A Real-World Observational Study of Hospitalization and Health Care Costs Among Nonvalvular Atrial Fibrillation Patients Prescribed Oral Anticoagulants in the U.S. Medicare Population

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ABSTRACT

BACKGROUND: Clinical trials have shown that direct oral anticoagulants (DOACs)—including dabigatran, rivaroxaban, apixaban, and edoxaban—are at least as effective and safe as warfarin for the risk of stroke/systemic embolism (SE) and major bleeding (MB) in patients with atrial fibrillation (AF). However, few studies have compared oral anticoagulants (OACs) among elderly patients.

OBJECTIVE: To compare hospitalization risks (all-cause, stroke/SE-related, and MB-related) and associated health care costs among elderly nonvalvular AF (NVAF) patients in the Medicare population who initiated warfarin, dabigatran, rivaroxaban, or apixaban.

METHODS: Patients (aged ≥65 years) initiating warfarin or DOACs (apixaban, rivaroxaban, and dabigatran) were selected from the Centers for Medicare & Medicaid Services database from January 1, 2013, to December 31, 2014. Patients initiating each OAC were matched 1:1 to apixaban patients using propensity score matching to balance demographic and clinical characteristics. Cox proportional hazards models were used to estimate the risk of hospitalization of each OAC versus apixaban. Generalized linear models and two-part models with bootstrapping were used to compare all-cause health care costs and stroke/SE- and MB-related medical costs between matched cohorts.

RESULTS: Of the 186,132 eligible patients, 41,606 warfarin-apixaban, 30,836 dabigatran-apixaban, and 41,608 rivaroxaban-apixaban pairs were matched. The OACs were associated with a significantly higher risk of all-cause hospitalization compared with apixaban (warfarin: HR = 1.33, 95% CI = 1.27-1.38, $P<0.001$; dabigatran: HR = 1.17, 95% CI = 1.11-1.23, $P<0.001$; and rivaroxaban: HR = 1.27, 95% CI = 1.22-1.32, $P<0.001$) and were associated with a significantly higher risk of hospitalization due to stroke/SE (warfarin: HR = 2.51, 95% CI = 1.92-3.29, $P<0.001$; dabigatran: HR = 2.24, 95% CI = 1.60-3.13, $P<0.001$; and rivaroxaban: HR = 1.74, 95% CI = 1.31-2.30, $P<0.001$). Also, the OACs were associated with significantly higher risk of hospitalization due to MB-related conditions compared with apixaban (warfarin: HR = 1.96, 95% CI = 1.71-2.23, $P<0.001$; dabigatran: HR = 1.48; 95% CI = 1.25-1.76, $P<0.001$; and rivaroxaban: HR = 2.17, 95% CI = 1.91-2.48, $P<0.001$). Compared with apixaban, warfarin ($3,747 vs. $3,061, $P<0.001$); dabigatran ($3,230 vs. $2,951, $P<0.001$); and rivaroxaban ($3,950 vs. $3,060, $P<0.001$) had significantly higher all-cause total health care costs per patient per month. Patients initiating the OACs also had significantly higher stroke/SE- and MB-related medical costs compared with apixaban: warfarin (stroke/SE = $135 vs. $60, $P=0.001$; MB = $537 vs. $286, $P<0.001$); dabigatran (stroke/SE = $94 vs. $62, $P=0.045$; MB = $373 vs. $277, $P=0.010$); and rivaroxaban (stroke/SE = $91 vs. $60, $P=0.008$; MB = $524 vs. $287, $P<0.001$).

CONCLUSIONS: This real-world study showed that among elderly NVAF patients in the Medicare population, apixaban was associated with significantly lower risks of all-cause, stroke/SE-related, and MB-related hospitalizations compared with warfarin, dabigatran, and rivaroxaban. Accordingly, apixaban showed significantly lower all-cause health care costs and stroke/SE- and MB-related medical costs.

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What is already known about this subject

- Clinical trials have shown that direct oral anticoagulants (DOACs) are at least as effective as warfarin for stroke risk reduction and are associated with similar or lower rates of major bleeding (MB) in patients with atrial fibrillation.
- Several real-world studies have compared the risks of stroke and MB between DOACs and warfarin in various databases; however, few real-world comparisons are available between DOACs.

What this study adds

- In the elderly Medicare population, apixaban initiation was associated with significantly lower risks of all-cause, stroke/systemic embolism (SE)-related, and MB-related hospitalizations compared with warfarin, dabigatran, or rivaroxaban initiation.
- The all-cause health care costs and stroke/SE- and MB-related medical costs were significantly higher for dabigatran, rivaroxaban, or warfarin initiators compared with apixaban initiators.

Atrial fibrillation (AF) is the most common sustained heart arrhythmia and is estimated to affect approximately 9% of the population aged ≥65 years in the United States.[1,2] The presence of AF increases the relative risk of stroke by 5-fold, with attributable risk increasing from 4.6% among patients aged 50-59 years to over 20% among those aged 80-89 years.[3] AF's annual national incremental costs were estimated at $26 million compared with patients without AF, and hospitalizations were the primary cost driver.[4] For Medicare beneficiaries, AF onset leads to an adjusted mean incremental treatment cost of $14,199 per patient per year.[5]

Warfarin, a vitamin K antagonist in use since the 1950s, has been proven to reduce ischemic and hemorrhagic stroke by 64% compared with placebo.[6] However, the narrow therapeutic window managed by the international normalized ratio and increased risk of bleeding have hindered the proper use of warfarin, especially in the elderly population.[2] Several new direct oral anticoagulants (DOACs) targeting key coagulation factors—including dabigatran, rivaroxaban, apixaban, and edoxaban—have been approved for stroke risk reduction in nonvalvular AF (NVAF) in recent years. Additionally, DOACs have demonstrated to be at least as effective as warfarin for the risk reduction of stroke and systemic embolism (SE) and are associated with similar or lower rates of major bleeding (MB).[7-10] While there are NVAF trials of DOACs versus warfarin, there are no head-to-head clinical trials comparing DOACs to each other. A few real-world studies have examined the risk of hospitalizations due to stroke/SE and MB among OACs. However, there is a dearth of real-world data for all-cause hospitalizations and health care costs.[11] Although warfarin has a lower pharmacy cost, using data from clinical trials and a Markov decision analysis model, apixaban, dabigatran, and rivaroxaban have shown to be more cost-effective than warfarin.[12] Real-world studies comparing health care costs among NVAF patients have also shown that apixaban patients had lower hospitalization costs compared with warfarin patients.[13,14]

The objective of this study was to compare the risk of hospitalizations (all-cause, stroke/SE-related, and MB-related) and associated health care costs among elderly NVAF patients who initiated warfarin, dabigatran, rivaroxaban, or apixaban in the Medicare population.

