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TITLE: Patterns and Factors Influencing Oral Anticoagulant Prescription in People with Atrial Fibrillation and Dementia: Results from UK Primary Care

SHORT RUNNING TITLE: Oral anticoagulant in dementia patients

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The authors confirm that the Principle Investigator for this paper is Professor Ian C.K. Wong and that he had responsibility for maintaining the confidentiality of patients involved in this database study.

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Abstract

AIMS: Oral anticoagulant (OAC) is recommended for preventing stroke in atrial fibrillation (AF). However, the OAC utilisation in AF patients with dementia or cognitive impairment (CI) is limited. This study aimed to examine the prevalence of OAC prescriptions in AF patients with dementia/CI and to identify factors associated with OAC treatment within 180 days after dementia/CI diagnosis.

METHODS: Using The Health Improvement Network database, the annual trends of OAC between 2000 and 2015 were calculated. Multivariable logistic regression was performed to identify factors associated with OAC treatment.

RESULTS: The prevalence rate of OAC prescriptions increased from 6.1% in 2000 to 45.9% in 2015. Among OAC users, the proportion of direct oral anticoagulants (DOACs) use increased significantly from 0.1% in 2011 to 33.8% in 2015 (P-trend < 0.001), while the proportion of vitamin K antagonist use decreased by 28.6% from 100% in 2000 to 71.4% in 2015 (P-trend <0.001). In the multivariable analysis, younger age, very old age, female sex, higher Charlson Comorbidity Index, having a HASBLED score ≥ 3, a history of intracranial bleeding, falls, and polypharmacy were significantly associated with lower odds of receiving OAC.

CONCLUSIONS: In the UK primary care**,** OAC use increased from 2000 to 2015 in AF patients with dementia/CI, with a substantial increase in DOACs use. Characteristics related to frailty are associated with lower odds of OAC prescription. Given the increasing use of DOACs in patients with dementia/CI, further studies are needed to investigate the safety and effectiveness of DOACs in this important patient group.

Keywords: Atrial fibrillation; cognitive impairment; dementia; direct oral anticoagulants; oral anticoagulant; warfarin

Statement 1: What is already known about this subject:

- Oral anticoagulants (OACs) are recommended for stroke prevention in atrial fibrillation (AF) patients.
- Although dementia is not a contraindication to OACs, dementia is a reason for not prescribing OACs.
- Data on OACs including direct oral anticoagulants (DOACs) prescription and predictors of OAC use in AF patients with dementia is lacking.

Statement 2: What this study adds:

- In AF patients with dementia, the use of OAC increased by 39.8% between 2000 and 2015 attributable to an increase of DOACs.
- Characteristics related to frailty are associated with lower odds of OAC prescription.
- Studies investigating the efficacy and safety of DOACs versus warfarin in AF with dementia are needed.

INTRODUCTION

Atrial fibrillation (AF) causes cardiac rhythm disturbances and consequently ineffective atrial contraction [1]. It is anticipated that by 2030, 17 million patients will have AF in Europe, with 200,000 new cases being diagnosed each year [2]. AF is associated with increased risk of mortality, stroke, and other cardiovascular comorbidities [3, 4], and accounted for 1% of total healthcare expenditure in the UK [5]. Dementia is defined as the development of severe cognitive decline that subsequently causes significant impairment in social and/or occupational functioning [6]. Similar to AF, dementia occurrence increases steadily with increasing age, of which the risk doubles every 5 years after 65 years of age [7]. It is projected that >100 million people globally will develop dementia by 2050 [8].

Oral anticoagulants (OACs) are recommended by the European Society of Cardiology (ESC) guidelines to decrease stroke risk related to AF [2]. However, the presence of dementia or cognitive impairment (CI) often results in underuse of OAC even in the absence of established contraindications [9-12]. ESC guidelines recommend withholding OACs in patients with dementia only when adherence cannot be assured by a caregiver [2]. Results from the UK general practice demonstrate that presence of dementia was independently associated with reduced use of warfarin in AF [13]. Patients with dementia/CI may have difficulties with medication adherence and monitoring, and may be at increased risk of falls, leading to haemorrhagic complications when using OAC. The introduction of the direct oral anticoagulants (DOACs) mitigates some of the issues associated with vitamin K antagonists (VKAs), such as fewer drug and food interactions, more predictable effects and no requirement for regular anticoagulation monitoring [1, 2]. However, few studies have focused on OAC utilisation among patient with AF and comorbid dementia/CI. There is little information available regarding factors that could influence OAC prescribing, particularly for the DOACs in AF and dementia/CI. The objective of this study was to examine the prevalence of OAC prescribing in AF with comorbid dementia/CI and to identify factors associated with OAC use versus non-use, and use of DOACs versus warfarin, within 180 days after dementia/CI diagnosis.

METHODS:

Data source

The study was conducted using The Health Improvement Network (THIN) database, which is one of the largest UK databases of primary care electronic health records. THIN covers approximately 6% of the UK population and is broadly representative of the UK population in terms of demographics, prescribing information, medical conditions, disease, and death rates [14]. The diagnosis data within THIN is recorded by general practitioners using the Read classification system [15]. The quality of THIN data has been validated [16] and diagnosis and prescribing information have been used in previous dementia and anticoagulant studies [17-21]. The protocol for this study was approved by the THIN Scientific Review Committee (reference number 18THIN043).

Study design and identification of the study cohort

A population-based longitudinal study was conducted. Patients were included if they were 18 years or older and had a first ever AF diagnosis between January 1, 2000 and December 31, 2015. Read codes for AF are shown in Supplemental Table S1. The entry date of patients was defined as the date at which THIN had adopted adequate methods for mortality reporting or patient's registration date [22]. To ensure data quality, patients were excluded if they had an observation period less than 12 months prior to the first AF diagnosis. Patients diagnosed with valvular heart disease and transient causes of AF (hyperthyroidism, pericarditis or myocarditis) were also excluded. To identify AF with concomitant dementia/CI, we included all patients with a dementia diagnosis or symptoms of dementia, patients who received a prescription of antidementia drugs (Anatomical Therapeutic Chemical (ATC) Classification System: code N06D), on or after AF diagnosis. Dementia and cognitive impairment codes were based on published dementia studies [23-25] and the Department of Health's Quality and Outcomes Framework list of business codes for dementia [26, 27] (Supplemental Table S2).

