protocol: 01-12; previously reported and anonymized data with institutional review board approval, ie, data from China[26]) or approval to use patient data was obtained during the conduct of the EUVAS trial,[27-30] a major contributing source of patients to this paper. The same database was used elsewhere.[31]

As described earlier in our previous multinational retrospective study,[31] organ involvement was evaluated using the Disease Extent Index, a simplified tool to assess disease extent in retrospective studies at the time of diagnosis.[32] The Birmingham Vasculitis Activity Score (BVAS) was collected only if it was provided by the investigators. We recorded age, sex, BMI, smoking status (never, current, previous), ANCA status (positive or negative), ANCA type, kidney function expressed as baseline creatinine and estimated glomerular filtration rate (eGFR; Chronic Kidney Disease Epidemiology Collaboration equation), duration of follow-up, treatment with glucocorticoids (GCs), cyclophosphamide (CYC), or rituximab (RTX), and time from disease onset to CVE. ANCA titers were not included in the dataset because of the differences in analytical techniques and reference values in the tertiary centers.[33,34] The diagnosis of MI and stroke was established using the local diagnostic algorithms of each tertiary center.

Statistical analysis. Characteristics of patients are presented as absolute values and percentages, mean (SD), or median (IQR) depending on the data distribution. The normality of distribution was tested using Shapiro-Wilk test. The data were compared by Welch *t* test or Mann-Whitney *U* test for continuous data, and chi-square test or Fisher exact test for categorical data, as appropriate. It was accepted that incidence rates have a Poisson distribution to calculate 95% CIs. To identify factors associated with CVEs, we used the Cox proportional hazards model. The proportional hazards assumption was checked using a Schoenfeld residuals assessment. If the proportional hazards assumption was rejected, we used a binary logistic regression model instead. Binomial proportion CIs were calculated using the Clopper-Pearson method. We performed univariate analysis for each variable adjusted for age and male sex, followed by a multivariate regression model with stepwise selection. The results of the univariate and multivariate analyses are presented as hazard ratios (HRs) and 95% CIs as appropriate. *P* values < 0.05 were considered significant. Statistical analysis was performed in R 4.1.0 (R Development Core Team).

RESULTS

Patients. In total, we included 2286 patients with AAV (53.4% female, median age 64.2 yrs) who were followed for a median of 62.0 months (IQR 22.6-100.0). Patients were distributed into 6 cohorts according to geographic region: EU, China, Russia, Turkey, the UK, and the USA. Most patients had MPA (51%) or GPA

Table 1. Clinical and demographic characteristics of patients recruited from different sites across the globe.

