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ORIGINAL RESEARCH

Oral Anticoagulant Treatment and the Risk of Dementia in Patients With Atrial Fibrillation: A Population-Based Cohort Study

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BACKGROUND: We compared the dementia incidence rate between users and nonusers of oral anticoagulants (OACs) in a large cohort of primary care patients with atrial fibrillation.

METHODS AND RESULTS: We performed a retrospective study using an Australia-wide primary care data set, MedicineInsight. Patients aged ≥18 years and newly diagnosed with atrial fibrillation between January 1, 2010, and December 31, 2017, and with no recorded history of dementia or stroke were included and followed until December 31, 2018. We applied a propensity score for 1:1 pair matching of baseline covariates and Cox regression for comparing the dementia incidence rates for OAC users and nonusers. Data were analyzed for 18 813 patients with atrial fibrillation (aged 71.9±12.6 years, 47.1% women); 11 419 had a recorded OAC prescription for at least 80% of their follow-up time. During the mean follow-up time of 3.7±2.0 years, 425 patients (2.3%; 95% CI, 2.1%–2.5%) had a documented diagnosis of dementia. After propensity matching, the incidence of dementia was significantly lower in OAC users (hazard ratio [HR], 0.59; 95% CI, 0.44–0.80; P<0.001) compared with nonusers. Direct-acting oral anticoagulant users had a lower incidence of dementia than non-OAC users (HR, 0.49; 95% CI, 0.33–0.73; P<0.001) or warfarin users (HR, 0.46; 95% CI, 0.28–0.74; P=0.002). No significant difference was seen between warfarin users and non-OAC users (HR, 1.08; 95% CI, 0.70–1.70; P=0.723).

CONCLUSIONS: In patients with atrial fibrillation, direct-acting oral anticoagulant use may result in a lower incidence of dementia compared with treatment with either warfarin or no anticoagulant.

Key Words: atrial fibrillation ■ dementia ■ direct-acting oral anticoagulants ■ oral anticoagulants ■ warfarin

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a 5-fold increase in stroke risk,[1] which is a common subsequent cause of dementia.[2] However, there is growing evidence to suggest an association between AF and dementia, even in patients with no previous history of ischemic stroke.[3] Dementia with AF is not limited to vascular dementia; other types of dementia, such as Alzheimer's, are also relatively common in patients with AF.[4] This is partly because AF and dementia have common risk factors, such as advancing age, congestive heart failure, hypertension, diabetes, and vascular diseases.[5,6] AF-related microbleeds and microemboli long term can also lead to dementia.[7]

Previous studies[8–13] that evaluated the incidence of dementia in patients with AF with and without oral anticoagulant (OAC) use had several limitations, and their findings are conflicting. For instance, none of the 5 studies

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CLINICAL PERSPECTIVE

What Is New?

- Based on a large Australian national primary care data set of patients with atrial fibrillation, the use of a direct-acting oral anticoagulant was associated with a significantly lower incidence of dementia compared with either use of warfarin or nonuse of an oral anticoagulant.
- The risk of dementia in patients with atrial fibrillation was halved in those taking a direct-acting oral anticoagulant compared with those on warfarin.

What Are the Clinical Implications?

- Use of direct-acting oral anticoagulants instead of warfarin in patients with atrial fibrillation may provide additional benefits by lowering the risk of dementia.

Nonstandard Abbreviations and Acronyms

DOAC	direct-acting oral anticoagulant
OAC	oral anticoagulant

included in a recent systematic review and meta-analysis that evaluated the incidence of dementia in patients with AF receiving OACs excluded patients with an early diagnosis of dementia (within a year) after OAC initiation.[8] Previous studies[9,10] also included patients with a history of stroke/transient ischemic attack who may have had an underlying increased risk of dementia.

Evidence concerning the association between the type of OAC (warfarin versus direct-acting oral anticoagulant [DOAC]) and the risk of developing dementia is also conflicting. A recent US study in 468 445 patients treated with OACs using 2 databases found that patients receiving DOACs experienced lower rates of dementia than warfarin users.[11] However, studies from Europe did not find a significant difference between warfarin and DOAC users in the risk of developing dementia.[12,13]

Given the conflicting evidence obtained from previous studies with several limitations, we aimed to compare the incidence of dementia in primary care patients with AF and no previous recorded stroke history based on the use and type of OAC.

METHODS

The authors license for using these data does not allow sharing raw data with third parties. However, other researchers are able to access these data in the same manner as the authors. Data access inquiries can be directed to NPS MedicineWise (https://medicineinsight@nps.org.au).

This study was an analysis of general practice data obtained from the NPS MedicineWise's data set, MedicineInsight. MedicineInsight extracts and collates deidentified patient health records from the electronic health records of consented Australian general practices. The information collected consists of patient demographics, encounters, diagnoses, prescriptions, observations, and pathology tests. The unstructured data in the electronic health records, "progress notes," were not extracted as these data may contain identifiable patient information. The data of 436 general practices across Australia that met the standard data quality criteria (described elsewhere[14]) were included. The data set represents the Australian population in terms of age and sex compared with national Medicare Benefits Schedule data.[14] Age was calculated at the date of AF diagnosis based on the patient's date of birth (defined as July 1 in the patient's year of birth). Further details about the MedicineInsight data set are available elsewhere.[15–19]

Patients were included in the study if they were aged ≥18 years; had their first recorded AF diagnosis between January 1, 2010, and December 31, 2017; had at least 3 visits to their general practice in 2 years (within the year either side of their AF diagnosis); were not prescribed an OAC before AF diagnosis; and had at least 1 year of follow-up data. Patients were required to have at least 1 recorded general practice visit each year during the follow-up period. Patients were excluded if they had a recorded diagnosis of dementia, epilepsy, or schizophrenia; antidementia drug prescription; or stroke before the diagnosis of AF.

We followed patients from AF diagnosis to either the incidence of dementia, last patient visit, death, or the end of follow-up (December 31, 2018), whichever occurred first. We also excluded patients who developed dementia within a year as these patients were more likely to have represented prevalent cases because of the prodromal phase before dementia onset.[20] OAC users were defined as those who received OAC therapy for at least 80% of their follow-up duration, based on recorded prescriptions, regardless of the type of OAC. OAC users included patients who continued on a single OAC or switched between OACs. Patients who received an OAC for <80% of their follow-up period were excluded. DOAC users were defined as patients who were prescribed a DOAC exclusively, with the duration on a DOAC covering at least 80% of their follow-up time. Similarly, those prescribed only warfarin during follow-up and with their treatment duration covering at least 80% of their follow-up time were grouped as warfarin users. Patients switched from their index DOAC prescription to warfarin or vice versa were not

included in the DOAC or warfarin group for analyses but were in the OAC user group. Non-OAC users were defined as patients who did not have a recorded OAC prescription during follow-up.

We identified baseline comorbidities, such as heart failure, hypertension, diabetes, vascular disease, and dementia based on condition flags provided by MedicineInsight.[21] Details of coded and noncoded terms used to identify conditions are shown in Table S1 and the MedicineInsight Data Dictionary.[21] Specific medicine active ingredients recorded in the data set for each class of baseline medications are shown in Table S1. All 3 DOACs available in Australia (dabigatran, rivaroxaban, apixaban) are listed on the Pharmaceutical Benefits Scheme and subsidized by the Australian government; the ability to pay for therapy does not distinguish DOAC users from warfarin users.

We calculated the stroke risk using the CHA_2DS_2-VA score and CHA_2DS_2-VASc at the time of AF diagnosis.[22] The CHA_2DS_2-VA score was used in this analysis as it is currently recommended by the relevant Australian guideline.[22]

We performed 2 subanalyses and 3 sensitivity analyses. In the first subanalysis, we included people aged ≥65 years, whereas people with CHA_2DS_2-VA scores ≥2 were included in the second subanalysis. These analyses were performed to examine whether the effects of the OACs on the incidence of dementia

Table 1. Baseline Characteristics of OAC Users and Non-OAC Users Before and After Propensity Score Matching

