Clinical and Applied Thrombosis/Hemostasis
Volume 25: 1-8

DOI: 10.1177/1076029619870249
journals.sagepub.com/home/cat
SAGE

Switching to Another Oral Anticoagulant and Drug Discontinuation Among Elderly Patients With Nonvalvular Atrial Fibrillation Treated With Different Direct Oral Anticoagulants

Christine L. Baker, JD, MPH[1], Amol D. Dhamane, BPharm, MS[2], Jigar Rajpura, PhD[2], Jack Mardekian, PhD[1], Oluwaseyi Dina, MPH[1], Cristina Russ, MD, PhD[1], Lisa Rosenblatt, MD, MPH[2], Melissa Lingohr-Smith, PhD[3], and Jay Lin, PhD, MBA[3]

Abstract

We compared the risks of switching to another oral anticoagulant (OAC) and discontinuation of direct oral anticoagulants (DOACs) among elderly patients with nonvalvular atrial fibrillation (NVAF) who were prescribed rivaroxaban or dabigatran versus apixaban. Patients (≥65 years of age) with NVAF prescribed DOACs (January 1, 2013 to September 30, 2017) were identified from the Humana research database and grouped into DOAC cohorts. Cox regression analyses were used to evaluate whether the risk for switching to another OAC or discontinuing index DOACs differed among cohorts. Of the study population (N = 38 250), 55.9% were prescribed apixaban (mean age: 78.6 years; 49.8% female), 37.3% rivaroxaban (mean age: 77.4 years; 46.7% female), and 6.8% dabigatran (mean age: 77.0 years; 44.0% female). Compared to patients prescribed apixaban, patients prescribed rivaroxaban (hazard ratio [HR]: 2.08; 95% confidence interval [CI], 1.92-2.25; $P < .001$) or dabigatran (HR: 3.74; 95% CI, 3.35-4.18, $P < .001$) had a significantly higher risk of switching to another OAC during the follow-up; compared to patients prescribed apixaban, the risks of discontinuation were also higher for patients treated with rivaroxaban (HR: 1.10; 95% CI, 1.07-1.13, $P < .001$) or dabigatran (HR: 1.29; 95% CI, 1.23-1.35, $P < .001$).

Keywords

nonvalvular atrial fibrillation, direct oral anticoagulants, apixaban, rivaroxaban, dabigatran, drug switching, drug discontinuation

Date received: 03 April 2019; revised: 25 June 2019; accepted: 23 July 2019.

Introduction

The common cardiac rhythm disorder of nonvalvular atrial fibrillation (NVAF) is more prevalent among older age groups.[1-3] In 2010, it was reported that among Medicare beneficiaries, 9% of patients ≥65 years of age had atrial fibrillation (AF).[4] The association of NVAF with stroke risk increases as well in older people, accounting for approximately 1 in 4 strokes among those ≥80 years.[3,4] Vitamin K antagonists, predominately warfarin, have been used for decades to reduce the risk of stroke in patients with NVAF; however, in older patients, they have been underutilized due to multiple barriers, including higher bleeding risk of this patient group.[5] Multiple new direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, and apixaban, have been developed to reduce stroke/systemic embolism (SE) risk in patients with NVAF. Based on their comparative efficacy and safety with warfarin shown in clinical trials, these 3 DOACs were approved by the Food and Drug Administration for stroke/SE risk reduction in patients with NVAF.[6-8] Several studies of patients with NVAF in real-world settings have further documented the efficacy and

[1] Pfizer Inc, New York, NY, USA
[2] Bristol-Myers Squibb, Lawrenceville, NJ, USA
[3] Novosys Health, Green Brook, NJ, USA

Corresponding Author:
Christine L. Baker, Health Economics & Outcomes Research, Internal Medicine, Pfizer, Inc 235 E 42nd St, New York, NY 10017, USA.
Email: christine.l.baker@pfizer.com

safety of dabigatran, rivaroxaban, and apixaban for stroke/SE prevention, with apixaban frequently yielding the most clinical benefits versus warfarin.[9-14] The availability of DOACs and their advantages over warfarin for the treatment of patients with NVAF may help to mitigate the underutilization of oral anticoagulants (OACs), especially among elderly patients. Early studies of OAC usage in the pre- and post-DOAC eras in the United States have suggested this is the case, although there remains room for further improvement.[15,16]

From 2010 onward, there has been an increase in the usage of DOACs for stroke risk reduction in patients with NVAF, while warfarin usage had declined.[16] Furthermore, other real-world studies have provided evidence that continuous adherence to DOACs is essential to maintain stroke risk reduction.[17-20] To gain a greater understanding of the usage patterns of DOACs among elderly patients with NVAF, in this study, we compared the risks of switching to another OAC and discontinuation of DOACs among elderly patients with NVAF who were prescribed rivaroxaban or dabigatran versus apixaban.

