ORIGINAL RESEARCH ARTICLE

Impact of Medication Adherence on the Association Between Oral Anticoagulant Use and Risk of Dementia: A Retrospective Cohort Study using the Japanese Claims Database

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Abstract

Background Atrial fibrillation (AF) is a major risk factor for the development of stroke and silent cerebral infarct (SCI). Additionally, AF is independently associated with neurological disorders, including cognitive impairment and dementia. Although oral anticoagulants (OACs) are used to reduce the risk of development of stroke and SCI in patients with AF, it is unclear whether OACs reduce the risk of dementia.

Objective This study aimed to investigate the association between OAC use and dementia in relatively young patients with AF. Moreover, the impact of medication adherence on the association between OAC use and the risk of dementia was examined.

Patients and Methods This retrospective cohort study was conducted using a large claims database—Japan Medical Data Center, Inc. (JMDC)—from which newly diagnosed patients with AF younger than 75 years of age were identified. We analyzed medication adherence using the medication possession ratio (MPR). The dementia risk was compared between the OAC and non-OAC groups using Cox proportional hazards regression analysis and the Kaplan–Meier method after propensity score matching. Similarly, the MPR-classified and non-OAC groups were also compared.

Results OAC administration was not associated with the risk of dementia in the entire cohort (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.40–1.08; $p = 0.098$); however, OAC administration in patients with an MPR $\geq$90% was significantly associated with a lower risk of dementia (HR 0.45, 95% CI 0.25–0.81; $p = 0.008$). Meanwhile, direct OAC (DOAC) and warfarin (WF) administration was not associated with the risk of dementia regardless of MPR. Kaplan–Meier analysis revealed a significant difference in the incidence of dementia between the MPR $\geq$ 90% OAC and non-OAC groups (log-rank test: $p = 0.006$). However, no difference was observed in the incidence of dementia between the MPR $\geq$ 90% WF and non-OAC groups, or between the MPR $\geq$ 90% DOAC and non-OAC groups.

Conclusions OAC administration was not associated with the risk of dementia in relatively young patients with AF; however, when limited to patients with an MPR $\geq$ 90%, OAC administration reduced the risk of dementia. Our results suggest that the association between OAC use and dementia should be evaluated while considering medication adherence.

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Key Summary Points

Oral anticoagulant (OAC) administration did not reduce the risk of dementia in patients with nonvalvular atrial fibrillation younger than 75 years of age.

OAC administration reduced the risk of dementia in patients with an MPR $\geq$ 90%.

In the separate analyses of direct OACs and warfarin, administration in patients with an MPR $\geq$ 90% did not reduce the risk of dementia.

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1 Introduction

The prevalence of atrial fibrillation (AF) in Japan is approximately 0.6% [1], and the number of patients with AF is increasing not only in Japan but also worldwide [2]. Recent studies have suggested that AF is independently associated with neurological disorders, including cognitive impairment and dementia, even after adjusting for previous ischemic stroke [3, 4]. Furthermore, AF has been reported to be associated with an increased risk of mild cognitive impairment and dementia, even among patients who had not experienced an overt stroke [5–7]. The aforementioned reports suggest that additional mechanisms other than stroke may be involved in the association between AF and dementia. Accordingly, nerve cell damage due to silent cerebral infarct (SCI), reduced cerebral blood flow, and chronic cerebral hypoperfusion due to complicated heart failure and irregular heartbeat have been presumed to be some of the mechanisms for the development of dementia.

A number of retrospective studies have reported that oral anticoagulants (OACs) reduce the development of stroke or SCI and subsequently reduce the risk of dementia or cognitive impairment in patients with AF [8–10]. However, no randomized controlled trial (RCT) has investigated the association between anticoagulant therapy and cognitive decline or dementia in patients with AF. Although RCT remains the gold standard for determining therapeutic efficacy, it would be difficult and unethical to investigate the risk of dementia in patients with AF. By contrast, a study using real-world data (RWD) may be invaluable. Studies using RWD such as registry, claims, prescription, and electronic healthcare record databases can provide valuable information about practice patterns and patient characteristics in actual clinical settings [11], if appropriately designed.

Dementia reduces the quality of life of caregivers, such as family members, as well as the patient. Because dementia is not completely curable, the onset of dementia in young patients is expected to require a longer duration of caregiving than that in older patients. Although it is generally known that older people are at a higher risk of dementia, some studies have reported that younger patients (aged < 70 years) with AF are at a greater risk of dementia than older patients [4, 12]. Therefore, further study is needed to clarify the association between the risk of dementia and OAC use in relatively young patients with AF.

Patient adherence and persistence to drug therapy are known to affect treatment effectiveness. Some observational studies reported that stroke reduction following direct OAC (DOAC) treatment in patients with AF is dependent on adherence and persistence in the real-world setting. Ozaki et al. reported that suboptimal adherence and persistence to DOACs were common in patients with AF, with one in three patients adhering to their DOAC < 80% of the time, which was associated with poor clinical outcomes in nonadherent patients [13]. Moreover, Obamiro et al. reported that approximately 50% of patients taking OACs had poor adherence to their therapy [14]. The association between OAC use and dementia risk should be investigated considering medication adherence, but few studies have considered adherence.

Therefore, this study aimed to investigate the association between OAC use and the risk of dementia in patients with nonvalvular AF. Additionally, we hypothesized that adherence to medication may be a significant protective factor for dementia in patients with nonvalvular AF who received OACs.

2 Methods

2.1 Study Design

A retrospective cohort study was conducted to investigate the association between OAC use and dementia using a large claims database constructed by the Japan Medical Data Center, Inc. (JMDC), one of the database vendors in Japan [15].

