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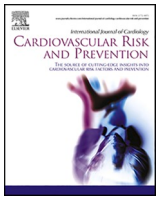

Assessment of cardiovascular risk in patients with ANCA-associated vasculitis: A systematic review and meta-analysis

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ABSTRACT

Background: Although many chronic inflammatory conditions are linked to elevated cardiovascular risk, the specific extent of this risk in ANCA-associated vasculitis (AAV) remains elusive, largely due to the disease's rarity. Our study sought to clarify the cardiovascular risks and mortality linked to AAV.

Methods: A systematic literature review was conducted across multiple databases from their inception until April 2024 to identify studies comparing cardiovascular outcomes in patients with and without AAV. R Studio's meta package was used to pool risk ratios under the random-effects model, and statistical significance was set at $p < 0.05$.

Results: Nine observational studies involving 45024 individuals were included in this analysis. Patients with AAV exhibited a significantly elevated risk of stroke (RR = 1.43, 95 % CI: 1.12–1.83, I2 = 62 %, p = 0.0048), myocardial infarction (RR = 1.49, 95 % CI: 1.25–1.79, $I^2 = 0$ %, $p < 0.0001$), ischemic heart disease (RR = 1.40, 95 % CI: 1.24–1.58, $I^2 = 1$ %, $p < 0.0001$), venous thromboembolism (RR = 2.57, 95 % CI: 1.70–3.90, $I^2 = 74$ %, $p < 0.0001$), and pulmonary embolism (RR = 3.53, 95 % CI: 2.82–4.42, $I^2 = 9$ %, $p < 0.0001$), deep vein thrombosis (RR: 4.21; 95 % CI: 2.00–8.86; p = 0.0002), heart failure (RR = 1.63, 95 % CI: 1.39–1.90, $I^2 = 0$ %, $p < 0.0001$), and cardiovascular disease-related mortality (RR = 1.79, 95 % CI: 1.07–3.00, I2 = 0 %, p = 0.0256) compared to patients without AAV.

Conclusion: This meta-analysis underscores a notable increase in adverse cardiovascular events among patients with AAV, underscoring the need for comprehensive cardiovascular care and diligent monitoring in this patient cohort.

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) encompasses a group of autoimmune conditions characterized by inflammation of small to medium-sized blood vessels. It includes three major subtypes: eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), and granulomatosis with polyangiitis (GPA) [1]. AAV is relatively rare, with an estimated prevalence of 200–400 cases per million people and an annual incidence of 15–20 cases per million [2]. Although AAV can occur at any age, it predominantly affects adults aged 65–74 years [3]. A recent meta-analysis revealed that cardiovascular events occur 65 % more frequently in patients with AAV than in the general population, although the study reported only a limited number of endpoints [4]. The exact risk of cardiovascular events in AAV remains inadequately defined in the literature, which was the aim of our study.

Although the lungs and kidneys are frequently affected, the clinical

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Abbreviations

Antineutrophilic cytoplasmic antibody (ANCA)
ANCA-associated vasculitis (AAV)
Eosinophilic granulomatosis with polyangiitis (EGPA)
Microscopic polyangiitis (MPA)
Granulomatosis with polyangiitis (GPA)
European Alliance of Associations for Rheumatology (EULAR)
Myocardial infarction (MI)
Ischemic heart disease (IHD)
Venous thromboembolism (VTE)
Pulmonary embolism (PE)
Deep vein thrombosis (DVT)
Heart failure (HF)
Birmingham vasculitis activity score (BVAS)
Myeloperoxidase (MPO)
Cardiovascular disease (CVD)

manifestations of ANCA-AAV are primarily dictated by the specific vascular bed involved [5]. AAV can affect multiple organs, including the cardiovascular system, depending on its severity and extent. Cardiovascular complications, such as coronary artery disease and stroke, represent a significant source of morbidity and mortality in patients with AAV [6–8]. Additionally, patients with AAV have an elevated risk of venous thromboembolic events, with approximately 10 % of the patients experiencing such events [9]. The proposed mechanisms for cardiovascular and thromboembolic complications include inflammation and ANCAs, which promote leukocyte adhesion, recruit neutrophils, and trigger extracellular trap formation, leading to tissue damage [10]. Recent studies have also highlighted that patients with AAV often develop cardiovascular risk factors owing to immunosuppressive therapy, as well as an increased risk of infections and malignancies [7].

Consequently, the latest guidelines from the European Alliance of Associations for Rheumatology (EULAR) emphasize the importance of thoroughly evaluating cardiovascular risk factors as a crucial aspect of managing patients with AAV [11]. Studies indicate that the prevalence of cardiovascular complications in these patients has been underestimated, underscoring the need for additional diagnostic methods such as electrocardiograms and echocardiograms, particularly for those at higher risk [12]. Regular comprehensive assessments of cardiovascular risk factors, recommended at intervals such as every six months, should be combined with appropriate management of hypercholesterolemia, hypertension, and diabetes mellitus to achieve the target outcomes [7]. This systematic review and meta-analysis aimed to quantify the cardiovascular risk associated with AAV by consolidating evidence from recent observational studies with the goal of identifying potential knowledge gaps.

2. Materials and methods

The meta-analysis was conducted following the recommended procedures outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis Statement (PRISMA 2020) guidelines [13]. The study protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42024538300).

