ORIGINAL RESEARCH

Effect of Rivaroxaban Versus Warfarin on Health Care Costs Among Nonvalvular Atrial Fibrillation Patients: Observations from Rivaroxaban Users and Matched Warfarin Users

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ABSTRACT

Introduction: New target-specific oral anticoagulants may have benefits, such as shorter hospital length of stay, compared to warfarin in patients with nonvalvular atrial fibrillation (NVAF). This study aimed to assess, among patients with NVAF, the effect of rivaroxaban versus warfarin on health care costs in a cohort of rivaroxaban users and matched warfarin users.

Methods: Health care claims from the Humana database from 5/2011 to 12/2012 were analyzed. Adult patients newly initiated on rivaroxaban or warfarin with ≥ 2 atrial fibrillation (AF) diagnoses (The International Classification of Diseases, Ninth Revision, Clinical Modification: 427.31) and without valvular AF were identified. Based on propensity score methods, warfarin patients were matched 1:1 to rivaroxaban patients. Patients were observed up to end of data, end of insurance coverage, death, a switch to another anticoagulant, or treatment nonpersistence. Health care costs [hospitalization, emergency room (ER), outpatient, and pharmacy costs] were evaluated using Lin's method.

Results: Matches were found for all rivaroxaban patients, and characteristics of the matched groups ($n = 2253$ per group) were well balanced. Estimated mean all-cause and AF-related hospitalization costs were significantly lower for rivaroxaban versus warfarin patients (all-cause: $5411 vs. $7427, $P = 0.047$; AF-related: $2872 vs. $4147, $P = 0.020$). Corresponding estimated mean all-cause outpatient visit costs were also significantly lower, but estimated mean pharmacy costs were significantly higher for rivaroxaban patients ($5316 vs. $2620, $P < 0.001$).

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Although estimated mean costs of ER visits were higher for rivaroxaban users compared to those of warfarin users, differences were not statistically significant. Including anticoagulant costs, mean overall total all-cause costs were comparable for rivaroxaban versus warfarin users due to cost offset from a reduction in the number and length of hospitalizations and number of outpatient visits ($17,590 vs. $18,676, $P = 0.542$).

Conclusion: Despite higher anticoagulant cost, mean overall total all-cause and AF-related cost remains comparable for patients with NVAF treated with rivaroxaban versus warfarin due to the cost offset from reduced health care resource utilization.

Keywords: Anticoagulant agents; Atrial fibrillation; Cost; Rivaroxaban; Warfarin

INTRODUCTION

Atrial fibrillation (AF) is the most common heart rhythm disturbance, with a prevalence estimated between 2.7 and 6.1 million cases in the United States [1]. Compared to non-AF patients, AF patients have been found to be at a near five-fold higher risk of stroke and at an eight-fold higher risk of having multiple cardiovascular hospitalizations [2, 3]. The associated health care costs of patients with AF are high. The incremental cost burden of AF patients versus non-AF patients was estimated at $26 billion in the United States in 2010, with more than 50% of this amount being hospitalization costs [3, 4]. Moreover, the AF-related hospitalization rate increased by 23% among US adults from 2000 to 2010 [5].

Chronic anticoagulation has been the standard of care for patients with chronic nonvalvular atrial fibrillation (NVAF) in the

previous decades and, until recently, warfarin and other vitamin K antagonists were the only available options [6, 7]. Recently, the target-specific oral anticoagulants rivaroxaban, dabigatran, and apixaban have been approved by the US Food and Drug Administration (FDA) for the treatment of NVAF [8–10]. These new agents have predictable pharmacokinetic properties, minimal food–drug interactions, and do not require frequent monitoring as compared to warfarin [11–14]. Recent studies have compared these new agents with warfarin and found that target-specific oral anticoagulants were a cost-effective option [15–17].

AF is a significant driver of hospitalizations [18] and a considerable burden for the health care system. Since the use of new target-specific oral anticoagulants may result in potential economic benefits, the aim of the present study was to compare health care costs between NVAF patients using rivaroxaban and a matched sample of patients using warfarin.

