

Risk of Stroke and Bleeding in Atrial Fibrillation Treated with Apixaban Compared with Warfarin



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BACKGROUND: A previous FDA study reported a favorable benefit risk for apixaban compared with warfarin for stroke prevention in older non-valvular atrial fibrillation (NVAF) patients (≥ 65 years). However, it remains unclear whether this favorable benefit risk persists in other populations including younger users. We examined if a similar benefit risk was observed in the Sentinel System and if it varied by age group.

OBJECTIVE: To examine the risk of ischemic stroke, gastrointestinal (GI) bleeding, and intracranial hemorrhage (ICH) in apixaban users compared with warfarin users in Sentinel Distributed Database (SDD).

DESIGN AND PARTICIPANTS: A retrospective new user cohort study was conducted among patients, 21 years and older initiating apixaban and warfarin for NVAF, between December 28, 2012, and June 30, 2018, in the SDD.

MAIN MEASURES: Cox proportional hazard regression was used to estimate the hazard ratios (HR) and 95% confidence intervals (95% CI) for each outcome (ischemic stroke, GI bleeding, and ICH) in propensity score matched apixaban users compared with the warfarin users. Subgroup analyses by age (21–64, 65–74, and 75+ years) were conducted.

KEY RESULTS: After matching, 55.3% and 58.4% ($n = 55,038$) of the apixaban and warfarin users were included in the main analysis. GI bleeding was the most common outcome. The HR (95% CI) for GI bleeding, ICH, and ischemic stroke in apixaban users compared with warfarin users were 0.57 (0.50–0.66), 0.53 (0.40–0.70), and 0.56 (0.45–0.71) respectively. The reduced risk of these outcomes in apixaban compared with warfarin users persisted across age groups.

CONCLUSION: In NVAF patients of all ages initiating either apixaban or warfarin for stroke prevention in the Sentinel System, apixaban was associated with a decreased risk of GI bleeding, ICH, and ischemic stroke compared with warfarin. Among patients less than 65 years of age, apixaban use was associated with a decreased risk of GI bleeding and ischemic stroke.

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INTRODUCTION

Non-valvular atrial fibrillation (NVAF) is a common arrhythmia that independently increases the risk of ischemic stroke by fivefold.^{1,2} Estimates suggest that around 2.7–6.1 million Americans have NVAF and prevalence increases with age, particularly after 65 years.^{3,4} Prior to 2010, the mainstay of stroke prevention in NVAF was oral vitamin K antagonists, such as warfarin.⁵ Since then, four non-vitamin K antagonist oral anticoagulants (NOACs) have been approved in the USA for stroke prevention in patients with NVAF and serve as an alternative to the traditional warfarin option. NOACs do not require therapeutic monitoring and have simpler dosing regimens than warfarin. Dabigatran (approved in 2010) is a direct thrombin inhibitor, while rivaroxaban (2011), apixaban (2012), and edoxaban (2015) are factor Xa inhibitors and all of them have been shown to be non-inferior to warfarin for stroke prevention.^{6–8}

NOAC use in the USA increased dramatically since 2010, especially in those aged under 65 years.⁹ A US study that examined NOAC use between 2010 and 2017 reported that from 2015, NOACs accounted for over 80% of new oral anticoagulant prescriptions among patients aged less than 65 years and that prescriptions for dabigatran, rivaroxaban, and apixaban exceeded warfarin.⁹ Across all age groups, apixaban was the most frequently prescribed oral anticoagulant since 2015 and accounted for half of new oral anticoagulant prescriptions in 2017.⁹ The increasing use of apixaban is likely related to increased evidence and recognition of its favorable benefit risk profile as recently reported in a large study among Medicare beneficiaries.¹⁰ That Medicare study, conducted among new users of NOACs and warfarin between 2010 and 2015, reported a lower risk of stroke, intracranial hemorrhage (ICH), major extracranial bleeding, and death