	All Countries	China	Russia	Turkey	EU[a]	UK	USA
Patients, n	2286	504	401	53	732	516	80
Female	1221 (53.4)	259 (51.4)	262 (65.3)	24 (45.3)	378 (51.6)	244 (47.3)	54 (67.5)
Median age, yrs (IQR)	64.2 (52.0-73.2)	69.3 (60.3-76.3)	53.8 (39.4-62.0)	58.1 (47.3-64.0)	65.6 (54.7-73.1)	65.6 (52.6-74.8)	68.0 (55.8-75.2)
Median age at onset, yrs (IQR)	59.0 (47.0-68.0)	65.5 (54.0-72.0)	48.0 (32.8-56.0)	53.0 (44.0-60.0)	60.0 (48.0-67.0)	60.0 (48.2-70.0)	63.0 (49.8-69.0)
Diagnosis							
GPA	983 (43)	116 (23)	244 (60.8)	34 (64.2)	356 (48.6)	185 (35.9)	48 (60)
MPA	1165 (51)	388 (77)	103 (25.7)	18 (34)	353 (48.2)	272 (52.7)	31 (38.8)
EGPA	138 (6)	0 (0)	54 (13.5)	1 (1.9)	23 (3.1)	59 (11.4)	1 (1.2)
ANCA[b]							
PR3	877 (38.7)	52 (10.3)	174 (43.4)	25 (47.2)	354 (48.4)	238 (46.1)	34 (42.5)
MPO	1140 (49.9)	445 (88.3)	117 (29.2)	17 (32.1)	317 (43.3)	198 (38.4)	46 (57.5)
PR3 + MPO	18 (0.8)	0 (0)	9 (2.2)	0 (0)	9 (1.2)	0 (0)	0 (0)
ANCA-negative	198 (8.7)	5 (1)	83 (20.7)	2 (3.8)	47 (6.4)	61 (11.8)	0 (0)
Undifferentiated[c]	67 (2.9)	2 (0.4)	19 (4.7)	9 (17.0)	20 (2.7)	17 (3.3)	0 (0)
Missing data	22 (1)	0 (0)	17 (4.2)	0 (0)	3 (0.4)	2 (0.4)	0 (0)
CYC any time	1565/1972 (79.4)	432 (85.7)	260/363 (71.6)	30 (56.6)	406/457 (88.8)	397/515 (77.1)	40 (50.0)
RTX any time	411/1468 (28)	0/504 (0)	91/363 (25.1)	31 (58.5)	12/457 (2.6)	222/515 (43.1)	55 (68.8)
eGFR at onset, mL/min/1.73 m^2, median (IQR)	26.0 (9.4-71.0)	13.4 (6.7-40.5)	60.3 (24.4-89.1)	37.5 (16.2-92.9)	22.9 (8.6-61.2)	35.2 (10.9-78.3)	19.5 (12.0-35.5)
eGFR, n/N (%)							
≥ 60 mL/min/1.73 m^2	566/1859 (30.5)	94/502 (18.7)	150/297 (50.5)	21 (39.6)	118/448 (26.3)	175/479 (36.5)	8 (10)
15-59.9 mL/min/1.73 m^2	612/1859 (32.9)	141/502 (28.1)	95/297 (32)	20 (37.7)	163/448 (36.4)	147/479 (30.7)	46 (57.5)
< 15 mL/min/1.73 m^2	681/1859 (36.6)	267/502 (53.2)	52/292 (17.5)	12 (22.6)	167/448 (37.3)	157/479 (32.8)	26 (32.5)
BMI[d], median (IQR)	24.4 (21.5-28.0)	23.0 (20.0-25.0)	26.2 (22.8-30.1)	25.6 (22.6-29.0)	25.9 (23.0-28.4)	25.9 (21.9-28.4)	27.7 (24.1-33.6)
History of smoking, n/N (%)	729/1370 (53.2)	161/504 (31.9)	62/273 (22.7)	26/46 (56.5)	154/434 (35.5)	289/419 (69)	37/80 (46.2)
HTN, n/N (%)	653/1371 (47.6)	121/503 (24.1)	237/374 (63.4)	26/46 (56.5)	129/204 (63.2)	76/157 (48.4)	64/80 (80)
Dyslipidemia or on statins, n/N (%)	503/1367 (36.8)	23/502 (4.6)	223/371 (60.1)	12/46 (26.1)	92/204 (45.1)	113/157 (72)	40/80 (50)

Values are n (%) unless otherwise indicated. [a] Includes Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Italy, Ireland, the Netherlands, Poland, Spain, and Sweden. [b] Patients with both PR3-ANCA and MPO-ANCA were counted in the 3 groups (PR3, MPO, and PR3+MPO). Therefore, the total number may exceed 100% in some columns. [c] Undifferentiated ANCA indicates that the ANCA test was positive, but the type of ANCA is unknown. [d] BMI calculated as weight in kilograms divided by height in meters squared. ANCA: antineutrophil cytoplasmic antibody; CYC: cyclophosphamide; eGFR: estimated glomerular filtration rate; EGPA: eosinophilic granulomatosis with polyangiitis; EU: European Union; GPA: granulomatosis with polyangiitis; HTN: hypertension; MPA: microscopic polyangiitis; MPO: myeloperoxidase, PR3: proteinase 3; RTX: rituximab.

(43%) and were positive for myeloperoxidase (MPO)-ANCA (49.9%) or proteinase 3 (PR3)-ANCA (38.4%; Table 1).

