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Treatment and persistence with oral anticoagulants among newly diagnosed patients with non-valvular atrial fibrillation: a retrospective observational study in a US commercially insured and Medicare Advantage population

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ABSTRACT

Objectives With the approval of new non-vitamin K antagonist oral anticoagulants for stroke prevention in non-valvular atrial fibrillation (NVAF), it is anticipated that their introduction may change NVAF treatment patterns; however, there is limited supporting real-world evidence. This study investigated guideline-recommended oral anticoagulation (OAC) treatment and persistence in newly diagnosed patients with NVAF to understand demographic and clinical characteristics.

Design Retrospective observational administrative claims study in the USA.

Setting Patients with NVAF with ≥1 pharmacy claim for OAC (warfarin, dabigatran, rivaroxaban or apixaban) and no atrial fibrillation diagnosis within 12 months prior to the first claim were identified in the HealthCore Integrated Research Database between 1 November 2010 and 30 November 2013.

Participants 45 092 patients with NVAF were included.

Outcomes The proportion of OAC-treated patients was stratified by $CHADS_2$ score. Treatment persistence was measured from OAC initiation to discontinuation, end of eligibility or end of study period (30 November 2014), whichever occurred first.

Results Almost half of the patients (41.1%) received an OAC. The proportion treated differed slightly in baseline stroke risk ($CHADS_2$<2: 39.8%; $CHADS_2$=2 or 3: 42.4%; and $CHADS_2$>3: 40.3%: p<0.001). Treated patients were slightly younger (70±12.2 vs 71±14.3 years; p<0.001), more likely male (59.7% vs 52.5%; p<0.001) and had a slightly elevated stroke risk ($CHADS_2$: 2.03±1.3 vs 1.98±1.4; p<0.001) and a lower bleeding risk ($HEMORR_2HAGES$: 2.55±1.8 vs 2.80±1.9; p<0.001) relative to untreated patients. Overall, patients with higher $CHADS_2$ scores had higher $HEMORR_2HAGES$ scores. The mean follow-up was 2.25 years (2.25±0.85) and 72.7% of patients discontinued OACs; nearly 25% within 3 months and 55% within 12 months. The mean time to discontinuation was 255±249 days.

Conclusions The proportion of patients with NVAF who received OAC treatment was lower than previously reported and differed slightly by stroke risk. Patients with an elevated stroke risk had a higher bleeding risk, suggesting that clinicians may incorporate both in the treatment decision.

Strengths and limitations of this study

- Large and representative sample, drawn from one of the largest national commercially insured/Medicare Advantage populations in the USA, representing over 40 million enrollees and providing significant follow-up time.
- A study time period that included the introduction of the non-vitamin K antagonist oral anticoagulants onto the market.
- The study results may not be generalisable to individuals not having US commercial/Medicare Advantage insurance or uninsured populations.
- Administrative claims data did not have information on over-the-counter medications such as aspirin.

INTRODUCTION

Atrial fibrillation (AF), the most common type of arrhythmia, affected an estimated 3.03 million people in the USA in 2005.[1] An important risk factor in stroke, AF increases the risk of stroke fivefold across all ages.[2] Stroke is more severe in patients with AF and is associated with greater functional disability and mortality relative to patients without the condition.[3] As a result, patients with AF have been shown to have higher stroke-related healthcare costs compared with patients without AF.[4]

Stroke prevention is central to the management of AF.[5] Clinical studies have shown that oral anticoagulation (OAC) therapy

substantially reduces the risk of stroke in patients with AF.[6–9] Evidence-based guidelines for stroke prevention in patients with AF recommend treatment with OACs for patients with moderate or high risk of stroke.[10 11] More than 95% of the cases in the USA are non-valvular atrial fibrillation (NVAF), defined as AF in the absence of mitral stenosis or valvular prostheses[12] and recent versions of the American College of Chest Physicians antithrombotic guidelines recommend OAC therapy for patients with NVAF at intermediate and high risk ($CHADS_2$ score of ≥2 or $CHA2DS_2$-VASc score ≥2) of stroke.[11–14]

Warfarin, an oral vitamin K antagonist (VKA), had been the only OAC option for more than half a century. Studies have shown that warfarin was significantly underused, with only 38.8%–64.6% of patients with NVAF with $CHADS_2$≥2 using the medication despite guideline indications that it reduced the danger of stroke in patients with NVAF at moderate and high risks.[15–18] Warfarin is associated with adverse food and drug interactions and requires frequent coagulation monitoring and dose adjustment, which may interfere with convenience and compliance in sustained, continued use.[19] Underutilisation has also been attributed to physicians' concerns with OAC-related bleeding.[20]

Since 2010, four new non-VKA oral anticoagulants (NOAC), including dabigatran, rivaroxaban, apixaban and edoxaban, that have either comparable or reduced rates of major bleeding for use have been approved for stroke prevention in patients with NVAF.[21–24] These medications have also been included in the recommendations of evidence-based guidelines to reduce the risk of stroke.[11] With the approval of four NOACs for stroke prevention in patients with NVAF, it is anticipated that a larger number of patients will receive treatment. However, there is limited supporting evidence.[25] Given the increasing AF population, appropriate treatment initiation coupled with persistence could help reduce the number of associated stroke events. Thus, this study seeks to understand current guideline-recommended treatment rates for OACs in real-world practice, and assess the baseline characteristics of newly diagnosed treated and untreated patients with NVAF. Noting the chronic nature of AF, and the importance of long-term treatment,[26] this study also aimed to evaluate persistence among patients receiving treatment.

