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RESEARCH PAPER

Comparing the risk of dementia in subjects with atrial fibrillation using non-vitamin K antagonist oral anticoagulants versus vitamin K antagonists: a Belgian nationwide cohort study

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Abstract

Background: Atrial fibrillation (AF) is associated with cognitive decline, with anticoagulated subjects potentially having a reduced risk compared with non-anticoagulated subjects. However, whether non-vitamin K antagonist oral anticoagulants (NOACs) may reduce the risk of dementia compared with vitamin K antagonists (VKAs) is unclear yet. Therefore, the risk of dementia was compared between AF subjects on NOACs versus VKAs.
Methods: AF subjects initiating anticoagulation between 2013 and 2019 were identified in Belgian nationwide data. Inverse probability of treatment weighted Cox regression was used to investigate cognitive outcomes.
Results: Among 237,012 AF subjects (310,850 person-years (PYs)), NOAC use was associated with a significantly lower risk of dementia (adjusted hazard ratio (aHR) 0.91, 95% confidence interval (CI) (0.85–0.98)) compared with VKAs. A trend towards a lower risk of vascular dementia (aHR 0.89, 95% CI (0.76–1.04)) and significantly lower risk of other/unspecified dementia (aHR 0.91, 95% CI (0.84–0.99)) were observed with NOACs compared with VKAs, whereas the risk of Alzheimer's disease was similar (aHR 0.99, 95% CI (0.88–1.11)). Apixaban (aHR 0.91, 95% CI (0.83–0.99)) and edoxaban (aHR 0.79, 95% CI (0.63–0.99)) were associated with significantly lower risks of dementia compared with VKAs, while risks were not significantly different with dabigatran (aHR 1.02, 95% CI (0.93–1.12)) and rivaroxaban (aHR 0.97, 95% CI (0.90–1.05)). Comparable risks of dementia were observed between individual NOACs, except for significantly lower risks of dementia (aHR 0.93, 95% CI (0.87–0.98)) and other/unspecified dementia (aHR 0.90 (0.84–0.97)) with apixaban compared with rivaroxaban.
Conclusion: NOACs were associated with a significantly lower risk of dementia compared with VKAs, likely driven by apixaban and edoxaban use.

Keywords: atrial fibrillation, non-vitamin K antagonist oral anticoagulants (NOAC), vitamin K antagonists (VKA), dementia, Alzheimer's disease

Key Points

- Non-vitamin K antagonist oral anticoagulants were associated with a 9% significantly lower risk of new-onset dementia compared with vitamin K antagonists (VKAs) among unselected Atrial fibrillation subjects.
- This was driven by lower risks of vascular and other/unspecified dementia, whereas the risk of Alzheimer's disease was similar.
- Compared with VKAs, lower risks of dementia were observed with apixaban and edoxaban, but not with dabigatran or rivaroxaban.

Introduction

Dementia, a condition with impaired memory and cognitive functions, increases with age and causes significant disability [1]. Atrial fibrillation (AF) also increases with age and has been associated with substantial morbidity and mortality [2]. Several studies have demonstrated that AF is an independent risk factor for dementia [3–10]. Moreover, emerging evidence associates long-term use of oral anticoagulants (OACs) in AF management with a significantly lower risk of new-onset dementia compared with non-anticoagulated AF subjects [9–15].

Following the rapid uptake of non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in AF [16, 17], the question has been raised whether NOACs may additionally reduce the risk of dementia compared with vitamin K antagonists (VKAs), given that they are associated with significantly lower risks of stroke and intracranial bleeding compared with VKAs [1, 2, 8, 11, 14, 18–21]. However, strong randomised evidence is currently lacking and previous real-world observational studies have reported conflicting results [1, 5, 12, 13, 20–24]. Studies often have been limited by a short follow-up, small sample size or inclusion of subjects with prior OAC use. Furthermore, differences between individual NOACs are even less established.

Therefore, we aimed to investigate the risk of dementia with NOACs compared with VKAs and between individual NOACs in unselected persons with AF on a full-population scale. Differences in the risk of dementia subtypes were explored.

Methods

Source population

Details on the study methodology have been published before and are provided in the supplemental materials [17, 25]. In brief, two nationwide databases provided the source population, namely the InterMutualistic Agency (IMA) database and Minimal Hospital Dataset (MHD). The IMA centralises all claims data from Belgian health insurance funds on reimbursed ambulatory and hospital care, including demographic characteristics, medical procedures and drug prescription claims, and represents all legal residents in Belgium [26, 27]. The MHD aggregates hospital discharge diagnoses of every hospital admission (hospitalisations, day-care stays and emergency room contacts), coded in International Classification of Diseases (ICD) codes (ICD-9 up to 2014, ICD-10 from 2015 onwards) [26, 28]. This study was approved by the Belgian Commission for the Protection of Privacy (approval code IVC/KSZG/20/344) [29]. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed (Table S1) [30].

Study population

From 1 January 2013 to 1 January 2019, persons aged ≥45 years old and with ≥1 year coverage by a health insurance fund were included from the IMA database on the first date of filling an OAC prescription (=index date) (Figure S1). NOAC users, namely dabigatran (approved in Belgium since August 2012), rivaroxaban (approved since September 2012), apixaban (approved since September 2013) and edoxaban (approved since October 2016), and VKA users (warfarin, acenocoumarol, phenprocoumon) were included [17]. Only OAC-naïve subjects were considered, excluding OAC-experienced subjects with an OAC prescription filled ≤1 year before the index date.

