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ORIGINAL RESEARCH

Lower Risk of Dementia in Patients With Atrial Fibrillation Taking Non-Vitamin K Antagonist Oral Anticoagulants: A Nationwide Population-Based Cohort Study

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BACKGROUND: A higher risk of developing dementia is observed in patients with atrial fibrillation (AF). Results are inconsistent regarding the risk of dementia when patients with AF use different anticoagulants. We aimed to investigate the risk of dementia in patients with AF receiving non-vitamin K antagonist oral anticoagulants (NOACs) compared with those receiving warfarin.

METHODS AND RESULTS: We conducted a nationwide population-based cohort study of incident cases using the Taiwan National Health Insurance Research Database. We initially enlisted all incident cases of AF and then selected those treated with either NOACs or warfarin for at least 90 days between 2012 and 2016. First-ever diagnosis of dementia was the primary outcome. We performed propensity score matching to minimize the difference between each cohort. We used the Fine and Gray competing risk regression model to calculate the hazard ratio (HR) for dementia. We recruited 12 068 patients with AF (6034 patients in each cohort). The mean follow-up time was 3.27 and 3.08 years in the groups using NOACs and warfarin, respectively. Compared with the HR for the group using warfarin, the HR for dementia was 0.82 (95% CI, 0.73–0.92; P=0.0004) in the group using NOACs. Subgroup analysis demonstrated that users of NOAC aged 65 to 74 years, with a high risk of stroke or bleeding were associated with a lower risk of dementia than users of warfarin with similar characteristics.

CONCLUSIONS: Patients with AF using NOACs were associated with a lower risk of dementia than those using warfarin. Further randomized clinical trials are greatly needed to prove these findings.

Key Words: atrial fibrillation ■ dementia ■ non-vitamin K antagonist oral anticoagulants ■ warfarin

The incidence of atrial fibrillation (AF) and dementia is increasing in an aging society.[1] The association of AF with a higher risk of developing dementia has been well documented.[2] Warfarin has been the cornerstone of stroke prevention for decades, until the introduction of non-vitamin K antagonist oral anticoagulants (NOACs).[3] Compared with warfarin, NOACs have an equal or superior efficacy for stroke prevention, lesser risk of major bleeding, and fewer adverse drug interactions.[4] Therefore, it is plausible that NOACs may decrease silent infarction, lower the risks of microbleeds, and consequently, delay the development of AF-related dementia more effectively than warfarin.

However, results are inconsistent regarding the risk of dementia in patients with AF using NOACs compared with those using warfarin.[5–9] Although some studies have suggested that NOACs are superior to warfarin,[5,7,8] others have reported contrasting observations.[6,9] This inconsistency could be attributed to methodological variations, such as differences in study population with prevalent AF case

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CLINICAL PERSPECTIVE

What Is New?

- This study demonstrated that patients with atrial fibrillation who were using non-vitamin K antagonist oral anticoagulants had a lower risk of developing dementia compared with those using warfarin.
- Patients taking non-vitamin K antagonist oral anticoagulants, aged 65 to 74 years, with a high risk of stroke (assessed by the congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category [CHA_2DS_2-VASc] score) or bleeding (assessed by the hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [>65 years], drugs/alcohol concomitantly [HAS-BLED] score) were significantly associated with a lower risk of dementia compared with patients with similar characteristics who were taking warfarin.

What Are the Clinical Implications?

- Patients with atrial fibrillation, particularly those who are aged 65 to 74 years, with a high risk of stroke or major bleeding, might have additional benefits on lower risk of dementia when using non-vitamin K antagonist oral anticoagulants than when using warfarin.

Nonstandard Abbreviations and Acronyms

NHIRD	National Health Insurance Research Database

design,[5–7,9] ill-defined outcome variables,[5,8] short duration of follow-up,[6] and definition of anticoagulant use.[7] Particularly, incident AF study design is seldom considered when evaluating the association between AF and dementia. This consideration is crucial because the association between prevalent AF and dementia may be inaccurately estimated because of delayed diagnosis of AF and survival effects.[10] An incident AF study design might directly investigate the relationship between AF and dementia and the effect of anticoagulant use to lower the risk of dementia in patients with AF.[11] Moreover, given that the majority of the existing evidence has been derived from the Western population, its general applicability to non-Western countries requires investigation.

Considering these caveats, we designed an incident case, real-world, nationwide, population-based cohort study. We aimed to examine whether the risk of dementia among patients with AF differs between users of warfarin and NOACs in incident AF cases.

METHODS

The Taiwan National Health Insurance Research Database (NHIRD) is an encrypted database that is regulated and maintained by the Health and Welfare Data Science Center at the Ministry of Health and Welfare in Taiwan. Therefore, the data set cannot be available publicly. Researchers interested in analyzing this data set can provide a formal application to the Taiwan Ministry of Health and Welfare to request access (website: https://dep.mohw.gov.tw/DOS/cp-2516-3591-113.html). All relevant data are within the article.

Study Design, Data Source, and Ethical Approval

This incident case, nationwide, population-based cohort study obtained data from the Taiwan NHIRD. The Taiwan National Health Insurance program represents nearly the entire population of Taiwan, as more than 99% of the inhabitants in Taiwan have joined this insurance program. The Taiwan NHIRD consists of comprehensive healthcare information, including all hospitalizations, emergency services, outpatient visits, and detailed medication prescription data, from all 23.6 million enrollees. It also provides an identical encrypted identity code to link all healthcare information longitudinally. The diagnostic and procedure codes applied were the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) before 2016 and *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) after 2016.[12] This study was approved by the Institutional Review Board of Hualien Tzu Chi Hospital (IRB-107-06C). The Institutional Review Board agreed that informed consent could be waived because the Taiwan NHIRD is an encrypted database.

Study Population

We initially identified all patients with AF older than 20 years of age in our research database, from 2010 to 2016. The AF diagnosis was defined as either discharge diagnosis or outpatient diagnoses confirmed at least twice by use of the *ICD-9-CM* code 427.31 and the *ICD-10-CM* code I48.0–I48.2 or I48.9. This definition of AF diagnosis in the Taiwan NHIRD has been previously validated.[13] To ensure that only newly diagnosed patients with AF were obtained to achieve an incident cohort, we defined a 2-year washout period (2010–2011) and excluded patients who received a diagnosis of AF before 2012. In Taiwan, NOACs

were approved for stroke prevention in patients with AF in 2012, and thus, we included only patients diagnosed with AF after 2012. To obtain a nonvalvular AF cohort, we also excluded patients with heart disease, including rheumatic heart disease, congenital heart disease, and patients with valvular disease that had received valvular replacement surgery. These approaches ensured that we included only patients with a nonvalvular AF between 2012 and 2016, and thus, they had similar opportunities to receive NOACs or warfarin.

We analyzed the risk of dementia in patients with AF receiving NOACs or warfarin by categorizing patients into NOAC or warfarin groups. The NOAC and warfarin cohorts comprised patients who had been receiving NOACs or warfarin, respectively, for at least 90 days after the diagnosis of AF. After categorizing patients into each cohort, we defined index date as the date when they completed 90 days of the respective anticoagulant regimen and follow-up initiated since then. To enable specific comparisons of the impacts of NOACs and warfarin on dementia risk, we excluded patients with AF who had been administered anticoagulants for more than 90 days within 1 year before having diagnosis of AF. We also excluded patients who have been administered more than 2 types of oral anticoagulants for more than 90 days, those who did not receive any oral anticoagulant, or those on oral anticoagulants for <90 days after having diagnosis of AF. To restrict our evaluation to first-ever dementia cases, we excluded patients with previous diagnosis of dementia, before the index date (Figure 1). To minimize the difference in baseline characteristics between the NOAC and warfarin cohorts, we adopted propensity score matching.

