



Differential Risk of Dementia Between Patients With Atrial Flutter and Atrial Fibrillation: A National Cohort Study

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Objectives: Atrial fibrillation (AF) is linked to an increased risk of stroke and dementia. Atrial flutter (AFL) is also linked to an increased risk of stroke but at a different level of risk as compared to AF. Little is known about the difference in the risk of dementia between AF and AFL. This study aims to investigate whether the risk of dementia is different between AF and AFL.

Methods: Patients with newly diagnosed AF and AFL during 2001–2013 were retrieved from Taiwan's National Health Insurance Research Database. Patients with incomplete demographic data, aged <20 years, history of valvular surgery, rheumatic heart disease, hyperthyroidism, and history of dementia were excluded. The incidence of new-onset dementia was set as the primary outcome and analyzed in patients with AF and AFL after propensity score matching (PSM).

Results: A total of 232,425 and 7,569 patients with AF and AFL, respectively, were eligible for analysis. After 4:1 PSM, we included 30,276 and 7,569 patients with AF and AFL, respectively, for analysis. Additionally, patients with AF ($n = 29,187$) and AFL ($n = 451$) who received oral anticoagulants were enrolled for comparison. The risk of dementia was higher in patients with AF compared with patients with AFL (subdistribution hazard ratio (SHR) = 1.52, 95% CI 1.39–1.66; $p < 0.0001$) before PSM and remained higher in patients with AF (SHR = 1.14, 95% CI 1.04–1.25; $p = 0.0064$) after PSM. The risk of dementia was higher in patients with AF without previous history of stroke after PSM but the risk did not differ between patients with AF and AFL with previous history of stroke. Among patients who received oral anticoagulants, the cumulative incidences of dementia were significantly higher in patients with AF than in patients with AFL before and after PSM (all $P < 0.05$).

Conclusions: This study found that, among patients without history of stroke, the risk of dementia was higher in patients with AF than in patients with AFL, and CHA₂DS₂-VASc score might be useful for risk stratification of dementia between patients with AF and AFL.

Keywords: atrial fibrillation, atrial flutter, dementia, stroke, CHA₂DS₂-VASc score

INTRODUCTION

Atrial fibrillation (AF) had been reported to be linked to an increased risk of ischemic stroke, thromboembolism, heart failure, myocardial infarction, and death (1, 2). Moreover, there is increasing evidence that AF is also a risk factor for cognitive decline and dementia, which might be independent of ischemic stroke (3–6). Atrial flutter (AFL) and AF share the common risk factors and therefore, should contribute to similar clinical events. Accordingly, clinical guidelines recommend AFL should be treated as AF in terms of anticoagulation to prevent stroke and systemic thromboembolism (7). However, our previous study showed that the incidence of ischemic stroke was significantly higher in the AF cohort than in the AFL cohort at a CHA₂DS₂-VASc score [Heart failure, Hypertension, Age \geq 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female)] \geq 1 (8). Therefore, differential risk of ischemic stroke exists between AF and AFL. There is no study to examine the risk of dementia between patients with AFL and AF. We hypothesized that patients with AF had a higher risk of dementia than patients with AFL independent of the previous history of stroke. Accordingly, we conducted this large population-based national cohort study to evaluate the incidence of dementia in patients with AF and AFL.

MATERIALS AND METHODS

Data Source

Taiwan's National Health Insurance started in 1995 and covers 99.5% (23 million) of the residents in Taiwan. The National Health Insurance Research Database (NHIRD) provides the data of all inpatient and outpatient services, diagnoses, emergency room visits, prescriptions, examinations, operations, and expenditures and are updated biannually. The diseases were diagnosed using the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) and version 2001 codes. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (202100865B1). The dataset used in this study was held by the Taiwan Ministry of Health and Welfare (MOHW). Any researcher interested in accessing this dataset can submit an application form to the MOHW requesting access. (Email: stcarol-wu@mohw.gov.tw).

Study Patients

Electronic medical records from the NHIRD between January 1, 2001 and December 31, 2013 were retrieved for patients with a discharge diagnosis or at least two consecutive outpatient clinic diagnoses of AF (ICD-9-CM: 427.31) and AFL (ICD-9-CM: 427.32). The time when AF or AFL was first diagnosed was assigned as the index date. The coverage period of our database was from 1997 to 2013; therefore, we excluded patients who were diagnosed with both AF and AFL between 1997 and 2000. Furthermore, we excluded patients who had incomplete demographic data (<0.1%), aged <20 years, history of valvular surgery, rheumatic heart disease, hyperthyroidism, and history of dementia (Figure 1). The remaining patients were categorized into two groups as newly diagnosed AF or newly diagnosed AFL

without history of dementia. Furthermore, we excluded those patients who received radiofrequency ablation because these factors might also affect the risk of stroke and dementia.

Study Design

The primary outcome of dementia was analyzed after propensity score matching (PSM) between AF and AFL population in three different cohorts. In cohort 1, patients with AF ($n = 232,425$) and AFL ($n = 7,569$) were eligible population after serial excluding criteria. Cohort 2 [patients with AF ($n = 200,646$) and AFL ($n = 6,683$)] enrolled those patients without any history of ischemic stroke in cohort 1, while cohort 3 [patients with AF ($n = 31,779$) and AFL ($n = 886$)] enrolled those patients with a history of ischemic stroke in cohort 1 (Figure 1). The PSM was performed with 4:1 ratio under adjusting covariates including age, sex, comorbidities, and medications between AF and AFL cohorts. Furthermore, the primary outcome was also analyzed by stratifying the groups by CHA₂DS₂-VASc score in cohort 1 (Figure 1).

Study Outcome, Covariates, and Follow-Up

The primary outcome was dementia, which was defined when the diagnosis was made during hospitalization or \geq 2 consecutive clinic visits. The diagnostic code of dementia was validated in previous NHIRD studies (9, 10). The first date when dementia was coded during follow-up was assigned as the date of the endpoint. Each patient in the three cohorts was followed up until the date of dementia occurrence, death, or December 31, 2013, whichever occurred first.

The covariates included comorbidities, namely hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, peripheral arterial disease, chronic obstructive pulmonary disease, renal function status, abnormal liver function, gout, systemic thromboembolism, myocardial infarction, stroke, and heart failure, and medications.

These comorbidities were ascertained according to the ICD-9-CM codes combined with medication use. The patients with systemic thromboembolism, myocardial infarction, stroke, and heart failure were defined as having any inpatient diagnosis before the index date. Most of these diagnostic codes were validated in previous NHIRD studies (11–15). Similarly, data on medication usage were retrieved on claim-based data of the previous year.

Ascertainment of AF/AFL and CHA₂DS₂-VASc Score

All patients who had AF or AFL diagnosis defined according to the diagnosis made at least once during hospitalization or \geq 2 consecutive clinic visits. The accuracy of AF or AFL diagnosis using ICD-9-CM code in the NHIRD has been confirmed in previous studies (16, 17).

Because CHA₂DS₂-VASc score has been reported to be useful for risk stratification regarding ischemic stroke and dementia among patients with AF and AFL (18–21), we stratified patients using CHA₂DS₂-VASc score to compare the risk of dementia between patients with AF and AFL before and after PSM. Comorbidities in CHA₂DS₂-VASc score were ascertained