2.2 Data Source

The JMDC claims database includes approximately 6 million insured individuals (approximately 5% of the population), consisting primarily of health insurance association members and their families (aged < 75 years). The JMDC database provides information on monthly claims (inpatient, outpatient, and dispensing) received from multiple health insurance associations. This information includes encrypted personal identifiers, age, sex, treatment, International Classification of Diseases 10th revision (ICD-10) codes, and standardized disease classification codes developed by the Medical Information System Development Center. The database also provides data about the name, dose, and number of days for which the drugs were prescribed and/or dispensed. All prescribed drugs are coded according to the Anatomical Therapeutic Chemical classification based on the European Pharmaceutical Market Research Association, with the ingredient and product names also being provided. Given that all claims are collected by the health insurance association, the same patient's claims are linked even when they visit multiple medical institutions. Additionally, all personal names and identification numbers from the JMDC claims database were replaced by a univocal numerical code. Therefore, obtaining informed consent was not required in this study. This study was approved by the Ethics Committee of Kindai University School of Pharmacy (approval numbers: 17-112).

2.3 Study Population

All patients who were diagnosed with AF between April 2010 and April 2019 were extracted from the JMDC claims database. To exclude prevalent cases of AF, the analysis was restricted to patients who were first diagnosed in April 2011 or later (after a run-in period of 12 months). Likewise, the analysis was restricted to OAC users who received their first prescription in April 2011 or later. Patients with incident AF and OAC users aged > 18 years were included in the study. For this study, patients included in the database were followed up until April 2019; therefore, they had different follow-up periods. Patients who did not have at least 6 months of follow-up after their AF diagnosis and at least 12 months of database history (pre-index period) before their AF diagnosis were excluded from the analysis. Additionally, patients who were prescribed OACs within 12 months before the diagnosis of AF and patients who were diagnosed with dementia prior to the diagnosis of AF were excluded from the analysis. Patients diagnosed with atrial flutter and valvular AF, who were identified using standardized disease classification codes (4273009 and 8846941), were excluded from the analysis because such diseases have not been approved as indications for DOACs in Japan. Patients with incomplete medical treatment data were excluded from the analysis. The ICD-10 code I48 was used to identify patients with AF. ICD-10 codes generally have high sensitivity and specificity [16]. The cohort study design is presented in Fig. 1.

Patients were then divided into two groups, the OAC and non-OAC groups, with the former being further divided into the warfarin (WF) and DOAC groups according to the type of OAC initially prescribed. Patients who were prescribed both WF and DOACs on the same day during the follow-up period were treated as censored cases. In total, 17 patients received both WF and DOAC prescriptions on the start date, but in these patients, both treatments were prescribed only on this date. Therefore, these patients were included in the continuously prescribed medications group. Patients were followed from the date of the first AF diagnosis to any of the following events, whichever occurred first: diagnosis of dementia defined by the ICD-10 codes F00–F03 and G30–G31, OAC discontinuation or change, and the end of the study period. A medication was deemed discontinued when the prescription intervals exceeded 3 months or when the medication was switched to another OAC. Deceased patients were considered as censor cases. The non-OAC group was followed from AF diagnosis to the diagnosis of dementia or the end of the study period. The ICD-10 codes F00–F03 and G30–G31 defined the following dementias: dementia in Alzheimer's disease, vascular dementia, dementia in other diseases classified elsewhere, unspecified dementia, Alzheimer's disease, other degenerative diseases of the nervous system, not elsewhere classified.

Patient characteristics were determined from the database during the baseline period, i.e., 12 months prior to AF diagnosis. The patient selection flowchart is presented in Fig. 2.

2.4 Adherence

The medication possession ratio (MPR), which was calculated as the total duration of supply (days) of the prescribed drug divided by the number of days from the first prescription date to the end date of the last prescription, was used as an indicator of medication adherence ("Appendix 1"). The MPR reflected whether anticoagulants were prescribed or dispensed but not whether patients actually took them. Although the MPR cannot directly evaluate adherence, there are days when patients with an MPR < 100% cannot take the medication because OACs cannot be purchased without a prescription in Japan. Although this is not a direct indicator of compliance, we considered it an indirect indicator. Patients with an MPR of 0 were categorized into the non-OAC group.

