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Long-term Risk of Heart Failure and Other Adverse Cardiovascular Outcomes in Granulomatosis With Polyangiitis: A Nationwide Cohort Study

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ABSTRACT. ***Objective.*** To examine the long-term rates of heart failure (HF) and other adverse cardiovascular (CV) outcomes in a nationwide cohort of patients diagnosed with granulomatosis with polyangiitis (GPA) compared with the general population.

Methods. Using Danish nationwide registries, patients with newly diagnosed GPA were identified and matched 1:4 by age, sex, and comorbidities with subjects from the general population. Outcomes were compared using Cox regression. Due to violation of the proportional hazard assumption, landmark analyses for the first year and from 1 year were performed.

Results. Of the 1923 patients with GPA, 1781 patients (median age 59 yrs, 47.9% men) were matched with 7124 subjects from the general population. The median follow-up was 6.4 years. The absolute 10-year risk of HF was 6.8% (95% CI 5.5–8.2%) for patients with GPA and 5.9% (5.3–6.6%) for the general population. During the first year after diagnosis, GPA was associated with a significantly higher rate of HF (hazard ratio [HR] 3.60, 95% CI, 2.28–5.67) and other adverse outcomes, including atrial fibrillation/flutter (HR 6.50, 95% CI 4.43–9.55) and ischemic stroke (HR 3.24, 95% CI 1.92–5.48), compared with the general population. After the first year, GPA was not associated with higher rates of HF or other CV outcomes compared with the general population, except atrial fibrillation/flutter (HR 1.38, 95% CI 1.12-1.70).

Conclusion. During the first year after diagnosis, the rates of HF and other CV outcomes were higher in patients with GPA compared with the general population. However, after the first year, the rates of HF and other CV outcomes, except atrial fibrillation/flutter, were similar to those in the general population.

Key Indexing Terms: cardiovascular diseases, granulomatosis with polyangiitis, heart failure

Granulomatosis with polyangiitis (GPA; previously known as Wegener) is a systemic autoimmune disease characterized by granulomatous inflammation and necrotizing vasculitis.[1,2] The most commonly involved organs of GPA include the upper and lower respiratory tract and the kidneys.[3,4] However, the disease can affect any organ system in the body, and cardiac manifestations, including acute myocardial infarction (MI), conduction system abnormalities, and pericarditis, have been described.[5,6,7] The evidence regarding the risk of adverse cardiovascular (CV) events in patients with GPA is conflicting. For example, an increased risk of ischemic heart disease and stroke has been observed in some cohorts of patients with GPA and other types of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) compared with the general population,[8,9,10] but not in other cohorts.[11,12,13] Moreover, data on the risk of other adverse CV outcomes such as heart failure (HF) and arrhythmia among patients with GPA are sparse and limited to case reports[14] or studies with a small sample size or lack of long-term follow-up.[4,5,15–20] Given the high morbidity and mortality associated with HF in particular,[21,22] it is important to assess the long-term burden of HF and other CV manifestations in a large and unselected GPA population. Accordingly, we performed a nationwide cohort study to investigate the long-term rates of HF and other adverse CV outcomes in patients diagnosed with GPA relative to a matched cohort from the Danish population.

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

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METHODS

Data sources. In Denmark, all residents are assigned a unique civil registration number that allows linkage of nationwide administrative registries

at an individual level. The present study was based on data obtained from the following 3 registries: (1) the Danish National Patient Registry, which holds data on all hospital admissions and outpatient contacts according to the International Classification of Diseases, 8th revision (ICD-8 until the end of 1993 and ICD-10 thereafter; each hospital contact is recorded with 1 primary and, if appropriate, ≥ 1 secondary diagnoses[23]); (2) the Danish National Prescription Registry, which contains information on dispensing date, strength, and quantity of all claimed drug prescriptions in Danish pharmacies[24]; and (3) the Danish Civil Registration System, which contains information on birth date, sex, and vital status (including date of death and emigration).[25]

