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ORIGINAL ARTICLE

Association of anti-neutrophil cytoplasmic antibody-associated vasculitis and cardiovascular events: a population-based cohort study

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ABSTRACT

Background. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is implicated in elevating the risk for cardiovascular (CV) disease; whether the elevated risk applies to all types of CV diseases or specific types is unclear. This study examined the association of AAV and adverse CV outcomes compared with the non-AAV population.
Methods. We conducted a population-based, retrospective cohort study of adults (mean age 61 years, 51% female) with a new diagnosis of AAV in Ontario, Canada from 2007 to 2017. Weighted models were used to examine the association of AAV ($n = 1520$) and CV events in a matched (1:4) control cohort ($n = 5834$). The main outcomes were major adverse CV events (MACE), defined as myocardial infarction (MI), stroke or CV death, its components, atrial fibrillation (AF) and congestive heart failure (CHF).
Results. Over a mean follow-up of 3.8 years, AAV (compared with non-AAV) was associated with a higher risk of stroke: cumulative incidence 7.0% versus 5.2%, sub-distribution hazard ratio (sHR) 1.49 [(95% confidence interval (95% CI) 1.10–2.02]; AF: cumulative incidence 16.4% versus 11.5%, sHR 1.51, 95% CI 1.30–1.75; and CHF: cumulative incidence 20.8% versus 13.3%, sHR 1.41, 95% CI 1.22–1.62; but not for MACE, MI or CV death. The risks for all CV events, except CV death, were significantly elevated in the early period after AAV diagnosis, in particular AF (365-day sHR 2.06, 95% CI 1.71–2.48; 90-day sHR 3.33, 95% CI 2.66–4.18) and CHF (365-day sHR 1.75, 95% CI 1.48–2.07; 90-day sHR 2.65, 95% CI 2.15–3.26).
Conclusion. AAV is associated with a high risk of certain types of CV events, particularly in the early period following diagnosis.

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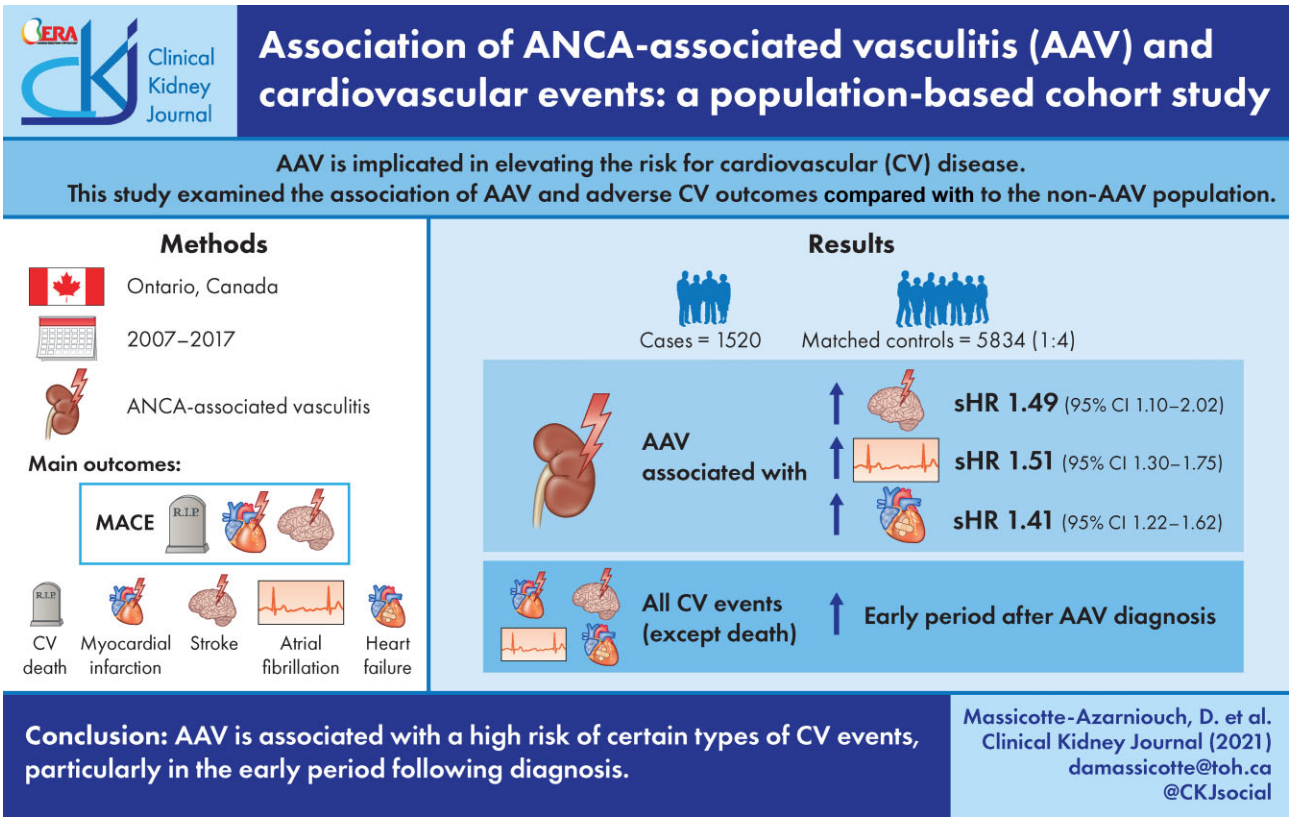
GRAPHICAL ABSTRACT



Keywords: ANCA-associated vasculitis, atrial fibrillation, cardiovascular events, congestive heart failure

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic inflammatory disease causing small vessel inflammation and organ damage [1]. Historically often fatal if untreated, current therapies achieve initial disease control in the majority of cases [2–4]. However, patients with AAV may be at higher risk for chronic diseases due to residual organ damage from AAV or its therapies [5–7]. The degree to which these indirect complications of AAV contribute to excess morbidity and mortality remains uncertain.

Cardiovascular (CV) disease appears to be a major contributor to excess mortality in AAV in the long-term [7, 8]. To better inform risk factor reduction, treatment and future CV trials in AAV, a broader understanding of the distinct types of CV illnesses and their timing of onset in AAV is required.

