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Full Length Article

Rivaroxaban versus warfarin treatment among morbidly obese patients with venous thromboembolism: Comparative effectiveness, safety, and costs

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ABSTRACT

Introduction: Limited data exist on direct-acting oral anticoagulants in morbidly obese patients with venous thromboembolism (VTE). We compared clinical and health/economic outcomes with rivaroxaban versus warfarin for VTE treatment in morbidly obese patients.

Materials and methods: This retrospective 1:1 propensity score matched cohort study analyzed data from 2 US claims databases. VTE patients initiating rivaroxaban or warfarin were identified who had diagnosis codes for morbid obesity (ICD-9:278.01,V85.4; ICD-10:E66.01,E66.2,Z68.4) 12 months pre- or 3 months post-initiation and followed ≥ 3 months. Intent-to-treat (ITT) and on-treatment (OT) analyses were conducted using conditional logistic regression and generalized linear models to compare recurrent VTE and major bleeding risks, healthcare resource utilization (HRU), and per patient per year (PPPY) costs.

Results: In total, 2890 matched pairs of morbidly obese VTE patients initiating rivaroxaban or warfarin were identified. Risks of recurrent VTE (ITT: OR: 0.99; 95% CI: 0.85–1.14) and major bleeding (OT: OR: 0.75; 95% CI: 0.47–1.19) were similar for cohorts. Anti-Factor Xa laboratory measurement was performed on < 1% of rivaroxaban cohort. Hospitalizations (OR: 0.86; 95% CI: 0.77–0.96) and outpatient visits (OR: 0.23; 95% CI: 0.10–0.56), were lower with rivaroxaban versus warfarin (ITT analysis). Average total medical costs PPPY were $2829 lower with rivaroxaban versus warfarin ($34,824 vs $37,653), mainly driven by hospitalization costs. Total healthcare costs (including pharmacy) were similar ($43,034 vs $44,565).

Conclusions: Morbidly obese VTE patients receiving rivaroxaban had similar risks of recurrent VTE and major bleeding versus warfarin. Rivaroxaban treatment yielded significantly less HRU and total medical costs, with similar total healthcare costs between groups.

1. Introduction

Obesity is an independent risk factor for venous thromboembolism (VTE), increasing the risk by 2- to 6-fold compared with nonobese patients [1]. Obesity amplifies the effects of other VTE risk factors, such as surgery, medical illness, and use of hormone therapy [2]. The risk of recurrent VTE was shown to be nearly linear in relationship to increasing body weight in the absence of anticoagulation [3]. Rivaroxaban is a direct-acting oral anticoagulant (DOAC) approved for acute VTE treatment, including deep-vein thrombosis (DVT) and pulmonary embolism (PE), using a fixed-dose regimen with no requirement for routine monitoring of anticoagulant activity [4–6]. Pharmacokinetic

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; DOAC, direct-acting oral anticoagulant; DVT, deep-vein thrombosis; ER, emergency room; HRU, healthcare resource utilization; *ICD*, *International Classification of Diseases*; ISTH, International Society of Thrombosis and Haemostasis; ITT, Intent-to-treat; NOAC, non-vitamin K antagonists oral anticoagulants; OR, odds ratio; OT, on-treatment; PE, pulmonary embolism; PPPY, per patient per year; QCI, Quan-Charlson Comorbidity Index; SD, standard deviation; SNF, skilled nursing facility; SSC, Scientific and Standardization Committee; VTE, venous thromboembolism

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and pharmacodynamic studies have found no effects of high body weight on the peak plasma concentration, distribution, or half-life of rivaroxaban, which is likely the result of a low volume of distribution of the drug [2,7–9]. Previous small studies that evaluated the risks of recurrent VTE and major bleeding relative to body weight comparing rivaroxaban with enoxaparin and vitamin K antagonist therapy found no association in adverse outcomes between body weight or body mass index (BMI) for patients who received rivaroxaban [2,10,11]. No dosage adjustment is indicated for patients with body weight > 120 kg in the rivaroxaban product labeling [4].