among apixaban users compared with warfarin users who were aged 65 years or older.¹⁰ These findings are in line with those from the pre-approval Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial which showed that patients who received apixaban were less likely to die within 30 days of a major hemorrhagic event, were less likely to have non-major bleeding, and had lower rates of ICH compared with those who received warfarin.⁸ However, it remains unclear whether the lower risk of bleeding associated with apixaban use, seen among older patients in the ARISTOTLE trial and the Medicare study, would also be seen in younger users. Therefore, we sought to examine if a similar benefit risk profile for apixaban compared with warfarin was observed in the FDA Sentinel System and if this varied by age group. Specifically, we compared risk of stroke and bleeding in NVAf patients who initiated apixaban or warfarin.

METHODS

Study Design

A retrospective cohort study was conducted.

Cohort

New initiators of apixaban or warfarin, aged 21 years or more with a diagnosis of atrial fibrillation (AF) in the previous 183 days, between December 28, 2012, and June 30, 2018, were identified in the Sentinel Distributed Database (SDD). Sentinel comprises electronic health care data from a distributed network of US-based data partners. These data partners, mostly commercial health insurers and integrated delivery care networks, convert their data into the Sentinel Common Data Model. The data domains include patient demographics; health insurance enrollment; diagnoses and procedures during inpatient, outpatient, and emergency room encounters; and outpatient pharmacy dispensing records.^{11–13} This study included data outside of the Medicare fee-for-service population in order to better differentiate our population from that in the prior Medicare study.¹⁰ Cohort members maintained continuous enrollment for at least 183 days before apixaban or warfarin initiation during which gaps in medical and prescription drug coverage of up to 45 days were allowed. Patients were excluded if they had evidence of the following conditions in the 183 days prior to and including date of drug initiation: any of the study outcomes (gastrointestinal (GI) bleeding, ICH, or ischemic stroke) as principal discharge diagnosis of an inpatient admission, an alternate indication for apixaban or warfarin use (deep vein thrombosis, pulmonary embolism, joint replacement, mitral stenosis, valve replacement, or valve repair), from any care setting. Those receiving dialysis in outpatient settings or who had a kidney replacement were excluded as there has been some controversy about the use of NOACs in dialysis patients and this might affect the use in

those with kidney transplants also (see flow diagram in the Appendix: Fig. 1). We identified the exclusion conditions, exposure, outcomes, and covariates via outpatient pharmacy dispensing encoded in the National Drug Codes and medical encounter diagnoses and procedures encoded in the International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification (ICD-9-CM or ICD-10-CM); the International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS); Healthcare Common Procedure Coding System (HCPCS); and Current Procedural Terminology (CPT) codes. We performed all analyses using the Sentinel's Cohort Identification and Descriptive Analysis (CIDA) and Propensity Score Analysis tools, Version 5.4.4, with additional programming to calculate the risk scores.

Exposure

New users of apixaban (standard 5 mg strength only) or warfarin (all strengths) whose first exposure occurred on or after December 28, 2012 (approval date for apixaban) were included. New use of apixaban or warfarin was defined as no use of any anticoagulant (apixaban, dabigatran, rivaroxaban, edoxaban, or warfarin) in the previous 183 days. The index date was defined as the dispensing date for the first eligible apixaban or warfarin dispensing during the study period. Each eligible member contributed only the earliest valid exposure episode in their entire health insurance enrollment history.