Kidney disease was present in 73.3% of included patients. Kidney function was impaired in most patients (median serum creatinine level = 182 μmol/L [IQR 81-452]). Approximately one-third (36.6%) of patients had severely impaired kidney function, defined as an eGFR < 15 mL/min/1.73 m^2 at baseline. The prevalence of traditional risk factors for CVEs was high in the studied cohort: 53.2% of patients had a history of smoking, 36.8% had dyslipidemia or were treated with statins, and 47.6% had arterial hypertension (HTN).

Prevalence of CVEs. In the total cohort, any CVE occurred in 245 (10.7%) of 2286 patients; MI in 185 (8.1%) patients, and stroke in 74 (3.2%) patients, including 14 (0.6%) patients who had both an MI and stroke. The reported frequencies of CVEs and MIs were higher in the Chinese (24.2% and 23.2%, respectively) and UK cohorts (9.7% and 5.4%, respectively; Table 2). Death from any cause occurred in 455 (19.9%) patients.

Incidence of CVEs. Median time from disease onset to CVE (known in 198 cases) was 17.5 months (IQR 3.0-40.0). There were no significant differences in the risk for all CVEs, MIs, and stroke between the first, second, and third years of follow-up after disease onset. There was a trend to a lower prevalence of CVEs during the second and third year of follow-up in comparison to the first year (age-, sex-, and region-adjusted HR 0.84, 95% CI 0.49-1.43, $P = 0.50$, and HR 0.68, 95% CI 0.40-1.14, $P = 0.15$, respectively).

The incidence rates for CVEs, MIs, and stroke varied by region and were higher in the Chinese and UK cohorts than in the other countries (Figure 1; Supplementary Table S1, available with the online version of this article). CVE-free, MI-free, and stroke-free survival for different geographic regions are presented on Kaplan-Meier curves (Supplementary Figure S1, S2, and S3). Log-rank test showed that CVE-free and MI-free survival was lower in China than in any other region (all P values < 0.005). Stroke-free survival in China was lower than in the EU ($P < 0.005$) and Russia ($P = 0.02$). In the UK, CVE-free and MI-free survivals were lower than in the EU ($P < 0.005$ for

Table 2. Prevalence of CVEs in all regions, and subdivided across different countries/regions.

	All Regions	China	Russia	Turkey	EU[a]	UK	USA
Patients, n	2286	504	401	53	732	516	80
Median follow up, months (IQR)	62.0 (22.7-100.0)	60.0 (23.0-98.0)	43.0 (18.0-70.0)	73.5 (38.0-110.0)	38.0 (4.8-87.2)	58.9 (34.8-85.3)	44.0 (29.8-81.5)
Any CVE	245 (10.7)	122 (24.2)	18 (4.5)	2 (3.8)	47 (6.4)	50 (9.7)	6 (7.5)
MI	185 (8.1)	117 (23.2)	13 (3.2)	2 (3.8)	20 (2.7)	28 (5.4)	5 (6.3)
Stroke	74 (3.2)	13 (2.6)	7 (1.7)	0 (0)	29 (4.0)	23 (5.4)	2 (2.5)
MI and stroke	14 (0.6)	8 (1.6)	2 (0.5)	0 (0)	2 (0.3)	1 (0.2)	1 (1.3)
Death from any cause	455 (19.9)	263 (52.2)	29 (7.6)	0 (0)	86 (11.7)	71 (13.8)	6 (7.5)

Values are n (%) unless otherwise indicated. [a]Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Italy, Ireland, the Netherlands, Poland, Spain, and Sweden. CVE: cardiovascular event; EU: European Union; MI: myocardial infarction.