Methods

Data Source

This real-world retrospective database analysis used data from the Centers for Medicare & Medicaid Services from January 1, 2012, to December 31, 2014. Medicare is the federal health insurance program for people aged ≥65 years, certain younger people with disabilities, and people with end-stage renal disease (permanent kidney failure requiring dialysis or a transplant). The database includes around 38 million fee-for-service beneficiaries.[15] It contains medical and pharmacy claims from 100% national Medicare data, which includes hospital inpatient, outpatient, Medicare carrier, Part D pharmacy, skilled nursing facility, home health agency, and durable medical equipment files. Medical claims were obtained through the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis and procedure codes, as well as Health Care Common Procedure Coding System and Current Procedural Terminology codes. Pharmacy claims were obtained through National Drug Code numbers. The comparative effectiveness research methods guidance documents aided researchers in designing the study.[16-19]

Patient Selection

OAC treatment-naive patients were included in the study if they had ≥1 prescription claim for apixaban, dabigatran, rivaroxaban, or warfarin during the identification period (January 1, 2013-December 31, 2014). Edoxaban was approved by the U.S. Food and Drug Administration in 2015; therefore, it was not included in our study. The first OAC pharmacy claim date was designated as the index date. Patients were required to be aged ≥65 years on the index date, have ≥1 AF medical claim (ICD-9-CM code 427.31), and have continuous health plan enrollment with medical and pharmacy benefits for 12 months before the index date (baseline period).[20]

Patients were excluded if they had evidence of rheumatic mitral valvular heart disease, mitral valve stenosis, heart valve replacement or surgery; transient AF (pericarditis, hyperthyroidism, and thyrotoxicity), venous thromboembolism, or an OAC pharmacy claim during the 12-month baseline period; pregnancy during the study period; or >1 OAC prescription claim on the index date.

Patients were followed from the index date until the earliest of the OAC prescription discontinuation date, switch date from index drug to another OAC, date of death, date of health plan disenrollment, or December 31, 2014. Discontinuation was defined as no evidence of an index prescription for 30 days from the last day of the supply of the last filled prescription (discontinuation date). Switching was defined as having a prescription for an OAC other than the index drug within 30 days before or after the discontinuation date.[21]

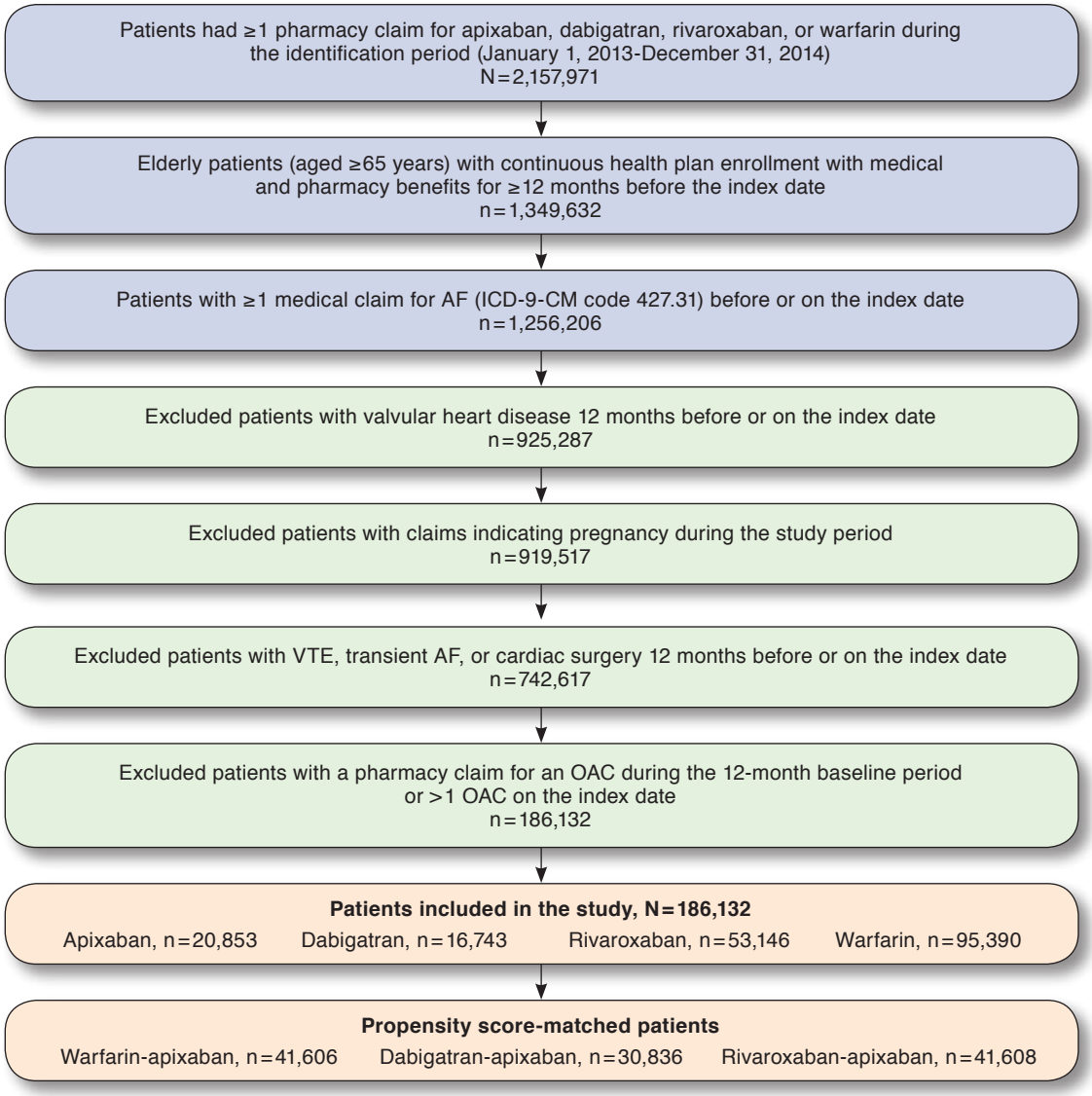
Outcomes

The primary outcomes were likelihood of all-cause hospitalization, hospitalization due to stroke/SE, hospitalization due to MB-related conditions, and health care costs, including all-cause health care, all-cause medical, all-cause pharmacy, all-cause hospitalization, all-cause emergency room (ER)/outpatient, stroke/SE-related medical, and MB-related medical costs.

Stroke/SE and MB hospitalization events were identified using hospital claims that had a stroke/SE or MB code as the primary discharge diagnosis.[22] The ICD-9-CM codes used for stroke and MB were based on a validated administrative claims-based algorithm as well as the clinical trial definition of stroke and MB.[7,23,24] Stroke/SE was stratified by ischemic stroke, hemorrhagic stroke, and SE; MB was stratified by gastrointestinal bleeding, intracranial hemorrhage, and other MB.

