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CLINICAL RESEARCH
Atrial fibrillation

Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a population-based cohort

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Aims Atrial fibrillation (AF) is generally regarded as a risk factor for dementia, though longitudinal studies assessing the association between AF and dementia have shown inconsistent results. This study aimed to determine the effect of AF on the risk of developing dementia using a longitudinal, community-based, and stroke-free elderly cohort.

Methods and results The association of incident AF with the development of incident dementia was assessed from 2005 to 2012 in 262 611 dementia- and stroke-free participants aged ≥60 years in the Korea National Health Insurance Service-Senior cohort. Incident AF was observed in 10 435 participants over an observational period of 1 629 903 person-years (0.64%/year). During the observational period, the incidence of dementia was 4.1 and 2.7 per 100 person-years in the incident AF and propensity score-matched AF-free groups, respectively. After adjustment, the risk of dementia was significantly increased by incident AF with a hazard ratio (HR) of 1.52 [95% confidence interval (CI) 1.43–1.63], even after censoring for stroke (1.27, 95% CI 1.18–1.37). Incident AF increased the risk of both Alzheimer (HR 1.31, 95% CI 1.20–1.43) and vascular dementia (HR 2.11, 95% CI 1.85–2.41). Among patients with incident AF, oral anticoagulant use was associated with a preventive effect on dementia development (HR 0.61, 95% CI 0.54–0.68), and an increasing CHA_2DS_2-VASc score was associated with a higher risk of dementia.

Conclusion Incident AF was associated with an increased risk of dementia, independent of clinical stroke in an elderly population. Oral anticoagulant use was linked with a decreased incidence of dementia.

Keywords Atrial fibrillation • Dementia • Anticoagulation • Aged • Prognosis

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general elderly population, with more than half of AF patients being aged ≥80 years, and leads to substantial public health and economic burdens.[1–3] The age distribution of populations in developed countries is expected to shift in the coming years, with older age groups becoming more prominent.[3] The presence of AF increases the risk of mortality and morbidity resulting from stroke, congestive heart failure, and

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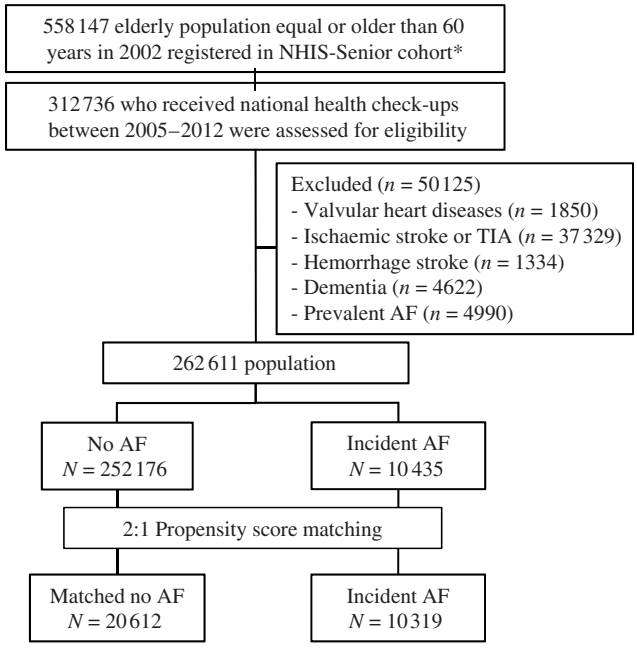


Figure 1 Flowchart of the study population enrolment and analyses.

hospitalization in association with an increase in comorbid chronic diseases.[1]

Worldwide, prevalence of dementia is ~40 million, and this number is expected to increase owing to the population aging.[4] Although the pathophysiologic mechanisms of dementia are largely unknown, there has been increasing evidence that AF may contribute to the development of cognitive dysfunction and dementia.[5–9] The Rotterdam Study demonstrated that cognitive dysfunction was approximately twice as common in subjects with AF than in those without.[5] However, the cross-sectional design of that study precluded definitive conclusions regarding a causal relationship. Since then, several longitudinal studies [6–9] have investigated the association between AF and incident dementia, with inconsistent results: some studies[6,7] found that AF was associated with an increased risk of cognitive decline or dementia, whereas others [8,9] found no association.

These inconsistencies may be due to methodological variation across studies. Most studies included prevalent AF, and the risk of dementia in relation to incident AF was not well identified. In addition, the age ranges differed substantially among studies, as did the assessment of AF and dementia. Overall, the effects of oral anticoagulants (OACs) on the prevention of dementia remain controversial.

In this study, we investigated the associations between incident AF in an elderly population and the risk of dementia using the database of the nationwide population-based National Health Insurance Service (NHIS)-senior cohort (NHIS-Senior). In addition, we evaluated whether these associations occurred independent of stroke and were influenced by OACs therapy.

Methods

Data were collected from the NHIS-Senior, which contains data on 558 147 individuals, ~10% of the entire elderly population in South Korea aged ≥60 years (~5.1 million) in 2002.[10] The NHIS-Senior database covered the following parameters: sociodemographic and socioeconomic information, insurance status, health check-up examinations, and records of patients' medical and dental history. These parameters were stratified to cover 12 years (2002–2013) and anonymized to protect individuals' privacy within the cohort study. This study was approved by the Institutional Review Board of Yonsei University Health System (4-2016-0179). Informed consent was waived. NHIS-Senior database used in this study (NHIS-2016-2-171) was made by NHIS of Korea.

Study population

From the Korean NHIS-Senior, a total of 312 736 patients who had a health check-up between 2005 and 2012 were enrolled and follow-up data were reviewed until December 2013. The exclusion criteria were as follows: (i) patients with valvular heart disease (diagnosis of mitral stenosis or prosthetic heart valves or with insurance claims for valve replacement or valvuloplasty) ($n = 1850$); (ii) those who had an ischaemic stroke or transient ischaemic attack before enrolment ($n = 37\,329$); (iii) those who had a haemorrhagic stroke before enrolment ($n = 1334$); (iv) those who had dementia before enrolment ($n = 4622$); and (v) those who had AF before enrolment ($n = 4990$). We excluded secondary AF related to valvular heart disease, given the higher stroke rate of associated valvular heart disease compared to non-valvular heart disease might increase the development of dementia and cognitive function impairment. Finally, we included 262 611 subjects, including 10 435 with incident AF during the follow-up period (*Figure 1*).