Characteristics	Before matching			Propensity-score matched		
	OAC users (n=11 419)	Non-OAC users (n=7394)	Standardized differences*	OAC users (n=4191)	Non-OAC users (n=4191)	Standardized differences*
Female sex	5242 (45.9)	3609 (48.8)	0.06	2017 (48.1)	2017 (48.1)	<0.01
Age, y	73.9±9.8	69.0±15.6	0.38	73.0±10.4	73.2±13.1	0.02
CHA_2DS_2-VA score	2.6±1.3	1.9±1.5	0.47	2.4±1.3	2.4±1.4	<0.01
CHA_2DS_2-VASc score†	3.0±1.4	2.4±1.6		2.9±1.4	2.9±1.5	
Duration of follow-up, y	3.8±2.1	3.6±2.0	0.12	3.6±2.0	3.6±2.0	0.01
Congestive heart failure	1531 (13.4)	628 (8.5)	0.16	465 (11.1)	460 (11.0)	<0.01
Hypertension	7047 (62.3)	3409 (46.5)	0.32	2451 (58.5)	2424 (57.8)	0.01
Diabetes	2377 (20.9)	990 (13.4)	0.20	717 (17.0)	713 (17.0)	<0.01
Vascular disease	3117 (27.4)	1574 (21.3)	0.14	1114 (26.6)	1102 (26.3)	0.01
Venous thromboembolism	700 (6.1)	201 (2.7)	0.17	162 (3.9)	154 (3.7)	0.01
Anxiety	1963 (17.2)	1497 (20.1)	0.08	790 (18.9)	797 (19.0)	<0.01
Arthritis	7325 (64.2)	3860 (52.2)	0.25	2481 (59.2)	2523 (60.2)	0.02
Asthma	2284 (20.0)	1390 (18.8)	0.03	750 (17.9)	799 (19.1)	0.03
Depression	2729 (23.9)	1901 (25.7)	0.04	1083 (25.8)	1029 (24.6)	0.03
Cancer	4824 (42.3)	2818 (38.1)	0.08	1753 (41.8)	1754 (41.9)	
Coronary heart disease	3481 (30.5)	1675 (22.7)	0.18	1175 (28.0)	1188 (28.4)	<0.01
Chronic liver disease	78 (0.7)	96 (1.3)	0.06	34 (0.8)	42 (1.0)	0.02
Chronic obstructive pulmonary disease	2084 (18.3)	1111 (15.0)	0.09	710 (16.9)	739 (17.6)	0.02
Antiplatelets	4138 (36.2)	3129 (42.3)	0.12	1813 (43.3)	1873 (44.7)	0.03
NSAIDs	4747 (41.6)	3045 (41.2)	0.01	1732 (41.3)	1790 (42.7)	0.03
RAAS inhibitors	8996 (78.8)	3883 (52.5)	0.58	2893 (69.0)	2920 (69.7)	0.01
Nitrates	2359 (20.7)	1082 (14.6)	0.16	766 (18.3)	773 (18.4)	<0.01
Statins	7310 (64.0)	3069 (41.5)	0.46	2281 (54.4)	2277 (54.3)	<0.01
β-blockers	8737 (76.5)	3723 (50.4)	0.56	2688 (64.1)	2729 (65.1)	<0.02
Digoxin	3506 (30.7)	1047 (14.2)	0.41	845 (20.2)	819 (19.5)	0.02
Antiarrhythmic drugs, class I or III‡	3692 (32.3)	1499 (20.3)	0.28	1051 (25.1)	1072 (25.6)	0.01

Data are provided as mean±SD or number (percentage). OAC indicates oral anticoagulant; and RAAS, renin-angiotensin-aldosterone system.

*Absolute standardized differences are reported.

†CHA_2DS_2-VASc was not included in the propensity score matching.

‡Only prescriptions for flecainide and disopyramide from class I antiarrhythmics and amiodarone and sotalol from class III antiarrhythmics were recorded in the MedicineInsight data set.

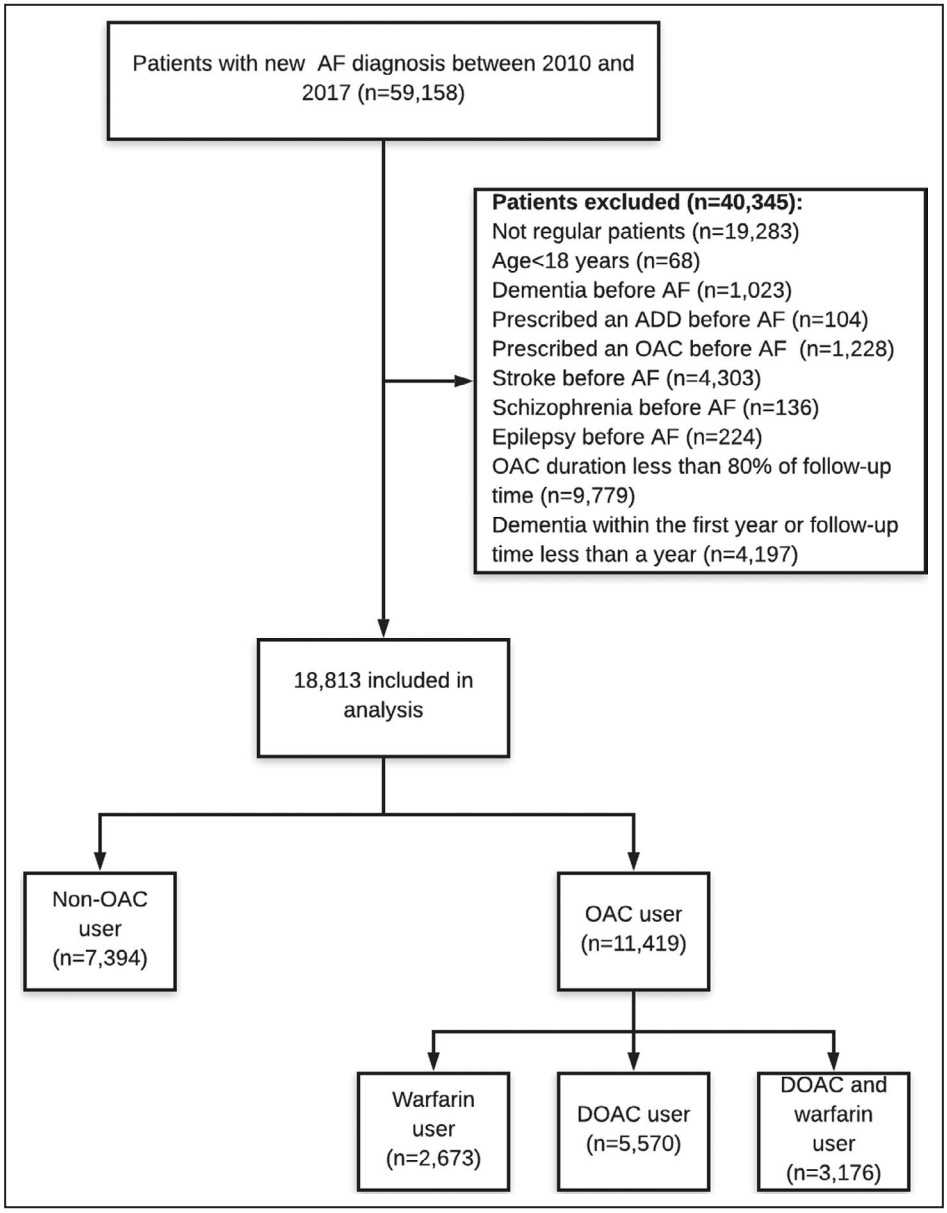

Figure. Selection of patients with AF.
ADD indicates antidementia drug; AF, atrial fibrillation; DOAC, direct-acting oral anticoagulant; and OAC, oral anticoagulant.

were any different in patients with a relatively high risk of dementia.

The first sensitivity analysis was performed without excluding patients who received an OAC for <80% of their follow-up period. The second sensitivity analysis was performed by including patients who had ≥3 recorded visits in 2 years before AF diagnosis (in 2 years within the year either side of their AF diagnosis for primary analysis) and a minimum of 6 months of follow-up. Patients who developed dementia within the first year of follow-up were not excluded in the second sensitivity analysis. Also, 4 additional baseline characteristics (in addition to the covariates listed in Table 1) were included in the propensity score matching of the cohorts for this sensitivity analysis. These were socioeconomic indexes for areas, rurality, selective serotonin/norepinephrine reuptake inhibitor use, and stroke during follow-up. The Australian Bureau of Statistics' socioeconomic indexes for areas quintile index ranks areas in Australia from 1 (most disadvantaged) to 5 (most advantaged),[23] whereas the Accessibility/Remoteness Index of Australia score[24] classifies areas into 5 categories of rurality: major cities, inner regional, outer regional, remote, and very remote.

Propensity score matching was used to address potential bias associated with the retrospective nature

of this study. It allowed us to construct 4 cohorts of patients who differed for treatment with anticoagulants but were similar for the remaining measured baseline characteristics. These cohorts were OAC users versus non-OAC users, DOAC users versus non-OAC users, warfarin users versus non-OAC users, and DOAC users versus warfarin users. The propensity scores were estimated and used for 1:1 pair matching in descending order without replacement for each of the 4 cohorts. A caliper width of 0.001 on the logit of propensity score was used for matching.[13,25] An absolute standardized difference of ≥0.10 was considered as a significant imbalance between the groups. The covariates and their standardized differences before and after matching for OAC users versus non-OAC users are shown in Table 1, DOAC users versus non-OAC users in Table S2, and DOAC users versus warfarin users in Table S3. The covariates for the remaining cohort (warfarin users versus non-OAC users) were the same as the previous 3, and we did not report standardized differences for this cohort.

The quality of 1-to-1 pair matching decreases as the sample size becomes smaller with subgroups.[26] We subclassified OAC users as warfarin users or DOAC users and performed separate matching for each with non-OAC users in our primary analysis. These subclassifications might have limited the efficiency and quality of the matchings. A third sensitivity analysis was therefore performed using the cohort constructed by matching OAC users and non-OAC users for comparing the risk of dementia in DOAC and warfarin users with non-OAC users.

Statistical Analysis

Descriptive statistics were used to compare baseline characteristics of unmatched and matched groups. Crude incidence rates were expressed as rates per 1000 person-years. Cox proportional hazards regression models stratified on the matched pairs were used to compare dementia outcomes. Robust standard errors were estimated for each Cox proportional hazards model. Data management and analysis were performed using SAS software (SAS version 9.4, SAS Institute Inc., Cary, NC).

Approvals were obtained from the University of Tasmania's Human Research Ethics Committee (H0017648) and the MedicineInsight independent Data Governance Committee (2018-033).

Reporting of the study conforms to broad Enhancing the QUAlity and Transparency Of health Research guidelines.[27]

RESULTS

A total of 18 813 eligible patients with newly diagnosed AF (47.1% [8851/18 813] women) were included in this study (Figure). The mean age was 71.9±12.6 years, and the follow-up duration was 3.7±2.0 years. More than half of these patients (60.7%, 11 419/18 813) had received OAC therapy for at least 80% of their follow-up time (Table 1). Of these, 5570 took a DOAC, whereas 2673 received warfarin (Table 2). The remaining 3176 patients had received either a DOAC or warfarin at different times during the follow-up. Patients with a recorded OAC prescription were more likely to have hypertension (62.3% versus 46.5%; $P<0.001$) and diabetes (20.9% versus 13.4%; $P<0.001$) than those without a recorded OAC prescription (Table 1). They also had a higher mean CHA_2DS_2-VA score (2.6±1.3 versus 1.9±1.5; $P<0.001$). The mean number of general practice visits after inclusion was 58±52.

