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Warfarin vs. apixaban in nonvalvular atrial fibrillation, and analysis by concomitant antiarrhythmic medication use: A national retrospective study

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Abstract

Background: No real-world data exist on outcomes in patients on anticoagulants and concomitant antiarrhythmic medications. This study aims to compare the safety and effectiveness of apixaban and warfarin, first in patients with nonvalvular atrial fibrillation (NVAF) and then in patients on concurrent antiarrhythmic medications.

Methods: A retrospective cohort study was conducted using a large US electronic medical record database (2012-2016). Patients with NVAF on warfarin or apixaban were included. The primary endpoint was a composite of stroke (ischemic or hemorrhagic) or systemic embolism. The primary safety endpoint was major bleeding (ISTH definition). Patients were matched using propensity scoring. Univariate survival analyses were conducted by using the log-rank test and Kaplan-Meier survival curves. A subgroup analysis was conducted to assess outcomes on patients on concurrent antiarrhythmic medications.

Results: A total of 332 100 patients with NVAF were identified, and 20 378 were included in the propensity-matching analysis. No baseline differences were seen in age, comorbidities, or CHA_2DS_2-VASc score. The primary endpoint occurred in 122 (1.2%) patients on apixaban compared to 166 (1.63%) on warfarin (hazard ratio, 0.84; 95% confidence interval [CI], 0.79-0.88). Major bleeding occurred at a lower rate in the apixaban group (n = 600, 5.89%) compared to warfarin (n = 887, 8.71%) (odds ratio, 0.65; 95% CI, 0.58-0.73). In patients on concurrent antiarrhythmic medications (n = 2498), there was no difference in thrombotic (1.04% vs. 1.37%; P = 0.42) or bleeding events (5.29% vs. 6.89%; P = 0.08).

Conclusion: Apixaban was associated with reduced stroke/systemic embolism and bleeding when compared with warfarin. No difference was seen in thrombotic or bleeding events in patients on concurrent antiarrhythmic medications.

KEYWORDS

anticoagulation, atrial fibrillation, bleeding, apixaban, stroke, warfarin

Essentials

- No real-world data exist in patients on anticoagulants and concomitant antiarrhythmic drugs.
- A retrospective cohort study was conducted using a US electronic medical record database (2012-2016).
- A total of 20 378 patients were included in this propensity matched analysis.
- There was no difference in thrombosis or bleeding in patients on concurrent antiarrhythmic medications.

1 | BACKGROUND

Atrial fibrillation (AF) is the most common arrhythmia in the United States. It is characterized by rapid and disorganized atrial activity increases the risk of heart failure (HF) and stroke, and reduce quality of life.[1] The risk of stroke increases up to 20-fold in patients with AF compared to those in sinus rhythm.[2] Optimizing anticoagulant therapy in patients with AF is essential to reduce the risk of thromboembolic events and improve quality of life. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines for the Management of Patients With Atrial Fibrillation recommend that the CHA_2DS_2-VASc score be used to assess stroke risk and guide choice of anticoagulant therapy.[3] For patients with risk factors such as congestive HF, diabetes mellitus, or previous stroke, warfarin or a direct oral anticoagulant (DOAC), such as dabigatran, rivaroxaban, or apixaban (guideline recommendation 1A and 1B, respectively) is recommended. However, the choice of anticoagulation is not a one-size-fits-all approach. Other factors such as renal and hepatic function, ability to maintain a therapeutic international normalized ratio, availability of a reversal agent, bleeding risk, and food and drug interactions must be considered when choosing the most appropriate agent for stroke prevention in AF.

Strategies to control symptoms from AF and prevent cardiac remodeling and hypertrophy include rate and/or rhythm control agents.[3] Rate control agents have similar outcomes on hospitalizations and mortality compared to rhythm control agents, with fewer side effects.[4] Patients often require the addition of rhythm control agents (also known as antiarrhythmic drugs) when symptoms become intolerable or the patient's heart rate cannot be adequately controlled with rate control agents. Many rhythm control agents have the potential for significant drug-drug interactions with oral anticoagulants and thus make management difficult.

