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Original article

Direct oral anticoagulants are associated with lower risk of dementia in patients with atrial fibrillation

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ABSTRACT

Background and aim: Atrial fibrillation (AF) is associated with increased risk of dementia. Whether direct oral anticoagulation (DOAC) reduce this risk compared to vitamin-K antagonist (VKA) is unclear. The aim of this study was to assess the risk of new all-cause dementia and vascular dementia in AF patients, treated with either DOAC or VKAs.

Methods: Anonymized electronic medical records from the TriNetX federated research network were used. AF patients treated with DOACs within 1 month of AF diagnosis, were 1:1 propensity score-matched with those treated with a VKA. The analysis included patients who completed 5 and 10 years of follow-up and were assessed for all-cause dementia and vascular dementia. Cox proportional hazard models were used to hazard ratios (HR), respectively with 95% confidence intervals (CIs).

Results: Among patients who completed 5 years of follow-up, after propensity score matching the final cohort consisted of 215,404 well-matched AF patients. All-cause dementia was diagnosed in 4,153 (3.9%) patients among those treated with DOACs and 4,150 (3.9%) among the VKA-treated patients (HR: 1.01, 95%CI: 0.96–1.05). Among patients 65–74 years old who were followed, DOAC treatment was associated with lower risk of dementia compared to VKAs (HR: 0.72; 95%CI: 0.59–0.86). Among patients who completed 10 years of follow-up, after propensity score matching the final cohort consisted of 19,208 well-matched AF patients. All-cause dementia was diagnosed in 314 (3.3%) patients among those treated with DOACs and 451 (4.7%) among the VKA-treated patients. DOAC treatment was associated with significantly lower risk of all-cause dementia during a follow-up period of 10 years compared to VKA treatment (HR: 0.72, 95%CI: 0.62–0.83), which remained consistent in patiens ≥65 years old.

Conclusion: This propensity-score matched analysis showed that among AF patients, treatment with a DOACs for a period of 10 years was associated with lower risk of all-cause dementia and vascular dementia compared to VKA treatment, an effect which was not apparent in those treated for shorter duration. This finding requires confirmation in ongoing randomised controlled trials.

1. Introduction

Both atrial fibrillation (AF) and dementia have evolved into silent epidemics which convey significant health-related, societal and financial burden. The number of patients with AF are expected to increase by 150% during the next four decades [1], and the number of patients with

Abbreviations: AF, atrial fibrillation; OAC, oral anticoagulation; direct oral anticoagulation, DOAC; vitamin-k antagonist, VKA; EMR, electronic; ICD-10CM, international classification of diseases; Ninth revision and tenth revision, clinical modification; HR, hazard ratios; CI, confidence interval.

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dementia is expected to exceed 135 million during the next 30 years [2]. AF and dementia frequently coexist, however it remains unclear whether AF is causally associated with dementia, or a mediating factor explained by shared risk factors such as age, hypertension, diabetes mellitus, dyslipidemia, sleep apnea, ischaemic heart disease, heart failure, chronic kidney disease, obesity, physical inactivity, and excessive alcohol consumption [3]. Several pathophysiological mechanisms may explain a putative casual association, including cerebral infarcts, decreased brain volume due to hypoperfusion of gray matter, silent cerebral infarcts, micro-bleeds and inflammation [3]. Importantly, since the presence of AF is associated with higher risk of cortical cerebral infarcts, which in turn may increase the risk of dementia [4,5], the use of oral anticoagulation (OAC) may be protective against dementia among AF patients [6–8].