Exposure

OAC was the exposure of interest. The term OAC included VKAs (warfarin, acenocoumarol, phenindione) and DOACs (dabigatran, rivaroxaban, apixaban or edoxaban). These medications were identified from drug codes from the British National Formulary and the drug dictionary provided by THIN. All VKAs available in the UK over the study period were identified. Dabigatran, rivaroxaban, apixaban, and edoxaban were authorized for non-valvular AF in the European Union in August 2011, December 2011, November 2012, and June 2015, respectively.

Study covariates

Patient characteristics included age, sex, history of congestive heart failure (CHF), hypertension, diabetes, ischaemic stroke/transient ischaemic attack (TIA)/systemic embolism (SE), intracranial bleeding, coronary artery disease (CAD), gastrointestinal (GI) bleeding, chronic kidney disease (CKD), hyperlipidaemia, and falls. These comorbidities were identified using Read codes up to 10 years before or on the date of dementia/CI diagnosis. Concomitant medication use was defined within 180 days after dementia/CI diagnosis and included antiplatelets (aspirin and clopidogrel), antihypertensive drugs, digoxin, lipid-lowering drugs, proton pump inhibitors (PPIs), amiodarone, and nonsteroidal anti-inflammatory drugs (NSAIDs). Polypharmacy was defined as the concomitant use of five or more medications [28]. In addition, a CHA_2DS_2-VASc score was calculated to estimate stroke risk [29] and a modified HAS-BLED score (labile international normalised ratio, not included) for bleeding risk [2, 30]. Finally, Charlson Comorbidity Index (CCI) was calculated to measure the risk mortality [31].

Statistical analysis

The prevalence of OAC use in AF patients with dementia/CI was examined annually from 2000 to 2015. Prevalence was calculated by dividing the total number of patients with AF and dementia/CI who were prescribed OAC by the total number of AF with dementia/CI in a particular year, accounting for deaths and transfers out of the general practice. The annual prevalence was calculated for overall OAC and subgrouped by OAC drug class (VKA and DOAC) and individual OACs (warfarin, acenocoumarol, phenindione, dabigatran, apixaban, rivaroxaban, and edoxaban). The use of OAC was further stratified by age and gender. We stratified patients into the following age group: less than 65 years, 65 to 74 years, 75 to 84 years, and 85 years or older. The Cochran-Armitage trend test [32] was used to examine temporal trends in OAC prescription over time.

To identify factors associated with OAC prescription, OAC treatment was determined from prescription fills within 180 days after or on a date of dementia/CI diagnosis. AF patients with dementia/CI who did not receive OAC treatment within 180 days after dementia/CI diagnosis were defined as non-OAC users. Comparisons of baseline characteristics between AF with dementia/CI who received OAC and those who did not receive OAC were performed using the t-test for continuous

variables and the $\chi 2$ test for categorical variables. Univariable and multivariable logistic regression was used to identify factors of OAC prescribing in AF with dementia/CI compared with no OAC treatment. Baseline covariates included age group (< 65 years, 65 to 74 years, 75 to 84 years, and ≥ 85 years), sex, CHA_2DS_2-VASc Score (0, 1, and ≥2), HASBLED score (<3 vs ≥3), CCI, CHF, hypertension, diabetes, ischaemic stroke/TIA/SE, intracranial bleeding, CAD, GI bleeding, CKD, hyperlipidaemia, falls, and polypharmacy. Concurrent medications included the use of antiplatelet drugs, antihypertensive drugs, digoxin, lipid-lowering drugs, PPIs, amiodarone, and NSAIDs. Unadjusted odds ratios (OR) with 95% confidence intervals (CIs) were estimated for all predictors. Adjusted OR with 95% CIs were estimated using all factors that were associated with a p value <0.20 in the bivariate comparisons, in which these factors were selected using a backward selection approach. Factors associated with DOAC versus VKA prescription were also identified using the same approach.

Data extraction and management and all analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). A P value <0.05 was considered statistically significant. Statistical analyses were conducted by PM and the results were cross-checked by HA for quality assurance.

RESULTS:

Patient characteristics

We identified 219,088 patients with newly diagnosed AF between 1st January 2000 and 31th December 2015. Of these, 209,243 patients were excluded as they did not meet the inclusion criteria. Finally, 9,845 patients with AF and dementia/CI were eligible. Among the patients, 3,801 (38.6%) were prescribed OAC within 180 days after dementia/CI diagnosis while 6,044 (61.4%) were not prescribed OAC (Figure 1). At baseline, the mean age [standard deviation; SD] was higher among non-OAC-users (84.5 years [7.3] years) compared to OAC users (mean age 81.5 [6.7] years). Across both groups, the proportion of AF patients with stroke/TIA/SE in OAC users was more than a proportion in non-OAC group (26.1% vs 22.0%), however, no difference was seen in CHA_2DS_2-VASc score (3.9 [SD 1.4] among OAC users and 3.9 [SD 1.4] among non-OAC users). Patients with prior intracranial bleeding not prescribed OAC was approximately three-fold that of OAC users (2.7% vs 1.0%). Patients receiving

OACs also were more likely to receive statins (59.6% vs 38.9%). In contrast, non-OAC users were more likely to be prescribed antiplatelet drugs (70.2% vs. 13.6%) (Table 1).

