Traditional and disease specific risk factors for cardiovascular events in ANCA-associated vasculitis: a multinational retrospective study

***Short title*: Cardiovascular events in ANCA-associated vasculitits**

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

Methods. Patients with a definite diagnosis of AAV who were followed ≥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 (interquartile range: 23, 100) months, CVE (mostly MI) occurred in 245 (10.7%) of 2286 AAV patients with a higher frequency in China and the UK. On multivariate regression analysis, older age (55-64.9 years; 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), 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 CVE.

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

Key words. ANCA-associated vasculitis, cardiovascular events, myocardial infarction, stroke, risk factors.

Introduction

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 was revived in recent decades when the role of inflammatory mechanisms in the pathophysiology of atherosclerosis was proved in multiple experimental studies [2]. Moreover, the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial 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-1α/β and interleukin-6R-related pathways and coronary heart disease [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 were shown to be associated with premature and accelerated atherosclerosis leading to an increased risk of cardiovascular events [7]. Antineutrophil cytoplasm 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 of MPA had at least one cardiovascular event within 5 years of diagnosis [11].

According to a recent meta-analysis, patients with AAV have a 1.65-fold risk of CVE compared to the general population [12]. Most of this risk was driven by an increase in coronary artery disease, with only a trend for cerebrovascular accidents. Cardiovascular morbidity in AAV contributes to overall mortality, which has decreased over the last few decades due to improvement in immunosuppressive regimens [13-15], but remains 2.7-times higher than in the general population [16]. An increased cardiovascular 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 pro-coagulant state and precedes atherosclerotic plaque formation [18]. Several other factors are implicated in diffuse endothelial dysfunction, including elevated levels of circulating pro-inflammatory 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 (NETs), 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]. Recent research suggests that myeloperoxidase (MPO), an enzyme that is mainly found in neutrophils and has the ability to modify LDL in the intima, may also contribute to atherogenesis in AAV patients due to enhanced MPO-mediated LDL oxidation [25].

The objective of this multinational retrospective study was to compare the incidence rates of MI and stroke in a large cohort of patients with AAV from various countries, including the European Union, China, Turkey, Russia, UK, and USA, and to define factors associated with higher risk of CVE in AAV.

Material and methods

Design and patients

Data on CVE, including fatal and non-fatal 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, UK, and 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 co-morbidities. Ethics approval was obtained in all centers involved (i.e. at Sechenov University, Moscow, on September 12th, Protocol: 01-12; previously reported and anonymized data with IRB approval, i.e. data from China[26]) or approval to use patient data was obtained during the conduct of the EUVAS trial [27-30], a major source contributing 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 (DEI), 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, gender, body mass index (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, cyclophosphamide or rituximab, time from disease onset to CVE. ANCA titers were not included in the data set 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 with interquartile range 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 test for continuous data and Chi-square test or Fisher's exact test for categorical data as appropriate. It was accepted that incidence rates have Poisson distribution to calculate 95% confidence intervals. To identify factors associated with CVE, we used the Cox proportional hazards model. The proportional hazards assumption was checked using Schoenfeld residuals assessment. If the proportional hazards assumption was rejected, we used a binary logistic regression model instead. Binomial proportion confidence intervals (CI) were calculated using Clopper-Pearson method. We performed univariate analysis for each variable adjusted for age and male gender, that was followed by a multivariate regression model with stepwise selection. The results of the univariate and multivariate analyses are presented as hazard ratios (HR) or odds ratios (ORs) and 95% CIs as appropriate. P values less than 0.05 were considered significant. Statistical analysis was performed in R 4.1.0 (R Development Core Team, 2021).

Results

Patients

In total, we included 2286 patients with AAV (53.4% females, median age 64.2 years) who were followed for a median of 62.0 (22.6; 100.0) months. Patients were distributed into six cohorts according to the geographic region: European Union, China, Russia, Turkey, UK, and USA. Most patients had MPA (51.0%) or GPA (43.0%) and were positive for myeloperoxidase (MPO)-ANCA (49.9%) or proteinase-3 (PR3)-ANCA (38.6%) (Table 1).

