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ORIGINAL RESEARCH

Incidence Rate of Cardiovascular Events in Rheumatoid Arthritis: An Observational Cohort Study in Saudi Arabia

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Purpose: Rheumatoid arthritis (RA) doubles the morbidity of cardiovascular disease (CVD) and leads to a 50% increase in mortality compared to the general population. This study aims to estimate the CVD incidence among RA patients in Saudi Arabia (SA), vital for assessing CVD burdens within this group.

Patients and Methods: This retrospective study took place at two centers in the Eastern Province of SA, including all adult RA patients who visited the rheumatology clinic from 2016 to 2021 and were prescribed disease-modifying antirheumatic drugs (DMARDs). CVD incidence was determined by the diagnosis of ischemic heart disease (IHD), stroke/transient ischemic attack (TIA), venous thromboembolism (VTE), heart failure (HF), and arrhythmia post-RA diagnosis. Additional data collected included demographics, CVD risk factors, comorbidities, RA-related factors, and medication usage.

Results: The study comprised 651 patients, 80.5% of whom were females with an average age of 51. The overall CVD incidence was 11.2 per 1000 person-years, with males experiencing five times more incidents than females. The prevalence of CVD risk factors included 18.7% with hypertension, 7.8% with hyperlipidemia, 18.9% with diabetes, and 42.9% with obesity. Significant predictors of CVD were male gender and RA duration, with adjusted odds ratios (aOR) of 3.17 (95% CI 1.10 to 9.14, P=0.033) and 64.81 (95% CI 3.68 to 1140.6, P=0.004), respectively.

Conclusion: This unique study from SA examined the CVD incidence in RA patients, identifying long disease duration and male gender as significant predictors. Effective reduction of CVD risk in RA patients requires aggressive management of modifiable risk factors and regular risk assessments.

Keywords: cardio-rheumatology, cardiovascular, arrhythmia, autoimmune arthritis, anti-rheumatic

Introduction

Rheumatoid arthritis (RA) is the most prevalent autoimmune inflammatory arthritis,[1] with an estimated prevalence rate of 460 per 100,000 population between 1980 and 2019.[2] In addition to affecting joints, RA induces a chronic systemic inflammatory state that impacts various tissues and organs, including the cardiovascular system.[3] RA is linked to an increased incidence of cardiovascular disease (CVD), which is the primary cause of death among RA patients, resulting in 50% excess mortality compared to the general population.[4] It is believed that RA patients are at heightened risk for sudden cardiac death due to ischemic and non-ischemic heart disease, and cardiac arrhythmias.[5] The

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inflammatory nature of RA may contribute to the connection between RA and CVD, due to the increased production of pro-inflammatory substances like erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukins, and tumor necrosis factors. These substances are known to promote endothelial dysfunction, atherosclerosis plaque formation, and cardiac remodeling.[6–9]

Previous studies on the relationship between CVD and RA within a Saudi Arabian cohort are scarce. One study from the western region of Saudi Arabia assessed hyperlipidemia prevalence in 180 RA patients, finding that 55.1% had elevated total cholesterol and 55.2% had elevated low-density lipoprotein cholesterol.[10] These rates surpass the 20–40% hyperlipidemia rates reported in the general Saudi population by Al-Kaabba et al.[11] Additionally, Al-Bishri et al analyzed 340 RA patients from three centers in Saudi Arabia, identifying hypertension (35.9%), diabetes (30.9%), and dyslipidemia (19.4%) as the most common comorbidities. Furthermore, 7.4% of these patients had ischemic heart disease, 3.3% had cerebrovascular disease, and 2.1% had deep venous thrombosis.[12] Another study involving 75 RA patients showed that 18.7% had diabetes, 26.7% had hypertension, and 6.7% had CVD, with a significantly higher risk of CVD found in those with highly active disease ($p < 0.001$).[13,14] Another study reported that among 116 RA patients in western Saudi Arabia, cardiovascular disease was the most significant cause of death, accounting for 58% of cases.[14]

To the best of our knowledge, there is no published data available in Saudi Arabia regarding the incidence rate of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA). It is critical to understand the epidemiology of CVD in RA to guide current and future healthcare policies. This study was conducted to estimate the incidence rate of CVD among Saudi RA patients and to identify the risk factors associated with CVD in this population.

Materials and Methods

Study Setting

This retrospective study analyzed electronic medical records of patients who attended rheumatology clinics and were prescribed disease-modifying antirheumatic drugs (DMARDs) at Dammam Medical Complex (DMC), as well as hospitalization records at Saud Al-Babtain Center for Cardiac Medicine and Surgery (SBCC) for those hospitalized with a CVD event. Additionally, patients were contacted by phone to collect further data that might have been missed due to incomplete documentation or loss of follow-up.

Dammam Medical Complex, managed by the Eastern Health Cluster, is a public hospital in Dammam with 51 clinics and centers offering a variety of medical services, including rheumatology. Specialized cardiac services are provided by Saud Al-Babtain Cardiac Center, which is part of DMC.[15]

The study received approval from the Institutional Review Board of Saud Al-Babtain Cardiac Center (SBCC-IRB-MC-2021-05). Since DMC lacked an independent IRB at the time of the study, approval was also obtained from the review board of King Fahad Specialist Hospital – Dammam (No. EXT0383). All participants provided verbal informed consent prior to participation, ensuring that they were not subjected to any undue pressure. The interviews were conducted with the utmost confidentiality and respect. IRB approved the verbal informed consent process and the study procedures adhered to the Declaration of Helsinki guidelines for good clinical practice.

Subjects and Procedures

In the current study, we screened all patients who visited rheumatology clinics at DMC from 2016 to 2021 and were treated with disease-modifying anti-rheumatic drugs (DMARDs). We excluded 856 subjects who received DMARDs for conditions other than rheumatoid arthritis (RA) and 9 subjects who were under 18 at the time of their RA diagnosis, from a total of 1516 screened subjects. Follow-ups were conducted via phone calls by three interviewers using a standardized questionnaire and continued until the last recorded notes in charts or the date of data collection on February 2, 2022, whichever came first. To verify cardiovascular disease (CVD) incidents, data were collected from three sources: DMC electronic records, SBCC hospitalization records, and patient self-reports, and were entered into the REDCap software. Discrepancies between records and patient-reported outcomes were resolved by prioritizing the documented chart information.

