



Increased ischemic stroke, acute coronary artery disease and mortality in patients with granulomatosis with polyangiitis and microscopic polyangiitis

M. Mourguet^{a,b,*}, D. Chauveau^{a,c}, S. Faguer^{a,c}, J.B. Ruidavets^d, Y. Béjot^{e,f}, D. Ribes^{a,c}, A. Huart^{a,c}, L. Alric^{a,g}, L. Balardy^{a,h}, L. Astudillo^{a,b}, D. Adoue^{a,i}, L. Sailer^{a,b}, G. Pugnet^{a,b}

^a Université de Toulouse Paul Sabatier, Toulouse, France

^b Service de Médecine Interne, CHU Toulouse Purpan, Toulouse, France

^c Département de néphrologie et transplantation d'organe, CHU Toulouse Rangueil, Toulouse, France

^d Laboratoire d'épidémiologie et santé communautaire – Unité INSERM UMR 1027, CHU Toulouse Purpan, Toulouse, France

^e Département de Neurologie, CHU Dijon Hôpital Le Bocage, Dijon, France

^f Dijon Stroke Registry, EA4184, Department of Neurology, University Hospital and Medical School of Dijon, University of Burgundy, France

^g Service de Médecine Interne - Fédération digestive, CHU Toulouse Purpan, Toulouse, France

^h Service de Médecine Interne et Oncologie Gériatrique, CHU Toulouse Purpan, Toulouse, France

ⁱ Service de Médecine Interne et Immunopathologie clinique, Institut Universitaire du Cancer Oncopôle CHU Toulouse, Toulouse, France

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ABSTRACT

Objective: The aim of our study was to assess major cardiovascular event incidence, predictors, and mortality in ANCA-associated vasculitis (AAV).

Methods: We conducted a retrospective cohort study of all GPA or MPA, according to Chapel Hill Consensus Conference classification criteria, diagnosed between 1981 and 2015. Major cardiovascular event was defined as acute coronary artery disease, or ischemic stroke, or peripheral vascular disease requiring a revascularization procedure. We calculated the comparative morbidity/mortality figure (CMF) and we used Cox proportional hazards regression models to assess the risk of coronary artery disease, ischemic stroke associated with AAV, after adjusting for covariates.

Results: 125 patients, 99 GPA (79,2%) and 26 MPA (20,8%), were followed 88.4 ± 78.3 months. Ischemic stroke incidence was four times higher than in the general population (CMF 4,65; 95% CI 4,06-5,31). Coronary artery disease incidence was four times higher than in the general population (CMF 4,22; 95% CI 1,52-11,68). Smoking habits and history of coronary artery disease were strongly associated with coronary artery disease occurrence (adjusted HR 8.8; 95% CI 2.12–36.56, and adjusted HR 10.3; 95% CI 1.02–104.5, respectively). ENT flare-up was an independent protective factor for coronary artery disease occurrence. We did not identify factors significantly associated with stroke occurrence. The age-adjusted mortality rate was 22.5 per 1000 person-years. Mortality in AAV was 1.5 times higher than in the general population (CMF 1.56; 95% CI 1.34–1.83).

Conclusion: AAV have a significantly increased risk of mortality, ischemic stroke, and coronary artery disease.

1. Introduction

ANCA-associated vasculitis (AAV) encompasses a group of autoimmune diseases, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EPGA) and pauci-immune glomerulonephritis that are characterized by inflammation and necrosis of small and medium-sized vessel [1]. Current treatment approaches have greatly improved the survival [2,3], however both morbidity and mortality are still

significant [4], from persistent low-grade activity and permanent damage caused by the acute phase of vasculitis or its treatment [5] and disease relapses. This increased risk is mainly due to cardiovascular complications.

As for other chronic systemic inflammatory diseases [6], premature and accelerated atherosclerosis has emerged during the last decade as an important facet of AAV. Experimental data showed that, in addition to lipid accumulation, arterial inflammation, attributable to Th1 and Th17 and resulting from increased cytokines production, were

* Corresponding author. Service de Médecine Interne - Fédération digestive, CHU Toulouse Purpan, 1 place du Dr Joseph Baylac, TSA40031, 31059 Toulouse, France.

E-mail address: mourguet.m@chu-toulouse.fr (M. Mourguet).

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associated with accelerated subclinical atherosclerosis [7,8]. Epidemiological studies showed the higher frequency of subclinical atherosclerosis in patients with AAV [9–12]. Whereas the increased risk of cardiovascular diseases is well established in other chronic systemic inflammatory diseases [13–16], data on cardiovascular disease risk in AAV patients are scarce [17–20].

The aim of this study was to assess the incidence of the first major cardiovascular event and its predictors in a cohort of GPA and MPA patients.