The total sum of years each person observed during follow-up, 425 (2.3%) patients developed dementia, resulting in a crude incidence rate of 6.1 per 1000 person-years (95% CI, 5.5–6.7). The incidence rate of dementia in OAC users was 6.5 per 1000 person-years (95% CI, 5.6–7.5), whereas a rate of 5.8 per 1000 person-years (95% CI, 5.1–6.6) was seen for nonusers (Table 2). The mean follow-up times for patients with and without OAC use were 3.8±2.1 years and 3.6±2.0 years, respectively.

A total of 2 equal-size groups of OAC users and nonusers (n=4191) were produced using propensity

Table 2. Dementia Incidence Rates With 95% CIs Across Unmatched Patient Groups

Group	Total, n (%)	No. of events (dementia diagnosis)	Person-y at risk	Follow-up time, y, mean±SD	Incidence rates per 1000 person-y (95% CI)
Total	18 813	425	69 882	3.7±2.0	6.1 (5.5–6.7)
Non-OAC	7394 (39.3)	254	43 525	3.6±2.0	5.8 (5.1–6.6)
OAC	11 419 (60.7)	171	26 356	3.8±2.1	6.5 (5.6–7.5)
Exclusive DOAC user	5570 (29.6)	73	15 952	2.9±1.3	4.6 (3.6–5.7)
Exclusive warfarin user	2673 (14.2)	92	14 420	4.3±2.2	6.4 (5.1–7.8)
DOAC and warfarin user	3176 (16.9)	89	16 152	5.1±2.1	5.5 (4.4–6.8)

DOAC indicates direct-acting oral anticoagulant; and OAC, oral anticoagulant.

score matching. They were similar on all tested covariates (Table 1). The incidence of dementia was significantly lower in OAC users (hazard ratio [HR], 0.59; 95% CI, 0.44–0.80; *P*<0.001) compared with nonusers (Table 3). Another propensity score–matching procedure was used to generate 2 equal-size samples (n=2850) of exclusively DOAC users and non-OAC users (Table S2). Exclusive DOAC use was significantly associated with a lower risk of dementia (HR, 0.49; 95% CI, 0.33–0.73; *P*<0.001) compared with non-OAC use (Table 3). Comparing propensity score–matched exclusive warfarin users (n=1377) with non-OAC users (n=1377) did not show a significant reduction in dementia risk (HR, 1.08; 95% CI, 0.70–1.70; *P*=0.723). Compared with exclusive warfarin users (n=1335), exclusive DOAC users (n=1335) (propensity score matching reported in Table S3) had a lower risk of dementia (HR, 0.46; 95% CI, 0.28–0.74; *P*=0.002; Table 3). This apparent protective effect of DOAC use was maintained after additional adjustment for baseline estimated glomerular filtration rate (n=871 each group; HR, 0.22; 95% CI, 0.11–0.47; *P*<0.001).

In our subanalyses, except for the OAC users versus non-OAC users, HRs for dementia diagnosis between propensity-matched groups in people aged ≥65 years (Table 4) and CHA_2DS_2-VA scores ≥2 (Table 5) were similar to HRs reported in Table 3. The incidence of dementia became nonsignificant for OAC users compared with non-OAC users in both subanalyses.

The results of the 3 sensitivity analyses are shown in Tables S4 through S6. The HRs of comparing groups (OAC users versus non-OAC users, DOAC users versus non-OAC users, warfarin users versus non-OAC users, and DOAC users versus warfarin users) for the first and second sensitivity analyses were similar to the primary analysis shown in Table 3. The results of the third sensitivity (OAC users versus non-OAC users, DOAC users versus non-OAC users, and warfarin users versus non-OAC users) were similar to the primary analysis.

DISCUSSION

In this nationwide retrospective follow-up study, we demonstrated that patients with no record of a prior stroke before AF diagnosis and receiving DOACs had a 50% lower risk of dementia than those receiving warfarin. We also found that OAC users (DOAC or warfarin users) had a 40% lower risk of new-onset dementia compared with nonusers. However, the latter finding became nonsignificant in 2 separate sensitivity subanalyses (aged ≥65 years and CHA_2DS_2-VA scores ≥2). The inclusion of more warfarin users likely drove this nonsignificance; warfarin use alone did not decrease the incidence of new-onset dementia in this study.

Table 3. HRs for Dementia Diagnosis With 95% CIs for Propensity Score–Matched Groups

Characteristics	OAC users	Non-OAC users	DOAC users	Non-OAC users	Warfarin users	Non-OAC users	DOAC users	Warfarin users
Total	4191	4191	2850	2850	1377	1377	1335	1335
Follow-up, y, mean±SD	3.6±2.0	3.7±2.0	3.0±1.4	3.0±1.7	3.9±2.1	3.9±2.1	3.2±1.4	3.2±1.7
Person-y at risk	15 209	15 242	8663	8637	5404	5423	4408	4288
Dementia diagnosis	67	114	36	74	43	40	24	51
Incidence rate per 1000 person-y (95% CI)	4.4 (3.4–5.6)	7.5 (6.2–9.0)	4.2 (2.9–5.7)	8.6 (6.7–10.7)	8.0 (5.8–10.7)	7.4 (5.3–10.0)	5.4 (3.5–8.1)	11.9 (8.9–15.6)
HRs (95% CI)	0.59 (0.44–0.80)	Reference	0.49 (0.33–0.73)	Reference	1.08 (0.70–1.66)	Reference	0.46 (0.28–0.74)	Reference

DOAC indicates direct-acting oral anticoagulant; HR, hazard ratio; and OAC, oral anticoagulant.

Table 4. HRs for Dementia Diagnosis With 95% CIs for Propensity Score–Matched Groups in People Aged ≥65 Years

Characteristics	OAC users	Non-OAC users	DOAC users	Non-OAC users	Warfarin users	Non-OAC users	DOAC users	Warfarin users
Total	2972	2972	1966	1966	1004	1004	672	672
Follow-up, y, mean±SD	3.5±1.9	3.6±2.0	3.0±1.3	3.0±1.7	3.8±2.0	3.8±2.1	3.3±1.4	3.2±1.7
Person-y at risk	10 571	10 473	5840	5910	3813	3791	2222	2145
Dementia diagnosis	70	92	31	68	38	31	8	41
Incidence rate per 1000 person-y (95% CI)	6.6 (5.2–8.4)	8.8 (7.1–10.8)	5.3 (3.6–7.5)	11.5 (8.9–14.6)	10.0 (7.1–13.7)	8.2 (5.6–11.6)	3.6 (1.6–7.1)	19.1 (13.8–25.8)
HRs (95% CI)	0.77 (0.57–1.05)	Reference	0.45 (0.29–0.68)	Reference	1.22 (0.76–1.96)	Reference	0.19 (0.09–0.40)	Reference

DOAC indicates direct-acting oral anticoagulant; HR, hazard ratio; and OAC, oral anticoagulant.

Our findings are in line with a previous study by Chen et al[11] that used 2 US databases and reported that DOACs significantly lowered the incidence of dementia compared with warfarin (meta-analyzed HRs from the 2 databases were dabigatran, 0.85 [95% CI, 0.71–1.01]; rivaroxaban, 0.85 [95% CI, 0.76–0.94]; and apixaban, 0.80 [95% CI, 0.65–0.97]). The mean follow-up of the cohorts from the 2 US databases ranged between 0.7 and 2.2 years.

A Danish study that followed patients for a mean of 3.4 years[12] found a nonsignificant lower incidence of dementia in patients aged 60 to 79 years initiated on DOAC therapy (weighted HR, 0.92; 95% CI, 0.48–1.72) compared with those taking warfarin. However, the incidence was significantly higher in patients on DOACs and aged ≥80 years (weighted HR, 1.31; 95% CI, 1.07–1.59).

A possible explanation for the higher risk of dementia in patients receiving warfarin may be difficulty in managing the time in therapeutic range for the international normalized ratio. Time outside the therapeutic range in these patients can lead to microemboli and microbleeds, which could cause chronic cerebral injury and finally lead to dementia.[28] However, according to a recent meta-analysis by Lee et al,[29] even patients who achieve a high time in therapeutic range (>66%) while taking warfarin are at increased risk of intracranial bleeding when compared with patients receiving a DOAC. This finding, combined with our results, suggests that the use of DOACs may be a promising approach to reduce the risk of dementia in patients with AF.[30] In contrast to the findings of Lee et al,[29] a systematic review and meta-analysis by Mongkhon et al[8] found that a higher time in therapeutic range was associated with a decrease in the incidence of dementia. Unfortunately, the international normalized ratio was not routinely recorded for all patients taking warfarin in our data set. We were therefore unable to determine the risk of dementia based on international normalized ratio control in these patients.

Compared with warfarin, the dementia protective effect of DOAC therapy should be interpreted with caution given this study's relatively short mean follow-up (3.7 years). The US study that followed patients for a shorter time (mean follow-up of individual DOAC cohorts ranged between 0.7 and 2.2 years) did find a significant reduction in the incidence of dementia in DOAC users compared with warfarin users.[11] However, the Denmark[12] and UK[9] studies that followed patients for more extended periods, 3.4 years and 5.9 years, respectively, did not find such significant differences. These 2 studies, however, had other limitations. For instance, the Denmark study[12] excluded only patients who developed dementia within the first 6 months of follow-up. On the other hand, the UK study[9] included patients with a stroke history at baseline.