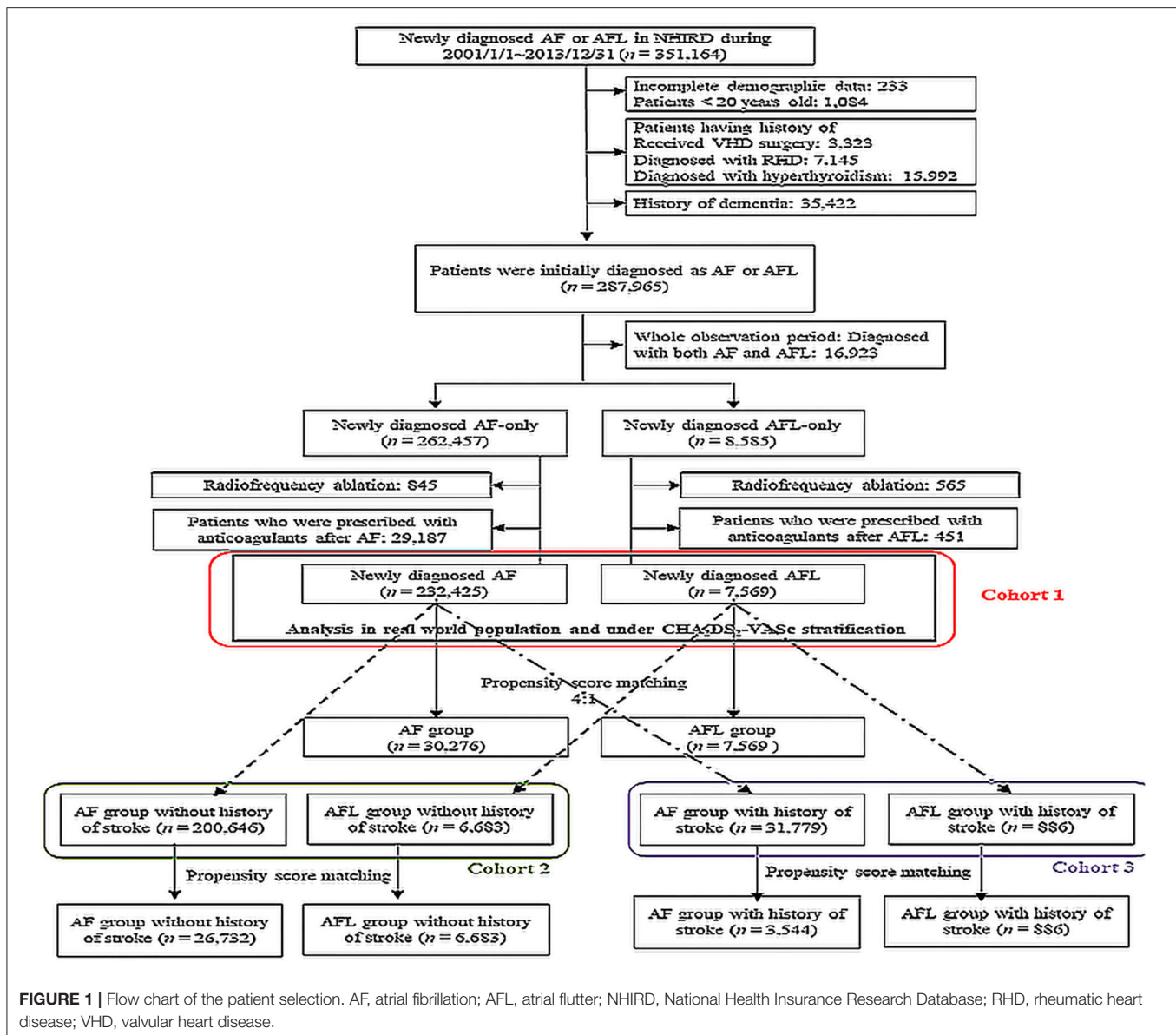


FIGURE 1 | Flow chart of the patient selection. AF, atrial fibrillation; AFL, atrial flutter; NHIRD, National Health Insurance Research Database; RHD, rheumatic heart disease; VHD, valvular heart disease.

according to the ICD-9-CM codes combined with medication use and the diagnostic codes were validated in previous NHIRD studies (12–15).

Statistical Analysis

The propensity score matching was performed with 4:1 ratio in patients with AF and AFL. The covariates in the propensity score calculation were the age, gender, 12 comorbidities, 10 types of medication, and index date. The matching was processed using a greedy nearest neighbor algorithm with a caliper of 0.2 times the SD of the logit of the propensity score. The quality of matching was assessed using the standardized mean difference (SMD) between the two groups after matching, where a value <0.1 indicated a negligible difference (Table 1). The risk of dementia was compared between patients with AF and AFL

before and after PSM. The risk of dementia between patients with AF and AFL was also compared after stratification by CHA₂DS₂-VASc score and previous history of stroke. A $P < 0.05$ was considered statistically significant. No adjustment for multiple testing (multiplicity) was performed in this study. All statistical analyses were performed using commercial software [Statistical Analysis System (SAS) V.9.4], including the “*psmatch*” procedure for PSM, “*phreg*” procedure for survival analysis, and “%*cif*” macro for generating a cumulative incidence function through Fine and Gray’s method.

Patient and Public Involvement

Since this study is a retrospective cohort study based on a national insurance database, in no part or stage of the research were the patients/public involved.

TABLE 1 | Baseline characteristics of the atrial fibrillation and atrial flutter groups before and after propensity score matching.

Variables	All patients			Propensity score matched	
	AFL (n = 7,569)	AF (n = 232,425)	P-value	AF (n = 30,276)	P-value
Age (years; mean ± SD)	67.41 ± 6.0	72.21 ± 3.3	<0.0001	67.31 ± 5.7	0.6889
Age group			<0.0001		0.725
< 65 years	2,841 (37.5%)	59,556 (25.6%)		11,449 (37.8%)	
65~74 years	1,883 (24.9%)	59,783 (25.7%)		7,399 (24.4%)	
≥ 75 years	2,845 (37.6%)	113,086 (48.7%)		11,428 (37.7%)	
Gender			<0.0001		0.6485
Male	4,689 (62.0%)	131,832 (56.7%)		18,842 (62.2%)	
Female	2,880 (38.0%)	100,593 (43.3%)		11,434 (37.8%)	
Comorbidities					
Hypertension	4,199 (55.5%)	139,437 (60.0%)	<0.0001	16,672 (55.1%)	0.5216
Diabetes Mellitus	1,463 (19.3%)	44,672 (19.2%)	0.813	5,834 (19.3%)	0.9066
Ischemic heart disease	2,546 (33.6%)	86,362 (37.2%)	<0.0001	10,111 (33.4%)	0.6909
Heart failure	901 (11.9%)	29,841 (12.8%)	0.0166	3,539 (11.7%)	0.6037
Dyslipidemia	1,086 (14.3%)	30,650 (13.2%)	0.0033	4,189 (13.8%)	0.25
Gout	753 (9.9%)	24,095 (10.4%)	0.2398	3,037 (10.0%)	0.8305
Chronic obstructive pulmonary disease	1,360 (18.0%)	45,954 (19.8%)	0.0001	5,419 (17.9%)	0.8881
Peripheral arterial disease	321 (4.2%)	11,007 (4.7%)	0.0458	1,242 (4.1%)	0.5875
Renal status			0.0137		0.717
Non-chronic kidney disease	6,384 (84.3%)	198,371 (85.3%)		25,649 (84.7%)	
Chronic kidney disease without dialysis	911 (12.0%)	26,833 (11.5%)		3,549 (11.7%)	
Chronic kidney disease with dialysis	274 (3.6%)	7,221 (3.1%)		1,078 (3.6%)	
Immune disease	147 (1.9%)	3,935 (1.7%)	0.0991	562 (1.9%)	0.6221
Abnormal liver function	904 (11.9%)	26,151 (11.3%)	0.061	3,603 (11.9%)	0.9178
Malignancy	683 (9.0%)	17,722 (7.6%)	<0.0001	2,811 (9.3%)	0.483
History of disease					
Prior stroke or systemic thromboembolism	977 (12.9%)	34,401 (14.8%)	<0.0001	3,928 (13.0%)	0.8784
Prior stroke	886 (11.7%)	31,779 (13.7%)	<0.0001	3,556 (11.7%)	0.9237
Old myocardial infarction	425 (5.6%)	10,307 (4.4%)	<0.0001	1,661 (5.5%)	0.6605
Medications					
ACEi/ARB	2,445 (32.3%)	91,378 (39.3%)	<0.0001	9,795 (32.4%)	0.9343
Calcium channel blockers	1,667 (22.0%)	58,046 (25.0%)	<0.0001	6,672 (22.0%)	0.9802
β-blockers	2,549 (33.7%)	75,683 (32.6%)	0.0418	9,531 (31.5%)	0.0002
Dipeptidyl peptidase 4 inhibitors	153 (2.0%)	4,518 (1.9%)	0.6308	568 (1.9%)	0.4081
Statins	832 (11.0%)	25,522 (11.0%)	0.975	3,095 (10.2%)	0.0496
Biguanides	697 (9.2%)	21,906 (9.4%)	0.5259	2,756 (9.1%)	0.7752
Sulfonylurea	758 (10.0%)	24,341 (10.5%)	0.2	3,004 (9.9%)	0.8099
Thiazolidinedione	106 (1.4%)	3,160 (1.4%)	0.7626	388 (1.3%)	0.415
Insulin	260 (3.4%)	7,366 (3.2%)	0.1944	946 (3.1%)	0.169
Antiplatelet	2,479 (32.8%)	104,861 (45.1%)	<0.0001	9,968 (32.9%)	0.776

ACEi, angiotensin converting enzyme inhibitors; AF, atrial fibrillation; AFL, atrial flutter; ARB, angiotensin II receptor blockers.

