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# Prevalence and the clinical outcome of atrial fibrillation in patients with Autoimmune Rheumatic Disease

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ABSTRACT

*Background:* Systemic inflammation plays an important role in the pathogenesis of atrial fibrillation (AF). However, little evidence exists whether the risk of AF is increased in autoimmune rheumatic disease (ARD).
*Methods:* In 20,772 consecutive ARD patients (mean age 42 ± 17 years, 13,683 female) in a tertiary hospital from 2005 to 2015, AF prevalence, comorbidities and cardiovascular (CV) outcomes were evaluated.
*Results:* AF was observed in 235 (1.1%) patients. The mean duration to AF diagnoses was 5.9 ± 2.4 years. Compared with patients without AF, AF patients were older, and had a higher CRP level (5.1 ± 0.7 vs. 2.7 ± 0.2 mg/L, $p = 0.01$), higher incidence of hypertension, heart failure and coronary artery disease. The AF prevalence was higher in inflammatory myositis (3.5%) and systemic sclerosis (2.3%) than that in other ARDs (all $p < 0.05$).
In the multivariate analysis, the independent predictors of AF were an older age (HR 1.05, 95% CI: 1.04–1.06, $p = 0.01$), hypertension (HR 2.28, 95% CI: 1.70–3.06, $p < 0.001$), high CRP levels (HR 1.75, 95% CI: 1.07–2.86, $p = 0.04$), and heart failure (HR 11.96, 95% CI: 8.13–17.60, $p = 0.03$). During a mean follow-up period of 6.8 ± 4.5 years, ARD patients with AF had a higher all cause death (16.5% vs. 2.1%, $p < 0.001$) and incidence of strokes (1.9% vs. 0.4%, $p = 0.001$) than non-AF patients.
*Conclusions:* The incidence of AF in ARD was affected by specific disease and an inflammatory status manifested by the CRP level. AF in ARD was related to a higher mortality and strokes mandating meticulous follow-up.


## 1. Introduction

The link between systemic inflammation and atherosclerosis and cardiovascular diseases (CVDs) such as myocardial infarctions and coronary artery disease has been well established [1,2]. Atrial fibrillation (AF) is the most common cardiac arrhythmia and is strongly related to cardiovascular disease (CVD) [3]. Previous research suggests a potential role of inflammation in the development and maintenance of AF [4]. Several epidemiological studies have shown a significant association between the serum inflammatory markers such as the tumor necrosis factor-α, interleukin (IL)-2, IL-6, and c reactive protein (CRP), and the risk of AF development, recurrence, or persistence [4–6]. The link between the inflammatory markers and AF seems clearest among patients with inflammatory cardiac conditions, such as pericarditis or myocarditis, but several large prospective cohort studies also found an association between systemic inflammation and the incident AF even after controlling for the traditional risk factors of CVD [7,8].

If systemic inflammation is one of the causes of AF, patients with chronic inflammatory conditions such as autoimmune rheumatic disease (ARD), including rheumatoid arthritis (RA), may have an increased risk of AF. It is still controversial whether RA is associated with the risk of AF. A recently published Danish cohort study noted a 40% increase in the risk of AF in patients with RA compared with the general population [9]. However, Kim et al. reported that data from a large US commercial insurance plan showed no increased risk of AF associated with RA. Active inflammatory bowel disease (IBD) is associated with an increased risk of AF and strokes [10]. The relationship with AF has not been reported in other types of ARD.

Autoimmune rheumatic diseases (ARDs) are associated with higher rates of cardiovascular morbidity and mortality, primarily secondary to accelerated atherosclerosis. This disease entity can be attributed to traditional risk factors for atherosclerosis and the use of specific drugs, such as corticosteroids, but also might be the result of other autoimmune and inflammatory mechanisms that are aggravated in ARDs. Recent publications have examined the relationship between atrial fibrillation (AF) and some ARDs including RA and IBD with variable results [9–11]. However, there has been a lack of evidence as to whether the risk of AF is increased in ARD. We examined the prevalence, and mortality impact of AF in a cohort of patients with ARDs from a tertiary hospital.