METHODS

Study design

Data source

Data for this study were drawn from the HealthCore Integrated Research Database (HIRD^{SM}), a broad, clinically rich and geographically diverse repository of longitudinal claims data from Anthem health insurance plans in the Northeastern, South, Midwest and Western regions of the USA. The database has been shown to be generally representative of the US Census population in terms of age and gender, though under-represents patients aged 65 years and older.[27] The database consisted of claims information from one of the largest commercially insured populations in the USA, and incorporated health maintenance organisations (HMO), point of service plans, Medicare Advantage and Part D plan, preferred provider organisations, and consumer directed health plans and indemnity plans. HMO patients with capitation and Part D plan members were not included. The claims included in the HIRD are fully adjudicated and are final paid claims. All data handling complied with federal and state requirements, and the privacy and security of individually identifiable personal health information, required by Health Insurance Portability and Accountability Act (HIPAA) Standards were preserved. As this non-experimental study did not require direct patient identification, a Limited Data Set, defined by the HIPAA Privacy Rule, was used.

Study population

This study focused on newly diagnosed patients with NVAF with ≥2 medical claims with a diagnosis of AF (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code: 427.31 in any position) in any setting (inpatient (INP), outpatient, emergency department (ED) or office visit (OV)) during the patient identification period, 1 November 2010 through 30 November 2013 with no evidence of AF diagnosis 12 months prior to the first observed AF diagnosis (newly diagnosed). Eligible patients were categorised into two cohorts based on treatment status: OAC treated and OAC untreated. The OAC treated cohort was defined as patients with ≥1 pharmacy claim(s) for any OAC including warfarin (Generic Product Identifier (GPI) code starting with 83200030), dabigatran (GPI code starting with 83337030), rivaroxaban (GPI code starting with 83370060) or apixaban (GPI code starting with 83370010) during the patient identification period, and a medical claim for an AF diagnosis on or within 90 days prior[28] to the first observed OAC fill date. The first observed fill date of any OAC during the patient identification period was defined as the index date. The OAC untreated cohort consisted of patients with no OAC pharmacy claim during the identification period but who had an AF diagnosis claim on or within 90 days prior to an iteratively simulated index date, which was computed using the average lag time between the first observed AF diagnosis and the first OAC pharmacy claim of corresponding treated patients. The first observed AF diagnosis date was used in the simulation to account for any regional, temporal and gender variation in treatment patterns. To this end, in the first iteration, treated and untreated patients with same region of residence, health plan type, commercial plan versus Medicare Advantage plan, calendar quarter and year of the first observed AF diagnosis, gender, age categories (18–64 years; 65–74 years; ≥75 years) and $CHADS_2$ score ($CHADS_2$ score <2; $CHADS_2$score=2 or 3; $CHADS_2$ score >3) were categorised. For each category with ≥1 treated and ≥1 untreated patients, the average lag time between first AF diagnosis and OAC pharmacy claim for treated patients was applied

to the corresponding untreated patients. In the second iteration, region of residence at the first AF diagnosis was dropped and the steps of the first iteration were repeated.

Inclusion criteria

To be included in the study, patients were required to be continuously enrolled in a health plan for a minimum of 12 months prior the index date, and have continuous coverage for at least 12 months after the index date. In addition, to facilitate the simulation of the index date of the untreated patients, all patients were also required to be continuously enrolled in a health plan for a minimum of 12 months prior to the first observed AF diagnosis.

Exclusion criteria

Patients younger than 18 years on the index date were excluded from the study. Also excluded were patients with a diagnosis of hyperthyroidism[7] (ICD-9-CM diagnosis code 242.x) within 12 months prior to the index date. To ensure the selection of patients with NVAF, patients with AF with a medical claim for valvular heart disease (ICD-9-CM diagnosis codes: 394.0x, 394.2x, 396.0x, 396.1x; ICD-9-CM procedure codes: 35.20, 35.22, 35.24, 35.26, 35.28) or valvular procedures (The Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) codes: 33999, 0257T, 0258T, 0259T, 33405, 33425, 33426, 33427, 33430, 0262T, 33475, 33460, 33463, 33464, 33465) within 12 months prior to the index date were not included. Similarly, patients with a claim within 3 months prior to the first observed diagnosis of AF for cardiac surgery (ICD-9-CM procedure codes: 00.5x, 35.xx, 36.xx or 37.xx), pericarditis (ICD-9-CM diagnosis codes: 391.x, 393, 420.x, 423.2, 0.36.41, 074.21, 093.81 or 098.83), myocarditis (ICD-9-CM diagnosis codes: 391.2, 422.xx, 074.23, 398.0, 429.0, 032.43, 093.82 or 130.3) or pulmonary embolism (ICD-9-CM diagnosis code: 415.1x) were excluded.

