Effect of Apixaban Versus Warfarin Use on Health Care Resource Utilization and Costs Among Elderly Patients with Nonvalvular Atrial Fibrillation

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ABSTRACT

BACKGROUND: The clinical trial ARISTOTLE showed that apixaban was superior to warfarin in reducing the risks of stroke and bleeding among patients with nonvalvular atrial fibrillation (NVAF). Further study of the effect of apixaban versus warfarin use on health care resource utilization (HCRU) and associated costs in the real-world setting is warranted, especially among elderly patients who are at higher risk of stroke and bleeding.

OBJECTIVE: To compare HCRU and costs among elderly NVAF patients treated with apixaban versus warfarin in the United States.

METHODS: Elderly patients (aged ≥65 years) with Medicare coverage who initiated apixaban or warfarin were identified from the Humana research database during January 1, 2013-September 30, 2015. Patients were required to have 12 months of continuous insurance coverage before drug initiation (baseline period) and an atrial fibrillation diagnosis during the baseline period or on the date of drug initiation. NVAF patients were grouped into cohorts depending on the drug initiated. Propensity score matching (PSM) was conducted to control for differences in demographics and clinical characteristics of study cohorts. Patients were followed after the index date for a variable length of follow-up. All-cause and disease-specific HCRU and costs during the follow-up were evaluated before and after PSM and reported as per patient per year.

RESULTS: Of the overall (unmatched) population, 8,250 patients (mean age: 78.0 years) initiated apixaban and 14,051 patients (mean age: 78.2 years) initiated warfarin. Among NVAF patients who initiated apixaban versus those who initiated warfarin, mean Charlson Comorbidity Index (CCI) scores (3.0 vs. 3.4, $P<0.001$); stroke risk scores, including $CHADS_2$ (2.7 vs. 2.9, $P<0.001$) and CHA_2DS_2-VASc (4.6 vs. 4.7, $P<0.001$); and bleeding risk scores, including HAS-BLED (3.1 vs. 3.2, $P<0.001$), were lower. Additionally, total annual all-cause health care costs were lower during the baseline period for patients treated with apixaban versus warfarin ($17,077 vs. $20,236, $P<0.001$). After PSM, 14,214 patients were matched, with 7,107 in each cohort. Mean age, CCI score, and stroke and bleeding risks were similar between matched cohorts, as were total all-cause health care costs during the baseline period. During the follow-up among matched cohorts, apixaban versus warfarin treatment was associated with higher annual pharmacy costs ($5,159 vs. $2,867, $P<0.001$) but lower annual inpatient ($8,327 vs. $14,296, $P<0.001$), outpatient ($9,655 vs. $11,469, $P<0.001$), and total all-cause health care costs ($23,141 vs. $28,633, $P<0.001$), which were reflective of lower inpatient, outpatient, and all-cause HCRU among apixaban-treated patients. Furthermore, bleeding-related ($2,101 vs. $3,963, $P<0.001$) and stroke-related ($652 vs. $1,178, $P=0.001$) annual medical costs were lower for patients treated with apixaban versus warfarin.

CONCLUSIONS: After controlling for differences in patient characteristics, in the real-world setting apixaban versus warfarin use was associated with less HCRU and lower total all-cause health care costs and costs for bleeding- and stroke-related medical services, but greater pharmacy costs, among elderly NVAF patients.

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What is already known about this subject

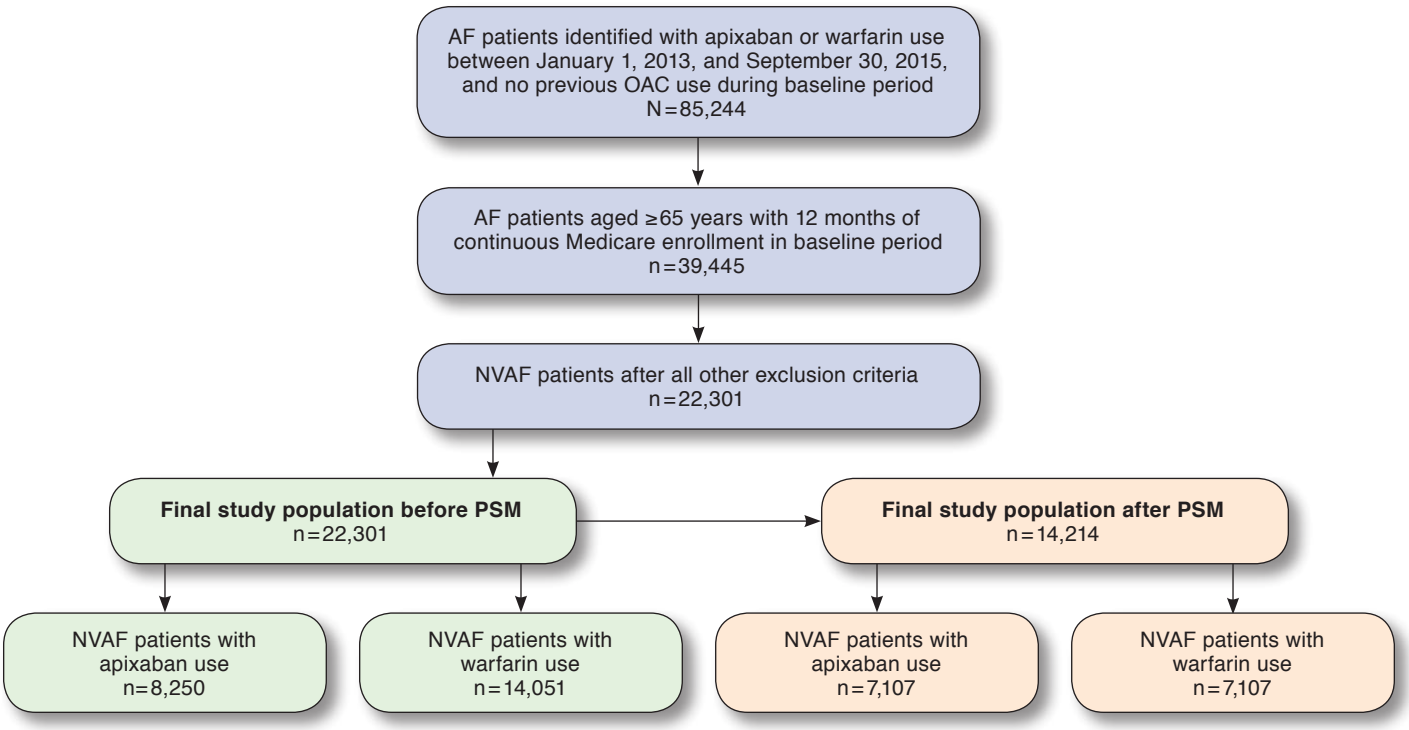
- Previous economic modeling studies, based on clinical trial event rates, predicted a cost savings to health care systems in the United States associated with apixaban versus warfarin use among nonvalvular atrial fibrillation (NVAF) patients.
- A study of NVAF patients hospitalized for AF showed that apixaban versus warfarin treatment was associated with a shorter hospital length of stay.

