Title

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Journal

Journal of managed care & specialty pharmacy, 26(5)

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Publication Date

2020-05-01

DOI

10.18553/jmcp.2020.26.5.639

Peer reviewed

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 264,479 eligible patients, 77,480 warfarin-apixaban, 41,580 dabigatran-apixaban, and 77,640 rivaroxaban-apixaban patients were matched. The OACs were associated with a significantly higher risk of all-cause hospitalization compared with apixaban (warfarin: HR = 1.27, 95% CI = 1.23-1.31, $P<0.001$; dabigatran: HR = 1.13, 95% CI = 1.08-1.18, $P<0.001$; and rivaroxaban: HR = 1.22, 95% CI = 1.18-1.26, $P<0.001$) and were associated with a significantly higher risk of hospitalization due to stroke/SE (warfarin: HR = 2.18, 95% CI = 1.80-2.64, $P<0.001$; dabigatran: HR = 1.45, 95% CI = 1.12-1.88, $P=0.006$; and rivaroxaban: HR = 1.40, 95% CI = 1.14-1.71, $P=0.001$). Also, the OACs were associated with significantly higher risk of hospitalization due to MB-related conditions compared with apixaban (warfarin: HR = 1.76, 95% CI = 1.59-1.95, $P<0.001$; dabigatran: HR = 1.44, 95% CI = 1.23-1.68, $P<0.001$; and rivaroxaban: HR = 1.89, 95% CI=1.71-2.09, P<0.001). Compared with apixaban, warfarin ($3,577 vs. $3,183, $P<0.001$); dabigatran ($3,217 vs. $3,060, $P<0.001$); and rivaroxaban ($3,878 vs. $3,180, $P<0.001$) had significantly higher all-cause total health care costs per patient per month. Patients initiating the OACs had significantly higher MB-related medical costs compared with apixaban: warfarin ($472 vs. $269; $P<0.001$); dabigatran ($364 vs. $245, $P<0.001$); and rivaroxaban ($493 vs. $270, $P<0.001$). Warfarin was also associated with higher stroke/SE-related medical costs compared with apixaban ($124 vs. $62, $P<0.001$).

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 MB-related medical costs.

J Manag Care Spec Pharm. 2020;26(5):639-51. A previous version of this article has been retracted and is available on request. See corrections in *J Manag Care Spec Pharm.* 2020;26(5):682.

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 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]