RESULTS

Study Population

We identified a total of 351,164 patients newly diagnosed with AF or AFL during 2001–2013 in the NHIRD. After exclusions, 232,425 patients with AF (aged 72.2 ± 13.3 years) and 7,569 patients with AFL (aged 67.41 ± 6.0 years) without receiving oral anticoagulants were eligible for analysis in the study cohort 1 (Table 1). The distribution of comorbidities was similar

between the patients with AF and AFL, except there was a higher prevalence of hypertension, ischemic heart disease, and history of thromboembolism/ischemic stroke in patients with AF compared with patients with AFL. After 4:1 ratio of PSM using all variables in Table 1 and there was a good balance between the patients with AF and AFL, except for β-blockers (right panel of Table 1), 30,276 patients with AF (aged 67.3 ± 15.7 years) and 7,569 patients with AFL were analyzed for comparison of the risk of dementia.

TABLE 2 | Clinical outcomes between the patients with atrial fibrillation and atrial flutter not receiving warfarin therapy before and after PSM.

Variable	Before PSM			After PSM		
	AF (n = 232,425)	AFL (n = 7,569)	P-value	AF (n = 30,276)	AFL (n = 7,569)	P-value
Dementia						
Number of events, n (%)	22,833 (9.82)	521 (6.88)		2,435 (8.04)	521 (6.88)	
Incidence density§	3.04 (3.00–3.08)	2.05 (1.87–2.22)		2.33 (2.24–2.43)	2.05 (1.87–2.22)	
Hazard ratio (95% CI)	1.52 (1.39–1.66)	Reference	<0.0001	1.14 (1.04–1.25)	Reference	0.0064
Ischemic stroke						
Number of events, n (%)	18,475 (7.95)	297 (3.92)		2,095 (6.92)	297 (3.92)	
Incidence density§	2.54 (2.50–2.58)	1.18 (1.04–1.31)		2.07 (1.98–2.16)	1.18 (1.04–1.31)	
Hazard ratio (95% CI)	2.15 (1.92–2.42)	Reference	<0.0001	1.76 (1.56–1.98)	Reference	<0.0001

AF, atrial fibrillation; AFL, atrial flutter; PSM, propensity score matching.

§ Incidence density: number of events per 100 person-years.

Moreover, we further categorized the original 232,425 patients with AF and 7,569 patients with AFL in the cohort 1 into cohorts 2 and 3 according to history without (cohort 2) or with stroke (cohort 3) and performed the additional PSM in each cohort. After PSM, there were 26,732 patients with AF and 6,683 patients with AFL in the cohort 2, and 3,544 patients with AF and 886 patients with AFL in the cohort 3 (Figure 1).

Difference in the Risk of Dementia and Ischemic Stroke Between Patients With AF and AFL Before and After PSM (Cohort 1)

Before PSM, the incidence densities of dementia (hazard ratio [HR], 1.52; 95% CI, 1.39–1.66; $P < 0.0001$) and ischemic stroke (HR, 2.15; 95% CI, 1.92–2.42; $P < 0.0001$) were higher in patients with AF than in patients with AFL (Table 2). After PSM, the incidence densities of dementia (HR, 1.14; 95% CI, 1.04–1.25; $P = 0.0064$) and ischemic stroke (HR, 1.76; 95% CI, 1.56–1.98; $P < 0.0001$) were still higher in patients with AF than in patients with AFL (Table 2). The cumulative incidences of dementia in patients with AF and AFL before and after PSM were shown in Figures 2A,B.

Difference in the Risk of Dementia and Ischemic Stroke Between Patients With AF and AFL Without Previous History of Stroke (Cohort 2)

There were 200,646 patients with AF without previous history of stroke and 6,683 patients with AFL without previous history of stroke (Table 3, Figure 1). After 4:1 PSM, 26,732 patients with AF and 6,683 patients with AFL were well balanced, except for β -blockers (Table 3). Before PSM, the incidence densities of dementia (HR, 1.54; 95% CI, 1.40–1.69; $P < 0.0001$) and ischemic stroke (HR, 2.32; 95% CI, 2.04–2.64; $P < 0.0001$) were higher in patients with AF than in patients with AFL (Table 4). After PSM, the incidence densities of dementia (HR, 1.15; 95% CI, 1.03–1.27; $P = 0.0098$) and ischemic stroke (HR, 1.82; 95% CI, 1.59–2.09; $P < 0.0001$) were higher in patients with AF than in patients with AFL (Table 4).

The cumulative incidences of dementia in patients with AF and AFL without previous history of stroke before and after PSM were shown in Figures 3A,B.

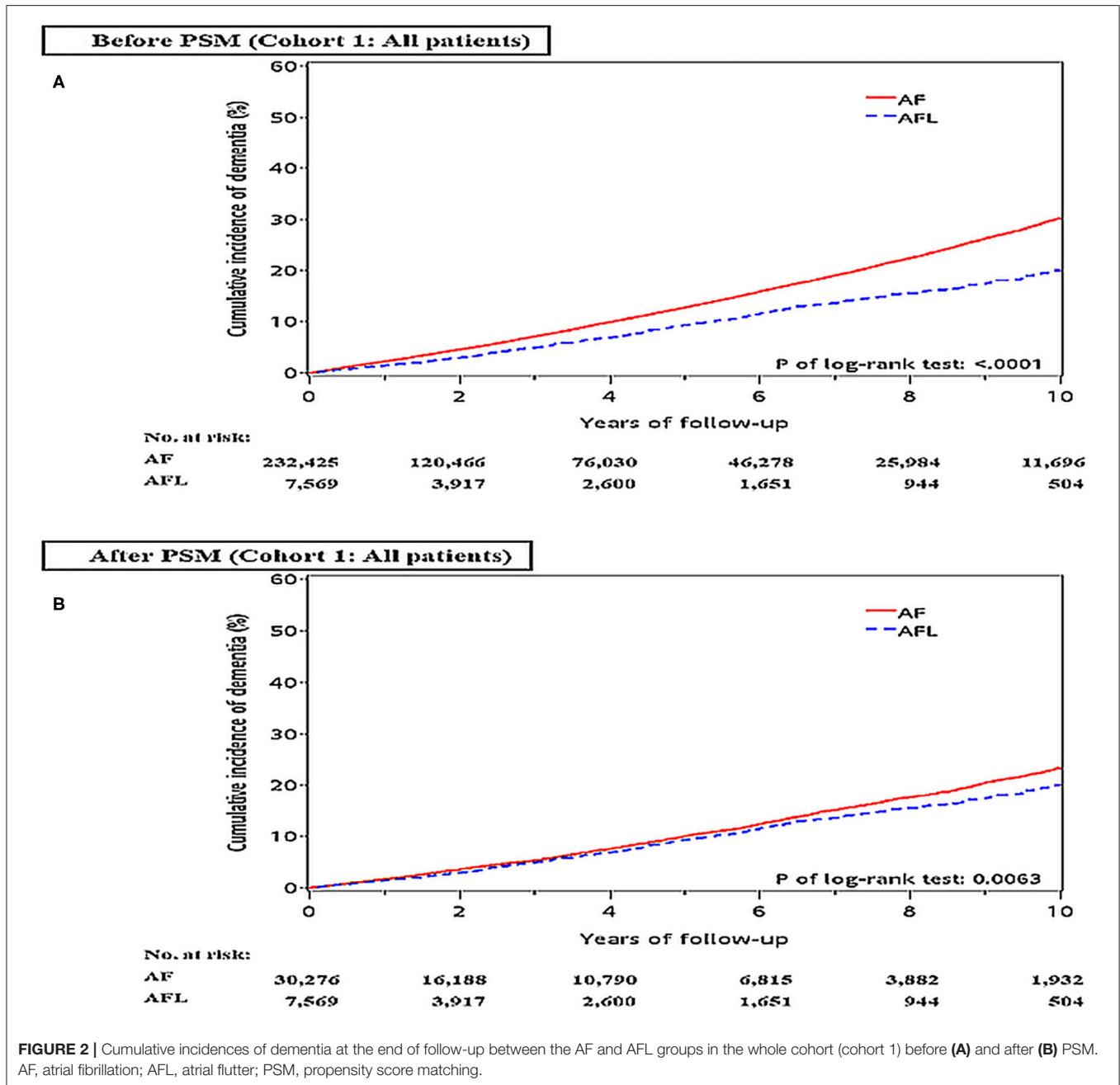
Difference in the Risk of Dementia and Recurrent Ischemic Stroke Between Patients With AF and AFL With Previous History of Stroke (Cohort 3)