The objective of this study was to examine the risks for specific types of CV diseases and the periods of heightened risk in patients with AAV. Specifically, we examined the association of AAV with major adverse CV events [MACE; composite of myocardial infarction (MI), stroke/transient ischemic attack (TIA) and CV death], its individual components, atrial fibrillation (AF) and congestive heart failure (CHF), compared with non-AAV patients using population-based administrative healthcare data. We hypothesized that patients with AAV would be at greater risk for CV events compared with those without AAV and that the risk would be highest in the first year following diagnosis when AAV is most active.

MATERIALS AND METHODS

Study design and setting

We conducted a population-based, retrospective cohort study using health administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES), in the province of Ontario, Canada. The use of data in this project was authorized under Section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. The reporting of this study follows guidelines for observational studies [9]. Details of the data sources used for this study are provided in Supplementary data, Table S1.

Population and study cohort

All adults (≥18 years) with a serum creatinine measurement, inpatient or out-patient (closest value to index date, defined below, in the 2 years prior to 30 days after), between 1 January 2007 (date since when serum creatinine has been captured in the Ontario Laboratory Information System) and 31 December 2017 who reside in Ontario, Canada were included. We excluded: (i) age <18 or >95 years at index date; (ii) diagnosis of AAV prior to index

date (see Supplementary data, Table S2); (iii) end-stage kidney disease (ESKD) prior to index date (defined as at least two outpatient claims for dialysis at least 90 days apart) and (iv) kidney transplant prior to index date.

Exposure and control groups

Patients with AAV were defined as any individual with a hospitalization or emergency room visit with a diagnosis of AAV [International Classification of Diseases 10th Revision (ICD10) AAV diagnostic code in any position; see Supplementary data, Table S3]. The ICD10 AAV codes have been shown to have a sensitivity, specificity and positive predictive value (PPV) of 52.6%, 93.1% and 89.0%, respectively [10]. The study index date was defined as the first hospitalization or emergency room visit with an AAV diagnostic code (incident AAV). Individuals with AAV were matched to controls without AAV in a 1:4 ratio based on age (±2 years), sex, estimated glomerular filtration rare (eGFR; ± 5 mL/min by Chronic Kidney Disease Epidemiology Collaboration), income quintile, rurality status and number of hospitalizations in the 3 years prior to index date (exact). The control group index date was obtained by randomly sampling the times from serum creatinine to index date in the AAV group and applying this to serum creatinine measurements in the control group. Censoring occurred at the first study outcome event, death, emigration from province or end of follow-up (end of study period: March 31 2019).

Outcomes

The study outcomes of interest were: MACE (composite of MI, stroke/TIA and CV death), its individual components, AF and CHF. Outcomes were defined by validated ICD discharge codes (see outcomes definitions with validation studies in Supplementary data, Table S4). We also examined all-cause mortality and ESKD as exploratory outcomes.

Baseline characteristics

The following characteristics were ascertained at index date for each study participant: age, sex, rural residence, neighbourhood income quintile, serum creatinine (and eGFR) defined as the closest value to index date in the 2 years prior to 30 days after index date, comorbidities [diabetes, hypertension, CHF, coronary artery disease, coronary artery bypass graft (CABG), AF, arrhythmia, peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), chronic liver disease, osteoarthritis and major cancer], 5-year look back and healthcare utilization [hospital admissions, emergency department (ED) visits, GP visits, nephrologist visits, rheumatologist visits, cardiologist visits] and 1-year look back.

Statistical analysis

Since individuals with AAV differ significantly from those without AAV, we undertook measures to reduce residual confounding. Along with greedy matching AAV in a 1:4 ratio with controls as detailed above, we used overlap propensity score (PS) weighting to create balance between the analytical study groups (AAV versus controls). A PS for AAV exposure was calculated followed by overlap-weighted analyses. Overlap weighting assigns each individual a weight of 1 – PS if they are exposed (AAV) and PS if they are unexposed (controls). In estimating hazard ratios, overlap weights assign less weight to observations with extreme propensity scores and more weight to those with propensity scores close to 0.5 (see Supplementary data, Figure S1). This method creates a balanced cohort in terms of the baseline variables included to calculate the propensity score and does

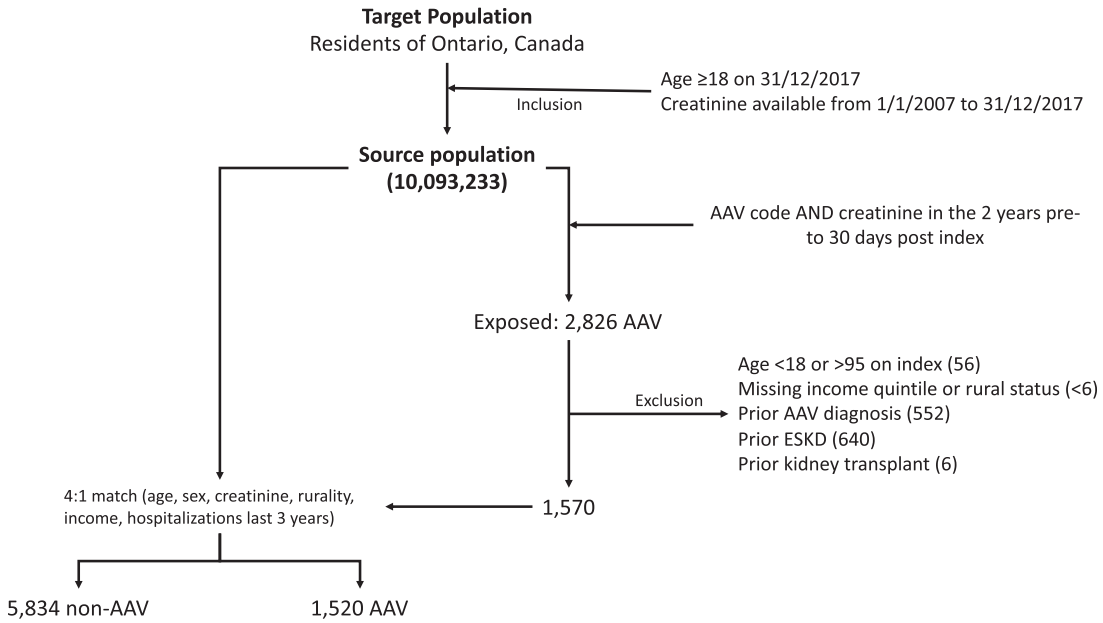


FIGURE 1: Study flow chart. Flow chart of cohort creation for the study project, with inclusion and exclusion criteria, from target population, to source population and then exposure and control group populations.

