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# Comorbidities and health-related quality of life in Patients with Antineutrophil Cytoplasmic Antibody (ANCA) - associated vasculitis

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ABSTRACT

*Background and objectives:* The optimization of immunosuppressive therapies has led to a marked improvement in the survival of ANCA-associated vasculitides (AAV). The main issue now appears to be the management of comorbidities and the improvement of quality of life. The objective of this review was to investigate the incidence and the impact of AAV-associated comorbidities, as well as the determinants of health-related quality of life (HRQoL).

*Methods:* We performed a systematic literature review of articles published in Medline from 2001 to 04/28/2020. We selected relevant articles about AAV-associated comorbidities as well as HRQoL and fatigue. For each selected article, data on the incidence of comorbidity were extracted, and factors associated with the Mental component score (MCS) and the Physical component score (PCS) were identified.

*Results:* Among the 10,993 references identified, 103 were retained for the final analysis. A significant increase in cardiovascular risk was evidenced, particularly for coronary artery disease and thromboembolic events, especially during the active phase of the disease. AAV was also associated with bronchiectasis, thyroid diseases and osteoporosis. A marked decrease in HRQoL and an increase in fatigue and anxiety were reported. Decrease in PCS and MCS was associated with fatigue, mood disorders, sleep disturbance, and/or unemployment.

*Conclusion:* The excess mortality of AAV is still a concern, partly in connection with cardiovascular and thromboembolic comorbidities. AAV patients also experiment a reduction in their HRQoL that requires integrated management. Patients with AAV need comorbidity management strategies to improve their quality of life and outcomes.

## 1. Introduction

Antineutrophil Cytoplasmic Antibody (ANCA)-associated vasculitides (AAV) is a heterogeneous group of inflammatory diseases which includes granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome) and renal-limited vasculitis (RLV). Each one has its own clinical features, involving the lungs, the kidneys, the ear nose and throat (ENT), the skin, the heart, and the central and peripheral nervous system. They are characterized by small and medium-sized vessel necrotizing vasculitis, and the presence of ANCA, either targeting proteinase 3 (PR3) or myeloperoxidase (MPO).

From a fatal disease with an average survival of 5 months, before the currently-available immunosuppressive treatments [1], it has become a chronic disease with the burden of the toxicity of long-term treatment, the risk of relapses and the accumulation of organ damage [2]. The AAV overall mortality has improved in the last decades [3–6] with a 1-year survival rate estimated between 77.4 and 95%, and a 5-year survival estimated between 61.9 and 97% respectively [4,5,7,8]. However,

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mortality of patients with AAV is still 2.7 times higher than in the general population [4], not only due to the disease itself or infections, but also due to comorbidities [9], particularly cardiovascular diseases [10]. Comorbidities are other disabling conditions co-occurring or co-existing with AAV, particularly cardiovascular diseases [5,7,8,11,12]. Comorbidities may impact morbidity and mortality, impair quality of life (QoL), and increase the complexity of AAV management as well as its costs. Having comorbidities at the time of diagnosis increases mortality [13–15] and comorbidities could also have an impact on patients' QoL, even after achievement of remission. This has become a major outcome studied in AAV patients.

In this review, the incidence and the impact of comorbidities in AAV, as well as the determinants of health-related quality of life (HRQoL), will be discussed, in order to highlight possible improvements in the management of these patients.

## 2. Methods

### 2.1. Data sources and study selection

We performed a systematic review of articles published in Medline (via Pubmed), until 04/28/2020, restricted to English and French languages, and to adults. We used the Mesh term "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis" combined with the Boolean operator "AND" with "Comorbidity" or various comorbidity-related terms including: "Cardiovascular diseases", "Myocardial Ischemia", "Myocardial Infarction", "Coronary Artery Disease", "Stroke", "Overweight", "Diabetes Mellitus", "Hypertension", "Metabolic syndrome", "Peripheral Arterial Disease", "Venous Thromboembolism", "Venous Thrombosis", "Quality of life", "Fatigue", "Depression", "Thyroid Diseases", "Osteoporosis", and "Bronchiectasis".

Abstracts of all of the articles of interest were reviewed for relevance, and articles dealing with the above comorbidities were included. Irrelevant references were excluded.

Given that AAV management has changed since the past decade, including the use of pulsed cyclophosphamide and rituximab, we decided not to include articles published before 2001. We also excluded case reports, pediatric references, articles dealing with infections and malignancy, which we considered more as complications of the treatments than as comorbidities of the disease itself. Similarly, references focusing on AAV characteristics rather than on their associated pathologies were excluded.

We also hand searched for relevant additional references. The bibliography of each of the articles found was checked. If a reference was relevant, it was also included.

### 2.2. Data extraction

The following data were extracted for each article using a predefined data collection form: study design and population, sample size, mean age, gender, mean duration of follow-up, incidence or prevalence of the comorbidity, statistical comparison with control group or general population when available. For the HRQoL articles, factors associated with the mental component score (MCS) and the physical component score (PCS), which are two subparts of QoL, were collected. We also recorded factors associated with fatigue.

In addition to these data, the main findings of each study were noted. We then summarized this information to provide clinicians with current evidence regarding the comorbidities of AAV patients, including their impact on QoL, in order to improve their overall management in daily practice.

## 3. Results of search

A total of 10,993 references were identified through database searching (Figure 1). An additional 26 references from hand-search screening were found. By cross-referencing the term MESH "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis" with the different comorbidities, we obtained respectively 77 results for "Comorbidity", 10,350 for "Cardiovascular diseases", 118 for "Myocardial Ischemia", 54 for "Myocardial Infarction", 12 for "Coronary Artery Disease", 60 for "Stroke", 4 for "Overweight", 46 for "Diabetes Mellitus", 40 for "Hypertension", 1 for "Metabolic syndrome", 2 for "Peripheral Arterial Disease", 15 for "Venous Thromboembolism", 46 for "Venous Thrombosis", 45 for "Quality of life", 22 for "Fatigue", 10 for "Depression", 73 for "Thyroid Diseases", 6 for "Osteoporosis", and 12 for "Bronchiectasis".

After removing duplicates, the first step of the systematic review excluded 5,816 references that were not relevant to our topic, 835 that were not in French or in English, and 4,181 that were published before 2001. Finally, 103 full references were selected for qualitative analysis.