There were 31,779 patients with AF with a history of stroke and 886 patients with AFL with a history of stroke (Table 5, Figure 1). After 4:1 PSM, 3,544 patients with AF and 886 patients with AFL were well balanced (Table 5). Before PSM, the incidence densities of dementia (HR, 1.25; 95% CI, 1.02–1.54; $P = 0.0351$) and recurrent ischemic stroke (HR, 1.39; 95% CI, 1.09–1.78; $P = 0.0083$) were higher in patients with AF than in patients with AFL (Table 6). After PSM, the incidence density of dementia did not differ between patients with AF and AFL (HR, 1.16; 95% CI, 0.92–1.45; $P = 0.2058$) (Table 6). However, the incidence density of recurrent ischemic stroke (HR, 1.40; 95% CI, 1.08–1.83; $P = 0.0118$) was higher in patients with AF than in patients with AFL (Table 6).

The cumulative incidences of dementia in patients with AF and AFL with a history of stroke before and after PSM were shown in Figures 3C,D.

The Risk of Dementia Stratified According to CHA₂DS₂-VASc Score Between Patients With AF and AFL (Cohort 1)

The risk of dementia in the cohort 1 was stratified according to CHA₂DS₂-VASc score. Before PSM, the incidence density of dementia was higher in patients with AF than in patients with AFL across CHA₂DS₂-VASc scores of 1–4 and 6–9 (Figure 4). After PSM, the cumulative incidences of dementia in patients with AF and AFL stratified according to different CHA₂DS₂-VASc scores were shown in Figure 5, and the cumulative incidences of dementia were significantly higher in patients with AF than patients with AFL in patients with CHA₂DS₂-VASc score ≤ 2 ($P < 0.0001$) and patients with CHA₂DS₂-VASc score between 3 and 4 ($P = 0.0104$), but not in patients with CHA₂DS₂-VASc score ≥ 5 .



Difference in the Risk of Dementia and Ischemic Stroke Between Patients With AF and AFL Receiving Oral Anticoagulants Therapy Before and After PSM

Because the usage of oral anticoagulant might affect the risk of dementia and ischemic stroke in patients with AF and AFL, we identified and analyzed the risk of dementia and ischemic stroke between patients newly diagnosed with AF ($n = 29,187$) and AFL ($n = 451$) who received oral anticoagulants (mainly vitamin K oral anticoagulant)

in another dataset during the same study period in the NHIRD.

Before PSM, the incidence densities of dementia (HR, 2.05; 95% CI, 1.35–3.11; $P = 0.0008$) and ischemic stroke (HR, 2.95; 95% CI, 1.86–4.62; $P < 0.0001$) were higher in patients with AF than in patients with AFL (Table 7). After PSM, the incidence density of dementia (HR, 1.57; 95% CI, 1.00–2.45; $P = 0.0501$) was higher with borderline significance in patients with AF than in patients with AFL, and the incidence density of ischemic stroke (HR, 2.54; 95% CI, 1.56–4.12; $P = 0.0002$) was significantly higher in patients with AF than in patients with AFL

TABLE 3 | Baseline characteristics of the atrial fibrillation and atrial flutter groups before and after PSM (without history of stroke).

Variables	Without history of stroke patients			Propensity score matched	
	AFL (n = 6,683)	AF (n = 200,646)	P-value	AF (n = 26,732)	P-value
Age (years; mean ± SD)	66.41 ± 6.3	71.51 ± 3.6	<0.0001	66.51 ± 6.0	0.8808
Age group			<0.0001		0.7103
< 65 years	2,694 (40.3%)	55,494 (27.7%)		10,751 (40.2%)	
65~74 years	1,640 (24.5%)	51,904 (25.9%)		6,457 (24.2%)	
≥ 75 years	2,349 (35.1%)	93,248 (46.5%)		9,524 (35.6%)	
Gender			<0.0001		0.6932
Male	4,130 (61.8%)	114,261 (56.9%)		16,590 (62.1%)	
Female	2,553 (38.2%)	86,385 (43.1%)		10,142 (37.9%)	
Comorbidities					
Hypertension	3,576 (53.5%)	116,639 (58.1%)	<0.0001	14,458 (54.1%)	0.398
Diabetes Mellitus	1,179 (17.6%)	35,701 (17.8%)	0.7504	4,790 (17.9%)	0.5972
Ischemic heart disease	2,168 (32.4%)	72,738 (36.3%)	<0.0001	8,717 (32.6%)	0.7928
Heart failure	705 (10.5%)	22,725 (11.3%)	0.0485	2,883 (10.8%)	0.5778
Dyslipidemia	918 (13.7%)	25,282 (12.6%)	0.006	3,670 (13.7%)	0.9873
Gout	662 (9.9%)	20,528 (10.2%)	0.3879	2,645 (9.9%)	0.9781
Chronic obstructive pulmonary disease	1,134 (17.0%)	37,762 (18.8%)	0.0001	4,489 (16.8%)	0.7311
Peripheral arterial disease	245 (3.7%)	8,668 (4.3%)	0.0095	960 (3.6%)	0.7692
Renal status			0.0191		0.809
Non-chronic kidney disease	5,702 (85.3%)	173,283 (86.4%)		22,725 (85.0%)	
Chronic kidney disease without dialysis	758 (11.3%)	21,634 (10.8%)		3,088 (11.6%)	
Chronic kidney disease with dialysis	223 (3.3%)	5,729 (2.9%)		919 (3.4%)	
Immune disease	132 (2.0%)	3,421 (1.7%)	0.0941	520 (1.9%)	0.8743
Abnormal liver function	812 (12.2%)	22,840 (11.4%)	0.0523	3,299 (12.3%)	0.6711
Malignancy	606 (9.1%)	15,458 (7.7%)	<0.0001	2,422 (9.1%)	0.9848
History of disease					
Prior systemic thromboembolism	91 (1.4%)	2,622 (1.3%)	0.6977	390 (1.5%)	0.5505
Old myocardial infarction	323 (4.8%)	7,614 (3.8%)	<0.0001	1,348 (5.0%)	0.4822
Medications					
ACEi/ARB	2,104 (31.5%)	78,575 (39.2%)	<0.0001	8,499 (31.8%)	0.6257
Calcium channel blockers	1,419 (21.2%)	48,585 (24.2%)	<0.0001	5,858 (21.9%)	0.2278
β-blockers	2,300 (34.4%)	67,200 (33.5%)	0.1155	8,644 (32.3%)	0.0012
Dipeptidyl peptidase 4 inhibitors	129 (1.9%)	3,748 (1.9%)	0.7115	458 (1.7%)	0.2272
Statins	736 (11.0%)	21,750 (10.8%)	0.6545	2,732 (10.2%)	0.0573
Biguanides	594 (8.9%)	18,483 (9.2%)	0.368	2,332 (8.7%)	0.6703
Sulfonylurea	645 (9.7%)	20,391 (10.2%)	0.1732	2,567 (9.6%)	0.904
Thiazolidinedione	95 (1.4%)	2,665 (1.3%)	0.5126	348 (1.3%)	0.4441
Insulin	188 (2.8%)	5,525 (2.8%)	0.77	798 (3.0%)	0.4572
Antiplatelet	2,118 (31.7%)	89,775 (44.7%)	<0.0001	8,524 (31.9%)	0.7601

ACEi, angiotensin converting enzyme inhibitors; AF, atrial fibrillation; AFL, atrial flutter; ARB, angiotensin II receptor blockers.