2. Materials and methods

2.1. Study population

We conducted a retrospective review of medical records of all patients diagnosed with a small and medium-sized vessels vasculitis at Toulouse University Hospital, a tertiary referral center for systemic vasculitis, between 1981 and 2015. After thorough medical chart review, patients were included if they 1) met the classification criteria proposed by the 2012 Chapel Hill Consensus Conference [1] for GPA or MPA with histologically confirmed necrotizing vasculitis and/or ANCA-positive serum, 2) were more than 18 years of age, 3) had at least 1 year of follow-up, in order to focus on events most likely to be due to atherosclerosis late morbidity 4) had at least quarterly visits. Patients with EGPA were excluded since this condition has its own cardiovascular risks [21]. The data analyzed were collected as part of routine clinical care in accordance to Good Clinical Practice.

2.2. Data collection

Demographics (including age, gender and body weight), clinical data at diagnosis and assessment of AAV severity (Birmingham Vasculitis Activity Score – BVAS) [22], and biological data (including C-reactive protein (CRP), renal function expressed as serum baseline creatinine and estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) formula) ANCA status (immunofluorescence and enzyme-linked immunoabsorbent assay) were retrieved. Also, cardiovascular risk factors like smoking habits (ever/never), cardiovascular heredity, cardiovascular history before AAV diagnosis, diabetes mellitus, hyperlipidemia, were assessed. On follow-up, key clinical events (relapse, organ involvement or damage), biological data (including renal function one year after AAV occurrence expressed as serum creatinine and eGFR), and drug exposure (including corticosteroid, immunosuppressant, rituximab, platelet aggregation inhibitor, angiotensin-converting enzyme (ACE) inhibitor, statins ...) were collected. Long-term follow-up data were retrieved from medical charts or patients' physicians to determine survival.

2.3. Outcomes

Major cardiovascular event was defined as acute coronary artery disease, or ischemic stroke, or peripheral vascular disease requiring a revascularization procedure.

Acute coronary artery disease had to meet the following criteria, increase and/or decrease of a cardiac biomarker (cardiac troponin) with at least one value above the 99th percentile for GFR and at least one of the following events: 1) symptoms suggestive of cardiac ischemia, and/or 2) significant new (or presumed new) changes in the ST segment or T-wave or new left bundle-branch block, and/or 3) appearance of Q waves on an electrocardiogram, and/or 4) Imaging evidence of new myocardial damage or regional contractile abnormality, and/or 5) Identification of an intracoronary thrombus by angiography [23].

Ischemic stroke was defined as any clinical or radiological sign consistent with a sudden episode of neurological dysfunction caused by

focal cerebral, medullary or retinal ischemia, with 1) a clinical evidence of focal cerebral, medullary or retinal ischemia based on persistent symptoms (≥ 24 h) or until the time of death, with other causes excluded, or 2) an objective pathological imaging evidence of a focal ischemic lesion with defined vascular distribution [24]. None of the patients with stroke had history of atrial fibrillation.

Peripheral vascular disease was defined as 1) peripheral arterial thrombosis defined as any other obstruction of an artery or an arterial branch by a blood clot following embolism or thrombus, with acute localized tissue ischemia or arterial stenosis, or 2) stage 2 or higher symptomatic peripheral vascular disease or acute lower limb ischemia, defined as arterial stenosis in the lower limbs with an ankle brachial index below 0.9 (when available), leading to pain during walking or discomfort in a limb (or its extremity) due to sudden lack of blood flow with skin circulation disorders, up to the ischemic rest pain stage [24] and requiring a revascularization procedure.

Finally, we collected occurrence of death, and its mechanisms: coronary artery disease, stroke, peripheral vascular disease or any other cause. We systematically called for each patient his/her referent AAV physician and/or General Practitioner to accurately assess vital status.

2.4. Statistical analysis

We compared the baseline characteristics of the major cardiovascular event group and no-major cardiovascular event group in the AAV cohort. Categorical variables were compared with the chi-squared test or Fisher exact test; equality of means in continuous variables was tested with the Wilcoxon test.

We identified incident coronary artery disease, ischemic stroke and peripheral vascular disease during the follow-up period and calculated the incidence rates per 1000 person-years for each outcome, individually as well as together (i.e., as major cardiovascular event). Kaplan-Meier survival curves were plotted to determine probability of survival, proportion of survivors not experiencing major cardiovascular event, coronary artery disease or stroke.

Then we calculated the comparative morbidity figure (CMF) and 95% Confidence Interval (CI) for coronary artery disease and stroke. For the general population comparison, we used two validated prospective registry one from the same area for mortality and coronary artery disease: the Midi-Pyrénées county mortality and acute coronary artery disease registries [25,26]. Since no stroke registry is available in the Toulouse area we used the Dijon stroke registry. This population-based registry complies with the criteria recommended for the running of 'ideal' stroke incidence studies [27], Dijon is a city in eastern France. Individual demographic characteristics, except age, or cardiovascular risk factor in these registries were not available for this study. CMF is the ratio of the standardized incidence (or death) rate to the crude incidence (or death) rate in the standard population. CMF is a weighted average of age-specific cohort to standard rate ratios.