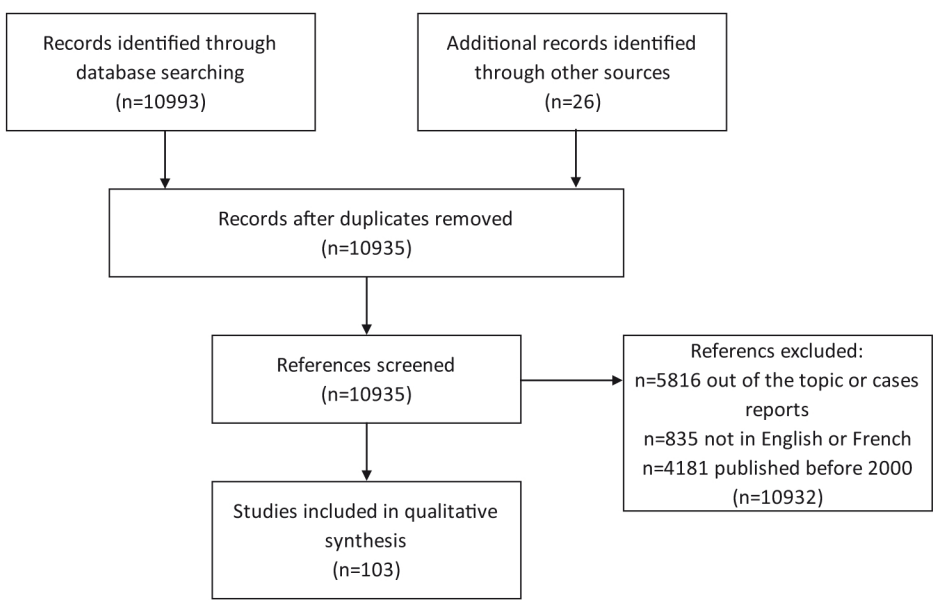


**Fig. 1.** Study identification and selection, n: number of references.

**Table 1**
Cardiovascular events in AAV patients.

| Ref | Type | Population | n | Age (mean) (years) | Follow-up | Males (%) | Prevalence/ incidence | RR/HR/ OR of occurrence [IC 95%] | p | Adjustment factors | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Cardiovascular events (CVE)*** | | | | | | | | | | | |
| [12] | 4 EUVAS RCT: MEPEX, CYCAZAREM, CYCLOPS, NORAM | AAV | 535 including 281 GPA 254 MPO | 58.4 | 5 years | 54 | 5-years cumulative incidence: 13.8% | - | - | | CVE= CV death, stroke, MI, coronary bypass or percutaneous coronary intervention |
| [16] | Meta-analysis Includes [17,101,102] | AAV | 803 | - | - | - | - | RR: 1.65 [1.23; 2.22] | - | | Includes [17,101,102] |
| [17] | Retrospective study population-based database | GPA | 504 | 57.4 | 3.8 years | 46.6 | Incidence: 18.97/ 1000 P.Y. | First year: HR 2.88 [1.37; 6.08] Overall: HR 1.64 [1.03; 2.60] | - | -Age, sex -Entry time-matched -Number of outpatient visits -Glucocorticoid use | CVE: MI, ischemic stroke. |
| [18] | Retrospective study | AAV | 204 including 111 GPA 38 MPA 14 EGPA 27 RLV | 55 (median) | 5.8 years | 46.1 | Overall incidence: 2.67/100 P.Y. First year incidence: 4.9/100 P.Y. | - | - | | CVE: MI, coronary bypass or percutaneous coronary intervention, ischemic stoke |
| [19] | Retrospective study | AAV | 504 including 349 MPA 119 GPA, 36 RLV | 62.1 (median) | 38 months | 48.4 | Cumulative incidence: 23.2% | - | - | | CVE: CV death, stroke, MI, coronary bypass or percutaneous coronary intervention |
| [32] | Retrospective study | AAV | 58 including 23 GPA 28 MPA 7 EGPA | 61.1 | 6.5 years | 52 | 10 years cumulative incidence: 39.6% | HR: 3.15 [1.51; 6.57] | 0.002 | -Age -Sex -Calendar year | CVE= Coronary artery disease, heart failure, atrial fibrillation, peripheral vascular disease, CVA, VTE |
| [37] | Retrospective study | AAV | 125 including 99 GPA 26 MPA | 61.3 | 88.4 months | 52 | 1-year, 5-years and 10-years cumulative incidence, respectively: 7%; 15 % and 23% Cumulative incidence: 27.8/ 1000 P.Y. | - | - | | CVE= acute coronary artery disease, ischemic stroke, peripheral vascular disease requiring revascularization |
| [102] | Retrospective study | AAV | 113 including 65 GPA, 46 MPA, 2 EGPA | 63 (median) | 3.4 years | 49.6 | 23 events | HR: 2.23 [1.1; 4.4] | 0.017 | No adjustment | CVE= acute coronary syndrome, new onset angina, symptomatic peripheral vascular disease, stroke, TIA |
| [103] | Prospective cohort study | Necrotizing vasculitis | 42 including 20 GPA 9 EGPA 8 MPA 5 PAN | 54 (median) | 7.1 years | 64 | 5-years and 10-years cumulative incidence, respectively: 9.5 % and 26.8% | - | - | | CVE= CV deaths, MI, stroke, arterial revascularisation, hospitalization for unstable angina |
| ***Coronary artery disease*** | | | | | | | | | | | |
| [16] | Meta-analysis Includes [17,33,101,104] | AAV | 13653 | - | - | - | - | RR 1.60 [1.39; 1.84] | - | | Includes [17,33,101,104] |
| [17] | Retrospective study population-based database | GPA | 504 | 57.4 | 3.8 years | 46.6 | Incidence: 11.72/ 1000 P.Y. | HR 1.86 [1.05; 3.31] | - | -Age, sex -Entry time-matched -Number of outpatient visits -Glucocorticoid use | Only MI included |
| [18] | Retrospective study | AAV | 204 including 111 GPA 38 MPA 14 EGPA 27 RLV | 55 (median) | 5.8 years | 46.1 | Incidence: 1.56/100 P.Y. | - | - | | |

(*continued on next page*)

**Table 1** (*continued*)

| Ref | Type | Population | n | Age (mean) (years) | Follow-up | Males (%) | Prevalence/ incidence | RR/HR/ OR of occurrence [IC 95%] | p | Adjustment factors | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [31] | Retrospective study | AAV | 53 | 61.3 | - | 52.8 | Cumulative incidence: 7.5% | - | - | | Only MI included |
| [32] | Retrospective study | AAV | 58 including 23 GPA 28 MPA 7 EGPA | 61.1 | 6.5 years | 52 | 10-years cumulative incidence: 11.6% | HR: 0.87 [0.29; 2.60] | - | -Age<br>-Sex<br>-Calendar year | **NS** |
| [33] | Retrospective study from nationwide database | GPA | 12670 | - | - | 32.8 | - | First year SIR: 2.21 [1.98; 2.46]<br>Overall SIR: 1.50 [1.46; 1.55] | - | Age, period, socioeconomic status, hospitalization of chronic lower respiratory diseases, obesity, alcohol, hypertension, diabetes, arterial flutter, heart failure, renal disease | Over-risk most important the first year after diagnosis, but remains significative afterwards. |
| [34] | 4 EUVAS RCT: NORAM, CYCAZAREM, MEPEX, and CYCLOPS | AAV | 302 | - | 7.1 years | - | 1-year cumulative incidence: 1.9%.<br>Overall cumulative incidence: 4.4% | - | - | | Only MI included |
| [35] | Prospective cohort study | AAV | 489 | 55 | 2.8 years | 52.5 | 2-years cumulative incidence: 5 % | - | - | | Only MI included<br>Patients included: chronic renal failure, not on dialysis. |
| [37] | Retrospective study | AAV | 125 including 99 GPA 26 MPA | 61.3 | 88.4 months | 52 | 1-year, 5-years and 10-years cumulative incidence, respectively: 2%, 8% and 12% | Comparative morbidity figure: 4.22 [1.52; 11.68] | - | Age | |
| [41] | Retrospective study population- based database | GPA | 570 | 58.4 | 5.9 years | 55.4 | 1-year, 5-years and 10-years cumulative incidence, respectively: 0.40, 3.13 and 5.36 | HR: 0.91 [0.60, 1.38] | - | -Age<br>-Sex<br>-General practice attended | **NS** |
| [101] | Retrospective study population- based database | AAV | 186 including 92 GPA 83 MPA 11 EGPA | 64.5 | 5.3 years | 48.9 | 30.9/1000 P.Y. | Comorbidity rate ratio: 1.5 [1.0; 2.3] | 0.07 | -Age<br>-Sex<br>-Index year-matched reference | **NS** |
| [104] | Retrospective study population- based database | GPA | 293 | 59 (median) | 8.4 years | 53.2 | 63 events | standardized ratios of observed to expected (O:E) events:<br>O/E= 1.9 [1.4-2.4] | - | -Time since the diagnosis<br>-Age<br>-Cumulative dose of cyclophosphamide | |
| [105] | Retrospective study | AAV ≥75 ans | 151 including 106 MPA 45 GPA | 79 (median) | 730 days | 50 | Cumulative incidence: 19% | - | - | | |
| ***Stroke*** | | | | | | | | | | | |
| [13] | Retrospective study | AAV | 30 including 16 GPA, 7 EGPA 4 MPA, 3 isolated organ involvement | 53.2 | 9 years | 23.3 | Cumulative incidence: 6.7 % | - | - | | Includes TIA |
| [16] | Meta-analysis Includes [17,38,48,101] | AAV | 2779 | - | - | - | - | RR: 1.20 [0.98; 1.48] | - | | **NS**<br>Includes [17,38,48,101] |
| [17] | Retrospective study population-based database | GPA | 504 | 57.4 | 3.8 years | 46.6 | Incidence: 8.99/ 1000 P.Y. | HR 1.50 [0.78;2.89] | - | -Age, sex<br>-Entry time-matched<br>-Number of outpatient visits<br>-Glucocorticoid use | **NS**<br>Only ischemic stroke |
| [18] | Retrospective study | AAV | | | | 46.1 | | - | - | | Only ischemic stroke |

