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Oral anticoagulants, cognition, and clinical outcomes in atrial fibrillation and Alzheimer's disease: a Swedish nationwide study

Nanbo Zhu [1,*], Hong Xu [1], Sara Garcia-Ptacek [1,2], Sumonto Mitra [1,†], and Maria Eriksdotter [1,2,*†]

[1]Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, 171 77 Stockholm, Sweden; and [2]Theme Inflammation and Aging, Karolinska University Hospital, 141 52 Huddinge, Sweden

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Abstract

Background and Aims Use of non-vitamin K oral anticoagulants (NOACs) is associated with reduced dementia risk in patients with atrial fibrillation (AF), but their impact on cognitive function and clinical outcomes in AF patients with Alzheimer's disease (AD) remains unclear.

Methods Based on the Swedish Registry for Cognitive/Dementia Disorders, individuals with incident AD during May 2007–December 2020 and pre-existing AF were identified. Anticoagulant use at baseline was categorized as non-use, warfarin, or NOACs. Inverse probability of treatment weighting was employed to balance covariates. Mixed-effects models were used to assess the association between anticoagulant use and cognitive decline measured by the Mini-Mental State Examination (MMSE). Cox proportional hazards models were used to examine risks of all-cause mortality, ischaemic stroke/systemic embolism, major bleeding, and fracture.

Results Among 7308 eligible individuals (3341 non-users, 2277 warfarin users, and 1690 NOAC users), NOAC users exhibited significantly slower cognitive decline compared to non-users (difference in MMSE scores $\beta = 0.23$ points/year, 95% confidence interval [CI] 0.11–0.36) and warfarin users ($\beta = 0.21$ points/year, 95% CI 0.10–0.33). Compared to non-use of anticoagulants, NOAC use was associated with significantly lower rates of mortality (hazard ratio [HR] 0.81; 95% CI 0.72–0.91), ischaemic stroke/systemic embolism (HR 0.66; 95% CI 0.53–0.82), and fracture (HR 0.79; 95% CI 0.64–0.97), without an increased rate of major bleeding (HR 1.05; 95% CI 0.84–1.32); in contrast, warfarin use was associated with significantly lower rates of mortality (HR 0.88; 95% CI 0.80–0.97) and ischaemic stroke/systemic embolism (HR 0.85; 95% CI 0.72–1.00), but a higher rate of major bleeding (HR 1.31; 95% CI 1.09–1.56). Compared to warfarin, NOAC use was associated with lower rates of ischaemic stroke/systemic embolism (HR 0.78; 95% CI 0.62–0.98) and major bleeding (HR 0.80; 95% CI 0.64–1.01), and non-significant reductions in mortality and fracture.

Conclusions In patients with AF and AD, NOAC use was associated with modestly slower cognitive decline and more favourable effectiveness and safety profiles, compared to warfarin or no anticoagulation.

* Corresponding authors. Email: nanbo.zhu@ki.se (N.Z.); Email: maria.eriksdotter@ki.se (M.E.)
† Equal last authorship.

Structured Graphical Abstract

Key Question

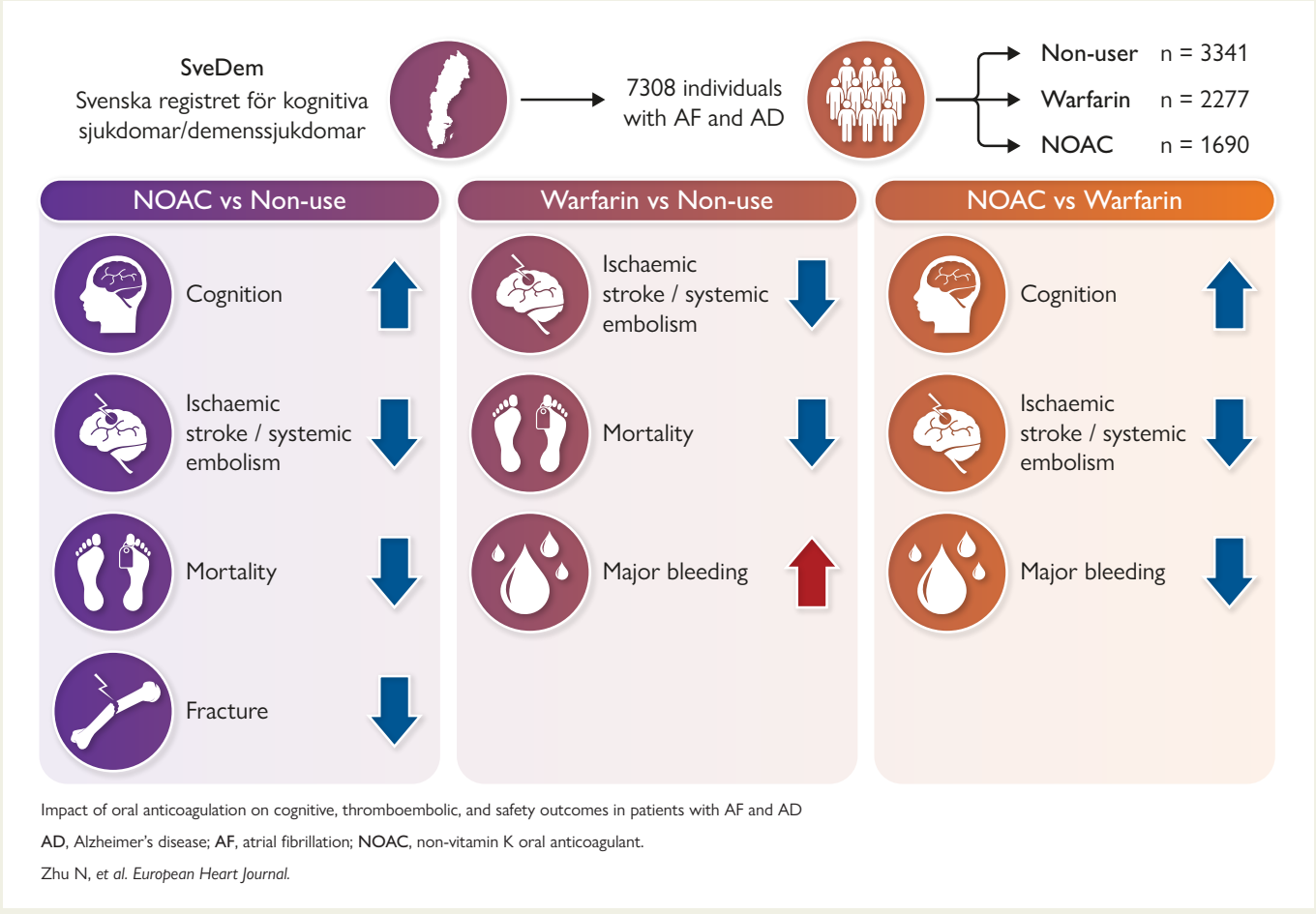
What is the impact of oral anticoagulants (OAC) on cognitive function and clinical outcomes in patients with atrial fibrillation (AF) and Alzheimer's disease (AD)? How do non-vitamin K OAC (NOAC) compare with warfarin?

Key Finding

In a Swedish nationwide registry, NOAC were associated with slower cognitive decline than warfarin or no anticoagulation. Both NOAC and warfarin use was associated with lower thromboembolic events and mortality rates. NOAC were associated with lower thromboembolic and major bleeding rates compared with warfarin.

Take Home Message

In patients with AF and AD, NOAC appear to be a better treatment option than warfarin in slowing cognitive decline.



Impact of oral anticoagulant use on cognitive, thromboembolic, and safety outcomes among patients with atrial fibrillation and Alzheimer's disease.

