Research Article

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Discontinuation and primary care visits in nonvalvular atrial fibrillation patients treated with apixaban or warfarin

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Aim: Nonvalvular atrial fibrillation (NVAF) requires long-term anticoagulation treatment, which may necessitate frequent primary care visits. **Materials & methods:** NVAF patients initiating warfarin or apixaban in 2012–2017 were identified from linked primary (Clinical Practice Research Datalink) and secondary care (Hospital Episode Statistics) data. A propensity score matched Cox regression model compared discontinuation risk. Primary care visits were compared via negative binomial regression. **Results:** A total of 2695 apixaban users were matched to warfarin patients. Discontinuation risk was lower with apixaban than warfarin (hazard ratio: 0.40; 95% CI: 0.35–0.46). Apixaban patients averaged 12.2 annual primary care visits, versus 17.1 for warfarin users ($p < 0.001$). **Conclusion:** Apixaban was associated with reduced rates of discontinuation and primary care visits compared with warfarin.

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Keywords: NVAF • oral anticoagulants • treatment persistence

Nonvalvular atrial fibrillation (NVAF) is a chronic condition and major contributor to cardiovascular disease morbidity and mortality. The risk of stroke in NVAF patients is five-times that of the general population [1]. Anticoagulation treatments have a well-established body of randomized controlled trial evidence supporting their effectiveness in reducing the risk of stroke in patients with NVAF [2]. Formerly, treatment with warfarin and other vitamin K antagonists (VKAs) was recommended to reduce the risk of stroke among patients with NVAF. However, to prevent serious side effects such as bleeding, patients treated with warfarin require regular coagulation monitoring to ensure they remain within the therapeutic range. Nonvitamin K antagonist oral anticoagulants (NOACs), including apixaban, are becoming the preferred treatment for NVAF; this was demonstrated in a recent retrospective study – conducted in the UK's Clinical Practice Research Datalink (CPRD) database – that reported that a decreasing percentage of NVAF patients initiated VKAs (from 50.8 to 31.8%) from 2012 to 2016 and an increasing percentage initiated NOACs (from 9.8 to 40.6%, including 16.6% apixaban) [3]. This evidence coincided with the National Institute for Health and Care Excellence (NICE) 2014 guidance, which emphasized the role of NOACs as an alternative to VKAs and addressed some of the limitations of VKAs [4].

NOACs, unlike warfarin, do not require routine coagulation monitoring, making treatment simpler and potentially more convenient for patients. These characteristics may improve treatment adherence and reduce the need for frequent medical visits. Initial assessment of NOAC use in real-world clinical practice in the UK suggested that apixaban was associated with higher rates of treatment persistence [5]. However, apixaban had recently gained market authorization at the time of the analyses, limiting the period within which their use could be evaluated.

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Furthermore, the analysis did not utilize linkage between primary and secondary care data, potentially missing hospital diagnoses or procedures that may be important for identifying NVAF and relevant comorbidities, nor did it assess primary care visit frequency [6,7]. Recent data from the USA suggest that apixaban is associated with reduced medical costs compared with warfarin [8]. However, information on the frequency of general practitioner (GP) and nurse visits among NVAF patients in the UK is lacking.

This study aimed to provide up-to-date estimates of the real-world treatment patterns and primary care visit frequency of NVAF patients treated with apixaban or warfarin in England using linked primary and secondary care data.

Materials & methods

Data source

We obtained primary care data from the CPRD, which was linked to Inpatient and Outpatient Hospital Episode Statistics (HES) and mortality data from the Office for National Statistics (ONS) [9]. The CPRD contains longitudinal data from real-life general practices, and HES contains diagnoses and procedural information from the secondary care setting. This study was reviewed by the Independent Scientific Advisory Committee (ISAC) and received approval (study protocol 17_188).

