Risk of Dementia in Stroke-Free Patients Diagnosed with Atrial Fibrillation: Data from a Population-Based Cohort

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Directed by Professor Boyoung Joung

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Dongmin Kim

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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, population-based, stroke-free elderly cohort.

Methods: The association of incident AF with the development of incident dementia was assessed from Jan 1, 2005 to Dec 31, 2012 in 260,638 dementia- and stroke-free participants aged ≥60 years in the Korea National Health Insurance Service-Senior cohort.

Results: Incident AF was observed in 10,975 participants over an observational period of 1,613,322 person-years (0.68% per year). During the observational period, the incidence of dementia was 2.5 and 1.6 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 1.84 [95% confidence interval (CI): 1.71-1.98], even after censoring for stroke (1.64, 95% CI: 1.51-1.79). Incident AF increased the risk of both Alzheimer (HR 1.63, 95% CI 1.50-1.78) and vascular dementia (HR 3.09, 95% CI 2.56-3.72). Among patients with incident AF, oral anticoagulant (OAC) use was associated with a preventive effect on dementia development (0.67, 95% CI: 0.57-0.79, $p<0.001$), 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. OAC use was linked with a decreased incidence of dementia.

Key words : atrial fibrillation, dementia, anticoagulation, aged, prognosis

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

Worldwide, prevalence of dementia is approximately 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 remains 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.

II. MATERIALS AND METHODS

Source of study data

Data were collected from the NHIS-Senior, which contains data on 558,147 individuals, approximately 10% of the entire elderly population in South Korea aged ≥60 years (about 5.1 million) in 2002.[10, 11] 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. The authors declare no conflict of interest with NHIS.

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=1,019); (ii) those who had an ischemic stroke or transient ischemic attack before enrollment (n=41,722); (iii) those who had a hemorrhagic stroke before enrollment (n=1,425); (iv) those who had dementia before enrollment (n=2,281); and (v) those who had AF before enrollment (n=5,651). 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 260,638 subjects, including 10,975 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%.[2, 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 (Table 1).[2, 12] 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.

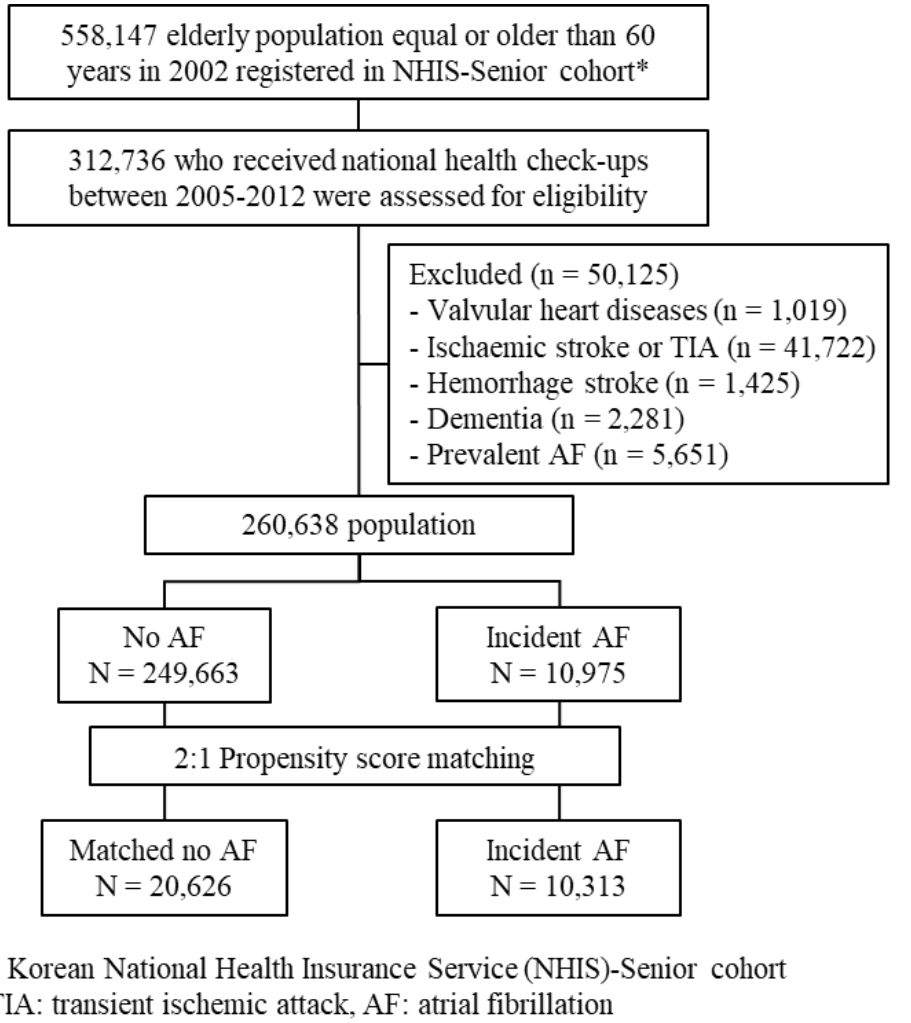

Figure 1. Flowchart of the study population enrollment and analyses.