AF was diagnosed using the International Classification of Disease (ICD)-10th Revision, code I48. To ensure diagnostic accuracy, patients

were defined as having AF only when it was a discharge diagnosis or had been confirmed at least twice in the outpatient department. This AF diagnosis definition has been previously validated in the NHIS database with a positive predictive value of 94.1%.[11,12]

Covariates

We obtained information on selected comorbid conditions from inpatient and outpatient hospital diagnoses. Baseline comorbidities were defined using the medical claims and prescription medication information prior to the index date. To ensure diagnostic accuracy, the patients were considered to have comorbidities when the condition was a discharge diagnosis or had been confirmed at least twice in an outpatient setting, in line with previous studies using the NHIS (see Supplementary material online, *Table S1*).[11,13] Baseline income status was evaluated based on the total amount of national health insurance premiums paid by the insured individual in the index year, proportional to the individual's income.

Assessment of dementia

Participants were screened for dementia at baseline using a Korean Dementia Screening Questionnaire (KDSQ). The KDSQ consists of questions for global memory function and instrumental activities of daily living, including five items that can detect early changes in cognitive decline to diagnose dementia.[14] Each item on the KDSQ is scored from 0 to 2, with a higher score indicating poorer function and a greater frequency. The KDSQ is not influenced by age or educational level and has shown a 0.79 sensitivity and 0.80 specificity for dementia.[14]

The Korean government covers medical expenditure for dementia patients diagnosed by the following ICD-10 codes: F00, G30 (Alzheimer's disease; AD), F01 (vascular dementia; VaD), F02 (dementia with other diseases classified elsewhere), and F03 (unspecified dementia). We used the same criteria to diagnose dementia. To ensure diagnostic accuracy, patients were defined as having dementia only when it was a discharge diagnosis or had been confirmed at least twice in the outpatient department.

Statistical analysis

Baseline characteristics of participants with and without incident AF were compared using logistic regression models. Incidence rates are events per 100 years at risk, but expressed as annualized rates in percentage for comprehensiveness. Furthermore, propensity scores (PS) were used to correct for potential systematic differences between AF and AF-free groups. Each study patient's PS for development of AF were computed and adjusted for the covariates in a logistic regression analysis. Propensity scores matching was made on logit-transformed PS matched to the nearest neighbour in a 2:1 fashion with a caliper of 0.1. No replacements were used.

We assessed the association between incident AF, which was entered into the models as a time-varying factor, and incident dementia using Cox proportional hazards regression models. The underlying time scale in these models was the observational period. Observation started on the date that participants enrolled in the study. Participants were censored at the date of dementia diagnosis, date of death, or end of the study period, defined as the last date of follow-up or 31 December 2013, whichever came first. We adjusted for age, sex, and clinical variables, including hypertension, diabetes mellitus, previous myocardial infarction (MI), heart failure, peripheral artery disease, dyslipidaemia, osteoporosis, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), liver disease, history of malignant neoplasm, economic status, cardiovascular medications (aspirin, P_2Y_{12} inhibitor, statin, anticoagulant, beta-blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker, calcium channel blocker, digoxin, diuretics), body mass index, systolic and diastolic blood pressure (BP), blood glucose level, total cholesterol, and alcohol and smoking habits.

In the sensitivity analyses, we additionally censored patients at the date of stroke, if the latter occurred before the end of the follow-up period. We examined potential effect modification by age using an interaction term and by stratifying analyses at the median age. In addition, we investigated whether the association between AF and dementia differed according to anticoagulation status. The effect of OAC use was evaluated only in AF patients.

All tests were two-tailed, and *P*-value <0.05 was considered significant. Statistical analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC, USA) and SPSS version 23.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Incident AF was diagnosed in 10 435 participants over an observational period of 1 629 903 person-years (0.64%/year). Patients with incident AF were older (aged 71.7 ± 5.7 vs. 70.7 ± 5.4 years, $P < 0.001$), had higher diastolic BP, and had more frequent heart failure and COPD compared to participants without incident AF. Hypertension was significantly higher in the AF group compared to controls. Duration of observation was longer in the AF group [median 86 months, interquartile range (IQR) 62–96 months] compared to the AF-free group (median 85 months, IQR 58–95 months) ($P < 0.001$) (*Table 1*).

Baseline cognitive function was not significantly different between the AF-free and AF groups, with no difference in the KDSQ (AF-free vs. AF groups; median 1, IQR 0–3 vs. median 1, IQR 0–3, $P = 0.659$) or the number of patients with a positive KDSQ screening (21.0% vs. 21.7%, $P = 0.626$) (*Table 1*).

After PS matching, baseline characteristics of the incident AF and AF-free groups became similar (*Table 1*).

Risk of dementia

In patients with incident AF, 2522 participants (24.4%) developed dementia during 61 834 person-years of follow-up, compared to 36 322 participants (14.4%) who developed dementia among the AF-free patients. The incidence of dementia was 4.1 and 2.7 per 100 person-years in the incident AF and PS-matched AF-free patients, respectively (*Table 2*). The incident AF group had a higher cumulative incidence of dementia compared to the overall (log-rank $P < 0.001$, *Figure 2A*) and PS-matched AF-free group (log-rank $P < 0.001$, *Figure 2C*). As quantified by the clinical variable-adjusted hazard ratios (HRs), subjects with incident AF had an increased risk of dementia [HR 1.63 95% confidence interval (CI) 1.54–1.72] (*Table 2*). After PS matching, the risk of dementia was still significantly increased by incident AF with clinical variable HR of 1.52 (95% CI 1.43–1.63) (*Table 2*). Incident AF increased the risk of dementia in both patients aged ≥70 years and those aged <70 years.