Study design

The study employed a retrospective cohort study design. Patients were included based on the presence of a diagnosis of atrial fibrillation (AF) and incident treatment with warfarin or apixaban between 1 December 2012 and 1 July 2017. AF was categorized as nonvalvular based on the absence of diagnostic codes indicating mitral stenosis or a procedural code for mechanical heart valve replacement. Patients were required to be aged ≥18 years and have at least 1 year of baseline data prior to index. Additional exclusion criteria are shown in Figure 1.

The index date was the date of the first prescription of either warfarin or apixaban during the study period, and patients were classified into treatment groups based on their index prescription. Patients were followed from index to the earliest of the following: date of death, date of patient transfer out of the general practice, end date of data contribution from the practice or end date of the data extract (31 July 2017).

Study measures

The study focused on the first continuous treatment episode. Days of supply of treatment were estimated using information on the number of prescriptions and the prescribed dosage recorded in CPRD. In the absence of dosage information, the median time between sequential prescriptions was assigned as the estimated days of supply. A gap of 60 days or fewer between the end of days of supply of one prescription and the next was ignored and counted as a continuous treatment episode; this was to account for the real-world setting and potential delays in gaining a repeat prescription. Treatment discontinuation was defined as no new prescription of the index medication within 60 days after the end of the estimated days of supply. A switch was defined as a treatment discontinuation and start of a new oral anticoagulant within 60 days after the end date of the prior treatment.

Statistical analyses

Propensity score (PS) matching was used to control for potential cofounding factors. The PS was estimated using a logistic regression model that included age, gender, ethnicity, quintile of socioeconomic deprivation (multiple deprivation index [MDI]) [10], body mass index (BMI), smoking status, alcohol intake, Charlson comorbidity score [11], HAS-BLED score [12], CHA_2DS_2-VASc score [13], prevalent hypertension and history of bleeding. Patients treated with apixaban were matched 1:1 to warfarin patients using the 'nearest neighbour' technique and by enforcing a calliper of 0.2-times the standard deviation of the logit of the PS.

Additional baseline variables examined that were considered potential confounders of the treatment outcome association included year of index date, time from NVAF diagnosis to index date, baseline hospitalizations and use during the prior year of proton pump inhibitors, antibiotics, antiplatelets, antidepressants, anticonvulsants (phenytoin or carbamazepine), systemic corticosteroids, nonsteroidal anti-inflammatory drugs, statins and hormones. Demographics and clinical characteristics were described using frequencies and percentages for categorical variables, and median and interquartile range for continuous variables. Characteristics were compared between matched apixaban and warfarin patients using standardized differences.