2.1. Data sources and search strategy

We conducted an extensive electronic search across multiple databases, including PubMed, EMBASE, Google Scholar, SCOPUS, and Web of Science, from their inception to April 2024. The objective of this study was to identify all relevant observational studies concerning the risk of adverse cardiovascular events in patients diagnosed with AAV. We did not impose any language or timeframe restrictions during the search.

For our search strategy, we employed predefined Medical Subject Headings (MeSH) terms and keywords, such as "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis," "ANCA-Associated Vasculitis," "Granulomatosis with Polyangiitis," "Wegener Granulomatosis," "Wegener's Granulomatosis," "Churg Strauss Syndrome," "Eosinophilic Granulomatosis with Polyangiitis," "Microscopic Polyangiitis," "survival," "mortality," "cardiovascular outcome," "MACE," "major adverse cardiovascular event," "Myocardial infarction," "heart attack," "Stroke" "cerebrovascular accident," "Heart failure," "Arrhythmia," "Sudden cardiac death," and "Cardiac arrest" in different combinations using Boolean operators 'AND' and 'OR' to enhance search precision. A comprehensive search strategy is provided in the Supplementary File. In addition, we manually searched the reference lists to retrieve articles that were missed during the initial search.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

The inclusion criteria were determined in accordance with the PICOs (population, intervention, control, and outcomes) format used in systematic reviews and meta-analyses. The population (P) consisted of patients diagnosed with ANCA-associated vasculitis. Intervention (I) was deemed inapplicable, while the control (C) group consisted of either the general population, healthy controls, or matched controls. The outcomes (O) of interest encompassed cardiovascular events, namely myocardial infarction (MI), ischemic heart disease (IHD), stroke, venous thromboembolism (VTE), pulmonary embolism (PE), and deep vein thrombosis (DVT), heart failure (HF), and cardiovascular disease (CVD)-related mortality.

2.2.2. Exclusion criteria

The exclusion criteria were studies lacking sufficient clinical data relevant to the outcomes under investigation and subjects without ANCA-associated vasculitis. Additionally, non-peer-reviewed articles, publications in languages other than English, case reports, case series, editorials, commentaries, review articles, and meta-analyses were excluded. Furthermore, studies failing to report cardiovascular events such as MI, IHD, stroke, HF, VTE, PE, DVT, and CVD-related mortality were also excluded.

2.3. Endpoints

This study aimed to assess the primary outcome of stroke. In addition, we examined the secondary outcomes, including myocardial infarction (MI), ischemic heart disease (IHD), VTE, PE, DVT, HF, and CVD-related mortality.

2.4. Data extraction and quality assessment

Two researchers (H.Q.A and A.G) independently reviewed the titles and abstracts of the potential studies to determine their eligibility. They excluded duplicates or studies that did not meet the predefined inclusion criteria. Subsequently, the full texts of the selected articles were reviewed to extract relevant data. Any discrepancies in screening and data extraction were resolved through discussions with a third reviewer (Y. M.). The extracted data were then entered into a standardized Microsoft Excel spreadsheet. Following this, all reviewers cross checked the extracted data for accuracy and consistency. Data extracted from the eligible studies included details such as the first author's name, year of publication, study design, sample size, baseline characteristics of the study population (including age, gender, and AAV type), and reported outcomes. Quality assessment of the selected studies was conducted using the New Ottawa Scale [14].

This scale evaluates the risk of bias in studies based on three domains: selection of study groups, comparability of study groups, and

outcome assessment. Two researchers (H.Q.A and A.G) independently evaluated the risk of bias for each study and disagreements were resolved by a third investigator (Y. M.).

2.5. Data synthesis

Data synthesis for this meta-analysis was conducted using RStudio's version (4.3.2) "meta" package [15]. The combined data from these studies were visually represented in forest plots. Risk ratios (RR) along with corresponding 95 % confidence intervals (CI) were pooled for all outcomes under DerSimonian and Laird random-effects models, with statistical significance set at $p < 0.05$. The degree of heterogeneity was assessed using Higgins I2 statistics, categorizing values as low (<25 %), moderate (25–75 %), or high (>75 %) [16]. Sensitivity analyses were conducted by systematically excluding one study at a time to investigate sources of heterogeneity. Publication bias was evaluated by visual inspection of funnel plots.

3. Results

3.1. Search results

A total of 8142 studies were identified using PubMed (n = 5664), EMBASE (n = 617), Scopus (n = 488), Web of Science (n = 425), and Google Scholar (n = 948). After initial screening of titles and abstracts, 7278 studies were excluded, and 104 studies were subjected to full-text screening. Nine studies met the predefined inclusion criteria and were therefore included in the current systematic review and meta-analysis [17–25]. The PRISMA flowchart of the study selection process is shown in Fig. 1.

3.2. Study and patient characteristics

All included studies were observational and published between 2009 and 2023. Eight were retrospective cohort studies [17–24] while one was a prospective cohort study [25]. The sample size of the included studies ranged between 61 and 20955, summing into a total population of 45024 study participants, 5643 and 39341 in the AAV and non-AAV groups, respectively. Geographically, two studies were conducted in Denmark [17,21], while the other two were conducted in Canada [19, 23]. The remaining studies were conducted in Korea [18], the United Kingdom [20], the United States [24], Sweden [22], and Finland [25]. The detailed baseline characteristics of the included studies and their patients are presented in Tables 1 and 2, respectively.

