Risk of sick sinus syndrome in patients diagnosed with atrial fibrillation: a population-based cohort

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Abstract

Background: Sinoatrial node dysfunction and atrial fibrillation (AF) frequently coexist and interact with each other, often to initiate and perpetuate each other. Objective: To determine the effect of AF on the incidence and risk of sick sinus syndrome (SSS). Methods: The association of incident AF with the development of incident SSS was assessed from 2004 to 2013 in 302,229 SSS- and pacemaker-free participants aged [?]60 years in the Korea National Health Insurance Service-Senior cohort. Results: During an observation period of 1,854,800 person-years, incident AF was observed in a total of 12,797 participants (0.69%/year). The incidence of SSS was 0.2 and 3.4 per 1000 person-years in the incident AF and the propensity score matched no-AF groups, respectively. After adjustment, the risk of SSS caused by incident AF was significantly increased, with a hazard ratio (HR) of 13.4 (95% confidence interval [CI]: 8.4–21.4). This finding was consistently observed after censoring for heart failure (HR, 16.0; 95% CI: 9.2–28.0) or heart failure/myocardial infarction (HR, 16.6; 95% CI: 9.3-29.7). Incident AF also was associated with an increased risk of pacemaker implantation related with both SSS (HR, 21.8; 95% CI: 8.7–18.4) and atrioventricular (AV) block (HR, 9.5; 95% CI: 4.9–18.4). These results were consistent regardless of sex and comorbidities. Conclusion: Incident AF was associated with more than ten times increased risk of SSS in an elderly population regardless of comorbidities. Risk of pacemaker implantations related with both sinus node dysfunction and AV block were increased in elderly population with incident AF.

1. INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population.[1, 2] The age distribution of AF is predicted to shift with an expected increase in its prevalence among the elderly.[1]. AF has tremendous socioeconomic implications as it increases the risk of morbidity and mortality due to stroke, congestive heart failure, and impaired quality of life.[1-4]

AF is associated with significant electrophysiologic and structural remodeling as well as sick sinus syndrome (SSS).[5-8] AF develops in up to 50% of patients with tachycardia-bradycardia syndrome.[9] Moreover, it is associated with SSS, manifested as sinus bradycardia without the component of tachycardia-bradycardia syndrome. In an animal study, persistent (>2 weeks) rapid atrial pacing and chronic AF resulted in sinoatrial node (SAN) dysfunction.[5] In AF, SAN dysfunction is associated with calcium (Ca^{2+}) clock malfunction, characterized by unresponsiveness to isoproterenol and caffeine and down-regulation of ryanodine receptor 2.[5, 10] Comparable data in humans have also been reported. SSS patients with tachycardia-bradycardia

syndrome showed lesser electrical and structural remodeling and better outcome after radiofrequency ablation of AF than those without it.[6, 11]

However, the effect of AF on the risk of SSS and pacemaker implantations is not revealed in general population. In this study, the association between incident AF and the risk of SSS was investigated in the cohort of elderly individuals. Additionally, we evaluated whether these associations occurred independent of heart failure or myocardial infarction, and whether they were influenced by medications for cardiac rhythm or rate control.

2. METHODS

2.1. Data source

Data were collected from the National Health Insurance Service (NHIS)-Senior database, which included data for 558,147 individuals, approximately 10% of the elderly population in South Korea aged [?]60 years in 2002 (about 5.1 million).[12] This study was approved by the institutional review board of Yonsei University Health System (4-2020-0798) and the need for informed consent was waived.

2.2. Study population

A total of 312,736 patients who underwent a health checkup between 2005 and 2013 were selected from the Korean NHIS-Senior database, and their follow-up data were reviewed until December 2014. The exclusion criteria were as follows: (i) those with valvular heart disease (mitral stenosis, prosthetic heart valves, valve replacement, or valvuloplasty) (n=1948); (ii) those who had AF before enrollment (n=8167); (iii) those who had a pacemaker implantation before enrollment (n=217); and (iv) those who had SSS before enrollment (n=175). Finally, 302,229 subjects were included (Figure 1).

The International Classification of Disease (ICD)-10th Revision, code I48 was used to diagnose AF. Patients were defined as having AF if it was present at the time of discharge, or its presence was confirmed at least twice in the outpatient clinic. This definition of AF diagnosis was previously validated in the NHIS database with a positive predictive value of 94.1%.[1, 2, 4]

For both the AF and the AF-free patients, the time at risk was estimated from the index date or the day of their enrollment in the study. Effect of incident AF was analyzed as a time-varying factor. Participants were censored on the date of diagnosis of SSS, death, or at the end of the study period, defined as the last date of follow-up or December 31, 2014, whichever came first.