Towards the reduction of silent and non-silent cerebral infarcts which may represent an important pathophysiological mechanism of dementia [3], previous studies have shown that the use of vitamin-K antagonists (VKAs) among AF patients was associated with lower risk of dementia, compared to non-anticoagulated [9,10]. Nevertheless, VKA non-adherence may lead to suboptimal times in therapeutic range (TTR), which has been associated with higher risk of dementia compared to those with high TTRs [11,12]. On the other hand, among AF patients, the use of VKAs was associated with the development of microbleeds [13] while supratherapeutic ranges of VKA were associated with an increased risk of dementia [12]. Direct oral anticoagulants (DOACs) have important advantages over VKAs, such as lack of dietary interactions, few drug interactions, no requirement to monitor the international normalised ratio (INR), equal or superior efficacy, and superior safety, increasing adherence to treatment [14], and simultaneously were not found to be associated with higher risk of microbleeds [13]. If there is a causal association between AF and dementia, it is plausible to hypothesize that the superior profile of DOACs could be translated into more efficient prevention of dementia compared to VKAs [3], by reducing the incidence of silent infarction or microbleeds. Previous studies have identified an association between dementia and the quality of VKA treatment, assessed by the time in therapeutic range [15].

Recently, a real-world data analysis based on the TriNetX database, including patients ≥80 years, showed that DOAC treatment was associated with lower risk of cardiovascular events and all-cause dementia in patients with AF [16]. The aim of this study was to compare the risk of all-cause dementia and dementia types between patients with AF, treated with either DOAC or VKA, using a real-world, global federated health network.

2. Methods

2.1. Data availability statement & ethical approval

The data underlying this article are available in TriNetX at https://live.trinetx.com. To gain access to the data in the TriNetX research network, requests are directed to TriNetX and a data sharing agreement is required. As a federated research network, studies using the TriNetX health research network do not need ethical approval as no patient identifiable information is received.

2.2. Study design

This was a retrospective observational study conducted within TriNetX, which is a global federated health research network with access to electronic medical records (EMRs) from participating health care organizations including academic medical centers, specialty physician practices, and community hospitals covering approximately 69.8 million individuals, mainly in the United States. Within this network, available data include demographics, diagnoses using International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-10-CM) codes, and medications. Further information can be found online (https://trinetx.com/company-overview/). Further details related to TriNetX database can be found in Supplemental material.

2.3. Cohort

The searches on the TriNetX online research platform were performed on 29 June 2023 for individuals with newly diagnosed atrial fibrillation or flutter (ICD-10-CM code I48) aged ≥18 years, who were treated within one month of atrial fibrillation or flutter diagnosis with either DOACs (e.g. dabigatran or apixaban or rivaroxaban or edoxaban) or VKAs (e.g.warfarin or phenprocumon). Patients with diagnosis of vascular dementia or dementia in other diseases classified elsewhere or unspecified dementia or Alzheimer's disease (ICD-10-CM codes F01, F02, F03, G30, respectively) in their electronic medical records prior to OAC initiation were excluded (Supplemental Table 1). At the time of the search, there were 67 participating health care organizations. The baseline index event date was the date that anticoagulation therapy with either DOACs or VKA was first recorded in the participant's electronic medical records within 1 month of AF diagnosis. Any diagnoses registered before this date were considered to be the individual's baseline characteristics.

The cohort was divided into two groups using electronic health records according to the type of oral anticoagulant recorded: i) AF patients treated with DOACs, (apixaban or rivaroxaban or dabigatran or edoxaban) during the study time-period excluding those treated with any VKA and those with dementia prior to DOAC initiation; and ii) AF patients treated with VKA during the study time-period, excluding those treated with any DOAC and those with dementia prior to VKA initiation. In order to have the same follow-up period for all patients, we performed two analyses. In the first analysis, we included AF patients who had data in their records for at least 5 years after AF diagnosis and initiation of OAC and in these patients we have investigated each outcome for a follow-up period of 5 years. In the second analysis we included AF patients who had data in their records for at least 10 years after AF diagnosis and initiation of OAC and in these patients we have investigated each outcome for a follow-up period of 10 years. Thus, in each analysis all patients were followed up for 5 and 10 years, respectively, or their death. The above periods were used to allow a long follow-up period in all included patients. Individuals with AF and no record of any OAC during the study time-period, and individuals who had a record of receiving both VKA and a DOAC during the study period, were excluded.