We also identified death from any cause during the follow-up period and calculated the crude all-cause mortality rates per 1000 person-years. Then we calculated the comparative mortality figure and 95% CI which compared the deaths to be expected in the registry population by ten-year stratum crude mortality rates in the cohort.

Finally, we used Cox proportional hazards regression models (backward-selection technique) to assess the risk of coronary artery disease, ischemic stroke or death associated with AAV, after adjusting for covariates (Table 1). The multivariate analyze was adjusted to age, gender and tobacco exposure. Patients were censored in the following cases: 1) occurrence of the event of interest (cardiovascular event); when the patient had several events, only the first one was considered; 2) death, 3) lost to follow-up (non-death censored); 4) date of last follow-up (non-death censored). Hazard ratios (HR) and 95% CI were estimated. All *P* values were 2-sided. For all statistical analyses, *P* < 0,05 was considered significant. Statistical analysis was performed with SAS® 9.3 software.

Table 1
 Characteristics of the cohort at diagnosis of ANCA-associated vasculitis and comparison according to occurrence of major cardiovascular event on follow up^a.

	All n = 125	Without MCVE n = 102	With MCVE n = 23	P value
Age at diagnosis, mean ± SD, years	61.3 ± 15.7	60.8 ± 15.9	63.2 ± 15.0	0.51
Men	65 (52)	52 (51)	13 (56.5)	0.63
Granulomatosis with polyangiitis	99 (79.2)	82 (82.4)	15 (65.2)	0.07
Mean follow-up ± SD, years	7.5 ± 6.4	7.0 ± 6.1	9.3 ± 7.7	0.13
Comorbidities				
Cardiovascular risk factors	78 (62.4)	62 (60.8)	16 (69.6)	0.43
- Hypertension	45 (36)	34 (33.3)	11 (47.8)	0.19
- Diabetes Mellitus	9 (7.2)	7 (6.9)	2 (8.7)	0.76
- Dyslipidemia	20 (16)	18 (17.7)	2 (8.7)	0.36
- History of stroke	6 (4.8)	4 (3.9)	2 (8.7)	0.30
- Peripheral artery disease	2 (1.6)	0	2 (8.7)	0.03
- History of coronary artery disease	3 (2.4)	2 (2.0)	1 (4.4)	0.46
- Tobacco use	37 (29.6)	26 (25.5)	11 (47.8)	0.03
Clinical AAV presentation at first flare				
- BVAS mean ± SD	8.8 ± 4.9	8.9 ± 5.0	8.4 ± 5.2	0.67
- Fever > 38°	21 (16.8)	17 (16.7)	4 (17.4)	0.93
- Asthenia	60 (48.0)	47 (46.1)	13 (56.5)	0.37
- Arthralgia	28 (22.4)	23 (22.6)	5 (21.7)	0.93
- Skin involvement	9 (7.2)	7 (6.9)	2 (8.7)	0.67
- ENT involvement	57 (45.6)	50 (49.0)	7 (30.4)	0.11
- Lung involvement	55 (44)	42 (41.2)	13 (56.5)	0.18