2.5 Variables for Propensity Score Matching

Propensity score matching was performed to balance confounding factors between the OAC and non-OAC groups. Factors associated with the development of dementia, (age; sex; comorbidities; diagnosis of stroke, systemic emboli, or transient ischemic attack; cancer; ischemic stroke; intracerebral hemorrhage; other intracranial bleed; myocardial infarction; peripheral artery disease; vascular disease; heart failure; any valvular disease; hypertension; diabetes; renal disease; liver disease; bleeding; venous thromboembolism; hypothyroidism; osteoarthritis; chronic obstructive pulmonary disease; alcohol index; pneumonia; thyrotoxicosis; Parkinson's disease; and prescription of an antiplatelet agent, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, diuretic, statin, nitrates, β-blocker, antiarrhythmic drug class 1 or 3, digoxin) were included as covariates for calculating propensity scores. The comorbidities were used the ICD-10 codes defined by Friberg and Rosenqvist [9]. We extracted from the database the covariates of the diagnoses and prescriptions within 12 months prior to the first diagnosis of AF. Individual propensity scores for the probability of OAC treatment were calculated using logistic regression, after which 1:1 propensity score-matched pairs were created by matching the OAC and non-OAC groups. A caliper of 0.2 on logit-transformed scores was used for propensity score matching. Differences in baseline characteristics between the OAC and non-OAC groups were evaluated using standardized differences. A standardized difference of <0.10 was used to indicate good balance between groups for a given covariate. Additionally, the 1:1 propensity score-matched pairs were created by matching
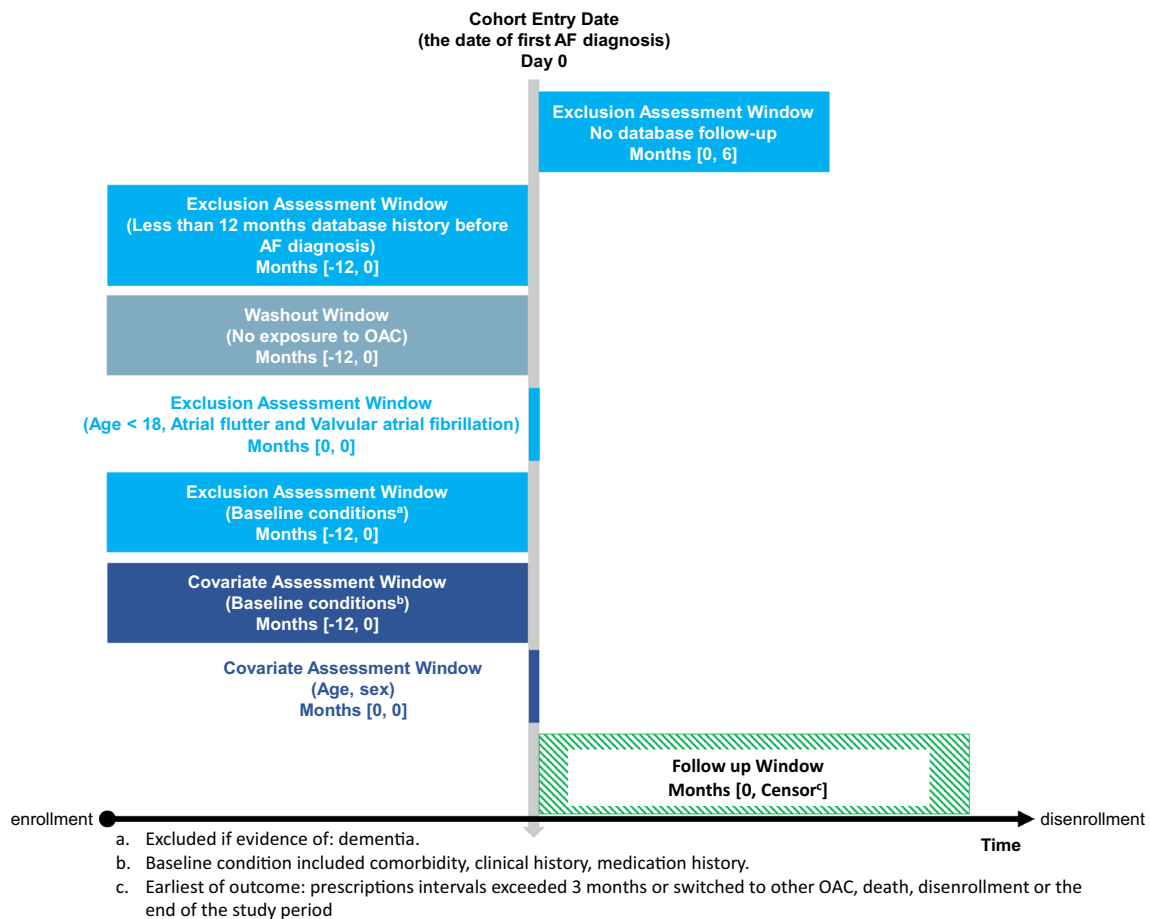
Fig. 1 Cohort study design. *AF* atrial fibrillation, *OAC* oral anticoagulant

the non-OAC group with the DOAC, WF group, and with the OAC, DOAC, or WF groups of patients with MPRs of $\geq 60\%$, $\geq 70\%$, $\geq 80\%$, and $\geq 90\%$.

2.6 Statistical Analysis

The incidence of dementia in the non-OAC group was compared with those in the OAC, DOAC, or WF groups, as well as with those in groups of patients with MPRs of $\geq 60\%$, $\geq 70\%$, $\geq 80\%$, and $\geq 90\%$. Crude incidence rates were expressed as rates per 1000 person-years. The 95% confidence interval (CI) of incidence rates was calculated using the Clopper–Pearson method. The incidence of dementia was compared between the OAC and non-OAC groups after propensity score matching, and the Cox proportional hazards regression model was used to estimate the risk of dementia for the OAC, DOAC, and WF groups. Similarly, the risk of dementia for the OAC, DOAC, and WF groups of patients with MPRs of $\geq 60\%$, $\geq 70\%$, $\geq 80\%$, and $\geq 90\%$ was also estimated. We used the univariate Cox proportional hazards models to obtain the unadjusted hazard ratio (HR) for each group. The Kaplan–Meier method was performed to compare the incidence of dementia between the propensity score-matched OAC, DOAC, and WF groups and the non-OAC group using the log-rank test. Additionally, the Cox proportional hazards regression model and Kaplan–Meier method were used to investigate the risk of stroke between the MPR $\geq 90\%$ OAC group and the non-OACs group.

Data extraction and management were performed using Visual Mining Studio software (version 8.0; Mathematical Systems, Inc., Tokyo, Japan). All analyses were conducted using JMP® version 14.2 (SAS Institute Inc., Cary, NC, USA), and a *p*-value of < 0.05 indicated statistical significance. Bonferroni's correction was applied to the analyses of the association between dementia and OAC use.

3 Results

3.1 Patient Characteristics

The JMDC claims database included 26,526 patients with AF, of whom 8564 patients were excluded from the analysis. Ultimately, 17,962 patients who satisfied the selection

Fig. 2 Patient selection process. *AF* atrial fibrillation, *DOAC* direct oral anticoagulant, *OAC* oral anticoagulant, *WF* warfarin

AF patients over 18 years old between April 2010 and April 2019 (N = 26,526)

8,564 excluded
· No database follow-up for at least 6 months (n = 3,237)
· Patients not in the database for more than 12 months before diagnosis of AF (n = 2,876)
· Patients who were prescribed OAC before their first diagnosis of AF (n = 1,885)
· Atrial flutter and Valvular atrial fibrillation (n = 230)
· Patients with a dementia diagnosis before their first diagnosis of AF (n = 208)
· Patients with incomplete medical treatment data (n = 128)

Enrolled patients (n = 17,962)

OAC (n = 7,895)
DOAC (n = 6,962)   WF (n = 933)

non-OAC (n = 10,067)

1:1 Propensity score matching

OAC — OAC (n = 5,587) — non-OAC (n = 5, 587)

DOAC — DOAC (n = 5,211) — non-OAC (n = 5,211)

WF — WF (n = 873) — non-OAC (n = 873)

criteria were included in the study. Among the included patients, 7895 (44.0%) were prescribed OACs (Fig. 2), with 6962 and 933 having been prescribed DOACs and WF, respectively. The baseline patient characteristics of the OAC and non-OAC groups are presented in Table 1. The mean ages of the OAC and non-OAC groups were 56.9 and 51.4 years, respectively. After propensity score matching, 5587 patients were selected from the OAC and non-OAC groups (Table 1); 5211 matched patients were selected from the DOAC and non-OAC groups (Table 2); and 873 matched patients were selected from the WF and non-OAC groups (Table 3). Sufficiently balanced cohorts were generated with a standardized difference of < 0.10 for almost all covariates. Additionally, sufficient balanced cohorts were generated using propensity score matching during the analysis of the OAC, DOAC, and WF groups limited to patients with MPRs of ≥ 60%, ≥ 70%, ≥ 80%, and ≥ 90%.