What this study adds

- This study examined the effect of apixaban versus warfarin use on health care resource utilization (HCRU) and the associated costs among elderly NVAF patients in the real-world setting in the United States.
- In comparison with NVAF patients who received warfarin, patients who initiated apixaban significantly differed in many patient characteristics, with age, bleeding and stroke risks, and previous HCRU and costs being lower for those who received apixaban.
- After controlling for differences in patient characteristics with propensity score matching, apixaban versus warfarin use was associated with less HCRU and lower total all-cause health care costs and costs for bleeding- and stroke-related medical services, but greater pharmacy costs, among elderly NVAF patients.

Atrial fibrillation (AF) is a common cardiac rhythm disorder that is associated with up to a 5-fold increase in stroke risk.[1,2] It is primarily nonvalvular, with less than 5% of AF patients having valvular heart disease.[1] In 2005, there were an estimated 3 million persons with AF in the United States.[3] With the growing elderly population in the United States, this number is expected to at least double by 2050.[1,3] The annual direct medical cost of nonvalvular atrial

FIGURE 1 Selection of Patients for Study Cohorts



AF = atrial fibrillation; NVAF = nonvalvular atrial fibrillation; PSM = propensity score matching.

fibrillation (NVAF) was estimated at $6 billion for NVAF-related costs only and $26 billion when including other concomitant cardiovascular and noncardiovascular costs in 2008 U.S. dollars.[4]

Vitamin K antagonists, mainly warfarin, have been used for decades to reduce stroke risk for NVAF patients.[5] However, warfarin has several disadvantages, including a limited therapeutic index, potential for drug and food interactions, and bleeding risk.[5,6] Furthermore, nearly half of AF patients in the United States do not receive warfarin therapy as recommended.[7] Four new oral anticoagulants (NOACs) have been introduced to the U.S. market within the past several years and are alternatives to warfarin for anticoagulation therapy among NVAF patients. In the randomized clinical trial, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), treatment with the NOAC apixaban was shown to be superior to warfarin for stroke prevention and also was associated with lower bleeding risk among NVAF patients.[8] Additionally, a recent retrospective cohort analysis conducted in the United States observed that apixaban use in comparison with warfarin was associated with significantly lower stroke and major bleeding risk in the real-world setting.[9]

Some economic modeling studies based on clinical event rates reported in the ARISTOTLE trial predicted apixaban versus warfarin use to be associated with a cost savings to health care systems in the United States.[10-13] Additionally, a study of 1,664 NVAF patients (aged ≥18 years) hospitalized for AF showed that apixaban versus warfarin treatment was associated with a shorter hospital length of stay.[14] Further study of the effect of apixaban versus warfarin use on health care resource utilization (HCRU) and associated costs in the real-world setting is warranted, especially among elderly patients with NVAF who are at higher risk of stroke and bleeding.[1,15] To address this need, we evaluated the effect of treatment with apixaban versus warfarin on HCRU and costs, specifically among elderly (aged ≥65 years) NVAF patients with Medicare insurance coverage, using a large retrospective database claims analysis.

Methods

Study Population

NVAF patients with Medicare insurance coverage and aged ≥65 years who were first prescribed apixaban or warfarin between January 1, 2013, and September 30, 2015, were identified from the Humana research database. The database comprises claims from millions of members with Medicare

Advantage coverage. The database is an integrated source of managed care medical and pharmacy claims and eligibility files. The medical file contains data on diagnostic and therapeutic services rendered in both inpatient and outpatient settings, including the emergency room. The pharmacy file contains data on outpatient prescription drugs dispensed (retail and mail order) with accompanying information on the characteristics of the drug dispensed, such as quantity and days supply. For both medical and pharmacy files, the dates of service are recorded. The eligibility file also contains data on demographic characteristics and periods of insurance eligibility for each patient.

The date of the earliest apixaban or warfarin prescription to occur (index event) between January 1, 2013, and September 30, 2015, was defined as the index date. The study start date was chosen since apixaban was approved by the U.S. Food and Drug Administration in December 2012. The study end date was chosen based on the availability of the most recent data when the study was conducted.