Table 1. Baseline characteristics of the study cohort

Variable	Controls ($n = 5834$)[a]	AAV ($n = 1520$)	Standardized difference (pre-weighting)[b]	Standardized difference (weighted)
Age at index date, mean (SD)	61.1 (17.3)	60.8 (17.4)	0.01928	0.000010
Female, %	50.5	50.5	0.00093	0.000000
Baseline eGFR, mean (SD)	62.9 (34.4)	61.7 (34.9)	0.03357	0.000017
eGFR at baseline <15, %	7.7	9.1	0.04925	0.000011
eGFR at baseline 15–29, %	16.3	16.3	0.00179	0.000010
eGFR at baseline 30–59, %	23.9	24.1	0.00586	0.000003
eGFR at baseline 60–89, %	24.2	23.3	0.02227	0.000010
eGFR at baseline ≥90, %	27.9	27.2	0.01644	0.000009
Income quintile 1, %	20.7	20.8	0.00205	0.000005
Income quintile 2, %	18.9	18.8	0.00144	0.000001
Income quintile 3, %	19.9	19.7	0.00490	0.000001
Income quintile 4, %	22.0	22.2	0.00349	0.000001
Income quintile 5, %	18.5	18.6	0.00060	0.000004
Rural living, %	12.0	12.7	0.02071	0.000003
Index date fiscal year 2006, %	0	< 0.4	0.03629	0.032452
Index date fiscal year 2007, %	1.4	1.1	0.03204	0.070778
Index date fiscal year 2008, %	4.3	4.1	0.01115	0.043811
Index date fiscal year 2009, %	7.0	7.5	0.02021	0.036131
Index date fiscal year 2010, %	7.2	7.8	0.02343	0.003075
Index date fiscal year 2011, %	6.8	9.0	0.08257	0.070839
Index date fiscal year 2012, %	8.1	10.2	0.07314	0.056 474
Index date fiscal year 2013, %	9.7	10.4	0.02363	0.028 870
Index date fiscal year 2014, %	12.0	12.8	0.02374	0.048566
Index date fiscal year 2015, %	14.0	12.2	0.05437	0.045784
Index date fiscal year 2016, %	15.6	12.9	0.07693	0.035369
Index date fiscal year 2017, %	14.0	12.1	0.05737	0.015663
Hospitalizations in year prior to baseline, mean (SD)	1.2 (1.4)	1.8 (1.4)	0.41933	0.000043
ED visits in year prior to baseline, mean (SD)	1.5 (2.4)	2.9 (3.3)	0.48539	0.000045
Visits to cardiologist in year prior to baseline, mean (SD)	2.0 (4.2)	2.3 (4.1)	0.07048	0.000021
Visits to nephrologist in year prior to baseline, mean (SD)	0.9 (2.7)	1.6 (4.1)	0.21164	0.000014
Visits to rheumatologist in year prior to baseline, mean (SD)	0.2 (1.4)	1.3 (3.1)	0.46540	0.000012
Diabetes mellitus, %	35.3	30.2	0.10946	0.000009
Hypertension, %	60.3	57.9	0.04897	0.000012
Ischemic stroke, %	3.4	3.4	0.00039	0.000007
Myocardial infarction, %	6.8	5.3	0.06343	0.000009
Arrhythmia, %	14.0	15.9	0.05327	0.000017
Atrial fibrillation, %	9.8	11.0	0.04047	0.000014
Congestive heart failure, %	17.9	19.5	0.03961	0.000018
Coronary artery disease, %	24.4	21.5	0.06889	0.000010
CABG, %	2.0	1.1	0.07158	0.000001
PVD, %	2.2	1.3	0.06577	0.000004
COPD, %	8.2	12.0	0.12579	0.000015
Major cancer, %	17.5	19.1	0.04128	0.000010
Chronic liver disease, %	8.5	9.1	0.02451	0.000007
Osteoarthritis, %	7.9	5.8	0.08246	0.000003

[a]Matched 4:1 to patients with AAV on age, sex, serum creatinine, income quintiles, rurality status and number of hospitalizations in the 3 years prior to index date.
[b]SD >0.1 were considered significant.

not exclude any potential study participants nor is it affected by extreme outliers over-dominating the analysis as can happen with inverse probability treatment weighting [11–13].

Baseline characteristics were examined pre- and post-weighting to assess for imbalance using standardized differences. Standardized differences describe differences between group means or proportions relative to the pooled standard deviation (SD) and are less sensitive to large sample sizes than traditional hypothesis testing [14]. A potentially important difference is considered to be 0.10 or greater [15]. We calculated the crude counts, cumulative incidence and incidence rates (IR) for outcomes. We used Fine and Gray models, which account for informative censoring and the competing risk of non-CV death [16, 17], to calculate sub-distribution hazard ratios (sHR), after overlap weighting, for all outcomes other than all-cause mortality where Cox proportional hazards models were used. The 95% confidence intervals (CIs) were estimated using bootstrapping to account for variability in the propensity scores used for weighting [18]. To examine if the CV risk differs in the early period after AAV diagnosis, as suggested by prior studies [19, 20], we also limited follow-up to 365 days after index date. After seeing a very early separation in cumulative incidence curves for most CV outcomes, we decided to also examine results limited to 90-day follow-up, since this is when AAV tends to be most

Table 2. Event counts and cumulative incidence for CV events at full study, 365-day and 90-day follow-up for AAV ($n = 1520$) compared with controls ($n = 5834$)