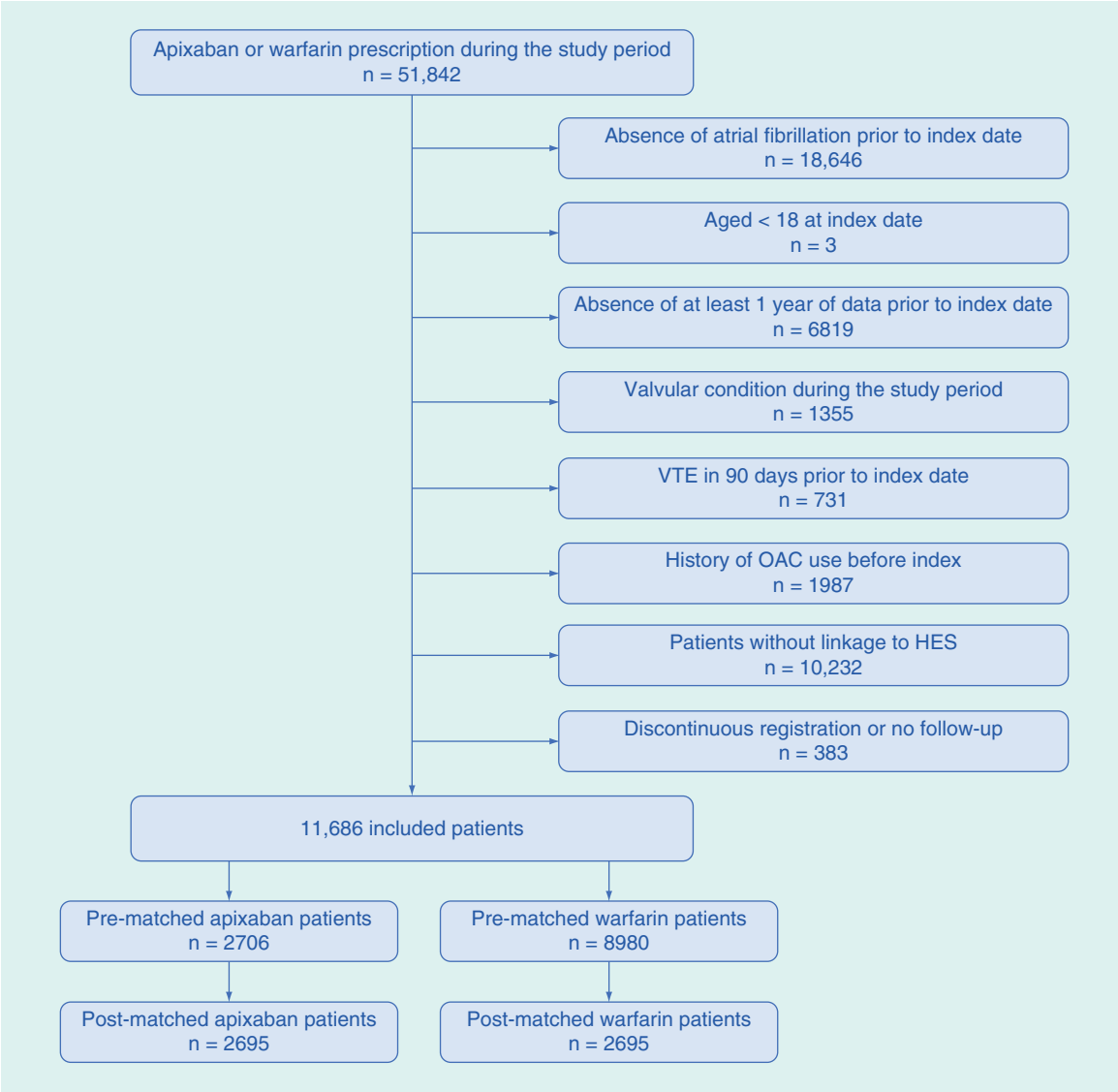

Figure 1. A flow chart of inclusion/exclusion criteria.
HES: Hospital episode statistics; OAC: Oral anticoagulant; VTE: Venous thromboembolism.

As apixaban was newly approved at the start of the study period, and market uptake was expected to occur gradually over the first few years, it was expected that warfarin users would have longer follow-up time available. To account for this pattern, in addition to adjusting for year of index date, the number and proportion of patients who discontinued treatment at each 3-month point after index, and those who switched therapies, were calculated among patients still under follow-up at each timepoint.

A Kaplan–Meier plot of time to discontinuation was created for the PS-matched patients, censoring at 60 days before the end of follow-up for patients still on treatment within 60 days prior to end of follow-up. Nonparametric log-rank tests compared time to discontinuation between treatment groups, and a Cox proportional hazards model estimated the relative risk of treatment discontinuation for apixaban versus warfarin. The Cox model adjusted for any baseline variable that differed between groups after matching by a standardized difference of >0.05.

The rate of primary care visits per patient-year was defined as the total number of GP or nurse visits during the first continuous treatment episode, divided by the time at risk (i.e., continuous time on treatment). A negative binomial model compared primary care visit rates between treatment groups; covariates were the same as in the model of treatment discontinuation.

