Clinical and Economic Outcomes Among Nonvalvular Atrial Fibrillation Patients With Coronary Artery Disease and/or Peripheral Artery Disease

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To address literature gaps on treatment with real-world evidence, this study compared effectiveness, safety, and cost outcomes in NVAF patients with coronary or peripheral artery disease (CAD, PAD) prescribed apixaban versus other oral anticoagulants. NVAF patients aged ≥65 years co-diagnosed with CAD/PAD initiating warfarin, apixaban, dabigatran, or rivaroxaban were selected from the US Medicare population (January 1, 2013 to September 30, 2015). Propensity score matching was used to match apixaban versus warfarin, dabigatran, and rivaroxaban cohorts. Cox models were used to evaluate the risk of stroke/systemic embolism (SE), major bleeding (MB), all-cause mortality, and a composite of stroke/myocardial infarction/all-cause mortality. Generalized linear and two-part models were used to compare stroke/SE, MB, and all-cause costs between cohorts. A total of 33,269 warfarin-apixaban, 9,335 dabigatran-apixaban, and 33,633 rivaroxaban-apixaban pairs were identified after matching. Compared with apixaban, stroke/SE risk was higher in warfarin (hazard ratio [HR]: 1.93; 95% confidence interval [CI]: 1.61 to 2.31), dabigatran (HR: 1.69; 95% CI: 1.18 to 2.43), and rivaroxaban (HR: 1.24; 95% CI: 1.01 to 1.51) patients. MB risk was higher in warfarin (HR: 1.67; 95% CI: 1.52 to 1.83), dabigatran (HR: 1.37; 95% CI: 1.13 to 1.68), and rivaroxaban (HR: 1.87; 95% CI: 1.71 to 2.05) patients vs apixaban. Stroke/SE- and MB-related medical costs per-patient per-month were higher in warfarin, dabigatran, and rivaroxaban patients versus apixaban. Total all-cause health care costs were higher in warfarin and rivaroxaban patients compared with apixaban patients. In conclusion, compared with apixaban, patients on dabigatran, rivaroxaban, or warfarin had a higher risk of stroke/SE, MB, and event-related costs. **(Am J Cardiol 2021;148:69−77)**

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Atrial fibrillation (AF) is associated with several complications and comorbidities of considerable clinical and economic concern, which is further exacerbated by comorbidities, such as coronary artery disease (CAD) and peripheral arterial disease (PAD), which are concomitant in 34% to 69% and 4% to 28% of AF diagnosed patients, respectively.[1−4] Evidence from multiple randomized clinical trials (RCTs) and real-world studies has shown that apixaban was noninferior to warfarin in reducing all-cause mortality, stroke, and major bleeding event rates in patients with nonvalvular AF (NVAF).[5−8] Further, real-world evidence has shown that use of apixaban in NVAF patients was associated with lower major bleeding event rates when compared with dabigatran and rivaroxaban, similar to lower stroke/systemic embolism (SE) risk, and lower healthcare costs.[7−13] The performance of direct oral anticoagulants (DOACs) compared to warfarin in patients with concomitant NVAF and CAD or PAD has been evaluated in a previous study.[14] However, there is little research comparing DOACs within a NVAF population with concomitant CAD or PAD. Therefore, this study compared the risk of stroke/SE, major bleeding, mortality, composite outcomes (stroke/

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myocardial infarction/all-cause mortality), and health care costs among US patients diagnosed with NVAF and CAD or PAD who were newly prescribed apixaban vs warfarin, dabigatran, or rivaroxaban.

Methods

This retrospective observational study used Medicare data from the Centers for Medicare and Medicaid Services. Medicare is a federal health insurance program for people aged ≥65 years, and those with qualifying disabilities, or end-stage renal disease. Over 38 million beneficiaries were enrolled in the fee-for-service Medicare insurance by 2015.[15]

Patients were required to have ≥1 pharmacy claim for warfarin, apixaban, dabigatran, or rivaroxaban between January 1, 2013 and September 30, 2015. The first prescription for an OAC during this period was designated as the index date. Edoxaban was not included in the study given its recent Food and Drug Administration approval in 2015, and hence a small sample size. Further, patients were required to have ≥1 diagnosis of AF and ≥1 diagnosis of CAD or PAD during the 12 months before (baseline period) or on the index date. All patients were aged ≥65 on the index date and had continuous medical and pharmacy health plan enrollment during the baseline period. Exclusion criteria are listed in Figure 1.

Patient data were assessed from the day after the index date until the earliest of discontinuation, treatment switch, death, study end, medical/pharmacy disenrollment, or 1 year from the index date. Discontinuation was defined as no evidence of index OAC prescription for 30 days from the last day of the last filled prescription days' supply. A switch was defined as the presence of a nonindex OAC prescription claim within ±30 days of the last days' supply.