	Follow-up	Group	Events	Cumulative incidence (%)	Crude IR (per 1000 person-years)
MACE	Full study	Controls	642	15.1	30.72
		AAV	192	15.4	32.13
	365-day	Controls	326	5.6	63.25
		AAV	126	8.3	96.98
	90-day	Controls	162	2.8	119.81
		AAV	89	5.9	260.68
MI	Full study	Controls	234	5.8	11.00
		AAV	77	6.6	12.54
	365-day	Controls	115	2.0	22.18
		AAV	54	3.6	40.71
	90-day	Controls	53	0.9	39.08
		AAV	42	2.8	120.67
Stroke/TIA	Full study	Controls	205	5.2	9.66
		AAV	85	7.0	13.81
	365-day	Controls	85	1.5	16.36
		AAV	47	3.1	35.35
	90-day	Controls	37	0.6	27.23
		AAV	37	2.4	106.27
CV death	Full study	Controls	285	6.2	13.20
		AAV	54	4.1	8.53
	365-day	Controls	158	2.7	30.21
		AAV	34	2.2	25.06
	90-day	Controls	85	1.5	62.36
		AAV	17	1.1	47.90
AF	Full study	Controls	460	11.5	21.95
		AAV	205	16.4	34.87
	365-day	Controls	236	4.1	46.02
		AAV	148	9.8	117.21
	90-day	Controls	131	2.2	97.37
		AAV	124	8.2	373.32
CHF	Full study	Controls	598	13.3	28.57
		AAV	240	20.8	40.94
	365-day	Controls	350	6.0	68.54
		AAV	177	11.7	141.05
	90-day	Controls	170	2.9	126.52
		AAV	143	9.4	435.15

active. All analyses were conducted with SAS Enterprise Guide 7.15 (SAS Institute Inc., Cary, NC, USA). Confidence intervals that did not overlap with 1 or $P \leq 0.05$ was considered statistically significant.

Additional analyses

We performed the following additional analyses. Firstly, we examined a more rigorous diagnosis of AAV defined as any hospitalization or ED visit with a diagnosis of AAV or nephritis (ICD10 code in any position; see Supplementary data, Table S3) and a positive ANCA serology (defined as a value above the manufacturer recommended reference range for the test used) within 365 days before or after the ICD10 diagnosis date. The addition of a positive ANCA serological test to an ICD diagnostic code has been shown to improve the accuracy for identifying AAV compared with only using ICD codes [10, 21]. This 'serological' AAV cohort was similarly 1:4 matched to controls and we analyzed the IRs for outcomes. Secondly, we repeated our analyses after excluding any outcomes occurring during the index hospitalization.

RESULTS

Study cohort and baseline characteristics

The study population consisted of 1520 patients with AAV and 5834 matched controls (Figure 1). For the study population, the mean duration of follow-up was 1387 days, mean age was 61 years, 51% were female, mean eGFR was 63 mL/min, 34% had a previous diagnosis of diabetes and 60% had a previous diagnosis of hypertension (Table 1). Overlap propensity score weighting led to no significant imbalances between AAV and non-AAV groups except for index year (see Table 1 and Supplementary data, Figure S1).

CV risk in AAV

The mean (SD) days of follow-up for the full study period was 1522 (1084) in AAV and 1352 (996) in non-AAV. The cumulative incidence for CV outcomes in AAV was 15.4% for MACE, 6.6% for MI, 7.0% for stroke/TIA, 4.1% for CV death, 16.4% for AF and 20.8% for CHF (Table 2). Individuals with AAV were found to be at significantly higher risk (sHR, 95% CI) for stroke/TIA (1.49,