3.3. Quality assessment and publication bias

Nine outcomes were evaluated in this study. The quality of the

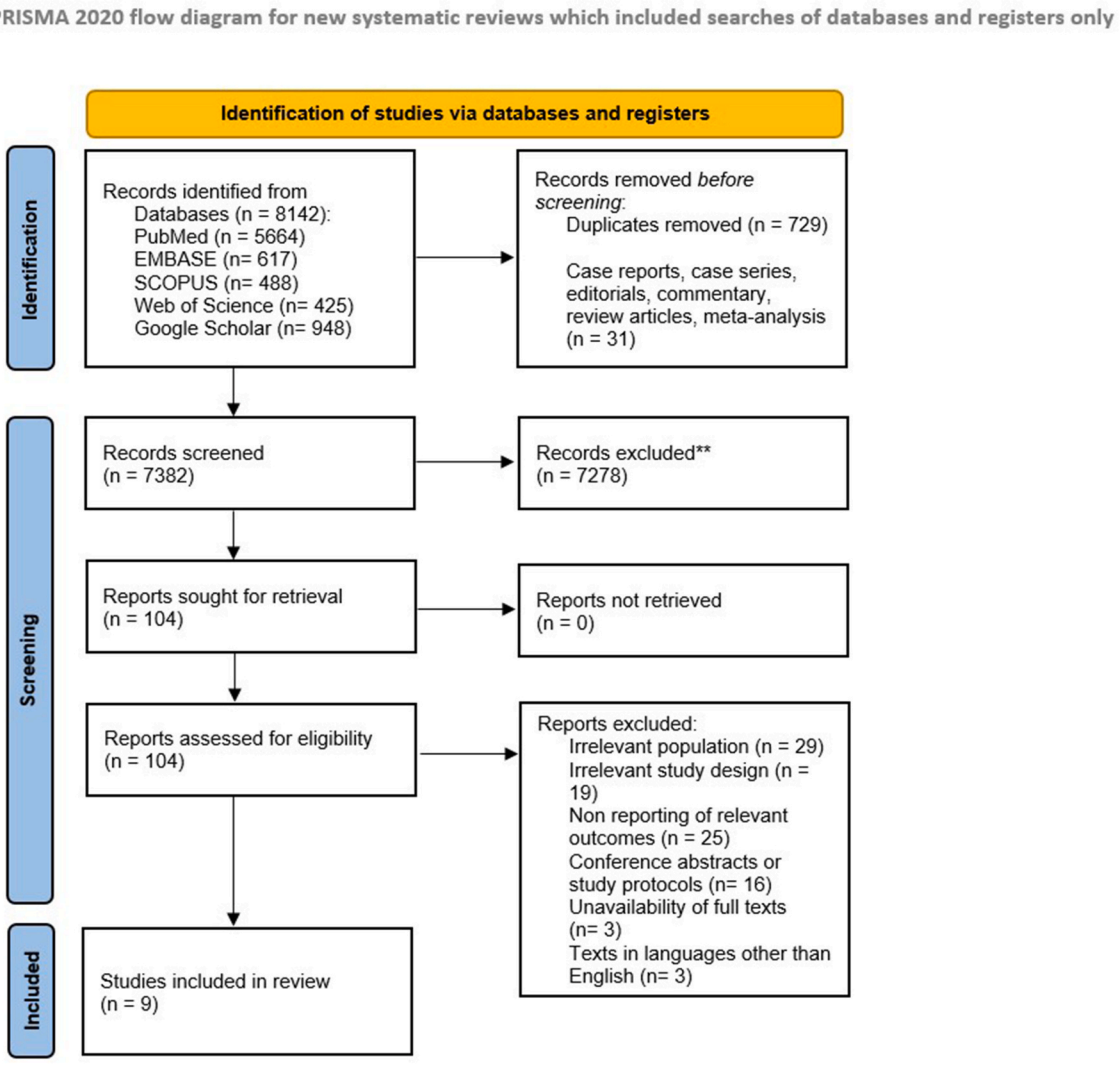


Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) Flow Diagram (2020) for systematic reviews and meta-analyses.

Table 1
Characteristics of the included studies.

Study ID	Country	Study Design	No of participants		Total no of participants	Patients with GPA, n	Patients with MPA, n	Patients with EGPA, n	Mean Follow-up (years)	
			AAV	Control					AAV	Control
Nygaard et al., 2023	Denmark	Retrospective cohort study	2306	6918	9224	NR	NR	0	10.23 ± 7.78	
Ahn et al., 2023	Korea	Retrospective cohort study	1905	19,050	20955	555	809	541	4.68 ± 3.36	5.48 ± 3.15
Tan et al., 2019	Canada	Retrospective cohort study	370	3700	4070	370	0	0	4.39	5.05
Morgan et al., 2009	United Kingdom	Retrospective cohort study	113	113	226	65	46	2	3.57 ± 3.23	5.04 ± 5.26
Faurschou et al., 2014	Denmark	Retrospective cohort study	180	3420	3600	180	0	0	7.34 ± 6.43	8.14 ± 6.30
Englund et al., 2016	Sweden	Retrospective cohort study	186	744	930	92	83	11	5.3 ± 3.9	NR
Aviña-Zubieta et al., 2016	Canada	Retrospective cohort study	504	5222	5726	504	0	0	3.8	4.6
Berti et al., 2018	United States	Retrospective cohort study	58	174	232	23	28	7	7.0 ± 4.8	6.9 ± 3.6
Salmela, 2015	Finland	Prospective cohort study	21	40	61	7	14	0	NR	NR