Subjects were excluded in case of (i) a prior diagnosis of dementia or use of anti-dementia drugs before OAC initiation, (ii) total hip or knee replacement, or diagnosis of deep vein thrombosis or pulmonary embolism ≤6 months before the index date, (iii) valvular AF (mechanical prosthetic heart valve or moderate/severe mitral stenosis), (iv) end-stage renal disease, (v) ≥2 prescription claims of different NOAC types or doses on the index date, or (vi) use of NOAC doses not approved for stroke prevention in AF (Table S2).

Outcomes

The primary outcome was new-onset dementia, defined as a new diagnosis of Alzheimer's disease, vascular dementia or other/unspecified dementia (e.g. Lewy body dementia). As a secondary outcome, dementia subtypes were investigated separately. Outcomes were identified using ICD-coded hospital discharge diagnoses (e.g. ICD-10 code G30 for Alzheimer's disease) and/or medication prescription claims for anti-dementia drugs (e.g. use of cholinesterase inhibitors for Alzheimer's disease) from the day after OAC initiation (Table S3). The incident date of outcomes was defined as the date of hospital admission related to ICD codes or first date of dispensing of anti-dementia drugs, whichever occurred first.

Follow-up

Subjects were followed from OAC initiation until the first occurrence of the investigated outcome, discontinuation (>60-day gap of drug supply) or switch of treatment, death, emigration or end of the study period (1 January 2019), whichever came first.

Covariables

Baseline characteristics were assessed on the index date and included age, sex, comorbidities, medication history and clinical risk scores. Comorbidities were identified with specific ICD-coded diagnoses, medical procedure codes and/or medication prescription claims ≤1 year before the index date (Table S2). Medication history was identified with medication prescription claims, considering recent use ≤6 months before the index date. Lastly, the CHA_2DS_2-VASc score, HAS-BLED score and age-adjusted Charlson Comorbidity Index were calculated [2, 31]. A modified HAS-BLED score was used without the 'labile INR' criterion.

Statistical analyses

Mean and standard deviation, and counts and percentages were presented for continuous and categorical variables, respectively. Crude incidence rates (IRs) were calculated as the total number of events per 100 person-years (PYs) at risk. Outcomes were compared between NOACs and VKAs, and between individual NOACs using stabilised inverse probability of treatment weighting (IPTW). In comparisons with apixaban and edoxaban, the study population was restricted to subjects having initiated treatment from September 2013 and from October 2016 onwards respectively, to improve comparability and avoid violations of the positivity assumption [20, 32]. Propensity scores (PS) were calculated with logistic regression models including the 41 confounding covariables described in Table 1, stratified by calendar year (to account for changes in prescribing practices over time). Based on the PS, stabilised weights were calculated and truncated at the 0.5 and 99.5 percentile. Covariable balance before and after weighting was checked using standardised mean differences (SMDs) with a ≥ 0.1 threshold to indicate imbalance. Weighted Cox proportional hazard regression models were used to calculate cause-specific adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs), treating death as a competing risk. The proportional hazard assumption was tested using scaled Schoenfeld residuals and was valid for all outcomes. A two-sided *P*-value of <0.05 was considered statistically significant. All analyses were performed in R (R version 3.6.0).

Sensitivity analyses

Sensitivity analyses were performed to check the robustness of results. First, only subjects with an ICD-coded hospital discharge diagnosis of AF before or up to 90 days after the index date were investigated, although this approach resulted in the exclusion of AF subjects treated exclusively in primary or ambulatory care [23]. Second, the study population was restricted to subjects having initiated treatment since October 2016, when all NOACs were commercially available in Belgium. Third, analyses were repeated using an intention-to-treat (ITT) approach, defining the end of follow-up as the first occurrence of an outcome, death, emigration or end of study period, whichever occurred first [24]. Lastly, subjects were additionally excluded in case of a new diagnosis of dementia ≤90 days after the index date or in case of a prior diagnosis of stroke, transient ischaemic attack (TIA) or intracranial bleeding before the index date, to exclude new dementia diagnoses unlikely to be associated with the recent initiation of anticoagulation [1, 24].

Results

Baseline characteristics

During a mean follow-up of 1.3 ± 1.5 years (310,850 PYs), 237,012 newly treated AF subjects were included (Figure S2). Baseline characteristics of the 179,237 NOAC and 57,775 VKA users are summarised in Table 1. Before weighting, NOAC users were older than VKA users (mean age 75.7 ± 10.1 versus 70.2 ± 12.0 years), had more prior stroke (11.6% versus 10.3%) and had higher CHA_2DS_2-VASc scores (mean score 3.4 ± 1.7 versus 3.1 ± 1.9). After weighting, covariable balance was achieved (Table 1, Figure S3).

Risk of dementia

The unadjusted number of events and IRs are summarised in Table 2. After multivariable adjustment using stabilised IPTW, NOACs were associated with a significantly lower risk of new-onset dementia (aHR 0.91, 95%CI (0.85–0.98)) compared with VKAs (Table 3, Figure 1). Apixaban (aHR 0.91, 95% CI (0.83–0.99)) and edoxaban (aHR 0.79, 95% CI (0.63–0.99)) were associated with significantly lower risks of new-onset dementia compared with VKAs, whereas the risk was not significantly different with dabigatran (aHR 1.02, 95% CI (0.93–1.12)) and rivaroxaban (aHR 0.97, 95% CI (0.90–1.05)). A trend towards a lower risk of vascular dementia (aHR 0.89, 95% CI (0.76–1.04)) and significantly lower risk of other/unspecified dementia (aHR 0.91, 95% CI (0.84–0.99)) were observed with NOACs compared with VKAs, whereas the risk of Alzheimer's disease was similar (HR 0.99, 95%CI (0.88–1.11)). No significant differences in the risk of dementia subtypes were observed between individual NOAC types and VKAs, except for a significantly lower risk of other/unspecified dementia with edoxaban (aHR 0.74, 95% CI (0.57–0.96)) and higher risk of Alzheimer's disease with dabigatran (aHR 1.17, 95% CI (1.01–1.35)) compared with VKAs.

