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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
Background: Dementia and atrial fibrillation (AF) have many shared risk factors. There are limited data on the risks of incident AF and AF-related clinical outcomes in patients with dementia.
Methods: Out study utilized the Taiwan National Health Insurance Research Database. A total of 544,074 patients with dementia were compared to 554,074 age- and sex-matched patients without dementia regarding the risk of incident AF. Among patients with dementia who experienced incident AF, the risks of clinical events of patients treated with warfarin or NOACs were compared to those without OACs.
Results: The risk of incident AF was greater for patients with dementia compared to those without (1.89 vs 1.78 per 100 person-years). Among patients with dementia and experienced incident AF, warfarin use was associated with a higher risk of ischemic stroke (aHR 1.290; 95%CI 1.156-1.440), intracranial hemorrhage (ICH)(aHR 1.678; 95%CI 1.346-2.090) and major bleeding (aHR 1.192; 95%CI 1.073-1.323) compared to non-OACs. NOAC use was associated with a lower risk of ischemic stroke (aHR 0.421; 95%CI 0.352-0.503) and composite risk of ischemic stroke or major bleeding (aHR 0.544; 95%CI 0.487-0.608) compared to non-OACs. These results were consistent among the patients after the propensity matching.
Conclusions: In this nationwide cohort, the risk of incident AF was higher in patients with dementia. For patients with dementia who experienced incident AF, NOAC use was associated with better clinical outcomes compared to non-OAC. Patients with dementia require a holistic approach to their care and management, including the use of NOACs to reduce risks of clinical events.

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"What is known about this topic?"

- Dementia and atrial fibrillation (AF) have many shared risk factors and patients with dementia were under-represented in randomized trials.
- Decisions about prescriptions of oral anticoagulants (OAC) are challenging for dementia patients who were diagnosed to have incident AF.

"What does this paper add?"

- The risk of incident AF was greater for patients with dementia compared to those without.
- Among patients with dementia and experienced incident AF, warfarin use was associated with a higher risk of ischemic stroke, intracranial hemorrhage and major bleeding compared to non-OACs, while NOAC use was associated with a better clinical outcome.
- Patients with dementia require a holistic approach to their care and management, including the use of NOACs to reduce risks of clinical events.

Risk of Incident Atrial Fibrillation and Subsequent Use of Oral Anticoagulants in Patients with Dementia

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Running title: Incident AF in dementia

Conflict of interest: The authors have no conflicts to disclose.

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Abstract

BACKGROUND: Dementia and atrial fibrillation (AF) have many shared risk factors. Besides, patients with dementia are under-represented in randomized trials, and even if AF is present, oral anticoagulants (OAC) are not prescribed frequently. This study aimed to report the incidence of newly-diagnosed AF in dementia patients, and the impacts of use of vitamin K antagonist (VKA, eg warfarin) and non-VKA OAC (NOACs) on stroke and bleeding outcomes.

METHODS: Out study utilized the Taiwan National Health Insurance Research Database. A total of 544,074 patients with dementia were compared to 554,074 age- and sex-matched patients without dementia regarding the risk of incident AF. Among patients with dementia who experienced incident AF, the risks of clinical events of patients treated with warfarin or NOACs were compared to those without OACs (reference group).

RESULTS: The risk of incident AF was greater for patients with dementia compared to those without (adjusted hazard ratio [aHR] 1.054; 95% confidence interval [CI] 1.040-1.068 for all types of dementia, aHR 1.035; 95%CI 1.020-1.051 for pre-senile/senile dementia, and aHR 1.125; 95%CI 1.091-1.159 for vascular dementia). Among patients with dementia and experienced incident AF, warfarin use was associated with a higher risk of ischemic stroke (aHR 1.290; 95% CI 1.156-1.440), intracranial hemorrhage (ICH)(aHR 1.678; 95%CI 1.346-2.090) and major

bleeding (aHR 1.192; 95%CI 1.073-1.323) compared to non-OACs. NOAC use was associated with a lower risk of ischemic stroke (aHR 0.421; 95%CI 0.352-0.503) and composite risk of ischemic stroke or major bleeding (aHR 0.544; 95%CI 0.487-0.608) compared to non-OACs. These results were consistent among the patients after the propensity matching.

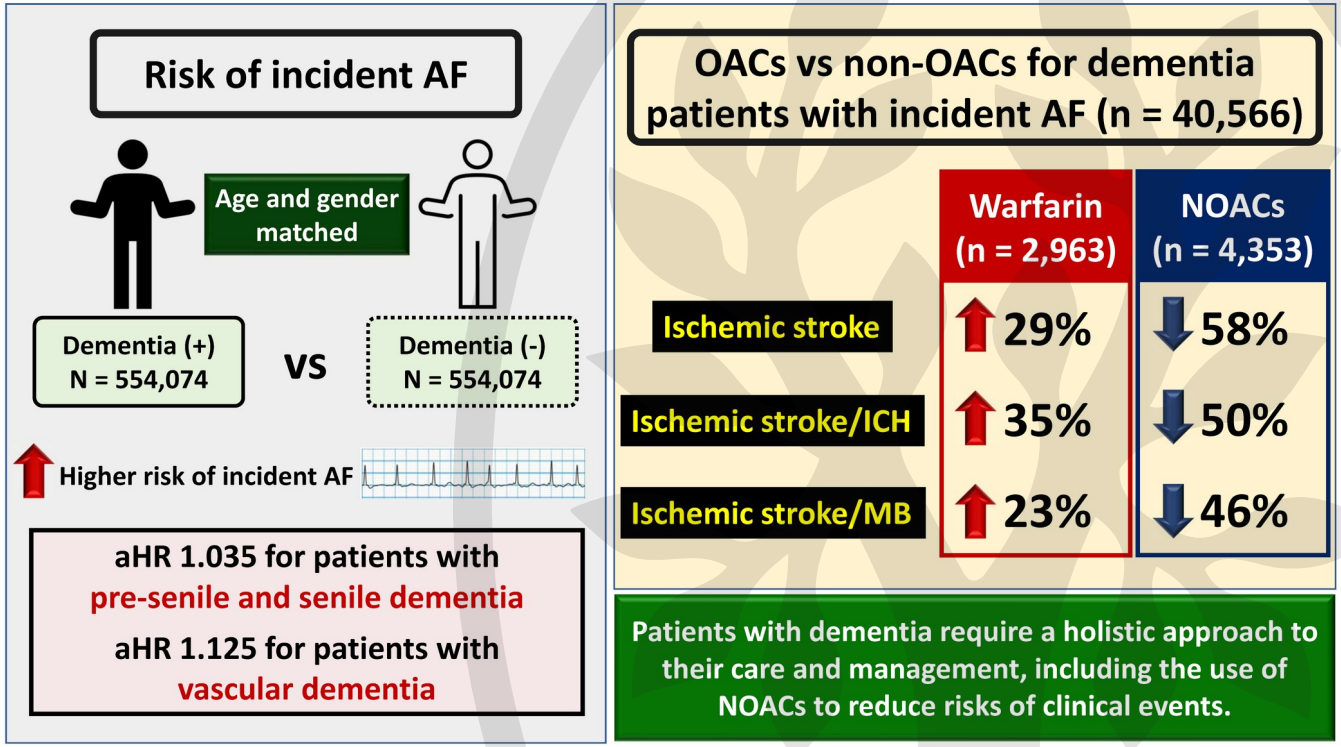
CONCLUSION: In this large nationwide cohort, the risk of newly-diagnosed AF was higher in patients with dementia (all dementia, pre-senile/senile dementia and vascular dementia) compared to those without dementia. For patients with dementia who experienced incident AF, NOAC use was associated with a better clinical outcome compared to non-OAC. Patients with dementia require a holistic approach to their care and management, including the use of NOACs to reduce the risks of clinical events.

