Real-World Comparative Effectiveness, Safety, and Health Care Costs of Oral Anticoagulants in Nonvalvular Atrial Fibrillation Patients in the U.S. Department of Defense Population

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ABSTRACT

BACKGROUND: The ARISTOTLE trial demonstrated that apixaban had significantly lower rates of stroke/systemic embolism (SE) and major bleeding than warfarin; however, no direct clinical trials between apixaban and other direct oral anticoagulants (DOACs) are available. Few real-world studies comparing the effectiveness and safety between DOACs have been conducted.

OBJECTIVE: To compare effectiveness, safety, and health care costs among oral anticoagulants (OACs) for nonvalvular atrial fibrillation (NVAF) patients in the U.S. Department of Defense (DoD) population.

METHODS: Adult NVAF patients initiating warfarin or DOACs (apixaban, rivaroxaban, and dabigatran) were selected from U.S. DoD data from January 1, 2013, to September 30, 2015. The first OAC claim date was designated as the index date. Patients initiating another OAC were matched 1:1 to apixaban patients using propensity score matching to balance demographics and clinical characteristics. Cox proportional hazards models were used to estimate the risk of stroke/SE and major bleeding for each OAC versus apixaban. Generalized linear and two-part models with bootstrapping were used to compare all-cause health care costs and stroke/SE-related and major bleeding-related medical costs.

RESULTS: Of the 41,001 eligible patients, 7,607 warfarin-apixaban, 4,129 dabigatran-apixaban, and 11,284 rivaroxaban-apixaban pairs were matched. Warfarin (HR = 1.84; 95% CI = 1.30-2.59; $P < 0.001$) and rivaroxaban (HR = 1.46; 95% CI = 1.08-1.98; $P = 0.015$) were associated with a significantly higher risk of stroke/SE compared with apixaban. Dabigatran (HR = 1.17; 95% CI = 0.68-2.03; $P = 0.573$) was associated with a numerically higher risk of stroke/SE compared with apixaban. Warfarin (HR = 1.53; 95% CI = 1.24-1.89; $P < 0.001$), dabigatran (HR = 1.76; 95% CI = 1.27-2.43; $P < 0.001$), and rivaroxaban (HR = 1.59; 95% CI = 1.34-1.89; $P < 0.001$) were associated with higher risks of major bleeding compared with apixaban.

Compared with apixaban, patients prescribed warfarin incurred numerically higher all-cause total health care costs per patient per month (PPPM) (\$2,498 vs. \$2,277; $P = 0.148$) and significantly higher stroke/SE-related (\$118 vs. \$46; $P = 0.012$) and major bleeding-related (\$166 vs. \$76; $P = 0.003$) medical costs. Dabigatran patients incurred numerically higher all-cause total health care PPPM costs (\$2,372 vs. \$2,143; $P = 0.150$) and stroke/SE-related medical costs (\$61 vs. \$32; $P = 0.240$) but significantly higher major bleeding-related costs (\$114 vs. \$58; $P = 0.025$). Rivaroxaban patients incurred significantly higher all-cause total health care costs (\$2,546 vs. \$2,200; $P < 0.001$) and major bleeding-related medical costs PPPM (\$137 vs. \$69; $P < 0.001$) but numerically higher stroke/SE-related medical costs PPPM (\$58 vs. \$38; $P = 0.057$).

CONCLUSIONS: Among NVAF patients in the U.S. DoD population, warfarin and rivaroxaban were associated with a significantly higher risk of stroke/SE and major bleeding compared with apixaban. Dabigatran use was associated with a numerically higher risk of stroke/SE and a significantly higher

risk of major bleeding compared with apixaban. Warfarin and dabigatran incurred numerically higher all-cause total health care costs compared with apixaban. Rivaroxaban was associated with significantly higher all-cause total health care costs compared with apixaban.

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What is already known about this subject

- Warfarin has been the standard oral anticoagulant for decades; several direct oral anticoagulants were approved for stroke prevention in atrial fibrillation patients in recent years.
- A prospective randomized clinical trial demonstrated that apixaban had significantly lower rates of stroke/systemic embolism (SE) and major bleeding than warfarin.

What this study adds

- In the U.S. Department of Defense population, apixaban initiation was associated with a significantly lower risk of stroke/SE and major bleeding compared with warfarin and rivaroxaban.
- Apixaban initiation was associated with a lower risk of stroke/SE that was not statistically significant but was also associated with significantly lower risk of major bleeding compared with dabigatran initiation.
- Compared with apixaban initiators, all-cause health care costs were significantly higher for rivaroxaban but similar for dabigatran and warfarin initiators.

Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with a nearly 5-fold excess risk of stroke.^{1,2} In the United States in 2010, the estimated prevalence of AF was approximately 5.2 million.³ The annual direct expenses for nonvalvular AF (NVAF) were estimated at approximately \$7 billion, which included \$3 billion to \$4 billion for hospitalizations.⁴

The American College of Cardiology/American Heart Association/Heart Rhythm Society Guideline recommends oral anticoagulants (OACs) for patients with NVAF and previous stroke, transient ischemic attack, or CHA₂DS₂-VASc score

≥ 2 .⁵ Adjusted-dose warfarin has been used prophylactically as an oral anticoagulant to reduce the risk of stroke among NVAF patients.⁶ In recent years, 4 direct OACs (DOACs; dabigatran, rivaroxaban, apixaban, and edoxaban) have been approved by the U.S. Food and Drug Administration for the prevention of stroke and systemic embolism (SE) in NVAF patients. These DOACs offer the advantages of fewer drug-drug interactions, an absence of major dietary effects, no requirement for regular international normalized ratio monitoring, and less risk of intracranial bleeding when compared with warfarin.⁶

In the phase 3 randomized clinical trials comparing the effectiveness and safety among DOACs and warfarin, DOAC patients had at least noninferior risks of stroke/SE than warfarin patients; however, risks of major bleeding varied between DOACs and warfarin.⁷⁻¹⁰ No direct clinical trials have compared dabigatran, rivaroxaban, and apixaban.

In addition to clinical trials, retrospective observational studies have also examined the comparative effectiveness and safety among OACs.^{11,12} A recent meta-analysis showed that apixaban was associated with a similar risk of stroke/SE versus warfarin, dabigatran, rivaroxaban, and edoxaban, as well as a lower risk of major bleeding compared with warfarin and rivaroxaban.¹² Several studies have reported that apixaban patients incurred lower health care costs (inpatient and/or outpatient) compared with warfarin and rivaroxaban, but incurred similar costs compared with dabigatran.¹³⁻¹⁵ However, additional large real-world studies are warranted to support these results.

The U.S. Department of Defense (DoD) health care system is one of the largest health care plans in the United States. To the best of our knowledge, this is the first study using this dataset to examine the risk of stroke/SE and major bleeding, as well as health care costs, among apixaban and other OACs. The purpose of this study was to provide additional information on clinical and economic outcomes of OAC-naïve patients newly prescribed apixaban, dabigatran, rivaroxaban, or warfarin in a real-world clinical practice setting.

Methods

Data Source

We conducted a retrospective analysis using the U.S. DoD data from January 1, 2012, to September 30, 2015. The DoD provides health care to more than 9.4 million beneficiaries located in all 50 U.S. states and multiple countries. Beneficiaries include active duty, activated Guard and Reserve, retirees, survivors, some inactive Guard and Reserve, and their family members.¹⁶ Most beneficiaries are retired service members and their family members (4.8 million, 51%), many of whom are Medicare eligible. The data include information about the inpatient, outpatient, emergency room, and pharmacy claims from U.S. DoD facilities and civilian/private sector care for eligible beneficiaries.

Patient Selection

Treatment-naïve patients with ≥ 1 pharmacy claim for warfarin, apixaban, rivaroxaban, or dabigatran from January 1, 2013, through September 30, 2015, were selected. Given the later market entry (and hence small sample size), edoxaban was not included in the study. The first DOAC prescription date was designated as the index date if patients had DOAC claims; the first warfarin prescription date was designated as the index date for patients without any DOAC claim. Patients were required to have continuous health plan enrollment for 12 months before the index date (baseline period) and ≥ 1 medical claim for AF (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 427.31) during the baseline period.¹⁷

Patients were excluded from the study if they had claims for valvular heart disease, heart valve replacement, or heart surgery; dialysis, kidney transplant, or end-stage chronic kidney disease; venous thromboembolism or reversible AF (pericarditis, hyperthyroidism, or thyrotoxicity); a pharmacy claim for an OAC during the baseline period; hip or knee replacement within 6 weeks before the index date; > 1 OAC claim on the index date; or indication of pregnancy during the study period.

Patient demographics, clinical risk scores (Charlson Comorbidity Index [CCI], CHA₂DS₂-VASc, and HAS-BLED), comorbidities, comedications, and hospitalizations during the 12-month baseline period were measured. Patient data were assessed from the day after the index date until the date of discontinuation, switch to an OAC other than the index drug, death, interruption in continuous enrollment (no gap was allowed), or the end of the study period (September 30, 2015), whichever occurred first. Discontinuation was defined as no evidence of an index OAC prescription for 30 days from the last day of supply of the last filled prescription. The discontinuation date was defined as the last day of supply of the last filled prescription. Switching was defined as a prescription for an OAC other than the index OAC prescription within 30 days before or after the discontinuation date.¹⁸

Outcome Measures

The primary outcomes were stroke/SE, major bleeding, and health care costs (all-cause, stroke/SE-related, and major bleeding-related). Stroke/SE and major bleeding were defined by the primary or secondary diagnosis position of inpatient claims. Stroke/SE included ischemic stroke, hemorrhagic stroke, and SE. Major bleeding included bleeding at key sites including—but not limited to—intracranial, gastrointestinal, liver, splenic, and ocular hemorrhage. The stroke/SE and major bleeding code lists were based on previously published studies and validated administrative claims-based algorithms.^{19,20}

FIGURE 1 Attrition Flowchart

AF=atrial fibrillation; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; OAC=oral anticoagulant.