Table 5. HRs for Dementia Diagnosis With 95% CIs for Propensity Score–Matched Groups in People With CHA_2DS_2-VA Score ≥2

Characteristics	OAC users	Non-OAC users	DOAC users	Non-OAC users	Warfarin users	Non-OAC users	DOAC users	Warfarin users
Total	2696	2696	1838	1838	921	921	1051	1051
Follow-up, y, mean±SD	3.5±1.9	3.5±2.0	3.0±1.4	2.9±1.7	3.8±2.1	3.8±2.1	3.2±1.3	3.1±1.5
Person-y at risk	9409	9560	5514	5418	3507	3534	3344	3208
Dementia diagnosis	86	70	36	56	41	35	17	49
Incidence rate per 1000 person-y (95% CI)	9.1 (7.3–11.3)	7.3 (5.7–9.2)	6.5 (4.6–9.0)	10.3 (7.8–13.4)	11.7 (8.4–15.8)	9.9 (6.9–13.7)	5.1 (3.0–8.1)	15.3 (11.3–20.1)
HRs (95% CI)	0.80 (0.58–1.09)	Reference	0.61 (0.40–0.93)	Reference	1.19 (0.76–1.87)	Reference	0.42 (0.21–0.83)	Reference

DOAC indicates direct-acting oral anticoagulant; HR, hazard ratio; and OAC, oral anticoagulant.

Our study had several strengths. It was the first of its kind in Australia, and we used the largest nationally representative data set.[14] Unlike some previous studies,[8] we excluded patients diagnosed with dementia within the first year of follow-up, as these patients were more likely prevalent cases. In this study, patients had no recorded stroke history before diagnosing AF. However, the study also had several limitations. For instance, treatment groups were not prospectively randomized and thus were subject to potential confounding bias. However, we performed a propensity score matching to adjust for baseline patient characteristics differences that could influence OAC treatment decisions. We also performed subanalyses and sensitivity analyses; the results were similar to the principal analysis.

Confounding by indication is a potential problem in this study. The likelihood of being prescribed an OAC might be influenced by unmeasured baseline cognitive function, although a recent study in people with AF and aged ≥65 years did not find a significant association between OAC prescribing and cognitive impairment (adjusted odds ratio, 0.75; 95% CI, 0.51–1.09).[31] In addition, our study cohorts (including OAC users versus non-OAC users) were adjusted for an extensive list of baseline characteristics using propensity score matching. This may lessen the concern of confounding by indication. As we excluded people with a recorded diagnosis of dementia at baseline, dementia was not included in the matchings. Warfarin was the preferred OAC in patients with valvular heart disease who have higher risks of stroke and cognitive decline.[32] Valvular heart disease was not flagged in the MedicineInsight data set and therefore could not be included in the propensity score matching; this might have introduced bias. However, the dementia-protective effect of DOACs compared with warfarin was maintained in our sensitivity analysis adjusted for follow-up stroke.

We did not include competing risks, such as death, in our survival analysis models. This might have led to an overestimation of dementia incidence. We performed matching for each pairwise comparison (OAC users versus non-OAC users, DOAC users versus non-OAC users, and warfarin users versus non-OAC users) instead of using the same cohort constructed by matching OAC users and non-OAC users for all of these 3 comparisons. These might have limited the efficiency of the matchings and altered the generalizability of our findings to all patients with AF who would be eligible to receive any of the OACs. However, the results of the third sensitivity analysis (using 1 cohort constructed by matching OAC users versus non-OAC users for the 3 pairwise comparisons) were similar to the primary analysis.

Patients in the treatment group were required to have recorded OAC prescriptions that could cover treatment for at least 80% of their follow-up period.

However, we performed a sensitivity analysis to evaluate the potential bias associated with this exclusion criterion using cohorts constructed regardless of treatment duration. The findings were similar to the primary analysis, and any bias related to this exclusion was minimal. We assumed that patients who had recorded OAC prescriptions were taking their medication as directed during follow-up. We did not have data on actual adherence with therapy.

CONCLUSIONS

In patients with AF, DOAC use may result in a lower incidence of dementia compared with treatment using either warfarin or no anticoagulant.

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Supplemental Material

Tables S1–S6

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SUPPLEMENTAL MATERIAL

Table S1. Clinical definitions used to identify conditions in MedicineInsight patients with atrial fibrillation

Comorbid condition	Coded terms (from Docle or Pyefinch) used to identify the condition
Atrial fibrillation	AF; AF (Atrial Fibrillation); Arrhythmia, Atrial Fibrillation; Atrial Fibrillation; Atrial Fibrillation - Isolated Episode; Atrial Fibrillation - Paroxysmal; Atrial Fibrillation Ablation; Atrial Fibrillation, Non-Valvular; Atrial Fibrillation, Valvular; Fibrillation – Atrial; Fibrillation Atrium - Paroxysmal; Fibrillation, Atrial; Non-Valvular Atrial Fibrillation; Paroxysmal Atrial Fibrillation; Rapid AF; Rapid Atrial Fibrillation; Valvular Atrial Fibrillation
Dementia	Alzheimer's Disease; Binswanger Disease; Binswanger's Encephalopathy; Dementia; Dementia – Frontotemporal; Dementia - Lewy-Body; Dementia - Multi Infarct; Dementia – Pick; Dementia – Vascular; Dementia Related Psychosis; Dementia With Lewy Bodies; Dementia,Early Onset; Dementia, Frontotemporal; Dementia, Multi Infarct; Dementia, Pick's; Dementia, Semantic; Dementia, Substance Induced; Dementia, Vascular; Early Onset Dementia; Frontotemporal Dementia; Korsakoff's Dementia; Korsakoff's Psychosis; Korsakov's Psychosis; Lewy Body Dementia; Major Neurocognitive Disorder Due To Alzheimer's Disease; Multi Infarct Dementia; Neurocognitive Disorder, Major, Due To Alzheimer's Disease; Parkinson's Disease - Lewy Body Dementia; Pick's Disease; Psychosis - Korsakoff's; Psychosis, Dementia Related; Semantic Dementia; Senile Dementia With Psychosis; Subcortical Arteriosclerotic Encephalopathy; Subcortical Dementia; Substance Induced Dementia; Vascular Dementia; Young Onset Dementia
Congestive heart failure	Acute Cardiac Failure; Acute Heart Failure; Biventricular Heart Failure; Cardiac Failure; Cardiac Failure, Acute; CCF; Chronic Heart Failure; Congestive Cardiac Failure; Congestive Heart Failure; Cor Pulmonale; Diastolic Cardiac Dysfunction; Diastolic Heart Failure; Heart Failure; Heart Failure – Acute; Heart Failure – Biventricular; Heart Failure - Chronic ; Heart Failure - High Output; Heart Failure – Left; Heart Failure - Mid Range Ejection Fraction; Heart Failure - Preserved Ejection Fraction; Heart Failure - Reduced Ejection Fraction; Heart Failure – Right; Heart Failure, Acute; Heart Failure, High Output; Heart Failure, Left; HFMREF; HFPEF; HFREF; High Output Cardiac Failure; High Output Heart Failure; Hypertensive Heart Failure; Left Heart Failure; Left Ventricular Failure; LHF; LHF (Left Heart Failure); LVF; LVF (Left Ventricular Failure); Pulmonary Oedema; RHF; RHF (Right Heart Failure); Right Heart Failure; Right Ventricular Failure; RVF; RVF (Right Ventricular Failure); Systolic Cardiac Dysfunction; Systolic Heart Failure; Ventricular Diastolic Dysfunction
Hypertenstion	Hypertension – Controlled; Essential Hypertension; HBP; High Blood Pressure; HT (Hypertension); Hypertension; Primary Hypertension; Hypertension – Malignant; Malignant Hypertension; Severe Refractory Hypertension; Hypertension – Pregnancy; PIH; Pregnancy Induced Hypertension; Hypertension – Renovascular; Renal Hypertension; Renovascular Hypertension; Hypertension - Isolated Systolic; Blood Pressure Labile; BP Labile; BP Unstable; Hypertension – Labile; Hypertension – Unstable; Labile Blood Pressure; Labile BP; Labile Hypertension; Hypertension - Life Style Management; Antihypertensive Agent Prescription; Blood Pressure Review; Hypertension Review; Review – BP; Hypertension, Essential; Hypertension, Malignant; Hypertension In Pregnancy; Hypertension, Renovascular; Hypertension, Isolated Systolic; Isolated Systolic Hypertension; Diastolic Hypertension; Hypertension, Diastolic
Diabetes mellitus	Diabetes Mellitus – IDDM; Diabetes Mellitus - Type I; Diabetes Mellitus, IDDM; Diabetes Mellitus, Type 1; IDDM; IDDM (Insulin Dependent Diabetes Mellitus); Insulin Dependent Diabetes Mellitus; Juvenile Onset Diabetes; Juvenile Onset Diabetes Mellitus; Diabetes Mellitus – NIDDM; Diabetes Mellitus - Type II; Diabetes Mellitus, NIDDM; Diabetes Mellitus, Type 2; Diabetes Type II