Measurements and Definitions

Baseline data collection included sociodemographic information, CVD history and risk factors, other comorbidities, RA history, and DMARD usage. Sociodemographic data captured age, gender, nationality, and smoking status. CVD risk factors included diagnosed hypertension, diabetes, family and personal history of CVD, previous coronary artery disease, stroke/transient ischemic attack, heart failure, atrial fibrillation, venous thromboembolism, treated dyslipidemia, and obesity (BMI ≥30 kg/m²).[16] RA diagnosis followed the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria.[17] Other disease-related data such as date of diagnosis, disease duration, and plasma levels of inflammatory markers (CRP and ESR) at diagnosis were collected. RA medications were categorized into four groups: conventional synthetic DMARDs (methotrexate and hydroxychloroquine), TNF inhibitors (adalimumab, infliximab, etanercept), non-TNF biologics (tocilizumab, abatacept, rituximab), and the JAK inhibitor tofacitinib. The study also examined exposure to oral corticosteroids and NSAIDs due to their potential relevance to RA and associated outcomes. Chronic use of NSAIDs and steroids was defined as continuous use for 6 months or more.

Outcomes

Incidence of cardiovascular events was defined as the occurrence and/or diagnosis of ischemic heart disease (myocardial infarction, unstable angina, coronary revascularization), stroke/transient ischemic attack, venous thromboembolism, heart failure, and arrhythmia/conduction abnormalities after the diagnosis of RA. Events were identified from hospitalization/procedural records and patient self-reports of CVD collected via telephone.

Statistical Analysis

Categorical variables were presented as counts and percentages, while continuous variables were presented as either mean ± standard deviation or median and interquartile range, depending on their distribution. Patient-years at risk for cardiovascular diseases were calculated for each subject from the baseline visit to the diagnosis of each outcome, the time of the last outpatient clinic visit, or the time of the telephone interview, whichever came first. Incidence rates were calculated by dividing the number of new events for each outcome by the respective patient-years at risk.

Our exploratory analysis included a univariable logistic regression to identify possible predictors of CVD or arrhythmia among RA patients. Results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Multivariable logistic regression analysis further supplemented our analysis. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using R software.[18]

Results

A total of 651 subjects were eligible for inclusion, of whom 52 had hospitalization records at SBCC for cardiovascular events and 365 were contacted by phone. Figure 1 showed the flowchart of study population.

Baseline Characteristics

Of the 651 included patients, 80.5% were female, and 93% were Saudis, with an average age of 51 (SD±13) years. The most prevalent comorbid diseases were obesity (42.9%), diabetes (18.9%), and hypertension (18.7%). Only a small proportion of patients (1.7%) had established cardiovascular disease before the diagnosis of RA. Regarding smoking status, twenty-three patients were current smokers, while nine reported a previous smoking history. Concerning rheumatoid arthritis history, the median duration since RA diagnosis was 9 years, with median baseline levels of inflammatory markers at 45.4 mm/hr for erythrocyte sedimentation rate and 4.8 mg/dL for C-reactive protein. The most commonly used therapies for RA were methotrexate (91.2%) and hydroxychloroquine (87.4%). Adalimumab was the most frequently prescribed biologic drug (24.6%), while Infliximab was the least frequently used (3.2%). Regarding adjunctive medication use, 47.5% were chronic steroid users and 22.3% were chronic NSAIDs users. Table 1 shows the cohort's baseline characteristics.

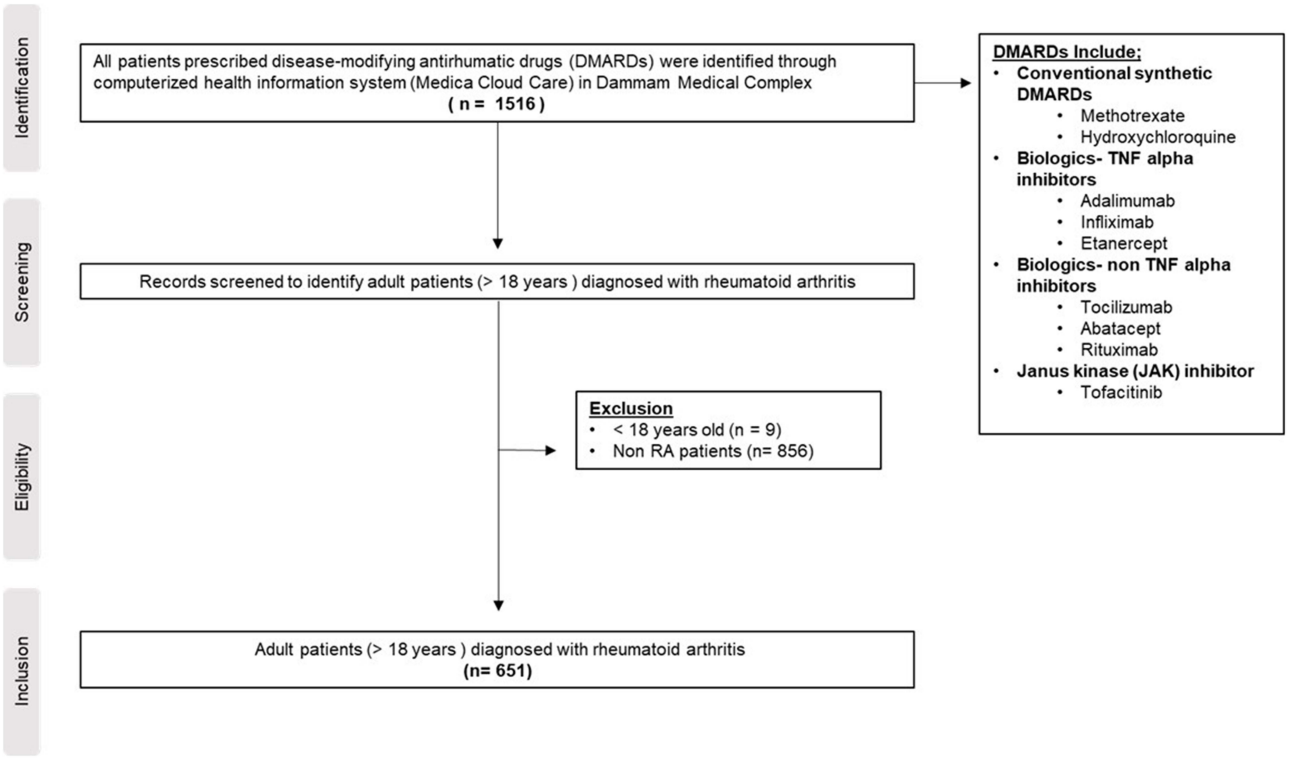

Figure 1 Participants Flowchart.

