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Comparison of healthcare costs among patients with non-valvular atrial fibrillation treated with warfarin who switched to a novel oral anticoagulant

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Abstract

Objective To compare all-cause healthcare costs among non-valvular atrial fibrillation (NVAF) patients who switched from warfarin to novel oral anticoagulants (NOAC).

Methods Adult NVAF patients who switched from warfarin to dabigatran, rivaroxaban or apixaban were identified in MarketScan claims databases between 10/01/2010 and 12/31/2015. Patients were continuously enrolled for 12 months before the first NOAC claim and followed for 12 months or until medication switch, discontinuation, inpatient death or 12/31/2016. Dabigatran patients were matched 1 : 1 separately to rivaroxaban and apixaban. All-cause costs were reported as per-patient-per-month (PPPM) in 2017 US dollars.

Key findings A total of 8679 and 5761 dabigatran switchers were matched to rivaroxaban and apixaban switchers respectively (mean age 73–74 years; mean CCI 1.8–2.0). Compared with rivaroxaban, dabigatran switchers had significantly lower PPPM mean outpatient (OP) ($1265 versus $1587, $P < 0.001$), emergency department (ED, $67 versus $95, $P < 0.001$), OP office ($114 versus $119, $P = 0.003$), other OP services ($1085 versus $1373, $P < 0.001$) and OP pharmacy costs ($624 versus $660, $P < 0.001$). Compared with apixaban, dabigatran switchers had significantly lower mean PPPM ED ($67 versus $123, $P < 0.001$), OP office ($116 versus $121, $P = 0.032$), other OP services ($1062 versus $1434, $P < 0.001$), OP pharmacy ($633 versus $706, $P < 0.001$) and total healthcare costs ($3254 versus $3805, $P = 0.016$).

Conclusions Outpatient costs were considerably lower among dabigatran switchers compared with rivaroxaban. Total and OP healthcare costs were significantly lower for patients switching from warfarin to dabigatran versus apixaban. Use of dabigatran following warfarin discontinuation may enable healthcare cost savings among NVAF patients, as compared with rivaroxaban or apixaban.

Keywords apixaban; dabigatran; healthcare costs; non-valvular atrial fibrillation; rivaroxaban; warfarin

Introduction

In the United States, close to 3–6 million adults present with non-valvular atrial fibrillation (NVAF), accounting for up to 95% of all atrial fibrillation (AF) cases.[1-3] The risk of stroke is 4–5 times higher among patients with untreated AF, with this chronic condition representing an independent risk factor for stroke severity, recurrence and mortality.[4,5] For patients at risk of stroke, treatment with oral anticoagulants (OAC) is highly advocated,[6,7] given that OACs are considered to mitigate the overall risk of stroke as well as all-cause mortality.[8,9]

Warfarin, a vitamin K antagonist, has been used for stroke prevention since the 1950s and has been shown to reduce the risk of stroke in patients with NVAF by over 60% as compared with placebo, and by 40% when compared with antiplatelet therapy.[9] Despite its long history of success, the use of warfarin and other vitamin K antagonists is limited by their numerous drug interactions, need for dietary management and narrow therapeutic window that requires frequent monitoring.[10-12] The approval of novel oral anticoagulants

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(NOAC), such as dabigatran, apixaban and rivaroxaban, that target the clotting cascade directly, has presented clinicians with alternative treatment options that have more predictable dosing profiles, fewer interactions and a reduced risk of intracranial bleeding.[13]

Although NOACs are approved as first-line agents and the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines recommend NOACs over warfarin,[14] many patients are initiated on warfarin due to its low cost and familiarity to both patients and physicians.[15] However, a portion of these patients may eventually switch to a NOAC due to complications, new comorbidities, discomfort with frequent blood draws or an inability to achieve International Normalized Ratio stability.[16,17] Several studies have shown that patients can be safely switched from warfarin to a NOAC without increased risk of bleeding or cardiac events, but to date, none have investigated the differences in healthcare costs among patients who switch to different NOACs.[18,19] This study set forth to examine the real-world differences in healthcare costs among patients diagnosed with NVAF who switched from warfarin to dabigatran, rivaroxaban or apixaban.

Methods

Data source

This retrospective matched cohort study used de-identified US administrative claims data from the MarketScan (IBM® Watson Health™, Cambridge, MA, USA) Commercial Claims and Encounters (commercial) Database and Medicare Supplemental and Coordination of Benefits (Medicare) Database during the timeframe of 1 October 2009 through 31 December 2016. Each database captures the inpatient medical, outpatient medical and outpatient prescription drug data for its respective covered population, and together form a nationally representative sample of insured individuals living in the United States. The commercial database includes 145.5 million employees and their dependents, including 26.9 million lives in 2015, covered under a variety of fee-for-service and managed care health plans. The Medicare database contains the pooled healthcare experience of approximately 10.4 million Medicare enrollees, including 2 million lives in 2015. All study data were obtained using International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes, Current Procedural Terminology 4th edition (CPT-4) codes, Healthcare Common Procedure Coding System (HCPCS) codes and National Drug Codes (NDC). Because this study used only Health Insurance Portability and Accountability Act compliant, de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board approval to conduct this study was not necessary.