- GI involvement	7 (5.6)	6 (5.9)	1 (4.4)	0.77
- Kidney involvement	82 (65.6)	67 (65.7)	15 (65.2)	0.97
- Central neurologic symptoms	4 (3.2)	3 (2.9)	1 (4.4)	0.73
- Peripheral neurologic symptoms	20 (16)	17 (16.7)	3 (13.0)	0.67
- Ophthalmologic involvement	15 (12)	14 (13.7)	1 (4.4)	0.21
Clinical AAV involvement during follow-up				
- Arthralgia	34 (27.2)	29 (28.4)	5 (21.7)	0.51
- Skin involvement	12 (9.6)	10 (9.8)	2 (8.7)	0.87
- ENT involvement	69 (55.2)	59 (57.8)	10 (43.5)	0.21
- Lung involvement	59 (47.2)	45 (44.1)	14 (60.9)	0.15
- GI involvement	8 (6.4)	6 (5.9)	2 (8.7)	0.64
- Kidney involvement	93 (74.4)	73 (71.6)	20 (87.0)	0.13
- Central neurologic symptoms	5 (4)	3 (2.9)	2 (8.7)	0.23
- Peripheral neurologic symptoms	42 (33.6)	36 (35.3)	6 (26.1)	0.40
- Ophthalmologic involvement	21 (16.8)	18 (17.7)	3 (13.0)	0.76
Serum creatinine at AAV diagnosis, mean ± SD, μmol/L	227.1 ± 191.2	230.8 ± 200	208.8 ± 143.9	0.17
Serum creatinine one year after AAV diagnosis mean ± SD, μmol/L	163.5 ± 154.6	163.9 ± 118.6	160.4 ± 89.1	0.07
Immunology profile				
- ANCA	123 (98.4)	100 (98.0)	23 (100)	0.50
- PR3	56 (44.8)	49 (48.0)	7 (30.4)	0.13
Histological profile				
Positive Biopsy	83 (86.5)	54 (83.1)	29 (93.6)	0.16
Medication use prior to AAV diagnosis				
Angiotensin-converting enzyme inhibitor	12 (9.6)	9 (8.8)	3 (13.0)	0.53
Statins	21 (16.8)	11 (10.8)	10 (43.5)	0.0002
Platelet aggregation inhibitor	13 (10.4)	4 (3.9)	9 (39.1)	0.0001
First induction of remission treatment for AAV				
- Steroids	123 (98.4)	100 (98.0)	23 (100)	0.50
- Cyclophosphamide	96 (76.8)	79 (77.6)	17 (73.9)	0.72
- Rituximab	12 (9.8)	9 (8.8)	3 (13.0)	0.53
- Plasma exchange	26 (20.8)	19 (18.6)	7 (30.4)	0.21
- Azathioprine	6 (4.8)	5 (4.9)	1 (4.4)	0.91
- Dialysis	6 (4.8)	6 (5.9)	0	0.59
- Methotrexate	5 (4.0)	5 (4.9)	0	0.58
AAV treatment exposition during follow-up				
- Steroids	125 (100)	102 (100)	23 (100)	1
- Cyclophosphamide	106 (84.8)	86 (84.3)	20 (87.0)	0.75
- Rituximab	64 (51.2)	50 (49.0)	14 (60.9)	0.30
- Plasma exchange	24 (19.2)	16 (15.7)	8 (34.8)	0.04
- Azathioprine	69 (55.2)	60 (58.8)	9 (39.1)	0.09
- MMF	26 (20.8)	19 (18.6)	7 (30.4)	0.21
- Dialysis	19 (15.2)	15 (14.7)	4 (17.4)	0.75
- Methotrexate	14 (11.2)	14 (13.7)	0	0.07
- Intravenous immunoglobulin	9 (7.2)	7 (6.9)	2 (8.7)	0.67
- Transplantation	7 (5.6)	6 (5.9)	1 (4.4)	0.77
Mean number of relapses	0,7 ± 1,3	0,7 ± 1,4	0,8 ± 1,0	0.88
Major relapses	45 (36)	33 (32.4)	12 (52.2)	0.07