Stroke/SE-related medical costs were defined as hospitalization costs associated with the first stroke/SE event plus all subsequent stroke/SE costs occurring in the inpatient or outpatient setting (primary or secondary diagnosis) after the first stroke/SE during the follow-up. MB-related medical costs were defined as the hospitalization costs associated with the first MB event plus all subsequent MB costs occurring in the inpatient or outpatient setting (primary or secondary diagnosis) after the

FIGURE 1 Patient Selection Criteria



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

first MB during the follow-up. Costs included all paid amounts, including Medicare payments, copayments, and deductibles incurred during the follow-up period. All-cause medical costs represent the sum of reimbursed costs for inpatient, outpatient (office, ER, and other outpatient costs), and other costs (durable medical equipment, skilled nursing facility, home health agency, and hospice costs); total health care costs represent the sum of medical and pharmacy costs. All cost outcomes were measured per patient per month (PPPM) and adjusted to 2014 U.S. dollars using the Consumer Price Index for medical care services.

Baseline Variables

Patient demographics (age, sex, and U.S. geographic region) and clinical characteristics (Charlson Comorbidity Index [CCI] score, $CHADS_2$ score, CHA_2DS_2-VASc score, HAS-BLED score, comorbid conditions, and comedication use), as well as health care resource utilization, were assessed during the baseline period. The CHA_2DS_2-VASc stroke risk score was calculated using ICD-9-CM codes in the claims data as the summed total of the points determined for each diagnosis or characteristic and based on the $CHADS_2$ score (congestive heart failure,

TABLE 1 PSM-Adjusted Baseline Characteristics and Outcomes

	Apixaban Cohort n = 20,803		Warfarin Cohort n = 20,803		Apixaban Cohort n = 15,418		Dabigatran Cohort n = 15,418		Apixaban Cohort n = 20,804		Rivaroxaban Cohort n = 20,804	
	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD
Age (years)	78.4	7.4	78.1	7.5	77.6	7.2	77.5	7.0	78.4	7.4	78.3	7.4
65-74	7,214	34.7%	7,506	36.1%	5,957	38.6%	5,951	38.6%	7,239	34.8%	7,149	34.4%
75-84	8,830	42.4%	8,660	41.6%	6,599	42.8%	6,613	42.9%	8,833	42.5%	8,903	42.8%
≥ 85	4,759	22.9%	4,637	22.3%	2,862	18.6%	2,854	18.5%	4,732	22.7%	4,752	22.8%
Gender												
Male	9,919	47.7%	9,971	47.9%	7,610	49.4%	7,643	49.6%	9,927	47.7%	9,910	47.6%
Female	10,884	52.3%	10,832	52.1%	7,808	50.6%	7,775	50.4%	10,877	52.3%	10,894	52.4%
U.S. geographic region												
Northeast	3,596	17.3%	3,918	18.8%	2,906	18.8%	2,949	19.1%	3,595	17.3%	3,513	16.9%
North Central	4,220	20.3%	6,079	29.2%	3,420	22.2%	3,420	22.2%	4,221	20.3%	4,260	20.5%
South	9,377	45.1%	7,300	35.1%	6,201	40.2%	6,163	40.0%	9,375	45.1%	9,440	45.4%
West	3,595	17.3%	3,491	16.8%	2,879	18.7%	2,878	18.7%	3,601	17.3%	3,583	17.2%
Other	15	0.1%	15	0.1%	12	0.1%	8	0.1%	12	0.1%	8	0.0%
Baseline comorbidity												
Baseline Charlson Comorbidity Index score	2.8	2.6	2.9	2.6	2.6	2.4	2.6	2.5	2.8	2.6	2.8	2.6
0-1	7,932	38.1%	7,372	35.4%	6,373	41.3%	6,312	40.9%	7,967	38.3%	7,852	37.7%
2-3	6,292	30.3%	6,534	31.4%	4,695	30.5%	4,721	30.6%	6,293	30.3%	6,386	30.7%
≥ 4	6,579	31.6%	6,897	33.2%	4,350	28.2%	4,385	28.4%	6,544	31.5%	6,566	31.6%
Baseline $CHADS_2$ score[a]	2.8	1.4	2.8	1.4	2.7	1.4	2.7	1.4	2.8	1.4	2.8	1.4
0 = low risk	625	3.0%	575	2.8%	547	3.5%	546	3.5%	626	3.0%	585	2.8%
1 = moderate risk	3,411	16.4%	3,378	16.2%	2,775	18.0%	2,774	18.0%	3,433	16.5%	3,372	16.2%
2 = high risk	6,042	29.0%	5,817	28.0%	4,620	30.0%	4,576	29.7%	6,047	29.1%	6,056	29.1%
≥ 2 = high risk	10,725	51.6%	11,033	53.0%	7,476	48.5%	7,522	48.8%	10,698	51.4%	10,791	51.9%
Baseline CHA_2DS_2-VASc score[b]	4.6	1.7	4.7	1.7	4.5	1.7	4.5	1.7	4.6	1.7	4.6	1.7
0 = low risk	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
1 = moderate risk	318	1.5%	264	1.3%	285	1.8%	275	1.8%	318	1.5%	299	1.4%
2 = high risk	1,787	8.6%	1,791	8.6%	1,501	9.7%	1,534	9.9%	1,803	8.7%	1,782	8.6%
≥ 2 = high risk	18,698	89.9%	18,748	90.1%	13,632	88.4%	13,609	88.3%	18,683	89.8%	18,723	90.0%
Baseline HAS-BLED score[c]	3.3	1.2	3.3	1.2	3.1	1.2	3.2	1.2	3.3	1.2	3.3	1.2
0 = low risk	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
1-2 = moderate risk	5,963	28.7%	5,521	26.5%	5,103	33.1%	5,056	32.8%	5,966	28.7%	5,868	28.2%
≥ 2 = high risk	14,840	71.3%	15,282	73.5%	10,315	66.9%	10,362	67.2%	14,838	71.3%	14,936	71.8%
Baseline prior bleed	4,548	21.9%	4,731	22.7%	3,081	20.0%	3,090	20.0%	4,542	21.8%	4,664	22.4%
Baseline prior stroke	2,686	12.9%	2,872	13.8%	1,827	11.8%	1,852	12.0%	2,675	12.9%	2,649	12.7%
Congestive heart failure	6,388	30.7%	6,698	32.2%	4,425	28.7%	4,459	28.9%	6,356	30.6%	6,371	30.6%
Diabetes	7,341	35.3%	7,467	35.9%	5,582	36.2%	5,560	36.1%	7,331	35.2%	7,374	35.4%
Hypertension	18,782	90.3%	18,980	91.2%	13,705	88.9%	13,727	89.0%	18,782	90.3%	18,848	90.6%
Renal disease	4,977	23.9%	5,312	25.5%	3,139	20.4%	3,130	20.3%	4,939	23.7%	4,865	23.4%
Myocardial infarction	2,659	12.8%	2,844	13.7%	1,696	11.0%	1,731	11.2%	2,649	12.7%	2,676	12.9%
Dyspepsia or stomach discomfort	4,640	22.3%	4,815	23.1%	3,166	20.5%	3,209	20.8%	4,637	22.3%	4,585	22.0%
Peripheral vascular disease	12,286	59.1%	12,617	60.6%	8,513	55.2%	8,483	55.0%	12,289	59.1%	12,298	59.1%
Transient ischemic attack	1,769	8.5%	1,842	8.9%	1,177	7.6%	1,180	7.7%	1,767	8.5%	1,749	8.4%
Coronary artery disease	10,758	51.7%	11,086	53.3%	7,357	47.7%	7,341	47.6%	10,760	51.7%	10,747	51.7%
Baseline medication use												
Angiotensin-converting enzyme inhibitor	7,420	35.7%	7,452	35.8%	5,710	37.0%	5,772	37.4%	7,431	35.7%	7,426	35.7%
Amiodarone	2,171	10.4%	2,158	10.4%	1,379	8.9%	1,396	9.1%	2,185	10.5%	2,202	10.6%
Angiotensin receptor blocker	5,558	26.7%	5,660	27.2%	3,934	25.5%	3,949	25.6%	5,576	26.8%	5,667	27.2%