No significant differences in the risks of new-onset dementia or dementia subtypes were observed between

Table 1. Baseline characteristics of OAC-naïve AF subjects

Baseline characteristics	VKA (n = 57,775)	NOAC					SMD[a]	
		Overall (n = 179,237)	Dabigatran (n = 26,509)	Rivaroxaban (n = 69,287)	Apixaban (n = 61,244)	Edoxaban (n = 22,197)	Before IPTW	After IPTW
Age (years)	70.2 ± 12.0	75.7 ± 10.1	75.5 ± 9.8	75.0 ± 10.4	76.7 ± 9.8	75.3 ± 10.2	0.493	0.017
<65 years	20,948 (36.3%)	24,569 (13.7%)	3,611 (13.6%)	10,766 (15.5%)	6,875 (11.2%)	3,317 (14.9%)	NA	NA
65–74 years	14,717 (25.5%)	54,527 (30.4%)	8,165 (30.8%)	21,194 (30.6%)	18,039 (29.5%)	7,129 (32.1%)		
75–84 years	15,241 (26.4%)	66,642 (37.2%)	10,140 (38.3%)	25,508 (36.8%)	23,303 (38.0%)	7,691 (34.6%)		
≥85 years	6,869 (11.9%)	33,499 (18.7%)	4,593 (17.3%)	11,819 (17.1%)	13,027 (21.3%)	4,060 (18.3%)		
Female	26,657 (46.1%)	83,475 (46.6%)	12,139 (45.8%)	32,055 (46.3%)	29,334 (47.9%)	9,947 (44.8%)	0.009	0.005
Reduced dose	NA	63,460 (35.4%)	14,127 (53.3%)	26,567 (38.3%)	16,611 (27.1%)	6,155 (27.7%)	NA	NA
Follow-up (years) (OT analysis)	0.9 ± 1.4	1.5 ± 1.5	1.6 ± 1.7	1.7 ± 1.7	1.4 ± 1.3	0.7 ± 0.6	NA	NA
Follow-up (years) (ITT analysis)	3.3 ± 1.8	2.4 ± 1.7	3.0 ± 1.8	3.0 ± 1.7	2.2 ± 1.4	0.9 ± 0.6	NA	NA
Comorbidities								
Hypertension	34,162 (59.1%)	117,445 (65.5%)	17,187 (64.8%)	43,979 (63.5%)	42,043 (68.6%)	14,236 (64.1%)	0.133	0.011
Coronary artery disease	12,899 (22.3%)	30,064 (16.8%)	3,926 (14.8%)	10,886 (15.7%)	11,399 (18.6%)	3,852 (17.4%)	0.139	0.012
Congestive heart failure	8,619 (14.9%)	25,976 (14.5%)	3,176 (12.0%)	9,320 (13.5%)	10,270 (16.8%)	3,210 (14.5%)	0.011	0.025
Valvular heart disease	10,809 (18.7%)	20,642 (11.5%)	2,735 (10.3%)	6,830 (9.9%)	8,082 (13.2%)	2,995 (13.5%)	0.207	0.001
Peripheral artery disease	6,054 (10.5%)	12,011 (6.7%)	1,641 (6.2%)	4,082 (5.9%)	4,865 (7.9%)	1,423 (6.4%)	0.129	0.006
Dyslipidaemia	32,222 (55.8%)	102,126 (57.0%)	15,400 (58.1%)	37,822 (54.6%)	36,237 (59.2%)	12,667 (57.1%)	0.024	0.004
Chronic kidney disease	7,208 (12.5%)	17,024 (9.5%)	1,553 (5.9%)	5,552 (8.0%)	7,468 (12.2%)	2,451 (11.0%)	0.089	0.009
Chronic liver disease	2,155 (3.7%)	4,916 (2.7%)	638 (2.4%)	1819 (2.6%)	1784 (2.9%)	675 (3.0%)	0.052	0.002
Chronic lung disease	7,428 (12.9%)	20,687 (11.5%)	2,708 (10.2%)	7,776 (11.2%)	7,654 (12.5%)	2,549 (11.5%)	0.036	0.004
Obstructive sleep apnoea	2,107 (3.6%)	6,087 (3.4%)	842 (3.2%)	2,307 (3.3%)	2,116 (3.5%)	822 (3.7%)	0.011	0.011
Cancer	5,267 (9.1%)	17,235 (9.6%)	2,269 (8.6%)	6,588 (9.5%)	6,085 (9.9%)	2,293 (10.3%)	0.020	0.011
Diabetes mellitus	20,416 (35.3%)	53,142 (29.6%)	7,154 (27.0%)	19,385 (28.0%)	19,940 (32.6%)	6,663 (30.0%)	0.120	0.026
Anaemia	5,387 (9.3%)	11,576 (6.5%)	1,318 (5.0%)	4,152 (6.0%)	4,634 (7.6%)	1,473 (6.6%)	0.098	0.003
Thyroid disease	8,070 (14.0%)	25,006 (14.0%)	3,559 (13.4%)	9,678 (14.0%)	8,972 (14.7%)	2,796 (12.6%)	<0.001	0.010
Depression	13,268 (23.0%)	35,818 (20.0%)	5,194 (19.6%)	14,123 (20.4%)	12,640 (20.6%)	3,861 (17.4%)	0.073	0.013
Parkinson's disease	1,247 (2.2%)	4,530 (2.5%)	669 (2.5%)	1,663 (2.4%)	1,680 (2.7%)	518 (2.3%)	0.024	0.002
History of falling	2,745 (4.8%)	11,286 (6.3%)	1,321 (5.0%)	3,587 (5.2%)	4,776 (7.8%)	1,601 (7.2%)	0.072	0.036