Temporal trends of OAC use among AF patients with dementia/CI

Among all patients with AF and dementia (n=9,845), OACs were prescribed for 4,168 (42.3%) of patients during the study period. The prevalence of OAC was significantly increased from 6.1% in 2000 to 45.9% in 2015 (P for trend < 0.001) (Figure 2). Among OAC users, DOACs were first prescribed in 2011 and the proportion of DOAC among the OAC prescribed increased from 0.1% from 2011 to 33.8% in 2015 (P for trend < 0.001), while the proportion of VKA use decreased from 100% in 2000 to 71.4% in 2015 (P for trend <0.001) (Figure 3A).

Figure 3B shows the changes in percentage of OAC prescribing between 2000 and 2015 stratified by individual OAC treatment. None of AF with dementia/CI was prescribed edoxaban during the study period. The prevalence of warfarin decreased significantly by 28.8% from 100% in 2000 to 71.2% in 2015 (P for trend < 0.001). In the contrary, the prevalence of rivaroxaban, which was the most commonly DOAC prescribing, increased dramatically by 21.2% from 0% in 2011 to 21.2% in 2015 (P for trend < 0.001). Acenocoumarol and phenindione were less likely to be prescribed (less than 0.1%) in the UK primary care.

Temporal trends of OAC use within different gender and age groups

Figure 4A illustrates an increase in the prevalence of OAC for both genders throughout the study period, however, the higher prevalence of OAC was observed among males compared to females. The prevalence of OAC in males increased from 10% in 2000 to 49.6% in 2015 (P for trend < 0.001) while the prevalence of OAC in female increased from 4.3% in 2000 to 42.7% in 2015 (P for trend < 0.001).

According to age group, the prevalence of OAC increased significantly among AF with dementia/CI aged 65 to 74, 75 to 84, and ≥ 85 years (P=0.007, < 0.001, and < 0.001 for trend, respectively), whereas for patients aged < 65 years, the prevalence of OAC use remained stable throughout the entire study period (P for trend = 0.668) (Figure 4B).

Factors associated with OAC prescription versus non-OAC in AF with dementia/CI

Table 2 presents the results of logistic regression model used to identify factors associated with OAC prescription versus non-OAC prescription, within 180 days after dementia/CI diagnosis. In multivariable analysis, patients who had a history of stroke/TIA/SE and CKD demonstrated higher odds of OAC prescription (adjusted OR 1.37; 95% CI 1.17-1.59 and adjusted OR 1.56; 95% CI 1.32-1.84, respectively). In addition, statin use was a strong predictor of OAC prescribing (adjusted OR 3.19; 95% CI 2.80-3.64). Other concomitant medications that were significantly associated with OAC prescription include ACEI/ARB, beta-blocker, calcium channel blocker, diuretics, and digoxin (Table 2). Younger age (< 65 years vs 65-74 years) was also negatively associated with the OAC prescription. Further, very old patients (≥ 85 years) were less likely to be prescribed OAC compared with patients aged 65-74 years (adjusted OR 0.56; 95% CI 0.45-0.70). Females were 41% less likely to be prescribed OAC compared to males (adjusted OR 0.59; 95% CI 0.53-0.66). Furthermore, for every 1-point increase in CCI, AF patients with dementia/CI were 6% less likely to receive OAC (adjusted OR 0.94; 95% CI 0.90-0.98). Having a HASBLED score ≥ 3, history of intracranial bleeding, fall, and polypharmacy was significantly associated with lower odds of receiving OAC (Table 2).

Factors associated with DOAC prescription versus VKA in AF with dementia/CI

Among 3,801 patients receiving OAC within 180 days after dementia/CI diagnosis, 87.8% were prescribed VKA and 12.2% were prescribed DOAC. DOAC users were older than VKA users (mean age 83.2 years vs 81.3 years). The proportion of females among DOAC users was 54.6% while among VKA users was 49.4%. The mean CCI in DOAC users was higher than CCI in VKA users (6.9 vs 6.7). Stroke/TIA/SE distribution was similar among both groups. Patients who received DOACs had a higher number of falls than those who received VKA (Table 1). In multivariable analysis, patients aged 75-84 years (adjusted OR 1.60; 95% CI 1.07-2.37) and ≥ 85 years (adjusted OR 2.35; 95% CI 1.56-3.55) were more likely to be prescribed a DOAC compared to those aged 65-74 years. In addition, patients who had a history of falls were more likely to receive a DOAC than VKA (adjusted OR 1.60; 95% CI 1.20-2.15). In contrast, having a history of hypertension (adjusted OR 0.71; 95% CI 0.57-0.88), CAD (adjusted OR 0.60; 95% CI 0.46-0.78), and hyperlipidaemia (adjusted OR 0.60; 95% CI 0.41-0.87) were significantly associated with lower odds of DOAC prescriptions. The use of statin and PPIs predicted

DOAC prescriptions while using ACEI/ARB and digoxin were less likely to be prescribed DOAC than VKA (Table 2).

DISCUSSION

Our findings showed that the prevalence of OAC use in AF with dementia/CI increased significantly over 15 years between 2000 and 2015. A substantial increase in the prescription of DOAC was observed, while the use of VKAs declined. The most commonly prescribed OAC among AF with dementia/CI was warfarin, followed by rivaroxaban then apixaban. In addition, the prevalence of OAC use remained higher among males when compared with females during the study period. In particular, female gender, patients aged < 65 years or ≥ 85 years, HASBLED score ≥ 3, increasing comorbidity burden, a history of intracranial bleeding, falls, polypharmacy, and concomitant use of antiplatelet drugs were factors associated with a lower prescription of OAC within 180 days after dementia/CI diagnosis. Finally, very old age (75-84 years and ≥ 85 years), a history of falls, the use of statin and PPIs were strong predictors for DOAC prescriptions in patients with AF and dementia/CI.

We found that none of the patients with AF and dementia/CI was prescribed edoxaban over the study period (2000-2015). The explanation for this is that edoxaban was first authorised for preventing stroke and systemic embolism throughout the EU in June 2015 [33] and it has subsequently been approved in the UK in September 2015 [34]. Given the fact that edoxaban was authorised for stroke prevention in patients with AF in the UK in the last half year of 2015, it is possible that none of the patients with dementia/CI was prescribed edoxaban was found in our analysis. The findings from our study are in line with a previous study using UK primary care data showing that none of the patients with type 2 diabetes mellitus was prescribed edoxaban during their study period (2001-2015) [21].