Table 1. Definitions and ICD-10 codes used for defining the comorbidities and clinical outcomes

	Definitions	**ICD-10 codes or conditions**
Comorbidities		
Hypertension	Defined from diagnosis* plus treatment	ICD-10: I10, I11, I12, I13, I15 Treatment: all kinds of blood pressure lowering medications
Diabetes mellitus	Defined from diagnosis* plus treatment	ICD-10: E10, E11, E12, E13, E14 Treatment: all kinds of oral antidiabetics and insulin.
Dyslipidemia	Defined from diagnosis*	ICD-10: E78
Heart failure	Defined from diagnosis*	ICD-10: I11.0, I50, I97.1
Peripheral arterial disease	Defined from diagnosis*	ICD-10: I70.0, I70.1, I70.2, I70.8, I70.9
Previous myocardial infarction	Defined from diagnosis*	ICD-10: I21, I22, I25.2
Chronic kidney disease	Defined from eGFR or diagnosis* (if laboratory value was not available, diagnosis code was used)	eGFR <60mL/min per 1.73 m^2 ICD-10: N18, N19
ESRD	Defined from the national registry for severe illness.	Patients undergoing chronic dialysis or those who had received a kidney transplant.
Malignancy	Defined from diagnoses of cancer (non-benign)	ICD-10: C00-C97
COPD	Defined from diagnosis* plus treatment	ICD-10: J42, J43(except J43.0), J44 Treatment: inhaled corticosteroid, inhaled bronchodilators, or oral methylxanthine (>1 months).

Chronic liver disease	Defined from diagnosis of chronic liver disease, cirrhosis, and hepatitis	B18, K70, K71, K72, K73, K74, K76.1
Clinical outcomes		
Dementia	Defined from diagnosis*	ICD-10: F00, G30, F01, F02, F03
New onset atrial fibrillation	Defined from diagnosis* without previous insurance claim for AF	I48
Exclusion Diagnosis		
Previous ischemic stroke	Defined from diagnosis*	ICD-10: I63, I64
Previous TIA	Defined from diagnosis*	ICD-10: G45
Previous intracranial hemorrhage	Defined from diagnosis*	ICD-10: I60, I61, I62
Potential absence of non-valvular atrial fibrillation	Defined from any diagnoses of mitral stenosis or heart valve surgery	I05.0, I05.2, I34.2, Z95.2-4, claim for valve replacement or valvuloplasty
Dementia	Defined from diagnosis*	F00, F01, F02, F03, G30

*To ensure accuracy, diagnosis was established based on one inpatient or two outpatient records of ICD-10 codes in the database.

ICD-10, International Classification of Disease-10th revision; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; TIA, transient ischemic attack

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 5 items that can detect early changes in cognitive decline to diagnose dementia [13]. 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.[13]

Newly diagnosed dementia was defined by ICD-10 codes and the prescription of medication for dementia (rivastigmine, galantamine, memantine, or donepezil). 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. Dementia was further classified as Alzheimer's disease (F00 or G30), vascular dementia (F01), or other dementia (F02, F03, or G31). When both codes for Alzheimer's disease and vascular dementia were recorded, we followed the principal diagnosis. If both were in the additional diagnosis up to the second claim DB, the subject was classified as other dementia[14].

To evaluate the accuracy of our definition of dementia, we conducted a validation study in three teaching hospitals with 1,220 patients who having ICD-10 code F00, F01, F02x, F03, or G30. The patient's medical records and the results of cognitive function test including the Mini Mental State Examination (MMSE) were reviewed. Patients were ascertained to have dementia if it was diagnosed by the cognitive function test. The positive predictive value was 95.3% (1163/1220). The most common case of false positive was mild cognitive dysfunction.

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 were used to correct for potential systematic differences between AF and AF-free groups. Each study patient's propensity scores for development of AF were computed and adjusted for the covariates in a logistic regression analysis based on baseline characteristics, including age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, heart failure, chronic kidney disease (CKD), osteoporosis, liver disease, history of malignant neoplasm, CHA_2DS_2-VASc score, economic status, cardiovascular medications (angiotensin converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, statin, aspirin, P2Y12 inhibitor), body mass index (BMI), systolic blood pressure, diastolic blood pressure, blood glucose level total cholesterol, hemoglobin, and alcohol, smoking and exercise habits habit. Propensity score matching was made on logit-transformed propensity scores matched with greedy method in a 2:1 fashion with a caliper of 0.05. 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 December 31, 2013, whichever came first. We adjusted for age, sex and clinical variables including hypertension, diabetes mellitus, dyslipidemia, heart failure, previous myocardial infarction (MI), heart failure, peripheral artery disease (PAD), CKD, chronic obstructive pulmonary disease(COPD), liver disease, history of malignant neoplasm, economic status, cardiovascular medications (angiotensin converting enzyme inhibitor or

angiotensin receptor blocker, beta-blocker, alpha-blocker, diuretics, k-sparing diuretics, calcium channel blocker, digoxin, antiarrhythmic agents, statin, aspirin, P2Y12 inhibitor, anticoagulants), BMI, blood glucose level, total cholesterol, and alcohol, smoking and exercise 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.

All tests were two-tailed, and $p < 0.05$ was considered significant. Statistical analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS version 24.0 statistical package (SPSS Inc., Chicago, IL, USA).

III. RESULTS

Baseline characteristics

Incident AF was diagnosed in 10, 975 participants over an observational period of 1,613,322 person-years (0.68%/year). Patients with incident AF were older (aged 71.7±5.7 vs. 70.8±5.4 years), had higher diastolic blood pressure, and had more comorbidities compared to participants without incident AF. Hypertension was significantly higher in the AF group compared to controls. Cardiovascular medications were used frequently in the AF group compared to the AF-free group (Table 2).

Table 2. Patient characteristics.