Patient selection

Patients were eligible for study inclusion if they had at least one non-diagnostic inpatient or outpatient claim between 1 October 2010 and 31 December 2015 with an AF diagnosis (ICD-9-CM 427.31; ICD-10-CM I48.0, I48.1, I48.2 and I48.91), at least one outpatient pharmacy claim for warfarin on or after the earliest observed AF claim, and at least one outpatient pharmacy claim for a NOAC (dabigatran, apixaban or rivaroxaban) after the first warfarin claim and before 31 December 2015. Patients were only eligible if their NOAC claim occurred on or after the launch date of the qualifying medication: 1 October 2010 for dabigatran, 1 November 2011 for rivaroxaban or 1 December 2012 for apixaban. Non-diagnostic claims were defined as those that are not potentially associated with a diagnostic workup used to rule out the presence of a condition, such as claims for laboratory tests or radiology.

Patients were assigned an index date based on the date of the first outpatient prescription claim for the qualifying NOAC. The baseline period was the 12-months immediately prior to the index date. A variable follow-up period was used for each patient from the index date to the earliest of the following: (1) 12-months post-index, (2) end of study period (12/31/2016), (3) inpatient death, (4) end of continuous enrolment, (5) discontinuation of the index NOAC or (6) switching to a different anticoagulant. The maximum length of follow-up was 12 months. Discontinuation was defined as the lack of subsequent claims for the index medication beyond 90 days following the exhaustion of the previous claim's days' supply. Switching was defined as initiation of a different NVAF medication within 30 days of exhausting the supply of the index NOAC. Qualifying NVAF medications included apixaban, dabigatran, edoxaban, rivaroxaban, warfarin, argatroban, dalteparin, enoxaparin, fondaparinux, heparin and tinzaparin.

Patients were required to be at least 18 years of age on the index date. Patients with an outpatient pharmacy claim for any OAC other than warfarin in the 6 months prior to the index date were excluded, as were patients with any evidence of cardiac surgery, hyperthyroidism, myocarditis, pericarditis, pregnancy, pulmonary embolism, valve replacement, valvular heart disease or chronic rheumatic heart disease during the 6 months prior to the earliest AF diagnosis. Patients also could not have an outpatient prescription for a 10 mg dose of rivaroxaban on the index date. Finally, patients must have discontinued warfarin during the follow-up period, while continuing their index medication, indicating that they had fully switched to the NOAC.

Patient characteristics

Demographic characteristics including age, sex, payer (Medicare or commercial) type, health plan type (comprehensive/indemnity, exclusive/preferred provider organization, point of service with and without capitation, health maintenance organization, consumer-driven/high-deductible health plan or unknown) and geographic region of residence (northeast, north central, south, west or unknown) were captured on the index date.

Clinical characteristics were measured during the baseline period. These included general comorbid conditions (chronic kidney disease, chronic obstructive pulmonary disease, cirrhosis/hepatitis, coronary artery disease, diabetes

mellitus, heart failure, myocardial infarction, paraplegia/hemiplegia, pneumonia, psychiatric disorders, venous thromboembolism), stroke conditions (ischaemic stroke, transient ischaemic attack and haemorrhagic stroke) and bleeding-related conditions (intracranial bleed, extracranial bleed and gastrointestinal bleed). Recorded baseline health status markers included the number of unique medications, the number of inpatient admissions, the number of physician office visits, evidence of hip fracture and evidence of home oxygen use. Costs were also measured during the baseline period and included total all-cause healthcare costs, inpatient costs, outpatient costs, emergency department costs and outpatient pharmacy costs.

The use of high-risk medications including antiarrhythmics, antidiabetics, antihyperlipidemic, antiplatelets, beta blockers, calcium channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor and other antihypertensives in the baseline period was also recorded.[20] Also measured were several indicators of clinical risk including the Deyo-Charlson Comorbidity Index (DCCI), two measures of stroke risk ($CHADS_2$ and CHA_2DS_2-VASc) and two measures of bleeding risk (HAS-BLED and ATRIA).[21-23]

Additional variables included the number of days between AF diagnosis and the first warfarin claim, the duration of warfarin therapy, and the number of days between the last warfarin claim and the index date. The duration and the reason for the end of the variable follow-up period were also recorded.