*Abbreviations:* AF, atrial fibrillation; ARD, autoimmune rheumatic disease; AS, ankylosing spondylitis; BD, Behçet's disease; CVD, cardiovascular disease; IBD, inflammatory bowel disease; IM, inflammatory myopathy; RA, rheumatoid arthritis; SD, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

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## 2. Methods

### 2.1. Patients

This was a retrospective study conducted at referral centers in South Korea. The study protocol was approved by the Institutional Review Board. We enrolled 20,772 consecutive ARD patients who visited and/or were admitted to Severance Hospital from 2005 to 2015. Patients were eligible for analysis if they were diagnosed with ARD (ICD-10 code M06, K50 to 51, M32, M35.2, M34, M33.0 to 33.9, G72.4, M45, M35), and had AF (ICD-9 code 427.31). ARDs included rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), Behçet's disease (BD), systemic sclerosis (SSc), inflammatory myopathy (IM), ankylosing spondylitis (AS), and Sjögren's syndrome (SD). We also excluded the patients with concomitant mitral stenosis or prosthetic heart valves (ICD-10 I05.0, to I05.9, Z95.0), previous valvular surgery (ICD-9 codes 35.10 to 35.14 or 35.20 to 35.28), renal/hepatic failure, malignancy, previous intracerebral hemorrhage, or insufficient clinical data.

AF was confirmed by a documented EKG or 24-hour Holter recording. The patients' medical records were reviewed for information on the age, sex, weight, height, drug therapy, and AF duration. The patients' medical records were also reviewed for information on the age, gender, weight, comorbidities, medication use, $CHA_2DS_2$-VASc (Congestive heart failure, hypertension, age ≥ 75 [doubled], Diabetes mellitus, prior Stroke or transient ischemic attack [doubled]-Vascular disease, Age 65–74 years and Sex category [female]) and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly [>65], Drugs/alcohol concomitantly) score.

### 2.2. Follow-up

We evaluated the causes of death in ARDs including the cardiovascular death, disease progression, infection, and others during the follow-up. Adverse cardiac events included ischemic strokes, myocardial infarctions, and pulmonary thromboembolisms. Ischemic strokes were defined as a neurological deficit of a sudden onset that persisted for >24 h corresponding to a vascular territory in the absence of a primary hemorrhage and was not explained by other causes, including trauma, infection, or vasculitis [12]. Myocardial infarctions were diagnosed according to the 2007 universal definition by the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation [13]. Pulmonary embolisms were diagnosed if there were at least two segmental defects without a ventilation defect on a ventilation-perfusion scan, a positive angiogram finding, or documented evidence on computed tomography or magnetic resonance imaging of the chest [14].

Major bleeding was defined as any central nervous system bleeding, including intracranial bleeding, subdural hemorrhage, subarachnoid hemorrhage, epidural hemorrhage, any bleeding requiring a transfusion of at least two units of red blood cells or the equivalent of whole blood over 24 h, or bleeding events that caused hypotension (systolic blood pressure < 90 mm Hg), multi-organ failure, or death. When a patient experienced both adverse cardiac events and major bleeding events during the follow-up period, each event was counted respectively. However, when analyzing the Kaplan–Meier cumulative event-free survival, we counted the first event only.

### 2.3. Statistical analysis

Continuous variables that were normally distributed were reported as the mean ± SD and were compared by the use of a Student's *t*-test for parametric data and a Mann–Whitney test for nonparametric data. Categorical variables were reported as the count (percentage) and were compared using a Chi-square or Fisher's exact test. We used a Cox proportional hazards model to compute the hazard ratio (HR) and its 95% confidence intervals (CI), and a sensitivity analysis adjusted for baseline covariates including the sex, hypertension, diabetes mellitus, strokes, and brain hemorrhages, which showed a difference between the study groups. Kaplan–Meier survival curves were plotted for the ARD group with AF and the groups without AF and compared by means of a log-rank test. The SPSS statistical package (SSPS Inc., Chicago, Illinois) version 21.0 was used to perform all statistical evaluations. A p value less than 0.05 was considered statistically significant.