Patients were required to have 12 months of continuous insurance coverage before drug initiation (baseline period). Patients were also required to have at least 1 inpatient or outpatient AF diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] diagnosis code 427.31) during the baseline period or on the date of drug initiation. Patients who had medical claims indicative of diagnoses of valvular heart disease or venous thromboembolism during the baseline period were excluded, as were patients with a diagnosis or procedure code for transient AF, cardiac surgery, hyperthyroidism or thyroid toxicity, or pregnancy (Appendix A, available in online article). Additionally, patients were excluded if they had a pharmacy claim for warfarin, apixaban, dabigatran, rivaroxaban, or edoxaban during the baseline period or had claims for > 1 type of oral anticoagulant (OAC) on the index date.

Eligible patients were grouped either in the apixaban or warfarin cohort based on which drug the patients newly initiated. Patients were followed-up after the index date for a variable length of time until the earliest of the following dates: 90 days after the index OAC treatment discontinuation, which was a grace period included to ensure potential stroke and bleeding events were captured after patients discontinued OAC treatment; the date that the patient switched from the index OAC treatment to another OAC; the health plan disenrollment date; or the end of the study period (September 30, 2015).

Discontinuation was defined as no prescription refill of the index OAC within 30 days from the end date of the last filled prescription. The date of discontinuation was the end date of the last filled prescription before the treatment gap. A switch among OACs was defined as a prescription filled for nonindex OACs within ± 30 days after the discontinuation date. Figure 1 shows the process of selection of patients for study cohorts.

Propensity Score Matching

Propensity scores were generated using a multivariate logistic regression, which controlled for patient characteristics identified from claims data: age, gender, race, U.S. geographic region, and Charlson Comorbidity Index (CCI) score—a measurement to reflect the patient's burden of comorbidities, which are correlated with the risk of death from comorbid disease, that involves calculating a score based on the degree of mortality attributed to each comorbid condition.[16] Other characteristics are CHA_2DS_2-VASc score—an estimate of stroke risk in patients with AF[17]; HAS-BLED score—an estimate of bleeding risk in patients with AF[18]; follow-up period duration; baseline total health care cost; baseline bleeding-related medical cost; baseline stroke-related medical cost; baseline comorbidities (thrombocytopenia, congestive heart failure, diabetes, hypertension, renal disease, myocardial infarction, dyspepsia/stomach discomfort, peripheral vascular disease, transient ischemic attack, coronary artery disease); and baseline medication use (angiotensin-converting enzyme inhibitors, amiodarone, angiotensin receptor blockers, beta blockers, H2-receptor antagonists, proton pump inhibitors, statins, and antiplatelet drugs).

As these patient characteristics were derived from claims within the database and based on diagnosis and drug codes, there is potential for miscoding. Matching was conducted 1:1 by using the nearest neighbor algorithm, which required matched patients to have propensity scores within 0.001 of each other. Additionally, matched patients were required to have HAS-BLED scores within 3 points of each other and baseline bleeding-related medical costs within $5,000 of each other in order for the matched patient cohorts to be well balanced (without statistically significant differences).

Demographics and Clinical Characteristics

Demographics, including age, gender, race, and U.S. geographic region and clinical characteristics, CCI score, $CHADS_2$ score, CHA_2DS_2-VASc score, HAS-BLED score, and previous bleeding and stroke diagnoses during the 12-month baseline period, were determined for each patient in the study cohorts before and after propensity score matching (PSM).

HCRU and Cost Measurements

HCRU and costs during the baseline (including index date) and follow-up periods were evaluated for the unmatched and propensity score matched study cohorts and normalized to per patient per year (PPPY). Health care resources evaluated included number of hospitalizations, hospital length of stay, number of outpatient claims (with breakdown into office visits, ER visits, outpatient hospital claims, and other outpatient claims), and number of outpatient prescription claims for all causes. Use of bleeding- and stroke-related medical services were evaluated and identified by the corresponding ICD-9-CM

TABLE 1 Baseline Demographics, Clinical Characteristics, and Health Care Costs of Study Cohorts Before and After Propensity Score Matching