Outcomes

All-cause costs for inpatient services, outpatient services (emergency department visits, outpatient office visits and other outpatient services) and outpatient pharmacy services were calculated per-patient per-month (PPPM) for the variable length follow-up period. Costs reflected the paid amounts of fully adjudicated claims, including insurer and health plan payments as well as patient cost-sharing in the form of copayment, deductible and coinsurance. All costs were inflated to 2017 US dollars using the medical care component of the Consumer Price Index.[24]

Statistical analysis

Propensity score matching was conducted to match dabigatran switchers 1 : 1 with apixaban switchers and separately 1 : 1 with rivaroxaban patients based on baseline demographic and clinical characteristics. For each comparison (dabigatran versus apixaban and dabigatran versus rivaroxaban), propensity score matching was conducted using a logistic regression model to predict the probability that a patient on warfarin switched to dabigatran or the comparator. Once each patient was assigned a propensity score, dabigatran switchers were matched, separately, with the pool of apixaban switchers and with rivaroxaban switchers, by propensity score.

Propensity score matching used the nearest neighbour approach with a caliper of one-fourth of the combined propensity scores' standard deviation without replacement. Standardized differences between the matching variables in each comparator group were used to examine the quality of the match, comparing the differences before and after matching.[25] Variables used in the propensity score models included age, payer type, sex, geographic region, health plan type, clinical risk scores (DCCI, $CHADS_2$ and HAS-BLED), number of International Normalized Ratio tests, presence of baseline comorbidities, baseline medication utilization, baseline total costs and baseline health status markers (number of unique medications, number of hospital admissions, number of physician office visits, evidence of hip fracture and evidence of home oxygen use).

All patient characteristics and outcome variables are reported descriptively. Means with standard deviations (SD) are reported for continuous variables, with statistical significance determined using Student's *t*-test. Frequencies and percentages are reported for categorical variables, with statistical significance determined using the chi-square test. The alpha level for all statistical tests was set *a priori* at $P < 0.05$. All data analyses were conducted using SAS (version 9.4; SAS Inc., Cary, NC, USA).

Results

Patient characteristics

A total of 11 825 dabigatran patients, 9999 rivaroxaban patients and 6522 apixaban patients met the selection criteria, and after propensity matching, there were 8579 dabigatran versus rivaroxaban pairs and 5761 dabigatran versus apixaban pairs (Figure 1). The matched cohorts had a mean age of 73.1–74.4 years and were 56.2–58.8% male (Table 1). Over three quarters had Medicare coverage (76.2–78.6%), and they were most likely to live in the south (34.7–35.7%).

On average, patients included in this study had a DCCI of 1.8–1.9, a moderate/high risk of stroke ($CHADS_2$: 1.9–2.2 and CHA_2DS_2-VASc: 3.2–3.5), and a low risk of bleeding (HAS-BLED: 1.5–1.7 and ATRIA: 2.1–2.6). The mean number of unique medications (12.2–12.9), inpatient admissions (0.6) and physician office visits (13.5–14.1) was similar across all groups, as was the prevalence of home oxygen use (6.1–6.9%) and hip fracture (1.1–1.3%). Total annual healthcare costs (mean) in the baseline period were lower for dabigatran switchers versus apixaban switchers ($32 275 versus $40 124, $P < 0.001$) and for dabigatran switchers versus rivaroxaban switchers ($29 624 versus $34 320, $P < 0.001$). It is worth noting that while the *P* values were significant, standardized difference on baseline costs was 6 for dabigatran versus apixaban and 9 for dabigatran versus rivaroxaban, which is considered well balanced post-matching.

The most common comorbid conditions across all groups were coronary artery disease (38.2–43.4%), diabetes (28.6–30.1%), and heart failure (26.6–31.4%; Table S1). Ischaemic strokes or transient ischaemic attacks occurred in 10.2–12.1% of the study groups; whereas, extracranial bleeding occurred in 15.6–19.2% and gastrointestinal bleeding occurred in 6.0–8.1% of patients. Beta blockers,