Study population. All Danish citizens aged ≥ 18 years with a first-time primary or secondary in- or outpatient diagnosis of GPA from January 1, 1996, to June 30, 2018, were eligible for inclusion. Patients were excluded from the study if they met the following exclusion criteria: prior implantable cardioverter defibrillator (ICD) or pacemaker implantation or a history (ie, primary or secondary in- or outpatient diagnosis) of HF, atrial fibrillation/flutter, ventricular arrhythmias (ventricular tachycardia, flutter, or fibrillation), cardiac arrest, atrioventricular block (advanced 2nd or 3rd degree), sinoatrial dysfunction, ischemic stroke, ischemic heart disease, pericarditis, myocarditis, or aortic aneurysm/dissection (Supplementary Table 1 for diagnosis and procedure codes, available with the online version of this article). We identified a cohort of controls from the general population in order to compare outcomes between patients with GPA and the general population. The controls did not have a history of GPA and did not develop this condition any time during follow-up. For patients with GPA, the index date was set at diagnosis of GPA; controls from the general population were randomly assigned the same index date as a case from the GPA population. Exclusion criteria were the same in the general population cohort as in the GPA cohort. Using risk-set matching,[26] each patient was matched with 4 controls from the general population by age (up to a 1-yr difference), sex, year of the index date, and each of the following comorbidities: hypertension, peripheral artery disease, diabetes, chronic kidney disease, and chronic obstructive pulmonary disease.

Comorbidity and concomitant pharmacotherapy. Comorbidities were identified using in- and outpatient primary and secondary diagnosis codes any time prior to the index date (Supplementary Table 1, available with the online version of this article), except for diabetes and hypertension, which were identified through drug prescriptions, as described previously.[27,28] Concomitant medical treatment was identified using claimed prescriptions within 6 months prior to the index date (Supplementary Table 2).

Outcomes. The primary outcome was incident HF, defined as a first-time in- or outpatient primary or secondary diagnosis of HF recorded in the Danish National Patient Registry. Secondary outcomes were atrial fibrillation/flutter; a composite of ICD implantation, ventricular arrhythmia, or cardiac arrest; a composite of pacemaker implantation, atrioventricular block (advanced 2nd or 3rd degree) or sinoatrial dysfunction; ischemic stroke; MI; pericarditis; myocarditis; aortic aneurysm/dissection; and all-cause mortality. All diagnosis codes for outcomes have previously been validated with high positive predictive values (PPVs) in the Danish National Patient Registry.[29,30,31,32,33] Patients were followed from the index date until the occurrence of the outcome of interest, death, emigration, or the end of the study (December 31, 2018), whichever came first.

Statistical analyses. Continuous variables are presented as medians with IQRs and categorical variables as frequencies with percentages. Differences in baseline characteristics were tested with the chi-square or Fisher exact test for categorical variables and the Wilcoxon test for continuous variables. Incidence rates (IRs) of outcomes were calculated as the number of events per 1000 person-years (PY). The 10-year absolute risks of HF and secondary outcomes other than all-cause mortality according to groups were calculated using the Aalen-Johansen estimator, with death from other causes treated as competing risk. Differences between groups were assessed using the Gray test.[34] The 10-year absolute risks of all-cause mortality according to groups were calculated using the Kaplan-Meier estimator, and differences between groups were assessed using the log-rank test. HRs with 95% CIs were estimated with Cox proportional hazards models conditional on the matching (ie, comparing cases with general population). HRs were adjusted for a history of liver disease and malignancy, as the populations were not matched on these. The assumption of proportional hazards was not fulfilled; therefore, analyses were split into 2 time periods (0–365 days and 366 days to full follow-up). Interactions between GPA and clinically relevant variables, including age and sex, on the rate of outcomes were tested for with the likelihood ratio test. The level of statistical significance was set at 5%. Data management and statistical analyses were performed with SAS (version 9.4, SAS Institute).

Sensitivity analysis. To test the robustness of our findings, we restricted the GPA cohort to patients who had at least 2 in- or outpatient hospital contacts of GPA within 18 months. For patients with GPA, the index date was set at the second diagnosis, while controls from the general population were randomly assigned the same index date as a case from the GPA population. As in the main analysis, each GPA patient was matched with 4 controls from the general population by age, sex, relevant comorbidities, and year of index date using risk-set matching. A comparable definition has previously been validated with a high PPV of 91% in the Danish National Patient Registry.[35] Although the PPV of the GPA diagnosis in the sensitivity analysis may be higher than that of the primary analysis, only 1 in- or outpatient hospital contact of GPA was required in the primary analysis in order to capture CV diagnoses in relation to or within 18 months after the GPA diagnosis.

