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Nemin Chen Date

Association of Oral Anticoagulant Type with Risk of Dementia among Patients with Atrial Fibrillation

By

Nemin Chen

Master of Public Health

Epidemiology

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Alvaro Alonso

Committee Chair

Association of Oral Anticoagulant Type with Risk of Dementia among Patients with Atrial Fibrillation

By

Nemin Chen

B.Sc.

Tsinghua University

2016

Faculty Thesis Advisor: Alvaro Alonso, MD, PhD

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Abstract

Association of Oral Anticoagulant Type with Risk of Dementia among Patients with Atrial Fibrillation

By Nemin Chen

Background

Oral anticoagulation (OAC) in patients with atrial fibrillation (AF), in addition to reducing stroke risk, could also prevent adverse cognitive outcomes.

Objectives

The purpose of this study was to compare the risk of dementia incidence across AF patients initiating different OACs.

Methods

We identified patients with non-valvular AF initiating OACs in two US healthcare claim databases, MarketScan (2007-2015) and Optum Clinformatics (2009-2015). Dementia, comorbidities and use of medications were defined based on inpatient and outpatient claims. We performed head-to-head comparisons of warfarin, dabigatran, rivaroxaban, and apixaban in propensity score-matched cohorts. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia for each propensity score-matched cohort, and meta-analyzed database-specific results.

Results

We analyzed 307,099 AF patients from the MarketScan database and 161,346 from the Optum database, of which 6,572 and 4,391 respectively had a diagnosis of incident dementia. Mean follow-up of each cohort ranged between 0.7 and 2.2 years. Patients initiating direct oral anticoagulants (DOACs) experienced lower rates of dementia than those initiating warfarin (dabigatran: HR 0.85, 95%CI 0.71, 1.01; rivaroxaban: HR 0.85, 95%CI 0.76, 0.94; apixaban: HR 0.80, 95%CI 0.65, 0.97). There were no differences in rates of dementia comparing DOAC user groups (dabigatran vs. rivaroxaban: HR 1.02, 95%CI 0.79, 1.32; dabigatran vs. apixaban: HR 0.92, 95%CI 0.63, 1.36; apixaban vs. rivaroxaban: HR 1.01, 95%CI 0.86, 1.19).

Conclusions

Patients with AF initiating DOACs experienced lower rates of incident dementia than warfarin users. No obvious benefit was observed for any particular DOAC in relation to dementia rates.

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Nemin Chen,[a] Pamela L. Lutsey, PhD,[b] Richard F. MacLehose, PhD,[b] J'Neka S. Claxton, MPH,[a] Faye L. Norby, MPH, MS,[b] Alanna M. Chamberlain, PhD,[c] Lindsay G. S. Bengtson, PhD,[d] Wesley T. O'Neal, MD, MPH,[e] Lin Y. Chen, MD, MS,[f] Alvaro Alonso, MD, PhD[a]

a. Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA
b. Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN
c. Department of Health Sciences Research, Mayo Clinic, Rochester, MN
d. Health Economics and Outcomes Research, Life Sciences, Optum, Eden Prairie, MN
e. Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, GA
f. Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN

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Contents

Background 1

Methods 3

Study population 3

OAC use 4

Outcome 4

Covariates 4

Statistical analysis 5

Results 8

Comparison of DOACs with warfarin 9

Comparisons among dabigatran, rivaroxaban, and apixaban 10

Sensitivity and subgroup analyses 10

Assessment of confounding by indication 11

Discussion 12

Study strengths and limitations 14

Conclusions 17

Perspectives 18

References 19

Figure Legends 23

Tables 24

Background

Atrial fibrillation (AF) is the most prevalent arrhythmia in clinical practice (1). Because of its high prevalence and the high risk of associated complications, such as stroke, AF is a major contributor to the burden of cardiovascular diseases in both the US and worldwide (2,3). In addition, growing evidence points to cognitive decline and dementia as additional outcomes associated with AF. An elevated stroke risk could partly mediate this association. Other mechanisms, such as repetitive cerebral injury due to lacunar infarcts or microbleeds, and brain hypoperfusion, are likely to play a role, but are not well characterized (4,5). Research on potential therapeutic targets to lower dementia risk are required to address this issue.