The patients were considered to have comorbidities, as previously described using data from the NHIS database, if their condition was diagnosed at the time of discharge or was confirmed at least twice in an outpatient setting (eTable 1 in the Supplement).[1, 2, 4]

2.3. Outcomes

The primary outcome was SSS. SSS was defined from any discharge diagnoses or two outpatients visits (ICD-10 codes for SSS and tachybradycardia syndrome [I495]). The secondary outcomes were pacemaker implantation or atrioventricular (AV) block. AV block was defined from any discharge diagnoses or two outpatient visits [I441 (Second-degree AV block, Mobitz type I and II), I442 (Complete AV block), I443 (AV block NOS), I453 (Trifascicular block), I458 (AV dissociation), I459 (Stokes-Adams syndrome, Heart block NOS)] (eTable 1 in the Supplement). To evaluate the accuracy of the outcome definitions, we conducted a validation study using hospital administrative data from two hospitals. The positive predictive values were found to be 91.1% (307/337) and 95.7% (264/276) for SSS and AV block, respectively.

2.4. Statistical analyses

Propensity scores (PS) were used to correct potential systematic differences between AF (n=12,797) and no-AF groups (n=289,432) (Figure 1). Each patient's PS to estimate the risk of developing AF was calculated and adjusted for the covariates in a logistic regression analysis model. PS matching was performed on

logit-transformed PS-matched to the nearest neighbor in a 1:1 fashion with a caliper of 0.1, without using replacement.

The details of methods are presented in method of supplementary material.

3. RESULTS

3.1. Distribution of SSS with the incident AF

Figure 2 shows the distribution of SSS with the incident AF. Among subjects with incident AF, 83 (42%) had SSS before the incident AF, and 115 (58%), afterwards. Forty-six (23%) patients had SSS 30 days before the incident AF and 16 (8%), after the incident AF. For the time-varying analysis, patients with SSS before incident AF were included into the no-AF group.

3.2. Baseline characteristics

Incident AF was diagnosed in 12,797 participants over an observational period of 1,869,266 person-years (0.69%/year). Patients who developed AF were older (aged, 71.7±5.6 vs. 72.0±5.7 years, p<0.001), and had more cases of heart failure, hypertension, and chronic obstructive pulmonary disease than those without incident AF. The observation period was longer in the AF group (median 85 months; interquartile range [IQR], 59–95 months) than in the no-AF group (median, 85 months; IQR, 55–95 months) (p<0.001) (Table 1). After PS matching, the baseline characteristics of the incident AF and no-AF groups became similar (Table 1).

3.3. Risk of SSS

A total of 115 patients with incident AF developed SSS during the follow-up period of 35,086 person-years, whereas among those without AF, 431 participants developed SSS. The incidence of SSS was 3.4 and 0.2 per 1000 person-years in the AF and PS-matched patients without AF, respectively (Table 2). Patients with AF had a higher cumulative incidence of SSS compared to the overall (log-rank p<0.001, Figure 3A) and PS-matched patients without AF (log-rank p<0.001, Figure 3B). After adjustment of clinical variables and competing risk of mortality, the subjects with incident AF had an increased risk of SSS with adjusted hazard ratio (HR) of 8.2 (95% CI: 6.5–10.3). After PS matching, incident AF was associated with significantly increased risk of SSS with adjusted HR of 13.4 (95% CI: 8.4–21.4) (Table 2).

The analysis of censoring for heart failure was performed in patients without history of heart failure (incident AF, 10,706; no-AF, 265,865). During the follow-up period, heart failure occurred in 13.2% and 1.4% patients in the AF and no-AF groups, respectively. After censoring for heart failure, the incidence of SSS was 2.7 and 0.2 per 1000 person-years in the AF and PS-matched no-AF groups, respectively (Table 2). The incident AF group had a higher cumulative incidence of SSS compared to the overall (log-rank p<0.001; Figure 3C) and PS-matched patients without AF (log-rank p<0.001; Figure 3D). After adjustment for clinical variables and competing risk of mortality, incident AF was associated with an increased risk of SSS (adjusted HR, 11.4; 95% CI: 8.7–14.9). After PS matching, compared with PS-matched no-AF group, incident AF was associated with increased the risk of SSS with adjusted HR of 16.0 (95% CI: 9.2–28.0) (Table 2).

After censoring for heart failure or acute myocardial infarction, incident AF had increased risk of SSS compared to the overall (adjusted HR, 11.6; 95% CI: 8.9–15.2) and PS-matched groups (adjusted HR, 16.9; 95% CI: 9.3–29.7) (Table 2).

In subgroup analysis, incident AF increased the risk of SSS regardless of sex, age, living in metropolitan cities, economic status, heart failure, hypertension, diabetes, ischemic stroke/transient ischemic attack, vascular disease, CHA_2DS_2-VASc score, medication for rate control, and antiarrhythmic drugs (Figure 4).

3.4. Risk of pacemaker implantation

In patients with incident AF, a total of 107 participants had pacemaker implantation during the follow-up period of 36,536 person-years, compared with 358 no-AF patients who needed pacemaker implantation. The

incidence of pacemaker implantation was 2.9 and 0.1 per 1000 person-years in the incident AF and PS-matched no-AF groups, respectively. As quantified by the clinical variable and competing risk of mortality, patients with incident AF had an increased risk of pacemaker implantation (adjusted HR, 9.4; 95% CI: 7.5–11.8). Even after PS matching, the risk of pacemaker implantation was still significantly high in those with incident AF (adjusted HR, 15.2; 95% CI: 9.1–25.6) (Table 3).