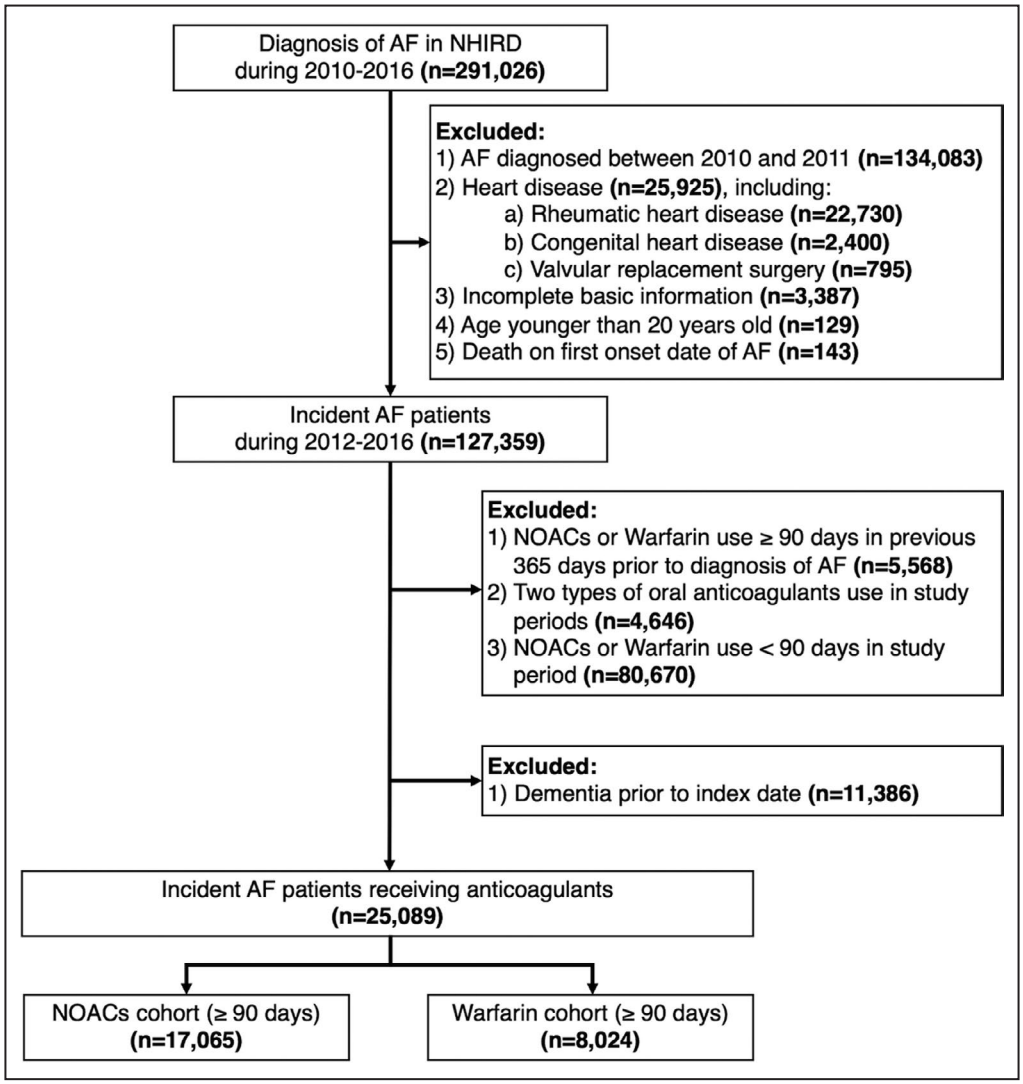

Figure 1. Study flow chart.
AF indicates atrial fibrillation; NHIRD, National Healthcare Insurance Research Database; and NOACs, non-vitamin K antagonist oral anticoagulants.

Outcomes

The primary outcome was defined as the incidence of dementia (*ICD-9-CM* codes: 290.0–290.4 and 331.0; *ICD-10-CM* codes: F01, F03, G30). We included only patients who visited the healthcare institutions at least 3 times with a diagnosis of dementia, with either inpatient or outpatient visits. We defined the date of the first diagnosis of dementia as the date of event occurrence. All individuals began the follow-up period from the index date until December 31, 2018, the development of dementia, or death.

We compared the risk of dementia in the NOAC group to that in the warfarin group. To investigate whether the risk of dementia in users of NOAC compared with that in users of warfarin differs in different stroke and bleeding risk group, we also conducted stratified analyses by stroke risk (assessed using the congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category [CHA_2DS_2-VASc] score) and bleeding risk (assessed using the hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR, left out because data are unavailable), elderly [>65 years], drugs/alcohol concomitantly [HAS-BLED] score). Stratified analyses of age and sex were also performed.

Covariates and Confounding Factors

We collected the baseline characteristics and clinical information of patients with AF on the date of initiation of anticoagulants. Comorbidities listed in Table 1 were identified either by inpatient or outpatient diagnoses and confirmed at least twice in the outpatient department. Preexisting medication use was defined as an existing drug prescription for longer than 30 days within the year before the date of initiation of anticoagulants. A previous study considered these baseline comorbidities and drug prescriptions as potential confounding variables in multivariable analyses.[6] The Charlson Comorbidity Index, CHA_2DS_2-VASc score, and HAS-BLED score were calculated according to baseline comorbidities and preexisting medication use. The Charlson Comorbidity Index represented the complexity of comorbidities in each patient.[14] The CHA_2DS_2-VASc score estimates the risk of ischemic stroke and determines the prescription of oral anticoagulants.[15] The HAS-BLED score assesses bleeding risk and guides physicians to prescribe relatively safer oral anticoagulants.[16] The income of participants was assessed from their insurance fee. Hospitalization history was evaluated by the number of hospitalizations 1 year before admission. Healthcare use was calculated as the number of outpatient and inpatient visits per year during the follow-up period; if there were several visits on the same day, they were counted as 1. Inpatient stroke events were identified by inpatient diagnosis of stroke, either ischemic or hemorrhagic stroke, during the follow-up period.

Statistical Analysis

We used propensity score matching to balance baseline characteristics, including age, sex, income level, index year, time interval between AF diagnosis and anticoagulant use, CHA_2DS_2-VASc score, HAS-BLED score, Charlson Comorbidity Index, comorbidities, and medication use. The propensity scores, which calculate the probability of a patient with AF using NOACs or warfarin, were estimated for NOACs versus warfarin comparison using a logistic regression model. Within the propensity score matching, we used nearest-neighbor matching algorithms without replacements and adopted a caliper width equal to 0.2 of the SD of the logit of the propensity score. Difference of baseline characteristics were assessed by standardized difference, and values with significant differences were defined as standardized difference values of >0.1. Considering that mortality is an important competing risk among elderly patients, the cumulative incidence of developing dementia was estimated using the cumulative incidence function with death as a competing event. The difference between cumulative incidence curves was examined using the Gray's test. For the analyses with propensity score matching, a univariable Fine and Gray competing risk regression model stratified by the matched pair was used to measure dementia risk with hazard ratios (HRs) and corresponding 95% CIs.[17,18] Statistical significance was defined as a 2-tailed probability value of <0.05.

The statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA) and Stata, version 14 (Stata Corporation LLC, College Station, TX, USA).