	Requiring Insulin; NIDDM; NIDDM - Requiring Insulin; NIDDM (Non Insulin Dependent Diabetes Mellitus); Non Insulin Dependent Diabetes Mellitus; T2DM; Type 2 Diabetes Mellitus
Stroke	Cerebral Haemorrhage; Cerebral Infarction; Cerebrovascular Accident; CVA; CVA (Cerebrovascular Accident); Haemorrhage – Intracerebral; Haemorrhage, Intracerebral; Haemorrhagic CVA; Haemorrhagic Stroke; Intracerebral Bleed; Intracerebral Haemorrhage; Intracranial Haemorrhage; Ischaemic Stroke; Lacunar Infarct; Lacunar Stroke; Migrainous Stroke; Migranous Stroke; Stroke; Stroke – Haemorrhagic; Stroke – Ischaemic; Stroke – Lacunar; Stroke – Migranous; Stroke – Thrombotic; Stroke, Haemorrhagic; Stroke, Ischaemic; Stroke, Lacunar; Stroke, Migrainous; Stroke, Thrombotic; Thrombotic – Stroke; Thrombotic Stroke; Visual Cortex Stroke
Vascular disease	Arteriosclerosis Obliterans; Arteritis - Diabetes Mellitus; Buerger's Disease; Diabetes With Vascular Changes; Diabetic Endarteritis; Diabetic Peripheral Vascular Disease; Diabetic Vascular Disease – Peripheral; Obliterative Vascular Disease; Occlusive Vascular Disease; Occlusive Vascular Disease (Buerger's Disease); Peripheral Arterial Disease; Peripheral Arterial Occlusive Disease (Buerger's Disease); Peripheral Vascular Disease; Peripheral Vascular Disease, Diabetic; PVD; Thrombangiitis Obliterans; Thromboangiitis Obliterans
Venous thromboembolism	Deep Venous Thrombosis; DVT; Thrombosis - Deep Vein
Anxiety	Adjustment Disorder With Anxiety; Adjustment Disorder With Mixed Anxiety And Depressed Mood: Anxiety; Anxiety- Generalised; Anxiety – PTSD; Anxiety – Social; Anxiety Disorder; Anxiety Disorder, Substance Induced; Anxiety Neurosis; Anxiety Phobia; Anxiety With Panic Attacks; Anxiety/Depression; Depression/Anxiety; Depressive Anxiety Disorder; GAD; GAD (Generalised Anxiety Disorder); Generalised Anxiety Disorder; Generalised Anxiety Disorder (GAD); Mixed Anxiety Depression; Mixed Anxiety/Depressive Disorder; Mixed Depression Anxiety; Nervous Anxiety; Neurotic Anxiety; Phobic Anxiety Disorder; Social Anxiety Disorder; Social Phobia; Substance Induced Anxiety Disorder
Arthritis	Ac Joint Arthritis; Acromioclavicular Joint Arthritis; Aneurysm-Osteoarthritis Syndrome; Ankle Osteoarthritis; Ankylosing Spondylitis; Arthritis; Arthritis – Gouty; Arthritis – Juvenile Rheumatoid; Arthritis Lisfranc; Arthritis Lupus; Arthritis Osteo; Arthritis Psoriatic; Arthritis Rheumatoid; Arthritis – Septic; Arthritis – Seronegative; Arthritis – Viral; Arthritis Of Spine; Arthritis Of The Acromioclavicular Joint; Arthritis, Inflammatory; Arthritis, Juvenile Rheumatoid; Arthritis, Psoriatic; Arthritis, Rheumatoid; Arthritis, Septic; Arthritis, Seronegative; Arthritis, Viral; Caplan Syndrome; Cervical - Osteo Arthritis; Cervical Spine Osteoarthritis; Elbow Osteoarthritis; Facet Joint Arthritis; Generalised Osteoarthritis; Giant Cell Reticulohistiocytosis; Gout; Gouty Arthritis; Hallux Rigidus; Hip Osteoarthritis; Hip Osteoarthrosis; Hyperuricaemia; Hyperuricemia; Inflammatory Polyarthritis; Joint Infection; Jra; Jra (Juvenile Rheumatoid Arthritis); Juvenile Idiopathic Arthritis; Juvenile Rheumatoid Arthritis; Knee Osteoarthritis; Knee Osteoarthrosis; Lipoid Dermatoarthritis; Lipoid Rheumatism; Lisfranc Arthritis; Loeys-Dietz Syndrome Type 3; Lumbar - Osteo Arthritis; Lumbar Spine Osteoarthritis; Lupus Arthritis; Lyme Arthritis; Midfoot Osteoarthritis; Monoarthritis; Multicentric Reticulohistiocytosis; Oa; Oa (Osteoarthritis); Oligoarthritis, Inflammatory; Osteoarthritis; Osteoarthritis – Ankle; Osteoarthritis – Elbow; Osteoarthritis – Fingers; Osteoarthritis - Glenohumeral Joint; Osteoarthritis – Hands; Osteoarthritis – Hip; Osteoarthritis – Knee; Osteoarthritis – Neck; Osteoarthritis – Shoulder; Osteoarthritis – Spine; Osteoarthritis Of 1st Carpometacarpal Joint; Osteoarthritis Of 1st Carpo-Metacarpal Joint; Osteoarthritis Of 1st Metatarsophalangeal Joint; Osteoarthritis

	Of Ankle; Osteoarthritis Of Cervical Spine; Osteoarthritis Of Elbow; Osteoarthritis Of Fingers; Osteoarthritis Of Foot; Osteoarthritis Of Hand; Osteoarthritis Of Hip; Osteoarthritis Of Knee; Osteoarthritis Of Lumbar Spine; Osteoarthritis Of Neck; Osteoarthritis Of Sacroiliac Joints; Osteoarthritis Of Shoulder; Osteoarthritis Of The Patellofemoral Joint; Osteoarthritis Of Thoracic Spine; Osteoarthritis Of Tmj; Osteoarthritis Of Wrist; Osteoarthritis Generalised; Osteoarthrosis; Patellofemoral Osteoarthritis; Podagra; Polyarthritis; Polyarthritis, Inflammatory; Psoriatic Arthritis; Psoriatic Arthropathy; RA; RA (Rheumatoid Arthritis); Reactive Arthritis; Reiter's Disease; Reiter's Syndrome; Rheumatoid Arthriti; Rheumatoid Arthritis Juvenile; Rheumatoid Arthritis – Pneumoconiosis; Rheumatoid Arthritis, Juvenile; Sacroiliac Joint Arthritis; Septic Arthritis; Seronegative Arthritis; Seronegative Rheumatoid Arthritis; Shoulder Osteoarthritis; Spondyloarthritis; Spondylosis; Stills Disease; Thoracic - Osteo Arthritis; Urate Crystal Deposition; Venereal Arthritis; Viral Arthritis - Waelsch's Syndrome; Wear And Tear Arthritis; Wrist Osteoarthritis
Asthma	Acute Severe Asthma; Allergic Asthma; Allergy Induced Asthma; Aspirin Sensitive Asthma; Asthma; Asthma - Allergy Induced; Asthma - Chronic Persistent; Asthma - Exercise Induced; Asthma - Frequent Episodic; Asthma - Infective Exacerbation; Asthma - Infrequent Episodic; Asthma - Precipitated By Bacterial Infection; Asthma - Precipitated By Viral Infection; Asthma Action Plan; Asthma Action Plan Performed; Asthma Action Plan Printed; Asthma Care Plan; Asthma Care Plan Review; Asthma Cycle Of Care; Asthma Exacerbation; Asthma Review; Asthma, Allergic; Asthma, Allergy Induced; Asthma, Childhood; Asthma, Exercise Induced; Asthma, Frequent Episodic; Asthma, Infective Exacerbation; Asthma, Infrequent Episodic; Asthma, Occupational; Asthma, Thunderstorm; Bronchial Asthma; Care Plan, Asthma; Check Up, Asthma; Exercise Induced Asthma; Exertional Asthma; Frequent Episodic Asthma; Infective Exacerbation Of Asthma; Infrequent Episodic Asthma; Occupational Asthma; Review – Asthma; Samter's Triad; Status Asthmaticus;Thunderstorm Asthma; Wheezy Bronchitis
Depression	Adjustment Disorder (Chronic) With Depressed And Anxious Mood; Adjustment Disorder (Chronic) With Depressed Mood; Adjustment Disorder With Depressed And Anxious Mood; Adjustment Disorder With Mixed Anxiety And Depressed Mood; Anxiety/Depression; Chronic Adjustment Disorder With Depressed And Anxious Mood; Chronic Adjustment Disorder With Depressed Mood; Depression; Depression – Endogenous; Depression – Minor; Depression - Post Natal; Depression – Reactive; Depression – Recurrent; Depression – Subsyndromal; Depression With Melancholic Features; Depression, Endogenous; Depression, Melancholic; Depression, Non Melancholic; Depression, Organic; Depression, Postnatal; Depression, Psychotic; Depression, Reactive; Depression/Anxiety; Depressive Anxiety Disorder; Depressive Episode, Major; Endogenous Depression; Insomnia - Depression-Related; Involutional Melancholia; Major Depression; Major Depressive Episode; Melancholia; Melancholia – Involutional; Melancholic Depression; Mixed Anxiety Depression; Mixed Anxiety/Depressive Disorder; Mixed Depression Anxiety; Neurotic Depression; Non Melancholic Depression; Organic Depression; Post Natal Depression; Postnatal Depression; Psychotic Depression; Reactive Depression
Cancer	Acute Granulocytic Leukaemia; Acute Lymphoblastic Leukaemia; Acute Lymphocytic Leukaemia; Acute Myelocytic Leukaemia; Acute Myeloid Leukaemia; Adamantinoma; Adenocarcinoma - Ampulla Of Vater; Adenocarcinoma – Breast; Adenocarcinoma – Colon; Adenocarcinoma – Endometrium; Adenocarcinoma – Gallbladder; Adenocarcinoma – Lung; Adenocarcinoma – Pancreas; Adenocarcinoma – Prostate; Adenocarcinoma - Small Bowel; Adenocarcinoma – Stomach; Adenocarcinoma - Unknown