Several pharmacokinetic studies have shown varying results about in vitro interactions with oral anticoagulants.[5–14] Most oral anticoagulants are primarily metabolized via multiple cytochrome P450 (CYP) enzymes and/or P-glycoprotein and may be susceptible to drug-drug interactions. A pharmacokinetics study by Wang and

colleagues[5] showed the metabolic drug-drug interaction potential between apixaban and other coadministered medications is low. In contrast, other studies have shown that coadministration of apixaban with either strong CYP3A4 inhibitors (diltiazem and ketoconazole) or drugs that increase its bioavailability may cause up to a 2-fold increase in the area under the curve of apixaban.[6,7] Similar concerns exist with warfarin. Two studies have demonstrated that administration of amiodarone, a potent CYP3A4 inhibitor, with warfarin reduced the clearance of warfarin.[8,9] The clinical significance of this interaction with DOACs warrants further assessment.

To date, no real-world data exist on clinical outcomes of concurrent use of apixaban and concomitant antiarrhythmic drugs. A subgroup analysis from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial evaluated patients in both study groups (warfarin or apixaban) on concomitant amiodarone and found a similar rate of thromboembolic events (1.24%/year for apixaban vs. 1.85%/year for warfarin; hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.40-1.15) but a higher rate of major bleeding events (2.18%/year for apixaban vs. 3.03%/year for warfarin; HR, 0.72; 95% CI, 0.62-0.84).[15] A separate subgroup analysis, however, showed no significant difference in both rates of thromboembolic events and major bleeding events in either group.[16] Another subgroup analysis demonstrated an increased risk of thromboembolic events and major bleeding with increased number of concomitant medications in both warfarin and apixaban groups.[17] However, apixaban was still more effective as compared to warfarin, while in terms of major bleeding, its benefits decreased with increasing number of concomitant drugs. A study in Taiwan found an increased bleeding risk in patients with nonvalvular atrial fibrillation (NVAF) taking a DOAC along with amiodarone, fluconazole, rifampin, or phenytoin (medications with a common metabolic pathway) compared to a DOAC alone.[18]

Several pivotal comparative studies demonstrated the superiority or noninferiority of DOACs over warfarin. However, none of these studies have addressed the safety and effectiveness outcomes of concomitant rhythm control agents. With the high prevalence of AF patients on antiarrhythmic medications, specifically amiodarone,

patients on warfarin may be at risk of worse outcomes compared to patients on apixaban. With 2.5 million Americans suffering from AF, of which 20% receive a concurrent antiarrhythmic medication, this represents a large portion of patients on high-risk pharmacotherapy.[19] Using a large national electronic medical record (EMR) database of patients, this study aimed to compare the safety and effectiveness of apixaban and warfarin, first in patients with NVAF and then in patients on concomitant antiarrhythmic medications.

2 | METHODS

2.1 | Data source, study design, and sample

The GE Centricity EMR database is a real-world observational, daily-updated and nationally representative clinical database, rich in information on millions of patients in the United States. It is used by >20 000 clinicians and contains longitudinal ambulatory electronic health data for >7.4 million patients, including demographic data, vital signs, laboratory orders and results, medication list entries and prescriptions, and diagnoses or problems. A variety of practice types are represented in the database, ranging from primary care practitioners to community clinics, academic medical centers, and large integrated health care networks. Both medications and prescriptions are documented in the database. The data are deidentified in accordance with Health Insurance Portability and Accountability Act standards and requirements.

This study was a retrospective cohort study using data from the GE EMR database from January 1, 2012, through December 31, 2016. Patients were included if they were aged 18 years or older with a diagnosis of NVAF and receiving either warfarin or apixaban. An index date was identified for each patient, defined as the date of the first prescription claim for apixaban or warfarin during 2013-2015. The patients were followed for 1 year from the index date, allowing follow-up through 2016. A washout period for each patient was defined as not receiving any prescription of apixaban or warfarin (or other DOAC) for 1 year prior to the index date. Incident and prevalent users were identified using the washout period. Inclusion criteria required patients to be continuously enrolled 1 year before and 1 year after the index date, defined as patients having at least 1 office visit in the 12 months prior to index date and in the 12 months after the study.

Patients were excluded from the study if they were pregnant, had valvular heart disease, venous thromboembolism, cardiac surgery, pericarditis, or thyrotoxicosis within the 12 months prior to the index date. Additionally, patients were excluded if they used rivaroxaban, edoxaban, or dabigatran during the study period.