Incidence of Cardiovascular Events

Over a median follow-up of 6 years (interquartile range: 3 to 9 years), the incidence of CVD events or arrhythmia was 54 (8.2%), including 17 (2.6%) cases of ischemic heart disease, 10 (1.53%) ischemic strokes or TIAs, 5 (0.76%) venous thromboembolisms (VTE), 17 (2.6%) arrhythmias, and 9 (1.38%) heart failure diagnoses. The crude incidence rates per 1000 person-years were 3.4 for ischemic heart disease, 2.02 for ischemic stroke or TIA, 1.02 for VTE, 3.5 for

Table 1 Patients' Baseline Characteristic (n=651)

Demographics	
Age, mean (SD)	51.43 (13.29)
Female, n (%)	524 (80.5)
Saudi, n (%)	607 (93.2)
Past medical history, n (%)	
Diabetes	123 (18.9)
Hypertension	122 (18.7)
Dyslipidemia	48 (7.4)
Obesity	279 (42.9)
History of established CVD	11 (1.7)
Family history of CVD	91 (14.0)
Arrhythmia	1 (0.2)
Osteoporosis	85 (13.1)

(*Continued*)

Table 1 (Continued).

Respiratory disease	52 (8.0)
Hypothyroidism	57 (8.8)
Liver disease	6 (0.9)
Chronic kidney disease	15 (2.3)
Cancer	4 (0.6)
Smoking status n (%)	
Current smokers	23 (3.5)
Past smokers	9 (1.4)
Home medications n (%)	
Aspirin	34 (5.2)
Other anti-platelet therapy	6 (0.9)
Angiotensin-converting enzyme inhibitors or Angiotensin receptor blockers	61 (9.4)
Calcium channel blockers	47 (7.2)
Beta blockers	38 (5.8)
Diuretics	24 (3.7)
Proton pump inhibitors	99 (15.2)
Warfarin	3 (0.5)
Direct oral anticoagulants	7 (1.1)
Insulin	83 (12.7)
Non-insulin diabetes medications	36 (5.5)
Statin	83 (12.7)
Rheumatoid Arthritis history	
Duration of disease (years), median (IQR)	9.2 (6 to 10)
Diagnosis in years categories, n (%)	
< 5 years	103 (16.0)
5 to 9 years	242 (37.6)
10 to 14 years	206 (32.0)
15 to 20	44 (6.8)
> 20 years	49 (7.6)
Inflammatory markers at baseline	
Erythrocyte sedimentation rate, median mm/h (IQR)	45.4 (22 to 64)
C reactive protein, median mg/dL(IQR)	4.8 (1.3 to 7.2)

(*Continued*)

Table 1 (Continued).

Rheumatoid Arthritis Medications n (%)	
Conventional synthetic DMARDs	
Methotrexate	594 (91.2)
Hydroxychloroquine	569 (87.4)
Targeted synthetic DMARDs	
Tofacitinib	47 (7.2)
Biologics - TNF alpha inhibitors	
Adalimumab	160 (24.6)
Infliximab	21 (3.2)
Etanercept	104 (16.0)
Biologics – Non-TNF alpha inhibitors	
Tocilizumab	28 (4.3)
Abatacept	84 (12.9)
Rituximab	27 (4.1)
Adjunctive medication use	
Steroids use n (%)	
Systemic glucocorticosteroids (prednisolone < 7.5 mg or equivalent)	431 (66.2)
Systemic glucocorticosteroids (prednisolone ≥ 7.5 mg or equivalent)	235 (36.1)
None	114 (17.5)
Frequency of steroid use, n (%)	
Chronic ≥ 6 months	227 (47.5)
Intermittent > 5 months/year	68 (14.2)
Intermittent < 5 months/year	183 (38.3)
NSAIDsd use	
Chronic NSAID users, n (%)	145 (22.3)

Notes: Missing %: years of diagnosis (1.1%), Erythrocyte sedimentation rate (2.3%), C reactive protein (91.2%), rheumatoid factor (59.2%).
Abbreviations: CVD, cardiovascular disease; DMARDs, disease-modifying antirheumatic drugs; SD, standard deviation; TNF, Tumor necrosis factor; NSAIDs, non-steroidal anti-inflammatory drugs; IQR, interquartile range.

arrhythmias, and 1.84 for heart failure. Overall, the cumulative 6-year incidence rate for CVD was 11.2 events per 1000 person-years. Males had a higher incidence rate compared to females (69.9 vs 13.3 per 1000 person-years). Table 2 shows the six-years cumulative incidence and incidence rates of cardiovascular disease in Rheumatoid Arthritis Patients from the Kingdom of Saudi Arabia.

Analyses of Risk Factors

Table 3 presents the results from the univariable multivariable logistic regression analyses of incident CVD. Statistically significant risk factors included hypertension (odds ratio [OR] 4.15, 95% CI 2.29–7.51), dyslipidemia (OR 3.67, 95% CI 1.77–7.59), diabetes (OR 2.93, 95% CI 1.57–5.46), and previous history of CVD events (OR 4.95, 95% CI 1.35–18.14).

Table 2 Six-Year Cumulative Incidence and Incidence Rates of Cardiovascular Disease in RA Patients

	Cumulative 6 Years Incidence N (%)	Incidence Rate (Events/1000 Person-Years)
Any cardiovascular event	54 (8.2%)	11.2
Ischemic heart disease	17 (2.6%)	3.4
Ischemic stroke or transient ischemic attack	10 (1.5%)	2.0
Venous Thromboembolism	5 (0.7%)	1.0
Arrhythmias	17 (2.6%)	3.5
Heart Failure	9 (1.3%)	1.8

Notes: Ischemic heart disease includes myocardial infarction, unstable angina, coronary revascularization (Coronary artery bypass graft, Percutaneous coronary intervention).