	Overall Population			Propensity score-matched population		
	AF-free (n=249,663)	**Incident AF (n=10,975)**	**SMD**	**AF-free (n=20,626)**	**Incident AF (n=10,313)**	**SMD**
Age, years	70.8±5.4	71.7±5.7	0.170	71.7±5.8	71.7±5.7	-0.005
Age over 75 years, n (%)	51,622 (20.7)	2,945 (26.8)	0.145	5,557 (26.9)	2,786 (27)	-0.002
Female, n (%)	140,169 (56.1)	5,215 (47.5)	0.173	10,032 (48.6)	5,016±48.6	-0.001
BMI, kg/m2	23.7±3.2	23.9±3.4	0.040	23.9±3.3	23.9±3.4	-0.003
SBP, mmHg	132.3±17.9	133.9±18.8	0.084	134.1±18.2	133.8±18.8	-0.01
DBP, mmHg	79.5± 10.8	80.2±11.3	0.064	80.3±11	80.2±11.3	-0.007
Blood glucose, mg/dL	102.8±31.1	104.6±35.5	0.052	104.8±33.7	104.6±35.4	0.003
Total cholesterol, mg/dL	199.1±39	194.1±39	-0.128	194.4±38.2	194.4±39.1	-0.002
Serum creatinine, mg/dL	0.98±0.85	1.05±0.96	0.076	1.03±0.98	1.05±0.97	0.021
Hypertension, n (%)	109,782 (44)	5,990 (54.6)	0.213	1,1403 (55.3)	5,636 (54.7)	-0.012
Diabetes, n (%)	36,064 (14.5)	1,823 (16.6)	0.060	3,525 (17.1)	1,719 (16.7)	-0.004

Dyslipidemia, n (%)	80,864 (32.4)	3,903 (35.6)	0.067	7,451 (36.1)	3,695 (35.8)	-0.004
Heart failure, n (%)	16,956 (6.8)	1,638 (14.9)	0.264	3,045 (14.8)	1,563 (15.2)	0.013
CKD or ESRD, n (%)	3,126 (1.3)	186 (1.7)	0.037	3,32 (1.6)	178 (1.7)	0.009
History of MI, n (%)	4,944 (2)	422 (3.9)	0.111	650 (3.2)	395 (3.8)	0.031
PAOD, n (%)	10,044 (4)	542 (4.9)	0.044	1,025 (5)	509 (4.9)	-0.005
Vascular disease, n (%)	14,312 (5.7)	906 (8.3)	0.099	1,576 (7.6)	849 (8.2)	0.016
COPD, n (%)	19,225 (7.7)	1,171 (10.7)	0.103	1,918 (9.3)	1,105 (10.7)	0.047
Liver disease, n (%)	56,559 (22.7)	2,738 (25)	0.054	5,266 (25.5)	2,561 (24.8)	-0.011
Malignancy, n (%)	27,311 (10.9)	1,347 (12.3)	0.042	2,558 (12.4)	1,250 (12.1)	-0.004
Osteoporosis, n (%)	74,211 (29.7)	3,029 (27.6)	-0.047	5,866 (28.4)	2,906 (28.2)	-0.005
CHA_2DS_2-VASc score	2.36±1.21	2.59±1.31	0.174	2.6±1.31	2.6±1.31	-0.002
Economic status			0.024			0.024
Low, n (%)	77,469 (31)	3,423 (31.2)		6,449 (31.3)	3,234 (31.4)	
Middle, n (%)	86,948 (34.8)	3,682 (33.6)		6,959 (33.7)	3,440 (33.4)	
High, n (%)	85,246 (34.1)	3,870 (35.3)		7,218 (35)	3,639 (35.3)	

Smoking			0.049			0.001
No, n (%)	188,018 (79.2)	7,924 (76.6)		15,757 (76.4)	7,903 (76.6)	
Former, n (%)	18,278 (7.7)	895 (8.7)		1,777 (8.6)	895 (8.7)	
Current, n (%)	31,132 (13.1)	1,521 (14.7)		3,092 (15)	1,515 (14.7)	
Alcohol consumption			0.108			0.001
Low, n (%)	206,717 (82.8)	8,711 (79.4)		1,6416 (79.6)	8,233 (79.8)	
Moderate, n (%)	20,154 (8.1)	969 (8.8)		1,779 (8.6)	901 (8.7)	
Heavy, n (%)	22,792 (9.1)	1,295 (11.8)		2,431 (11.8)	1,179 (11.4)	
Exercise			0.202			0.001
No, n (%)	17,463 (7)	433 (4)		847 (4.1)	425 (4.1)	
Seldom, n (%)	15,723 (6.3)	382 (3.5)		741 (3.6)	375 (3.6)	
Regular, n (%)	216,477 (86.7)	10,160 (92.6)		1,9038 (92.3)	9,513 (92.2)	
Cognitive Function[§]						
KDSQ (positive rate)	6,811 (20.9)	220 (22.6)	0.041	410 (19.6)	201 (22)	0.059
KDSQ score	1 (0, 3)	1 (0, 3)	0.053	1 (0, 3)	1 (0, 3)	0.076