(*continued on next page*)

**Table 1** (*continued*)

| Ref | Type | Population | n | Age (mean) (years) | Follow-up | Males (%) | Prevalence/ incidence | RR/HR/ OR of occurrence [IC 95%] | p | Adjustment factors | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 204 including 111 GPA 38 MPA 14 EGPA 27 RLV | 55 (median) | 5.8 years | | Incidence: 1.10/100 P.Y. | | | | |
| [31] | Retrospective study | AAV | 53 | 61.3 | - | 52.8 | Cumulative incidence: 9.4% | - | - | | |
| [32] | Retrospective study | AAV | 58 including 23 GPA 28 MPA 7 EGPA | 61.1 | 6.5 years | 52 | 10-years cumulative incidence: 21.5% | HR: 8.49 [2.54; 28.30] | <0.001 | -Age<br>-Sex<br>-Calendar year | Includes ischemic and hemorrhagic stroke, subarachnoid hemorrhage, TIA, amaurosis fugax or death from CVA |
| [34] | 4 EUVAS RCT: NORAM, CYCAZAREM, MEPEX, and CYCLOPS | AAV | 302 | - | 7.1 years | - | Cumulative incidence: 3.7% | - | - | | |
| [35] | Prospective cohort study | AAV | 489 | 55 | 2.8 years | 52.5 | 2-years cumulative incidence: 4 % | - | - | | Patients included: chronic renal failure, not on dialysis. |
| [37] | Retrospective study | AAV | 125 including 99 GPA 26 MPA | 61.3 | 88.4 months | 52 | 1-year, 5-years and 10-years cumulative incidence, respectively: 2%; 3% and 11% | Comparative morbidity figure: 4.65 [4.06; 5.31] | - | -Age | Only ischemic stroke |
| [38] | Retrospective study from nationwide database | GPA | 1909 | - | - | 53.7 | - | First year SIR only for hemorrhagic stroke: 5.83 [2.10; 12.76] | | | No over-risk for ischemic stroke |
| [41] | Retrospective study population- based database | GPA | 570 | 58.4 | 5.9 years | 55.4 | 1-year, 5-years and 10-years cumulative incidence, respectively: 0.96; 3.31 and 5.15 | HR 1.08 [0.70, 1.67] | - | -Age<br>-Sex<br>-General practice attended | **NS**<br>Includes ischemic stroke and TIA |
| [48] | Retrospective study | GPA | 180 | 54.9 (median) | 7.2 years | 20.6 | - | Incidence rate ratio: 1.4 [0.3; 5.7] | - | -Age<br>-Sex | **NS**<br>Both ischemic and hemorrhagic stroke |
| [101] | Retrospective study population- based database | AAV | 186 including 92 GPA 83 MPA 11 EGPA | 64.5 | 5.3 years | 48.9 | 13.2/1000 P.Y. | Comorbidity rate ratio: 1.1 [0.56; 2] | 0.7 | -Age<br>-Sex<br>-Index year-matched reference | **NS**<br>Includes ischemic, hemorrhagic and, subarachnoid bleeding |
| [105] | Retrospective study | AAV ≥75 ans | 151 including 106 MPA 45 GPA | 79 (median) | 730 days | 50 | Cumulative incidence: 13 % | - | - | | |
| ***Peripheral Arterial Disease*** | | | | | | | | | | | |
| [32] | Retrospective study | AAV | 58 including 23 GPA 28 MPA 7 EGPA | 61.1 | 6.5 years | 52 | 10-years cumulative incidence: 2% | HR: 0.70 [0.08; 6.40] | 0.75 | -Age<br>-Sex<br>-Calendar year | **NS**<br>Includes peripheral arterial disease, abdominal aortic aneurysm, and renal artery stenosis or arterial thromboembolism |
| [41] | Retrospective study population- based database | GPA | 570 | 58.4 | 5.9 years | 55.4 | 3-years and 5-years cumulative incidence, respectively: 0.21 % and 0.99 % | HR: 0.96 [0.45, 2.09] | - | -Age<br>-Sex<br>-General practice attended | **NS** |

RR: relative risk; HR: hazard ratio; OR: odds radio; EUVAS : European vasculitis study group; RCT : randomized controlled trial ; P.Y: person.years ; MI: myocardial infarction ; AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis granulomatosis with polyangiitis ; MPA : microscopic polyangiitis ; EGPA : eosinophilic granulomatosis with polyangiitis ; RLV :renal-limited vasculitis ; CV : cardiovascular ; CVA : cerebrovascular accident ; VTE : venous thromboembolism event ; PAN : polyarteritis nodosa ; TIA : transient ischemic attack ; SIR : standardized incidence ratio; NS: not significant; O/E: ratio of observed to expected events.

## 4. Discussion

### 4.1. Increased cardiovascular risk

#### 4.1.1. Cardiovascular events (CVE)

CVE, including cardiovascular (CV) death, stroke, heart failure, myocardial infarction (MI) and/or coronary artery disease (CAD), occur 1.65 to 3.15 times more frequently in AAV patients than in the general population (Table 1). In their meta-analysis, Houben et al. found an overall increased risk of 65% of CVE (relative risk (RR) of 1.65 IC 95% = [1.23; 2.22]) compared to the general population [16]. This increased risk of CVE is at its highest rate within the first year after diagnosis [17,18], probably related to inflammation and disease activity. Bai et al. showed that the Birmingham Vasculitis Activity Score (BVAS) at diagnosis, which reflects disease activity, was a risk factor for the development of CVE and mortality [19], independently of traditional cardiovascular risk factors. The 5-year and 10-year cumulative incidence of CVE ranges from 9.5 to 15%, and 23 to 39.6% respectively (Table 1). Excess mortality due to CVE ranges from 2.30 to 3.70 [5,12,18] [10], and is higher in the elderly [15]. Several pathophysiological mechanisms are involved in the development of CVE. ANCA seems to have its own pathogenicity, for instance through the liberation of Neutrophil Extracellular Traps (NETs) from neutrophils, a process named NETosis. Released NETs may contain bioactive molecules involved in inflammation, thrombosis, fibrosis, and endothelial activation [20]. Pacholczak et al. showed that this endothelial dysfunction was greater in AAV and EGPA patients compared to healthy controls, both via biomarkers (increased serum levels

of Vascular cell adherence molecule-1 (VCAM-1) and thrombomodulin) and ultrasound parameters (decrease of flow-mediated dilatation). It was associated with inflammatory markers, which are usually more important during disease flares [21,22]. Endothelial activation then induces thrombosis and fibrosis, but also an upregulation of adhesion molecules, leading to lymphocytes recruitment and thus to the genesis of atherosclerosis, subclinical then clinical, as well as inflammation of the vessels. Several studies have shown that subclinical atherosclerosis, assessed by carotid intima-media thickness (IMT), was greater in GPA compared to control patients [23,24], although this result was not found in all studies [25]. A correlation between IMT and the duration of the disease has been reported, in favour of the role of prolonged inflammation in this accelerated atherosclerosis [21]. Leukocytes-derived microparticles, which are higher in patients in relapse than in those in remission, could also participate in atherosclerosis via platelet activation and endothelial activation [26]. Particularly in EGPA patients, eosinophils could have a direct role on endothelial-cell injury [22].

Of note, cyclophosphamide itself can also induce endothelial cell damage [27]. The increasing use of rituximab in the management of AAV could therefore lead to a decrease in atherosclerosis, but this needs to be evaluated over the next few years.