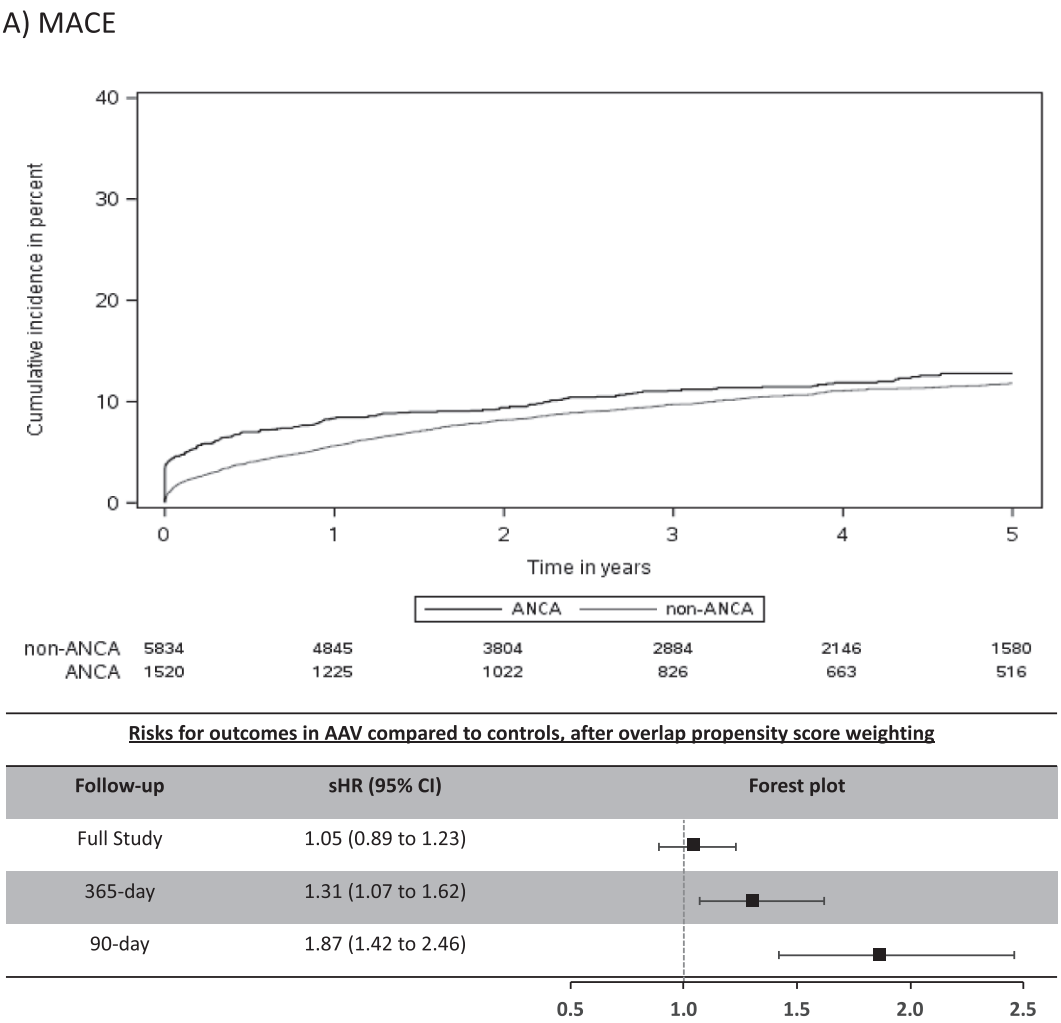


FIGURE 2: Cumulative incidence function curves and forest plots with adjusted risks for outcomes. Cumulative incidence curves for each CV outcome by AAV status, along with forest plots of the sHR or outcomes in AAV group for 90-day, 365-day and full-study follow-up time. The sHR are adjusted for index year due to imbalances in this baseline characteristics between the two groups despite overlap propensity weighting. (**A**) MACE; (**B**) MI; (**C**) stroke/TIA; (**D**) CV death; (**E**) AF; (**F**) CHF.

1.10–2.02), AF (1.51, 1.30–1.75) and CHF (1.41, 1.22–1.62), whereas there was no significantly increased risk for MACE, MI or CV death (Figure 2).

Early risk period after AAV diagnosis

Most CV events occurred in the early period after AAV diagnosis (Table 2) and this was a period of heightened risk. In the first 365 days after diagnosis, AAV was associated with an increased risk (sHR, 95% CI) for MACE (1.31, 1.07–1.62), MI (1.52, 1.10–2.10), stroke/TIA (1.87, 1.25–2.80), AF (2.06, 1.71–2.48) and CHF (1.75, 1.48–2.07), but not for CV death (Figure 2). CV risks were predominantly elevated in the first 90 days of diagnosis of AAV, particularly for AF and CHF, where the sHR (95% CI) was 3.33 (2.66–4.18) for AF and 2.65 (2.15–3.26) for CHF (Table 2 and Figure 2).

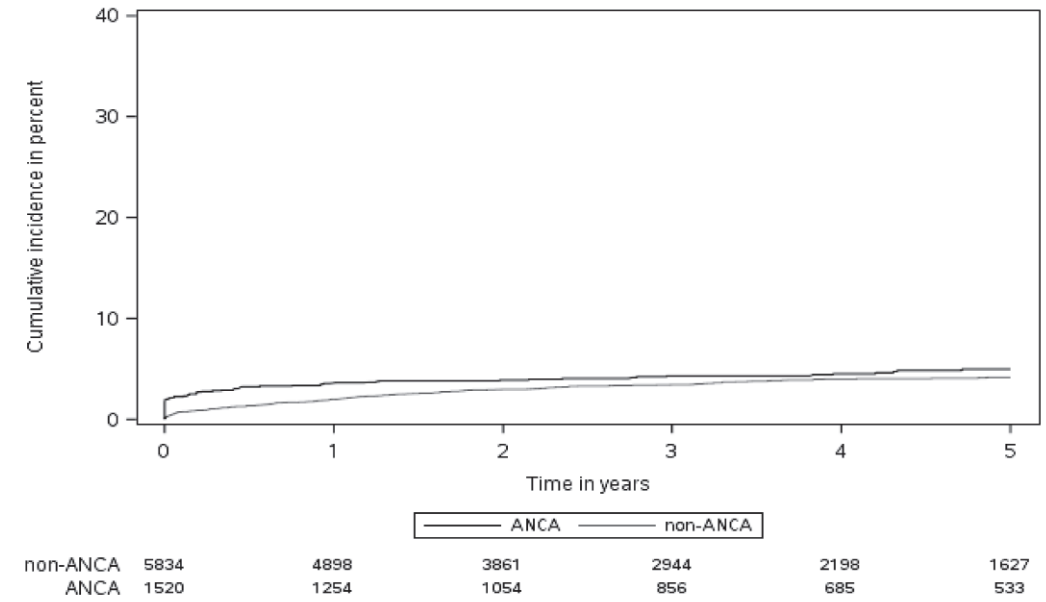
All-cause mortality and ESKD in AAV

The cumulative incidences and IRs for all-cause mortality and ESKD were similar between AAV patients and controls. AAV was associated with a lower all-cause mortality throughout the full study follow-up (HR 0.82, 95% CI 0.74–0.90), in the first 365 days (HR 0.82, 95% CI 0.71–0.95) and in the first 90 days (HR 0.82, 95% CI 0.66–1.01) after AAV diagnosis. The risks for ESKD were not significantly different between AAV patients and controls regardless of follow-up time (Supplementary data, Table S5).

Additional analysis

Using our more stringent AAV diagnosis definition incorporating a positive ANCA serology ($n = 89$; Supplementary data, Figure S2), individuals with AAV demonstrated similarly elevated rates for CV events in the period after AAV diagnosis as was seen in the original analysis (Supplementary data, Table S6 and Figure S3). After excluding events captured during the index hospitalization of AAV diagnosis, the risks for each outcome attenuated, but remained elevated for AF and CHF (Supplementary data, Table S7).