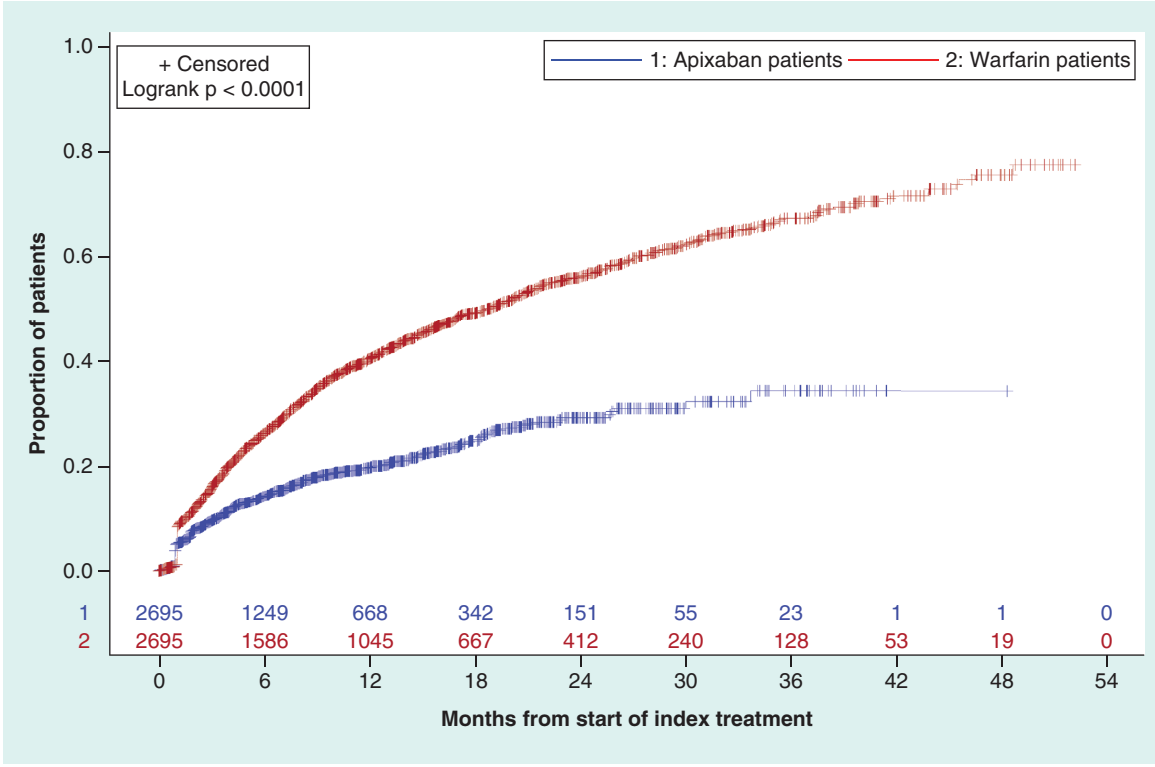

Figure 2. Cumulative incidence of discontinuation among propensity score-matched (unadjusted) apixaban and warfarin users. The plot shows the numbers of patients at risk of treatment discontinuation at each 6-month interval.

Results

A total of 8980 warfarin patients and 2706 apixaban patients fulfilled all inclusion and no exclusion criteria for this study (Figure 1). Of these, 2695 (>99%, 2695/2706) apixaban patients were successfully matched to a patient treated with warfarin.

Baseline characteristics

Many patient characteristics differed between the treatment groups prior to matching, but the PS matching was generally successful in creating balanced groups (Table 1). The prevalence of potential confounding factors appeared well balanced, with standardized differences all <0.10 for variables included in the PS, but age groups, year of index date and several individual comorbidities demonstrated sufficient imbalance (standardized difference >0.05) to warrant further adjustment in outcome models. The most prevalent comorbidities at baseline were hypertension, cerebrovascular disease, congestive heart failure and renal disease. More than a third of patients in both cohorts had history of bleeding (major or clinically relevant nonmajor) recorded. The median follow-up time was shorter in apixaban than warfarin patients (median: 265 days vs 580 days, respectively; $p < 0.001$).

Outcomes

Kaplan–Meier estimates indicated that patients treated with apixaban persisted on treatment for longer than warfarin patients (Figure 2, log rank $p < 0.001$). The adjusted Cox model estimated that apixaban treatment was associated with a 60% reduction in the risk of treatment discontinuation compared with warfarin (hazard ratio [HR]: 0.40; 95% CI: 0.36–0.46; $p < 0.001$).