Keywords: atrial fibrillation, dementia, NOACs

Nonstandard Abbreviations and Acronyms

AF, Atrial fibrillation; OAC, oral anticoagulant; TTR, time in therapeutic range; NOAC, non-vitamin K antagonist OAC; VKA, vitamin K antagonist; NHIRD, National Health Insurance Research Database; HWDC, Health and Welfare Data Science Centre; NHI, National Health Insurance; INR, labile international normalized ratio; ICH, intracranial hemorrhage; SD, standard deviation; aHR, adjusted hazard ratio.

Visual Summary – Incident atrial fibrillation and use of oral anticoagulants in patients with dementia. AF = atrial fibrillation; aHR = adjusted hazard ratio; ICH = intracranial hemorrhage; MB = major bleeding; NOACs = non-vitamin K antagonist OACs; OACs = oral anticoagulants



Introduction

Dementia and atrial fibrillation (AF) shared various common risk factors, and the presence of AF increased risk of incident dementia via multiple different mechanisms.[1] While the most common cause of death in patients with dementia was cardiovascular related,[2] there are sparse report on the risks of incident AF, and the associated AF-related clinical outcomes in patients with dementia. In addition, those patients represented minor population in randomized trials. Even though AF is present, decision about prescription of oral anticoagulants (OAC) is challenging as warfarin was reported to be associated with increased traumatic intracranial bleeding from fall and co-existing co-morbidities such as abnormal liver or renal function in patients with dementia.[3]

Prior studies have focused on incident dementia in AF patients, and the relation to risk factors such as hypertension burden, smoking and alcohol, as well as the impact of OAC use on dementia onset in AF patients, and the differences in efficacy between warfarin and non-vitamin K antagonist OAC (NOACs).[4,5] With warfarin users, one study showed a clear relationship to the quality of anticoagulation control, as reflected by the time in therapeutic range (TTR).[5] While many studies reported marginal differences between warfarin and NOACs for incident dementia, one Danish study reported that amongst AF patients aged ≥80 years, NOACs were less effective than warfarin for incident dementia.[6] Studies on the converse relationship, that is, of dementia patients developing new onset AF, and the impact on AF-related complications are sparse.

The aim of this nationwide study was to report the incidence of newly diagnosed AF in dementia patients, and secondly, the impacts of use of vitamin K antagonist (VKA, e.g., warfarin) and NOACs on stroke and bleeding outcomes.

Methods

Database

This study used the "National Health Insurance Research Database (NHIRD)" provided by the Health and Welfare Data Science Centre (HWDC), Ministry of Health and Welfare (MOHW), Taiwan. The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. NHIRD consists of detailed health care data from over 23 million enrollees, representing more than 99% of Taiwan's population. In this cohort dataset, the patients' original identification numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent, so that a linkage of the claims belonging to the same patient was feasible within the NHI database and can be followed continuously. The descriptions about Taiwan NHIRD have been reported in our previous studies.[7-14]

Study population

The flowchart of patient enrollment is shown in **Figure 1**. From January 1st, 2007 to December 31st, 2018, a total of 554,074 patients aged ≥20 years with newly-diagnosed dementia who didn't have previous history of AF was identified from the NHIRD as the "dementia population". Alzheimer's disease, vascular dementia and pre-senile/senile dementia were diagnosed in 11,518, 109,056 and 433,500 patients, respectively. At the same index date when the patients were diagnosed as having dementia, 554,074 age- and gender-matched subjects without previous history of dementia and AF were identified to constitute the "non-dementia population". The risk of new-onset AF was compared between dementia and non-dementia groups.

Stroke prevention strategies after newly-diagnosed AF among the dementia population

Among the dementia population, 40,566 patients experienced incident AF during the follow up with an incidence rate of 1.89 per 100 person-years. Among these patients, the risks of clinical events were compared between patients receiving different stroke prevention strategies; that is, “without OACs” (n = 33,250), “warfarin” (n = 2,963) and “NOACs” (n = 4,353).

Calculation of scores and definitions of clinical endpoints

The calculation rules of CHA_2DS_2-VASc score, HAS-BLED score and the definitions of clinical endpoints have been published in our previous works.[12,15,16] Notably, the component of “labile international normalized ratio (INR)” was excluded from the calculation of HAS-BLED score in the present study because the information on INR of warfarin was not available in the Taiwan registry database. Also, abnormal renal and liver functions were defined by the ICD-9-CM codes rather than laboratory data.

The clinical endpoints of the present study included the occurrences of ischemic stroke, major bleeding, intracranial hemorrhage (ICH), composite events of ischemic stroke or major bleeding, and ischemic stroke or ICH. The accuracy of diagnosis of ischemic stroke in Taiwan’s NHIRD has been reported to be around 94%.[17] Another validation study also demonstrated that the diagnostic accuracy of ischemic stroke in NHIRD was high, with the positive predictive value and sensitivity of 88.4% and 97.3%, respectively.[18] Major bleeding was defined as ICH or bleeding from gastrointestinal or genitourinary or respiratory tract requiring hospitalization.

Falsification analysis (sensitivity analysis)

The statements about the falsification analysis have been published in our previous works.[9,14] In order to further assess the likelihood of confounding by indication, we analyzed three falsification endpoints (cellulitis, gastric cancer and extremity fracture/dislocation) which were unlikely to be affected by different stroke prevention strategies. A finding of an association between different stroke prevention strategies and these falsification endpoints would therefore indicate the presence of unmeasured confounders. On contrary, if risks of these falsification endpoints of different patients' groups did not differ significantly, the differences between different stroke prevention strategies with regard to clinical outcomes in which we were interested may be less likely due to treatment selection bias.