Oral anticoagulants (OACs) are recommended for stroke prevention in patients with nonvalvular AF at moderate or high stroke risk (6). This has been commonly achieved with vitamin K antagonists (i.e. warfarin in the United States). Since October 2010, several direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, have been approved by the U.S. Food and Drug Administration (FDA) for the prevention of stroke and systemic embolism among nonvalvular AF patients based on the results of large phase 3 randomized trials (7). Observational studies have generated results similar to randomized trials, showing noninferiority of DOACs versus warfarin for stroke prevention, and provided evidence of DOAC effectiveness in usual clinical practice (8-11). Limited additional evidence suggests an association between risk of dementia and type of OAC (DOACs versus warfarin) in patients with AF. A previous study in 5,254 anticoagulated patients managed by the Intermountain Healthcare Clinical Pharmacist Anticoagulation Service in Utah, documented a lower rate of dementia in patients taking a DOAC compared with warfarin (12). However, a recent study with a

larger sample size using data from Swedish registers found no difference of dementia risk between DOACs and warfarin users after adjusting for multiple baseline characteristics (13). Neither of these studies, however, evaluated the risk of dementia comparing warfarin with individual DOACs, or between individual DOACs.

Based on this previous suggestive but inconclusive evidence, we analyzed data from two large US healthcare utilization databases to evaluate whether the risk of dementia incidence among patients with AF differs between warfarin users and DOAC users, as well as across DOAC user groups.

Methods

Study population

The study population was identified from two databases (MarketScan and Optum Clinformatics). The Truven Health MarketScan Commercial Claims and Encounter Database and the Medicare Supplemental and Coordination of Benefits Database (Truven Health Analytics Inc., Ann Arbor, MI, USA) included data from 1 January 2007 to 30 September 2015. The MarketScan databases contain claims data and linked patient enrollment information from insured employees and their dependents for active employees as well as Medicare-eligible retirees with employer-provided Medicare Supplemental plans. Similarly, Optum Clinformatics™ Data Mart included data from 1 January 2009 to 30 September 2015. The Optum database contains health insurance medical and pharmacy claims as well as linked patient enrollment data from privately insured and Medicare Advantage enrollees throughout the United States.

We restricted the analysis to non-valvular AF patients with a prescription for an OAC. Enrollees were included if they had at least one inpatient claim or two outpatient claims with an AF diagnosis separated at least 7 days but less than 1 year, defined by an International Classification of Disease Ninth Revision, Clinical Modification (ICD-9-CM) code 427.31 or 427.32 in any position, without history of mitral stenosis (ICD-9-CM 394.0) or mitral valve disorder (ICD-9-CM 424.0) (14). At least one prescription for warfarin or one of the DOACs (dabigatran, rivaroxaban, or apixaban) was required, restricting the data to 678,683 and 362,357 patients in MarketScan and Optum, respectively. We excluded enrollees with less than 90 days of enrollment before the first OAC prescription (328,300 in MarketScan and 178,656 in Optum) to enhance the ability to identify comorbidities and other medications prior to OAC initiation. Those who took

OACs 90 days before (or earlier) their AF diagnosis were excluded, since they may have been using OACs for other indications. Enrollees with a dementia diagnosis before or at the time of their first OAC prescription (4,458 in MarketScan and 3,674 in Optum) were excluded. The inclusion procedure is shown in **Figure 1**.

OAC use

Outpatient pharmaceutical claim data includes, among other variables, the National Drug Code and prescription fill date. Enrollees were classified in exclusive categories according to their first filled OAC prescription: warfarin initiators, dabigatran initiators, rivaroxaban initiators, or apixaban initiators. We did not consider edoxaban use, since it was approved by the FDA in January 2015 and very few patients in our population received this medication.

Outcome

The primary outcome of interest was a diagnosis code for dementia on an inpatient claim, defined with the following ICD-9-CM codes in any position: 290.xx (dementia); 294.xx (persistent mental disorders due to conditions classified elsewhere); 331.0 (Alzheimer's disease). Positive predictive values (PPVs) for these codes have been shown to be greater than 80% in a previous study (15). In a sensitivity analysis, we defined dementia with an inpatient or an outpatient claim, using the diagnosis codes in any position.