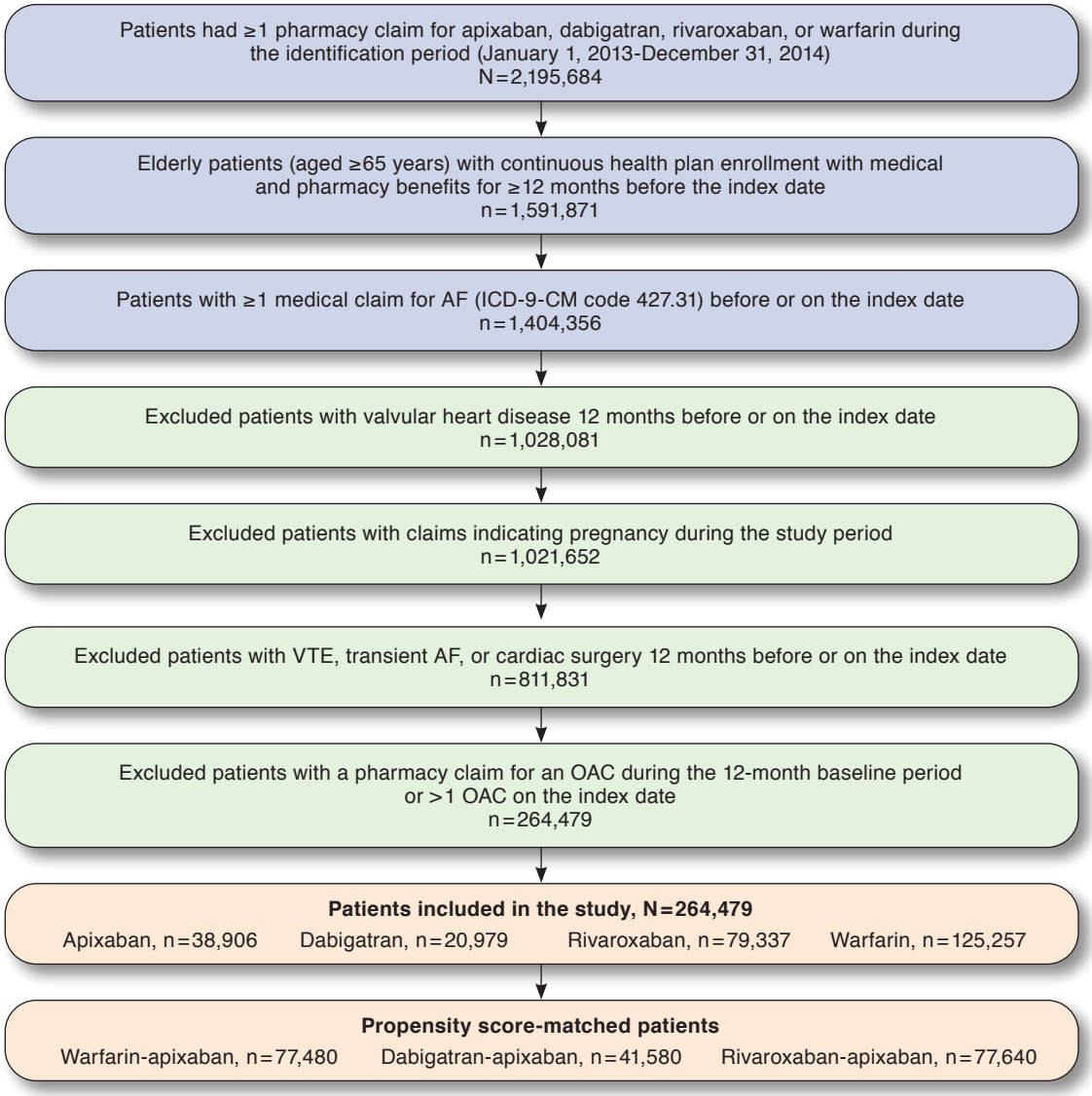
Outcomes

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 = 38,740		Warfarin Cohort n = 38,740		Apixaban Cohort n = 20,790		Dabigatran Cohort n = 20,790		Apixaban Cohort n = 38,820		Rivaroxaban Cohort n = 38,820	
	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD
Age (years)	78.3	7.4	78.2	7.3	77.2	7.2	77.1	7.0	78.3	7.4	78.3	7.2
65-74	13,578	35.0%	13,888	35.8%	8,529	41.0%	8,435	40.6%	13,644	35.1%	13,596	35.0%
75-84	16,407	42.4%	16,179	41.8%	8,707	41.9%	8,796	42.3%	16,454	42.4%	16,523	42.6%
≥85	8,755	22.6%	8,673	22.4%	3,554	17.1%	3,559	17.1%	8,722	22.5%	8,701	22.4%
Gender												
Male	18,365	47.4%	18,179	46.9%	10,417	50.1%	10,503	50.5%	18,414	47.4%	18,334	47.2%
Female	20,375	52.6%	20,561	53.1%	10,373	49.9%	10,287	49.5%	20,406	52.6%	20,486	52.8%
U.S. geographic region												
Northeast	7,107	18.3%	7,191	18.6%	4,130	19.9%	4,183	20.1%	7,098	18.3%	7,052	18.2%
North Central	8,114	20.9%	7,987	20.6%	4,805	23.1%	4,827	23.2%	8,110	20.9%	8,167	21.0%
South	17,227	44.5%	17,367	44.8%	7,997	38.5%	7,980	38.4%	17,318	44.6%	17,307	44.6%
West	6,266	16.2%	6,164	15.9%	3,848	18.5%	3,790	18.2%	6,268	16.1%	6,245	16.1%
Other	26	0.1%	31	0.1%	10	0.1%	10	0.1%	26	0.1%	49	0.1%
Baseline comorbidity												
Baseline Charlson Comorbidity Index score	2.7	2.6	2.8	2.6	2.5	2.4	2.5	2.4	2.7	2.5	2.7	2.5
0-1	15,365	39.7%	15,094	39.0%	9,127	43.9%	8,955	43.1%	15,451	39.8%	15,293	39.4%
2-3	11,618	30.0%	11,639	30.0%	6,175	29.7%	6,373	30.7%	11,640	30.0%	11,865	30.6%
≥4	11,757	30.3%	12,007	31.0%	5,488	26.4%	5,462	26.2%	11,729	30.2%	11,662	30.0%
Baseline $CHADS_2$ score[a]	2.7	1.4	2.7	1.4	2.6	1.4	2.6	1.4	2.7	1.4	2.7	1.4
0 = low risk	1,453	3.8%	1,474	3.8%	1,024	4.9%	986	4.7%	1,455	3.7%	1,450	3.7%
1 = moderate risk	6,548	16.9%	6,286	16.2%	3,881	18.7%	3,867	18.6%	6,592	17.0%	6,577	16.9%
2 = high risk	11,279	29.1%	11,163	28.8%	6,298	30.3%	6,251	30.1%	11,318	29.2%	11,263	29.0%
≥2 = high risk	19,460	50.2%	19,817	51.2%	9,587	46.1%	9,686	46.6%	19,455	50.1%	19,530	50.3%