Discontinuation and switching patterns in subgroups of patients who remained under follow-up at 3-month intervals for the first year after the index date are shown in Table 2. At 3 months, 9.1% of apixaban patients who were still under follow-up had discontinued treatment compared with 15.5% in matched warfarin patients. The same values were 13.4 and 25.8% at 6 months and 19.2 and 38.7% at 12 months, respectively.

Table 1. Baseline characteristics in prematch and postmatched patients.

Characteristics	Prematch			Postmatch		
	Apixaban (N = 2706)	Warfarin (N = 8980)	Standardized difference	Apixaban (N = 2695)	Warfarin (N = 2695)	Standardized difference
Female, N (%)	1272 (47.0)	3944 (43.9)	-0.0620	1263 (46.9)	1236 (45.9)	-0.0201
Age at index (years), median (IQR)	78 (70–85)	76 (69–83)	0.0734	78 (70–85)	78 (71–84)	0.0092
Ethnicity, N (%)						
– White	2510 (92.8)	8356 (93.1)	-0.0620	2500 (92.8)	2488 (92.3)	-0.0201
– Black	19 (0.7)	49 (0.5)		19 (0.7)	24 (0.9)	
– Asian	21 (0.8)	84 (0.9)		21 (0.8)	25 (0.9)	
– Mixed	5 (0.2)	12 (0.1)		5 (0.2)	5 (0.2)	
– Other	19 (0.7)	63 (0.7)		18 (0.7)	20 (0.7)	
– Unknown	132 (4.9)	416 (4.6)		132 (4.9)	133 (4.9)	
Social deprivation, N (%)						
– 1 (least deprived)	766 (28.3)	2151 (24.0)	-0.0620	758 (28.1)	784 (29.1)	-0.0201
– 2	635 (23.5)	2168 (24.2)		634 (23.5)	623 (23.1)	
– 3	535 (19.8)	1912 (21.3)		534 (19.8)	563 (20.9)	
– 4	418 (15.4)	1608 (17.9)		418 (15.5)	419 (15.5)	
– 5 (most deprived)	352 (13.0)	1137 (12.7)		351 (13.0)	306 (11.4)	
BMI in the 12 months prior, median (IQR)	27.6 (24.1–31.8)	28.3 (25–32.4)	-0.0620	27.6 (24.1–31.9)	27.6 (24.1–31.8)	-0.0201
Days from NVAF diagnosis to index date, median (IQR)	47 (14–864)	51 (16–391)	0.1206	46 (14–859)	54 (17–413)	0.1105
Smoking status, N (%) among patients with data						
– Current	180 (6.8)	690 (7.8)	-0.0620	180 (6.8)	191 (7.2)	-0.0201
– Past	1395 (52.4)	4638 (52.2)		1394 (52.5)	1352 (51.0)	
– Never	1088 (40.9)	3555 (40.0)		1081 (40.7)	1110 (41.8)	
Alcohol intake in the 12 months prior, N (%) among patients with data						
– Nondrinker (0 units per day)	280 (28.7)	913 (27.3)	-0.0620	279 (28.7)	305 (31.7)	-0.0201
– Light drinker (>0 to <3 units per day)	519 (53.2)	1844 (55.2)		518 (53.2)	494 (51.4)	
– Moderate drinker (≥3 to <7 units per day)	71 (7.3)	239 (7.2)		71 (7.3)	67 (7.0)	
– Heavy drinker (≥7 units per day)	46 (4.7)	155 (4.6)		46 (4.7)	43 (4.5)	
– Drinker whose category is unknown	59 (6.1)	188 (5.6)		59 (6.1)	52 (5.4)	
Hospitalized in year up to index date, N (%)	1481 (54.7)	4149 (46.2)	0.1501	1472 (54.6)	1334 (49.5)	0.0834
Charlson comorbidity index, N (%)						
– <2	1348 (49.8)	4787 (53.3)	0.0807	1347 (50.0)	1316 (48.8)	-0.014
– ≥2	1358 (50.2)	4193 (46.7)		1348 (50.0)	1379 (51.2)	
Comorbidities, N (%)						
– Myocardial infarction	454 (16.8)	1357 (15.1)	0.0455	450 (16.7)	411 (15.3)	0.0395
– Congestive heart failure	738 (27.3)	2409 (26.8)	0.0101	730 (27.1)	820 (30.4)	-0.0738
– Peripheral vascular disease	328 (12.1)	1078 (12.0)	0.0036	323 (12.0)	384 (14.2)	-0.0671
– Cerebrovascular disease	791 (29.2)	1693 (18.9)	0.2447	782 (29.0)	676 (25.1)	0.0886
– Dementia	152 (5.6)	208 (2.3)	0.1697	150 (5.6)	72 (2.7)	0.1460
– Chronic pulmonary disease	564 (20.8)	1945 (21.7)	-0.02	563 (20.9)	588 (21.8)	-0.0226
– Rheumatic disease	156 (5.8)	416 (4.6)	0.051	156 (5.8)	142 (5.3)	0.0227
– Peptic ulcer disease	236 (8.7)	627 (7.0)	0.0647	234 (8.7)	203 (7.5)	0.0422
– Mild liver disease	46 (1.7)	117 (1.3)	0.0327	46 (1.7)	37 (1.4)	0.0269