Methods

Study Design and Data Source

Using the Humana research database, we conducted a retrospective claims database analysis of elderly patients with NVAF during a study period beginning on January 1, 2012, and ending on December 31, 2017. The Humana research database is an integrated source of managed care medical and pharmacy insurance claims and eligibility files of over 10 million members with Medicare coverage. The medical file contains data on diagnostic and therapeutic services obtained in both inpatient and outpatient settings. The pharmacy file contains data on outpatient prescription drugs dispensed with information on quantity and days' supply. An eligibility file contains data on demographic characteristics and periods of insurance enrollment. The claims data of the Humana research database are deidentified and comply with the patient requirements of the Health Insurance Portability and Accountability Act.

Study Population

Elderly patients ($\geq$65 years of age) with Medicare coverage who had $\geq$1 pharmacy claim for rivaroxaban, dabigatran, or apixaban between January 1, 2013, and September 30, 2017, were identified from the Humana research database. The first date of the pharmacy claim for the DOAC was designated as the index date. Patients were required to have an NVAF diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] diagnosis code of 427.31 or the corresponding 10th Revision [*ICD-10*] code I48.x) in the 12-month baseline period prior to the index date or on the index date. If patients had a medical claim indicative of valvular heart disease, kidney disease, venous thromboembolism, or reversible AF during the 12-month baseline period or on the index date, they were excluded from the study population. Patients were also excluded if they had hip or knee surgery within a 6-week period prior to the index date or if they had a claim indicating pregnancy at any time during the study period. Additionally, if any patient had a prior pharmacy claim for apixaban, rivaroxaban, dabigatran, edoxaban, or warfarin during the baseline period, or if they had prescription claims of $\geq$1 type of OAC on the index date, they were excluded from the study population.

After inclusion and exclusion criteria were applied, the remaining patients were grouped into study cohorts based on the index DOAC prescribed (rivaroxaban, dabigatran, or apixaban). Patients prescribed edoxaban were not analyzed in this study due to its later entry into the US market and consequently small patient sample size. For the study cohorts, the baseline period was 12-months prior to the index date, in which patients were required to have continuous health insurance coverage. The follow-up period lasted a minimum of 3 months after the index date and ended either at the end of OAC treatment date, health plan disenrollment date, or the end of the study period (December 31, 2017), whichever came first. Patients were required to have continuous health insurance coverage throughout the follow-up period.

Demographics and Clinical Characteristics of Study Cohorts

During the 12-month baseline period or on the index date, demographics and clinical characteristics were collected for patients in the study cohorts. The clinical characteristics evaluated included Charlson Comorbidity Index (CCI) score, an indicator of the degree of general comorbidity; $CHADS_2$ and CHA_2DS_2 VASc scores, indicators of stroke risk; and HAS-BLED score, an indicator of bleeding risk. The proportions of patients with prior bleeding, stroke, and usage of certain comedications during the baseline period were additionally determined. The prescribed DOAC dosage level was reported as standard or low; a low-dosage level was considered a dosage below the standard dosage indicated in the US drug package insert.

Rates of Switching to Another OAC and Discontinuation of Index DOACs

The rates of switching to another OAC and discontinuation of index DOACs were evaluated during the follow-up period and reported as the number of patients and proportion of each study cohort. Switching was defined as when a patient had a prescription claim for another OAC, which was not their index DOAC, occurring prior to the date of discontinuation of the index DOAC or the end of study period. Among those who switched, the OACs switched to (other DOACs, including edoxaban, and warfarin) were determined. Discontinuation was defined as when a patient had a >30-day gap in the days' supply of their index DOAC prescription.

Statistical Analyses

Descriptive statistics, with analysis of variance tests and χ^2 tests to detect statistically significant differences in continuous and categorical variables, respectively, were employed to describe and compare patient demographics, clinical characteristics, switching rates, and discontinuation rates of the study cohorts. The times to switching to another OAC and discontinuation of index DOACs from the index date were examined by Kaplan-Meier analyses. Multivariable Cox regression analyses were used to evaluate whether the risks of switching to another OAC and discontinuation of index DOACs differed among the study cohorts (rivaroxaban vs apixaban, dabigatran vs apixaban). The models incorporated the following patient characteristics as covariates: gender, US geographic region, CCI score group, CHA_2DS_2-VASc score group, HAS-BLED score group, prior bleeding in baseline, prior stroke in baseline, select baseline comedications, and index DOAC dosage level (standard vs low). An α value of .05 was used to determine statistical significance. All statistical analyses were carried out with SAS version 9.4.