Sensitivity Analyses

Sensitivity analysis A was conducted using all patients, without propensity score matching, because including only part of the study population might introduce bias. Univariable and multivariable Fine and Gray competing risk regression models were used to measure dementia risk with HRs and corresponding 95% CIs.[18] The multivariable regression model was performed with adjustment for age, sex, income level, index year, time interval between AF diagnosis and anticoagulant use, CHA_2DS_2-VASc score, HAS-BLED score, Charlson Comorbidity Index, comorbidities, and medication use to calculate adjusted hazard ratios (aHRs). We also performed additional sensitivity analyses, adjusting for inpatient stroke events (sensitivity analysis B), healthcare use (sensitivity analysis C), and hospitalization history (sensitivity analysis D). Sensitivity analysis E was conducted by changing the number of diagnoses of dementia, from only 1 to at least 5 times. The sensitivity analyses B to E were analyzed using propensity-score-matched cohorts. For the various definitions of

Table 1. Baseline Characteristics After Propensity Score Matching

	Non-Vitamin K Antagonist Oral Anticoagulants (n=6034)	Warfarin (n=6034)	Standardized Difference
Sex			
Male	3592 (59.5)	3560 (59.0)	0.0108
Female	2442 (40.5)	2474 (41.0)	0.0108
Age, y*	70.3 (11.7)	70.4 (11.6)	0.0034
<65	1790 (29.7)	1964 (32.6)	0.0622
65–74	1929 (32.0)	1715 (28.4)	0.0774
≥75	2315 (38.4)	2355 (39.0)	0.0136
Income level (new Taiwan dollar)			
Dependence	1560 (25.9)	1552 (25.7)	0.0030
15 840–29 999	2786 (46.2)	2799 (46.4)	0.0044
30 000–44 999	933 (15.5)	955 (15.8)	0.0102
≥45 000	755 (12.5)	728 (12.1)	0.0137
Index year†			
2012	122 (2.0)	122 (2.0)	0.0000
2013	997 (16.5)	997 (16.5)	0.0000
2014	1461 (24.2)	1461 (24.2)	0.0000
2015	1742 (28.9)	1742 (28.9)	0.0000
2016	1712 (28.4)	1712 (28.4)	0.0000
Time interval between AF diagnosis and anticoagulant use, d‡	26 (166)	20 (179)	n/a
CHA_2DS_2-VASc score*	2.9 (1.8)	3.0 (1.9)	0.0481
Low stroke risk§	729 (12.1)	696 (11.5)	0.0170
Middle stroke risk	1060 (17.6)	1062 (17.6)	0.0008
High stroke risk	4245 (70.4)	4276 (70.9)	0.0114
HAS-BLED score*	2.2 (1.2)	2.3 (1.2)	0.0418
Low bleeding risk‖	3566 (59.1)	3546 (58.8)	0.0067
High bleeding risk	2468 (40.9)	2488 (41.2)	0.0067
Charlson Comorbidity Index‡	4.7 (3.2)	5.0 (3.3)	0.0675
0	408 (6.8)	411 (6.8)	0.0020
1	546 (9.1)	528 (8.8)	0.0105
≥2	5080 (84.2)	5095 (84.4)	0.0069
Comorbidities			
Hypertension	4884 (80.9)	4904 (81.3)	0.0084
Diabetes mellitus	2316 (38.4)	2346 (38.9)	0.0103
Coronary artery disease	2828 (46.9)	2889 (47.9)	0.0202
Congestive heart failure	2153 (35.7)	2228 (36.9)	0.0258
Chronic obstructive pulmonary disease	1608 (26.7)	1626 (27.0)	0.0068
Chronic kidney disease	1399 (23.2)	1451 (24.1)	0.0202
Cirrhosis	954 (15.8)	977 (16.2)	0.0104
Depression	402 (6.7)	409 (6.8)	0.0048
Parkinsonism	183 (3.0)	192 (3.2)	0.0086
Epilepsy	136 (2.3)	137 (2.3)	0.0013
Stroke, ischemic	2101 (34.8)	2064 (34.2)	0.0128
Stroke, hemorrhage	237 (3.9)	233 (3.9)	0.0036
Malignancy	671 (11.1)	701 (11.6)	0.0158
Hypothyroidism	145 (2.4)	165 (2.7)	0.0209

(*Continued*)

Table 1. Continued

	Non-Vitamin K Antagonist Oral Anticoagulants (n=6034)	Warfarin (n=6034)	Standardized Difference
Thyrotoxicosis	300 (5.0)	288 (4.8)	0.0093
Medication			
Angiotensin-converting-enzyme inhibitor and angiotensin receptor blocker	3699 (61.3)	3656 (60.6)	0.0146
Beta blocker	3611 (59.8)	3660 (60.7)	0.0168
Diuretics	2286 (37.9)	2285 (37.9)	0.0004
Class 1 and Class 3 antiarrhythmic	2123 (35.2)	2181 (36.2)	0.0203
Digoxin	1035 (17.2)	1017 (16.9)	0.0080
Statin	1973 (32.7)	1974 (32.7)	0.0002
Antiepileptic	489 (8.1)	524 (8.7)	0.0209
Antiparkinsonism	131 (2.2)	134 (2.2)	0.0034
Antipsychotics	233 (3.9)	247 (4.1)	0.0118
Anxiolytics, hypnotics, and sedatives	2030 (33.6)	2044 (33.9)	0.0049
Antidepressants	480 (8.0)	470 (7.8)	0.0059
Thyroxine	129 (2.1)	138 (2.3)	0.0102
Antithyroid drugs	211 (3.5)	202 (3.4)	0.0082
Hospitalization history¶	1.6 (2.4)	1.9 (2.9)	0.0947
Inpatient stroke events#			
Overall stroke	443 (7.3)	565 (9.4)	0.0731
Ischemic stroke	389 (6.5)	461 (7.6)	0.0465
Hemorrhage stroke	92 (1.5)	144 (2.4)	0.0629
Healthcare use**			
Outpatient department	23.2 (15.7)	24.7 (16.4)	0.0972
Inpatient department	0.7 (1.7)	1.0 (2.2)	0.1398

Data are expressed as n (%) unless otherwise indicated. CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category; and HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR, left out because data are unavailable), elderly (>65 years), drugs/alcohol concomitantly.

*Expressed as mean (SD).

†Index year: the year each patient started to receive follow-up.

‡Expressed as median (interquartile range).

§CHA_2DS_2-VASc score: high stroke risk was defined as a score of ≥3 in women and a score of ≥2 in men; middle stroke risk was defined as a score of 2 in women and a score of 1 in men; low stroke risk was defined as a score of 1 or 0 in women and a score of 0 in men.

‖HAS-BLED score: high bleeding risk: score ≥3; low bleeding risk: score <3.

¶Hospitalization history: the number of hospitalizations 1 year before admission.

#Inpatient stroke events: the proportion of patients who had been admitted for stroke during follow-up period.

**Healthcare use: the number of outpatient and inpatient visits per year during follow-up.

dementia diagnosis, we calculated the curves of cumulative incidence with similar methods as in our main analysis.

Supplemental Analyses

To compare the risk of dementia between patients with AF receiving oral anticoagulants and those not receiving oral anticoagulants, we performed additional analyses that are described in Data S1.