Table 3 Univariable and Multivariable Logistic Regression for Cardiovascular Disease in Rheumatoid Arthritis Patients

Predictor	Odds Ratio (95% CI, P value)	Adjusted Odds Ratio (95% CI, P value)
Demographics		
Age (years)	1.07 (1.04 to 1.10, P <0.001)	1.03 (0.98 to 1.07, P= 0.247)
Male sex	1.88 (0.98 to 3.16, P = 0.058)	3.17 (1.10 to 9.14, **P = 0.033)**
Past medical history and risk factors		
Diabetes	2.93 (1.57 to 5.46, P= 0.001)	2.34 (0.67 to 1.16, P= 0.137)
Hypertension	4.15 (2.29 to 7.51, P < 0.001)	3.40 (1.09 to 10.61, **P= 0.035**)
Dyslipidemia	3.67 (1.77 to 7.59, P< 0.001)	2.44 (0.56 to 10.63, P= 0.234)
Cardiovascular disease history	4.95 (1.35 to 18.14, P= 0.016)	2.29 (0.19 to 27.93, P= 0.548)
Obesity	1.17 (0.66 to 2.06, P= 0.596)	1.41 (0.57 to 3.47, P= 0.452)
Family history of CVD	1.32 (0.67 to 2.59, P= 0.419)	1.42 (0.50 to 4.03, P= 0.507)
Rheumatoid Arthritis history		
Rheumatoid arthritis duration		
< 5 years	Reference	
5 to 9 years	2.65 (0.75 to 9.40, P= 0.132)	9.75 (0.87 to 126.2, P= 0.081)
10 to 14 years	3.33 (0.95 to 11.72, P= 0.061)	12.82 (0.75 to 190.18, P= 0.064)
15 to 20 years	7.33 (1.8 to 29.94, P= 0.005)	64.81 (3.68 to 1140.6, **P= 0.004**)
> 20 years	4.97 (1.20 to 20.51, P= 0.027)	24.23 (1.35 to 433.9, **P= 0.030**)
Erythrocyte sedimentation rate	0.99 (0.99 to 1.01, P= 0.912)	1.00 (0.98 to 1.01, P= 0.618)
C reactive protein	1.04 (0.94 to 1.15, P= 0.417)	*

(*Continued*)

Table 3 (Continued).

Predictor	Odds Ratio (95% CI, P value)	Adjusted Odds Ratio (95% CI, P value)
Rheumatoid Arthritis Medications		
Methotrexate	0.76 (0.28 to 2.05, P= 0.584)	0.99 (0.19 to 5.25, P= 0.995)
Hydroxychloroquine	0.58 (0.27 to 1.24, P= 0.159)	0.71 (0.20 to 2.45, P=0.826)
Tofacitinib	0.36 (0.09 to 1.56, P= 0.173)	0.54 (0.09 to 3.35, P=0.508)
Biologics - TNF alpha inhibitors	0.83 (0.46 to 1.48, P= 0.524)	1.76 (0.64 to 4.820, P=0.272)
Biologics - Non-TNF alpha inhibitors	0.56 (0.25 to 1.29, P=0.174)	0.32 (0.09 to 1.065, P=0.063)
Steroid and NSAIDs use		
Systemic glucocorticosteroids (prednisolone < 7.5 mg or equivalent)	1.56 (0.81 to 3.03, P= 0.184)	9.50 (1.348 to 66.89, **P=0.024**)
Systemic glucocorticosteroids (prednisolone ≥ 7.5 mg or equivalent)	0.89 (0.49 to 1.62, P=0.694	1.842 (0.65 to 5.25, P=0.252)
Any NSAID use	0.58 (0.24 to 1.39, P= 0.224)	0.43 (0.081 to 2.33, P= 0.330)

Notes: P-value in Bold; statistically significant values. *C-reactive protein was not included in the multivariable logistic regression model due to large missing data.
Abbreviations: CVD; cardiovascular disease, NSAID; non-steroidal anti-inflammatory drug, TNF; tumor necrosis factor.

Age (OR 1.07, 95% CI 1.04–1.10) and a RA duration of 15 years or more were also significant predictors of incident CVD. After adjustment, significant predictors included male sex (adjusted OR 3.17, 95% CI 1.10–9.14), hypertension (adjusted OR 3.40, 95% CI 1.09–10.61), and a RA duration of 15 years or more (adjusted OR 64.81, 95% CI 3.68–1140.6).

Discussion

This study is the first to explore the incidence rates of CVD among RA patients in Saudi Arabia. The overall incidence was 11.2 per 1000 person-years over six years. Demographically, 80.5% of the participants were female, 93% were Saudis, and the mean age was 51 years. The prevalence of traditional CVD risk factors was 18.9% for diabetes, 18.7% for hypertension, 42.9% for obesity, and 7.4% for dyslipidemia. Globally, CVD incidence varies by country and population. The Global Burden of Disease study reported a global incidence of 684.33 per 100,000 population (6.8 per 1000), and in Central Asia, the age-adjusted incidence was 1100 per 100,000 population.[19] Locally, a one-year study from a tertiary center in Jeddah (2019–2020) reported a lower incidence of ischemic heart diseases at 2.2 per 1000 person-years in the general population.[20]

Several studies around the world have investigated the incidence of cardiovascular disease (CVD) among rheumatoid arthritis (RA) populations, revealing varied rates. For instance, a national Korean study reported an incidence rate of 18.2 per 1000 person-years.[21] In Sweden, the rate was 21 per 1000 person-years,[22] while a Canadian inception cohort study revealed a rate of 7.1 per 1000 person-years.[23] Similarly, a Portuguese cohort of RA women reported a rate of 7 per 1000 person-years.[24] In England, the incidence rate was 35.33 per 1000 person-years, using a broader definition of CVD that included twelve different presentations.[25] Note that all rates were standardized to per 1000 person-years for comparison. These rates indicate higher incidences in RA patients compared to the general population, which may be attributed to differences in study methodologies, inclusion criteria, CVD definitions, follow-up durations, and variations in genetic, environmental, and lifestyle risk factors.

Ischemic Heart Disease (I.e Coronary Heart Disease)

As previously mentioned, a retrospective study conducted by Albeladi et al in Jeddah, Saudi Arabia, reported the incidence of coronary artery disease (CAD) in 2019 as 2.20 per 1000 person-years.[20] This rate is lower than the 3.4 per 1000 person-years reported for ischemic heart diseases. Interestingly, Albeladi et al also reported a rate of 303 per 1000 person-years in 2020, a significant increase likely due to COVID-19, which is known to exacerbate CVD.[26] Our study, which followed up until 2021, did not account for the COVID-19 virus. Additionally, gender differences may have influenced these findings, as men, who comprised 77% of the study's participants, have a twofold higher incidence of CAD than women.[27] In our study, 80.5% of participants were females, reflecting the higher prevalence of RA among women.[28] Cho et al reported a CAD incidence of 5.2 per 1000 person-years in males versus 1.5 in females,[21] and Chung et al reported 3.36 per 1000 person-years in males versus 1.36 in females.[29] These findings suggest a two- to threefold increase in CAD among RA males compared to females, mirroring trends seen in the general population. Our study also confirmed a higher incidence of CVD or arrhythmia in males, with rates of 69.9 per 1000 person-years versus 13.3 per 1000 person-years in females.