Frailty	10,755 (18.6%)	46,741 (26.1%)	6,373 (24.0%)	16,453 (23.7%)	18,590 (30.4%)	5,325 (24.0%)	0.181	0.021
Prior stroke/SE	7,438 (12.9%)	22,035 (12.3%)	4,217 (15.9%)	6,229 (9.0%)	9,690 (15.8%)	1899 (8.6%)	0.012	0.014
Prior stroke	5,961 (10.3%)	20,744 (11.6%)	4,038 (15.2%)	5,693 (8.2%)	9,231 (15.1%)	1781 (8.0%)	0.044	0.010
Prior TIA	763 (1.3%)	3,479 (1.9%)	738 (2.8%)	871 (1.3%)	1,541 (2.5%)	329 (1.5%)	0.049	<0.001
Prior MB/CRNMB	3,284 (5.7%)	8,261 (4.6%)	1,151 (4.3%)	2,817 (4.1%)	3,283 (5.4%)	1,011 (4.6%)	0.042	0.007
Prior ICH	290 (0.5%)	1,016 (0.6%)	221 (0.8%)	255 (0.4%)	461 (0.8%)	79 (0.4%)	0.011	0.005
Medication history								
Number of concomitant drugs	6.7 ± 4.5	6.5 ± 4.0	6.1 ± 3.7	6.4 ± 4.0	6.8 ± 4.2	6.2 ± 4.0	0.049	0.006
Polypharmacy (5-9)	24,355 (42.2%)	82,498 (46.0%)	12,521 (47.2%)	31,964 (46.1%)	28,152 (46.0%)	9,861 (44.4%)	NA	NA
Hyperpolypharmacy (≥10)	12,730 (22.0%)	33,824 (18.9%)	4,182 (15.8%)	12,687 (18.3%)	13,089 (21.4%)	3,866 (17.4%)		
Beta blockers	29,735 (51.5%)	111,125 (62.0%)	16,195 (61.1%)	41,504 (59.9%)	39,358 (64.3%)	14,068 (63.4%)	0.214	0.008
Verapamil, diltiazem	2,013 (3.5%)	7,290 (4.1%)	1,102 (4.2%)	2,994 (4.3%)	2,447 (4.0%)	747 (3.4%)	0.031	0.016
Digoxin	3,262 (5.6%)	16,685 (9.3%)	2,333 (8.8%)	6,142 (8.9%)	6,205 (10.1%)	2,005 (9.0%)	0.140	0.010
Class I AAD	3,386 (5.9%)	19,163 (10.7%)	2,982 (11.2%)	7,929 (11.4%)	5,784 (9.4%)	2,468 (11.1%)	0.176	0.007
Class III AAD	10,802 (18.7%)	46,630 (26.0%)	6,880 (26.0%)	18,844 (27.2%)	15,911 (26.0%)	4,995 (22.5%)	0.176	0.026
Acetylsalicylic acid	20,048 (34.7%)	72,253 (40.3%)	10,699 (40.4%)	27,368 (39.5%)	25,533 (41.7%)	8,653 (39.0%)	0.116	0.009
P2Y12 inhibitor	3,137 (5.4%)	10,417 (5.8%)	1,410 (5.3%)	3,613 (5.2%)	3,829 (6.3%)	1,565 (7.1%)	0.017	0.011
Proton pump inhibitor	23,722 (41.1%)	69,538 (38.8%)	9,656 (36.4%)	26,399 (38.1%)	24,863 (40.6%)	8,620 (38.8%)	0.046	0.016
NSAID	15,814 (27.4%)	44,043 (24.6%)	6,581 (24.8%)	17,599 (25.4%)	14,553 (23.8%)	5,310 (23.9%)	0.064	0.005
Oral corticosteroids	12,940 (22.4%)	35,111 (19.6%)	4,780 (18.0%)	13,791 (19.9%)	12,191 (19.9%)	4,349 (19.6%)	0.069	0.001
SSRI/SNRI	7,227 (12.5%)	19,573 (10.9%)	2,848 (10.7%)	7,810 (11.3%)	6,893 (11.3%)	2,022 (9.1%)	0.049	0.012
Lipid-lowering drugs	26,941 (46.6%)	87,365 (48.7%)	13,146 (49.6%)	32,509 (46.9%)	30,929 (50.5%)	10,781 (48.6%)	0.042	0.010
Clinical risk score								
CHA_2DS_2-VASc score	3.1 ± 1.9	3.4 ± 1.7	3.4 ± 1.7	3.3 ± 1.7	3.7 ± 1.7	3.3 ± 1.7	0.187	0.016
HAS-BLED score	2.2 ± 1.4	2.5 ± 1.2	2.4 ± 1.1	2.4 ± 1.2	2.6 ± 1.2	2.4 ± 1.2	0.197	0.010
Charlson Comorbidity Index	3.8 ± 2.3	4.2 ± 2.0	4.2 ± 1.9	4.1 ± 2.0	4.5 ± 2.1	4.2 ± 2.1	0.190	0.003

Data shown as mean ± standard deviation, or counts and percentages. VKA users included 27,721 acenocoumarol, 15,794 warfarin and 14,260 phenprocoumon users. AAD: antiarrhythmic drug; CRNMB: clinically relevant non-major bleeding; MB: major bleeding; NA: not applicable; NSAID: non-steroidal anti-inflammatory drug; OT: on-treatment; SE: systemic embolism; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.
[a]Absolute SMDs illustrated for comparison of NOACs versus VKAs before and after IPTW.