During the follow-up period, stroke developed in 20.0% and 4.4% patients in the AF and AF-free groups, respectively. The incidence of dementia after censoring for stroke was 3.5 and 2.5 per 100 person-years in the incident AF and PS-matched AF-free groups, respectively (*Table 2*). After censoring for stroke, the incident AF group had a higher cumulative incidence of dementia compared to the overall (log-rank $P < 0.001$; *Figure 2B*) and PS-matched AF-free group (log-rank $P < 0.001$; *Figure 2D*). Incident AF increased the risk of dementia

Table 1 Patient characteristics

	Overall population			Propensity-matched population		
	AF-free (*n* = 252 176)	Incident AF (*n* = 10 435)	*P*-value	AF-free (*n* = 20 612)	Incident AF (*n* = 10 319)	*P*-value
Age (years)	70.7 ± 5.4	71.7 ± 5.7	<0.001	71.7 ± 5.8	71.7 ± 5.7	0.710
Female gender	141 492 (56.1)	4931 (47.3)	<0.001	9606 (46.6)	4865 (47.1)	0.872
BMI (kg/m^2)	23.8 ± 3.2	23.9 ± 3.4	<0.001	23.9 ± 3.2	23.9 ± 3.4	0.086
SBP (mmHg)	132.3 ± 17.9	134 ± 18.9	0.083	134.3 ± 18.4	134.0 ± 18.8	0.251
DBP (mmHg)	79.5 ± 10.8	80.3 ± 11.3	0.003	80.4 ± 11.1	80.3 ± 11.3	0.416
Blood glucose (mg/dL)	102.9 ± 31.1	104.5 ± 35.0	0.009	103.9 ± 31.5	104.5 ± 35.0	0.108
Total cholesterol (mg/dL)	199.1 ± 39.0	194.1 ± 38.8	<0.001	193.9 ± 38.2	194.1 ± 38.8	0.854
Serum creatinine (mg/dL)	0.98 ± 0.86	1.07 ± 1.08	0.003	1.02 ± 0.87	1.07 ± 1.08	0.107
Hypertension (with med)	109 164 (43.5)	5637 (54.3)	0.004	11 251 (54.6)	5592 (54.2)	0.373
Diabetes	35 933 (14.3)	1688 (16.3)	0.151	3277 (15.9)	1675 (16.2)	0.909
Dyslipidaemia	73 564 (29.3)	3373 (32.5)	0.218	6651 (32.3)	3345 (32.4)	0.843
Heart failure	15 091 (6.0)	1429 (13.8)	<0.001	2722 (13.2)	1404 (13.6)	0.005
CKD or ESRD	2658 (1.1)	154 (1.5)	0.327	311 (1. 5)	153 (1.5)	0.833
History of MI	4247 (1.7)	346 (3.3)	0.271	662 (3.2)	338 (3.3)	0.523
PAOD	8863 (3.5)	461 (4.4)	0.947	918 (4.5)	457 (4.4)	0.408
COPD	43 215 (17.2)	2394 (23.1)	<0.001	4746 (23.0)	2370 (23.0)	0.771
Liver disease	48 226 (19.2)	2230 (21.5)	0.485	4416 (21.4)	2212 (21.4)	0.869
Malignancy	23 364 (9.3)	1096 (10.6)	0.363	2163 (10.5)	1087 (10.5)	0.828
CHA_2DS_2-VASc score	2.3 ± 1.2	2.6 ± 1.3	0.097	2.6 ± 1.3	2.6 ± 1.3	0.600
Economic status			0.602			0.668
Low	77 760 (31.0)	3268 (31.5)		6396 (31.0)	3247 (31.5)	
Middle	87 461 (34.9)	3435 (33.1)		7059 (34.2)	3418 (33.1)	
High	85 547 (34.1)	3673 (35.4)		7157 (34.7)	3654 (35.4)	
Smoking			0.227			0.871
No	188 793 (79.2)	7489 (76.6)		14 835 (76.2)	7446 (76.5)	
Former	18 353 (7.7)	868 (8.9)		1845 (9.5)	865 (8.9)	
Current	31 293 (13.1)	1426 (14.6)		2793 (14.3)	1417 (14.6)	
Alcohol consumption			<0.001			0.060
Low	220 198 (87.8)	8839 (85.2)		17 738 (86.1)	8790 (85.2)	
Moderate	10 934 (4.4)	553 (5.3)		1015 (4.9)	552 (5.3)	
Heavy	19 636 (7.8)	984 (9.5)		1859 (9.0)	977 (9.5)	
Cognitive function[a]						
KDSQ (positive rate)	7337 (21.0)	201 (21.7)	0.626	457 (20.5)	210 (22.5)	0.214
KDSQ score	1 (0–3)	1 (0–3)	0.659	1 (0–3)	1 (0–3)	0.130
ADL score	0 (0–3)	0 (0–1)	0.430	0 (0–1)	0 (0–1)	0.200
History of recent fall	4870 (13.9)	135 (14.5)	0.600	313 (14.0)	138 (14.7)	0.616
Depression (positive rate)	17 797 (51.1)	496 (53.7)	0.125	1073 (52.5)	511 (54.7)	0.275
Medication						
ACE inhibitor or ARB	41 899 (16.7)	2325 (22.4)	0.454	4573 (22.2)	2300 (22.3)	0.429
Beta-blocker	38 885 (15.5)	2287 (22.0)	<0.001	4481 (21.7)	2269 (22.0)	0.731
Diuretic	52 139 (20.8)	2962 (28.5)	0.266	5665 (27.5)	2935 (28.4)	0.201
K-sparing diuretics	4725 (1.9)	401 (3.9)	0.283	621 (3.0)	397 (3.8)	0.600
Calcium channel blocker						
DHP	62 002 (24.7)	3051 (29.4)	0.121	6383 (30.0)	3029 (29.4)	0.072
Non-DHP	4562 (1.8)	379 (3.7)	<0.001	531 (2.6)	369 (3.6)	<0.001
Digoxin	1877 (0.7)	406 (3.9)	<0.001	329 (1.6)	399 (3.9)	<0.001
Statin	23 562 (9.4)	984 (9.5)	<0.001	2052 (10.0)	979 (9.5)	0.066
Aspirin	43 079 (17.2)	2457 (23.7)	0.022	4903 (23.8)	2439 (23.6)	0.194

Continued

Table 1 *Continued*

	Overall population			Propensity-matched population		
	AF-free (*n* = 252 176)	Incident AF (*n* = 10 435)	*P*-value	AF-free (*n* = 20 612)	Incident AF (*n* = 10 319)	*P*-value
P_2Y_{12} inhibitor	2957 (1.2)	194 (1.9)	0.776	397 (1.9)	193 (1.9)	0.888
Anticoagulant	259 (0.1)	58 (0.6)	<0.001	39 (0.2)	56 (0.5)	<0.001
Antiarrhythmic agents	487 (0.2)	1016 (9.8)	<0.001	51 (0.2)	1009 (9.8)	<0.001