Ethics and consent. This study was approved by the Capital Region of Denmark (approval number: P-2019-348) in accordance with the General Data Protection Regulation. Registry-based studies in which individuals cannot be identified do not require ethics committee approval in Denmark.

RESULTS

From January 1, 1996, to June 30, 2018, there were 2393 patients diagnosed with GPA in Denmark. After exclusion criteria were applied, 1923 patients were eligible for inclusion in the present study (Supplementary Table 3 for baseline characteristics of excluded patients with GPA, available with the online version of this article). Of these patients, 60.3% were diagnosed in an inpatient setting. Of the 1923 patients eligible for matching, 1781 patients were matched with 7124 subjects from the general population based on age, sex, and comorbidities. Baseline characteristics for the GPA population and general population are summarized in Table 1. The median age of the study population was 59 (IQR 47–70) years, and 47.9% were men. The GPA population was characterized by a lower prevalence of liver disease and history of malignancy compared with the general population.

Incident HF. The median follow-up from the index date until diagnosis of HF, death, emigration, or end of the study period was 6.4 (IQR 2.6–11.5) years for the GPA population and 7.2 (IQR 3.4–12.4) years for the general population. The absolute risk of incident HF according to groups is displayed in Figure 1 and Table 2. During the first 365 days after index, the IR of HF was significantly higher in patients with GPA compared with the general population (IR per 1000 PY 21.93, 95% CI 15.82–30.41 and 6.59, 95% CI 4.94–8.81, respectively; adjusted HR 3.60, 95% CI 2.28–5.67). However, from day 366 until the end of follow-up, the IR of HF was not significantly different in patients with GPA compared with the general population (IR per 1000 PY 6.98, 95% CI 5.61–8.69 and 7.13, 95% CI 6.43–7.91, respectively; adjusted HR 1.11 95% CI 0.85–1.44;

Table 1. Baseline characteristics of the study population.

	General Population, n = 7124	GPA Population, n = 1781	*P*
Demographics			
Age, yrs, median (IQR)	59 (47–70)	59 (47–70)	N/A
Male, n (%)	3412 (47.9)	853 (47.9)	N/A
Comorbidities, n (%)			
Hypertension	1496 (21.0)	374 (21.0)	N/A
Peripheral artery disease	32 (0.5)	8 (0.5)	N/A
Diabetes	368 (5.2)	92 (5.2)	N/A
Malignancy	815 (11.4)	167 (9.4)	0.01
Chronic kidney disease	5928 (83.2)	1482 (83.2)	N/A
Chronic obstructive pulmonary disease	192 (2.7)	48 (2.7)	N/A
Liver disease	269 (3.8)	33 (1.9)	< 0.001
Medical treatment at baseline, n (%)			
Lipid-lowering medication	953 (13.4)	172 (9.7)	< 0.001
Acetylsalicylic acid	582 (8.2)	133 (7.5)	0.33
Beta blockers	773 (10.9)	167 (9.4)	0.07
Calcium channel blockers	1040 (14.6)	229 (12.9)	0.06
RAS inhibitors	1622 (22.8)	348 (19.5)	0.003

N/A indicates not applicable as these were the variables both groups were matched on. GPA: granulomatosis with polyangiitis; RAS: renin-angiotensin system.

Figure 2 and Figure 3). There was no interaction during the first year after GPA diagnosis between GPA and sex (women: HR 4.58, 95% CI 2.32–9.03; men: HR 2.96, 95% CI 1.57–5.56, $P_{interaction}$ = 0.33), as well as GPA and age (age ≥ 59 yrs: HR 3.39, 95% CI 2.04–5.65; age < 59 yrs: HR 5.63, 95% CI 1.83–17.33, $P_{interaction}$ = 0.61) on the rate of HF. After the first year, there was also no interaction between GPA and sex or age on the rate of HF (Supplementary Table 4, available with the online version of this article).

Secondary outcomes. The absolute risks of secondary outcomes are depicted in Table 2, Figures 1B–D, and Supplementary Figure 1A–F (available with the online version of this article). Figure 2 and Figure 3 show unadjusted IRs per 1000 PY and adjusted HRs of outcomes stratified by time period (0–365 days and 366 days to full follow-up). In Cox regression analysis, GPA was associated with a higher rate of all outcomes during the first 365 days after index date, except the composite of pacemaker implantation, atrioventricular block, or sinoatrial dysfunction; MI; and aortic aneurysm/dissection (Figure 2). However, from day 366 until the end of follow-up, GPA was not associated with a significantly increased rate of outcomes, except atrial fibrillation/flutter and all-cause mortality (Figure 3).