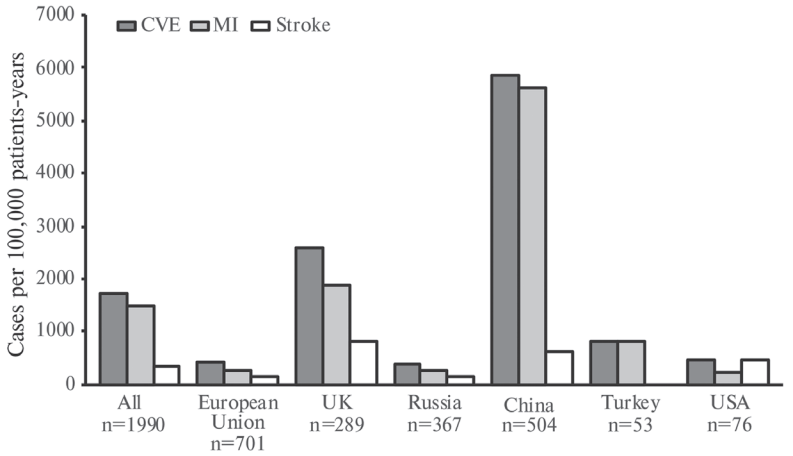

Figure 1. Cases per 100,000 patient-years of CVEs, and subdivision into MI and stroke in the whole sample and in the different countries/regions. CVE: cardiovascular events; MI: myocardial infarction.

both), Russia ($P < 0.005$ for both), and the US ($P = 0.02$ and $P = 0.03$, respectively). Stroke-free survival was lower in the UK than in the EU ($P < 0.005$) and Russia ($P = 0.01$). Survival in all other regions was comparable ($P > 0.05$ for all).

Factors associated with a higher risk of CVE. On age- and sex-adjusted univariate Cox regression analysis, traditional risk factors, including male sex, older age, BMI, smoking, and HTN, were associated with a higher risk of CVEs (Supplementary Table S2, available with the online version of this article). Several AAV-related factors adjusted for age and sex were also associated with a higher risk of CVEs: MPA diagnosis, ANCA-positivity, MPO-ANCA-positivity, higher BVAS at onset, history of rapidly progressive glomerulonephritis, CV, kidney, and nervous system involvement, eGFR < 15 mL/min/1.73 m^2 at onset, and treatment with CYC in comparison to other therapies used to induce remission. PR3-ANCA-positivity and GPA diagnosis were associated with a lower risk of CVEs. The risk of CVEs also depended on the geographic region and was the highest in China.

On multivariate Cox regression analysis, only age ≥ 55 years, smoking, Chinese origin, and pulmonary and kidney involvement retained their significance as risk factors for CVEs (Figure 2). The results of univariate Cox regression analysis

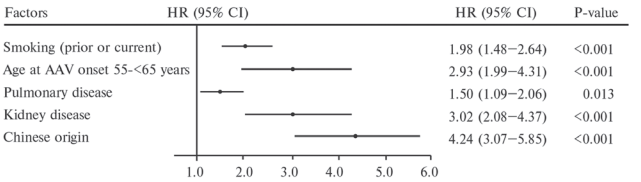

Figure 2. Multivariate Cox proportional HRs for CVEs. The list of factors for backwise selection included: sex, age, geographic region, diagnosis, PR3-ANCA, MPO-ANCA, smoking, HTN, dyslipidemia, RPGN, eGFR at onset (≥ 60, 15-59.9, or < 15), cyclophosphamide treatment, ENT, ocular, pulmonary, kidney, gastrointestinal, peripheral nervous system, skin, joint involvement, and general manifestations. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; CVE: cardiovascular event; eGFR: estimated glomerular filtration rate; ENT: ear, nose, and throat; HR: hazard ratio; HTN: hypertension; MPO: myeloperoxidase; PR3: proteinase 3; RPGN: rapidly progressive glomerulonephritis.

of factors that were associated with either MI or stroke are presented in Supplementary Tables S3 and S4 (available with the online version of this article).

Given the regional differences in the CVE occurrence, we conducted a separate univariate Cox regression analysis to evaluate the risk factors for CVEs in China and other regions of the world separately (Supplementary Tables S5 and S6, available

with the online version of this article). In China, male sex, smoking, HTN, pulmonary, nervous system, kidney disease, and eGFR < 15 mL/min/1.73 m^2 were associated with a higher risk of CVEs; whereas, in other regions, adverse outcomes were associated with male sex, older age, HTN, CV involvement, BVAS at onset of AAV, and eGFR < 15 mL/min/1.73 m^2.