Covariates

Covariates included demographic characteristics, as well as cognitive impairment, comorbidities and use of medications at baseline. Baseline demographic information included in our study were age and sex, as well as (in the Optum database only) race, education, and household income. Approximately 30% of the race/ethnicity data in Optum were collected from public records (e.g., driver's license records), and the

remaining were imputed by the E-Tech commercial software using individuals' names and zip codes. This validated imputation method has 97% specificity and 48% sensitivity for estimating the race of black individuals (16). Enrollees with missing values were categorized into the unknown group for race, education, and household income in Optum. We included the following baseline comorbidities that might affect both OAC type and dementia: heart failure, hypertension, diabetes, myocardial infarction, peripheral artery disease, kidney disease, ischemic stroke, gastrointestinal bleeding, cerebral bleeding, other bleeding, anemia, coagulopathy, cancer, mood disorders. We also included use of the following medications: antiplatelet therapy, diuretics, antiarrhythmic drugs, digoxin, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and lipid lowering medications. Cognitive impairment, comorbidities and prescription fills of medications were defined based on inpatient and outpatient claims, and outpatient pharmacy claims before first OAC prescription since their enrollment. The ICD-9-CM codes to define cognitive impairment and comorbidities have been used in previous analyses and are provided in **Supplemental Table s1**.(14) Stroke and bleeding risk stratification scores of CHA_2DS_2-VASc and HAS-BLED were calculated for each individual (17,18).

Statistical analysis

For each database, we performed all pairwise comparisons of different OACs (warfarin versus dabigatran, warfarin versus rivaroxaban, warfarin versus apixaban, dabigatran versus rivaroxaban, dabigatran versus apixaban, and rivaroxaban versus apixaban). For each analysis, we restricted the initial cohort to enrollees initiating OAC after the date when both anticoagulants were available (19 October 2010 for dabigatran, 4 November

2011 for rivaroxaban, 28 December 2013 for apixaban). We calculated propensity scores for treatment with a particular anticoagulant at the time of OAC initiation for each comparison in each cohort, using logistic regression models that included all the comorbidities and medications described above. Finally, we matched enrollees 1:1 on propensity score with calipers of 0.2 of standard deviation (SD) of the propensity scores, using a greedy matching algorithm implemented with the *gmatch* SAS macro (19). Any patient without a match was excluded from the analysis.

We assessed the association between anticoagulant type and incidence of dementia using Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Time to dementia was calculated from time of first anticoagulant prescription (index date) to September 30, 2015, database disenrollment, or dementia diagnosis, whichever occurred earlier. In model 1, we adjusted for age, sex, and cognitive impairment, as well as (only in the Optum database) race, education, and household income. In model 2, we additionally adjusted for comorbidities and medications listed in **Supplemental Table s2**, and CHA_2DS_2-VASc and HAS-BLED scores. In a supplementary analysis, we added incident ischemic stroke to our model as model 3. We tested the proportional hazards assumption by introducing an interaction term of OAC group and logarithmic scale of time in the model. No violation of the proportionality assumption was detected in both MarketScan and Optum databases across the comparisons. We meta-analyzed the database-specific results using a random effects model. Homogeneity of results between the databases was tested. We performed a sensitivity analysis by defining dementia incidence using both inpatient and outpatient claims to evaluate the robustness of our primary results to changes in endpoint definition.

Effect measure modification by age (≤75 and >75), sex (male and female), and CHA_2DS_2-VASc score (<2 as low risk and ≥2 as moderate/high risk) between OAC therapy and risk of dementia was assessed, after adjusting for other covariates in model 2 in each database. The significance of effect measure modifications is reported as p-values.

We conducted an additional analysis to address the concern that patients prescribed warfarin may have inherently different cognitive status at baseline from those prescribed DOACs in ways that our adjustment cannot control (confounding by indication). Specifically, we included all eligible enrollees from our primary analysis, plus patients previously excluded because of a dementia diagnosis before or at the time of their first OAC prescription (311,557 in MarketScan and 165,020 in Optum). We calculated, at the time of anticoagulant initiation, the odds ratios (ORs) of being prescribed a DOAC (versus warfarin) in patients with prevalent dementia (defined by an inpatient claim) or cognitive impairment (defined by an inpatient or outpatient claim) compared to cognitively normal patients. Logistic regression was used, adjusting for all the other covariates mentioned above, to determine if underlying cognitive status likely influenced the type of prescribed anticoagulant.

Results

The MarketScan database included 1,194,111 patients with non-valvular AF. After excluding ineligible patients using the criteria described above, 307,099 enrollees remained. The Optum database included 727,935 identified non-valvular AF patients and 161,346 remained in the cohort after excluding enrollees who did not meet the study criteria. The inclusion procedure is shown as a flow chart in **Figure 1**. In both cohorts, the majority of enrollees took warfarin as their first OAC (71% and 69%, respectively), while few of them were apixaban initiators (6% and 7%, respectively). We performed propensity score matching separately in MarketScan and Optum, obtaining six cohorts each as our final analytical datasets. Overall, there were 62,608 MarketScan and 30,358 Optum enrollees in the warfarin-dabigatran matched cohorts, 78,404 and 44,878 in the warfarin-rivaroxaban matched cohorts, 38,610 and 23,568 in the warfarin-apixaban matched cohorts, 36,114 and 20,356 in the dabigatran-rivaroxaban matched cohorts, 14,250 and 9,514 in the dabigatran-apixaban matched cohorts, and 38,716 and 23,570 in the rivaroxaban-apixaban matched cohorts, respectively **(Figure 1)**.