Table 2. The unadjusted number of events and IRs per 100 PYs of follow-up with 95% CIs for each investigated outcome

	Dementia		Alzheimer's disease		Vascular dementia		Other/unspecified dementia	
	Events	IR per 100 PY (95%CI)	Events	IR per 100 PY (95%CI)	Events	IR per 100 PY (95%CI)	Events	IR per 100 PY (95%CI)
VKA	1,062	2.18 (2.05–2.32)	394	0.80 (0.72–0.88)	214	0.43 (0.38–0.49)	814	1.67 (1.55–1.78)
NOAC	6,815	2.66 (2.59–2.72)	2,934	1.13 (1.09–1.17)	1,450	0.55 (0.53–0.58)	5,118	1.98 (1.93–2.03)
Dabigatran	1,101	2.58 (2.43–2.74)	508	1.18 (1.08–1.28)	230	0.53 (0.46–0.60)	796	1.85 (1.72–1.98)
Rivaroxaban	2,946	2.60 (2.50–2.69)	1,269	1.11 (1.04–1.17)	614	0.53 (0.49–0.57)	2,270	1.99 (1.90–2.07)
Apixaban	2,338	2.77 (2.65–2.88)	976	1.14 (1.07–1.21)	519	0.60 (0.55-0.65)	1,729	2.03 (1.93–2.13)
Edoxaban	430	2.70 (2.45–2.96)	181	1.13 (0.97–1.29)	87	0.54 (0.43-0.65)	323	2.02 (1.80–2.24)

Table 3. aHRs with 95% CIs of the risk of dementia between NOACs and VKAs or between NOAC types after IPTW

	Dementia	Alzheimer's disease	Vascular dementia	Other/unspecified dementia
	aHR (95%CI)	aHR (95%CI)	aHR (95%CI)	aHR (95%CI)
NOAC vs VKA				
NOAC vs VKA	0.91 (0.85–0.98)	0.99 (0.88–1.11)	0.89 (0.76–1.04)	0.91 (0.84–0.99)
Dabigatran vs VKA	1.02 (0.93–1.12)	1.17 (1.01–1.35)	0.92 (0.74–1.13)	0.99 (0.88–1.10)
Rivaroxaban vs VKA	0.97 (0.90–1.05)	1.04 (0.92–1.17)	0.96 (0.81–1.14)	0.98 (0.90–1.07)
Apixaban vs VKA	0.91 (0.83–0.99)	0.91 (0.79–1.05)	0.89 (0.73–1.09)	0.92 (0.83–1.02)
Edoxaban vs VKA	0.79 (0.63–0.99)	0.82 (0.56–1.21)	0.93 (0.56–1.55)	0.74 (0.57–0.96)
NOAC vs NOAC				
Rivaroxaban vs dabigatran	1.02 (0.95–1.09)	0.96 (0.86–1.06)	1.08 (0.92–1.26)	1.07 (0.98–1.16)
Apixaban vs dabigatran	0.94 (0.87–1.03)	0.89 (0.79–1.01)	0.97 (0.81–1.16)	0.97 (0.88–1.07)
Edoxaban vs dabigatran	0.87 (0.72–1.04)	0.83 (0.63–1.10)	0.95 (0.63–1.44)	0.93 (0.75–1.16)
Apixaban vs rivaroxaban	0.93 (0.87–0.98)	0.95 (0.86–1.04)	0.89 (0.78–1.01)	0.90 (0.84–0.97)
Edoxaban vs rivaroxaban	0.90 (0.78–1.03)	0.92 (0.74–1.14)	0.86 (0.63–1.17)	0.94 (0.80–1.11)
Apixaban vs edoxaban	0.98 (0.87–1.11)	0.90 (0.74–1.09)	1.08 (0.82–1.41)	0.94 (0.82–1.09)