Sensitivity analysis. To test the robustness of our findings, the GPA cohort was restricted to 1196 patients who had at least 2 in- or outpatient hospital contacts of GPA within 18 months. Of these, 1121 patients were matched with 4484 patients from the general population based on age, sex, and comorbidities. Supplementary Table 5 (available with the online version of this article) displays adjusted HRs of outcomes in patients with at least 2 diagnosis codes of GPA vs a matched general population. As in the main analysis, the IRs of HF, several other CV outcomes, and mortality were significantly higher in patients with GPA compared with the general population during the first 365 days after index, but not significantly different from day 366 until the end of follow-up.

DISCUSSION

This nationwide cohort study explored the association between new-onset GPA and HF and other adverse CV outcomes compared with a matched cohort from the general population. The main finding was that patients with GPA had increased rates of HF and other adverse CV outcomes, including atrial fibrillation; a composite of ICD implantation, ventricular arrhythmia, or cardiac arrest; ischemic stroke; myocarditis; and pericarditis, within the first year after the diagnosis. However, beyond the first year, patients with GPA had rates of HF and other adverse CV outcomes similar to those of a matched general population, except for atrial fibrillation/flutter.

The prevalence and effect of HF in patients with GPA have been examined in several studies. For example, a retrospective cross-sectional study found an almost 2-fold higher prevalence of HF in more than 100,000 GPA hospitalizations compared with non-GPA hospitalizations.[4] In another observational study, HF was an independent predictor for 30-day readmission among 9749 patients admitted with GPA.[18] However, longitudinal studies investigating the long-term risk of HF in patients with GPA are sparse. In an observational study including 58 patients with newly diagnosed AAV, of whom 23 were diagnosed with GPA, AAV overall was associated with an increased risk of CV diseases, including HF, compared with age- and sex-matched controls during a median follow-up of 6.5 years.[36] To our knowledge, our study is the first to explore the long-term risk of HF in a large nationwide cohort of patients with GPA compared with thoroughly matched controls from the general population. We found that patients with GPA had an almost 4-fold higher associated rate of HF within the first year after diagnosis compared

Table 2. Ten-year absolute risks of cardiovascular outcomes in patients with GPA and a matched general population.

Outcomes	10-year Absolute Risk, % (95% CI)
Heart failure	
GPA population	6.77 (5.50–8.21)
General population	5.91 (5.28–6.59)
Atrial fibrillation or flutter	
GPA population	12.19 (10.47–14.06)
General population	8.20 (7.45–8.99)
ICD, ventricular arrhythmia, or cardiac arrest	
GPA population	1.33 (0.83–2.04)
General population	0.99 (0.74–1.29)
Pacemaker, atrioventricular block, or sinoatrial dysfunction	
GPA population	1.37 (0.83–2.15)
General population	1.68 (1.34–2.09)
Ischemic stroke	
GPA population	5.78 (4.58–7.16)
General population	4.85 (4.28–5.46)
Acute myocardial infarction	
GPA population	3.89 (2.92–5.07)
General population	3.49 (3.01–4.02)
Pericarditis	
GPA population	0.66 (0.35–1.15)
General population	0.37 (0.23–0.58)
Myocarditis	
GPA population	0.38 (0.16–0.80)
General population	0.04 (0.01–0.14)
Aortic aneurysm/dissection	
GPA population	1.00 (0.55–1.68)
General population	0.83 (0.60–1.12)
All–cause mortality	
GPA population	30.95 (28.3–33.54)
General population	24.24 (23.04–25.45)

GPA: granulomatosis with polyangiitis; ICD: implantable cardioverter defibrillator.

with a matched population. However, after the first year, the rate of HF in patients with GPA was similar to that of the matched general population. A similar pattern has also been observed in patients with other inflammatory diseases. For example, a Swedish study from Mantel et al found that new-onset rheumatoid arthritis was associated with an increased short-term risk of HF compared with a matched population, with a less pronounced long-term risk.[37] Taken together, our findings support the notion of an increased surveillance of CV diseases in patients with GPA in the first year after diagnosis. However, further studies are warranted to examine whether GPA is associated with a greater risk of HF within the first year and whether this association is modified by the degree of systemic inflammation and by medical therapy for GPA, including corticosteroids.