Baseline characteristics in MarketScan before propensity score matching by prescribed first OAC are presented in **Supplemental Table s2**. In general, dabigatran and rivaroxaban initiators had similar demographic, health and medication use profiles. Warfarin and apixaban initiators were slightly older, more likely to be female, and had higher CHA_2DS_2-VASc and HAS-BLED scores compared to dabigatran and rivaroxaban initiators. Prevalence of comorbidities was generally higher among warfarin users compared to DOAC users. Similar results were observed in Optum, which are shown in **Supplemental Table s3**. Characteristics at baseline after propensity score matching were similar between OAC treatment groups in each cohort. Across the cohorts the average

age ranged between 67 in MarketScan and 73 in Optum (SD around 12), percentage of female enrollees ranged between 35 in MarketScan and 45 in Optum, and the average CHA_2DS_2-VASc score ranged between 2.9 in MarketScan and 4.3 in Optum (SD around 2.0). Additionally, race was distributed similarly across the Optum cohorts, with approximately 77% white enrollees. Patients in Optum were generally older and had higher predicted risk of stroke and bleeding than those in MarketScan. Distribution of age, sex, race (in Optum database only), and CHA_2DS_2-VASc and HAS-BLED scores in each study after propensity score matching are shown in **Table 1** and **Table 2**.

Comparison of DOACs with warfarin

Table 3 shows the meta-analyzed HRs and 95%CIs of dementia comparing DOAC initiators to warfarin initiators. Mean follow-up ranged between 0.7 years for analyses comparing apixaban to warfarin in MarketScan to 2.2 years in the analyses comparing dabigatran to warfarin in Optum. Total numbers of 1,463, 1,592, and 751 dementia cases were identified in warfarin-dabigatran matched cohorts, warfarin-rivaroxaban matched cohorts, and warfarin-apixaban matched cohorts, respectively. Rate of dementia was lower among dabigatran users compared with warfarin users (model 1: HR 0.85, 95%CI 0.74, 0.97) after adjusting for demographic characteristics and prior cognitive impairment. Results were similar after additional adjustment for comorbidities, non-anticoagulant medication use, and CHA_2DS_2-VASc and HAS-BLED scores (model 2: HR 0.85, 95%CI 0.71, 1.01). Similar results also were observed for rivaroxaban and apixaban when compared to warfarin users, with HRs (95%CIs) of 0.85 (0.76, 0.94) for rivaroxaban users and 0.80 (0.65, 0.97) for apixaban users after full adjustment **(Table 3)**. There was no evidence of heterogeneity across databases. Database-specific results are presented in **Supplemental Tables s4** and **s5**. In a supplementary analysis, after

additional adjustment for incident ischemic stroke, results remained similar to what we observed from model 2 (**Supplemental Table s6**).

Comparisons among dabigatran, rivaroxaban, and apixaban

Meta-analyzed results from database-specific analysis showed comparable hazards of dementia across different DOAC groups (**Table 3**, model 2, dabigatran vs. rivaroxaban: HR 1.02, 95%CI 0.79, 1.32; dabigatran vs. apixaban: HR 0.92, 95%CI 0.63, 1.36; apixaban vs. rivaroxaban: HR 1.01, 95%CI 0.86, 1.19). There was no evidence of significant heterogeneity across database-specific results (**Supplemental Tables s7** and **s8**).

Sensitivity and subgroup analyses

We identified more than two times the number of dementia cases when ascertaining dementia diagnoses using both inpatient and outpatient ICD-9 codes instead of only using inpatient claims, with the number of enrollees comparable to the number in primary analyses in each comparison cohort **(Supplemental Tables s9 - Table s12)**. Results were similar to the primary analyses. DOACs were associated with a lower incidence of dementia compared with warfarin initiation, with HRs (95%CIs) of 0.79 (0.63, 0.88), 0.79 (0.63, 0.99), and 0.73 (0.52, 1.02) in the comparisons of dabigatran, rivaroxaban, and apixaban with warfarin, respectively (**Table 4**). Incidence of dementia was similar in head-to-head comparisons of the different DOACs. However, some of these comparisons showed evidence of heterogeneity across databases, most notably for the comparison of dabigatran with other DOACs, which had opposite direction of association in each database (**Supplemental Tables s11** and **s12**).