continued on next page

TABLE 1 PSM-Adjusted Baseline Characteristics and Outcomes *(continued)*

	Apixaban Cohort n = 20,803		Warfarin Cohort n = 20,803		Apixaban Cohort n = 15,418		Dabigatran Cohort n = 15,418		Apixaban Cohort n = 20,804		Rivaroxaban Cohort n = 20,804	
	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD
Baseline medication use												
Beta blockers	11,880	57.1%	12,273	59.0%	8,507	55.2%	8,508	55.2%	11,887	57.1%	11,889	57.1%
H_2-receptor antagonist	1,446	7.0%	1,546	7.4%	1,007	6.5%	1,013	6.6%	1,444	6.9%	1,427	6.9%
Proton pump inhibitor	6,907	33.2%	7,104	34.1%	4,714	30.6%	4,742	30.8%	6,913	33.2%	6,875	33.0%
Antiplatelets	4,100	19.7%	4,196	20.2%	2,492	16.2%	2,480	16.1%	4,114	19.8%	4,065	19.5%
Statins	12,791	61.5%	13,075	62.9%	9,064	58.8%	9,060	58.8%	12,797	61.5%	12,818	61.6%
Index drug dose[d]												
Standard dose	14,980	72.0%			11,584	75.1%	12,139	78.7%	15,007	72.1%	13,009	62.5%
Low dose	5,838	28.1%			3,843	24.9%	3,282	21.3%	5,812	27.9%	7,835	37.7%
Follow-up time (days)	171	153	196	184	172	154	196	192	171	153	205	191
Median	115		122		115		113		115		133	
Switch during follow-up	914	4.4%	1,364	6.6%	696	4.5%	1,798	11.7%	913	4.4%	1,342	6.5%

[a]*$CHADS_2$: congestive heart failure, hypertension, aged ≥ 75 years, diabetes mellitus, prior stroke, transient ischemic attack, or venous thromboembolism.*

[b]*CHA_2DS_2-VASc: congestive heart failure, hypertension, aged ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, aged 65-74 years, sex category.*

[c]*HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, drugs and alcohol.*

[d]*Standard dose: 5 mg twice a day apixaban, 150 mg twice a day dabigatran, 20 mg every day rivaroxaban; low dose: 2.5 mg twice a day apixaban, 75 mg twice a day dabigatran, 10 mg or 15 mg every day rivaroxaban.*

PSM = propensity score matching; SD = standard deviation.

hypertension, aged > 75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism) plus vascular disease, aged 65-74 years, and sex.[25] The HAS-BLED bleeding risk score was based on evidence of hypertension, abnormal kidney or liver function, stroke, bleeding, aged > 65 years, and drugs/alcohol abuse or dependence.[26]

Statistical Methods

All study variables were analyzed descriptively in each cohort, using apixaban as the reference. Means and standard deviations were reported for continuous variables, and student's t-tests were used to detect differences. Percentages were reported for categorical variables, and chi-square tests were used to detect differences in these variables. A *P* value of 0.05 was used as the threshold for statistical significance.

Propensity score matching (PSM) was conducted to balance identified baseline demographics and clinical characteristics when comparing apixaban to dabigatran, rivaroxaban, or warfarin. Patients were matched 1:1 on the propensity scores generated by multivariable logistic regressions based on age, sex, geographic region, CCI score, CHA_2DS_2-VASc score, HAS-BLED score, prior bleed and stroke, comorbidities, baseline comedications, and baseline hospitalization. The covariates included in the PSM were determined based on clinical rationale. Nearest neighbor without replacement with a caliper of 0.01 was used to match the patients.[27] The balance of covariates was checked based on standardized differences with a threshold of 10%.[28]

The incidence rates of hospitalization (all-cause, stroke-related, and MB-related) in the matched cohorts were calculated using the number of hospitalized patients divided by total person-years of exposure and multiplied by 100. Cox proportional hazards regression models were used to assess the likelihood of all-cause hospitalization, hospitalization due to stroke/SE, and hospitalization due to MB-related conditions in patients treated with other OACs relative to apixaban.[27] Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each outcome of interest.

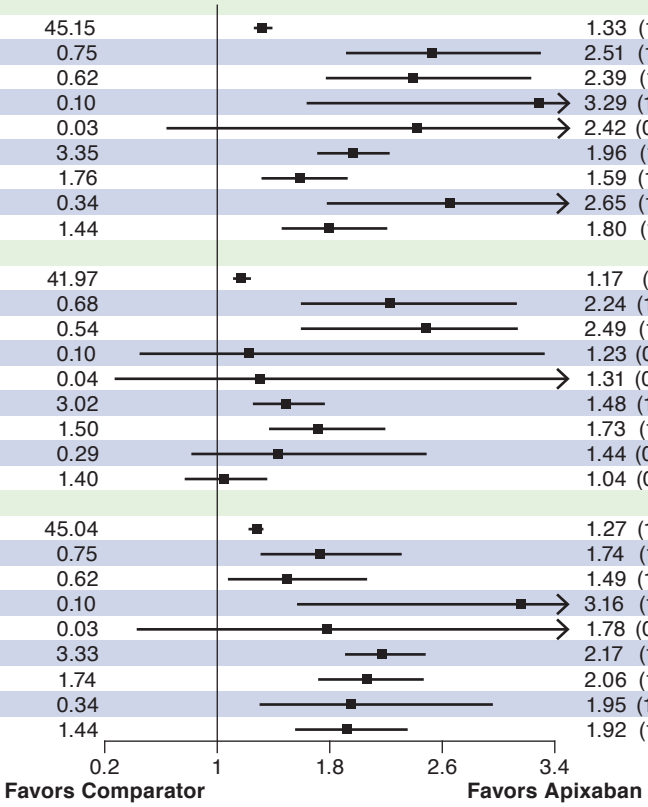
Generalized linear models with log-link and a gamma distribution were used for the analysis of health care costs among the cohorts.[29] Additionally, two-part models with bootstrapping were used in the analysis of MB- and stroke-related medical costs, given the high proportion of cost fields with 0 values. The marginal effect of costs, 95% CIs, and *P* values for each matched cohort were reported.