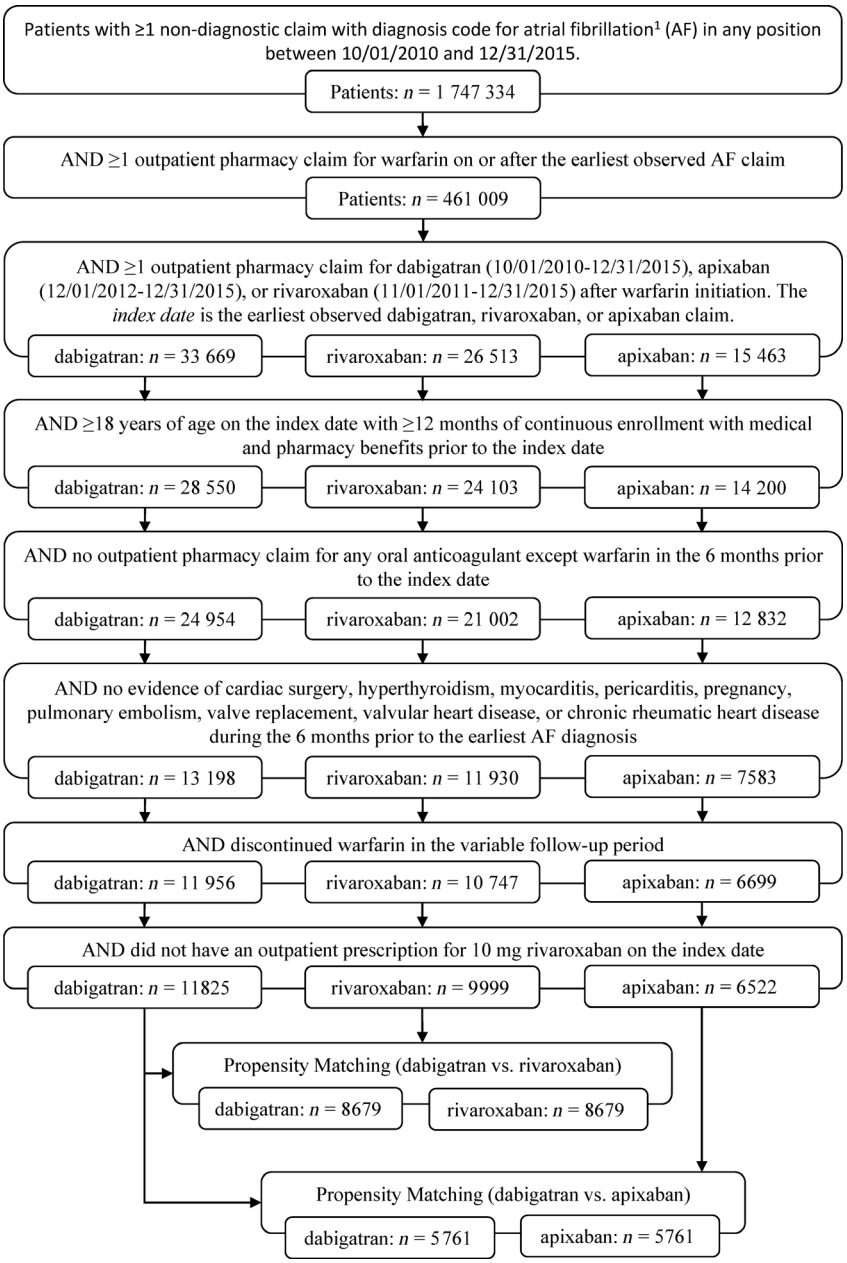

Figure 1 Patient attrition.

antihyperlipidemics and diuretics were used by over half of all patients included in the study. A full list of evaluated comorbid conditions and baseline medication usage can be found in Table S1.

Treatment patterns

After matching, dabigatran switchers had, on average, less time between their AF diagnosis and first warfarin claim, a shorter duration of warfarin therapy, and less time between their last warfarin claim and their first index medication claim than either rivaroxaban or apixaban switchers (Table 2). This resulted in a shorter span of time between the AF diagnosis and index date for dabigatran versus rivaroxaban switchers (0.93 versus 2.16 years, $P < 0.001$) or dabigatran versus apixaban switchers (0.98 versus 2.92, $P < 0.001$).

Across all groups, 42.2–47.7% of patients had a full year of follow-up data and the mean duration of the variable follow-up period ranged from 224.5 to 233.3 days. The most common reason for not achieving a full year of follow-up was discontinuation for dabigatran switchers (20.6%) and end of continuous enrolment for rivaroxaban switchers (22.7%) and apixaban switchers (34.3%).