Outcomes

The outcomes of interest in this study included the proportion of patients treated with OAC among newly diagnosed patients with NVAF for whom treatment was recommended (baseline $CHADS_2$ score ≥2) as well as stratified by baseline $CHADS_2$ score. The latest guidelines (2014), for the first time, recommend using CHA_2DS_2-VASc,[11] however prior guidelines recommended using $CHADS_2$, to classify patients who should be treated with OAC.[29] Since this study used data before the 2014 guidelines were published, the adherence to evidence-based guidelines was evaluated using baseline $CHADS_2$ and was stratified by $CHADS_2$ score <2; $CHADS_2$score=2 or 3; and $CHADS_2$ score >3.[29]

Treatment persistence, a key outcome of interest, was calculated for the treated cohort. Patients were categorised as treated once they had a pharmacy claim for an OAC treatment, regardless of the specific medication (warfarin, dabigatran, rivaroxaban or apixaban). Treatment persistence was defined as the duration from the index date to discontinuation of OAC treatment. Patients who did not discontinue before the end of continuous enrolment, the end of the study observation period or death, whichever was earlier, were considered censored at the end of the follow-up period, and persistence was defined as the duration from the index date to the censored date. Patients were allowed to switch between OACs and still be considered persistent with therapy. For any NOAC segment of the treatment, discontinuation was defined as the failure to refill an OAC prescription within 30 days from the run-out date of the previous prescription for an OAC. Patients on warfarin have to adjust the dose frequently based on their international normalised ratio (INR) test results. Therefore, for any warfarin segment of treatment, discontinuation was determined similarly to the approach used by Go *et al*[30] and was based on a combination of prescription fills from pharmacy claims and indicators of INR measurements from the medical claims. Dates of service for CPT code 85610 (prothrombin time/INR) in the medical claims were used to identify INR tests. For any consecutive prescriptions with a gap of no more than 60 days, a patient was considered continually taking warfarin. For gaps longer than 60 days, the patient was considered continually taking warfarin if there were intervening INR tests at least every 42 days. If a patient did not have another INR test within 42 days after the previous INR test or end of the previous warfarin fill, the patient was considered discontinued from the warfarin segment of treatment. The discontinuation date was defined as the run-out date of the last warfarin fill or the last INR test date, whichever came later. A grace period of 30 days at the end of each warfarin fill was selected since changes in warfarin dosages were common. To examine the robustness of the findings, a sensitivity analysis using 45 days as a permissible gap for all OACs for the persistence measure was conducted in addition to the primary analysis.

Baseline characteristics

At the baseline, comorbidities were evaluated using the Deyo-Charlson Comorbidity Index (DCI)[31] and the Elixhauser Comorbidity Index (ECI).[32] Other specific comorbidities assessed at baseline included cardiovascular, renal, hepatic and gastrointestinal (GI) conditions and diabetes. Stroke risk was assessed for the preindex period using the $CHADS_2$,[29] and bleeding risk was assessed using the $HEMORR_2HAGES$.[17] Baseline use of cardiovascular and diabetes medications, non-oral anticoagulants, antiplatelets and medications that affect hepatic metabolism was also assessed.

Statistical analysis

All study outcomes were analysed descriptively. Means (±SD) and medians were reported for continuous variables, and frequencies (%) were reported for categorical variables. Statistical significance was assessed with the Student's t-test or Wilcoxon rank-sum test or Kruskal-Wallis test for continuous variables and X^2 test for categorical variables. The Marascuilo procedure was used

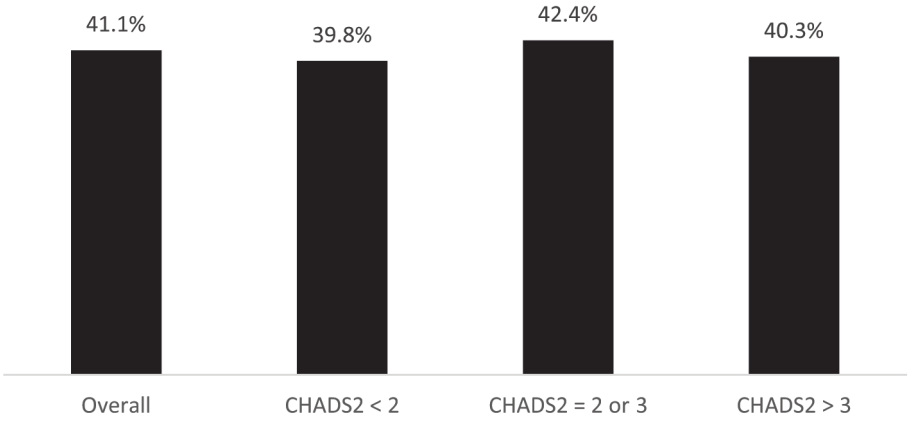

Figure 1 Proportion of patients with non-valvular atrial fibrillation (NVAF) treated with oral anticoagulation (OAC)—stratified by $CHADS_2$ score. Overall, a difference was observed in the proportion of patients with NVAF treated with OAC based on $CHADS_2$ score ($p<0.001$). Specifically, patients with NVAF with a $CHADS_2$ score=2 or 3 were treated with an OAC compared with patients with a $CHADS_2$ score of <2 or >3 (both $p<0.05$).

to test the treatment rates between the two groups based on $CHADS_2$.