The incidence of SSS-related pacemaker implantation was 0.05 and 1.3 per 1000 person-years in the incident AF and PS-matched no-AF patients, respectively. Incident AF was associated with an increased risk of SSS-related pacemaker implantation (adjusted HR, 21.8; 95% CI: 8.7–18.4). The incidence of pacemaker implantation associated with AV block was 0.1 and 1.3 per 1000 person-years in the incident AF and PS-matched no-AF groups, respectively. Incident AF was associated with an increased risk of pacemaker implantation due to AV block (adjusted HR, 9.5; 95% CI: 4.9–18.4, p<0.001) (Table 3).

3.5. Factors associated with SSS in AF patients

The characteristics of AF patients with and without SSS are presented in eTable 2 in the supplement. On multivariable analysis, residence in the use of antiarrhythmic drugs (OR, 1.03; 95% CI: 1.01–1.05, p=0.002) and the living in metropolitan cities (OR, 1.0; 95% CI: 1.0–1.01, p=0.04) were identified as the factors independently associated with the likelihood of SSS (eTable 3 in the supplement).

4. DISCUSSION

Our principal findings from this elderly population-based cohort study were as follows: (i) About a third of SSS occurred 30 days before or after the diagnosis of incident AF; (ii) incident AF was associated with an increased risk of SSS, independent of heart failure or myocardial infarction; (iii) incident AF increased the risk of SSS in all subgroups regardless of sex, age, economic status, and comorbidities; and (iv) Among patient with AF, the use of antiarrhythmic drugs was associated with an increased risk of SSS. These findings support the strong association between AF and SSS.

4.1. The development of SSS in patients with AF

The prevalence of SSS is estimated to be 1 in 1000 in adults over 45 years of age,[13] with the incidence rate increasing with age, up to 1 in 600 patients over 65 years of age. SSS accounts for significant healthcare use, including hospitalization and pacemaker implantation (about half of implant indications in the United States).[13] However, a characteristic feature of SSS is the development of supraventricular arrhythmias, among which, AF is the most common.[9, 14, 15] In a large population study, the estimated HR for new-onset AF in patients with SSS was 4.[14] At initial diagnosis of SSS, AF can appear simultaneously in 40–70% of patients.[9, 14, 15] In patients without clinical AF, incident AF occurs in 4–22% of patients during follow-up.[9, 14, 15]During long-term follow-up, 68% of patients had AF recorded in their pacemakers.[14]

AF can change a normal SAN or promote preexisting SSS. However, the incident of SSS in patients with incident AF has not been well elucidated. This study showed that about a third of SSS occurred before or after 30 days of incident AF. After regarding AF as time-varying covariate, the estimated HR for the newly developed SSS in patients with incident AF was 8.2 and 13.4, compared with the overall and PS-matched patients without AF. The concept of a single pacemaker dominating the cardiac rhythm of the atria is effective wherein AF blocks the SAN by long-term overdrive suppression of its activity. Patients with paroxysmal AF and prolonged sinus pauses (>3 s) had improved SAN function after ablation of AF. Sinus pauses were caused by long-term suppression of the SAN activity.[16]

4.2. Typical electrophysiologic remodeling in AF and SSS

Typical electrophysiologic remodeling in AF includes down-regulation of L-type Ca^{2+} channel (ICa,L), down-regulation ofI_{to}, and upregulation ofI_{KACh} andI_{K1}.[17, 18] The remodeling of ionic current could reduce the slope of phase 0, hyperpolarize membrane voltage, and reduce heart rate. Funny current down-regulation might contribute to the association between SAN dysfunction and supraventricular tachyarrhythmias.[19]Compared with the normal SANs, those of patients or animals with AF did not ex-

hibit spontaneous late diastolic Ca^{2+} elevation or cranial shifting of the earliest atrial activation sites upon isoproterenol infusion, suggesting impaired spontaneous sarcoplasmic reticulum Ca^{2+}release.[5, 20]

Patients with conditions associated with atrial remodeling, ischemia, and atrial stretch (e.g., congestive heart failure) manifest altered SAN function.[21, 22] Therefore, we excluded heart failure and myocardial ischemia cases but without affecting the final results. Moreover, there is evidence to indicate that antiarrhythmic drugs used for the treatment of AF can cause SAN dysfunction.[23] In this study, antiarrhythmic drug was a factor associated with SSS in patients with AF.

SSS might also be accompanied by intra-atrial conduction delay, AV nodal conduction disturbances, and paroxysmal atrial tachycardia as part of the tachycardia-bradycardia syndrome. Damage to SAN is an important factor for the formation of AF. When sinus impulse formation is depressed in the presence of SSS, during the slow atrial cycle, an atrial extrasystole may occur. Moreover, SAN may also facilitate re-entry. Thus, ischemic damage to the SAN alone, without atrial wall disturbances, such as fibrosis, stretch, or muscle loss, may result in chronic AF.