All-cause medical costs represent the sum of outpatient, emergency room, and inpatient costs. Total health care costs represent the sum of medical and pharmacy costs. Patients with insurance through the DoD do not have to pay for prescriptions filled through the DoD system; therefore, there is no cost value for those prescriptions. The pharmacy costs observed in this study were from TRICARE Mail Order Pharmacy and retail pharmacies. Patients pay copays for prescriptions filled through mail order or a traditional retail pharmacy.

Stroke/SE-related and major bleeding-related medical costs were defined as the hospitalization costs associated with the

first stroke/SE or major bleeding event plus all subsequent stroke/SE or major bleeding costs occurring in the inpatient or outpatient setting. Per patient per month (PPPM) costs were measured and adjusted to 2015 U.S. dollars using the medical care component of the Consumer Price Index.

Statistical Methods

The design, analytical methods, and presentation of this study were informed by the guidelines for comparative effectiveness research.^{21,22} All study variables, including baseline and outcome measures, were analyzed descriptively and stratified by cohort.

**Real-World Comparative Effectiveness, Safety, and Health Care Costs of Oral Anticoagulants
in Nonvalvular Atrial Fibrillation Patients in the U.S. Department of Defense Population**

TABLE 1 Baseline Characteristics of NVAf Patients in the Propensity Score-Matched Cohorts