Stroke and/or Transient Ischemic Attack

On a national level, the incidence of first-ever stroke was estimated through five cross-sectional studies across different regions of Saudi Arabia. Our findings indicated a rate of 1.53% (2.02 per 1000 person-years) for ischemic stroke or TIA in patients with RA, which is higher than previously reported in the general population: 0.0139% (13.9 per 100,000 people) over 1 year,[30] 0.0159% (15.9 per 100,000 people) over two years,[31] 0.0298% (29.8 per 100,000 people) over 3 years,[32] 0.0438% (43.8 per 100,000 people) over ten years,[33] and 0.0576% (57.6 per 100,000 people) over one year.[34] A systematic review and meta-analysis of these studies found an annual incidence of 29 strokes per 100,000 people (95% CI: 15 to 47), yielding a pooled rate of 0.029% (95% CI: 0.015 to 0.047), which is lower than in other high-income countries.[35]

Internationally, stroke rate for women with RA, as indicated by the Nurses' Health Study (1.12 per 1000 person-years), is not considered statistically significant compared to the general population, with a multivariable-adjusted relative risk of 1.48 (95% CI, 0.70 to 3.12).[36] However, our results align with other studies that explored the association between stroke and RA. For example, a study in the Korean population revealed a stroke incidence rate of 2.85 per 1000 person-years in RA patients, with a more pronounced association in females (adjusted HR: 1.27) compared to males (adjusted HR: 1.14; $p = 0.037$).[37] Conversely, our rates are lower than those reported in a Danish nationwide cohort study, which showed a stroke incidence rate of 7.6 per 1000 person-years among 718 subjects with RA.[38]

Venous Thromboembolism

Regarding venous thromboembolism (VTE) events, a single-center cohort study among the Saudi population reported a cumulative incidence of 0.17% (1.7 per 1000 patients) over 3 years, with an overall incidence of 158 per 1000 person-years for recurrent VTE.[39] These findings are higher than those in the current study, reported an event rate of 0.76% (1.02 per 1000 person-years). Contrarily, a Swedish register-based cohort study found a VTE incidence of 0.71% among RA patients, compared to 0.36% in the matched general population.[40] An earlier study in Sweden observed even higher rates of VTE, with 5.9 per 1000 person-years in RA patients versus 2.8 in the general population, noting that the increased risk remained consistent up to 10 years from RA diagnosis.[41] Meanwhile, a cohort of 609 RA patients showed a VTE incidence of 7.2% over 30 years via ultrasound.[42] The relatively short median follow-up of 6 years in our study may account for the lower rate observed.

Arrhythmias

We reported an incidence rate of 3.5 per 1000 person-years with a total of 17 events (2.6%) for arrhythmias, which included various types such as supraventricular tachycardia, atrial flutter, atrial fibrillation, ventricular tachycardia, premature ventricular contraction, and left bundle branch block. The incidence rate of atrial fibrillation (AF) in rheumatoid arthritis (RA) patients was investigated through a nationwide, longitudinal, register-based cohort study in Denmark. The study found an incidence rate of 8.2 per 1000 person-years among 18,247 RA patients, compared to

6.0 per 1000 person-years in age- and sex-matched controls. Women exhibited a slightly higher relative risk than men, and AF was more prevalent in the youngest age groups.[38] Another smaller inception cohort of 813 RA subjects reported a cumulative incidence of AF at 18.3% over an average follow-up of 9.6 (± 6.9) years.[43] Furthermore, an Italian retrospective study noted an AF incidence rate of 7.01 per 1000 person-years among 21,201 RA patients, higher than the 5.98 per 1000 person-years in a non-RA cohort. The risk remained significant even after adjusting for cardiovascular comorbidities such as hypertension and diabetes, which were more prevalent in the RA cohort.[44] Despite a broader definition of arrhythmia used in our study, the resultant incidence rate was lower. However, a similar rate was reported by Kim et al in a US retrospective cohort of 20,852 RA patients from a commercial health plan, with an AF incidence rate of 4.0 (95% CI 3.4 to 4.7) per 1000 person-years over a two-year follow-up. This study did not demonstrate an increased risk of AF in the RA cohort compared to non-RA, with a hazard ratio (HR) of 1.1 (95% CI 0.9 to 1.4) adjusted for diabetes, cardiovascular disease, and medications.[45] Similarly, Jang et al did not establish an association between AF and RA, with a cumulative incidence of AF over 10 years of follow-up at 4.01 per 1000 person-years (95% CI 329–489) in RA versus 3.79 (95% CI 329–437) in matched controls.[46]

Heart Failure

The study identified 9 (1.38%) cases of heart failure diagnosis, corresponding to an incidence rate of 1.84 per 1000 person-years, which is low compared to other studies. For instance, a retrospective population-based study in Minnesota including 575 RA subjects reported a heart failure (HF) incidence rate of 19.9 per 1000 person-years over a median follow-up of 11.8 years, with a higher risk among rheumatoid factor-positive patients.[47] The positive correlation between HF and elevated rheumatologic biomarkers such as ESR, CRP, rheumatoid factor, and TNF was described in several other studies.[48–50] In another prospective study evaluating the effect of anti-TNF medications on HF rates among 13,171 RA patients, the reported rate of HF was 3.9%, significantly ($P < 0.05$) less common in anti-TNF-treated patients (3.1%) compared to the remaining patients (3.8%).[51]

Risk Factors

In rheumatoid arthritis (RA), accelerated atherosclerosis might be due to a higher occurrence of conventional CVD risk factors, including smoking, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, and obesity.[52] Our study recorded the prevalence of these risk factors as follows: 18.9% for diabetes, 18.7% for hypertension, 7.4% for dyslipidemia, and 49.2% for obesity. The Saudi National Heart Center reported lower prevalences in the general population of Saudi Arabia, including 12.3% for diabetes mellitus, 16% for smoking, 22% for hypertension, and 35–40% for dyslipidemia.[53] Our RA cohort showed higher diabetes rates, but lower rates of hypertension and dyslipidemia compared to the general population. Notably, the lower dyslipidemia rates in our RA patients align with previous findings that RA patients do not generally have higher hyperlipidemia than the general population, and their cholesterol levels are often lower when the disease is active.[54] This phenomenon, known as the "lipid paradox", suggests that reduced lipid levels in RA patients are paradoxically linked to an increased CVD risk.[55] Regarding obesity, our findings were double those of the Arab Teens Lifestyle Study, which reported a 23% obesity rate among adults in the general Saudi population.[56] In contrast, we observed a lower prevalence of all risk factors compared to another cohort of 340 RA patients in Saudi Arabia, which reported higher rates of hypertension (35.9%), diabetes (30.9%), and dyslipidemia (19.4%) in a cross-sectional study.[12] These variations could be due to demographic, regional, and study design differences. In our study, hypertension was identified as the most significant predictor of incident CVD in the multivariable analysis.

