



Healthcare Resource Utilization and Costs of Rivaroxaban Versus Warfarin Among Nonvalvular Atrial Fibrillation Patients with Obesity and Diabetes

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ABSTRACT

Introduction: Nonvalvular atrial fibrillation (NVAf) is associated with a substantial economic burden, particularly in patients with comorbid conditions. This study compared healthcare resource utilization (HRU) and costs of rivaroxaban and warfarin in patients with NVAf, obesity, and diabetes.

Methods: A de-identified healthcare claims database was used to identify adult patients newly initiating rivaroxaban or warfarin and having at least one medical claim with a diagnosis of AF, obesity determined by validated algorithm, and at least one claim with a diagnosis of diabetes or for antidiabetic medication from December 2011 to March 2020. Propensity score matching was used to balance the treatment cohorts on the basis of demographics and baseline characteristics. All-cause and NVAf-related HRU rates and costs were compared

between treatments using rate ratios, and mean cost differences were calculated on a per patient per year (PPPY) basis.

Results: A total of 9999 matched pairs of patients with NVAf, obesity, and diabetes were identified in the rivaroxaban and warfarin cohorts. Rate ratios of all-cause HRU were significantly reduced with rivaroxaban versus warfarin in all healthcare settings evaluated, except emergency room visits. The greatest impact was on physician office visits followed by hospital outpatient and inpatient visits. NVAf-related HRU was significantly lower for rivaroxaban versus warfarin in all care settings. Consistent with these findings, the length of hospital stay was significantly reduced by approximately 4 days among all patients for both all-cause and NVAf-related hospitalizations in the rivaroxaban cohort compared with the warfarin cohort. Rivaroxaban was associated with reductions in all-cause total healthcare costs by more than \$5000 PPPY and NVAf-related medical costs by approximately \$1100 PPPY.

Conclusion: In comparison with warfarin, rivaroxaban reduced HRU and costs, particularly hospital inpatient and outpatient visits and physician office visits, in patients with NVAf and comorbidities of obesity and diabetes.

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PLAIN LANGUAGE SUMMARY

People who are overweight or obese are at risk of developing atrial fibrillation (AF) along with other medical conditions, such as diabetes. Standard therapy with oral anticoagulants or blood thinners is recommended to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF (NVAF). In this study, we evaluated healthcare insurance claims for people with NVAF, obesity, and diabetes who started therapy with warfarin or rivaroxaban from 2011 to 2020 to compare the use and cost of healthcare services, such as hospitalizations and doctor visits, using diagnosis and procedure codes. The study included nearly 20,000 patients with similar characteristics. Patients who started treatment with rivaroxaban used fewer healthcare services for any cause and for those related to NVAF than those who started treatment with warfarin. The difference in use of services was largest for hospital outpatient and inpatient visits and doctor office visits; emergency room visits were only different for those related to NVAF. Length of hospital stay was also shorter for patients receiving rivaroxaban versus those receiving warfarin. These differences in healthcare service use translated into lower costs associated with rivaroxaban versus warfarin. The findings of this study suggest that treatment with rivaroxaban reduces the use of healthcare services compared with warfarin. This difference may be related, in part, to the reduced risks of stroke and systemic embolism observed in other real-world studies with rivaroxaban compared to warfarin. In addition, rivaroxaban does not require routine blood testing, which is required with warfarin treatment.

Keywords: Nonvalvular atrial fibrillation; Obesity; Diabetes mellitus; Anticoagulation; Rivaroxaban; Warfarin; Real-world evidence; Healthcare resource utilization; Costs

Key Summary Points

Why carry out this study?

The risk of nonvalvular atrial fibrillation (NVAF) is increased among individuals with obesity and diabetes.

Obesity is a worldwide public health crisis that increases the risk of comorbidities and contributes substantially to healthcare expenditures.

What did the study ask?

This real-world study evaluated and compared healthcare resource utilization (HRU) and costs of rivaroxaban and warfarin in patients with NVAF, obesity, and diabetes.

What were the study outcomes?

All-cause HRU rate ratios were significantly reduced with rivaroxaban versus warfarin in all healthcare settings evaluated, except emergency room visits.

NVAF-related HRU was significantly lower for rivaroxaban versus warfarin in all healthcare settings.

Rivaroxaban was associated with reductions in all-cause and NVAF-related costs.

What was learned from the study?

HRU and costs were lower with rivaroxaban compared with warfarin in patients with NVAF and concurrent obesity and diabetes.

Treatment differences in HRU and costs were mainly observed for hospital inpatient and outpatient visits and physician office visits, supporting the need for fewer healthcare interactions during rivaroxaban therapy compared with warfarin therapy.

INTRODUCTION

Atrial fibrillation (AF) is associated with substantial burden to patients, caregivers, and the healthcare system, with increased risks of stroke, heart failure, cognitive and mental health problems, and death, which contribute to an annual hospitalization rate of up to 40% [1]. The incidence of chronic diseases, particularly cardiovascular diseases and diabetes, is increased in overweight or obese individuals [2]. Similarly, the risk of developing nonvalvular atrial fibrillation (NVAF) and thrombotic events is higher in obese individuals, and NVAF in obese patients is associated with more severe symptoms, more persistent AF, and poorer outcomes [3–5]. Obesity is the leading risk factor for type 2 diabetes, and prevalence rates of diabetes increase in parallel with rates of obesity [6, 7]. Diabetes is also a well-established risk factor for stroke among patients with AF [8]. The co-occurrence of diabetes and AF is associated with worsened symptoms of AF, an increased risk of all-cause and cardiovascular mortality, an increased risk of hospitalizations, and excess morbidity [9, 10]. Patients with obesity and diabetes have an increased risk of AF [11–13].

Obesity and associated medical conditions lead to substantial medical expenditures, which are expected to increase with the increasing prevalence of obesity worldwide [14–16]. The global economic impact of obesity was estimated at 2 trillion US dollars in 2014 [16]. A recent study using the 2001–2016 Medical Expenditure Panel Survey found that total direct medical costs of obesity in US adults doubled from 2001 (\$124.2 billion) to 2016 (\$260.6 billion), and total annual medical expenditures of obese adults (\$5010) were double those of people of normal weight (\$2504) [17]. Overweight and obese individuals have increased utilization of primary and secondary healthcare services compared with those of normal body weight [2, 17, 18]. In addition, obese individuals are prescribed nearly twice as many medications and are nearly four times more likely to be hospitalized compared with nonobese individuals [2]. Obesity may also

increase societal costs associated with lost productivity, disability, and mortality [16].