Patient involvement

No patients were directly involved in the development of the research question, selection of the outcome measures, design and implementation of the study, or interpretation of the results.

RESULTS

Patient attrition

A total of 287 802 patients had at least one INP, OV or ED visit with diagnosis of AF during the patient identification period. Following the requirement of ≥2 diagnoses of AF in INP, OV or ED visits and applying the additional inclusion/exclusion criteria, a total of 89 875 patients with NVAF remained. Of those, 45 092 patients were classified as newly diagnosed and included in the analysis: $CHADS_2<2$ were 17 053 (37.8%); $CHADS_2=2$ or 3 were 22 060 (48.9%); and $CHADS_2>3$ were 5979 (13.3%).

Treatment status

Of the newly diagnosed patients with NVAF, 41.1% were classified as treated, as shown in figure 1. Among patients recommended for treatment in accordance with evidence-based guidelines based on a baseline $CHADS_2$ score ≥2 (n=28 039), 42.0% were treated. The proportion of patients treated with OAC differed slightly by baseline risk for stroke ($p<0.001$): $CHADS_2<2=39.8\%$; $CHADS_2=2$ or 3=42.4%; and $CHADS_2>3=40.3\%$. Marascuilo pairwise testing (at alpha=5%) showed that the proportions of patients treated with OAC were similar between $CHADS_2<2$ and $CHADS_2>3$ groups; statistically higher for $CHADS_2=2$ or 3 relative to $CHADS_2<2$ group; and statistically higher for $CHADS_2=2$ or 3 relative to $CHADS_2>3$.

Baseline characteristics

Demographics

The treated patients were slightly younger than the untreated patients (treated vs untreated (mean±SD) 70±12.2 years vs 71±14.3 years ($p<0.001$)). Men accounted for over half in both cohorts, however, the percentage of women in the treated cohort was lower than in the untreated cohort (treated vs untreated: women 40% vs 48% ($p<0.001$)), as shown in table 1.

Comorbidities

The top three most frequently occurring comorbidities of interest, as shown in table 2, were hypertension (treated vs untreated: 80.9% vs 78.9% ($p<0.001$)), hyperlipidaemia (treated vs untreated: 65.9% vs 64.2% ($p<0.001$)) and coronary artery disease (treated vs untreated: 38.7% vs 40.9% ($p<0.001$)). Several comorbid conditions were significantly different between the treated and untreated groups, however, the numerical differences were small as with the most frequent conditions above. Differences in the prevalence of cardiovascular conditions were mixed between the treated and untreated groups. The treated group had more comorbid cerebrovascular disease than the untreated group, and in the treated group lower percentages of baseline renal, liver and GI disease (table 2).

OAC-treated patients were more aggressively treated with all medications in general. The numerical differences in various medication use were much greater in magnitude than the differences in the prevalence of comorbidities between the groups, as shown in table 3. DCI of the untreated patients was higher than the treated group (treated vs untreated: 2.11±2.2 vs 2.26±2.5 ($p<0.001$)). Untreated patients with NVAF also had higher ECI (treated vs untreated: 4.67±2.6 vs 4.96±2.8 ($p<0.001$)) (table 2).

Stroke and bleeding risk

Treated patients had a slightly higher risk of stroke as measured by $CHADS_2$ score than patients in the untreated

Table 1 Baseline demographic characteristics

Variables	Treated cohort n/mean	Treated cohort %/SD	Treated cohort Median	Untreated cohort n/mean	Untreated cohort %/SD	Untreated cohort Median	P values*
Number of patients	18549	100%		26543	100%		
Sex, n (%)							
Male	11081	59.7%		13921	52.5%		
Female	7468	40.3%		12622	47.6%		<0.001
Age							
Age (mean, SD, median)	70	±12.2	72	71	±14.3	74	<0.001
Age category, n (%)							
18–44	437	2.4%		1215	4.6%		
45–54	1542	8.3%		2233	8.4%		
55–64	4032	21.7%		4360	16.4%		
65–74	4876	26.3%		6157	23.2%		
75–79	5575	30.1%		7607	28.7%		
80+	2087	11.3%		4971	18.7%		<0.001
Region of residence, n (%)							
Northeast	3720	20.1%		3686	13.9%		
Midwest	6088	32.8%		10067	37.9%		
South	4685	25.3%		7377	27.8%		
West	4056	21.9%		5413	20.4%		<0.001
Medicare plan type, n (%)							
Medicare Advantage only	5015	27.0%		4707	17.7%		<0.001
Commercial health plan type, n (%)							
HMO	4373	23.6%		4413	16.6%		
PPO	13316	71.8%		20876	78.7%		
Other†	860	4.6%		1254	4.7%		<0.001

*T-test or Wilcoxon rank-sum test was used for continuous variables and X^2 test was used for categorical variables.
†Other plans include consumer directed health plans (CDHP) and indemnity plans.
HMO, health maintenance organisation; PPO, preferred provider organisation.

group (treated vs untreated: 2.03±1.3 vs 1.98±1.4 (p<0.001)) and slightly lower risk of stroke as measured by CHA_2DS_2VASc score than patients in the untreated group (treated vs untreated: 3.34±1.9 vs 3.42±1.9 (p<0.001)). Untreated patients had higher $HEMORR_2HAGES$ Bleeding Risk Score (treated vs untreated: 2.55±1.8 vs 2.80±1.9 (p<0.001)) as shown in table 2. For both treated and untreated patients, those in higher $CHADS_2$ score categories also had higher $HEMORR_2HAGES$ scores as shown in figure 2.