Results of subgroup analyses from each database are shown in **Supplemental Tables s13** and **s14**. No multiplicative interactions of OAC treatment with age, sex, and CHA_2DS_2-

VASc score were detected. In the Optum database, we observed that dabigatran initiation was associated with a lower hazard of dementia than warfarin initiation among younger patients ≤75 (HR 0.61, 95%CI 0.41, 0.89) but not among patients >75 (HR 1.04, 95%CI 0.87, 1.25, p for interaction=0.01). Rivaroxaban was associated with lower dementia hazard compared with warfarin among female enrollees (HR 0.70, 95%CI 0.56, 0.87) but not among male enrollees (HR 0.96, 95%CI 0.76, 1.21, p for interaction=0.04). For the dabigatran-rivaroxaban comparison, we observed a lower hazard of dementia for dabigatran among younger patients (HR 0.54, 95%CI 0.32, 0.91) and a higher hazard of dementia for dabigatran among older patients (HR 1.41, 95%CI 1.09, 1.84), with a p for interaction of 0.002. However, despite identifying several significant interactions in the Optum database, additional confirmatory evidence is required because of the inconsistency between the two databases, the limited number of cases in subgroups from each cohort, and multiple comparisons. Finally, HRs and 95% CIs were not calculated for CHA_2DS_2-VASc-categorized subgroups in the apixaban-dabigatran cohort from MarketScan, and all six cohorts from Optum database, because few dementia occurrences were identified among enrollees with CHA_2DS_2-VASc of 0 or 1.

Assessment of confounding by indication

In the analysis that included AF patients with prevalent dementia or cognitive impairment at the time of anticoagulant initiation, the odds of receiving DOACs vs warfarin was similar regardless of baseline cognitive status. In MarketScan, the OR (95%CI) of DOAC initiation was 0.99 (0.90, 1.10) comparing those with dementia/cognitive impairment to cognitively normal individuals, while the corresponding OR (95%CI) in Optum was 0.91 (0.81, 1.03), for a combined OR (95%) of 0.96 (0.88, 1.04) (**Supplemental Table s15**).

Discussion

In this study, which used data from two independent large healthcare claims databases, we found that patients with non-valvular AF initiating DOACs (dabigatran, rivaroxaban, and apixaban) had consistently lower rates of dementia compared to warfarin initiators. In head-to-head DOAC comparisons, however, we found that the hazard of dementia did not vary according to DOAC prescribed. Our findings suggest that (1) DOACs may be superior to warfarin with respect to outcome of dementia, which is considered as an important adverse outcome of AF; and (2) future risk of dementia does not appear to be influenced by choice of DOAC, therefore DOAC choice should be driven by other efficacy, safety, and preference considerations (20,21).

Growing evidence indicates that cognitive decline and dementia are frequent adverse outcomes in AF patients (4). Although preventing dementia is not the primary focus of antithrombotic treatment in patients with AF, concerns exist about higher risk of microbleeds in patient receiving suboptimal management of anticoagulation with warfarin, either due to under or over anticoagulation. These microbleeds could cause chronic cerebral injury and finally lead to dementia (22,23). On the other hand, the role that DOACs can play in the prevention of dementia is of considerable interest. Through prevention of ischemic stroke, both warfarin and DOACs can reduce the risk of vascular dementia. Moreover, DOAC users experience lower risk of intracranial bleeding compared to warfarin users. As shown in pivotal clinical trials, dabigatran, rivaroxaban, and apixaban were all reported noninferior in preventing ischemic stroke or systemic embolism, and had lower rates of intracranial hemorrhage compared with warfarin (24-26). Lastly, DOACs provide steady therapeutic levels without the fluctuations that are common among warfarin users, and may be a promising approach to reduce the risk of

dementia among AF patients (5). To have a better understanding of potential mechanisms that underlie the association between DOACs versus warfarin and incidence of dementia in this study, we further adjusted for incidence of ischemic stroke in the multivariate regression analysis, and detected no change compared with the primary results. Although the number of incident stroke events in each cohort is limited, it might indicate that mechanisms other than the reduction in risk of clinically recognized stroke, and possibly reduction of intracranial bleeding, is the primary factor underlying the observed beneficial association of DOACs versus warfarin in dementia risk.