2.4. Outcome

The primary outcome of interest was the diagnosis of the composite outcome of all-cause dementia, including vascular dementia or dementia in other diseases classified elsewhere or unspecified dementia or Alzheimer's disease (ICD-10-CM codes F01, F02, F03, G30, respectively) after OAC initiation. Secondary outcomes were the diagnosis of vascular dementia, ischemic stroke, myocardial infarction, intracerebral bleeding and death. Two pre-specified exploratory analyses were performed for the primary outcome. One analysis was performed based on the age of the included patients at the time of AF diagnosis, in which the cohort was divided in 3 groups: i) <65 years, ii) 65–74 years and iii) ≥75 years. A second exploratory analysis was performed based on the different types of DOACs in patients who were treated with the same DOAC during the study period.

2.5. Statistical analysis

All statistical analyses were performed on the TriNetX online research platform. Baseline characteristics were compared using chi-squared tests for categorical variables and independent-sample *t*-tests for continuous variables. We performed 1:1 propensity score matching

(PSM) to create balanced cohorts. We included the following variables in the propensity score matching: age, gender, ethnicity, co-morbidities (heart failure, arterial hypertension, ischaemic heart disease, cerebral infarction, dyslipidemia, diabetes mellitus, chronic kidney disease, non-traumatic intracerebral hemorrhage, extrapyramidal movement disorders and depression) and concomitant medication (lipid-lowering treatments, beta blockers, anti-arrhythmics, angiotensin converting enzyme [ACE] inhibitors, angiotensin II inhibitors) (Supplemental Table 1). After propensity score matching Chi square test and T-test were used to assess the balance between the two groups for each characteristic, while Cox-proportional hazard models were used to calculate hazard ratios (HRs) and 95% CIs to assess the associations between the type of OAC (i.e. DOAC or VKA) and the outcome of interest. Participants were censored when they experienced the outcome of interest or when they died. In this study all analyses were performed within the TriNetX platform, which utilizes the R's survival package v3.2–3, without any direct access to crude data.

3. Results

3.1. Cohort characteristics before and after propensity score matching

The initial cohort including patients who completed 5 years follow-up consisted of 264,071 patients with atrial fibrillation or flutter. Of these, 117,960 (44.7%) were treated with DOACs and 146,111 (55.3%) were treated with VKAs (Supplemental Table 2). After propensity score matching on a 1:1 ratio, the final cohort consisted of 215,404 AF patients, mean (SD) age 70.2 (12.1); 90,216 (41.8%) females (Supplemental Fig. 1). The main characteristics of this cohort are summarized in Table 1.

The cohort which included patients with 10 years of follow-up consisted of 90,686 patients with atrial fibrillation or flutter. Of these, 9604 (10.5%) were treated with DOACs and 81,082 (89.5%) were treated with VKAs (Supplemental Table 3). After propensity score matching on a 1:1 ratio, the final cohort consisted of 19,208 well-matched AF patients, mean (SD) age 67 (12.1); 6797 (35.4%) female (Supplemental Fig. 1). The main characteristics of this cohort are summarized in Table 2.

3.2. DOAC vs. VKA and risk of all-cause dementia

After propensity-score matching, among patients who completed 5 years of follow-up, 8303 (3.9%) were diagnosed with all-cause dementia. All-cause dementia was diagnosed in 4153 (3.9%) patients among those treated with DOACs and 4150 (3.9%) among the VKA-treated patients [Table 3]. In the Cox-regression analysis, DOAC treatment was not associated with a lower risk of all-cause dementia during a follow-up period of 5 years compared to VKA treatment (HR: 1.01, 95% CI: 0.96–1.05).

After propensity-score matching, among 19,208 patients who completed 10 years of follow-up, 765 (4%) were diagnosed with all-cause dementia. All-cause dementia was diagnosed in 314 (3.3%) patients among those treated with DOACs and 451 (4.7%) among the VKA-treated patients. In the Cox-regression analysis, DOAC treatment was associated with significantly lower risk of all-cause dementia during a follow-up period of 10 years compared to VKA treatment (HR: 0.72, 95% CI: 0.62–0.83).