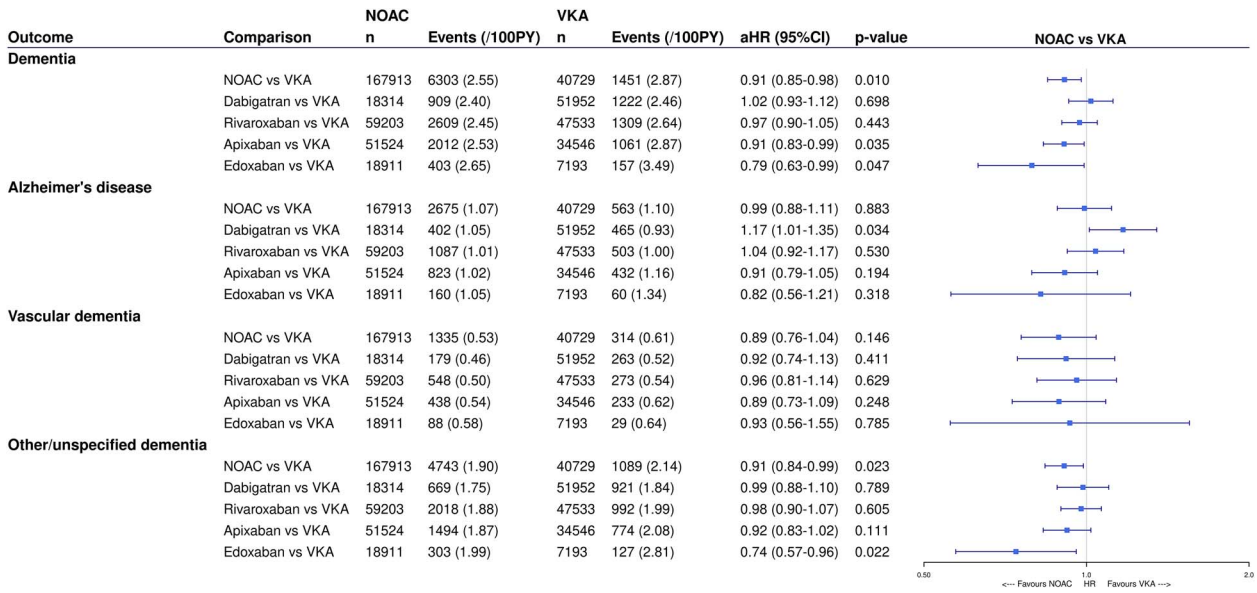

Figure 1. The risk of dementia in AF subjects treated with (individual) NOACs versus VKAs after IPTW. The weighted number of subjects at risk in the pseudopopulation, weighted number of events, weighted IRs per 100 PY and adjusted HRs with 95%CIs after IPTW are illustrated. AF: atrial fibrillation; vs: versus.

individual NOACs, except for significantly lower risks of dementia (aHR 0.93, 95% CI (0.87–0.98)) and other/unspecified dementia (aHR 0.90 (0.84–0.97)) with apixaban compared with rivaroxaban (Table 3, Figure 2). Risk estimates of new-onset dementia with apixaban compared with dabigatran (aHR 0.94, 95% CI (0.87–1.03)), and with edoxaban compared with dabigatran (aHR 0.87, 95% CI (0.72–1.04)) and rivaroxaban (aHR 0.90,

Outcome	Comparison	Comparator n	Comparator Events (/100PY)	Reference n	Reference Events (/100PY)	aHR (95%CI)	p-value
Dementia							
	Rivaroxaban vs Dabigatran (ref)	68573	2984 (2.62)	25211	1071 (2.57)	1.02 (0.95-1.09)	0.585
	Apixaban vs Dabigatran (ref)	60845	2289 (2.69)	19848	829 (2.85)	0.94 (0.87-1.03)	0.178
	Edoxaban vs Dabigatran (ref)	21869	434 (2.73)	6926	175 (3.07)	0.87 (0.72-1.04)	0.134
	Apixaban vs Rivaroxaban (ref)	59454	2200 (2.62)	55072	2399 (2.81)	0.93 (0.87-0.98)	0.010
	Edoxaban vs Rivaroxaban (ref)	21731	427 (2.72)	17631	413 (2.97)	0.90 (0.78-1.03)	0.125
	Apixaban vs Edoxaban (ref)	27706	630 (2.90)	21243	472 (3.01)	0.98 (0.87-1.11)	0.795
Alzheimer's disease							
	Rivaroxaban vs Dabigatran (ref)	68573	1288 (1.12)	25211	492 (1.17)	0.96 (0.86-1.06)	0.396
	Apixaban vs Dabigatran (ref)	60845	966 (1.12)	19848	372 (1.26)	0.89 (0.79-1.01)	0.068
	Edoxaban vs Dabigatran (ref)	21869	182 (1.14)	6926	78 (1.35)	0.83 (0.63-1.10)	0.201
	Apixaban vs Rivaroxaban (ref)	59454	932 (1.10)	55072	1002 (1.16)	0.95 (0.86-1.04)	0.234
	Edoxaban vs Rivaroxaban (ref)	21731	181 (1.15)	17631	171 (1.22)	0.92 (0.74-1.14)	0.459
	Apixaban vs Edoxaban (ref)	27706	240 (1.10)	21243	194 (1.23)	0.90 (0.74-1.09)	0.282
Vascular dementia							
	Rivaroxaban vs Dabigatran (ref)	68573	631 (0.54)	25211	214 (0.50)	1.08 (0.92-1.26)	0.344
	Apixaban vs Dabigatran (ref)	60845	505 (0.58)	19848	178 (0.60)	0.97 (0.81-1.16)	0.752
	Edoxaban vs Dabigatran (ref)	21869	90 (0.56)	6926	34 (0.58)	0.95 (0.63-1.44)	0.818
	Apixaban vs Rivaroxaban (ref)	59454	469 (0.55)	55072	531 (0.61)	0.89 (0.78-1.01)	0.074
	Edoxaban vs Rivaroxaban (ref)	21731	86 (0.54)	17631	87 (0.62)	0.86 (0.63-1.17)	0.332
	Apixaban vs Edoxaban (ref)	27706	146 (0.67)	21243	100 (0.63)	1.08 (0.82-1.41)	0.587
Other/unspecified dementia							
	Rivaroxaban vs Dabigatran (ref)	68573	2290 (1.99)	25211	784 (1.87)	1.07 (0.98-1.16)	0.111
	Apixaban vs Dabigatran (ref)	60845	1691 (1.98)	19848	600 (2.04)	0.97 (0.88-1.07)	0.510
	Edoxaban vs Dabigatran (ref)	21869	325 (2.04)	6926	123 (2.15)	0.93 (0.75-1.16)	0.523
	Apixaban vs Rivaroxaban (ref)	59454	1638 (1.93)	55072	1843 (2.15)	0.90 (0.84-0.97)	0.003
	Edoxaban vs Rivaroxaban (ref)	21731	324 (2.05)	17631	300 (2.14)	0.94 (0.80-1.11)	0.472
	Apixaban vs Edoxaban (ref)	27706	464 (2.13)	21243	360 (2.29)	0.94 (0.82-1.09)	0.424

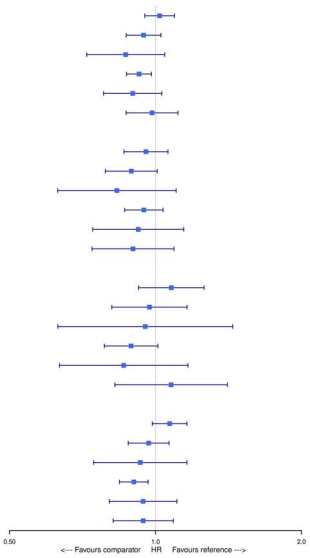

Figure 2. The risk of dementia between (individual) NOACs in persons with AF after IPTW. The weighted number of subjects at risk in the pseudopopulation, weighted number of events, weighted IRs per 100 PY and adjusted HRs with 95%CIs after IPTW are illustrated. Ref: reference category.