Outcomes and Follow-Up

The primary outcomes were an inpatient principal diagnosis for GI bleeding, ICH, or ischemic stroke. Outcomes were defined using previously validated algorithms based on ICD-9-CM diagnosis codes in claim databases. These algorithms have reported positive predictive values ranging from 86 to 97%.^{14–18} These ICD-9-CM-based algorithms were mapped to the ICD-10-CM coding system via forward-backward mapping^{19,20} using the 2017 General Equivalence Mappings.²¹ Follow-up began on the day after the first dispensing of a study drug and continued until the first occurrence of any of the following: (1) outcome occurrence, (2) switching to a different anticoagulant, (3) disenrollment, (4) recorded death, (5) end of exposure episode, and (6) end of query period (June 30, 2018) or end of available data for data partners. Exposure episodes were considered continuous if gaps in days supplied were 3 days or less. Three days were chosen as an appropriate gap allowance based on the half-life of NOACs and the requirement that patients remain anticoagulated during follow-up. An episode extension of 3 days was added to the end of each exposure episode. A 14-day gap allowance and extension were applied in sensitivity analyses.

Statistical Analysis

Confounding Adjustment. Logistic regression was used to estimate the propensity score (PS) of initiating apixaban

Table 1 Characteristics of New Initiators of Apixaban and Warfarin After Propensity Score Matching from December 28, 2012, to June 30, 2018

Characteristic*	Apixaban		Warfarin		Absolute difference	Stanardized mean difference
	N/ mean	%/Std Dev [†]	N/ mean	%/Std Dev [†]		
Patients (N)	55,038	55.3%	55,038	58.4%	–	–
Demographics						
Mean age	71.3	9.7	71.3	10.6	–0.056	–0.006
Age: 21–64 years	14,473	26.3%	15,203	27.6%	–1.326	–0.030
Age: 65–74 years	19,315	35.1%	17,894	32.5%	2.582	0.055
Age: 75+ years	21,250	38.6%	21,941	39.9%	–1.255	–0.026
Gender (male)	33,394	60.7%	33,476	60.8%	–0.149	–0.003
Race (White)	25,454	46.2%	26,059	47.3%	–1.099	–0.022
Race (Black or African American)	2231	4.1%	2288	4.2%	–0.104	–0.005
Race (Unknown)	26,810	48.7%	26,186	47.6%	1.134	0.023
Race (American Indian or Alaska Native)	56	0.1%	69	0.1%	–0.024	–0.007
Race (Asian)	240	0.4%	222	0.4%	0.033	0.005
Race (Native Hawaiian or other Pacific Islander)	247	0.4%	214	0.4%	0.060	0.009
Year (2012)	–	0.0%	98	0.2%	–0.178	–
Year (2013)	3021	5.5%	10,985	20.0%	–14.47	–0.445
Year (2014)	9648	17.5%	8337	15.1%	2.382	0.064
Year (2015)	14,566	26.5%	9339	17.0%	9.497	0.232
Year (2016)	10,764	19.6%	13,175	23.9%	–4.381	–0.106
