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CLINICAL REVIEW

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Association between rheumatoid arthritis and atrial fibrillation: A systematic review and meta-analysis

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Abstract

Rheumatoid arthritis (RA) is an autoimmune disorder with a varying range of organs involved leading to adverse outcomes. However, very little is known, with conflicting results about the association between RA and atrial fibrillation (AF). We aim to evaluate the association between RA and AF, and other clinical outcomes. We performed a systematic literature search using PubMed, Embase, and Scopus for relevant articles from inception until September 10, 2023. Primary clinical outcomes were AF. Secondary outcomes were acute coronary syndrome (ACS), stroke, and all-cause mortality (ACM). A total of 4 679 930 patients were included in the analysis, with 81 677 patients in the RA group and 4 493 993 patients in the nonrheumatoid arthritis (NRA) group. The mean age of the patients was 57.2 years. Pooled analysis of primary outcomes shows that RA groups of patients had a significantly higher risk of AF (odds ratios [OR], 1.53; 95% confidence interval [CI]: [1.16–2.03], $p < .001$) compared with NRA groups. Secondary Outcomes show that the RA group of patients had significantly higher odds of ACS (OR, 1.39; 95% CI: [1.26–1.52], $p < .001$), and ACM (OR, 1.19; 95% CI: [1.03–1.37], $p = .02$) compared with the NRA groups. However, the likelihood of stroke (OR, 1.02; 95% CI: [0.94–1.11], $p = .61$) was comparable between both groups of patients. Our study shows that RA groups of patients are at increased risk of having AF, ACS, and ACM.

KEYWORDS
acute coronary syndrome, atrial fibrillation, mortality, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and systemic autoimmune disorder characterized by progressive polyarthritis that primarily affects the small joints and gradually extends to larger joints.[1] Although relatively rare, cutaneous, cardiovascular, and ocular manifestations may also occur in some cases.[2] While RA predominantly affects individuals in the age range of 35–60 years, instances of juvenile RA, affecting individuals under the age of 16, have also been documented.[3] Many etiological factors like genetic predisposition, environmental exposure, and dynamic lifestyle choices act in conjugation, contributing to the onset and progression of RA. Globally, the estimated prevalence of RA stands at 0.24%, with notably higher rates observed in the United States and certain regions of Northern Europe, ranging from 0.5% to 1%.[4–6] The incidence of RA in these areas hovers around 40 cases per 100 000 individuals,[6,7] with a marked predilection towards females who experience an approximately twofold greater incidence and prevalence compared to males. The lifetime risk of developing RA is reported to be 3.6% in women and 1.7% in men.[8] Classic clinical presentations of RA include fever, weight loss, tender joints, and characteristic rheumatoid nodules beneath the skin.[1]

The pathogenesis of RA is a multifaceted process involving a complex interplay of genetic and environmental factors that contribute to immune system dysregulation, synovial fluid inflammation, and joint tissue damage.[9] The genetic component of RA is intricate, encompassing numerous genes that exhibit varying degrees of association with the disease.[10] In addition to synovitis, individuals with RA face an elevated risk of developing cardiovascular disease (CVD) because of the pivotal role of inflammation in CVD pathogenesis.[11] The progression towards CVD is attributed to the presence of several proinflammatory cytokines, including Tumor Necrosis Factor-alpha, interleukin (IL)-1β, IL-6, and IL-17, which are notably elevated in RA patients.[12] The prognosis and severity of RA significantly impact cardiovascular risk, with each year of heightened disease severity associated with a 7% increase in the risk of developing CVD. These factors not only affect morbidity but also influence patient outcomes.[13,14]

Upon conducting an extensive literature search, we discovered inconsistent findings regarding the risk of atrial fibrillation (AF) and cardiovascular outcomes associated with RA. Consequently, the aim of this meta-analysis is to elucidate the association between RA and various severe CVD outcomes. By doing so, we aim to provide valuable insights into the multifactorial causation of CVD in individuals with RA, which will aid in the development of appropriate therapeutic strategies and screening measures for vulnerable populations.

2 | METHODS

This meta-analysis was conducted and reported following the Cochrane and PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) 2020 guidelines and performed according to established methods, as described previously.[15–17] The pre-specified study protocol has been registered in the PROSPERO (CRD42023424652).

2.1 | Outcomes

The primary outcome of interest was AF. Secondary endpoints included acute coronary syndrome (ACS), stroke, and all-cause mortality (ACM).