ADL score	0 (0, 1)	0 (0, 1)	0.086	0 (0, 1)	0 (0, 1)	0.107
History of recent fall	4,549 (13.9)	142 (14.5)	0.017	299 (14.2)	134 (14.6)	0.011
Depression (positive rate)	16,594 (50.9)	529 (54.4)	0.069	1,042 (49.9)	503 (55.1)	0.105
Medication						
ACE inhibitor or ARB, n (%)	46,952 (18.8)	2,769 (25.2)	0.156	5,226 (25.3)	2,597 (25.2)	-0.005
Beta-blocker, n (%)	43,661 (17.5)	2,668 (24.3)	0.168	5,056 (24.5)	2,514 (24.4)	-0.002
Alpha-blocker, n (%)	12,053 (4.8)	673 (6.1)	0.057	1,341 (6.5)	632 (6.1)	-0.015
Diuretic, n (%)	59,194 (23.7)	3,478 (31.7)	0.179	6,454 (31.3)	3,268 (31.7)	0.010
K-sparing diuretics, n (%)	6,037 (2.4)	527 (4.8)	0.128	769 (3.7)	496 (4.8)	0.049
Calcium channel blocker, n (%)						
DHP, n (%)	67,353 (27)	3,496 (31.9)	0.107	6,994 (33.9)	3,291 (31.9)	-0.039
Non-DHP, n (%)	5,233 (2.1)	444 (4.1)	0.113	610 (3)	420 (4.1)	0.061
Digoxin, n (%)	2,237 (0.9)	475 (4.3)	0.216	382 (1.9)	444 (4.3)	0.137
AADs, n (%)	256 (0.1)	78 (0.7)	0.096	43 (0.2)	74 (0.7)	0.077
Statin, n (%)	28,383 (11.4)	1,242 (11.3)	-0.002	2,410 (11.7)	1,179 (11.4)	-0.011

Aspirin, n (%)	47,426 (19)	2,857 (26)	0.169	5,306 (25.7)	2,684 (26)	0.004
P2Y12 inhibitor, n (%)	3,513 (1.4)	240 (2.2)	0.059	431 (2.1)	220 (2.1)	-0.003
Anticoagulant, n (%)	315 (0.1)	66 (0.6)	0.079	36 (0.2)	57 (0.6)	0.062
F/U duration, month (median, IQR)	85 (58, 95)	86 (62, 96)	0.042	85 (59, 95)	86 (61, 96)	0.064

Values are expressed in n (%), mean ± SD, or median (interquartile range). SMD, standardized mean difference

AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; ESRD, end-stage renal disease; MI, myocardial infarction; PAOD, peripheral artery occlusive disease; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARB, angiotensin type II receptor blocker; DHP, dihydropyridine; AADs, antiarrhythmic drugs; CHA_2DS_2-VASc, (congestive heart failure, blood pressure consistently above 140/90 mm Hg or treated hypertension on medication, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism)–(vascular disease [e.g., peripheral artery disease, myocardial infarction, aortic plaque], age 65–74 years, female sex); F/U, follow-up; IQR, interquartile range.

[§]KDSQ, Korean Dementia Screening Questionnaires, including 5 items. Each item on the KDSQ is scored from 0 to 2, with a higher score indicating poorer function and a greater frequency; ADL, Activity of Daily Living, a questionnaire that combines 4 items from the Korean Activity of Daily Living (K-ADL) and 2 items from the Korean Instrumental ADL (K-IADL) scales; Depression screening, 4 selected questions from the Center for Epidemiologic Studies Depression scale, and 3 selected questions from the Geriatric Depression Scale.

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 (20.9% vs. 22.6%, p=0.626) (Table 2).

After propensity score (PS) matching, baseline characteristics of the incident AF and AF-free groups became similar (Table 2).

Risk of dementia

In overall patients with incident AF, 1,635 participants (14.9%) developed dementia during 67,103 person-years of follow-up, compared to 21,469 participants (8.6%) who developed dementia among the AF-free patients. The incidence of dementia was 2.5 and 1.6 per 100 person-years in the incident AF and PS-matched AF-free patients, respectively (Table 3). 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 1.84, 95% CI: 1.73-1.96) (Table 2). After propensity score matching, the risk of dementia was still significantly increased by incident AF with clinical variable HR of 1.84 (95% CI: 1.71-1.98) (Table 3). 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 21.2% and 4.8% patients in the AF and AF-free groups, respectively. The incidence of dementia after censoring for stroke was 2.0 and 1.5 per 100 person-years in the incident AF and PS-matched AF-free groups, respectively (Table 3). 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 with a clinical variable-adjusted HR of 1.63 (95% CI: 1.52-1.76)

Table 3. Incidences of dementia during follow-up period according to AF status in overall and propensity score matched population.

Dementia	Overall population			Propensity score-matched population		
	Cases, n (%)	Incidence§	Clinical variable-adjusted HR (95% CI)	Cases, n (%)	Incidence§	Clinical variable-adjusted HR (95% CI)
Including Stroke						
No AF (n=249,663)	21,469 (8.6)	1.4	1.00 (Reference)	2,023 (9.8)	1.6	1.00 (Reference)
Incident AF (n=10,975)	1,635 (14.9)	2.4	1.84 (1.73-1.96)	1,549 (15.0)	2.5	1.84 (1.71-1.98)
Age subgroup						
Age ≥ 70 years						
No AF (n=133,918)	15,825 (11.8)	2.2	1.00 (Reference)	1,602 (12.8)	2.3	1.00 (Reference)
Incident AF (n=6,693)	1242 (18.6)	3.5	1.76 (1.64-1.89)	1,179 (18.7)	3.3	1.77 (1.62-1.93)
Age < 70 years						
No AF (n=115,745)	5,644 (4.9)	0.7	1.00 (Reference)	421 (5.2)	0.8	1.00 (Reference)
Incident AF (n=4,282)	393 (9.2)	1.3	2.09 (1.84-2.36)	370 (9.2)	1.4	2.07 (1.78-2.42)
Censored for stroke						
No AF (n=249,663)	19,603 (7.9)	1.3	1.00 (Reference)	1,818 (8.8)	1.5	1.00 (Reference)
Incident AF (n=10,975)	1,259 (11.5)	2.0	1.63 (1.52-1.76)	1,194 (11.6)	2.0	1.64 (1.51-1.79)
Age subgroup						
Age ≥ 70 years						
No AF (n=133,918)	14,510 (10.8)	2	1.00 (Reference)	1,446 (11.6)	2.2	1.00 (Reference)
Incident AF (n=6,693)	977 (14.6)	2.8	1.61 (1.48-1.75)	929 (14.7)	2.8	1.63 (1.48-1.80)
Age < 70 years						