Baseline CHA_2DS_2-VASc score[b]	4.6	1.7	4.6	1.7	4.3	1.7	4.4	1.7	4.5	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	729	1.9%	683	1.8%	538	2.6%	539	2.6%	727	1.9%	686	1.8%
2 = high risk	3,549	9.2%	3,410	8.8%	2,279	11.0%	2,260	10.9%	3,568	9.2%	3,590	9.2%
≥2 = high risk	34,462	89.0%	34,647	89.4%	17,973	86.5%	17,991	86.5%	34,525	88.9%	34,544	89.0%
Baseline HAS-BLED score[c]	3.2	1.2	3.3	1.2	3.1	1.2	3.1	1.2	3.2	1.2	3.2	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	12,002	31.0%	11,602	29.9%	7,498	36.1%	7,406	35.6%	12,027	31.0%	12,197	31.4%
≥2 = high risk	26,738	69.0%	27,138	70.1%	13,292	63.9%	13,384	64.4%	26,793	69.0%	26,623	68.6%
Baseline prior bleed	7,914	20.4%	8,065	20.8%	3,882	18.7%	3,858	18.6%	7,906	20.4%	7,922	20.4%
Baseline prior stroke	4,742	12.2%	4,928	12.7%	2,338	11.2%	2,353	11.3%	4,729	12.2%	4,769	12.3%
Congestive heart failure	11,277	29.1%	11,545	29.8%	5,656	27.2%	5,688	27.4%	11,246	29.0%	11,234	28.9%
Diabetes	13,850	35.8%	14,007	36.2%	7,557	36.3%	7,572	36.4%	13,855	35.7%	13,935	35.9%
Hypertension	34,117	88.1%	34,357	88.7%	17,970	86.4%	18,004	86.6%	34,195	88.1%	34,173	88.0%
Renal disease	9,158	23.6%	9,344	24.1%	3,906	18.8%	3,893	18.7%	9,107	23.5%	9,086	23.4%
Myocardial infarction	4,895	12.6%	4,979	12.9%	2,234	10.7%	2,243	10.8%	4,891	12.6%	4,895	12.6%
Dyspepsia or stomach discomfort	8,164	21.1%	8,427	21.8%	3,983	19.2%	4,031	19.4%	8,193	21.1%	8,155	21.0%
Peripheral vascular disease	21,370	55.2%	21,683	56.0%	10,713	51.5%	10,692	51.4%	21,432	55.2%	21,387	55.1%
Transient ischemic attack	3,032	7.8%	3,117	8.0%	1,528	7.3%	1,513	7.3%	3,032	7.8%	3,100	8.0%
Coronary artery disease	18,572	47.9%	18,876	48.7%	9,288	44.7%	9,214	44.3%	18,626	48.0%	18,597	47.9%
Baseline medication use												
Angiotensin-converting enzyme inhibitor	14,261	36.8%	14,410	37.2%	7,928	38.1%	7,972	38.3%	14,289	36.8%	14,349	37.0%
Amiodarone	3,248	8.4%	3,193	8.2%	1,599	7.7%	1,631	7.8%	3,303	8.5%	3,253	8.4%
Angiotensin receptor blocker	10,467	27.0%	10,538	27.2%	5,227	25.1%	5,248	25.2%	10,550	27.2%	10,552	27.2%