NB: Patient groups <5 are not reported.
BMI: Body mass index; CHA_2DS_2-VASc: Congestive heart failure (or left ventricular systolic dysfunction); hypertension; age ≥75 years; diabetes mellitus; prior stroke, TIA, or thromboembolism; vascular disease; age 65–74 years; sex category; CRNM: Clinically relevant nonmajor; HAS-BLED: Hypertension; abnormal renal and liver function; stroke; bleeding; labile INR; elderly; drugs or alcohol; IQR: Interquartile range; NSAID: Nonsteroidal anti-inflammatory drug; NVAF: Nonvalvular atrial fibrillation.

Table 1. Baseline characteristics in prematch and postmatched patients (cont.).

Characteristics	Prematch			Postmatch		
	Apixaban (N = 2706)	Warfarin (N = 8980)	Standardized difference	Apixaban (N = 2695)	Warfarin (N = 2695)	Standardized difference
– Diabetes without chronic complications	392 (14.5)	1219 (13.6)	-0.0142	387 (14.4)	347 (12.9)	0.0411
– Diabetes with chronic complications	174 (6.4)	609 (6.8)	0.0256	173 (6.4)	197 (7.3)	-0.0352
– Hemiplegia or paraplegia	82 (3)	124 (1.4)	0.1125	80 (3.0)	49 (1.8)	0.0753
– Renal disease	816 (30.2)	2571 (28.6)	0.0335	810 (30.1)	861 (31.9)	-0.0409
– Malignancy	471 (17.4)	1496 (16.7)	0.0199	470 (17.4)	473 (17.6)	-0.0029
– Moderate or severe liver disease	16 (0.6)	59 (0.7)	-0.0083	16 (0.6)	24 (0.9)	-0.0346
– Metastatic solid tumor	56 (2.1)	164 (1.8)	0.0176	56 (2.1)	54 (2.0)	0.0052
– History of major or CRNM bleeding	1042 (38.5)	3191 (35.5)	0.0616	1031 (38.3)	1010 (37.5)	0.0161
– Prevalent hypertension	2537 (93.8)	8390 (93.4)	0.0133	2526 (93.7)	2534 (94.0)	-0.0124
Medications used in year up to index date, N (%)						
– Proton pump inhibitors	1274 (47.1)	3995 (44.5)	0.0521	1269 (47.1)	1227 (45.5)	0.0313
– Antibiotics	291 (10.8)	873 (9.7)	0.0341	288 (10.7)	287 (10.6)	0.0012
– Antiplatelets	453 (16.7)	1251 (13.9)	0.078	451 (16.7)	439 (16.3)	0.0120
– Antidepressants	289 (10.7)	850 (9.5)	0.0404	288 (10.7)	258 (9.6)	0.0369
– Anticonvulsants (phenytoin or carbamazepine)	15 (0.6)	80 (0.9)	-0.0397	15 (0.6)	19 (0.7)	-0.0187
– Corticosteroids	424 (15.7)	1460 (16.3)	-0.0161	424 (15.7)	428 (15.9)	-0.0041
– NSAIDs	349 (12.9)	1298 (14.5)	-0.0453	348 (12.9)	401 (14.9)	-0.0569
– Statins	1558 (57.6)	4843 (53.9)	0.0734	1552 (57.6)	1473 (54.7)	0.0591
– Hormones	69 (2.5)	176 (2.0)	0.0397	69 (2.6)	50 (1.9)	0.0480
CHA_2DS_2-VASc score, N (%)						
– <2	139 (5.2)	573 (6.4)	-0.0620	139 (5.2)	130 (4.8)	-0.0201
– ≥2	2567 (94.8)	8407 (93.6)		2556 (94.8)	2565 (95.2)	
HAS-BLED score, N (%)						
– <3	808 (29.9)	2739 (30.5)	0.1384	806 (29.9)	791 (29.4)	0.0206
– ≥3	1898 (70.2)	6241 (69.5)		1889 (70.1)	1904 (70.6)	