RESULTS

Patient Characteristics

We recruited 25 089 patients with incident AF, including 17 065 patients in the NOAC cohort and 8024 patients in the warfarin cohort. Compared with the warfarin cohort, the NOAC cohort had individuals who were older and had higher CHA_2DS_2-VASc scores (Table S1). After propensity score matching, each cohort comprised 6034 patients. The baseline characteristics between the NOAC and warfarin cohorts were mostly comparable, with a standardized difference <0.1 (Table 1). However, the warfarin cohort accessed health care at the inpatient department more frequently than did the NOAC cohort. The mean follow-up duration in the NOAC and warfarin groups were 3.27 and 3.08 years, respectively.

Risk of Dementia

Dementia was diagnosed in 304 patients from the NOAC cohort and in 360 patients from the warfarin cohort. On cumulative incidence analysis, the NOAC

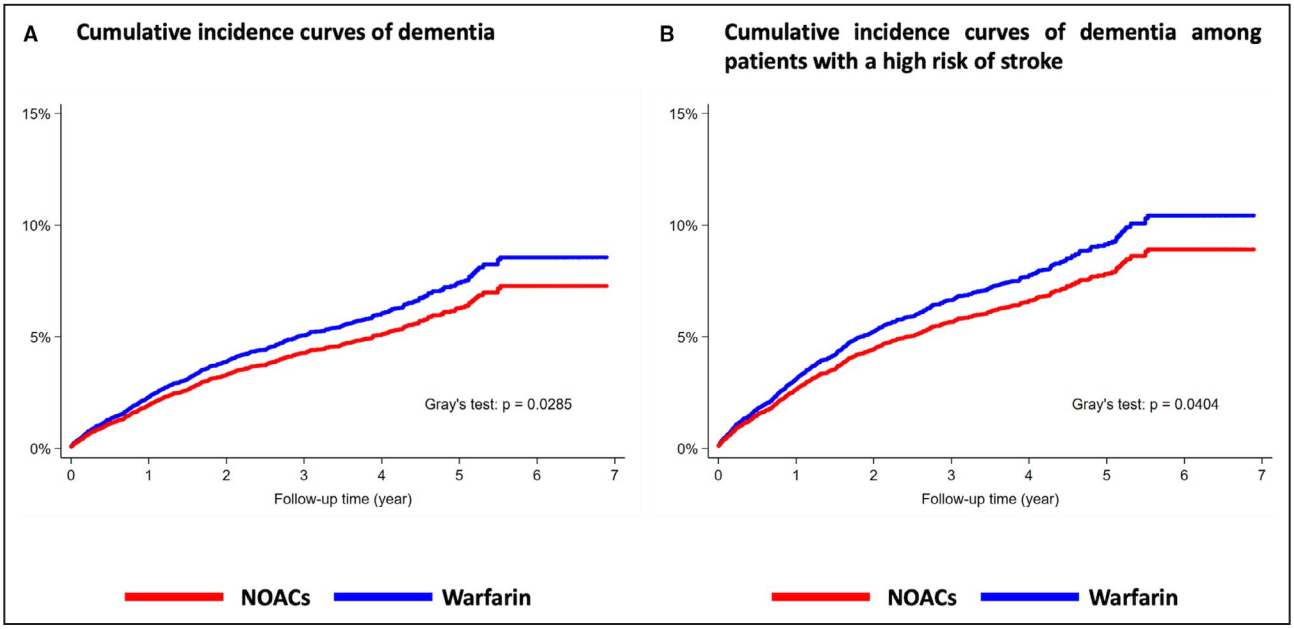

Figure 2. Cumulative incidence curves of dementia risk.
A, Patients with incident AF using NOACs had a lower risk of dementia than those using warfarin (Gray's test, *P*=0.0285). **B**, In addition, compared with the patients on warfarin, patients with AF with a high risk of stroke, as determined by their CHA_2DS_2-VASc score, presented a lower risk of dementia when they received NOACs (Gray's test, *P*=0.0404). AF indicates atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age (75 years or old), diabetes mellitus, stroke-vascular disease, age (65–74 years), sex category; and NOACs, non-vitamin K antagonist oral anticoagulants.

cohort had a lower risk of developing dementia (Gray's test, *P*=0.0285; Figure 2A) than the warfarin cohort. Additionally, NOAC cohort with a high risk of stroke had a lower risk of dementia compared with warfarin cohort with a high risk of stroke (Gray's test, *P*=0.0404; Figure 2B). The univariable Fine and Gray competing risks regression model stratified by the matched pair revealed that use of NOACs was associated with a lower risk of developing dementia (HR, 0.82; 95% CI, 0.73–0.92; *P*=0.0004) compared with warfarin use (Table 2).

Table 2. Risk of Dementia in Patients With Atrial Fibrillation Receiving Different Anticoagulants After Propensity Score Matching

	Non-Vitamin K Antagonist Oral Anticoagulants (n=6034)	Warfarin (n=6034)
Event number	304	360
Person-years	19 701	18 580
Incidence rate*	15.40	19.40
Univariable model		
HR†	0.82	1.00
95% CI	0.73–0.92	Reference
P value	0.0004	

HR indicates hazard ratio.
*Incidence rate: per 1000 person-years.
†The HRs were calculated using a univariable Fine and Gray competing risks regression model stratified by the matched pair.

Stratified Analyses by Sex, Age, Stroke Risk, and Bleeding Risk

Stratified analyses were performed with different cohorts to further define the association between NOAC or warfarin use and the risk of dementia. We stratified the cohorts by age, sex, stroke risk as assessed by the CHA_2DS_2-VASc score, and bleeding risk as assessed by the HAS-BLED score. Patients aged 65 to 74 years using NOACs had a lower risk of dementia than patients of the same age using warfarin. Compared with users of warfarin with a high risk of stroke, users of NOACs with a high risk of stroke had a lower risk of dementia. Moreover, users of NOACs with a high risk of bleeding also had a lower risk of dementia than users of warfarin with a high risk of bleeding (Table 3).

Sensitivity Analyses

To remedy possible selection bias, sensitivity analysis A, using all study participants, without propensity score matching, was performed, which revealed similar findings. The NOAC cohort had a lower risk of dementia compared with the warfarin cohort (aHR, 0.86; 95% CI, 0.77–0.97; *P*=0.0106) (Table 4). The detailed results of additional sensitivity analyses (sensitivity analyses B through E) are in Tables S2 and S3. The cumulative incidence curves for various definitions of dementia are reported in Figure S1.

Supplemental Analyses

The detailed results of the supplemental analyses, which compared the risk of dementia between patients with and without oral anticoagulant treatment, were shown in Tables S4 and S5. In brief, users of NOACs were associated with a lower risk of dementia than those who did not use oral anticoagulants. Users of warfarin had a similar risk of dementia as those who did not use oral anticoagulants.

DISCUSSION

Summary of Findings

Our study revealed that patients with AF using NOACs had a lower risk of developing dementia than those using warfarin. During the mean follow-up of around 3.17 years, users of NOACs showed an association with a lower risk of dementia than users of warfarin. Users of NOACs aged 65 to 74 years, with a high risk of stroke or bleeding had a significantly lower risk of dementia than users of warfarin with similar characteristics.

Table 3. Stratified Analysis to Assess Risk of Dementia in Patients With Atrial Fibrillation Receiving Non-Vitamin K Antagonist Oral Anticoagulants Versus Those Receiving Warfarin

	Hazard Ratio*	95% CI	*P* Value
Sex			
Male	0.88	0.70–1.11	0.2879
Female	0.82	0.67–1.00	0.0529
Age, y			
≤64	0.57	0.29–1.15	0.1191
65–74	0.74	0.54–0.99	0.0476
≥75	0.90	0.75–1.08	0.2558
CHA_2DS_2-VASc score†			
Low stroke risk	0.49	0.09–2.67	0.4077
Middle stroke risk	0.92	0.49–1.73	0.7893
High stroke risk	0.85	0.72–0.99	0.0404
HAS-BLED score‡			
Low bleeding risk	0.89	0.69–1.13	0.3366
High bleeding risk	0.82	0.67–0.99	0.0451

CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category; and HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR, left out because data are unavailable), elderly (>65 years), drugs/alcohol concomitantly.