Values are expressed in *n* (%), mean ± SD, or median (interquartile range).
ACE, angiotensin-converting enzyme; ADL: activities of daily living; AF, atrial fibrillation; 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; SD, standard deviation; CHA_2DS_2-VASc (congestive heart failure, BP consistently above 140/90 mm Hg or treated hypertension on medication, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack or thromboembolism)–[vascular disease (e.g. peripheral artery disease, MI, aortic plaque), age 65–74 years, female sex].
[a]KDSQ, Korean Dementia Screening Questionnaires, including five items. Each item on the KDSQ is scored from 0 to 2, with a higher score indicating poorer function and a greater frequency.

Table 2 Incidences of dementia during observational period according to atrial fibrillation status in overall and propensity score-matched population

Dementia	Overall population			Propensity score-matched population		
	Cases, *n* (%)	Incidence (/100 person-years)	Adjusted hazard ratio (95% CI)	Cases, *n* (%)	Incidence (/100 person-years)	Adjusted hazard ratio (95% CI)
Including stroke						
No AF (*n* = 252 176)	36 322 (14.4)	2.4	1.00 (reference)	3164 (15.4)	2.7	1.00 (reference)
Incident AF (*n* = 10 435)	2522 (24.4)	4.1	1.63 (1.54–1.72)	2505 (24.3)	4.1	1.52 (1.43–1.63)
Age subgroup						
Age ≥70 years						
No AF (*n* = 135 269)	25 158 (18.6)	3.5	1.00 (reference)	2399 (19.3)	3.7	1.00 (reference)
Incident AF (*n* = 6391)	1906 (29.8)	5.5	1.65 (1.54–1.76)	1877 (29.8)	5.4	1.52 (1.41–1.65)
Age <70 years						
No AF (*n* = 116 907)	11 164 (9.5)	1.4	1.00 (reference)	765 (9.4)	1.4	1.00 (reference)
Incident AF (*n* = 4044)	638 (15.8)	2.4	1.57 (1.40–1.75)	628 (15.6)	2.4	1.47 (1.29–1.68)
Censored for stroke						
No AF (*n* = 252 176)	33 980 (13.5)	2.3	1.00 (reference)	2 948 (14.3)	2.5	1.00 (reference)
Incident AF (*n* = 10 435)	2065 (19.8)	3.5	1.37 (1.28–1.47)	2034 (19.7)	3.5	1.27 (1.18–1.37)
Age subgroup						
Age ≥70 years						
No AF (*n* = 135 269)	23 565 (17.4)	3.3	1.00 (reference)	2228 (17.9)	3.5	1.00 (reference)
Incident AF (*n* = 6391)	1559 (24.4)	4.7	1.41 (1.30–1.52)	1535 (24.3)	4.7	1.30 (1.19–1.42)
Age <70 years						
No AF (*n* = 116 907)	10 415 (8.9)	1.3	1.00 (reference)	720 (8.8)	1.3	1.00 (reference)
Incident AF (*n* = 4044)	506 (12.5)	2.0	1.27 (1.12–1. 45)	499 (12.4)	2.0	1.17 (1.01–1.36)

with a clinical variable-adjusted HR of 1.37 (95% CI 1.28–1.47) (*Table 2*). After PS matching, incident AF increased the risk of dementia with clinical variable-adjusted HR of 1.27 (95% CI 1.18–1.37) (*Table 2*). After censoring for stroke, incident AF increased the risk of dementia in patients aged ≥70 years and those aged <70 years.

Risks of dementia according to BP control status and number of BP medication are presented in Supplementary material online, *Tables S2 and S3* and *Figure S1*. Uncontrolled BP status was not related with the increased risk of dementia in this senior cohort (age > 60 years).

Risk of dementia according to the type of dementia

Overall dementia, 61.6% and 18.5% were AD and VaD, respectively. The incidence of AD was 2.2 and 1.6 per 100 person-years in the