Treatment type and physician specialty

Among the treated cohort, 37.3% of patients were initially (OAC prescription on the index date) prescribed an OAC by a cardiologist, followed by primary care physicians for 32.5% of the patients. For a majority of patients, index OAC was warfarin (60.1%), followed by dabigatran (23.8%), rivaroxaban (14.2%) and apixaban (2.0%) as shown in table 3.

Medication persistence among the treated patients

Patients were followed for an average of 2.25 years (2.25±0.85 (median=2.11 years)). During the follow-up, 72.7% of patients discontinued OAC treatment. Mean time to discontinuation was 255±249 days. Nearly one-fourth (23.1%) of patients discontinued within 3 months, and more than half (54.7%) did within 12 months, as shown in figure 3. The sensitivity analysis using a 45-day permissible gap also showed similar results.

DISCUSSION

This study found that nearly 60% of newly diagnosed patients with NVAF recommended for treatment with OAC by evidence-based guidelines remained untreated an average of over 2 years after their diagnosis. Additionally, more than half of the patients initiating OAC treatment discontinued their treatment within the first year of treatment.

Table 2 Baseline specific comorbid conditions and clinical indices

Variables	Treated cohort n/mean	%/SD	Median	Untreated cohort n/mean	%/SD	Median	P values*
Number of patients	18549	100%		26543	100%		
Comorbidities, n (%)							
Cardiovascular disease							
Hypertension	15002	80.90%		20948	78.90%		<0.001
Hyperlipidaemia	12228	65.90%		17028	64.20%		<0.001
Coronary artery disease	7173	38.70%		10858	40.90%		<0.001
Heart failure	5101	27.50%		6579	24.80%		<0.001
Atrial flutter	2691	14.50%		2681	10.10%		<0.001
Peripheral artery disease	2662	14.40%		4745	17.90%		<0.001
Cardiomyopathy	2140	11.50%		2274	8.60%		<0.001
Venous thromboembolism	1186	6.40%		1152	4.30%		<0.001
Acute myocardial infarction	1148	6.20%		1684	6.30%		0.503
Left ventricular heart failure	406	2.20%		485	1.80%		0.007
Cerebrovascular disease							
Ischaemic stroke	1762	9.50%		1987	7.50%		<0.001
TIA	1182	6.40%		1452	5.50%		<0.001
Gastrointestinal disease							
Peptic ulcer/GORD	3841	20.70%		6449	24.30%		<0.001
Dyspepsia	256	1.40%		433	1.60%		0.032
Other relevant disease states							
Diabetes	5508	29.70%		7114	26.80%		<0.001
Renal disease	4441	23.90%		6962	26.20%		<0.001
COPD/emphysema	3700	20.00%		5896	22.20%		<0.001
Liver disease	832	4.50%		1373	5.20%		0.001
Deyo-Charlson Comorbidity Index (DCI)							
DCI—mean (SD), median	2.11	±2.2	2	2.26	±2.5	2	<0.001
Categorical DCI distribution							
Patients with DCI of 0	5031	27.10%		7622	28.70%		
Patients with DCI of 1	4227	22.80%		5425	20.40%		
Patients with DCI of 2 or higher	9291	50.10%		13496	50.90%		<0.001
Elixhauser Comorbidity Index (ECI)							
ECI—mean (SD), median	4.67	±2.6	4	4.96	±2.8	4	<0.001
Categorical ECI distribution							
Patients with ECI of 0–3	6805	36.70%		9336	35.20%		
Patients with ECI of 4–6	7739	41.70%		10392	39.20%		
Patients with ECI of 7 or higher	4005	21.60%		6815	25.70%		<0.001
$CHADS_2$ Stroke Risk Score							
$CHADS_2$—mean (SD), median	2.03	±1.3	2	1.98	±1.4	2	<0.001
Categorical $CHADS_2$ distribution							
Patients with low risk ($CHADS_2$: 0–1)	6785	36.60%		10268	38.70%		
Patients with intermediate risk ($CHADS_2$: 2–3)	9353	50.40%		12707	47.90%		