AAV = ANCA-associated Vascuilitis; GPA = Granulomatosis with polyangiitis; MPA = Microscopic polyangiitis; EGPA = Eosinophilic granulomatosis with polyangiitis.

included observational studies that reported these outcomes was assessed (Supplementary Table 1). The studies included in the analysis were deemed high quality, with scores ranging from 7 to 9 out of a total of 9 points on the Newcastle-Ottawa Scale. Publication bias was assessed using visual inspection of funnel plots, which indicated a low risk of bias (Supplementary Fig. 1).

4. Outcomes

4.1. Primary endpoint

Seven of the included studies reported stroke as an outcome [17,18,20–24]. The risk of stroke was significantly higher in patients with AAV than in those without AAV (RR: 1.43; 95 % CI: 1.12–1.83; p = 0.0048). However, moderate heterogeneity was observed (I2 = 62 %; p = 0.02) (Fig. 2A). After excluding the study conducted by Ahn et al. [18] through leave-one-out sensitivity analysis, heterogeneity decreased to 26 %.

4.2. Secondary endpoints

Four of the nine studies reported the outcome of IHD [17,20,22,24], which was significantly increased in patients with AAV compared to those without AAV (RR: 1.40; 95 % CI: 1.24–1.58; p < 0.0001). Mild heterogeneity was reported among studies (I2 = 1 %; p = 0.39) (Fig. 2B). Four studies reported the outcome of MI [17,18,21,22], which was found to be significantly higher in patients with AAV than in those without AAV (RR: 1.49; 95 % CI: 1.25–1.79; p < 0.0001). No heterogeneity was found among the studies (I2 = 0 %; p = 0.60) (Fig. 2C). Five studies reported VTE as an outcome [17,18,22,24,25] and were found to be significantly increased in patients with AAV compared to those without AAV (RR: 2.57; 95 % CI: 1.70–3.90; p < 0.0001). Moderate heterogeneity was observed among the studies (I2 = 74 %; p < 0.01) (Fig. 2D). After excluding the study conducted by Nygaard et al. [17] using leaving-one-out sensitivity analysis, the heterogeneity decreased to 0 %. Furthermore, four studies specifically reported the risk of PE [17,18,21,24]. Patients with AAV were found to be at an increased risk of PE compared to those without AAV (RR: 3.53; 95 % CI: 2.82–4.42; p < 0.0001). Mild heterogeneity was reported among the studies (I2 = 9 %; p = 0.35) (Fig. 2E). Three studies reported DVT [17,21,24], which was significantly increased in patients with AAV compared to those without AAV (RR: 4.21; 95 % CI: 2.00–8.86; p = 0.0002). Moderate heterogeneity was observed among the studies (I2 = 68 %; p = 0.04) (Fig. 2F). After excluding the study conducted by Nygaard et al. [17] by utilizing leaving-one-out sensitivity analysis, heterogeneity decreased to 0 %. Two studies reported the risk of HF [17,24]. Our analysis revealed a significantly increased risk of HF among patients with AAV compared to those without AAV (RR: 1.63; 95 % CI: 1.39–1.90; p < 0.0001). No heterogeneity was observed among the studies (I2 = 0 %; p = 0.90) (Fig. 2G). Two studies reported CVD-related mortality [19,25]. Patients with AAV had a statistically significant increased risk of CVD-related mortality compared to patients without AAV (RR: 1.79; 95 % CI: 1.07–3.00; p = 0.0256). No heterogeneity was observed among the studies (I2 = 0 %; p = 0.47) (Fig. 2H).

5. Discussion

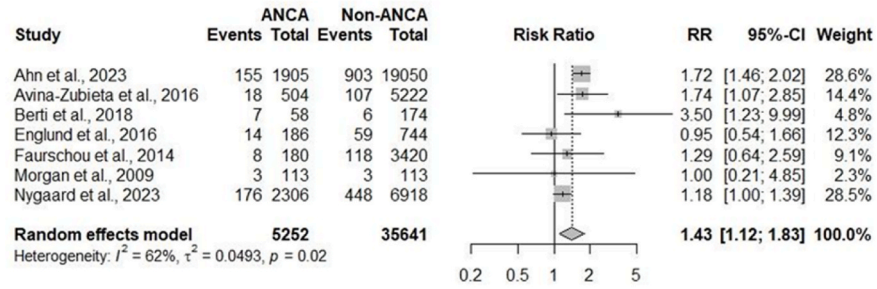
Our study indicated that individuals with AAV faced higher risks of stroke, IHD, MI, HF, and CVD-related mortality compared to those without AAV. Additionally, AAV patients had more than a three-fold elevated risk of VTE, predominantly manifesting as PE and DVT. Previous meta-analyses on cardiovascular outcomes in AAV patients faced limitations due to smaller sample sizes, fewer outcomes, and high heterogeneity [11,26–29]. To address these issues, we conducted the largest meta-analysis to date, including 45,024 patients, demonstrating a significant association between AAV and various cardiovascular outcomes. Our study also examined more outcomes than previous analyses [29]. A recent systematic review by Xie et al. [29] reported increased risks of cardiovascular and cerebrovascular diseases in patients with AAV, including elevated risks of MI, stroke, and HF. These findings are consistent with our own results. However, our study provides a more comprehensive assessment by reporting additional outcomes such as the risk of IHD, PE, DVT, and CVD-related mortality in patients with AAV. This broader scope offers a more complete review of the cardiovascular and thromboembolic risks associated with this condition. A key strength of our meta-analysis is the low heterogeneity for most outcomes, with sensitivity analyses further reducing heterogeneity for those with initially high variability, thereby enhancing the robustness of our findings. Vasculitis is a rare cause of stroke; however, its incidence varies globally [30]. Epidemiological data may depend on the local diagnostic strategies [30]. Patients with primary systemic vasculitis (PSV), such as ANCA-associated vasculitis and Behçet's disease, exhibit a higher risk of cerebrovascular disease, potentially due to vasculitis involvement in the central nervous system (CNS) [31], extracranial organs [32], accelerated atherosclerosis rates [33], or vasculitis treatment. Stroke early in the disease course may be more directly related to vasculitis than to