Given this increased cardiovascular risk in AAV, AAV could be considered as an independent risk of CVE [28], like rheumatoid arthritis [29] and systemic lupus erythematosus [30]. Overall, cardiovascular risk should therefore be assessed at an early stage of follow-up, and then regularly, by screening and assessing traditional cardiovascular risk factors, in order to reduce the increased cardiovascular risk and to improve the global management of patients with AAV. Currently, there is room for improvement in the screening and treatment of traditional cardiovascular risk factors. Indeed, Bramlage et al. showed that among the AAV patients with an indication for lipid-lowering treatment (72.5 % of patients included), only 24.3% received it. Similarly, the blood pressure target of 130/80 mmHg (in the presence of proteinuria or

chronic renal failure) was not achieved in 65% of patients [31]. These findings are consistent with those reported by Houben et al., with 36% of patients showing an unmet blood pressure target and 25% with an indication for lipid-lowering treatment who did not receive appropriate treatment [28]. There is therefore a need for regular and systematic assessment of cardiovascular risk in patients with AAV, with appropriate subsequent management.

#### 4.1.2. Coronary artery disease (CAD)

Although the statistical threshold is not always reached, most studies report an increased risk of CAD compared to the general population (Table 1). Houben et al. found an increased risk of CAD of 60% in their meta-analysis (RR=1.60; IC 95% [1.39-1.84]) [16]. The 1-year, 5-years, and 10-years incidences of CAD were from 0.4 to 2%, 3.13 to 8%, and 5.36 to 12%, respectively (Table 1). This risk is at its greatest in the first years after the diagnosis of AAV [32,33].

Particularly for MI, the cumulative incidence at 1 year was 1.9% in Robson's study, which pooled several EUVAS clinical trials [34], and 5% at 2 years in McGregor's study [35]. In Aviña-Zubieta's cohort study, using a population database, patients with GPA had an incidence rate of MI of 11.7 per1000 person-years, with an adjusted HR of 1.86 (IC 95% 1.05-3.31) compared to age- and sex-matched controls [17]. MI, in the majority of cases, appears to be related to accelerated atherosclerosis in these patients, but may sometimes be related to coronary vasculitis or rarely to cardiac damage secondary to the vasculitis itself, such as in GPA [36].

#### 4.1.3. Stroke

Patients with AAV appear to also have an increased risk of stroke ranging from 1.08 to 8.49 times higher than the general population (Table 1), although this increased risk was found statistically significant in only 2 studies [32,37]. The 1-year, 5-years and 10-years incidences were from 0.96 to 2%, 3 to 3.31%, and 5.15 to 11% respectively (Table 1). In the meta-analysis previously cited, Houben et al. found a non-significant increased risk of 20% (RR=1.20; IC 95% = [0.98; 1.48]) [16]. Interestingly, Zoller et al. distinguished ischemic strokes from hemorrhagic strokes, and AAV patients were found to be at increased risk only for hemorrhagic strokes [38].

#### 4.1.4. Peripheral arterial disease (PAD)

There is only a small amount of data in the literature on the risk of PAD in AAV patients. In the studies found, there does not appear to be any increase in this risk (Table 1). Further studies would be necessary to explore this association.

### 4.2. Cardiovascular risk factors

#### 4.2.1. Diabetes mellitus

Diabetes is 2 to 10 times more frequent in AAV patients than in the general population. It was reported in 7.2 to 29% of patients (Table 2). This comorbidity is related both to the inflammation that occurs during disease flares and to the treatment, particularly glucocorticoids (GC), as diabetes is a well-known adverse event [39].

#### 4.2.2. Hypertension

The results of studies assessing the prevalence of hypertension in AAV patients are very heterogeneous, depending on their recruitment. For example, high blood pressure is much more common when patients come from nephrology departments. The prevalence therefore varies between 9% and 83% (Table 2). Several factors explain this high prevalence: the side effects of treatment such as GC [40], but also renal damages linked to vasculitis, who can, via kidney failure, increase cardiovascular morbidity.

#### 4.2.3. Dyslipidemia

Few studies have evaluated this endpoint, but AAV patients seem to experience some changes in the lipid profile [28,41,42]. Interestingly, Wallace et al. found in their study of patients included in the RAVE trial, an increase of total cholesterol level, low density of lipoprotein and apoliproteine B from baseline to month 6, with no statistical correlation

**Table 2**
Cardiovascular risk factors in AAV patients.

| Ref | Type | Population | n | Age (mean) (years) | Follow-up | Males (%) | Prevalence/ incidence | RR/HR/OR of occurrence [IC 95%] | p | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Diabetes*** | | | | | | | | | | |
| [2] | RCT (WGET trial) | GPA | 180 | 47 | - | 60 | Prevalence at one year of diagnosis: 7.2% | - | - | |
| [13] | Retrospective study | AAV | 30: 16 GPA, 7 EGPA 4 MPA, 3 isolated organ involvement | 53.2 | 9 years | 23.3 | Prevalence: 23.3% | - | - | |
| [25] | Retrospective study | Necrotizing vasculitis | 50 : 26 GPA 11 EGPA 8 MPA 5 PAN | 55 | - | 66 | Prevalence: 8% | - | - | |
| [34] | 4 EUVAS RCT: NORAM, CYCAZAREM, MEPEX, and CYCLOPS | AAV | 302 | - | 7.1 years | - | Cumulative incidence: 10.4% | - | - | |
| [35] | Prospective cohort study | AAV | 489 | 55 | 2.8 years | 52.5 | 2-years cumulative incidence: 29% | - | - | |
| [37] | Retrospective study | AAV | 125: 99 GPA 26 MPA | 61.3 | 88.4 months | 52 | Prevalence: 7.2% | - | - | |
| [41] | Retrospective study population- based database | GPA | 570 | 58.4 | 5.9 years | 55.4 | 1-year, 5-years and 10-years cumulative incidence, respectively: 2.71, 6.55 and 10.6 | HR: 2.13 [1.36-3.32] | - | Over-risk greater in the first 3 years. |
| [101] | Retrospective study population- based database | AAV | 186: 92 GPA 83 MPA 11 EGPA | 64.5 | 5.3 years | 48.9 | 44.3/1000 P.Y. | Comorbidity rate ratio: 2.0 [1.3; 2.9] | 0.003 | |
| [105] | Retrospective study | AAV ≥75 ans | 151: 106 MPA 45 GPA | 79 (median) | 730 days | 50 | Cumulative incidence: 15% | - | - | |
| [106] | Retrospective study population- based database | GPA | 342 | 55 (median) | 5.8 years | 50.3 | 28 events | Incidence rate ratio the first year after diagnosis: 10.4 % [4.4; 24] | - | |
| ***Hypertension*** | | | | | | | | | | |
| [2] | RCT (WGET trial) | GPA | 180 | 47 | - | 60 | Prevalence at one year of diagnosis: 9.4% | - | - | |
| [13] | Retrospective study | AAV | 30: 16 GPA, 7 EGPA 4 MPA, 3 isolated organ involvement | 53.2 | 9 years | 23.3 | Cumulative incidence: 40% | - | - | |
| [19] | Retrospective study | AAV | 504: 349 MPA 119 GPA, 36 RLV | 62.1 (median) | 38 months | 48.4 | Prevalence at diagnosis and after treatment, respectively: 53.4% and 67.9% | - | - | |
| [24] | Retrospective study | GPA | 23 | 47.9 | 72 months | 60.9 | Cumulative incidence: 57% | - | - | |
| [25] | Retrospective study | Necrotizing vasculitis | 50: 26 GPA 11 EGPA 8 MPA 5 PAN | 55 | - | 66 | Prevalence: 60% | - | - | |
| [28] | Retrospective study | AAV | 144: 99 GPA 25 MPA 20 EGPA | 62 | - | 56 | Prevalence: 72% | - | - | |
| [31] | Retrospective study | AAV (from a nephrology ward) | 53 | 61.3 | - | 52.8 | Cumulative incidence: 83% | - | - | |
| [34] | 4 EUVAS RCT: NORAM, CYCAZAREM, MEPEX, and CYCLOPS | AAV | 302 | - | 7.1 years | - | Cumulative incidence: 41.5% | - | - | |
| [41] | Retrospective study population- based database | GPA | 570 | 58.4 | 5.9 years | 55.4 | 1-year, 5-years and 10-years cumulative incidence, respectively: 8.55%; 19.9% and 27.8% | HR for the first 3 years after diagnosis: 2.45 [1.84, 3.26] | - | |
| [42] | Retrospective study | AAV | 268: 163 GPA, 80 MPA, 25 EGPA | 45.3 | 62 months | 35.1 | Prevalence: 63.8% | - | - | |
| [101] | Retrospective study population- based database | AAV | 186: 92 GPA 83 MPA 11 EGPA | 64.5 | 5.3 years | 48.9 | 98.8/1000 P.Y. | Comorbidity rate ratio: 1.4 [1.1; 1.8] | 0.02 | |