Keywords Alzheimer's disease • Atrial fibrillation • NOAC • Warfarin • Cognition • Clinical outcomes

Introduction

Atrial fibrillation (AF) has been consistently associated with Alzheimer's disease (AD) and related dementias, independent of clinically overt stroke.[1,2] AF is present in nearly 20% of individuals at the time of dementia diagnosis,[3] highlighting the frequent coexistence of the two conditions. Proposed mechanisms linking AF to cognitive dysfunction include cerebral infarction, hypoperfusion, and microbleeds.[2,4]

This close relationship has prompted substantial interest in whether oral anticoagulation, a cornerstone of AF management for stroke and thromboembolism prevention,[5] can protect against cognitive impairment and dementia.[6,7] Meta-analyses of observational studies suggest that patients with AF receiving oral anticoagulants have a lower risk of developing dementia compared with untreated individuals,[8] with a potential greater benefit for non-vitamin K oral anticoagulants (NOACs) than vitamin K antagonists (VKAs; mainly warfarin).[9,10] Nevertheless,

recent randomized trials comparing dabigatran with warfarin and rivaroxaban with placebo in AF patients without dementia have not demonstrated cognitive benefit.[11–13]

In patients with coexisting AF and AD, a population underrepresented in clinical research, the benefits and risks of anticoagulation remain uncertain.[5] This uncertainty reflects both the influence of impaired cognition on anticoagulation decisions and outcomes,[14] and emerging biological links between Alzheimer's pathology and hemostasis.[15] Notably, amyloid-β (Aβ), a core pathological feature of AD, has been shown to interact with the haemostatic system through several pathways, including platelet activation,[16] thrombin formation,[17] and fibrin(ogen) deposition.[18,19] Such interactions may exacerbate haemostatic dysregulation, impair Aβ clearance, and contribute to cognitive decline.[20] Conversely, experimental studies suggest that normalizing the hypercoagulable state may delay disease progression in preclinical AD models.[21–23] However, to date, no population-based studies have evaluated whether anticoagulant use influences cognitive trajectories among patients with both AF and AD. Together, these evidence gaps and mechanistic insights underscore the need for further studies evaluating the cognitive, thromboembolic, and safety consequences of anticoagulation in this high-risk population.

To address this, we examined the associations of anticoagulant use with cognitive decline and clinical outcomes in a Swedish nationwide cohort of patients with incident AD and pre-existing AF, comparing NOACs, warfarin, and no anticoagulation.

Methods

Data source

This study was based on the linkage of multiple Swedish national registers through unique personal identification numbers. The Swedish Registry for Cognitive/Dementia Disorders (SveDem) is a national quality registry initiated in 2007 that enrols patients diagnosed with incident dementia from either primary care or specialist memory clinics and collects demographic and diagnostic information, including date of diagnosis, type of dementia, and cognitive function assessed by the Mini-Mental State Examination (MMSE).[24] All memory clinics and 78% of primary care units in Sweden currently participate in SveDem.[25] The National Patient Register provided clinical diagnoses coded according to the 10th revision of the International Classification of Diseases (ICD-10) from hospital admissions since 1997 and from outpatient specialist consultations since 2001;[26] the Cause of Death Register provided information on the dates and underlying causes of all deaths in Sweden;[27] the Prescribed Drug Register provided complete information on all prescribed drugs dispensed at Swedish pharmacies since July 2005, including details such as date of dispensing, drug's identity categorized by the Anatomical Therapeutic Chemical (ATC) classification system, amount, and dosage.[28] Healthcare in Sweden is primarily tax-funded with nearly equal access, and these national registers are generally considered to have near-universal coverage and good overall quality for epidemiologic research.[29]

This study was approved by the Swedish Ethical Review Authority (Dnr: 2021/03304) and adhered to the Declaration of Helsinki. Participants were informed about their registration in SveDem and could decline participation or withdraw registration. Informed consent for this study was waived, as the register data were pseudonymized before delivery to the research team. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[30]

Study design and population

This was a longitudinal cohort study. Among 95 701 patients registered in SveDem between May 2007 and December 2020, we identified 7595 individuals with AD or mixed AD dementia who had a prior AF diagnosis recorded in the National Patient Register. The index date was defined as the date of AD diagnosis at the first registration in SveDem, with the 4 months preceding this date serving as the exposure assessment period. This span was chosen based on the Swedish '90-day rule' limiting medication dispensing to ≤90 days per prescription, plus an additional 30 days to accommodate non-adherence. A graphical depiction of the study design is shown in Supplementary data online, *Figure S1*. After excluding individuals who died on the index date, those with a missing baseline MMSE score, and those dispensed both warfarin and NOACs, a total of 7308 eligible individuals were included in the analysis. A flowchart illustrating the sample selection is presented in *Figure 1*.

Exposure

The baseline exposure was anticoagulant use on the index date, estimated as non-use, warfarin, or NOACs, based on the most recent dispensation of oral anticoagulants within the exposure assessment window (see Method *S1*). Our primary analysis followed the intention-to-treat principle, assuming the study exposure to be constant throughout follow-up, regardless of changes in medication use after baseline.

Outcomes

Cognitive trajectory was modelled using MMSE scores from baseline registration and annual follow-ups over the first 5 years, due to sparse data at later time points. Clinical outcomes included ischaemic stroke/systemic embolism, major bleeding, and fracture, identified through ICD-10 coded inpatient visits or death records (listed in Supplementary data online, *Table S1*), as well as all-cause mortality. Outcome definitions based on the National Patient Register generally demonstrate high diagnostic validity, with sensitivity and positive predictive value (PPV) around 90% for stroke,[31] PPV 59%–97% across fracture sites,[31] and sensitivity and PPV >95% for major bleeding in AF patients.[32] Follow-up for time-to-event analyses started on the index date and ended at the earliest occurrence of an event, death, 5 years after baseline, or study end (31 December 2020).

Covariates

Covariates used to predict baseline anticoagulant exposure were defined using information before the exposure assessment window to ensure temporality, including age, sex, duration of AF, MMSE score, healthcare utilization, comorbidities, and concurrent use of medications. Definitions of comorbidities and medications are provided in Supplementary data online, *Table S2*.

Statistical analysis

Continuous variables are reported as either mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables are presented as frequencies with percentages.

To address confounding by indication, we applied inverse probability of treatment weighting (IPTW) for a three-level exposure.[33] Conditional probabilities of each exposure group were estimated using multinomial logistic regression that included all aforementioned covariates. Each individual was assigned a weight equal to the inverse of the probability of their observed exposure. Weights were truncated at the 99th percentile to reduce the impact of extreme values. Covariate balance was defined as a standardized mean difference (SMD) ≤ 0.1 after applying IPTW.