	Apixaban Cohort (n = 7,607)		Warfarin Cohort (n = 7,607)		STD ^a	Apixaban Cohort (n = 4,129)		Dabigatran Cohort (n = 4,129)		STD ^a	Apixaban Cohort (n = 11,284)		Rivaroxaban Cohort (n = 11,284)		STD ^a
	n/Mean	%/SD	n/Mean	%/SD		n/Mean	%/SD	n/Mean	%/SD		n/Mean	%/SD	n/Mean	%/SD	
Age	76.5	9.5	76.6	9.8	0.95	73.0	10.0	73.0	9.9	0.05	75.3	9.6	75.3	9.5	0.12
18-54	172	2.3	178	2.3	0.53	183	4.4	160	3.9	2.79	315	2.8	293	2.6	1.20
55-64	558	7.3	563	7.4	0.25	523	12.7	561	13.6	2.73	993	8.8	1,007	8.9	0.44
65-74	2,157	28.4	2,057	27.0	2.94	1,472	35.7	1,487	36.0	0.76	3,518	31.2	3,493	31.0	0.48
≥ 75	4,720	62.0	4,809	63.2	2.42	1,951	47.3	1,921	46.5	1.46	6,458	57.2	6,491	57.5	0.59
Sex															
Male	4,431	58.2	4,430	58.2	0.03	2,551	61.8	2,538	61.5	0.65	6,431	57.0	6,411	56.8	0.36
Female	3,176	41.8	3,177	41.8	0.03	1,578	38.2	1,591	38.5	0.65	4,853	43.0	4,873	43.2	0.36
Geographic region															
Northeast	632	8.3	644	8.5	0.57	283	6.9	275	6.7	0.77	690	6.1	685	6.1	0.19
North Central	1,182	15.5	1,191	15.7	0.33	564	13.7	562	13.6	0.14	1,309	11.6	1,325	11.7	0.44
South	3,672	48.3	3,688	48.5	0.42	2,271	55.0	2,284	55.3	0.63	6,722	59.6	6,680	59.2	0.76
West	1,966	25.8	1,933	25.4	0.99	939	22.7	938	22.7	0.06	2,380	21.1	2,407	21.3	0.59
Other	155	2.0	151	2.0	0.37	72	1.7	70	1.7	0.37	183	1.6	187	1.7	0.28
Dose															
Standard	5,714	75.1				3,452	83.6	3,535	85.6		8,856	78.5	8,044	71.3	
Reduced	1,893	24.9				677	16.4	594	14.4		2,428	21.5	3,240	28.7	
Baseline comorbidity															
Deyo-Charlson Comorbidity Index score	2.5	2.4	2.5	2.4	1.51	1.92	2.09	1.92	2.07	0.05	2.2	2.3	2.2	2.3	0.24
CHADS ₂ score	2.6	1.4	2.6	1.4	1.28	2.2	1.3	2.2	1.4	0.73	2.4	1.4	2.4	1.4	0.27
0 = low risk	422	5.5	408	5.4	0.81	340	8.2	348	8.4	0.70	675	6.0	637	5.6	1.44
1 = moderate risk	1,318	17.3	1,294	17.0	0.84	1,030	24.9	1,048	25.4	1.00	2,344	20.8	2,362	20.9	0.39
2 = high risk	2,247	29.5	2,360	31.0	3.23	1,287	31.2	1,289	31.2	0.10	3,513	31.1	3,555	31.5	0.80
> 2 = high risk	3,620	47.6	3,545	46.6	1.98	1,472	35.7	1,444	35.0	1.42	4,752	42.1	4,730	41.9	0.39
CHA ₂ DS ₂ -VASc score	4.2	1.8	4.1	1.8	0.81	3.6	1.7	3.6	1.8	0.82	4.0	1.7	4.0	1.7	0.16
0 = low risk	108	1.4	111	1.5	0.33	89	2.2	127	3.1	5.77	183	1.6	170	1.5	0.93
1 = moderate risk	363	4.8	377	5.0	0.86	353	8.5	332	8.0	1.84	610	5.4	643	5.7	1.28
2 = high risk	872	11.5	832	10.9	1.67	694	16.8	689	16.7	0.32	1,509	13.4	1,452	12.9	1.50
> 2 = high risk	6,264	82.3	6,287	82.6	0.80	2,993	72.5	2,981	72.2	0.65	8,982	79.6	9,019	79.9	0.82
HAS-BLED score	3.0	1.3	3.0	1.3	1.65	2.8	1.2	2.8	1.2	0.14	3.0	1.2	3.0	1.2	0.71
0 = low risk	100	1.3	110	1.4	1.13	75	1.8	84	2.0	1.59	139	1.2	129	1.1	0.82
1-2 = moderate risk	2,606	34.3	2,737	36.0	3.61	1,782	43.2	1,704	41.3	3.83	4,043	35.8	4,041	35.8	0.04
> 2 = high risk	4,901	64.4	4,760	62.6	3.85	2,272	55.0	2,341	56.7	3.37	7,102	62.9	7,114	63.0	0.22
Baseline prior bleed	1,525	20.0	1,484	19.5	1.35	606	14.7	602	14.6	0.27	1,903	16.9	1,907	16.9	0.09
Baseline prior stroke	931	12.2	907	11.9	0.97	365	8.8	354	8.6	0.94	1,090	9.7	1,113	9.9	0.69
Congestive heart failure	2,052	27.0	2,033	26.7	0.56	823	19.9	777	18.8	2.82	2,469	21.9	2,490	22.1	0.45
Diabetes	2,631	34.6	2,593	34.1	1.05	1,303	31.6	1,313	31.8	0.52	3,544	31.4	3,529	31.3	0.29
Hypertension	6,469	85.0	6,450	84.8	0.70	3,423	82.9	3,442	83.4	1.23	9,694	85.9	9,741	86.3	1.20
Renal disease	1,852	24.3	1,839	24.2	0.40	654	15.8	653	15.8	0.07	2,170	19.2	2,202	19.5	0.72
Myocardial infarction	485	6.4	479	6.3	0.32	226	5.5	208	5.0	1.95	603	5.3	622	5.5	0.74
Dyspepsia or stomach discomfort	1,404	18.5	1,398	18.4	0.20	746	18.1	729	17.7	1.07	2,068	18.3	2,074	18.4	0.14
Peripheral vascular disease	3,755	49.4	3,742	49.2	0.34	1,786	43.3	1,746	42.3	1.96	5,324	47.2	5,308	47.0	0.28
Transient ischemic attack	599	7.9	596	7.8	0.15	251	6.1	257	6.2	0.60	824	7.3	827	7.3	0.10
Coronary artery disease	3,146	41.4	3,126	41.1	0.53	1,512	36.6	1,478	35.8	1.71	4,534	40.2	4,544	40.3	0.18
Baseline medication use															
Angiotensin-converting enzyme inhibitor	2,696	35.4	2,714	35.7	0.49	1,383	33.5	1,411	34.2	1.43	3,876	34.3	3,866	34.3	0.19
Angiotensin receptor blocker	1,983	26.1	1,921	25.3	1.87	1,126	27.3	1,126	27.3	0.00	3,195	28.3	3,218	28.5	0.45
Amiodarone	772	10.1	765	10.1	0.31	365	8.8	359	8.7	0.51	1,119	9.9	1,127	10.0	0.24

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Real-World Comparative Effectiveness, Safety, and Health Care Costs of Oral Anticoagulants in Nonvalvular Atrial Fibrillation Patients in the U.S. Department of Defense Population

TABLE 1 Baseline Characteristics of NVAF Patients in the Propensity Score-Matched Cohorts (continued)

	Apixaban Cohort (n = 7,607)		Warfarin Cohort (n=7,607)		STD ^a	Apixaban Cohort (n = 4,129)		Dabigatran Cohort (n = 4,129)		STD ^a	Apixaban Cohort (n = 11,284)		Rivaroxaban Cohort (n = 11,284)		STD ^a
	n/Mean	%/SD	n/Mean	%/SD		n/Mean	%/SD	n/Mean	%/SD		n/Mean	%/SD	n/Mean	%/SD	
Baseline medication use															
Dronedarone	140	1.8	151	2.0	1.06	211	5.1	197	4.8	1.56	526	4.7	521	4.6	0.21
Beta blockers	5,286	69.5	5,304	69.7	0.51	2,894	70.1	2,865	69.4	1.53	8,076	71.6	8,074	71.6	0.04
Statins	4,616	60.7	4,572	60.1	1.18	2,420	58.6	2,446	59.2	1.28	6,915	61.3	6,885	61.0	0.55
Calcium channel blockers	3,000	39.4	3,001	39.5	0.03	1,602	38.8	1,655	40.1	2.63	4,580	40.6	4,600	40.8	0.36
H ₂ -receptor antagonist	521	6.8	521	6.8	0.00	240	5.8	244	5.9	0.41	782	6.9	773	6.9	0.31
Proton pump inhibitor	2,813	37.0	2,817	37.0	0.11	1,558	37.7	1,545	37.4	0.65	4,467	39.6	4,472	39.6	0.09
Antiplatelets	1,740	22.9	1,668	21.9	2.27	985	23.9	1,001	24.2	0.91	2,800	24.8	2,824	25.0	0.49
Baseline inpatient admission	3,237	42.6	3,217	42.3	0.53	1,521	36.8	1,485	36.0	1.81	4,387	38.9	4,391	38.9	0.07