Table 2
Baseline characteristics of the study participants.

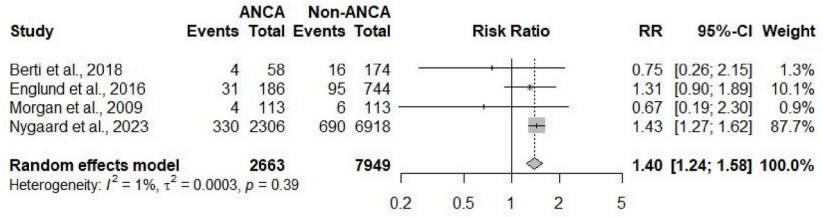
Study ID	Age in years (mean SD)		Male n (%)	BMI, kg/m2	Hypertension, n (%)	HLD, n (%)	PAD, n (%)	Diabetes, n (%)	COPD, n (%)	CLD, n (%)	CKD, n (%)	Pulmonary Hemorrhage, n (%)	IHD, n (%)	MI, n (%)	HF, n (%)	CAG, n (%)	PCI, n (%)	DVT, n (%)	PE, n (%)	AFib, n (%)	IS, n (%)	Cardiac arrest, n (%)
	AAV	Control	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C	AAV/C
Nygaard et al., 2023	62.9 (50.9–72.0)	62.9 (50.9–72.0)	1212 (52.6)/3636 (52.6)	NR	692 (30.0)/1568 (22.7)	341 (14.8)/997 (14.4)	42 (1.8)/120 (1.7)	180 (7.8)/473 (6.8)	351 (15.2)/498 (7.2)	41 (1.8)/113 (1.6)	529 [23]/46 (0.7)	180 (7.8)/108 (1.6)	264 (11.4)/613 (8.9)	101 (4.4)/241 (3.5)	89 (3.9)/162 (2.3)	129 (5.6)/308 (4.5)	51 (2.2)/132 (1.9)	63 (2.7)/110 (1.6)	39 (1.7)/56 (0.8)	131 (5.7)/286 (4.1)	96 (4.2)/318 (4.6)	5 (0.2)/4 (0.1)
Ahn et al., 2023	59.9 ± 14.7	59.9 ± 14.7	842 (44.2)/8420 (44.2)	NR	1026 (53.9)/7409 (38.9)	NR	NR	951 (49.9)/4127 (21.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tan et al., 2019	Early cohort (1997–2004) = 56.8 (16.9) Late cohort (2005–2012) = 54.9 (15.6)	Early cohort (1997–2004) = 56.8 (16.9) Late cohort (2005–2012) = 54.8 (15.5)	158 (42.7)/1580 (42.7)	NR	89 (24.0)/847 (22.9)	NR	NR	NR	89 [24]/255 (6.9)	NR	NR	NR	NR	NR	21/69	NR	NR	NR	NR	NR	NR	NR
Morgan et al., 2009	63 (52–70)	62 (52–72)	56/56	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Faurschou et al., 2014	54.5 (41.2–62.1)	54.5 (41.2–62.1)	91 [51]/1729 [51]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Englund et al., 2016	64.5 ± 15.8	64.5 ± 15.8	91 (49.6)/364 (49.6)	NR	NR	NR	NR	NR	NR	NR	32 [17]/NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Aviña-Zubieta et al., 2016	57.37 ± 16.57	57.33 ± 16.3	235 (46.6)/2484 (47.6)	NR	NR	NR	NR	NR	121 [24]/400 (7.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Berti et al., 2018	61.1 ± 16.5	61.2 ± 16.3	30 [52]/90 [52]	28.2 ± 6.3/29.5 ± 7.6	34 (59)/85 [49]	28 [48]/89 [51]	NR	9 [16]/19 (11)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Salmela et al., 2015	60 (18–84)	Control group1 = 44 (21–66) Control group 2 = 57.5 (25–77)	16/25	NR	12/21	NR	NR	NR	NR	NR	0/20	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

AAV = ANCA-associated Vasculitis; C = Control; HLD = Hyperlipidemia; CLD = Chronic liver disease; CKD = Chronic Kidney Disease; IHD = Ischemic Heart Disease; MI = Myocardial Infarction; HF = Heart Failure; PCI = Percutaneous Coronary Intervention; DVT = Deep Vein Thrombosis; PE = Pulmonary Embolism; AFib = Atrial Fibrillation; IS = Ischemic stroke.