Year (2017)	12,299	22.3%	10,193	18.5%	3.826	0.095
Year (2018)	4740	8.6%	2911	5.3%	3.734	0.139
Recorded history of:						
Prior combined comorbidity score	2.9	2.5	3.0	2.6	–0.109	–0.043
CHA ₂ DS ₂ VaSc						
Mean, Std	3.2	1.5	3.2	1.5	–0.016	–0.010
0–1	8559	15.6%	8363	15.2%	0.356	0.010
2	10,146	18.4%	10,110	18.4%	0.065	0.002
3	13,272	24.1%	13,294	24.2%	–0.040	–0.001
4	11,911	21.6%	12,008	21.8%	–0.176	–0.004
5	7067	12.8%	7142	13.0%	–0.136	–0.004
≥6	4083	7.4%	4121	7.5%	–0.069	–0.003
HAS-BLED						
Mean, Std	2.2	1.0	2.2	1.1	–0.014	–0.013
0–1	14,764	26.8%	14,455	26.3%	0.561	0.013
2	20,771	37.7%	20,819	37.8%	–0.087	–0.002
3	13,308	24.2%	13,345	24.2%	–0.067	–0.002
≥4	6195	11.3%	6419	11.7%	–0.407	–0.013
Acute myocardial infarction—prior 1–30 days	2609	4.7%	2700	4.9%	–0.165	–0.008
Acute myocardial infarction—prior 31–183 days	1457	2.6%	1516	2.8%	–0.107	–0.007
Cardiac ablation	1115	2.0%	1055	1.9%	0.109	0.008
Cardioversion	4310	7.8%	4038	7.3%	0.494	0.019
Coronary revascularization	7656	13.9%	7973	14.5%	–0.576	–0.017
Diabetes	19,141	34.8%	19,284	35.0%	–0.260	–0.005
Falls	1770	3.2%	1888	3.4%	–0.214	–0.012
Fractures	759	1.4%	735	1.3%	0.044	0.004
Heart failure—hospitalized	9726	17.7%	9604	17.4%	0.222	0.006
Heart failure—outpatient	11,035	20.0%	11,374	20.7%	–0.616	–0.015
Hospitalized bleeding	5594	10.2%	5637	10.2%	–0.078	–0.003
Hyperlipidemia	35,822	65.1%	35,657	64.8%	0.300	0.006
Hypertension	45,243	82.2%	45,509	82.7%	–0.483	–0.013
Obesity	12,344	22.4%	13,209	24.0%	–1.572	–0.037
Other ischemic heart disease	22,685	41.2%	22,769	41.4%	–0.153	–0.003
Peptic ulcer disease	234	0.4%	258	0.5%	–0.044	–0.007
Renal disease—acute	5795	10.5%	6042	11.0%	–0.449	–0.014
Renal disease—chronic	9602	17.4%	10,130	18.4%	–0.959	–0.025
Smoking	10,148	18.4%	10,947	19.9%	–1.452	–0.037
Stroke, non-inpatient—prior 1–30 days	1901	3.5%	1815	3.3%	0.156	0.009
Stroke, non-inpatient—prior 31–183 days	2028	3.7%	2058	3.7%	–0.055	–0.003
Syncope	4165	7.6%	4139	7.5%	0.047	0.002
Transient ischemic attack	2270	4.1%	2089	3.8%	0.329	0.017
Walker use	1296	2.4%	1256	2.3%	0.073	0.005
History of use:						
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	31,920	58.0%	31,913	58.0%	0.013	0.000
Amiodarone	6688	12.2%	6726	12.2%	–0.069	–0.002
Anti-anginal vasodilators	5600	10.2%	5595	10.2%	0.009	0.000
Anticoagulants	6319	11.5%	6252	11.4%	0.122	0.004
Antiplatelet agents (non-aspirin)	6908	12.6%	6974	12.7%	–0.120	–0.004
Aspirin	954	1.7%	1070	1.9%	–0.211	–0.016
Beta blockers	39,686	72.1%	39,851	72.4%	–0.300	–0.007
Cyclooxygenase (COX-2) inhibitors	787	1.4%	750	1.4%	0.067	0.006