Despite these data, concerns about the use of anticoagulation in morbidly obese patients stem from the potential for altered drug pharmacokinetics at body weight extremes and a lack of robust clinical data with the DOACs in this population [2,9,12]. In 2016, the Scientific and Standardization Committee (SSC) of the International Society of Thrombosis and Haemostasis (ISTH) conducted an obesity subgroup analysis of available phase 3 clinical trial data on DOACs [12]. The committee concluded that DOACs are safe and effective in obese patients with BMI ≤40 kg/m^2 or body weight ≤120 kg. However, limited data were available for patients with morbid obesity, defined as BMI > 40 kg/m^2 or body weight > 120 kg. Based on the theoretical potential for decreased drug exposures, reduced peak concentrations, and shorter half-lives among morbidly obese patients and a lack of robust clinical data, the committee suggested that DOACs should not be used in this population for fear of potential underdosing. The committee also indicated that if DOACs are used in patients with morbid obesity, measurement of anticoagulant activity should be considered using specific monitoring, including anti-FXa for apixaban, edoxaban, and rivaroxaban; ecarin clotting time or dilute thrombin time with appropriate calibrators for dabigatran; or mass spectrometry drug level for any of the DOACs.

Given these concerns, large scale studies are needed in morbidly obese patients that focus on clinical outcomes such as VTE recurrence and major bleeding related to DOAC treatment for VTE. In addition, healthcare resource utilization and cost analyses between DOACs and conventional therapy with warfarin for VTE management are lacking in this population. Using a large US healthcare claims database, we compared the effectiveness, safety, healthcare resource utilization, and costs of rivaroxaban and warfarin in morbidly obese patients.

2. Materials and methods

2.1. Study design

We conducted a retrospective cohort study that combined 2 databases providing data for a 5-year period from 2011 to 2016. The Truven MarketScan Commercial Claims and Encounters database contained inpatient admission records, outpatient services, prescription drugs, enrollment status, and costs of medical services and drugs for approximately 138 million unique de-identified persons insured by employer-sponsored plans. The Truven MarketScan Medicare Supplemental database contained person-specific clinical utilization, cost, and enrollment across inpatient, outpatient, prescription drug, and carve-out services for Medicare-eligible active and retired employees and their dependents from employer-sponsored supplemental plans. Two analyses were conducted: an intent-to-treat (ITT) analysis, in which patients were followed until the first event of interest or censored at the end of the 12-month observation period, and an on-treatment analysis that included patients from treatment initiation to discontinuation.

2.2. Study population

Adult patients with ≥1 medical claim with a VTE diagnosis (ICD-9: 451.1, 451.2, 453.4, 453.8, 453.9 for DVT and 415.1 for PE; ICD-10: I80.1, I80.2, I80.3, I82.4, I82.6, I82.A1, I82.B1, I82.C1, I82.90 for DVT and I26 for PE) were identified from December 1, 2012 (post-approval of rivaroxaban for VTE) to September 30, 2016. The date of first qualified VTE diagnosis at any place of service and in any position was the diagnosis index date. Patients were required to have initiated treatment with either rivaroxaban or warfarin, based on ≥1 pharmacy claim for either agent, within 28 days of the VTE diagnosis index date. The first pharmacy claim date for rivaroxaban or warfarin was the drug index date. The baseline period was a minimum continuous health plan enrollment period of 12 months before the diagnosis index date. Due to a lack of BMI data in claims databases, ≥1 diagnosis of morbid obesity based on ICD-9/10 codes (ICD-9: 278.01, V85.4; ICD-10: E66.01, E66.2, Z68.4) was required during the 12-month baseline period through 3 months after the drug index date (follow-up period) for study inclusion [13]. Patients were excluded if they had a diagnosis of VTE or atrial fibrillation (AF) at any time prior to the diagnosis index date or if they had an oral anticoagulant prescription prior to the drug index date.

2.3. Study outcomes and variables

The primary outcome compared between treatment cohorts was the risk of recurrent VTE, defined as a hospitalization (inpatient service) or emergency room (ER) visit with a primary diagnosis of VTE during the follow-up period and calculated as the number of patients with recurrent VTE (DVT or PE) divided by the total number of patients in the treatment cohort. The mean (standard deviation [SD]) number of recurrent VTE events per patient per year (PPPY) and the time-to-first event (from drug index date to first event during follow-up) were determined. Secondary outcomes included major bleeding risk, healthcare resource utilization, and costs. A major bleeding event was defined using a validated claims-based algorithm [14] during the follow-up period in the primary position, and risk, number of events, and time-to-event measures were calculated as per the primary outcome.

All-cause healthcare resource utilization and costs incurred during the follow-up period were reported for each treatment cohort. The frequency and proportion of patients who had ≥1 visit and the mean (SD) number of visits for hospitalization (including mean [SD] length of stay), ER, physician office, outpatient visits (which included INR monitoring), skilled nursing facility (SNF) and pharmacy prescription (s) were included in all-cause healthcare resource utilization. All costs were inflated to 2016 US dollars and reported as total medical cost (i.e., costs for hospitalization, ER, physician office, outpatient visits, and SNF/long-term care), and total pharmacy prescription cost for all medications. Limited data on anti-FXa measurement for rivaroxaban were available in the databases.