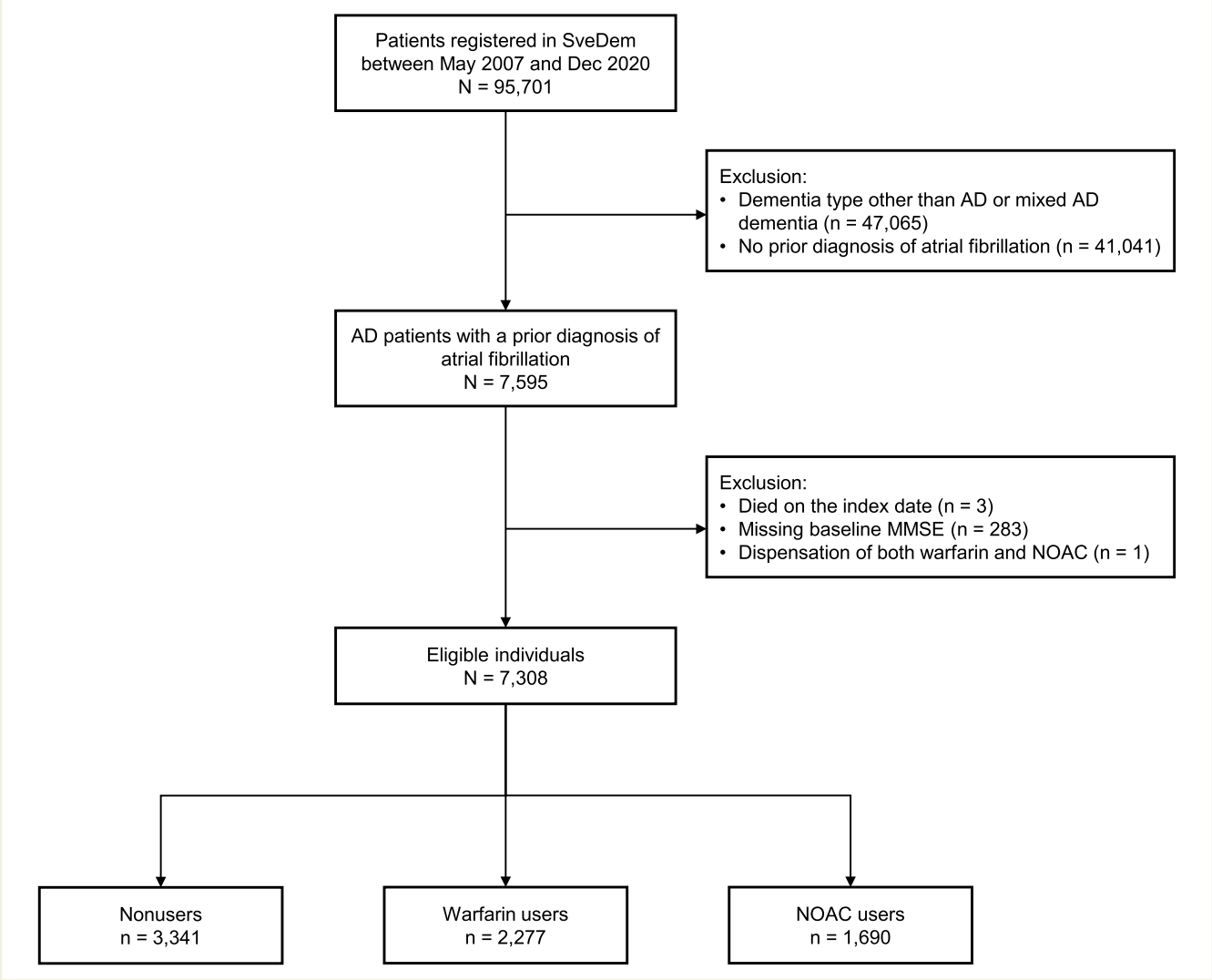


Figure 1 Flowchart of sample selection. AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; NOAC, non-vitamin K oral anticoagulant; SveDem, Swedish registry for cognitive/dementia disorders. The index date was the date of AD diagnosis at the first registration in SveDem

In the analysis of MMSE score trajectories, dropout was defined as the last observed MMSE measurement, in the absence of death or study end within the subsequent year. We employed inverse probability of censoring weighting (IPCW) to control for informative attrition due to dropout or death.[34] Variables used to estimate the probability of censoring included the exposure group, along with baseline and post-baseline characteristics: age, sex, MMSE score at diagnosis, type of diagnostic unit (memory clinic or primary care), rating of global cognition (stable, improved, or declined), coresident status (cohabiting or living alone), nursing home residence (yes or no), and home care (yes or no). The definition of dropout and selection of covariates were informed by previous research using SveDem.[34]

We used linear mixed-effects models with random intercepts, in conjunction with IPTW and IPCW, to examine the association between anticoagulant use and cognitive decline. MMSE scores were regressed on exposure group, follow-up time (time since baseline), and their interaction, with further adjustments for baseline MMSE score, type of diagnostic unit, coresident status, nursing home residence, home care, and anti-dementia drugs × time interaction. The β coefficients and 95% confidence intervals (CIs) for the exposure × time interaction were of primary interest, which quantify differences in the rate of cognitive decline between exposure groups. In addition, we estimated the marginal mean MMSE scores and 95% CIs at each year of follow-up.

We used IPTW-weighted Cox regression to examine the associations between anticoagulant use and 3-year clinical outcomes, reporting weighted cause-specific hazard ratios (csHRs) with 95% CIs. For outcomes subject to the competing risk of death (i.e. ischaemic stroke/systemic embolism, major bleeding, and fracture), we additionally applied IPTW-weighted Fine-Gray models to estimate sub-distribution hazard ratios (HRs). To enhance clinical interpretability, we further calculated cumulative incidence, risk differences, and restricted mean time lost (RMTL) differences over 5 years using the weighted Aalen-Johansen estimator, which does not assume proportional hazards, with 95% CIs obtained via 500 bootstrap resamples. The RMTL difference quantifies the absolute difference in cumulative time lost up to a specified follow-up time between groups.[35] Multiple testing was not performed because outcomes were prespecified based on clinical relevance.

Sensitivity analysis

Several sensitivity analyses were conducted to test the robustness of the results. For both cognitive decline and time-to-event outcomes: (i) 54% of anticoagulant non-users who received antiplatelets during the exposure assessment period were analysed as the comparison group; (ii) 23% of anticoagulant non-users who had been dispensed anticoagulants within 1 year before the index date (considered as recent discontinuers) were excluded from the comparison group; (iii) since NOACs were first marketed in Sweden in 2011 and rarely prescribed before 2013, we restricted the analysis to individuals diagnosed with AD during 2013–20, when clinical equipoise was more plausible between NOACs and warfarin.

For cognitive decline specifically, we modelled follow-up time using cubic splines to capture potential non-linear trajectories, and applied multiple transformations to MMSE scores to address the instrument's non-linear scaling properties[36] or to provide additional clinical insights (see Method *S2*).[37] For time-to-event outcomes, we conducted per-protocol analyses accounting for changes in anticoagulant exposure during follow-up (see Method *S3*).

Data management was performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and statistical analyses were conducted using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed $P < .05$ was considered statistically significant.

Results

The analysis included 7308 individuals, comprising 3341 non-users of anticoagulants, 2277 warfarin users, and 1690 NOAC users (*Figure 1*). The mean age at AD diagnosis was 82.6 ± 6.2 years, and 52.7% were female (*Table 1*). Compared with either warfarin or NOAC users, non-users were slightly older, had a lower MMSE score, had a lower prevalence of hypertension, dyslipidaemia, and pacemaker implantation; lower use of renin-angiotensin system inhibitors, beta-blockers, and statins; and higher use of antiplatelets and non-steroidal anti-inflammatory drugs. Covariates were more similar between warfarin and NOAC users.

There was a good overlap in the distribution of propensity scores across exposure groups (see Supplementary data online, *Figure S2*). After applying IPTW, all included covariates were well balanced in each pairwise comparison (*Table 1* and Supplementary data online, *Figure S3*).

Anticoagulant use and cognitive decline

Supplementary data online, *Figure S4* shows the number of individuals and crude mean MMSE scores at baseline and during follow-up visits. After applying IPTW and IPCW, there were differences in baseline MMSE scores (i.e. intercept) among the three groups, with warfarin and NOAC users showing slightly higher baseline MMSE scores (*Table 2*). No significant difference in the annual change of MMSE scores (i.e. slope) was found between warfarin users and non-users, while NOAC users exhibited a slower decline in MMSE scores compared to both non-users and warfarin users. Further adjustment for baseline covariates reduced the differences in the intercepts but had minimal impact on the slopes. In the final model, warfarin use was associated with a similar rate of cognitive decline compared to non-users ($\beta = 0.02$, 95% CI −0.08, 0.12), whereas NOAC users exhibited significantly slower cognitive decline than both non-users ($\beta = 0.23$, 95% CI 0.11, 0.36) and warfarin users ($\beta = 0.21$, 95% CI 0.10, 0.33).

The linear trajectories and marginal means of MMSE scores based on the final model are shown in *Figure 2*. The predicted mean baseline MMSE scores were approximately 21.5 across all three groups. At 5 years of follow-up, the estimated MMSE scores were 14.3 (95% CI 13.9, 14.6) in non-users, 14.5 (95% CI 14.2, 14.8) in warfarin users, and 15.3 (95% CI 14.9, 15.8) in NOAC users.