Clinical outcomes were stroke/SE, major bleeding, all-cause mortality, and stroke/myocardial infarction/all-cause mortality. Outcomes were determined using primary diagnoses on discharge records from hospitalizations. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes used to identify stroke/SE (ischemic stroke, hemorrhagic stroke, and SE) and major bleeding (gastrointestinal bleeding, intracranial hemorrhage, and other major bleeding sites) were based on validated administrative-claim based algorithms and can be

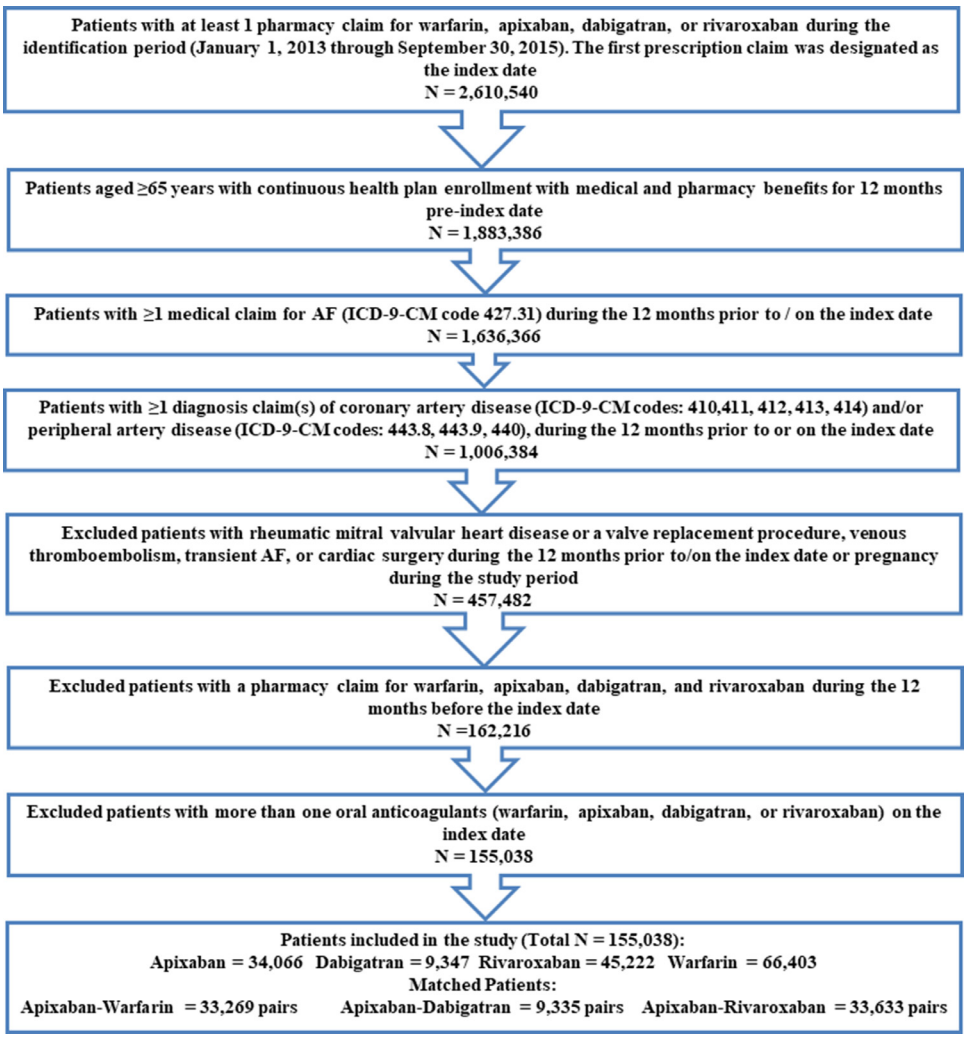

Figure 1. Patient selection figure. AF = atrial fibrillation; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

found in S1 Table.[16,17] Death was obtained by validated Social Security records that included the date of death.[18]

Total all-cause health care costs were defined as the sum of medical and pharmacy costs. All-cause medical costs included inpatient, outpatient/ER, and other costs (durable medical equipment, skilled nursing facility, home health agency, and hospice). 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 and secondary diagnoses). Major bleeding-related medical costs were defined as hospitalization costs associated with the first major bleeding event plus all subsequent bleeding costs occurring in the inpatient or outpatient (primary and secondary diagnoses) setting. Costs included all paid amounts, including Medicare payments, copayments, and deductibles incurred during the follow-up period.