^aStandardized difference = 100 actual standardized difference. Standardized difference > 10 is considered significant.

SD = standard deviation; STD = standardized difference.

One-to-one propensity score matching (PSM) was used to balance demographics and clinical characteristics between each matched cohort (warfarin vs. apixaban, dabigatran vs. apixaban, and rivaroxaban vs. apixaban). Age, sex, U.S. geographic region, CCI score, CHA₂DS₂-VAsC score, HAS-BLED score, stroke and bleeding history, comorbidities, baseline medication use, and inpatient admissions were used to calculate propensity scores for each patient using logistic regression.²³ The nearest neighbor method without replacement with a caliper of 0.01 was used to match patients. Mean standardized differences were used to assess the balance of baseline patient characteristics; values > 10% were used as the threshold for statistical significance.²⁴

Incidence rates of stroke/SE and major bleeding in PSM cohorts were calculated as the number of stroke/SE and major bleeding events, respectively, per 100 person-years. Cox proportional hazards models with robust sandwich estimates were used to compare the risk of stroke/SE and major bleeding in each of the matched cohorts. No additional variables except treatment were included in the models since all the baseline variables were balanced.

The association between treatments and the all-cause health care cost outcomes was evaluated using generalized linear models with log-link and a gamma distribution, wherein the dependent variable was costs.²⁵ The association between treatment and the stroke/SE-related and major bleeding-related medical costs was evaluated using 2-part models with bootstrapping, which took the cost fields with 0 values into account.²⁶ The costs and differences in costs, 95% confidence interval (CI), and *P* values for each model are reported.

Sensitivity Analyses

Sensitivity analyses were conducted to test the robustness of the main results. In the first sensitivity analysis, the cohorts

were stratified by dose (reduced and standard) to determine if the treatment effects were modified by dose. Patients prescribed DOACs were stratified into subgroups of standard dose (apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg) and reduced dose (apixaban 2.5 mg, dabigatran 75 mg, and rivaroxaban 10 mg or 15 mg) based on the index dose. Each warfarin patient was assigned to 1 of the 2 subgroups per the dose of the matched apixaban patient. In each subgroup, the balance of baseline characteristics was evaluated; when imbalance was detected (standardized difference >10%), the variable was included in the multivariate model. The statistical significance of the interaction between treatment and dose was evaluated.

Second, patients who had catheter ablation within 2 months before the index prescription and those who had cardioversion 1 month before or after the index drug initiation date were excluded, as they likely had a low risk of stroke/SE and were administered an OAC for their procedure, not for long-term stroke prevention.^{27,28}

Third, a sensitivity analysis for the 6 months postindex date as follow-up was also conducted. In this analysis, patients were censored at OAC discontinuation, switch, death, disenrollment date, end of the study period (September 30, 2015), or 6 months after the index date, whichever occurred the earliest. Sensitivity analysis allowed for the follow-up period to be more balanced between the cohorts. Finally, a sensitivity analysis using the intent-to-treat method was implemented, where patient data were assessed based on the index drug regardless of discontinuation or switch.

Results

Baseline Characteristics

A total of 41,001 patients were eligible for the study, including 9,255 (22.6%) warfarin, 4,312 (10.5%) dabigatran, 15,680

FIGURE 2 Risk of Stroke/SE and Major Bleeding in the Propensity Score-Matched Populations

CI=confidence interval; SE=systemic embolism.

(38.2%) rivaroxaban, and 11,754 (28.7%) apixaban patients. Patients initiating apixaban were younger and had lower baseline mean CHA₂DS₂-VASc, HAS-BLED, and CCI scores than warfarin patients. However, compared with those initiating dabigatran and rivaroxaban, patients initiating apixaban were older and had higher baseline mean CHA₂DS₂-VASc, HAS-BLED, and CCI scores.

After 1:1 PSM, there were 7,607 warfarin-apixaban, 4,129 dabigatran-apixaban, and 11,284 rivaroxaban-apixaban matched pairs (Figure 1). Baseline demographic and clinical characteristics were balanced between the matched cohorts with standardized difference $\leq 10\%$. Warfarin-apixaban, dabigatran-apixaban, and rivaroxaban-apixaban cohorts had mean ages of 77, 73, and 75 years, respectively. Across the 3 matched cohorts, the mean CHA₂DS₂-VASc score was 3.6-4.2, and the mean HAS-BLED score was 2.8-3.0 (Table 1). Patients were followed for a mean of 7-9 months.