(Supplemental Table 5). The cumulative incidences of dementia in patients with AF and AFL before and after PSM were shown in **Figures 6A,B** and the cumulative incidences of dementia were significantly higher in patients with AF than in patients with AFL before and after PSM.

DISCUSSIONS

The main findings of this study were (1) among patients without oral anticoagulants, the incidence densities of dementia and

ischemic stroke were significantly higher in patients with AF than in patients with AFL before and after PSM; (2) among patients without oral anticoagulants, the incidence densities of dementia and ischemic stroke were significantly higher in patients with AF than in patients with AFL among patients without previous history of stroke before and after PSM; (3) among patients without oral anticoagulants, the incidence density of dementia did not differ between patients with AF and AFL among patients with previous history of stroke after PSM; (4) among patients without oral anticoagulants, the cumulative incidence

TABLE 4 | Clinical outcomes between the patients with atrial fibrillation and atrial flutter before and after PSM (without history of stroke).

Variable	Before PSM			After PSM		
	AF (n = 200,646)	AFL (n = 6,683)	P-value	AF (n = 26,732)	AFL (n = 6,683)	P-value
Dementia						
Number of events, n (%)	18,693 (9.32)	431 (6.45)		1,983 (7.42)	431 (6.45)	
Incidence density§	2.77 (2.73–2.81)	1.85 (1.67–2.02)		2.11 (2.02–2.20)	1.85 (1.67–2.02)	
Hazard ratio (95% CI)	1.54 (1.40–1.69)	Reference	<0.0001	1.15 (1.03–1.27)	Reference	0.0098
Ischemic stroke						
Number of events, n (%)	15,119 (7.54)	232 (3.47)		1,661 (6.21)	232 (3.47)	
Incidence density§	2.31 (2.28–2.35)	1.00 (0.87–1.13)		1.82 (1.73–1.91)	1.00 (0.87–1.13)	
Hazard ratio (95% CI)	2.32 (2.04–2.64)	Reference	<0.0001	1.82 (1.59–2.09)	Reference	<0.0001

AF, atrial fibrillation; AFL, atrial flutter; PSM, propensity score matching.

§ Incidence density: number of events per 100 person-years.

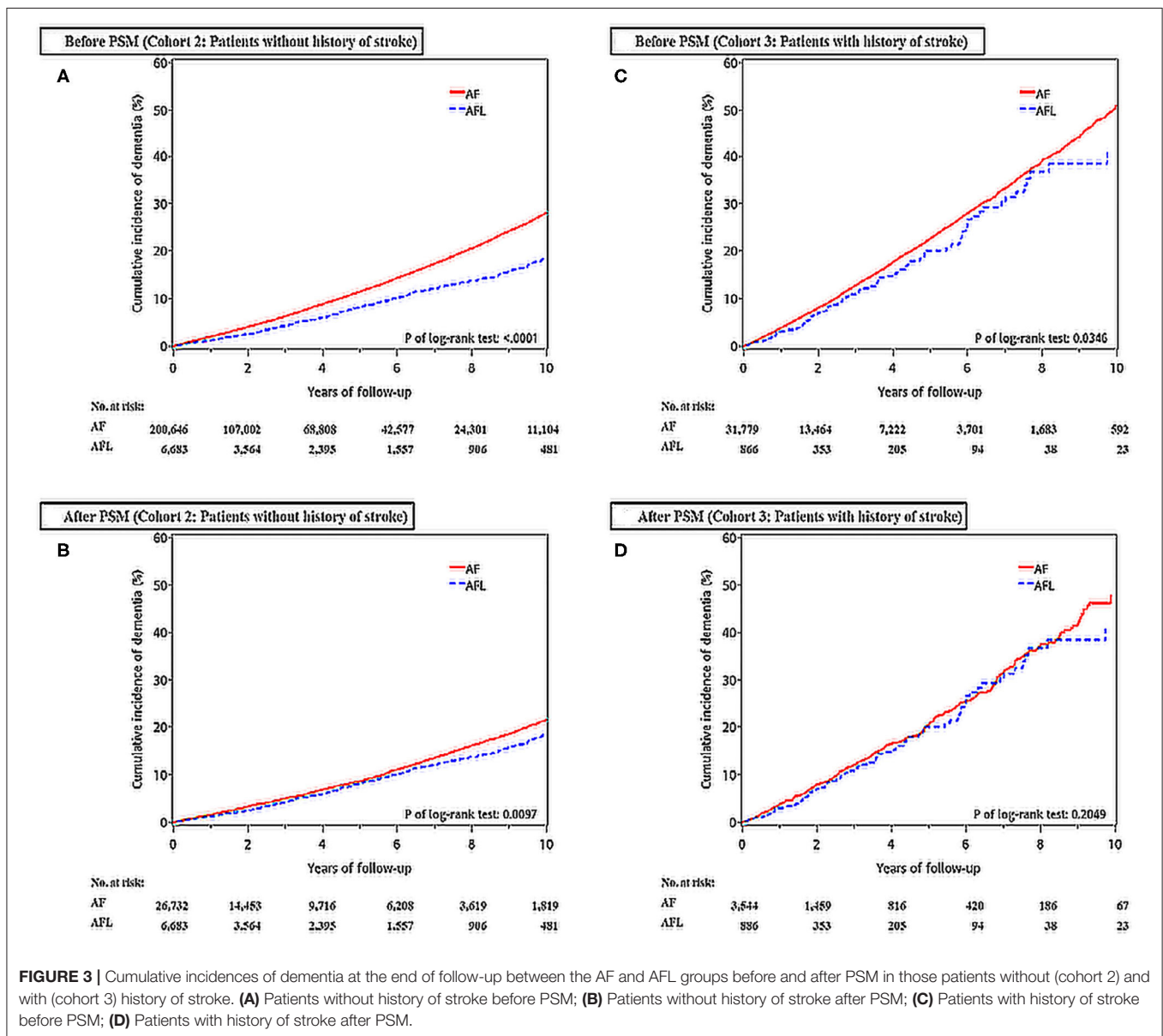


FIGURE 3 | Cumulative incidences of dementia at the end of follow-up between the AF and AFL groups before and after PSM in those patients without (cohort 2) and with (cohort 3) history of stroke. (A) Patients without history of stroke before PSM; (B) Patients without history of stroke after PSM; (C) Patients with history of stroke before PSM; (D) Patients with history of stroke after PSM.

TABLE 5 | Baseline characteristics of the atrial fibrillation and atrial flutter groups before and after PSM (with history of stroke).