Results

Demographics and Clinical Characteristics of Study Cohorts

Demographics and clinical characteristics of the study cohorts are shown in Table 1. Of the elderly patients with NVAF identified from the Humana research database and included in the study population (N = 38 250), 55.9% were prescribed apixaban (N = 21 376; mean age: 78.6 years; 49.8% female), 37.3% rivaroxaban (N = 14 277; mean age: 77.4 years; 46.7% female), and 6.8% dabigatran (N = 2597; mean age: 77.0 years; 44.0% female).

General comorbidity, as measured by CCI score, was greater among the apixaban cohort compared to the rivaroxaban and dabigatran cohorts (mean 3.0 vs 2.7 vs 2.6, $P < .001$). Also, stroke risk (mean CHA_2DS_2-VASc score: 4.5 vs 4.3 vs 4.2, $P < .001$) and bleeding risk (mean HAS-BLED score: 3.3 vs 3.1 vs 3.1, $P < .001$) were highest among patients in the apixaban cohort. During the baseline period, a prior bleeding diagnosis had occurred most frequently among the apixaban cohort (20.9% vs 19.0% vs 18.9%, $P < .001$), as had a prior stroke diagnosis (12.8% vs 10.5% vs 11.7%, $P < .001$).

Unadjusted Rates of Switching to Another OAC and Discontinuation of Index DOACs

Prior to adjusting for differences in patient characteristics, during the follow-up periods, patients treated with apixaban had a lower rate of switching to another OAC compared to those treated with either rivaroxaban or dabigatran (5.2% vs 10.6% vs 16.9%, $P < .001$); the rate of discontinuation of apixaban was also lower than that of rivaroxaban or dabigatran (63.2% vs 68.7% vs 71.7%, $P < .001$; Figure 1). Figures 2 and 3 show the times to switching to another OAC and discontinuation of index DOACs for study cohorts based on the Kaplan-Meier analyses.

Table 2 shows the proportions of patients who switched to other OACs from their index DOACs. Among those who switched from apixaban, the majority switched to warfarin (61.5%), 32.2% switched to rivaroxaban, and 6.3% switched to dabigatran. Among those who switched from rivaroxaban, the majority (53.9%) also switched to warfarin, 40.8% switched to apixaban, and 5.3% switched to dabigatran. In the case of dabigatran, the most patients (40.4%) switched to apixaban, 30.4% switched to rivaroxaban, and 29.2% switched to warfarin.

Adjusted Analyses: Risks for Switching to Another OAC and Discontinuation of Index DOACs

After adjusting for differences in patient characteristics via the multivariable Cox regression analysis, compared to patients treated with apixaban, elderly patients with NVAF prescribed rivaroxaban (hazard ratio [HR]: 2.08; 95% confidence interval [CI], 1.92-2.25; $P < .001$) or dabigatran (HR: 3.74; 95% CI, 3.35-4.18, $P < .001$) had a significantly higher risk of switching to another OAC during the follow-up periods (Table 3). Also, compared to patients prescribed apixaban, those prescribed rivaroxaban (HR: 1.10; 95% CI, 1.07-1.13, $P < .001$) or dabigatran (HR: 1.29; 95% CI, 1.23-1.35, $P < .001$) had a significantly higher risk of discontinuing treatment during the follow-up periods (Table 4).

Discussion

Using a large, nationally representative claims database, we identified nearly 40 000 elderly patients with NVAF who were prescribed DOACs. Apixaban was prescribed to over one-half (56%) of the study population, 37% were treated with rivaroxaban, and less than 7% were treated with dabigatran. Compared to the findings of our previous study of younger patients with NVAF (mean age: 61 years), a greater proportion of the elderly study population received apixaban; 37% was observed previously among the younger patient population.[21] However, the data on the prescribing pattern of apixaban complement our other findings in that we have observed before that of the DOACs, apixaban is generally prescribed to older patients with greater comorbidity and higher stroke and bleeding risks.[11,21,22] Among the elderly patients with NVAF in the current study who were prescribed DOACs, after adjusting for the differences in patient characteristics, those treated with rivaroxaban and dabigatran had a 2-fold and nearly a 4-fold higher risk, respectively, to switch to another OAC than patients treated with apixaban. The relative risks of switching to another OAC are consistent with that of our previous study of younger patients with NVAF, although the unadjusted rates of switching among the elderly study population were numerically higher.[21] For elderly patients treated either with apixaban or rivaroxaban, warfarin was the most frequent OAC switched to, while of those treated with dabigatran, the most frequent

Table 1. Demographics and Clinical Characteristics of Study Cohorts.