Sensitivity Analyses

Three sensitivity analyses were conducted. First, for the DOAC cohorts, standard-dose (dabigatran 150 mg, rivaroxaban 20 mg, and apixaban 5 mg) and reduced-dose (dabigatran 75 mg, rivaroxaban 10 mg/15 mg, and apixaban 2.5 mg) cohorts were created based on the index dosage. Each patient initiating warfarin was assigned to one of the 2 subgroups according to the dose of the matched DOAC patient (standard and low dose). The balance of baseline characteristics was tested in each subgroup; when imbalance was detected

FIGURE 2 Hazard Ratios of All-Cause Hospitalization, Hospitalization Due to Stroke/SE, and Hospitalization Due to Major Bleeding for Propensity Score-Matched Patients

	Comparator	Apixaban	HR (95% CI)	*P* Value
	Incidence Rate (per 100 person-years)			
Warfarin vs. apixaban				
All-cause hospitalization	57.23	45.15	1.33 (1.27-1.38)	<0.001
Stroke/SE	1.80	0.75	2.51 (1.92-3.29)	<0.001
Ischemic	1.39	0.62	2.39 (1.77-3.22)	<0.001
Hemorrhagic	0.33	0.10	3.29 (1.63-6.63)	<0.001
SE	0.07	0.03	2.42 (0.64-9.15)	0.194
Major bleeding	6.24	3.35	1.96 (1.71-2.23)	<0.001
GI bleeding	2.96	1.76	1.59 (1.32-1.92)	<0.001
ICH	0.89	0.34	2.65 (1.78-3.94)	<0.001
Other bleeding	2.83	1.44	1.80 (1.47-2.20)	<0.001
Dabigatran vs. apixaban				
All-cause hospitalization	46.58	41.97	1.17 (1.11-1.23)	<0.001
Stroke/SE	1.41	0.68	2.24 (1.60-3.13)	<0.001
Ischemic	1.25	0.54	2.49 (1.72-3.60)	<0.001
Hemorragic	0.11	0.10	1.23 (0.46-3.32)	0.676
SE	0.05	0.04	1.31 (0.29-5.88)	0.721
Major bleeding	4.22	3.02	1.48 (1.25-1.76)	<0.001
GI bleeding	2.64	1.50	1.73 (1.37-2.18)	<0.001
ICH	0.41	0.29	1.44 (0.83-2.49)	0.193
Other bleeding	1.52	1.40	1.04 (0.79-1.35)	0.791
Rivaroxaban vs. apixaban				
All-cause hospitalization	53.18	45.04	1.27 (1.22-1.32)	<0.001
Stroke/SE	1.26	0.75	1.74 (1.31-2.30)	<0.001
Ischemic	0.88	0.62	1.49 (1.08-2.06)	0.015
Hemorrhagic	0.33	0.10	3.16 (1.57-6.38)	0.001
SE	0.05	0.03	1.78 (0.44-7.25)	0.423
Major bleeding	6.75	3.33	2.17 (1.91-2.48)	<0.001
GI bleeding	3.69	1.74	2.06 (1.72-2.47)	<0.001
ICH	0.67	0.34	1.95 (1.30-2.95)	0.001
Other bleeding	2.86	1.44	1.92 (1.57-2.34)	<0.001



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

(standardized difference >10%), the variable was included in the multivariate model. Risk of hospitalization (all-cause health care, stroke-related, and MB-related) was compared between the study cohorts, and the statistical significance of the interaction between treatments and subgroups was evaluated.

Second, patients were censored at 6 months to create a more balanced length of follow-up between the treatment groups. Third, only patients with ≥30 days of follow-up were evaluated to exclude patients with too short of a follow-up to develop any stroke/SE or MB event. The second and third analyses were to help address the more recent approval of apixaban relative to dabigatran and rivaroxaban.

Results

After applying the selection criteria, a total of 186,132 patients were identified: 95,390 warfarin, 16,743 dabigatran, 53,146 rivaroxaban, and 20,853 apixaban patients (Figure 1). Before matching, patients prescribed warfarin were older and had poorer health status compared with apixaban patients, and apixaban patients were older with poorer health status compared with dabigatran and rivaroxaban patients (Appendix A, available in online article). After 1:1 PSM, 41,606 warfarin-apixaban, 30,836 dabigatran-apixaban, and 41,608 rivaroxaban-apixaban matched patients were included in the study (Table 1). Patients were followed for a median of 122 and 115 days for warfarin-apixaban cohorts, 113 and 115 days for dabigatran-apixaban cohorts, and 133 and 115 days for rivaroxaban-apixaban cohorts, respectively.

Baseline Characteristics

In the 3 postmatching cohorts, the mean age was around 78 years. The dabigatran-apixaban patients had the lowest mean CCI score (2.6), followed by rivaroxaban-apixaban (2.8) and warfarin-apixaban (2.9 and 2.8) patients. The CHA_2DS_2-VASc scores ranged from 4.5 to 4.7 across

TABLE 2 Adjusted Health Care Cost Comparisons

PPPM Costs[a]	Apixaban Cohort (n = 20,803)	Warfarin Cohort (n = 20,803)		Apixaban Cohort (n = 15,418)	Dabigatran Cohort (n = 15,418)		Apixaban Cohort (n = 20,804)	Rivaroxaban Cohort (n = 20,804)	
	Marginal Effect ($)	Marginal Effect ($)	*P* Value	Marginal Effect ($)	Marginal Effect ($)	*P* Value	Marginal Effect ($)	Marginal Effect ($)	*P* Value
All-cause ER/outpatient medical costs	886	1,025	<0.001	872	886	0.517	887	981	0.001
All-cause hospitalization medical costs	1,101	1,692	<0.001	1,036	1,294	<0.001	1,101	1,669	<0.001
All-cause medical costs[b]	2,328	3,379	<0.001	2,224	2,583	<0.001	2,326	3,285	<0.001
Pharmacy costs	733	368	<0.001	727	647	<0.001	733	665	<0.001
All-cause health care costs[b]	3,061	3,747	<0.001	2,951	3,230	<0.001	3,060	3,950	<0.001

[a]Generalized linear models were used for the analysis of all-cause health care costs.
[b]All-cause medical costs include all-cause ER/outpatient and hospitalization medical costs; all-cause health care costs include all-cause medical and pharmacy costs.
ER = emergency room; PPPM = per patient per month.

the cohorts. About 20% of all matched patients had baseline bleeding, and more than 10% had baseline stroke/SE (Table 1).