3.3. DOAC vs. VKA and secondary outcomes

Among patients who completed 5 years of follow-up, DOAC treatment was associated with statistically significant reduction of the risk of intracerebral bleeding and death (HR:0.66; 95%CI: 0.61–0.71 and HR:0.69; 95%CI: 0.68–1.05, respectively) and a marginal reduction of the risk of ischemic stroke (HR:0.95; 95%CI: 0.93–0.99), whereas there was no association the risk of vascular dementia, and myocardial infarction compared to VKAs (HR:0.94; 95%CI: 0.86–1.04 and HR: 1.01;95%CI: 0.98–1.05, respectively) (Table 3).

Among patients who completed 10 years of follow-up, DOAC treatment was associated with statistically significant reduction of the risk of vascular dementia and death (HR:0.64; 95%CI: 0.47–0.86 and HR:0.68; 95%CI: 0.65–0.72, respectively), whereas there was no association with the risk of ischemic stroke, myocardial infarction and intracerebral

Table 1
Baseline characteristics of DOAC- and VKA-treated patients who completed 5 years of follow-up after propensity score matching.

	DOAC-treated patients $n = 107,702$	VKA-treated patients $n = 107,702$	p-value
Demographics			
Age, years (±SD)	70.3 (±11.9)	70 (±12.3)	<0.001
White, n (%)	86,524 (80.3)	86,092 (79.9)	<0.001
Black/African American, n (%)	7056 (8.9)	7170 (6.7)	<0.001
Asian, n (%)	1395 (1.3)	1475 (1.4)	0.133
Female, n (%)	45,026 (41.8)	45,190 (6.7)	<0.001
Comorbidities			
Heart failure, n (%)	18,479 (17.2)	19,020 (17.7)	0.002
Arterial hypertension, n (%)	42,950 (39.9)	44,176 (41)	<0.001
Ischemic heart disease, n (%)	25,233 (23.4)	26,090 (24.2)	<0.001
Cerebral infarction, n (%)	6113 (5.7)	6162 (5.7)	0.649
Dyslipidaemia, n (%)	33,536 (31.1)	34,412 (32)	<0.001
Diabetes mellitus, n (%)	18,936 (17.6)	19,395 (18)	0.010
Chronic kidney disease, n (%)	9218 (8.6)	9375 (8.7)	0.228
Intracerebral hemorrhage, n (%)	531 (0.5)	544 (0.5)	0.691
Extrapyramidal movement disorders, n (%)	2068 (1.9)	2048 (1.9)	0.753
Depression, n (%)	6748 (1.9)	6819 (1.9)	0.753
Concomitant medications			
Lipid-lowering treatment, n (%)	32,986 (30.6)	33,759 (31.3)	<0.001
Beta-blockers, n (%)	39,213 (36.4)	40,238 (37.4)	<0.001
Anti-arrhythmics, n (%)	24,626 (22.9)	25,237 (23.4)	0.002
ACE inhibitors, n (%)	20,933 (19.4)	21,433 (19.9)	0.007
Angiotensin II inhibitors, n (%)	10,570 (9.8)	10,730 (10)	0.248

DOAC: direct oral anticoagulants, VKA: vitamin K antagonists, ACE: angiotensin converting enzyme.

Table 2
Baseline characteristics of DOAC- and VKA-treated patients who completed 10 years of follow-up after propensity score matching.