Beyond the traditional risk factors, RA patients also face increased CVD morbidity due to disease-related factors such as systemic inflammation and vascular endothelial activation caused by immune dysregulation and inflammation, as well as treatment-related factors including corticosteroids that can accelerate atherosclerotic disease.[57–59] Additionally, RA patients with elevated erythrocyte sedimentation rates are at heightened risk for cardiovascular complications.[60] Unlike previous studies, we found no significant association between CVD incidence and inflammation measured by baseline C-reactive protein (OR 1.04, CI: 0.94 to 1.15, P-value = 0.417) or erythrocyte sedimentation rate (OR: 0.99, CI: 0.99 to 1.01, P-value = 0.417). These findings may be attributable to our cohort selection criteria, which required at least one

DMARD prescription before inclusion, suggesting low systemic inflammation as all RA patients received DMARDs. Additionally, the values obtained at a single point may not adequately reflect the severity of the disease since some patients may experience flare-ups and progressions over time.

Generally, we found no significant association between the use of DMARDs and the incidence of CVD, although the odds ratios suggest a protective effect. These results align with previous studies investigating the impact of treatments on CVD. Methotrexate (MTX) was the most used DMARD in our cohort and is a highly recommended agent according to the 2015 and 2021 American College of Rheumatology Guidelines for the treatment of RA.[1,61] A 2015 analysis found that MTX use was associated with a 21% reduction in cardiovascular events compared to non-MTX use, including other DMARDs or no therapy at all.[62] This improvement in CVD outcomes was also observed with TNF-alpha inhibitors,[63] abatacept,[64] and Janus kinase inhibitors.[65] Additionally, the use of low-dose glucocorticoids (GC) showed a significant association with CVD incidence in the current study, with an adjusted odds ratio (aOR) of 9.50 (95% CI: 1.348 to 66.89, P=0.024). There is conflicting evidence regarding the effect of GC on incident CVD; while a reduced CVD risk with low-dose corticosteroids was observed in a US registry-based study,[66] a more recent analysis reported an increased risk associated with GC use, even at low doses, in a study involving 87,794 adults with immune-mediated inflammatory diseases and no prior CVD over a 5-year median follow-up.[67]

Study Limitations

The retrospective design of our study may have led to some subjects being lost to follow-up, which could have resulted in an underestimation of CVD incidence. Although we made every effort to ensure complete data collection, information loss is possible due to the nature of the study design. Additionally, the lack of a non-RA control group limits our ability to definitively attribute CVD incidence to RA alone. Instead, we relied on previously published literature to contextualize our results. This study was conducted in eastern Saudi Arabia, which may limit the generalizability of the findings to other regions or populations with different genetic, environmental, and lifestyle factors.

The median follow-up period of 6 years may not fully capture the long-term cardiovascular risks in patients with RA. Extended follow-up is necessary to more accurately determine the lifetime risk and the effects of RA management on cardiovascular outcomes. The impact of different RA treatment regimens on CVD risk was not thoroughly examined in the current study. As RA management evolves, it is critical to understand how various treatments affect cardiovascular outcomes, especially as treatment approaches can change over time and establishing a causal relationship was challenging with the study's design. Additionally, the study did not deeply analyze the role of lifestyle factors like diet, physical activity, and stress, which are crucial to cardiovascular health. Our univariable analysis aimed to be exploratory and identify predictors. This approach was limited by residual confounding due to variables like socioeconomic status or medication adherence, which were either unmeasured or inadequately measured, impacting our ability to establish a clear link between RA and CVD. The retrospective nature of the study also meant that we could not assess disease activity and severity indicators, such as the disease activity score in 28 joints (DAS28-CRP or DAS28-ESR), during data collection, nor were these examined as predictors of CVD in our cohort. We did, however, obtain baseline values of inflammatory markers ESR and CRP, which did not emerge as significant predictors of CVD. Likewise, data on rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) were largely absent from our dataset and thus were excluded from the analysis. Care should be taken when interpreting the results of multivariable logistic regression analysis due to potential misinterpretations known as the "Table 2 fallacy".[68]