*The hazard ratios were calculated using patients who received warfarin as the reference group.

†CHA_2DS_2-VASc score: high stroke risk was defined as a score of ≥3 in women and score of ≥2 in men; middle stroke risk was defined as a score of 2 in women and score of 1 in men; low stroke risk was defined as a score of 1 in women and score of 0 in men.

‡HAS-BLED score: high bleeding risk was defined as a score ≧ 3; low bleeding risk was defined as a score <3.

Comparison With Prior Knowledge

Previous studies have shown that warfarin can prevent dementia in patients with AF, triggering growing interest in related issues in the scientific community.[6,10,19,20] However, these studies have failed to determine whether NOACs lower the risk of dementia in patients with AF compared with those with warfarin.[5–9] These studies used a prevalent AF case design, which may present some inevitable bias.[5–7,9] These prevalent patients of AF have longer exposure duration than the observation period. Thus, these patients might have already experienced a few microthromboembolic events that decreased the brain reserve or induced irreversible damage before initiation of anticoagulants. We speculated that delayed initiation of anticoagulants after diagnosis of AF corresponds to decreased preservation of brain reserve. Therefore, despite variations in the protective effect of different oral anticoagulants, it may be difficult to slow the decline of cognitive impairment. Moreover, patients with AF with a risk of developing dementia before the observation period are excluded in prevalent AF study design. Therefore, we used an incident AF cohort to clarify this question. It has been recommended that an incident AF cohort may be more accurate in estimating the risk of dementia in these patients, and patients with incident AF using NOACs revealed a consistently lower risk of dementia.[10,11] Jacobs et al revealed that patients with prevalent AF using NOACs had a lower risk of developing dementia than those using warfarin (0.3% versus 0.7%, *P*=0.02).[5] However, the primary outcomes of this study were the composite end points of dementia, stroke/transient ischemic attack, and death, rather than the risk of dementia alone. The risk of dementia might have been misestimated because of competing outcomes with stroke/transient ischemic attack. Friberg et al directly compared the risk of dementia in patients with prevalent AF taking NOACs and those taking warfarin after propensity score matching; yet the mean follow-up duration was only 0.26 and 0.20 years in the groups taking NOACs and warfarin, respectively. Their study revealed a similar risk of developing dementia in patients with AF using NOACs and those using warfarin (aHR, 0.97, 95% CI, 0.67–1.40).[6] This could possibly be due to the follow-up period being too short to reveal any differences in dementia risk between users of NOACs and warfarin. Søgaard et al conducted a prevalent AF, oral anticoagulant naïve user cohort study with propensity weighting. Their sensitivity analysis revealed inconsistent results between incident AF design and prevalent AF design. Users of NOACs older than 80 years revealed a higher risk of dementia in the incident AF design (aHR, 1.40; 95% CI, 1.07–1.84) and revealed similar risk of dementia in prevalent AF design (aHR, 1.20; 95% CI, 0.90–1.61) compared with users of warfarin.[9]

Discontinuing or switching oral anticoagulants is very common in patients with AF and therefore must be taken into account.[21] Chen et al adopted a prevalent AF cohort and head-to-head comparisons between those taking different NOACs and those taking warfarin after a propensity score matching. Their study found a lower risk of inpatient diagnosis of dementia in patients with AF using NOACs (dabigatran: HR, 0.85; 95% CI, 0.71–1.01; rivaroxaban: HR, 0.85; 95% CI, 0.76–0.94; apixaban: HR, 0.80; 95% CI, 0.65–0.97) than in those using warfarin.[7] Patients with AF were classified into different NOAC groups or warfarin group based solely on the first prescription of anticoagulants after the diagnosis of AF; however, the minimum duration of anticoagulant use was not reported in their study. Anticoagulants may have a cumulative effect to lower the risk of dementia and this may be related to the anticoagulant exposure time. Therefore, in this study, we investigated patients with AF on NOACs or warfarin for at least 90 days during the study period; thereafter, follow-up was initiated after patients fulfilled the minimal exposure of anticoagulant use for 90 days.

Our study indicated that NOACs might be a more appropriate option for patients with AF that require oral anticoagulants other than warfarin because users of NOACs had a lower risk of dementia than users of warfarin. The potential benefit of NOACs on the risk of dementia might decrease the disability rate in the aging population. As both AF and dementia are major global threats for the aging population, the findings of our present study are clinically relevant and have implications for public health.

Table 4. Sensitivity Analyses A: Risk of Dementia in Patients With Atrial fibrillation Receiving Non-Vitamin K Antagonist Oral Anticoagulants Versus Those Receiving Warfarin

	Non-Vitamin K Antagonist Oral Anticoagulants (n=17 065)	Warfarin (n=8024)
Event number	965	487
Person-years	49 762	27 212
Incidence rate*	19.39	17.90
Univariable model		
Crude HR	1.06	1.00
95% CI	0.95–1.18	Ref.
P value	0.3168	
Multivariable model		
Adjusted HR†	0.86	1.00
95% CI	0.77–0.97	Reference
P value	0.0106	

The sensitivity analysis A was conducted by including all eligible patients for analyses without propensity score matching. HR indicates hazard ratio.

*Incidence rate: per 1000 person-years.

† The hazard ratios were calculated using a multivariable Fine and Gray competing risk regression model with adjustments for age, sex, income level, index year, time interval between atrial fibrillation diagnosis and anticoagulant use, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA_2DS_2-VASc) score, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR, left out because data are unavailable), elderly (>65 years), drugs/alcohol concomitantly (HAS-BLED) score, Charlson Comorbidity Index, comorbidities, and medication use.

Three important issues are worthwhile to be discussed. First, there was a difference in the prescription pattern of warfarin and NOACs in this study. It should be noted that our insurance system does not limit physicians regarding the prescribing of these types of drugs to patients. Moreover, the patients who received NOACs might have needed to spend more out-of-pocket money than those who received warfarin. However, the maximum difference of out-of-pocket money per visit between these 2 cohorts is ≈7 US dollars, which probably is affordable to most of these patients. Thus, this difference in the prescription pattern of warfarin and NOACs is probably owing to the preference of physicians or patients. Second, in the supplemental analysis, the results revealed no difference in the risk of dementia between users of warfarin and those who did not use oral anticoagulants. In addition to the effect on prevention of microthrombotic events, users of warfarin might face the risk of microbleeds,[22] which might be associated with a higher risk of dementia than for nonusers of warfarin. Thus, the net benefit of microthrombi and microbleeds in patients with AF using warfarin is unknown and might need further large-scale evaluations, especially in the Asian population. Third, our analysis revealed a wide 95% CI for the reduced risk of dementia with its upper limit close to 1 in patients with AF using NOACs. This may reflect the possible marginal efficacy or diversity of potential impact of these drugs on the risk of dementia in a real-world setting. Further large-scale studies with a longer follow-up period will be necessary to investigate this important topic.