What might be the mechanisms behind the increased risk of HF soon after diagnosis in patients with GPA? Although we can only speculate on the association between GPA and HF, there may be several explanations. First, inflammatory processes are thought to be involved in the pathogenesis of HF,[38,39] and severe systemic inflammation may be particularly pronounced soon after diagnosis in patients with GPA. The use of corticosteroids (which is particularly high during initial treatment phases) and disease-modifying drugs may reduce the systemic inflammation, thereby potentially lowering the risk of developing HF in the long term. Second, treatment with corticosteroids has been associated with an increased risk of HF. Although speculative, it is possible that the higher rate of HF within the first year after GPA diagnosis may be caused by the widespread use of corticosteroids.[40] Third, patients could be diagnosed with HF along with the GPA diagnosis or during the first year after diagnosis due to frequent hospital contacts; thus, it is possible that the increased rate of HF during the first year may be at least partly due to detection bias.

In terms of secondary outcomes, a prospective study of 41 patients with GPA showed that abnormalities in both electrocardiograms (such as atrioventricular block and atrial fibrillation) and echocardiograms (including valvular disease and pericardial effusion) were common and observed in up to 46% of the patients.[20] However, longitudinal data on the risk of clinically significant arrhythmias in patients with GPA are lacking. Whereas the rate of the composite of pacemaker implantation, atrioventricular block, or sinoatrial dysfunction was not significantly higher in patients with GPA compared with the general population, we found an increased rate of atrial fibrillation/flutter and the composite of ICD implantation, ventricular arrhythmia, and cardiac arrest in the GPA population within the first year after diagnosis. Interestingly, and unlike the other CV outcomes assessed in this study, the rate of atrial fibrillation/flutter remained increased beyond first year. Possible explanations may not only include inflammation and treatment with corticosteroids[41] but also detection bias, as new-onset arrhythmias, in particular silent atrial fibrillation/flutter, may be detected due to more frequent hospital visits and electrocardiograms in the GPA population.

There is some evidence of an increased risk of MI and ischemic stroke in patients with GPA, although the data are limited and conflicting.[8,9,10] In line with observations made in a French cohort of patients with AAV,[9] our study demonstrated that GPA was associated with an increased rate of ischemic stroke compared with a matched general population, though the increased rate was only present the first year after diagnosis. Interestingly, and in contrast to previous studies,[8,9,10] we did not find GPA to be associated with a significantly higher rate of MI compared with a matched general population. This observation could potentially reflect a decreasing relative risk of MI across recent calendar periods among patients treated for GPA, as also suggested by observations made in other cohort studies,[8,9,13] although not consistently.[10]

Pericarditis has been described as a common cardiac manifestation in GPA.[15] Although we found pericarditis to be more common in patients with GPA within the first year after diagnosis compared with a matched general population, the number of pericarditis cases was low, which may limit the interpretation of this analysis. Moreover, we found that the rates of myocarditis and aortic aneurysm/dissection were not significantly increased in patients with GPA compared with general