DISCUSSION

In our multinational retrospective study, 10.7% of 2286 patients with AAV developed an MI or stroke within the first few years after diagnosis, although the occurrence of CVEs varied widely depending on geographic region from 3.8% in Turkey to up to 24.2% in China. In total, MI was more common than stroke. In patients with a known duration of follow-up, the incidence of CVEs was similar in the EU, Russia, and the US and > 10- and 6-fold higher in China and the UK, respectively. The differences in the incidence of CVEs were driven mostly by the variable occurrence of MI, whereas the differences in the incidence of stroke between countries were less striking.

An increased CV risk in patients with AAV has been previously shown in several population-based studies.[12,35] For example, in a matched cohort study, 504 patients with newly diagnosed GPA had an almost 2-fold increased risk of MI and a nonstatistically significant trend toward an increased risk of ischemic stroke compared to 5222 matching subjects without GPA who were selected from a population database of a Canadian population from British Columbia.[36]

High CV morbidity in China seems to represent the country's current situation, in which there is an evolving epidemic of atherosclerotic CV disease (CVD).[37] The prevalence and incidence of CVD in China, including CAD and ischemic stroke, have been increasing continuously since 2006 owing to population aging, lifestyle changes, urbanization, and the gaps between guideline-recommended targets of major risk factors and their current levels.[38] Notably, the median age of Chinese patients in our study was 69.3 years and thus close to the overall life expectancy in this country of 73.3 years in 2007 and 76.3 years in 2017.[39] Moreover, greater than half of the patients with AAV from China had an eGFR < 15 mL/min/1.73 m^2 at onset of disease, whereas the percentage of such patients in the other regions ranged from only 17.5% in Russia to up to 37.3% in the European countries. Severe kidney disease in AAV predicts kidney replacement therapy in a significant proportion of patients, which is in turn a risk factor for CVEs.[40] On the contrary, a higher CV risk in patients with AAV from the UK was an unexpected finding. The difference in CV morbidity between the UK and other European countries could not be explained by the age of patients, which was similar in the 2 cohorts. It could be partly attributed to a higher prevalence of other traditional CV risk factors (that is, smoking and dyslipidemia) in the former cohort, although we cannot exclude the role of unaccounted confounders in our study (eg, better documented follow-up in the UK and China).

In our previous study involving a multinational cohort of 2869 patients with AAV, we showed a higher frequency of venous thromboembolic events within the first year after diagnosis of systemic vasculitis.[31] Population-based studies suggested that the risk of CVEs is also higher in the first year after diagnosis of AAV and decreases in subsequent years.[36,41,42] However, we did not confirm this finding in our study. Outcome data from randomized controlled trials in 535 patients with AAV showed that CVD was one of the leading causes of death only after the first year of follow-up, whereas patients usually died within the first year from infection and active vasculitis.[43] These data argue against an immediate effect of disease activity on the risk of CVEs, although the persistence of inflammation despite a remission state or a later manifestation of inflammation-driven acceleration of atherosclerosis cannot be ruled out.

On univariate analysis, geographic region and various traditional and disease-specific factors were associated with a higher risk of CVEs. However, most of these, with the exception of age, smoking, Chinese origin, and pulmonary and kidney disease, lost statistical significance on multivariate analysis. Our data are in line with previous studies[44,45] and support a significant contribution of traditional risk factors (age in particular) to the development of CVEs in patients with AAV. Of note, these factors, including male sex, smoking, and HTN, contributed significantly to the risk of CVEs both in China and other regions of the world in a separate univariate regression analysis. This confirms the finding of a previous prospective study, showing that major CVEs in patients with AAV relate to established CV risk factors, such as older age, a history of CVD, dyslipidemia, HTN, and a sedentary lifestyle.[46] Noteworthy, metabolic syndrome, a cluster of CV risk factors, was shown to occur more frequently in AAV when compared to age- and sex-matched controls.[47]

In AAV, the disease itself and prolonged immunosuppression result in a progressive accumulation of damage and treatment-related complications that can expose patients to CVEs. For example, during a 7-year follow-up of 302 patients from the EUVAS trials, the frequency of HTN and diabetes mellitus increased from 4.8% to 41.5% and from 1.1% to 10.4%, respectively, over time.[48] These unfavorable changes in the CV risk profile can explain a later increase in the risk of CVEs in patients with AAV. Houben et al studied guideline adherence in the management of CV risk in 144 patients with AAV from the Netherlands and Canada.[49] Approximately one-third of patients had indications for blood pressure or lipid-lowering therapy but were either not treated or not at target levels. This study highlights a need for periodic assessment and modification of a patient's individual CV risk profile as recommended by the 2016 European Alliance of Associations for Rheumatology/European Renal Association – European Dialysis and Transplant Association guidelines for the management of AAV.[17]