95% CI (0.78–1.03)) were numerically lower but not significantly different.

Sensitivity analyses

Among subjects with an ICD-coded hospital discharge diagnosis of AF ($n = 112{,}198$; baseline characteristics summarised in Table S4), trends were consistent and even more pronounced with NOACs being associated with significantly lower risks of dementia (aHR 0.81, 95% CI (0.73–0.90)), vascular dementia (aHR 0.78, 95% CI (0.63–0.97)) and other/unspecified dementia (aHR 0.83, 95% CI (0.74–0.93)) compared with VKAs, while the risk of Alzheimer's disease was lower but non-significantly different (aHR 0.84, 95% CI (0.71–1.00), *P*-value 0.051) (Table S5, Figure S4). Likewise, NOACs were associated with significantly lower risks of dementia (aHR 0.74, 95% CI (0.60–0.91)) and other/unspecified dementia (aHR 0.68, 95% CI (0.53–0.86)), and trends towards lower risks of Alzheimer's disease (aHR 0.73, 95% CI (0.51–1.05)) and vascular dementia (aHR 0.85, 95% CI (0.54–1.33)), compared with VKAs, and differences in the risk of dementia between individual NOACs were consistent when restricting the study population to subjects having initiated treatment since October 2016 ($n = 87{,}295$) (Table S6, Figure S5).

However, differences in the risk of dementia with NOACs compared with VKAs were no longer statistically significant with an ITT approach (aHR 0.97, 95% CI (0.93–1.01)) (Table S7, Figure S6) and when excluding subjects with a new diagnosis of dementia ≤90 days after the index date or in case of prior stroke, TIA or intracranial bleeding ($n = 204{,}503$) (aHR 0.93, 95% CI (0.85–1.02)) (Table S8, Figure S7). Nevertheless, comparative differences between individual NOACs were mostly consistent.

Discussion

In this nationwide cohort study including nearly 240,000 unselected AF subjects up to 6 years of on-treatment follow-up, NOACs were associated with a 9% significantly lower risk of new-onset dementia compared with VKAs. Results were most pronounced among apixaban and edoxaban users, and among recently hospitalised subjects with an ICD-coded hospital discharge diagnosis of AF.

Several studies have demonstrated that AF is associated with an increased risk of dementia [3–10]. Besides sharing several risk factors, the pathophysiological mechanism linking AF to dementia development is likely multifactorial [1, 13, 22]. Proposed mechanisms include clinically overt and silent brain infarcts, cerebral micro- and macrobleeds, chronic cerebral hypoperfusion, systemic inflammation and genetic variants [1, 3, 6–9, 12, 20, 22, 24, 33]. New overt and silent brain infarcts have indeed been associated with cognitive decline in AF subjects, corroborating the hypothesis of cerebral infarcts being the predominant contributor to new-onset dementia in AF [34–36].

Consequently, oral anticoagulation may have a pivotal role to reduce cognitive decline in AF subjects [7]. Indeed, lower risks of dementia have been observed with VKA use compared with non-anticoagulated AF subjects [9–15]. Optimal therapy adherence seems crucial, as a low time in therapeutic range (TTR) among VKA users has been associated with a significantly higher risk of dementia compared with persons with high TTRs [6, 11, 14].

Compared with VKAs, NOACs may additionally reduce the risk of dementia in AF subjects, given their predictable pharmacological profile with less fluctuations in anticoagulation effects, ease of use with improved therapy adherence [25] and significantly lower risks of stroke and intracranial bleeding [1, 2, 8, 11, 14, 18–21]. Indeed, NOACs were associated with a 9% significantly lower risk of dementia compared with VKAs among unselected AF subjects treated in primary and secondary care. Remarkably, results were even more pronounced among recently hospitalised subjects with an ICD-coded diagnosis of AF, observing a 19% significantly lower risk of dementia with NOACs compared with VKAs.

Previous observational studies have demonstrated conflicting results. Some studies [5, 20–23] observed significantly lower risks of dementia with NOACs versus VKAs, while other studies [1, 12, 13, 24] did not. Conflicting findings are in part driven by methodological differences between studies due to short follow-up durations, small sample sizes without inclusion of apixaban and/or edoxaban users, exposure misclassification when only using an ITT approach, inclusion of subjects with prior OAC use, not taking into account death as a competing risk to develop dementia and genetic differences. By including a large sample of unselected, newly treated AF subjects on a full-population scale during long-term follow-up, shortcomings were largely tackled in the present study. Moreover, the robustness of results was checked in several sensitivity analyses, as methodological differences may impact results. Exemplary, when using an ITT approach, trends were comparable but no longer significantly different. However, given that VKAs are more frequently discontinued and switched to NOACs than vice versa [25], the risk of exposure misclassification may have been considerably increased among VKA users in the ITT analysis. Consequently, the potential protective effect of NOACs on cognitive outcomes compared with VKAs, as observed in the on-treatment analysis, may have been attenuated in the ITT analysis due to the combined effect of persistent anticoagulant use, treatment discontinuation and switching between anticoagulants.