continued on next page

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

	Apixaban Cohort n = 38,740		Warfarin Cohort n = 38,740		Apixaban Cohort n = 20,790		Dabigatran Cohort n = 20,790		Apixaban Cohort n = 38,820		Rivaroxaban Cohort n = 38,820	
	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD
Baseline medication use												
Beta blockers	21,834	56.4%	21,927	56.6%	11,100	53.4%	11,175	53.8%	21,899	56.4%	22,071	56.9%
H2-receptor antagonist	2,598	6.7%	2,624	6.8%	1,291	6.2%	1,331	6.4%	2,603	6.7%	2,638	6.8%
Proton pump inhibitor	12,475	32.2%	12,646	32.6%	6,126	29.5%	6,137	29.5%	12,524	32.3%	12,473	32.1%
Antiplatelets	7,030	18.1%	7,127	18.4%	3,119	15.0%	3,094	14.9%	7,087	18.3%	7,016	18.1%
Statins	23,692	61.2%	23,916	61.7%	12,049	58.0%	12,036	57.9%	23,761	61.2%	23,755	61.2%
Index drug dose[d]												
Standard dose	28,130	72.6%			16,037	77.1%	16,626	80.0%	28,229	72.7%	24,801	63.9%
Low dose	10,610	27.4%			4,753	22.9%	4,164	20.0%	10,591	27.3%	14,019	36.1%
Follow-up time (days)	144.6	133.3	181.1	173.6	145.4	133.2	185.2	183.9	144.7	133.3	182.3	176.5
Median	97		113		98		106		97		117	
Switch during follow-up	1,461	3.8%	2,553	6.6%	771	3.7%	2,318	11.1%	1,460	3.8%	2,346	6.0%