Results from our analysis were consistent with the prior study using healthcare clinical data in Utah, where a lower rate of dementia was observed in patients taking a DOAC compared with warfarin users (12). In contrast, no difference between warfarin and DOACs was observed in a study using registry data from Sweden, in which patients treated with warfarin had a mean time in therapeutic range well above 70%. The mean time spent in therapeutic range in the US is much lower, at approximately 54% (27). This inconsistency might indicate that DOACs offer better protection than warfarin in the US compared with Sweden, possibly because of the difference in the time in therapeutic range for warfarin users (13).

We did not observe differences in the hazard of dementia among users of different DOACs, though there was some between-database heterogeneity in the comparisons of dabigatran with rivaroxaban and apixaban. Several previous analyses, including both direct and indirect comparisons between DOACs, found a more favorable profile of effectiveness and safety for dabigatran and apixaban users over rivaroxaban users, with no differences in risk of stroke or systemic embolism and lower risk of intracranial

bleeding (10,20). Comparisons including apixaban, however, need to be interpreted with caution given the shorter follow-up period and the limited number of events in this group because of the later FDA approval date. In addition, we have the fewest enrollees in the dabigatran-apixaban cohort due to limited number of dabigatran users since the approval of apixaban. Future analyses comparing dementia risk in apixaban users versus dabigatran and rivaroxaban users need to be based on a larger sample size and longer follow-up to generate a better understanding of dementia incidence across DOAC groups. We did not identify consistent effect measure modification in the association of OAC use with rates of dementia by age, sex, or CHA_2DS_2-VASc score. Rates of dementia incidence were lower in DOAC users among both younger and older patients, men and women, and low-risk patients and patients of high risk.

Study strengths and limitations

Our study has some important limitations. First, we relied on claims data to define dementia and baseline characteristics, which may lack clinical fidelity compared with using clinical criteria and detailed evaluation of cognitive function. In our primary analysis, we used inpatient claims to define dementia diagnosis, likely leading to an underestimate of dementia rates, as cases of dementia that were less severe were not captured by hospitalization records. Although we assumed a low sensitivity in this analysis, the specificity was expected to be high, as ICD codes of high validity were utilized to define dementia diagnosis (15). We also repeated the analysis using an alternative definition of incident dementia, using dementia codes in either inpatient or outpatient records—which did not have a major impact on the results. In addition to outcome misclassification, we categorized OAC user groups based on their first prescription of OACs, regardless of whether they stopped taking them or switched to

other OACs later. Furthermore, patterns of discontinuation and switching may not be random across OACs (e.g. patients prescribed warfarin were more likely to switch to other OAC therapies or to stop taking their medication). As a result, using initiation of prescription to represent OAC usage in this study would have limitations. Misclassifications of covariates, including race, were also possible.

Confounding by indication is a concern in this analysis. Individuals who were prescribed DOACs may be inherently different from those who were prescribed warfarin, and there may be uncontrolled confounding, due to unmeasured information at the time of prescription. Of particular concern is baseline cognitive status if the likelihood of being prescribed a DOAC or warfarin is affected by perceived cognitive function. To address this limitation, we conducted an analysis evaluating type of OAC prescribed in AF patients with dementia or cognitive impairment codes compared to patients without dementia or cognitive impairment codes. This analysis showed that baseline cognition status had only a weak association with the OAC prescribed (i.e. a DOAC or warfarin). In addition, in the main analysis, we adjusted for an extensive list of potential confounders by conducting propensity score matching and including the confounders in the Cox model, which makes the problem of confounding by indication less of a concern.

Other limitations of the present analysis include the potential lack of generalizability, since the population was restricted to individuals with commercial insurance, Medicare Supplemental insurance (MarketScan) or Medicare Advantage (Optum). Restricting analyses to patients matched on propensity score could be an additional source of restricted generalizability, especially for those initiating warfarin. Finally, the limited follow-up led to a small number of events, particularly for some comparisons, and to

uncertainties about long-term effects of anticoagulation. Because dementia-associated diseases can begin decades before they are clinically obvious, it will be important to assess the long-term effect of OACs on risk of dementia in future analyses.

Despite the limitations discussed above, our analysis has considerable strengths. We were able to assess a relatively rare event in two independent, large populations using administrative claims data. The large number of enrollees in each group of anticoagulant users enabled us to perform head-to-head comparisons between different anticoagulants and use of propensity score matching to generate exchangeable cohorts with practice-based claims data. The results were robust, since they were comparable in the MarketScan and Optum databases, even after adjustment for several markers of social economic status, and were consistent across diverse definitions of the outcome.