(*continued on next page*)

**Table 2** (*continued*)

| Ref | Type | Population | n | Age (mean) (years) | Follow-up | Males (%) | Prevalence/ incidence | RR/HR/OR of occurrence [IC 95%] | p | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| [105] | Retrospective study | AAV ≥75 ans | 151: 106 MPA 45 GPA | 79 (median) | 730 days | 50 | Cumulative incidence: 50% | - | - | |

RR: relative risk; HR: hazard ratio; OR: odds radio; AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis granulomatosis with polyangiitis ; MPA : microscopic polyangiitis ; EGPA : eosinophilic granulomatosis with polyangiitis ; RLV :renal-limited vasculitis ; EUVAS: European vasculitis study group; RCT: randomized controlled trial; polyarteritis nodosa; P.Y.: person. years.

with the GC dose. These modifications could be linked to the inflammatory state [43].

#### 4.2.4. Overweight

Probably as a side effect of treatments such as GC, some studies have shown that AAV patients often gain weight, especially during the first year after diagnosis. In the cohort of patients included in Wegener's Granulomatosis Etanercept Trial (WGET), Wung et al. showed that 22.3% of GPA patients gained at least 10 kg in the first year after diagnosis [44]. Similarly, in Moiseev's AAV patient cohort (n=268), 25.7% of the patients were overweight, and 19.4% were obese [42].

#### 4.2.5. Metabolic syndrome

The parameters assessed above belong to the definition of metabolic syndrome. However, we found only one study that has explored this entity in itself. Petermann et al. found that metabolic syndrome was more frequent in AAV patients compared to controls (43% vs 25%), and was not associated with the dose of GC that the patients had received [45]. This highlights a paradox concerning GC therapy in AAV like in other inflammatory diseases such as rheumatoid arthritis. On the one hand, it can increase CVE. On the other hand, GC allow the control of systemic inflammation, hence of disease and relapses, and may therefore reduce the process of atherosclerosis caused by the vasculitis.

Interestingly, the PEXIVAS trial recently showed a non-inferiority of a reduced-dose regimen of GC (cumulative dose at 6 months decreased by 60%) compared to a standard-dose regimen regarding overall survival and progression to end-stage renal disease in severe AAV [46]. Decreasing GC therapy could therefore reduce this increase in overall cardiovascular risk while being effective on the disease itself.

### 4.3. Venous thromboembolic events (VTE)

AAVs have an increased risk of VTE, between 4 and 5.24 times higher than the general population (Table 3). In their meta-analysis assessing the occurrence of VTE in rheumatic diseases, Lee et al. demonstrated that VTE were common in most of the auto immune diseases, and that AAV was the condition with the highest cumulative incidence of VTE (7.97% IC 95%

= [5.67; 10.68]) [47]. The incidence is estimated to be between 1.47 and 7/100 person-years, and is significantly higher during the active phase of the disease, particularly during the first 2 years after diagnosis [18,41,48–51]. In the post-hoc analysis of the RAVE trial, VTE occurred in average 1.5 months after inclusion [51]. However, excessive risk persists over time, particularly for deep venous thrombosis (DVT) [48], arguing for a procoagulant state, even in remission. Indeed, Hilhorst et al. showed that patients with AAV in remission had a higher Endogenous Thrombin Potential (ETP), reflecting a higher *in vivo* procoagulant state than controls, as well as a higher factor VIII activity in favor of endothelial system activation [52]. This procoagulant state appears to be independent of the classic risk factors for VTE [50]. NETose in neutrophils, which induces the transformation of pentameric C-reactive protein (CRP) into monomeric CRP, promoting platelet activation, could participate in this hypercoagulability [53]. Faced with this observation of an excess risk of VTE, a potentially fatal complication, the use of systematic preventive anticoagulation could be discussed during the active phases of vasculitis.

### 4.4. Bronchiectasis

Some studies show an association between AAV and bronchiectasis, evidenced in about 35% of patients [54,55]. Pearce et al. showed that the risk of developing GPA in patients with bronchiectasis was increased by a factor of 5 (OR 5.1; IC 95 = [ 2.7; 9.4]) [56]. In the study of Lhote et al., 41% of bronchiectasis diagnoses took place before the diagnosis of AAV, 20% were concomitant, and 39% were post-diagnosis. AAV patients with prior bronchiectasis had poorer prognosis and increased mortality. Interestingly, intensive immunosuppressive therapy for relapses seemed to have a positive effect on bronchiectasis [57].

One of the hypotheses that could explain this association is that bronchiectasis could be a condition favoring the appearance of AAV, via bronchial chronic suppuration, leading to auto- immunity [54,55]. It can therefore be suggested that at the time of the diagnosis of bronchiectasis, an ANCA test could be performed, as well as close monitoring for signs of extra-respiratory vasculitis.

### 4.5. Thyroid diseases

Thyroid diseases seem to be more frequent in patients with AAV than in the general population, with a prevalence of between 6.3 and 21.5% (Table 4), both via local autoimmunity, but also because of the use of synthetic antithyroid drugs (ATD) such as propylthiouracil (PTU).

First, autoimmunity responsible for AAV is a breeding ground for the development of certain dysthyroidism such as Grave's disease or Hashimoto's thyroiditis. In their study, Pearce et al. showed that, similarly to having rheumatoid arthritis or inflammatory bowel disease, patients with thyroid diseases were almost twice as likely to develop AAV compared to controls [56]. This common predisposition could be related to CTLA-4 polymorphism [58]. The hypothesis of a nucleotide sequence analogy between MPO and thyroperoxidase was also suggested to explain this association [59].

On the other hand, ATD used to treat certain hyperthyroidism, such as Grave's disease, are now known to induce ANCA and sometimes AAV. It is particularly described for PTU, but also, to a much lesser extent, with carbimazole and methimazole [60,61]. For PTU, it is estimated that between 11 and 41.3% of patients will develop MPO-ANCA [62–65], and that only a small proportion of patients will develop the symptoms of AAV, estimated at 3% of patients with PTU in the review of Balavoine et al. [66]. Compared to primitive-AAV, PTU-induced AAV is often less severe, with fewer organs affected and with less severe kidney damage. It has a better overall and renal prognosis [67–69], often with regression simply on stopping PTU [59,70]. Nevertheless, there are severe forms, sometimes with progression to death or end-stage renal disease, justifying conventional immunosuppressive drugs [59,71–73].

In view of these observations, attention should be paid to the presence of signs of vasculitis in patients with ATD, and ANCA should be investigated in the case of doubt.