Propensity scores were used to obtain estimates of the average treatment effect using a logistic model with two treatment cohorts.[19] Each patient in the reference cohort (apixaban) was matched with a patient in the comparison cohort (warfarin, dabigatran, or rivaroxaban) using nearest neighbor matching with a caliper of 0.01 without replacement.[20] The included covariates are noted in Table 1 and were considered balanced between the treatment groups if the absolute standardized difference of the mean was ≤ 10.[21]

Cox proportional hazards models with robust sandwich estimates were used to compare the time-to-clinical outcomes in matched cohorts (warfarin, dabigatran, or rivaroxaban vs apixaban).[20] OAC treatment was included as the independent variable; other covariates were not included because the cohorts were balanced. Statistical significance was set at 0.05 *a priori*. Generalized linear models with gamma distribution were used to compare marginal mean health care costs between warfarin, dabigatran, and rivaroxaban cohorts versus apixaban. Given the high proportion of cost fields with 0 values, bootstrapping with a two-part model was conducted at the pair level to generate the 95% confidence interval (CI).

To assess the robustness of the findings based on propensity score matching, a sensitivity analysis was conducted to compare clinical outcomes between cohorts using inverse probability treatment weighting to balance potential confounding factors for treatment choice (warfarin, dabigatran, or rivaroxaban vs apixaban).[22,23] The inverse of propensity scores was used to generate patient-specific weights to control for covariate imbalances. After weighting, no significant differences were observed between patient cohorts. Cox proportional hazards models were then used to estimate the risk of clinical outcomes.

Results

After application of the selection criteria, 155,038 NVAF patients were diagnosed with either CAD, PAD, or both. Among these, there were 34,066 (22.0%) apixaban, 66,403 (42.8%) warfarin, 9,347 (6.0%) dabigatran, and 45,222 (29.2%) rivaroxaban patients. Before matching, dabigatran and rivaroxaban patients were younger and apixaban and warfarin patients were of similar age. Prematching results are shown in the S2 Table.

Following propensity score matching, there were 33,269 apixaban-warfarin, 9,335 apixaban-dabigatran, and 33,633 apixaban-rivaroxaban pairs. All potential confounding variables that have been evaluated were well balanced within the matched cohorts with the absolute standardized difference of the mean for each of the variables being less than 0.1. Postmatching baseline results are presented in Table 1. The median follow-up times ranged from 119 to 139 days (4 to 4.6 months) (Table 1).

When compared with apixaban, warfarin patients had a significantly higher risk of stroke/SE, major bleeding, all-cause mortality, and composite stroke/myocardial infarction/all-cause mortality (Figure 2). When compared with the apixaban cohort, patients prescribed dabigatran had a significantly higher risk of stroke/SE and major bleeding, but similar risk of all-cause mortality, and stroke/myocardial infarction/all-cause mortality (Figure 2). When compared with the apixaban cohort, patients prescribed rivaroxaban had a significantly higher risk of stroke/SE, major bleeding, all-cause mortality, and stroke/myocardial infarction/all-cause mortality (Figure 2). The results stratified by types of stroke/SE and major bleeding are in S3 Table.

The results of sensitivity analyses were generally consistent with the above findings; however, dabigatran was associated with a significantly higher risk of stroke/myocardial infarction/all-cause mortality compared with apixaban (S4 Table).

When compared with the apixaban cohort, patients in the warfarin cohort had significantly higher average per-patient per-month total health care costs, stroke/SE-, and major bleeding-related medical costs. When compared with apixaban, dabigatran patients had significantly higher average per-patient per-month costs for stroke/SE and major bleeding. When compared with apixaban, rivaroxaban patients had significantly higher total health care costs as well as stroke/SE- and major bleeding-related medical costs per-patient per-month (Table 2).

Discussion

This analysis of Medicare data shows that when compared with patients prescribed apixaban, patients prescribed warfarin and rivaroxaban had a higher risk of stroke/SE, major bleeding, all-cause mortality, and stroke/myocardial infarction/all-cause mortality. Compared to apixaban, patients prescribed dabigatran had higher risk of stroke/SE and major bleeding but similar risk of all-cause mortality and stroke/myocardial infarction/all-cause mortality. The higher risk of adverse clinical outcomes associated with patients prescribed warfarin and rivaroxaban was further associated with higher all-cause health care costs when compared with patients prescribed apixaban. Stroke/SE- and major bleeding-related medical costs were also higher for the warfarin, dabigatran, and rivaroxaban cohorts when compared with the apixaban cohort.