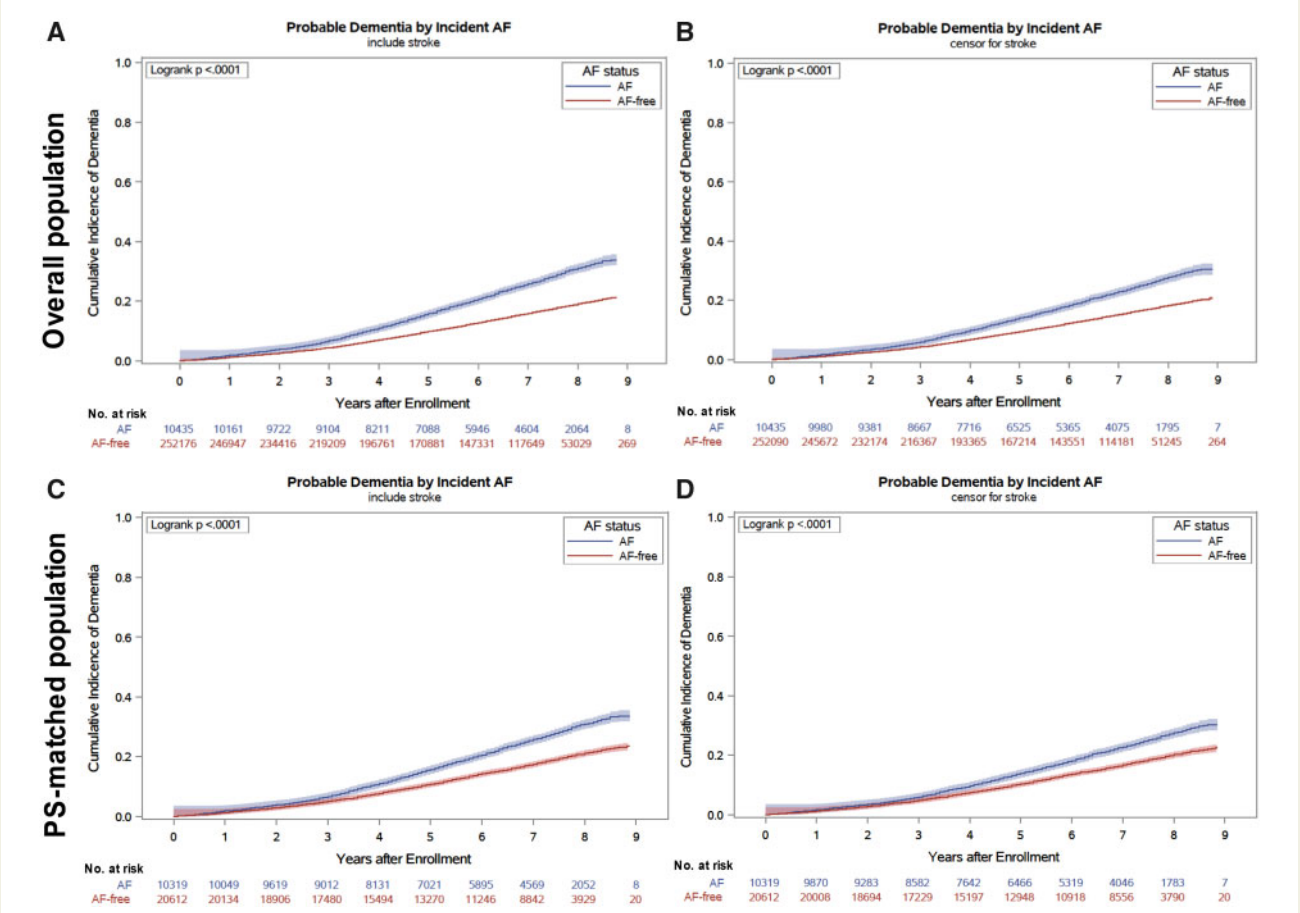


Figure 2 The cumulative incidence of dementia before (*A* and *C*) and after censoring for stroke (*B* and *D*) in overall population (*A* and *B*) and propensity score-matched population (*C* and *D*). Shaded regions indicate 95% confidence intervals.

incident AF and PS-matched AF-free patients, respectively. After PS matching, the clinical variable-adjusted HR for AD was 1.31 (95% CI 1.20–1.43) and 1.24 (95% CI 1.13–1.37) including and censoring stroke event during observational periods (*Table 3*).

The incidence of VaD was 1.1 and 0.5 per 100 person-years in the incident AF and PS-matched AF-free patients, respectively. Risk of VaD was significantly high in AF group (2.11, 95% CI 1.85–2.41). After censoring stroke, the risk for VaD was still higher in AF group with an HR of 1.36 (95% CI 1.15–1.62).

Subgroup analyses and relation to CHA_2DS_2-VASc score in overall population

Compared with the AF-free group, the risk of dementia was significantly increased in the AF group in all subgroups except in subjects with CKD, malignancy, heavy alcohol consumption and previous MI (*Figure 3*).

At each CHA_2DS_2-VASc score point, in OAC naïve patients, the stroke-censored incidence of dementia was higher in the AF group than in the AF-free group. With increasing CHA_2DS_2-VASc scores, the incidence of dementia increased gradually, up to 9.6% per year for CHA_2DS_2-VASc scores of 6 and 7 (*Figure 4*). Each 1-point increment of the CHA_2DS_2-VASc score in patients with incident AF was associated with a higher risk of dementia with an adjusted HR of 1.11 (95% CI 1.07–1.14, $P < 0.001$).

Effect of oral anticoagulants on dementia in patients with atrial fibrillation

In the AF group excluding patient with stroke during following, OACs were used in 3092 patients (29.6%), including 152 (4.9%) patients taking non-vitamin K oral anticoagulants (NOACs). The OAC group had a lower cumulative incidence of dementia compared to the OAC-free group (log-rank $P < 0.001$, *Figure 5*). Compared with AF patients without OAC, those taking OAC was associated with lower risk of dementia development (0.61, 95% CI 0.54–0.68, $P < 0.001$). Moreover, those taking OAC was associated with lower risk of AD and VaD with clinical variable-adjusted HR of 0.53 (95% CI 0.50–0.63) and 0.77 (95% CI 0.61–0.97), respectively.

Table 3 Incidences of Alzheimer and vascular dementia

	Overall population			Propensity score-matched population		
	Cases, *n* (%)	Incidence (/100 person-years)	Adjusted hazard ratio (95% CI)	Cases, *n* (%)	Incidence (/100 person-years)	Adjusted hazard ratio (95% CI)
Alzheimer dementia						
Including stroke						
No AF (*n* = 252 176)	22 562 (8.9)	1.5	1.00 (reference)	1953 (9.5)	1.6	1.00 (reference)
Incident AF (*n* = 10 435)	1372 (13.1)	2.2	1.39 (1.29–1.50)	1346 (13.0)	2.2	1.31 (1.20–1.43)
Censored for stroke						
No AF (*n* = 252 176)	21 650 (8.6)	1.4	1.00 (reference)	1857 (9.0)	1.6	1.00 (reference)
Incident AF (*n* = 10 435)	1221 (11.7)	2.1	1.32 (1.22–1.44)	1196 (11.6)	2.0	1.24 (1.13–1.37)
Vascular dementia						
Including stroke						
No AF (*n* = 252 176)	6490 (2.6)	0.4	1.00 (reference)	583 (2.8)	0.5	1.00 (reference)
Incident AF (*n* = 10 435)	684 (6.6)	1.1	2.46 (2.20–2.75)	676 (6.6)	1.1	2.11 (1.85–2.41)
Censored for stroke						
No AF (*n* = 252 176)	5593 (2.2)	0.4	1.00 (reference)	510 (2.5)	0.4	1.00 (reference)
Incident AF (*n* = 10 435)	464 (4.4)	0.8	1.63 (1.40–1.90)	461 (4.5)	0.8	1.36 (1.15–1.62)

Discussion

In this elderly population-based study, our principal findings were as follows: (i) incident AF was associated with an increased risk of dementia, independent of clinical stroke; (ii) incident AF increased the risk of dementia in all subgroups except in subjects with CKD, malignancy, heavy alcohol consumption and previous MI; and (iii) OAC use was associated with a lower cumulative incidence of dementia compared to no OAC use. These findings suggest that the strong link between AF and dementia might be weakened by OAC use.