Continued

Table 2 Continued

Variables	Treated cohort n/mean	%/SD	Median	Untreated cohort n/mean	%/SD	Median	P values*
Patients with high risk ($CHADS_2$≥4)	2411	13.00%		3568	13.40%		<0.001
CHA_2DS_2-VASc Stroke Risk Score							
CHA_2DS_2-VASc—mean (SD), median	3.34	±1.9	3	3.42	±1.9	3	<0.001
Categorical CHA_2DS_2-VASc distribution							
Patients with low risk (CHA_2DS_2-VASc: 0)	1061	5.70%		1802	6.80%		
Patients with intermediate risk (CHA_2DS_2-VASc: 1)	2220	12.00%		3309	12.50%		
Patients with high risk (CHA_2DS2-VASc≥2)	15268	82.30%		21432	80.70%		<0.001
$HEMORR_2HAGES$ Bleeding Risk Score							
HEMORR2HAGES—mean (SD), median	2.55	±1.8	2	2.8	±1.9	3	<0.001
Categorical HEMORR2HAGES distribution							
Patients with low risk ($HEMORR_2HAGES$: 0–1)	5989	32.30%		7616	28.70%		
Patients with intermediate risk ($HEMORR_2HAGES$: 2–3)	7609	41.00%		10249	38.60%		
Patients with high risk ($HEMORR_2HAGES$: ≥4)	4951	26.70%		8678	32.70%		<0.001

*T-test or Wilcoxon rank-sum test was used for continuous variables and X^2 test was used for categorical variables.
COPD, chronic obstructive pulmonary disease; GORD, gastro-oesophageal reflux disease; TIA, transient ischaemic attack.

Warfarin had been the only oral anticoagulant option indicated for NVAF for several decades. Since 2010, however, several new NOACs were approved for use by patients with NVAF for stroke prevention. In addition to comparable or superior prevention of stroke and comparable or reduced risk of major bleeding,[7–9] the new medications offered advantages versus warfarin that included ease of use, no requirement for routine coagulation monitoring and minimised food–drug and drug–drug interactions.[10 22 33 34]

Despite comparatively more beneficial profiles of the newer OACs relative to warfarin, this study found that 59% of newly diagnosed patients with NVAF did not receive any OAC treatment for more than 2 years (average 27 months) following their diagnosis. Among newly diagnosed patients with NVAF who were recommended OAC treatment for stroke prevention, in keeping with evidence-based guidelines (baseline $CHADS_2$ score ≥2), more than half (58%) remained untreated. Although the introduction of NOACs increased expectations of treatment rate improvement among patients with NVAF, our results indicated similar rates to those of studies conducted before the availability of NOACs.[15–18]

Warfarin was the dominant medication among newly diagnosed and treated patients even though approval of the first NOAC predated the start of our patient identification period. A combination of residual inconvenience with warfarin treatment along with a history of patient non-adherence, however, might have influenced OAC underprescribing by providers.[35] However, an apparent NOAC advantage could well limit the use of warfarin. Although the laboratory monitoring required with warfarin is largely eliminated with NOACs, patients and providers express concerns about their long-term use in the absence of regular healthcare encounters as required due to warfarin laboratory monitoring.[13 35]

In this study, no consistent relationship was found between treatment rate and baseline $CHADS_2$ score. A higher risk of stroke would imply a greater need for treatment, however highest risk for stroke category did not have the highest treatment rate. Additionally, this study also found that for both treated and untreated patients, those in the higher $CHADS_2$ score category also had a higher average $HEMORR_2HAGES$ score, suggesting that a higher risk of stroke was also associated with a higher risk of bleeding. This could complicate treatment decisions as both factors weigh heavily in treatment decision-making. A physician survey study indicated that concern about OAC-related bleeding in patients with NVAF factored strongly in decisions to not prescribe OACs.[20 33]

Table 3 Baseline medication use and provider and prescriber specialty and index OAC

Variables	Treated cohort		Untreated cohort		P values*
	n/mean	%/SD	n/mean	%/SD	
Number of patients	18549	100%	26543	100%	
Medication use other than OAC, n (%)					
Beta blockers	10207	55.00%	11339	42.70%	<0.001
Calcium channel blockers	5811	31.30%	6072	22.90%	<0.001
Diuretics	6458	34.80%	5994	22.60%	<0.001
ACE inhibitors	5279	28.50%	4774	18.00%	<0.001
Angiotensin-II receptor blockers (ARB)	2628	14.20%	2537	9.60%	<0.001
Other antihypertensives†	1589	8.60%	1430	5.40%	<0.001
Antihyperlipidaemics	9616	51.80%	9066	34.20%	<0.001
Corticosteroids	3542	19.10%	3831	14.40%	<0.001
Antidiabetics	3726	20.10%	3010	11.30%	<0.001
Antiarrhythmics‡	3530	19.00%	5162	19.50%	0.269
Ketoconazole	26	0.10%	35	0.10%	0.813
Cytochrome P450 inhibitors	45	0.20%	80	0.30%	0.243
Cytochrome P450 inducers	142	0.80%	183	0.70%	0.347
P-gp inhibitors	7951	42.90%	8956	33.70%	<0.001
P-gp inducers	145	0.80%	190	0.70%	0.423
Antiplatelets					
Clopidogrel	1861	10.00%	2262	8.50%	<0.001
Ticagrelor	6	0.00%	11	0.00%	0.624
Prasugrel	75	0.40%	115	0.40%	0.641
Ticlopidine	5	0.00%	9	0.00%	0.68
Cilostazol	115	0.60%	136	0.50%	0.131
Dipyridamole	19	0.10%	25	0.10%	0.783
Aspirin-dipyridamole	133	0.70%	124	0.50%	0.001
Other anticoagulant agents, n (%)	356	1.90%	246	0.90%	<0.001
Argatroban	0	0.00%	0	0.00%	<0.001
Unfractionated heparin (heparin)	7	0.00%	20	0.10%	0.108
Low molecular weight heparin					
Enoxaparin	328	1.80%	209	0.80%	<0.001
Tinzaparin	0	0.00%	1	0.00%	0.403
Dalteparin	10	0.10%	5	0.00%	0.044
Fondaparinux	14	0.10%	13	0.10%	0.258
Dyspepsia medications, n (%)					
Proton pump inhibitors (PPI)	3965	21.40%	4815	18.10%	<0.001
Histamine receptor antagonists (H2RAs)	683	3.70%	873	3.30%	0.024
Other gastrointestinal medication	262	1.40%	387	1.50%	0.69
Index provider specialty§, n (%)					
Cardiology	13794	74.40%	18079	68.10%	
Primary care physicians	2665	14.40%	5479	20.60%	
Other	639	3.40%	1306	4.90%	
Unknown	1451	7.80%	1679	6.30%	<0.001
The index OAC exposure, n (%)					
Apixaban	361	2.00%			