Risk of Stroke/SE and Major Bleeding

The incidence rates of stroke/SE and major bleeding are shown in Figure 2. Warfarin (hazard ratio [HR]=1.84; 95% CI=1.30-2.59; $P<0.001$) and rivaroxaban (HR=1.46; 95% CI=1.08-1.98; $P=0.015$) were associated with a significantly higher risk of stroke/SE compared with apixaban. Dabigatran (HR=1.17;

95% CI=0.68-2.03; $P=0.573$) patients had a nonstatistically significant higher risk of stroke/SE compared with apixaban (Figure 2).

Warfarin (HR=1.53; 95% CI=1.24-1.89; $P<0.001$), dabigatran (HR=1.76; 95% CI=1.27-2.43; $P<0.001$), and rivaroxaban (HR=1.59; 95% CI=1.34-1.89; $P<0.001$) were associated with a significantly higher risk of major bleeding compared with apixaban (Figure 2).

Health Care Costs

Warfarin initiation was associated with similar all-cause PPPM outpatient costs (\$1,157 vs. \$1,206; $P=0.341$), significantly higher all-cause inpatient (\$1,092 vs. \$711; $P=0.002$) and medical (inpatient and outpatient; \$2,249 vs. \$1,917; $P=0.026$) costs, and significantly lower pharmacy costs (\$248 vs. \$360; $P<0.001$) compared with apixaban. The total all-cause health care costs (\$2,498 vs. \$2,277; $P=0.148$) were higher for warfarin than apixaban patients but were not statistically significant. Dabigatran initiation was associated with significantly higher inpatient costs (\$781 vs. \$565; $P=0.034$), but numerically higher total all-cause health care costs (\$2,372 vs. \$2,143; $P=0.150$) compared with apixaban. Rivaroxaban was associated with significantly higher inpatient (\$939 vs. \$658; $P<0.001$), medical (inpatient and outpatient; \$2,156 vs.

Real-World Comparative Effectiveness, Safety, and Health Care Costs of Oral Anticoagulants in Nonvalvular Atrial Fibrillation Patients in the U.S. Department of Defense Population

TABLE 2 Comparisons of All-Cause Health Care Costs After PSM

PPPM Costs	Apixaban Cohort n = 7,607	Warfarin Cohort n = 7,607		Apixaban Cohort n = 4,129	Dabigatran Cohort n = 4,129		Apixaban Cohort n = 11,284	Rivaroxaban Cohort n = 11,284	
	Marginal Effect ^a (\$)	Marginal Effect (\$)	P Value	Marginal Effect (\$)	Marginal Effect (\$)	P Value	Marginal Effect (\$)	Marginal Effect (\$)	P Value
All-cause outpatient medical costs	1,206	1,157	0.341	1,222	1,236	0.888	1,174	1,217	0.284
All-cause inpatient medical costs	711	1,092	0.002	565	781	0.034	658	939	<0.001
All-cause medical costs	1,917	2,249	0.026	1,787	2,018	0.143	1,832	2,156	<0.001
Pharmacy costs	360	248	<0.001	356	354	0.904	368	390	0.032
All-cause health care costs	2,277	2,498	0.148	2,143	2,372	0.150	2,200	2,546	<0.001

^aMarginal effect measures the marginal contribution of each variable (in this case, each oral anticoagulant drug in the matched pairs) on the scale of the linear predictor. PPPM = per patient per month; PSM = propensity score matching.

\$1,832; $P < 0.001$), pharmacy (\$390 vs. \$368; $P = 0.032$), and total health care costs (\$2,546 vs. \$2,200, $P < 0.001$) compared with apixaban (Table 2).

Warfarin patients had significantly higher PPPM stroke/SE-related medical costs (\$118 vs. \$46; $P = 0.012$) compared with apixaban patients. Dabigatran (\$61 vs. \$32; $P = 0.240$) and rivaroxaban (\$58 vs. \$38; $P = 0.057$) patients had numerically higher stroke/SE-related medical costs compared with apixaban. Warfarin (\$166 vs. \$76; $P = 0.003$), dabigatran (\$114 vs. \$58; $P = 0.025$), and rivaroxaban (\$137 vs. \$69; $P < 0.001$) patients had significantly higher PPPM major bleeding-related medical costs compared with apixaban patients (Figure 3).

Sensitivity Analyses

The sensitivity analyses were generally consistent with the primary study results. A significant interaction was found for the dose of rivaroxaban and apixaban for major bleeding ($P = 0.039$). Standard-dose rivaroxaban was associated with a significantly higher risk of major bleeding (HR=1.81; 95% CI=1.47-2.24) compared with standard-dose apixaban, whereas reduced-dose rivaroxaban was associated with a similar risk of major bleeding (HR=1.23; 95% CI=0.91-1.67) compared with reduced-dose apixaban (Appendix A, available in online article). The other sensitivity analyses showed results similar to the results of the main analysis (Appendix B, available in online article).

