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Ankylosing spondylitis: A novel risk factor for atrial fibrillation — A nationwide population-based study

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ABSTRACT

Background: Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease, associated with a number of cardiovascular diseases. We sought to investigate whether AS increases the risk of atrial fibrillation (AF) in a nationwide population-based study.

Methods: A total of 14,129 patients newly diagnosed with AS (mean age 41.8 ± 15.3 years, 72% male) were recruited from the Korean National Health Insurance Service database between 2010 and 2014 and followed up for new onset AF. Age- and sex-matched non-AS subjects (1:5, n = 70,645) were selected and compared with the AS patients.

Results: During a mean follow-up of 3.5 years, AF was newly diagnosed in 486 patients (114 patients of the AS group). The AS patients developed AF more frequently than the non-AS subjects (2.32 vs. 1.51 per 1000 person-years). In multivariate Cox regression analysis, AS was an independent risk factor for AF (Hazard ratio [HR] 1.28, 95% confidence interval [1.03–1.58]). The AS with tumor necrosis factor inhibitor (TNFi) therapy group showed higher risk for AF (HR 1.60 [1.02–2.39]). In younger patients of the AS group (patients <40 years old), the risk for AF was three times higher than patients at same age in the non-AS group. AS was an independent risk factor for AF in men, but not in women (HR 1.53 [1.18–1.95]; HR 1.42 [0.94–2.08], respectively).

Conclusions: AS was an independent risk factor for AF, especially in those under 40 years of age and those administered TNFi. It would be reasonable to screen for AF and stroke prevention in these high-risk patients.

1. Introduction

Ankylosing spondylitis (AS) is known to increase the risk of cardiovascular diseases such as aortitis, valvular disease, and conduction abnormalities [1]. Aortitis associated with AS is characterized as increased wall thickness of the aortic root caused by plasma cells and lymphocytes and the prevalence ranges from 3 to 18% [2,3]. Valvular diseases, especially aortic regurgitation and mitral regurgitation, are considered common cardiac manifestations, and their prevalence is reported to be 5–10% and 20–30%, respectively [3–6]. The prevalence of conduction abnormalities, such as atrioventricular block, varies among studies and ranges from 5 to 30%, but the prognosis and severity of conduction abnormalities in AS patients are much worse [5,7–9]. A recent study reported an increased risk of ischemic heart disease and stroke in AS patients [10].

Atrial fibrillation (AF) is the most common cardiac arrhythmia and increases the burden of public health cost as members of the society grow older [11–14]. The pathogenesis of AF is complex and related to multiple disease pathways [15]. Inflammation is one of the multiple factors supported by the association of AF and inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) [16,17]. AF is frequently associated with inflammatory conditions, such as myocarditis, pericarditis, and cardiac surgeries [18]. Furthermore, chronic inflammatory diseases, such as rheumatic disease and inflammatory bowel disease, are known to be associated with AF development [19,20].

There is a paucity of information regarding the association between AS and AF. A recent Swedish cohort study reported the risk of cardiac rhythm disturbances and aortic regurgitation in different

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spondyloarthritis subtypes [21]. It found that the age- and sex-adjusted risk was increased in AS patients compared to non-AS subjects. However, other cardiovascular comorbidities could increase the risk of AF, so more meticulous adjustments would be needed to accurately determine if AS patients have an increased risk of AF. Also, the study included not only AS patients but also undifferentiated spondyloarthritis and psoriatic arthritis patients, and the severity of AS was not clearly defined. Therefore, we sought to focus on the effect of AS on the risk of AF development while adjusting for other cardiovascular risk factors and considering the severity of AS based on medication in a Korean nationwide population.