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

Prevalence of CVE

In the total cohort, any CVE occurred in 245 (10.7%) of 2286 patients, MI in 185 (8.1%), and stroke in 74 (3.2%), including 14 (0.6%) patients who had both MI and stroke. The reported

frequencies of CVE and MI 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 CVE

Median time from disease onset to CVE (known in 198 cases) was 17.5 (3.0; 40.0) months. There were no significant differences in the risk for all CVE, MI and stroke between the first, second and third years of follow-up after disease onset. There was a trend to a lower prevalence of CVE 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 0.68 (95% CI 0.40-1.14, p=0.15). The incidence rates for CVE, MI and stroke varied by region and were higher in the Chinese and UK cohorts than in the other countries (Fig. 1, supplementary Table 1). CVE-free, MI-free, and stroke-free survival for different geographic regions are presented on Kaplan-Meier curves (Supplementary Fig. 1, 2, 3). 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 European Union ($p < 0.005$) and Russia ($p = 0.02$). In the UK, CVE-free and MI-free survival were lower than in the European Union (both $p<0.005$), Russia (both $p<0.005$), and the USA ($p=0.02$ 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 (all $p>0.05$).

Factors associated with a higher risk of CVE

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

On multivariate Cox regression analysis, only age of ≥ 55 years, smoking, Chinese origin, pulmonary and kidney involvement retained their significance as risk factors for CVE (Fig. 2). The results of univariate Cox regression analysis of factors that were associated with either MI or stroke are presented in Supplementary Tables 3 and 4.

Given the regional differences in the CVE occurrence, we conducted a separate univariate Cox regression analysis to evaluate the risk factors for CVE in China and other regions of the world separately (Supplementary Tables 5 and 6). In China, male sex, smoking, hypertension, pulmonary, nervous system, and kidney disease, and eGFR<15 mL/min/1.73 m^2 were associated with a higher risk of CVE, whereas in other regions, adverse outcomes were associated with male sex, older age, hypertension, cardiovascular 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 AAV patients developed MI or stroke within the first few years after diagnosis, although the occurrence of CVE 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 known duration of follow-up, the incidence of CVE was similar in the European Union, Russia, and the USA and more than ten- and six-fold higher in China and the UK, respectively. The differences in the incidence of CVE were driven mostly by the variable occurrence of MI, whereas the differences in the incidence of stroke between countries were less striking.

An increased cardiovascular risk in AAV patients was 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 two-fold increased risk of MI and a non-statistically significant trend toward an increased risk of ischemic stroke compared to 5,222 matching subjects without GPA who were selected from the British Columbia (Canada) population database [36].

High cardiovascular morbidity in China seems to represent the current situation in this country that goes through the evolving epidemic of atherosclerotic cardiovascular disease [37]. The prevalence and incidence of cardiovascular disease, including coronary artery disease and ischemic stroke, in China 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 overall life expectancy in this country with 73.3 years in the year 2007 and 76.3 years in 2017 [39]. Moreover, more than half of AAV patients from China had eGFR of less than 15 ml/min/1.73 m^2 at onset of disease whereas the percentage of such patients in the other regions ranged from only 18% in Russia to up to 37% 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 CVE [40]. On the contrary, a higher

cardiovascular risk in AAV patients from the UK was an unexpected finding. The difference in cardiovascular morbidity between the UK and other European countries could not be explained by the age of patients, which was similar in the two cohorts. It could be partly attributed to a higher prevalence of other traditional cardiovascular risk factors, that is, smoking and dyslipidemia, in the former cohort, although we cannot exclude a role of unaccounted confounders in our study, e.g. better documented follow-up in the UK and China.

In our previous study in 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 CVE 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 cardiovascular disease was one of the leading causes of death only after the first year of follow-up, whereas within the first-year patients usually died from infection and active vasculitis [43]. These data argue against an immediate effect of disease activity on the risk of CVE, 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 CVE. However, most of them, except age, smoking, Chinese origin, 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 CVE in AAV patients. Of note, these factors, including male sex, smoking and hypertension, contributed significantly to the risk of CVE both in China and other regions of the world in a separate univariate regression analysis. This confirms the finding of a recent prospective study, showing that major CVE in AAV patients relates to established cardiovascular risk factors, such as older age, a history of cardiovascular disease, dyslipidemia, hypertension, and a sedentary lifestyle [46]. Noteworthy, metabolic syndrome, a cluster of cardiovascular risk factors, was shown to occur more frequently in AAV when compared to age- and sex-matched controls [47].