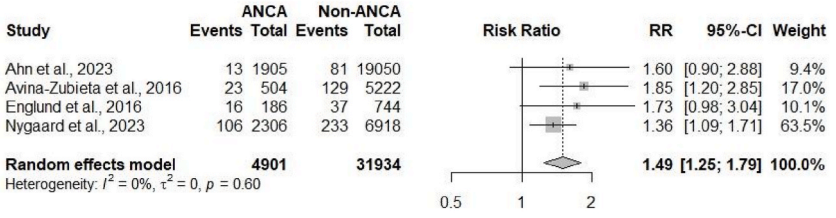
(A) Stroke



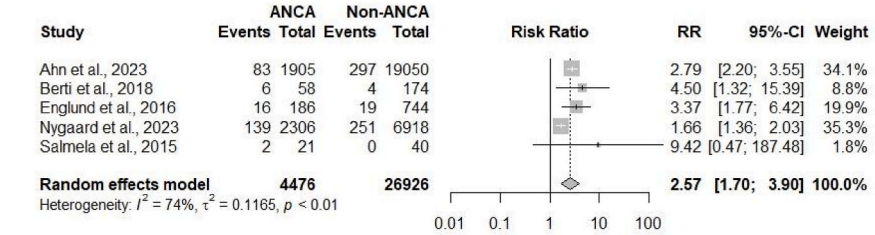
(B) Ischemic heart disease



(C) Myocardial infarction

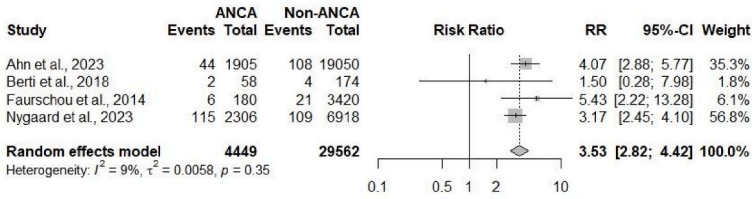


(D) Venous thromboembolism

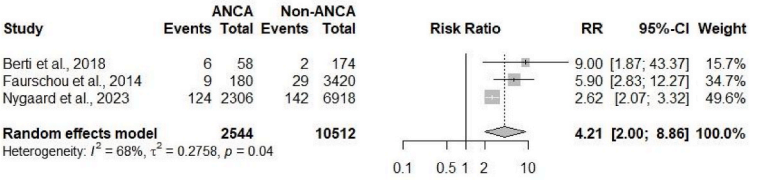


(E) Pulmonary embolism

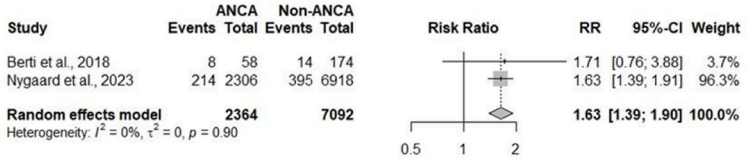
Fig. 2. Forest plots were employed for the pooled analysis of data. Risk Ratio (RR) was used for binary variables, with statistical significance set at a 95 % confidence interval (CI). The weight of each included study is represented by the size of the square adjacent to the study, and the diamond illustrates the results of the pooled analysis of all studies. The width of the diamond represents the pooled confidence interval. Forest plots were generated for various outcomes, ranging from stroke (A) and ischemic heart disease (B) to myocardial infarction (C), venous thromboembolism (D), pulmonary embolism (E), deep vein thrombosis (F), heart failure (G), and cardiovascular disease-related mortality (H).



(F) Deep vein thrombosis



(G) Heart failure



(H) Cardiovascular disease-related mortality

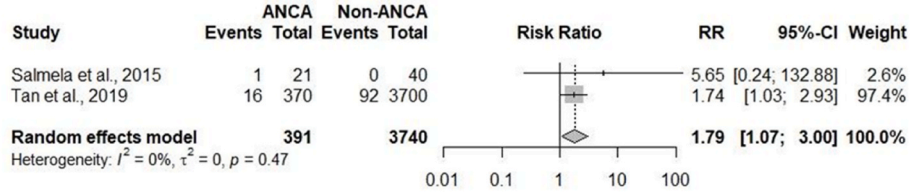


Fig. 2. (*continued*).

other factors, with complications potentially becoming more significant later in disease progression.

Our study found a heightened risk of stroke in AAV patients compared with controls, consistent with previous meta-analyses [11,26] and observational studies [17,18,20–24]. This increased risk can be attributed to the inflammatory burden associated with vasculitis. As for IHD, inflammation, a key player in atherosclerotic plaque development, leads to modifications in low-density lipoprotein particles, stimulating endothelial cells to express leukocyte adhesion molecules and activating macrophages and mast cells in plaques [26]. Furthermore, comorbidities associated with AAV, such as hypertension due to glomerulonephritis and increased risk of diabetes associated with glucocorticoid treatment, may contribute to an elevated stroke risk [26]. While nervous system involvement in AAV is common, CNS vasculitis is rare and unlikely to be the primary reason for the increased stroke risk [26]. Interestingly, prior research has also suggested that myocarditis/cardiomyopathy should be considered as a potential cause of ischemic stroke or transient ischemic attacks in systemic vasculitis such as AAV [30].