5. LIMITATIONS

This study has several limitations. First, studies using administrative databases might be susceptible to errors arising from coding inaccuracies. To minimize this problem, we applied the definition validated in previous studies that used the Korean NHIS sample cohort.[1, 2, 12, 24, 25]Second, we were unable to define the type (paroxysmal vs. persistent) of AF. AF can occur without symptoms, and although numerous electrocardiography measurements were performed at the study center, some participants with asymptomatic AF might have been missed. Third, despite the adjustment for differences in baseline characteristics, residual unidentified confounders may remain.

6. CONCLUSION

Incident AF was associated with more than ten times increased risk of SSS in an elderly population regardless of comorbidities. Pacemaker implantations due to both sinus node dysfunction and AV block were increased in the elderly population with incident AF.

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Table 1. Characteristics of patients with and without incident AF

	No-AF (n=289,432)	**AF (n=12,797)**	**SMD**	**No-AF (n=11,759)**	**AF (n=11,759)**	**SMD**
Age (years)	71.1 ± 5.6	72.0 ± 5.7	0.16	72.0 ± 5.9	72.0 ± 5.8	0.003
Female gender	124931 (43.2)	6630 (51.8)	0.174	6014 (51.1)	5940 (50.5)	0.013
BMI (kg/m^2)	23.8 ± 3.2	23.9 ± 3.4	0.05	24.0 ± 3.3	24.0 ± 3.4	0.005
SBP (mmHg)	132.4 ±17.9	133.9 ±18.8	0.083	134.1 ±18.2	133.9 ±18.7	0.01
DBP (mmHg)	79.5 ±10.8	80.2 ±11.3	0.069	80.2 ±11.0	80.2 ±11.3	0.006
Blood glucose (mg/dL)	103.3 ±31.7	105.2 ±35.8	0.055	104.8 ±33.3	105.3 ±35.8	0.013
Total cholesterol (mg/dL)	198.7 ±39.3	194.0 ±39.2	0.121	194.0 ±38.6	194.4 ±39.3	0.008
Serum creatinine (mg/dL)	1.0 ± 1.0	1.1 ± 1.2	0.107	1.0 ± 1.0	1.1 ± 1.2	0.081
Hypertension	139939 (48.3)	7507 (58.7)	0.208	6909 (58.8)	6898 (58.7)	0.002
Diabetes mellitus	46104 (15.9)	2348 (18.3)	0.064	2125 (18.1)	2170 (18.5)	0.01
Dyslipidemia	104746 (36.2)	5092 (39.8)	0.074	4797 (40.8)	4699 (40.0)	0.017
Heart failure	23567 (8.1)	2091 (16.3)	0.252	1899 (16.1)	1906 (16.2)	0.002
CKD or ESRD	4421 (1.5)	281 (2.2)	0.049	249 (2.1)	259 (2.2)	0.006
History of MI	7328 (2.5)	622 (4.9)	0.124	564 (4.8)	543 (4.6)	0.008
PAOD	20622 (7.1)	1291 (10.1)	0.106	1139 (9.7)	1158 (9.8)	0.005
COPD	24048 (8.3)	1423 (11.1)	0.095	1363 (11.6)	1297 (11.0)	0.018
Liver disease	69450 (24.0)	3298 (25.8)	0.041	3030 (25.8)	3004 (25.5)	0.005
Malignancy	33811 (11.7)	1667 (13.0)	0.041	1563 (13.3)	1509 (12.8)	0.014
Ischemic stroke or TIA	36917 (12.8)	2042 (16.0)	0.091	1864 (15.9)	1871 (15.9)	0.002
CHA_2DS_2-VASc score*	2.7 ± 1.6	3.0 ± 1.7	0.188	3.0 ± 1.7	3.0 ± 1.6	0.006