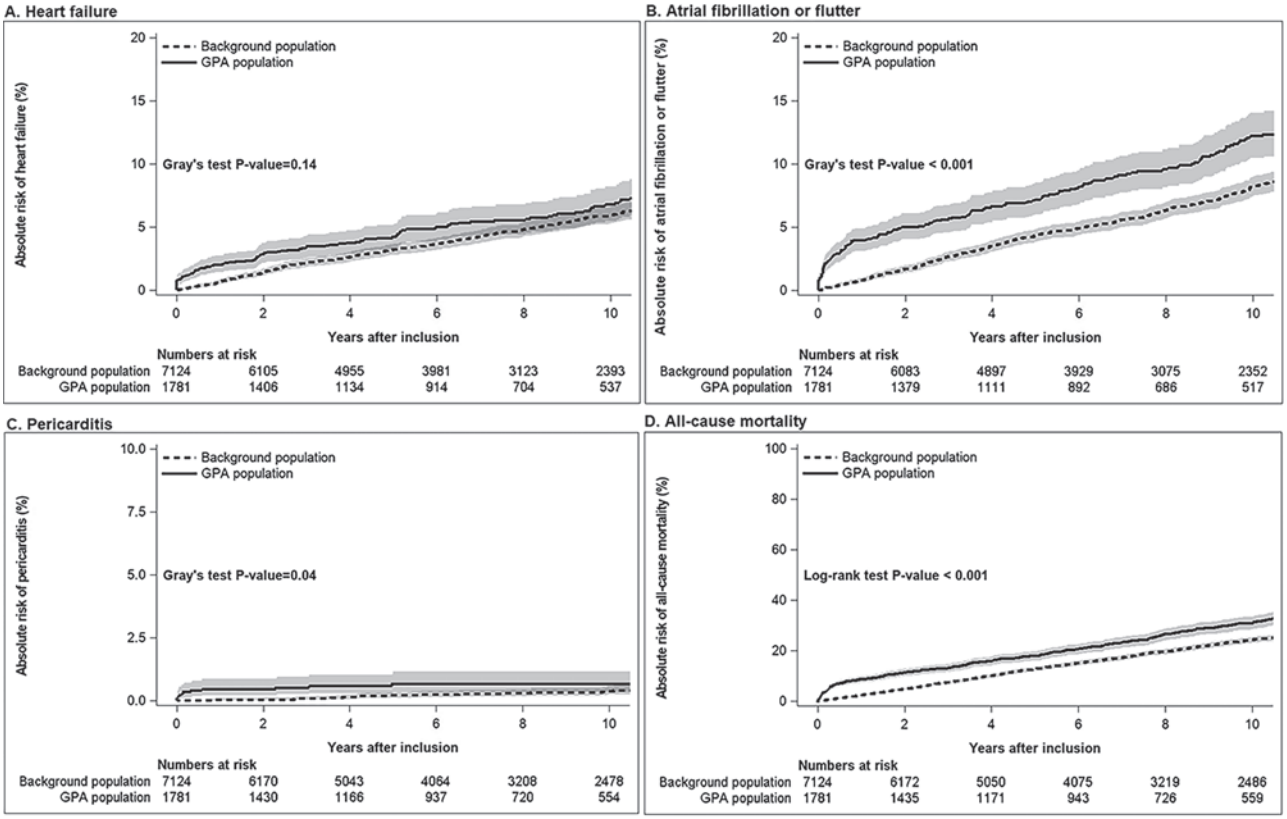

Figure 1. Absolute risks of heart failure and some adverse cardiovascular outcomes in patients with GPA and a matched general population. (A) Heart failure; (B) atrial fibrillation or flutter; (C) pericarditis; and (D) all-cause mortality. GPA: granulomatosis with polyangiitis.

population, although the estimates pointed toward an increased rate within the first year. However, the low number of patients with myocarditis and aortic aneurysm/dissection and a possible underestimation of myocarditis due to subclinical cases limit the interpretation of these analyses. Finally, our study demonstrated that patients with GPA have an increased long-term rate of all-cause mortality compared with general population, particularly within the first year after diagnosis, which is in line with previous studies.[9,16] Although the explanations for this finding are not clear, it is possible that non-CV conditions such as cancer and infections, both of which have been shown to be some of the most common causes of death in this population, may contribute to the observed excess risk in patients with GPA.[42]

The strengths of the present study are the large cohort of patients with GPA, long-term follow-up with no loss to follow-up, and complete data from nationwide registries. Our study has several limitations, which deserve acknowledgment. First, as a registry-based study, we were able to report only associations rather than causal relationships. Despite thorough matching and adjustments, the possibility of residual confounding cannot be excluded. Second, the identification of patients with GPA was based on ICD-8 and ICD-10 codes rather than the verification of individual medical records, and identification of GPA patients with 1 in- or outpatient diagnosis (the primary analysis) has not been validated. However, we performed a sensitivity analysis in which patients were only included if they had at least 2 in- or outpatient hospital contacts with a diagnosis of GPA, and this analysis yielded similar results as the primary analysis. Third, data on important clinical variables, including left ventricular ejection fraction and left ventricular mass obtained from echocardiograms and other imaging modalities (eg, cardiac magnetic resonance imaging and positron emission tomography/computed tomography), natriuretic peptides, smoking, and BMI were not available. Fourth, we found a lower prevalence of liver disease and malignancy in patients with GPA compared with the matched general population, although GPA appears to be associated with a worse liver function and an increased risk of cancer.[43,44] This finding is therefore likely to be a play by chance. It is important to emphasize that although we did not match on liver disease or malignancy, we adjusted for these potential confounders in the Cox regression models.