The primary independent variable was prescription of either apixaban or warfarin. The primary outcome variables were efficacy and safety. The primary efficacy endpoint was identified using *International Classification of Diseases*, *Ninth Revision* (ICD-9) or *10th Revision* (ICD-10) codes for stroke (ischemic or hemorrhagic) or systemic embolism during the follow-up period. The primary safety outcome was identified using ICD-9 and ICD-10 codes for bleeding

during the follow-up period. It was defined as symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of ≥2 g/dL or leading to transfusion of ≥2 units of whole blood or red cells (International Society of Thrombosis and Hemostasis definition).

2.2 | Statistical analysis

Descriptive statistics were provided for baseline sample characteristics. T test and chi-square were performed to assess the group difference for continuous and categorical variables, respectively. One-to-one propensity score matching was conducted to reduce the impact of treatment-selection bias. McNemar chi-square test for the matched-pair cohort was performed to assess the association between treatment exposure and risk of bleeding for the 1-year follow-up period.

A Cox proportional hazards model was used to compare the risk of stroke for patients taking apixaban vs. warfarin in the propensity score matched cohort. In the Cox proportional hazards model, outcome was defined as time to the first event of stroke. Patients who discontinued their initial index medication or switched to another anticoagulant medication (defined as 90 days with no prescription or a new prescription for rivaroxaban, edoxaban, or dabigatran) or did not experience the event of stroke during the follow-up period were censored at the time of discontinuation, switch, and the end of the follow-up period. Baseline variables that were not balanced after matching and treatment exposure were included in the Cox regression model. Covariates, measured over the 1-year baseline period prior to index date or at the index date, that were included in the propensity score matching included patient age, gender, physician specialty, geographic region, major comorbidities (such as hypertension, HF, diabetes mellitus, myocardial infarction, renal disease), baseline HAS-BLED score, baseline CHA_2DS_2-VASc score, having stroke or systemic embolism 1 year prior to the index date, and having a major bleed 1 year prior to the index date. Bleeding was categorized as a binary variable (yes/no). A multivariate logistic regression model, used instead of a Cox regression model as time to bleeding event could not be accurately measured with the laboratory data, was performed to assess factors associated with risk of bleeding. Baseline variables that were not balanced after matching and treatment exposure were included in the logistic regression model.

A subgroup analysis was established a priori to compare the risk of thrombotic (stroke and/or systemic embolism) and major bleeding events in patients with AF receiving a concurrent antiarrhythmic medication (identified by National Drug Code numbers) and either warfarin or apixaban. Patients from the original study population were included in this subgroup analysis if they had at least 30 days' overlap of prescription claims of anticoagulant (apixaban or warfarin) and an antiarrhythmic medication. The new index date was defined as the start date of the patient being on both an anticoagulant and antiarrhythmic medication. The baseline period was defined as

12 months prior to the index date, and these patients were also in-cident users of anticoagulation therapy, as defined in the primary analysis. The patients were followed for 1 year after the index date. One-to-one propensity score matching was also conducted in the subgroup analysis. McNemar chi-square test for the matched-pair cohort was performed to assess the association between treatment exposure and risk of bleeding for the 1-year follow-up period. Cox regression analysis was performed for the matched data to compare the risk of stroke of patients taking apixaban vs. warfarin and con-current antiarrhythmic medication.

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) statistical package at a priori significance level of 0.05.

3 | RESULTS

A total of 332 100 patients were identified as having a diagnosis of AF. Among these, 146 294 patients were prescribed either warfarin or apixaban. After applying the washout period of 12 months, a total of 47 100 incident users of warfarin or apixaban were identified. Among those incident users, 36 538 patients had at least 1 physician visit 1 year prior to the index date and at least 1 physician visit 1 year after the index date. After applying the exclusion criteria, the final cohort consisted of 31 612 incident users of warfarin or apixaban. Of these, 21 319 were incident users of warfarin and 10 293 were incident users of apixaban. The cohort identification process is sum-marized in Figure 1.