2.2 | Search strategy

We conducted a systematic literature search across the following databases: PubMed, Embase, Cochrane Library, and Scopus. Predefined MeSH terms were used by applying the BOOLEAN ("AND" and "OR") logic. The following search terms were used: "rheumatoid arthritis" OR "rheumatology" AND "arrhythmia" OR "atrial fibrillation" AND "acute coronary syndrome" AND "mortality" AND "stroke." The search was performed from inception until September 10, 2023, without any language or date restrictions. All the studies were carefully screened and exported to the Endnote 2020 library (Clarivate Analytics, USA). Two reviewers (VJ and PR) reviewed the studies based on the title and abstract. A third author (SA) arbitrated discrepancies regarding the inclusion of studies.

2.3 | Eligibility criteria

2.3.1 | Inclusion criteria

1. Studies with patients aged ≥18 years.
2. Studies with two arms where one arm is of RA patients while another is of nonrheumatoid arthritis patients.
3. Studies were required to report at least one of the desired outcomes of Interest.
4. Studies such as propensity score-matched studies and prospective and retrospective studies were sought to be eligible.

2.3.2 | Exclusion criteria

1. Animal studies, abstracts, editorials, commentaries, systematic reviews, single-patient case studies, letters, and studies with insufficient data were excluded.
2. Studies where a single arm was presented without comparators and with noncompliant outcomes were also excluded.

2.4 | Data extraction, quality assessment, and statistical analysis

Data from the eligible selected studies, such as demographics, comorbidities, risk factors, follow-up, and outcomes of both groups, were extracted into a shared spreadsheet by two authors (VJ and PR). Baseline continuous variables were summarized as mean (SD),

whereas dichotomous variables were described as frequencies or percentages. A conventional, two-arm meta-analysis for primary and secondary outcomes was performed by adopting the Dersimonian and Laird random-effects model for the study variations. The primary endpoint in this meta-analysis was AF, and the effect size was determined by HR with 95% confidence interval [CI]. However, dichotomous variables were assessed by pooled odds ratios (OR) and their corresponding 95% CI. Statistical significance was met if 95% CI did not cross the numeric "1" and the two-tailed *p* value was less than .05. The heterogeneity among studies was assessed using the Higgins I-squared (I^2) statistical model, with I^2 values < 75% considered mild–moderate and ≥75% considered high.[18] All statistical work, including analyses and graphical illustrations, was conducted using Review Manager software (RevMan) Version 5.4.

SA independently assessed the quality of the included studies using the Newcastle-Ottawa Scale (NOS) for cohort and cross-sectional studies.[19] A study with a score of 7–9 was considered high quality; a score of 4–6 was considered high risk, whereas a score of 0–3 indicated a high risk of bias. In case of disagreement, a group-based discussion was conducted.

3 | RESULTS

3.1 | Study characteristics

Our initial comprehensive search identified a total of 451 articles. After excluding duplicates (157), 294 articles were further screened based on title and abstract. Two hundred fifty-nine studies were further excluded after reviewing the title and abstract, and 35 studies were reviewed in full-text form. However, 28 studies were further excluded as lacking outcomes of interest, abstract, overlapping data from the same database of the same year, and different populations of interest. A total of seven studies qualified for quantitative analysis, of which all were observational studies.[20–26] The details of the screening and selection process are shown in the PRISMA flow diagram (Figure 1). Besides, the NOS score ranges from 7 to 9, indicating a high quality of all included cohort studies (Table S1).