	Apixaban, N = 21 376		Rivaroxaban, N = 14 277		Dabigatran, N = 2597		*P* Value
Age, years, mean (SD)	78.6 (10.2)		77.4 (9.5)		77.0 (9.3)		<.001
Age group, years	n	%	n	%	n	%	<.001
65-74	8426	39.4	6360	44.6	1208	46.5	
≥75	12 950	60.6	7917	55.5	1389	53.5	
Gender	n	%	n	%	n	%	<.001
Female	10 645	49.8	6665	46.7	1143	44.0	
Male	10 731	50.2	7612	53.3	1454	56.0	
Geographic region	n	%	n	%	n	%	<.001
Midwest	4343	20.3	3222	22.6	530	20.4	
Northeast	594	2.8	411	2.9	78	3.0	
South	14 380	67.3	9093	63.7	1711	65.9	
West	2059	9.6	1551	10.9	278	10.7	
Follow-up duration in months, mean (SD)	9.2 (9.4)		11.3 (12.8)		12.3 (15.3)		<.001
Charlson Comorbidity Index (CCI) score, mean (SD)	3.0 (2.4)		2.7 (2.4)		2.6 (2.4)		<.001
CCI score group	n	%	n	%	n	%	<.001
CCI = 0	3148	14.7	2599	18.2	486	18.7	
CCI = 1-2	7574	35.4	5314	37.2	978	37.7	
CCI = 3-4	5563	26.0	3511	24.6	629	24.2	
CCI ≥5	5091	23.8	2853	20.0	504	19.4	
$CHADS_2$ score, mean (SD)	2.7 (1.4)		2.5 (1.3)		2.5 (1.3)		<.001
$CHADS_2$ score group	n	%	n	%	n	%	<.001
$CHADS_2$ = 0	600	2.8	500	3.5	103	4.0	
$CHADS_2$ = 1-2	9963	46.6	7421	52.0	1330	51.2	
$CHADS_2$ = 3-4	8487	39.7	5204	36.5	944	36.4	
$CHADS_2$ = 5-6	2326	10.9	1152	8.1	220	8.5	
CHA_2DS_2-VASc score, mean (SD)	4.5 (1.6)		4.3 (1.6)		4.2 (1.6)		<.001
CHA_2DS_2-VASc score group	n	%	n	%	n	%	<.001
CHA_2DS_2-VASc = 1-2	1966	9.2	1722	12.1	343	13.2	
CHA_2DS_2-VASc = 3-4	9125	42.7	6674	46.8	1200	46.2	
CHA_2DS_2-VASc = 5-6	7639	35.7	4528	31.7	826	31.8	
CHA_2DS_2-VASc ≥7	2646	12.4	1353	9.5	228	8.8	
HAS-BLED score, mean (SD)	3.3 (1.2)		3.1 (1.1)		3.1 (1.2)		<.001
HAS-BLED score group	n	%	n	%	n	%	<.001
HAS-BLED = 0-2	6209	29.1	4721	33.1	915	35.2	
HAS-BLED ≥3	15 167	71.0	9556	66.9	1682	64.8	
Prior bleeding in baseline	4458	20.9	2712	19.0	490	18.9	<.001
Prior stroke in baseline	2725	12.8	1493	10.5	304	11.7	<.001
Baseline comedications	n	%	n	%	n	%	
ACE inhibitor	8771	41.0	6023	42.2	1057	40.7	.07
Amiodarone	2459	11.5	1479	10.4	253	9.7	<.001
Angiotensin receptor blocker	5353	25.0	3416	23.9	597	23.0	.01
β-Blocker	15 730	73.6	10 268	71.9	1841	70.9	<.001
H_2-receptor antagonist	1535	7.2	917	6.4	162	6.2	.01
Proton pump inhibitor	6705	31.4	4,062	28.5	739	28.5	<.001
Statin	13 332	62.4	8646	60.6	1538	59.2	<.001
Antiplatelet	3191	14.9	1960	13.7	344	13.3	.002
Index DOAC dosage level	n	%	n	%	n	%	<.001
Low	4621	21.6	3516	24.6	387	14.9	
Standard	16 755	78.4	10 761	75.4	2210	85.1	

Abbreviations: ACE, angiotensin-converting enzyme; CCI, Charlson Comorbidity Index; DOAC, direct oral anticoagulant; SD, standard deviation.

OAC switched to was apixaban. In addition to which DOAC was initiated, the regression analysis indicated that the risk for switching to another OAC may have been influenced by the geographic region of care and having significant comorbidity (CCI ≥5).

The rates of discontinuation of index DOACs of elderly patients with NVAF observed in this study were high, averaging 66% across the different DOACs. After adjusting for the differences in patient characteristics, the risks for discontinuation were approximately 10% and 29%, respectively, higher for those treated with rivaroxaban and dabigatran compared to those treated with apixaban. These relative risks for rivaroxaban and dabigatran discontinuation compared with apixaban are also consistent with that reported in our previous study of

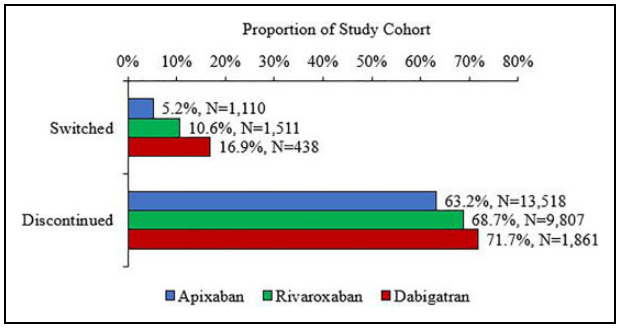

Figure 1. Unadjusted comparison of rates of switching to another OAC and discontinuation of index DOACs of elderly patients with NVAF in study cohorts. Across the 3 patient cohorts, *P* values were <.001 for both switching to another OAC and discontinuing index DOACs. DOAC indicates direct oral anticoagulant; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant.