METHODS

Data Source

The analysis was conducted using health insurance claims from the Humana database during the period from May 2011 through December 2012, in line with other retrospective studies [19–22]. The Humana database includes over 11.3 million lives of commercial and Medicare members, and covers all census regions in the United States. The database contains information on patient demographics; enrollment history; and claims for inpatient, outpatient, emergency room (ER), and other medical services. In addition, the Humana database contains information on

pharmacy and laboratory claims. Data are de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA). Institutional review board approval was not required for this study. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Study Design

A retrospective matched-cohort design was used to quantify the difference in health care costs between patients with NVAF who used rivaroxaban versus warfarin among rivaroxaban-treated-like patients. Patients included in the study were newly initiated on rivaroxaban or warfarin after November 2011 (the time of rivaroxaban approval for NVAF in the United States), were 18 years of age or older, had a baseline period of at least 6 months of continuous health plan enrollment before the index date (i.e., the date of the first rivaroxaban or warfarin dispensing), and had at least two primary or secondary AF diagnoses [The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 427.31] during the baseline or the follow-up period. Patients were excluded if they were diagnosed at baseline with valvular involvement [ICD-9-CM: 394.x-397.x, 424.x, 746.0x-746.7x, V42.2, V43.3; Current Procedural Terminology, 4th Edition (CPT-4): 33400-33478], pregnancy (ICD-9-CM: V22, V23, V27, 630.x-676.x), malignant cancer (ICD-9-CM: 140.x-208.xx, 230.x-234.x), or transient cause of AF (ICD-9-CM: 415.x, 429.4; CPT-4: 33400-33999).

Similarly to three recent phase III clinical trials on the target-specific oral anticoagulants rivaroxaban, dabigatran, and apixaban (i.e., ROCKET AF, NCT00403767; RE-LY,

NCT00262600; ARISTOTLE, NCT00412984), patients in the current study who were treated with rivaroxaban after its approval in November 2011, but with previous use of warfarin, were classified in the rivaroxaban cohort [23–25]. In each of the phase III trials, a total of 50–62% of patients had used warfarin before enrollment and randomization.

The observation period spanned from the date of the first dispensing (i.e., the first filled pharmacy prescription) of rivaroxaban or warfarin, defined as the index date, to the earliest among the end of data availability, end of insurance coverage, death, a switch to another anticoagulant, or 14 days after treatment nonpersistence (i.e., 14 days after the end of the days of supply of the first dispensing for which the next dispensing of the index medication, if any, was more than 60 days later). The nonpersistence criterion increased the certainty that health care costs were evaluated during exposure to the medications of interest.

Study Endpoints

The primary endpoint of this study was all-cause health care costs, which included hospitalizations, ER visits, outpatient visits, and pharmacy costs. Health care costs were calculated as the sum of the following elements: amount paid by insurance, copay amount, coinsurance amount, deductible amount, and secondary insurance amount. AF-related costs were also evaluated. Costs for AF-related hospitalizations, ER visits, and outpatient visits were defined as costs associated with claims that had a primary or secondary diagnosis for AF. AF-related pharmacy costs were the costs of anticoagulant or antiplatelet agents that were dispensed.

Statistical Analysis

Propensity score matching was performed to adjust for confounding bias. Patients in the warfarin group were matched 1:1 to patients in the rivaroxaban group based on random selection among propensity score calipers of 5%. Propensity scores were calculated using a multivariate logistic regression model that incorporated the following baseline characteristics: age, gender, type of insurance, comorbidity index scores (i.e., Quan-Charlson Comorbidity Index, $CHADS_2$ score, CHA_2DS_2-VASc score, ATRIA score, and HAS-BLED score), baseline resource utilization, baseline costs, the month of the index date, and specific comorbidities (>5%; Table 1).