Table 1 Post-matching baseline demographic and clinical characteristics

	Dabigatran *N* = 8679	Rivaroxaban *N* = 8679	*P* value	Dabigatran *N* = 5761	Apixaban *N* = 5761	*P* value
Age, mean (SD)	73.1 (11.3)	73.3 (11.3)	0.229	74.1 (11.2)	74.4 (11.3)	0.106
Male, *N* (%)	5101 (58.8%)	5036 (58.0%)	0.317	3267 (56.7%)	3237 (56.2%)	0.573
Medicare, *N* (%)	6612 (76.2%)	6642 (76.5%)	0.592	4523 (78.5%)	4528 (78.6%)	0.910
Health plan type, *N* (%)						
Comprehensive/Indemnity	3196 (36.8%)	3243 (37.4%)	0.460	2194 (38.1%)	2239 (38.9%)	0.389
EPO/PPO	4120 (47.5%)	4116 (47.4%)	0.952	2618 (45.4%)	2595 (45.0%)	0.667
POS w/ and w/o capitation	460 (5.3%)	440 (5.1%)	0.494	293 (5.1%)	281 (4.9%)	0.607
HMO	549 (6.3%)	541 (6.2%)	0.802	382 (6.6%)	375 (6.5%)	0.792
CDHP/HDHP	206 (2.4%)	202 (2.3%)	0.841	194 (3.4%)	186 (3.2%)	0.676
Other/unknown	148 (1.7%)	137 (1.6%)	0.511	80 (1.4%)	85 (1.5%)	0.695
Geographic region, *N* (%)						
Northeast	1816 (20.9%)	1831 (21.1%)	0.780	1334 (23.2%)	1327 (23.0%)	0.877
North Central	2313 (26.7%)	2346 (27.0%)	0.572	1541 (26.8%)	1532 (26.6%)	0.850
South	3094 (35.7%)	3046 (35.1%)	0.446	1996 (34.7%)	2049 (35.6%)	0.301
West	1405 (16.2%)	1408 (16.2%)	0.951	875 (15.2%)	838 (14.6%)	0.333
Unknown	51 (0.6%)	48 (0.6%)	0.762	15 (0.3%)	15 (0.3%)	1.000
Clinical risk scores, mean (SD)						
DCCI	1.8 (1.9)	1.8 (2.0)	0.518	1.9 (1.9)	1.9 (2.2)	0.556
$CHADS_2$	2.0 (1.3)	1.9 (1.3)	0.622	2.2 (1.3)	2.2 (1.3)	0.865
CHA_2DS_2-VASc	3.2 (2.0)	3.2 (2.0)	0.753	3.5 (1.9)	3.5 (1.9)	0.246
HAS-BLED	1.6 (1.1)	1.5 (1.1)	0.700	1.7 (1.1)	1.7 (1.1)	0.522
ATRIA	2.1 (1.9)	2.2 (2.0)	0.004	2.5 (2.0)	2.6 (2.1)	<0.001
Health status markers						
Number of unique medications, mean (SD)	12.4 (6.1)	12.2 (6.2)	0.017	12.9 (6.2)	12.5 (6.2)	<0.001
Number of inpatient admissions, mean (SD)	0.6 (0.8)	0.6 (0.8)	0.738	0.6 (0.8)	0.6 (0.9)	0.575
Number of physician visits, mean (SD)	13.5 (9.2)	13.6 (10.3)	0.474	14.0 (9.4)	14.1 (10.6)	0.633
Evidence of home oxygen use, *N* (%)	531 (6.1%)	535 (6.2%)	0.899	376 (6.5%)	396 (6.9%)	0.456
Evidence of hip fracture, *N* (%)	113 (1.3%)	116 (1.3%)	0.842	62 (1.1%)	63 (1.1%)	0.928
Baseline annual total healthcare costs, mean (SD)	$29 624 ($44 714)	$34 320 ($62 214)	<0.001	$32 275 ($47 132)	$40 124 ($92 041)	<0.001
Inpatient costs	$12 458 ($35 219)	$14 985 ($45 173)	<0.001	$14 034 ($37 441)	$17 586 ($71 319)	<0.001
Outpatient costs	$12 832 ($19 729)	$15 358 ($32 763)	<0.001	$13 783 ($20 861)	$18 348 ($45 148)	<0.001
Emergency department costs	$610 ($2086)	$846 ($3032)	<0.001	$697 ($2306)	$1149 ($4376)	<0.001
Outpatient pharmacy costs	$4334 ($5493)	$3977 ($7320)	<0.001	$4458 ($5350)	$4190 ($8591)	0.045

ATRIA, anticoagulation and risk factors in atrial fibrillation; CDHP, consumer-driven health plan; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischaemic attack or thromboembolism (doubled), vascular disease, age 65–74 and sex category; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus and stroke prior stroke or transient ischaemic attack or thromboembolism (doubled); DCCI, Deyo-Charlson Comorbidity Index; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; SD, standard deviation.

Cost analysis

Compared with rivaroxaban switchers, dabigatran switchers had significantly lower mean PPPM all-cause outpatient pharmacy costs ($624 versus $660, $P < 0.001$) and outpatient services costs ($1265 versus $1587, $P < 0.001$) including emergency department ($67 versus $95, $P < 0.001$), outpatient office ($114 versus $119, $P < 0.01$) and other outpatient ($1085 versus $1373, $P < 0.001$) costs (Table 3). There was, however, no statistical difference in inpatient costs between dabigatran and rivaroxaban switchers ($1405 versus $1326, $P = 0.676$). Collectively, total all-cause healthcare costs PPPM were lower for dabigatran switchers than rivaroxaban switchers; albeit, this difference was not statistically significant ($3294 versus $3572, $P = 0.170$; Figure 2).