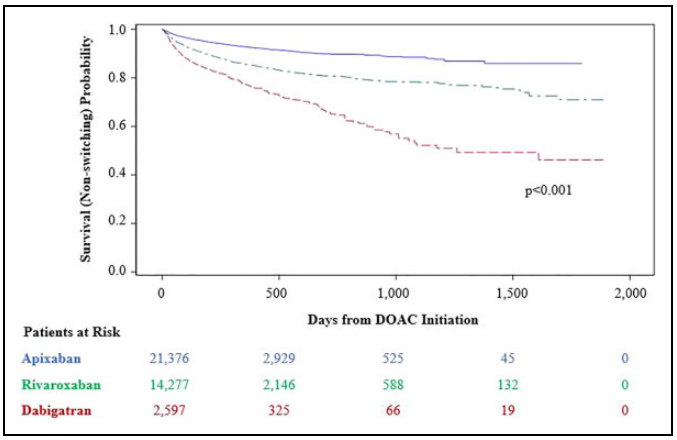

Figure 2. Kaplan-Meier analysis: time to switching to another OAC. DOAC indicates direct oral anticoagulant; OAC, oral anticoagulant.

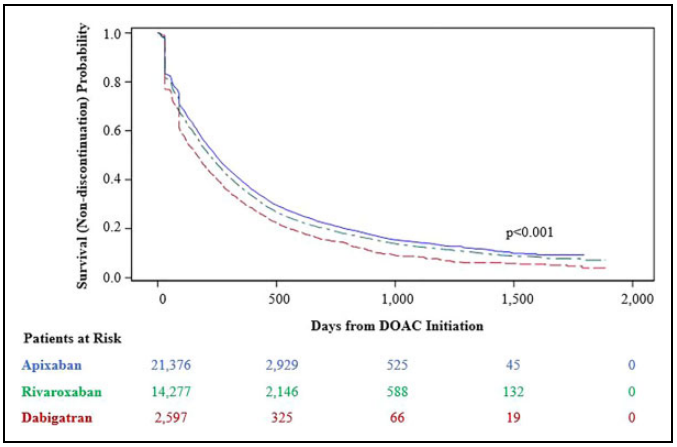

Figure 3. Kaplan-Meier analysis: time to discontinuation of index DOAC. DOAC indicates direct oral anticoagulant.

younger patients with NVAF.[21] Additionally, they are directionally consistent with the findings of Lip et al, who reported 23% and 46% increased risks for discontinuation of

Table 2. Oral Anticoagulants That Patients Switched to From Index DOACs.

	Apixaban, N = 1110		Rivaroxaban, N = 1511		Dabigatran, N = 438	
	n	%	n	%	n	%
OAC switched to						
Apixaban	–	–	617	40.8	177	40.4
Rivaroxaban	357	32.2	–	–	133	30.4
Dabigatran	70	6.3	80	5.3	–	–
Warfarin	683	61.5	814	53.9	128	29.2

Abbreviations: DOAC, direct oral anticoagulant; OAC, oral anticoagulant.

rivaroxaban and dabigatran, respectively, compared to apixaban among patients with NVAF.[23] In the study of Lip et al, discontinuation rates of DOACs were also high, averaging 50% to 72%, with apixaban having the lowest discontinuation rate.[23] In the study by Lip et al and for this current study, a similar definition of discontinuation was used (ie, having a gap >30 days in the days' supply of index DOAC prescription), which may also be indicative of an interruption in therapy and not permanent discontinuation.

The rates of discontinuation of DOACs of elderly patients with NVAF are somewhat higher than those we reported previously among younger patients, which were 53%, 60%, and 63% for apixaban, rivaroxaban, and dabigatran, respectively.[21] Although we have not directly compared the 2 study populations, it may be hypothesized that older patients with NVAF may require even greater oversight or intervention in their DOAC therapy so that the most suitable options when switching are provided to avoid treatment discontinuation. Further study of these adherence issues and whether they are different between older and younger patients with NVAF are warranted. In the current study, other possible factors that may influence discontinuation of DOACs included geographic region of care, having significant comorbidity (CCI = 3-4, ≥5), having prior bleeding, taking certain comedications, and DOAC dosage level. These patient variables also deserve further study using other data sources.