2. Methods

2.1. Data source and study population

We used the national claim data established by the National Health Insurance Service (NHIS) of Korea. Detailed information about the NHIS claim database has been made available [22,23]. Briefly, the NHIS database has access to the medical records of the entire Korean population. The NHIS claims database contains information on diagnoses, procedures, prescription records, and demographics. NHIS in Korea has a registration system for Rare Intractable Diseases (RID) that provides support for patients with rare and intractable diseases, including AS (V14.0). To be included in the RID system, AS patients have to meet the following criteria: (1) over stage 3 sacroiliitis on one side in radiologic test or (2) over stage 2 on both sides in radiologic test and more than one of the following conditions: (a) lumbar pain of >3 months relieved by exercise but not by rest, (b) decreased movement of lumbar area in both sagittal and frontal planes, (c) decreased thoracic expansion than expected for patient age.

In this study, the diagnosis of AS was confirmed in both the NHIS and the RID systems. The authors confirmed the diagnoses using the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes. This study was exempt from review by the Seoul National University Hospital Institutional Review Board (1711-018-897).

2.2. Study cohort and propensity score matched cohort

Among 50,455,745 subjects registered in 2010, 15,547 subjects with newly diagnosed AS (ICD-10-CM code M45 and RID code V14.0) [24] were identified between January 2010 and December 2014. We excluded 222 subjects who had previous history of AF, and 1196 subjects under the age of 20. Finally, 14,129 subjects with AS were analyzed. For comparison, 1:5 age- and sex-matched subjects (n = 70,645) without AS were selected as the non-AS group. Both groups were followed until December 31, 2015 and the follow-up durations were 3.49 ± 1.45 and 3.48 ± 1.46 years, respectively ($P = 0.587$).

Study cohort had imbalanced baseline characteristics and it could confound the outcomes, we performed propensity score matching for verifying our results. Variables that could be confounding factors for outcomes were chosen and absolute standardized differences (ASD) of each variable were corrected to <0.1. The detail of propensity score matching results demonstrated in supplement table and figure.

2.3. Defining the severity of ankylosing spondylitis with anti-tumor necrosis factor therapy, outcomes, comorbidities and medication

The Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) are well-known systems used to stratify the severity of AS, but these could not be applied to our study population due to the lack of clinical information regarding patient symptoms [25]. Instead, we classified AS patients according to the prescription of tumor necrosis factor inhibitor (TNFi) therapy based on the relationship between the use of TNFi therapy and its use in high disease activity even after conventional treatments [26]. The primary outcome was the development of non-valvular AF, defined using ICD-10 codes (I48.0-I48.4, I48.9). AF with rheumatic mitral stenosis (I05.0, I05.2, I05.9) and mechanical heart valves (Z95.2-Z95.4) were regarded as valvular AF and excluded as in our previous study [13]. Comorbidities including hypertension (I10-13, I15), diabetes mellitus (DM) (E11-14), dyslipidemia (E78), congestive heart failure (CHF) (I50), peripheral artery disease (PAD) (I70, I73), chronic obstructive pulmonary disease (COPD) (J43-44), end stage renal disease (ESRD) (N18-19, Z49, Z905, Z94, Z992), previous history of ischemic stroke (I63-64) and myocardial infarction (MI) (I21-22) were also defined by ICD-10 codes. The CHA_2DS_2-VASc score was calculated for each patient by assigning 1 point each for age between 65 and 74 years, female sex, the presence of hypertension, DM, CHF, and vascular disease (prior MI or PAD) and 2 points each for a history of stroke, transient ischemic attack (TIA) or thromboembolism, and age of ≥75 years [27]. We gathered information about prescription of AS-related medication (non-steroidal anti-inflammatory drugs [NSAIDs], methotrexate, sulfasalazine, TNF inhibitors [Adalimumab, Etanercept, Golimumab, Infliximab]). Definition of outcomes, comorbidities, medications, and the individual components of the CHA_2DS_2-VASc score are described in detail in Supplementary Table 1.