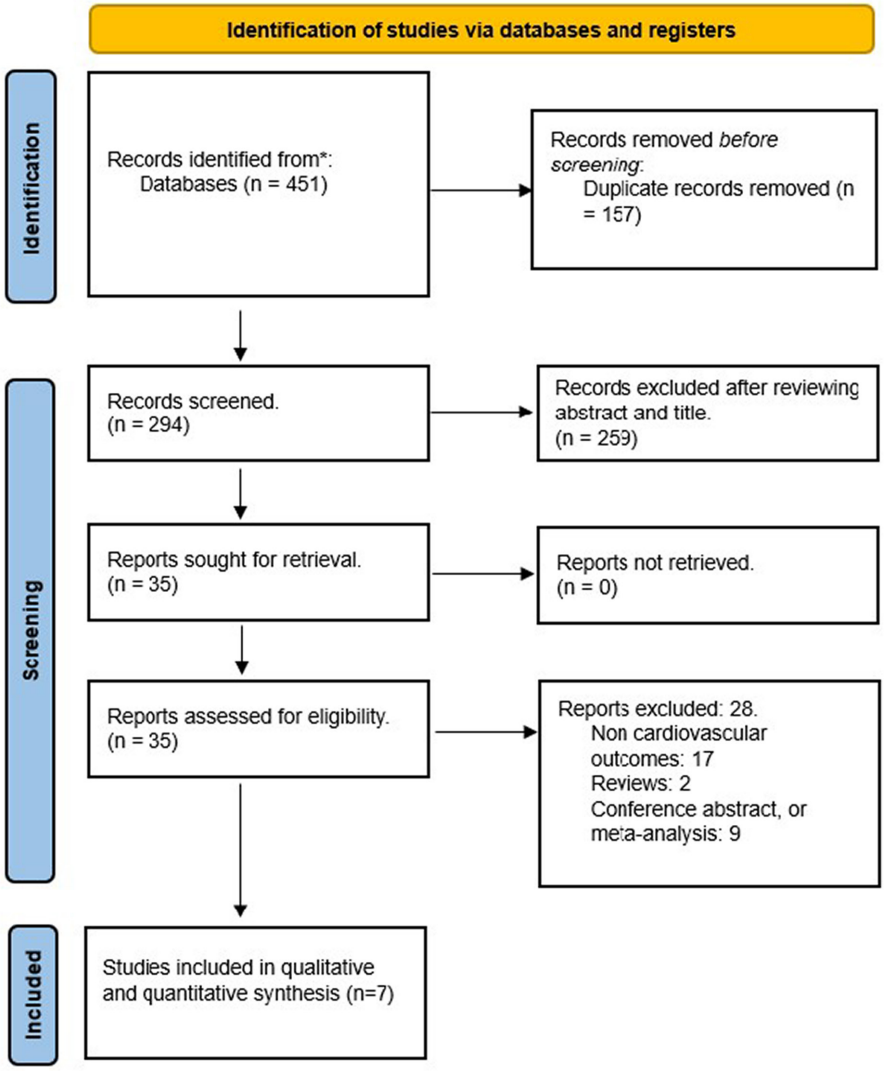

FIGURE 1 The details of the screening and selection process are shown in the PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis.

3.2 | Baseline characteristics of included studies

A total of 4 679 930 patients were included in the analysis, with 81 677 patients in the RA group and 4 493 993 patients in the nonrheumatoid arthritis (NRA) group. The mean age of the patients was 57.2 years. The most common comorbidity among RA and NRA patients was HTN (94% vs. 6%) and DM (88.1% vs. 11.9%). The study characteristics, demographics, and comorbidities are presented in Table 1.

3.3 | Meta-analysis of primary and secondary clinical outcomes

Pooled analysis of primary outcomes shows that the RA group of patients had a significantly higher risk of AF (OR, 1.53; 95% CI: [1.16–2.03], $p < .001$) compared with NRA groups (Figure 2).

Pooled analysis of secondary Outcomes shows that the RA group of patients were having significantly higher odds of ACS (OR, 1.39; 95% CI: [1.26–1.52], $p < .001$), and ACM (OR, 1.19; 95% CI: [1.03–1.37], $p = .02$) compared with the NRA groups (Figure 3A,B). However, the likelihood of stroke (OR, 1.02; 95% CI: [0.94–1.11], $p = .61$) was comparable between both groups of patients (Figure 4).

4 | DISCUSSION

4.1 | Summary findings

This study reveals compelling evidence supporting a higher risk of AF among individuals with RA. Moreover, we also found that RA patients exhibit higher odds of ACS and ACM. However, the risk of stroke was not significant between the RA and NRA group of patients. Previous meta-analysis with three cohort studies and with small sample size could have contributed to a less comprehensive and representative overview of the topic under investigation.[27] Thus, to ensure more robust and reliable results, an updated analysis should ideally include a larger and more diverse pool of studies to draw meaningful and generalizable conclusions.

4.2 | Interpretation of findings

Our meta-analysis presents compelling evidence supporting a strong association between RA and an increased risk of CVD outcomes. Notably, individuals with RA face a significantly elevated risk of developing AF and ACS, both of which contribute to mortality in these patients.[28] The observed heterogeneity across studies may stem from variations in study design, population characteristics, and adjustments for confounding factors. While the precise mechanisms underlying the heightened cardiovascular risk in RA are not yet fully elucidated, several factors are believed to contribute. Inflammation, a hallmark feature of RA, is thought to play a crucial role. Additionally, traditional cardiovascular risk factors such as hypertension, diabetes mellitus, a history of previous myocardial infarction and stroke, along with RA-specific factors such as anti-citrullinated protein antibodies, may collectively contribute to the increased cardiovascular risk observed in RA patients.