Among OAC users, we observed an increasing of DOAC prescriptions and decreasing of VKAs use in which the results were in line with previous studies using the UK's Clinical Practice Research Datalink (CPRD) [35], French health insurance databases [36], and Norway national registries [37], even though these studies focused on general AF population. Recently, published data from the Australian Pharmaceutical Benefits Scheme investigated the prevalence of OAC in older people (age > 65 years) with Alzheimer's disease. The results showed increasing rates of DOAC prescriptions while

warfarin prevalence declined between 2013/2014 and 2016/2017 [38]. The explanation for the increasing of DOAC uptake is that in 2009, several large randomized trials have demonstrated a non-inferiority of DOAC compared to warfarin [39-41]. After that, they were approved for use in non-valvular AF in the EU in 2011. Therefore, is the most likely reason that we observed a significant increase in DOAC prescriptions from 2011 onwards. Furthermore, the safety profile of DOACs might be another reason for the popularity of DOAC among AF with dementia/CI. DOACs have more predictable pharmacokinetics [42], are simpler to use, and do not require routine monitoring of the degree of anticoagulation effect, which may improve adherence [43]. Physicians might perceive that dementia/CI is a factor limiting VKA treatment in AF and increased bleeding risk or lack of adherence [44]. Therefore, in patients with dementia/CI, DOACs might be a preferred alternative for stroke prevention for patients with both AF and dementia because of the easier manageability and the lower risk of major bleeding [45]. However, the information regarding the effectiveness of DOACs for stroke prevention or mortality risk reduction in AF with dementia/CI compared to VKA is limited. We urge further study to be investigated to understand the risk and benefit of DOAC in AF patients with dementia/CI.

Even though DOACs have advantages over VKA, a risk of bleeding associated with the use of these agents do occur. Considering the demonstrated trend of increased DOAC use in the UK, reversal of DOACs may be required in the context of life-threatening bleeding, major bleeding, or supportive measures fail. Idarucizumab and andexanet, approved by the US FDA, are the specific reversal agents for dabigatran and FXa inhibitors (apixaban and rivaroxaban), respectively [46]. Alternative nonspecific agents (e.g. fresh frozen plasma, prothrombin complex concentrate) are also available. However, the use of DOAC reversal agents requires appropriate use, knowledge of how the agents are stored, and multidisciplinary stewardship programs [46].

The results from our current study are in line with previous studies using UK primary care data showing no changes of OAC use between 2001 and 2015 among younger patients [21, 47]. Given AF is a condition of older age, and people are now living longer, it is reasonable that the prevalence of OAC prescribing in patients less than 65 years is unchanged, as the disease in this population group should not be changing, but more people are getting AF as they age. In addition, prevalence of OAC

prescribing increased mainly due to DOACs, but the introduction of CHA_2DS_2-VASc risk score and changes in guidelines also may have affected this and caused increased prescribing. Patients aged <65 years also have a relatively low risk of developing stroke according the CHA_2DS_2-VASc score. Therefore, we would expect that the indication for use of OAC in this group remained the same throughout the study period.

We found higher prevalence of OAC prescriptions in males compared to females. Our findings from multivariable analysis also illustrated that females were 41% less likely to be prescribed OAC compared to males even though female gender has been associated with an increased risk of stroke [1]. This was consistent with the previous studies using the UK CPRD database [13], Norwegian nationwide registries [37], Danish registries [48], and Korean [49] nationwide data demonstrating that females are less likely to be prescribed OAC than males. In addition, a national survey in Scotland revealed that females were 18% less likely to receive warfarin compared with males [50]. The reasons why OAC is underused in females is not fully understood. However, it has been suggested that female sex is a risk factor for poorer anticoagulation control [51]. In addition, females are generally older than males at the time of their first AF and stroke which might lead to fewer females being prescribed OAC [48, 52].

We found differences in baseline characteristic of AF with dementia/CI who received OAC and those who did not receive OAC within 180 days after dementia/CI diagnosis. It should be noted that non-OAC users were more vulnerable compared to OAC users. Non-OAC users were older and had a greater risk of bleeding. The proportion of AF with dementia/CI who aged ≥ 85 years in non-OAC group was greater than a proportion in OAC group (55.0% vs 36.2%). It was clearly observed in our current study that the temporal trend in OAC prescriptions in patients aged ≥ 85 years was lowest among all age groups. Multivariable analysis demonstrated that advanced age (≥ 85 years), HASBLED score ≥ 3, a higher CCI, having a history of intracranial bleeding, falls and polypharmacy significantly affected the decision to not prescribe OACs. It may be because these factors are associated with increased risk of bleeding complications. Elderly patients have several comorbidities which increase bleeding and thromboembolism risks. Comorbidities present in the elderly such as frailty, falls, polypharmacy and impaired renal and liver function results in changed in body composition which

subsequently interfere with medication pharmacokinetics and pharmacodynamics. Warfarin, the most common OAC prescribed, requires dose adjustment and frequently monitoring, and has the potential to interact with numerous drugs. Accordingly, physicians might perceive that warfarin is difficult to manage in patients with dementia/CI, and concern for treatment adherence may account for the lower use of OAC prescription in this population.