Anticoagulant use and clinical outcomes

For the 3-year outcomes, over a median follow-up of 2.7 years (IQR 1.3–3.0), a total of 2588 deaths were recorded in the study population, along with 833 ischaemic stroke/systemic embolism events, 683 major bleeding events, and 824 fracture events (*Table 3*). Compared to non-use of anticoagulants, warfarin use was associated with significantly lower rates of mortality (csHR 0.88; 95% CI 0.80, 0.97) and ischaemic stroke/systemic embolism (csHR 0.85; 95% CI 0.72, 1.00), but a higher rate of major bleeding (csHR 1.31; 95% CI 1.09, 1.56), with no significant association observed for fracture (csHR 0.89; 95% CI 0.76, 1.06) (*Table 3*). In contrast, NOAC use was associated with significantly lower rates of mortality (csHR 0.81; 95% CI 0.72, 0.91), ischaemic stroke/systemic embolism (csHR 0.66; 95% CI 0.53, 0.82), and fracture (csHR 0.79; 95% CI 0.64, 0.97), without a significant increase in major bleeding (csHR 1.05; 95% CI 0.84, 1.32). Compared directly to warfarin, NOAC use was associated with a significantly lower rate of ischaemic stroke/systemic embolism (csHR 0.78; 95% CI 0.62, 0.98), as well as non-significant reductions in mortality (csHR 0.92; 95% CI 0.81, 1.05), major bleeding (csHR 0.80; 95% CI 0.64, 1.01), and fracture (csHR 0.88; 95% CI 0.70, 1.11). For non-death outcomes, subdistribution HRs from Fine–Gray models were largely similar.

Weighted cumulative incidence and risk differences are presented in *Figure 3* and Supplementary data online, *Figure S5*, respectively. At 3 years, compared with non-use of anticoagulants, warfarin use was associated with a 3.7% lower mortality risk (95% CI −6.6, −0.8) but a 3.1% higher risk of major bleeding (95% CI 1.2, 4.9); NOAC use was associated with a 5.9% lower mortality risk (95% CI −9.6, −2.1) and a 4.7% lower risk of ischaemic stroke/systemic embolism (95% CI −6.8, −2.7). Compared with warfarin, NOAC use was associated with a 3.0% lower risk of ischaemic stroke/systemic embolism (95% CI −5.4, −1.0) and a 2.7% lower risk of major bleeding (95% CI −5.0, −0.3). Weighted RMTL differences (see Supplementary data online, *Figure S6*), a measure of time lost, were generally consistent with the risk differences.

Sensitivity analysis

Comparison between NOAC and warfarin users remained robust in sensitivity analyses, yet some variability was observed when compared to non-users of anticoagulants. When using antiplatelet use as reference, both warfarin and NOAC use were associated with slower cognitive decline (see Supplementary data online, *Table S3* and Supplementary data online, *Figure S7*). Antiplatelet users experienced a higher rate of ischaemic stroke/systemic embolism, in turn resulting in a stronger protective association for this condition among warfarin and NOAC users (see Supplementary data online, *Table S4*). Associations with other clinical outcomes were similar

Table 1 Characteristics of the study population before and after inverse probability of treatment weighting

Characteristics	Overall	Before weighting						After weighting					
		Nonuse	Warfarin	NOAC	Warfarin vs nonuse	SMD NOAC vs nonuse	NOAC vs warfarin	Nonuse	Warfarin	NOAC	Warfarin vs nonuse	SMD NOAC vs nonuse	NOAC vs warfarin
N	7308	3341	2277	1690				7335	7190	7225			
Age, years	82.6 ± 6.2	83.1 ± 6.5	82.1 ± 5.8	82.5 ± 6.0	0.16	0.09	0.07	82.6 ± 6.5	82.5 ± 5.7	82.7 ± 6.1	0.01	0.02	0.03
Female	3852 (52.7)	1827 (54.7)	1126 (49.5)	899 (53.2)	0.10	0.03	0.07	3860 (52.6)	3751 (52.2)	3759 (52.0)	0.01	0.01	<0.01
Atrial fibrillation duration, years					0.26	0.16	0.40				0.01	0.01	0.01
0 to <1	1108 (15.2)	547 (16.4)	210 (9.2)	351 (20.8)				1088 (14.8)	1049 (14.6)	1078 (14.9)			
1 to <5	2489 (34.1)	1145 (34.3)	718 (31.5)	626 (37.0)				2507 (34.2)	2485 (34.6)	2457 (34.0)			
5 to <10	2093 (28.6)	971 (29.1)	731 (32.1)	391 (23.1)				2101 (28.6)	2046 (28.5)	2059 (28.5)			
≥10	1618 (22.1)	678 (20.3)	618 (27.1)	322 (19.1)				1640 (22.4)	1610 (22.4)	1631 (22.6)			
MMSE score	20.8 ± 4.8	20.3 ± 5.0	21.4 ± 4.6	20.9 ± 4.7	0.23	0.13	0.10	20.8 ± 4.8	20.9 ± 4.8	20.8 ± 4.8	0.02	0.01	0.01
No. of MMSE test[a,b]													
1	4092 (56.0)	1975 (59.1)	1160 (50.9)	957 (56.6)									
2	1976 (27.0)	846 (25.3)	648 (28.5)	482 (28.5)									
≥3	1240 (17.0)	520 (15.6)	469 (20.6)	251 (14.9)									
Outpatient visits within 1 year													
Number	2 (1–4)	2 (0–4)	2 (1–4)	3 (1–5)	0.01	0.13	0.16	2 (1–4)	2 (1–4)	2 (1–4)	0.03	0.02	0.02
Any	5569 (76.2)	2419 (72.4)	1743 (76.5)	1407 (83.3)	0.10	0.26	0.17	5613 (76.5)	5536 (77.0)	5573 (77.1)	0.01	0.01	<0.01

Continued

Table 1 *Continued*

Characteristics	Overall	Before weighting						After weighting					
		Nonuse	Warfarin	NOAC	Warfarin vs nonuse	SMD NOAC vs nonuse	NOAC vs warfarin	Nonuse	Warfarin	NOAC	Warfarin vs nonuse	SMD NOAC vs nonuse	NOAC vs warfarin
Inpatient visits within 1 year													
Number	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0.18	<0.01	0.18	0 (0–1)	0 (0–1)	0 (0–1)	0.01	0.01	<0.01
Any	3168 (43.3)	1496 (44.8)	884 (38.8)	788 (46.6)	0.12	0.04	0.16	3175 (43.3)	3114 (43.3)	3080 (42.6)	<0.01	0.01	0.01
CHA_2DS_2-VASc score[a]	4.5 ± 1.5	4.5 ± 1.5	4.6 ± 1.4	4.6 ± 1.4	0.10	0.08	0.02						
HAS-BLED score[a]	2.7 ± 0.9	2.9 ± 1.0	2.5 ± 0.8	2.5 ± 0.8	0.52	0.42	0.09						
Comorbidities													
Alcohol-related disorders	183 (2.5)	104 (3.1)	26 (1.1)	53 (3.1)	0.14	<0.01	0.14	186 (2.5)	173 (2.4)	179 (2.5)	0.01	<0.01	<0.01
Hypertension	6642 (90.9)	2931 (87.7)	2149 (94.4)	1562 (92.4)	0.23	0.16	0.08	6679 (91.0)	6570 (91.4)	6570 (90.9)	0.01	<0.01	0.02
Diabetes	1413 (19.3)	628 (18.8)	431 (18.9)	354 (20.9)	<0.01	0.05	0.05	1403 (19.1)	1400 (19.5)	1404 (19.4)	0.01	0.01	<0.01
Dyslipidaemia	1485 (20.3)	570 (17.1)	501 (22.0)	414 (24.5)	0.12	0.18	0.06	1506 (20.5)	1480 (20.6)	1503 (20.8)	<0.01	0.01	0.01
Myocardial infarction	1320 (18.1)	650 (19.5)	382 (16.8)	288 (17.0)	0.07	0.06	0.01	1335 (18.2)	1293 (18.0)	1326 (18.4)	0.01	<0.01	0.01
Congestive heart failure	2345 (32.1)	1004 (30.1)	819 (36.0)	522 (30.9)	0.13	0.02	0.11	2326 (31.7)	2300 (32.0)	2293 (31.7)	0.01	<0.01	0.01
Peripheral vascular disease	629 (8.6)	278 (8.3)	191 (8.4)	160 (9.5)	<0.01	0.04	0.04	665 (9.1)	665 (9.2)	619 (8.6)	0.01	0.02	0.02
Arterial embolism	100 (1.4)	43 (1.3)	36 (1.6)	21 (1.2)	0.02	<0.01	0.03	103 (1.4)	93 (1.3)	88 (1.2)	0.01	0.02	0.01
Venous thromboembolism	581 (8.0)	227 (6.8)	195 (8.6)	159 (9.4)	0.07	0.10	0.03	589 (8.0)	575 (8.0)	564 (7.8)	<0.01	0.01	0.01
Valve disease	1000 (13.7)	403 (12.1)	371 (16.3)	226 (13.4)	0.12	0.04	0.08	1026 (14.0)	981 (13.6)	968 (13.4)	0.01	0.02	0.01