Oral anticoagulation therapy with a direct oral anticoagulant (DOAC) is the standard of care to prevent embolic events in patients with NVAF [19]. Standard dosing of DOACs in patients with body mass index (BMI) of 40 kg/m² or less was recommended by the International Society of Thrombosis and Haemostasis in 2016; however, the use of DOACs in morbidly obese patients (BMI > 40 kg/m²) was not recommended because of limited clinical evidence [20]. A number of studies and three systematic reviews have subsequently assessed the use of DOACs in patients with morbid obesity (body weight ≥ 120 kg or BMI ≥ 40 kg/m²) and support the benefit–risk profile of DOACs, particularly rivaroxaban and apixaban, in this population [21–23]. Rivaroxaban, an oral direct factor Xa inhibitor, was approved for the prevention of stroke and systemic embolism in patients with NVAF in November 2011 on the basis of the ROCKET-AF trial [24, 25].

There is a need to understand the healthcare resource utilization (HRU) and costs associated with anticoagulation therapy in patients with NVAF and common comorbidities. This study evaluated the HRU and costs of rivaroxaban compared with warfarin in patients with NVAF, obesity, and diabetes.

METHODS

Study Design

This retrospective cohort study was conducted from December 1, 2010 to March 1, 2020 (Fig. 1). The patient identification period began on December 1, 2011, aligning with the approval date of rivaroxaban in November 2011, and ended on March 1, 2020. The first pharmacy dispensing for rivaroxaban or warfarin during the patient identification period was defined as the index date. The baseline period was defined as a 12-month period with continuous health plan enrollment prior to the index date. This analysis was designed to evaluate and compare all-cause and NVAF-related HRU and costs between rivaroxaban and

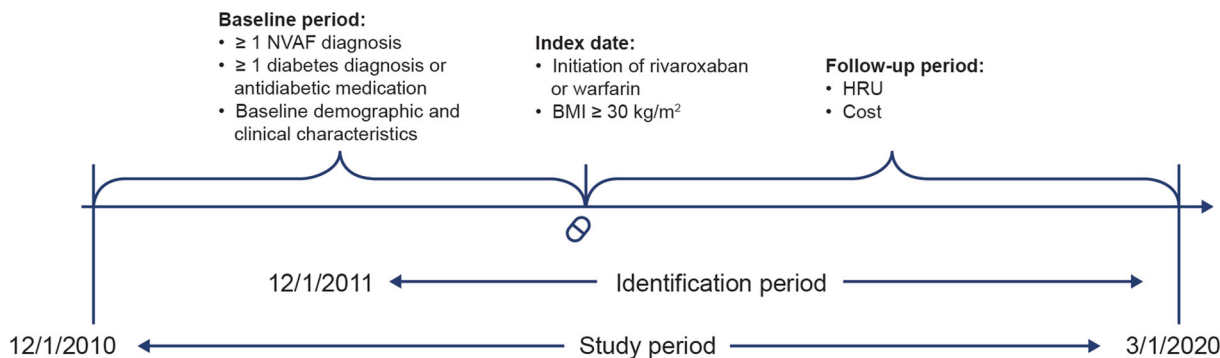


Fig. 1 Study design. *BMI* body mass index, *HRU* healthcare resource utilization, *NVAf* nonvalvular atrial fibrillation. The identification period was from December 1, 2011 to March 1, 2020. The index event was the first pharmacy dispensing for rivaroxaban or warfarin during the identification period. The index date was the first claim date for rivaroxaban or warfarin. The baseline

period was a 12-month period with continuous health plan enrollment prior to the index date, and criteria for inclusion could be met at any time during this time. Patients with stroke/systemic embolism or major bleeding within 30 days prior to the index date were excluded from the analysis

warfarin among patients with NVAf, obesity, and diabetes.

Data Sources

The outcomes in this study were assessed using Optum's de-identified Clinformatics® Data Mart Database—Date of Death (DOD) database, an adjudicated US administrative health claims database. Members include people with private health insurance, who are fully insured in commercial plans or in administrative services only, and Medicare Advantage (starting January 2006). Commercial claims patients (age 0–65 years) make up the majority of the population, with some Medicare patients (age 65–90 years) also included. The database includes information from inpatient and outpatient medical services, prescriptions as dispensed, and outpatient laboratory tests processed by large national vendors who participate in data exchange with Optum.

Patients

Adult patients newly initiating rivaroxaban or warfarin were identified from the database with the following inclusion criteria: at least one pharmacy claim for rivaroxaban or warfarin

(generic product identifier [GPI] code 83370060 and 83200030, respectively) during the patient identification period; at least 12 months continuous medical and pharmacy benefit enrollment prior to and on the index date; at least one medical claim with a diagnosis of AF during the 12-month baseline period prior to or on the index date (International Classification of Diseases [ICD]-9 code 427.31 and ICD-10 codes I48.0%–I48.2%, I48.91%); and at least 18 years of age on the index date.

Patient height and weight data were not available in the claims databases. Thus, the presence of obesity, defined as BMI ≥ 30 kg/m², was determined on the basis of a proprietary validated BMI interpolation algorithm [26]. Using a novel automated weighted prediction approach (Super Learner algorithm), the predictions from four different machine learning algorithms (Catboost, random forest, least absolute shrinkage, and selection operator [LASSO] regression, and artificial neural networks) were leveraged through logistic regression. Features included diagnoses, procedures, and medication uses during the 12-month baseline period and patient demographics. The Optum DOD database was used for training and internally validating the algorithm. The IBM® MarketScan® Commercial Claims and Encounters database was used for external validation

based on assessments of area under the receiver operating characteristic curve (ROC AUC), F1 score, accuracy, negative predictive value, specificity, positive predictive value or precision, and sensitivity or recall. Two predictive models were developed: model 1 included the selected features along with baseline BMI features for patients who had historical BMI data available (diagnosis codes are provided in Table S1 of the supplementary material), and model 2 included only the selected features and was trained on patients who did not have baseline BMI data. Internal validation of model 1 yielded ROC AUC of 88%, with accuracy ranging from 88% to 93% and specificity ranging from 92% to 95% for predicting BMI classifications of ≥ 30 , ≥ 35 , and ≥ 40 kg/m². Model 2 was internally validated with ROC AUC of 73%, with accuracy ranging from 74% to 80% and specificity ranging from 72% to 86% [26].

Patients were also required to have at least one claim with a diagnosis of diabetes (ICD-9: 250.; ICD-10: E10., E11., E13.) or at least one claim for antidiabetic medication (GPI code 27% Healthcare Common Procedure Coding System codes J1815, J1817, E0784, S5550-S5571, G9147, S9353) during the 12-month baseline period prior to or on the index date.