(continued on next page)

Table 1. (continued)

Characteristic*	Apixaban		Warfarin		Absolute difference	Stanardized mean difference
	N/ mean	%/Std Dev [†]	N/ mean	%/Std Dev [†]		
Calcium channel blockers	21,971	39.9%	21,772	39.6%	0.362	0.007
Digoxin	5209	9.5%	4922	8.9%	0.521	0.018
Disopyramide	35	0.1%	30	0.1%	0.009	0.004
Dronedarone	1113	2.0%	1003	1.8%	0.200	0.015
Estrogen replacement	636	1.2%	623	1.1%	0.024	0.002
Flecainide	1933	3.5%	1889	3.4%	0.080	0.004
H2 antagonists	2611	4.7%	2666	4.8%	-0.100	-0.005
Insulin	4855	8.8%	4809	8.7%	0.084	0.003
Loop diuretics	15,866	28.8%	16,147	29.3%	-0.511	-0.011
Metformin	9344	17.0%	9436	17.1%	-0.167	-0.004
Non-statin lipid-lowering agents	4353	7.9%	4216	7.7%	0.249	0.009
Other anti-diabetic drugs	3280	6.0%	3342	6.1%	-0.113	-0.005
Potassium-sparing diuretics	5266	9.6%	5429	9.9%	-0.296	-0.010
Prescription non-steroidal anti-inflammatory drugs (NSAIDs)	6901	12.5%	6671	12.1%	0.418	0.013
Propafenone	1095	2.0%	1009	1.8%	0.156	0.011
Proton pump inhibitors	13,981	25.4%	14,037	25.5%	-0.102	-0.002
Statins	31,098	56.5%	31,360	57.0%	-0.476	-0.010
Sulfonylureas	5398	9.8%	5299	9.6%	0.180	0.006
Thiazide diuretics	13,916	25.3%	13,753	25.0%	0.296	0.007
Health service utilization intensity:						
Mean number of ambulatory encounters	11.8	9.6	11.8	9.4	-0.052	-0.005
Mean number of emergency room encounters	0.5	0.9	0.5	1.1	-0.008	-0.007
Mean number of inpatient hospital encounters	0.5	0.7	0.5	0.8	0.020	0.027
Mean number of generics	9.5	4.9	9.5	4.9	0.053	0.011

*Covariates in italics were not included in the propensity score logistic regression model

[†]Value represents standard deviation where no % follows the value

versus warfarin using the baseline characteristics and potential confounders, including CHA₂DS₂-VASc²² and HAS-BLED²³ scores, existing risk factors for bleeding, measures of overall health status, and medication use (Table 1) within data partners. New apixaban and warfarin initiators were 1:1 PS-matched using a nearest neighbor matching algorithm with a maximum caliper of 0.05 within each DP and within ICD-9-CM or ICD-10 CM era. The PS distributions and covariate balance between apixaban and warfarin cohorts were examined before and after PS matching using standardized mean differences (SMD), with absolute values >0.10 indicating imbalance.

For the main analysis, Cox proportional hazard regression was used to estimate the hazard ratios (HR) and 95% confidence intervals (95% CI) for each outcome in the matched cohort of apixaban users compared with the warfarin users. A subgroup analysis by age group (21–64, 65–74, and 75+ years) was conducted.

RESULTS

A total of 99,442 apixaban and 94,189 warfarin initiators were identified for potential study inclusion from seven data partners who had full propensity score model convergence. Before matching, there were minor differences between cohorts for combined comorbidity score, CHA₂DS₂VaSc score, HAS-BLED score, cardiac ablation, cardioversion, diabetes, heart failure, hospitalized

bleeding, obesity, other ischemic heart disease, renal disease, smoking, anti-anginal vasodilator, digoxin, dronedarone, flecainide, loop diuretic, and prescription non-steroidal anti-inflammatory drug (NSAID) use; for example, the prior combined comorbidity score was 2.7 in apixaban users and 3.2 in warfarin users, SMD -0.198. There were also slight differences in the number of ambulatory encounters (11.2 apixaban vs. 12.5 warfarin, SMD -0.132) (Appendix: Table 1). After matching, 55.3% and 58.4% of the apixaban and warfarin cohorts respectively were included ($n=55,038$ in each cohort). Both matched exposure groups were closely balanced for all covariates (Table 1 and Appendix: Fig. 2) and there were 14,172, 17,804, and 20,977 apixaban and warfarin users rematched within subgroups aged 21–64, 65–74, and ≥75 years respectively.

The incidence rate for GI bleeding in the matched apixaban group was 14.85 per 1000 person-years compared with 25 per 1000 person-years in the matched warfarin group (Appendix: Fig. 2). Overall, the HR for GI bleeding in apixaban users compared with warfarin users was 0.57 (95% CIs 0.50–0.66) (Table 2 and Fig. 1).