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

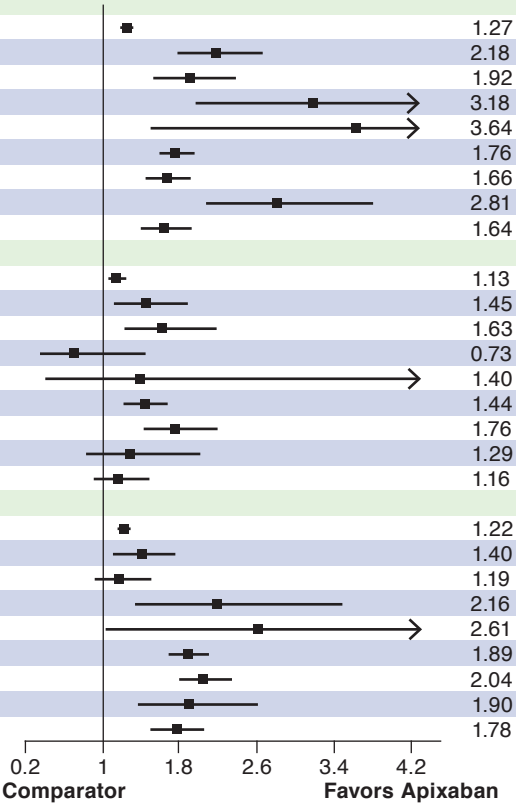
Generalized linear models with log-link and a gamma distribution were used for the analysis of health care costs among the cohorts.[29] Additionally, two-part models with bootstrapping were used in the analysis of MB- and stroke-related medical costs, given the high proportion of cost fields with 0 values. 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 low-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	55.12	47.31	1.27 (1.23-1.31)	<0.001
Stroke/SE	1.96	0.97	2.18 (1.80-2.64)	<0.001
Ischemic	1.39	0.79	1.92 (1.55-2.38)	<0.001
Hemorrhagic	0.43	0.14	3.18 (1.99-5.09)	<0.001
SE	0.14	0.04	3.64 (1.51-8.80)	0.004
Major bleeding	5.94	3.66	1.76 (1.59-1.95)	<0.001
GI bleeding	2.80	1.84	1.66 (1.44-1.92)	<0.001
ICH	0.95	0.36	2.81 (2.08-3.80)	<0.001
Other bleeding	2.51	1.67	1.64 (1.41-1.91)	<0.001
Dabigatran vs. apixaban				
All-cause hospitalization	45.35	44.38	1.13 (1.08-1.18)	<0.001
Stroke/SE	1.41	1.10	1.45 (1.12-1.88)	0.006
Ischemic	1.22	0.85	1.63 (1.21-2.18)	0.001
Hemorragic	0.13	0.21	0.73 (0.37-1.46)	0.375
SE	0.06	0.05	1.40 (0.40-4.87)	0.596
Major bleeding	4.20	3.20	1.44 (1.23-1.68)	<0.001
GI bleeding	2.59	1.61	1.76 (1.43-2.18)	<0.001
ICH	0.45	0.37	1.29 (0.83-2.02)	0.264
Other bleeding	1.48	1.40	1.16 (0.91-1.47)	0.240
Rivaroxaban vs. apixaban				
All-cause hospitalization	52.35	47.22	1.22 (1.18-1.26)	<0.001
Stroke/SE	1.27	0.97	1.40 (1.14-1.71)	0.001
Ischemic	0.86	0.79	1.19 (0.94-1.51)	0.141
Hemorrhagic	0.31	0.14	2.16 (1.34-3.49)	0.002
SE	0.09	0.04	2.61 (1.04-6.55)	0.041
Major bleeding	6.29	3.63	1.89 (1.71-2.09)	<0.001
GI bleeding	3.38	1.82	2.04 (1.77-2.35)	<0.001
ICH	0.66	0.36	1.90 (1.39-2.60)	<0.001
Other bleeding	2.68	1.66	1.78 (1.53-2.06)	<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 events. 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 264,479 patients were identified: 125,257 warfarin, 20,979 dabigatran, 79,337 rivaroxaban, and 38,906 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, 77,480 warfarin-apixaban, 41,580 dabigatran-apixaban, and 77,640 rivaroxaban-apixaban matched patients were included in the study (Table 1). Patients were followed for a median of 113 and 97 days for warfarin-apixaban cohorts, 106 and 98 days for dabigatran-apixaban cohorts, and 117 and 97 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 (2.5), followed by rivaroxaban-apixaban (2.7) and warfarin-apixaban (2.8 and 2.7) patients. The CHA_2DS_2-VASc scores ranged from 4.3 to 4.6 across

TABLE 2 Adjusted Health Care Cost Comparisons

PPPM Costs[a]	Apixaban Cohort (n = 38,470)	Warfarin Cohort (n = 38,470)		Apixaban Cohort (n = 20,790)	Dabigatran Cohort (n = 20,790)		Apixaban Cohort (n = 38,820)	Rivaroxaban Cohort (n = 38,820)	
	Marginal Effect ($)	Marginal Effect ($)	*P* Value	Marginal Effect ($)	Marginal Effect ($)	*P* Value	Marginal Effect ($)	Marginal Effect ($)	*P* Value
All-cause ER/outpatient medical costs	901	956	<0.001	895	873	0.010	902	932	<0.001
All-cause hospitalization medical costs	1,147	1,599	<0.001	1,080	1,307	<0.001	1,145	1,632	<0.001
All-cause medical costs[b]	2,402	3,207	<0.001	2,290	2,556	<0.001	2,399	3,178	<0.001
Pharmacy costs	781	370	<0.001	770	660	<0.001	781	701	<0.001
All-cause health care costs[b]	3,183	3,577	<0.001	3,060	3,217	<0.001	3,180	3,878	<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 = 1.27, 95% CI = 1.23-1.31; dabigatran: HR = 1.13, 95% CI = 1.08-1.18; and rivaroxaban: HR = 1.22, 95% CI = 1.18-1.26).