In AAV, disease itself and prolonged immunosuppression result in a progressive accumulation of damage and treatment-related complications that can expose patients to CVE, e.g. during 7-year follow-up of 302 patients from EUVAS trials the frequency of hypertension and diabetes increased from 4.8% to 41.5% and from 1.1% to 10.4%, respectively, over time [48]. These unfavorable changes in the cardiovascular risk profile can explain a later increase in the risk of

CVE in AAV patients. Houben et al. studied guideline adherence in the management of cardiovascular risk in 144 AAV patients from 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 in periodic assessment and modification of a patient's individual cardiovascular risk profile as recommended by the 2016 EULAR/ERA-EDTA guidelines for the management of AAV [17].

Among disease-specific factors, a higher risk of CVE in multivariate analysis was associated only with kidney and pulmonary disease. In the general population, cardiovascular risk increases exponentially with impaired kidney function [50]. The risk of cardiovascular complications and death is particularly high in dialysis patients. 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 CVE 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 non-fatal CVE, 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 CVE. A total of 455 patients died during follow-up. Causes of death were not captured by our case report form. The infrequent use of rituximab and missing cumulative glucocorticoids doses should also be noted. Nevertheless, our study was conducted in a large international cohort of AAV patients and provides a picture of cardiovascular 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 AAV patients 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 CVE. Therefore, timely control of disease activity is critical to prevent accrual of organ damage in AAV patients. However, better management of modifiable cardiovascular risk factors will also be beneficial for AAV patients and seems to be a more practical approach to prevent

cardiovascular morbidity and mortality. Glucocorticoid minimization strategies may be one step forward in managing modifiable cardiovascular risk factors. In addition, cardio- and nephroprotection, e.g. with the use of sodium-glucose cotransporter-2 inhibitors proven to be effective in large outcome trials, may be another promising option to improve cardiovascular health in AAV [52], but trial data specifically focusing on AAV are missing.

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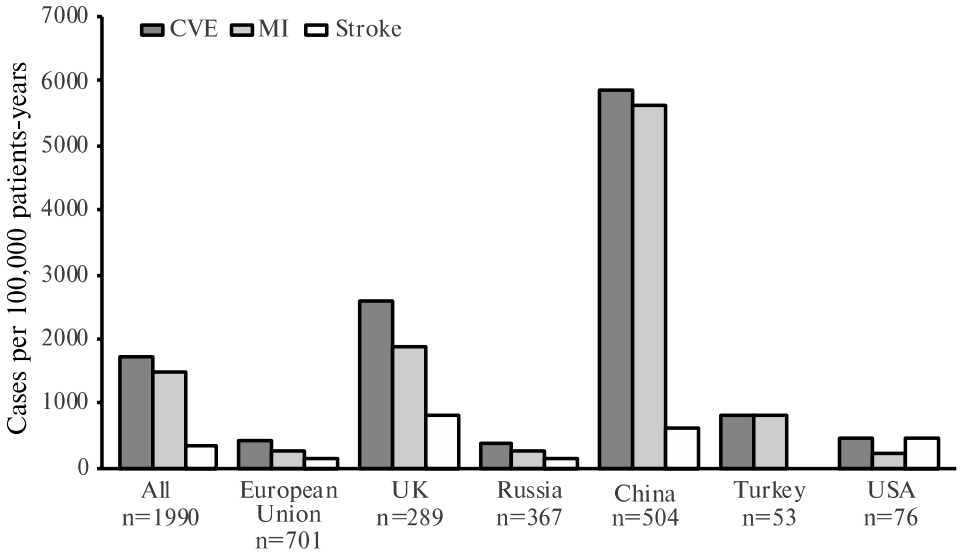
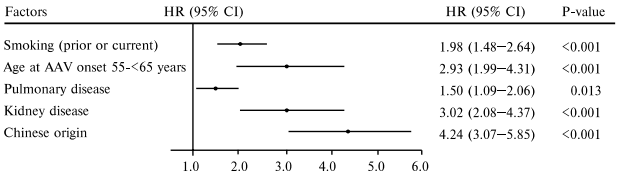
Figure 1. Cases per 100,000 patient years of cardiovascular events (CVE), and subdivision into myocardial infarction (MI) and stroke in the whole sample and in the difference countries/regions.



Abbreviations: CVE – cardiovascular events, MI – myocardial infarction, UK – United Kingdom, USA – United States of America.

Figure 2. Multivariate Cox proportional hazards ratios (HRs) for cardiovascular events.