Propensity matched analysis

We performed propensity score–matched analyses for 2 kinds of comparisons among patients with dementia who experienced AF: "warfarin versus without OACs" and "NOACs versus without OACs". We calculated propensity scores for the likelihoods of receiving warfarin compared to without OACs by multivariate logistic regression analyses, conditional on baseline covariates. After that, we matched patients in the warfarin group to those in the no OAC group with a 1:1 ratio on the basis of the closest propensity score for the use of warfarin within a threshold of ±0.01 using the greedy algorithm. If more than one patient in the no OAC group could be matched to the corresponding subject in the warfarin group, 1 patient from the no OAC group was selected randomly without repeat sampling. Similar matching processes were performed for the comparisons of "NOACs versus no OACs".

Statistical analysis

Data are presented as the mean value and standard deviation (SD) for continuous variables, and proportions for categorical variables. Differences between continuous values and nominal variables were assessed using the unpaired two-tailed *t*-test and chi-squared test, respectively. The incidences of clinical events were calculated from dividing the number of events by person-time at risk. The risks of adverse events were assessed using the Cox regression analysis adjusted for age, sex and clinical variables which were significantly different between the comparison's groups. The cumulative incidences curves of events were plotted via the Kaplan-Meier method with statistical significance examined by the log-rank test. All statistical significances were set at a $p < 0.05$.

Results

Baseline characteristics of patients with or without dementia are shown in **Table 1**, and the flowchart of patients' enrollment is shown in **Figure 1**. The age- and sex-matched 544,074 patients with dementia, compared to 554,074 patients without dementia. Compared to those without dementia, patients with dementia were of similar age and had statistically significant but marginal differences in various comorbidities. Patients with dementia had more co-morbidities such as hypertension, diabetes mellitus, heart failure, stroke, chronic obstructive pulmonary disease and abnormal renal function but lesser co-morbidities such as hyperlipidemia, autoimmune diseases, cancer, abnormal liver function and anemia compared to those without dementia.

Risk of incident AF in patients with dementia

Figure 2 compares the rates of newly diagnosed or incident AF in patients with and without dementia, being 1.89/100 person-years in patients with dementia compared to 1.78/100 person-years in patients without dementia. When comparing patients with and without dementia, the adjusted risk of incident AF was greater in all types of dementia (adjusted hazard ratio, aHR, 1.054; 95% confidence interval (CI), 1.040 - 1.068), pre-senile/senile dementia (aHR, 1.035; 95% CI, 1.020 - 1.051) and vascular dementia (aHR, 1.125; 95% CI, 1.091 - 1.159). For Alzheimer's dementia, the aHR was 1.104, with wide 95% CI (0.931 – 1.309) due to small patients' numbers.

Antithrombotic strategies and clinical events in dementia patients with incident AF

Table 2 shows baseline characteristics of patients with dementia, in relation to warfarin (n=2963), NOAC (n=4353) and non-OAC (n=33250) use. When compared to non-OAC users, both warfarin and NOAC users were younger (with lower proportion with age ≥75), lower proportions with anemia or history of bleeding, a higher mean CHA_2DS_2-VASc score and marginally lower mean HAS-BLED score, as well as small differences in various comorbidities.

Figure 3 illustrates the risks of clinical events of ischemic stroke, ICH, major bleeding and composite outcomes. Using non-OAC users as reference, warfarin use was associated with a higher risk of ischemic stroke (aHR, 1.290; 95% CI, 1.156 - 1.440) while NOAC use was associated with a lower ischemic stroke risk (aHR, 0.42; 95% CI, 0.352 - 0.501). For ICH, warfarin use was associated with higher ICH risk

(aHR, 1.678; 95% CI, 1.346 - 2.09) while NOACs had a non-significant difference for ICH compared to non-OAC use (aHR, 0.971; 95% CI, 0.725 – 1.301). For major bleeding, there was a higher risk for warfarin user (aHR, 1.192; 95% CI, 1.073 - 1.323) and lower risk for NOACs (aHR, 0.665; 95% CI, 0.580 – 0.761), when compared to non-OAC use. Warfarin use was associated with higher risk of composite ischemic stroke and ICH (aHR, 1.347; 95% CI, 0433 – 0587) than those without OAC use. A similar pattern was seen for the composite outcome of 'ischemic stroke and major bleeding'. Kaplan-Meier curves of cumulative incidence of ischemic stroke or ICH are shown in **Figure 4**).

Falsification analysis

The risks of 3 falsification endpoints (cellulitis, gastric cancer and fracture/dislocation) did not differ significantly between different stroke prevention strategies (warfarin, NOAC) compared to the "without OAC" group (**Table 3**). The results of falsification analyses suggested that the significant differences between different treatment groups with regard to clinical outcomes of interest may be less likely due to treatment selection bias.

Propensity matched analysis

After propensity matching, there were no significant differences about propensity scores in matched paired comparisons between "warfarin vs non-OAC users" and "NOACs vs non-OAC users" (**Supplemental Table 1** and **Supplemental Table 2**). The principal results were generally consistent to that of multivariable Cox regression analyses performed among the pre-matched cohort (**Supplemental Figure 1**).

Discussion

In this nationwide study, our principal findings are as follows: (i) The incidence rate of newly diagnosed or incident AF was 1.89/100 person-years in patients with dementia while that is lower in patients without dementia, 1.78/100 person-years; (ii) When comparing patients with and without dementia, the adjusted risk of incident AF was greater in all kinds of dementia, pre-senile/senile dementia and vascular dementia, with a trend for Alzheimer's dementia; and (iii) Compared to non-OAC users, warfarin use was associated with a higher risk of ischemic stroke, ICH and major bleeding, while NOAC use was associated with a lower ischemic stroke and major bleeding; and (iv) NOAC monotherapy was the only approach associated with a positive net clinical benefit, a lower composite outcome of 'ischemic stroke and ICH, ischemic stroke and major bleeding', while warfarin was associated with a higher composite outcome.

As far as we are aware, this is the largest cohort study of patients with dementia, in relation to their risks of incident AF as well as the impact on stroke and major bleeding outcomes with warfarin and NOAC use. Our data clearly show the higher rate of incident AF amongst patients with dementia, compared to those without history of dementia. This greater risk of incident AF, adjusted for confounders, was evident for all types of dementia, pre-senile/senile dementia and vascular dementia, with a non significant trend for Alzheimer's dementia. The highest aHR was seen for vascular dementia, perhaps reflecting the associations of vascular dementia and AF through mechanisms of overt or subclinical stroke, AF-induced systemic inflammation, chronic brain hypoperfusion, side effects of AF-specific medications.[19-22]

Patients with dementia are under-represented in randomized trials, and if AF is present, OAC is often not prescribed. The latter perception may relate to the need for good anticoagulation control if warfarin is used, given the close relationship between TTR for INR 2.0-3.0 and stroke

or bleeding outcomes.[23] In the present study, we did not have TTR data, but prior studies from Taiwan have indicated an overall poor TTR (around 50%).[24] This may partly explain why warfarin users in our AF patients with dementia had a higher risk of stroke, ICH and major bleeding, when compared to non-OAC users. In contrast, NOACs do not require anticoagulation monitoring, and very few drug-drug, drug-food interaction. Our data are consistent with improved effectiveness and safety of NOACs when used in AF patients, but extending the evidence to dementia population.