Patients' baseline characteristics evaluated during the 6 months prior to the index date were summarized using means [±standard deviation (SD)] for continuous variables, and frequencies and percentages for categorical variables. Baseline characteristics were compared between cohorts using standardized differences. Baseline characteristics with standardized differences of less than 10% were considered well balanced [26–28].

Health care costs (i.e., hospitalizations, ER visits, outpatient visits, and pharmacy costs) between rivaroxaban and warfarin users were reported and compared using Lin's method to account for death and the censored observation periods of patients [29]. For the calculation of health care costs based on Lin's method, the follow-up period of each patient was partitioned in small intervals (i.e., days in the current study), and health care costs were calculated across all patients still observed (i.e., in plan and not censored) for a given interval. Hospitalizations, ER visits, outpatient visits, and pharmacy costs were estimated as the sum over intervals of the Kaplan–Meier estimator for the conditional probability of surviving to the start of the interval multiplied by the average studied outcome over the interval.

Health care costs were compared between cohorts through mean differences. Nonparametric bootstrap procedures with 999 replications were used to evaluate confidence intervals and to compare rivaroxaban and warfarin mean all-cause and AF-related costs. All costs were inflation adjusted to 2012 US dollars based on the medical care component of the Consumer Price Index. Statistical significance was assessed at a significance level of 0.05. All statistical analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

A total of 2253 rivaroxaban and 10,796 warfarin users were identified (Fig. 1). All rivaroxaban users were propensity matched with the same number of warfarin users to form the study cohorts. Overall, baseline characteristics were well balanced (i.e., standardized difference below 10%) between rivaroxaban and warfarin users. The baseline characteristics of the matched cohorts are summarized in Table 1. Mean age of both cohorts was 74 years, and 46% of patients were female. All comorbidity index scores between cohorts were similar, with standardized differences below 10%, and the most prevalent comorbidities were hypertension, hyperlipidemia, diabetes, and abdominal surgery (>30%). A total of 517 (23%) rivaroxaban users had previous use of warfarin at baseline. The mean observation period was 114.0 and 123.7 days for rivaroxaban and warfarin users (standardized difference = 10.5%), respectively.

Table 1 Demographic and clinical characteristics—matched rivaroxaban and warfarin users

Characteristics	Rivaroxaban cohort (N = 2253)	Warfarin cohort (N = 2253)	Standardized difference (%)[a,b]
Matching factors			
Demographics			
Age, years, mean (SD)	74.2 (9.0)	74.5 (8.7)	4.0
Gender, female, n (%)	1040 (46.2)	1031 (45.8)	0.8
Insurance type, n (%)			
Commercial			
POS	73 (3.2)	74 (3.3)	0.2
PPO	72 (3.2)	71 (3.2)	0.3
HMO	55 (2.4)	45 (2.0)	3.0
IMM metavance	20 (0.9)	20 (0.9)	0.0
IHMO	2 (0.1)	2 (0.1)	0.0
Medicare			
Medicare PPO	931 (41.3)	934 (41.5)	0.3
Medicare HMO	770 (34.2)	778 (34.5)	0.7
Medicare PFFS	259 (11.5)	257 (11.4)	0.3
Medicare POS	59 (2.6)	59 (2.6)	0.0
Medicare risk	10 (0.4)	11 (0.5)	0.7
Medicaid	1 (0.0)	1 (0.0)	0.0
Unknown	1 (0.0)	1 (0.0)	0.0
Comorbidity index scores, mean [MDN] (SD)[c]			
Quan-Charlson comorbidity index	1.5 [1.0] (1.6)	1.5 [1.0] (1.6)	0.5
CHADS$_2$ score	2.3 [2.0] (1.3)	2.3 [2.0] (1.3)	1.8
CHA$_2$DS$_2$-VASc score	3.9 [4.0] (1.7)	3.9 [4.0] (1.7)	1.9
ATRIA score	3.3 [3.0] (2.4)	3.3 [3.0] (2.4)	1.4
HAS-BLED score	1.4 [1.0] (0.9)	1.4 [1.0] (0.9)	0.9
Comorbidities and risk factors, n (%)[c]			
Hypertension	1919 (85.2)	1932 (85.8)	1.6
Age >70	1588 (70.5)	1598 (70.9)	1.0
Hyperlipidemia	1551 (68.8)	1554 (69.0)	0.3
Diabetes	825 (36.6)	837 (37.2)	1.1
Abdominal surgery	704 (31.2)	722 (32.0)	1.7
Heart failure	556 (24.7)	559 (24.8)	0.3