Among disease-specific factors, a higher risk of CVEs in multivariate analysis was associated only with kidney and pulmonary disease. In the general population, CV risk increases exponentially with impaired kidney function.[50] The risk of CV complications and death is particularly high in patients receiving dialysis. In our study, 70% of patients with AAV had reduced eGFR (< 60 mL/min/1.73 m^2) at baseline. New regimens of remission induction and maintenance therapy have improved the outcomes in AAV with kidney involvement, although a

significant proportion of them still ultimately reach end-stage kidney disease.[51]

The limitations of our study are inherent with the retrospective design. The information about traditional and potential disease-specific risk factors for CVEs was in part missing, and we had limited data on certain clinical features of AAV. The missing country-based control groups limit our potential to calculate risk ratios of CVEs in comparison to a matched background population. We did not calculate BVAS retrospectively as a high level of inaccuracy might be expected, but we used these data if provided by investigators. More importantly, we could not differentiate fatal and nonfatal CVEs, since the exact causes of death were not reported. Information on disease relapses is missing, which might also have an influence on the frequency of CVEs. A total of 455 patients died during follow-up. Causes of death were not identified by our case report form. The infrequent use of RTX and missing cumulative GC doses should also be noted. Nevertheless, our study was conducted in a large international cohort of patients with AAV and provides a picture of CV morbidity in this population in different regions of the world.