The findings of our study differ from some findings of others, such as those of the study of Brown et al and McHorney et al.[24,25] A few explanations for the differences in findings and reasons that it is difficult to directly compare the results of these studies with our study results include that DOAC discontinuation does not equate with nonadherence as it may be interpreted from these other 2 studies; also there were different patient inclusion criteria across the studies that would likely have impacted the study results, such as the requirement for more than 1 NVAF diagnosis in the study by Brown et al and that patients were not required to be naïve to OAC treatment in the study by McHorney et al. Furthermore, study periods differed, with our index identification period being from January 2013 to September 2017, while for Brown et al the study period was from January 2013 to September 2014, and for McHorney et al it was from January 2013 to June 2015; thus, these other

Table 3. Multivariable Cox Regression Analysis: Risk for Switching to Another OAC for Elderly NVAF Patients Treated With Rivaroxaban and Dabigatran Versus Apixaban.

Variable	Reference	Hazard Ratio	Lower 95% CI	Upper 95% CI	*P* Value
Index DOAC	Apixaban				
Rivaroxaban		2.08	1.92	2.25	<.001
Dabigatran		3.74	3.35	4.18	<.001
Gender					
Male	Female	0.97	0.90	1.05	.46
Geographic region	Midwest				
West		0.87	0.76	1.00	.05
South		0.90	0.83	0.98	.01
Northeast		1.00	0.80	1.24	.97
Charlson Comorbidity Index (CCI) score group	CCI = 0				
CCI = 1-2		1.10	0.98	1.23	.10
CCI = 3-4		1.11	0.97	1.26	.14
CCI ≥5		1.16	1.01	1.35	.04
CHA_2DS_2-VASc score group	CHA_2DS_2-VASc = 1-2				
CHA_2DS_2-VASc = 3-4		1.04	0.91	1.19	.53
CHA_2DS_2-VASc = 5-6		1.14	0.97	1.33	.12
CHA_2DS_2-VASc ≥7		1.10	0.90	1.35	.34
HAS-BLED score group					
HAS-BLED ≥3	HAS-BLED = 0-2	0.99	0.90	1.08	.79
Prior bleeding in baseline	Yes vs No	0.92	0.84	1.02	.10
Prior stroke in baseline	Yes vs No	0.92	0.81	1.04	.16
Baseline comedication usage	Yes vs No				
ACE inhibitor		1.02	0.94	1.10	.68
Amiodarone		1.05	0.93	1.18	.42
Angiotensin receptor blocker		1.03	0.95	1.13	.47
β-Blocker		1.07	0.98	1.16	.14
H_2-receptor antagonist		0.91	0.78	1.05	.19
Proton pump inhibitor		1.04	0.96	1.12	.37
Statin		0.99	0.92	1.07	.87
Antiplatelet		1.06	0.95	1.18	.29
Index DOAC dosage level					
Standard	Low	0.96	0.88	1.05	.39

Abbreviations: ACE, angiotensin-converting enzyme; CCI, Charlson Comorbidity Index; CI, confidence interval; DOAC, direct oral anticoagulant; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant.

Table 4. Multivariable Cox Regression Analysis: Risk for Discontinuation of Index DOACs for Elderly NVAF Patients Treated With Rivaroxaban and Dabigatran Versus Apixaban.

Variable	Reference	Hazard Ratio	Lower 95% CI	Upper 95% CI	*P* Value
Index DOAC	Apixaban				
Rivaroxaban		1.10	1.07	1.13	<.001
Dabigatran		1.29	1.23	1.35	<.001
Gender					
Male	Female	1.15	1.12	1.18	<.001
Geographic region	Midwest				
West		1.13	1.08	1.19	<.001
South		1.16	1.12	1.19	<.001
Northeast		1.03	0.94	1.11	.56
Charlson Comorbidity Index (CCI) score group	CCI = 0				
CCI = 1-2		1.07	1.03	1.11	.002
CCI = 3-4		1.13	1.08	1.19	<.001
CCI ≥5		1.25	1.19	1.32	<.001
CHA_2DS_2-VASc score group	CHA_2DS_2-VASc = 1-2				
CHA_2DS_2-VASc = 3-4		1.03	0.98	1.07	.30
CHA_2DS_2-VASc = 5-6		1.05	0.99	1.11	.11
CHA_2DS_2-VASc ≥7		1.06	0.98	1.13	.13
HAS-BLED score group					
HAS-BLED ≥3	HAS-BLED = 0-2	1.05	1.01	1.08	.01
Prior bleeding in baseline	Yes vs No	1.06	1.03	1.10	<.001
Prior stroke in baseline	Yes vs No	0.86	0.82	0.89	<.001
Baseline comedication usage	Yes vs No				
ACE inhibitor		0.99	0.96	1.01	.32
Amiodarone		1.22	1.18	1.27	<.001
Angiotensin receptor blocker		0.97	0.94	1.01	.10
β-Blocker		0.95	0.92	0.97	<.001
H_2-receptor antagonist		1.01	0.96	1.06	.69
Proton pump inhibitor		1.03	1.00	1.05	.08
Statin		0.90	0.88	0.92	<.001
Antiplatelet		0.95	0.92	0.99	.01
Index DOAC dosage level					
Standard	Low	0.96	0.93	0.99	.01