Table 1 continued

Characteristics	Rivaroxaban cohort (N = 2253)	Warfarin cohort (N = 2253)	Standardized difference (%)[a,b]
Renal disease	546 (24.2)	541 (24.0)	0.5
COPD	431 (19.1)	439 (19.5)	0.9
Chronic kidney disease	395 (17.5)	390 (17.3)	0.6
Anemia	382 (17.0)	392 (17.4)	1.2
Multiple trauma	375 (16.6)	357 (15.8)	2.2
Other serious infections	332 (14.7)	337 (15.0)	0.6
Cerebrovascular accident (stroke)	331 (14.7)	333 (14.8)	0.3
Obesity	318 (14.1)	309 (13.7)	1.2
NSAID use	311 (13.8)	282 (12.5)	3.8
Excessive fall risk (Parkinson's disease, etc.)	309 (13.7)	305 (13.5)	0.5
Depression	224 (9.9)	218 (9.7)	0.9
Drugs	153 (6.8)	150 (6.7)	0.5
Pneumonia	151 (6.7)	159 (7.1)	1.4
Baseline health care utilization, mean (SD)[c]			
Hospitalizations	0.53 (0.99)	0.54 (0.98)	0.9
ER visits	0.44 (0.96)	0.44 (1.21)	0.1
Outpatient visits	12.68 (10.85)	12.43 (11.43)	2.2
Baseline health care cost, US$ 2012 mean (SD)[c]			
Hospitalizations	4534 (10,570)	4720 (9989)	1.8
ER visits	452 (1497)	418 (1375)	2.4
Outpatient visits	2922 (5121)	2834 (5584)	1.6
Pharmacy	1498 (2091)	1368 (3177)	4.8
Total health care cost	9406 (12,921)	9341 (13,140)	0.5
Nonmatching factors			
Observation period, days, mean (SD)	114.0 (93.9)	123.7 (91.4)	10.5
Dosing patterns, mean (SD)			
Number of dispensings per patient	3.3 (2.8)	3.3 (2.9)	1.9
Day supply per dispensing	37.6 (19.4)	50.2 (26.1)	54.6

Table 1 continued

Characteristics	Rivaroxaban cohort (N = 2253)	Warfarin cohort (N = 2253)	Standardized difference (%)[a,b]
Baseline warfarin use[c]	517 (23)		

Additional propensity score–matching factors not reported in this table include the following variables: month of index date; family history of CVD; myocardial infarction; coagulation defect; hepatic disease; left ventricular dysfunction; previous VTE; thrombocytopenia (low platelet count); thrombophilia; hip, pelvis, or leg fracture; rheumatoid arthritis; varicose veins; major bleeding; GI bleeding; total knee replacement; ETOH abuse; peptic ulcer; central venous catheter; inflammatory bowel disease; antiplatelet use; total hip replacement; treatment with erythropoiesis-stimulating agents; treatment with SERMs; treatment with aromatase inhibitors; genitourinary bleeding; cerebral bleeding; other bleeding; immobility; spinal cord injury; surgical resection of abdominal or pelvic cancer; bleeding diathesis; contraceptive pill

COPD chronic obstructive pulmonary disease, *CVD* cardiovascular disease, *ER* emergency room, *ETOH* ethanol (alcohol), *GI* gastrointestinal, *HMO* health maintenance organization, *IHMO* individual health maintenance organization, *MDN* median, *NSAID* nonsteroidal anti-inflammatory drugs, *PFFS* private fee-for-service, *POS* point of service, *PPO* preferred provider organization, *SD* standard deviation, *SERMs* selective estrogen receptor modulators, *VTE* venous thromboembolism