No AF (n=115,745)	5,093 (4.4)	0.7	1.00 (Reference)	372 (4.6)	0.7	1.00 (Reference)
Incident AF (n=4,282)	282 (6.6)	1.0	1.68 (1.44-1. 96)	265 (6.6)	1.0	1.66 (1.38-1.99)

§100 person-years

Abbreviation: HR, hazard ratio; AF, atrial fibrillation.

Clinical variable-adjusted HR was adjusted for age, sex, and clinical variables including hypertension, diabetes mellitus, dyslipidemia, heart failure, previous myocardial infarction, heart failure, peripheral artery disease, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, history of malignant neoplasm, economic status, cardiovascular medications (angiotensin converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, alpha-blocker, diuretics, k-sparing diuretics, calcium channel blocker, digoxin, antiarrhythmic agents, statin, aspirin, P2Y12 inhibitor, anticoagulants), body mass index, systolic blood pressure, diastolic blood pressure, blood glucose level, total cholesterol, and alcohol, smoking and exercise habits.

Table 4. Incidences of Alzheimer and vascular dementia during follow-up period according to AF status in overall and propensity score matched population.

	Overall population			Propensity score-matched population		
	Cases, n (%)	Incidence[§]	Clinical variable-adjusted HR (95% CI)	Cases, n (%)	Incidence[§]	Clinical variable-adjusted HR (95% CI)
Alzheimer Dementia Including Stroke						
No AF (n=249,663)	16,147 (6.5)	1.1	1.00 (Reference)	1,540 (7.5)	1.2	1.00 (Reference)
Incident AF (n=10,975)	1,150 (10.5)	1.7	1.66 (1.54-1.79)	1,089 (10.6)	1.7	1.63 (1.50-1.78)
Censored for stroke						
No AF (n=249,663)	15,028 (6.0)	1.0	1.00 (Reference)	1,409 (6.8)	1.2	1.00 (Reference)
Incident AF (n=10,975)	951 (8.7)	1.5	1.59 (1.46-1.73)	903 (8.8)	1.5	1.57 (1.42-1.73)
Vascular Dementia Including Stroke						
No AF (n=249,663)	2,444 (1.0)	0.2	1.00 (Reference)	235 (1.1)	0.2	1.00 (Reference)
Incident AF (n=10,975)	282 (2.6)	0.4	3.17 (2.74-3.66)	265 (2.6)	0.4	3.09 (2.56-3.72)
Censored for stroke						
No AF (n=249,663)	1956 (0.8)	0.1	1.00 (Reference)	186 (0.9)	0.1	1.00 (Reference)
Incident AF (n=10,975)	146 (1.3)	0.2	2.01 (1.63-2.48)	136 (1.3)	0.2	2.00 (1.57-2.57)

[§]100 person-years

Abbreviation: HR, hazard ratio; AF, atrial fibrillation.

Clinical variable-adjusted HR was adjusted for same variables used in Table 2.

(Table 3). After propensity score matching, incident AF increased the risk of dementia with clinical variable-adjusted HR of 1.64 (95% CI: 1.51-1.79) (Table 3). After censoring for stroke, incident AF increased the risk of dementia in patients aged ≥70 years and those aged <70 years.