Abbreviations: AAV – anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, CI – confidence interval, eGFR – estimated glomerular filtration rate, ENT – ear, nose and throat, MPO – myeloperoxidase, PR3 – proteinase 3, RPGN – rapidly progressive glomerulonephritis.
The list of factors for backwise selection included: sex, age, geographic region, diagnosis, PR3-ANCA, MPO-ANCA, smoking, hypertension, dyslipidemia, RPGN, eGFR at onset (60 or higher, 15-59.9, <15), cyclophosphamide treatment, ENT, ocular, pulmonary, kidney, gastrointestinal, peripheral nervous system, skin, joint involvement, general manifestations.

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

	All countries	China	Russia	Turkey	European Union**	UK	USA
Patients, n	2286	504	401	53	732	516	80
Female, n (%)	1221 (53.4)	259 (51.4)	262 (65.3)	24 (45.3)	378 (51.6)	244 (47.3)	54 (67.5)
Median age, years	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, years	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, n (%)							
GPA	983 (43.0)	116 (23.0)	244 (60.8)	34 (64.2)	356 (48.6)	185 (35.9)	48 (60.0)
MPA	1165 (51.0)	388 (77.0)	103 (25.7)	18 (34.0)	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, n (%)*							
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	9 (2.2)	0	9 (1.2)	0 (0)	0 (0)
ANCA-negative	198 (8.7)	5 (1.0)	83 (20.7)	2 (3.8)	47 (6.4)	61 (11.8)	0 (0)
Undifferentiated	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 (7.7)	0 (0)	3 (0.4)	2 (0.4)	0 (0)
CYC any time, n (%)	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, n (%)	411/1468 (28.0)	0/504 (0.0)	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	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 (%)							
≥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 (10.0)
15-59.9 ml/min/1.73 m^2	612/1859 (32.9)	141/502 (28.1)	95/297 (32.0)	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, kg/m^2	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 (%)	729/1370 (53.2)	161 (31.9)	62/273 (22.7)	26/46 (56.5)	154/434 (35.5)	289/419 (69.0)	37 (46.2)
Hypertension, n (%)	653/1371 (47.6)	121/503 (24.1)	237/374 (63.4)	26 (49.1)	129/204 (63.2)	76/157 (48.4)	64 (80.0)
Dyslipidemia or on statins, n (%)	503/1367 (36.8)	23/502 (4.6)	223/371 (60.1)	12 (22.6)	92/204 (45.1)	113/157 (72.0)	40 (50.0)

Note: *Patients with both PR3-ANCA and MPO-ANCA were counted in the three groups (PR3, MPO, and PR3+MPO). Therefore, the total number may exceed 100% in some columns. **Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Italy, Ireland, the Netherlands, Poland, Spain, Sweden.

Abbreviations: BMI – body mass index, CYC – cyclophosphamide, eGFR (estimated glomerular filtration rate), EGPA – eosinophilic granulomatosis with polyangiitis, GPA – granulomatosis with polyangiitis, MPA – microscopic polyangiitis, MPO – myeloperoxidase, NA – not available, PR3 – proteinase 3, RTX – rituximab, UK – United Kingdom, undifferentiated ANCA: ANCA test was positive, but the type of ANCA is unknown, USA – United States of America.

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

	All regions	China	Russia	Turkey	European Union*	UK	USA
Patients, n	2286	504	401	53	732	516	80
Median follow up, months	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, n (%)	245 (10.7)	122 (24.2)	18 (4.5)	2 (3.8)	47 (6.4)	50 (9.7)	6 (7.5)
MI, n (%)	185 (8.1)	117 (23.2)	13 (3.2)	2 (3.8)	20 (2.7)	28 (5.4)	5 (6.3)
Stroke, n (%)	74 (3.2)	13 (2.6)	7 (1.7)	0	29 (4.0)	23 (5.4)	2 (2.5)
MI and stroke, n (%)	14 (0.6)	8 (1.6)	2 (0.5)	0	2 (0.3)	1 (0.2)	1 (1.3)
Death from any cause, n (%)	455 (19.9)	263 (52.2)	29 (7.6)	0	86 (11.7)	71 (13.8)	6 (7.5)

*Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Italy, Ireland, the Netherlands, Poland, Spain, Sweden.

Abbreviations: CVE – cardiovascular event, MI – myocardial infarction, UK – United Kingdom, USA – United States of America.

Correction

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

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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.

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