Interestingly, our results showed that the NOAC group was associated with a lower risk of major bleeding than the non-OAC group. Since our investigation was a retrospective analysis rather than a randomized trial, it may be possible that AF patients receiving NOACs were under more comprehensive medical care for close monitoring and corrections of modifiable bleeding risk factors which may lead to a lower bleeding risk.

The risk of incident AF amongst dementia patients highlights the current approach for a more holistic or integrated care approach for managing AF patients,[25] especially since such management is associated with less incident dementia amongst AF patients.[25] Also, a reduced risk of incident dementia in AF patients is associated with better risk factor management (e.g., smoking cessation, lower hypertension burden) and possibly, rhythm control.[26] Indeed, a holistic or integrated care approach for managing AF patients has been associated with improved clinical outcomes[27] and incorporated into guidelines.[28,29]

Study limitations

There are several limitations of the present study mainly owing to the nature of the database we used. First, the diagnosis of AF and occurrence of ischemic stroke were based on the diagnostic codes registered by the physicians responsible for the treatments of patients; nonetheless, the accuracy of these diagnoses has been previously validated.[17,18,30] Second, since our study was an observational study rather than a randomized trial, the presence of unmeasured confounders and selection bias is highly probable which could alter the result. Although the results of falsification analyses may suggest that significant differences between different treatment groups with regard to clinical outcomes in which we were interested may be less likely due to treatment selection bias. Third, we can only report "associations" and do not imply causality. Our findings would need to be confirmed in large prospective randomized trials comparing different antithrombotic strategies.

Conclusion

In this large nationwide cohort, the risk of newly-diagnosed AF was higher in patients with dementia (all dementia, pre-senile/senile dementia and vascular dementia) compared to those without dementia. For patients with dementia who experienced incident AF, NOAC use was associated with a better clinical outcome compared to non-OAC. Patients with dementia require a holistic approach to their care and management, including the use of NOACs to reduce the risks of clinical events.

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2. This study is based on data from the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare (MOHW), Taiwan. The interpretation and conclusions contained herein do not represent those of HWDC, MOHW, Taiwan.

Conflicts of Interest and Financial Disclosures

None

Author Contributions

Study concept and design: Chuan-Tsai Tsai, Tze-Fan Chao, Gregory Y. H. Lip, Shih-Ann Chen

Acquisition of data: Tzeng-Ji Chen, Yi-Hsin Chan

Analysis and interpretation of data: Tze-Fan Chao, Gregory Y. H. Lip, Shih-Ann Chen

Drafting of the manuscript: Chuan-Tsai Tsai, Tze-Fan Chao, Gregory Y. H. Lip

Critical revision of the manuscript for important intellectual content: Gregory Y. H. Lip, Shih-Ann Chen

Statistical analysis: Tze-Fan Chao, Jo-Nan Liao

Study supervision: Gregory Y. H. Lip, Shih-Ann Chen

Data availability statement

The data underlying this article cannot be shared publicly due to ethical/privacy reasons.

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Table 1. Baseline characteristics of AF patients with or without dementia

Variables	Without dementia (n = 554,074)	With dementia (n = 554,074)	p
Age, years; mean value (SD)	79.58 (8.7)	79.58 (8.7)	0.9891
Age ≥ 75 years, *n* (%)	407525 (73.55)	407526 (73.55)	0.9983
Age 65–74 years, *n* (%)	132205 (23.86)	132205 (23.86)	1.000
Male gender, *n* (%)	247441 (44.66)	247441 (44.66)	1.000
Comorbidities, *n* (%)			
Hypertension	403440 (72.81)	394349 (71.17)	<.0001
Diabetes mellitus	187356 (33.81)	198703 (35.86)	<.0001
Heart failure	78330 (14.14)	83839 (15.13)	<.0001
Prior stroke/TIA	89426 (16.14)	159424 (28.77)	<.0001
Vascular diseases	40242 (7.26)	40674 (7.34)	0.1147
COPD	128672 (23.22)	133566 (24.11)	<.0001
Hyperlipidemia	220523 (39.8)	201612 (36.39)	<.0001
Autoimmune diseases	34688 (6.26)	30667 (5.53)	<.0001
Cancer	75928 (13.7)	61208 (11.05)	<.0001
Abnormal renal function	82823 (14.95)	87180 (15.73)	<.0001
Abnormal liver function	89214 (16.1)	81483 (14.71)	<.0001

Anemia	70154 (12.66)	82570 (14.9)	<.0001

AF = atrial fibrillation; SD = standard deviation; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

Table 2. Clinical characteristics of patients with dementia experiencing incident AF receiving different stroke prevention strategy

Variables	**Without OACs (n = 33,250)**	**Warfarin* (n = 2,963)**	**NOACs[#] (n = 4,353)**	**P***	**P[#]**
Age, years; mean value (SD)	85.00 (7.27)	82.26 (7.3)	83.92 (6.91)	<.0001	<.0001
Age ≥ 75 years, *n* (%)	30493 (91.71)	2538 (85.66)	3947 (90.67)	<.0001	0.020
Age 65–74 years, *n* (%)	2615 (7.86)	392 (13.23)	396 (9.1)	<.0001	0.005
Male gender, *n* (%)	15213 (45.75)	1303 (43.98)	1779 (40.87)	0.064	<.0001
Comorbidities, *n* (%)					
Hypertension	28204 (84.82)	2543 (85.83)	3932 (90.33)	0.141	<.0001
Diabetes mellitus	13426 (40.38)	1188 (40.09)	1944 (44.66)	0.758	<.0001
Heart failure	14923 (44.88)	1511 (51)	1928 (44.29)	<.0001	0.462
Prior stroke/TIA	14983 (45.06)	1522 (51.37)	2023 (46.47)	<.0001	0.079
Vascular diseases	4528 (13.62)	401 (13.53)	658 (15.12)	0.891	0.007
COPD	15170 (45.62)	984 (33.21)	1602 (36.8)	<.0001	<.0001
Hyperlipidemia	10777 (32.41)	1212 (40.9)	2391 (54.93)	<.0001	<.0001
Autoimmune diseases	1906 (5.73)	212 (7.15)	394 (9.05)	0.002	<.0001
Cancer	4936 (14.85)	366 (12.35)	741 (17.02)	<.0001	<.0001
Abnormal renal function	8255 (24.83)	761 (25.68)	1152 (26.46)	0.305	0.020
Abnormal liver function	4937 (14.85)	445 (15.02)	922 (21.18)	0.803	<.0001
Anemia	9246 (27.81)	615 (20.76)	816 (18.75)	<.0001	<.0001
History of bleeding	12702 (38.2)	931 (31.42)	1522 (34.96)	<.0001	<.0001
Alcohol excess/abuse	306 (0.92)	16 (0.54)	49 (1.13)	0.035	0.178
CHA_2DS_2-VASc score; mean values (SD)	5.19 (1.6)	5.34 (1.56)	5.37 (1.54)	<.0001	<.0001
HAS-BLED score, mean value (SD)	3.5 (1.23)	3.41 (1.18)	3.44 (1.19)	<.0001	0.002

*P value between Warfarin and “Without OACs”

[#]P value between NOACs and “Without OACs”

AF = atrial fibrillation; OACs = oral anticoagulants; NOACs = non–vitamin K antagonist oral anticoagulants; SD = standard deviation; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease.