In agreement with previous studies [11,17,18,21,22,34,35], our study underscores that patients with AAV face heightened morbidity linked to IHD and MI compared to the general population. Atherosclerosis, characterized by arterial intimal inflammation, is a major contributor to the development of IHD and is accelerated in AAV due to systemic inflammation. C-reactive protein (CRP), an independent marker and an active contributor to inflammation, induces endothelial adhesion molecule expression and promotes leukocyte adherence and atherosclerosis [36]. Elevated D-dimer levels in AAV also correlate with disease activity and inflammation, implicating these as markers of AAV severity [25,37]. Moreover, a previous study identified a biphasic pattern of IHD risk in AAV patients [38]. Within the first five years post-diagnosis, the risk of IHD events, including MI, notably increases. However, between the fifth and ninth years, the risk aligns with that of the general population before doubling ten years after post-diagnosis [38]. This unique pattern contrasts with other autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, where IHD risk typically increases with disease duration [39,40].

This early increase in the risk of IHD in AAV patients may stem from both disease-specific and therapeutic factors. Necrotizing vasculitis in cardiac vessels could precipitate acute MI in AAV [41], and high-dose corticosteroid therapy, often a primary immunosuppressive regimen for the induction of remission, may further elevate IHD risk [42]. In the later years, as many patients achieve remission or experience reduced disease activity, systemic inflammation decreases, and the risk of IHD aligns more closely with that of the general population. However, the risk of IHD in AAV patients is characteristically biphasic. The significantly increased risk of IHD after ten years is likely due to the cumulative effects of chronic low-grade inflammation, long-term vascular damage, and extended use of immunosuppressive treatments [38]. Furthermore, while cyclophosphamide has demonstrated a cardioprotective effect in cohorts of SLE patients [40], its use in AAV patients requiring prolonged treatment appears to exacerbate the risk study due to the combined effects of sustained inflammation [43] and corticosteroid therapy [42]. Further investigations are warranted to elucidate the contributions of systemic inflammation and corticosteroid treatment to the development of IHD in patients with AAV, akin to what has been explored in SLE and RA cohorts [44].

Consistent with previous meta-analyses [11,27] and observational studies [17,18,22,24,25], our study also revealed a significantly increased risk of VTE in patients with AAV, with the majority of cases comprising DVT and PE; thus, automatically translated into heightened risk of DVT and PE among AAV patients in comparison to the general population. Furthermore, a prior study showed that the incidence and burden of VTE in AAV were higher than those previously reported in SLE patients, suggesting a more pronounced inflammatory process in AAV [45]. Previous research also indicated that older age, higher Birmingham vasculitis activity score (BVAS), positive myeloperoxidase (MPO)-ANCA, and renal involvement are significant risk factors for VTE, while positive proteinase 3 (PR3)-ANCA is inversely associated with VTE risk [27]. Interestingly, the serological subtype (MPO vs. PR3) rather than the clinical subtype (e.g., MPA vs. GPE) was associated with increased VTE risk, highlighting the importance of serological classification in AAV [46–48].

Nephrotic proteinuria, often observed in AAV-associated glomerulonephritis, may also contribute to hypercoagulability, and increase VTE risk by reducing circulating anticoagulant levels [27]. Interestingly, many studies have indicated that increasing follow-up duration was not associated with increased VTE risk, suggesting that VTE events in AAV may occur when disease activity is high, typically within the first year of diagnosis [49]. Prospective trials are needed to determine the efficacy of anticoagulation in preventing VTE in AAV patients, particularly within the first year of diagnosis, when disease activity is heightened. Thus, the combination of inflammation-driven atherosclerosis and a heightened tendency for thrombosis creates a vicious cycle, significantly elevating the long-term risk of CVD in individuals with chronic inflammatory conditions like AAV. This necessitates vigilant monitoring and proactive management to mitigate future cardiovascular risks [36–38,49].

Several studies have investigated the prevalence and impact of HF in patients with AAV [17,24,50–52]. Our analysis has also revealed a significantly increased risk of HF in the AAV patients which is in agreement with prior research [17,24,50–52]. Retrospective analyses have shown that GPA hospitalizations have nearly double the prevalence of HF compared with non-GPA hospitalizations [50], especially within the first year after diagnosis compared with matched controls, followed by a normalized rate thereafter [52]. Additionally, HF has been identified as an independent predictor of 30-day readmission among patients admitted with GPA [51]. Similar patterns have been observed in other inflammatory diseases, such as rheumatoid arthritis, suggesting heightened surveillance for CVD, including HF, in the initial post-diagnosis period [53].

Several potential explanations have been proposed for the association between AAV and HF. First, the combination of direct inflammatory damage to the heart muscle, acceleration of coronary atherosclerosis, and systemic inflammation collectively reduces the pumping ability of the heart [52]. Second, corticosteroid and cytotoxic drug therapies commonly used in AAV management may increase the risk of HF. The heightened rate of HF in the first year after AAV diagnosis could be linked to extensive corticosteroid use during the initial treatment phase [52]. Third, frequent hospital contact around AAV diagnosis might lead to HF detection bias, wherein HF cases are more likely to be identified in the early post-diagnosis period [52].