4.3 | RA and AF

RA primarily affects the small joints, causing limited movement. The prevalence of RA varies, but it can range from 180 to 1070 cases per 100 000 people.[29] Among RA patients, the most common arrhythmia is AF, especially in young females under 50 with specific factors.[23] Smaller cohort studies have mentioned other arrhythmias like premature ventricular contractions and ventricular tachycardia (VT) among RA patients. These arrhythmias can be linked to cardiac involvement, coronary issues, and autoantibodies affecting the cardiac conduction system. Additionally, increased sympathetic and decreased parasympathetic activity may contribute to VT in RA patients. Some reports suggest that the anti-inflammatory drug infliximab could be associated with new-onset ventricular tachyarrhythmias.[30] Early treatment with disease-modifying antirheumatic drugs can positively impact the lipid profile and reduce atherosclerosis by lowering inflammation. While catheter ablation for AF in RA patients can be successful, they tend to experience early atrial tachyarrhythmia recurrence after the procedure compared to those without RA.[31]

CVD is a well-known complication of RA and can significantly impact disease outcomes. While the association between arrhythmias, specifically AF, and RA has been investigated in previous studies, there remains a paucity of comprehensive data on the risk of arrhythmia in RA patients. While studies conducted by Lindhardsen et al.[20], Kim et al.[32] and Bacani et al.[23] have demonstrated an increased risk of AF in individuals with RA, other studies have not established a clear-cut association.[21] This lack of consensus can be attributed to various factors. The inflammatory processes triggered by RA can affect the atrial myocardium in multiple ways, potentially acting as both triggers and perpetuators of AF. Patients with AF often exhibit elevated levels of inflammatory markers such as C-reactive protein, IL-1, IL-6, and tumor necrosis factor (TNF), which have been linked to reduced success rates for cardioversion.[28,33,34] Wang et al. further suggest that RA patients with AF may have significant changes in their peripheral T cell profiles, including higher percentages of Th1 cells, higher absolute numbers of Th17 cells, and altered Th1/Treg ratios, which are associated with a higher risk of AF.[35] It highlights the potential role of Th cell immunological derangements in the development of AF in RA patients and the importance of early diagnosis and intervention to prevent AF initiation and progression in this population.

Atrial fibrosis, resulting from structural remodeling induced by TNF and platelet-derived growth factor-A (PDGF-A), activates the transforming growth factor-beta (TGF-b) signaling system, promotes matrix metalloproteinase secretion, and stimulates cell proliferation and collagen expression in cardiac fibroblasts.[36] Additionally, TNF and PDGF-A contribute significantly to electrical remodeling by modifying calcium

TABLE 1 Baseline demographics, comorbidities, and study characteristics of studies included in the meta-analysis.

Author	Sample size	Country	Age	Year	Study design	Follow up, years	Diabetes mellitus, *n*	Hypertension, *n*	H/O myocardial infarction, *n*	H/O stroke	H/O heart failure
Kim et al.[21]											
RA	20852	USA	51.9	2014	Retrospective cohort	2	1935	5876	1439	497	–
Non-RA	104260		51.9				9279	26360	5355	1983	
Jang et al.[26]											
RA	4217	Korea	66.4	2020	Prospective cohort	5.9	321	1340	–	93	46
Non-RA	8434		66.4				533	2646	–	175	87
Lindhardsen et al.[20]											
RA	18247	Denmark	52.4	2012	Retrospective cohort	4.8	–	936	620	–	101
Non-RA	4164088		45.6				–	148893	109382	–	27221
Bacani et al.[23]											
RA	813	USA	55.9	2015	Retrospective cohort	9.6	79	307	87	–	23
Non-RA	813		55.9				67	275	89	–	23
Argnani et al.[25]											
RA	21201	Italy	61.7	2021	Retrospective cohort	5	2162	7823	–	–	–
Non-RA	249156		62.5				23918	83218	–	–	
Holmqvist et al.[22]											
RA	15744	Sweden	57	2017	Nationwide population-based cohort	5.7	–	–	–	–	–
Non-RA	70899		57				–	–	–	–	
Maradit-Kremers et al.[24]											
RA	603	USA	58	2005	Retrospective long cohort study	14.7	44	312	–	–	–
Non-RA	603		58.2				41	298	–	–	