2.4. Statistical analysis

Categorical variables are presented as numbers and relative frequencies (percentages) and were compared using the Chi-squared test. Continuous variables are expressed as mean ± standard deviation and were analyzed by using the Student's *t*-test. Comparison of cumulative event rates between the AS and non-AS groups was based on Kaplan-Meier censoring estimates and compared with the log-rank test. Annual event rates were described as the number of events per 1000 person-years (PY). Hazard ratios (HR) and the corresponding 95% confidence intervals (CI) were calculated using Cox proportional hazard models for investigating association between AS and AF, after adjusting for age, sex, DM, hypertension, dyslipidemia and CHF, PAD, COPD, ESRD and a history of ischemic stroke, and MI. The results were confirmed in a propensity score matched cohort. Subgroup analyses differentiated by multiple cardiovascular risk factors were subsequently performed. All *P*-values were two-sided, and a value <0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline characteristics of the cohort

The baseline characteristics of our study cohort are summarized in Table 1. The mean age was 41.8 years and males made up 71.5% of subjects in both groups. The AS group had more comorbidities such as hypertension, DM, dyslipidemia, CHF, PAD, COPD and ESRD. Previous stroke and MI were also more prevalent in the AS group. The proportion of patients with CHA_2DS_2-VASc score >2 points was higher in the AS group than in the non-AS group (18.1% vs 13.9%, respectively). NSAIDs were prescribed to most of the AS patients (95%), and a quarter of the AS group patients (n = 3899, 27.6%) received TNFi therapy. Methotrexate and sulfasalazine were prescribed to 2635 (18.7%) and 8699 (61.6%) patients, respectively.

3.2. Incidence rates and relative risks of AF

During a mean follow-up of 3.5 years, new onset AF was diagnosed in 114 patients (2.3%) of the AS group and 372 patients (1.5%) of the non-AS group. The AS group had a higher incidence of AF than the non-AS group (log-rank test $P < 0.0001$, Fig. 1). Table 2 shows the crude and adjusted incidence rates of AF, and the adjusted HR of AF risk in the AS group. AS patients showed higher incidence of AF compared to non-AS subjects (1.03 vs. 0.69 per 1000 PY in adjusted incidence). After using Cox proportional hazard models, AS patients had 28% increased risk of AF compared to non-AS subjects (adjusted HR = 1.28, 95% CI: 1.03–1.58).

We divided the AS group according to TNF inhibitor (TNFi) therapy. In the baseline characteristics of the three groups, the AS group with TNFi therapy was younger and had more male subjects and lower cardiovascular risk factors compared to the AS group without TNFi therapy (Supplementary Table 2). Also, the TNFi therapy group used more NSAIDs, methotrexate (33.6%), and sulfasalazine (79.8%) than the group not on TNFi therapy. The adjusted AF incidence rates for both AS groups were higher than that for the non-AS group (0.99 per 1000 PY in the AS group without TNFi therapy, 1.16 per 1000 PY in the AS group with TNFi therapy and 0.69 per 1000 PY in the non-AS group). In Cox proportional hazard models, the AS group with TNFi therapy group showed significantly higher HR for AF (HR = 1.60, 95% CI: 1.02–2.39), while the AS group without TNFi therapy did not show statistical significance (HR = 1.21, 95% CI: 0.95–1.53). On the contrary, AS patients taking either methotrexate or sulfasalazine did not show an increased risk of AF compared to those without these medications (Supplementary Table 3).

3.3. Propensity score matching results and relative risks of AF

After propensity score matching, all baseline clinical covariate differences were reduced to less than ASD 0.1 between the AS and non-AS groups (Supplementary Table 4). Successfully distributed individual

Table 1
Baseline characteristics of study population.