Exclusion criteria included the following: a hospitalization or emergency room (ER) visit with a primary diagnosis code for stroke or systemic embolism, or an event of major bleeding defined by the Cunningham algorithm [27] within 30 days prior to index date; pharmacy claims for at least two oral anticoagulant medications on the index date; and at least one pharmacy claim for an oral anticoagulant at any time prior to the index date (Table S2 in the supplementary material). If patients had evidence of another indication for anticoagulation (i.e., acute venous thromboembolism, prophylaxis after hip/knee replacement surgery) during the baseline period or a diagnosis code for mitral stenosis or a diagnosis or procedure code for a mechanical heart valve procedure at any time prior to the index date, they were also excluded from the analysis (Table S2).

Outcomes

All-cause and NVAf-related (i.e., associated with a diagnosis code for NVAf in any position) HRU were evaluated for the following settings: inpatient hospitalization, including length of stay in days; proportion of patients with 30-day rehospitalization (all-cause hospitalization only); ER visits; hospital outpatient visits; physician office visits (primary and specialty care); and skilled nursing facility (SNF) visits. All-cause and NVAf-related medical costs were evaluated as total medical costs for inpatient hospitalization, ER visits, hospital outpatient visits, physician office visits (primary and specialty care), and SNF visits. Total pharmacy costs were evaluated for all-cause costs only. All-cause total healthcare costs were defined as all-cause medical costs plus all-cause pharmacy costs. Two analyses of HRU and costs were conducted on the basis of the duration of follow-up. The first was an intent-to-treat analysis, including data through the earliest of health plan disenrollment or latest data availability. A second analysis (sensitivity analysis) followed an as-treated approach, including data from treatment initiation (index date) to treatment discontinuation, health plan disenrollment, or end of study, whichever came first.

Statistical Analysis

The propensity of receiving rivaroxaban was predicted using a logistic regression model with potential confounders of age; gender; geographic region; health plan type; insurance type; index year; baseline comorbidities and comorbidity risk scores (i.e., Quan-Charlson comorbidity index [QCI] [28], CHA₂DS₂-VASc [29], and HAS-BLED [30]); baseline procedures (gastric bypass surgery and cardiovascular procedures); baseline medication use (non-oral anticoagulants, antihyperlipidemics, antihypertensives, antiplatelet agents); and baseline HRU and costs (Table S3 in the supplementary material).

To reduce potential bias and create more comparable cohorts based on baseline characteristics, propensity score matching was used in

which rivaroxaban users were matched 1:1 with warfarin users without replacement on the logit of the propensity score using calipers of width equal to 20% of the standard deviation of the logit of the propensity score [31]. To indicate sufficient overlap and use of propensity score matching, calculation of equipoise greater than 50% was used.

Descriptive statistics were used to summarize demographics and baseline characteristics for each treatment cohort. Standardized differences in baseline characteristics of less than 10% were considered a negligible imbalance. Rates of all-cause and NVAf-related HRU and costs were calculated as the number of events or costs incurred over the follow-up period divided by the patient-years of observation. HRU was compared between treatment cohorts using rate ratios, and mean cost differences per patient per year (PPPY) between cohorts were calculated. All costs were inflated to 2020 US dollars based on the medical care component of the Consumer Price Index. For both HRU and costs, nonparametric bootstrap procedures were used to estimate 95% confidence intervals and *P* values.

Compliance with Ethics Guidelines

This study is based on de-identified data collected from a healthcare claims database and does not contain any experimental data with human or animal participants; this analysis was deemed exempt from institutional review board oversight and informed consent was not obtained as per guidance from the Office for Human Research Protections [32].

RESULTS

Patient Characteristics

Among 258,475 adult patients who had at least one claim for either rivaroxaban or warfarin, at least one claim for AF, and at least 12 months of continuous health plan enrollment, obesity (BMI ≥ 30 kg/m²) was identified in 103,342 (40.0%) patients using the BMI algorithm tool

(Table 1). Of these, 57,340 (55.5%) were identified as having diabetes. Exclusion criteria removed 26,262 patients, leaving an analysis population of 31,078 patients, of which 12,663 initiated rivaroxaban and 18,415 initiated warfarin (Table 1).

Demographics and baseline clinical characteristics before and after propensity score matching are shown in Table 2. Rivaroxaban patients were younger than warfarin patients and had lower scores for QCI [28], CHA₂DS₂-VASc [29], and HAS-BLED [30]. Baseline HRU and costs were generally lower for rivaroxaban compared with warfarin, except ER visits and pharmacy fills. Matching provided 9999 pairs of patients with AF, obesity, and diabetes that were well balanced (Table 2). The mean (standard deviation [SD]) follow-up time from index date to the earlier of health plan disenrollment or end of study was 2.3 (1.9) years for the rivaroxaban cohort and 2.5 (2.0) years for the warfarin cohort.

Outcomes

In the intent-to-treat analysis, rate ratios for all-cause HRU were significantly lower in the rivaroxaban cohort compared with the warfarin cohort for all settings, except ER visits (Table 3). The proportion of patients with 30-day rehospitalization was significantly lower with rivaroxaban versus warfarin (24% vs 26%; odds ratio = 0.93; *P* = 0.0189). The mean (SD) length of hospital stay was 16 (34) days for rivaroxaban and 21 (41) days for warfarin for all patients (*P* < 0.0001) and 25 (40) days versus 31 (47) days, respectively, for patients with at least one hospitalization (*P* < 0.0001).

Similar results were obtained for NVAf-related HRU, with rate ratios significantly lower in the rivaroxaban cohort versus the warfarin cohort for inpatient hospitalizations, ER visits, hospital outpatient visits, and physician office visits (Table 3). NVAf-related mean (SD) lengths of hospital stay were significantly shorter with rivaroxaban versus warfarin for all patients (15 [34] days vs 19 [40] days) and patients with at least one hospitalization (28 [42] days vs 33 [48] days).

Table 1 Patient disposition

Criteria	N (%) ^a	
1. Retain patients with ≥ 1 claim for either warfarin or rivaroxaban from December 1, 2011 to March 1, 2020	1,032,008	
2. Retain patients ≥ 18 years old on the index date	1,030,910 (99.9%)	
3. Retain patients with ≥ 12 months continuous medical and pharmacy benefit enrollment prior to and on the index date	550,203 (53.4%)	
4. Retain patients with ≥ 1 claim with an ICD-9/10-CM diagnosis code for AF during the 12 months prior to or on the index date	258,475 (47.0%)	
5. Retain patients with predicted BMI ≥ 30 kg/m ² on the index date per the previously validated BMI algorithm tool	103,342 (40.0%)	
6. Retain patients with ≥ 1 claim with a diagnosis of diabetes or ≥ 1 claim for antidiabetic medication during the 12 months prior to or on the index date	57,340 (55.5%)	
7. Exclude patients with ≥ 1 hospitalization or ER visit with a primary diagnosis for stroke/SE during the 30 days prior to the index date	55,565 (96.9%)	
8. Exclude patients with ≥ 1 major bleeding event ^b during the 30 days prior to the index date	55,398 (99.7%)	
9. Exclude patients with claims for ≥ 2 different OACs on the index date	55,337 (99.9%)	
	Rivaroxaban cohort	Warfarin cohort
10. Exclude patients with ≥ 1 claim for any OAC during the 12 months prior to the index date	13,913 (86.1%)	20,639 (52.7%)
11. Exclude patients with ≥ 1 claim with a procedure code for knee or hip replacement during the 12 months prior to the index date	13,461 (96.8%)	20,120 (97.5%)
12. Exclude patients with ≥ 1 claim with an ICD-9/10-CM diagnosis code for VTE during the 12 months prior to the index date	13,454 (99.9%)	20,093 (99.9%)
13. Exclude patients with ≥ 1 claim with an ICD-9/10-CM diagnosis code for mitral stenosis during the 12 months prior to the index date	12,663 (94.1%)	18,415 (91.6%)
14. Exclude patients with ≥ 1 claim with a procedure or diagnosis code for mechanical heart valve procedure during the 12 months prior to the index date	12,663 (100.0%)	18,415 (100.0%)