In conclusion, in a nationwide cohort of patients with new-onset GPA, the rates of HF and other adverse CV outcomes were increased within the first year after diagnosis compared with a matched general population. However, after the first year, patients with GPA had rates of HF and other adverse CV outcomes similar to those of a matched general population, except for atrial fibrillation/flutter. While our findings support the notion of an increased surveillance of CV diseases in patients with GPA in the first year after diagnosis, further studies are warranted to confirm these findings and to assess whether these associations are modified by the degree of systemic inflammation or by medical therapy for GPA, including corticosteroids.

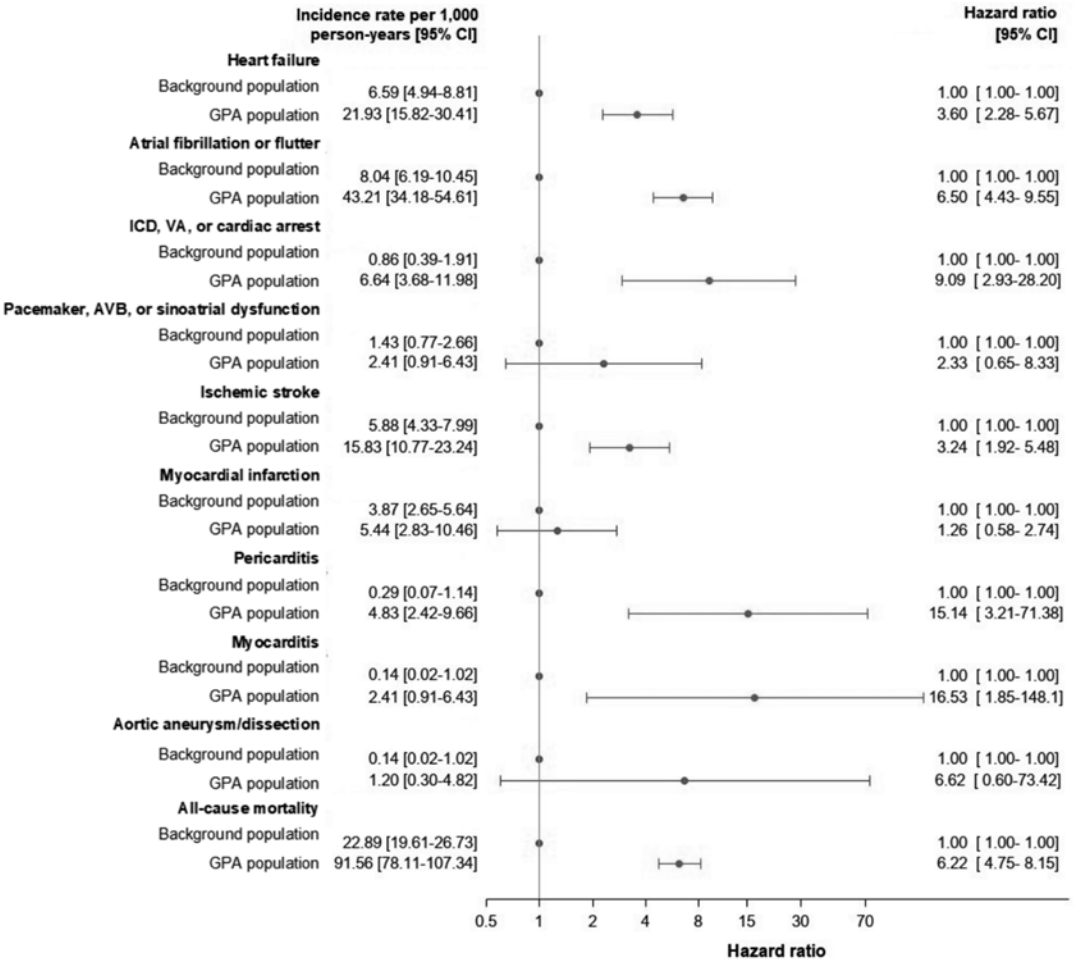

Figure 2. Unadjusted incidence rates and adjusted hazard ratios of outcomes in patients with GPA and a matched general population in the first year. AVB: atrioventricular block; GPA: granulomatosis with polyangiitis; ICD: implantable cardioverter defibrillator; VA: ventricular arrhythmia.