^a Values are the number (percentage) unless otherwise indicated; MCVE: major cardiovascular event; SD: standard deviation; AAV: ANCA-associated vasculitis; ENT: ear nose throat, GI: gastro intestinal.

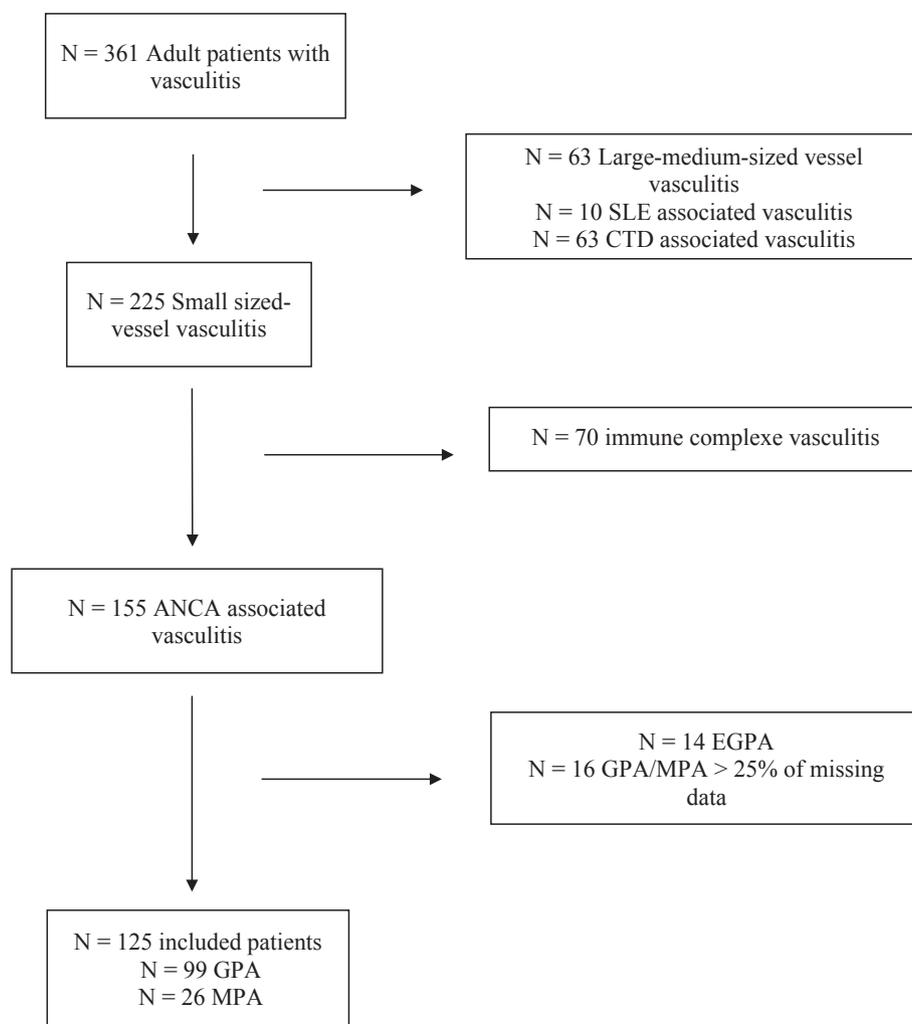


Fig. 1. Flow chart for inclusion of adult AAV patients from Toulouse university hospital*. *SLE: Systemic lupus erythematosus; CTD: connective tissue disease; ANCA: antineutrophil cytoplasmic antibody; EGPA: Eosinophilic granulomatosis with polyangiitis; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis.

3. Results

3.1. Demographics and cardiovascular risk factors

We identified 361 relevant medical records for the 1981–2015 period. One hundred twenty-five of these patients met the selection criteria for study inclusion (Fig. 1), 99 GPA (79,2%) and 26 MPA (20,2%) with a mean follow-up of 88.4 ± 78.3 months. There were 65 males (52%) and 60 females (48%). Mean age at disease onset was of 61.3 ± 15.7 years. Prior to AAV recognition, 45 (36%) had high blood pressure, 20 (16%) had hyperlipidemia, 37 (29.6%) were smokers, 9 (7.2%) had diabetes mellitus, 6 (4.8%) had a history of ischemic stroke, 2 (1.6%) had peripheral vascular disease and 3 (2.4%) had a history of coronary artery disease (Table 1). None of the patients had atrial fibrillation or a history of atrial fibrillation.

3.2. Incident major cardiovascular event

During follow-up, 10 patients developed coronary artery disease, 9 suffered from an ischemic stroke and 11 developed peripheral vascular disease. None of these major cardiovascular event occurred during a disease flare. For the combined outcome of coronary artery disease or stroke or peripheral vascular disease, the incident rate was evaluated at 27.8 per 1000 person-years. Cumulative major cardiovascular event incidence at 1, 5 and 10 years were 7% (95% CI 4–9), 15% (95% CI 12–19) and 23% (95% CI 18–28), respectively (Fig. 2A).

As compared to general population included in the Midi-Pyrénées and Dijon registries, the AAV cohort was associated with a higher incidence of coronary artery disease and stroke. Cumulative coronary artery disease incidence at 1, 5 and 10 years were 2% (95% CI 1–4), 8% (95% CI 5–10) and 12% (95% CI 8–18), respectively (Fig. 2B). Using direct standardization, the age-adjusted incidence rate for coronary artery disease in the AAV cohort was 8.5 per 1000 person-years and 2.2 per 1000 person-years in the general population using the Midi-Pyrénées county coronary artery disease registry [28] as a reference. This indicates that coronary artery disease incidence for AAV patients is four times more that in the general population, independent of age differences between the two populations (CMF = 4,22; 95% CI 1,52 to 11,68). The sensitivity analyses for coronary artery disease incidence in MPA and GPA patients were consistent with the main analysis (CMF = 5,84 95% CI 1,65 to 20,65 and CMF = 3,32 95% CI 0,94 to 11,67 respectively).

Cumulative ischemic stroke incidence at 1, 5 and 10 years was 2% (95% CI 1%–4%), 3% (95% CI 2%–5%) and 11% (95% CI 6%–15%), respectively (Fig. 2C). The age adjusted incidence rate for ischemic stroke in the AAV cohort was 10.2 per 1000 person-years and 1.9 per 1000 person-years in the general population using the Dijon Stroke Registry [27] as a reference. This indicates that ischemic stroke incidence for AAV patients is four times more than in the general population, independent of age differences between the two populations (CMF = 4,65; 95% CI 4,06 to 5,31). The sensitivity analyses for ischemic stroke incidence in MPA and GPA patients were consistent with