[a] For continuous variables, the standardized difference is calculated by dividing the absolute difference in means of the warfarin and the rivaroxaban cohorts by the pooled SD of both groups. The pooled SD is the square root of the average of the squared SDs

[b] For categorical variables with 2 levels, the standardized difference is calculated using the equation below where p is the respective proportion of participants in each group: $(P_{warfarin} - P_{rivaroxaban})/\sqrt{[p(1-p)]}$, where $p = (P_{warfarin} + P_{rivaroxaban})/2$

[c] Evaluated during the 6-month baseline period

Health Care Costs

Table 2 [30] presents estimated mean health care costs. The estimated mean all-cause and AF-related hospitalization costs were significantly lower for patients treated with rivaroxaban compared to patients treated with warfarin (all-cause: $5411 vs. $7427, $P = 0.047$; AF-related: $2872 vs. $4147, $P = 0.020$). Similarly, estimated mean all-cause outpatient visit costs were significantly lower for rivaroxaban users ($6025 vs. $7999, $P = 0.040$), while mean AF-related outpatient visit costs were lower but not statistically significant for rivaroxaban users ($1799 vs. $2845, $P = 0.167$).

Estimated mean pharmacy costs were significantly higher for rivaroxaban patients compared to warfarin patients (all-cause: $5316 vs. $2620, $P < 0.001$; AF-related: $2355 vs. $121, $P < 0.001$). Estimated mean ER visit costs were also higher for rivaroxaban users compared to warfarin users, but the differences were not statistically significant (all-cause: $838 vs. $630, $P = 0.201$; AF-related: $369 vs. $208, $P = 0.054$). The estimated mean all-cause total cost was lower for rivaroxaban users compared to warfarin users, but not statistically different ($17,590 vs. $18,676, $P = 0.542$), while the estimated mean AF-related total cost was not significantly higher for rivaroxaban users ($7394 vs. $7319, $P = 0.943$).

DISCUSSION

This retrospective matched-cohort analysis compared health care costs between a sample of NVAF patients treated with the target-specific oral anticoagulant rivaroxaban and a matched sample of NVAF patients treated with warfarin based on real-world data.
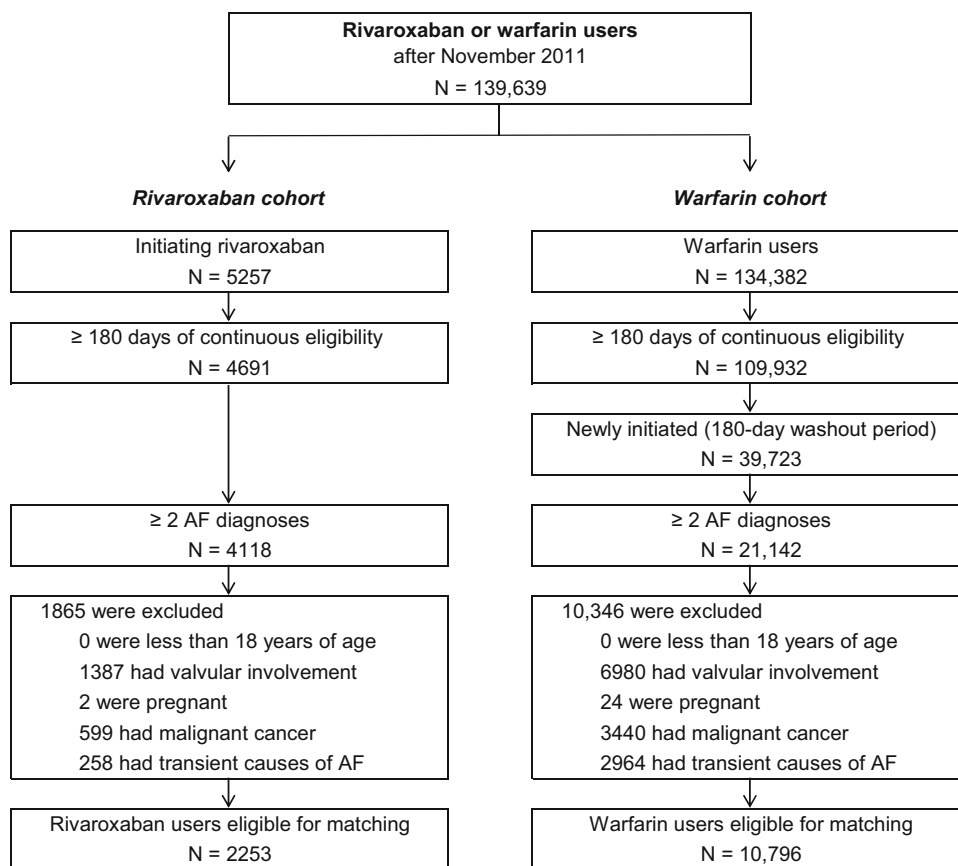
Fig. 1 Patient disposition. *AF* atrial fibrillation