The mean (SD) duration of index treatment was measured during the follow-up period and defined as the number of days that elapsed between the prescription index data and the time of discontinuation of index medication. Discontinuation was defined as no subsequent index medication dispensing prior to the end of the 60-day maximum permissible gap of dispensing. Switching or adding another anticoagulant was not considered discontinuation of the index medication in the ITT analysis. The proportion of days covered as calculated as the ratio of the number of days covered by the index medication prescription dispensed during the follow-up period divided by the number of days of follow-up. Patients with a proportion of days covered ratio ≥0.80 were considered adherent to index therapy.

The mean (SD) time from diagnosis index date to drug index date was determined. Demographic variables, including age, gender, and insurance type (commercial or Medicare), were evaluated on the drug index date. During the 12-month baseline period, the Quan-Charlson Comorbidity Index (QCI) [15] was used to measure the general status of comorbid conditions, individual comorbid conditions were identified by diagnosis codes, and the modified RIETE score (for lack of data for creatinine variable) stratified a patient's risk of major bleeding with anticoagulation for DVT or PE [16]. The RIETE score ranges from 0 to 8, with 0 indicating low risk, 1 to 4 indicating moderate risk, and 4.5 to 8

indicating high risk. The frequency and proportion of patients who had ≥1 prescription medication and mean (SD) number of different pharmacy prescriptions used were reported.

2.4. Statistical analysis

Propensity score matching techniques were used to create comparable rivaroxaban and warfarin cohorts at a 1:1 ratio. All demographic and baseline clinical characteristics (Supplemental Table 1) were considered as potential confounders and used to construct the logistic regression model that calculated propensity scores for each patient. Treatment cohorts were considered well-balanced for a given variable if the standardized difference between the groups was ≤10%.

Multivariable regression models compared outcomes between propensity score matched treatment cohorts. Outcomes were reported as PPPY to adjust for various lengths of follow-up time. Conditional logistic regression models were used to model the expected risk of events as a function of the independent variable (rivaroxaban vs warfarin) and covariates. Odds ratios (OR), 95% confidence intervals (CI), and *P* values were calculated. For the number of events and visits, general linear models using negative binomial or Poisson distribution and a logarithm link function were used to report mean difference, 95% CI, and *P* values. Conditional Cox proportional hazards models were used to calculate the hazard ratio and corresponding 95% CIs and *P* values for time-to-first event. The multivariable model was adjusted for index VTE type (DVT, PE, or both) and time between treatment initiation and VTE diagnosis (≤7 days vs > 7 days) for risk and number of events and time-to-first event. Costs were compared using general linear models with gamma distribution and a logarithm link function. All statistical analyses were conducted using SAS Enterprise Guide 7 (Cary, NC).

2.5. Sensitivity analyses

A sensitivity analysis was conducted to evaluate the effect of a 30-day permissible gap for discontinuation of index medication. Two additional sensitivity analyses were performed to restrict recurrent VTE events to 1) patients with recurrent VTE as primary diagnosis code in the inpatient setting during the follow-up period (i.e., excluding those with only ER claims) and 2) patients with recurrent VTE as primary diagnosis code in the inpatient setting and imaging code in the primary position during follow-up.

3. Results

Across the 2 databases, 125,267 adult patients met entry criteria with ≥1 medical claim for a diagnosis of VTE, ≥1 pharmacy claim for rivaroxaban or warfarin within 28 days of VTE diagnosis, and 12 months of continuous plan enrollment prior to the index date. Patients were excluded for prior diagnosis of VTE or AF (n = 40,850) and oral anticoagulant use before the drug index date (n = 12,622). Of the 64,997 with continuous enrollment within 3 months following the drug index date, morbid obesity was present in 7342 (11%) patients. Demographic and baseline characteristics for patients before propensity score matching are shown in Table 1. Patients receiving warfarin were older, were more likely to be female, had ≥1 hospitalization, and had higher risk scores and more comorbidities compared with those receiving rivaroxaban. Significant differences between treatment cohorts were found for all characteristics, except for average number of different pharmacy prescriptions. Propensity score matching was successful for 2890 matched pairs of patients with VTE and morbid obesity who initiated treatment with either rivaroxaban or warfarin (Table 1).