In summary, depending on geographic region and duration of follow-up, up to 24% of patients with AAV develop MI or stroke within the first 5 years after diagnosis. On multivariate analysis, geographic (Chinese origin), and both traditional (older age and smoking) and disease-specific (pulmonary and kidney disease) factors were significantly associated with a higher risk of CVEs. Therefore, timely control of disease activity is critical to prevent accrual of organ damage in patients with AAV. However, better management of modifiable CV risk factors will also be beneficial for patients with AAV and seems to be a more practical approach to prevent CV morbidity and mortality. GC minimization strategies may be one step forward in managing modifiable CV risk factors. In addition, cardio- and nephroprotection (eg, with the use of sodium-glucose cotransporter-2 inhibitors proven to be effective in large outcome trials), may be another promising option to improve CV health in AAV,[52] but trial data specifically focusing on AAV are missing.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Virchow R. Cellular pathology. As based upon physiological and pathological histology. Lecture XVI--Atheromatous affection of arteries. 1858. Nutr Rev 1989;47:23-5.
2. Mayerl C, Lukasser M, Sedivy R, Niederegger H, Seiler R, Wick G. Atherosclerosis research from past to present--on the track of two pathologists with opposing views, Carl von Rokitansky and Rudolf Virchow. Virchows Arch 2006;449:96-103.
3. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-31.
4. Sarwar N, Butterworth AS, Freitag DF, et al; IL6R Genetics Consortium Emerging Risk Factors Collaboration. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet 2012;379:1205-13.
5. Interleukin 1 Genetics Consortium. Cardiometabolic effects of genetic upregulation of the interleukin 1 receptor antagonist: a Mendelian randomisation analysis. Lancet Diabetes Endocrinol 2015;3:243-53.
6. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999;340:115-26.
7. Clifford AH, Cohen Tervaert JW. Cardiovascular events and the role of accelerated atherosclerosis in systemic vasculitis. Atherosclerosis 2021;325:8-15.
8. Morgan MD, Turnbull J, Selamet U, et al. Increased incidence of cardiovascular events in patients with antineutrophil cytoplasmic antibody-associated vasculitides: a matched-pair cohort study. Arthritis Rheum 2009;60:3493-500.
9. Houben E, Mendel A, Carette S, Voskuyl AE, Penne EL, Pagnoux C. Predictors of fatal and non-fatal cardiovascular events in ANCA-associated vasculitis: data from the Toronto CanVasc cohort. Joint Bone Spine 2020;87:221-4.
10. Kronbichler A, Leierer J, Gauckler P, Shin JI. Comorbidities in ANCA-associated vasculitis. Rheumatology 2020;59 Suppl 3:iii79-83.
11. Suppiah R, Judge A, Batra R, et al. A model to predict cardiovascular events in patients with newly diagnosed Wegener's granulomatosis and microscopic polyangiitis. Arthritis Care Res 2011;63:588-96.
12. Houben E, Penne EL, Voskuyl AE, et al. Cardiovascular events in anti-neutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis of observational studies. Rheumatology 2018; 57:555-62.
13. Novikov PI, Moiseev SV, Kuznetsova EI, Semenkova EN, Mukhin NA. Changing patterns of clinical severity and risk of mortality in granulomatosis with polyangiitis over four decades: the Russian experience. Rheumatol Int 2015;35:891-8.
14. Wallace ZS, Lu N, Unizony S, Stone JH, Choi HK. Improved survival in granulomatosis with polyangiitis: a general population-based study. Semin Arthritis Rheum 2016;45:483-9.
15. Hilhorst M, Wilde B, van Paassen P, et al. Improved outcome in anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis: a 30-year follow-up study. Nephrol Dial Transplant 2013;28:373-9.
16. Tan JA, Dehghan N, Chen W, Xie H, Esdaile JM, Avina-Zubieta JA. Mortality in ANCA-associated vasculitis: a meta-analysis of observational studies. Ann Rheum Dis 2017;76:1566-74.
17. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583-94.
18. Hilhorst M, Winckers K, Wilde B, van Oerle R, ten Cate H, Cohen Tervaert JW. Patients with antineutrophil cytoplasmic antibodies associated vasculitis in remission are hypercoagulable. J Rheumatol 2013;40:2042-6.
19. Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. Circ Res 2016;118:145-56.
20. Shirai T, Hilhorst M Harrison DG, Goronzy JJ, Weyand CM. Macrophages in vascular inflammation--from atherosclerosis to vasculitis. Autoimmunity 2015;48:139-51.
21. Moiseev S, Lee JM, Zykova A, et al. The alternative complement pathway in ANCA-associated vasculitis: further evidence and a meta-analysis. Clin Exp Immunol 2020;202:394-402.
22. Lee KH, Kronbichler A, Park DDY, et al. Neutrophil extracellular traps (NETs) in autoimmune diseases: a comprehensive review. Autoimmun Rev 2017;16:1160-73.
23. Miao D, Ma TT, Chen M, Zhao MH. Platelets release proinflammatory microparticles in anti-neutrophil cytoplasmic antibody-associated vasculitis. Rheumatology 2019; 58:1432-42.