	Before Matching					After Matching				
	Apixaban n = 8,250		Warfarin n = 14,051		*P* Value[a]	Apixaban n = 7,107		Warfarin n = 7,107		*P* Value[a]
Demographics										
Age										
Mean (SD)	78.0 (9.0)		78.2 (9.0)		0.03	78.2 (9.1)		78.1 (8.8)		0.54
Median	76		77			77		77		
	n	%	n	%		n	%	n	%	
Gender										
Male	4,249	51.5	7,757	55.2	<0.001	3,740	52.6	3,688	51.9	0.38
U.S. geographic region					<0.001					0.82
South	5,707	69.2	7,807	55.6		4,675	65.8	4,717	66.4	
Midwest	1,582	19.2	4,168	29.7		1,514	21.3	1,504	21.2	
West	775	9.4	1,640	11.7		737	10.4	705	9.9	
Northeast	186	2.3	436	3.1		181	2.6	181	2.6	
Race/ethnicity					<0.001					0.85
White	7,385	89.5	12,507	89.0		6,373	89.7	6,371	89.6	
Black	481	5.8	977	7.0		440	6.2	436	6.1	
Other	192	2.3	329	2.3		167	2.4	160	2.3	
Unknown	192	2.3	238	1.7		127	1.8	140	2.0	
Clinical characteristics										
Charlson Comorbidity Index score										
Mean (SD)	3.0 (2.5)		3.4 (2.6)		<0.001	3.0 (2.4)		3.0 (2.4)		0.97
Median	3		3			3		3		
$CHADS_2$ score										
Mean (SD)	2.7 (1.4)		2.9 (1.4)		<0.001	2.7 (1.4)		2.7 (1.3)		0.37
Median	3		3			3		3		
CHA_2DS_2-Vasc score										
Mean (SD)	4.6 (1.6)		4.7 (1.6)		<0.001	4.6 (1.6)		4.6 (1.6)		0.66
Median	4		5			4		4		
HAS-BLED score										
Mean (SD)	3.1 (1.2)		3.2 (1.2)		<0.001	3.0 (1.1)		3.1 (1.1)		0.22
Median	3		3			3		3		
Baseline conditions	n	%	n	%		n	%	n	%	
Previous bleeding	1,561	18.9	3,375	24.0	<0.001	1,339	18.8	1,350	19.0	0.81
Previous stroke	970	11.8	2,216	15.8	<0.001	842	11.9	834	11.7	0.84
Thrombocytopenia	316	3.8	691	4.9	<0.001	252	3.6	274	3.9	0.33
CHF	2,580	31.3	5,045	35.9	<0.001	2,224	31.3	2,234	31.4	0.86
Diabetes	3,165	38.4	6,204	44.2	<0.001	2,775	39.1	2,717	38.2	0.32
Hypertension	7,543	91.4	12,841	91.4	0.91	6,469	91.0	6,513	91.6	0.19
Renal disease	2,580	31.3	5,135	36.6	<0.001	2,231	31.4	2,227	31.3	0.94
MI	1,362	16.5	2,597	18.5	<0.001	1,141	16.1	1,115	15.7	0.55
Dyspepsia	1,771	21.5	3,022	21.5	0.94	1,449	20.4	1,436	20.2	0.79
PVD	4,724	57.3	8,494	60.5	<0.001	4,076	57.4	4,010	56.4	0.26
TIA	590	7.2	1,115	7.9	0.03	495	7.0	504	7.1	0.77
CAD	4,075	49.4	7,167	51.0	0.02	3,485	49.0	3,435	48.3	0.40
Baseline medications	n	%	n	%		n	%	n	%	
ACE inhibitor	3,589	43.5	6,479	46.1	<0.001	3,130	44.0	3,136	44.1	0.92
Amiodarone	1,115	13.5	1,638	11.7	<0.001	839	11.8	819	11.5	0.60
ARB	1,999	24.2	2,801	19.9	<0.001	1,576	22.2	1,590	22.4	0.78
Beta blocker	6,190	75.0	10,166	72.4	<0.001	5,235	73.7	5,276	74.2	0.43
H2-receptor antagonist	592	7.2	1,013	7.2	0.93	474	6.7	515	7.3	0.18
PPI	2,697	32.7	4,372	31.1	0.01	2,198	30.9	2,254	31.7	0.31
Statin	5,165	62.6	8,722	62.1	0.43	4,387	61.7	4,378	61.6	0.88
Antiplatelet	1,454	17.6	2,299	16.4	0.01	1,173	16.5	1,144	16.1	0.51

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TABLE 1 Baseline Demographics, Clinical Characteristics, and Health Care Costs of Study Cohorts Before and After Propensity Score Matching *(continued)*

	Before Matching			After Matching		
	Apixaban n = 8,250	Warfarin n= 14,051	*P* Value[a]	Apixaban n = 7,107	Warfarin n= 7,107	*P* Value[a]
Clinical characteristics						
Duration of follow-up (months)						
Mean (SD)	6.3 (5.2)	8.3 (6.8)	<0.001	6.7 (5.3)	6.6 (5.4)	0.67
Median	5	6		5	5	
Total all-cause health care cost ($)						
Mean (SD)	17,077 (20,794)	20,236 (27,688)	<0.001	14,317 (14,314)	13,971 (14,499)	0.15
Median	10,128	10,982		9,367	9,075	
Total all-cause medical cost ($)						
Mean (SD)	14,098 (19,277)	17,834 (26,418)	<0.001	11,816 (13,678)	11,899 (13,885)	0.72
Median	7,436	8,605		6,936	6,960	
Bleeding-related medical cost ($)						
Mean (SD)	876 (6,073)	1,798 (8,078)	<0.001	670 (3,447)	740 (3,695)	0.24
Median	0	0		0	0	
Stroke-related medical cost ($)						
Mean (SD)	862 (4,796)	1,466 (6,990)	<0.001	725 (3,651)	724 (3,605)	0.99
Median	0	0		0	0	

[a]*P values were calculated for the differences in mean values.*

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction; PPI = proton pump inhibitor; PVD = peripheral vascular disease; SD = standard deviation; TIA = transient ischemic attack.

codes on either inpatient or outpatient health care encounters for a primary or secondary diagnosis of the medical condition (Appendix B, available in online article). Health care costs were measured for all evaluated HCRU categories as the following: all-cause total health care costs; all-cause medical costs; all-cause inpatient costs; all-cause outpatient medical costs (with breakdown into office visit costs, ER costs, outpatient hospital costs, and other outpatient costs); all-cause prescription costs; bleeding-related medical costs; and stroke-related medical costs. All costs were inflation-adjusted to 2015 cost levels using the medical care component of the Consumer Price Index.[19]

Statistical Analyses

Descriptive statistics were used to evaluate differences between the study cohorts in demographics, clinical characteristics, and HCRU and costs before and after matching. T-tests and chi-square tests were used to detect statistically significant differences in continuous and categorical variables, respectively, as commonly used in similar studies evaluating such data with and without PSM.[20,21] All data analyses were executed using SAS statistical software package 9.3 (SAS Institute, Cary, NC).