Rivaroxaban was associated with a significant reduction in all-cause and AF-related estimated costs of hospitalization compared to warfarin (27% and 31%, respectively). Significant differences between costs incurred by rivaroxaban and warfarin users were also found for estimated all-cause and AF-related outpatient visits (25% and 37%, respectively). Estimated pharmacy costs were significantly lower for warfarin users compared to rivaroxaban users (51% lower costs for all-cause pharmacy costs and 95% for AF-related pharmacy costs).

Patients in the current study treated with rivaroxaban who had previous use of warfarin were classified in the rivaroxaban cohort. Since the results of the ROCKET AF trial suggested that rivaroxaban users who were naïve to warfarin experienced better primary efficacy and safety endpoints relative to warfarin-exposed patients [24], including warfarin-experienced patients in the rivaroxaban cohort likely produced more conservative estimates of differences between groups in the current study. The proportion of rivaroxaban patients with prior use of warfarin in the current study at 23% was lower than the proportion reported in the ROCKET AF trial, where 62% of rivaroxaban patients had previous use of vitamin K antagonists [24]. Since the current study was conducted with real-world data, it may be more representative of the real rivaroxaban patient population than a clinical trial with more strict inclusion criteria.

Table 2 Health care cost—matched rivaroxaban and warfarin users[a]

Health care cost (US$ 2012)	Rivaroxaban cohort (N = 2253)	Warfarin cohort (N = 2253)	Mean cost difference [95% CI][b]	P value[c]
All-cause, mean				
Hospitalizations	5411	7427	−2016 [−3900; −21]	0.0468
ER visits	838	630	208 [−102; 665]	0.2007
Outpatient visits	6025	7999	−1973 [−4358; −128]	0.0401
Pharmacy	5316	2620	2695 [1915; 3419]	<0.0001
Total	17,590	18,676	−1086 [−3815; 1944]	0.5418
AF-related, mean				
Hospitalizations	2872	4147	−1274 [−2454; −177]	0.0201
ER visits	369	208	161 [−10; 416]	0.0535
Outpatient visits	1799	2845	−1046 [−3186; 164]	0.1672
Pharmacy[d]	2355	121	2234 [2148; 2318]	<0.0001
Total	7394	7319	74 [−2185; 1945]	0.9431

AF atrial fibrillation, *ER* emergency room, *CI* confidence interval
[a] Calculated using Lin's method
[b] 95% CIs were obtained using nonparametric bootstraps with 999 replications
[c] P values were estimated using the achieved significance level as reported in Efron and Tibshirani [30]
[d] AF-related pharmacy claims were identified as dispensings for either anticoagulant or antiplatelet agents