Hospitalization: All-Cause, Stroke/SE, and MB

Incidence of all-cause hospitalizations and hospitalizations related to MB and stroke/SE are shown in Figure 2.

After PSM, OAC patients were significantly more likely to have an all-cause hospitalization compared with apixaban patients (warfarin: HR = 1.33, 95% CI = 1.27-1.38; dabigatran: HR = 1.17, 95% CI = 1.11-1.23; and rivaroxaban: HR = 1.27, 95% CI = 1.22-1.32).

Warfarin, dabigatran, and rivaroxaban treatment were each associated with a significantly higher likelihood of having a hospitalization due to stroke/SE compared with apixaban treatment (warfarin: HR = 2.51, 95% CI = 1.92-3.29; dabigatran: HR = 2.24, 95% CI = 1.60-3.13; and rivaroxaban: HR = 1.74, 95% CI = 1.31-2.30). They were also associated with a significantly higher risk of hospitalization due to MB-related conditions compared with apixaban treatment (warfarin: HR = 1.96, 95% CI = 1.71-2.23; dabigatran: HR = 1.48, 95% CI = 1.25-1.76; and rivaroxaban: HR = 2.17, 95% CI = 1.91-2.48).

Health Care Costs

Patients prescribed warfarin, dabigatran, and rivaroxaban had significantly higher all-cause total health care costs PPPM compared with apixaban patients (Table 2). Inpatient and outpatient costs were the main drivers for health care costs.

Warfarin, dabigatran, and rivaroxaban patients had significantly higher stroke/SE- and MB-related medical costs compared with apixaban patients (Figure 3).

Subgroup and Sensitivity Analyses Results

Results of the subgroup and sensitivity analyses were generally consistent with those of the main analysis (Appendix B, available in online article). A significant interaction was found for dose and all-cause hospitalization among apixaban and warfarin patients ($P < 0.001$). Warfarin was associated with a higher risk of all-cause hospitalization compared with both standard-dose and low-dose apixaban, with a difference in magnitude. No other interactions were significant. The other sensitivity analyses were consistent with the main analysis.

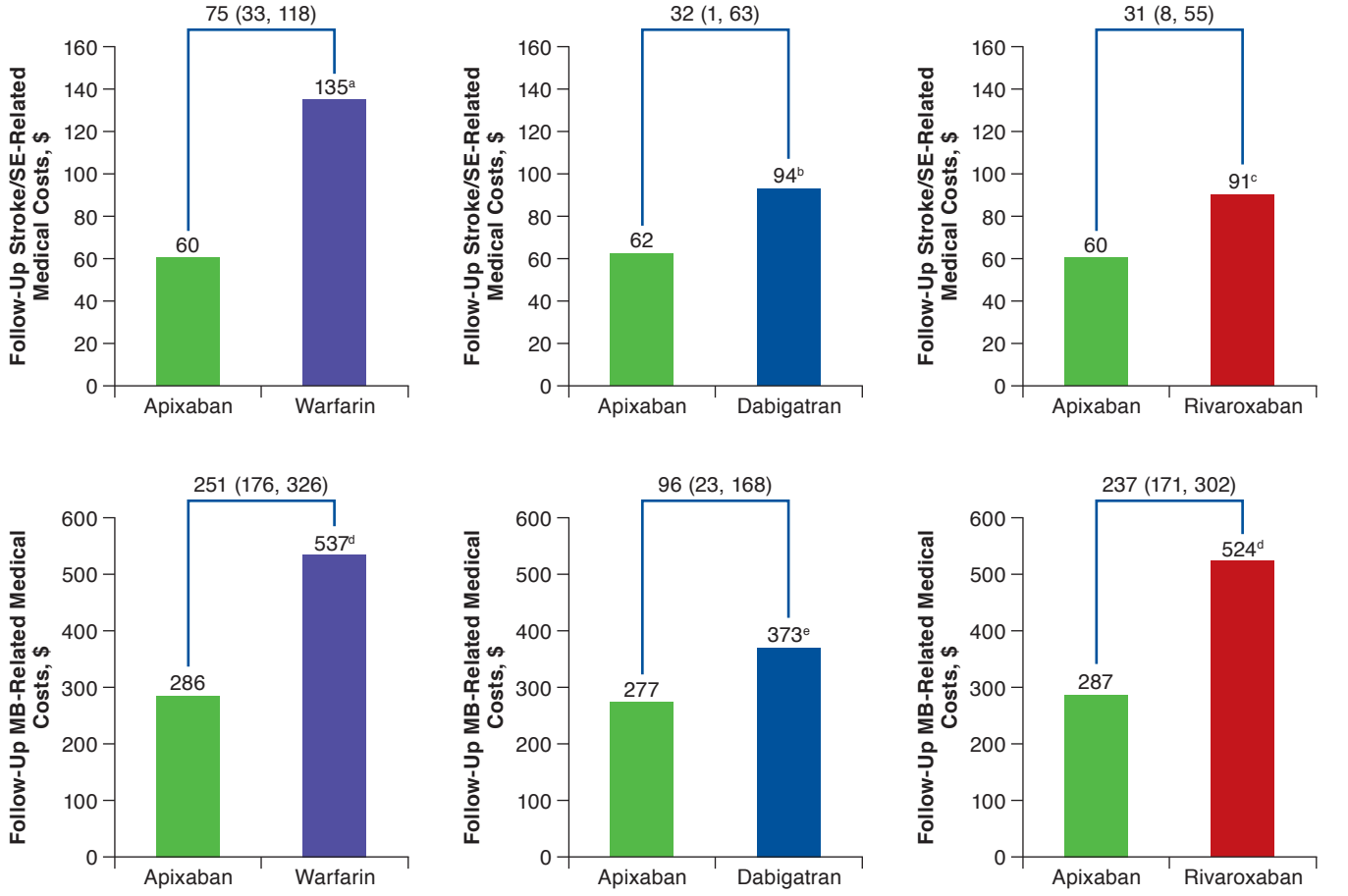
Discussion

Using national Medicare data, we found that NVAF patients initiating warfarin, dabigatran, or rivaroxaban had a higher risk of all-cause, stroke/SE-related, and MB-related hospitalization compared with patients initiating apixaban. In addition, patients initiating warfarin, dabigatran, and rivaroxaban had significantly higher all-cause, MB-related, and stroke/SE-related health care costs compared with patients initiating apixaban.