Prior stoke/TIA/SE was associated with a greater likelihood of being prescribed OAC, with a 37% increased likelihood of prior stroke (adjusted OR 1.37; 95% CI 1.17-1.59) in OAC-users compared with non-OAC users, while CHF, hypertension, diabetes, and CAD did not show an important role influencing OAC prescribing. We also found that patients with CKD were 56% more likely to receive OAC than those who had no history of CKD even though the efficacy and safety of OAC have been poorly defined in AF with CKD. However, current evidence suggests that CKD is an independent risk factor for stroke in patients with AF [53, 54]. In a previous RCT (Stroke Prevention in Atrial Fibrillation III: SPAF III trials), adjusted-dose warfarin reduced the incidence of stroke by 76% in stage 3 CKD patients with AF compared with aspirin/low-dose warfarin [54]. In addition, patients with CKD may have underlying conditions such as hypertension and diabetes and theses conditions are known as risk factors for stroke. For these reasons, patients with CKD may be more likely to be prescribed OAC compared with non-CKD patients, as observed in our study. It is also important to note that, unlike VKAs, DOACs require dose adjustments and/or should be avoided in severe CKD. Therefore, in order to be better understand about OAC in AF with CKD, we urge future studies to be conducted to investigate the efficacy and safety of OAC including DOAC in AF with CKD.

Among AF patients with dementia/CI who received OAC, we found that an advanced age (≥75 years) and falls were significant predictors of DOAC prescriptions. Even though warfarin is beneficial for stroke prevention in all age groups, the risk of bleeding associated with warfarin remains a major concern in older people. Recently, data from the National Health Insurance Research Database in Taiwan demonstrated that DOACs were associated with a lower risk of intracranial haemorrhage compared with warfarin among patients with AF ≥90 years of age [55]. In people with dementia, warfarin was associated with increased any cause of haemorrhage compared to antiplatelets [56]. In addition, in older patients with non-valvular AF, a history of fall was associated with a risk of

intracranial haemorrhage [57]. Accordingly, the concern of increased risk of bleeding could make VKA a less appealing option for physicians compared to DOAC in AF with dementia/CI.

Strengths and limitations

Our study has several strengths. This study was conducted using electronic health records from the THIN database, which is representative of the UK general population and the findings reflect the real-world clinical practice patterns of OAC use among patients with AF and dementia/CI at a nationwide scale. Moreover, we examined trends in OAC use over a period of 15 years which covered time before and after the introduction of the DOACs. To our knowledge, this is the first study to describe the trend of OAC use in AF with dementia/CI in the UK while previous studies [13, 58] provided information of OAC use from subgroup analyses and did not examine OAC in relation to cognitive status as the main objective. Our study also has limitations. THIN database records prescriptions issued, so that it is not possible to confirm whether patients actually had their medication dispensed or took their medications. Furthermore, due to the observational nature of this study (as is the case with other population-based studies using large electronic health databases), the causal relationship between predictors and OAC treatment could not be drawn.

In conclusion, the overall prevalence of OAC in AF with dementia/CI increased significantly between 2000 and 2015 in the UK. A substantial increase in DOAC prescriptions was observed, while VKA prescriptions declined. Baseline characteristics of patients who were prescribed OAC differed from those who were not prescribed OAC. Age < 65 years, advanced age (≥ 85 years), being females, HASBLED score ≥ 3, having a higher CCI, intracranial bleeding, falls and polypharmacy were associated with lower odds of OAC prescription in patients with AF and dementia/CI.

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Competing Interests:

ICKW has received funding from Research Grant Council of Hong Kong, Pfizer and Bayer to evaluate use of anticoagulants in Hong Kong. However, these grants were not associated with the current study and had no role in the design of the study; the collection, analysis, or interpretation of the data; or the decision to approve publication of the final manuscript. Authors not named here have disclosed no conflicts of interest.

Contributions:

ICKW, PM, and WL were involved in the study concept and design. PM undertook the primary analysis. HA performed independent analysis for quality control. All authors involved in the acquisition, analysis or interpretation of data. PM wrote the manuscript with input from all authors. All authors were involved in the critical revision of the manuscript for important intellectual content.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1. Characteristics of AF patients with dementia/CI who were prescribed OAC and not prescribed OAC within 180 days after dementia/CI diagnosis

Characteristic	OAC versus non-OAC				DOAC versus VKA		
	Number (%)				Number (%)		
	All AF patients with dementia/CI (n=9845)	OAC (n=3801)	Non-OAC (n=6044)	P-Value	DOAC (n=465)	VKA (n=3336)	P-Value
Age (years), mean (SD)	83.4 (7.2)	81.5 (6.7)	84.5 (7.3)	<0.001	83.2 (6.3)	81.3 (6.8)	<0.001
< 65 y	139 (1.4)	57 (1.5)	82 (1.4)		3 (0.7)	54 (1.6)	
65-74 y	852 (8.7)	451 (11.9)	401 (6.6)		32 (6.9)	419 (12.6)	
75-84 y	4156 (42.2)	1916 (50.4)	2240 (37.1)		215 (46.2)	1701 (51.0)	
≥ 85 y	4698 (47.7)	1377 (36.2)	3321 (55.0)		215 (46.2)	1162 (34.8)	
Female (%)	5600 (56.9)	1903 (50.1)	3697 (61.2)	<0.001	254 (54.6)	1649 (49.4)	0.036
CHA_2DS_2-VASc Score[a]				0.161			0.504
0	28 (0.3)	9 (0.2)	19 (0.3)		1 (0.2)	8 (0.2)	
1	168 (1.7)	76 (2.0)	92 (1.5)		6 (1.3)	70 (2.1)	
≥2	9649 (98.0)	3716 (97.8)	5933 (98.2)		458 (98.5)	3258 (97.7)	
Mean CHA_2DS_2-VASc Score (SD)	3.9 (1.4)	3.9 (1.4)	3.9 (1.4)	0.274	3.9 (1.3)	3.9 (1.4)	0.928
HASBLED[b]				<0.001			0.728
<3	4958 (50.4)	2382 (62.7)	2576 (42.6)		288 (61.9)	2094 (62.8)	
≥3	4887 (49.6)	1419 (37.3)	3468 (57.4)		177 (38.1)	1242 (37.2)	
Mean HASBLED (SD)	2.6 (1.0)	2.3 (1.0)	2.8 (1.0)	<0.001	2.3 (1.0)	2.3 (1.0)	0.537
Mean Charlson Comorbidity Index (SD)	6.6 (1.8)	6.7 (1.9)	6.6 (1.8)	0.171	6.9 (1.9)	6.7 (1.9)	0.028
Baseline comorbidity, n (%)							
Congestive heart failure	1855 (18.8)	744 (19.6)	1111 (18.4)	0.141	82 (17.6)	662 (19.8)	0.261
Hypertension	3479 (35.3)	1346 (35.4)	2133 (35.3)	0.903	128 (27.5)	1218 (36.5)	<0.001
Diabetes mellitus	1514 (15.4)	656 (17.3)	858 (14.2)	<0.001	70 (15.1)	586 (17.6)	0.179
Stroke/TIA/SE	2320 (23.6)	992 (26.1)	1328 (22.0)	<0.001	135 (29.0)	857 (25.7)	0.124
Intracranial bleeding	197 (2.0)	37 (1.0)	160 (2.7)	<0.001	4 (0.9)	33 (1.0)	0.791
Coronary artery disease	2279 (23.2)	892 (23.5)	1387 (23.0)	0.552	83 (17.9)	809 (24.3)	0.002
Gastrointestinal bleeding	956 (9.7)	337 (8.9)	619 (10.2)	0.025	39 (8.4)	298 (8.9)	0.698
Chronic kidney disease	3438 (34.9)	1454 (38.3)	1984 (32.8)	<0.001	202 (43.4)	1252 (37.5)	0.014