	Primary; Adenocarcinoma – Uterine; Adenocarcinoma Or Carcinoma-Nonspecific; Adenoid Cystic Carcinoma; Adrenal Carcinoma; ALL (Acute Lymphocytic Leukaemia); Ameloblastoma; AML (Acute Myelocytic Leukaemia); Ampullary Adenocarcinoma; Ampullary Carcinoma; Astrocytoma - Biliary Carcinoma; Bladder Cancer; Bowel Cancer; Brain Carcinoma; Breast Cancer; Breast Cancer – Male; Breast Carcinoma; Bronchogenic Carcinoma; Caecal Carcinoma; Cancer - Unknown Primary; Cancer Of Ovary; Cancer Of Pancreas; Carcinoma - Ampulla Of Vater; Carcinoma - Bile Duct; Carcinoma – Bladder; Carcinoma – Brain; Carcinoma – Breast; Carcinoma - Breast – Male; Carcinoma – Caecal; Carcinoma – Cervix; Carcinoma – Chorion; Carcinoma – Colon; Carcinoma – Gallbladder; Carcinoma – Hypothalamus; Carcinoma – Kidney; Carcinoma – Larynx; Carcinoma – Liver; Carcinoma - Liver – Fibrolamellar; Carcinoma – Lung; Carcinoma - Lung – Adenocarcinoma; Carcinoma - Lung - Alveolar Cell; Carcinoma - Lung - Large Cell; Carcinoma - Lung - Small Cell; Carcinoma - Lymph Vessel; Carcinoma – Mouth; Carcinoma – Nasopharynx; Carcinoma – Oesophagus; Carcinoma – Oropharynx; Carcinoma – Ovary; Carcinoma – Pancreas; Carcinoma – Parotid; Carcinoma - Parotid – Mixed; Carcinoma – Pituitary; Carcinoma – Prostate; Carcinoma - Rathke's Pouch; Carcinoma – Rectum; Carcinoma – Retina; Carcinoma - Salivary Gland; Carcinoma – Stomach; Carcinoma – Testis; Carcinoma – Thyroid; Carcinoma – Tongue; Carcinoma – Tonsil; Carcinoma – Uterus; Carcinoma – Vagina; Carcinoma – Vulva; Carcinoma Or Adenocarcinoma – Nonspecific; Cervical Cancer; Cervical Carcinoma; Cholangiocarcinoma; Choriocarcinoma; Chronic Lymphatic Leukaemia; Chronic Lymphocytic Leukaemia; Cll (Chronic Lymphocytic Leukaemia); Colon – Adenocarcinoma; Colonic Cancer; Colonic Carcinoma; Common Bile Duct Cancer; Craniopharyngioma; Endometrial Adenocarcinoma; Gallbladder – Cancer; Gallbladder – Carcinoma; Gastric Adenocarcinoma; Gastric Cancer - Gastric Carcinoma; Gestational Choriocarcinoma; Glioblastoma Multiforme – Glioma; Hepatocellular Carcinoma; Hepatoma; Hereditary Non-Polyposis Colon Cancer; Histiocytoma; HNPCC (Hereditary Non-Polyposis Colon Cancer); Hypernephroma; Hypothalamic Carcinoma; Kidney Cancer; Laryngeal Carcinoma; Leukaemia; Leukaemia - Acute Lymphocytic – Leukaemia; Acute Myeloid - Leukaemia - Chronic Lymphocytic; Linitus Plastica; Lobular Carcinoma In-Situ; Lung Adenocarcinoma; Lung Cancer; Lymphangitis Carcinomatosa; Lymphangitis Carcinomatosis; Malignant Glioma; Mammary Carcinoma In The Male; Medullary Thyroid Carcinoma; Mixed Parotid Tumor; Nasopharyngeal Carcinoma; Nasopharyngeal Lymphoepithelioma; Nephrectomy – Cancer; Nephrectomy – Tumor; Nodular Thyroid Carcinoma; Oesophageal Adenocarcinoma; Oesophageal Carcinoma; Oligodendroglioma; Oropharyngeal Carcinoma; Ovarian Adenocarcinoma; Ovarian Cancer; Ovarian Carcinoma; Pancreatic Adenocarcinoma; Pancreatic Cancer; Pancreatic Carcinoma; Papillary Thyroid Carcinoma; Parotid Adenocarcinoma; Parotid Adenolymphoma; Parotid Carcinoma; Peri-Ampullary Carcinoma; Phobia - Breast Cancer; Phobia – Cancer; Post Nasal Cancer; Primary Unknown Adinocarcinoma; Prostate Cancer; Prostatic Adenocarcinoma; Rectal Adenocarcinoma; Rectal Cancer; Rectal Carcinoma; Renal Carcinoma; Retinal Cancer; Small Bowel Adenocarcinoma; Spindle Cell Cancer; Stomach Cancer; Testicular Carcinoma; Thyroid Cancer; Thyroid Carcinoma; Tongue Carcinoma; Tonsillar Carcinoma; Tonsillar Lymphoma; Undifferentiated Thyroid Cancer; Undifferentiated Thyroid Carcinoma; Unknown Primary Adinocarcinoma; Urinary Bladder Carcinoma; Uterine Adenocarcinoma; Uterine Cancer; Vaginal Carcinoma; Vaginal Malignancy; Vesical Adenocarcinoma; Vulval Carcinoma
Coronary heart disease	AAA; AAA Rupture; Abdominal Aortic Aneurysm; Abdominal Aortic Aneurysm Rupture; Acs (Acute Coronary Syndrome); Acute Coronary Insufficiency; Acute

	Coronary Syndrome; Acute Myocardial Infarction; AMI; AMI (Acute Myocardial Infarction); Aneurysm Of Abdominal Aorta; Aneurysm Of Thoracic Aorta; Angina; Angina Pectoris; Angina Pectoris – Unstable; Angina, Stable; Angina, Unstable; Anterior Myocardial Infarct; Anterolateral Myocardial Infarct; Aortofemoral Bypass Occlusion; Aortoiliac Bypass Occlusion; Aortoiliac Stent Blockage; Aortoiliac Stent Occlusion ; Arterial Insufficiency; Arteriosclerotic Arterial Insufficiency; Atherosclerotic Heart Disease; Blockage Coronary Artery; Blocked Aortofemoral Bypass; Blocked Aortoiliac Bypass; Blocked Aortoiliac Stent; Blocked Coronary Artery Bypass Graft; Blocked Femoro-Popliteal Bypass; Blocked Popliteal Artery Stent; Chronic Stable Angina; Coronary Artery Bypass Graft Blockage; Coronary Artery Bypass Graft Occlusion; Coronary Artery Disease; Coronary Artery Stent Blocked; Coronary Heart Disease; Coronary Insufficiency; Coronary Occlusion; Femoro-Popliteal Bypass Blockage; Femoro-Popliteal Bypass Occlusion; Heart Attack; Heart Disease, Atherosclerotic; Heart Disease, Coronary; Heart Disease, Ischaemic; IHD; IHD (Ischaemic Heart Disease); Inferior Myocardial Infarction; Ischaemic Heart Disease; Ischaemic Vascular Disease; Mi; Myocardial Damage; Myocardial Infarction; Myocardial Infarction – Anterior; Myocardial Infarction – Anterolateral; Myocardial Infarction- Inferior; Myocardial Infarction – Posterior; Myocardial Infarction – Silent; Myocardial Infarction – Subendocardial; Myocardial Infarction – Superior; Myocardial Infarction - With St Elevation; Myocardial Infarction - Without St Elevation; Myocardial Infarction, Anterior; Myocardial Infarction, Anterolateral; Myocardial Infarction, Inferior; Myocardial Infarction, Non Stemi; Myocardial Infarction, Posterior; Myocardial Infarction, Stemi; Myocardial Infarction, Subendocardial; Myocardial Infarction, Superior; Myocardial Insufficiency - Non St Elevation; Myocardial Infarction - Non-St-Elevation; Myocardial Infarction (NSTEMI); NSTEMI; NSTEMI (Non-St-Elevation Myocardial Infarction); Obstructed Aortofemoral Bypass; Obstructed Aortoiliac Bypass; Obstructed Aortoiliac Stent; Obstructed Coronary Artery Bypass Graft; Obstructed Femoro-Popliteal Bypass; Obstructed Popliteal Artery Stent; Occluded Aortofemoral Bypass; Occluded Aortoiliac Bypass; Occluded Aortoiliac Stent; Occluded Popliteal Artery Stent; Occlusion - Coronary Artery; Occlusion Of Aortic Bifurcation Bypass Graft; Occlusion Of Femoropopliteal Bypass Graft – Occlusion; Coronary Artery - Popliteal Artery Stent Blockage; Popliteal Artery Stent Occlusion; Posterior Myocardial Infarct; Preinfarction Syndrome; Rupture Of Abdominal Aortic Aneurysm; Ruptured Aaa; Silent Myocardial Infarction; St Elevation Myocardial Infarction; Stable Angina; Stemi; Stemi (St-Elevation Myocardial Infarction); Subendocardial Infarct; Subendocardial Myocardial Infarct; Superior Myocardial Infarct; Thoracic Aortic Aneurysm; Unstable Angina; Unstable Angina - High Risk; Unstable Angina - Low Risk; Unstable Angina - Moderate Risk
Chronic liver disease	Cirrhosis; Cirrhosis - Alpha1 Antitrypsin Deficiency; Cirrhosis Of The Liver; Cirrhosis With Acute Renal Failure; Coma – Hepatic; Copper Storage Disease; Encephalopathy – Hepatic; Encephalopathy Liver Failure; Failure – Liver; Fibrosis Of Liver; Hepatic Cirrhosis; Hepatic Coma; Hepatic Failure; Hepatic Fibrosis; Hepatic Pre-Coma; Hepatolenticular Degeneration; Hepatorenal Syndrome; Liver Cirrhosis; Liver Failure; Liver Failure – Encephalopathy; Liver Fibrosis; Renal Failure Due To Cirrhosis; Wilson's Degeneration; Wilson's Disease; Wilson's Syndrome
Chronic obstructive pulmonary disease	Acute Exacerbation Of Copd; Bronchitis – Chronic; Bronchitis, Chronic; CAL (Chronic Airways Limitation); Chronic Airways Limitation; Chronic Bronchitis; Chronic Bronchitis - Infective Exacerbation; Chronic Bronchitis, Infective Exacerbation; Chronic Obstructive Airways Disease; Chronic Obstructive Pulmonary Disease; COAD; COAD - Infective Exacerbation; COAD (Chronic Obstructive Airways Disease); COAD, Infective Exacerbation; COPD; COPD -