Characteristics	Non- ankylosing spondylitis (n = 70,645)	Ankylosing spondylitis (n = 14,129)	*P* value
Age (years)	41.8 ± 15.3	41.8 ± 15.3	1
20–39	35,895 (50.8%)	7179 (50.8%)	1
40–64	27,940 (39.6%)	5588 (39.6%)	
≥ 65	6810 (9.6%)	1362 (9.6%)	
Male	50,535 (71.5%)	10,107 (71.5%)	1
Low income[a]	15,620 (22.1%)	3500 (24.8%)	<0.0001
Hypertension	8835 (12.5%)	2335 (16.5%)	<0.0001
Diabetes mellitus	3602 (5.1%)	849 (6.0%)	<0.0001
Dyslipidemia	5534 (7.8%)	1530 (10.8%)	<0.0001
Congestive heart failure	375 (0.5%)	181 (1.3%)	<0.0001
Peripheral arterial disease	2044 (2.9%)	686 (4.9%)	<0.0001
COPD	3117 (4.4%)	1368 (9.7%)	<0.0001
End stage renal disease	85 (0.1%)	66 (0.5%)	<0.0001
Previous stroke	933 (1.3%)	310 (2.2%)	<0.0001
Previous myocardial infarction	226 (0.3%)	110 (0.8%)	<0.0001
CHA_2DS_2-VASc score			
0 or 1	60,815 (86.1%)	11,567 (81.9%)	
≥ 2	9830 (13.9%)	2562 (18.1%)	<0.0001
Medication			
NSAIDs	31,839 (45.1%)	13,453 (95.2%)	<0.0001
Methotrexate	198 (0.3%)	2635 (18.7%)	<0.0001
Sulfasalazine	92 (0.1%)	8699 (61.6%)	<0.0001
TNF-α inhibitor	18 (0.03%)	3899 (27.6%)	<0.0001
Follow-up duration (year)	3.49 ± 1.45	3.48 ± 1.46	0.5868
Number of patient-years	246,662.0	49,229.4	

Abbreviations: COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs; TNF, tumor necrosis factor.
[a] Denotes subjects with annual income lower than 20% among total population.

propensity scores and well-balanced assessments are demonstrated in the Supplementary Figure. In line with our main results, the risk of AF was significantly higher in the AS group (hazard ratio = 1.31, 95% confidence interval [1.02–1.67]).

3.4. Subgroup analyses

In the subgroup analyses, the AS group showed consistently higher risk of AF development compared to the non-AS group in most of the subgroups (Fig. 2). The risk of AF in the male subgroup was higher in the AS group than in the non-AS group, whereas there was no significant difference in the risk of AS between the female AS and non-AS groups. Significant interaction was observed in the age subgroups (P for interaction = 0.009). Although older AS patients showed higher incidence of AF compared to the younger AS patients, the effect of AS on AF development was relatively weaker in the subgroups of older age patients than in those of younger age patients. Also, the absolute incidence rates were higher in those with cardiovascular risk factors, and the effect of AS on AF risk was relatively weaker in subgroups with well-known cardiovascular risk factors than in those without such risk factors.

Table 2
Risk of the atrial fibrillation events in Ankylosing Spondylitis (AS) patients and divided by anti-TNF therapy.

Groups	N	No. of events	Incidence rate (IR)[a]		Hazard ratio (95% CI)
			Crude IR	Adjusted IR[b]	Adjusted HR[c]
Non-AS	70,645	372	1.51	0.69	1.00 (Ref.)
AS	14,129	114	2.32	1.03	1.28 (1.03,1.58)
Anti-TNF therapy					
Non-AS	70,645	372	1.51	0.69	1.00 (Ref.)
AS without TNFi	10,230	91	2.58	0.99	1.21 (0.95,1.53)
AS with TNFi	3899	23	1.65	1.16	1.60 (1.02,2.39)

Abbreviations: TNF, tumor necrosis factor; CI, confidence interval.
[a] Incidence rates were calculated per 1000 patient-years.
[b] Adjusted for age, sex, diabetes mellitus, hypertension and dyslipidemia.
[c] Adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, end stage renal disease, previous stroke, and previous myocardial infarction.

4. Discussion

This study investigated the risk of AF in AS patients using a nationwide population database. To the best of our knowledge, this is the largest study reporting the association of AS with the development of AF with adjustment for other cardiovascular risk factors. Among AS patients, those administered TNFi therapy showed significantly higher risk of AF than those who did not receive TNFi therapy.