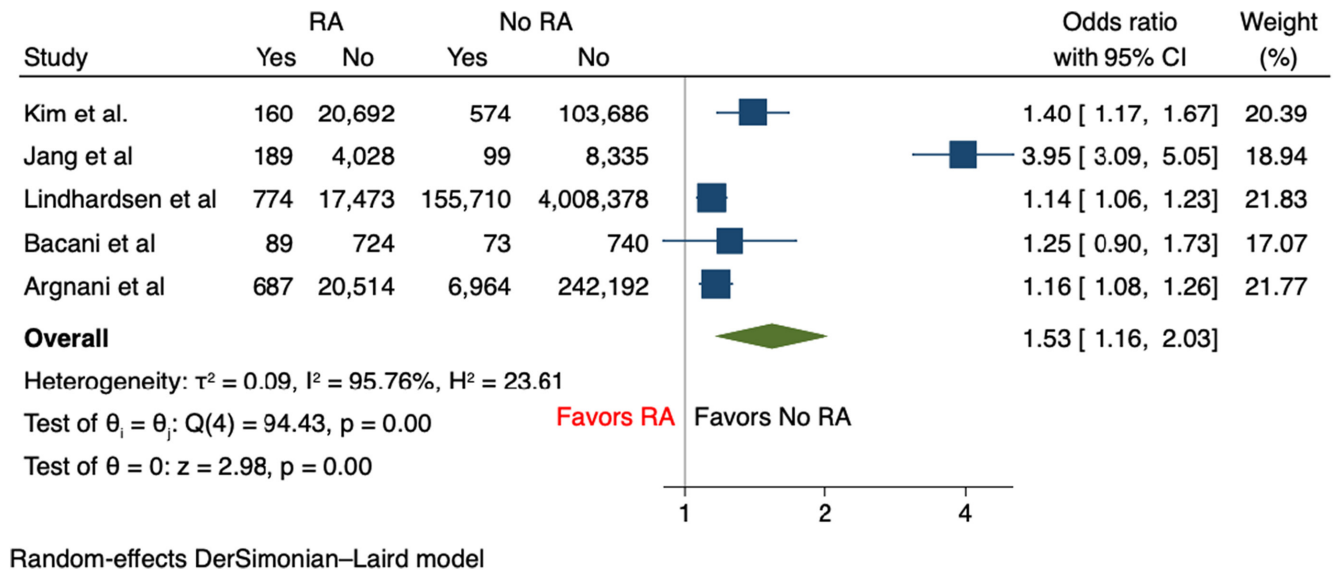

FIGURE 2 Forest plot showing meta-analysis result of primary outcome: atrial fibrillation.

handling, shortening action potentials and calcium transients, and increasing arrhythmogenicity.[37] Inflammation also exerts detrimental effects on atrial electrophysiology by altering the expression of gap junction proteins, including connexin-40 and connexin-43, which can lead to conduction heterogeneity. These changes result in conduction abnormalities and disturbances in the atrial action potential waveform, ultimately contributing to the development of AF. These pathological alterations in the atrial structure and electrical properties represent early pathophysiological events in the initiation of AF.[38]

Several other factors may contribute to the association between RA and AF. Shared risk factors, including age, hypertension, and obesity, are prevalent in both conditions and may contribute to an increased risk of developing AF.[32,39] Furthermore, genetic factors have been implicated in both RA and AF, with specific gene variants linked to the susceptibility of developing these conditions. In the presence of ethnic-specific risk factors, both common and rare genetic variations can heighten an individual's vulnerability to AF. Studies focusing on isolated forms of AF have revealed a conventional monogenic disease pattern with low penetrance.[40] Moreover, it is widely recognized that patients with RA have higher rates of coronary artery disease (CAD) and congestive heart failure (CHF) compared to individuals without RA.[41] This observation may partially explain the elevated risk of AF in RA patients, as both CHF and CAD are significant risk factors for AF.[42] The risk of developing AF was significantly increased by Leflunomide use and disease-modifying antirheumatic drugs (DMARDs), while Methotrexate decreased the risk.[32]

While the precise etiological pathways linking RA and AF are not yet fully understood, several hypothetical factors have been proposed as potential drivers of this association. The onset of AF in RA patients may be influenced by a combination of common risk factors, genetic variables, and chronic inflammation. To develop effective management and prevention strategies for AF in individuals with RA, it is crucial to gain a comprehensive understanding of these underlying mechanisms.