Increased risk of dementia by atrial fibrillation

In this study, the risk of dementia was increased, with an adjusted HR of 1.63 in individuals with AF but without stroke at baseline when compared to those without AF, even after censoring for incident stroke. Previous studies have shown that the risk of dementia and cognitive decline was more modest in individuals with AF but without stroke at baseline,[15] and dementia was also more common in patients diagnosed with AF even in the absence of stroke.[5,16]

Our study showed that incident AF was associated with the increased risk of both AD and VaD. AF may be related to dementia via various pathways.[16] Given the relationship between AF and stroke, VaD may be an obvious contributor to cognitive decline, encompassing both multi-infarct dementia and small vessel disease dementia.[5,16] Although our results remained similar after censoring for stroke, it remains possible that asymptomatic strokes explain the link between AF and dementia.[17]

The second form of dementia in AF patients is AD, which is a more common type of dementia overall. Indeed, AF has been identified as a risk factor for AD.[6,7,16] In the majority of cases, the brains of AD have vascular microinfarcts, white matter lesions, or vessel wall alterations.[18] Increased beta-amyloid and hyperphosphorylated tau reactivity in both infarcted and adjacent brain areas were followed experimentally induced cerebral microemboli in aged rats,[19] suggesting a possible association with Alzheimer's pathophysiology. Vascular risk factors have been linked to risk for AD in many epidemiological studies.[18,20] These evidences have suggested a role for cerebrovascular disease in the onset and progression of AD. Consistently, compared with AF patients without OAC, OAC use was associated with decreased risk of overall dementia, and both AD and VaD. Other studies have suggested that the occurrence of AD is related to hypoperfusion, inflammation, oxidative stress, and endothelial dysfunction.[16]

One recent study suggested that incident AF was a risk factor for dementia only in participants aged younger than 67 years.[21] Since dementia develops gradually over many years, it is likely that AF needs to occur at a younger age to contribute to the onset of dementia. Similarly, the associations of other dementia risk factors, such as hypertension, hypercholesterolaemia, and obesity, also appears to differ with age, with a stronger effect evident earlier in life.[22] Accordingly, if AF is a causal factor in the aetiology of dementia, one would expect that the longer a person has the condition, the higher the risk of dementia. However, in this elderly cohort, we demonstrated that the risk of dementia was increased by incident AF even in the more elderly subjects aged ≥70 years.

Predictors of dementia in atrial fibrillation

Since AF patients show a higher risk of dementia, the ability to predict its occurrence in the AF population is critical. In the present study using the NHIS-Senior, the CHA_2DS_2-VASc score was a significant predictor of dementia in AF subjects even after censoring for stroke.

Based on the findings of the present study, physicians should be vigilant for clinical manifestations implying any cognitive decline and functional impairment in AF patients, especially those with a

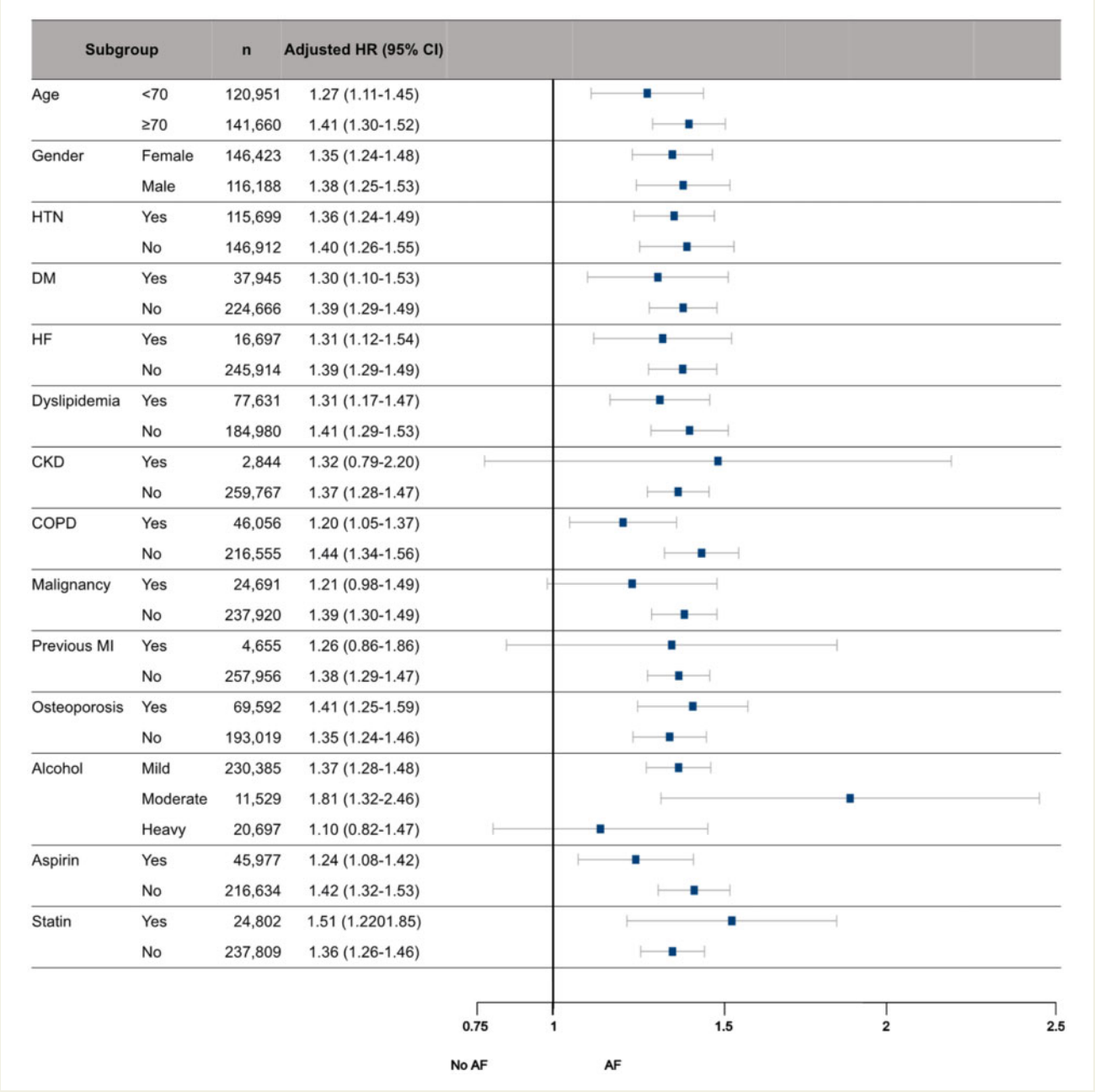


Figure 3 Hazard ratios for dementia in different subgroups in overall population. Boxes indicate the hazard ratio, limit lines indicate the 95% confidence interval, and the horizontal line (at hazard ratio 1) indicates no difference in the hazard ratios between atrial fibrillation and no atrial fibrillation.