4.1. Risk of AF in AS patients

Previous studies have reported the association between AS and ischemic heart disease or stroke [10,24,28,29]. The relative risk of ischemic heart disease in AS was 1.2 to 2.7 (HR), that for stroke was 1.0 to 2.4 and 1.3 to 3.0 for all cardiovascular diseases. A recent Swedish population study reported the association between AF and ankylosing spondylitis [21]. In this study, not only AS patients, but also those with

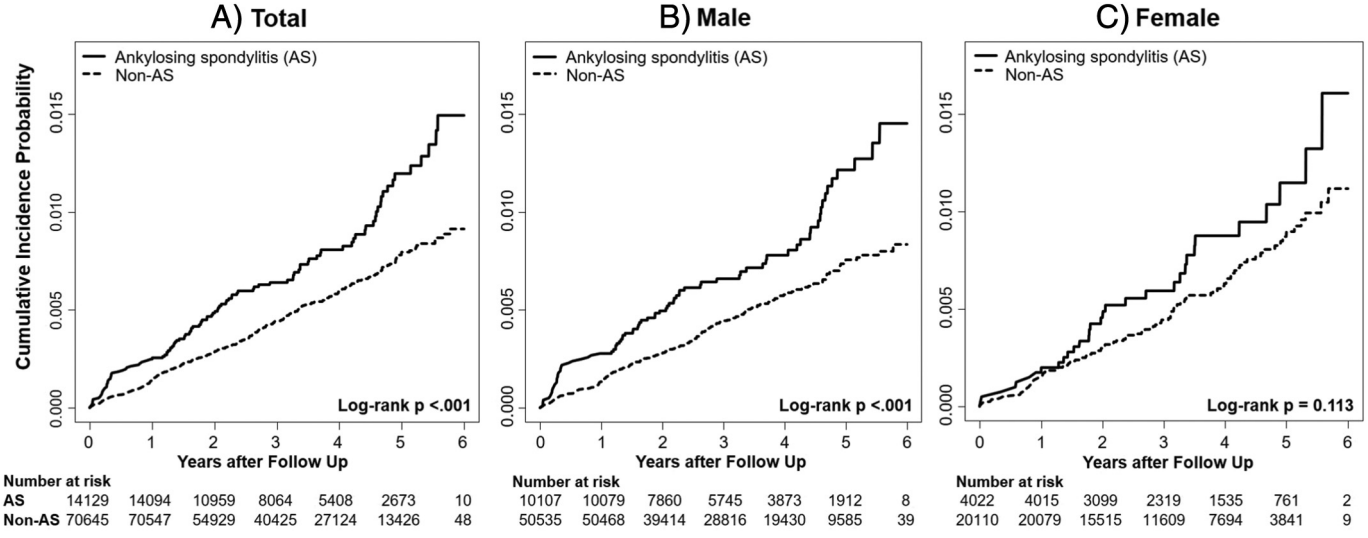

Fig. 1. Comparison of cumulative incidence of atrial fibrillation events depending on the presence or absence of ankylosing spondylitis. Abbreviations: AS, ankylosing spondylitis.