Wen et al. in their study studied the effects of catheter ablation in patients with RA, implying that the success rate of ablation was comparable in the study and control groups. In addition, the relapse of Atrial Tachycardia was more common among the RA group following the index procedure.[43] Similarly, Haq et al. found that after ablation, RA patients had significantly higher rates of AF recurrence, were more likely to be taking antiarrhythmic drugs, and were more likely to undergo repeat ablations.[44]

In contrast to our findings, which indicated that RA patients have a higher risk of AF and ACS, Edigin's study presents different results. Edigin's research suggests that patients admitted for AF with coexisting RA experienced similar inpatient mortality rates compared to those without RA. Additionally, AF patients with RA had shorter hospital stays and lower charges.[45]

4.4 | RA and ACS

RA is a chronic inflammatory disorder primarily affecting the joints. However, emerging evidence indicates a significant association between RA and an increased risk of CVD, including ACS. This correlation has been investigated in two population-based cohort studies conducted by Maradit-Kremers et al. and Holmqvist et al. shedding light on the underlying mechanisms linking RA and ACS.[22,24]

The mechanisms underlying the association between RA and ACS are intricate and multifaceted. RA patients exhibit a heightened susceptibility to developing atherosclerosis, characterized by the narrowing and stiffening of arteries, which ultimately contributes to the development of CVD. Several pathological processes contribute to this increased risk, including oxidative lipid imbalance, insulin resistance, abnormal blood clotting, elevated levels of homocysteine, and T-cell immune activation. These factors collectively contribute to endothelial dysfunction and arterial stiffness, thereby accelerating the progression of atherosclerosis and subsequently leading to a higher incidence of

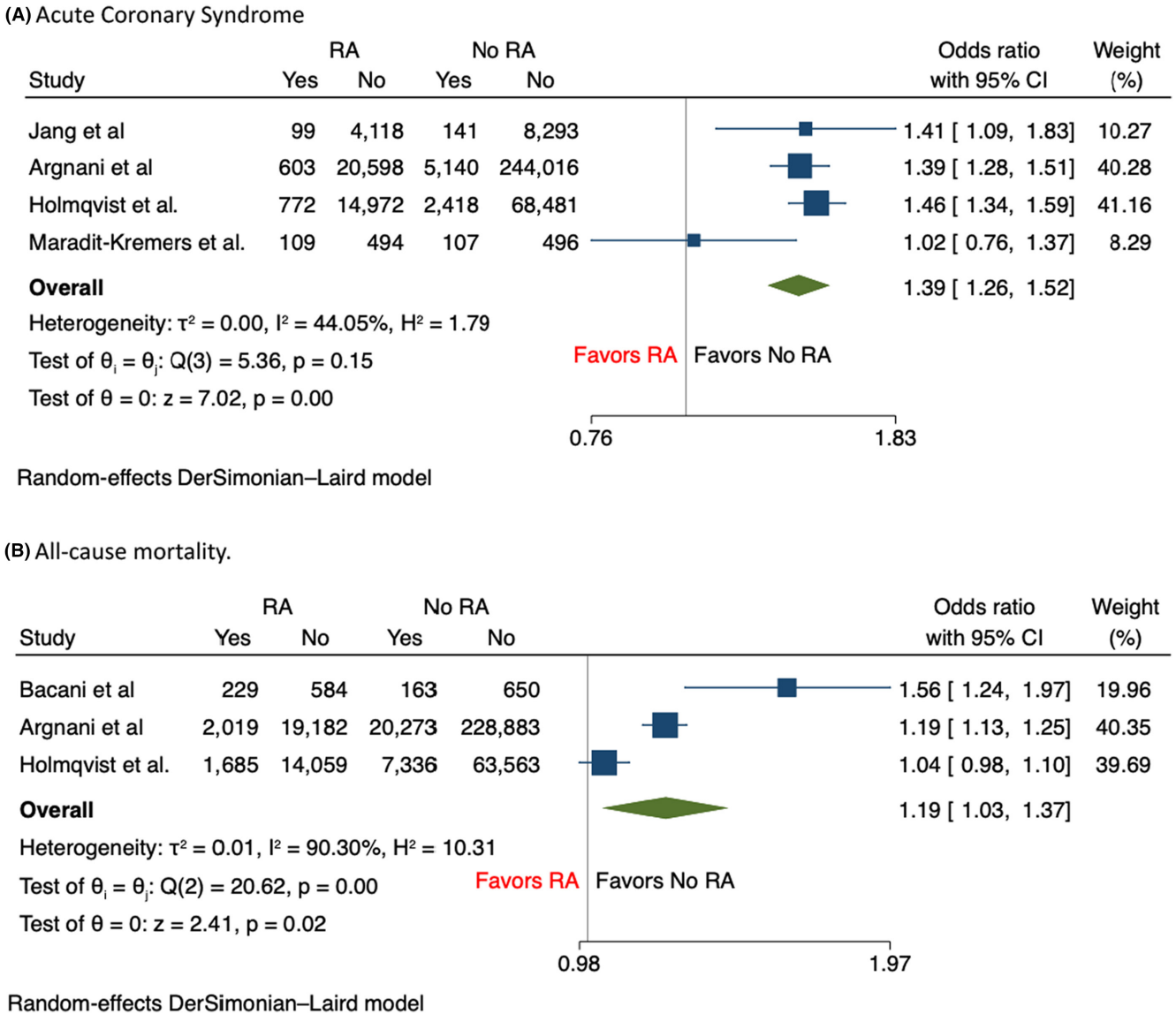

FIGURE 3 Forest plot showing meta-analysis result of secondary outcome: (A) acute coronary syndrome, (B) all-cause mortality.