Abbreviations: ACE, angiotensin-converting enzyme; CCI, Charlson Comorbidity Index; CI, confidence interval; DOAC, direct oral anticoagulant; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant.

studies had older time frames. In relationship to the differences in study periods, among our study population, over one-half were prescribed apixaban; while in the study of Brown et al, 13% in 2013 and 31% in 2014 were treated with apixaban; and in the study of McHorney et al, it was 27% of the DOAC treated population, both of which reflected more outdated treatment patterns among patients with NVAF. Taken together, these studies show the evolving prescribing patterns of DOACs.

Although there can be a number of potential reasons for making changes to OAC therapy, the lower bleeding rate frequently observed with apixaban treatment in comparison to rivaroxaban and dabigatran in multiple real-world studies may have some influence on treatment-related decisions, especially among elderly patients.[9-14] Further study of DOAC usage patterns among patients with NVAF and across different patient groups is warranted, since suboptimal adherence, interruptions in therapy, and/or discontinuation of DOACs are associated with poor patient outcomes.[17-20,26,27]

Limitations

Due to limitations of the data source, we were unable to discern why patients may have switched to another OAC or discontinued DOAC treatment. The potential causes of these events may involve several factors, such as patient choice, copay changes/financial considerations, potential adverse events associated with drugs, change in patient comorbidity profiles, and so on. Further study utilizing data sources that may have available the descriptions of the reasons concerning medication changes (eg, electronic medical records database) with longer follow-up periods is needed to more completely understand DOAC usage patterns. Such data may also be useful for building a framework to improve the management of elderly patients with NVAF who are treated with these anticoagulants. Although for this study we used the term "discontinuation," the study definition may not indicate permanent DOAC discontinuation and possibly only an interruption in therapy. Such a definition for drug discontinuation has been used in other previous studies.[18,21,23] We used prescription claims as a proxy for medication usage and the presence of a claim for a filled prescription does not actually indicate that the medication was taken as prescribed. Additionally, taking aspirin sold over the counter that may be used for stroke prevention was not captured in the claims data and may have influenced the treatment patterns we observed for the different DOACs in this study. Due to the later commercial availability of apixaban in the United States, the mean duration of the follow-up period for patients treated with apixaban was less than that of those treated with rivaroxaban and dabigatran. Such differences in the follow-up durations (apixaban: 9.2 months; rivaroxaban: 11.3 months; dabigatran: 12.3 months) were expected and generally align with the US market launch sequence of the DOACs; first dabigatran, followed by rivaroxaban, and then apixaban. For the switching and discontinuation outcome Cox regression analyses, we used censoring indicators to account for the differences in follow-up durations of the study cohorts treated with the different DOACs. Also, the unadjusted and adjusted data were relatively consistent in regard to the observations of the lower rate/risk of switching and discontinuation among patients treated with apixaban compared to that of those treated with rivaroxaban and dabigatran. Future additional study of such outcomes with longer follow-up periods may be needed to further confirm these findings. As this analysis was based on a claims database, there may have been coding errors and inaccuracies in the data. The Human research database is a large nationally representative claims database; however, the data collected in this study may not be representative of the entire US population of elderly patients with NVAF. Lastly, there may be other confounding factors that are not well captured in the data source and residual bias may remain for the measured outcomes of the multivariable Cox regression analyses.

Conclusions

Based on this large-scale study of nearly 40 000 elderly patients with NVAF in the United States who were prescribed DOACs, there were significant risks for switching to another OAC and discontinuation of index treatment. The risks for such events were lower for those treated with apixaban compared to those treated with rivaroxaban and dabigatran. As DOAC prescribing and usage patterns continue to evolve, it is important for future studies to monitor DOAC usage patterns alongside evaluating the associated patient outcomes to ensure optimal oral anticoagulation therapy is provided to patients with NVAF.

Authors' Note

In compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the database utilized for this study consists of fully deidentified data sets with synthetic identifiers applied to patient- and provider-level data to protect the identities of both the patients and data contributors. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Christine L. Baker, Jack Mardekian, Oluwaseyi Dina, and Cristina Russ are employees and stockholders of Pfizer, Inc. Amol Dhamane, Jigar Rajpura, and Lisa Rosenblatt are employees of Bristol-Myers Squibb. Melissa Lingohr-Smith and Jay Lin are employees of Novosys Health, which has received research funds from Pfizer and Bristol-Myers Squibb in connection with conducting this study and development of this manuscript.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was sponsored by Pfizer and Bristol-Myers Squibb.