Continued

Table 3 Continued

Variables	Treated cohort n/mean	Treated cohort %/SD	Untreated cohort n/mean	Untreated cohort %/SD	P values*
Dabigatran	4407	23.80%			
Rivaroxaban	2625	14.20%			
Warfarin	11 156	60.10%			
Index prescriber specialty¶, n (%)					
Cardiology	6914	37.30%			
Primary care physicians	6028	32.50%			
Other	1587	8.60%			
Unknown	4020	21.70%			
Duration of follow-up period, mean (median)±SD, median					
Time from index date to the end of follow-up (in days)**	821 (770)	±309.5	804 (785)	±271.9	0.011

*T-test or Wilcoxon rank-sum test was used for continuous variables and X^2 test was used for categorical variables.
†Includes direct renin inhibitors, and so on.
‡Includes amiodarone HCl, propafenone and flecainide, dronedarone, sotalol (Betapace), Tikosyn, disopyramide (Norpace), quinidine.
§The specialists are mutually exclusive; primary care physicians include internal medicine, family/general practice; others include pulmonary medicine, haematology, geriatrics, surgery (all types, including vascular surgery), neurology, emergency medicine, other physician types, other non-physician specialty; for the index provider specialty, the specialty is based on the provider whom patients have seen within 90 days prior to/on the index date; if multiple providers, the hierarchy is applied as follows: cardiology, primary care physicians, others.
¶The index prescriber specialty is only available for the treated cohort.
**The follow-up period is from the index date, for a minimum of 12 months and until the end of the study period, disenrolment or death, whichever occurs first.
OAC, oral anticoagulation.

We found that a larger proportion of patients in the treated cohort had baseline cerebrovascular disease. Also, patients in the treated cohort were more likely to receive medication for other comorbid conditions at baseline. The potential for drug–drug interactions among such patients presents important challenges for continued treatment with warfarin, and may drive medication discontinuation.

Acknowledging the value of treatment continuation in chronic conditions,[26] our analysis of treatment persistence found that among patients receiving OACs, the majority of the patients initiated treatment on warfarin (60.1%). Among these patients initiating any OAC treatment, 55% discontinued their medication within 1 year, and nearly 25% within 3 months. While this result is consistent with prior findings, many earlier studies analysed medication

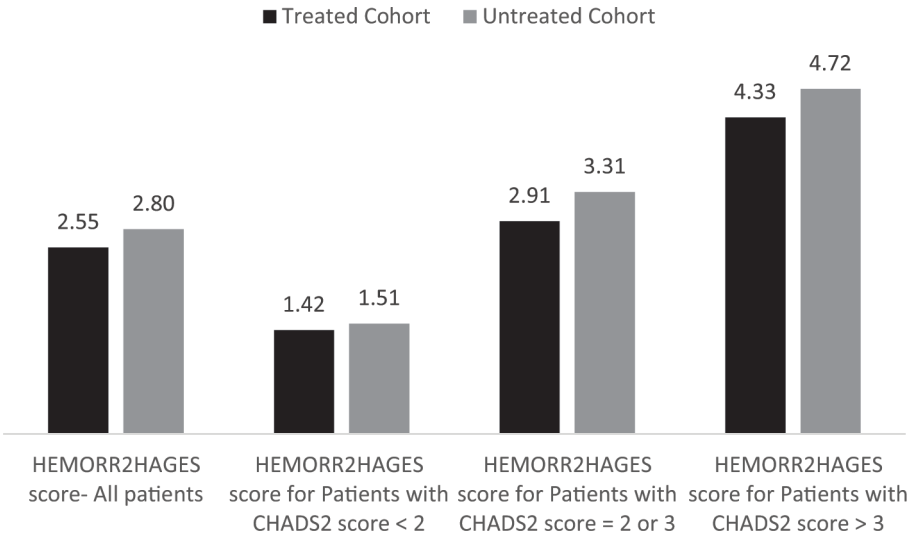

Figure 2 Baseline HEMORR$_2$HAGES score by baseline CHADS$_2$ score. Patients with non-valvular atrial fibrillation (NVAF) treated with oral anticoagulations (OAC), both overall and by all levels of CHADS$_2$ scores, had a lower bleed risk compared with those not treated by OACs as reflected by the HEMORR$_2$HAGES score (all p<0.001).