	Infective Exacerbation; COPD (Chronic Obstructive Pulmonary Disease); COPD, Infective Exacerbation; Emphysema; Emphysema - Infective Exacerbation; Infective Exacerbation Of Chronic Bronchitis; Infective Exacerbation Of COAD; Infective Exacerbation Of COPD
Medications	Coded medicine active ingriedents names alone or incombination
Oral anticoagulants	Warfarin; Warfarin sodium; Apixaban; Dabigatran; Dabigatran etexilate; Rivaroxaban;
Antiplatelets	Clopidogrel; Clopidogrel hydrogen sulfate; Clopidogrel, Aspirin; Aspirin/clopidogrel; Ticlopidine; Ticlopidine hydrochloride; Prasugrel; Ticagrelor; dipyridamole; Dipyridamole, Aspirin; Aspirin/Dipyridamole; Abciximab; Aspirin; Aspirin, Glycine; Eptifibatide; tirofiban
NSAIDs	Celecoxib; Etoricoxib; Lumiracoxib; Parecoxib sodium; Rofecoxib; Diclofenac; Diclofenac diethylammonium; Diclofenac potassium; Diclofenac sodium, misoprostol; Diclofenac/misoprostol; Nepafenac, Solifenacin; Solifenacin succinate; Diflunisal; Codeine/Ibuprofen; Ibuprofen,Codeine phosphate; Ibuprofen, Paracetamol; Ibuprofen, Phenylephrine hydrochloride; Ibuprofen, Pseduoephedrine Hydrocholride; Ibuprofen/Paracetamol; Ibuprofen/Pseudoephedrine; Paracetamol, Ibuprofen; Pseudoephedrine hydrochloride, Ibuprofen; Indomethacin; Indometacin; Ketoprofen; Esomeprazole/Naproxen; Naproxen; Naproxen sodium; Naproxen;Esomeprazole; Sulindac, Meloxicam; Piroxicam; Tiaprofenic acid; Phenylbutazone
RAAS inhibitors	Amlodipine,Perindopril; Amlodipine/Perindopril; Captopril; Cilazapril; Enalapril; Enalapril maleate; Enalapril maleate, hydrochlorothiazide; Enalapril maleate/ hydrochlorothiazide; Enalapril/lercanidipine; Felodipine/Ramipril; Fosinopril; Fosinopril sodium; Fosinopril sodium, Hydrochlorothiazide; Fosinopril sodium/Hydrochlorothiazide; Hydrochlorothiazide/Quinapril; Indapamide/Perindopril; Lercanidipine, Enalapril; Lisinopril; Perindopril; Perindopril arginine; Perindopril erbumine; Perindopril erbumine, Indapamide hemihydrate; Perindopril, Amlodipine; Quinapril; Quinapril, Hydrochlorothiazide; Ramipril; Ramipril, Felodipine; Trandolapril, Verapamil; Trandolapril/Verapamil; Amelodipine/Valsartan; Amelodipine, Valsartan, Hydrochlorothiazide; Amelodipine/Hydrochlorothiazide/Olmesartan; Amelodipine/Hydrochlorothiazide/Valsartan; Amelodipine/ Olmesartan; Amelodipine/Telmisartan; Amelodipine/Valsartan; Candeartan; Candeartan cilexetil, Hydrochlorothiazide; Candeartan cilexetil/Hydrochlorothiazide; Eprosartan; Eprosartan mesylate; Eprosartan mesylate, Hydrochlorothiazide; Eprosartan/Hydrochlorothiazide; Hydrochlorothiazide/Irbesartan; Hydrochlorothiazide/Olmesartan; Hydrochlorothiazide/Telmisartan; Hydrochlorothiazide/Valsartan; Ibresartan; Ibresartan, hydrochlorothiazide; Losartan; Losartan potassium; Olmesartan; Olmesartan medoxomil; Olmesartan medoxomil, Hydrochlorothiazide; Olmesartan medoxomil, Amlodipine beysylate; Olmesartan medoxomil, Amelodipine, hydrochlorothiazide; Olmesartan medoxomil, hydrochlorothiazide; Sacubitril, Valsartan; Sacubitril/Valsartan; Telmisartan, Amlodipine; Telmisartan, Amlodipine besylate; Telmisartan, hydrochlorothiazide; Valsartan; Valsartan, Hydrochlorothiazide
Nitrate	Isosorbide dinitrate; Isosorbide mononitrate; Isosorbide trinitrate
Statin	Amlodipine Besylate, Atorvastatin; Amlodipine,Atorvastatin; Amlodipine/Atorvastatin; Atorvastatin; Atrovastatin/Ezetimibe; Cerivastatin; Ezetimibe, atorvastatin; ezetimibe, rosuvastatin; Ezetimibe, Simvastatin; Ezetimibe/Rosuvastatin; Ezetimibe/ Simvastatin; Fluvastatin; Pravastatin; Pravastatin sodium; Rosuvastatin; Simvastatin; Simvastatin/Sitagliptin; Sitagliptin, Simvastatin.
Beta-blockers	Alprenolol; Atenolol; Bisoprolol; Bisoprolol fumarate; Carvedilol; Labetalol; Labetalol hydrochloride; Metoprolol; Metoprolol succinate; Metoprolol tartrate;

	Nebivolol; Oxprenolol; Oxprenolol hydrochloride; Pindolol; Propranolol; Propranolol hydrochloride; Sotalol; Sotalol hydrochloride
Digoxin	Digoxin
Antiarrhythmic drugs class I or III	Amiodarone; Amiodarone hydrochloridce; Sotalol; Sotalol hydrochloride; Disopyramide; Flecainide; Flecainide acetate
Antidementia drugs	Donepezil; Memantine; Memantine hydrochloride; Rivastigmine; Rivastigmine hydrogen tartrate

Table S2. Baseline characteristics of DOAC users and non-OAC users before and after propensity score matching

	Before Matching			Propensity-score matched		
Characteristics	DOAC users (n=5,570)	Non-OAC users (n=7,394)	*Standardised differences	DOAC users (n=2,850)	Non-OAC users (n=2,850)	*Standardised differences
Female sex, n (%)	2,631 (47.2)	3,609 (48.8)	0.03	1,346 (47.2)	1,346 (47.2)	<0.01
Age, mean (years)	73.7±9.6	69.0±15.6	0.37	72.7±9.9	72.8±13.6	<0.01
CHA_2DS_2-VA, mean score	2.5±1.2	1.9±1.5	0.45	2.4±1.3	2.4±1.4	<0.01
Duration of follow-up, mean (years)	2.9±1.3	3.6±2.0	0.41	3.0±1.4	3.0±1.7	0.01
Congestive heart failure, n (%)	600 (10.8)	628 (8.5)	0.08	307 (10.7)	299 (10.5)	<0.01
Hypertension, n (%)	3,576 (64.7)	3,409 (46.5)	0.37	1,715 (60.2)	1,707 (59.9)	0.01
Diabetes mellitus, n (%)	1,116 (20.1)	990 (13.4)	0.18	503 (17.7)	505 (17.7)	<0.01
Vascular disease, n (%)	1,460 (26.3)	1,574 (21.3)	0.12	754 (26.5)	738 (25.9)	<0.01
Venous thromboembolism, n (%)	238 (4.3)	201 (2.7)	0.09	110 (3.9)	102 (3.6)	0.02
Anxiety, n (%)	966 (17.3)	1,497 (20.1)	0.08	507 (17.8)	526 (18.5)	0.02
Arthritis, n (%)	3,860 (52.2)	3,860 (52.2)	0.22	1,665 (58.4)	1,675 (58.8)	0.01
Asthma, n (%)	1,095 (19.7)	1,390 (18.8)	0.02	542 (19.0)	547 (19.2)	<0.01
Depression, n (%)	1,261 (22.6)	1,901 (25.7)	0.07	667 (23.4)	687 (23.4)	0.02
Cancer, n (%)	2,274 (40.8)	2,818 (38.1)	0.06	1,156 (40.6)	1,152 (40.4)	<0.01
Coronary heart disease, n (%)	1,515 (27.2)	1,675 (22.7)	0.11	770 (27.0)	761 (26.7)	0.01
Chronic liver disease, n (%)	28 (0.5)	96 (1.3)	0.08	22 (0.8)	20 (0.7)	0.01
Chronic obstructive pulmonary disease, n (%)	906 (16.3)	1,111 (15.0)	0.03	486 (17.1)	481 (17.0)	0.01
Antiplatelets, n (%)	1,857 (33.3)	3,129 (42.3)	0.18	1,175 (41.2)	1,161 (40.7)	0.01
NSAIDs, n (%)	2,544 (45.7)	3,045 (41.2)	0.09	1,230 (43.2)	1,208 (42.4)	0.02
RAAS inhibitors, n (%)	4,244 (76.2)	3,883 (52.5)	0.51	1,960 (68.8)	1,928 (67.7)	0.02

Nitrates, n (%)	966 (17.3)	1,082 (14.6)	0.08	482 (16.9)	476 (16.7)	0.01
Statins, n (%)	3,341 (60.0)	3,069 (41.5)	0.38	1,542 (54.1)	1,502 (52.7)	0.03
Beta-blockers, n (%)	4,138 (74.3)	3,723 (50.4)	0.51	1,855 (65.1)	1,867 (65.5)	0.01
Digoxin, n (%)	1,230 (22.1)	1,047 (14.2)	0.21	518 (18.2)	526 (18.5)	0.01
Antiarrhythmic drugs class I or III, n (%)	1,710 (30.7)	1,499 (20.3)	0.25	720 (25.3)	737 (25.9)	0.01

NSAIDs, non-steroidal anti-inflammatory drugs (NSAIDs); OAC, oral anticoagulant; RAAS, renin-angiotensin-aldosterone system.
Only prescriptions for flecainide and disopyramide from class I antiarrhythmics and amiodarone and sotalol from class III antiarrhythmics were recorded in the MedicineInsight dataset. CHA_2DS_2-VA (congestive heart failure (1 point), hypertension (1 point), age≥75 years (2 points), diabetes mellitus (1 point), stroke/transient ischaemic attack (2 points), vascular disease (1 point), and age 65-74 years (1 point). *Absolute values of standardised differences are reported.