Limitations of This Study

Our study has some limitations that should be noted. First, we tried to match the most common risk factors for dementia, although not all variables associated with dementia were assessed in our study. Namely, the administrative database did not provide information regarding education level, diet, environmental factors, physical conditions, laboratory data, history of smoking, or drinking, which are potential confounding factors for dementia risk in patients with AF. However, the key mechanisms underlying the development of dementia in patients with AF are silent cerebral infarct and cerebral microbleeds.[1] Our study revealed a lower risk of developing dementia in the NOAC cohort than the warfarin cohort after

propensity score matching by CHA_2DS_2-VASc score and HAS-BLED score. Second, although dementia is a clinical diagnosis that is characterized by a cluster of symptoms, neuropsychiatric examinations and brain imaging may help clinicians to confirm the diagnosis and assess the severity of dementia. We were unable to obtain the results of any neuropsychiatric tests or brain imaging from the database; additionally, we could not retrieve the exact time point of dementia onset. Therefore, to ensure the accuracy of the dementia diagnosis, we included only patients who were definitively diagnosed with dementia through at least 3 times of visits with a diagnosis of dementia during the study period. We also performed a sensitivity analysis based on different definitions of the diagnosis of dementia, and we obtained similar results. Third, some selection bias might exist in our study design owing to the exclusion of a large portion of patients with AF who did not use anticoagulants for at least 90 days. However, a lower prescription rate of anticoagulants is very common and a bias in the administrative database, reflecting the real-world situation, in either Western[23,24] or Eastern countries is inevitable.[25] A randomized controlled trial may need to be conducted to avoid this selection bias. Fourth, although, we hoped to minimize the difference between the NOAC and warfarin cohorts, some information bias on the diagnosis of valvular disease may exist as we could trace back our database only to 2010. If the conditions of those patients were stable for more than 2 years, and if no diagnostic code was assigned during the follow-up period, we might not exclude these patients from our study population and include them in the warfarin cohort. Fifth, in the stratified analyses, we could not disclose the number of events officially and publicly if the number of events is smaller than 3 in order to protect patient privacy and data security depending on the regulation rules of the Health and Welfare Data Science Center. The inadequate sample size and small number of events in the stratified analyses might have resulted in the lack of statistical power to reveal the association between NOACs or warfarin use and risk of dementia. Sixth, more frequent healthcare use may have increased the chances of dementia diagnosis in the patients of the warfarin cohort. However, the sensitivity analysis C with adjustment for healthcare use still demonstrated similar results to that of our main analysis, indicating the robustness of our finding.

CONCLUSIONS

In this incident case, real-world, nationwide population-based cohort study, patients with AF using NOACs were found to have a lower risk of dementia than those using warfarin, significantly among patients aged 65 to 74 years, with a high risk of stroke as assessed by the CHA_2DS_2-VASc score, and those with a high risk of bleeding assessed by the HAS-BLED score. NOACs might have additional benefit to lower the risk of dementia than warfarin if those patients require oral anticoagulants. However, further research is greatly needed to shed additional light on these initial findings. Whether individualized best medical therapy for AF holds the promise of preventing dementia should be tested further in randomized clinical trials.

ARTICLE INFORMATION

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None.

Supplementary Material

Data S1
Tables S1–S5
Figure S1

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods for Tables S4 and S5

We performed additional analyses to compare the risk of dementia between patients with atrial fibrillation (AF) receiving oral anticoagulants, including the non-vitamin K antagonist oral anticoagulant (NOAC) and warfarin groups, and those not receiving oral anticoagulants. In addition to the NOAC and warfarin groups, which are already defined in our main analyses (patients who had been receiving NOACs or warfarin for at least 90 days after the diagnosis of AF), we further enrolled a no oral anticoagulant group. The no oral anticoagulant group included patients who did not use any NOAC or warfarin after the diagnosis of AF. We excluded patients with AF who had been administered more than two types of oral anticoagulants for ≥90 days and those had used oral anticoagulants but for less than 90 days. The index date was defined as the date of AF diagnosis, and the follow-up began since the index date. To restrict our evaluation to first-ever dementia cases, we excluded patients with previous diagnoses of dementia before the index date. The outcomes, covariates, and confounding factors were defined as they were in the main analysis. The statistical analysis was conducted by using univariable and multivariable Fine and Gray competing risk regression models to measure risk of dementia with hazard ratio and corresponding 95% confidence intervals. The multivariable regression model was performed with adjustment for age, sex, income level, index year, CHA_2DS_2-VASc score, HAS-BLED score, CCI, comorbidities, medication use, inpatient stroke events, and healthcare use during the follow-up period to calculate adjusted hazard ratios.

Table S1. Baseline Characteristics without Propensity Score Matching.

	NOACs (n=17,065)	Warfarin (n=8,024)	Standardized difference
Sex			
Male	9,653 (56.6)	4,781 (59.6)	0.0610
Female	7,412 (43.4)	3,243 (40.4)	0.0610
Age, years*	73.7 (10.3)	69.0 (12.3)	0.4101
<65	2,878 (16.9)	2,998 (37.4)	0.4739
65-74	5,558 (32.6)	2,146 (26.7)	0.1279
≥75	8,629 (50.6)	2,880 (35.9)	0.2996
Income level (NTD)			
Dependence	4,935 (28.9)	2,004 (25.0)	0.0889
15,840-29,999	7,934 (46.5)	3,703 (46.2)	0.0068
30,000-44,999	2,280 (13.4)	1,320 (16.5)	0.0868
≥45,000	1,916 (11.2)	997 (12.4)	0.0372
Index year‡			
2012	129 (0.8)	1,086 (13.5)	0.5118
2013	1,221 (7.2)	1,584 (19.7)	0.3755
2014	2,943 (17.3)	1,750 (21.8)	0.1152
2015	5,362 (31.4)	1,846 (23.0)	0.1898
2016	7,410 (43.4)	1,758 (21.9)	0.4712
Time interval between AF diagnosis and anticoagulant use (Days) †	28.0 (270.0)	16.0 (111.5)	n/a
CHA_2DS_2-VASc score*	3.2 (1.7)	2.9 (1.9)	0.1650
Low stroke risk§	971 (5.7)	1,123 (14.0)	0.2817
Middle stroke risk	2,388 (14.0)	1,420 (17.7)	0.1017
High stroke risk	13,706 (80.3)	5,481 (68.3)	0.2775
HASBLED score*	2.3 (1.1)	2.2 (1.3)	0.0597
Low bleeding risk‖	9,994 (58.6)	4,729 (58.9)	0.0077
High bleeding risk	7,071 (41.4)	3,295 (41.1)	0.0077
Charlson comorbidity index†	4.6 (3.1)	5.1 (3.4)	0.1491
0	1,220 (7.2)	502 (6.3)	0.0356
1	1,583 (9.3)	688 (8.6)	0.0249
≥2	14,262 (83.6)	6,834 (85.2)	0.0441
Comorbidities			
Hypertension	14,019 (82.2)	6,464 (80.6)	0.0408
Diabetes mellitus	6,205 (36.4)	3,119 (38.9)	0.0518