### 4.6. Osteoporosis

Osteoporosis and the resulting risk of fracture are important in

**Table 3**
Venous thromboembolic events in AAV patients.

| Ref | Type | Population | n | Age (mean) (years) | Follow-up | Males (%) | Prevalence/ incidence | RR/HR/OR | p | Adjustment factors | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [18] | Retrospective study | AAV | 204 whom 111 GPA 38 MPA 14 EGPA 27 RLV | 55 (median) | 5.8 years | 46.1 | Fist year incidence: 3.8/100 P.Y. Overall incidence: 1.47/100 P.Y. | - | - | | |
| [32] | Retrospective study | AAV | 58: 23 GPA 28 MPA 7 EGPA | 61.1 | 6.5 years | 52 | 10-years cumulative incidence for DVP and EP respectively: 9.8% and 4.8% | HR for only DVT: 6.25 [1.16; 33.60] | 0.03 | -Age<br>-Sex<br>-Calendar year | Significant over-risk only for DVT. NS for PE and VTE |
| [35] | Prospective cohort study | AAV | 489 | 55 | 2.8 years | 52.5 | 2-years cumulative incidence: 11% | - | - | | Patients included: chronic renal failure, not on dialysis. |
| [41] | Retrospective study population-based database | GPA | 570 | 58.4 | 5.9 years | 55.4 | 1-year, 3-years and 5-years cumulative incidence, respectively: 2.27; 5.18 and 6.11 | HR : 5.24 [2.83-9.71] | - | -Age<br>-Sex<br>-General practice attended | |
| [47] | Meta-analysis Includes [49,50,107,108] | AAV | 16295 | - | - | - | Cumulative incidence : 7.97% [5.67; 10.68] | - | - | | Includes [49,50,107,108] |
| [48] | Retrospective study | GPA | 180 | 54.9 (median) | 7.2 years | 20.6 | - | IRR within 2 years after diagnosis for PE and DVT respectively: 25.7 [6.9; 96] and 20.2 [5.1; 81] | - | -Age<br>-Sex | After the second year after diagnosis, NS for PE. For DVT: IRR: 4.5 [1.7; 11.8] |
| [49] | Retrospective study from nationwide database | GPA | 15085 | - | - | 35.3 | - | First-year SIR: 6.57 [5.66; 7.58]<br>Overall SIR: 1.41 [1.31; 1.50] | - | -Age<br>-Sex<br>-Period of occurrence<br>-Comorbidities (chronic obstructive pulmonary disease, alcoholism and alcohol related liver disease; coronary heart disease; stroke; hypertension; sepsis; varicose veins; peripheral vascular disease; and congestive heart failure | Only deals with PE.<br>After the 5th year, NS over risk |
| [50] | Retrospective study | AAV | 198 | 60 (median) | 6.1 years | 57 | Overall incidence 1.8/100 P.Y. Incidence while active disease: 6.7/ 100 P.Y. | - | - | | |
| [51] | RCT (RAVE trial) | AAV | 197 | 52 (median) | - | 50.7 | Cumulative incidence: 8.1% | - | - | | |
| [52] | Prospective cohort study | AAV | 31: 29 GPA 1 | 51.4 | 5 years | 51.6 | Incidence: 2.5 /100 P.Y. | - | - | | |

(*continued on next page*)

**Table 3** (*continued*)

| Ref | Type | Population | n | Age (mean) (years) | Follow-up | Males (%) | Prevalence/ incidence | RR/HR/OR | p | Adjustment factors | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | MPA 1 EGPA | | | | | | | | |
| [101] | Retrospective study population-based database | AAV | 186: 92 GPA 83 MPA 11 EGPA | 64.5 | 5.3 years | 48.9 | Incidence : 15.6/1000 P. Y. | Comorbidity rate ratio : 4.0 [1.9; 8.3] | 0.003 | -Age -Sex -Index year-matched reference | |
| [107] | RCT (WGET trail) | GPA | 180 | 50 | 1.5 years | 60 | Cumulative incidence: 7.0/100 P.Y. | - | - | | |
| [108] | Retrospective study | Necrotizing vasculitis | 1130: 377 GPA, 236 MPA, 232 EGPA, 285 PAN | 52.5 | 58.4 months | 52.8 | Overall prevalence (within the 6 months before and after the diagnosis): 6.5%. GPA: 8% EGPA 8% MPA 7.6% | - | - | | |
| [109] | 4 EUVAS RCT: NORAM, CYCAZAREM, MEPEX, and CYCLOPS | AAV | 417 | 60 (median) | - | 54.4 | Cumulative incidence: 9.8% | - | - | | |
| [110] | Retrospective study | AAV | 105 | - | - | - | Incidence: 4.3/100 P.Y. | - | - | | |

RR: relative risk; HR: hazard ratio; OR: odds radio; AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis granulomatosis with polyangiitis ; MPA : microscopic polyangiitis ; EGPA : eosinophilic granulomatosis with polyangiitis ; RLV :renal-limited vasculitis; P.Y.: person.years; DVT: deep venous thrombosis; PE: pulmonary embolism; NS: not significant; IRR: incidence rate ratio; SIR: standardized incidence radio; RCT: randomized controlled trial; RAVE trial: Rituximab in ANCA-associated vasculitis trial; WGET trial: Wegener's Granulomatosis Etanercept Trial; EUVAS : European vasculitis study group; PAN : polyarteritis nodosa.

**Table 4**
Thyroid diseases in AAV patients.

| References | Type | Population | n | Age (mean) (years) | Follow-up | Males (%) | Prevalence/incidence | RR/HR/OR | p |
|---|---|---|---|---|---|---|---|---|---|
| [41] | Retrospective study population- based database | GPA | 570 | 58.4 | 5.9 years | 55.4 | Prevalence (hypothyroidy before diagnosis of AAV): 6.3% | - | 0.0003 |
| [58] | Retrospective study | AAV | 158 | 62.7 | - | 59 | Prevalence before diagnostic of AAV: 20% | OR : 3.7 [1.5-9.2] | 0.002 |
| [101] | Retrospective study population- based database | AAV | 186: 92 GPA 83 MPA 11 EGPA | 64.5 | 5.3 years | 48.9 | Incidence : 27.9/1000 P.Y. | Comorbidity rate ratio : 2.1 [1.3; 3.3] | 0.09 |
| [111] | Retrospective study | AAV | 279 | - | - | 48.4 | Prevalence : 21.5% | - | - |

RR: relative risk; HR: hazard ratio; OR: odds radio; AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis granulomatosis with polyangiitis ; MPA : microscopic polyangiitis ; EGPA : eosinophilic granulomatosis with polyangiitis; P.Y.: person.years.

patients with AAV (Table 5) and deserve to be screened. This increased risk [74] [75] is especially true for men over 55 years of age [75]. It is related in particular to the high-dose GC therapy used, but can also be reported to renal insufficiency and to inflammation. The physician must therefore be aware of this complication and prevent it. Hygieno-dietetic advice, such as smoking cessation, physical activity, limiting alcohol intake and phospho-calcium supplementation seems to be appropriate.

### *4.7. Psychosocial factors*

#### *4.7.1. Health relative quality of life (HRQoL)*

Decreased QoL in patients with AAV is consistently found in studies using the physical component scale (PCS), and in most of the studies using the mental component scale (MCS) (table 6) [76–80]. Classical AAV scores such as the Vasculitis damage index (VDI) and the BVAS, assessing respectively the sequelae and activity of vasculitis, are associated with QoL in only a few studies [2,79,81–83]. Most studies, including Walsh's meta- analysis [84], did not find such an association [77,78,85–87]. This observation suggests that there are other factors that may worsen patients' QoL. The main components associated with PCS identified in our research are fatigue, mood disorders, and sleep disturbances. Those associated with MCS are fatigue, mood disorders, and unemployment. To improve the overall management of the patient, including QoL, the physician should therefore be attentive to these elements, which are less often evaluated in daily practice. Neurological involvement, which can lead to neuropathic pain [77,78], and ENT involvement [88] are also parameters that impact QoL. Better physician and partner support, known to significantly improve the QoL [79], should also be integrated. It should be noted that rituximab, increasingly used in this pathology, seems to have a positive effect on QoL, as found in the study carried out in parallel to the MAINRITSAN trial [89]. However, further studies will be needed to confirm these data.