Variables	With history of stroke patients			Propensity score matched	
	AFL (n = 886)	AF (n = 31,779)	P-value	AF (n = 3,544)	P-value
Age (years; mean ± SD)	75.01 ± 1.1	76.61 ± 0.0	<0.0001	75.01 ± 0.7	0.9391
Age group			0.0001		0.9949
< 65 years	147 (16.6%)	4,062 (12.8%)		589 (16.6%)	
65~74 years	243 (27.4%)	7,879 (24.8%)		966 (27.3%)	
≥ 75 years	496 (56.0%)	19,838 (62.4%)		1,989 (56.1%)	
Gender			<0.0001		0.9504
Male	559 (63.1%)	17,571 (55.3%)		2,232 (63.0%)	
Female	327 (36.9%)	14,208 (44.7%)		1,312 (37.0%)	
Comorbidities					
Hypertension	623 (70.3%)	22,798 (71.7%)	0.3536	2,478 (69.9%)	0.8185
Diabetes Mellitus	284 (32.1%)	8,971 (28.2%)	0.0127	1,167 (32.9%)	0.6197
Ischemic heart disease	378 (42.7%)	13,624 (42.9%)	0.9021	1,523 (43.0%)	0.8674
Heart failure	196 (22.1%)	7,116 (22.4%)	0.849	769 (21.7%)	0.7849
Dyslipidemia	168 (19.0%)	5,368 (16.9%)	0.1053	697 (19.7%)	0.6357
Gout	91 (10.3%)	3,567 (11.2%)	0.3747	360 (10.2%)	0.9208
Chronic obstructive pulmonary disease	226 (25.5%)	8,192 (25.8%)	0.8561	899 (25.4%)	0.9312
Peripheral arterial disease	76 (8.6%)	2,339 (7.4%)	0.1719	302 (8.5%)	0.9571
Renal status			0.233		0.7953
Non-chronic kidney disease	682 (77.0%)	25,088 (78.9%)		2,691 (75.9%)	
Chronic kidney disease without dialysis	153 (17.3%)	5,199 (16.4%)		645 (18.2%)	
Chronic kidney disease with dialysis	51 (5.8%)	1,492 (4.7%)		208 (5.9%)	
Immune disease	15 (1.7%)	514 (1.6%)	0.8604	65 (1.8%)	0.7779
Abnormal liver function	92 (10.4%)	3,311 (10.4%)	0.9731	345 (9.7%)	0.5623
Malignancy	77 (8.7%)	2,264 (7.1%)	0.0746	301 (8.5%)	0.8507
History of disease					
Old myocardial infarction	102 (11.5%)	2,693 (8.5%)	0.0014	423 (11.9%)	0.7274
Medications					
ACEi/ARB	341 (38.5%)	12,803 (40.3%)	0.2812	1,319 (37.2%)	0.4849
Calcium channel blockers	248 (28%)	9,461 (29.8%)	0.2528	1,039 (29.3%)	0.4367
β-blockers	249 (28.1%)	8,483 (26.7%)	0.3496	932 (26.3%)	0.2769
Dipeptidyl peptidase 4 inhibitors	24 (2.7%)	770 (2.4%)	0.5858	106 (3.0%)	0.6562
Statins	96 (10.8%)	3,772 (11.9%)	0.3473	460 (13.0%)	0.0848
Biguanides	103 (11.6%)	3,423 (10.8%)	0.4191	422 (11.9%)	0.8162
Sulfonylurea	113 (12.8%)	3,950 (12.4%)	0.7729	532 (15.0%)	0.0884
Thiazolidinedione	11 (1.2%)	495 (1.6%)	0.4524	71 (2.0%)	0.1324
Insulin	72 (8.1%)	1,841 (5.8%)	0.0035	234 (6.6%)	0.1097
Antiplatelet	361 (40.7%)	15,086 (47.5%)	<0.0001	1,461 (41.2%)	0.7952

ACEi, angiotensin converting enzyme inhibitors; AF, atrial fibrillation; AFL, atrial flutter; ARB, angiotensin II receptor blockers.

of dementia was significantly higher in patients with AF than patients with AFL only in patients with CHA₂DS₂-VASc score ≤4; (5) among patients who received oral anticoagulants, the cumulative incidences of dementia were significantly higher in patients with AF than in patients with AFL before and after PSM.

Atrial fibrillation provides five-fold increase in the risk of stroke and AF is associated with more severe ischemic strokes than emboli from carotid disease (18, 22). It has been reported that AF is associated with cognitive dysfunction and dementia, and may increase the risk of developing dementia (4, 23–26). Several pathophysiologic mechanisms have been proposed to

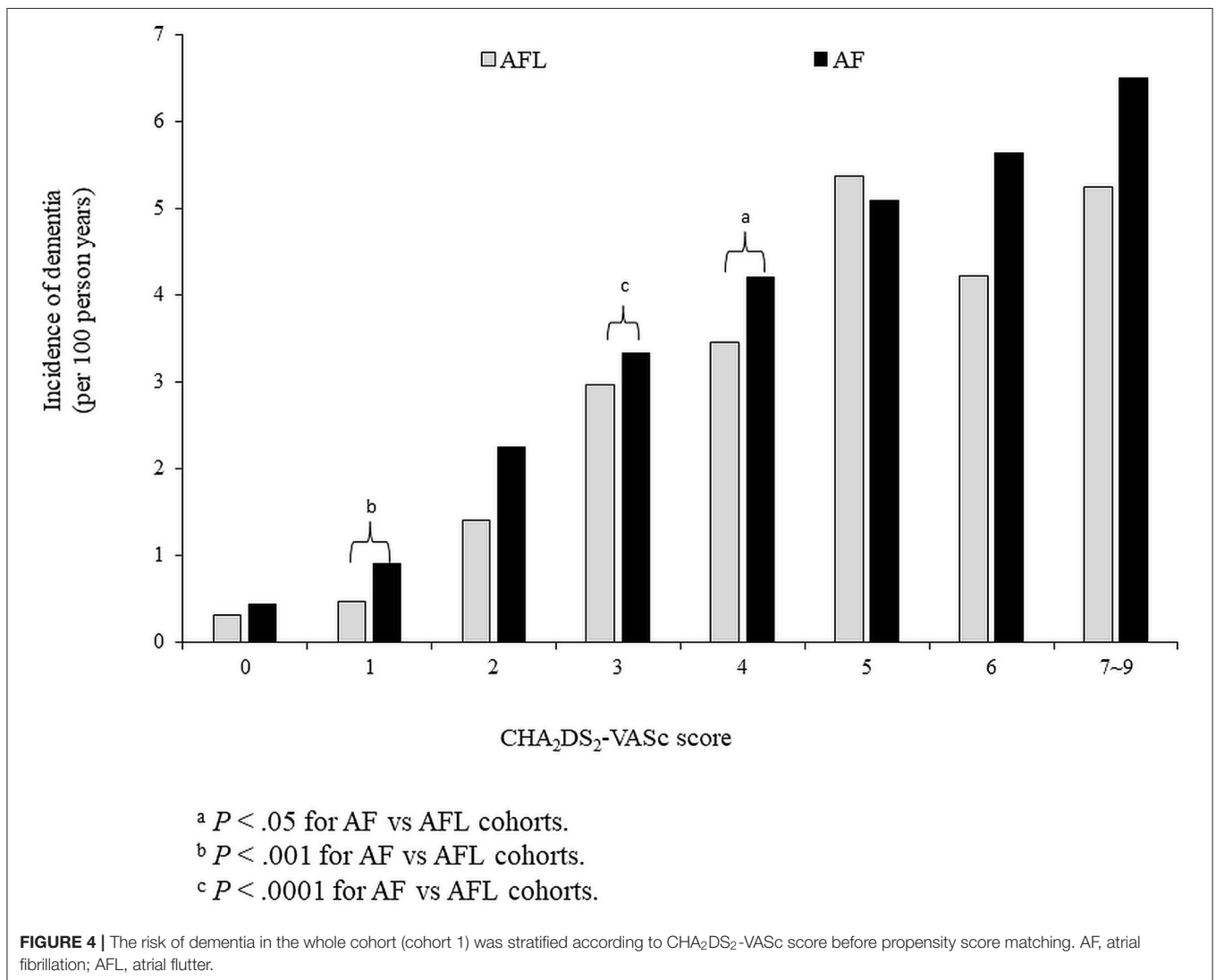
explain the complex association between AF and dementia, which include cerebral hypoperfusion, vascular inflammation, cerebral small vessel disease, microbleeds, brain atrophy, and AF-related ischemic stroke (3, 5, 23, 27, 28). AF and AFL share some common risk factors for cognitive dysfunction or dementia. When more cardiovascular disease risks coexist, the risk of dementia in patients with AF will increase significantly. CHA₂DS₂-VASc score has been reported to be useful for risk stratification regarding ischemic stroke and dementia among patients with AF and AFL (18–21, 29). Study conducted by Chou et al. reported that CHADS₂ score had a good prediction

TABLE 6 | Clinical outcomes between the patients with atrial fibrillation and atrial flutter before and after PSM (with history of stroke).