AF atrial fibrillation, BMI body mass index, ER emergency room, ICD-9/10-CM International Classification of Diseases, 9th and 10th Revisions, Clinical Modification, OAC oral anticoagulant, SE systemic embolism, VTE venous thromboembolism

^a The exclusion criteria are presented as a funnel approach in which the number of patients in each row reflects those who were retained after applying the respective exclusion criteria in sequential order; the percentages were calculated using the number of patients from the prior row as the denominator

^b A major bleeding event was identified during the follow-up period using a validated claims-based algorithm developed by Cunningham et al. [27]

Table 2 Demographic and baseline characteristics before and after matching

Characteristic	Prior to matching		Post matching		Standard difference ^a
	Rivaroxaban (<i>n</i> = 12,663)	Warfarin (<i>n</i> = 18,415)	Rivaroxaban (<i>n</i> = 9999)	Warfarin (<i>n</i> = 9999)	
Age, years, mean (SD)	68.9 (9.5)	70.8 (8.5)	70.0 (8.9)	70.2 (8.9)	2.6%
Sex, <i>n</i> (%)					
Male	7603 (60.0%)	10,655 (57.9%)	5876 (58.8%)	5796 (58.0%)	1.6%
Female	5060 (40.0%)	7760 (42.1%)	4123 (41.2%)	4203 (42.0%)	1.6%
Insurance type, <i>n</i> (%)					
Commercial	3865 (30.5%)	3521 (19.1%)	2470 (24.7%)	2374 (23.7%)	2.2%
Medicare	8798 (69.5%)	14,894 (80.9%)	7529 (75.3%)	7625 (76.3%)	2.2%
Baseline risk scores, mean (SD)					
QCI	2.59 (2.24)	3.23 (2.31)	2.80 (2.28)	2.89 (2.22)	4.0%
CHA ₂ -DS ₂ -VASC	4.27 (1.69)	4.79 (1.69)	4.47 (1.68)	4.55 (1.66)	4.8%
HAS-BLED	3.18 (1.44)	3.49 (1.50)	3.27 (1.46)	3.32 (1.46)	3.4%
Baseline obesity class, <i>n</i> (%)					
Class I (BMI 30.0–34.9 kg/m ²)	5107 (40.3%)	8130 (44.2%)	4143 (41.4%)	4309 (43.1%)	3.4%
Class II (BMI 35.0–39.9 kg/m ²)	1937 (15.3%)	2512 (13.6%)	1472 (14.7%)	1426 (14.3%)	1.3%
Class III (BMI ≥ 40.0 kg/m ²)	5619 (44.4%)	7773 (42.2%)	4384 (43.8%)	4264 (42.6%)	2.4%
Baseline comorbidities, <i>n</i> (%)					
Hypertension	12,130 (95.8%)	17,704 (96.1%)	9594 (96.0%)	9577 (95.8%)	0.9%
Hyperlipidemia	10,866 (85.8%)	15,681 (85.2%)	8610 (86.1%)	8485 (84.9%)	3.6%
Congestive heart failure	4687 (37.0%)	9420 (51.2%)	4175 (41.8%)	4371 (43.7%)	4.0%
Osteoarthritis	4407 (34.8%)	6312 (34.3%)	3599 (36.0%)	3402 (34.0%)	4.1%

Table 2 continued

Characteristic	Prior to matching			Post matching		
	Rivaroxaban (<i>n</i> = 12,663)	Warfarin (<i>n</i> = 18,415)	Standard difference ^a	Rivaroxaban (<i>n</i> = 9999)	Warfarin (<i>n</i> = 9999)	Standard difference ^a
Coronary artery disease	4208 (33.2%)	6405 (34.8%)	3.3%	3404 (34.0%)	3462 (34.6%)	1.2%
Chronic kidney disease	3484 (27.5%)	7617 (41.4%)	29.5%	3197 (32.0%)	3404 (34.0%)	4.4%
Thyroid disease	3466 (27.4%)	4879 (26.5%)	2.0%	2801 (28.0%)	2594 (25.9%)	4.7%
Anemia	3332 (26.3%)	7417 (40.3%)	30.0%	3040 (30.4%)	3267 (32.7%)	4.9%
COPD	3183 (25.1%)	5753 (31.2%)	13.6%	2732 (27.3%)	2794 (27.9%)	1.4%
Stroke/TIA	1960 (15.5%)	3967 (21.5%)	15.7%	1696 (17.0%)	1819 (18.2%)	3.2%
Peripheral vascular disease	1936 (15.3%)	3872 (21.0%)	14.9%	1691 (16.9%)	1814 (18.1%)	3.2%
Depression	2448 (19.3%)	3644 (19.8%)	1.2%	1976 (19.8%)	1934 (19.3%)	1.1%
Nonalcoholic fatty liver disease	2233 (17.6%)	3184 (17.3%)	0.9%	1925 (19.3%)	1891 (18.9%)	0.9%
Cancer ^b	2040 (16.1%)	3093 (16.8%)	1.9%	1640 (16.4%)	1681 (16.8%)	1.1%
Lung cancer	175 (1.4%)	264 (1.4%)	0.4%	156 (1.6%)	129 (1.3%)	2.3%
Prostate cancer	391 (3.1%)	609 (3.3%)	1.3%	309 (3.1%)	355 (3.6%)	2.6%
Breast cancer	266 (2.1%)	395 (2.1%)	0.3%	209 (2.1%)	210 (2.1%)	0.1%
Colorectal cancer	132 (1.0%)	224 (1.2%)	1.7%	116 (1.2%)	110 (1.1%)	0.6%
Other solid cancers	1876 (14.8%)	2812 (15.3%)	1.3%	1501 (15.0%)	1536 (15.4%)	1.0%
Hematologic cancers	248 (2.0%)	420 (2.3%)	2.2%	211 (2.1%)	213 (2.1%)	0.1%
Metastasis	225 (1.8%)	366 (2.0%)	1.6%	188 (1.9%)	166 (1.7%)	1.7%
Anxiety	1927 (15.2%)	2577 (14.0%)	3.5%	1501 (15.0%)	1453 (14.5%)	1.4%
Asthma	1714 (13.5%)	2632 (14.3%)	2.2%	1390 (13.9%)	1326 (13.3%)	1.9%
Old MI	1246 (9.8%)	2355 (12.8%)	9.3%	1081 (10.8%)	1117 (11.2%)	1.2%
Diverticulosis	1223 (9.7%)	1933 (10.5%)	2.8%	995 (10.0%)	996 (10.0%)	< 0.1%