3.2 Outcomes

The number of events, follow-up duration, and incidence rates for dementia are summarized in Table 4. After propensity score matching, the crude incidence of dementia per 1000 person-years was 2.76 and 4.00 in the OAC and non-OAC groups, respectively, with the MPR ≥ 90% OAC group having the lowest crude incidence per 1000 person-years at 1.97. After analyzing the DOAC group, our findings showed a 3.14 and 3.69 crude incidence of dementia per 1000 person-years in the DOAC and non-OAC groups, respectively, with the MPR ≥ 90% DOAC group having the lowest crude incidence per 1000 person-years at 2.75. After analyzing the WF group, our findings showed a 3.69 and 5.47 crude incidence of dementia per 1000 person-years in the WF and non-OAC groups, respectively, with the MPR ≥ 90% WF group having a crude incidence per 1000 person-years of 3.32. Results of OAC and DOAC analyses showed that the groups with MPR ≥ 90% had the lowest crude incidences per 1000 person-years.

Table 1 Characteristics of the study patients before and after propensity score matching (OAC and non-OAC groups)

	Before matching			Propensity score–matched		
	Non-OAC ($n = 10{,}067$)	OAC ($n = 7895$)	Standardized differences	Non-OAC ($n = 5587$)	OAC ($n = 5587$)	Standardized differences
Age, years [mean ± SD]	51.4 ± 11.7	56.9 ± 9.5	0.03	55.7 ± 9.8	55.5 ± 9.8	0.03
Female sex	36.6	17.7	0.43	19.6	21.3	0.04
Stroke/systemic emboli/TIA	15.5	15.5	0.00	16.1	15.5	0.02
Cancer	21.1	16.5	0.12	18.3	18.3	0.00
Ischemic stroke	12.1	11.7	0.01	12.5	12.0	0.02
Intracerebral hemorrhage	3.2	1.6	0.10	2.1	1.9	0.01
Other intracranial bleed	1.2	0.5	0.08	0.6	0.6	0.00
Myocardial infarction	16.8	17.6	0.02	17.5	17.4	0.00
Peripheral artery disease	13.3	12.9	0.01	13.8	13.4	0.01
Vascular disease	25.9	26.8	0.02	27.2	26.8	0.01
Heart failure	41.8	59.6	0.36	51.0	51.9	0.02
Any valvular disease	25.4	33.0	0.17	29.4	29.6	0.00
Hypertension	42.5	59.6	0.35	53.5	53.9	0.01
Diabetes	46.9	54.4	0.15	51.5	51.6	0.00
Renal disease	4.3	3.7	0.03	4.3	4.3	0.00
Liver disease	22.9	22.4	0.01	21.7	22.2	0.01
Bleeding	9.5	6.6	0.11	7.6	7.3	0.01
Venous thromboembolism	8.5	13.6	0.16	11.1	11.0	0.00
Hypothyroidism	9.4	9.5	0.00	8.9	9.2	0.01
Osteoarthritis	5.3	6.6	0.05	6.2	6.3	0.00
Chronic obstructive pulmonary disease	11.4	10.7	0.02	10.6	10.8	0.01
Alcohol index	1.3	1.5	0.02	1.3	1.4	0.01
Pneumonia	8.3	6.5	0.07	6.8	6.8	0.00
Thyrotoxicosis	22.0	25.1	0.07	21.7	22.3	0.01
Parkinson's disease	0.4	0.3	0.02	0.3	0.3	0.00
Antiplatelet	14.1	15.3	0.03	16.6	16.0	0.02
ACE inhibitor or ARB	21.8	36.3	0.32	30.0	30.9	0.02
Diuretic	7.1	16.5	0.29	10.5	11.3	0.03
Statin	18.3	19.5	0.03	20.6	20.4	0.00
Nitrates	8.2	11.6	0.11	9.8	10.4	0.02
β-blocker	23.5	39.5	0.35	30.4	31.7	0.03
Antiarrhythmic drug, class 1 or 3	13.8	29.0	0.38	21.2	21.9	0.02
Digoxin	2.1	7.1	0.24	3.5	4.0	0.03

Data are expressed as percentages unless otherwise specified

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *OAC* oral anticoagulant, *SD* standard deviation (OAC and non-OAC groups), *TIA* transient ischemic attack

Table 4 details the results of Cox proportional hazards analysis. Although OAC administration was not associated with a lower risk of dementia (HR 0.66, 95% CI 0.40–1.08; $p = 0.098$), OAC administration in patients with MPR ≥90% was significantly associated with a lower risk of dementia (HR 0.45, 95% CI 0.25–0.81; $p = 0.008$). The DOAC (HR 0.80, 95% CI 0.48–1.34; $p = 0.393$) and WF (HR 0.68, 95% CI 0.23–1.98; $p = 0.475$) groups were not associated with the risk of dementia. Consequently, neither DOAC nor WF administration reduced the risk of dementia regardless of MPR.

Additionally, no significant difference was found in the risk of dementia between OAC administration in patients with an MPR ≥ 90% and those with an MPR < 90%, between DOAC administration in patients with an MPR ≥ 90% and those with an MPR < 90%, and between WF administration in patients with an MPR ≥ 90% and those with an MPR < 90% (Table 5).