high CHA_2DS_2-VASc score. This finding also implies that subclinical stroke and shared risk factors play significant roles in the development of dementia in patients with AF. The increasing risk of dementia with rising CHA_2DS_2-VASc score would not support the deployment of NOAC therapy in anticipation of AF before a diagnosis of AF. To answer this question, a well-designed specific study is needed.

Uncontrolled BP status was not related with the increased risk of dementia in this senior cohort (age > 60 years). This result is consistent with previous reports showing that BP effects on dementia were significant in younger, but not in elderly population (age > 60 years).[23,24]

Lowering the risk of dementia with oral anticoagulants

Our findings suggest that OAC users had a lower cumulative incidence of dementia compared to non-users. Unfortunately, there are no randomized data examining the efficacy of various therapies or of individualized management in preventing dementia in individuals with

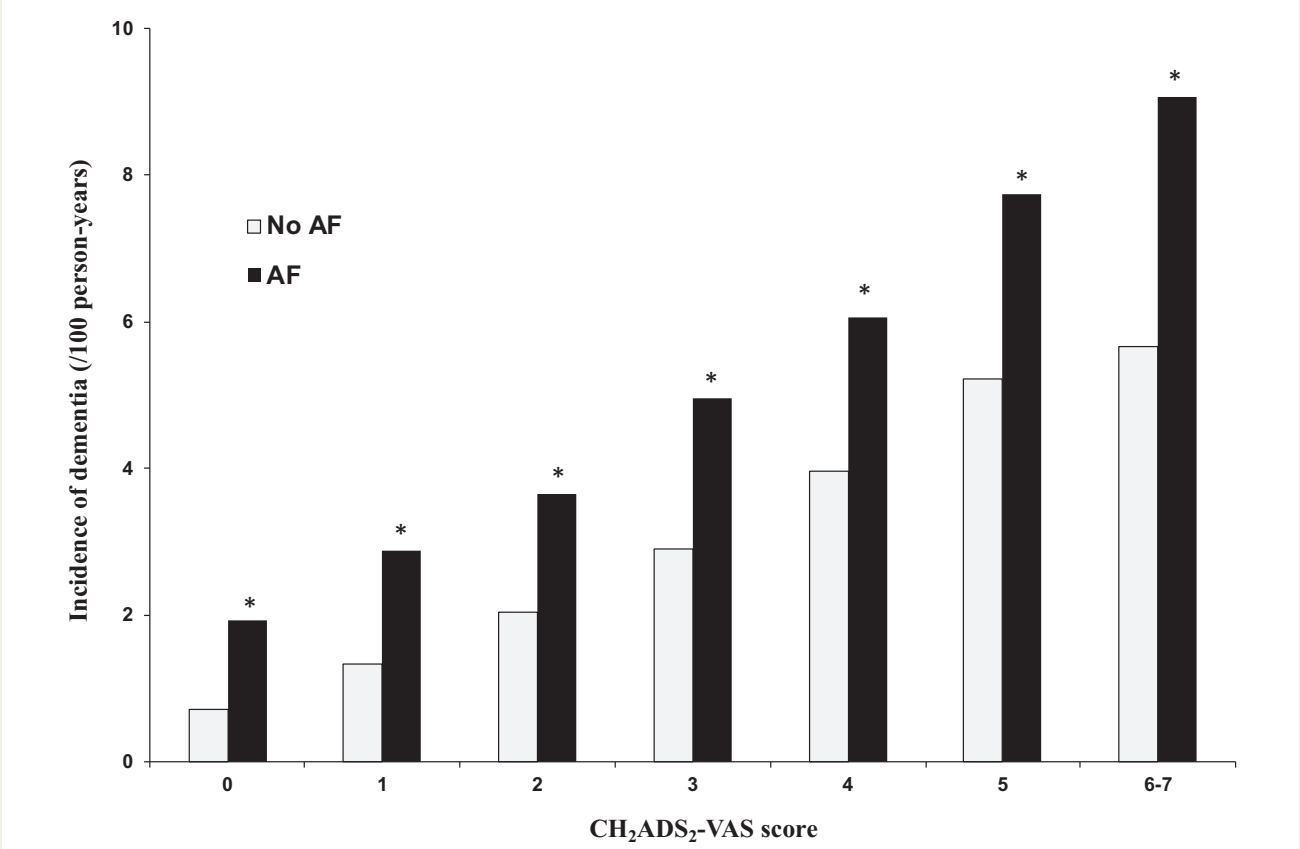


Figure 4 The incidence of dementia according to different CHA_2DS_2-VASc scores in participants with or without incident atrial fibrillation.