	DOAC-treated patients $n = 9604$	VKA-treated patients $n = 9604$	p-value
Demographics			
Age, years (±SD)	67.1 (±11.9)	66.9 (±12.3)	0.132
White, n (%)	7992 (83.2)	8072 (84)	0.119
Black/African American, n (%)	438 (4.6)	405 (4.2)	0.245
Asian, n (%)	112 (1.2)	113 (1.2)	0.947
Female, n (%)	3441 (35.8)	3356 (34.9)	0.200
Comorbidities			
Heart failure, n (%)	910 (9.5)	923 (9.6)	0.750
Arterial hypertension, n (%)	3091 (32.2)	3025 (31.5)	0.307
Ischemic heart disease, n (%)	1699 (17.7)	1700 (17.7)	0.985
Cerebral infarction, n (%)	285 (3)	253 (2.6)	0.162
Dyslipidaemia, n (%)	2562 (26.7)	2510 (26.1)	0.395
Diabetes mellitus, n (%)	1193 (12.4)	1124 (11.7)	0.126
Chronic kidney disease, n (%)	309 (3.2)	314 (3.3)	0.839
Intracerebral hemorrhage, n (%)	12 (0.1)	17 (0.2)	0.353
Extrapyramidal movement disorders, n (%)	97 (1)	94 (1)	0.827
Depression, n (%)	303 (3.2)	253 (2.6)	0.031
Concomitant medications			
Lipid-lowering treatment, n (%)	2771 (28.9)	2626 (27.3)	0,020
Beta-blockers, n (%)	3138 (32.7)	3083 (32.1)	0,396
Anti-arrhythmics, n (%)	1412 (14,7)	1415 (14.7)	0,951
ACE inhibitors, n (%)	1723 (17.9)	1621 (16.9)	0.052
Angiotensin II inhibitors, n (%)	994 (10.3)	8.9 (851)	<0.001

DOAC: direct oral anticoagulants, VKA: vitamin K antagonists, ACE: angiotensin converting enzyme.

Table 3
Outcomes among included patients in each cohort.

	DOAC n (%)		VKA n (%)		
5 years of follow-up	**108,119**		**108,119**		**HR (95%CI)**
All-cause dementia	4153	(3.8)	4166	(3.9)	1.01 (0.96–1.05)
Vascular dementia	793	(0.7)	848	(0.8)	0.94 (0.86–1.04)
Ischemic stroke	8651	(8.0)	8955	(8.3)	0.95 (0.93–0.99)
myocardial infarction	7498	(6.9)	7405	(6.8)	1.01(0.98–1.05)
Intracerebral bleeding	997	(0.9)	1515	(1.4)	0.66 (0.61–0.71)
Death	19,003	(17.6)	27,171	(25.1)	0.69 (0.68–0.70)
10 years of follow-up	**9683**		**9683**		
All-cause dementia	322	(3.3)	463	(4.8)	0.71 (0.61–0.81)
Vascular dementia	70	(0.7)	113	(1.2)	0.64 (0.47–0.86)
Ischemic stroke	716	(7.4)	787	(8.1)	0.92 (0.83–1.01)
myocardial infarction	93	(1.0)	124	(1.3)	0.76 (0.56–1.00)
Intracerebral bleeding	584	(6.0)	632	(6.5)	0.94 (0.84–1.05)
Death	2250	(23.2)	3307	(34.2)	0.68 (0.65–0.72)

DOAC, direct oral anticoagulants; VKA, vitamin K antagonists; HR, hazard ratio; CI, confidence intervals.

bleeding, compared to VKAs (HR:0.92; 95%CI: 0.83–1.01, HR: 0.76;95% CI: 0.56–1.00 and HR: 0.94;95%CI: 0.84–1.05 respectively) (Table 3).

3.4. Exploratory analyses based on patients age and type of DOAC on all-cause dementia

In the *exploratory analysis* based on the age of the included patients, among patients who have completed 5 years of follow-up, DOAC treatment was associated with lower risk of all-cause dementia among patients aged 65–74 years at the time of AF diagnosis (HR: 0.72; 95%CI: 0.59–0.86), while among those who completed 10 years of follow-up, DOAC treatment was associated with lower risk of all-cause dementia among patients 65–74 years and ≥75 years old at the time of AF diagnosis (HR: 0.38; 95%CI: 0.21–0.69, HR:0.76, 95% CI:0.65–0.88) (Table 3). In the *exploratory analysis* based on the type of DOAC, after propensity score matching, neither anti-Xa inhibitors (apixaban, rivaroxaban, edoxaban), nor dabigatran were associated with lower risk of all-cause dementia, among patients with 5 or 10years of follow-up. (Table 4).