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 = 2.18, 95% CI = 1.80-2.64; dabigatran: HR = 1.45, 95% CI = 1.12-1.88; and rivaroxaban: HR = 1.40, 95% CI = 1.14-1.71). They were also associated with a significantly higher risk of hospitalization due to MB-related conditions compared with apixaban treatment (warfarin: HR = 1.76, 95% CI = 1.59-1.95; dabigatran: HR = 1.44, 95% CI = 1.23-1.68; and rivaroxaban: HR = 1.89, 95% CI = 1.71-2.09).

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

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). Significant interactions were found for dose and all-cause, stroke/SE-related, and MB-related hospitalizations among apixaban and warfarin patients. Warfarin was associated with a higher risk of all-cause, stroke/SE-related, and MB-related hospitalizations 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.

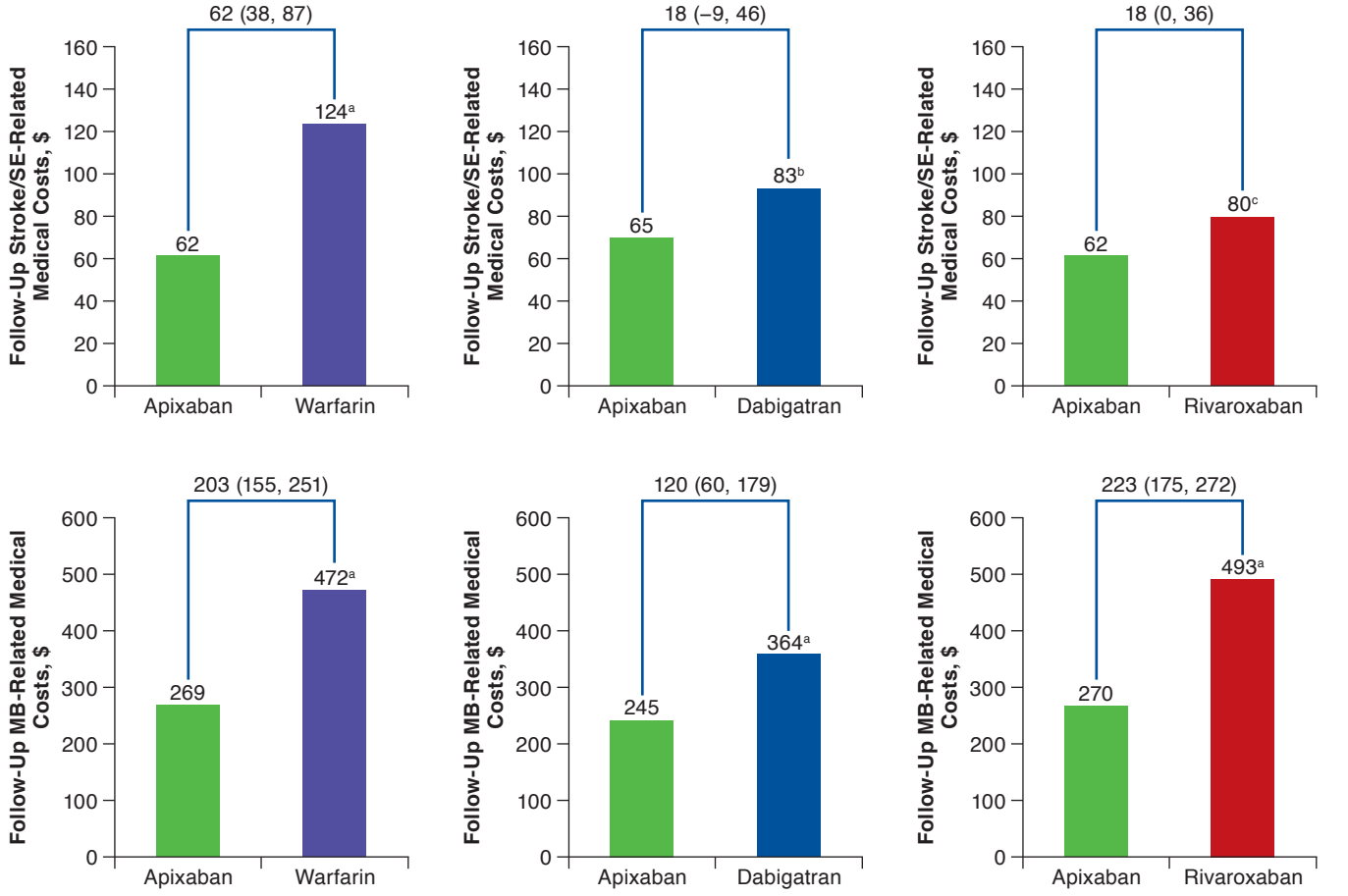
Discussion

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 and MB-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

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



[a]*P* < 0.001.
[b]*P* = 0.189.
[c]*P* = 0.051.
MB = major bleeding; PPPM = per patient per month; SE = systemic embolism.

DOACs. In a study of the MarketScan population by Lip et al. (2016), patients who initiated dabigatran had a numerically 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 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. He has served as a consultant and/or speaker for Bristol Myers Squibb, Pfizer, and Boehringer Ingelheim. 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 = 125,257)		Apixaban Cohort (N = 38,906)		Dabigatran Cohort (N = 20,979)		Rivaroxaban Cohort (N = 79,337)	
	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD
Age (years)	78.56	7.37	78.30	7.38	77.07	7.00	77.53	7.16
65-74	41,678	33.27%	13,648	35.08%	8,585	40.92%	30,663	38.65%
75-84	54,186	43.26%	16,470	42.33%	8,830	42.09%	33,772	42.57%
≥85	29,393	23.47%	8,788	22.59%	3,564	16.99%	14,902	18.78%
Gender								
Male	60,638	48.41%	18,438	47.39%	10,647	50.75%	38,518	48.55%
Female	64,619	51.59%	20,468	52.61%	10,332	49.25%	40,819	51.45%
Geographic region								
Northeast	24,944	19.91%	7,110	18.27%	4,239	20.21%	14,298	18.02%