NB: Patient groups <5 are not reported.
BMI: Body mass index; CHA_2DS_2-VASc: Congestive heart failure (or left ventricular systolic dysfunction); hypertension; age ≥75 years; diabetes mellitus; prior stroke, TIA, or thromboembolism; vascular disease; age 65–74 years; sex category; CRNM: Clinically relevant nonmajor; HAS-BLED: Hypertension; abnormal renal and liver function; stroke; bleeding; labile INR; elderly; drugs or alcohol; IQR: Interquartile range; NSAID: Nonsteroidal anti-inflammatory drug; NVAF: Nonvalvular atrial fibrillation.

The rate of primary care visits (GP or nurse visits) was 12.2 per person-year in apixaban patients compared with 17.1 per person-year in warfarin patients. The adjusted negative binomial model estimated a 31.7% (95% CI: 27.6–35.6) lower rate of visits for apixaban users compared with warfarin ($p < 0.001$).

Discussion

In this retrospective cohort study of treatment patterns in NVAF patients, we found evidence that those treated with apixaban had a lower risk of discontinuation compared with warfarin-treated patients. In patients with NVAF, treatment persistence with anticoagulants is important in reducing the risk of stroke. The results of our study are in line with early findings following the initial release of NOACs in the UK, which suggested NVAF patients were more likely to remain persistent on treatment with apixaban compared with warfarin [5]. In this early analysis, 88.2% (95% CI: 84.5–91.3) of NVAF patients remained persistent at 6 months of treatment, an estimate that is very similar to this study (86.6%).

Persistence with anticoagulation therapy is essential, as stopping treatment can put patients at high risk of thromboembolic events [14]. For example, in a study conducted in the Truven MarketScan claims database [15], warfarin patients who discontinued treatment for 45 days or longer had higher rates of ischemic stroke (HR: 2.04; 95% CI: 1.47–2.84) and transient ischemic attack (HR: 1.36; 95% CI: 1.04–1.78) compared with those who

Table 2. Discontinuation and switching in subgroups of patients with 3, 6, 9 and 12 months of follow-up.

Patient subgroup and outcome		Apixaban (N = 2695)	Warfarin (N = 2695)
Patients with 3 months follow-up		2163 (80.3)	2489 (92.4)
Persistence during first 3 months	Persistence	1966 (90.9)	2104 (84.5)
	Discontinuation	197 (9.1)	385 (15.5)
	Switch†	48 (24.4)	69 (17.9)
Patients with 6 months follow-up		1712 (63.5)	2265 (84)
Persistence during first 6 months	Persistence	1483 (86.6)	1681 (74.2)
	Discontinuation	229 (13.4)	584 (25.8)
	Switch†	50 (21.8)	102 (17.5)
Patients with 9 months follow-up		1318 (48.9)	2070 (75.8)
Persistence during first 9 months	Persistence	1098 (83.3)	1370 (66.2)
	Discontinuation	220 (16.7)	700 (33.8)
	Switch†	45 (20.5)	122 (17.4)
Patients with 12 months follow-up		1004 (37.3)	1852 (68.7)
Persistence during first 12 months	Persistence	811 (80.8)	1135 (61.3)
	Discontinuation	193 (19.2)	717 (38.7)
	Switch†	41 (21.2)	117 (16.3)