Discussion

In this real-world study of NVAf patients initiating OAC treatment in the U.S. DoD population, warfarin and rivaroxaban were associated with a significantly higher risk of stroke/SE and major bleeding compared with apixaban. Dabigatran initiation was associated with a numerically higher risk of stroke/SE and a significantly higher risk of major bleeding compared with apixaban. Correspondingly, stroke/SE-related medical costs were significantly higher for warfarin patients

compared with apixaban. Major bleeding-related medical costs were significantly higher for those prescribed warfarin, dabigatran, and rivaroxaban compared with apixaban. Rivaroxaban was associated with significantly higher total all-cause health care costs compared with apixaban. Warfarin and dabigatran patients had similar total all-cause health care costs compared with apixaban. The robustness of the clinical results was tested by several sensitivity analyses, which were consistent with the main analysis.

The results of this observational study are generally consistent with clinical trials and real-world studies with a focus on apixaban. In the ARISTOTLE trial, apixaban treatment was superior to warfarin in reducing the risk of stroke/SE (HR=0.79; 95% CI=0.66-0.95; $P = 0.011$) with fewer major bleeding events (HR=0.69; 95% CI=0.60-0.80; $P < 0.001$).⁷ Our study also demonstrated the same associations between apixaban and warfarin for the risk of stroke/SE and major bleeding.

No head-to-head clinical trials are available for DOAC comparisons. Indirect DOAC comparisons using clinical trial data showed that apixaban had a similar risk of stroke/SE compared with rivaroxaban and reduced- or standard-dose dabigatran and a significantly lower risk of major bleeding compared with rivaroxaban and standard-dose dabigatran.²⁹ In addition, few real-world studies examined the risk of stroke/SE and major bleeding among apixaban, dabigatran, and rivaroxaban. In the Noseworthy et al. study (2016), no significant differences were found regarding the risk of stroke/SE for patients prescribed apixaban, dabigatran, or rivaroxaban; however, apixaban use was associated with a 50% lower risk of major bleeding compared with dabigatran and a 61% lower risk of major bleeding compared with rivaroxaban.¹¹ Similarly, in the Amin et al. study (2018) using OptumInsight data, dabigatran and rivaroxaban were associated with a similar risk of stroke/SE but a significantly higher risk of major bleeding compared with apixaban.¹⁵ Our study showed consistent results except that

FIGURE 3 PPPM Stroke/SE-Related and Major Bleeding-Related Medical Costs Among Propensity Score-Matched Populations

^aP=0.012.

^bP=0.240.

^cP=0.057.

^dP=0.003.

^eP=0.025.

^fP<0.001.

Δ=differences in costs; CI=confidence interval; PPPM=per patient per month; SE=systemic embolism.

rivaroxaban was associated with a significantly higher risk of stroke/SE compared with apixaban. This may be because of the different patient population across studies. For example, this DoD population had a higher mean age compared with the populations in the other studies.

In real-world studies comparing the effectiveness and safety between apixaban and warfarin, apixaban showed consistent results of significantly lower risks of stroke/SE and major bleeding compared with warfarin.^{15,19,30-32} Several studies using the clinical trials data and Markov decision models have shown that DOACs are cost-effective alternatives to warfarin, with apixaban providing the greatest cost-effectiveness compared with dabigatran, rivaroxaban, and warfarin.³³⁻³⁵ However, limited real-world data are available regarding comparative health care costs for OACs. The all-cause medical cost results found here are similar to previous studies.^{15,34} For example, in the Deitelzweig et al. (2016) evaluation of DOACs using Premier

data, rivaroxaban patients incurred significantly higher all-cause hospitalization readmission costs (difference=\$413; P=0.003) compared with apixaban patients.¹⁴ Also, in Amin et al., apixaban was associated with significantly lower all-cause health care costs PPPM and major bleeding-related medical costs compared with warfarin and significantly lower major bleeding-related medical costs compared with dabigatran.¹⁵ Our study showed similar total all-cause health care costs between warfarin and apixaban patients; however, in a study using Medicare data, warfarin patients were found to have significantly higher all-cause health care costs compared with apixaban patients.³⁴ The difference in results may be because of the potential underestimation of pharmacy costs in the DoD data. As more longitudinal data become available and as treatment practices change over time, additional studies are warranted regarding the comparative economic outcomes between OACs among NVAf patients.

Limitations

This study has several limitations. Because of the nature of claims studies, diagnoses and procedures in this study were identified using ICD-9-CM, Current Procedural Terminology, and Healthcare Common Procedure Coding System codes and National Drug Code numbers. These coding systems were originally designed for billing purposes rather than research. For example, the presence of a claim for a filled prescription does not indicate whether the medication was consumed or taken as prescribed, and no international normalized ratio value is available for the prescription of warfarin. Moreover, the pharmacy costs in military facilities are not captured in the DoD data. Only the TRICARE Mail Order Pharmacy and retail pharmacy expenditures are available, which may have caused the underestimation of the pharmacy cost calculation in our analysis.