B) MI



Risks for outcomes in AAV compared to controls, after overlap propensity score weighting

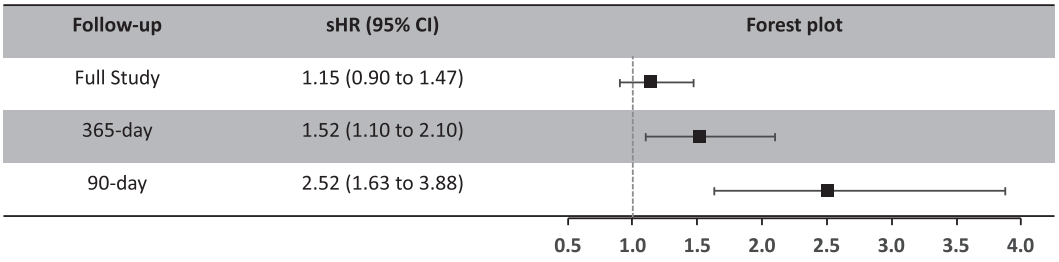


FIGURE 2: (Continued)

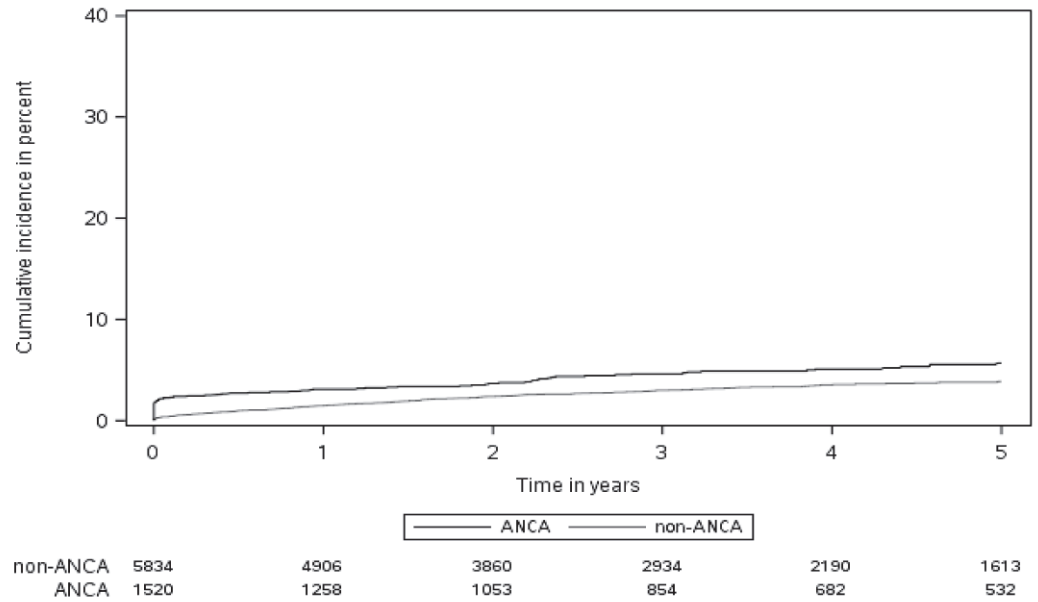
DISCUSSION

In this population-based, cohort study of 1520 individuals with incident AAV diagnosed during a hospital encounter and followed for a mean duration of 3.8 years, we found similar rates of MACE and MI, but higher rates of stroke/TIA (1.5-fold risk), AF (1.5-fold risk) and CHF (1.4-fold risk) in those with AAV compared with controls matched on important prognostic variables. The majority of excess risk occurred immediately after the diagnosis of AAV, particularly for AF and CHF. At 90 days a 3.3-fold risk for AF and 2.7-fold risk for CHF were observed for individuals with AAV and by 1-year these attenuated to a 2.1-fold and 1.8-fold risk for AF and CHF, respectively. Our study reveals important, under-recognized adverse CV outcomes associated with AAV and identifies a key period of heightened risk.

Our findings are consistent with and expand on previous studies examining CV risks in AAV, underscoring the high-risk nature of this population for adverse CV outcomes. Long-term follow-up of clinical trials in AAV demonstrated CV disease as a major contributor to mortality after 1 year [7]. We found that individuals with AAV have high rates of CV events immediately after the diagnosis of AAV, comparable to previous observational studies [19, 20, 22–24]. Furthermore, our finding of a cumulative incidence of 15.4% for MACE over approximately 4 years identifies individuals with AAV as being high-risk for CV events [25, 26], and they appear to be at an especially high risk for AF and CHF. A case-control study recently reported 2.9-fold odds for AF with small-vessel vasculitis [27]. Berti *et al.* reported 10-year cumulative incidences for AF and CHF of 14.4% and 20.0%, respectively [24]. Both of these studies were small cohorts with few events and the case-control study included other types of vasculitis. Our findings in 1520 individuals with AAV capturing over 200 events each of AF and CHF are consistent with the previous smaller studies and demonstrate high rates of AF and CHF, particularly in the period immediately following AAV diagnosis. Monitoring, heightened awareness and multi-disciplinary care could improve morbidity related to these under-recognized problems.

We found that individuals with AAV were at significantly higher risk for CV events compared with matched controls. Retrospective cohort studies found that AAV was associated with 1.5 to 3-fold greater risk for ischemic heart disease, MI and stroke, and that this was greatest in the first year after diagnosis, similar to our study [19, 20, 22–24]. Moreover, we

C) Stroke/TIA



Risks for outcomes in AAV compared to controls, after overlap propensity score weighting

Follow-up	sHR (95% CI)	Forest plot
Full Study	1.49 (1.10 to 2.02)	
365-day	1.87 (1.25 to 2.80)	
90-day	2.92 (1.76 to 4.85)	

FIGURE 2: (Continued)

demonstrated the first 3 months after onset of AAV as the most crucial period when individuals with AAV are at greatest risk for CV events. Although many CV events seemed to occur at time of AAV diagnosis, risk of AF and CHF remained elevated after excluding events occurring during the index AAV hospitalization. When an individual is diagnosed with AAV, this has likely been active for weeks to months prior to diagnosis, therefore it is likely that CV events diagnosed during the index hospitalization are a consequence of active vasculitis. That being said, the increased risk for AF and CHF even after excluding such events strengthens our study findings in regard to AF and CHF. To our knowledge, prior studies on CV risks in AAV did not address this issue.