Characteristic	OAC versus non-OAC				DOAC versus VKA		
	Number (%)				Number (%)		
	All AF patients with dementia/CI (n=9845)	OAC (n=3801)	Non-OAC (n=6044)	P-Value	DOAC (n=465)	VKA (n=3336)	P-Value
Hyperlipidaemia	1018 (10.3)	425 (11.2)	593 (9.8)	0.030	33 (7.1)	392 (11.8)	0.003
Falls	1164 (11.8)	352 (9.3)	812 (13.4)	<0.001	69 (14.8)	283 (8.5)	<0.001
Polypharmacy	2244 (22.8)	813 (21.4)	1431 (23.7)	0.008	104 (22.4)	709 (21.3)	0.584
Concomitant medication use n (%)							
Antiplatelet	4756 (48.3)	515 (13.6)	4241 (70.2)	<0.001	68 (14.6)	447 (13.4)	0.470
ACEI/ARB	4321 (43.9)	2096 (55.1)	2225 (36.8)	<0.001	212 (45.6)	1884 (56.5)	<0.001
Beta blocker	4238 (43.1)	2113 (55.6)	2125 (35.2)	<0.001	275 (59.1)	1838 (55.1)	0.100
CCBs	2169 (22.0)	993 (26.1)	1176 (19.5)	<0.001	114 (24.5)	879 (26.4)	0.399
Diuretics	3803 (38.6)	1594 (41.9)	2209 (36.6)	<0.001	182 (39.1)	1412 (42.3)	0.192
Digoxin	3331 (33.8)	1361 (35.8)	1970 (32.6)	0.001	116 (25.0)	1245 (37.3)	<0.001
Statin	4615 (46.9)	2266 (59.6)	2349 (38.9)	<0.001	293 (63.0)	1973 (59.1)	0.111
Amiodarone	348 (3.5)	133 (3.5)	215 (3.6)	0.879	14 (3.0)	119 (3.6)	0.541
PPIs	3622 (36.8)	1348 (35.5)	2274 (37.6)	0.031	206 (44.3)	1142 (34.2)	<0.001
NSAIDs	507 (5.2)	155 (4.1)	352 (5.8)	<0.001	24 (5.2)	131 (3.9)	0.207

Abbreviations: AF=atrial fibrillation; CI=cognitive impairment; SD=standard deviation; OAC=oral anticoagulant; DOAC=direct oral anticoagulant; VKA=vitamin K antagonist; TIA=transient ischaemic attack; SE=systemic embolism; ACEI=angiotensin-converting-enzyme inhibitor; ARB=angiotensin II receptor blocker; CCBs=calcium channel blockers; PPIs=proton-pump inhibitors; NSAIDs= Nonsteroidal anti-inflammatory drugs

[a]CHA_2DS_2-VASc indicates patients with congestive cardiac failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65 to 74 years, prior stroke or TIA or SE (doubled), vascular disease, and gender category (women). CHA_2DS_2-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke); [b]HAS-BLED indicates patients with hypertension, renal disease, liver disease, prior stroke, prior major bleeding, age > 65 years, medications that predispose to bleeding (NSAIDs or antiplatelet drugs), alcohol use (labile INR not included). HAS-BLED score ranges from 0 to 8 (as labile INR not included in calculation), a higher score indicates a higher risk for bleeding.

Table 2. Results of analysis evaluating factors associated with oral anticoagulation prescribing within 180 days after dementia/CI diagnosis: univariate and multivariate analysis