Results of baseline sample characteristics for the matched co-hort are presented in Table 1. After propensity score matching, the matched cohort consisted of 20 378 patients, 10 189 patients in the apixaban group and 10 189 in the warfarin group. A total of 121 (1.20%) of patients in the apixaban group experienced stroke or systemic embolism, compared to 167 (1.63%) of patients in the warfarin group (HR, 0.84; 95% CI, 0.79-0.88) (Figure 2). In patients with covariates that differed at baseline between the 2 groups (dys-pepsia, renal disease, or HAS-BLED score), there was no difference in stroke or systemic embolism seen (Table 2). Regarding bleeding, 600 (5.89%) patients experienced bleeding in the apixaban group compared to 887 (8.71%) patients in the warfarin group (odds ratio [OR], 0.65; 95% CI, 0.58-0.73). Patients with a history of dyspep-sia (OR, 0.54; 95% CI, 0.37-0.79) and higher HAS-BLED score (OR, 0.78; 95% CI, 0.72-0.92) were at a higher risk of having a bleeding event (Table 3). A total of 2423 (11.89%) patients switched to other anticoagulants.

3.1 | Antiarrhythmic medication subgroup analysis results

A total of 3774 patients with concomitant apixaban or warfarin and antiarrhythmic drug use were identified. After propensity score matching, the matched cohort consisted of 2496 patients, 1248 in the apixaban group and 1248 in the warfarin group

(Figure 3; Table 4). Among the matched cohort, there were 13 (1.04%) strokes in the apixaban group compared to 17 (1.37%) in the warfarin group (P = 0.42). No patient in the subgroup expe-rienced a systemic embolism. Regarding bleeding outcomes, 66 (5.29%) patients in the apixaban group and 86 (6.89%) patients in the warfarin group experienced a bleeding event (P = 0.08).

4 | DISCUSSION

In this national cohort of patients diagnosed with NVAF, we assessed the real-world safety and effectiveness of newly initiated apixaban compared to warfarin. We further evaluated the safety and effec-tiveness in those patients receiving concomitant antiarrhythmic medications. The principal findings were that, given similar baseline characteristics with propensity score matching, apixaban was asso-ciated with a reduced risk of bleeding and stroke and/or systemic embolism as compared to warfarin. Further, for patients on concomi-tant antiarrhythmic medications, there was no significant difference in the risk of bleeding and stroke between patients on apixaban or warfarin.

We are not aware of other national-based studies that investi-gated the risk of bleeding and stroke among newly initiated apixaban and warfarin users with concomitant antiarrhythmic medications in a clinical real-world setting. Propensity score matching ensured that patients with similar demographic and clinical characteristics were compared. Bleeding risk (HAS-BLED) scores and thrombotic risk (CHA_2DS_2-VASc) scores were calculated for both the groups. While CHA_2DS_2-VASc scores were equally balanced across matched cohorts, thereby reflecting equivalent baseline thrombosis risks, HAS-BLED scores were controlled in the final regression model to eliminate potential confounding effects from this measure. Further, this is the first real-world comparative study using EMR data. EMR, a much richer database, is an amalgamation of clinical, administrative, and laboratory encounters between a patient and a provider.[20] Key components include electronic prescribing, laboratory, and radiology results as well as provider notes (Dean et al[21]). By providing a wealth of data for outcomes research, EMR-based research studies increased 6-fold from 2000 to 2006.[21] In the present study, laboratory results, such as hemoglobin levels, were extracted from EMR data, thereby providing a complete understanding of a patient's health status.