The trends were similar between dabigatran and apixaban switchers (Table 3). That is, dabigatran switchers were documented as having significantly lower mean PPPM all-cause outpatient pharmacy costs ($633 versus $706, $P < 0.001$) and outpatient services costs ($1244 versus $16 478, $P < 0.001$), including emergency department ($67 versus $123, $P < 0.001$), outpatient office ($116 versus $121, $P < 0.05$) and other outpatient services ($1062 versus $1434, $P < 0.001$) costs. Inpatient costs did not differ materially between dabigatran and apixaban switchers ($1377 versus $1421, $P = 0.831$). Though notably, total all-cause healthcare costs were significantly lower for dabigatran switchers as compared with apixaban switchers ($3254 versus $3805, $P = 0.016$; Figure 2).

Table 2 Post-matching treatment patterns

	Dabigatran *N* = 8679	Rivaroxaban *N* = 8679	*P* value	Dabigatran *N* = 5761	Apixaban *N* = 5761	*P* value
Days between AF diagnosis and index date, mean (SD)	339.2 (332.1)	790.2 (478.1)	<0.001	358.2 (353.5)	1064.9 (552.7)	<0.001
Days between AF diagnosis and first warfarin claim	59.7 (129.5)	115.6 (227.9)	<0.001	62.9 (138.8)	150.8 (292.9)	<0.001
Duration of warfarin therapy	250.1 (272.3)	559.3 (466.4)	<0.001	262.6 (289.0)	733.9 (580.0)	<0.001
Days between last warfarin claim and index date	29.4 (162.4)	115.2 (304.5)	<0.001	32.6 (172.3)	180.2 (398.5)	<0.001
Duration of variable follow-up period, mean (SD)	228 (144.4)	231.3 (139.7)	0.123	224.5 (145.1)	233.3 (134.0)	<0.001
Reason for end, *N* (%)						
Inpatient death	55 (0.6%)	84 (1.0%)	0.014	46 (0.8%)	62 (1.1%)	0.122
End of continuous enrolment	1214 (14.0%)	1969 (22.7%)	<0.001	839 (14.6%)	1973 (34.3%)	<0.001
End of study period	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	NA
Switch	1483 (17.1%)	946 (10.9%)	<0.001	1013 (17.6%)	384 (6.7%)	<0.001
Discontinuation	1790 (20.6%)	1692 (19.5%)	0.063	1186 (20.6%)	911 (15.8%)	<0.001
Full year of follow-up	4137 (47.7%)	3988 (46.0%)	0.023	2677 (46.5%)	2431 (42.2%)	<.0001

AF, atrial fibrillation; NA, not applicable; SD, standard deviation.

Table 3 All-cause healthcare costs per-patient per-month in matched patients

	Dabigatran *N* = 8679	Rivaroxaban *N* = 8679	*P* value	Dabigatran *N* = 5761	Apixaban *N* = 5761	*P* value
Inpatient costs, mean (SD)	$1405 ($15 824)	$1326 ($7693)	0.676	$1377 ($12 765)	$1421 ($9277)	0.831
Outpatient costs, mean (SD)	$1265 ($3222)	$1587 ($4140)	<0.001	$1244 ($3002)	$1678 ($4977)	<0.001
Emergency department costs, mean (SD)	$67 ($414)	$95 ($444)	<0.001	$67 ($375)	$123 ($1228)	<0.001
Outpatient office costs, mean (SD)	$114 ($112)	$119 ($121)	0.003	$116 ($111)	$121 ($154)	0.032
Other outpatient service costs, mean (SD)	$1085 ($3118)	$1373 ($3993)	<0.001	$1062 ($2910)	$1434 ($4628)	<0.001
Outpatient pharmacy costs, mean (SD)	$624 ($549)	$660 ($725)	<0.001	$633 ($513)	$706 ($901)	<0.001

SD, standard deviation.