These findings accord with evidence in the literature, including the ARISTOTLE trial, which demonstrated that warfarin patients had higher rates of stroke/SE and major bleeding than apixaban patients.[5] In the ARISTOTLE trial, this trend did not change with the presence of concomitant CAD or PAD.[24,25] Several real-world studies have also found

Table 1
Baseline characteristics and follow-up time for nonvalvular atrial fibrillation patients with coronary artery disease/peripheral artery disease after propensity score matching

	Apixaban cohort N = 33,269 N(%), Mean (SD)	Warfarin cohort N = 33, 269 N(%), Mean (SD)	Std Difference	Apixaban cohort N = 9,335 N(%), Mean (SD)	Dabigatran cohort N = 9,335 N(%), Mean (SD)	Std Difference	Apixaban cohort N = 33,633 N(%), Mean (SD)	Rivaroxaban cohort N = 33,633 N(%), Mean(SD)	Std Difference
Age (years)	78.9 (7.4)	78.9 (7.4)	0.07	78.1 (7.3)	77.7 (7.1)	5.03	78.8 (7.4)	78.7 (7.3)	1.15
65-74	10,696 (32.2%)	10,628 (31.9%)	0.44	3,357 (36.0%)	3,461 (37.1%)	2.31	11,013 (32.7%)	10,901 (32.4%)	0.71
75-79	7,296 (21.9%)	7,330 (22.0%)	0.25	2,287 (24.5%)	2,288 (24.5%)	0.02	7,433 (22.1%)	7,412 (22.0%)	0.15
≥80	15,277 (45.9%)	15,311 (46.0%)	0.21	3,691 (39.5%)	3,586 (38.4%)	2.31	15,187 (45.2%)	15,320 (45.6%)	0.79
Gender									
Male	17,910 (53.8%)	17,931 (53.9%)	0.13	5,144 (55.1%)	5,236 (56.1%)	1.98	18,178 (54.0%)	18,131 (53.9%)	0.28
Female	15,359 (46.2%)	15,338 (46.1%)	0.13	4,191 (44.9%)	4,099 (43.9%)	1.98	15,455 (46.0%)	15,502 (46.1%)	0.28
Race									
White	30,261 (91.0%)	30,283 (91.0%)	0.23	8,391 (89.9%)	8,390 (89.9%)	0.04	30,603 (91.0%)	30,632 (91.1%)	0.30
Black	1,516 (4.6%)	1,511 (4.5%)	0.07	442 (4.7%)	439 (4.7%)	0.15	1,488 (4.4%)	1,466 (4.4%)	0.32
Hispanic	420 (1.3%)	401 (1.2%)	0.52	156 (1.7%)	149 (1.6%)	0.59	424 (1.3%)	422 (1.3%)	0.05
Other	1,072 (3.2%)	1,074 (3.2%)	0.03	346 (3.7%)	357 (3.8%)	0.62	1,118 (3.3%)	1,113 (3.3%)	0.08
U.S. Geographic Region									
Northeast	6,496 (19.5%)	6,415 (19.3%)	0.62	1,834 (19.6%)	1,888 (20.2%)	1.45	6,423 (19.1%)	6,414 (19.1%)	0.07
Midwest	7,700 (23.1%)	8,052 (24.2%)	2.49	2,251 (24.1%)	2,279 (24.4%)	0.70	7,658 (22.8%)	7,593 (22.6%)	0.46
South	14,186 (42.6%)	14,055 (42.2%)	0.80	3,769 (40.4%)	3,662 (39.2%)	2.34	14,670 (43.6%)	14,848 (44.1%)	1.07
West	4,866 (14.6%)	4,726 (14.2%)	1.20	1,468 (15.7%)	1,496 (16.0%)	0.82	4,861 (14.5%)	4,760 (14.2%)	0.86