Variables	OAC versus non-OAC prescription				DOAC versus VKA prescription			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age < 65 y	0.62 (0.43-0.89)	0.010	0.57 (0.33-0.98)	0.043	0.73 (0.22-2.46)	0.609	0.83 (0.24-2.83)	0.766
65-74 y	Ref		Ref		Ref		Ref	
75-84 y	0.76 (0.66-0.88)	<0.001	0.87 (0.70-1.08)	0.211	1.66 (1.13-2.44)	0.011	1.60 (1.07-2.37)	0.021
≥ 85 y	0.37 (0.32-0.43)	<0.001	0.56 (0.45-0.70)	<0.001	2.42 (1.64-3.57)	<0.001	2.35 (1.56-3.55)	<0.001
Female sex (%)	0.64 (0.59-0.69)	<0.001	0.59 (0.53-0.66)	<0.001	1.23 (1.01-1.50)	0.0361		
CHA_2DS_2-VASc Score[a]								
0	Ref		Ref		Ref			
1	1.74 (0.75-4.08)	0.199	1.46 (0.48-4.47)	0.511	0.69 (0.07-6.44)	0.741		
≥2	1.32 (0.60-2.93)	0.491	2.11 (0.70-6.32)	0.184	1.13 (0.14-9.01)	0.912		
HASBLED[b]								
<3	Ref		Ref		Ref			
≥3	0.44 (0.41-0.48)	<0.001	0.72 (0.62-0.85)	<0.001	1.04 (0.85-1.27)	0.727		
Charlson Comorbidity Index	1.02 (0.99-1.04)	0.170	0.94 (0.90-0.98)	0.008	1.06 (1.01-1.11)	0.029	1.06 (0.99-1.13)	0.103
Baseline comorbidity								
Congestive heart failure	1.08 (0.98-1.20)	0.141	0.86 (0.73-1.01)	0.067	0.87 (0.67-1.11)	0.261		
Hypertension	1.01 (0.92-1.09)	0.903			0.66 (0.53-0.82)	<0.001	0.71 (0.57-0.88)	0.002
Diabetes mellitus	1.26 (1.13-1.41)	<0.001			0.83 (0.64-1.09)	0.180	0.80 (0.59-1.10)	0.165
Stroke/TIA/SE	1.25 (1.14-1.38)	<0.001	1.37 (1.17-1.59)	<0.001	1.18 (0.96-1.47)	0.124		
Intracranial bleeding	0.36 (0.25-0.52)	<0.001	0.16 (0.11-0.25)	<0.001	0.87 (0.31-2.46)	0.791		
Coronary artery disease	1.03 (0.94-1.13)	0.552			0.68 (0.53-0.87)	0.002	0.60 (0.46-0.78)	<0.001
Gastrointestinal bleeding	0.85 (0.74-0.98)	0.025			0.93 (0.66-1.32)	0.698		
Chronic kidney disease	1.27 (1.17-1.38)	<0.001	1.56 (1.32-1.84)	<0.001	1.28 (1.05-1.56)	0.014		
Hyperlipidaemia	1.16 (1.01-1.32)	0.030			0.57 (0.40-0.83)	0.003	0.60 (0.41-0.87)	0.007
Falls	0.66 (0.58-0.75)	<0.001	0.82 (0.69-0.98)	0.026	1.88 (1.42-2.50)	<0.001	1.60 (1.20-2.15)	0.002
Polypharmacy	0.88 (0.80-0.97)	0.009	0.62 (0.51-0.75)	<0.001	1.07 (0.85-1.35)	0.584		

Variables	OAC versus non-OAC prescription				DOAC versus VKA prescription			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Concomitant medication use								
Antiplatelet	0.07 (0.06-0.07)	<0.001	0.04 (0.04-0.05)	<0.001	1.11 (0.84-1.46)	0.470		
ACEI/ARB	2.11 (1.94-2.29)	<0.001	2.16 (1.91-2.45)	<0.001	0.65 (0.53-0.79)	<0.001	0.69 (0.56-0.84)	<0.001
Beta blocker	2.31 (2.13-2.51)	<0.001	3.18 (2.81-3.58)	<0.001	1.18 (0.97-1.44)	0.100	1.18 (0.96-1.45)	0.107
CCBs	1.46 (1.33-1.61)	<0.001	1.73 (1.50-1.99)	<0.001	0.91 (0.73-1.14)	0.400		
Diuretics	1.25 (1.15-1.36)	<0.001	1.54 (1.35-1.75)	<0.001	0.88 (0.72-1.07)	0.192		
Digoxin	1.15 (1.06-1.26)	0.001	1.95 (1.72-2.22)	<0.001	0.56 (0.45-0.70)	<0.001	0.57 (0.46-0.72)	<0.001
Statin	2.32 (2.14-2.52)	<0.001	3.19 (2.80-3.64)	<0.001	1.18 (0.96-1.44)	0.112	1.38 (1.11-1.72)	0.004
Amiodarone	0.98 (0.79-1.23)	0.879			0.84 (0.48-1.47)	0.541		
PPIs	0.91 (0.84-0.99)	0.031			1.53 (1.26-1.86)	<0.001	1.50 (1.22-1.84)	<0.001
NSAIDs	0.69 (0.57-0.83)	<0.001			1.33 (0.85-2.08)	0.208		

Abbreviations: OR=odd ratio; CI=confidence interval; OAC=oral anticoagulant; DOAC=direct oral anticoagulant; VKA=vitamin K antagonist; TIA=transient ischaemic attack; SE=systemic embolism; ACEI=angiotensin-converting-enzyme inhibitor; ARB=angiotensin II receptor blocker; CCBs=calcium channel blockers; PPIs=proton-pump inhibitors; NSAIDs= Nonsteroidal anti-inflammatory drugs

[a]CHA_2DS_2-VASc indicates patients with congestive cardiac failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65 to 74 years, prior stroke or TIA or SE (doubled), vascular disease, and gender category (women). CHA_2DS_2-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke); [b]HAS-BLED indicates patients with hypertension, renal disease, liver disease, prior stroke, prior major bleeding, age > 65 years, medications that predispose to bleeding (NSAIDs or antiplatelet drugs), alcohol use (labile INR not included). HAS-BLED score ranges from 0 to 8 (as labile INR not included in calculation), a higher score indicates a higher risk for bleeding.