Table 3. Risks of 3 falsification endpoints of patients receiving warfarin or NOACs compared to "without OACs"

	Event rate (%/year)	Adjusted HR (95%CI)	P value
Cellulitis			
Without OACs	3.18		
Warfarin	2.92	1.002 (0.880 - 1.140)	0.982
NOACs	2.54	1.013 (0.866 - 1.185)	0.876
Gastric cancer			
Without OACs	0.26		
Warfarin	0.30	1.126 (0.693-1.828)	0.595
NOACs	0.24	1.016 (0.624-1.654)	0.459
Extremity fracture/dislocation			
Without OACs	3.41		
Warfarin	3.21	1.265 (0.904-1.769)	0.123
NOACs	2.82	0.946 (0.598-1.496)	0.698

NOACs = non–vitamin K antagonist oral anticoagulants; OACs = oral anticoagulants; HR = hazard ratio; CI = confidence interval.

Supplemental Table 1. Clinical characteristics of patients with dementia experiencing incident AF receiving warfarin and without OACs after the propensity match

Variables	Without OACs (n = 2,963)	Warfarin (n = 2,963)	P
Age, years; mean value (SD)	82.21 (7.54)	82.26 (7.3)	0.806

Age ≥ 75 years, *n* (%)	2503 (84.48)	2538 (85.66)	0.202
Age 65–74 years, *n* (%)	421 (14.21)	392 (13.23)	0.274
Male gender, *n* (%)	1277 (43.1)	1303 (43.98)	0.496
Comorbidities, *n* (%)			
Hypertension	2533 (85.49)	2543 (85.83)	0.711
Diabetes mellitus	1198 (40.43)	1188 (40.09)	0.791
Heart failure	1484 (50.08)	1511 (51)	0.483
Prior stroke/TIA	1557 (52.55)	1522 (51.37)	0.363
Vascular diseases	424 (14.31)	401 (13.53)	0.388
COPD	979 (33.04)	984 (33.21)	0.890
Hyperlipidemia	1222 (41.24)	1212 (40.9)	0.792
Autoimmune diseases	152 (5.13)	212 (7.15)	0.001
Cancer	328 (11.07)	366 (12.35)	0.123
Abnormal renal function	765 (25.82)	761 (25.68)	0.905
Abnormal liver function	444 (14.98)	445 (15.02)	0.971
Anemia	564 (19.03)	615 (20.76)	0.097
History of bleeding	911 (30.75)	931 (31.42)	0.575
Alcohol excess/abuse	5 (0.17)	16 (0.54)	0.016
CHA_2DS_2-VASc score; mean values (SD)	5.35 (1.59)	5.34 (1.56)	0.674
HAS-BLED score, mean value (SD)	3.39 (1.18)	3.41 (1.18)	0.644
Propensity score (SD)	0.88 (0.07)	0.88 (0.07)	0.983

AF = atrial fibrillation; OACs = oral anticoagulants; SD = standard deviation; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease.

Supplemental Table 2. Clinical characteristics of patients with dementia experiencing incident AF receiving NOACs and without OACs after the propensity match

Variables	**Without OACs (n = 4,353)**	**NOACs (n = 4,353)**	**P**
Age, years; mean value (SD)	83.53 (7.14)	83.92 (6.91)	0.010

Age ≥ 75 years, *n* (%)	3882 (89.18)	3947 (90.67)	0.021
Age 65–74 years, *n* (%)	449 (10.31)	396 (9.1)	0.055
Male gender, *n* (%)	1796 (41.26)	1779 (40.87)	0.711
Comorbidities, *n* (%)			
Hypertension	3962 (91.02)	3932 (90.33)	0.269
Diabetes mellitus	1938 (44.52)	1944 (44.66)	0.897
Heart failure	1962 (45.07)	1928 (44.29)	0.464
Prior stroke/TIA	2068 (47.51)	2023 (46.47)	0.334
Vascular diseases	643 (14.77)	658 (15.12)	0.652
COPD	1597 (36.69)	1602 (36.8)	0.912
Hyperlipidemia	2379 (54.65)	2391 (54.93)	0.796
Autoimmune diseases	345 (7.93)	394 (9.05)	0.060
Cancer	605 (13.9)	741 (17.02)	<.0001
Abnormal renal function	1160 (26.65)	1152 (26.46)	0.846
Abnormal liver function	859 (19.73)	922 (21.18)	0.094
Anemia	720 (16.54)	816 (18.75)	0.007
History of bleeding	1537 (35.31)	1522 (34.96)	0.736
Alcohol excess/abuse	66 (1.52)	49 (1.13)	0.111
CHA_2DS_2-VASc score; mean values (SD)	5.38 (1.54)	5.37 (1.54)	0.786
HAS-BLED score, mean value (SD)	3.44 (1.17)	3.44 (1.19)	0.885
Propensity score (SD)	0.82 (0.1)	0.82 (0.1)	0.967

AF = atrial fibrillation; OACs = oral anticoagulants; NOACs = non–vitamin K antagonist oral anticoagulants; SD = standard deviation; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease.

Figure 1. Study concept and the flowchart of the enrollment of study population.

AF = atrial fibrillation; NHIRD = National Health Insurance Research Database; NOACs = non–vitamin K antagonist oral anticoagulants

Figure 2. Risks of incident AF in patients with or without dementia.

aHR = adjusted hazard ratio; AF = atrial fibrillation; CI = confidence interval;

Figure 3. Risks of clinical events of patients with dementia receiving different stroke prevention strategies after AF was newly diagnosed.

aHR = adjusted hazard ratio; CI = confidence interval; ICH = intra-cranial hemorrhage; NOACs = non–vitamin K antagonist oral anticoagulants

Figure 4. Cumulative incidence curves of ischemic stroke/ICH of different stroke prevention strategies.

aHR = adjusted hazard ratio; CI = confidence interval; ICH = intra-cranial hemorrhage; NOACs = non–vitamin K antagonist oral anticoagulants

Supplemental Figure 1. Risks of clinical events of patients with dementia receiving different stroke prevention strategies after AF was newly diagnosed.