The mean time between VTE diagnosis and treatment start was 14 days. A low proportion of patients received low molecular weight heparin (rivaroxaban: 8.0%; warfarin: 12.7%) or unfractionated heparin (rivaroxaban: 2.7%; warfarin: 3.4%) prior to initiating treatment. Most patients in the rivaroxaban cohort (~80%) were initiated on the 15-mg BID dose. The mean duration of index treatment was 181 days for the rivaroxaban cohort and 193 days for the warfarin cohort (difference in means, −11.93; 95% CI: −17.98, −5.89; $P = 0.0001$). The treatment groups had a similar proportion of days covered, with a mean of 0.62 for rivaroxaban and 0.63 for warfarin, and 40% and 41% of patients, respectively, achieved > 0.80 days covered. A sensitivity analysis using a 30-day permissible gap for discontinuation found a similar average proportion of days covered (0.61–0.63) in both cohorts. The mean follow-up time was 10.0 months and 10.5 months for rivaroxaban and warfarin, respectively, in the ITT analysis. The rivaroxaban cohort averaged 1 anti-FXa test PPPY (with 0.8% of rivaroxaban patients receiving this test), while the average number of INR tests PPPY for warfarin users was 14.

Table 1
Demographic and baseline characteristics.

	Prior to matching		Post matching		
Characteristic	Rivaroxaban (n = 3035)	Warfarin (n = 4307)	Rivaroxaban (n = 2890)	Warfarin (n = 2890)	Standard difference[a]
Age, years, mean (SD)	53.2 (12.7)	54.6 (13.4)	53.3 (12.9)	53.1 (13.1)	1.4%
Gender, n (%)					
Male	1232 (40.6)	1613 (37.5)	1141 (39.5)	1150 (39.8)	0.6%
Female	1803 (59.4)	2694 (62.5)	1749 (60.5)	1740 (60.2)	0.6%
Insurance type, n (%)					
Commercial only	2582 (85.1)	3468 (80.5)	2441 (84.5)	2434 (84.2)	0.7%
Medicare	453 (14.9)	839 (19.5)	449 (15.5)	456 (15.8)	0.7%
Modified RIETE score, mean (SD)	0.80 (1.19)	0.92 (1.30)	0.81 (1.19)	0.82 (1.22)	0.8%
QCI, mean (SD)	1.24 (2.11)	1.38 (2.13)	1.22 (2.05)	1.23 (2.01)	0.5%
Common comorbid conditions (> 5%), n (%)					
Hypertension	1906 (62.8)	2803 (65.1)	1816 (62.8)	1815 (62.8)	0.1%
Hyperlipidemia	1246 (41.1)	1876 (43.6)	1194 (41.3)	1183 (40.9)	0.8%
Diabetes	962 (31.7)	1523 (35.4)	920 (31.8)	941 (32.6)	1.6%
Peripheral vascular disease	232 (7.6)	361 (8.4)	220 (7.6)	217 (7.5)	0.4%
Congestive heart failure	210 (6.9)	398 (9.2)	207 (7.2)	224 (7.8)	2.2%
Solid cancers	235 (7.7)	338 (7.8)	211 (7.3)	199 (6.9)	1.6%
Chronic kidney disease	184 (6.1)	448 (10.4)	182 (6.3)	203 (7.0)	2.9%
Diverticulosis	202 (6.7)	316 (7.3)	195 (6.7)	200 (6.9)	0.7%
Number of different pharmacy prescriptions, mean (SD)	11.51 (7.70)	11.46 (7.60)	11.38 (7.53)	11.35 (7.68)	0.4%
Patients with ≥1 hospitalization at baseline, n (%)	1232 (40.6)	1996 (46.3)	1196 (41.4)	1200 (41.5)	0.3%

QCI, Quan-Charlson comorbidity index; SD, standard deviation.
[a] A standard difference ≥ 10% was considered significant.

Table 2
Risk of recurrent VTE with rivaroxaban and warfarin.