A reduced risk of GI bleeding in apixaban compared with warfarin users was seen in all age groups: 21–64 years (HR 0.34, 95% CI 0.21–0.54), 65–74 years (HR 0.51, 95% CI 0.40–0.65), and ≥75 years (HR 0.68, 95% CI 0.56–0.82) (Table 3 and Fig. 1).

The incidence rate for ICH in the matched apixaban group was 3.46 per 1000 person-years compared with 6.73 per 1000

Table 2 Adjusted HRs (95% CIs) for GI Bleeding, ICH, and Ischemic Stroke in Apixaban Compared with Warfarin Users, in Sentinel, from December 28, 2012, to June 30, 2018

	Number of new users	Person years at risk	Number of events	Incidence rate per 1000 person-years	Hazard ratio (95% CI)	Wald P value
GI bleeding						
Apixaban	55,038	20,470.14	304	14.85	0.57 (0.50–0.66)	<0.001
Warfarin	55,038	25,243.38	631	25.00		
ICH						
Apixaban	55,038	20,517.02	71	3.46	0.53 (0.40–0.70)	<0.001
Warfarin	55,038	25,411.13	171	6.73		
Ischemic stroke						
Apixaban	55,038	20,493.77	108	5.27	0.56 (0.45–0.71)	<0.001
Warfarin	55,038	25,381.00	226	8.90		

person-years in the matched warfarin group (Appendix: Fig. 3). Overall, the HR for ICH in apixaban users compared with warfarin users was 0.53 (95% CI 0.40–0.70) (Table 2). The HR was non-significantly reduced in users aged 21–64 years (HR 0.38, 95% CI 0.14–1.05) and in those aged 65–74 years (HR 0.63, 95% CI 0.39–1.03) and was significantly reduced in those aged ≥ 75 years (HR 0.52, 95% CI 0.36–0.76) (Table 4 and Fig. 1). Of note, there were only five events among apixaban users aged 21–64 years.

The incidence rate for ischemic stroke in the matched apixaban group was 5.27 per 1000 person-years compared with 8.90 per 1000 person-years in the matched warfarin group (Appendix: Fig. 4). Overall, the HR for ischemic stroke in apixaban users compared with warfarin users was 0.56 (95% CI 0.45–0.71) (Table 2). The HR was significantly reduced in users aged 21–64 years (HR 0.29, 95% CI 0.13–0.68) and users aged ≥ 75 years (HR 0.57, 95% CI 0.42–0.77) and non-significantly reduced in those aged 65–74 years (HR 0.70, 95% CI 0.46–1.07) (Table 5 and Fig. 1).

Results for GI bleeding, ICH, and ischemic stroke overall and across age groups remained consistent in sensitivity analyses when the episode gap was extended to 14 days (data not shown).

DISCUSSION

Overall, among patients with NVAf, in seven Sentinel data partners, between 2012 and 2018, apixaban use was associated with a statistically significant decreased risk of GI bleeding, ICH, and ischemic stroke compared with warfarin use. When analyses were stratified by age, the risk of GI bleeding and stroke were significantly reduced in apixaban users aged less than 65 years of age. The risk of ICH was also reduced in younger apixaban users, but not significantly so. There were only 20 ICH events in this age group (5 in apixaban users), giving us reduced statistical power to show a significant reduction in risk. GI bleeding was the most commonly observed outcome irrespective of age group and the incidence rate of all outcomes increased with age in both apixaban and warfarin cohorts.