Table 2 continued

Characteristic	Prior to matching		Post matching			
	Rivaroxaban (<i>n</i> = 12,663)	Warfarin (<i>n</i> = 18,415)	Standard difference ^a	Rivaroxaban (<i>n</i> = 9999)	Warfarin (<i>n</i> = 9999)	Standard difference ^a
Acute MI	977 (7.7%)	2419 (13.1%)	17.8%	887 (8.9%)	970 (9.7%)	2.9%
Stable angina	812 (6.4%)	1658 (9.0%)	9.7%	690 (6.9%)	776 (7.8%)	3.3%
Unstable angina	502 (4.0%)	1279 (7.0%)	13.2%	446 (4.5%)	481 (4.8%)	1.7%
Osteoporosis	502 (4.0%)	789 (4.3%)	1.6%	427 (4.3%)	407 (4.1%)	1.0%
Rheumatoid arthritis	413 (3.3%)	584 (3.2%)	0.5%	346 (3.5%)	313 (3.1%)	1.9%
Liver cirrhosis	168 (1.3%)	355 (1.9%)	4.8%	144 (1.4%)	192 (1.9%)	3.7%
GI bleeding	59 (0.5%)	218 (1.2%)	7.9%	58 (0.6%)	88 (0.9%)	3.5%
<i>H. pylori</i> infection	51 (0.4%)	91 (0.5%)	1.4%	44 (0.4%)	44 (0.4%)	0.0%
Uveitis	47 (0.4%)	71 (0.4%)	0.2%	35 (0.4%)	42 (0.4%)	1.1%
Baseline procedures, <i>n</i> (%)						
Gastric bypass surgery	37 (0.3%)	52 (0.3%)	0.2%	32 (0.3%)	29 (0.3%)	0.5%
Cardiovascular procedure	977 (7.7%)	2480 (13.5%)	18.8%	892 (8.9%)	980 (9.8%)	3.0%
Baseline medication use, <i>n</i> (%)						
Nonoral anticoagulant	1801 (14.2%)	3060 (16.6%)	6.6%	1477 (14.8%)	1535 (15.4%)	1.6%
Antihyperlipidemics	9163 (72.4%)	12,932 (70.2%)	4.7%	7206 (72.1%)	7216 (72.2%)	0.2%
Antihypertensives	11,738 (92.7%)	16,721 (90.8%)	6.9%	9230 (92.3%)	9197 (92.0%)	1.2%
Antiplatelet agents	1937 (15.3%)	3183 (17.3%)	5.4%	1608 (16.1%)	1665 (16.7%)	1.5%
Baseline all-cause HRU (counts), mean (SD)						
Inpatient hospitalization	1.54 (3.58)	2.18 (4.00)	16.9%	1.69 (3.60)	1.80 (3.69)	3.0%
ER visit	0.65 (1.77)	0.57 (1.55)	4.8%	0.62 (1.67)	0.61 (1.69)	0.6%
Office visit	15.26 (12.02)	16.22 (13.44)	7.5%	15.72 (12.56)	15.87 (12.54)	1.2%
Outpatient visit	21.96 (20.03)	24.33 (26.08)	10.2%	22.34 (20.94)	22.88 (22.36)	2.5%

Table 2 continued

Characteristic	Prior to matching		Post matching		Standard difference ^a
	Rivaroxaban (<i>n</i> = 12,663)	Warfarin (<i>n</i> = 18,415)	Rivaroxaban (<i>n</i> = 9999)	Warfarin (<i>n</i> = 9999)	
Pharmacy fill	52.77 (41.18)	51.91 (41.13)	52.60 (41.30)	52.34 (41.16)	0.6%
Baseline all-cause SNF visit, <i>n</i> (%)	2202 (17.4%)	3739 (20.3%)	1764 (17.6%)	1838 (18.4%)	1.9%
Baseline costs (\$), mean (SD)					
Inpatient hospitalization	24,570 (50,448)	49,559 (94,025)	28,942 (55,262)	34,733 (75,730)	8.7%
ER visit	1123 (3908)	1044 (3137)	1114 (4164)	1053 (2918)	1.7%
Office visit	2406 (4960)	2549 (6174)	2494 (5249)	2569 (6043)	1.3%
Outpatient visit	11,477 (27,296)	18,463 (63,487)	11,777 (28,842)	15,066 (49,903)	8.1%
SNF visit	963 (4534)	1421 (5795)	1073 (4860)	1184 (5241)	2.2%
Pharmacy fill	5886 (11,761)	5317 (12,645)	5553 (11,393)	5659 (15,299)	0.8%

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *ER* emergency room, *HRU* healthcare resource utilization, *QCI* Quan–Charlson comorbidity index, *SD* standard deviation, *SNF* skilled nursing facility, *TIA* transient ischemic attack

^a Standard difference < 10% was considered a negligible imbalance

^b A diagnosis of cancer required two diagnosis codes for the same type of cancer on separate dates ≥ 30 days apart. Patients could have a diagnosis for more than one type of cancer

Table 3 All-cause and NVAF-related HRU for patients with NVAF, obesity, and diabetes newly initiating rivaroxaban or warfarin