HR = hazard ratio; CI = confidence interval; ICH = intra-cranial hemorrhage; NOACs = non–vitamin K antagonist oral anticoagulants

Figure 1

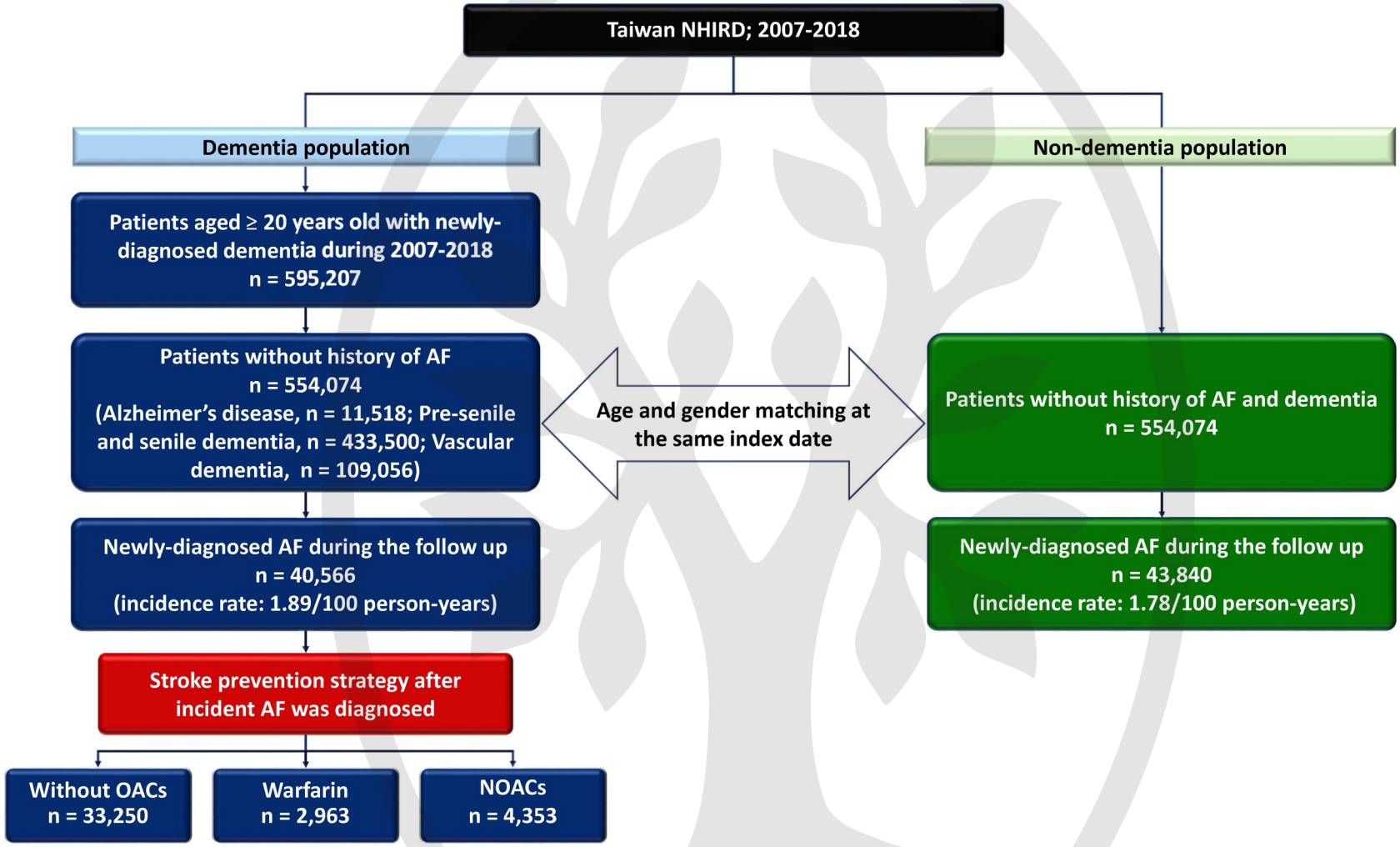


Figure 2. Risks of incident AF in patients with or without dementia.

aHR = adjusted hazard ratio; AF = atrial fibrillation; CI = confidence interval;

	Risk of incident AF Event number (%/yr)		aHR (95%CI)	Dementia (+) vs Dementia (-)	P value
Types of dementia	Dementia (+)	Dementia (-)			
All types	40,566 (1.89)	43,840 (1.78)	1.054 (1.040 – 1.068)		<.0001
Alzheimer's disease	278 (1.50)	254 (1.36)	1.104 (0.931 – 1.309)		0.2541
Pre-senile and senile dementia	31,970 (1.95)	35,008 (1.87)	1.035 (1.020 – 1.051)		<.0001
Vascular Dementia	8,318 (1.71)	8,578 (1.50)	1.125 (1.091 – 1.159)		<.0001