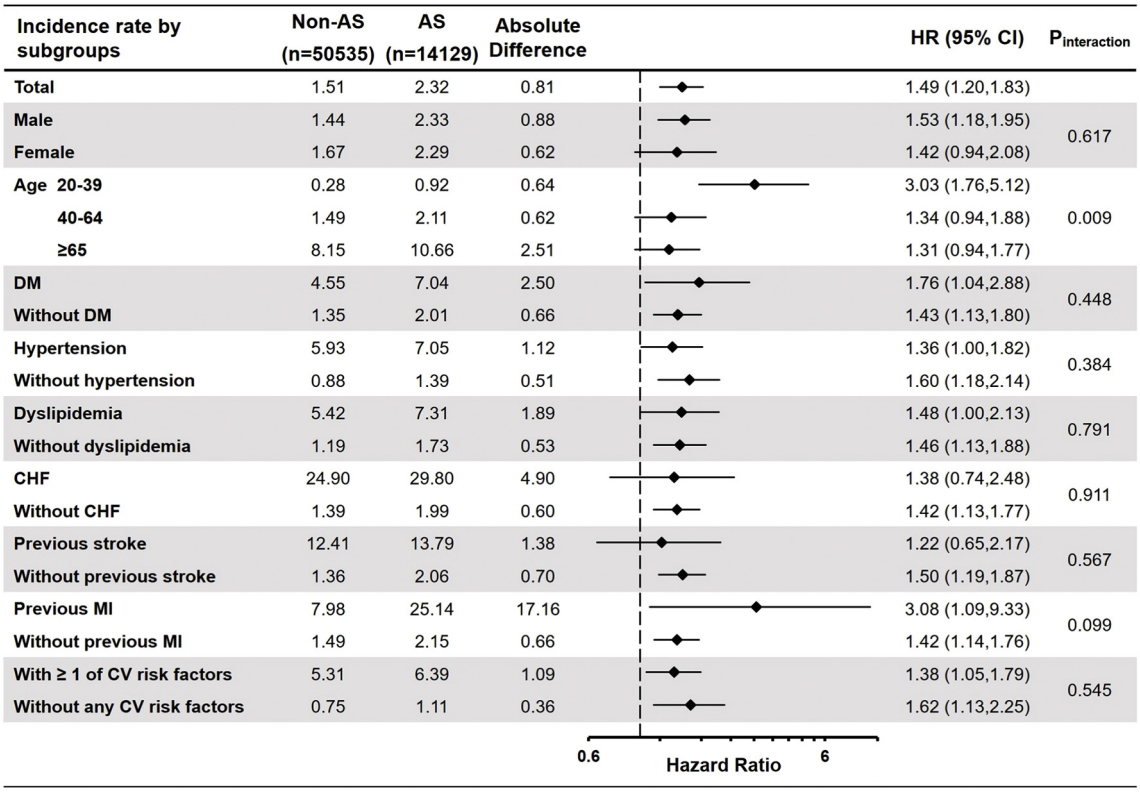

Fig. 2. Subgroup analyses for risk of atrial fibrillation in ankylosing spondylitis patients. All subgroup analyses were adjusted with age, sex, hypertension, DM and dyslipidemia. Cardiovascular risk factors included hypertension, DM and dyslipidemia. Abbreviations: AS, ankylosing spondylitis; HR, hazard ratios; CI, confidence interval; DM, diabetes mellitus; CHF, congestive heart failure; MI, myocardial infarction; CV, cardiovascular.

undifferentiated spondyloarthritis and psoriatic arthritis were analyzed and compared with the general population. They found that AS patients showed 35% increased risk of AF compared to non-AS subjects. In accordance with the Swedish study, we found that AS showed an increased risk of AF compared to non-AS patients even after adjustments for various cardiovascular comorbidities. Interestingly, the age- and sex-adjusted incidence rates of the Swedish study were 7.1 per 1000 PY in the AS group and 5.5 per 1000 PY in the general population, which were higher than we recorded in our study. Also, we could not find statistical significance in female AS patients in the risk of AF, whereas both male and female AS patients showed consistently increased risk of AF in the Swedish study (HR = 1.27, 95% CI: 1.07–1.51 in males, and HR = 1.58, 95% CI: 1.16–2.14 in females) [21]. In our study, most of the AS population was male, and the female AS patients made up only 30% of the study population, which might affect the statistical significance. A previous study showed that, in a cross-sectional study of AS patients, arrhythmia and/or valvular heart disease were strongly correlated with male sex [30]. There were several observational studies [31–33] and meta-analysis of clinical treatment trial [34] for gender difference of AS presentation. Generally, male AS patients had more HLA-B27 positivity, axial symptoms, and radiographic findings. However, the trends of increased risk of AF was similar in male and female AS patients in our study. Overall, the increased risk of AF in AS patients is in line with the previous studies reporting the incremental risk of stroke in AS patients [10,28,29,35].