Other	21 (0.1%)	21 (0.1%)	0.00	13 (0.1%)	<11	0.92	21 (0.1%)	18 (0.1%)	0.37
Baseline Comorbidity									
Deyo-Charlson Comorbidity Index	3.9 (2.6)	3.9 (2.5)	0.12	3.7 (2.5)	3.6 (2.5)	3.92	3.8 (2.5)	3.8 (2.5)	0.27
CHA_2DS_2-VASc Score	4.4 (1.4)	4.4 (1.3)	0.09	4.3 (1.4)	4.2 (1.4)	2.30	4.3 (1.4)	4.3 (1.4)	0.65
HAS-BLED Score*	3.6 (1.2)	3.6 (1.2)	1.41	3.5 (1.2)	3.4 (1.2)	2.00	3.6 (1.2)	3.6 (1.2)	0.89
Bleeding history	8,187 (24.6%)	8,252 (24.8%)	0.45	2,213 (23.7%)	2,134 (22.9%)	0.38	8,148 (24.2%)	8,076 (24.0%)	0.50
Congestive Heart Failure	12,869 (38.7%)	12,950 (38.9%)	0.50	3,493 (37.4%)	3,476 (37.2%)	0.65	12,704 (37.8%)	12,713 (37.8%)	0.06
Diabetes Mellitus	14,667 (44.1%)	14,712 (44.2%)	0.27	4,191 (44.9%)	4,221 (45.2%)	2.39	14,661 (43.6%)	14,668 (43.6%)	0.04
Hypertension	31,355 (94.2%)	31,359 (94.3%)	0.05	8,823 (94.5%)	8,771 (94.0%)	4.93	31,711 (94.3%)	31,706 (94.3%)	0.06
Renal Disease	9,383 (28.2%)	9,393 (28.2%)	0.07	2,326 (24.9%)	2,130 (22.8%)	1.52	9,185 (27.3%)	9,268 (27.6%)	0.55
Liver Disease	1,869 (5.6%)	1,841 (5.5%)	0.37	550 (5.9%)	517 (5.5%)	2.18	1,877 (5.6%)	1,903 (5.7%)	0.34
Myocardial Infarction	5,883 (17.7%)	5,946 (17.9%)	0.50	1,507 (16.1%)	1,433 (15.4%)	2.20	5,850 (17.4%)	5,926 (17.6%)	0.59
Dyspepsia or Stomach Discomfort	8,179 (24.6%)	8,109 (24.4%)	0.49	2,221 (23.8%)	2,134 (22.9%)	1.05	8,223 (24.4%)	8,260 (24.6%)	0.26
Stroke/SE	5,230 (15.7%)	5,143 (15.5%)	0.72	1,408 (15.1%)	1,377 (14.8%)	0.93	5,127 (15.2%)	5,173 (15.4%)	0.10
Transient ischemic attack	3,117 (9.4%)	3,037 (9.1%)	0.83	814 (8.7%)	822 (8.8%)	0.30	3,133 (9.3%)	3,163 (9.4%)	0.38
Anemia and Coagulation Defects	12,288 (36.9%)	12,306 (37.0%)	0.11	3,161 (33.9%)	3,093 (33.1%)	1.54	12,184 (36.2%)	12,145 (36.1%)	0.31
Alcoholism	715 (2.1%)	684 (2.1%)	0.65	242 (2.6%)	251 (2.7%)	0.60	719 (2.1%)	704 (2.1%)	0.24
PAD only	4,598 (13.8%)	4,777 (14.4%)	1.55	1,310 (14.0%)	1,319 (14.1%)	0.28	4,638 (13.8%)	4,831 (14.4%)	1.65
CAD only	20,242 (60.8%)	19,844 (59.6%)	2.44	5,721 (61.3%)	5,805 (62.2%)	1.85	20,571 (61.2%)	20,348 (60.5%)	1.36
CAD and PAD	8,429 (25.3%)	8,648 (26.0%)	1.51	2,304 (24.7%)	2,211 (23.7%)	2.33	8,424 (25.0%)	8,454 (25.1%)	0.21
Baseline Medication Use									
ACE/ARB	22,131 (66.5%)	22,099 (66.4%)	0.20	6,328 (67.8%)	6,264 (67.0%)	1.46	22,428 (66.7%)	22,548 (67.0%)	0.76
Amiodarone	4,804 (14.4%)	4,934 (14.8%)	1.11	1,341 (14.4%)	1,322 (14.2%)	0.58	4,917 (14.6%)	4,907 (14.6%)	0.08