Results

Unmatched Study Cohorts

Table 1 presents the baseline demographics, clinical characteristics, and health care costs of study cohorts before matching. Of the overall unmatched population, 8,250 patients (mean age: 78.0 years) initiated apixaban, and 14,051 patients (mean age: 78.2 years) initiated warfarin. Before matching, among NVAF patients who initiated apixaban versus those who initiated warfarin, mean CCI score (3.0 vs. 3.4, $P<0.001$); $CHADS_2$ score (2.7 vs. 2.9, $P<0.001$); CHA_2DS_2-VASc score (4.6 vs. 4.7, $P<0.001$); and HAS-BLED score (3.1 vs. 3.2, $P<0.001$) were lower. The proportions of patients with bleeding (18.9% vs. 24.0%, $P<0.001$) and stroke (11.8% vs. 15.8%, $P<0.001$) diagnoses during the baseline period were lower for NVAF patients treated with apixaban versus warfarin.

Among unmatched patients during the baseline period, the total all-cause mean medical (inpatient + outpatient) and prescription costs were lower for patients treated with apixaban versus warfarin ($17,077 vs. $20,236 PPPY, $P<0.001$; Table 1). In addition, mean costs for bleeding-related ($876 vs. $1,798 PPPY, $P<0.001$) and stroke-related ($862 vs. $1,466 PPPY, $P<0.001$) medical services were lower for patients treated with apixaban versus warfarin during the baseline period (Table 1).

During the follow-up period, the number of hospitalizations (0.8 vs. 1.2, $P<0.001$); hospital length of stay (4.6 vs. 7.5 days, $P<0.001$); number of outpatient claims (total: 34.4 vs. 54.6, $P<0.001$); and number of outpatient prescription claims (54.8 vs. 56.8, $P<0.001$) based on PPPY for all causes were lower for unmatched patients treated with apixaban versus warfarin (Table 2). Apixaban treatment was also associated with lower mean inpatient and outpatient costs based on PPPY for all causes as compared with warfarin (Table 2).

TABLE 2 Unmatched Study Cohorts: HCRU and Associated Costs per Patient per Year During the Follow-up Period

	Apixaban n = 8,250 Mean (SD) Median	Warfarin n = 14,051 Mean (SD) Median	*P* Value[a]
All causes			
Inpatient			
Number of hospitalizations	0.8 (2.3) 0	1.2 (2.9) 0	<0.001
Hospital length of stay (days)	4.6 (21.5) 0	7.5 (27.4) 0	<0.001
Total inpatient cost ($)	9,453 (38,068) 0	14,572 (48,344) 0	<0.001
Outpatient			
Number of outpatient claims	34.4 (33.3) 24	54.6 (43.1) 43	<0.001
Total outpatient cost ($)	10,538 (18,968) 4,386	13,003 (22,083) 5,804	<0.001
Number of office visit claims	17.3 (15.2) 14	24.2 (19.7) 21	<0.001
Office visit cost ($)	2,292 (5,457) 1,365	2,390 (5,477) 1,411	0.20
Number of emergency room claims	1.9 (4.8) 0	2.4 (5.1) 0	<0.001
Emergency room cost ($)	912 (2,990) 0	1,177 (4,181) 0	<0.001
Outpatient hospital claims	7.3 (15.4) 3	14.2 (26.6) 5	<0.001
Outpatient hospital cost ($)	4,088 (12,705) 345	4,294 (12,796) 579	0.24
Other outpatient claims	12.8 (25.0) 4	22.7 (33.8) 11	<0.001
Other outpatient cost ($)	3,246 (10,400) 216	5,141 (13,993) 637	<0.001
Prescription			
Number of outpatient prescription claims	54.8 (39.1) 48	56.8 (41.7) 48	<0.001
Total outpatient prescription cost ($)	5,619 (9,226) 4,327	3,198 (7,720) 1,539	<0.001
Total medical cost ($; inpatient + outpatient)	19,991 (47,549) 5,162	27,575 (59,315) 7,659	<0.001
Total medical and prescription cost ($)	25,611 (48,874) 10,924	30,772 (60,252) 10,804	<0.001
Bleeding-related			
Total medical cost ($; inpatient + outpatient)	2,428 (20,554) 0	4,068 (25,632) 0	<0.001
Stroke-related			
Total medical cost ($; inpatient + outpatient)	817 (10,038) 0	1,499 (14,472) 0	<0.001

[a]*P values were calculated for the differences in mean values.*
HCRU = health care resource utilization; SD = standard deviation.

Although patients treated with apixaban had higher mean prescription costs ($5,619 vs. $3,198 PPPY, $P<0.001$), total mean costs (inpatient + outpatient + prescription) based on PPPY for all causes were lower for patients treated with apixaban versus warfarin ($25,611 vs. $30,772 PPPY, $P<0.001$), as were inpatient costs ($9,453 vs. $14,572 PPPY, $P<0.001$) and total outpatient costs ($10,538 vs. $13,003 PPPY, $P<0.001$; Table 2). Also, costs for bleeding-related ($2,428 vs. $4,068 PPPY, $P<0.001$) and stroke-related ($817 vs. $1,499 PPPY, $P<0.001$) medical services were lower for patients treated with apixaban versus warfarin during the follow-up period (Table 2).