Continued

Table 1 *Continued*

Characteristics	Overall	Before weighting						After weighting					
		Nonuse	Warfarin	NOAC	Warfarin vs nonuse	SMD NOAC vs nonuse	NOAC vs warfarin	Nonuse	Warfarin	NOAC	Warfarin vs nonuse	SMD NOAC vs nonuse	NOAC vs warfarin
Cardiac pacemaker	858 (11.7)	315 (9.4)	313 (13.7)	230 (13.6)	0.14	0.13	<0.01	870 (11.9)	871 (12.1)	876 (12.1)	0.01	0.01	<0.01
Transient ischaemic attack	739 (10.1)	282 (8.4)	257 (11.3)	200 (11.8)	0.10	0.11	0.02	736 (10.0)	745 (10.4)	733 (10.1)	0.01	<0.01	0.01
Ischaemic stroke	1149 (15.7)	492 (14.7)	393 (17.3)	264 (15.6)	0.07	0.02	0.04	1158 (15.8)	1153 (16.0)	1091 (15.1)	0.01	0.02	0.03
Intracranial haemorrhage	185 (2.5)	109 (3.3)	34 (1.5)	42 (2.5)	0.12	0.05	0.07	191 (2.6)	165 (2.3)	185 (2.6)	0.02	<0.01	0.02
Traumatic intracranial haemorrhage	138 (1.9)	70 (2.1)	31 (1.4)	37 (2.2)	0.06	0.01	0.06	136 (1.9)	130 (1.8)	133 (1.8)	<0.01	<0.01	<0.01
Bleeding within 6 months	193 (2.6)	115 (3.4)	38 (1.7)	40 (2.4)	0.11	0.06	0.05	192 (2.6)	183 (2.5)	175 (2.4)	<0.01	0.01	0.01
Bleeding within 7–24 months	369 (5.0)	188 (5.6)	98 (4.3)	83 (4.9)	0.06	0.03	0.03	370 (5.0)	363 (5.0)	398 (5.5)	<0.01	0.02	0.02
Paresis/plegia	103 (1.4)	35 (1.0)	31 (1.4)	37 (2.2)	0.03	0.09	0.06	99 (1.4)	96 (1.3)	98 (1.4)	<0.01	<0.01	<0.01
Cancer	1431 (19.6)	626 (18.7)	448 (19.7)	357 (21.1)	0.02	0.06	0.04	1470 (20.0)	1403 (19.5)	1451 (20.1)	0.01	<0.01	0.01
Chronic pulmonary disease	915 (12.5)	443 (13.3)	237 (10.4)	235 (13.9)	0.09	0.02	0.11	911 (12.4)	889 (12.4)	897 (12.4)	<0.01	<0.01	<0.01
Chronic kidney disease	413 (5.7)	191 (5.7)	116 (5.1)	106 (6.3)	0.03	0.02	0.05	413 (5.6)	413 (5.8)	446 (6.2)	0.01	0.02	0.02
Liver disease	130 (1.8)	68 (2.0)	27 (1.2)	35 (2.1)	0.07	<0.01	0.07	128 (1.7)	106 (1.5)	141 (2.0)	0.02	0.02	0.04
Hypothyroidism	704 (9.6)	329 (9.8)	203 (8.9)	172 (10.2)	0.03	0.01	0.04	713 (9.7)	695 (9.7)	691 (9.6)	<0.01	0.01	<0.01
Thyrotoxicosis	196 (2.7)	92 (2.8)	56 (2.5)	48 (2.8)	0.02	0.01	0.02	196 (2.7)	181 (2.5)	184 (2.5)	0.01	0.01	<0.01
Rheumatic disease	734 (10.0)	324 (9.7)	216 (9.5)	194 (11.5)	0.01	0.06	0.07	725 (9.9)	692 (9.6)	741 (10.3)	0.01	0.01	0.02
Osteoporosis	479 (6.6)	241 (7.2)	139 (6.1)	99 (5.9)	0.04	0.05	0.01	486 (6.6)	471 (6.5)	508 (7.0)	<0.01	0.02	0.02

Continued

Table 1 *Continued*

Characteristics	Overall	Before weighting						After weighting					
		Nonuse	Warfarin	NOAC	SMD Warfarin vs nonuse	SMD NOAC vs nonuse	SMD NOAC vs warfarin	Nonuse	Warfarin	NOAC	SMD Warfarin vs nonuse	SMD NOAC vs nonuse	SMD NOAC vs warfarin
Fracture	1484 (20.3)	743 (22.2)	375 (16.5)	366 (21.7)	0.15	0.01	0.13	1478 (20.1)	1403 (19.5)	1452 (20.1)	0.02	<0.01	0.01
Hearing loss	991 (13.6)	394 (11.8)	298 (13.1)	299 (17.7)	0.04	0.17	0.13	988 (13.5)	958 (13.3)	990 (13.7)	<0.01	0.01	0.01
Depression	458 (6.3)	209 (6.3)	133 (5.8)	116 (6.9)	0.02	0.02	0.04	453 (6.2)	459 (6.4)	432 (6.0)	0.01	0.01	0.02
Anxiety disorders	286 (3.9)	128 (3.8)	73 (3.2)	85 (5.0)	0.03	0.06	0.09	274 (3.7)	299 (4.2)	289 (4.0)	0.02	0.01	0.01
Medications													
Renin-angiotensin system inhibitors	3770 (51.6)	1501 (44.9)	1309 (57.5)	960 (56.8)	0.25	0.24	0.01	3822 (52.1)	3815 (53.1)	3743 (51.8)	0.02	0.01	0.03
Beta-blockers	5099 (69.8)	2123 (63.5)	1721 (75.6)	1255 (74.3)	0.26	0.23	0.03	5139 (70.1)	5036 (70.0)	5050 (69.9)	<0.01	<0.01	<0.01
Calcium channel blockers	1680 (23.0)	712 (21.3)	539 (23.7)	429 (25.4)	0.06	0.10	0.04	1724 (23.5)	1697 (23.6)	1672 (23.1)	<0.01	0.01	0.01
Diuretics	2966 (40.6)	1337 (40.0)	996 (43.7)	633 (37.5)	0.08	0.05	0.13	2972 (40.5)	2925 (40.7)	2897 (40.1)	<0.01	0.01	0.01
Digoxin	1083 (14.8)	423 (12.7)	449 (19.7)	211 (12.5)	0.19	0.01	0.20	1080 (14.7)	1094 (15.2)	1030 (14.3)	0.01	0.01	0.03
Antiarrhythmics	134 (1.8)	57 (1.7)	46 (2.0)	31 (1.8)	0.02	0.01	0.01	133 (1.8)	139 (1.9)	132 (1.8)	0.01	<0.01	0.01
Antidiabetic drugs	1031 (14.1)	424 (12.7)	340 (14.9)	267 (15.8)	0.06	0.09	0.02	1022 (13.9)	1029 (14.3)	1035 (14.3)	0.01	0.01	<0.01
Statins	2881 (39.4)	1132 (33.9)	991 (43.5)	758 (44.9)	0.20	0.23	0.03	2926 (39.9)	2922 (40.6)	2845 (39.4)	0.02	0.01	0.03
Non-steroidal anti-inflammatory drugs	288 (3.9)	187 (5.6)	59 (2.6)	42 (2.5)	0.15	0.16	0.01	289 (3.9)	262 (3.6)	256 (3.5)	0.02	0.02	0.01
Proton-pump inhibitors	1483 (20.3)	732 (21.9)	378 (16.6)	373 (22.1)	0.13	<0.01	0.14	1503 (20.5)	1471 (20.4)	1454 (20.1)	<0.01	0.01	0.01
Anxiolytics, hypnotics, and sedatives	2104 (28.8)	1012 (30.3)	636 (27.9)	456 (27.0)	0.05	0.07	0.02	2105 (28.7)	2060 (28.7)	2065 (28.6)	<0.01	<0.01	<0.01