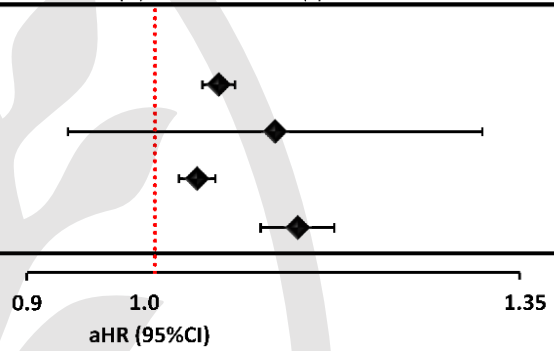


Figure 3

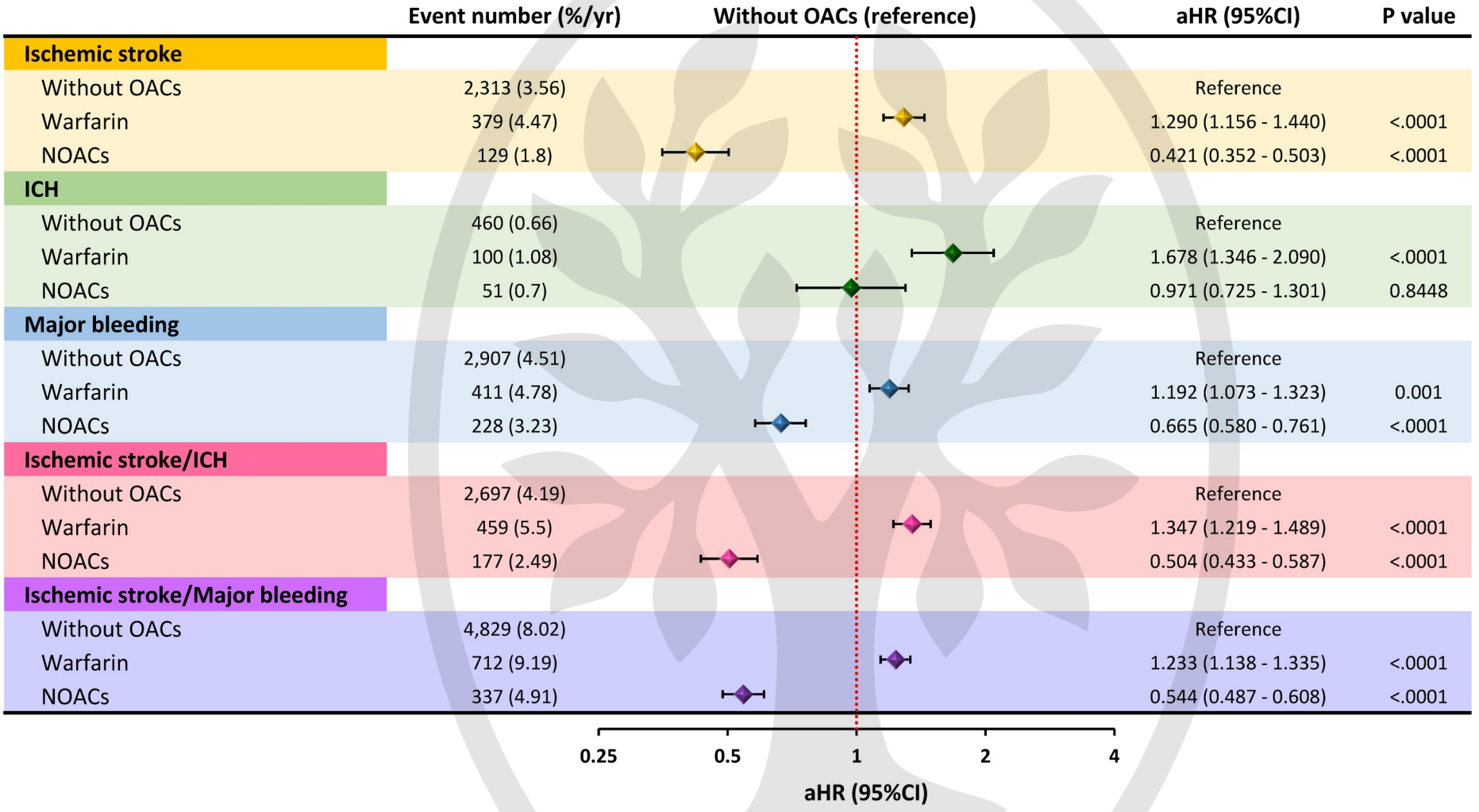
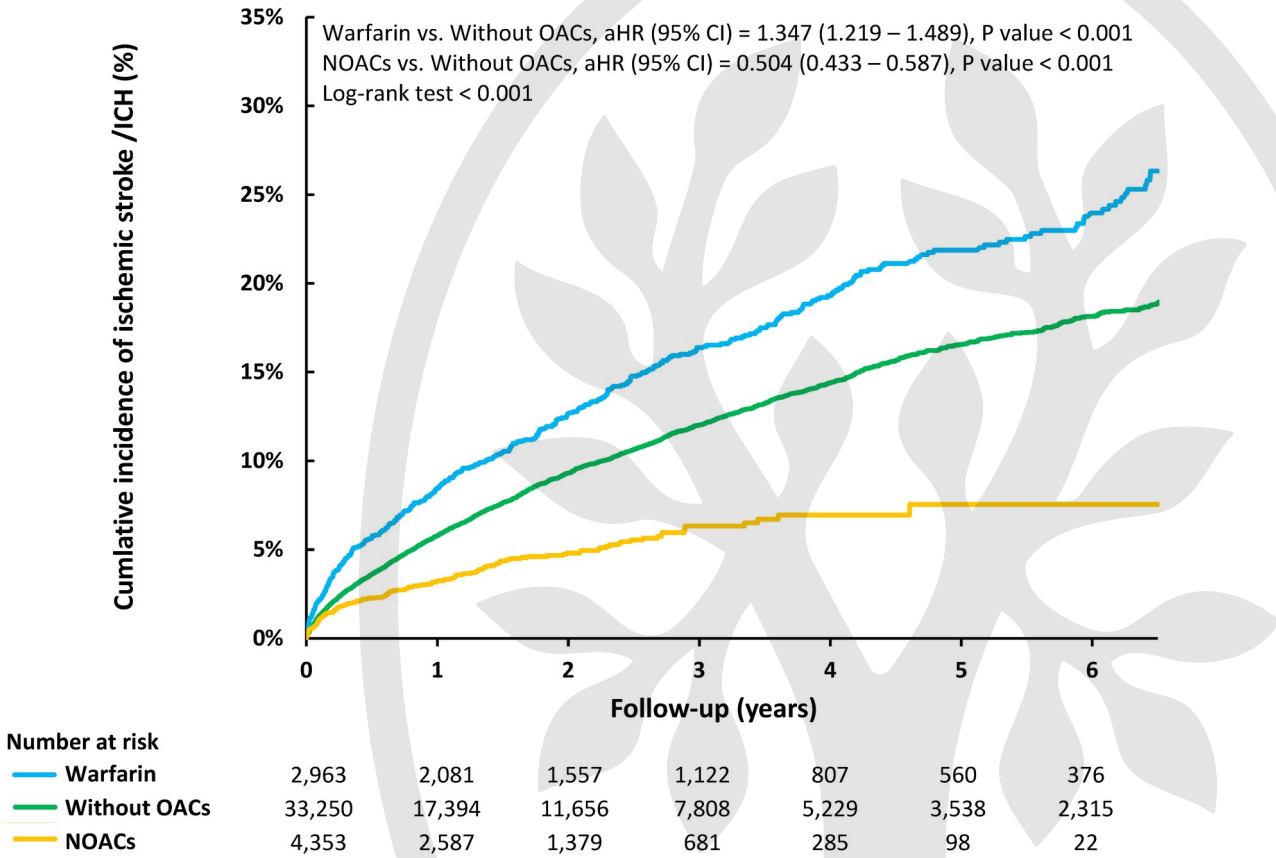
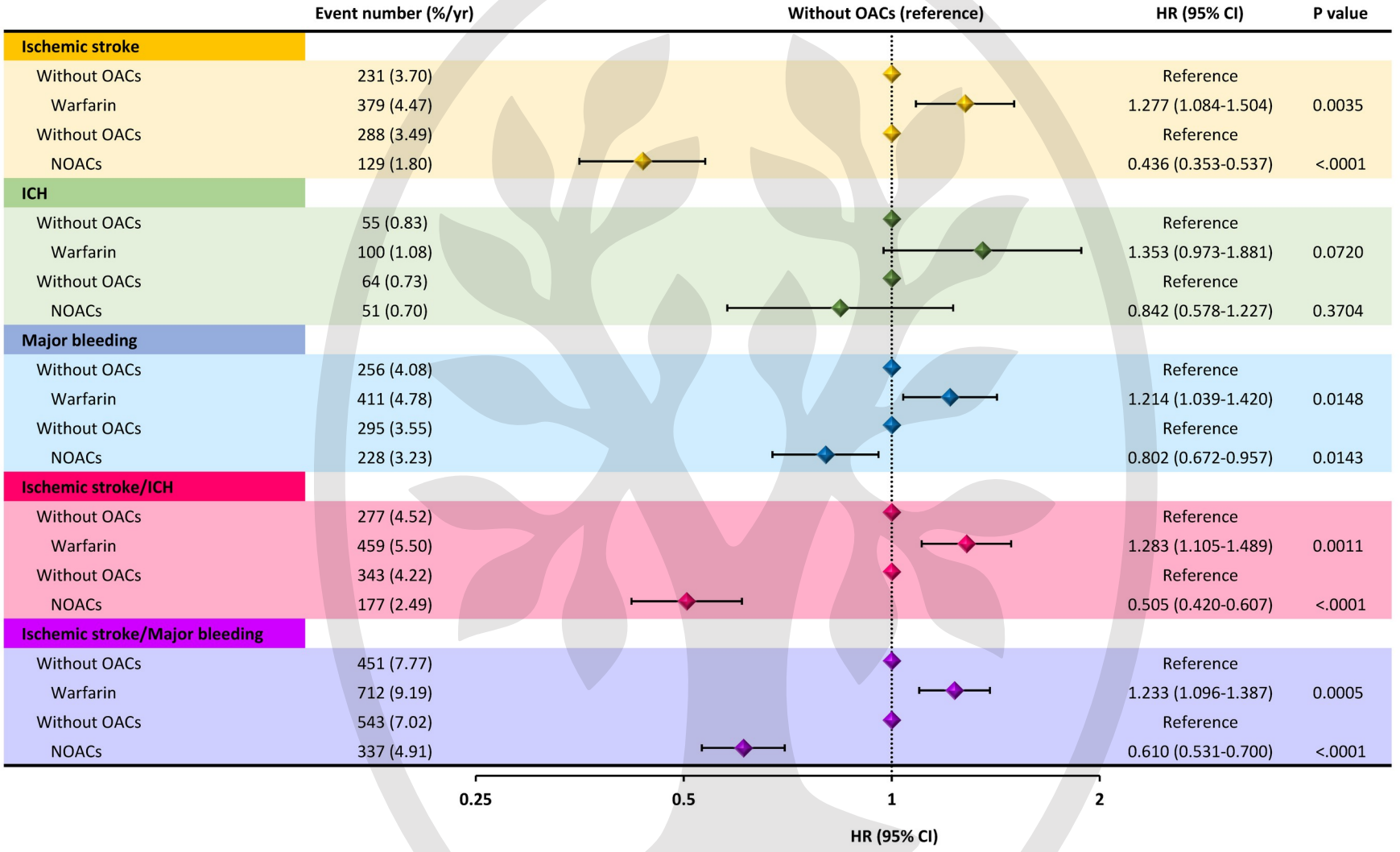
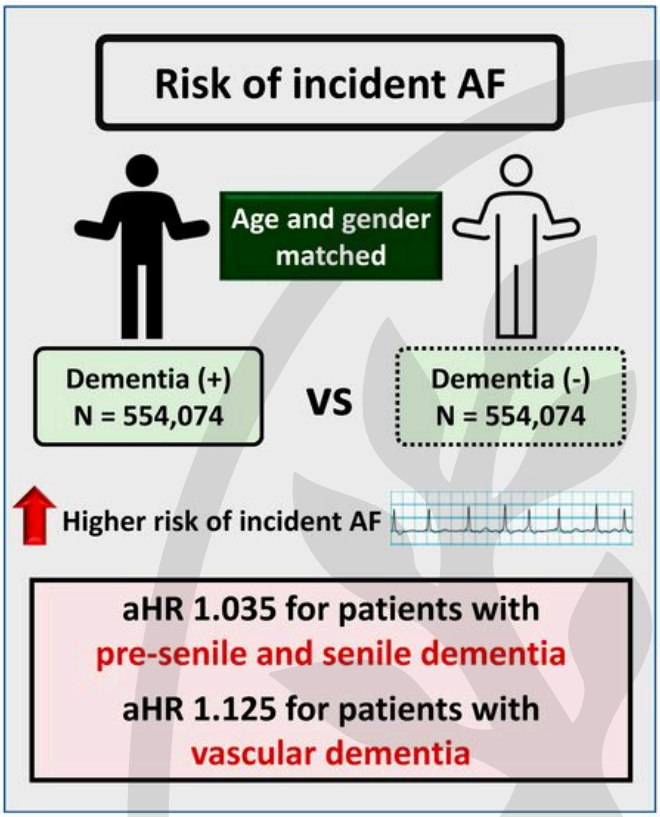