The results were consistent with the findings of a recent FDA study in Medicare among older anticoagulant users (aged ≥ 65 years) which compared apixaban users to warfarin users from 2010 to 2015 and reported a reduced risk of thromboembolic stroke (HR 0.71, 0.60–0.83), ICH (HR 0.54, 0.43–0.68), and major GI bleeding (HR 0.52, 0.45–0.60).¹⁰ Two previous studies^{24,25} were identified that

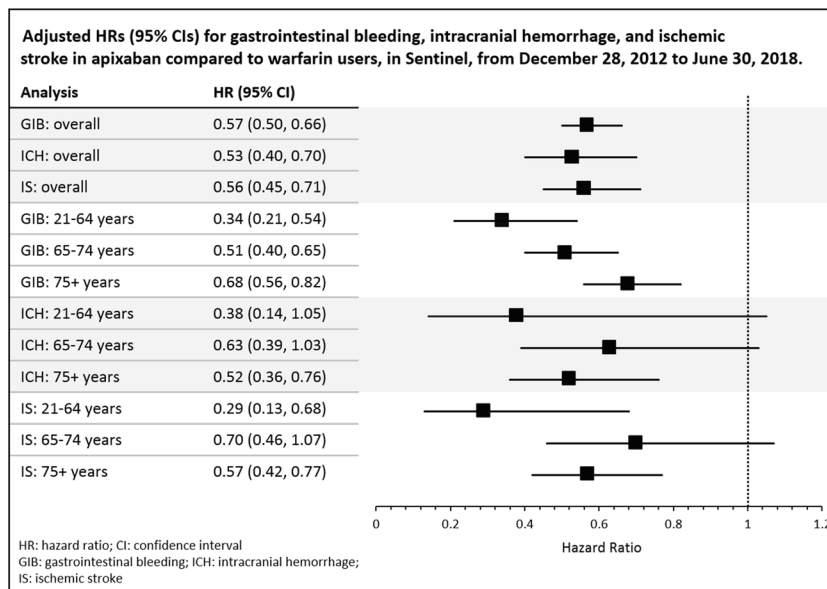


Figure 1 Forest plot showing estimates for each outcome overall and by age group.

Table 3 Adjusted HRs (95% CIs) for GI Bleeding, in Apixaban Compared with Warfarin Users, in Sentinel, from December 28, 2012, to June 30, 2018, by Age Group

Medical product	Number of new users	Person years at risk	Number of events	Incidence rate per 1000 person-years	Hazard ratio (95% CI)	Wald P value
Age group: 21–64 years						
Apixaban	14,172	4863.16	23	4.73	0.34 (0.21–0.54)	< 0.001
Warfarin	14,172	5197.32	77	14.82		
Age group: 65–74 years						
Apixaban	17,804	7041.44	93	13.21	0.51 (0.40–0.65)	< 0.001
Warfarin	17,804	9032.03	220	24.36		
Age group: 75+ years						
Apixaban	20,977	7778.84	175	22.50	0.68 (0.56–0.82)	< 0.001
Warfarin	20,977	10,139.88	310	30.57		

included some patients with AF below the age of 65 years. However, in the study by Gupta et al.,²⁵ the proportion of apixaban users aged 18–54 was only 2.3% (just 172 patients) and the proportion aged 18–65 was 9.6% (558 patients) compared with 26.3% aged 21–64 in our analysis, with over 14,400 patients in this age group. Yao et al.²⁵ included slightly more younger users with 22.7% of apixaban users (1747 patients) aged between 18 and 64 years. The findings of both studies were consistent with our study and showed that among those with AF, apixaban was associated with lower risks of both stroke and major bleeding compared with warfarin. However, in both studies, the risk estimates provided for stroke and bleeding events were for the entire study population. Neither study provided risk estimates for the stratum of patients below age 65 years. This highlights the need for a large study such as ours to provide evidence of safety and effectiveness of apixaban in younger users.