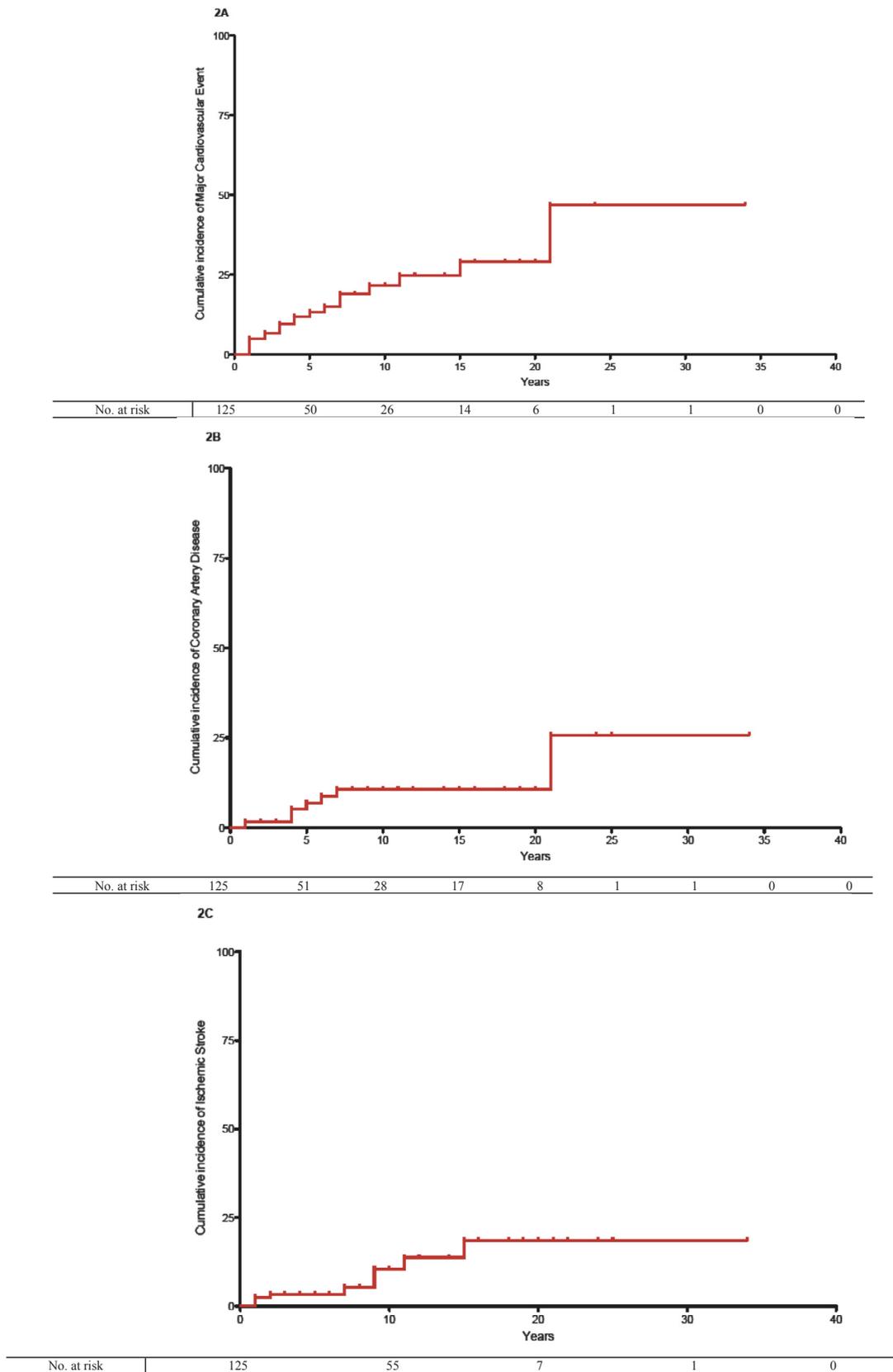


Fig. 2. Cumulative incidence of major cardiovascular event (2A), coronary artery disease (2B) and ischemic stroke (2C) in the 125 ANCA-associated vasculitis cohort.

Table 2

Independent associated factors with first major cardiovascular event, coronary artery disease, or stroke occurrence in 125 ANCA-associated vasculitis (COX multivariate model stepwise descending procedure).

	Adjusted Hazard Ratio	95% CI	P value
<i>Major cardiovascular event occurrence</i>			
- Age over 62 years	2.0	[0.85–4.90]	0.11
- Smoking status, ever	2.7	[1.07–6.66]	0.036
- Platelet Aggregation Inhibitor at AAV diagnosis	6.8	[2.57–18.13]	0.0001
- Azathioprine exposure, ever	0.4	[0.16–0.91]	0.03
<i>Coronary artery disease occurrence</i>			
- Smoking status, ever	8.8	[2.12–36.56]	0.003
- History of coronary artery disease	10.3	[1.02–104.5]	0.048
- AAV ENT flare, ever	0.12	[0.03–0.57]	0.007
<i>Stroke occurrence</i>			
- Age over 62 years	1.6	[0.37–6.51]	0.54
- Male	1.03	[0.27–3.86]	0.97
- AAV CNS flare, ever	3.9	[0.71–21.1]	0.12

CI: confidence interval, AAV: ANCA associated vasculitis, CNS: central nervous system.

the main analysis (CMF = 4,76 95% CI 4,73 to 4,79 and CMF = 4,69 95% CI 3,74 to 5,87 respectively).