There are multiple potential mechanisms for CVD in patients with AAV. First, glucocorticoids, a mainstay of treatment of AAV, are known to cause dyslipidemia and hypertension and are associated with coronary artery disease in patients with systemic inflammatory conditions [28–30]. Second, a systemic inflammatory response in of itself is thought to be a risk factor for CV disease, possibly mediated by inflammatory cytokines [31–33]. Third, in regard to stroke/TIA, the heightened early risk for AF may indicate cardioembolism as a culprit. Fourth, being a disease of small vessels, AAV causes direct endothelial damage that may promote diffuse atherosclerosis and vascular stiffening [34–37]. Such changes could directly affect coronary vessels and lead to increased strain on cardiac myocytes, predisposing to MI, AF and CHF. Interestingly, it has been suggested that endothelial damage may be reversible with suppression of inflammation in AAV [37]. Also, AAV often causes glomerulonephritis, manifesting with acute kidney injury and hypertension, both risk factors for CV events including AF and CHF [38–42]. Taken together, these hypotheses could explain why the highest risks for CV events occur in the early period following diagnosis, when organ involvement, systemic inflammation and doses of corticosteroids are at their highest.

Our study has limitations. First, since we defined AAV patients based on hospital ICD discharge codes, our findings may not be generalizable to individuals with less severe disease diagnosed in the outpatient setting. Second, as an observational study using administrative data, it has limitations inherent to the study design such as misclassification and unmeasured confounding (for example, we lacked certain clinical parameters such as the type of AAV organ involvement, or the types and

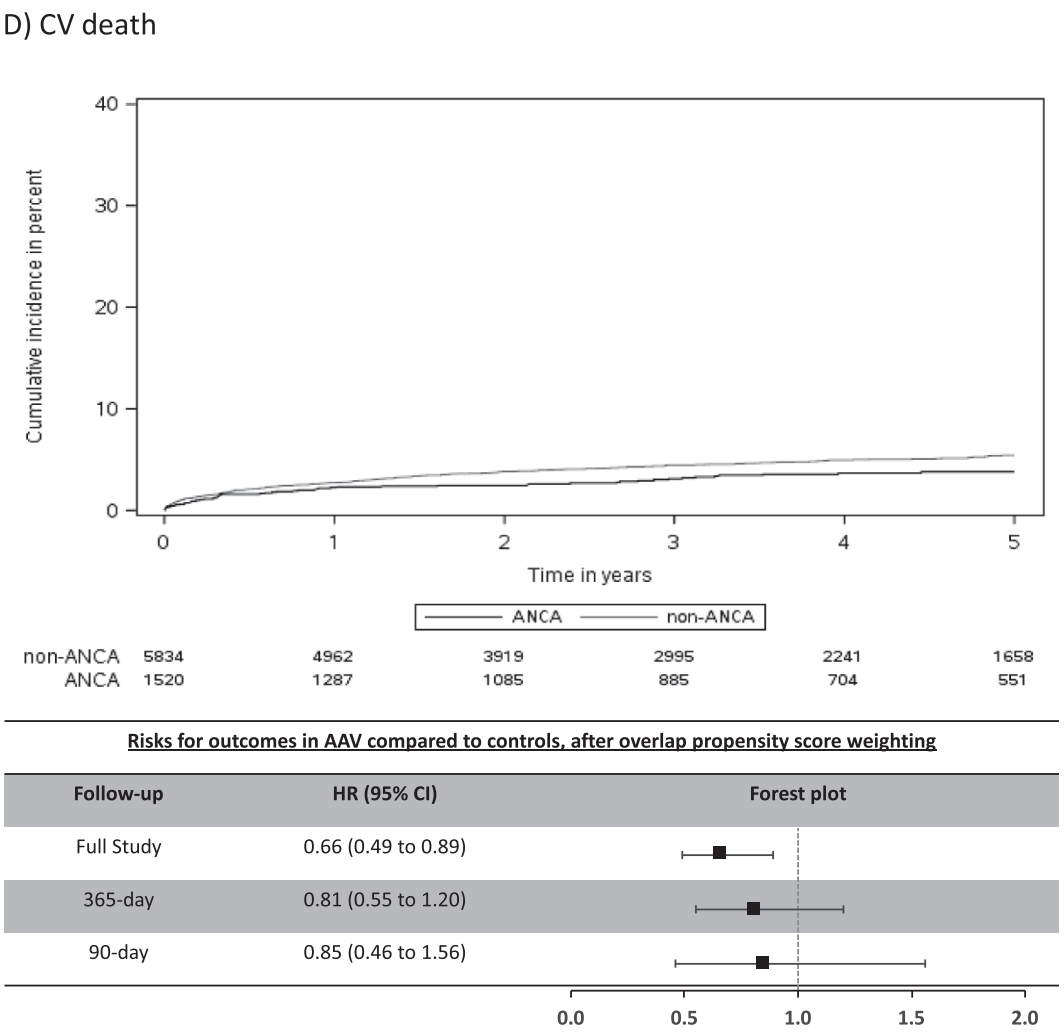


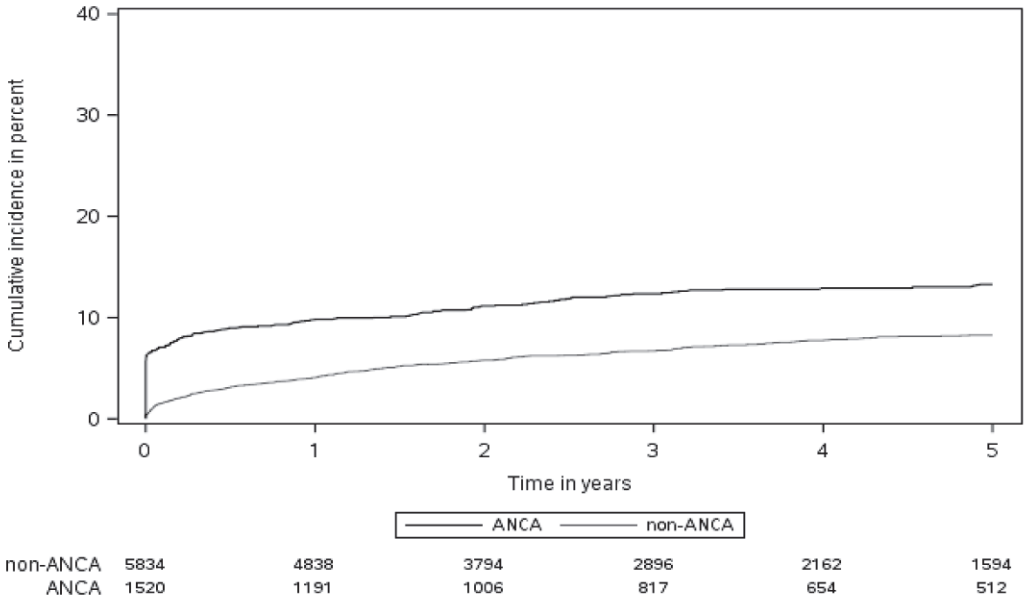
FIGURE 2: (Continued)