Table 4
All-cause dementia based on age group and DOAC type.

5 years of follow-up	DOAC n (%)		VKA n (%)		HR (95%CI)
<65	46/11,285	(0.4)	55/11,285	(0.5)	0.83 (0.56–1.23)
65–74	192/17,280	(1.1)	254/17,280	(1.5)	0.72 (0.59–0.86)
>75	3806/69,978	(5.4)	3790/69,978	(5.4)	0.99 (0.95–1.04)
Anti-Xa*	3873/97,713	(4.0)	3763/19,713	(3.9)	1.04 (0.99–1.01)
Dabigatran	499/15,444	(3.2)	485/15,444	(3.1)	0.99 (0.87–1.12)
10 years of follow-up					
<65	10/1151	(0.9)	10/1151	(0.9)	6.1 (0.73–50.8)
65–74	16/2148	(0.7)	33/2148	(1.5)	0.38 (0.21–0.69)
>75	296/6325	(4.7)	399/6325	(6.3)	0.76 (0.65–0.88)
Anti-Xa*	119/3218	(3.7)	156/3218	(4.8)	0.81 (0.64–1.04)
Dabigatran	244/6458	(3.8)	284/6458	(4.4)	0.86 (0.73–1.02)

DOAC, direct oral anticoagulants; VKA, vitamin K antagonists; HR, hazard ratio; CI, confidence intervals.
* apixaban, rivaroxaban, edoxaban.

4. Discussion

In this propensity-score matched analysis the risk of all-cause dementia and vascular dementia was lower among AF patients treated with a DOAC compared to those treated with a VKA, when they were followed up for 10 years from OAC initiation. Among patients who completed 5 years of follow up, DOAC treatment was associated with lower risk of dementia compared to VKAs, only among those aged 65–74 years on AF diagnosis.

Previous studies aiming to assess whether the risk of dementia differs between DOAC- and VKA-treated patients, have been inconclusive [8,10,17,18]. A retrospective population-based propensity-score-matched analysis from Sweden with >440,000 AF patients without previous diagnosis of dementia, reported that dementia occurred more frequently in patients without OAC, but DOAC treatment did not significantly reduce the risk of dementia compared to VKA [10,18]. In a propensity-score matched analysis of a nationwide Danish population-based study, which was limited by a relative short duration follow-up (mean 3.4 years), a direct comparison between DOACs and warfarin showed no difference regarding dementia risk, where patients ≥80 years old had a higher risk of dementia while being treated on DOACs [8]. A report from the randomized-control Cognitive Impairment Related to Atrial Fibrillation Prevention Trial (GIRAF trial), which assessed the effects of dabigatran compared with warfarin on cognitive outcomes in older adults with AF or atrial flutter, showed that two years after randomization dabigatran was not superior to warfarin in attenuating cognitive decline [19]. However, the conclusions were limited by the small sample size ($n = 200$) and that only 149 patients were assessed for cognitive function at two years [19].

Several observational and real-world data show that there may be an association of DOAC treatment with lower risk of dementia. A nationwide population-based study with administrative data from Taiwan showed that patients treated with DOAC, and especially those with higher thromboembolic and bleeding risk, were benefit more from the use of DOAC compared to VKAs [20]. Another observational study suggested that the use of DOAC was associated with lower risk of cardiovascular events and dementia compared to VKAs [21]. A previous analysis from TrinetX database which focused on patients ≥80 years old, showed that DOAC treatment reduced cardiovascular events and all-cause dementia [16]. Our findings extend these results beyond this age restriction and show that DOAC treatment is associated with lower risk of all-cause dementia and vascular dementia for those patients with longer treatment periods with DOAC and this effect is even more profound in patients 65–74 years old at the time of OAC initiation.