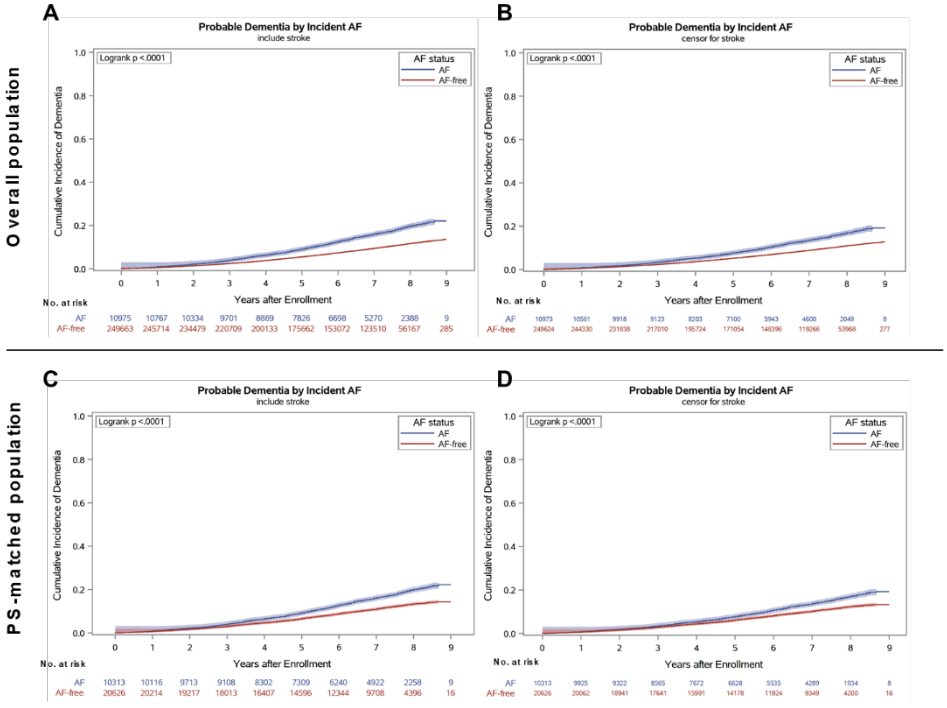

Figure 2. The cumulative incidence of dementia before (A and C) and after censoring for stroke (B and D) in overall population (A and B) and propensity score-matched population (C and D). Shaded regions indicate 95% confidence intervals.

Risk of dementia according to the type of dementia

Overall dementia, 86.9% and 13.1% were AD and VaD, respectively. The incidence of AD was 1.7 and 1.2 per 100 person-years in the incident AF and PS-matched AF-free patients, respectively. After PS matching, the clinical variable-adjusted HR for AD was 1.63 (95% CI: 1.50-1.78) and 1.57 (95% CI: 1.42-1.73)

when censoring stroke event during observational periods (Table 4).

The incidence of VaD was 0.4 and 0.2 per 100 person-years in the incident AF and PS-matched AF-free patients, respectively. Risk of vascular dementia was significantly high in AF group (3.09, 95% CI: 2.56-3.72). After censoring stroke, the risk for vascular dementia was still higher in AF group with an HR of 2.00 (95% CI: 1.57-2.57) (Table 4).

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 incident AF group in all subgroups except in subjects with CKD (Figure 4).

At each CHA_2DS_2-VASc score point, in OAC naïve patients, the stroke-censored incidence of dementia was higher in the incident AF group than in the AF-free group. With increasing CHA_2DS_2-VASc scores, the incidence of dementia increased gradually, up to 5.2% and 3.7% per year for CHA_2DS_2-VASc scores of 6 and 7 in AF and AF-free group, respectively (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 hazard ratio of 1.22 (95% CI: 1.16-1.27, $p<0.001$).

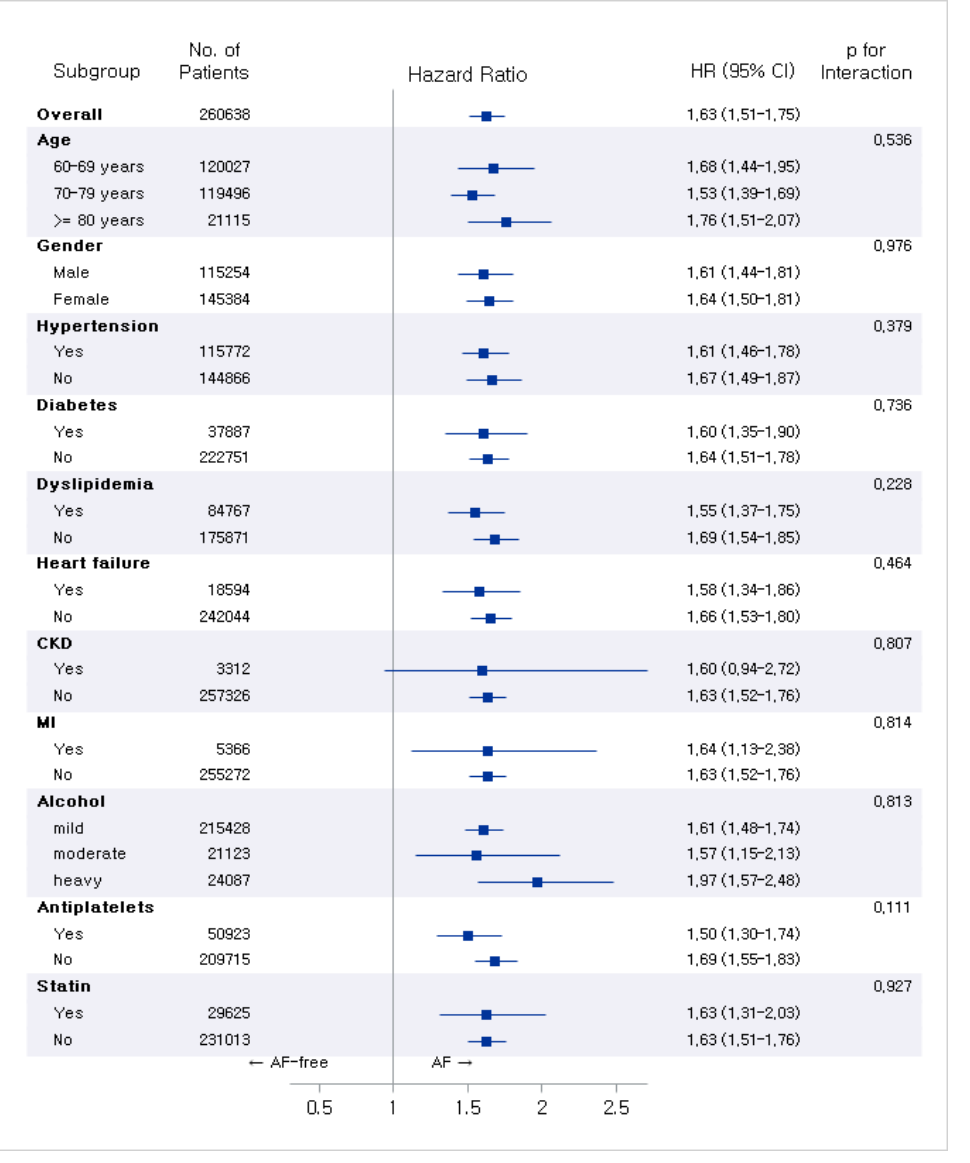

Figure 3. Hazard ratios for dementia in different subgroups in overall population. Boxes indicate the hazard ratio, limit lines indicate the 95% CI, and the vertical line (at hazard ratio 1) indicates no difference in the hazard ratios between AF and no AF.