	Rivaroxaban (<i>n</i> = 9999)	Warfarin (<i>n</i> = 9999)	Rate ratio/mean difference (95% CI)^a	<i>P</i> value
Intent-to-treat analysis				
All-cause HRU				
Number of events of interest (PPPY), mean (SD)				
Inpatient hospitalizations	1.39 (3.41)	1.62 (3.83)	0.86 (0.85, 0.88)	< 0.0001
ER visits	0.64 (1.56)	0.61 (1.25)	1.02 (0.99, 1.05)	0.2064
Hospital outpatient visits	17.38 (12.18)	21.33 (15.02)	0.80 (0.79, 0.80)	< 0.0001
Physician office visits	24.36 (20.11)	29.15 (24.39)	0.77 (0.77, 0.78)	< 0.0001
Pharmacy fills	60.92 (39.93)	61.21 (42.44)	0.97 (0.97, 0.97)	< 0.0001
30-day rehospitalization rate, ^b <i>n</i> (%)	2439 (24.4%)	2583 (25.8%)	0.93 (0.87, 0.99) ^b	0.0189
Length of hospital stay, mean (SD)				
All patients	16.16 (34.30)	20.57 (40.74)	−4.41 (−5.45, −3.37)	< 0.0001
Patients with ≥ 1 hospitalization ^c	25.47 (40.22)	30.66 (46.53)	−5.18 (−6.68, −3.69)	< 0.0001
NVAF-related^d HRU				
Number of events of interest (PPPY), mean (SD)				
Inpatient hospitalizations	0.82 (1.64)	0.89 (1.68)	0.93 (0.90, 0.95)	< 0.0001
ER visits	0.17 (0.52)	0.18 (0.51)	0.93 (0.87, 0.98)	0.0103
Hospital outpatient visits	4.34 (3.83)	7.19 (7.43)	0.60 (0.60, 0.61)	< 0.0001
Physician office visits	3.68 (4.52)	6.96 (8.40)	0.50 (0.49, 0.50)	< 0.0001
Length of hospital stay, mean (SD)				
All patients	15.47 (34.15)	19.38 (40.43)	−3.92 (−4.95, −2.88)	< 0.0001
Patients with ≥ 1 hospitalization ^c	27.51 (41.76)	33.21 (48.39)	−5.70 (−7.36, −4.04)	< 0.0001
As-treated sensitivity analysis				
All-cause HRU				
Number of events of interest (PPPY), mean (SD)				
Inpatient hospitalizations	1.29 (3.79)	1.62 (4.68)	0.83 (0.82, 0.84)	< 0.0001
ER visits	0.64 (1.64)	0.65 (1.64)	0.97 (0.94, 1.00)	0.048
Hospital outpatient visits	18.35 (13.35)	26.88 (18.48)	0.71 (0.71, 0.72)	< 0.0001
Physician office visits	26.21 (22.26)	36.69 (29.16)	0.71 (0.70, 0.71)	< 0.0001
Pharmacy fills	71.94 (44.84)	73.23 (47.56)	0.92 (0.91, 0.92)	< 0.0001

Table 3 continued

	Rivaroxaban (<i>n</i> = 9999)	Warfarin (<i>n</i> = 9999)	Rate ratio/mean difference (95% CI) ^a	<i>P</i> value
Length of hospital stay, mean (SD)				
All patients	5.94 (14.94)	7.91 (18.97)	−1.97 (−2.45, −1.50)	< 0.0001
Patients with ≥ 1 hospitalization ^c	9.36 (17.88)	11.79 (22.14)	−2.43 (−3.12, −1.74)	< 0.0001
NVAF-related ^d HRU				
Number of events of interest (PPPY), mean (SD)				
Inpatient hospitalizations	0.80 (2.12)	0.95 (2.33)	0.89 (0.87, 0.91)	< 0.0001
ER visits	0.18 (0.69)	0.20 (0.71)	0.94 (0.90, 0.99)	0.0265
Hospital outpatient visits	5.11 (4.69)	11.09 (10.64)	0.53 (0.53, 0.54)	< 0.0001
Physician office visits	4.36 (5.90)	11.10 (12.11)	0.45 (0.45, 0.46)	< 0.0001
Length of hospital stay, mean (SD)				
All patients	5.53 (14.69)	7.25 (18.64)	−1.72 (−2.19, −1.26)	< 0.0001
Patients with ≥ 1 hospitalization ^c	9.84 (18.48)	12.43 (23.05)	−2.58 (−3.35, −1.82)	< 0.0001

CI confidence interval, ER emergency room, HRU healthcare resource utilization, NVAF nonvalvular atrial fibrillation, PPPY per person per year, SD standard deviation

^a Rate ratio was used to compare the number of events PPPY, and difference in means was used to compare length of hospital stay; statistical comparisons are comparing rivaroxaban to warfarin (reference group)

^b 30-day rehospitalization rate was defined as having another hospitalization within 30 days after the first all-cause hospitalization during the follow-up period; odds ratio was used to compare the proportion of patients with 30-day rehospitalization

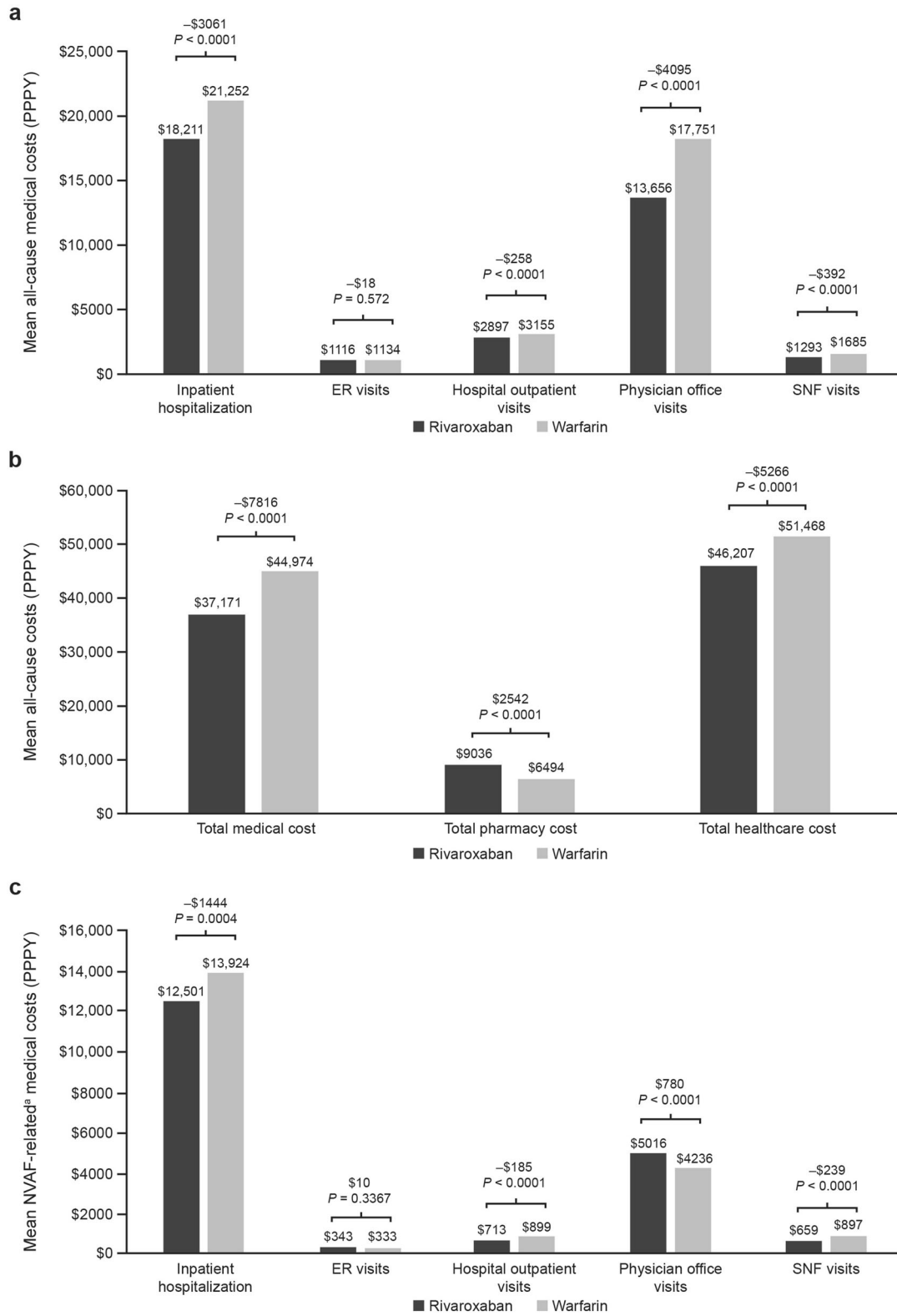
^c Number of patients with ≥ 1 hospitalization: intent-to-treat: all-cause (rivaroxaban, 6342; warfarin, 6708), NVAF-related (rivaroxaban, 5621; warfarin, 5836); as-treated: all-cause (rivaroxaban, 4315; warfarin, 4707), NVAF-related (rivaroxaban, 3669; warfarin, 3941)