PSM Study Cohorts

Table 1 presents the baseline demographics, clinical characteristics, and health care costs of study cohorts after matching. By implementing PSM, 14,214 patients were matched, with 7,107 patients in each cohort. After PSM, mean ages (78.2 years vs. 78.1 years, $P=0.54$); CCI scores (3.0 vs. 3.0, $P=0.97$); and stroke and bleeding risks, based on $CHADS_2$ score (2.7 vs. 2.7, $P=0.37$), CHA_2DS_2-VASc score (4.6 vs. 4.6, $P=0.66$), and HAS-BLED score (3.0 vs. 3.1, $P=0.22$), were similar (no statistically significant differences) between matched cohorts.

The proportions of patients with bleeding (18.8% vs. 19.0%, $P=0.81$) and stroke (11.9% vs. 11.7%, $P=0.84$) diagnoses during the baseline period were also similar for NVAF patients treated with apixaban versus warfarin. Additionally, total all-cause medical costs ($11,816 vs. $11,899 PPPY, $P=0.72$); total all-cause medical costs plus outpatient prescription costs ($14,317 vs. $13,971 PPPY, $P=0.15$); bleeding-related medical services costs ($670 vs. $740 PPPY, $P=0.24$); and stroke-related medical services costs ($725 vs. $724 PPPY, $P=0.99$) during the baseline period were similar for matched NVAF patients treated with apixaban versus warfarin.

The mean durations of follow-up for matched study cohorts were similar (mean: 6.7 vs. 6.6 months, $P=0.67$; median: 5 vs. 5 months). During the follow-up period, the number of hospitalizations (0.7 vs. 1.1, $P<0.001$; difference: -0.4); hospital length of stay (4.0 vs. 7.1 days, $P<0.001$; difference: -3.1 days); number of outpatient claims (32.7 vs. 51.0, $P<0.001$; difference: -18.3); and number of outpatient prescription claims (53.0 vs. 54.7, $P=0.006$; difference: -1.8) based on PPPY for all causes were lower for matched patients treated with apixaban versus warfarin (Table 3).

Apixaban treatment was also associated with lower mean inpatient and outpatient costs versus warfarin (Table 3 and Figure 2). While patients treated with apixaban had higher mean prescription costs ($5,159 vs. $2,867 PPPY, $P<0.001$), total mean costs (inpatient + outpatient + prescription) based on PPPY for all causes were $5,493 lower for patients treated with apixaban versus warfarin ($23,141 vs. $28,633 PPPY, $P<0.001$; Table 3 and Figure 2). Inpatient costs ($8,327 vs. $14,296 PPPY, $P<0.001$) and total outpatient costs ($9,655 vs. $11,469 PPPY, $P<0.001$) were also lower (Table 3). Additionally, costs for bleeding-related ($2,101 vs. $3,963 PPPY, $P<0.001$; difference: -$1,862) and stroke-related ($652 vs. $1,178 PPPY, $P=0.001$; difference: -$525) medical services were lower for patients treated with apixaban versus warfarin during the follow-up period (Table 3).

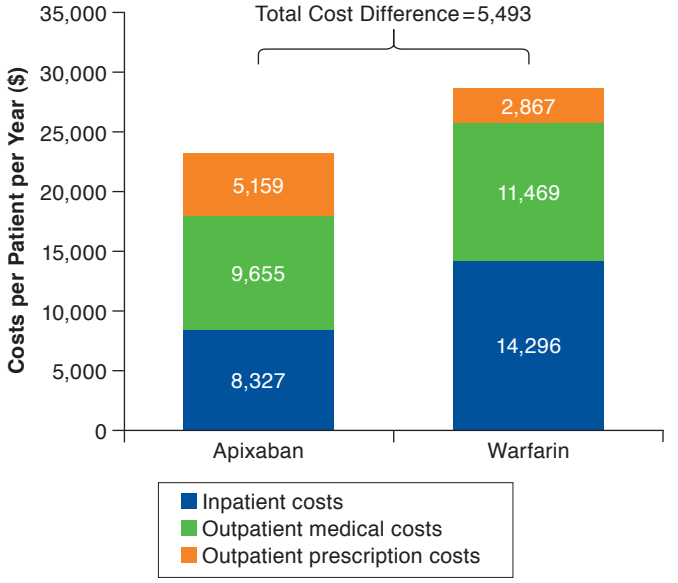
TABLE 3 Propensity Score Matched Study Cohorts: HCRU and Associated Costs per Patient per Year During the Follow-up Period