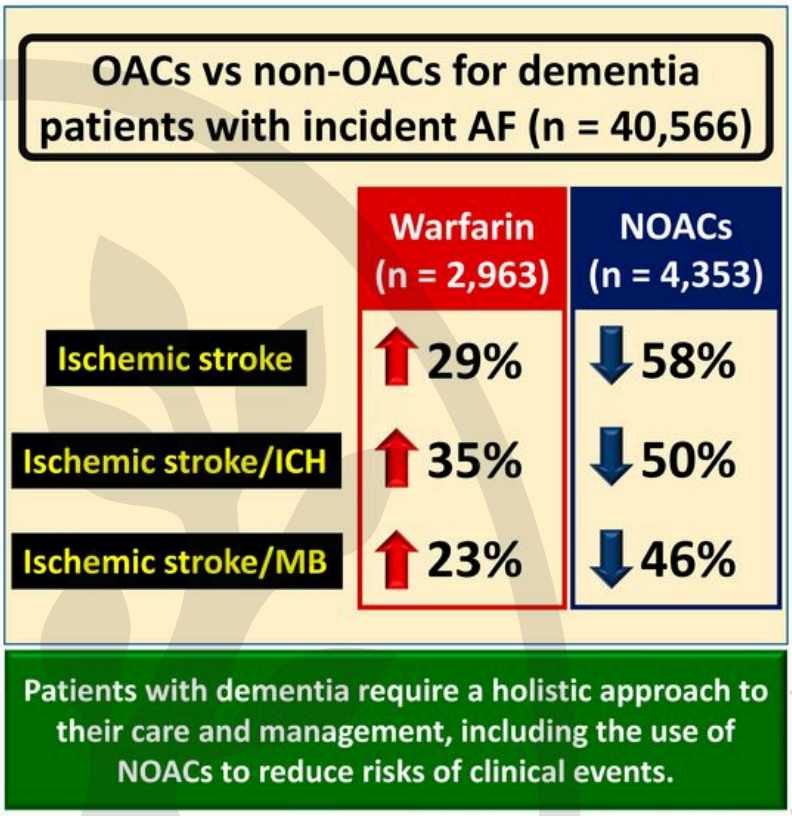
Figure 4



Supplemental Figure 1







Patients with dementia require a holistic approach to their care and management, including the use of NOACs to reduce risks of clinical events.