Recent studies have found that patients with NVAF who used target-specific oral anticoagulants had lower health care costs than patients who used warfarin during hospitalizations [31, 32]. More specifically, Fonseca et al. examined total hospital costs associated with warfarin and dabigatran use in a treatment-naïve NVAF population. The authors reported total hospitalization costs of $14,794 for dabigatran users and $16,826 for warfarin users ($P < 0.01$) [31]. Laliberté et al. [32], who studied a Premier database sample of NVAF patients administered rivaroxaban or warfarin during a hospitalization, also found significantly lower hospitalization costs for rivaroxaban compared to warfarin users ($11,993 vs. $13,255, respectively; $P < 0.001$). Although patients with NVAF in the current study were not administered rivaroxaban or warfarin in a hospital setting, significantly lower hospitalization costs were also found for rivaroxaban compared to warfarin users ($5411 vs. $7427, respectively; $P = 0.047$) during the observation period. In addition, in the current study, total health care costs were not significantly different between rivaroxaban and warfarin users despite the significantly higher pharmacy costs of rivaroxaban users. This suggests an offset of the higher cost of rivaroxaban therapy compared to warfarin.

Recent cost-effectiveness studies have also been conducted to compare new target-specific agents with warfarin [15, 16, 33–35]. Harrington et al. [16] constructed a Markov decision analysis model using data from clinical trials and found that new agents (apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg) were all cost-effective alternatives to warfarin.

In the base case, warfarin had both the lowest cost and the lowest quality-adjusted life-years estimate compared to all three new agents. Moreover, rivaroxaban was consistently reported as a cost-effective alternative to warfarin among AF populations in recent publications [15, 16, 33, 35]. Rivaroxaban was also shown to be cost-effective compared to warfarin in a Singapore health care setting, which suggests that the cost-effectiveness of rivaroxaban versus warfarin is global [36]. To be cost-effective means that the new product provides sufficient benefits to justify the added cost. The results of the current study provide additional real-world evidence, and suggest that the use of rivaroxaban may be cost-saving or cost-neutral as compared to warfarin. The overall nondrug lower costs for rivaroxaban users suggest that treatment with rivaroxaban results in less interaction with health care systems, especially in terms of hospitalizations, compared to treatment with warfarin. Therefore, the use of rivaroxaban may have clinical benefits without incurring higher overall health care costs.

This matched-cohort analysis has a number of limitations. First, in spite of information accuracy and completeness required by administrative databases for payment purposes, billing inaccuracies and missing data may still occur. Second, a general limitation of observational studies is that adjustments can be made only for observable factors; adjustments cannot be made for unmeasured confounders. Third, this study was conducted with data obtained from the time period immediately after rivaroxaban became available, and utilization patterns may have changed over time. Fourth, these findings only apply to rivaroxaban since the other target-specific oral anticoagulants were not evaluated. Lastly, the observational design of the study was susceptible to additional potential biases, such as information or classification bias (e.g., identification of false positive or negative AF events). Despite these limitations, observational studies that use statistical techniques to adjust for potentially observed confounding factors through matching techniques provide valuable information, with real-life scenarios and high generalizability.

CONCLUSION

In this real-world study, the estimated cost burden associated with rivaroxaban for all-cause and AF-related hospitalization costs, as well as all-cause outpatient visit costs, was significantly lower than that associated with warfarin in patients with NVAF. With the inclusion of drug costs, both all-cause and AF-related total costs were comparable between groups. Despite higher anticoagulant cost, overall total all-cause and AF-related cost remains comparable due to the cost offset from reduced health care resource utilization.

ACKNOWLEDGMENTS

Group, Inc. Analysis Group, Inc. is a consulting company that has received research grants from Janssen Scientific Affairs, LLC. Concetta Crivera, Winnie W. Nelson, William H. Olson, and Jeffrey Schein are employees of Janssen Scientific Affairs, LLC. Julie Vanderpoel was an employee of Janssen Scientific Affairs, LLC at the time this study was conducted.

Compliance with ethics guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

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