(*continued on next page*)

Table 1 (*Continued*)

	Apixaban cohort N = 33,269 N(%), Mean (SD)	Warfarin cohort N = 33, 269 N(%), Mean (SD)	Std Difference	Apixaban cohort N = 9,335 N(%), Mean (SD)	Dabigatran cohort N = 9,335 N(%), Mean (SD)	Std Difference	Apixaban cohort N = 33,633 N(%), Mean (SD)	Rivaroxaban cohort N = 33,633 N(%), Mean(SD)	Std Difference
Beta Blockers	21,195 (63.7%)	21,205 (63.7%)	0.06	5,823 (62.4%)	5,787 (62.0%)	0.80	21,444 (63.8%)	21,470 (63.8%)	0.16
H2-receptor Antagonist	2,789 (8.4%)	2,807 (8.4%)	0.19	791 (8.5%)	757 (8.1%)	1.32	2,798 (8.3%)	2,794 (8.3%)	0.04
Proton Pump Inhibitor	12,016 (36.1%)	11,798 (35.5%)	1.37	3,212 (34.4%)	3,239 (34.7%)	0.61	12,199 (36.3%)	12,244 (36.4%)	0.28
Statins	23,995 (72.1%)	23,961 (72.0%)	0.23	6,556 (70.2%)	6,473 (69.3%)	1.94	24,319 (72.3%)	24,472 (72.8%)	1.02
Anti-platelets	8,688 (26.1%)	8,683 (26.1%)	0.03	2,277 (24.4%)	2,197 (23.5%)	2.01	8,918 (26.5%)	9,030 (26.8%)	0.75
NSAIDs	8,068 (24.3%)	8,056 (24.2%)	0.08	2,313 (24.8%)	2,299 (24.6%)	0.35	8,347 (24.8%)	8,345 (24.8%)	0.01
Baseline Procedures									
Coronary Bypass surgery	569 (1.7%)	639 (1.9%)	1.58	148 (1.6%)	159 (1.7%)	0.93	561 (1.7%)	551 (1.6%)	0.23
Percutaneous Coronary Intervention	912 (2.7%)	921 (2.8%)	0.17	251 (2.7%)	239 (2.6%)	0.80	892 (2.7%)	915 (2.7%)	0.42
Index Dose[†]									
Low Dose	10,265 (30.9%)	-	-	2,574 (27.6%)	2,215 (23.7%)	8.81	10,166 (30.2%)	13,295 (39.5%)	0.05
Standard Dose	23,018 (69.2%)	-	-	6,763 (72.4%)	7,123 (76.3%)	8.84	23,481 (69.8%)	20,422 (60.7%)	19.19
Baseline All-cause Health Care Costs (PPPM)									
Inpatient Admission Costs	$903 ($1,480)	$1,106 ($1,809)	12.31	$879 ($1,491)	$830 ($1,481)	3.27	$884 ($1,464)	$995 ($1,612)	7.26
Outpatient Costs (ER, Office, and other)	$677 ($838)	$659 ($926)	2.10	$663 ($824)	$602 ($699)	8.02	$676 ($835)	$637 ($822)	4.67
Prescription Costs	$351 ($613)	$272 ($502)	14.24	$350 ($627)	$313 ($432)	7.05	$351 ($613)	$333 ($522)	3.18
Other Costs (DME, SNF, HHA, Hospice)	$342 ($894)	$456 ($1,088)	11.37	$323 ($887)	$375 ($987)	5.45	$334 ($885)	$415 ($1,054)	8.31
Total Costs	$2,274 ($2,412)	$2,492 ($2,830)	8.31	$2,216 ($2,403)	$2,119 ($2,384)	4.04	$2,244 ($2,392)	$2,380 ($2,572)	5.47
Follow-up Time (Mean)	183.5	227.6	-	183.6	244.1	-	183.9	225.2	-
SD	177.9	229.8	-	178.4	255.1	-	178.1	234.3	-
25th Percentile	44	56	-	45	30	-	44	31	-
Median	120	139	-	119	131	-	121	132	-
75th Percentile	262	330	-	265	372	-	263	339	-

ACE = angiotensin-converting enzyme inhibitors; ARB = angiotensin-receptor blockers; CAD = coronary artery disease; 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 to 74years, sex category; DME = durable medical equipment; ER = Emergency room; HAS-BLED = hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, drugs and alcohol; HHA = home health agency; NSAIDs = nonsteroidal anti-inflammatory drugs; PAD = peripheral artery disease; PPPM = per patient per month; SD = standard deviation; SE = systemic embolism; SNF = skilled nursing facility.

* As the international normalized ratio value was not available in the databases, a modified HAS-BLED score was calculated with a range of 0 to 8.

[†] Standard dose: 5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban; Low dose: 2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban. Patients could have received more than 1 dose on the index date.