	No-AF (n=289,432)	**AF (n=12,797)**	**SMD**	**No-AF (n=11,759)**	**AF (n=11,759)**	**SMD**
Charlson comorbidity index	2.2 ± 2.2	2.6 ± 2.3	0.154	2.6 ± 2.4	2.6 ± 2.3	0.005
Economic status			0.01			0.008
Low	88544 (30.6)	3940 (30.8)		3513 (29.9)	3626 (30.8)	
Middle	65999 (22.8)	2761 (21.6)		2678 (22.8)	2531 (21.5)	
High	134889 (46.6)	6096 (47.6)		5568 (47.4)	5602 (47.6)	
Living area			0.054			0.01
Small city or rural area	176895 (61.1)	8156 (63.7)		7540 (64.1)	7482 (63.6)	
Metropolitan city	112537 (38.9)	4641 (36.3)		4219 (35.9)	4277 (36.4)	
Smoking			0.057			<0.001
No	219680 (79.7)	9316 (77.1)		9050 (77.0)	9083 (77.2)	
Former	21409 (7.8)	1077 (8.9)		1091 (9.3)	1028 (8.7)	
Current	34477 (12.5)	1684 (13.9)		1618 (13.8)	1648 (14.0)	
Alcohol consumption+			0.079			0.014
No drinking	216400 (76.3)	9096 (72.8)		8661 (73.7)	8676 (73.8)	
Moderate	50670 (17.9)	2548 (20.4)		2241 (19.1)	2307 (19.6)	
Heavy	16442 (5.8)	857 (6.9)		857 (7.3)	776 (6.6)	
Physical activity++			0.157			0.017
Low	138539 (49.2)	7113 (57.1)		6778 (57.3)	6766 (57.2)	
Moderate	74421 (26.5)	2923 (23.4)		2906 (24.6)	2769 (23.4)	
High	68393 (24.3)	2429 (19.5)		2148 (18.2)	2297 (19.4)	
Medication use						
ACE inhibitor or ARB	64926 (22.4)	3707 (29.0)	0.15	3396 (28.9)	3377 (28.7)	0.004
β-blocker	57475 (19.9)	3457 (27.0)	0.17	3136 (26.7)	3170 (27.0)	0.007
Diuretic	77237 (26.7)	4452 (34.8)	0.176	3995 (34.0)	4085 (34.7)	0.016
Calcium channel blocker						
DHP	88895 (30.7)	4593 (35.9)	0.11	4282 (36.4)	4240 (36.1)	0.007
Non-DHP	9350 (3.2)	728 (5.7)	0.119	680 (5.8)	637 (5.4)	0.016
Digoxin	3041 (1.1)	562 (4.4)	0.206	466 (4.0)	483 (4.1)	0.007
Statin	40827 (14.1)	1806 (14.1)	<0.001	1705 (14.5)	1677 (14.3)	0.007
Antiplatelet agents	72803 (25.2)	4234 (33.1)	0.175	3879 (33.0)	3856 (32.8)	0.004
Anticoagulant	691 (0.2)	129 (1.0)	0.098	66 (0.6)	95 (0.8)	0.03

	No-AF (n=289,432)	**AF (n=12,797)**	**SMD**	**No-AF (n=11,759)**	**AF (n=11,759)**	**SMD**
Antiarrhythmic agents	353 (0.1)	115 (0.9)	0.071	51 (0.4)	70 (0.6)	0.021

Values are expressed in n (%), mean ± standard deviation, or median (interquartile range)

ACE, angiotensin-converting enzyme; ARB, angiotensin type II receptor blocker; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DHP, dihydropyridine; ESRD, end-stage renal disease; MI, myocardial infarction; PAOD, peripheral artery occlusive disease; SBP, systolic blood pressure; SMD, Standardized mean difference; TIA, transient ischemic attack.

*CHA_2DS_2-VASc scores range from 0 to 9, with higher scores indicating a greater risk of stroke. Previous stroke or transient ischemic attack and an age of 75 years or older are each assigned 2 points, and congestive heart failure, hypertension, diabetes, an age of 65–74 years, female sex, and history of vascular disease are each assigned 1 point toward the total score.

+ Heavy alcohol consumption: male >8 glass/week (or >3 glass/day), female >4 glass/week (or >2 glass/day), Moderate alcohol consumption: male [?]8 glass/week (or [?]3 glass/day), female [?]4 glass/week (or [?]2 glass/day)

++ high physical activity: [?]75 min/week of vigorous activity, [?]150 min/week of moderate activity or a combination of the two, moderate physical activity: 1–74 min/week vigorous activity, 1–149 min/week moderate activity or a combination of the two

Table 2. The incidence and risk of sick sinus syndrome in the AF and no-AF groups before and after propensity score matching.

	Number of events	Person Years	Event rate (1000 person-years)	Number of events	Person years	Event rate (1000 person-years)	Absolute increase in event rate (95% CI)	Adjusted hazard ratio (95% CI) *	p-v
Before propensity score matching Overall	Before propensity score matching No-AF (N= 289,432)	Before propensity score matching No-AF (N= 289,432)	Before propensity score matching No-AF (N= 289,432)	Before propensity score matching AF (N= 12,797)	Before propensity score matching AF (N= 12,797)	Before propensity score matching AF (N= 12,797)	Before propensity score matching	Before propensity score matching	Be pro sit sco ma
	431	1,819,714	0.2	115	35,086	3.3	3.0 (2.9-3.2)	8.2 (6.5-10.3)	<0
Censoring HF+	No-AF (N= 265,865)	No-AF (N= 265,865)	No-AF (N= 265,865)	AF (N= 10,706)	AF (N= 10,706)	AF (N= 10,706)			
	332	1,659,206	0.2	82	29,904	2.7	2.5 (2.4-2.7)	11.4 (8.7-14.9)	<0