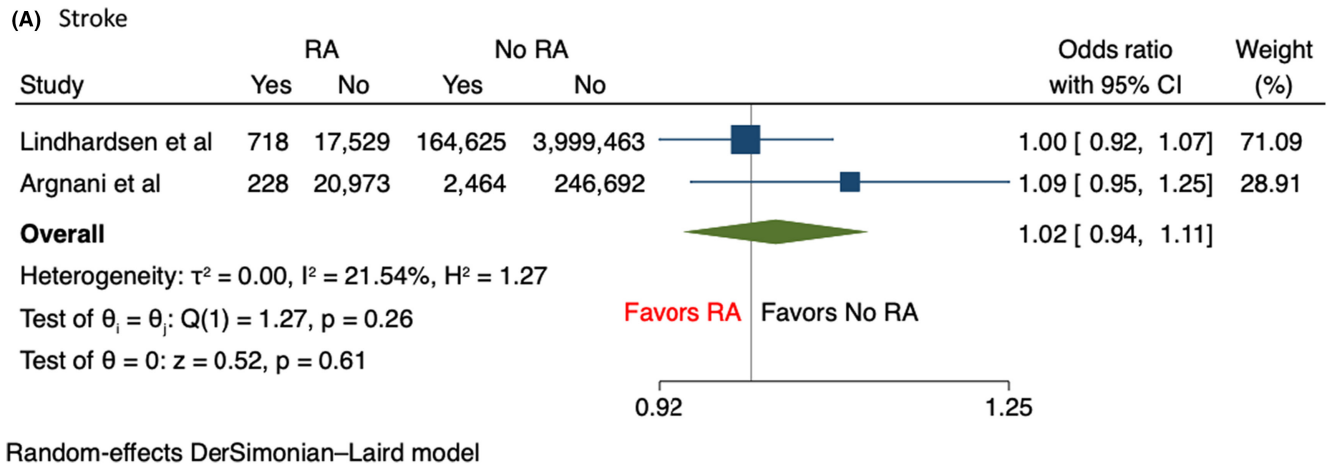

FIGURE 4 Forest plot of stroke.

heart disease in individuals with RA.[46] Furthermore, the activation of inflammatory cells in chronic inflammation observed in RA results in the production of proinflammatory cytokines, such as TNF-α and IL-6. These cytokines have been shown to promote atherosclerosis, impair endothelial function, and contribute to plaque instability, all of which can ultimately lead to the development of ACS.[47] Additionally, RA patients have a higher prevalence of traditional CVD risk factors, including hypertension, dyslipidemia, and diabetes, which further contribute to the increased likelihood of developing ACS.[48]

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids in the treatment of RA may potentially contribute to the elevated risk of ACS. NSAIDs, for instance, have been associated with an increased risk of cardiovascular events, including ACS, owing to their impact on platelet aggregation and blood pressure regulation.[49]

The findings of our meta-analysis have provided compelling evidence supporting the notion that RA patients face a heightened risk of ACS compared to the general population. Given this increased risk, it is imperative for clinicians to be cognizant of the association between RA and ACS. Early screening and the implementation of aggressive management strategies targeting traditional CVD risk factors are crucial in the care of RA patients. By addressing factors such as hypertension, dyslipidemia, and diabetes, healthcare professionals can potentially mitigate the risk of ACS in this patient population. Further research efforts are warranted to gain a comprehensive understanding of the underlying pathophysiology of RA-associated ACS. This understanding is essential in the development of targeted preventive and treatment strategies specifically tailored for RA patients. It is imperative to explore alternative treatment options for RA that do not carry an increased risk of ACS. For instance, biologic DMARDs that selectively target specific inflammatory pathways, without adversely affecting the cardiovascular system, hold promise in this regard. Ultimately, to effectively manage the heightened cardiovascular risk in RA patients and improve overall outcomes, a multidisciplinary approach involving rheumatologists, cardiologists, and primary care physicians is indispensable. Collaboration among these healthcare professionals will enable comprehensive and holistic care, ensuring that both RA and CVD risk factors are adequately addressed. Continued research, clinical vigilance, and a patient-centered approach are essential to optimize the management of ACS risk in RA patients and improve their long-term health outcomes.