The results of the main study analyzing apixaban and warfarin only were consistent with phase 3 clinical trials as well as claims-based observational studies. As indicated through our study find-ings, matched cohorts on apixaban had reduced risk of bleeding and stroke as compared to warfarin. This trend is consistent with the ARISTOTLE trial, which showed that apixaban reduced the rate of stroke or systemic embolism by 21% and major bleeding by 31% among patients with AF and at least 1 additional risk factor for stroke.[22] On a similar note, claims-based observational studies have provided complementary evidence on safety and effectiveness of apixaban compared to warfarin. Lip et al[23] demonstrated that among newly initiated NVAF patients, apixaban was associated with a lower
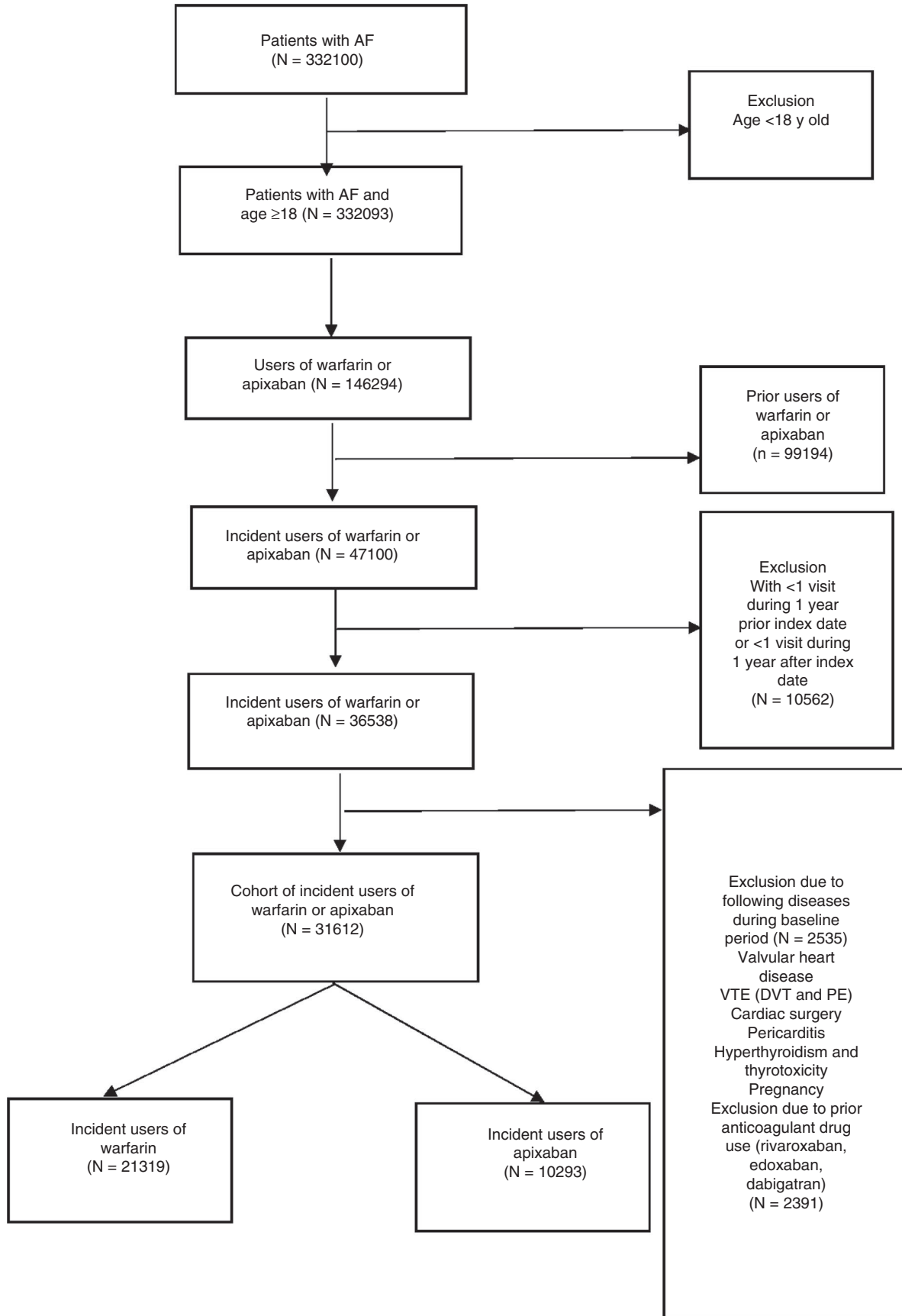
FIGURE 1 Cohort selection flowchart

TABLE 1 Baseline characteristics of patients with nonvalvular atrial fibrillation (n = 20 378)

Baseline characteristics	Apixaban (n = 10 189)	Warfarin (n = 10 189)	P value
Age (±SD)	72.1 (±9.1)	72.2 (±9.2)	0.56
Sex			
Female	4778 (46.9)	4752 (46.6)	0.57
Male	5411 (53.1)	5437 (53.4)	
HAS-BLED score	1.5 (±0.9)	1.5 (±0.9)	0.02
CHADS$_2$VASc score	2.5 (±1.3)	2.4 (±1.3)	0.20
Heart failure	1039 (10.2)	1053 (10.3)	0.75
Diabetes mellitus	880 (8.6)	805 (7.9)	0.06
Hypertension	2332 (22.9)	2228 (21.9)	0.08
Hemodialysis	7 (0.1)	7 (0.1)	0.99
Thrombocytopenia	59 (0.6)	42 (0.4)	0.09
Renal disease	559 (5.5)	464 (4.6)	0.002
Myocardial infarction	182 (1.8)	194 (1.9)	0.53
Dyspepsia	281 (2.7)	329 (3.2)	0.05
Peripheral vascular disease	1679 (16.5)	1646 (16.2)	0.53
Coronary artery disease	1375 (13.5)	1329 (13.0)	0.34
TIA	188 (1.9)	165 (1.6)	0.22
ESRD	31 (0.3)	29 (0.3)	0.80
Stroke	387 (3.8)	376 (3.7)	0.68
Bleeding	579 (5.7)	577 (5.7)	0.95
NSAID use	2699 (26.5)	2653 (26.0)	0.46
Clopidogrel use	554 (5.4)	526 (5.2)	0.38
Ticagrelor use	21 (0.2)	18 (0.2)	0.63
Prasugrel use	33 (0.3)	21 (0.2)	0.10
Aspirin use	2265 (22.2)	2247 (22.1)	0.76