North Central	38,533	30.76%	8,115	20.86%	4,882	23.27%	18,387	23.18%
South	40,386	32.24%	17,383	44.68%	7,987	38.07%	32,912	41.48%
West	21,241	16.96%	6,272	16.12%	3,837	18.29%	13,592	17.13%
Other	153	0.12%	26	0.07%	34	0.16%	148	0.19%
Baseline comorbidity								
Charlson Comorbidity Index	3.10	2.76	2.70	2.55	2.46	2.40	2.58	2.49
$CHADS_2$ score[a]	2.84	1.45	2.70	1.43	2.57	1.41	2.60	1.43
CHA_2DS_2-VASc score[b]	4.71	1.75	4.55	1.73	4.35	1.71	4.43	1.72
HAS-BLED score[c]	3.29	1.30	3.23	1.24	3.07	1.21	3.17	1.23
Baseline prior bleed	31,052	24.79%	7,921	20.36%	3,878	18.49%	16,932	21.34%
Baseline prior stroke	19,297	15.41%	4,746	12.20%	2,377	11.33%	9,021	11.37%
Congestive heart failure	43,374	34.63%	11,295	29.03%	5,753	27.42%	21,517	27.12%
Diabetes	50,006	39.92%	13,884	35.69%	7,683	36.62%	28,152	35.48%
Hypertension	108,611	86.71%	34,276	88.10%	18,152	86.52%	69,011	86.98%
Renal disease	36,657	29.27%	9,175	23.58%	3,902	18.60%	16,045	20.22%
Myocardial infarction	18,638	14.88%	4,906	12.61%	2,253	10.74%	9,400	11.85%
Dyspepsia or stomach discomfort	26,535	21.18%	8,215	21.11%	4,049	19.30%	16,489	20.78%
Peripheral vascular disease	69,381	55.39%	21,502	55.27%	10,762	51.30%	41,938	52.86%
Transient ischemic attack	9,789	7.82%	3,044	7.82%	1,527	7.28%	5,829	7.35%
Coronary artery disease	59,249	47.30%	18,698	48.06%	9,276	44.22%	35,963	45.33%
Follow-up time (days)	179.31	173.59	144.66	133.32	185.02	183.82	178.76	174.67
Median	111		97		106		113	
All-cause hospitalization incidence rate (per 100 person-years)	60.72		47.25		45.27		53.31	
Stroke/SE incidence rate (per 100 person-years)	1.98		0.97		1.40		1.25	
Ischemic stroke	1.43		0.79		1.21		0.87	
Hemorrhage stroke	0.42		0.14		0.13		0.29	
SE	0.13		0.04		0.06		0.08	
Major bleeding incidence rate (per 100 person-years)	6.56		3.64		4.18		6.30	
Gastrointestinal bleeding	3.12		1.83		2.58		3.53	
Intracranial hemorrhage	0.99		0.36		0.44		0.61	
Other bleeding	2.80		1.67		1.48		2.65	
Follow-up all-cause health care costs ($ PPPM)								
All-cause ER/outpatient medical costs	1,826	8,058	1,145	5,333	1,301	6,081	1,645	7,310
All-cause hospitalization medical costs	1,024	2,571	901	1,893	874	1,893	966	2,920
Pharmacy costs	375	885	780	1,690	659	1,046	701	1,097
All-cause health care costs	3,987	9,904	3,179	6,733	3,210	7,310	3,941	9,030