4.2. Mechanism of AF development in AS: Inflammation

Inflammation is one of the possible mechanisms of AF development [18,36]. Several inflammatory markers, such as CRP, IL-2, IL-6, IL-8, monocyte chemoattractant protein-1 and TNF-α, were related to the pathogenesis of AF [18]. TNF-α is known to play a significant role in the pathogenesis and treatment of AS. In this study, we found that AS patients on TNFi therapy showed higher risk of AF development, whereas for those not treated with TNFi, the risk was statistically insignificant. Furthermore, AS patients taking methotrexate or sulfasalazine did not show an increased risk of AF. These results suggested that TNF-α may be the pathological link between AS and AF.

We assumed that patients who were prescribed TNFi would have more severe symptoms that could not be controlled by NSAIDs and conventional disease-modifying anti-rheumatic drugs [26]. Although the AS patients with TNFi therapy were younger and had less comorbidities, the adjusted risk of AF was 60% higher in this group than in the non-AS group. These results mean that the greater the inflammation, the greater the incidence of AF and this strongly supports the view that inflammation is associated with AF.

4.3. Clinical implication with subgroup analyses

In the subgroup analyses, there were some points with clinical implications to be focused on. First, in the younger age group (20 to 39 years old), there was a three-fold increment in AF incidence and a significantly higher risk of AF than in the non-AS patients of the same age. Second, in the older age group (over 40 years old), the absolute incidence of AF increased, but the impact of AS on AF development was not as strong as in the younger age group. However, as AS commonly develops in young age, this result emphasizes the need for early AF screening. Third, the relative effect of AS on AF development is consistently smaller in those with cardiovascular risk factors. Although AS patients with CHF or previous stroke history showed no significant difference compared to the non-AS group, the absolute difference and incidence was higher in the AS patients, which should not be misinterpreted because of the numerically lower relative risk.

4.4. Study limitation

This study has several limitations that should be acknowledged. First, selection bias from frequent medical contact in patients with AS may have enhanced the risk of AF associated to AS. However, AF usually causes significant symptoms, so many patients visit hospital complaining of symptoms which finally diagnosed as AF regardless of routine check-up. And results were consistent in patients with previous cardiovascular disease which have similar level of exposure to medical use in both AS and non-AS group. For this reason, we considered that routine medical contact might not affect the results. Moreover, previous studies reporting the risk of AF in patients with rheumatoid disease had not adjusted the frequency of hospital visit [19,21,37]. For minimizing this bias, we restricted definition of AF that at least one of admission or two of outpatient office. Second, AS and other comorbidities were defined by only diagnostic codes in the claims data from NHIS without clinical or laboratory data, so we cannot exclude misclassification. However, we used both NHIS and RID systems and our definitions have been validated in previous studies [20,22,23,38,39]. Third, the severity of AS measured by clinical symptom score could not be analyzed due to the innate limitation of the claims data. Although TNF inhibitors are usually prescribed to AS patients refractory to other medications, their use does not directly correlate with the severity of disease. Forth, we did not adjust for other confounders that we could not receive from the claims data, such as obesity, low body weight, obstructive sleep apnea, alcohol consumption, duration from onset of AS and other laboratory findings. However, we adjusted for well-known and major cardiovascular risk factors, so the effect of other variables might be small.

5. Conclusion

We found that AS was associated with increased risk of AF, especially in those undertaking treatments with TNF inhibitors. The relative risk effect of AS was greater in young and male AS patients, while AS patients with cardiovascular risk factors seemed not to be adequately treated despite the associated higher absolute risk.

Conflict of interest statement

All authors declare that there is no conflict of interest relevant to the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.024.

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