doses of medications used for treatment). That being said, we used validated definitions for exposure and outcomes and the ICD10 AAV codes have a high specificity. Also, we undertook a number of measures to limit confounding including hard matching on a number of important risk factors for CVD, such as kidney function and the use of overlap propensity score weighting, a fairly new but recognized and valid method, to create near perfect balance in our analytical groups with regard to baseline characteristics [11–13, 43]. Third, since AAV is a treatable condition where the patient's clinical condition, including acute kidney injury, may improve with treatment, the controls matched on eGFR at time of AAV diagnosis may be at inherently greater risk for adverse outcomes since their kidney function would not be expected to improve. This could explain the unexpected lack of increased ESKD and lower all-cause and CV mortality in AAV. On the other hand, this means we had an appropriate high-risk control group whereby we were able to dampen the confounding effect from impaired kidney function, a major risk factor for CV disease. Finally, since AAV was diagnosed in hospital, there may be detection bias since an acutely ill individual with AAV is more likely to get diagnosed with a CV event than someone without AAV. We performed sensitivity analyses excluding events occurring on index hospitalization, thereby limiting detection bias, however we could not account for the more frequent follow-up afforded to individuals with new onset AAV and therefore cannot rule out the presence of detection bias.

CONCLUSION

In conclusion, individuals with incident AAV are at high risk for adverse CV events, in particular AF and CHF. These risks are highest in the immediate 3 months and 1 year following diagnosis. Our study demonstrates a key 'high-risk window' that should prompt careful monitoring for CV disease and aggressive risk factor reduction. Future prospective studies targeting the prevention of CV events in AAV may be warranted. This study highlights the complexity of caring for patients with AAV and additional benefits that may be derived from focused, multidisciplinary care in specialty clinics.

E) AF



Risks for outcomes in AAV compared to controls, after overlap propensity score weighting

Follow-up	sHR (95% CI)	Forest plot
Full Study	1.51 (1.30 to 1.75)	
365-day	2.06 (1.71 to 2.48)	
90-day	3.33 (2.66 to 4.18)	

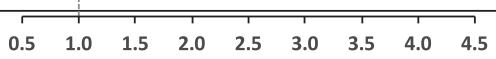


FIGURE 2: (Continued)

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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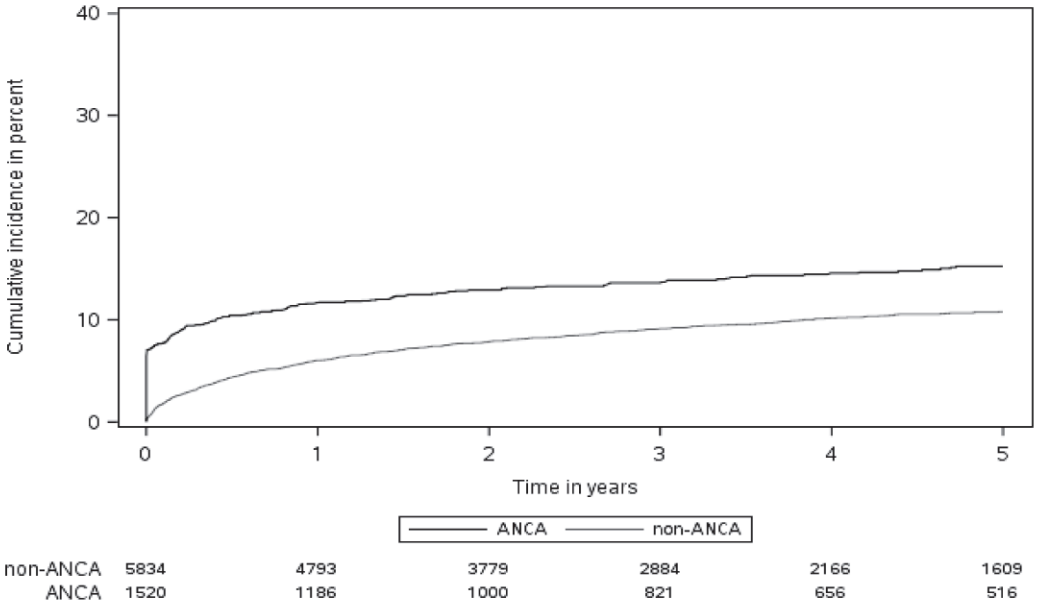
AUTHORS' CONTRIBUTIONS

D.M.-A., M.W. and M.M.S. came up with the study design. W.P. was responsible for conceiving and carrying out the statistical analysis. D.M.-A. and M.M.S. were responsible for the analysis and interpretation of the data. D.M.-A. and M.M.S. drafted the first manuscript. All co-authors provided revisions for the manuscript. Each author contributed important intellectual content and approved the final manuscript version.

F) CHF



Risks for outcomes in AAV compared to controls, after overlap propensity score weighting

Follow-up	sHR (95% CI)	Forest plot
Full Study	1.41 (1.22 to 1.62)	
365-day	1.75 (1.48 to 2.07)	
90-day	2.65 (2.15 to 3.26)	

FIGURE 2: (Continued)

CONFLICT OF INTEREST STATEMENT

M.M.S. received a speaker fee from AstraZeneca. All other authors have nothing to declare.

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