	Number of events	Person Years	Event rate (1000 person-years)	Number of events	Person years	Event rate (1000 person-years)	Absolute increase in event rate (95% CI)	Adjusted hazard ratio (95% CI) *	p-v
Censoring HF or MI++	No-AF (N= 260,773)	No-AF (N= 260,773)	No-AF (N= 260,773)	AF (N= 10,342)	AF (N= 10,342)	AF (N= 10,342)			
	320	1,630,117	0.2	79	28,920	2.7	2.5 (2.4-2.7)	11.6 (8.9-15.2)	<0
After propensity score matching Overall	After propensity score matching No-AF (N= 11,759)	After propensity score matching No-AF (N= 11,759)	After propensity score matching No-AF (N= 11,759)	After propensity score matching AF (N= 11,759)	After propensity score matching AF (N= 11,759)	After propensity score matching AF (N= 11,759)	After propensity score matching	After propensity score matching	Af pro sit sc ma
	20	112,021	0.2	108	32,113	3.4	3.2 (2.8-3.6)	13.4 (8.4-21.4)	<0
Censoring HF+	No-AF (N= 9,860)	No-AF (N= 9,860)	No-AF (N= 9,860)	AF (N= 9,853)	AF (N= 9,853)	AF (N= 9,853)			
	14	91,268	0.2	75	27,378	2.7	2.6 (2.2-3.0)	16.0 (9.2-28.0)	<0
Censoring HF or MI++	No-AF (N= 9,568)	No-AF (N= 9,568)	No-AF (N= 9,568)	AF (N= 9,534)	AF (N= 9,534)	AF (N= 9,534)			
	13	88,656	0.1	73	26,503	2.8	2.6 (2.2-3.0)	16.6 (9.3-29.7)	<0

Abbreviations: AF, atrial fibrillation; HF, Heart failure; MI, myocardial infarction

* Adjusted for age, sex, economic status, body mass index, systolic and diastolic blood pressure, blood glucose level, total cholesterol, alcohol, smoking habits, as well as comorbidities, including hypertension, diabetes mellitus, ischemic stroke/transient ischemic attack, previous myocardial infarction, heart failure, peripheral artery disease, dyslipidemia, osteoporosis, chronic kidney disease, chronic obstructive lung disease, liver disease, history of malignant neoplasm, and cardiovascular medications.

+ Before censoring heart failure, patients with heart failure were excluded.

++ Before censoring heart failure or myocardial infarction, patients with heart failure or myocardial infarction were excluded.

Table 3. The incidence and risk of pacemaker implantation in the AF and no-AF groups before and after propensity score matching.

	Number of events	Person years	Event rate (1000 person-years)	Number of events	Person years	Event rate (1000 person-years)	Absolute increase in event rate (95% CI)	Adjusted hazard ratio (95% CI) *	p-v
Before propensity score matching Pacemaker implantation	Before propensity score matching No-AF (N= 289,432)	Before propensity score matching No-AF (N= 289,432)	Before propensity score matching No-AF (N= 289,432)	Before propensity score matching AF (N= 12,797)	Before propensity score matching AF (N= 12,797)	Before propensity score matching AF (N= 12,797)	Before propensity score matching	Before propensity score matching	Be pro sit sco ma
	358	1,805,810	0.2	107	36,536	2.9	2.7 (2.6-2.9)	9.4 (7.5-11.8)	<0
Pacemaker implantation for SSS	No-AF (N= 289,432)	No-AF (N= 289,432)	No-AF (N= 289,432)	AF (N= 12,797)	AF (N= 12,797)	AF (N= 12,797)			
	93	1,805,810	0.1	49	36,536	1.3	1.3 (1.2-1.4)	17.9 (12.3-26.2)	<0
Pacemaker implantation for AV block	No-AF (N= 289,432)	No-AF (N= 289,432)	No-AF (N= 289,432)	AF (N= 12,797)	AF (N= 12,797)	AF (N= 12,797)			
	259	1,805,810	0.1	45	36,536	1.2	5.2 (3.8-7.3)	13.9 (11.0-17.4)	<0
After propensity score matching Pacemaker implantation	After propensity score matching No-AF (N= 11,759)	After propensity score matching No-AF (N= 11,759)	After propensity score matching No-AF (N= 11,759)	After propensity score matching AF (N= 11,759)	After propensity score matching AF (N= 11,759)	After propensity score matching AF (N= 11,759)	After propensity score matching	After propensity score matching	Af pro sit sco ma
	16	109,741	0.1	98	33,403	2.9	2.8 (2.4-3.1)	15.2 (9.1-25.6)	<0
Pacemaker implantation for SSS	No-AF (N= 11,759)	No-AF (N= 11,759)	No-AF (N= 11,759)	AF (N= 11,759)	AF (N= 11,759)	AF (N= 11,759)			
	5	109,741	0.05	45	33,403	1.3	1.3 (1.1-1.5)	21.8 (8.7-54.5)	<0