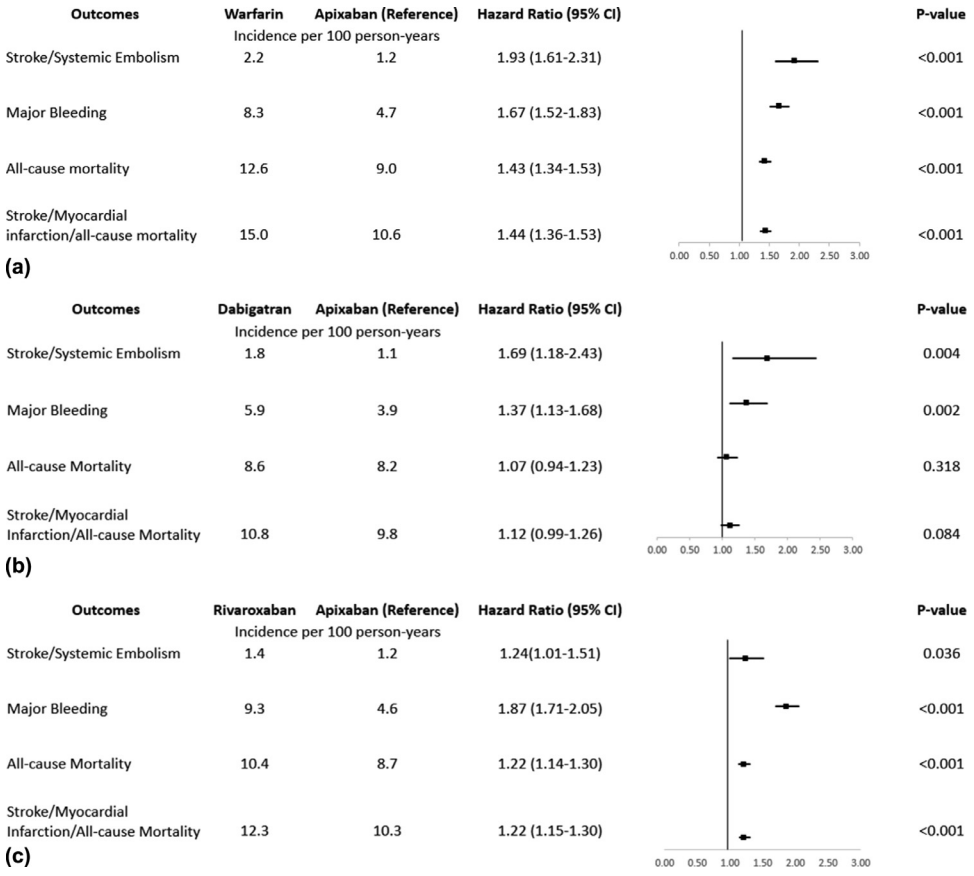

Figure 2. (a) Incidence rate and hazard ratios for warfarin vs apixaban. (b) Incidence rate and hazard ratios for dabigatran vs apixaban. (c) Incidence rate and hazard ratios for rivaroxaban vs apixaban. CI = confidence interval.

that warfarin use is associated with a higher risk of stroke/SE and major bleeding when compared with apixaban use.[6–8] A meta-analysis of RCTs comparing DOACs reported higher rates of major bleeding with dabigatran and rivaroxaban treatment compared with apixaban, supporting our major bleeding findings regarding dabigatran and rivaroxaban vs apixaban.[26] However, an indirect comparison analysis of several RCTs showed that there were no significant differences between dabigatran versus apixaban in preventing stroke/SE and major bleeding,[27] whereas rivaroxaban was associated with higher major bleeding rates and similar stroke/SE rates, compared with apixaban.[27] These discrepancies may be attributable to differences in the study design (RCT vs observational study) and study population.

Real-world studies have reported mixed results in the comparisons between dabigatran and rivaroxaban versus apixaban. One retrospective study using claims data found higher rates of stroke/SE and major bleeding with dabigatran and rivaroxaban treatment, compared with apixaban; in the CAD and PAD interaction analysis, there was no difference in effect between patients with and without CAD and PAD.[6] Additionally, a study using Medicare data found that dabigatran and rivaroxaban were associated with a higher risk of major extracranial bleeding compared to apixaban whereas rivaroxaban was also associated with a higher risk of intracranial hemorrhage, and death compared to apixaban.[11]

One Medicare study of elderly NVAF patients showed that warfarin, dabigatran, and rivaroxaban are associated with higher total all-cause health care costs as well as stroke/SE- and major bleeding-related medical costs, compared with apixaban.[13] Another study of the elderly NVAF population showed that, compared with apixaban, rivaroxaban had higher all-cause and major bleeding-related health care costs, dabigatran had higher all-cause health care costs, and warfarin patients incurred higher all-cause, stroke, and major bleeding-related health care costs.[9] Our current analysis of the subgroup of patients with CAD or PAD showed generally consistent findings, suggesting similar trends in NVAF patients with concomitant CAD or PAD.

This retrospective cohort study, using the available Medicare data, compared clinical outcomes and health care costs of patients who were prescribed apixaban and other OACs. Sample sizes for each cohort were large enough to provide adequate statistical power for comparisons. Considering the high prevalence of these comorbidities in patients with AF and the increasing prevalence of the disease, our findings will have applicability to a wide population.