Although most patients (>85%) in our study had Medicare as their primary insurance, all medical claims and costs should have been included in the DoD data. For patients with Medicare insurance, the DoD pays for any costs that are not covered by Medicare in military and civilian medical facilities, with the complete cost information in the data.³⁶

Also, although PSM was used with the cohorts, potential residual confounders existed, so no causal inferences could be drawn. In addition, PSM was conducted between each matched pair; thus, 1 patient may have been included in multiple comparisons, so no conclusions could be drawn across the matched cohorts.

Although no direct comparison to the clinical trials can be made given the nature of retrospective observational studies, our findings from the main analysis, as well as subgroup and sensitivity analyses, provided additional real-world evidence and support for the clinical trial study results. Finally, only treatment-naïve patients and patients in the DoD population were studied, which may have affected the generalization of the study results.

Conclusions

Using U.S. DoD data, this study adds real-world evidence to help compare the effectiveness, safety, and health care costs of apixaban to warfarin, dabigatran, and rivaroxaban. Among NVAf patients, warfarin and rivaroxaban were associated with a significantly higher risk of stroke/SE and major bleeding when compared with apixaban. Dabigatran use was associated with a numerically higher risk of stroke/SE and a significantly higher risk of major bleeding compared with apixaban.

Warfarin patients incurred significantly higher stroke/SE-related, major bleeding-related, and all-cause medical costs compared with apixaban patients. Dabigatran and rivaroxaban patients incurred numerically higher stroke/SE-related medical costs and significantly higher major bleeding-related medical costs compared with apixaban patients. Total all-cause health care costs were similar between patients prescribed dabigatran

and apixaban but were significantly higher for those prescribed rivaroxaban compared with apixaban.

This observational study supplements the clinical trial findings on the effectiveness and safety of apixaban relative to warfarin. In addition, it provides evidence on the clinical and economic comparisons of apixaban with other DOACs, which will potentially facilitate the decision-making process in the prevention of stroke/SE among NVAf patients.

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DISCLOSURES

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Real-World Comparative Effectiveness, Safety, and Health Care Costs of Oral Anticoagulants in Nonvalvular Atrial Fibrillation Patients in the U.S. Department of Defense Population

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Real-World Comparative Effectiveness, Safety, and Health Care Costs of Oral Anticoagulants in Nonvalvular Atrial Fibrillation Patients in the U.S. Department of Defense Population

APPENDIX A Dose Sensitivity Analysis for Propensity Score-Matched Patients

	Warfarin vs. Apixaban	P Value ^a	Dabigatran vs. Apixaban	P Value ^a	Rivaroxaban vs. Apixaban	P Value ^a
Stroke/SE, HR (95% CI)						
Reduced dose ^b	1.39 (0.72-2.67)	0.315	0.82 (0.29-2.28)	0.409	1.42 (0.83-2.42)	0.911
Standard dose ^c	2.06 (1.37-3.10)		1.37 (0.71-2.65)		1.47 (1.01-2.13)	
Major bleeding, HR (95% CI)						
Reduced dose ^b	1.52 (1.06-2.19)	0.803	1.89 (1.00-3.57)	0.763	1.23 (0.91-1.67)	0.039
Standard dose ^c	1.61 (1.24-2.09)		1.69 (1.16-2.47)		1.81 (1.47-2.24)	

^aP value is for interaction.

^bReduced dose: 2.5 mg apixaban, 75 mg dabigatran, 10 mg or 15 mg rivaroxaban.

^cStandard dose: 5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban.

CI=confidence interval; HR=hazard ratio; SE=systemic embolism.

APPENDIX B Sensitivity Analyses for Propensity Score-Matched Patients

	Warfarin vs. Apixaban	P Value	Dabigatran vs. Apixaban	P Value	Rivaroxaban vs. Apixaban	P Value
Excluding patients with catheter ablation or cardioversion, HR (95% CI)						
Stroke/SE	1.84 (1.03-2.59)	<0.001	1.17 (0.68-2.03)	0.573	1.46 (1.08-1.98)	0.015
Major bleeding	1.53 (1.24-1.89)	<0.001	1.76 (1.27-2.43)	<0.001	1.59 (1.34-1.89)	<0.001
Censoring at 6 months, HR (95% CI)						
Stroke/SE	1.95 (1.26-3.01)	0.003	1.14 (0.58-2.23)	0.711	1.64 (1.13-2.39)	0.009
Major bleeding	1.70 (1.31-2.22)	<0.001	1.81 (1.18-2.77)	0.006	1.85 (1.48-2.32)	<0.001
Intent to treat, HR (95% CI)						
Stroke/SE	1.58 (1.23-2.04)	<0.001	1.18 (0.82-1.69)	0.387	1.57 (1.25-1.96)	<0.001
Major bleeding	1.34 (1.14-1.57)	<0.001	1.35 (1.06-1.71)	0.015	1.38 (1.20-1.58)	<0.001

CI=confidence interval; HR=hazard ratio; SE=systemic embolism.