Continued

Table 1 *Continued*

Characteristics	Overall	Before weighting						After weighting					
		Nonuse	Warfarin	NOAC	Warfarin vs nonuse	SMD NOAC vs nonuse	NOAC vs warfarin	Nonuse	Warfarin	NOAC	Warfarin vs nonuse	SMD NOAC vs nonuse	NOAC vs warfarin
Antidepressants	1647 (22.5)	756 (22.6)	516 (22.7)	375 (22.2)	<0.01	0.01	0.01	1643 (22.4)	1644 (22.9)	1595 (22.1)	0.01	0.01	0.02
Antiplatelets[a]	2121 (29.0)	1783 (53.4)	155 (6.8)	183 (10.8)	1.18	1.02	0.14						
Anti-dementia drugs[a,c]	5434 (74.4)	2363 (70.7)	1791 (78.7)	1280 (75.7)	0.18	0.11	0.07						

Abbreviations: MMSE, mini-mental state examination; NOAC, non-vitamin K oral anticoagulant; SMD, standardized mean difference.
Values are presented as mean ± standard deviation, median (interquartile range), or frequency (%).
[a]Not included in the propensity score model for inverse probability of treatment weighting.
[b]Number of MMSE tests during the study period, including the baseline assessment.
[c]Use of anti-dementia drugs within six months after the index date.

Table 2 **Associations between oral anticoagulant use and MMSE score trajectories**

	Warfarin vs nonuse		NOAC vs nonuse		NOAC vs warfarin	
	Intercept	Slope	Intercept	Slope	Intercept	Slope
IPTW + IPCW[a]	0.80 (0.53, 1.07)	−0.03 (−0.15, 0.09)	0.24 (−0.05, 0.53)	0.21 (0.08, 0.34)	−0.56 (−0.86, −0.26)	0.24 (0.12, 0.36)
+ baseline variables[b]	0.13 (−0.12, 0.39)	0.02 (−0.08, 0.12)	−0.10 (−0.36, 0.16)	0.23 (0.11, 0.35)	−0.23 (−0.49, 0.03)	0.21 (0.10, 0.33)
+ interaction terms[c]	0.12 (−0.13, 0.38)	0.02 (−0.08, 0.12)	−0.10 (−0.36, 0.16)	0.23 (0.11, 0.36)	−0.23 (−0.49, 0.04)	0.21 (0.10, 0.33)

Abbreviations: MMSE, mini-mental state examination; NOAC, non-vitamin K oral anticoagulant.
[a]Estimation was obtained using a linear mixed model, combined with inverse probability of treatment weights and inverse probability of censoring weights.
[b]Linear mixed model was additionally adjusted for baseline variables, including baseline MMSE, diagnostic unit, coresident status, nursing home residence, and home care.
[c]Linear mixed model was further adjusted for the interaction term time × anti-dementia drugs.

Table 3 Associations between oral anticoagulant use and 3-year clinical outcomes

	No. of events	Person-year	Incidence rate (per 1000 person-years)	Weighted cause-specific HR (95% CI)		Weighted subdistribution HR (95% CI)	
All-cause mortality							
Non-use	1383	7411	186.6	1 (Ref)	–	–	–
Warfarin	795	5401	147.2	0.88 (0.80, 0.97)	1 (Ref)	–	–
NOAC	410	3035	135.1	0.81 (0.72, 0.91)	0.92 (0.81, 1.05)	–	–
Ischaemic stroke or systemic embolism							
Non-use	437	6996	62.5	1 (Ref)	–	1 (Ref)	–
Warfarin	268	5129	52.2	0.85 (0.72, 1.00)	1 (Ref)	0.87 (0.74, 1.02)	
NOAC	128	2910	44.0	0.66 (0.53, 0.82)	0.78 (0.62, 0.98)	0.66 (0.53, 0.82)	0.76 (0.60, 0.96)
Major bleeding							
Non-use	293	7167	40.9	1 (Ref)	–	1 (Ref)	–
Warfarin	265	5175	51.2	1.31 (1.09, 1.56)	1 (Ref)	1.35 (1.13, 1.61)	
NOAC	125	2935	42.6	1.05 (0.84, 1.32)	0.80 (0.64, 1.01)	1.07 (0.85, 1.34)	0.79 (0.63, 1.00)
Fracture							
Non-use	436	6923	63.0	1 (Ref)	–	1 (Ref)	–
Warfarin	253	5132	49.3	0.89 (0.76, 1.06)	1 (Ref)	0.93 (0.78, 1.09)	
NOAC	135	2920	46.2	0.79 (0.64, 0.97)	0.88 (0.70, 1.11)	0.80 (0.65, 0.99)	0.87 (0.69, 1.09)

Abbreviations: CI, confidence interval; HR, hazard ratio; NOAC, non-vitamin K oral anticoagulant.

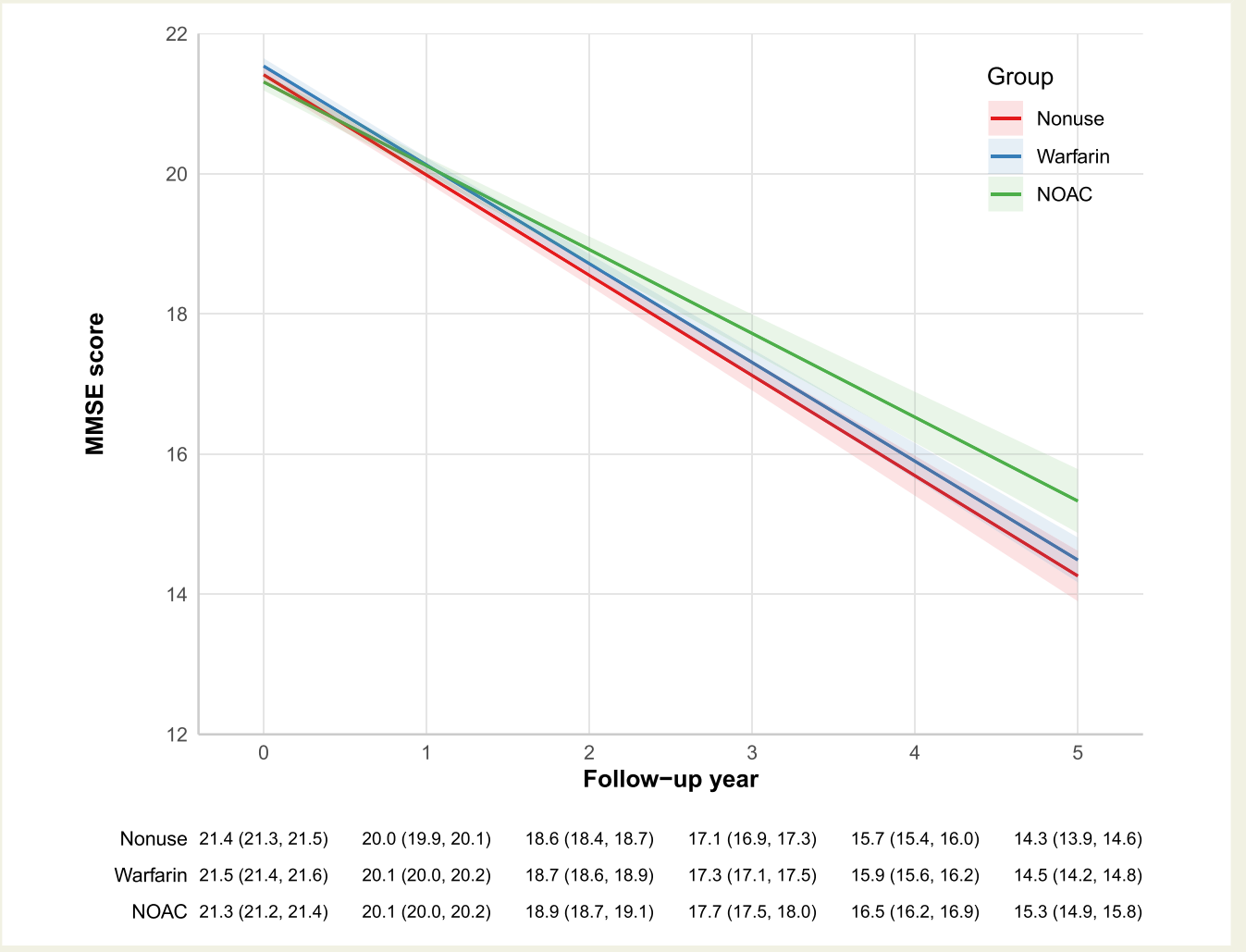


Figure 2 Estimated MMSE score trajectories by oral anticoagulant use. MMSE, Mini-Mental State Examination; NOAC, non-vitamin K oral anticoagulant. Marginal mean values of MMSE score were estimated based on the final model in *Table 2*

to the main analysis. When excluding individuals who recently discontinued anticoagulants or restricting to individuals diagnosed with AD during 2013–20, both cognitive and clinical outcomes aligned with those observed in the main analysis (see Supplementary data online, *Figures S8–S9* and Supplementary data online, *Tables S5–S6*).