3.3. Predictors of major cardiovascular event in the AAV cohort (Table 2)

Being a smoker at the time of AAV diagnosis was the best independent positive predictor of major cardiovascular event and coronary artery disease (adjusted HR 2.7; 95% CI 1.07 to 6.66, p = 0.04 and adjusted HR 8.8; 95% CI 2.12 to 36.56, p = 0.003 respectively). Platelet aggregation inhibitors exposure at AAV diagnosis (adjusted HR 6.8) was independently associated with major cardiovascular event occurrence while azathioprine exposure (adjusted HR 0.4) was inversely associated with major cardiovascular event occurrence.

History of coronary artery disease was strongly associated with coronary artery disease (adjusted HR 10.3; 95% CI 1.02 to 104.5, p = 0.003). ENT flare-up (adjusted HR 0.12) was an independent protective factor for coronary artery disease in this AAV cohort.

We did not find any factors that were statistically significant associated with stroke occurrence in our cohort. Statins exposure at AAV diagnosis did not have any impact in major cardiovascular event, coronary artery disease or ischemic stroke occurrence.

3.4. Mortality in AAV

During the follow-up period, 21 AAV (17,6%) patients died. The causes of death were: fatal cardiovascular events in 23% (n = 5),

infections in 23% (n = 5), cancer in 13% (n = 3), disease-related causes in 9% (n = 2), and other causes in 33% (n = 7). Probability of over all survival at 1, 5 and 10 years was 95% (95% CI 93–97), 90% (95% CI 87–93) and 77% (95% CI 72–83), respectively (Fig. 3). Comparing age-specific mortality rates in AAV patients to age-specific mortality rates calculated in the general population of the Midi-Pyrénées county of southwest France, we found that the mortality rates in all age bands were substantially higher in AAV patients compared to the general population. Using direct standardization, the age-adjusted mortality rate for the AAV cohort was 22.5 per 1000 person-years and 10.2 per 1000 person-years for the general population. This indicates the mortality rate in AAV patients is 1.5 times higher than in the general population, independent of age differences between the two populations (CMF = 1.56; 95% CI 1.34 to 1,83). The sensitivity analyses for death from any cause up to the end of the study in MPA and GPA patients were consistent with the main analysis (CMF 1,90; 95% CI 1,48-2,44 and CMF = 1,39; 95% CI 1,13 to 1,70 respectively).

4. Discussion

The main findings of this study are as follows. First, ischemic stroke incidence in our AAV cohort was four times higher than in the general population. These results remained significant in each MPA and GPA group. This study provides the first evidence that ischemic stroke is an important complication of AAV. Second, smoking habits and a history of coronary artery disease before AAV diagnosis were strongly associated with coronary artery disease occurrence during follow-up, while ENT flare-ups were associated with lower risk of any major cardiovascular event occurrence during the study period. Third, AAV patients had a 1.5 times greater mortality rate than the general population. These results remained significant in each MPA and GPA group.

The incidence of overall cardiovascular events in our study was 27.8 per 1000 person-years. Of the 131 AAV patients in Morgan's study, with a median follow-up of 3.4 years, 23 cardiovascular events occurred, which is almost twice our findings [18]. These differences could be related to the definition of the cardiovascular event, the studied population or the follow-up period and AAV severity. In comparison, the EUVAS study [19] with 535 AAV followed 5 years, and the Avina-Zubieta's study [20] with 504 GPA followed for 1897 person-years patients, reported cardiovascular event incidences similar to our study.

An increased risk of incident coronary artery disease in AAV, especially for GPA, has been reported in previous studies. In Denmark, GPA patients experienced increased morbidity due to coronary artery disease by 3.6 fold at 5 years and 2.2 fold at 10 years after GPA diagnosis [17]. A milder increased risk was reported in a real-life population-based study in Canada (RR 1.86 (1.05–3.31)) in the 5 years following GPA diagnosis [20]. This is consistent with our findings, since coronary artery disease incidence in our cohort was close to Faurschou

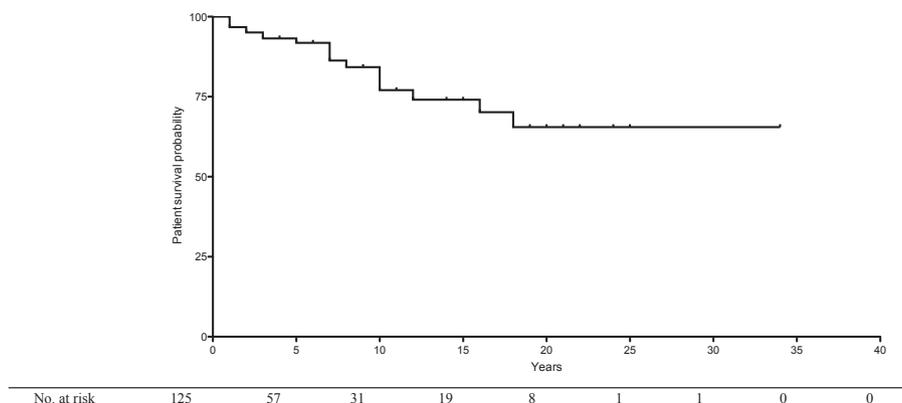


Fig. 3. Patient overall survival.

et al. study. Even if our cohort is from the South West of France, where the residents' cardiovascular risk for coronary artery disease differs from those of North-American and Northern European populations, known as the “French paradox” [29], associated factors with major cardiovascular event or coronary artery disease occurrence in this study were not different from established cardiovascular risk factors or from those previously reported in AAV [17,18], nevertheless, to the best of our knowledge this the first study which identified ENT flare associated with a lower risk for coronary artery disease occurrence in AAV. As describe in the revisited five-factor score [30] ENT involvement is associated with more relapses but a better AAV outcome [31], this particular phenotype could be associated with a less severe systemic inflammation responsible for fewer coronary artery disease.