ESRD, end-stage renal disease; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; TIA, transient ischemic attack.
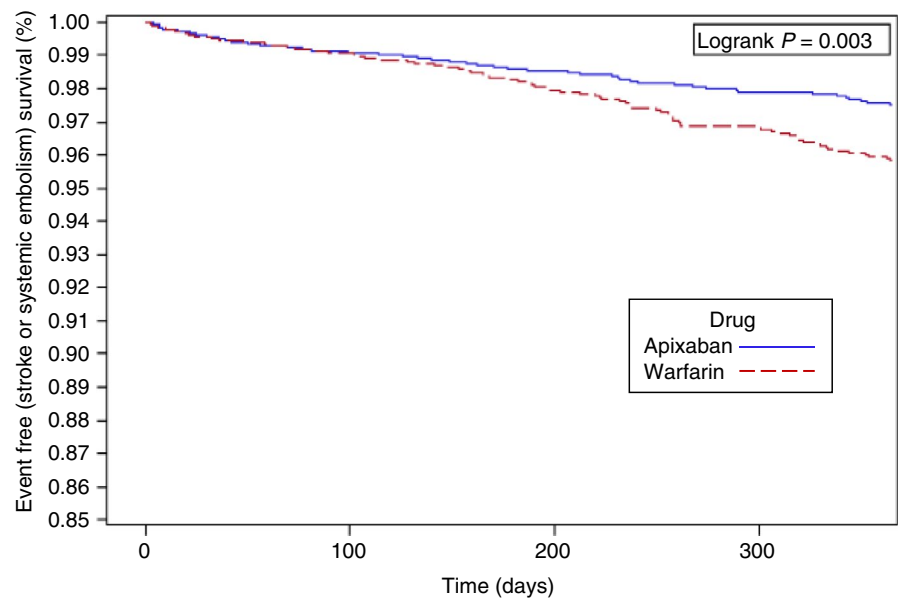

FIGURE 2 Time to stroke/systemic embolism in patients with NVAF on warfarin or apixaban (n = 20 378; 10 189/warfarin and 10 189/apixaban). NVAF, nonvalvular atrial fibrillation

	Stroke or systemic embolism, n (%)	HR (95% CI)	P value
Treatment			
Apixaban (n = 10 189)	121 (1.20)	0.84 (0.79-0.88)	<0.00
Warfarin (n = 10 189)	167 (1.63)		
Variables with baseline differences between groups			
Dyspepsia		0.85 (0.72-1.02)	0.09
Renal disease		1.02 (0.87-1.20)	0.73
HAS-BLED score		0.97 (0.93-1.03)	0.32

CI, confidence interval; HR, hazard ratio.

TABLE 3 Logistic regression model to assess risk of bleeding in patients with nonvalvular atrial fibrillation (n = 20 378)

	Major bleeding, n (%)	OR (95% CI)	P value
Treatment			
Apixaban	600 (5.89)	0.65 (0.58-0.73)	<0.00
Warfarin	887 (8.71)		
Variables with baseline differences between groups			
Dyspepsia		0.54 (0.37-0.79)	0.001
Renal disease		0.88 (0.62-1.26)	0.47
HAS-BLED score		0.78 (0.72-0.92)	0.001

CI, confidence interval; OR, odds ratio.

risk of major bleeding as compared to warfarin using a US claims database. Another US-based study revealed that apixaban effectively lowered the risk of both stroke and major bleeding as compared to warfarin among patients with NVAF.[24] Superiority of apixaban over warfarin was also validated in studies carried out in Japan and Taiwan, thereby demonstrating the robustness of these results.[25,26]