Conclusion

To the best of our knowledge, this is the only study estimating the incidence of CVD and associated risk factors in RA patients in Saudi Arabia. Our findings indicate that male gender, longer disease duration, and comorbid hypertension are significant predictors of CVD in this group. Therefore, aggressive management of modifiable CVD risk factors, coupled with regular and early risk assessments, is recommended to reduce the risk of CVD in the RA population.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res*. 2016;68(1):1–25. doi:10.1002/acr.22783
2. Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. *Rheumatol Int*. 2021;41(5):863–877. doi:10.1007/s00296-020-04731-0
3. Peters MJL, Symmons DPM, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis*. 2010;69(2):325–331. doi:10.1136/ard.2009.113696
4. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis*. 2012;71(9):1524–1529. doi:10.1136/annrheumdis-2011-200726
5. Mantel Ä, Holmqvist M, Andersson DC, Lund LH, Askling J. Association between rheumatoid arthritis and risk of ischemic and nonischemic heart failure. *J Am Coll Cardiol*. 2017;69(10):1275–1285. doi:10.1016/j.jacc.2016.12.033
6. DeMizio DJ, Geraldino-Pardilla LB. Autoimmunity and inflammation link to cardiovascular disease risk in rheumatoid arthritis. *Rheumatol Ther*. 2020;7(1):19–33. doi:10.1007/s40744-019-00189-0
7. Prasad M, Hermann J, Gabriel SE, et al. Cardiorheumatology: cardiac involvement in systemic rheumatic disease. *Nat Rev Cardiol*. 2015;12(3):168–176. doi:10.1038/nrcardio.2014.206
8. Murdaca G, Colombo BM, Cagnati P, Gulli R, Spanò F, Puppo F. Endothelial dysfunction in rheumatic autoimmune diseases. *Atherosclerosis*. 2012;224(2):309–317. doi:10.1016/j.atherosclerosis.2012.05.013
9. Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. *Ann Rheum Dis*. 2011;70(1):8–14. doi:10.1136/ard.2010.142133
10. Attar SM. Hyperlipidemia in rheumatoid arthritis patients in Saudi Arabia. Correlation with C-reactive protein levels and disease activity. *Saudi Med J*. 2015;36(6):685–691. doi:10.15537/smj.2015.6.10557
11. Al-Kaabba AF, Al-Hamdan NA, El Tahir A, et al. Prevalence and correlates of dyslipidemia among adults in Saudi Arabia: results from a national survey. *Open J Endocr Metab Dis*. 2012;02(04):89–97. doi:10.4236/ojemd.2012.24014
12. Al-Bishri J, Attar S, Bassuni N, et al. Comorbidity profile among patients with rheumatoid arthritis and the impact on prescriptions trend. *Clin Med Insights Arthritis Musculoskelet Disord*. 2013;6:11–18. doi:10.4137/CMAMD.S11481
13. Bawazir YM. Clinicodemographic profiles of rheumatoid arthritis patients from a single center in Saudi Arabia. *Open Access Rheumatol*. 2020;12:267–275. doi:10.2147/OARRR.S277956
14. Al-Ghamdi A. The co-morbidities and mortality rate among rheumatoid arthritis patients at the western region of Saudi Arabia a retrospective cross-sectional study. *J King Abdulaziz Univ Med Sci*. 2009;16(3):15–29.
15. Eastern Health Cluster. Available from: https://ehc.med.sa/en/Pages/default.aspx. Acessed 01 Feburary, 2024. About EHC.
16. WH Consultation. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:1–253.
17. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2010;69(9):1580–1588. doi:10.1136/ard.2010.138461
18. R Core Team. The R Project for Statistical Computing. Available from: https://www.R-project.org/. Accessed July 4, 2024.
19. Li Y, Cao G, Jing W, Liu J, Liu M. Global trends and regional differences in incidence and mortality of cardiovascular disease, 1990−2019: findings from 2019 global burden of disease study. *Eur J Prev Cardiol*. 2023;30(3):276–286. doi:10.1093/eurjpc/zwac285
20. Albeladi F, Wahby salem I, Zahrani M, et al. Incidence of coronary artery disease in King Abdulaziz University Hospital, Jeddah, Saudi Arabia, 2019–2020: a retrospective cohort study. *Cureus*. 2022. doi:10.7759/cureus.28770
21. Cho SK, Kim D, Won S, et al. Impact of anti-rheumatic treatment on cardiovascular risk in Asian patients with rheumatoid arthritis. *Semin Arthritis Rheum*. 2018;47(4):501–506. doi:10.1016/j.semarthrit.2017.08.002
22. Ajeganova S, Andersson MLE, Frostegård J, Hafström I. Disease factors in early rheumatoid arthritis are associated with differential risks for cardiovascular events and mortality depending on age at onset: a 10-year observational cohort study. *J Rheumatol*. 2013;40(12):1958–1966. doi:10.3899/jrheum.130365
23. Barra LJ, Pope JE, Hitchon C, et al. The effect of rheumatoid arthritis–associated autoantibodies on the incidence of cardiovascular events in a large inception cohort of early inflammatory arthritis. *Rheumatology*. 2017:kew474. doi:10.1093/rheumatology/kew474
24. Castro AM, Carmona-Fernandes D, Rodrigues AM, et al. Incidence and predictors of cardiovascular events in a cohort of patients with rheumatoid arthritis. *Acta Reumatol Port*. 2016;41(3):213–219.
25. Pujades-Rodriguez M, Duyx B, Thomas SL, et al. Rheumatoid arthritis and incidence of twelve initial presentations of cardiovascular disease: a population record-linkage cohort study in England. *PLoS One*. 2016;11(3). doi:10.1371/journal.pone.0151245
26. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol*. 2020;17(9):543–558. doi:10.1038/s41569-020-0413-9
27. Gao Z, Chen Z, Sun A, Deng X. Gender differences in cardiovascular disease. *Med Nov Technol Devices*. 2019;4:100025. doi:10.1016/j.medntd.2019.100025