	Number of events	Person years	Event rate (1000 person-years)	Number of events	Person years	Event rate (1000 person-years)	Absolute increase in event rate (95% CI)	Adjusted hazard ratio (95% CI) *	p-v
Pacemaker implantation for block	No-AF (N= 11,759)	No-AF (N= 11,759)	No-AF (N= 11,759)	AF (N= 11,759)	AF (N= 11,759)	AF (N= 11,759)			
	11	109,741	0.1	42	33,403	1.3	4.4 (3.9-4.9)	9.5 (4.9-18.4)	<0

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; SSS, sick sinus syndrome

* Adjusted for age, sex, economic status, body mass index, systolic and diastolic blood pressure, blood glucose level, total cholesterol, alcohol, smoking habits, as well as comorbidities, including hypertension, diabetes mellitus, ischemic stroke/transient ischemic attack, previous myocardial infarction, heart failure, peripheral artery disease, dyslipidemia, osteoporosis, chronic kidney disease, chronic obstructive lung disease, liver disease, history of malignant neoplasm, and cardiovascular medications.

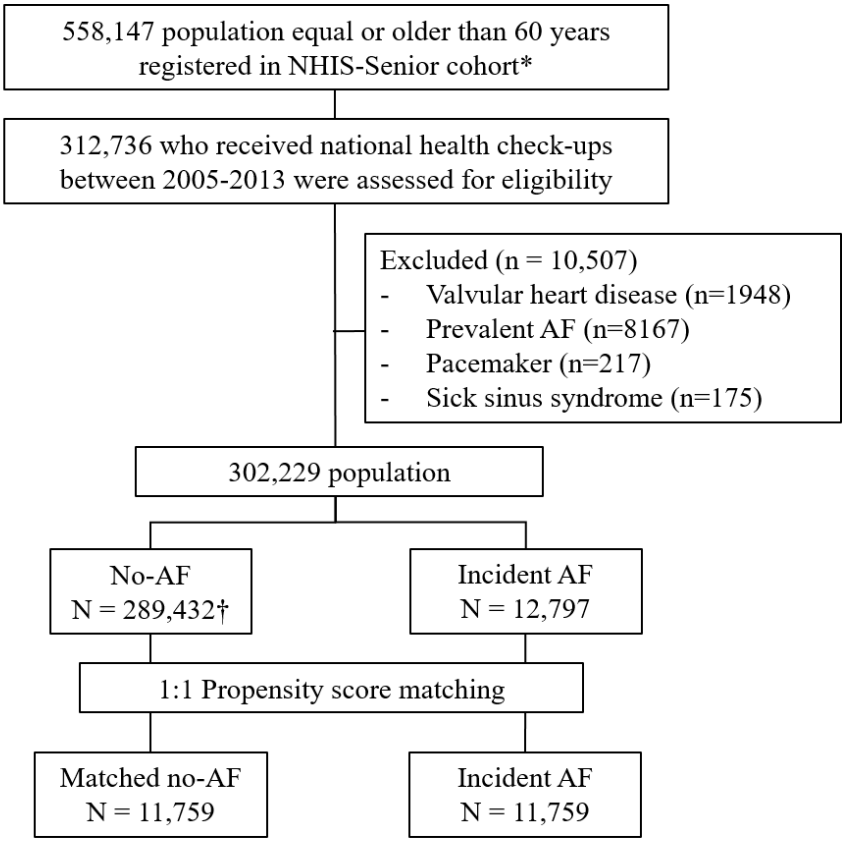
FIGURE LEGENDS

Figure 1. Flowchart depicting the enrollment and analyses of the study population.

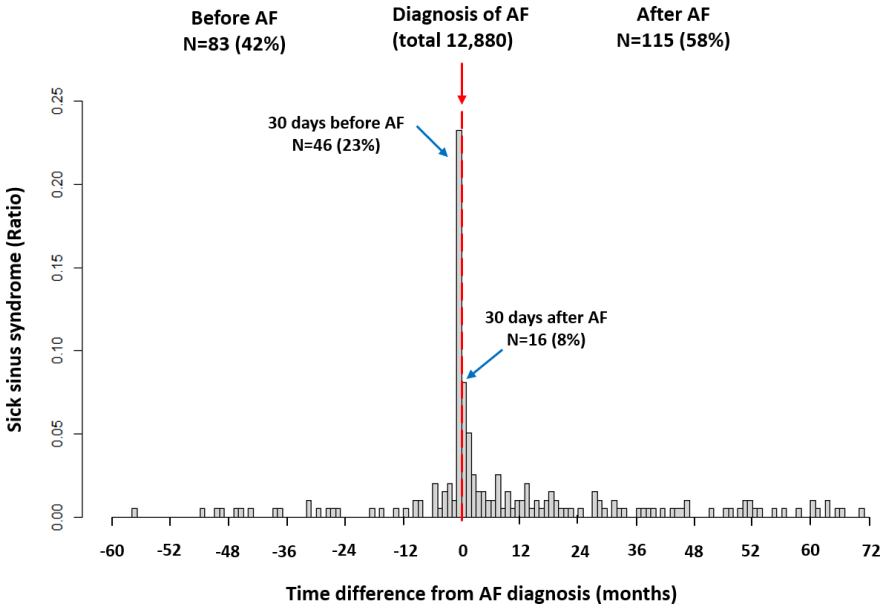
Figure 2. The distribution of sick sinus syndrome from the incident atrial fibrillation (AF). The red line indicates AF diagnosis.