Figure 3 shows the Kaplan–Meier curves for the incidence of dementia in the MPR ≥ 90% OAC, DOAC, and WF groups. Accordingly, differences in the incidences of dementia were observed between the MPR ≥ 90% OAC

Table 2 Characteristics of the study patients before and after propensity score matching (DOAC and non-OAC groups)

	Before matching			Propensity score–matched		
	Non-OAC ($n = 10{,}067$)	DOAC ($n = 6962$)	Standardized differences	Non-OAC ($n = 5211$)	DOAC ($n = 5211$)	Standardized differences
Age, years [mean ± SD]	51.4 ± 11.7	57.0 ± 9.4	0.03	55.9 ± 9.7	55.8 ± 9.6	0.03
Female sex	36.6	17.4	0.44	19.7	20.6	0.02
Stroke/systemic emboli/TIA	15.5	14.4	0.03	84.9	85.2	0.01
Cancer	21.1	16.2	0.13	82.0	81.7	0.01
Ischemic stroke	12.1	10.9	0.04	88.1	88.6	0.02
Intracerebral hemorrhage	3.2	1.6	0.10	98.1	98.2	0.01
Other intracranial bleed	1.2	0.5	0.08	99.3	99.4	0.01
Myocardial infarction	16.8	17.3	0.01	82.8	82.5	0.01
Peripheral artery disease	13.3	11.4	0.06	87.8	87.0	0.02
Vascular disease	25.9	25.7	0.00	74.2	73.2	0.02
Heart failure	41.8	59.0	0.35	49.0	47.2	0.04
Any valvular disease	25.4	31.4	0.13	71.3	71.0	0.01
Hypertension	42.5	58.5	0.32	47.2	46.8	0.01
Diabetes	46.9	54.0	0.14	49.1	48.1	0.02
Renal disease	4.3	2.9	0.08	96.7	96.6	0.01
Liver disease	22.9	22.5	0.01	78.3	77.2	0.03
Bleeding	9.5	5.6	0.15	92.9	93.6	0.03
Venous thromboembolism	8.5	14.0	0.17	88.7	88.8	0.00
Hypothyroidism	9.4	9.6	0.01	91.2	90.6	0.02
Osteoarthritis	5.3	6.7	0.06	93.9	93.7	0.01
Chronic obstructive pulmonary disease	11.4	10.3	0.04	89.9	89.7	0.01
Alcohol index	1.3	1.5	0.02	98.6	98.5	0.01
Pneumonia	8.3	6.2	0.08	93.4	93.3	0.00
Thyrotoxicosis	22.0	26.2	0.10	77.3	76.4	0.02
Parkinson's disease	0.4	0.3	0.02	99.7	99.7	0.00
Antiplatelet	14.1	13.4	0.02	84.9	85.2	0.01
ACE inhibitor or ARB	21.8	35.5	0.31	69.6	69.4	0.00
Diuretic	7.1	13.8	0.22	89.9	89.6	0.01
Statin	18.3	18.8	0.01	80.1	80.0	0.00
Nitrates	8.2	9.2	0.04	90.9	90.9	0.00
β-blocker	23.5	38.2	0.32	69.2	68.4	0.02
Antiarrhythmic drug, class 1 or 3	13.8	27.7	0.35	78.4	77.5	0.02
Digoxin	2.1	6.5	0.22	96.4	96.1	0.02

Data are expressed as percentages unless otherwise specified

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *DOAC* direct oral anticoagulant, *OAC* oral anticoagulant, *SD* standard deviation (DOAC and non-OAC groups), *TIA* transient ischemic attack

and non-OAC groups (log-rank test: $p = 0.006$). Meanwhile, no difference in the incidence of dementia was noted between the MPR ≥ 90% DOAC and non-OAC groups (log-rank test: $p = 0.250$) and between the MPR ≥ 90% WF and non-OAC groups (log-rank test: $p = 0.346$).

In an additional analysis for stroke risk, OAC administration carried a significantly higher risk of stroke in the MPR ≥90% group than in the non-OAC group (HR 1.16, 95% CI 1.08–1.26; $p < 0.001$) (Table 6). Furthermore, OAC administration was linked to a significantly higher

cumulative incidence of stroke in the MPR ≥ 90% group than in the non-OAC group (log-rank test: $p < 0.001$) (Fig. 4).

4 Discussion

The current study revealed that administration of OACs, be it DOAC or WF, did not reduce the risk of dementia in patients with nonvalvular AF. However, OAC administration with

Table 3 Characteristics of the study patients before and after propensity score matching (WF and non-OAC groups)

	Before matching			Propensity score–matched		
	Non-OAC (n = 10,067)	WF (n = 933)	Standardized differences	Non-OAC (n = 873)	WF (n = 873)	Standardized differences
Age, years [mean ± SD]	51.4 ± 11.7	56.3 ± 10.1	0.03	56.6 ± 9.9	56.2 ± 10.2	0.03
Female sex	36.6	19.7	0.38	18.6	20.6	0.05
Stroke/systemic emboli/TIA	15.5	23.3	0.20	22.7	21.8	0.02
Cancer	21.1	18.5	0.07	19.8	18.9	0.02
Ischemic stroke	12.1	17.6	0.16	17.2	16.4	0.02
Intracerebral hemorrhage	3.2	2.4	0.05	1.3	2.3	0.08
Other intracranial bleed	1.2	0.3	0.10	0.3	0.3	0.00
Myocardial infarction	16.8	19.4	0.07	19.2	18.9	0.01
Peripheral artery disease	13.3	24.2	0.28	22.5	22.7	0.00
Vascular disease	25.9	35.4	0.21	33.7	33.6	0.00
Heart failure	41.8	63.9	0.45	59.6	61.7	0.04
Any valvular disease	25.4	45.2	0.42	41.7	42.4	0.01
Hypertension	42.5	67.3	0.51	66.7	65.9	0.02
Diabetes	46.9	58.0	0.22	57.5	57.0	0.01
Renal disease	4.3	10.3	0.23	10.0	10.4	0.01
Liver disease	22.9	22.1	0.02	21.2	22.5	0.03
Bleeding	9.5	14.3	0.15	12.3	13.5	0.04
Venous thromboembolism	8.5	10.8	0.08	10.5	10.2	0.01
Hypothyroidism	9.4	9.1	0.01	10.7	9.2	0.05
Osteoarthritis	5.3	6.0	0.03	6.1	6.2	0.00
Chronic obstructive pulmonary disease	11.4	13.8	0.07	10.3	12.6	0.07
Alcohol index	1.3	1.8	0.04	1.6	1.8	0.02
Pneumonia	8.3	8.7	0.01	8.4	8.8	0.01
Thyrotoxicosis	22.0	16.8	0.13	16.4	17.2	0.02
Parkinson's disease	0.4	0.3	0.02	0.6	0.3	0.04
Antiplatelet	14.1	29.4	0.38	26.6	28.1	0.03
ACE inhibitor or ARB	21.8	42.6	0.46	43.3	40.9	0.05
Diuretic	7.1	36.9	0.77	34.0	32.5	0.03
Statin	18.3	24.5	0.15	24.6	25.0	0.01
Nitrates	8.2	29.3	0.56	22.6	25.5	0.07
β-blocker	23.5	49.0	0.55	44.8	46.2	0.03
Antiarrhythmic drug, class 1 or 3	13.8	38.6	0.59	33.9	35.3	0.03
Digoxin	2.1	10.8	0.36	9.0	9.5	0.02