#### *4.7.2. Fatigue*

Fatigue, which is one of the major components involved in the reduction of QoL in patients with AAV, has a high prevalence, ranging

**Table 5**
Osteoporosis and fractures in AAV patients.

| References | Type | Population | n | Age (mean) (years) | Follow-up | Males (%) | Prevalence/incidence | RR/HR/OR | p |
|---|---|---|---|---|---|---|---|---|---|
| ***Osteoporosis*** | | | | | | | | | |
| [74] | Retrospective study | AAV | 99: 80 GPA 6 EGPA 2 RLV | 55 | 50 months | 48.5 | Cumulative prevalence of osteoporosis (at least 1 site) and osteopenia, respectively: 21 and 57% | - | - |
| [101] | Retrospective study population- based database | AAV | 186: 92 GPA 83 MPA 11 EGPA | 64.5 | 5.3 years | 48.9 | Incidence : 47.0/1000 P.Y. | Comorbidity rate ratio : 4.6 [3.0; 7.0] | <0.0001 |
| ***Fractures*** | | | | | | | | | |
| [34] | 4 EUVAS RCT: NORAM, CYCAZAREM, MEPEX, and CYCLOPS | AAV | 302 | - | 7.1 years | - | Cumulative incidence : 14.1% [9.9; 18.2]] | - | - |
| [74] | Retrospective study | AAV | 99: 80GPA 6 EGPA 2 RLV | 55 | 50 months | 48.5 | Prevalence: 6% | - | - |
| [75] | Retrospective study | GPA | 159 | 55 | 5.7 years | 50 | | Overall incidence rate ratio: 1.2 [0.7-2.0] **NS** For males ≥ 55 years-old: Incidence rate ratio 3.5 [1.6; 7.6] | - |

RR: relative risk; HR: hazard ratio; OR: odds radio; AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis granulomatosis with polyangiitis ; MPA : microscopic polyangiitis ; EGPA : eosinophilic granulomatosis with polyangiitis; P.Y.: person.years; EUVAS : European vasculitis study group; NS: not significant.

from 68.4 to 76.4% (Table 7). The variables most often associated with fatigue are anxiety and depression, pain, and sleep disturbances. The latter is indeed very frequent (between 29 and 57.3% of patients) [83,90–92]. These three parameters deserve to be detected because they are elements for which treatment is possible. Although Hessels et al.'s study showed a significant decrease of muscle strength in patients with AAV compared to healthy patients [93], most studies support a central rather than peripheral cause for this fatigue. McClean et al. showed that the increase in fatigue observed in their patients was in fact not explained by poorer cardiorespiratory condition nor reduced

muscle mass or function, but was rather related to central causes [83], although no cerebral MRI correlation has yet been found [94].

There is also often a decrease in physical activity in AAV patients, which may contribute to this fatigue [90]. Interestingly, Tuin et al. showed that androgen deficiency, which is more common in these patients because of the disease itself and the treatments, such as cyclophosphamide, was correlated with decreased physical activity [95]. Encouraging physical activity, for example through a program to increase it, could therefore also be a way to improve the management of these patients. An open randomized trial is planned to evaluate the benefit of an intervention program of physical activity techniques and behavior change compared to the standard of care [96].

#### *4.7.3. Depression and anxiety*

Depressive disorders are found more frequently in AAV patients than in the general population (between 15 and 46% of patients) (Table 8), as is anxiety, found in 28.8 to 43% of patients [78,83,90,92]. These disorders explain part of the fatigue and the alteration of patients' QoL. GC, at the doses used in AAV, may also exacerbate underlying mood disorders.

Mood disorders, impaired QoL, sleep disturbance and fatigue are common in chronic diseases such as other inflammatory rheumatism and chronic kidney failure [90], where these parameters are maybe more explored and therefore better managed. The search for and management of these elements in AAV is nevertheless recommended [97].

#### *4.7.4. Work disability*

Unemployment and job loss related to vasculitis are common, contributing to a poor experience of the disease [98]. Between 26% and 43% of working-age patients with AAV are unemployed [98–100]. In Reinhold-Keller's study, 55% of patients had been hospitalized in the year prior to inclusion. Job loss due to vasculitis appears to be more frequent among women than men, with an estimated over-risk of 2.67% (IC 95%= [1.38; 5.14]) [98]. Benarous et al. found that 50% of patients thought that the disease hindered their career [100].

## 5. Conclusion

In summary, the excess mortality observed in AAV is partly related to comorbidities, particularly cardiovascular and thromboembolic events, which are significantly present, especially during the active phase of the disease. This increase in arterial thrombotic events is not only due to endothelial activation and inflammation, but also to a higher prevalence of cardiovascular risk factors (diabetes, obesity, overweight, dyslipidemia), that increases the risk of accelerated atherosclerosis. Clinical trials evaluating the benefit of primary prevention by aspirin or statin for cardiovascular events, but also by preventive anticoagulation during the active phases of the disease, could be interesting.

Osteoporosis, especially corticosteroid-induced osteoporosis, thyroid diseases and bronchiectasis are also more prevalent in AAV patients and should be screened.

Interestingly, it seems well-established that AAV patients suffer from a decrease in QoL, in relation to mood disorders, unemployment, and fatigue, the latter being itself associated with anxiety, depression, pain, and sleep disorders. All of these factors are available for screening (medical questioning, scales, screening for sleep disorders including sleep apnea) and may benefit from pharmacologic or non-pharmacologic treatment.

It should be noted that most studies are retrospective or post-hoc analyses of randomized clinical trials. Prospective studies on these comorbidities and their management, in primary or secondary prevention, are needed. To improve the overall management of patients, a program of systematic screening and management, not only of cardiovascular risk factors and subclinical atherosclerosis, but also of elements related to QoL and its above-mentioned determinants, could be beneficial. It can be hypothesized that this could help to improve cardiovascular risk and thus mortality, but also the patient's experience of this now chronic disease. Patients with AAV need comorbidity management strategies to improve their QoL and outcomes.

**Table 6**
Quality of life in AAV patients

| Ref | Type | Population | n | Age (mean) (years) | Follow-up | Males (%) | HRQOL score used | MCS (mean +/- SD) | RR/ HR/ OR | p | Factors associated with MCS | PCS (mean +/- SD) | RR/HR/ OR | p | Factors associated with PCS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [81] | RCT (WGET trial) | GPA | 180 | 49.9 | 2.3 years | 60 | SF-36 | 44.2+/-11.6 | - | - | - BVAS/WG | 33.5 +/-9.7 | - | - | - BVAS/WG<br>-VDI (when adjusted on BVAS/WG) |
| [81] | Prospective cohort study (VCRC-LS) | GPA | 237 | 49.1 | 2 years | 47.4 | SF-36 | 46.5 +/- 11.7 | - | - | - BVAS/WG | 43.6 +/- 10.3 | - | - | - BVAS/WG<br>-VDI |
| [83] | Retrospective study | AAV | 48 | 58 | - | 54 | SF-36 | 48.4 | - | <0.001 | | 42.5 | - | <0.001 | |
| [84] | Meta-analysis with the clinical trials CYCLOPS, MEPEX, NORAM, and CYCAZAREM | AAV | 346 | 57.1 | - | 56.1 | SF-36 | 40.4 +/- 11.9 | - | - | - Chest involvement p=0.027 | 27.6 +/- 12.5 | - | - | - Older age p=0.029<br>- Neurologic involvement |
| [85] | Retrospective study | AAV | 72: 45 GPA 12 MPA 15 EGPA | 59 | - | 59 | SF-8 | 49.3 (vs 49.0) | - | 0.84 **NS** | | 46.7 (vs 46.1) | 2.63 [1.28; 4.43] | <0.0001 | -moderate /severe fatigue p<0.001<br>-mood disturbance p=0.021 |
| [86] | Retrospective study | GPA | 68 | 58 (median) | - | 53 | SF-36 | 51.5 +/- 9.3 (vs 55.1) | - | <0.001 | | 44.9 +/- 10.5 (vs 52.0) | | <0.001 | |
| [87] | Retrospective study | Primary systemic vasculitis | 122, whom 63 GPA, 15 MPA, 14 EGPA) | 56.2 | - | 43.4 | SF-36 | For males 43.7 +/- 11.6<br>For female: 47.6 +/- 11.2 | - | - | -Depression | For males: 35.2 +/- 11.3<br>For females: 38.5 +/- 13 | | | -Depression<br>-Fatigue<br>-Widowed marital status |
| [89] | RCT MAINRITSAN | AAV | 115: 87 GPA 23 MPA 7 RLV | 55 | - | 56.5 | SF-36 | 41.8 +/- 10.1 | | | | 43.4 +/- 9.5 | | | |
| [90] | Retrospective study | AAV | 60: 53 GPA 5 MPA 2 RLV | 54 (median) | - | 40 | SF-36 | 62.42 | - | - | -worse PtGA (p=0.014)<br>-fatigue (p=0.002)<br>-HADS score (p=0.005) | 62.34 | - | - | -worse PtGA (p=0.01=<br>-worse PhGA (p=0.019)<br>- fatigue (p<0.001) |
| [93] | Retrospective study | AAV | 48 | 62 (median) | - | 52 | RAND-36 | 46+/- 9 (vs 50 in general population) | - | 0.01 | -Lower Baecke total index (physical activity)<br>-Higher dose of prednisolone > 5mg/day<br>-ENT involvement | 42 +/- 10 vs 50 in general population | - | <0.001 | -Lower muscle strength (knee extension)<br>-Younger age<br>-Previous relapses<br>-Higher CRP levels |
| [95] | Retrospective study | AAV | 70: 54 GPA 14 MPA 2 EGPA | 59 | - | 100 | RAND-36 | 47.8 +/- 9.5 | | 0.055 **NS** | | 41.4 +/- 11.4 | | <0.001 | -Testosterone level p=0.024<br>- Older age p= 0.007 |
| [100] | Retrospective study | AAV | 189: 126 GPA 22 MPA 41 EGPA | 58.6 | - | 43 | SF-36 | 14% had MCS <30 | | | -Unemployment (OR 3.28 [1.33; 8.11] p=0.01) | 19% had PCS <30 | | | -Diagnosis of EGPA (OR 3.22 [1.43; 7.26] p= 0.005)<br>- Long disease duration (OR 1.005 [1.00; 1.01] |
| [112] | Retrospective study | AAV | 410: 265 GPA 95 MPA 44 EGPA | 61.4 | - | 49 | SF-36 | | 2.5 [1.7; 3.6] | <0.00001 | -Fatigue<br>-Self distraction and self blame (coping strategies)<br>-Hypoalbuminemia<br>- Anxiety<br>-Depression<br>-Unemployment | | 7.0 [4.0; 11.1] | <0.00001 | -Fatigue<br>-Sleep disorders<br>-Pain<br>-Higher current dose prednisolone<br>-Older age<br>-Raised CRP |