Coronary artery disease	7,748 (45.4)	3,923 (48.9)	0.0700
Congestive heart failure	5,129 (30.1)	3,075 (38.3)	0.1748
COPD	4,669 (27.4)	2,162 (26.9)	0.0094
Chronic kidney disease	2,703 (15.8)	2,090 (26.1)	0.2529
Cirrhosis	2,595 (15.2)	1,334 (16.6)	0.0388
Depression	1,095 (6.4)	556 (6.9)	0.0204
Parkinsonism	540 (3.2)	272 (3.4)	0.0129
Epilepsy	338 (2.0)	197 (2.5)	0.0326
Stroke, ischemic	6,395 (37.5)	2,753 (34.3)	0.0659
Stroke, hemorrhage	557 (3.3)	328 (4.1)	0.0441
Malignancy	1,927 (11.3)	979 (12.2)	0.0283
Hypothyroidism	434 (2.5)	227 (2.8)	0.0179
Thyrotoxicosis	632 (3.7)	415 (5.2)	0.0714
Medication			
ACEI and ARB	10,748 (63.0)	4,810 (60.0)	0.0623
Beta-blocker	9,743 (57.1)	4,833 (60.2)	0.0638
Diuretics	5,844 (34.3)	3,098 (38.6)	0.0907
Class 1 and Class 3 antiarrhythmic	5,572 (32.7)	2,976 (37.1)	0.0933
Digoxin	2,214 (13.0)	1,387 (17.3)	0.1208
Statin	6,337 (37.1)	2,445 (30.5)	0.1411
Antiepileptic	1,317 (7.7)	689 (8.6)	0.0318
Antiparkinsonism	477 (2.8)	172 (2.1)	0.0425
Antipsychotics	631 (3.7)	315 (3.9)	0.0120
Anxiolytics, hypnotics and sedatives	5,811 (34.1)	2,680 (33.4)	0.0137
Antidepressants	1,382 (8.1)	609 (7.6)	0.0190
Thyroxine	390 (2.3)	176 (2.2)	0.0068
Antithyroid drugs	425 (2.5)	280 (3.5)	0.0587
Hospitalization history[#]	1.5 (2.3)	2.0 (3.0)	0.1715
Inpatient stroke events[**]			
Overall stroke	1,238 (7.3)	781 (9.7)	0.0891
Ischemic stroke	1,080 (6.3)	634 (7.9)	0.0611
Hemorrhage stroke	250 (1.5)	201 (2.5)	0.0747
Healthcare use[&]			
Outpatient department	24.1(16.0)	24.3(16.3)	0.0112
Inpatient department	0.8(1.7)	1.0(2.1)	0.1198

Data are presented as n (%) unless otherwise indicated.

*Expressed as mean (SD).

†Expressed as median (IQR).

‡Index year: the year each patient started to receive follow-up

§CHA_2DS_2-VASc score: high stroke risk was defined as a score of ≥ 3 in women and a score of ≥ 2 in men; middle stroke risk was defined as a score of 2 in women and a score of 1 in men; low stroke risk was defined as a score of 1 or 0 in women and a score of 0 in men.

‖HAS-BLED score: high bleeding risk: score ≥ 3; low bleeding risk: score < 3.

#Hospitalization history: the number of hospitalizations one year prior to admission

**Inpatient stroke events: The proportion of patients who had been admitted for stroke during follow-up period.

&Healthcare use: the number of outpatient and inpatient visits per year during follow-up.

Abbreviations: ACEI and ARB: angiotensin-converting-enzyme inhibitor and angiotensin receptor blocker; COPD: chronic pulmonary obstructive disease; IQR: interquartile range; NOACs: non-vitamin K antagonist oral anticoagulants; NTD: new Taiwan dollar; SD: standard deviation

Table S2. Sensitivity Analyses B, C, and D: Risk of Dementia in Patients with Atrial Fibrillation Receiving Non-Vitamin K Antagonist Oral Anticoagulants versus Those Receiving Warfarin.

	Model B*		Model C†		Model D‡	
	NOACs	Warfarin	NOACs	Warfarin	NOACs	Warfarin
HR	0.82	1.00	0.83	1.00	0.81	1.00
95% CI	0.73−0.92	ref.	0.74−0.94	ref.	0.72−0.91	ref.
p value	0.0004		0.0021		0.0003	

*Model B: The hazard ratios were calculated using a Fine and Gray competing risks regression model stratified by the matched pair, with adjustment for inpatient stroke events during the follow-up.

†Model C: The hazard ratios were calculated using a Fine and Gray competing risks regression model stratified by the matched pair, with adjustment for healthcare use during the follow-up.

‡Model D: The hazard ratios were calculated using a Fine and Gray competing risks regression model stratified by the matched pair, with adjustment for hospitalizations one year before the index date.

Abbreviations: HR: hazard ratio; CI: confidence interval; NOACs: non-vitamin K antagonist oral anticoagulants; ref: reference.

Table S3. **Sensitivity Analysis E: Risk of Dementia in Patients with Atrial Fibrillation Receiving Different Anticoagulants, Sensitivity Analysis by Changing the Number of Diagnoses of Dementia.**

Number of diagnoses	Group	Events	IR*	Univariable model		
				HR†	95% CI	*p* value
1	Warfarin	562	30.69	1.00	ref.	
	NOACs	511	26.38	0.88	0.80−0.96	0.0062
2	Warfarin	434	23.49	1.00	ref.	
	NOACs	368	18.78	0.81	0.73−0.89	< 0.0001
3	Warfarin	360	19.38	1.00	ref.	
	NOACs	304	15.43	0.82	0.73−0.92	0.0004
4	Warfarin	311	16.67	1.00	ref.	
	NOACs	259	13.09	0.81	0.72−0.91	0.0005
5	Warfarin	276	14.75	1.00	ref.	
	NOACs	215	10.83	0.77	0.68−0.88	< 0.0001

* Incidence rate: per 1,000 person-years.

†The hazard ratios were calculated using a Fine and Gray competing risks regression model stratified by the matched pair.

Abbreviations: IR: incidence rate; HR: hazard ratio; CI: confidence interval; NOACs: non-vitamin K antagonist oral anticoagulants; ref: reference.

Table S4. Baseline Characteristics for NOACs, Warfarin, and No OAC Cohorts.

	NOACs	Warfarin	No OAC	Standardized difference	Standardized difference
	(n=17,065)	(n=8,024)	(n=69,197)	NOACs VS. No OAC	Warfarin VS. No OAC
Sex					
Male	9,653 (56.6)	4,781 (59.6)	39,557 (57.2)	0.0121	0.0489
Female	7,412 (43.4)	3,243 (40.4)	29,640 (42.8)	0.0121	0.0489
Age, years*	73.1 (10.4)	68.7 (12.4)	70.9 (14.7)	0.1716	0.1667
<65	3,222 (18.9)	3,085 (38.5)	22,679 (32.8)	0.3214	0.1188
65-74	5,588 (32.8)	2,127 (26.5)	14,546 (21.0)	0.2669	0.1293
≥ 75	8,255 (48.4)	2,812 (35)	31,972 (46.2)	0.0435	0.2287
Income level (NTD)					
Dependence	4,935 (28.9)	2,004 (25.0)	19,391 (28.0)	0.0199	0.0689
15,840-29,999	7,934 (46.5)	3,703 (46.2)	32,346 (46.7)	0.0050	0.0118
30,000-44,999	2,280 (13.4)	1,320 (16.5)	9,966 (14.4)	0.0301	0.0568
≥45,000	1,916 (11.2)	997 (12.4)	7,494 (10.8)	0.0128	0.0499
Index year‡					
2012	1,941 (11.4)	2,148 (26.8)	14,619 (21.1)	0.2669	0.1324
2013	2,699 (15.8)	1,841 (22.9)	13,807 (20.0)	0.1079	0.0729
2014	3,676 (21.5)	1,664 (20.7)	13,484 (19.5)	0.0508	0.0312
2015	4,832 (28.3)	1,480 (18.4)	13,982 (20.2)	0.1900	0.0448
2016	3,917 (23.0)	891 (11.1)	13,305 (19.2)	0.0913	0.2281
CHA_2DS_2-VASc score*	3.2 (1.7)	2.9 (1.9)	2.8 (1.9)	0.1925	0.0365
Low stroke risk‡	1,098 (6.4)	1,164 (14.5)	12,871 (18.6)	0.3742	0.1102
Middle stroke risk	2,482 (14.5)	1,431 (17.8)	10,223 (14.8)	0.0065	0.0829
High stroke risk	13,485 (79.0)	5,429 (67.7)	46,103 (66.6)	0.2813	0.0219
HASBLED score*	2.4 (1.1)	2.3 (1.3)	2.2 (1.3)	0.1336	0.0471
Low bleeding risk§	9,378 (55.0)	4,616 (57.5)	41,040 (59.3)	0.0882	0.0361
High bleeding risk	7,687 (45.1)	3,408 (42.5)	28,157 (40.7)	0.0882	0.0361
Charlson comorbidity index*	4.6 (3.1)	5.1 (3.4)	5.0 (3.6)	0.1266	0.0174
0	1,220 (7.2)	502 (6.3)	6,215 (9.0)	0.0672	0.1027
1	1,583 (9.3)	688 (8.6)	5,993 (8.7)	0.0217	0.0032
≥ 2	14,262 (83.6)	6,834 (85.2)	56,989 (82.4)	0.0322	0.0763
Comorbidities					
Hypertension	14,019 (82.2)	6,464 (80.6)	51,860 (75.0)	0.1761	0.1352