Our study, in alignment with previous research [11,19,25], also showed a significantly increased risk of cardiovascular mortality in patients with AAV.Survival outcomes in AAV vary based on factors such as ethnicity [24,25], AAV subtype [46–48], and accessibility to biological treatment [12,54]. Poor prognostic factors for survival include old age, ANCA status, higher initial BVAS, lung and renal involvement, nonstandard treatment, and delayed administration of cyclophosphamide [55]. The BVAS is a strong, unmodifiable prognostic factor for AAV mortality, with specific cardiovascular-related items predicting cardiovascular event risk. It evaluates symptoms and signs across nine organ systems: the skin, mucous membranes, eyes, ears, nose, throat, lungs, cardiovascular system, gastrointestinal tract, kidneys, and nervous system. Each organ system is scored based on the presence and severity of vasculitis features. In short, it reflects disease activity and correlates with endothelial cell dysfunction, which is partly driven by complement system activation and inflammatory responses [56]. While some CV mortality occurs shortly after diagnosis due to acute disease, the majority occurs after achieving remission, with almost half occurring two years after diagnosis. Thus, despite achieving remission with immunosuppressive therapy, the persisting endothelial dysfunction contributes to the ongoing risk of cardiovascular mortality in AAV patients [56].

The treatment landscape for AAV has evolved significantly, from corticosteroids alone in 1969 to current guidelines recommending combinations of corticosteroids with either cyclophosphamide or rituximab with adjunctive therapeutic plasma exchange for rapidly progressive glomerulonephritis or diffuse alveolar hemorrhage [12]. Despite these advancements, AAV patients still have a high mortality rate compared to the general population, primarily due to the disease itself or complications of immunosuppressive drugs [7]. For instance, corticosteroids, a cornerstone of AAV treatment, contribute to CVD risk by inducing hypertension, dyslipidemia, glucose intolerance, weight gain, and metabolic syndrome, all of which elevate the likelihood of IHD and HF [57]. Cyclophosphamide, another key treatment, is associated with cardiotoxicity, leading to arrhythmias, myocarditis, and MI, especially with prolonged use. It can also cause neutropenia and infections, increasing cardiovascular stress [57]. Rituximab, though less cardiotoxic, heightens the risk of VTE, including DVT and PE. Thus, while AAV treatments have improved survival, they also increase risk of CVE, requiring vigilant monitoring [57].

6. Future implications

The results of our meta-analysis underscore the need for a refined approach to managing AAV due to its significant cardiovascular risks. Given the heightened odds of stroke, myocardial infarction, heart failure, and venous thromboembolism in AAV patients, the emerging subspecialty of Cardio-Rheumatology becomes increasingly relevant. Integrating cardiovascular care into rheumatological practice is essential to address the dual burden of chronic inflammation and its cardiovascular repercussions [58]. Future management strategies should focus on proactive cardiovascular risk assessment and monitoring, especially in the early stages of AAV and during long-term treatment with immunosuppressive therapies. Routine cardiovascular evaluations and tailored treatment regimens can help mitigate these risks. This interdisciplinary approach could lead to substantial improvements in long-term outcomes and quality of life for AAV patients.

6.1. Limitations

Our meta-analysis has several limitations. The analysis may not have accounted for all potential confounding factors, such as comorbidities and treatment modalities, which could have affected the association between AAV and cardiovascular outcomes. As all included studies were observational, biases, such as selection bias and information bias, may have influenced the results. The lack of randomized controlled trials limits the ability to establish causality. Variability in outcome definitions across studies, particularly for IHD, could lead to inconsistencies in reporting and affect comparability. Some outcomes exhibited moderate to high heterogeneity among the studies. To mitigate this, sensitivity analyses were conducted to explore the potential sources of inconsistency that adequately reduced the heterogeneity of our outcomes. Additionally, owing to the limited number of studies available for analysis, we were unable to evaluate publication bias using Egger's regression and Begg and Mazumdar's rank correlation test. Additionally, most studies were retrospective and based on national registry databases, potentially introducing inaccuracies, and limiting generalizability. The absence of treatment status reporting in retrospective studies may underestimate the disease activity. Further studies addressing these limitations are warranted to provide a more comprehensive understanding of the association between AAV and cardiovascular outcome.

7. Conclusion

In conclusion, this meta-analysis underscores the significant association between AAV and heightened cardiovascular morbidity including stroke, ischemic heart disease, myocardial infarction, venous thromboembolism, pulmonary embolism, deep vein thrombosis, and heart failure. These findings highlight the importance of vigilant cardiovascular monitoring in AAV patients, particularly during the initial post-diagnosis period. Further research is needed to elucidate the underlying mechanisms driving these associations and optimize management strategies aimed at reducing cardiovascular complications in AAV.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

The authors declare no conflict of interest.

Ethical approval

No ethical approval was required for this study design, as all data were obtained from publicly available sources.

CRediT authorship contribution statement

Aman Goyal: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Haleema Qayyum Abbasi:** Writing – review & editing, Writing – original draft, Visualization, Methodology. **Yusra Mashkoor:** Writing – review & editing, Writing – original draft. **Abdul Moiz Khan:** Writing – review & editing, Writing – original draft, Methodology. **Samia Aziz Sulaiman:** Writing – review & editing, Writing – original draft. **Mohamed Daoud:** Writing – review & editing, Writing – original draft, Supervision. **Kamna Bansal:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2024.200334.

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