## 3. Results

### 3.1. Comparison of the characteristics between the patients with and without AF

In total, 13,683 (65.9%) patients were women, and had a mean age was 42 ± 17 years. AF was observed in 235 (1.1%). The mean age of the ARD patients with AF was 60.9 ± 12.8 years. The mean duration from the ARD diagnoses to the AF diagnoses was 6.8 ± 4.4 years. Table 1 shows the comparison of the characteristic between the patients with and without AF. Compared with the ARD patients without AF, the ARD patients with AF were composed more of female patients (65.8% vs. 76.2%, $p < 0.001$), had a higher prevalence of hypertension (14.6% vs. 68.1%, $p < 0.001$), diabetes (7.0% vs. 31.9%, $p < 0.001$), dyslipidemia (9.0% vs. 36.2%, $p < 0.001$), CHF (0.8% vs. 26.4%, $p < 0.001$), coronary artery disease (0.5% vs. 1.2%, $p < 0.001$), and obstructive sleep apnea (0.5% vs. 1.2%, $p = 0.410$). Compare with the patients without AF, the AF patients had a higher CRP level (5.1 ± 0.7 vs. 2.7 ± 0.2 mg/L, $p = 0.010$).

The independent predictors of newly diagnosed AF in ARD patients are listed in Table 2. The age, hypertension, dyslipidemia, CHF, and high CRP level were univariate predictors of AF in ARD. In the multivariate analysis, the predictors of AF were CHF (HR = 11.96, 95% CI: 8.13–17.60, $p < 0.001$, $p = 0.039$), hypertension (HR = 2.28, 95% CI: 1.70–3.06, $p < 0.001$), a high CRP level (HR = 1.75, CI: 1.07–2.86, $p = 0.04$), and the age (Hazard ratio (HR) = 1.05, 95% confidence interval (CI): 1.04–1.06, $p = 0.01$).

### 3.2. Prevalence of AF in ARD

Among ARDs, RA was the most common diagnosis (7490 patients; 36.1%), followed by BD (5290; 25.5%), IBD (3143;15.1%), SLE (2217; 10.7%), AS (1699; 8.0%), IM (343; 1.7%), Sjögren's syndrome (317;

**Table 1**
Comparison of the baseline characteristics between the patients with and without atrial fibrillation.

| | All (n = 20,772) | ARD with AF (n = 235) | ARD without AF (n = 20,537) | p-Value |
|---|---|---|---|---|
| Age, years | 42.0 ± 17.4 | 60.9 ± 12.8 | 41.8 ± 17.4 | <**0.001** |
| Male | 13,683 (65.9) | 56(23.8) | 7033(34.2) | **0.001** |
| Hypertension | 3157 (15.2) | 160(68.1) | 2997(14.6) | <**0.001** |
| Diabetes | 1520 (7.3) | 75(31.9) | 1445(7.0) | <**0.001** |
| Dyslipidemia | 1934 (9.3) | 85 (36.2) | 1849(9.0) | <**0.001** |
| HF | 231 (1.1) | 62(26.4) | 169(0.8) | <**0.001** |
| Coronary artery disease | 249(1.2) | 29(12.3) | 220(1.1) | <**0.001** |
| Obesity | 123(0.5) | 3 (1.2) | 120 (0.5) | 0.410 |
| Obstructive sleep apnea | 54 (0.2) | 3 (1.2) | 51 (0.2) | **0.005** |
| CRP, mg/L | 5.0 ± 0.7 | 5.1 ± 0.7 | 2.7 ± 0.2 | **0.010** |
| Medication | | | | |
| Aspirin | 448(2.2) | 33(14.0) | 415(2.0) | <**0.001** |
| Warfarin | 247(1.2) | 79(33.6) | 168(0.8) | <**0.001** |
| ARB or ACEi | 378(1.8) | 33(14.0) | 345(1.7) | <**0.001** |
| BB | 395(1.9) | 34(14.5) | 361(1.8) | <**0.001** |
| Statin | 771(3.7) | 38(16.2) | 733(3.6) | <**0.001** |

Data are expressed as the mean ± SD or number (percentage).
AF, atrial fibrillation; ARB, angiotensin receptor blocker; ACEi, angiotensin-converting-enzyme inhibitor; BB, beta-adrenergic blocking agents; CRP, C-reactive protein; CHF, congestive heart failure.
P-values less than 0.05 are listed in bold type.