The ARISTOTLE trial demonstrated a significantly lower risk of stroke/SE (HR = 0.79, 95% CI = 0.66-0.95, $P = 0.01$) and MB (HR = 0.69, 95% CI = 0.60-0.80, $P < 0.001$) for apixaban patients compared with warfarin patients, which is consistent with our results.[7,30] In addition to clinical trials, a few observational studies comparing apixaban and warfarin have added real-world evidence in different patient populations.[22,31-34] In a study of OptumLabs data by Yao et al. (2016), apixaban users had a 33% lower risk of stroke/SE and 55% lower risk of MB compared with warfarin.[31] In a study of 4 pooled datasets by Li et al. (2017), apixaban demonstrated lower risks of stroke/SE (HR = 0.67, 95% CI = 0.59-0.76) and MB (HR = 0.60, 95% CI = 0.54-0.65) compared with warfarin.[32]

Although no head-to-head DOAC clinical trials are available, several real-world studies have compared the risks of stroke/SE and MB among dabigatran, rivaroxaban, and apixaban.[33,35] In our analysis, apixaban had a lower risk of hospitalization due to stroke/SE and MB compared with the other DOACs. In a study of the MarketScan population by Lip et al. (2016), patients who initiated dabigatran had a numerically

FIGURE 3 Comparisons of Stroke/SE-Related and MB-Related Medical Costs PPPM for Propensity Score-Matched Patients



[a]*P = 0.001.*
[b]*P = 0.045.*
[c]*P = 0.008.*
[d]*P < 0.001.*
[e]*P = 0.010.*
MB = major bleeding; PPPM = per patient per month; SE = systemic embolism.

higher risk of MB, and those who initiated rivaroxaban had a significantly higher risk of MB compared with those who initiated apixaban.[33] In Noseworthy et al. (2016), apixaban demonstrated a significantly lower risk of MB and a numerically lower risk of stroke/SE compared with dabigatran and rivaroxaban.[35] However, we found in our study that dabigatran and rivaroxaban patients had a statistically significantly higher risk of both stroke/SE and MB than apixaban, which may be due to the larger sample size and hence increased power and different study populations.

The results of the sensitivity analyses showed consistent results with the primary analysis, which showed that standard-dose or low-dose apixaban was associated with a lower risk of all-cause, stroke/SE-related, and MB-related hospitalization compared with other OACs.

There are a few economic studies that have compared apixaban to warfarin, dabigatran, and rivaroxaban among NVAF patients. In studies using IMS PharMetrics Plus, Humana, and Optum claims databases, warfarin patients had significantly higher total all-cause health care costs, stroke/SE-related costs, and MB-related medical costs compared with apixaban.[22,36-38] In Amin et al.'s (2013) observational claims database study, patients treated with apixaban versus warfarin had medical cost reductions of $493 for stroke, $752 for MB (excluding intracranial

hemorrhage), and $1,245 for the combined outcome of both events.[39] In claims studies comparing rivaroxaban and apixaban, rivaroxaban patients had higher all-cause hospitalization costs, all-cause health care costs, and MB-related medical costs compared with apixaban.[22,36,37] Dabigatran patients were associated with similar stroke/SE- and MB-related medical costs and similar or higher all-cause health care costs compared with apixaban.[22,36,37] In Deitelzweig et al.'s (2016) study comparing the all-cause hospitalization readmission costs of DOACs, rivaroxaban had significantly higher costs compared with apixaban (difference: $413; $P=0.003$), and dabigatran had numerically higher costs versus apixaban ($142; $P=0.31$).[40] These studies are generally aligned with our findings on health care costs associated with apixaban relative to other oral anticoagulants.

Limitations

This study has several limitations. Given the nature of retrospective observational studies, only associations were assessed, and no causality can be concluded. This database contains information from the Medicare population and may not be generalizable to the entire U.S. population of NVAF patients. Additionally, administrative claims data are primarily collected for billing purposes rather than research, and the analysis is constrained by codes that may contain coding errors and missing data. In addition, the cause of stroke/SE and major bleeding is not available in the claims data. Moreover, unobserved confounders such as compliance, AF duration, and over-the-counter aspirin use may exist for which the analysis did not control. Nevertheless, we used PSM to balance observed demographics and clinical characteristics. The follow-up time was short, not uniform, and was not consistent with the clinical trials. Therefore, the sensitivity analysis with patients censored at 6 months was conducted to address the issue of imbalanced follow-up times. Sensitivity analysis results for MB and stroke/SE were consistent with those in the main analysis. Finally, the interpretation of stroke/SE-related outcomes should be carefully considered because of the low number of stroke/SE events.

Conclusions

This real-world observational study is one of the largest that has compared the risks of stroke/SE and MB and the associated health care costs between OACs in elderly NVAF patients.

In this study, apixaban was associated with significantly lower risks of all-cause, stroke/SE-related, and MB-related hospitalizations compared with warfarin, dabigatran, and rivaroxaban. Accordingly, apixaban showed significantly lower all-cause health care costs as well as stroke/SE- and MB-related medical costs. This study may assist clinicians in determining the appropriate OAC for OAC-naive elderly NVAF patients and could be informative to decision makers managing Medicare populations.

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DISCLOSURES

This study was funded by Bristol-Myers Squibb and Pfizer. Amin is an employee of the University of California, Irvine, and was a paid consultant to Bristol-Myers Squibb in connection with this study and the development of this manuscript. Keshishian and Zhang are employees of STATinMED Research, a paid consultant to Pfizer and Bristol-Myers Squibb in connection with this study and the development of this manuscript. Trocio, Dina, Mardekian, and Liu are employees of Pfizer, with ownership of stocks in Pfizer. Le, Rosenblatt, Nadkarni, and Vo are employees of Bristol-Myers Squibb. Rosenblatt and Vo have ownership of stocks in Bristol-Myers Squibb. Baser has no conflicts to disclose.

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APPENDIX A Pre-PSM Descriptive Baseline Characteristics and Outcomes