	Apixaban n = 7,107 Mean (SD) Median	Warfarin n = 7,107 Mean (SD) Median	*P* Value[a]
All causes			
Inpatient			
Number of hospitalizations	0.7 (2.1) 0	1.1 (2.9) 0	<0.001
Hospital length of stay (days)	4.0 (19.8) 0	7.1 (25.6) 0	<0.001
Total inpatient cost ($)	8,327 (34,325) 0	14,296 (49,994) 0	<0.001
Outpatient			
Number of outpatient claims	32.7 (31.0) 24	51.0 (37.7) 42	<0.001
Total outpatient cost ($)	9,655 (16,922) 4,158	11,469 (19,582) 5,295	<0.001
Number of office visit claims	16.9 (14.4) 14	24.9 (20.4) 21	<0.001
Office visit cost ($)	2,150 (4,583) 1,333	2,358 (5,168) 1,433	0.01
Number of emergency room claims	1.8 (4.3) 0	2.4 (5.3) 0	<0.001
Emergency room cost ($)	864 (2,715) 0	1,155 (3,817) 0	<0.001
Outpatient hospital claims	6.8 (14.0) 3	11.4 (19.3) 4	<0.001
Outpatient hospital cost ($)	3,782 (11,751) 354	3,515 (11,264) 384	0.17
Other outpatient claims	11.7 (22.8) 4	20.4 (30.8) 9	<0.001
Other outpatient cost ($)	2,858 (9,159) 204	4,441 (12,723) 458	<0.001
Prescription			
Number of outpatient prescription claims	53.0 (36.4) 46	54.7 (39.2) 48	0.006
Total outpatient prescription cost ($)	5,159 (5,909) 4,296	2,867 (4,857) 1,545	<0.001
Total medical cost ($; inpatient + outpatient)	17,981 (43,039) 4,878	25,766 (59,220) 6,793	<0.001
Total medical and prescription cost	23,141 (43,595) 10,452	28,633 (59,650) 9,967	<0.001
Bleeding-related			
Total medical cost ($; inpatient + outpatient)	2,101 (17,867) 0	3,963 (27,424) 0	<0.001
Stroke-related			
Total medical cost ($; inpatient + outpatient)	652 (7,192) 0	1,178 (11,695) 0	0.001

[a]*P values were calculated for the differences in mean values.*

HCRU = health care resource utilization; SD = standard deviation.

FIGURE 2 Propensity Score Matched Study Cohorts: Health Care Costs per Patient per Year During the Follow-up Period Among Nonvalvular Atrial Fibrillation Patients Treated with Apixaban Versus Warfarin



Discussion

The current study analyzed claims data from the Humana research database to evaluate the effect of treatment with apixaban versus warfarin on HCRU and costs among elderly NVAF patients. The results of the study show that elderly NVAF patients who initiated apixaban significantly differed in many patient characteristics compared with those who received warfarin, with age, bleeding and stroke risks, prevalence of comorbidities, and previous HCRU and costs being lower for those who received apixaban. These differences may in part be attributed to the fact that apixaban is a new drug and clinicians might be more inclined to "play safe" and prescribe the new drug to healthier patients first until they gain more experience with it. After controlling for key significant differences in patient characteristics with PSM, including age, bleeding and stroke risks, and comorbidities, our study demonstrated that apixaban treatment was associated with greater pharmacy costs than treatment with warfarin but less HCRU, as well as lower total all-cause health care costs and bleeding- and stroke-related medical service costs, in comparison with warfarin treatment. The difference in mean total health care costs based on PPPY for all causes between apixaban and warfarin treatment reached $5,493 (Figure 2).

For the statistical analysis after the post hoc PSM, as in this current analysis, most of the analyses in the published literature used unpaired statistical methods.[22] While some researchers advocate that paired statistical methods can be used in the PSM cohort comparison to use the higher statistical sensitivity

of paired method, simulation analysis has shown that the paired methods in comparison with nonpaired methods tend to have higher type I (false positive) error.[23] Additionally, other researchers recommend that the paired methods should not be used in the cohorts generated by post hoc matching methods such as PSM, as there is little theoretical foundation to support that the PSM cohorts are truly paired cohorts and that "matching" erroneously suggests that the resulting data should be analyzed as if they were matched pairs.[24] Since there are many confounding factors in the data analysis of retrospective real-world data analyses already, we chose to use the more conservative methods of unpaired statistical analyses to avoid the higher false positive rate associated with the paired methods.

To our knowledge, the current study is one of the first comprehensive analyses to compare all types (inpatient, outpatient, and prescriptions) of HCRU and associated costs between apixaban and warfarin treatment among elderly NVAF patients. Recently, Xie et al. (2016) evaluated hospitalized NVAF patients treated with apixaban or warfarin using a large U.S. claims database and observed that apixaban treatment was associated with shorter length of stay and lower hospital costs versus warfarin.[25] Similarly, an earlier study by Farr et al. (2015) found that patients hospitalized for NVAF and treated with apixaban had a shorter length of stay than patients treated with warfarin.[14] Our findings are generally consistent with these other published studies. Additionally, our study provides data on other types of HCRU, such as outpatient and prescriptions, and evaluated the costs of NVAF patients treated with apixaban and warfarin for a longer period after initiating treatment than the earlier studies did.

Despite having higher prescription costs, apixaban treatment was associated with lower total health care costs versus warfarin. Most of the cost savings associated with apixaban versus warfarin treatment was attributed to less hospital resource use (inpatient cost difference = $5,970). The less resource use for hospital as well as outpatient services among patients treated with apixaban may be due to fewer bleeding and stroke events associated with apixaban treatment versus warfarin, as both bleeding-related and stroke-related medical costs were lower for patients treated with apixaban versus warfarin. Since bleeding and stroke-related medical costs only captured inpatient and outpatient services that could be identified by relevant bleeding and stroke diagnosis codes, some of the economic benefits associated with apixaban versus warfarin treatment, such as the lack of need for warfarin monitoring, were not included in these costs.