The results of our subanalysis were in contrast to the ARISTOTLE trial analysis by Flaker and colleagues, which reported that AF patients on apixaban and concurrent amiodarone had a reduced rate of stroke, systemic embolism, and major bleeding as compared to patients on warfarin and concurrent amiodarone. Our study showed that for patients on concomitant antiarrhythmic medications, there was no significant difference in the risk of bleeding and stroke between apixaban and warfarin users. In the Flaker study, there was a statistically significant decrease in time in therapeutic range for patients on warfarin and concurrent amiodarone (warfarin+amiodarone 56.5% vs. warfarin 63%; P < 0.0001). Our study did not capture time in therapeutic range, which may have an effect on outcomes seen. Further, our results report a decreased rate of stroke in the concomitant antiarrhythmic medication subanalysis group as compared to patients on apixaban or warfarin only. This result may be seen because amiodarone is a weak CYP3A4 and P-glycoprotein inhibitor, which would result in increased exposure to apixaban and more protection from systemic embolism. While there is no evidence for decreased metabolic clearance of apixaban by antiarrhythmic medications, studies have established an interaction between warfarin and amiodarone. O'Reilly et al[27] reported that amiodarone intensified the anticoagulant activity of warfarin nonstereoselectively by reduced metabolic clearance. Further, it also reported that addition of amiodarone to a stabilized regimen of warfarin can augment the anticoagulant activity and result in
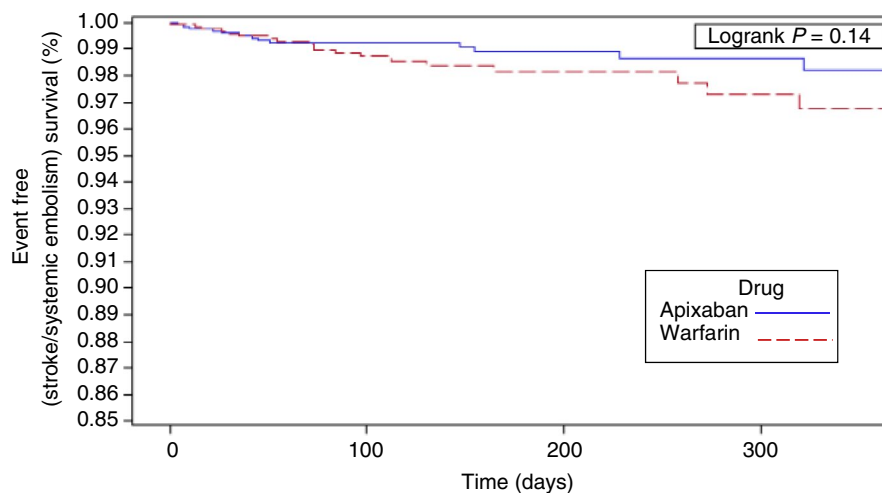

FIGURE 3 Time to stroke/systemic embolism in patients with NVAF on warfarin or apixaban, and concurrent antiarrhythmic medications (n = 2496; 1248/warfarin and 1248/apixaban). NVAF, nonvalvular atrial fibrillation

TABLE 4 Baseline characteristics of patients with nonvalvular atrial fibrillation and on concurrent antiarrhythmic medication (n = 2498)