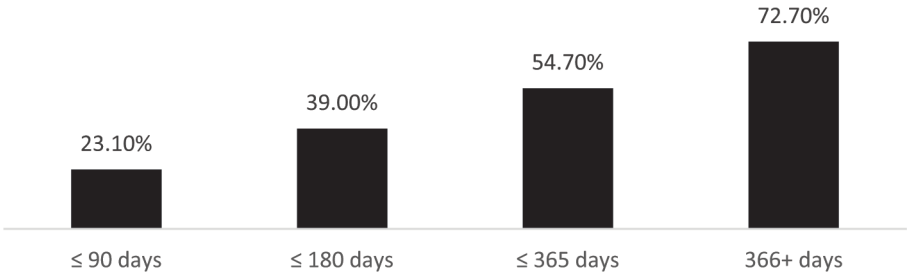

Figure 3 Proportion of discontinuation of oral anticoagulation (OAC) treatment by time after index date. Among patients with non-valvular atrial fibrillation (NVAF) treated with an OAC, discontinuation of this treatment occurred often. During the first 3 months of treatment, approximately one-quarter of patients with NVAF (23.1%) had discontinued therapy. This increased to over half (54.7%) by the 1-year mark, and almost three-quarters of patients with NVAF (72.7%) had discontinued OAC therapy by the end of the study.

persistence by individual drug, typically reporting higher discontinuation rates for warfarin relative to the NOACs.[36 37] Our results may be considered even more concerning as we did not consider switching between OACs to be a discontinuation event. The undertreatment and low persistence may, in part, be linked to the economics of the healthcare system. The average out-of-pocket cost of NOACs was nearly fivefold higher than for warfarin.[38] Additionally, the major side effect of OAC use is bleeding; access to reversal agents for the OACs may be beneficial and lack of these for some NOACs may deter some physicians from prescribing them.

The reasons underlying high undertreatment rates could be linked to the treatment decision process between physicians and patients. Physicians' attitudes, accessibility and use of evidence-based guidelines likely influence how disease is managed in patients with NVAF. In fact, evidence-based guidelines recommend the use of OACs but do not emphasise long-term treatment persistence.[39] Additionally, physicians' perceptions of patient anticoagulation adherence, barriers and challenges of NVAF management may contribute to low treatment rates. Similarly, understanding patients' perspectives on barriers associated with disease management and OAC treatment, including medication adherence/persistence and reasons for change of therapy (discontinuation/switching) and their OAC treatment experience will likely shed light on the suboptimal treatment and persistence rates observed in this study. One recent study highlighted how the physician and patient preference would influence the selection of OAC.[34] Insights into physician and patient's perceptions are key to implementing interventions that could maximise the utility of OACs in the NVAF population.

Limitations

These results should be assessed within the context that the secondary data used in this study were repurposed for research from their original transactional role. As a result, these administrative claims data do not have information on over-the-counter medications (ie, low-dose aspirin), which could have been purchased independently by patients, and may have overestimated the number of untreated patients due to unobservable low-dose aspirin use. Other important clinical information, such as disease severity and reasons of not starting treatment or discontinuation of treatment, is not available from the data source. Similar to any other studies using administrative data, identification of AF using ICD-9-CM diagnosis code might have included false positives. A previously published systematic review showed the positive predicted value of ICD-9 427.31 ranges from 70% to 96% (median 89%).[28] In addition, the requirement of two or more AF diagnosis on different dates in this study would minimise chances of false positives. Also, the presence of a claim for a filled prescription does not indicate that the medication was consumed. In addition, the study results may not be generalisable to the overall population, as patients who have commercial health insurance/Medicare Advantage may have different healthcare considerations from those with other types of health insurance or are uninsured. The results and implications may not be generalisable to other countries as well, as other countries may have different drug coverage and/or different cost-sharing structure.

CONCLUSION

This study found that nearly 60% of patients with NVAF recommended for OAC treatment for stroke prevention per evidence-based guidelines were not receiving treatment. Additionally, among the treated cohort, more than a half of the patients discontinued their treatment within 1 year. As the risk of stroke increased, the risk of bleeding increased as well, suggesting that bleeding risk may be a critical component in OAC treatment decision and may have contributed to lower treatment rates. The initiation and persistence with OAC therapy among newly diagnosed patients with NVAF in this real-world population appear to face challenges. Future research is important to better understand the drivers of low OAC initiation and persistence to optimise the potential benefits of OACs in stroke prevention among the increasing population of patients with NVAF.

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