Moreover, a trend towards a lower risk of vascular dementia and significantly lower risk of other/unspecified dementia were observed with NOACs compared with VKAs, whereas the risk of Alzheimer's disease was comparable, as observed before [24]. However, two other observational studies illustrated trends towards lower risks of Alzheimer's disease and vascular dementia with NOACs compared with VKAs [1, 22]. Therefore, more data are needed to explore whether NOACs may reduce the risk of every dementia subtype compared with VKAs.

Furthermore, potential differences between NOAC types are even less established. In this study, lower risks of dementia were only observed with apixaban and edoxaban compared with VKAs, while not with dabigatran and rivaroxaban. Likewise, apixaban was associated with a significantly lower risk of dementia compared with rivaroxaban, and risk estimates were numerically lower but non-significantly different with apixaban compared with dabigatran, and edoxaban compared with dabigatran and rivaroxaban. Proposed hypotheses for observed differences in cognitive outcomes may include differential risks of cerebral micro- and/or macrobleeds (e.g. significantly lower risks of intracranial bleeding with apixaban compared with rivaroxaban have been noted before) [37, 38]; predominant use of reduced dose dabigatran (53% of subjects, as compared with 38%, 27% and 28% of rivaroxaban, apixaban and edoxaban users, respectively) potentially influencing the risk of cerebral micro- and/or macro-emboli [34–36] (e.g. similar risks of stroke/SE were observed with reduced dose dabigatran compared with warfarin in the RE-LY trial, whereas significantly lower risks with standard dose dabigatran) [39]; and differences in therapy adherence (e.g. higher adherence to edoxaban than other NOACs has been observed before) [25].

Only three observational studies [20, 22, 24] have investigated cognitive outcomes of individual NOAC types compared with VKAs, among which only two studies [20, 22] explored outcomes between three NOACs (i.e. not including edoxaban yet). Results were however conflicting, as lower risks of dementia were observed with edoxaban compared with warfarin [24] and with rivaroxaban compared with dabigatran [22], while no differences were noted between dabigatran, rivaroxaban and apixaban in another study [20]. To the best of our knowledge, this is the first nationwide cohort study with long-term follow-up exploring cognitive outcomes between all four NOAC types. Nevertheless, given the sparsity of data and conflicting results compared with prior research, observed differences between NOAC types in this study should be interpreted with caution and seen as exploratory, while awaiting future research.

Strengths and limitations

Strengths of this study include the large sample size, long-term follow-up up to 6 years, inclusion of unselected OAC-naïve AF subjects treated in primary and secondary care on a full-population scale including all four NOACs to eliminate selection bias, use of an on-treatment analysis to reduce exposure misclassification, and adjustment for several confounders using stabilised IPTW taking into account the competing risk of death.

Several limitations should be mentioned. First, treatment allocation was non-randomised and therefore propensity scores were calculated based on 41 potential confounding covariables stratified by calendar year, to account for prescribing practices over time. However, there is a risk of unmeasured confounding due to missing lifestyle characteristics (e.g. weight, smoking) and laboratory values (e.g. renal function, INR), or coding errors in these healthcare databases. In line, (in)appropriate NOAC dosing and time in therapeutic range of VKA users could not be assessed. However, by identifying comorbidities based on ICD, medical procedure codes and/or medication prescription claims, missing data and misclassification of characteristics were reduced. Second, due to the assessment of dementia based on

ICD codes and medication prescription claims, milder forms of dementia not resulting in hospitalisation or initiation of anti-dementia drugs may have been missed. In line, the exact date of symptom onset and severity of dementia were not available. Moreover, dementia subtypes were identified using specific ICD codes, instead of neuropsychiatric tests, brain imaging and/or autopsy, which may have impacted the accuracy of dementia subtype diagnoses. Third, although subjects with prevalent dementia were excluded, data were lacking on the baseline cognitive status. This may have resulted in an overestimation of new-onset dementia diagnoses, especially if diagnosed shortly after OAC initiation. Nevertheless, trends were consistent, albeit not significantly different, in a sensitivity analysis in which subjects with a new diagnosis of dementia up to 90 days after the index date were excluded. Fourth, the follow-up duration of edoxaban users was shorter than other NOACs due to variable approval dates. Nevertheless, results were consistent among subjects having initiated treatment since October, 2016. Lastly, follow-up may have been too short to detect meaningful differences in the risk of new-onset dementia between NOACs and VKAs, given that AF may be detected and treated decades before new-onset dementia is clinically diagnosed [1, 20].

Conclusion

NOACs were associated with a 9% significantly lower risk of dementia compared with VKAs in the general AF population, which was most pronounced among apixaban and edoxaban users. A trend towards a lower risk of vascular dementia and significantly lower risk of other/unspecified dementia were observed with NOACs compared with VKAs, whereas the risk of Alzheimer's disease was comparable.

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Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: Outside this manuscript, T.D.B. has served as a chairperson during a lecture for Bayer and Daiichi Sankyo and participated in an expert meeting for Pfizer. Outside this manuscript, L.L. has been consulted as an expert for AstraZeneca, M.P. and S.S. have given a lecture sponsored by BMS, L.L. a lecture sponsored by Chiesi and S.S., L.L. and M.G. lectures sponsored by IPSA vzw, a non-profit organisation facilitating lifelong learning for health care providers. Neither author has received any fees personally.

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Data Availability Statement: Requests for the data underlying this article should be directed to the administrators of the InterMutualistic Agency (IMA) database or Minimal Hospital Dataset and is subject to approval.

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