[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 = 76,940**	***P* Value[a]**	**n = 41,580**	***P* Value[a]**	**n = 77,640**	***P* Value[a]**
All-cause hospitalization						
Standard dose[b]	1.33 (1.28-1.38)	<0.001	1.13 (1.07-1.19)	0.409	1.21 (1.17-1.26)	0.230
Low dose[b]	1.09 (1.03-1.16)		1.18 (1.08-1.28)		1.17 (1.11-1.23)	
Stroke/SE						
Standard dose	2.55 (1.99-3.26)	0.039	1.50 (1.08-2.10)	0.914	1.48 (1.13-1.94)	0.408
Low dose	1.67 (1.22-2.29)		1.46 (0.95-2.23)		1.25 (0.92-1.69)	
Major bleeding						
Standard dose	1.93 (1.70-2.19)	0.003	1.44 (1.19-1.74)	0.782	1.90 (1.67-2.17)	0.678
Low dose	1.38 (1.16-1.65)		1.51 (1.16-1.97)		1.82 (1.55-2.13)	
Censoring at 6 months	**n = 76,940**	***P* Value**	**n = 41,580**	***P* Value**	**n = 77,640**	***P* Value**
All-cause hospitalization	1.28 (1.24-1.32)	<0.001	1.14 (1.09-1.20)	<0.001	1.24 (1.20-1.29)	<0.001
Stroke/SE	2.22 (1.80-2.74)	<0.001	1.43 (1.08-1.90)	0.013	1.33 (1.05-1.67)	0.017
Major bleeding	1.74 (1.56-1.95)	<0.001	1.39 (1.18-1.65)	<0.001	1.85 (1.65-2.06)	<0.001
At least 30-day follow up	**n = 68,536**	***P* Value**	**n = 36,882**	***P* Value**	**n = 68,684**	***P* Value**
All-cause hospitalization	1.25 (1.21-1.29)	<0.001	1.11 (1.06-1.16)	<0.001	1.19 (1.15-1.23)	<0.001
Stroke/SE	2.21 (1.81-2.70)	<0.001	1.43 (1.08-1.88)	0.001	1.43 (1.16-1.77)	<0.001
Major bleeding	1.72 (1.55-1.91)	<0.001	1.42 (1.21-1.66)	<0.001	1.87 (1.69-2.07)	<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.