Analyses of non-linear MMSE trajectories (see Supplementary data online, *Figure S10*) and transformed MMSE scores (see Supplementary data online, *Figure S11*) similarly indicated a slower cognitive decline associated with NOAC use. Supplementary data online, *Figure S12* presents the cumulative incidence of first deviation from baseline exposure during follow-up, with warfarin users exhibiting a notably higher occurrence of exposure change than the other two groups. Nevertheless, per-protocol analyses for clinical outcomes yielded results consistent with the main analysis, with a larger effect size for mortality (see Supplementary data online, *Table S7*).

Discussion

In this nationwide cohort of patients with incident AD and pre-existing AF, compared with non-use of anticoagulants, use of NOACs, but not warfarin, was significantly associated with slower cognitive decline. Both NOAC and warfarin use were associated with lower rates of ischaemic stroke/systemic embolism and all-cause mortality. Additionally, NOAC use was associated with a lower rate of fracture, while warfarin use was associated with a higher rate of major bleeding. In direct comparison with warfarin, NOAC use was associated with slower cognitive decline, as well as lower rates of ischaemic stroke/systemic embolism and major bleeding (*Structured Graphical Abstract*).

Despite the high prevalence of AF among patients with AD,[3] to the best of our knowledge, no prior research has investigated the impact of anticoagulation on cognition in this population. In our study, NOAC use was associated with a modest but statistically significant attenuation in MMSE score decline (about 0.2 points/year), compared with either non-use of anticoagulants or use of warfarin, with no significant difference observed between the latter two. This difference is comparable to previously reported estimates for cholinesterase inhibitors,[38] a symptomatic treatment for AD, and may have meaningful implications at the population level. Most existing observational studies

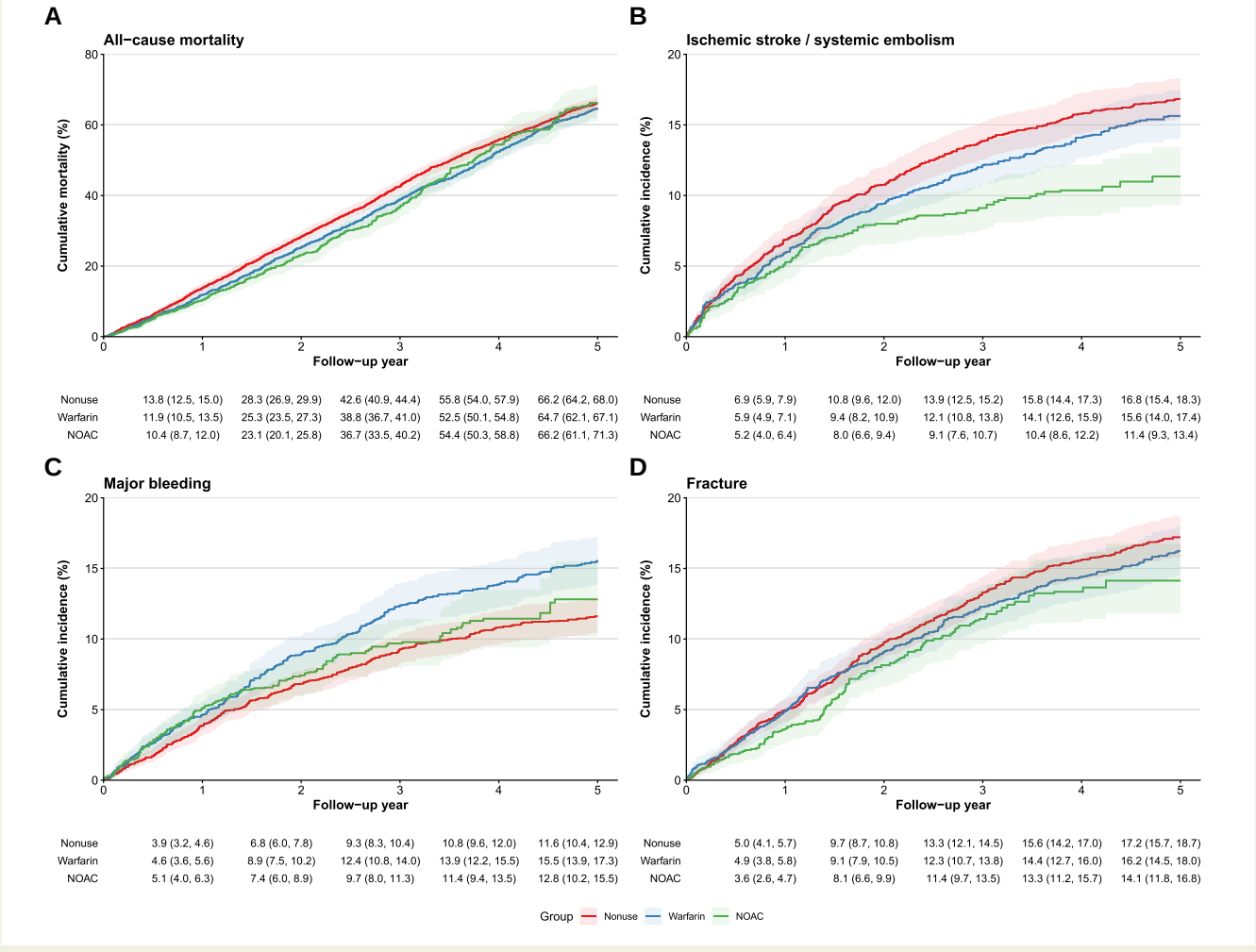


Figure 3 Weighted cumulative incidence of clinical outcomes by oral anticoagulant use. NOAC, non-vitamin K oral anticoagulant

relied on clinically diagnosed dementia as the outcome and indicated a protective role of anticoagulants against dementia risk,[8] with NOACs potentially favoured over warfarin.[9,10] However, the overall certainty of the evidence remains low.[8,9] Few studies have utilized longitudinal data to assess cognitive trajectories. Notably, a 7-year follow-up study by Armentaro *et al.* in older patients with AF reported less cognitive decline among NOAC users compared with those initiating VKAs,[39] which aligns with our findings in patients with coexisting AF and AD.

A meta-analysis of over 90 000 patients with AF, including four pivotal phase 3 trials where cognition-related adverse events were collected as safety outcomes, suggested that NOAC use may reduce the risk of cognitive impairment compared to warfarin or aspirin, particularly in studies with follow-up exceeding 1 year.[40] Nevertheless, two randomized controlled trials specifically designed to evaluate the cognitive benefits of dabigatran vs warfarin in patients with AF without dementia found no significant difference over a 2-year period.[11,12] Both trials featured well-managed warfarin therapy but were limited by small sample sizes (≤200 participants) and relatively short follow-up durations, potentially restricting their statistical power. The BRAIN-AF trial comparing rivaroxaban with standard care for preventing stroke and cognitive decline was terminated early due to futility;[13] however, it enrolled younger patients (30–60 years) with AF who had low stroke risk and preserved cognitive function, which limits its generalizability to higher-risk populations. A definitive causal link between NOAC use and cognitive outcomes requires further investigation, particularly in high stroke risk and/or cognitively vulnerable patients.