Data are expressed as percentages unless otherwise specified

ACE, angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *OAC* oral anticoagulant, *SD* standard deviation (WF and non-OAC groups), *WF* warfarin, *TIA* transient ischemic attack

an adherence of MPR ≥ 90% reduced the risk of dementia among the same patients, suggesting that medication adherence may be a significant protective factor for dementia in patients with AF receiving OACs. In this study, MPR was used as the total duration of supply (days) of the prescribed drug divided by the number of days from the first prescription date to the end date of the last prescription. MPR is a commonly used calculation in health research and is supported by the International Society for Pharmaceutical and Outcomes Research [17–19].

In the separate analyses of DOAC and WF, administration in patients with an MPR ≥ 90% did not reduce the risk of dementia. Consequently, our study could not detect any difference in the effects of DOAC and WF on dementia prevention. Therefore, whether differences exist in the effects of WF and DOACs on dementia remains unclear. Indeed, several contradictory reports have been published on the association between OAC administration and the risk of dementia. Some studies reported that DOAC users had a lower risk of dementia than WF users

Table 4 Number of events, follow-up time, incidence rates, and hazard ratios for dementia impairment for a primary analysis

Types of OAC	Group	Propensity score–matched						
		No.	No. of events	Person-years at risk	Follow-up time (years) [mean ± SD]	IR per 1000 person-years (95% CI)	HR (95% CI)	p-Value
OAC vs. non-OAC								
All OACs	OAC	5587	23	8321	1.5 ± 1.3	2.76 (1.75–4.14)	0.66 (0.40–1.08)	0.098
	Non-OAC	5587	50	12,511	2.2 ± 1.6	4.00 (2.97–5.27)		
MPR ≥ 60% OAC	MPR ≥ 60% OAC	5476	28	8360	1.5 ± 1.4	3.35 (2.23–4.84)	0.86 (0.54–1.39)	0.548
	Non-OAC	5476	44	12,112	2.2 ± 1.5	3.63 (2.64–4.87)		
MPR ≥ 70% OAC	MPR ≥ 70% OAC	5403	26	8244	1.5 ± 1.4	3.15 (2.06–4.62)	0.83 (0.51–1.35)	0.447
	Non-OAC	5403	43	12,011	2.2 ± 1.5	3.58 (2.59–4.82)		
MPR ≥ 80% OAC	MPR ≥ 80% OAC	5293	24	8080	1.5 ± 1.4	2.97 (1.90–4.42)	0.76 (0.46–1.26)	0.292
	Non-OAC	5293	43	11,824	2.2 ± 1.6	3.64 (2.63–4.90)		
MPR ≥ 90% OAC	MPR ≥ 90% OAC	5032	15	7620	1.5 ± 1.4	1.97 (1.10–3.24)	0.45 (0.25–0.81)	0.008
	Non-OAC	5032	45	11,202	2.2 ± 1.6	4.02 (2.93–5.37)		
DOAC vs. non-OAC								
All DOACs	DOAC	5211	23	7315	1.4 ± 1.3	3.14 (1.99–4.71)	0.80 (0.48–1.34)	0.393
	Non-OAC	5211	43	11,641	2.2 ± 1.5	3.69 (2.67–4.97)		
MPR ≥60% DOAC	MPR ≥60% DOAC	5102	22	7243	1.4 ± 1.3	3.04 (1.90–4.60)	0.64 (0.39–1.07)	0.086
	Non-OAC	5102	49	11,438	2.2 ± 1.5	4.28 (3.17–5.66)		
MPR ≥ 70% DOAC	MPR ≥70% DOAC	5029	20	7170	1.4 ± 1.3	2.79 (1.70–4.30)	0.54(0.32–0.91)	0.022
	Non-OAC	5029	51	11,135	2.2 ± 1.5	4.58 (3.41–6.02)		
MPR ≥ 80% DOAC	MPR ≥ 80% DOAC	4928	20	7087	1.4 ± 1.3	2.82 (1.72–4.36)	0.64 (0.38–1.09)	0.102
	Non-OAC	4928	45	10,991	2.2 ± 1.5	4.09 (2.99–5.47)		
MPR ≥ 90% DOAC	MPR ≥ 90% DOAC	4647	18	6543	1.4 ± 1.3	2.75 (1.63–4.34)	0.72 (0.40–1.27)	0.252
	Non-OAC	4647	36	10,322	2.2 ± 1.5	3.49 (2.44–4.83)		
WF vs. non-OAC								
All WF	WF	873	5	1355	1.6 ± 1.5	3.69 (1.20–8.59)	0.68 (0.23–1.98)	0.475
	Non-OAC	873	10	1828	2.1 ± 1.5	5.47 (2.63–10.04)		
MPR ≥ 60% WF	MPR ≥ 60% WF	872	5	1355	1.6 ± 1.5	3.69 (1.20–8.59)	0.83 (0.28–2.47)	0.736
	Non-OAC	872	9	1945	2.2 ± 1.6	4.63 (2.12–8.77)		
MPR ≥ 70% WF	MPR ≥ 70% WF	844	4	1327	1.6 ± 1.5	3.01 (0.82–7.70)	0.58 (0.18–1.90)	0.371
	Non-OAC	844	9	1781	2.1 ± 1.5	5.05 (2.31–9.57)		
MPR ≥ 80% WF	MPR ≥ 80% WF	830	5	1301	1.6 ± 1.5	3.84 (1.25–8.95)	0.71 (0.24–2.08)	0.531
	Non-OAC	830	10	1783	2.2 ± 1.5	5.61 (2.69–10.29)		
MPR ≥ 90% WF	MPR ≥ 90% WF	780	4	1205	1.5 ± 1.5	3.32 (0.91–8.48)	0.58 (0.18–1.84)	0.352
	Non-OAC	780	10	1746	2.2 ± 1.5	5.73 (2.75–10.51)		