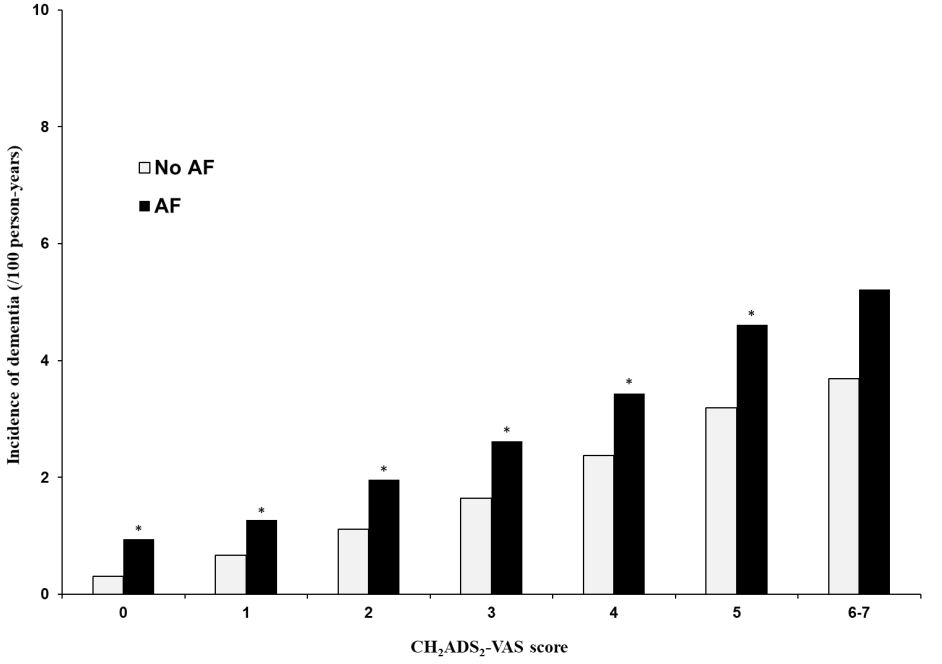

Figure 4. The incidence of dementia according to different CHA_2DS_2-VASc scores in participants with or without incident AF. Asterisk makers indicate statistical significance.

Effect of OACs on dementia in patients with AF

In the incident AF group excluding patient with stroke during following, OACs were used in 2,526 patients (23.0%), including 95 (3.7%) 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 oral anticoagulation (OAC), those taking OAC was associated with lower risk of dementia development (0.62, 95% CI: 0.52-0.73, p<0.001). Moreover, those taking OAC was associated with lower risk of AD and VaD with clinical variable adjusted HR of 0.56 (95% CI: 0.45-0.68) and 0.76 (95% CI: 0.48-0.99), respectively.

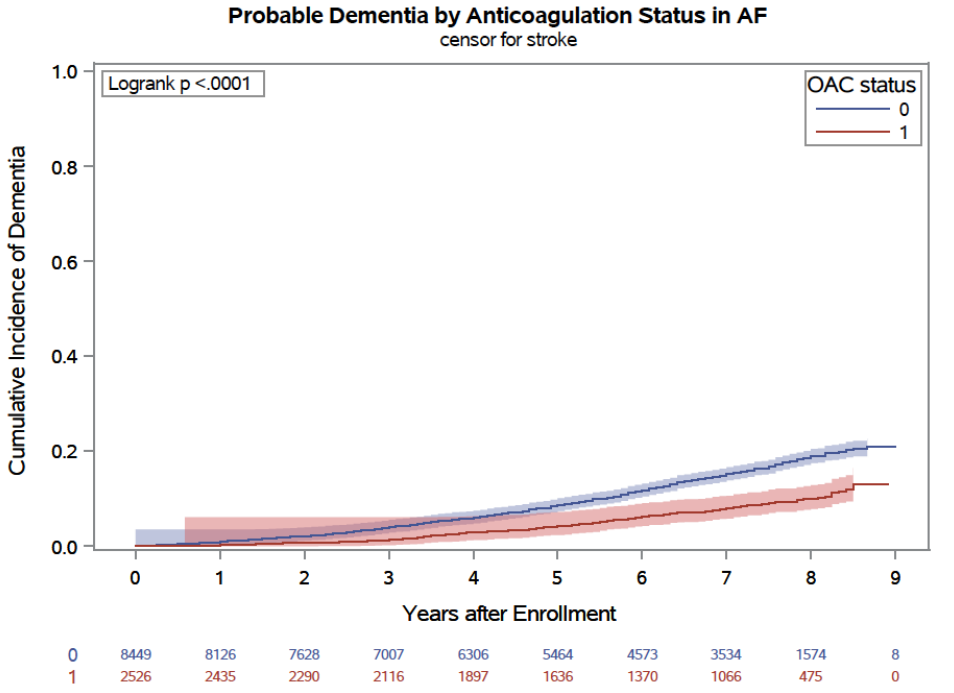

Figure 5. The cumulative incidence of dementia in patients with incident AF with or without oral anticoagulation. Shaded regions indicate 95% confidence intervals.