Conclusions

In this analysis comparing dementia rates by type of OAC in two large, independent retrospective health care use databases, we observed lower hazards of dementia among AF patients initiating DOACs compared to warfarin initiators and similar hazards of dementia across different DOAC user groups. Future long-term studies assessing dementia risk in AF patients initiating OACs are needed.

Perspectives

Competency in Medical Knowledge and Patient Care: DOACs including dabigatran, rivaroxaban, and apixaban contribute to a lower risk of dementia incidence among AF patients compared to warfarin. This association is consistent across AF patients of different age, gender, and stroke risk.

Translational Outlook: Future studies are needed to explore strategies to prevent adverse cognitive outcomes in AF patients by assessing the long-term risks of dementia incidence among patients initiating different OACs, as well as the potential mechanisms underlying the association.

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Figure Legends

Central illustration. Comparisons of dementia incidence among AF Patients Initiating Different OACs

In a meta-analysis combining the MarketScan and Optum claim databases, we compared the rate of dementia incidence among AF patients initiating different OACs in head-to-head propensity score-matched cohorts. HRs with 95%CIs from each database were calculated and meta-analyzed, adjusted for age, sex, prevalent cognitive impairment, comorbidities, medications, and CHA2DS2-VASc and HAS-BLED score, as well as (in the Optum only) race, education, and household income.

Figure 1. Flowchart of enrollees' selection to final analysis sample.

Inclusion criteria was applied to the MarketScan and Optum databases and all the eligible enrollees were matched 1:1 on propensity score to generate 6 final head-to-head OAC comparison cohorts.

Tables

Table 1. Baseline characteristics of patients with atrial fibrillation according to first prescribed oral anticoagulant after propensity score matching: MarketScan, 2010-2015. Comparison groups are matched 1:1.

	Comparison of DOACs with Warfarin		Comparison among Dabigatran, Rivaroxaban, and Apixaban	
	Warfarin	Dabigatran	Dabigatran	Rivaroxaban
n	31,304	31,304	18,057	18,057
Age, years, mean (SD)	67 (13)	67 (13)	67 (12)	66 (13)
Women, %	35	35	35	34
CHA_2DS_2-VASc, mean (SD)	3.0 (2.0)	3.1 (2.0)	3.0 (2.0)	2.9 (1.9)
HAS-BLED, mean (SD)	1.8 (1.1)	1.8 (1.2)	1.7 (1.1)	1.7 (1.1)

	Warfarin	Rivaroxaban	Dabigatran	Apixaban
n	39,202	39,202	7,125	7,125
Age, years, mean (SD)	68 (13)	67 (13)	67 (12)	67 (13)
Women, %	39	38	35	36
CHA_2DS_2-VASc, mean (SD)	3.1 (1.9)	3.1 (1.9)	3.0 (1.9)	2.9 (1.9)
HAS-BLED, mean (SD)	1.8 (1.1)	1.8 (1.1)	1.7 (1.1)	1.7 (1.1)

	Warfarin	Apixaban	Rivaroxaban	Apixaban
n	19,305	19,305	19,358	19,358

Age, years, mean (SD)	69 (13)	69 (13)	69 (12)	69 (13)
Women, %	40	40	40	40
CHA_2DS_2-VASc, mean (SD)	3.4 (1.9)	3.4 (2.0)	3.3 (2.0)	3.4 (2.0)
HAS-BLED, mean (SD)	1.9 (1.1)	1.9 (1.2)	1.9 (1.2)	1.9 (1.2)

Table 2. Baseline characteristics of patients with atrial fibrillation according to first prescribed oral anticoagulant after propensity score matching: Optum, 2010-2015. Comparison groups are matched 1:1.