24. Cohen Tervaert JW. Translational mini-review series on immunology of vascular disease: accelerated atherosclerosis in vasculitis. Clin Exp Immunol 2009;156:377-85.
25. Slot MC, Theunissen R, van Paassen P, Damoiseaux JG, Cohen Tervaert JW, Limburg Nephrology Working Group. Anti-oxidized low-density lipoprotein antibodies in myeloperoxidase-positive vasculitis patients preferentially recognize hypochlorite-modified low density lipoproteins. Clin Exp Immunol 2007;149:257-64.
26. Bai YH, Li ZY, Chang DY, Chen M, Kallenberg CG, Zhao MH. The BVAS is an independent predictor of cardiovascular events and cardiovascular disease-related mortality in patients with ANCA-associated vasculitis: a study of 504 cases in a single Chinese center. Semin Arthritis Rheum 2018;47:524-9.
27. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36-44.
28. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461-9.
29. de Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670-80.
30. Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007; 18:2180-8.
31. Moiseev S, Kronbichler A, Makarov E, et al. Association of venous thromboembolic events with skin, pulmonary and kidney involvement in ANCA-associated vasculitis: a multinational study. Rheumatology 2021;60:4654-61.
32. de Groot K, Gross WL, Herlyn K, Reinhold-Keller E. Development and validation of a disease extent index for Wegener's granulomatosis. Clin Nephrol 2001;55:31-8.
33. Bossuyt X, Cohen Tervaert JW, Arimura Y, et al. Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol 2017;13:683-92.
34. Moiseev S, Cohen Tervaert JW, Arimura Y, et al. 2020 international consensus on ANCA testing beyond systemic vasculitis. Autoimmun Rev 2020;19:102618.
35. Mercuzot C, Letertre S, Daien CI, et al. Comorbidities and health-related quality of life in patients with antineutrophil cytoplasmic antibody (ANCA) - associated vasculitis. Autoimmun Rev 2021;20:102708.
36. Aviña-Zubieta JA, Mai A, Amiri N, et al. Risk of myocardial infarction and stroke in patients with granulomatosis with polyangiitis (Wegener's): a population-based study. Arthritis Rheumatol 2016;68:2752-9.
37. Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. Nat Rev Cardiol 2019;16:203-12.
38. Ma LY, Chen WW, Gao RL, et al. China cardiovascular diseases report 2018: an updated summary. J Geriatr Cardiol 2020;17:1-8.
39. Chen H, Qian Y, Dong Y, et al. Patterns and changes in life expectancy in China, 1990-2016. PLoS One 2020;15:e0231007.
40. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
41. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent coronary heart disease in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. PLoS One 2012;7:e33442.
42. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. BMC Neurol 2012;12:41.
43. Flossmann O, Berden A, de Groot K, et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 2011;70:488-94.
44. Terrier B, Chironi G, Pagnoux C, et al. Factors associated with major cardiovascular events in patients with systemic necrotizing vasculitides: results of a longterm followup study. J Rheumatol 2014;41:723-9.
45. Kang A, Antonelou M, Wong NL, et al. High incidence of arterial and venous thrombosis in antineutrophil cytoplasmic antibody-associated vasculitis. J Rheumatol 2019;46:285-93.
46. Roubille C, Henriquez S, Mercuzot C, et al. Impact of cardiovascular risk factors on the occurrence of cardiovascular events in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides. J Clin Med 2021;10:2299.
47. Petermann Smits DR, Wilde B, Kianersi Adegani M, de Jongh H, van Paassen P, Cohen Tervaert JW. Metabolic syndrome in ANCA-associated vasculitis. Rheumatology 2013;52:197-203.
48. Robson J, Doll H, Suppiah R, et al. Damage in the ANCA-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. Ann Rheum Dis 2015;74:177-84.
49. Houben E, Mendel A, van der Heijden JW, et al. Prevalence and management of cardiovascular risk factors in ANCA-associated vasculitis. Rheumatology 2019;58:2333-5.
50. Go AS. Cardiovascular disease consequences of CKD. Semin Nephrol 2016;36:293-304.
51. Moiseev S, Novikov P, Jayne D, Mukhin N. End-stage renal disease in ANCA-associated vasculitis. Nephrol Dial Transplant 2017;32:248-53.
52. Säemann M, Kronbichler A. Call for action in ANCA-associated vasculitis and lupus nephritis: promises and challenges of SGLT-2 inhibitors. Ann Rheum Dis 2022;81:614-7.

Correction

Traditional and Disease Specific Risk Factors for Cardiovascular Events in ANCA-Associated Vasculitis: A Multinational Retrospective Study

Sergey Moiseev, Nikolay Bulanov, Matija Crnogorac, Haner Direskeneli, Kresimir Galesic, Ummugulsum Gazel, Duvuru Geetha, Loic Guillevin, Zdenka Hrušková, Mark A. Little, Liam O'Neill, Egor Makarov, Stephen P. McAdoo, Aladdin J. Mohammad, Sarah Moran, Pavel Novikov, Charles D. Pusey, Chinar Rahmattulla, Veronika Satrapová, Joana Silva, Alexander Suvorov, Vladimír Tesar, Benjamin Terrier, Peter Willeit, Ming-Hui Zhao, Andreas Kronbichler, and David R.W. Jayne
J Rheumatol 2023; doi:10.3899/jrheum.220851

The affiliation for Nikolay Bulanov and Pavel Novikov should be Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia. This correction applies only to the February 15 First Release. The correct affiliation appears in the print and online issues.

doi:10.3899/jrheum.220851.C1