^d NVAF-related was defined as an encounter associated with an AF diagnosis in any position

The as-treated sensitivity analysis results for all-cause and NVAF-related HRU rate ratios were consistent with the intent-to-treat analysis, with the additional finding that ER visits were significantly lower in the rivaroxaban cohort versus the warfarin cohort ($P < 0.05$; Table 3). The length of hospital stay was significantly shorter for rivaroxaban compared with warfarin. For all-cause hospitalizations, the length of stay was 2 days shorter both in all patients and in patients with at least one hospitalization.

For NVAF-related hospitalizations, the length of stay was 2 and 3 days shorter, respectively.

In the intent-to-treat analysis, all-cause total medical costs were \$7816 PPPY lower in the rivaroxaban cohort compared with the warfarin cohort, with significantly lower costs in all settings, except ER visits (Fig. 2a). Total pharmacy costs were higher for rivaroxaban versus warfarin by \$2542 PPPY, but the difference was offset by the larger reduction in medical costs (Fig. 2b). The total healthcare costs of medical



◀**Fig. 2** All-cause **a** medical costs, **b** total costs, and **c** NVAF-related^a medical costs (2020 US dollars) for patients with NVAF, obesity, and diabetes newly initiating rivaroxaban or warfarin. *ER* emergency room, *NVAF* nonvalvular atrial fibrillation, *PPPY* per patient per year, *SNF* skilled nursing facility. ^aNVAF-related was defined as an encounter associated with an AF diagnosis in any position

and pharmacy costs combined were lower by \$5266 PPPY for rivaroxaban compared with warfarin ($P < 0.0001$). NVAF-related medical costs were approximately half of the all-cause medical costs and were also lower for rivaroxaban versus warfarin (\$1056 PPPY; $P = 0.01$; Fig. 2c). The drivers of medical costs related to NVAF were inpatient hospitalizations and physician office visits, with the latter being higher in the rivaroxaban cohort compared with the warfarin cohort.

The total cost advantage of rivaroxaban versus warfarin was maintained in the as-treated sensitivity analysis. All-cause total healthcare costs were reduced by \$5459 for rivaroxaban versus warfarin, with total medical costs reduced by \$10,879 and pharmacy costs increased by \$5399 (Table 4). NVAF-related medical costs were reduced by \$3466 in the rivaroxaban cohort compared with the warfarin cohort. For both all-cause and NVAF-related costs on an as-treated basis, medical costs were driven by inpatient hospitalizations and physician office visits. However, NVAF-related physician office visit costs were significantly higher in the rivaroxaban cohort versus the warfarin cohort (\$518 PPPY; $P = 0.0013$).

DISCUSSION

This real-world study compared HRU and costs of oral anticoagulation therapy with rivaroxaban versus warfarin in patients with NVAF who have concurrent obesity and diabetes. All-cause HRU was reduced with rivaroxaban versus warfarin in all settings, except ER visits. NVAF-related HRU remained significantly lower for rivaroxaban versus warfarin in all settings, particularly physician office visits and hospital

outpatient visits. The length of hospital stay was significantly reduced by approximately 4–5 days in the rivaroxaban cohort compared with the warfarin cohort for both all-cause and NVAF-related hospitalizations. All-cause total healthcare costs were reduced by more than \$5000 PPPY with rivaroxaban, and NVAF-related medical costs were reduced by approximately \$1100 PPPY with rivaroxaban. The difference was driven mainly by lower costs for inpatient hospitalizations and physician office visits for rivaroxaban versus warfarin.

The efficacy of rivaroxaban and warfarin in overweight and obese patients with NVAF was analyzed using data from the ROCKET-AF trial, in which stroke and systemic embolism outcomes were lower compared with normal weight patients in both rivaroxaban and warfarin treatment groups [33]. Among patients with diabetes in ROCKET-AF, similar rates of stroke/systemic embolism were observed compared with patients who did not have diabetes [33, 34]. In addition, previously published real-world evidence studies demonstrated similar or improved effectiveness and safety of rivaroxaban versus warfarin in obese patients with NVAF [35–39]. Studies have also demonstrated the effectiveness and safety of rivaroxaban in patients with NVAF and concurrent diabetes [34, 40–45].