CI confidence interval, *DOAC* direct oral anticoagulant, *HR* hazard ratio, *IR* incidence rate, *MPR* medication possession ratio, *OAC* oral anticoagulant, *SD* standard deviation, *WF* warfarin

[20, 21]. In contrast, studies in Sweden [9, 22], the UK [23], and Korea [7] showed that OACs, including DOACs and WF, reduced the risk of dementia. Among the aforementioned studies, the Sweden study alone accounted for adherence to medication [9, 22]. Therefore, it cannot be denied that the presence or absence of medication adherence consideration may affect the results.

Anticoagulant therapy with WF requires dose adjustment based on the prothrombin time-international normalized ratio (PT-INR) to ensure sufficient efficacy and to prevent adverse effects, including bleeding. Additionally, the time in therapeutic range (TTR) has been used to evaluate the quality of WF therapy. A study reported that patients with a high TTR had a lower risk of dementia [24]. Although PT-INR or TTR would be a relevant parameter for assessing adherence, these laboratory data were not included in the JMDC database.

The current study found fewer incident WF users than incident DOAC users. Notably, DOACs are easier to use than WF because the former does not require PT-INR

Table 5 Number of events, follow-up time, incidence rates, and hazard ratios for dementia

		No.	No. of events	Person-years at risk	Follow-up time (years) [mean ± SD]	IR per 1000 person-years (95% CI)	HR (95% CI)	p-Value
OAC	MPR ≥ 90%	6675	28	10,038	1.5 ± 1.3	2.79 (1.85–4.03)	0.59 (0.27–1.30)	0.191
	MPR < 90%	1220	8	1690	1.4 ± 1.3	4.73 (2.05–9.31)		
DOAC	MPR ≥ 90%	5862	23	8249	1.4 ± 1.3	2.79 (1.77–4.18)	0.59 (0.25–1.38)	0.223
	MPR < 90%	1100	7	1461	1.3 ± 1.2	4.79 (1.93–9.85)		
WF	MPR ≥ 90%	830	5	1274	1.5 ± 1.5	3.92 (1.28–9.13)	0.63 (0.07–5.39)	0.673
	MPR < 90%	103	1	160	1.6 ± 1.5	6.25 (0.16–34.33)		

CI confidence interval, *DOAC* direct oral anticoagulant, *HR* hazard ratio, *IR* incidence rate, *MPR* medication possession ratio, *OAC* oral anticoagulant, *SD* standard deviation, *WF* warfarin
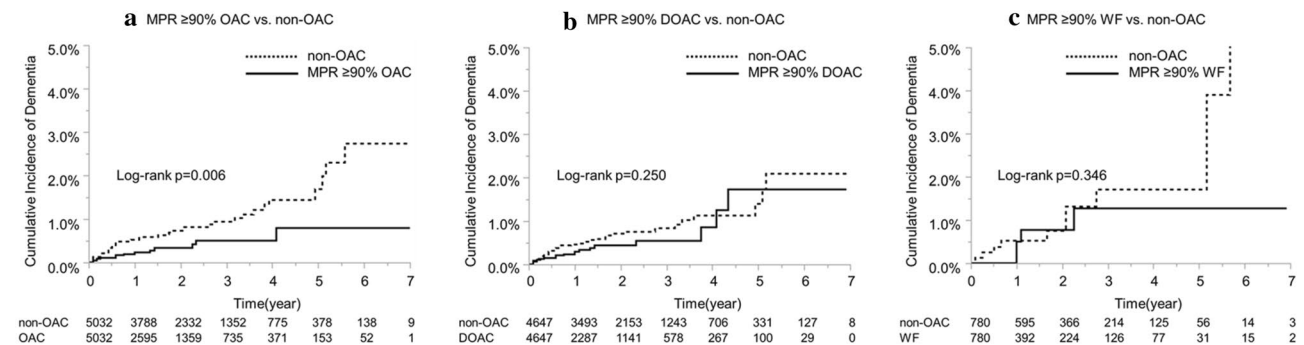
Fig. 3 Cumulative incidence of dementia in patients with incident atrial fibrillation after propensity score matching. *DOAC* direct oral anticoagulant, *MPR* medication possession ratio, *OAC* oral anticoagulant, *WF* warfarin

Table 6 Number of events, follow-up time, incidence rates, and hazard ratios for stroke

		No.	No. of events	Person-years at risk	Follow-up time (years) [mean ± SD]	IR per 1000 person-years (95% CI)	HR (95% CI)	p-Value
OAC vs. non-OAC	MPR ≥ 90% OAC	6675	1165	8301	1.2 ± 1.3	140.34 (132.94–148.00)	1.16 (1.08–1.26)	<0.001
	Non-OAC	10,067	1716	19,595	1.9 ± 1.6	87.57 (83.65–91.62)		

CI confidence interval, *HR* hazard ratio, *IR* incidence rate, *MPR* medication possession ratio, *OAC* oral anticoagulant, *SD* standard deviation

measurements and have fewer interactions with drugs and food. Several recent treatment guidelines have recommended the use of DOACs instead of WF for anticoagulant therapy in patients with nonvalvular AF [25–28]. Meanwhile, a study in Japan showed that WF users had higher CHADS$_2$ (congestive heart failure, hypertension, 75 years of age or older, diabetes mellitus, and previous stroke or transient ischemic attack) and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs/alcohol concomitantly) scores and several other comorbidities compared with DOAC users [29]. In Japan, WF is likely

used more than DOACs in patients with severe AF. Therefore, the difference in dementia risk between WF and DOAC use in patients with AF needs to be carefully studied.