Unlike clinical trials which are conducted in a controlled environment, real-world data has many factors that may have affected the study outcomes[28]; hence retrospective observational studies are limited to associations rather than causal inferences. Health coverage claims data is also limited by the use of diagnostic and procedure codes, which are subject to coding errors and inconsistencies as well as missing clinical information. The possibility of selection

Table 2
Major bleeding, stroke/systemic embolism, and all-cause health care costs between warfarin, dabigatran, and rivaroxaban cohorts versus apixaban cohort

Apixaban vs warfarin	Apixaban cohort Marginal effect	Warfarin cohort Marginal effect	Difference between marginal effects	95% CI for difference between marginal effects		p value
Follow-up major bleeding-related medical costs (PPPM)	$390	$574	$184	$125	$243	<0.0001
Follow-up stroke/SE-related medical costs (PPPM)	$66	$137	$70	$51	$90	<0.0001
All cause costs						
Inpatient admission costs	$1,495	$1,820	$325	$218	$432	<0.0001
Outpatient costs (ER, Office, and other)	$947	$942	−$5	−$30	$21	0.529
Other costs (DME, SNF, HHA, Hospice)	$531	$808	$277	$242	$313	<0.0001
Total medical costs	$2,972	$3,571	$599	$475	$722	<0.0001
Prescription costs	$532	$295	−$237	−$249	−$224	<0.0001
Total health care costs	$3,504	$3,866	$362	$238	$486	<0.0001
Apixaban vs Dabigatran	**Apixaban Cohort Marginal Effect**	**Dabigatran Cohort Marginal Effect**	**Difference between Marginal Effects**	**95% CI for Difference between Marginal Effects**		**p-value**
Follow-up major bleeding-related medical costs (PPPM)	$342	$469	$128	$31	$224	0.010
Follow-up stroke/SE-related medical costs (PPPM)	$51	$104	$52	$21	$84	0.001
All cause Costs						
Inpatient admission costs	$1,345	$1,506	$161	$11	$311	0.029
Outpatient costs (ER, Office, and other)	$922	$843	-$79	-$125	-$37	0.001
Other costs (DME, SNF, HHA, Hospice)	$493	$506	$13	-$66	$92	0.484
Total medical costs	$2,761	$2,855	$95	-$165	$355	0.303
Prescription costs	$537	$470	-$67	-$86	-$46	<.0001
Total health care costs	$3,298	$3,326	$28	-$207	$258	0.762
Apixaban vs Rivaroxaban	**Apixaban Cohort Marginal Effect**	**Rivaroxaban Cohort Marginal Effect**	**Difference between Marginal Effects**	**95% CI for Difference between Marginal Effects**		**P-Value**
Follow-up major bleeding-related medical costs (PPPM)	$374	$622	$248	$60	$436	0.010
Follow-up stroke/SE-related medical costs (PPPM)	$65	$109	$44	$18	$70	0.001
All cause costs						
Inpatient admission costs	$1,457	$1,871	$414	$306	$521	<0.0001
Outpatient costs (ER, Office, and other)	$944	$963	$19	$2	$37	0.031
Other costs (DME, SNF, HHA, Hospice)	$520	$760	$240	$204	$275	<0.0001
Total medical costs	$2,921	$3,593	$672	$547	$798	<0.0001
Prescription costs	$531	$497	−$34	−$46	−$21	<0.0001
Total health care costs	$3,451	$4,090	$639	$513	$765	<0.0001

CI = confidence interval; DME = durable medical equipment; HHA = home health agency; ER = emergency room; PPPM = per patient per month; SE = systemic embolism; SNF = skilled nursing facility.

bias cannot be ruled out because physicians' reasons for selecting a specific DOAC are not available in the Medicare database. And despite our usage of propensity score matching to mitigate bias, some residual confounding may have occurred due to unaccounted variables such as over-the-counter aspirin and dosage changes in warfarin treatment. Moreover, the data do not include laboratory test results (e.g., creatinine clearance, international normalized ratio values), which provide valuable clinical information. Finally, Medicare coverage is primarily limited to enrollees aged ≥65 years and this study is strictly limited to this age group, so the findings may not be generalizable to younger populations and those with non-Medicare fee-for-service insurance (Medicare Advantage, Medicaid, uninsured, etc.), in particular those with lower CHA_2DS_2-VASc scores. Nonetheless, patients aged ≥65 account for approximately 80% of all patients with AF.[11,13] All of the above mentioned limitations may have restricted clinical accuracy and incorporated bias into the study, and the results should be interpreted accordingly.

Among this large US Medicare population of NVAF patients who were also diagnosed with CAD or PAD, results from the current study indicate that when compared with apixaban, warfarin, dabigatran, and rivaroxaban use was associated with higher rates of stroke/SE and major bleeding. When compared with apixaban, stroke/SE and major bleeding-related medical costs were higher for warfarin, dabigatran, and rivaroxaban cohorts. These findings provide an assessment of OAC treatment in NVAF patients with coexisting CAD/PAD, which may offer valuable information for clinical and policy decision making.

Author Contributions

Conceptualization: all authors, Formal Analysis: Keshishian, Methodology: Lopes, Thomas, Di Fusco,

Keshishian, Luo, Li, Pan; Writing- original: Keshishian, Di Fusco; Writing- review and editing: all authors.

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Supplementary materials

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