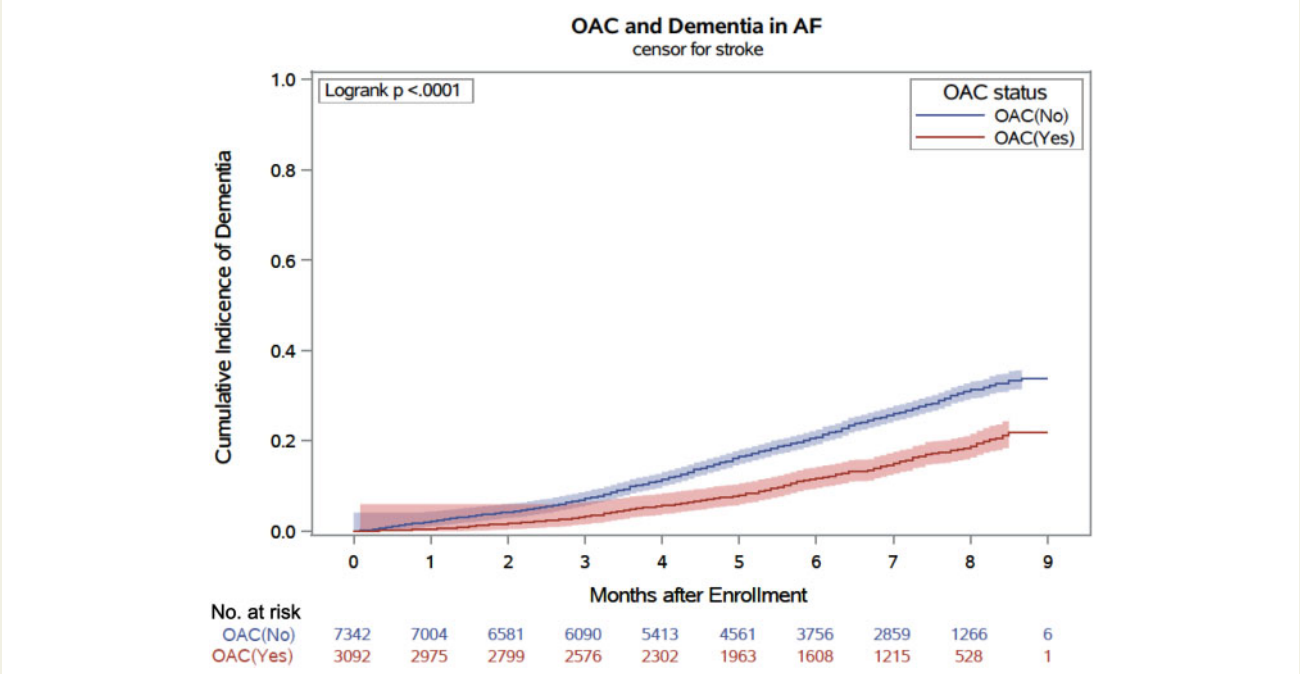
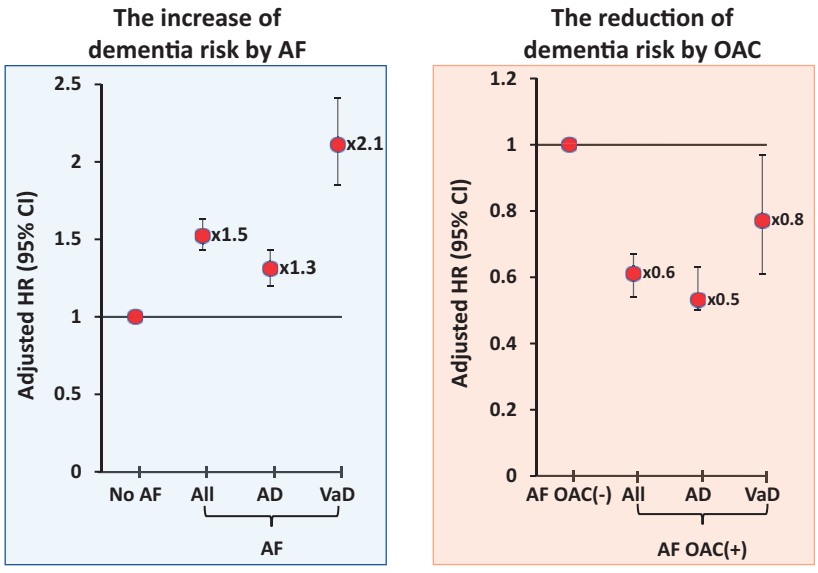


Figure 5 The cumulative incidence of dementia in patients with incident atrial fibrillation with or without oral anticoagulation. Shaded regions indicate 95% confidence intervals.



* AD: Alzheimer disease, VaD: Vascular dementia

Take home figure Risk of dementia according to atrial fibrillation (AF) status in the study population (left). Effects of oral anticoagulation (OAC) on risk of dementia in AF group (right).

AF. The risk of ischaemic stroke following AF declined by 9% (adjusted HR 0.91, 95% CI 0.88–0.93) in Korea for a decade from 2006 to 2015,[2,3] which was speculated to have been attributable to improved anticoagulation and treatment of risk factors in individuals with AF.

In previous retrospective observational studies, the risk of dementia increased with poor vitamin K antagonist management (a low time in therapeutic range),[25] whereas in the other study indicated that the use of OACs was associated with a lower risk of dementia compared to without use of OACs in patients with AF.[26] In a retrospective register-based study, NOACs use was associated with a reduced risk of dementia compared with warfarin.[27] A meta-analysis of the four randomized trials comparing NOACs to warfarin demonstrated that the NOACs were associated with a significant risk reduction in terms of overall stroke and systemic emboli,[28] with a greater effect observed in Asians compared to non-Asians.[29]

Large longitudinal studies with longer follow-up time are needed to clarify the effect of NOACs on cognitive function, and currently randomized-controlled clinical trial focusing on cognitive outcomes in patients with AF have been initiated.[16]

Limitations

The present study has several limitations. Although administrative databases are increasingly used for clinical research, such studies are potentially susceptible to errors arising from coding inaccuracies. To minimize this problem, we applied the definition that we had validated in previous studies using a Korean NHIS cohort.[2,3] Second, we were unable to define the type (paroxysmal vs. persistent) of AF. Atrial fibrillation can occur without symptoms, and although numerous electrocardiography measurements were performed at the research centre, we may have missed some participants with asymptomatic AF. Third, we did not have information regarding treatment following AF. It is possible that the risk of dementia in patients with AF may be attenuated after successful treatment. Forth, despite the adjustment for some differences in baseline characteristics, residual unidentified confounders may remain. Finally, there was no available information about ambulatory BP monitoring data, given this is a 'real world' nationwide population cohort.

Conclusions

Incident AF was associated with an increased risk of dementia, independent of clinical stroke, in an elderly population. Oral anticoagulant use was linked to a lower incidence of dementia.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No fees were received personally. JBY: Speaker for Bayer, BMS/Pfizer, Medtronic and Daiichi-Sankyo. Research fund from Medtronic, Boston scientifics and Abbott. None of the other authors have any disclosures to make.

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