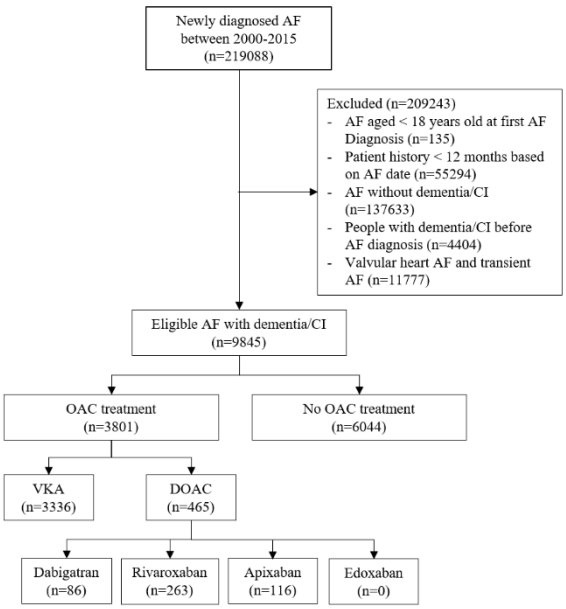

Figure 1. Cohort identification and OAC treatment within 180 days after dementia/CI diagnosis

Abbreviation: AF=atrial fibrillation; CI=cognitive impairment; OAC=oral anticoagulant; VKA=vitamin K antagonist; DOAC=direct oral anticoagulant

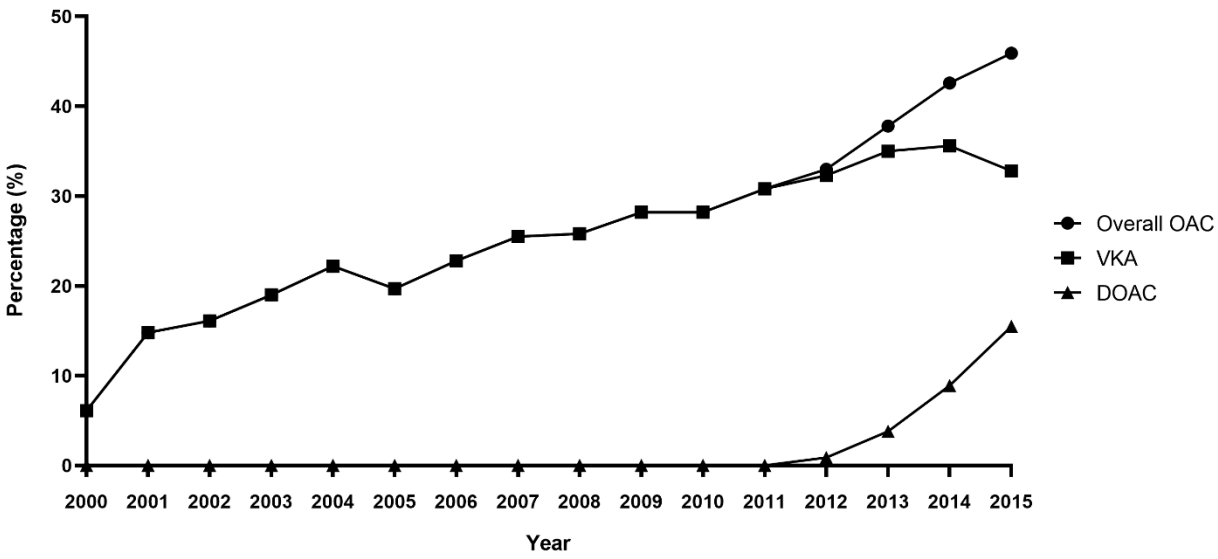

Figure 2. Annual trend of overall OAC, VKA, and DOAC among AF with dementia/CI between 2000 and 2015

Abbreviations: OAC=oral anticoagulant; VKA=vitamin K antagonist; DOAC=direct oral anticoagulant; AF=atrial fibrillation; CI=cognitive impairment

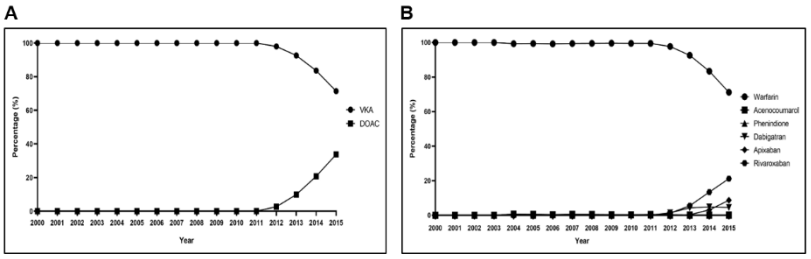

Figure 3. Annual trend of VKA and DOAC (A), and individual OAC (B) among OAC users between 2000 and 2015

Abbreviations: VKA=vitamin K antagonist; DOAC=direct oral anticoagulant; OAC=oral anticoagulant

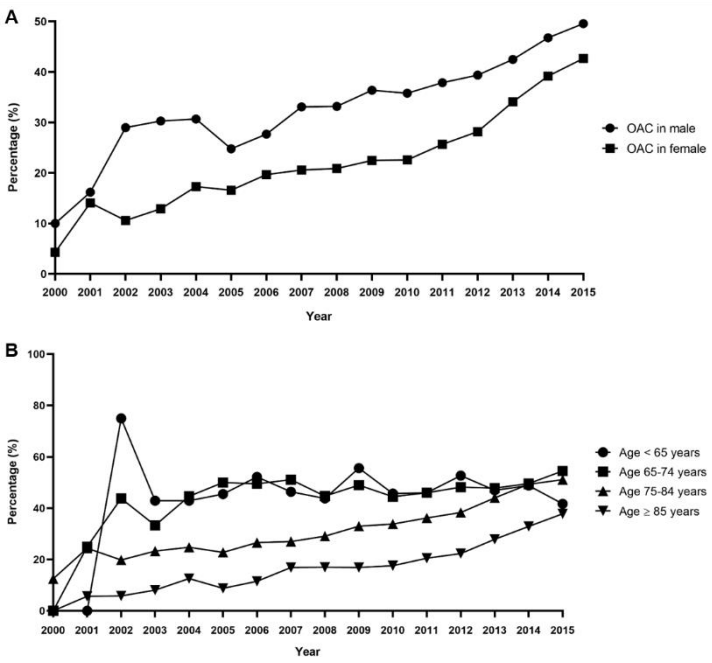

Figure 4. Temporal trends of OAC from 2000 to 2015 according to gender (A) and age group (B)

Abbreviations: OAC=oral anticoagulant