DATA AVAILABILITY STATEMENT

Data for this study are derived from Statistics Denmark. By law, these data are not allowed to be shared. Therefore, data cannot be made available to other researchers.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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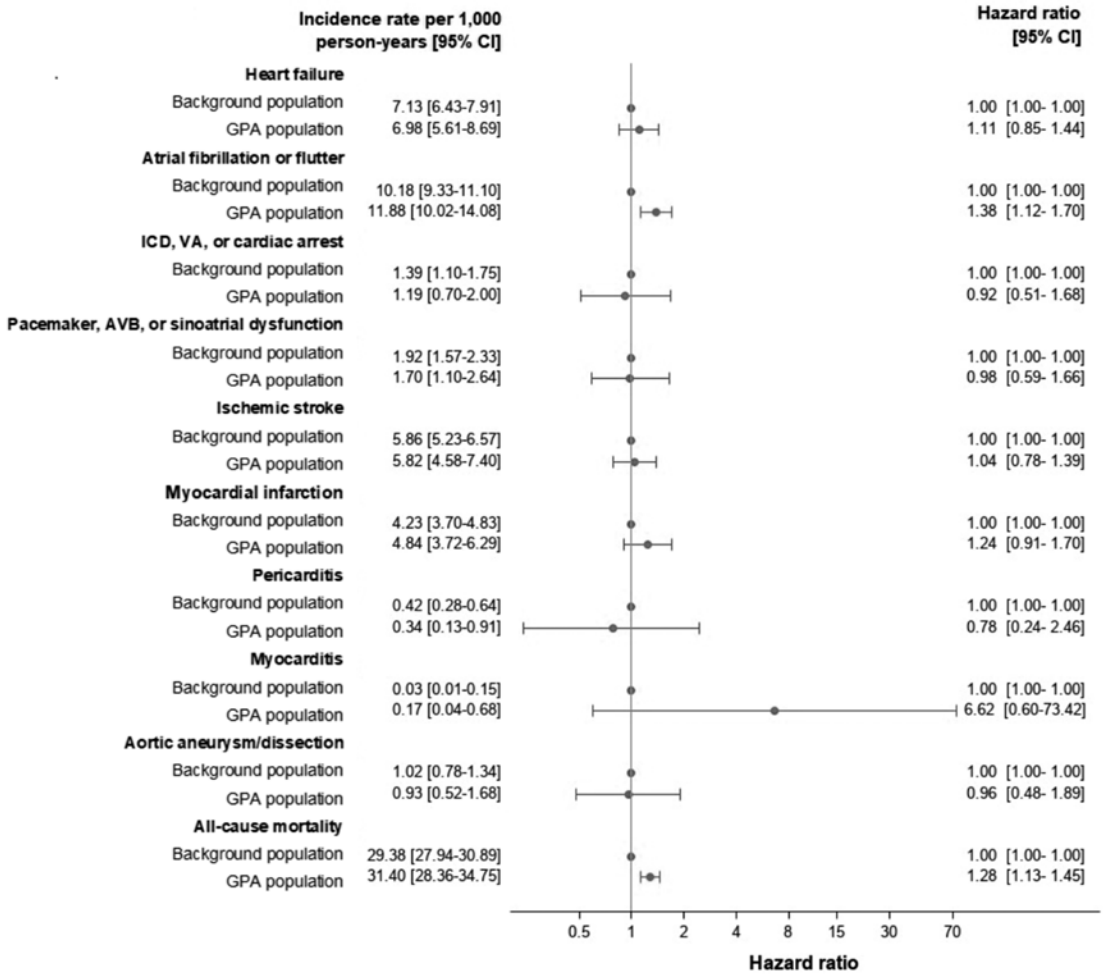

Figure 3. Unadjusted incidence rates and adjusted hazard ratios of outcomes in patients with GPA and a matched general population for 366 days until full follow-up. AVB: atrioventricular block; GPA: granulomatosis with polyangiitis; ICD: implantable cardioverter defibrillator.

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