References

1. Kistler P, Sanders P, Fynn S, et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J Am Coll Cardiol*. 2004;44(1):109-116.
2. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64(21):e1-e76.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22(8):983-988.
4. McManus DD, Rienstra M, Benjamin EJ. An update on the prognosis of patients with atrial fibrillation. *Circulation*. 2012; 126(10):e143-e146.
5. Mitrousi K, Lip GYH, Apostolakis S. Age as a risk factor for stroke in atrial fibrillation patients: implication in thromboprophylaxis in the era of novel oral anticoagulants. *J Atr Fibrillation*. 2013;6(1):783.
6. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011; 365(11):981-992.
7. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011; 365(10):883-891.
8. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009; 361:1139-1151.
9. Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. *Stroke*. 2017;48(9):2494-2503.
10. Lin J, Trocio J, Gupta K, et al. Major bleeding risk and healthcare economic outcomes of non-valvular atrial fibrillation patients newly-initiated with oral anticoagulant therapy in the real-world setting. *J Med Econ*. 2017;20(9):952-961.
11. Deitelzweig S, Luo X, Gupta K, et al. Comparison of effectiveness and safety of treatment with apixaban vs. other oral anticoagulants among elderly nonvalvular atrial fibrillation patients. *Curr Med Res Opin*. 2017;33(10):1745-1754.
12. Adeboyeje G, Sylwestrzak G, Barron JJ, et al. Major bleeding risk during anticoagulation with warfarin, dabigatran, apixaban, or rivaroxaban in patients with nonvalvular atrial fibrillation. *J Manag Care Spec Pharm*. 2017;23(9):968-978.
13. Yao X, Abraham NS, Sanaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc*. 2016;5(6): e003725.
14. Lip GY, Keshishian A, Kamble S, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. *Thromb Haemost*. 2016; 116(5):975-986.
15. Marzec LN, Wang J, Shah ND, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol*. 2017;69(20):2475-2484.
16. Brown JD, Shewale AR, Dherange P, Talbert JC. A comparison of oral anticoagulant use for atrial fibrillation in the pre- and post-DOAC eras. *Drugs Aging*. 2016;33(6):427-436.
17. Borne RT, O'Donnel C, Turakhia MP, et al. Adherence and outcomes to direct oral anticoagulants among patients with atrial fibrillation: findings from the Veterans health administration. *BMC Cardiovasc Disord*. 2017;17(1):236.
18. Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc*. 2016;5(2): e003074.
19. Vene N, Mavri A, Gubenšek M, et al. Risk of thromboembolic events in patients with non-valvular atrial fibrillation after dabigatran or rivaroxaban discontinuation—data from the Ljubljana registry. *PLoS One*. 2016;11(6):e0156943.
20. Amin A, Marrs JC. Direct oral anticoagulants for the management of thromboembolic disorders: the importance of adherence and persistence in achieving beneficial outcomes. *Clin Appl Thromb Hemost*. 2016;22(7):605-616.
21. Baker CL, Dhamane AD, Mardekian J, et al. Comparison of drug switching and discontinuation rates in patients with nonvalvular atrial fibrillation treated with direct oral anticoagulants in the United States. *Adv Ther*. 2019;36(1):162-174.
22. Deitelzweig S, Bruno A, Trocio J, et al. An early evaluation of bleeding-related hospital readmissions among hospitalized patients with nonvalvular atrial fibrillation treated with direct oral anticoagulants. *Curr Med Res Opin*. 2016;32(3):573-582.
23. Lip GYH, Pan X, Kamble S, et al. Discontinuation risk comparison among 'real-world' newly anticoagulated atrial fibrillation patients: apixaban, warfarin, dabigatran, or rivaroxaban. *PLoS One*. 2018;13(4):e0195950.
24. Brown JD, Shewale AR, Talbert JC. Adherence to rivaroxaban, dabigatran, and apixaban for stroke prevention for newly diagnosed and treatment-naïve atrial fibrillation: an update using 2013–2014 data. *J Manag Care Spec Pharm*. 2017;23(9): 958-967.
25. McHorney CA, Ashton V, Laliberté F, et al. Adherence to rivaroxaban compared with other oral anticoagulant agents among patients with nonvalvular atrial fibrillation. *J Manag Care Spec Pharm*. 2017;23(9):980-988.
26. Patel MR, Hellkamp AS, Lokhnygina Y, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol*. 2013;61(6):651-658.
27. Sherwood MW, Douketis JD, Patel MR, et al. Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from ROCKET AF. *Circulation*. 2014;129(18):1850-1859.