The present analysis point towards the potential beneficial effect of DOACs on the future dementia risk of patients diagnosed with AF, compared to VKAs. This was universally evident among patients with 10 years of follow-up, pointing towards the potential benefit of DOACs among patients with AF, which may be evident after a long period on treatment, irrespective of the age at the time of OAC initiation. On the other hand, among patients with 5 years of follow-up, DOACs were found to be associated with lower risk of dementia compared to VKAs, only in those aged 65–74 years at the time of OAC initiation. This interesting finding may be associated with the higher risk of dementia among patients older than 65 years [22], who may be benefited by the initiation of DOACs, compared to younger patients with lower dementia

risk or older patients who due to the late initiation of OAC, may have not be benefited from treatment. Nevertheless, in the present study patients >75 years old with 10 years of follow-up were benefited from DOAC treatment, underlying the importance of long-term treatment, which may be beneficial even among older patients with AF. This study increases the bulk of real-world evidence which supports that the use of DOAC in patients may exert a beneficial effect on the risk of future dementia compared to VKAs. The results of the present study are in agreement with the results of recent meta-analysis of observational data, which included 342,624 patients and showed that DOAC treatment was associated with lower risk of dementia compared to VKAs, especially among patients 65–75 years old [23]. In the present study DOAC treatment was associated with significantly lower risk of death compared to VKAs with high death rates in both groups, while the effect of DOACs on other competing events such as ischemic stroke or intracerebral hemorrhage was not consistent among those with 5 and 10 years of follow-up. In the analysis based on the different types of DOACs, neither Factor-Xa inhibitors nor dabigatran were associated with significantly lower risk of all-cause dementia, which can potentially be attributed to low statistical power due to the number of included patients rather than lack of true effect. Therefore, this observational retrospective analysis cannot prove a causal relationship. Definitive answers may be provided by ongoing trials of DOACs versus warfarin for the reduction of cognitive decline in AF patients. The ARISTA trial [Trial of Apixaban Versus Warfarin in Reducing Rate of Cognitive Decline, Silent Cerebral Ischemia and Cerebral Microbleeds in Patients With Atrial Fibrillation; NCT03839355] is a phase III trial testing the hypothesis that among AF patients, OAC with apixaban reduces the rate of decline in cognitive function compared to warfarin. The CAF trial (Cognitive Decline and Dementia in Atrial Fibrillation Patients; NCT03061006) is currently recruiting AF patients who will be randomized to dabigatran or warfarin and will assess the risk of incident dementia [24]. The ACCOG trial (AntiCoagulants and COGnition; NCT04073316) is comparing the change in global cognitive performance after 52 weeks of OAC treatment among participants with AF treated with either rivaroxaban or warfarin.

If the aforementioned ongoing randomized trials of DOACs versus warfarin for prevention of dementia in AF patients identify a beneficial effect of DOACs, it would add further support for the preference for DOACs over VKAs in patients with AF. The ongoing BRAIN-AF trial (Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in AF; NCT02387229) is exploring the efficacy and safety of rivaroxaban compared to standard of care in reducing neurocognitive decline (among other outcomes) in subjects with AF and with low risk of stroke (CHA_2DS_2VASc score of 0 for men and 1 for women) [25]. In addition, the Neurocognitive Sub-study of the ongoing ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; NCT01938248) [26] and the NOAH (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes; NCT02618577) trial [27] are assessing the role of NOACs to prevent change in cognitive function, in addition to cardiovascular outcomes such as stroke, systemic embolism or cardiovascular death in patients with subclinical atrial fibrillation and high CHA_2DS_2VASc score.