Baseline characteristics	Apixaban (n = 1248)	Warfarin (n = 1248)	P value
Age (±SD)	71.3 (±9.6)	71.1 (±9.4)	0.68
Sex			
Female	563 (45.1)	582 (46.6)	0.40
Male	685 (54.9)	666 (53.4)	
Region			
Northeast	119 (9.5)	123 (9.9)	0.84
Midwest	273 (21.9)	285 (22.8)	
South	665 (53.3)	642 (51.4)	
West	191 (15.3)	198 (15.9)	
Antiarrhythmic medication			
Amiodarone	679 (54.4)	701 (56.2)	0.91
Sotalol	211 (16.9)	202 (16.2)	
Flecainide	139 (11.1)	141 (11.3)	
Dronedarone	105 (8.4)	102 (8.2)	
Propafenone	98 (7.9)	85 (6.8)	
Dofetilide	16 (1.3)	17 (1.4)	
HAS-BLED score	1.54 (±0.9)	1.5 (±0.9)	0.98
$CHADS_2$ VASc score	2.45 (±1.4)	2.46 (±1.4)	0.90
Heart failure	152 (12.2)	167 (13.4)	0.37
Diabetes mellitus	104 (8.3)	108 (8.7)	0.77
Hypertension	306 (24.5)	310 (24.8)	0.85
Hemodialysis	1 (0.0)	0 (0.0)	0.32
Thrombocytopenia	7 (0.6)	3 (0.2)	0.21
Renal disease	79 (6.3)	87 (7.0)	0.52
Myocardial infarction	24 (1.9)	37 (3.0)	0.09
Dyspepsia	31 (2.5)	38 (3.0)	0.39
Peripheral vascular disease	265 (21.2)	273 (21.9)	0.70
Coronary artery disease	236 (18.5)	231 (18.7)	0.80
Transient ischemic attack	13 (1.0)	22 (1.8)	0.13
Stroke history	38 (3.0)	45 (3.6)	0.43
Bleeding history	78 (6.3)	88 (7.1)	0.42
NSAID use	362 (29.0)	361 (28.9)	0.96
Clopidogrel use	75 (6.0)	75 (6.0)	0.99
Ticagrelor use	3 (0.2)	3 (0.2)	0.99
Prasugrel use	6 (0.5)	4 (0.3)	0.53
Aspirin use	308 (24.7)	305 (24.4)	0.89

NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

severe bleeding. Thus, it is possible that the anticoagulant activity of both apixaban and warfarin, or warfarin alone, increased with a concomitant antiarrhythmic medication that potentially may have diminished apixaban's relative reduction in the risk of stroke. As the interaction between warfarin and amiodarone is well established, there is a possibility that clinicians could have monitored the prothrombin time more closely in patients on concurrent antiarrhythmic medications, thereby reducing the risk of bleeding for warfarin. The subgroup analysis, which looked at over 3700 patients on a concomitant antiarrhythmic medication, was powered to detect small to moderate effect sizes. This secondary analysis should be used to warrant future randomized studies assessing outcomes in this patient population.

The present study supports the results of prior clinical trials and claims-based observational studies demonstrating the superiority of apixaban over warfarin in patients with NVAF. For patients with concomitant antiarrhythmic medications, our study adds a novel observation of no significant difference in safety and effectiveness between apixaban and warfarin users. Future studies should validate this finding in a larger cohort of patients with NVAF.

The retrospective, observational study design has limitations that may reduce interpretation of these results as causal effects. Uncontrolled confounding due to nonrandomized prescribing of drugs by a physician is frequent in observational studies. However, our study employed propensity score methodology to mitigate confounding and bias and improve causal inference. Moreover, selection bias including depletion of susceptibles or lost to follow-up could have affected our results. Patients lost to follow-up with a negative impact from their anticoagulant medication, such as bleeding or thrombosis, would not have a documented event when the medication could have caused harm. Additionally, our study did not consider dosage of warfarin or apixaban, as this was difficult to reliably capture from the medical record. Future studies should evaluate the effect of different doses and dosing strategies, including the empiric under/overdosing of anticoagulants commonly seen in clinical practice based on perceived risk factors. Our study did not include other DOACs, such as dabigatran and rivaroxaban. Thus, these results cannot be applied for other DOACs and may have resulted in selection bias among the cohort. Additionally, the majority of patients in the subgroup received amiodarone as their antiarrhythmic medication, limiting the generalizability of results across other drugs. As with all EMR data, analysis of data requires complete and correct data entry by health care providers. Similarly, these data are based on the US health care system and thus has restricted external validity outside the United States.

5 | CONCLUSION

In a large national cohort of patients with nonvalvular AF, anticoagulation with apixaban was associated with reduced risk of stroke and/or systemic embolism and bleeding events when compared with warfarin. In a subgroup analysis of patients on concurrent antiarrhythmic medications, there was no difference seen in stroke or bleeding events. Future randomized studies should assess the impact of concurrent antiarrhythmic medications on patient outcomes.

AUTHOR CONTRIBUTIONS

MW was the primary investigator of the study, involved in study methodology, analysis of results, manuscript publication, and research assistant oversight. SA was a co–principal investigator, involved in study methodology, analysis of results, manuscript publication, and research assistant oversight. XW and RP were involved in data analysis and manuscript preparation. HC, MJ, and MF were involved in study methodology, data analysis, and manuscript preparation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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