IV. 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, in an elderly nationwide population cohort; (ii) incident AF increased the risk of dementia in all subgroups except in subjects with CKD; 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 AF

In this study, the risk of dementia was increased, with an adjusted HR of 1.65, 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.[17-19] 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. Such asymptomatic strokes are often lacunes, which are related to an increased risk of dementia.[20]

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, 21, 22] In the majority of cases, the brains of AD have vascular microinfarcts, white matter lesions, or vessel wall alterations.[23] Increased beta-amyloid and hyperphosphorylated tau reactivity in both infarcted and adjacent brain areas were followed experimentally induced cerebral microemboli in aged rats,[24] suggesting a possible association with Alzheimer's pathophysiology. Vascular risk factors have been linked to risk for AD in many epidemiological studies.[23, 25, 26] 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.[27, 28]

One recent study suggested that incident AF was a risk factor for dementia only in participants aged younger than 67 years.[22] 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, hypercholesterolemia, and obesity, also appears to differ with age, with a stronger effect evident earlier in life.[29, 30] Accordingly, if AF is a causal factor in the etiology 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 AF

Since AF patients show a higher risk of dementia, the ability to predict its occurrence in the AF population is critical. In a Taiwan AF cohort,[31] the CHA_2DS_2-VASc score was predictive of dementia; however, these authors did not report incident stroke events during follow-up. 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 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 dementia before a diagnosis of dementia. To answer this question, a well-designed specific study to answer the question 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).[32, 33]

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 AF.

The Framingham Heart Study reported that the risk of dementia associated with AF declined over 3 decades from 1970s to the early 2010s,[34] which was speculated to have been attributable to improved anticoagulation and treatment of risk factors in individuals with AF. The risk of ischemic 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.[3]

In previous retrospective observational studies, the risk of dementia increased with poor vitamin K antagonist management (a low time in therapeutic range),[18] whereas NOACs use was associated with a reduced risk of dementia compared with warfarin.[35] 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,[36] with a greater effect observed in Asians compared to non-Asians.[37]

Several retrospective observational studies have recently indicated that the use of NOACs was associated with a lower risk of dementia compared to warfarin in patients with AF [35, 38]. To clarify the effect of NOACs on cognitive function, well designed longitudinal studies with longer follow-up time are needed and currently several randomized-controlled clinical trials focusing on cognitive outcomes in patients with AF have been initiated[39].

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, especially hypertension which considered as significant risk factor for dementia. To minimize this problem, we applied the definition that we had validated in previous studies using a Korean NHIS sample cohort.[2, 40] Second, we were unable to define the type (paroxysmal vs. persistent) of AF. AF can occur without symptoms, and although numerous ECG measurements were performed at the research center, 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. Finally, despite the adjustment for some differences in baseline characteristics, residual unidentified confounders may remain.

V. CONCLUSION

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

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ABSTRACT(IN KOREAN)

뇌경색이 없는 환자에서 심방세동 발생이 치매 발생에 미치는 영향: 건강보험공단 노인코호트 분석

<지도교수 정보영>

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김동민

배경 및 목적: 심방세동은 일반적으로 치매 발생의 위험인자로 알려져 있으나 아직까지 전향적인 연구에서는 일관적인 결과를 보이고 있지는 못하다. 본 연구는 노인 인구로 구성된 전향적인 자료를 통해, 뇌경색이 없었던 인구에서도 심방세동이 치매 발생과 연관이 있는지 확인하고자 한다.

방법: 심방세동과 치매 발생과의 연관성을 확인하기 위해 건강보험관리공단의 노인코호트를 이용하였다. 2005년 1월 1일부터 2012년 12월 31일까지 등록된 환자 중 기존에 뇌경색 및 치매가 없는 260,638 명의 참가자를 분석하였다.

결과: 심방세동은 관찰 기간 1,613,322 인-년 동안 10,975 명에서 발생하였다(0.68%/년). 관찰 기간 동안 치매 발생 건수는 심방세동 군에서 2.5건/100인-년, 성향 점수 매칭 일반 인구에서

1.6건/100인-년으로 나타났다. Cox 회귀분석을 통해 기타 독립변수를 보정한 후, 심방세동의 치매 발생 위험비는 1.84 [95% 신뢰구간: 1.71-1.98]이었으며 이는 추적관찰 중 발생한 뇌경색을 제외하고도 유의하였다(1.64, 95% 신뢰구간: 1.51-1.79). 심방세동은 알츠하이머 치매(위험비 1.63, 95% 신뢰구간 1.50-1.78) 및 혈관성 치매를(위험비 3.09, 95% 신뢰구간 2.56-3.72) 모두 증가시키는 것으로 나타났다. 심방세동 환자 중, 경구 항응고제를 사용한 경우 치매 발생이 적었다(위험비 0.67, 95% 신뢰구간: 0.57-0.79, $p<0.001$), 또한 높은 CHA_2DS_2-VASc 점수는 치매 발생의 위험도를 높이는 것으로 나타났다.

결론: 추적관찰 중 발생한 심방세동은 임상적인 뇌경색과는 독립적으로 치매 발생의 위험성을 증가시켰다. 경구 항응고제 치료를 통해 심방세동으로 인한 치매 발생을 감소시킬 수 있었다.

핵심되는 말 : 심방세동, 치매, 항응고치료, 노인, 예후

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