Nevertheless, the prevention of cognitive decline and dementia among patients with AF is not only based on the anticoagulation therapy. Since dementia and cognitive impairment, is a heterogenous disease comprised by several pathophysiological mechanisms such as cerebral small vessels disease [28] and age-related vascular changes, the accumulation of cardiovascular risk factors as projected by the CHA_2DS_2-VASc score is associated with higher risk of dementia among AF patients [9]. Thus, a holistic approach in the treatment of patients with AF, including cardiovascular risk factors management, optimal blood pressure control and rhythm-control management, is essential for the reduction of cardiovascular and cognitive disease burden [29,30,31]. Based on this during the recent years the management of AF has moved towards an integrated care management approach [32], that is now recommended in guidelines [33], given the better prognosis in such patients (including less dementia) by adherence to such a strategy [33,34].

4.1. Strengths and limitations

The main strengths of this study are the large number of individuals included in the analysis, the long follow-up, and the use of propensity score matching to control for clinically and prognostically relevant factors, to minimize the risk of bias from confounding. Nonetheless, several limitations of this analysis are noteworthy. Health care organization EMR data are subject to entry errors and data gaps, and some health conditions may be underreported. Especially for the diagnosis of dementia this may have been even more profound, since patients were not universally screened for dementia and there were no data on how dementia was diagnosed. This may have led in difficulties to discriminate between Alzheimer's and vascular forms, and it is possible that only the more severe cases of dementia were captured in the administrative database. The TriNetX platform does not provide data on CHA_2DS_2VASc, the TTR of the patients treated with VKAs or the severity of each of the concomitant diseases, such as the severity of heart failure. Although competing events such as ischemic stroke or death were reported in this analysis, it was not possible to perform competing risk analysis in the TriNetX platform, which may have led to an underestimation of unaccounted competing events, and could raise some uncertainty regarding the effect of OACs on the risk of all-cause dementia. Although in the present analysis we performed two analyses, with 5 and 10 years of follow-up, these were two PSM analyses including different individuals, the results are not directly comparable. Moreover, since the TriNetX platform does not provide direct access to crude data, it was not possible to perform further analyses in order to investigate if there was statistically significant interaction between age-stratified subgroups. Patients treated both with a VKA and a DOAC were excluded from this analysis, nevertheless, changes in their medications, switching from DOAC to VKA or whether the patients were adherent to treatment was not reported in the study and may have potentially affected our results. Additionally, there were no information on how the glomerular filtration rate was calculated and how patients were categorized in chronic kidney disease stages, which may have affected the balance of the cohort in the propensity score matching. Also, outcomes which occurred outside the TriNetX network may have not been well captured. Some prescription changes may have taken place outside of the healthcare organizations captured within the TriNetX health research network and therefore, these patients might have been erroneously included in the analysis. Moreover, residual confounding may have influenced our results, including socioeconomic status, risk factor control, quality of anticoagulation control, use of AF interventions and lifestyle factors [35–37], which are not available in EMR data. Also, the data originate predominantly from the USA and may not be representative of the wider global population, therefore the generalizability of these results needs to be confirmed beyond this cohort. Finally, the use of ICD codes to identify people living with dementia within the TriNetX research network has not been previously validated. In the present analysis we performed an exploratory analysis on the effect of each DOAC on dementia, but we could not further analyze whether there was a statistically significant difference between each subgroup, due to restrictions of the TrinetX platform.

5. Conclusion

In conclusion, this real-world propensity-score matched analysis showed that among AF patients, treatment with a DOAC for 10 years was associated with a lower risk of all-cause dementia and vascular dementia irrespective of patients age compared to treatment with a VKA, a

beneficial effect which was not apparent in those treated for shorter duration. This finding requires confirmation in ongoing randomised controlled trials.

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Dr Underhill is an employee of TriNetX LLC.

Prof Lane has received investigator-initiated educational grants from Bristol-Myers Squibb (BMS), has been a speaker for Bayer, Boehringer Ingeheim, and BMS/Pfizer and has consulted for BMS, and Boehringer Ingelheim.

Prof Lip reports being a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Anthos and Daiichi-Sankyo. No fees are received personally.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.10.033.

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