Several interrelated pathways highlight a vital role of coagulation processes in cognitive function. First, anticoagulants prevent clot formation and reduce the incidence of both overt strokes and subclinical brain infarcts, which are well-recognized contributors to cognitive decline.[8] Second, anticoagulant use may improve cerebral perfusion and maintain blood-brain barrier integrity, thereby supporting neurovascular health.[41] Third, there is extensive cross-talk between coagulation and inflammation,[42] and inhibition of thrombin generation and fibrin deposition ameliorates neuroinflammation.[23] Fourth, growing evidence implicates the coagulation cascade as a molecular link between vascular and Aβ-related pathology in AD.[43] The co-deposition of fibrin and Aβ impairs fibrinolysis and Aβ clearance.[44,45] Importantly, pharmacological strategies such as

fibrinogen reduction,[18] blockade of Aβ-fibrin interaction,[21] and particularly thrombin inhibition with dabigatran,[23] have been shown to attenuate amyloid burden and improve cognition in AD mice. Of note, the differences observed between NOACs and warfarin may be attributed to both pharmacological mechanisms and medication adherence. In this study, warfarin users had a substantially higher occurrence of treatment deviations than NOAC users, possibly reflecting the greater management burden of warfarin therapy. Such adherence differences affect anticoagulation control and may partly explain the more favourable real-world outcomes with NOACs, while also highlighting the practical advantages of NOAC therapy.

In addition to cognitive outcomes, this study assessed the comparative effectiveness and safety of anticoagulants in patients with AF and AD. Compared with non-use of anticoagulants, both NOAC and warfarin use were associated with lower rates of ischaemic stroke/systemic embolism and all-cause mortality, with more pronounced associations for NOACs. A meta-analysis similarly suggested benefits of oral anticoagulation vs non-use in patients with AF and dementia.[46] The finding that use of warfarin, but not NOACs, was associated with a higher rate of major bleeding compared with no anticoagulation warrants consideration. About half of the patients in the non-user group received antiplatelet agents, which are known to increase bleeding risk and may obscure differences in major bleeding that would otherwise be observed when compared with non-use of antithrombotic drugs. This interpretation is supported by the AVERROES trial, in which apixaban reduced stroke risk compared with aspirin without a significant increase in major bleeding among patients with AF unsuitable for VKA therapy.[47] Residual and unmeasured confounding can also influence the comparisons, as non-use of anticoagulants in our cohort may reflect clinical concerns such as bleeding risk, fall risk, comorbidity burden, and frailty, which are difficult to fully capture in register data. Consequently, comparisons with non-users should be interpreted with caution but remain important in studies reflecting routine clinical practice.

Comparison between two active regimens with similar clinical purposes is less prone to confounding by indication. We found that NOAC use was associated with lower risks of ischaemic stroke/systemic embolism and major bleeding than warfarin. These findings align with existing evidence supporting the superior effectiveness and non-inferior safety of NOACs in older adults with AF,[48] though the associations are less certain in AF patients with dementia.[46] The effect size for ischaemic stroke/systemic embolism appeared larger in our study (HR 0.78; 95% CI 0.62–0.98) than in a meta-analysis of four pivotal NOAC trials (HR 0.92; 95% CI 0.83–1.03),[49] which could be due to differences in patient characteristics, treatment regimens, and adherence patterns, in addition to residual confounding. Specifically, unlike those pivotal trials conducted in the general AF population, our study focused on patients with coexisting AF and AD. Prior research found that before the widespread use of NOACs in Sweden, only 27% of dementia patients with AF were treated with warfarin, while most received antiplatelet or no antithrombotic treatment.[3] In the present cohort, 54% received anticoagulants (31% warfarin, 23% NOACs), indicating that, although undertreatment persists, anticoagulant use has improved in this population. Given the challenges of managing warfarin in individuals with cognitive impairment, our findings support the preferential use of NOACs in patients with AF and AD, in line with recommendations for the general population.[50]

Although not statistically significant, our findings are directionally consistent with previous research suggesting a lower fracture risk among NOAC users compared with warfarin.[51,52] Individuals with AD are particularly vulnerable to fractures, which relates to adverse clinical outcomes.[53] The impact of anticoagulation on bone health remains uncertain. Concerns about warfarin arise from its antagonism of vitamin K-dependent processes involved in bone formation, though population-based studies have yielded mixed results.[54] In contrast, NOACs do not interfere with these pathways and have shown a favourable bone-safety profile.[54] Furthermore, our study found NOAC use to be associated with slower cognitive decline, a known risk factor for falls and fractures. Taken together, NOACs may be a safer option regarding fracture risk, which could be an important consideration in the management of older adults with both AF and AD.

NOACs are now the first-line therapy for stroke prevention in AF and have largely replaced warfarin. Our study in patients with AF and AD suggests more favourable thromboembolic and bleeding outcomes with NOACs than with warfarin, consistent with findings in populations without dementia.[48,49] We also found a slower rate of cognitive decline associated with NOAC use, but further studies are warranted. While awaiting more evidence on cognitive outcomes, anticoagulation decisions should remain primarily guided by stroke prevention rather than anticipated cognitive benefit. Overall, these findings support NOACs as preferred over warfarin in patients with AF and AD in contemporary clinical practice.

Strengths and limitations

Strengths of this study include a large cohort of individuals with both AF and AD, comprehensive data on diagnoses and prescriptions, and, notably, longitudinal assessments of cognitive function. Several limitations should be acknowledged. First, because anticoagulation treatment is typically initiated before an AD diagnosis in patients with AF, our analyses were based on ongoing anticoagulant use at the index date rather than a new-user design. An alternative approach would be to evaluate the effects of anticoagulant continuation/discontinuation among treated patients, which would require a larger accrued population of patients with AF and AD. Second, although we used IPTW to balance observed covariates, unmeasured or residual confounding cannot be ruled out. In routine care, anticoagulant use is influenced by not only clinical judgment (e.g. stroke risk, bleeding risk, functional status, and frailty) but also patient preference and medication uptake, factors not fully captured in health registers. Some differences between our population-based study of patients with AF and AD and existing clinical trials in AF may partly reflect residual confounding, but should also be interpreted in the context of both methodological and clinical differences. Third, anticoagulant exposure was estimated with assumptions, and constant exposure was assumed throughout follow-up; while exposure changes were common, results from per-protocol sensitivity analyses were largely consistent. Fourth, cognitive assessments were obtained from routine clinical practice, leading to variability in the number and timing of MMSE tests. Given that attrition was likely not

random, we applied IPCW to mitigate potential bias. Fifth, some degree of misclassification of diagnosis-based outcomes is inevitable in register-based studies. However, there is no strong reason to expect systematic differences by anticoagulant group in this study; thus, any largely non-differential misclassification would be expected to attenuate associations towards the null. Finally, we were unable to evaluate the effects of individual NOAC agents due to insufficient statistical power. Our analyses focused on AD and mixed AD dementia, while other dementia subtypes with distinct pathophysiological mechanisms were not examined. Further studies are needed to confirm and extend our findings.

Conclusions

Among patients with incident AD and pre-existing AF, NOAC use was associated with modestly slower cognitive decline compared to non-use of anticoagulants or use of warfarin, with no significant difference between the latter two groups. Both NOAC and warfarin use were associated with lower rates of ischaemic stroke/systemic embolism and mortality relative to non-use, with stronger associations for NOACs. Moreover, NOAC users experienced a lower rate of fracture, whereas warfarin users experienced a higher rate of major bleeding.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

M.E. has served as a consultant for BioArctic AB, Roche, Eli Lilly, Biogen/Eisai, and Novo Nordisk and has given lectures in symposia sponsored by Roche. The other authors have nothing to disclose.

Data Availability

In accordance with Swedish and EU legislation, the supporting data cannot be made publicly available. Access to data from Swedish registries requires ethical approval and subsequent application to the registry steering committees (www.svedem.se) and relevant government authorities.

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Ethical Approval

This study was approved by the Swedish Ethical Review Authority (Dnr: 2021/03304). Individual informed consent was not required due to the register data being pseudonymized before delivery to the research group.

Pre-registered Clinical Trial Number

Not applicable.

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