28. Gerosa M, De Angelis V, Riboldi P, Meroni PL. Rheumatoid arthritis: a female challenge. *Womens Health*. 2008;4(2):195–201. doi:10.2217/17455057.4.2.195
29. Chung WS, Lin CL, Peng CL, et al. Rheumatoid arthritis and risk of acute myocardial infarction—A nationwide retrospective cohort study. *Int J Cardiol*. 2013;168(5):4750–4754. doi:10.1016/j.ijcard.2013.07.233
30. Al-Shenqiti AM, Ibrahim SR, Khaled OA, Ali ARH, Ahmed MS. Incidence of first time stroke: a Saudi experience. *Eur Neurol*. 2017;77(3–4):147–151. doi:10.1159/000455094
31. Ayoola AE, Banzal SS, Elamin AK, Gadour MO, Elsammani EW, Al-Hazmi MH. Profile of stroke in Gizan, Kingdom of Saudi Arabia. *Neurosciences*. 2003;8(4):229–232.
32. Al-Rajeh S, Larbi EB, Bademosi O, et al. Stroke Register: experience from the Eastern Province of Saudi Arabia. *Cerebrovascular Dis*. 1998;8(2):86–89. doi:10.1159/000015823
33. Al Rajeh S, Awada A, Niazi G, Larbi E; Stroke in a Saudi Arabian National Guard community. Analysis of 500 consecutive cases from a population-based hospital. *Stroke*. 1993;24(11):1635–1639. doi:10.1161/01.STR.24.11.1635
34. Alhazzani A, Mahfouz A, Abolyazid A, et al. Study of stroke incidence in the Aseer Region, Southwestern Saudi Arabia. *Int J Environ Res Public Health*. 2018;15(2):215. doi:10.3390/ijerph15020215
35. Alqahtani BA, Alenazi AM, Hoover JC, et al. Incidence of stroke among Saudi population: a systematic review and meta-analysis. *Neurol Sci*. 2020;41(11):3099–3104. doi:10.1007/s10072-020-04520-4
36. Solomon DH, Karlson EW, Rimm EB, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation*. 2003;107(9):1303–1307. doi:10.1161/01.CIR.0000054612.26458.B2
37. Kang S, Han K, Jung JH, et al. Associations between cardiovascular outcomes and rheumatoid arthritis: a nationwide population-based cohort study. *J Clin Med*. 2022;11(22):6812. doi:10.3390/jcm11226812
38. Lindhardsen J, Ahlehoff O, Gislason GH, et al. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ*. 2012;344(mar08 2):e1257. doi:10.1136/bmj.e1257
39. AlEidan FAS, AlManea RK, AlMoneef AT, et al. Incidence and predictors of recurrence and mortality following first venous thromboembolism among the Saudi population: single-center cohort study. *Int J Gen Med*. 2022;15:7559–7568. doi:10.2147/IJGM.S359893
40. Molander V, Bower H, Frisell T, Askling J. Risk of venous thromboembolism in rheumatoid arthritis, and its association with disease activity: a nationwide cohort study from Sweden. *Ann Rheum Dis*. 2021;80(2):169–175. doi:10.1136/ANNRHEUMDIS-2020-218419
41. Holmqvist ME, Neovius M, Eriksson J, et al. Risk of venous thromboembolism in patients with rheumatoid arthritis and association with disease duration and hospitalization. *JAMA*. 2012;308(13):1350. doi:10.1001/2012.jama.11741
42. Liang KP, Liang KV, Matteson EL, McClelland RL, Christianson TJH, Turesson C. Incidence of noncardiac vascular disease in rheumatoid arthritis and relationship to extraarticular disease manifestations. *Arthritis Rheum*. 2006;54(2):642–648. doi:10.1002/art.21628
43. Bacani AK, Crowson CS, Roger VL, Gabriel SE, Matteson EL. Increased incidence of atrial fibrillation in patients with rheumatoid arthritis. *Biomed Res Int*. 2015;2015:809514. doi:10.1155/2015/809514
44. Argnani L, Zanetti A, Carrara G, et al. Rheumatoid arthritis and cardiovascular risk: retrospective matched-cohort analysis based on the RECORD study of the Italian Society for Rheumatology. *Front Med*. 2021:8. doi:10.3389/fmed.2021.745601
45. Kim SC, Liu J, Solomon DH. The risk of atrial fibrillation in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2014;73(6):1091–1095. doi:10.1136/annrheumdis-2013-203343
46. Jang SY, Kang KW, Jo M, Park M. Risk of new-onset acute coronary syndrome and atrial fibrillation in patients with rheumatoid arthritis compared with a risk-set and propensity score-matched cohort— A nationwide cohort study. *Circ J*. 2021;85(2):194–200. doi:10.1253/circj.CJ-20-0825
47. Nicola PJ, Maradit-Kremers H, Roger VL, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. *Arthritis Rheum*. 2005;52(2):412–420. doi:10.1002/art.20855
48. Biskup M, Biskup W, Majdan M, Targońska-Stępniak B. Cardiovascular system changes in rheumatoid arthritis patients with continued low disease activity. *Rheumatol Int*. 2018;38(7):1207–1215. doi:10.1007/s00296-018-4053-x
49. Ahlers MJ, Lowery BD, Farber-Eger E, et al. Heart failure risk associated with rheumatoid arthritis–related chronic inflammation. *J Am Heart Assoc*. 2020;9(10). doi:10.1161/JAHA.119.014661
50. Ferreira MB, Fonseca T, Costa R, et al. Prevalence, risk factors and proteomic bioprofiles associated with heart failure in rheumatoid arthritis: the RA-HF study. *Eur J Intern Med*. 2021;85:41–49. doi:10.1016/j.ejim.2020.11.002
51. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. *Am J Med*. 2004;116(5):305–311. doi:10.1016/j.amjmed.2003.09.039
52. Baghdadi LR, Woodman RJ, Shanahan EM, Mangoni AA. The impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: a systematic review and meta-analysis. *PLoS One*. 2015;10(2):e0117952. doi:10.1371/journal.pone.0117952
53. National Heart Center. *Cardiovascular Disease: A Public Health Priority*. National Heart Center; 2022.
54. Kraakman MJ, Dragoljevic D, Kammoun HL, Murphy AJ. Is the risk of cardiovascular disease altered with anti-inflammatory therapies? Insights from rheumatoid arthritis. *Clin Transl Immunology*. 2016;5(5):e84. doi:10.1038/cti.2016.31
55. Myasoedova E, Crowson CS, Kremers HM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. *Ann Rheum Dis*. 2011;70(3):482–487. doi:10.1136/ard.2010.135871
56. Alsulami S, Baig M, Ahmad T, et al. Obesity prevalence, physical activity, and dietary practices among adults in Saudi Arabia. *Front Public Health*. 2023;11:1124051. doi:10.3389/fpubh.2023.1124051
57. Kaplan MJ, McCune WJ. New evidence for vascular disease in patients with early rheumatoid arthritis. *Lancet*. 2003;361(9363):1068–1069. doi:10.1016/S0140-6736(03)12901-7
58. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? *Arthritis Rheum*. 2002;46(4):862–873. doi:10.1002/art.10089
59. Pasceri V, Yeh ET. A tale of two diseases: atherosclerosis and rheumatoid arthritis. *Circulation*. 1999;100(21):2124–2126. doi:10.1161/01.cir.100.21.2124
60. Wållberg-Jonsson S, Johansson H, Ohman ML, Rantapää-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. *J Rheumatol*. 1999;26(12):2562–2571.

61. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res*. 2021;73(7):924–939. doi:10.1002/acr.24596
62. Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? *Nat Rev Rheumatol*. 2015;11(7):390–400. doi:10.1038/nrrheum.2015.40
63. Sattin M, Towheed T. The effect of TNFα-inhibitors on cardiovascular events in patients with rheumatoid arthritis: an updated systematic review of the literature. *Curr Rheumatol Rev*. 2016;12(3):208–222.
64. Giollo A, Bissell LA, Buch MH. Cardiovascular outcomes of patients with rheumatoid arthritis prescribed disease modifying anti-rheumatic drugs: a review. *Expert Opin Drug Saf*. 2018;17(7):697–708. doi:10.1080/14740338.2018.1483331
65. Kang EH, Liao KP, Kim SC. Cardiovascular Safety of biologics and JAK inhibitors in patients with rheumatoid arthritis. *Curr Rheumatol Rep*. 2018;20(7):42. doi:10.1007/s11926-018-0752-2
66. Solomon DH, Reed GW, Kremer JM, et al. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. *Arthritis Rheumatol*. 2015;67(6):1449–1455. doi:10.1002/art.39098
67. Pujades-Rodriguez M, Morgan AW, Cubbon RM, Wu J. Dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases: a population-based cohort study. *PLoS Med*. 2020;17(12):e1003432. doi:10.1371/journal.pmed.1003432
68. Westreich D, Greenland S. The table 2 fallacy: presenting and interpreting confounder and modifier coefficients. *Am J Epidemiol*. 2013;177(4):292–298. doi:10.1093/aje/kws412