The health care and economic burdens of AF-related stroke, especially among the elderly, are projected to increase.[1-4] Furthermore, the risk for bleeding also increases with age.[15,26] Hylek et al. (2007) additionally reported that among AF patients aged ≥80 years, 26% stopped taking warfarin within the first year.[26] Concerns related to safety were responsible for most of the discontinuations.[26] New pharmacotherapies provide alternative options for anticoagulation therapy and stroke prevention for NVAF patients. Apixaban demonstrated superior efficacy to warfarin and a significant reduction in risk for major bleeding in both a clinical trial and the real-world setting.[8,9] Our study additionally shows that the superior efficacy and safety of apixaban versus warfarin use among elderly NVAF patients translate to a reduced health care and economic burden. Future additional studies with larger sample sizes and longer follow-up may be needed to further confirm the results of this early evaluation of the effect of apixaban versus warfarin on HCRU and costs. Also, although we comprehensively evaluated all HCRU and associated costs, including inpatient, outpatient, and pharmacy use of elderly patients treated with apixaban versus warfarin, we believe that further assessment of the costs related to caregiver burden among elderly NVAF patients is warranted.

Limitations

Retrospective, observational analyses using claims databases have certain inherent limitations, as the claims are collected for the purpose of payment and not research. First, presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Second, medications filled over the counter or provided as samples by the physician are not captured in the claims data. Third, presence of a diagnosis code on a medical claim is not positive presence of disease, as the diagnosis code may be incorrectly coded or included as a rule-out criterion rather than indicate actual disease. Fourth, although we used PSM to control for multiple confounders, there is potential for residual bias and no causal relationship can be inferred from this study.

Fifth, since apixaban was a newly approved drug and warfarin has been used for many years, NVAF patients treated with apixaban had shorter follow-up durations than did warfarin-treated patients. While we aimed to adjust for the follow-up duration by calculating PPPY data, this may not fully adjust for the effect of the follow-up durations. For instance, in the occurence of a bleeding event, HCRU and cost data may not be linearly (uniformally) distributed over time, as it is possible that more events and costs may occur during the early months of the follow-up periods. In our study, the follow-up durations were similar between the patient cohorts after the PSM to minimize such potential effects.

Finally, the Humana research database comprises claims of persons primarily residing in the southern and midwestern regions of the United States, and therefore the results of this study may not be representative of the entire U.S. population.

Conclusions

In comparison with NVAF patients who received warfarin, patients who initiated apixaban significantly differed in many

patient characteristics. After controlling for these differences, we found that although treatment with apixaban was associated with higher pharmacy costs than treatment with warfarin, NVAF patients treated with apixaban had less HCRU, as well as lower total all-cause health care costs and bleeding- and stroke-related medical service costs, in comparison with patients treated with warfarin.

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DISCLOSURES

This study was sponsored by Pfizer and Bristol-Myers Squibb. Deitelzweig is a consultant for Pfizer and Bristol-Myers Squibb and has served on their advisory boards and received speaker fees. Deitelzweig also serves as consultant and advisory board member to Portola and Janssen. Luo, Trocio, and Mardekian are employees of Pfizer and own stock in the company. Gupta and Curtice are employees of Bristol-Myers Squibb and own stock in the company. Lingohr-Smith, Menges, and Lin are employees of Novosys Health, which received research funds from Pfizer and Bristol-Myers Squibb to conduct this study and develop the manuscript.

Study concept and design were primarily contributed by Deitelzweig, Luo, and Gupta, along with Trocio, Mardekian, Curtice, and Lin. Lin, Menges, and Lingohr-Smith took the lead in data collection, with assistance from the other authors. Data interpretation was performed by Deitelzweig, Menges, and Lin, with assistance from the other authors. The manuscript was written by Lingohr-Smith and Menges, along with the other authors, and revised by all the authors.

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APPENDIX A Claim Codes for Excluded Conditions

Condition	ICD-9-CM Code/Procedure Code/ HCPCS Code
Valvular heart disease	394.0, 394.1, 394.2, 394.9, 396.0, 396.1, 396.8, 396.9, 424.0, 745.xx, V42.2, V43.3
Venous thromboembolism	DVT: 451-453, 671.3, 671.4, 671.9 PE: 415.1, 673.2, 673.8
Transient atrial fibrillation or cardiac surgery	V422, V433, 35.05-35.09, 35.20-35.28 and 35.97; Pericarditis: 006.8, 017.9, 036.41, 074.21, 093.81, 098.83, 115.93, 390, 391, 392.0, 393, 411.0, 420.90, 420.91, 420.99, 423.0, 423.1, 423.2, 423.8, 423.9
Hyperthyroidism or thyroid toxicity	242.0, 242.1, 242.2, 242.3, 242.4, 242.8, 242.9
Pregnancy	630-679, V22, V23, V24, V27, V28, V61.6, V61.7, 792.3, 796.5, ICD-9-CM procedure code 72-75.99, or HCPCS codes 59000-59350, 76801-76828, 83661-83664

DVT = deep vein thrombosis; HCPCS = Healthcare Common Procedure Coding System; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; PE = pulmonary embolism.

APPENDIX B Stroke and Bleeding Claim Codes

Type of Stroke	ICD-9-CM Code
Hemorrhagic stroke	430.xx-432.xx Cases excluded if traumatic brain injury (ICD-9: 800-804, 850-854) was present during hospitalization
Ischemic stroke	433.x1, 434.x1, 436.xx
Systemic embolism	444.x, 445.x
Type of Bleeding	**ICD-9-CM Code**
Gastrointestinal bleeding	456.0x, 456.20, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x
Intracranial bleeding	430.xx, 431.xx, 432.0x, 432.1x, 432.9x, 852.0x, 852.2x, 852.4x, 853.0x
Other bleeding	285.1, 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 423.0x, 596.7x, 599.7x, 602.1x, 620.1, 621.4, 626.2, 626.5, 626.7, 626.8, 626.9, 719.1x, 782.7, 784.7, 784.8, 786.3x, 958.2, 997.02, 998.11 Procedure codes: 99.04, 44.43

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.