4.5 | RA and stroke

RA patients face an elevated risk of cerebrovascular disease, particularly stroke. This increased risk can be attributed to a variety of factors associated with RA, including chronic systemic inflammation, immunological dysregulation, and endothelial dysfunction. Our study revealed comparable likelihood of stroke between the RA and control groups, which is consistent with findings from Wiseman et al.[50] Lindhardsen et al. and others.[20,51–53] However, this result cannot be generalized as results were derived mainly from two studies and one of them holds a higher weight compared with another with a smaller sample size.

A Danish study by Lindhardsen's et al. links RA to an increased risk of AF. RA also shows a heightened risk of stroke, with respective incidence rate ratios of 1.33 for women and 1.34 for men.[20,53] These findings mirror the QRISK2 study, which demonstrated increased CVD risk in RA patients, with hazard ratios of 1.50 for women and 1.38 for men. Notably, QRISK2 considers AF, which exhibited high hazard ratios of 3.06 for women and 2.40 for men.

Chronic systemic inflammation, a hallmark of RA, leads to the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1. This inflammatory environment contributes to the development and progression of atherosclerosis, a major risk factor for stroke. Atherosclerosis involves the formation of fatty plaques in the arterial walls, which can restrict or block blood flow to the brain, resulting in ischemic stroke. Several studies have demonstrated a higher prevalence and severity of atherosclerosis in RA patients compared to healthy individuals.[46,54] Furthermore, it has been shown that RA patients with subclinical atherosclerosis are more susceptible to cerebrovascular events, including stroke and transient ischemic attacks.[55] In addition to atherosclerosis, RA is associated with endothelial dysfunction, which further increases the risk of stroke. Endothelial dysfunction is characterized by impaired vasodilation, increased vascular permeability, and a pro-thrombotic state. These abnormalities can lead to the formation of blood clots that may migrate to the brain and cause strokes. Studies have reported higher levels of endothelial dysfunction markers, such as von Willebrand factor and soluble E-selectin, as well as reduced flow-mediated dilation, increased intima-media thickness, and altered endothelial function in RA patients.[56,57] Moreover, RA patients exhibit elevated levels of procoagulant factors like fibrinogen and factor VIII, which contribute to an increased risk of thrombosis.[58]

In addition to the factors mentioned earlier, cardioembolism plays a significant role in the occurrence of stroke among patients with RA. Cardiac conditions such as AF or valvular heart disease (VHD) can lead to the formation of blood clots that can migrate to the brain and cause a stroke.[59] RA patients are more prone to developing VHDs, including conditions such as aortic regurgitation and mitral valve prolapse, which increase the likelihood of clot formation and subsequent stroke.

5 | STRENGTH AND LIMITATIONS

To our knowledge, this meta-analysis is most comprehensive and updated, with the highest sample size showing robust findings among RA patients with increased risk of AF, ACM, and ACS. The results of our meta-analyses should be interpreted in the context of these limitations. The major limitation is the lack of large, randomized controlled trials. The included studies were observational cohort studies where the possibility of confounding could not be ruled out. We were not able to perform subgroup analysis based on follow-up duration, high-risk cardiovascular group RA patients, and

type of studies because of lack of long term follow up data. Finally, there was a limited number of studies included with varying sample sizes making the weight of each study in the analysis vary considerably. The results of stroke have mainly been pooled with two studies hence results it can't be generalized among patients with RA.

6 | CONCLUSION

Our study shows that RA groups of patients are at increased risk of having AF, ACS, and ACM. Further research is much needed to know the risk factors, the role of gender, and race among such patients.

AUTHOR CONTRIBUTIONS

N.S. and V.J.: contributed to the conception or design of the work. A.M.T., S.P.A., and V.J.: contributed to the acquisition, analysis, or interpretation of data. V.J., P.R., N.S., K.R, Z.W., A.H., S.P.A., A.S., N.D., M.D., A.S., and A.H.: drafted the manuscript. V.A. and P.R.: referenced the manuscript. V.J., P.R., N.D., S.P.A., and M.B.: critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

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CONFLICT OF INTEREST STATEMENT

Vikash Jaiswal serves as an Associate editor section of Cardiology in the European Journal of Medical Research, Frontiers in Cardiology, European Heart Journal Imaging Methods and Practice, and Plos One.

DATA AVAILABILITY STATEMENT

All data related to this study has been uploaded as supplementary material.

ETHICS STATEMENT

Not required.

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