Our analysis was restricted to a subset of Sentinel data partners as we wanted to examine the association in a different data source from Medicare that also included younger anticoagulant users. However, given that anticoagulants tend to be used more in older age, the proportion of those aged less than 65 years in matched analyses was low (26–28%). These findings are also consistent with those from the pre-approval ARISTOTLE randomized controlled trial comparing apixaban with warfarin which reported a reduced risk of stroke (HR 0.79, 95% CI 0.65–0.95), ICH

(0.42, 95% CI 0.30–0.58), and GI bleeding (0.89, 95% CI 0.70–1.15) among older users (median age 70 years).⁸

This study identified almost 100,000 apixaban users in the Sentinel System reflecting the increasing use of apixaban across time, in all age groups, in the USA since its approval.⁹ Increasing use of apixaban has also been seen in European countries such as Denmark,²⁶ Norway,²⁷ and Sweden²⁸ and this is likely due to its favorable benefit risk compared with warfarin that was also observed in this study.

Our study had a number of strengths including the ability to capture large numbers of anticoagulant users of different ages, the use of propensity score estimation and matching within ICD-specific eras, the use of a new user design to minimize bias, and the ability to span both ICD eras. There were also noteworthy limitations including inability to include all data partners in the analyses due to model convergence issues in the smaller data partners, although the largest were included and as with all observational studies not all confounding factors may have been accounted for in the analysis. Year of cohort entry was not included in the propensity score model and so the effect of secular trends within each ICD era might not have been accounted for. The study was conducted in a US population and therefore the findings may not be generalizable to non-US populations. We included only patients using the 5-mg apixaban strength, assuming a dose of 10 mg daily, which is the standard dose for AF and in doing so may have excluded some patients with AF using the 2.5-mg apixaban strength. However, further work in the Sentinel System suggested that

Table 4 Adjusted HRs (95% CIs) for ICH, in Apixaban Compared with Warfarin Users, in Sentinel, from December 28, 2012, to June 30, 2018, by Age Group

Medical product	Number of new users	Person years at risk	Number of events	Incidence rate per 1000 person-years	Hazard ratio (95% CI)	Wald P value
Age group: 21–64 years						
Apixaban	14,172	4865.61	5	1.03	0.38 (0.14–1.05)	0.063
Warfarin	14,172	5212.11	15	2.88		
Age group: 65–74 years						
Apixaban	17,804	7060.23	24	3.40	0.63 (0.39–1.03)	0.067
Warfarin	17,804	9092.44	50	5.50		
Age group: 75+ years						
Apixaban	20,977	7803.61	40	5.13	0.52 (0.36–0.76)	< 0.001
Warfarin	20,977	10,226.84	98	9.58		

Table 5 Adjusted HRs (95% CIs) for Ischemic Stroke, in Apixaban Compared with Warfarin Users, in Sentinel, from December 28, 2012, to June 30, 2018, by Age Group

Medical product	Number of new users	Person years at risk	Number of events	Incidence rate per 1000 person-years	Hazard ratio (95% CI)	Wald P value
Age group: 21–64 years						
Apixaban	14,172	4861.33	7	1.44	0.29 (0.13–0.68)	0.004
Warfarin	14,172	5206.03	25	4.80		
Age group: 65–74 years						
Apixaban	17,804	7049.96	35	4.96	0.70 (0.46–1.07)	0.098
Warfarin	17,804	9091.32	61	6.71		
Age group: 75+ years						
Apixaban	20,977	7796.20	63	8.08	0.57 (0.42–0.77)	< 0.001
Warfarin	20,977	10,204.43	131	12.84		

the proportion of apixaban 2.5 mg users who had AF was low (21%) compared with 5 mg users who had AF (80%).

CONCLUSION

In NVAF patients of all ages initiating either apixaban or warfarin for stroke prevention in the Sentinel System, apixaban was associated with a decreased risk of GI bleeding, ICH, and ischemic stroke compared with warfarin. Among patients less than 65 years of age, apixaban was associated with a decreased risk of GI bleeding and ischemic stroke.

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Compliance with Ethical Standards:

This study was classified as public health surveillance by the Food and Drug Administration (FDA) and was exempt from review by its Research in Human Subjects Committee. It was not appropriate to involve patients or the public in the design, conduct, reporting, or dissemination plans of this work.

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