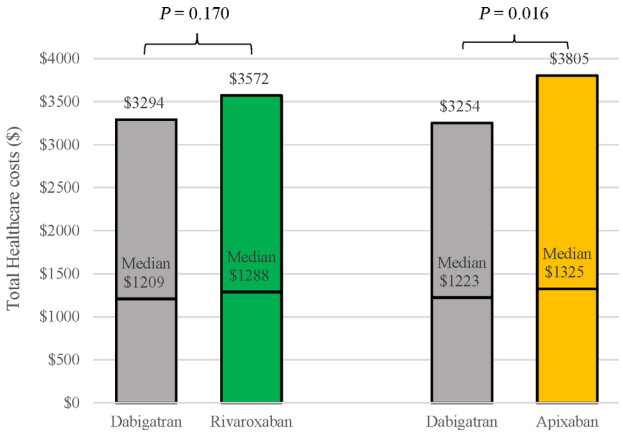

Figure 2 Total all-cause healthcare costs per-patient per-month in matched patients.

Discussion

Although warfarin has long been the first line of therapy in the AF population, many patients are expected to switch to NOACs following the 2019 AHA/ACC/HRS guidelines which recommend NOACs over warfarin. It is therefore important to understand the economic opportunity that may be associated with warfarin users switching to the various NOACs. This retrospective matched cohort study is the first to assess NVAF patients treated with warfarin who eventually switched to dabigatran and compared real-world healthcare costs with those who switched from warfarin to rivaroxaban or apixaban. Notably, patients treated with dabigatran had lower all-cause total healthcare monthly costs compared with those treated with apixaban and those treated with rivaroxaban. To this end, mean all-cause total healthcare costs for dabigatran switchers were approximately $551 and $278 less PPPM than those observed for apixaban and rivaroxaban switchers respectively.

Several studies have investigated the cost benefits of NOACs compared with warfarin using real-world claims data or Markov models[26-28]; however, there are less data comparing costs between different NOACs.[29,30] Using the IMS Pharmetrics Plus database, Lin *et al.*[29] reported that among matched newly diagnosed NVAF patients initiating on either dabigatran or apixaban there was no significant difference in total all-cause healthcare costs ($3683 versus $3572 PPPM, $P = 0.397$). However, the patient population in that study was on average 11 years younger and had lower mean $CHADS_2$ and CHA_2DS_2-VASc scores by 0.8 and 1.4 points indicating a less at-risk population. In a previous study using the MarketScan database, lower total ($4093 versus $4636, $P < 0.01$), inpatient ($1476 versus $1862, $P < 0.01$) and outpatient

($2016 versus $2121, $P < 0.01$) costs for dabigatran initiators compared with matched rivaroxaban initiators were reported. There was no significant difference in costs between dabigatran and apixaban initiators.[30] As documented within the Lin study, these patients were slightly younger and had lower $CHADS_2$ and CHA_2DS_2-VASc scores, though the differences were smaller (5 years, 0.4 points and 0.7 points respectively).[29] This difference in patient population is to be expected when evaluating initiators rather than switchers, but it highlights the challenges of making direct comparisons.

A challenge to retrospective cohort studies in general – and to this study in particular – is the question of comparability of patient groups. Differences in patient characteristics that influence development and management of NVAF can confound outcomes such as costs. Because dabigatran, apixaban and rivaroxaban patients are likely to have dissimilar demographic and clinical characteristics that may influence clinical outcomes, healthcare utilization and costs, propensity score matching was employed to 'fit' apixaban switchers and rivaroxaban switchers to dabigatran switchers. However, not all factors that can influence medication selection such as creatine clearance or the reason for switching from warfarin were available from administrative claims records.[17]

Limitations

The limitations of this study include those inherent to all retrospective, administrative claims-based cohort studies. First, this study was limited to only those individuals with commercial or private Medicare supplemental coverage, and, as a result, the conclusions may not be generalizable to patients with other insurance or without health insurance coverage. Second, there is the potential for misclassification of NVAF, covariates and study outcomes as patients were identified through administrative claims data, which is not collected with the same rigour as clinical trial data. Claims data are subject to data coding limitations and data entry error. Third, claims data only accounts for a prescription that was filled, and not whether the medication was taken as prescribed. Fourth, the potential for bias is higher in this patient population compared with treatment-naïve patients, in part, because treatment history may not be as accurately captured prior to switching and this study was limited to a defined study period in order to measure treatment history. This may contribute to the variation in time seen between AF diagnosis, warfarin discontinuation and initiation of the indexing NOAC as patients may have been treated with a therapy other than anticoagulants during this time. Fifth, propensity score matching provided adjustments for differences between cohorts, but matching was limited to variables that can be measured in administrative claims. On this basis, residual confounding due to certain unmeasured characteristics could perhaps still bias the observed comparisons reported in the present study.