Although AAV can involve the central nervous system [32,33], the risk of stroke associated with this disease is not well characterized. Two recent studies evaluated the risk of stroke and did not find a significant increased risk in AAV patients [20,34]. In a recent meta-analysis included seven studies comprising almost 14000 AAV patients versus general population controls, the relative risk is 1.65 (95% CI: 1.23, 2.22) for all cardiovascular events, 1.60 (95% CI: 1.39, 1.84) for ischaemic heart disease and 1.20 (95% CI: 0.98, 1.48) for cerebrovascular accidents [35]. Our study is the first to find a statistically increased risk of stroke in an AAV cohort. This is one of the major finding of our study, which corroborate as well the increase risk of cardiovascular diseases in this population.

Although the pathophysiology responsible for the enhanced risk of major cardiovascular event observed in the present AAV cohort cannot be determined from our data, many potential reasons could be raised in addition to the established cardiovascular risk factors. First, disease-specific factors: (1) inflammation has been increasingly recognized as a cardiovascular risk factor and AAV patients because of their chronic vascular inflammation should also bear an increased risk [36]; (2) atherosclerosis is increasingly demonstrated to be an inflammatory process, and studies have shown a relationship between markers of inflammation and surrogate markers of atherosclerotic cardiovascular diseases like increased carotid intima-media thickness in AAV [11]; (3) endothelial dysfunction has been shown in AAV [37]; (4) and impaired renal function, a key feature of AAV, is also associated with higher cardiovascular risks [38]. Second, therapeutic factors, mainly corticosteroids exposure, could be implicated. Since corticosteroids are associated with an increased risk of cardiovascular events [39–43], this treatment may have promoted a cardiovascular risk increase.

This study shows that AAV patients continue to have a slightly higher mortality [2,3]. However this mortality rate steadily declines, and its explanation is likely multifactorial, related to evolving management strategies such as early AAV treatment, expanding availability of plasma exchanges, updated vaccination guidelines or early antibiotic prophylaxis, and the expanding availability of improved diagnostic tools for disease flare identification or early infection detection. Our estimate of mortality is among the lowest reported in AAV but it is consistent with recent studies from tertiary referral center where 1-year mortality was between 1 and 7% [44,45] or European cohorts [32,46,47], while mortality-rate often reached 10–17% [33,47–49].

4.1. Strengths

To our knowledge this is the first study that compared general-population and a hospital-based cohort, using the comparative mortality/morbidity figure method, to assert cardiovascular diseases incidence in a French AAV cohort. Our method used direct age standardized rates. CMF is calculated with reference to the standard population and it is more accurate because age sub-group weights used in the denominator do not depend on the characteristics of the study population and then allows to reduce age differences influences.

Although this study was of retrospective design, the thorough medical chart review enables us to use stringent criteria, based on the

latest international consensus, to ensure coronary artery disease, ischemic stroke and peripheral vascular disease diagnosis. We also systematically called for each patient his/her referent AAV physician and/or General Practitioner to accurately assess vital status.

4.2. Limits

Our study had several limitations. Our clinic is a tertiary referral center, consequently a referral bias may also have occurred. However, major findings of this study, such as the increase mortality risk is in line with those of recent population-based studies. Major cardiovascular event or death identification may have been subject to information or recall bias. In order to limit that inherent bias we interviewed all the physicians involved in the patients' care of those lost to follow-up from our center to identified vital status or major cardiovascular event occurred elsewhere.

5. Conclusion

Despite recent advances, AAV patients still have a significantly increased risk of mortality, ischemic stroke, and coronary artery disease. Further studies are required to validate these results. However, monitoring for these complications and attempts strict management of cardiovascular risk factors are warranted in this population as part of the long-term management of these conditions.

Conflicts of interest and funding

The authors have no conflict of interest regarding this work or any other financial interests.

Declarations of interest

None.

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Author contributions

- 1) conceived and designed the study: MM, GP,
- 2) analyzed and interpreted the data: MM, GP
- 3) contributed reagents, materials, analysis tools or data: all authors
- 4) wrote the paper: MM, GP

Ethics approval

This study received approval and authorization from the *Commission Nationale de l'Informatique et des Libertés* (n°DR-2017-2097045v0).

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