NB: Cell entries are n (%).
†The denominator for % with switch is the number of patients who discontinued at that time point.

persisted on treatment. Similarly, a study conducted in the United States Veterans Affairs database found that lower adherence to dabigatran was associated with increased all-cause mortality and stroke (HR 1.13; 95% CI: 1.07–1.19) [16].

The present study found that the frequency of visits to primary care (GP or nurse visits) was reduced in patients treated with apixaban compared with warfarin. These findings are likely related to the requirement of warfarin patients to undergo blood testing for regular monitoring of coagulation levels. Such monitoring is not required for patients treated with NOACs, which appears to translate into substantially fewer primary care visits.

A recent network meta-analysis of randomized trials provides further evidence related to the net benefit associated with NOAC treatment [17]. This analysis of 23 randomized trials found that all NOACs were associated with improved efficacy, safety and cost–effectiveness relative to warfarin. Apixaban was found to have the greatest cost–effectiveness of the NOACs studied.

When interpreting the results of this study, it should be noted that the average available follow-up time from index in the warfarin treatment group was over twice as long compared with apixaban users. The differing follow-up time is likely because of the slow uptake of apixaban in the UK after approval [18]. The analyses accounted for the different durations of follow-up through restricted time-point analysis of discontinuation and through examining rates of primary care visits per year of follow-up and only during the first treatment episode.

Although this study included a large population that reflected real-world prescribing patterns, there are some limitations that should be acknowledged. As with all observational analyses, unmeasured differences in the characteristics of treatment groups may have introduced bias to our findings. Treatment persistence was estimated from prescription data and may be inaccurate; prescriptions received may not have been filled and taken as prescribed. Warfarin exposure dates are especially subject to error, as prescription details were often missing. Reasons for treatment discontinuation were not available in the database. Still, the study is strengthened by its large representative sample and through its use of linked electronic medical records from general practice and hospital data, which allowed us to obtain a comprehensive cohort of NVAF patients.

Conclusion

The findings from this study suggest that NVAF patients are less likely to discontinue treatment when prescribed apixaban compared with warfarin. In the primary care setting, visit frequency was reduced in NVAF patients treated with apixaban. Our findings suggest apixaban is associated with improved treatment persistence and reduced primary care visit rates.

Summary points

- Patients with nonvalvular atrial fibrillation need long-term treatment with anticoagulants to reduce the risk of stroke.
- Treatment may comprise warfarin or nonvitamin K antagonist oral anticoagulants (NOACs) such as apixaban.
- Frequent blood monitoring is required for warfarin but not for NOACs, and may lead to higher frequency of visits to primary care providers.
- This retrospective cohort study was conducted using linked primary and secondary care data from England.
- Patients initiating warfarin or apixaban in 2012–2017 were followed through the data to estimate time to discontinuation and annual rates of primary care visits.
- Because patients may be preferentially prescribed one drug rather than another based on various characteristics, propensity score matching was used to create balanced groups.
- Apixaban users showed a 60% reduced risk of treatment discontinuation than warfarin users, indicating longer continuous exposure to the recommended preventive therapy.
- Rates of primary care visits were 32% lower in apixaban than warfarin users.

Author contributions

All authors met the four standards for Authorship Credit as published in the Future Science Group Author Disclosure Form, and contributed sufficiently to the work to take responsibility for the article content.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This retrospective study was reviewed and approved by the Independent Scientific Advisory Committee (ISAC).

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