Variable	Before PSM			After PSM		
	AF (n = 31,779)	AFL (n = 886)	P-value	AF (n = 3,544)	AFL (n = 886)	P-value
Dementia						
Number of events, n (%)	4,140 (13.03)	90 (10.16)		427 (12.05)	90 (10.16)	
Incidence density§	5.33 (5.17–5.49)	4.31 (3.42–5.20)		4.97 (4.50–5.44)	4.31 (3.42–5.20)	
Hazard ratio (95% CI)	1.25 (1.02–1.54)	Reference	0.0351	1.16 (0.92–1.45)	Reference	0.2058
Ischemic stroke						
Number of events, n (%)	3,356 (10.56)	65 (7.34)		368 (10.38)	65 (7.34)	
Incidence density§	4.59 (4.43–4.74)	3.27 (2.48–4.07)		4.60 (4.13–5.07)	3.27 (2.48–4.07)	
Hazard ratio (95% CI)	1.39 (1.09–1.78)	Reference	0.0083	1.40 (1.08–1.83)	Reference	0.0118

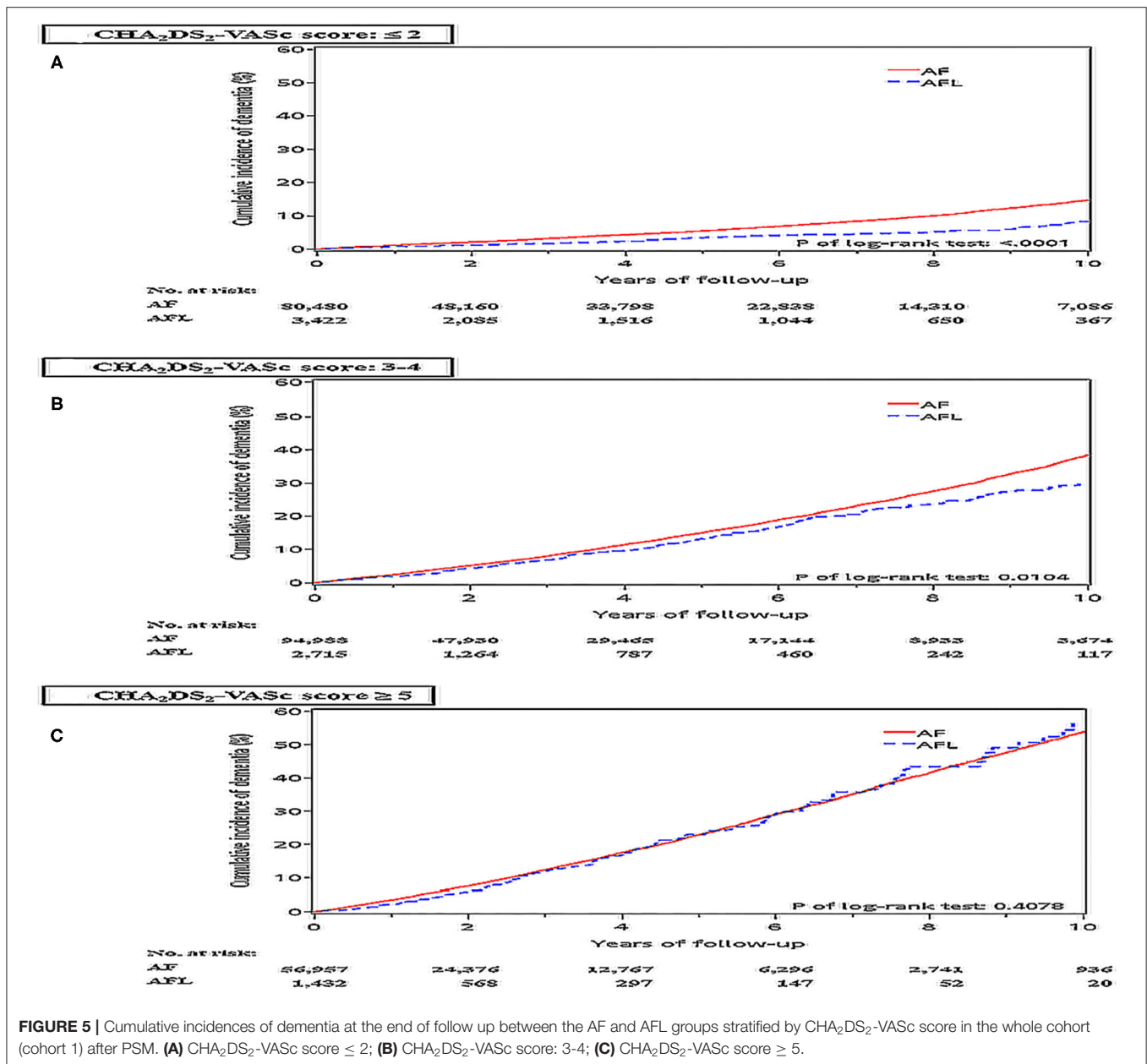
AF, atrial fibrillation; AFL, atrial flutter; PSM, propensity score matching.

§ Incidence density: number of events per 100 person-years.



of vascular dementia in patients with AF and AFL (3). The higher the score, the higher the number of patients suffering from dementia. CHA₂DS₂-VASc score is composed of chronic

diseases and also a history of stroke. Therefore, not only AF or AFL alone might contribute to the development of dementia, but all the comorbidities do. In this study, we also showed that



the risk of dementia is higher in both AF and AFL cohort with higher CHA₂DS₂-VASc scores. Based on our and other studies, the CHA₂DS₂-VASc score might be a useful risk scoring system for predicting future risk of development of vascular dementia and for risk stratification in patients with AF and AFL at risk of developing dementia (18). In this study, patients with AF were older than patients with AFL and had more comorbidities, including prior stroke, hypertension, ischemic heart disease, heart failure, and a higher average CHA₂DS₂-VASc score. All of these differences may contribute to a higher incidence of dementia in patients with AF than in patients with AFL before adjusting the comorbidities in this study. However, the incidence of dementia is still higher in patients with AF than in patients

with AFL even after adjusting the comorbidities and medications by PSM, especially in those patients without previous history of stroke. Therefore, differential risk of dementia existed between AF and AFL patients without previous history of stroke.

Although AF and AFL share some common risk factors and can both be risk stratified by CHA₂DS₂-VASc score, the pathophysiological mechanisms of AF and AFL are different. The initiation and maintenance of AF usually involved the pulmonary veins and depended on multiple chaotic rotors in the arrhythmogenic substrate in the left or right atrium for maintenance. In contrast, the maintenance of AFL depended on a single reentry circuit, such as single reentry circuit in the right atrium of a typical AFL. Our previous study showed that the

TABLE 7 | Clinical outcomes between the patients with atrial fibrillation and atrial flutter who received oral anticoagulants before and after PSM.

Variable	Before PSM			After PSM		
	AF (n = 29,187)	AFL (n = 451)	P-value	AF (n = 1,840)	AFL (n = 451)	P-value
Dementia						
Number of events, n (%)	2,830 (9.70)	22 (4.88)		144 (7.98)	22 (4.88)	
Incidence density§	2.81 (2.71–2.91)	1.39 (0.81–1.97)		2.20 (1.84–2.56)	1.39 (0.81–1.97)	
Hazard ratio (95% CI)	2.05 (1.35–3.11)	Reference	0.0008	1.57 (1.00–2.45)	Reference	0.0501
Ischemic stroke						
Number of events, n (%)	3,255 (11.15)	18 (3.99)		181 (10.03)	18 (3.99)	
Incidence density§	3.43 (3.31–3.54)	1.16 (0.62–1.70)		2.95 (2.52–3.38)	1.16 (0.62–1.70)	
Hazard ratio (95% CI)	2.95 (1.86–4.62)	Reference	<0.0001	2.54 (1.56–4.12)	Reference	0.0002

AF, atrial fibrillation; AFL, atrial flutter; PSM, propensity score matching.