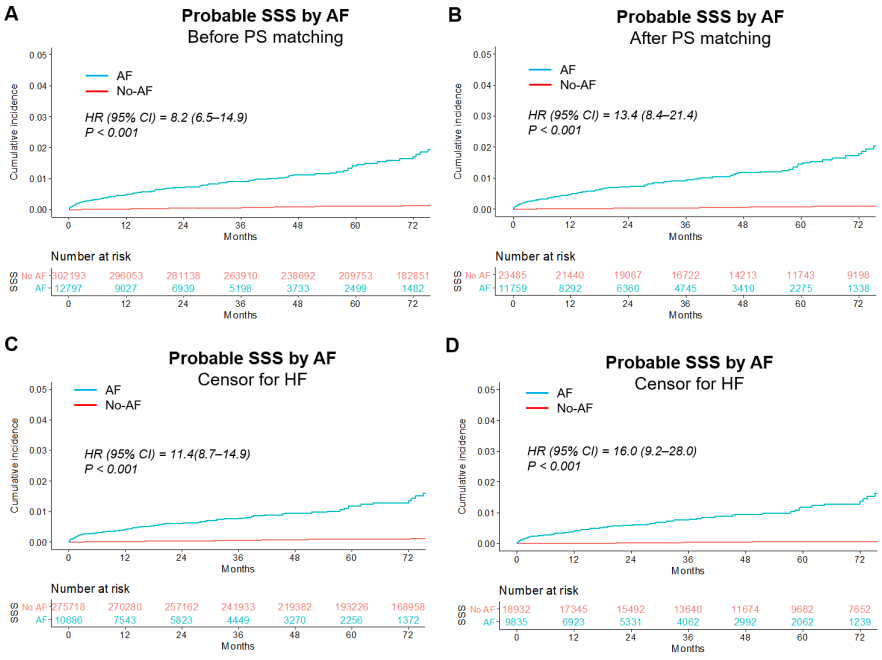
Figure 3. The cumulative incidence of the sick sinus syndrome (SSS) before (A and B) and after censoring for stroke (C and D) in the overall population (A and C) and propensity score (PS)-matched population (B and D).

Figure 4. Hazard ratios (HR) for sick sinus syndrome (SSS) in different subgroups in the overall population. Boxes indicate the HR, limit lines indicate the 95% confidence interval (CI), and the horizontal line (at HR 1) indicates no difference in the HR between atrial fibrillation (AF) and no-AF.



* Korean National Health Insurance Service (NHIS)-Senior cohort
† 83 patients had sick sinus syndrome before incident AF





Covariables	Ablation		Medical therapy		HR (95% CI)	P for interaction
	Patient N	Event rate	Patient N	Event rate		
Sex						0.905
Female	5745	10	5819	57	14.4 (7.5-27.5)	
Male	6014	10	5940	51	18.4 (8.7-39.1)	
Age ≥ 75						0.543
No	8383	14	8409	84	15.9 (9.2-27.6)	
Yes	3376	6	3350	24	8.7 (3.6-21.0)	
Living in a metropolitan city						0.536
No	7540	12	7482	56	11.7 (6.3-21.8)	
Yes	4219	8	4277	52	16.0 (7.7-33.1)	
Economic status						0.054
Low	6191	6	6157	61	25.2 (11.0-57.7)	
High	5568	14	5602	47	8.6 (3.6-21.0)	
Heart failure						0.084
No	9860	14	9853	91	16.2 (9.4-28.1)	
Yes	1899	6	1906	17	6.5 (2.6-16.4)	
Hypertension						0.017
No	4850	3	4861	48	39.7 (12.9-122.0)	
Yes	6909	17	6898	60	8.7 (5.1-14.8)	
Diabetes						0.229
No	9634	19	93078.3	91	11.9 (7.4-19.4)	
Yes	2125	1	2170	17	40.0 (5.4-298.0)	
Stroke/transient ischemic attack						0.614
No	9895	16	9888	90	14.1 (8.4-23.8)	
Yes	1864	4	1871	18	10.3 (3.5-29.9)	
Vascular disease						-
No	10620	19	10601	100	13.0 (8.0-21.1)	
Yes	1139	1	1158	8	18.5 (2.43-141)	
CHA_2DS_2-VASc						0.347
0,1,2	5058	20	4953	108	13.4 (8.4-21.4)	
>=3	6701	13	6806	59	10.6 (5.8-19.3)	
Rate control						0.013
No	6144	5	6188	60	29.3 (12.1-71.3)	
Yes	5615	15	5571	48	7.9 (4.4-14.0)	
Antiarrhythmic drugs						-
No	11709	20	11689	105	13.0 (8.1-20.7)	
Yes	50	0	70	3	-	