p: comparison vs general population or healthy subjects; HRQOL: Health relative quality of life; MCS: mental component score; PCS: physical component score; RR: relative risk; HR: hazard ratio; OR: odds radio; AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis granulomatosis with polyangiitis ; MPA : microscopic polyangiitis ; EGPA : eosinophilic granulomatosis with polyangiitis; P.Y.: person.years; RCT: randomized controlled trial; WGET trial: Wegener's Granulomatosis Etanercept Trial; BVAS/WG: Birmingham Vasculitis Activity Score for Wegener's granulomatosis; VDI: Vasculitis damage index; VCRC-LS : Vasculitis Clinical research Consortium longitudinal Study; PtGA: patient's global assessment, PhGA: physician's global assessment; SF-36: 36-item Short Form Survey; RAND-36.

**Table 7**
Fatigue in AAV patients.

| References | Type | Population | n | Age (mean) (years) | Males (%) | Fatigue score used | Prevalence | RR/HR/OR | p | Factors associated with fatigue |
|---|---|---|---|---|---|---|---|---|---|---|
| [83] | Retrospective study | AAV | 48 | 58 | 54 | MFI-20 | - | - | <0.001 | -Depression and anxiety<br>-Sleep disorders<br>-Pain<br>-Perception of exertion |
| [85] | Retrospective study | AAV | 72: 45 GPA 12 MPA 15 EGPA | 59 | 59 | Chalder fatigue scale (CFS) | Mild: 30.1% Moderate/ severe: 38.4% | Mild: OR 2.01 [1.1; 3.8] Moderate /severe: OR 2.5 [1.4; 4.5] | | - History of renal involvement p=0.012<br>-Mood disturbances p<0.0001 |
| [90] | Retrospective study | AAV | 60: 53 GPA 5 MPA 2 RLV | 54 (median) | 40 | Multidimensional fatigue Inventory-20 (MFI-20) | - | - | <0.0001 | -Depression (p=0.01) |
| [91] | Retrospective study | GPA | 55 | 53 (median) | 66 | Visual Analog Scale (VAS) fatigue | 76.4% | - | - | -Depression<br>-Sleep disorders<br>-Fibromyalgia syndrome |
| [92] | Retrospective study | AAV | 410: 265 GPA 95 MPA 44 EGPA | 63.5 (median) | 49 | CFS | High level of fatigue: 74.8% | - | - | -Sleep disorders (OR 5.3 [2.7; 10.5])<br>- Pain (OR 3.8 [2.0; 7.3]<br>- High CRP level (OR 3.7 [1.7; 8.1]<br>- Dysfunctional coping strategies of behavioral disengagement (OR 2.4)<br>-Female sex (OR 2.1) |
| [95] | Retrospective study | AAV | 70: 54 GPA 14 MPA 2 EGPA | 59 | 100 | MFI-20 | - | - | 0.001 | -Testosterone level<br>-VDI<br>-Older age<br>-High CRP level |

RR: relative risk; HR: hazard ratio; OR: odds radio; AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis granulomatosis with polyangiitis ; MPA : microscopic polyangiitis ; EGPA : eosinophilic granulomatosis with polyangiitis; RLV :renal-limited vasculitis.

**Table 8**
Depression in AAV patients.

| Ref | Type | Population | n | Age (mean) (years) | Follow-up | Males (%) | Prevalence/ incidence | RR/HR/OR | p | Depression score used |
|---|---|---|---|---|---|---|---|---|---|---|
| [41] | Retrospective study | GPA | 570 | 58.4 | 5.9 years | 55.4 | 1-year; 5-years and 10-years incidence, respectively: 2.12; 6.67 and 8.39 | HR 1.77 [1.10, 2.86] within the 3 first years | - | |
| [78] | Retrospective study | AAV | 51 : 31 GPA 9 MPA 11 EGPA | 60.06 | - | 59 | Prevalence : 25.5% | - | - | Hospital Anxiety and Depression Scale (HADS) |
| [85] | Retrospective study | AAV | 72 : 45 GPA 12 MPA 15 EGPA | 59 | - | 59 | Prevalence : 15% | - | 0.50 **NS** | Beck depression inventory (BDI) |
| [87] | Retrospective study | Primary systemic vasculitis | 122 including 63 GPA 15 MPA 14 EGPA | 56.2 | - | 43.4 | Prevalence: 46% had depression at least mild; 19 % had severe depression | - | - | BDI |
| [90] | Retrospective study | AAV | 60 : 53 GPA 5 MPA 2 RLV | 54 (median) | - | 40 | Prevalence : 15% | - | - | HADS |
| [91] | Retrospective study | GPA | 55 | 53 (median) | - | 66 | Prevalence : 22% (vs 7.6%) | - | <0.001 | Brief patient health questionnaire 9 |
| [92] | Retrospective study | AAV | 410 (265 GPA 95 MPA 44 EGPA) | 63.5 (median) | - | 49 | Prevalence : 24.6% | - | - | HADS |

P: comparison with general population or healthy subjects
RR: relative risk; HR: hazard ratio; OR: odds radio; AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis granulomatosis with polyangiitis ; MPA : microscopic polyangiitis ; EGPA : eosinophilic granulomatosis with polyangiitis; RLV :renal-limited vasculitis.

## Author contributions

All authors had full access to the data and reviewed and approved the manuscript for publication. C Mercuzot, P Fesler and C Roubille take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Mercuzot, Fesler, Roubille
Acquisition, analysis, or interpretation of data: All authors
Drafting of the manuscript: Mercuzot, Roubille
Critical revision of the manuscript: All authors
Agreement to be accountable for all aspects of the work: All authors

## Declaration of Competing Interest

CM has no conflict of interest to declare. SL has no conflict of interest to declare. CD has no conflict of interest to declare. LZ has no conflict of interest to declare.

PG has been a medical expert for LFB (Laboratoire Français du Biofractionnement) and has received fees from AbbVie, Actelion, Boehringer Ingelheim France, Bouchara-Recordati, Novartis, Pfizer and Roche in the last 5 years.

BT has received consulting fees or grants from Roche/Chugai, AstraZeneca, GlaxoSmithKine, Bristol-Myers Squibb, Lilly, Vifor Pharma and Terumo BCT.

PF has received fees from Servier, and Actelion in the last 5 years. CR has received fees from Servier, and Pfizer in the last 5 years.

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