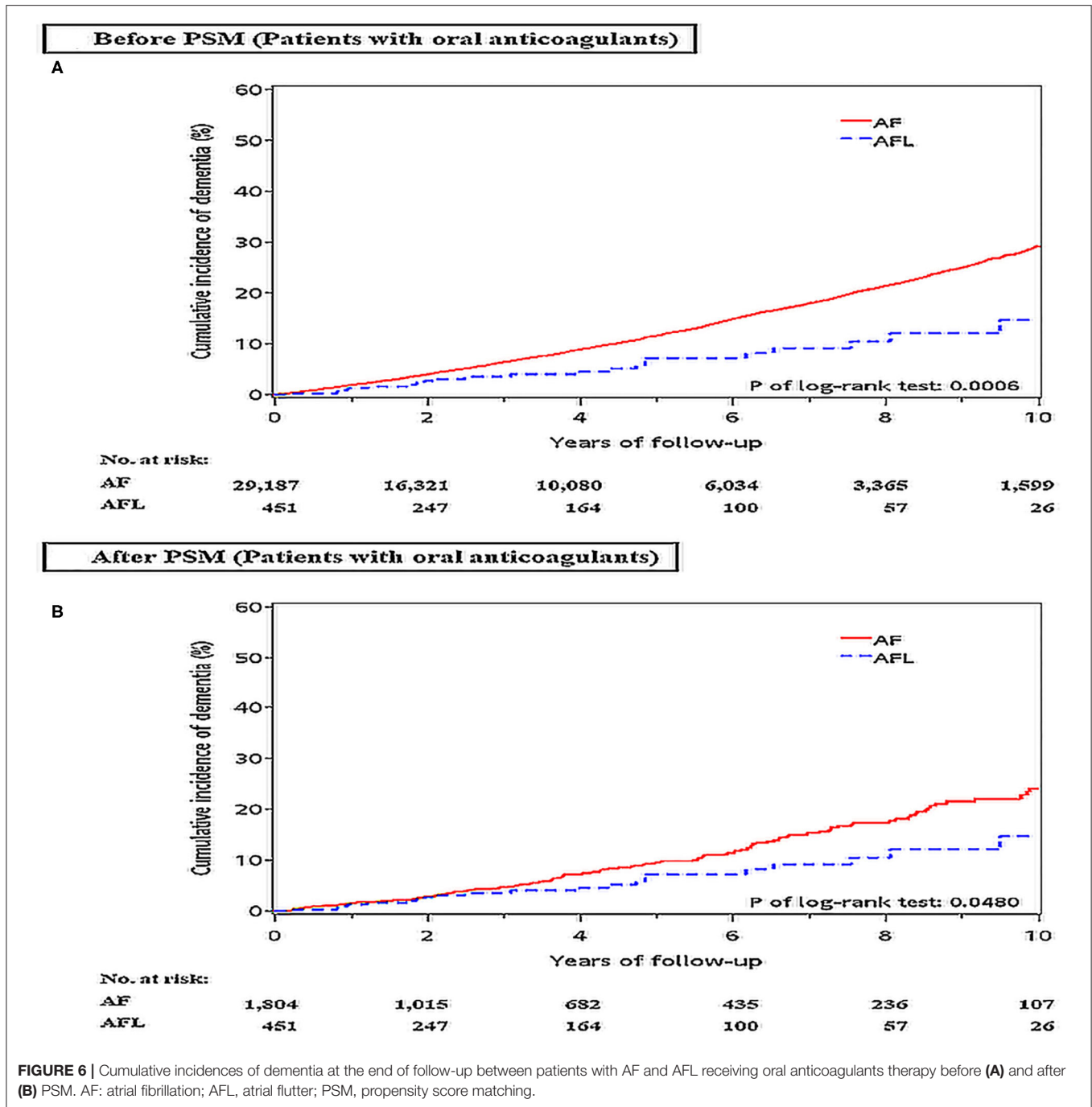
§ Incidence density: number of events per 100 person-years.

incidences of ischemic stroke, hospitalization for heart failure, and all-cause mortality are different between AF and AFL, which might be related to the different pathophysiological mechanisms between AF and AFL (8, 30). Although the risk of dementia is higher in patients with AF than in patients with AFL in this present study, further studies should be conducted to explore the pathophysiologic mechanisms of differential risk of dementia between patients with AF and AFL.

The previous studies showed that there were conflicting data regarding the therapeutic effect of oral anticoagulants on the risk of dementia in patients with AF (31). Although oral anticoagulants might decrease the risk of dementia by reducing the risk of silent infarct and microembolism, microhemorrhages, especially due to suprathreshold range of anticoagulation, may have implications for the mechanism of dementia (32, 33). In contrast, non-vitamin K oral anticoagulants may significantly reduce the occurrence of dementia (33–35). This may explain the discrepancy of oral anticoagulants on the risk of dementia in patients with AF. Our studies showed that among patients who received oral anticoagulants (mainly vitamin K oral anticoagulant), the cumulative incidence of dementia was significantly higher in patients with AF than in patients with AFL. Accordingly, the usage of oral anticoagulants may not affect the differential risk of dementia between patients with AF and AFL. Further prospective randomized studies are warranted to validate our findings and to investigate the effect of different oral anticoagulants on the risk of dementia in patients with AF and AFL.

Several limitations are associated with epidemiologic data from the NHIRD. First, using ICD-9-CM codes for patient selection may result in some missing cases due to incorrect coding. Some patients who had dementia with indistinct symptoms may be also missed due to the unavailability of clinical characteristics or image studies. Second, certain misclassification of disease leading to the miscalculation of the CHA₂DS₂-VASC score may have occurred due to the retrospective nature of the study. However, the highly diagnostic accuracy of comorbidities in CHA₂DS₂-VASC score has been validated in previous studies. Third, we could not categorize the mechanisms of AFL into

typical or atypical AFL and right or left AFL by ICD-9-CM codes. The clinical outcome may be different between patients with typical and atypical AFL and also between patients with left and right AFL. Further investigation should be conducted to clarify this issue. Fourth, AF was developed in around 30% AFL during follow-up according to previous studies (36). Although we have excluded those patients who have concomitant AF and AFL, there is still the possibility that some patients with AFL who developed AF during follow-up might not be diagnosed in the clinical follow-up. Despite this concern, we showed that the incidence density of dementia was significantly higher in patients with AF than in patients with AFL without previous history of stroke. Fifth, this study showed that among patients who received oral anticoagulants (mainly vitamin K oral anticoagulants), the cumulative incidence of dementia was significantly higher in patients with AF than in patients with AFL. However, this study did not analyze the effect of non-vitamin K oral anticoagulants on the risk of dementia in patients with AF and AFL. A previous study showed that non-vitamin K oral anticoagulants may lower the risk of dementia in patients with AF (33–35). Further prospective randomized studies are warranted to investigate the effect of different non-vitamin K oral anticoagulants on the risk of dementia in patients with AF and AFL. Sixth, although HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [age ≥65 years], drugs/alcohol concomitantly) and CHA₂DS₂-VASC score share many common risk factors, in a real-world population with AF, the CHA₂DS₂-VASC and HAS-BLED risk classifications are correlated but not exchangeable (37). Future research should be conducted to investigate the risk of dementia stratified according to HAS-BLED score alone or combined CHA₂DS₂-VASC score and HAS-BLED score between patients with AF and AFL. Seventh, although this study used PSM with all known variables to achieve a good balance between patients with AF and AFL, unavailable confounding risk factors might be still present. Finally, this study did not subclassify all subtypes of dementia. There might be a difference in the risk of developing different subtypes of dementia between



AF and AFL. Further studies could be conducted to clarify this issue.

CONCLUSIONS

This large nationwide cohort study showed that among patients without oral anticoagulants, the risk of dementia was higher in patients with AF than in patients with AFL. Among patients without oral anticoagulants, the risk of dementia was higher in patients with AF than in patients with AFL

with CHA₂DS₂-VASc score ≤4. Among patients without oral anticoagulants, the risk of dementia was higher in patients with AF than in patients with AFL among patients without previous history of stroke before and after PSM but the risk did not differ between patients with AF and AFL among patients with a previous history of stroke after PSM. Among patients who received oral anticoagulants, the cumulative incidences of dementia were significantly higher in patients with AF than in patients with AFL before and after PSM. Our study implicated that CHA₂DS₂-VASc score might be useful

for risk stratification of dementia between patients with AF and AFL.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Chang Gung Memorial Hospital. Written informed consent for participation

was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

C-MC and M-CC led in the conception and design of the study, revised the draft of the manuscript, and supervised and validated the clinical work and results. H-TW, Y-LC, and Y-SL collected research data, prepared the draft of the manuscript, performed the statistical analysis, and drafted the manuscript. H-CC, S-ZC, and SH organized the collected data. All authors have read and agreed to the published version of the manuscript.

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