Table S3. Baseline characteristics of DOAC users and warfarin users before and after propensity score matching

	Before Matching			Propensity-score matched		
Characteristics	DOAC users (n=5,570)	Warfarin users (n=2,673)	*Standardised differences	DOAC users (n=1,335)	Warfarin users (n=1,335)	*Standardised differences
Female sex, n (%)	2,631 (47.2)	1,214 (45.4)	0.03	583 (43.7)	583 (43.7)	<0.01
Age, mean (years)	73.7±9.6	75.0±10.2	0.13	74.8±9.2	75.0±10.6	0.02
CHA_2DS_2-VA, mean score	2.5±1.2	2.7±1.3	0.15	2.7±1.3	2.7±1.3	0.04
Duration of follow-up, mean (years)	2.9±1.3	4.3±2.2	0.75	3.2±1.7	3.3±1.4	0.05
Congestive heart failure, n (%)	600 (10.8)	543 (20.3)	0.26	191 (14.3)	224 (16.8)	0.07
Hypertension, n (%)	3,576 (64.7)	1,568 (59.3)	0.11	807 (60.5)	818 (61.3)	0.02
Diabetes mellitus, n (%)	1,116 (20.1)	623 (23.4)	0.08	290 (21.7)	297(22.3)	0.01
Vascular disease, n (%)	1,460 (26.3)	782 (29.4)	0.07	382 (28.6)	386 (28.9)	0.01
Venous thromboembolism, n (%)	238 (4.3)	208 (7.8)	0.14	76 (5.7)	77 (5.8)	<0.01
Anxiety, n (%)	966 (17.3)	424 (15.9)	0.04	205 (15.4)	204 (15.3)	<0.01
Arthritis, n (%)	3,860 (52.2)	1,690 (63.2)	0.01	819 (61.4)	826 (61.9)	0.01
Asthma, n (%)	1,095 (19.7)	498 (18.6)	0.02	249 (18.7)	228 (17.1)	0.04
Depression, n (%)	1,261 (22.6)	640 (23.9)	0.03	294 (22.0)	312 (23.4)	0.03
Cancer, n (%)	2,274 (40.8)	1,127 (42.2)	0.03	572 (42.9)	569 (42.6)	0.01
Coronary heart disease, n (%)	1,515 (27.2)	935 (35.0)	0.16	414 (31.0)	407 (30.5)	0.01
Chronic liver disease, n (%)	28 (0.5)	28 (1.1)	0.03	10 (0.8)	13 (1.0)	0.03
Chronic obstructive pulmonary disease, n (%)	906 (16.3)	510 (19.1)	0.07	236 (17.7)	249 (18.7)	0.03
Antiplatelets, n (%)	1,857 (33.3)	954 (35.7)	0.04	451 (33.8)	447 (33.5)	0.01
NSAIDs, n (%)	2,544 (45.7)	835 (31.2)	0.30	502 (37.6)	487 (36.5)	0.02
RAAS inhibitors, n (%)	4,244 (76.2)	2,153 (80.6)	0.10	1,024 (76.7)	1,045 (78.3)	0.04
Nitrates, n (%)	966 (17.3)	673 (25.2)	0.18	269 (20.2)	278 (20.8)	0.02

Statins, n (%)	3,341 (60.0)	1,785 (32.4)	0.14	852 (63.8)	856 (64.1)	0.01
Beta-blockers, n (%)	4,138 (74.3)	2,070 (77.4)	0.07	990 (74.2)	1,007 (75.4)	0.03
Digoxin, n (%)	1,230 (22.1)	1,073 (40.1)	0.39	399 (29.9)	407 (30.5)	0.01
Antiarrhythmic drugs class I or III, n (%)	1,710 (30.7)	742 (27.8)	0.07	374 (28.0)	381 (28.5)	0.01

NSAIDs, non-steroidal anti-inflammatory drugs (NSAIDs); OAC, oral anticoagulant; RAAS, renin-angiotensin-aldosterone system.
Only prescriptions for flecainide and disopyramide from class I antiarrhythmics and amiodarone and sotalol from class III antiarrhythmics were recorded in the MedicineInsight dataset. CHA_2DS_2-VA (congestive heart failure (1 point), hypertension (1 point), age≥75 years (2 points), diabetes mellitus (1 point), stroke/transient ischaemic attack (2 points), vascular disease (1 point), and age 65-74 years (1 point). *Absolute values of standardised differences are reported.

Table S4. Hazard ratios (HRs) for dementia diagnosis, with 95% confidence intervals (CIs), for propensity score-matched groups regardless of treatment duration during follow-up

Characteristics	OAC users	Non-OAC users	DOAC users	Non-OAC users	Warfarin users	Non-OAC users	DOAC users	Warfarin users
N	5,335	5,335	4,367	4,367	2,146	2,146	2,886	2,886
Follow-up, mean ± SD, y	3.6±2.0	3.6±2.0	3.4±1.9	3.4±1.9	3.8±2.1	3.9±2.1	3.6±1.9	3.6±2.0
Person-years at risk	19,220	19,284	14,804	14,708	8,241	8,409	10,493	10,382
Dementia diagnosis	105	145	48	112	62	58	54	102
Incidence rate (per 1000 person-years)	5.5 (4.5-6.6)	7.5 (6.3-8.8)	3.2 (2.4-4.3)	7.6 (6.3-9.2)	7.5 (5.8-9.6)	6.9 (5.2-8.9)	5.1 (3.9-6.7)	9.8 (8.0-11.9)
HRs (95% CIs)	0.73 (0.57-0.94)	Ref	0.42 (0.30-0.60)	Ref	1.10 (0.77-1.57)	Ref	0.52 (0.38-0.73)	Ref
OAC, oral anticoagulant; direct-acting oral anticoagulant (DOAC).								

Table S5. Hazard ratios (HRs) for dementia diagnosis, with 95% confidence intervals (CIs), for propensity score-matched groups in patients with AF who had recorded three or more visits within two years before AF diagnosis

Characteristics	OAC users	Non-OAC users	DOAC users	Non-OAC users	Warfarin users	Non-OAC users	DOAC users	Warfarin users
N	5,261	5,261	3,540	3,540	1,760	1,760	1,632	1,632
Follow-up, mean ± SD, y	3.1±1.9	3.1±2.3	2.7±1.4	2.7±2.2	3.3±2.3	3.3±2.4	3.0±1.5	2.8±2.0
Person-years at risk	16,136	16,382	9,672	9,679	5,793	5,852	4,914	4,725
Dementia diagnosis	155	192	70	136	76	65	33	72
Incidence rate (per 1000 person-years)	9.6 (8.2-11.2)	11.7 (10.1-13.5)	7.2 (5.6-9.1)	14.1 (11.8-16.6)	13.1 (10.3-16.4)	11.1 (8.6-14.1)	6.7 (4.6-9.4)	15.2 (11.9-19.1)
HRs (95% CIs)	0.81 (0.65-0.99)	Ref	0.51 (0.38-0.69)	Ref	1.18 (0.85-1.65)	Ref	0.45 (0.30-0.68)	Ref

OAC, oral anticoagulant; direct-acting oral anticoagulant (DOAC). Inclusion criteria for this sensitivity analysis were modified from the main analysis. We required patients to have at least three recorded visits before AF diagnosis and at least a recorded six months follow-up duration. Patients who developed dementia within a year were also included. In addition to variables listed in Table 1, the cohorts were matched with four additional variables (SEIFA, Rurality, SSRIs/SNRIs, and stroke that occurred during follow-up).

Table S6. Hazard ratios (HRs) for dementia diagnosis, with 95% confidence intervals (CIs), for propensity score-matched groups

Characteristics	OAC users	DOAC users	Warfarin users	Non-OAC users
N	3,651	2,538	1,113	3,651
Follow-up, mean ± SD, y	3.3±1.8	2.9±1.4	4.4±2.2	3.4±1.9
Person-years at risk	12,319	7,346	4,879	12,224
Dementia diagnosis	64	29	35	104
Incidence rate (per 1000 person-years)	5.2 (4.0-6.6)	3.9 (2.6-5.7)	7.2 (5.0-10.0)	8.5 (7.0-10.3)
HRs (95% CIs)	0.62 (0.46-0.85)	0.70 (0.57-0.87)	0.78 (0.54-1.14)	Ref
CI, confidence interval; DOAC, direct-acting oral anticoagulant; HR, hazard ratio; OAC, oral anticoagulant				