Diabetes mellitus	6,205 (36.4)	3,119 (38.9)	24,533 (35.5)	0.0190	0.0708
Coronary artery disease	7,748 (45.4)	3,923 (48.9)	31,292 (45.2)	0.0036	0.0736
Congestive heart failure	5,129 (30.1)	3,075 (38.3)	20,386 (29.5)	0.0131	0.1880
COPD	4,669 (27.4)	2,162 (26.9)	21,965 (31.7)	0.0961	0.1056
Chronic kidney disease	2,703 (15.8)	2,090 (26.1)	15,211 (22.0)	0.1573	0.0954
Cirrhosis	2,595 (15.2)	1,334 (16.6)	10,922 (15.8)	0.0158	0.0231
Depression	1,095 (6.4)	556 (6.9)	5,314 (7.7)	0.0492	0.0288
Parkinsonism	540 (3.2)	272 (3.4)	2,872 (4.2)	0.0528	0.0399
Epilepsy	338 (2.0)	197 (2.5)	1,829 (2.6)	0.0439	0.0114
Stroke, ischemic	6,395 (37.5)	2,753 (34.3)	19,597 (28.3)	0.1957	0.1294
Stroke, hemorrhage	557 (3.3)	328 (4.1)	2,779 (4.0)	0.0406	0.0035
Malignancy	1,927 (11.3)	979 (12.2)	10,946 (15.8)	0.1326	0.1044
Hypothyroidism	434 (2.5)	227 (2.8)	1,734 (2.5)	0.0019	0.0199
Thyrotoxicosis	632 (3.7)	415 (5.2)	3,028 (4.4)	0.0345	0.0371
Baseline medication					
ACEI and ARB	8,029 (47.1)	3,532 (44.0)	27,653 (40.0)	0.1434	0.0823
Beta-blocker	6,219 (36.4)	3,032 (37.8)	22,008 (31.8)	0.0980	0.1260
Diuretics	3,118 (18.3)	1,673 (20.9)	14,335 (20.7)	0.0619	0.0032
Class 1 and Class 3 Antiarrhythmic	1,303 (7.6)	591 (7.4)	5,205 (7.5)	0.0045	0.0057
Digoxin	582 (3.4)	348 (4.3)	2,519 (3.6)	0.0125	0.0358
Statin	4,366 (25.6)	1,827 (22.8)	13,979 (20.2)	0.1283	0.0626
Antiepileptic	909 (5.3)	493 (6.1)	5,032 (7.3)	0.0799	0.0452
Antiparkinsonism	347 (2.0)	147 (1.8)	1,903 (2.8)	0.0472	0.0615
Antipsychotics	324 (1.9)	179 (2.2)	2,655 (3.8)	0.1164	0.0940
Anxiolytics, Hypnotics, and sedatives	4,863 (28.5)	2,215 (27.6)	21,013 (30.4)	0.0410	0.0611
Antidepressants	985 (5.8)	462 (5.8)	4,747 (6.9)	0.0448	0.0453
Thyroxine	253 (1.5)	106 (1.3)	1,069 (1.5)	0.0049	0.0185
Antithyroid drugs	139 (0.8)	113 (1.4)	781 (1.1)	0.0327	0.0250
Inpatient stroke events‖					
Overall stroke	2,571 (15.1)	1,180 (14.7)	4,921 (7.1)	0.2556	0.2456
Ischemic stroke	2,409 (14.1)	1,038 (12.9)	4,301 (6.2)	0.2636	0.2298
Hemorrhage stroke	387 (2.3)	230 (2.9)	991 (1.4)	0.0624	0.0994
Healthcare use#					
Outpatient department	24.9(15.2)	25.1(15.6)	23(17.7)	0.1142	0.1266
Inpatient department	0.7(1.2)	0.9(1.4)	1.7(4.5)	0.2801	0.2216

Data are presented as n (%) unless otherwise indicated.

*Expressed as mean (SD).

†Index year: the year each patient has diagnosis of atrial fibrillation

‡CHA_2DS_2-VASc score: high stroke risk was defined as a score of ≥ 3 in women and a score of ≥ 2 in men; middle stroke risk was defined as a score of 2 in women and a score of 1 in men; low stroke risk was defined as a score of 1 or 0 in women and a score of 0 in men.

§HAS-BLED score: high bleeding risk: score ≥ 3; low bleeding risk: score < 3.

‖Inpatient stroke events: The proportion of patients who had been admitted for stroke during follow-up period.

&Healthcare use: the number of outpatient and inpatient visits per year during follow-up.

Abbreviations: ACEI and ARB: angiotensin-converting-enzyme inhibitor and angiotensin receptor blocker; COPD: chronic pulmonary obstructive disease; NOACs: non-vitamin K antagonist oral anticoagulants; NTD: new Taiwan dollar; OAC: oral anticoagulant; SD: standard deviation

Table S5. **Risk of Dementia in Patients with Atrial Fibrillation Receiving Different Oral Anticoagulants Compared with Those Not Receiving Oral Anticoagulants.**

	Incidence rate*	Univariable model			Multivariable model†		
		HR	95% CI	*p* value	Adjusted HR	95% CI	*p* value
No OAC	19.48	1.00	ref.		1.00	ref.	
Warfarin	15.20	0.97	0.88−1.06	0.4866	1.05	0.96−1.16	0.2903
NOACs	15.29	0.97	0.90−1.04	0.3480	0.87	0.81−0.93	0.0001

*Incidence rate: per 1,000 person-years.

†The hazard ratios were calculated using a multivariable Fine and Gray competing risk regression model with adjustments for age, sex, income level, index year, CHA_2DS_2-VASc score, HAS-BLED score, CCI, comorbidities, medication use, inpatient stroke events, and healthcare use during the follow-up period

Abbreviations: HR: hazard ratio; CI: confidence interval; OAC: oral anticoagulant; NOACs: non-vitamin K antagonist oral anticoagulants; ref: reference.

Figure S1. Cumulative incidence curves of dementia risk, based on various definitions of dementia.
Dementia was defined as having been diagnosed: (A) at least one time, (B) at least two times, (C) at least three times, (D) at least four times, and (E) at least five times.