	Warfarin Cohort (n = 95,390)		Apixaban Cohort (n = 20,853)		Dabigatran Cohort (n = 16,743)		Rivaroxaban Cohort (n = 53,146)	
	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD
Age (years)	78.72	7.40%	78.36	7.40%	77.16	7.01%	77.65	7.23%
65-74	31,061	32.56%	7,244	34.74%	6,788	40.54%	20,361	38.31%
75-84	41,254	43.25%	8,846	42.42%	7,062	42.18%	22,420	42.19%
≥ 85	23,075	24.19%	4,763	22.84%	2,893	17.28%	10,365	19.50%
Gender								
Male	46,183	48.41%	9,949	47.71%	8,472	50.60%	25,685	48.33%
Female	49,207	51.59%	10,904	52.29%	8,271	49.40%	27,461	51.67%
Geographic region								
Northeast	18,881	19.79%	3,599	17.26%	3,415	20.40%	9,308	17.51%
North Central	28,704	30.09%	4,225	20.26%	3,861	23.06%	11,915	22.42%
South	31,594	33.12%	9,407	45.11%	6,303	37.65%	22,469	42.28%
West	16,121	16.90%	3,607	17.30%	3,137	18.74%	9,355	17.60%
Other	90	0.09%	15	0.07%	27	0.16%	99	0.19%
Baseline comorbidity								
Charlson Comorbidity Index	3.15	2.76%	2.79	2.57%	2.54	2.42%	2.68	2.52%
$CHADS_2$ score[a]	2.89	1.44%	2.76	1.44%	2.62	1.41%	2.66	1.43%
CHA_2DS_2-VASc score[b]	4.76	1.74%	4.62	1.74%	4.41	1.71%	4.51	1.73%
HAS-BLED score[c]	3.30	1.27%	3.29	1.21%	3.10	1.19%	3.22	1.21%
Baseline prior bleed	24,393	25.57%	4,553	21.83%	3,264	19.49%	11,898	22.39%
Baseline prior stroke	15,023	15.75%	2,687	12.89%	1,975	11.80%	6,348	11.94%
Congestive heart failure	34,205	35.86%	6,393	30.66%	4,785	28.58%	15,275	28.74%
Diabetes	38,449	40.31%	7,346	35.23%	6,216	37.13%	19,092	35.92%
Hypertension	84,107	88.17%	18,831	90.30%	14,753	88.11%	47,186	88.79%
Renal disease	27,693	29.03%	4,977	23.87%	3,199	19.11%	11,085	20.86%
Myocardial infarction	14,004	14.68%	2,659	12.75%	1,811	10.82%	6,463	12.16%
Dyspepsia or stomach discomfort	20,902	21.91%	4,649	22.29%	3,367	20.11%	11,695	22.01%
Peripheral vascular disease	54,621	57.26%	12,332	59.14%	8,923	53.29%	29,797	56.07%
Transient ischemic attack	7,653	8.02%	1,773	8.50%	1,231	7.35%	4,122	7.76%
Coronary artery disease	46,691	48.95%	10,803	51.81%	7,700	45.99%	25,709	48.37%
Follow-up time (days)	196	184	171	153	196	192	203	192
Median	121		115		113		130	
All-cause hospitalization incidence rate (per 100 person-years)	59.0		44.5		45.1		52.5	
Stroke/SE incidence rate (per 100 person-years)	1.83		0.75		1.35		1.19	
Ischemic stroke	1.33		0.61		1.21		0.83	
Hemorrhagic stroke	0.38		0.10		0.10		0.30	
SE	0.11		0.03		0.04		0.05	
Major bleeding incidence rate (per 100 person-years)	6.28		3.34		4.03		6.30	
Gastrointestinal bleeding	3.00		1.76		2.55		3.54	
Intracranial hemorrhage	0.93		0.34		0.38		0.59	
Other bleeding	2.75		1.44		1.42		2.66	
Follow-up all-cause health care costs ($ PPPM)								
All-cause ER/outpatient medical costs	1,018	2,615	887	1,783	879	1,935	973	2,728
All-cause hospitalization medical costs	1,821	8,111	1,100	5,072	1,277	5,943	1,718	7,589
Pharmacy costs	368	825	733	1,546	642	946	664	915
All-cause health care costs	3,973	9,917	3,060	6,291	3,192	7,144	4,019	9,291

[a]*$CHADS_2$: congestive heart failure, hypertension, aged ≥ 75 years, diabetes mellitus, prior stroke, transient ischemic attack, or venous thromboembolism.*

[b]*CHA_2DS_2-VASc: congestive heart failure, hypertension, aged ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, aged 65-74 years, sex category.*

[c]*HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, drugs and alcohol.*

ER = emergency room; PPPM = per patient per month; PSM = propensity score matching; SD = standard deviation; SE = systemic embolism.

APPENDIX B Risk of Hospitalization in Sensitivity Analyses Among Propensity Score-Matched Patients

	Warfarin vs. Apixaban		Dabigatran vs. Apixaban		Rivaroxaban vs. Apixaban	
Dosing form	**n = 41,606**	***P* Value[a]**	**n = 30,836**	***P* Value[a]**	**n = 41,608**	***P* Value[a]**
All-cause hospitalization						
Standard dose[b]	1.36 (1.29-1.43)	<0.001	1.16 (1.10-1.24)	0.229	1.23 (1.17-1.30)	0.792
Low dose[b]	1.17 (1.08-1.26)		1.25 (1.14-1.37)		1.25 (1.17-1.34)	
Stroke/SE						
Standard dose	2.92 (2.07-4.13)	0.063	2.32 (1.52-3.53)	0.967	1.57 (1.07-2.31)	0.576
Low dose	1.69 (1.07-2.68)		2.28 (0.99-3.96)		1.85 (1.21-2.82)	
Major bleeding						
Standard dose	1.89 (1.60-2.24)	0.586	1.45 (1.18-1.78)	0.502	2.07 (1.75-2.45)	0.554
Low dose	2.04 (1.64-2.55)		1.64 (1.40-2.12)		2.25 (1.83-2.76)	
Censoring at 6 months	**n = 41,606**	***P* Value**	**n = 30,836**	***P* Value**	**n = 41,608**	***P* Value**
All-cause hospitalization	1.37 (1.30-1.43)	<0.001	1.20 (1.13-1.27)	<0.001	1.32 (1.26-1.38)	<0.001
Stroke/SE	2.39 (1.78-3.22)	<0.001	2.12 (1.49-3.02)	<0.001	1.71 (1.25-2.34)	<0.001
Major bleeding	1.91 (1.65-2.22)	<0.001	1.44 (1.19-1.74)	<0.001	2.09 (1.81-2.42)	<0.001
At least 30-day follow-up	**n = 41,576**	***P* Value**	**n = 30,824**	***P* Value**	**n = 41,539**	***P* Value**
All-cause hospitalization	1.30 (1.25-1.36)	<0.001	1.15 (1.09-1.21)	<0.001	1.23 (1.18-1.28)	<0.001
Stroke/SE	2.47 (1.87-3.26)	<0.001	2.16 (1.52-3.05)	<0.001	1.71 (1.28-2.29)	<0.001
Major bleeding	1.93 (1.69-2.22)	<0.001	1.47 (1.24-1.75)	<0.001	2.15 (1.88-2.45)	<0.001

Note: In the sensitivity analysis of dosing forms, standard-dose and low-dose dabigatran and rivaroxaban were compared with apixaban patients with the same dose.

[a]*P value is for interaction in the dosing form sensitivity analysis.*

[b]*Standard dose: 5 mg twice a day apixaban, 150 mg twice a day dabigatran, 20 mg every day rivaroxaban; low dose: 2.5 mg twice a day apixaban, 75 mg twice a day dabigatran, 10 mg or 15 mg every day rivaroxaban.*

SE = systemic embolism.