	Comparison of DOACs with Warfarin		Comparison among Dabigatran, Rivaroxaban, and Apixaban	
	Warfarin	Dabigatran	Dabigatran	Rivaroxaban
n	15,179	15,179	10,178	10,178
Age, years, mean (SD)	69 (12)	69 (12)	69 (12)	69 (12)
Women, %	37	37	37	37
Race, % White	79	79	78	78
CHA_2DS_2-VASc, mean (SD)	3.6 (2.0)	3.6 (2.0)	3.7 (2.0)	3.7 (2.1)
HAS-BLED, mean (SD)	2.3 (1.3)	2.3 (1.3)	2.3 (1.3)	2.3 (1.3)

	Warfarin	Rivaroxaban	Dabigatran	Apixaban
n	22,439	22,439	4,757	4,757
Age, years, mean (SD)	71 (11)	70 (12)	70 (11)	70 (12)
Women, %	40	40	38	38
Race, % White	77	78	76	76
CHA_2DS_2-VASc, mean (SD)	3.8 (2.0)	3.8 (2.1)	3.8 (2.0)	3.8 (2.1)
HAS-BLED, mean (SD)	2.5 (1.3)	2.5 (1.3)	2.4 (1.3)	2.4 (1.3)

	Warfarin	Apixaban	Rivaroxaban	Apixaban
n	11,784	11,784	11,785	11,785
Age, years, mean (SD)	73 (10)	73 (11)	72 (11)	73 (11)
Women, %	45	45	45	45
Race, % White	77	77	77	77
CHA_2DS_2-VASc, mean (SD)	4.3 (2.0)	4.2 (2.1)	4.2 (2.1)	4.2 (2.1)
HAS-BLED, mean (SD)	2.7 (1.3)	2.7 (1.3)	2.7 (1.3)	2.7 (1.3)

Table 3. Meta-analyzed hazard ratios and 95% confidence intervals of incident dementia in OAC comparison cohorts: MarketScan and Optum, 2010-2015.

	Warfarin	Dabigatran	Warfarin	Rivaroxaban	Warfarin	Apixaban
N	46,483	46,483	61,641	61,641	31,089	31,089
Dementia, N	739	724	944	648	474	277
		Hazard ratios (95% confidence intervals)				
Model 1*	1	0.85 (0.74, 0.97)	1	0.85 (0.77, 0.94)	1	0.80 (0.63, 1.03)
Model 2 †	1	0.85 (0.71, 1.01)	1	0.85 (0.76, 0.94)	1	0.80 (0.65, 0.97)

	Rivaroxaban	Dabigatran	Apixaban	Dabigatran	Rivaroxaban	Apixaban
N	28,235	28,235	11,882	11,882	31,143	31,143
Dementia, N	290	399	87	119	360	279
		Hazard ratios (95% confidence intervals)				
Model 1*	1	1.03 (0.85, 1.24)	1	0.95 (0.65, 1.38)	1	0.99 (0.85, 1.16)
Model 2†	1	1.02 (0.79, 1.32)	1	0.92 (0.63, 1.36)	1	1.01 (0.86, 1.19)

* Model 1 adjusted for age, sex, and prevalent cognitive impairment in study from MarketScan and age, sex,

race, education level, household income level, and prevalent cognitive impairment in study from Optum; †Model 2 additionally adjusted for comorbidities, medications, CHA_2DS_2-VASc and HAS-BLED score.

Table 4. Meta-analyzed hazard ratios and 95% confidence intervals of incident dementia in OAC comparison cohorts: MarketScan and Optum, 2010-2015. Dementia defined based on inpatient and outpatient diagnoses.

	Warfarin	Dabigatran	Warfarin	Rivaroxaban	Warfarin	Apixaban
N	45,439	45,439	60,178	60,178	30,218	30,218
Dementia, N	1,877	1,709	2,352	1,587	1,143	660
		Hazard ratios (95% confidence intervals)				
Model 1†	1	0.79 (0.74, 0.84)	1	0.80 (0.62, 1.04)*	1	0.75 (0.52, 1.06)*
Model 2‡	1	0.79 (0.71, 0.88)	1	0.79 (0.63, 0.99)*	1	0.73 (0.52, 1.02)*

	Rivaroxaban	Dabigatran	Apixaban	Dabigatran	Rivaroxaban	Apixaban
N	27,596	27,596	11,582	11,582	30,271	30,271
Dementia, N	690	900	186	321	869	660
		Hazard ratios (95% confidence intervals)				
Model 1†	1	1.01 (0.72, 1.41)*	1	1.22 (0.77, 1.92)*	1	0.94 (0.85, 1.04)
Model 2‡	1	1.00 (0.71, 1.42)*	1	1.19 (0.74, 1.92)*	1	0.96 (0.86, 1.06)

* Heterogeneous between studies.

†Model 1 adjusted for age, sex, and prevalent cognitive impairment in study from MarketScan and age, sex, race, education level, household income level, and prevalent cognitive impairment in study from Optum; ‡Model 2 additionally adjusted for comorbidities, medications, CHA_2DS_2-VASc and HAS-BLED score.