Aging is a significant risk factor for the development of dementia. In the study, the OAC and non-OAC groups had crude incidences of dementia of 2.76 and 4.00 per 1000 person-years, respectively, which were lower than previously reported data [7, 9, 22, 23]. The JMDC database contains claims data for relatively young working patients and their families collected from multiple health insurance associations. Consequently, the aforementioned database, which includes patients aged 0–75 years, demonstrated that the
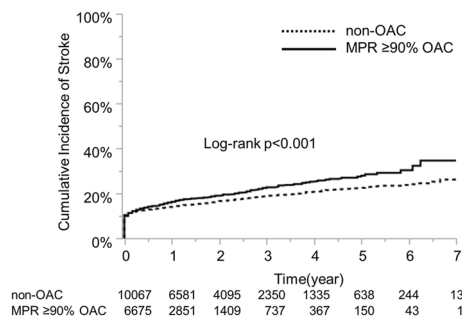
Fig. 4 Cumulative incidence of stroke in patients with incident atrial fibrillation. *MPR* medication possession ratio, *OAC* oral anticoagulant

OAC and non-OAC groups had mean ages of 56.9 ± 9.5 and 51.4 ± 11.7 years, respectively. Conversely, Friberg and Rosenqvist [9] reported that the OAC and non-OAC groups had mean ages of 73.7 and 75.7 years, respectively, with Mongkhon et al. [23] reporting mean ages of 73.3 and 72.9 years, respectively, for the same groups. Although Kim et al. [7] did not provide patient background data for the OAC and non-OAC groups, the mean age of patients with AF included in their study was 70.7 years. The lower incidence of dementia obtained in this study than in previous studies may be attributable to our relatively young study population. Our study revealed that OAC therapy with high adherence reduced the risk of dementia even in relatively young patients, who had a lower risk of dementia.

One hypothesis suggests that effective anticoagulant therapy maintains cognitive function in patients with AF by reducing the risks of stroke and SCI. Indeed, a number of retrospective studies reported that OACs reduced the development of stroke or SCI and subsequently reduced the risk of dementia or cognitive impairment in patients with AF [8–10]. However, the study revealed that OAC administration was linked to a significantly higher risk of stroke in the MPR ≥ 90% group than in the non-OAC group, suggesting that OAC administration reduced the risk of dementia in patients with an MPR ≥ 90% regardless of the history of stroke. It is assumed that the patients with an MPR ≥ 90% may have a high risk of stroke. The increased risk of stroke associated with OAC administration in patients with an MPR ≥ 90% may be attributable to indication bias. Furthermore, it seemed paradoxical that the MPR ≥ 90% OAC group is associated with an increased risk of stroke, but a reduced risk of dementia. It is hypothesized that high adherence to OAC therapy in patients with a high risk of stroke contributes to the reduced risk of dementia by additional mechanisms other than stroke. Further studies are needed to evaluate this hypothesis.

The current study has several limitations worth considering when interpreting our results. First, MPR was used as an indirect indicator of adherence to anticoagulants. The study determined whether anticoagulants were prescribed or dispensed but not whether patients actually took them. Furthermore, the time-dependent variance of MPR was not considered in the study. Therefore, it remains unclear whether MPR can accurately determine adherence to anticoagulant therapy. Second, the study was performed using a claims database as secondary data. We note that the diagnosis stated in the claim could have been listed to justify the health insurance claim or that the diagnosis of AF or dementia using ICD-10 codes may be higher than that reported because of subclinical events. Although some studies reported that ICD-10 codes generally have high sensitivity and specificity [16, 30], it remains unclear whether ICD-10 code I48 accurately identifies AF in the JMDC claims database. Nevertheless, the JMDC claims database used in this study includes approximately 6 million insured individuals in Japan (approximately 5% of the population). Third, given that our study population comprised relatively young working adults and their family members, while patients aged > 75 years were not included, the results presented herein may not be applicable to all populations. Fourth, most patients were followed for approximately 2 years. This follow-up may not be sufficient to identify the full risk or benefit to OAC over a longer course. Lastly, the WF group was significantly smaller than the DOAC group. As a result, the HR estimates may be inaccurate owing to the limited sample size of subjects using WF.

5 Conclusion

This retrospective cohort study demonstrated that OAC use did not affect the risk of dementia among relatively young patients with AF. However, OAC administration reduced the risk of dementia in patients with an MPR ≥ 90%. Therefore, the association between OAC administration and dementia should be evaluated while considering medication adherence. Further studies are needed to investigate the differences between the effects of DOACs and WF on dementia.

Appendix 1

MPR

$$MPR = \frac{\text{Total Day's Supply in Period}}{\text{Last Fill Date} - \text{First Fill Date} + \text{Last Fill Day's Supply}}$$

Declarations

Conflicts of interest Yuika Komatsu, Satoshi Yokoyama, Kouichi Hosomi, and Mitsutaka Takada declare they have no conflicts of interest.

Ethics approval This study was approved by the Ethics Committee of Kindai University School of Pharmacy (approval number: 17-112).

Consent to participate Not applicable.

Consent for publication Not applicable.

Informed consent Informed consent was not required for this study since all personal names and identification numbers from the JMDC claims database were replaced by a univocal numerical code.

Data availability The data that support the findings of this study are available at https://www.jmdc.co.jp/, with the permission from JMDC, Inc. Restrictions apply to the availability of these data, which were used under license for this study.

Code availability Not applicable.

Author Contributions All authors contributed to the study conception and design. Material preparation and data collection and analysis were performed by YK, SY, and KH. The draft of the manuscript was written by YK and MT. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

Permission to Reproduce Material from Other Sources Not applicable.

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