Our study findings are aligned with other retrospective analyses among patients with NVAF overall and in obese patients [35, 46, 47]. Among 2253 matched pairs of patients with NVAF newly initiating rivaroxaban or warfarin, all-cause and NVAF-related hospitalization costs were significantly lower with rivaroxaban compared with warfarin [47]. All-cause costs of outpatient visits were also significantly lower with rivaroxaban versus warfarin, while NVAF-related outpatient visit costs were lower but not statistically significant. Lower HRU and costs were also demonstrated with rivaroxaban versus warfarin in patients with NVAF who were morbidly obese despite similar effectiveness and safety of the anticoagulants [35]. Lower costs were driven by a lower hospitalization rate, shorter length of stay, and less outpatient and physician office service encounters for rivaroxaban versus warfarin [35]. Another recently

Table 4 Sensitivity analysis of as-treated patients: All-cause and NVAF-related healthcare costs (2020 US dollars) for patients with NVAF, obesity, and diabetes newly initiating rivaroxaban or warfarin

	Rivaroxaban (n = 9999)	Warfarin (n = 9999)	Mean difference (95% CI)^a	P value
As-treated analysis				
All-cause costs (PPPY), mean (SD)				
Total medical cost	\$36,010 (71,743)	\$46,829 (99,242)	−\$10,879 (−11,988, −9734)	< 0.0001
Inpatient hospitalizations	\$15,572 (55,081)	\$20,351 (65,097)	−\$4869 (−5842, −3832)	< 0.0001
ER visits	\$1122 (3707)	\$1237 (3743)	−\$115 (−181, −45)	0.0016
Hospital outpatient visits	\$2856 (5907)	\$3573 (9040)	−\$717 (−784, −648)	< 0.0001
Physician office visits	\$15,259 (36,646)	\$19,779 (64,263)	−\$4521 (−5057, −3966)	< 0.0001
SNF visits	\$1202 (5424)	\$1889 (7352)	−\$688 (−768, −602)	< 0.0001
Total pharmacy cost	\$11,972 (14,018)	\$6573 (13,000)	\$5399 (5127, 5679)	< 0.0001
Total cost (medical + pharmacy)	\$47,982 (74,149)	\$53,401 (101,549)	−\$5459 (−6704, −4181)	< 0.0001
NVAF-related costs (PPPY), mean (SD)				
Total medical cost	\$19,416 (50,505)	\$22,830 (57,213)	−\$3466 (−4248, −2651)	< 0.0001
Inpatient hospitalizations	\$11,263 (41,516)	\$14,270 (49,708)	−\$3079 (−3809, −2298)	< 0.0001
ER visits	\$376 (1937)	\$385 (1815)	−\$10 (−33, 16)	0.446
Hospital outpatient visits	\$846 (2084)	\$1320 (5493)	−\$474 (−501, −446)	< 0.0001
Physician office visits	\$6334 (24,003)	\$5816 (21,814)	\$518 (196, 857)	0.0013
SNF visits	\$600 (3416)	\$1041 (5174)	−\$422 (−483, −398)	< 0.0001

CI confidence interval, ER emergency room, HRU healthcare resource utilization, NVAF nonvalvular atrial fibrillation, PPPY per person per year, SD standard deviation, SNF skilled nursing facility

^a Difference in means was used to compare healthcare costs; statistical comparisons are comparing rivaroxaban to warfarin (reference group)

published study evaluated HRU and costs in patients with NVAF and obesity who were newly initiating rivaroxaban or warfarin [46]. At 12 and 36 months, rivaroxaban was associated with lower all-cause and NVAF-related HRU driven primarily by lower outpatient visits. All-cause and NVAF-related costs were also lower with rivaroxaban versus warfarin as a result of lower hospitalization costs. Outpatient office visits and other visit costs were also lower with rivaroxaban versus warfarin. This claims-based study was extended to evaluate HRU and costs for patients with NVAF, obesity, and polypharmacy (defined as five or more concurrent

outpatient prescriptions) [48]. Rivaroxaban was associated with significantly lower 12- and 36-month HRU and 12-month costs, driven by lower hospitalizations [48]. The lower hospitalization rates and shorter lengths of hospital stay associated with rivaroxaban versus warfarin suggest fewer healthcare interactions in patients treated with rivaroxaban [35, 47, 48]. These findings may be related to lack of need for routine monitoring and fewer drug–drug interactions with rivaroxaban in comparison to nearly monthly international normalized ratio monitoring that occurs with warfarin [35, 46, 48].

Although no data have specifically examined HRU and costs associated with anticoagulation therapy in patients with NVAF and diabetes, the Nationwide Inpatient Sample registry data found that 29% of AF-related hospitalizations occurred in patients with concurrent diabetes, and there was a temporal increase in the AF hospitalization rate among patients with diabetes [49]. No differences in costs were identified for patients with AF with and without diabetes, but there was a higher 30-day readmission risk for patients with diabetes. In our analysis, rivaroxaban was associated with a significantly lower 30-day rehospitalization rate. On the basis of results obtained using the National Readmission Database, readmitted patients with AF had a higher burden of comorbidities, and diabetes was among the most common comorbidities of hospitalized patients [50]. A higher burden of comorbidities was also predictive of higher cost of hospitalization for AF [50].

This study included the use of a geographically diverse healthcare claims database that represents both commercially insured and Medicare Advantage beneficiaries across the USA and 12 months of continuous health plan enrollment to better understand patient characteristics and outcomes over time. Propensity score matching was used to reduce selection biases, but there may be residual confounding as some factors were not available in the claims data; for example, we did not control for diabetes control, exercise, and smoking status. In this analysis, BMI was calculated using a validated machine learning algorithm, which allowed us to leverage the BMI information from claims data to assess HRU and costs. However, the algorithm may misclassify patients' BMI category. Other limitations of administrative claims data include coding errors and inconsistencies. The time in therapeutic international normalized ratio range was not assessed for warfarin patients because of limited laboratory data. HRU and costs were limited to the patient population studied and may not be generalizable to the broader US population, such as those who are uninsured or have a different insurance coverage (e.g., Medicaid). Moreover, prescription claims do not indicate

that the medication was taken as prescribed, and medications provided as samples by physicians or over-the-counter medications are not captured in these data. Costs provided in the Optum DOD database are standardized costs, which may underestimate the actual costs for commercial plans and overestimate the actual costs for Medicare Advantage plans. Finally, even with propensity score matching to balance the study cohorts, residual confounding cannot be excluded.

CONCLUSIONS

The results of this analysis provide valuable information on HRU and costs among patients with NVAF, obesity, and diabetes, showing that rivaroxaban is associated with lower HRU and costs compared with warfarin.

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contributed to study conception/design and data interpretation. Yen-Wen Chen and Jinghua He contributed to collection and assembly of data, and data analysis. All authors reviewed and approved the final content of this manuscript.

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Compliance with Ethics Guidelines. This study is based on de-identified data collected from a healthcare claims database and does not contain any experimental data with human or animal participants; this analysis was deemed exempt from institutional review board oversight and informed consent was not obtained as per guidance from the Office for Human Research Protections [32].

Data Availability. Data for this study were available to the authors via third-party license from Optum, a commercial data provider in the United States, and Janssen Pharmaceuticals, which has a license for analysis of Optum's de-identified Clinformatics® Data Mart Database—Date of Death database. As such, the authors cannot provide the raw data; however, other researchers may access the data by purchase through Optum, and the inclusion criteria specified in the methods would allow them to identify the same cohort of patients. Interested individuals may visit www.optum.com/contact.html for more information on accessing Optum's de-identified Clinformatics® Data Mart Database—Date of Death database.

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