Conclusion

All-cause outpatient services and pharmacy costs tended to be lower among dabigatran users who switched from warfarin as compared with those switching to rivaroxaban or apixaban. Although total all-cause healthcare costs were similar with rivaroxaban switchers, these costs were significantly lower for dabigatran when compared with apixaban switchers. The current observations provide some indication that switching to dabigatran following warfarin therapy discontinuation may enable favourable healthcare costs savings for patients with NVAF, particularly when compared with those who instead switched to rivaroxaban or apixaban.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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Authors' contributions

JF-E, CW, AG, XS, and AS-N participated in study design, data interpretation, and manuscript development and revisions. CH took the lead in data analysis. BOH contributed to substantial revisions of the manuscript.

References

1. Go AS *et al*. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *JAMA* 2001; 285: 2370–2375.
2. Miyasaka Y *et al*. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006; 114: 119–125.
3. Benjamin EJ *et al*. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation* 2018; 137: e67.
4. Lin H-J *et al*. Stroke severity in atrial fibrillation. *Stroke* 1996; 27: 1760–1764.
5. Wolf PA *et al*. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; 22: 983–988.
6. January CT *et al*. 2014 AHA/ACC/HRS guideline for the management of patients wth atrial fibrillation. *J Am Coll Cardiol* 2014; 64: e1.
7. Kirchhof P *et al*. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016; 18: 1609–1678.
8. Ruff CT *et al*. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; 383: 955–962.
9. Hart RG *et al*. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; 146: 857–867.
10. Ansell J *et al*. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133: 160S–198S.
11. Holbrook AM *et al*. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005; 165: 1095–1106.
12. Booth SL, Centurelli MA. Vitamin K: a practical guide to the dietary management of patients on warfarin. *Nutr Rev* 1999; 57: 288–296.
13. Verheugt FWA, Granger CB. Oral anticoagulants for stroke prevention in atrial fibrillation: current status, special situations, and unmet needs. *Lancet* 2015; 386: 303–310.
14. January CT *et al*. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association

Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019; 74: 104–132.
15. Palacio AM *et al*. Patient values and preferences when choosing anticoagulants. *Patient Pref Adherence* 2015; 9: 133–138.
16. Verdecchia P *et al*. Why switch from warfarin to NOACs? *Intern Emerg Med* 2016; 11: 289–293.
17. Diener H-C *et al*. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. *Eur Heart J* 2017; 38: 860–868.
18. Bouillon K *et al*. Risk of bleeding and arterial thromboembolism in patients with non-valvular atrial fibrillation either maintained on a vitamin K antagonist or switched to a non-vitamin K-antagonist oral anticoagulant: a retrospective, matched-cohort study. *Lancet Haematol* 2015; 2: e150–e159.
19. Beyer-Westendorf J *et al*. Safety of switching from vitamin K antagonists to dabigatran or rivaroxaban in daily care – results from the Dresden NOAC registry. *Br J Clin Pharmacol* 2014; 78: 908–917.
20. Centers for Medicare and Medicaid Services. *High-Risk Medication Risk-Priority Health 2016*. https://www.priorityhealth.com/provider/clinical-resources/medication-resources/~/media/documents/pharmacy/cms-high-risk-medications.pdf (accessed 28 March 2016).
21. van den Ham HA *et al*. Comparative performance of ATRIA, CHADS2, and CHA2DS2-VASc risk scores predicting stroke in patients with atrial fibrillation: results from a national primary care database. *J Am Coll Cardiol* 2015; 66: 1851–1859.
22. Lip GYH *et al*. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) score. *J Am Coll Cardiol* 2011; 57: 173–180.
23. Gage BF *et al*. Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. *JAMA* 2001; 285: 2864–2870.
24. *Consumer Price Index Details Report Tables Annual Average 2017*. 2018. https://www.bls.gov/cpi/tables.htm (accessed 22 February 2018).
25. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; 17: 2265–2281.
26. Margolis JM *et al*. Shorter hospital stays and lower costs for rivaroxaban compared with warfarin for venous thrombosis admissions. *J Am Heart Assoc* 2016; 5. https://doi.org/10.1161/JAHA.116.003788 (accessed 21 March 2020).
27. Harrington AR *et al*. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. *Stroke* 2013; 44: 1676–1681.
28. Kansal AR *et al*. Cost-effectiveness of new oral anticoagulants in the prevention of stroke in patients with atrial fibrillation. *Best Pract Res Clin Haematol* 2013; 26: 225–237.
29. Lin J *et al*. Major bleeding risk and healthcare economic outcomes of non-valvular atrial fibrillation patients newly-initiated with oral anticoagulant therapy in the real-world setting. *J Med Econ* 2017; 20: 952–961.
30. Gilligan AM *et al*. Comparison of all-cause costs and healthcare resource use among patients with newly-diagnosed non-valvular atrial fibrillation newly treated with oral anticoagulants. *Curr Med Res Opin* 2018; 34: 285–295.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Post-matching baseline comorbidities and medication utilization.