	Rivaroxaban	Warfarin	Estimate[a] (95% CI)	*P* value
ITT analysis	n = 2890	n = 2890		
Follow-up time, months, mean (SD)	10.04 (3.01)	10.51 (2.77)	Mean difference: −0.47 (−0.61, −0.32)	< 0.0001
Risk of recurrent VTE,[b] n (%)	485 (16.8%)	459 (15.9%)	OR: 0.99 (0.85, 1.14)	0.8443
Number of recurrent VTE events (PPPY), mean (SD)	0.24 (0.63)	0.25 (0.84)	Mean difference: −0.02 (−0.05, 0.01)	0.2234
Time-to-first recurrent VTE event, days, mean (SD)	52 (91)	58 (93)	HR: 1.20 (0.90, 1.16)	0.7259
On-treatment analysis[c]	n = 2832	n = 2832		
Follow-up time, months, mean (SD)	6.04 (3.80)	6.43 (3.98)		
Risk of recurrent VTE, [b] n (%)	418 (14.8%)	380 (13.4%)	OR: 1.02 (0.87, 1.20)	0.8343
Number of recurrent VTE events (PPPY), mean (SD)	0.34 (1.48)	0.32 (1.46)	Mean difference: −0.01 (−0.07, 0.05)	0.6370
Time-to-first recurrent VTE event, days, mean (SD)	30 (64)	30 (56)	HR: 1.06 (0.92, 1.21)	0.4429

CI, confidence interval; HR: hazard ratio; ITT, intent-to-treat; OR, odds ratio; PPPY, per patient per year; SD, standard deviation; VTE, venous thromboembolism.
[a] Odds ratio, difference in means, and hazard ratios were used for recurrent VTE risk, number of recurrent VTE events, and time-to-first event, respectively. Statistical comparisons are comparing rivaroxaban to warfarin (reference group). The model was adjusted for index VTE type (DVT, PE, or both) and time between treatment initiation and VTE diagnosis (≤7 days vs > 7 days).
[b] A recurrent VTE event was defined as a hospitalization or ER visit with a primary diagnosis of VTE during follow-up. Risk of recurrent VTE was measured by estimating the proportion of at-risk patients who had ≥1 recurrent VTE (DVT or PE) event during follow-up.
[c] Patients were followed from treatment initiation to discontinuation (switching or adding another anticoagulant was censored in the on-treatment analysis).

3.1. Intent-to-treat analysis

Among 944 patients with recurrent VTE, 43.8% were inpatients, 49.1% were in the emergency room, and 7.2% had inpatient and ER claims. The risk of recurrent VTE, defined by inpatient and ER claims, was not significantly different between patients receiving rivaroxaban (16.8%) and those receiving warfarin (15.9%) in the ITT analysis (OR: 0.99; 95% CI: 0.85, 1.14; $P = 0.8443$) (Table 2). The number of recurrent VTE events PPPY was also similar between groups (rivaroxaban, 0.24; warfarin, 0.25; $P = 0.2234$). The time-to-first recurrent VTE event was 52 days with rivaroxaban compared with 58 days with warfarin, and the difference between treatment cohorts was not significant ($P = 0.7259$).

Sensitivity analyses restricted to recurrent VTE events in the inpatient setting that included a primary diagnostic code for imaging to differentiate recurrent VTE from history of VTE substantially reduced the overall rates of recurrent VTE. The risk of recurrent VTE for patients with ≥1 inpatient hospitalization with a primary diagnosis code for VTE during follow-up was 8.1% with rivaroxaban and 8.6% with warfarin (OR: 0.93; 95% CI: 0.77, 1.12; $P = 0.4388$) (Table 3). The risk of recurrent VTE was further reduced by including the requirement for a primary imaging code among patients with ≥1 inpatient hospitalization and a primary diagnosis code for VTE during follow-up: rivaroxaban, 3.0% and warfarin, 2.6% (OR: 0.94; 95% CI: 0.37, 2.38; $P = 0.8877$) (Table 3).

Table 3
Sensitivity analysis results (ITT analysis).

	Rivaroxaban n = 2890	Warfarin n = 2890	OR (95% CI)	*P* value
Risk of recurrent VTE (inpatient diagnosis only),[a] n (%)	233 (8.1%)	248 (8.6%)	0.93 (0.77, 1.12)	0.4388
Risk of recurrent VTE (inpatient diagnosis and imaging code),[b] n (%)	87 (3.0%)	75 (2.6%)	0.94 (0.37, 2.38)	0.8877

CI, confidence interval; ITT, intent-to-treat; OR, odds ratio; VTE, venous thromboembolism.
[a] Recurrent VTE was defined as having ≥1 inpatient hospitalization with primary diagnosis code for VTE during the follow-up period.
[b] Recurrent VTE was defined as having ≥1 inpatient hospitalization with diagnosis and image code at primary position for VTE during the follow-up period.

The risk of major bleeding was significantly lower with rivaroxaban compared with warfarin in the ITT analysis (1.8% vs 2.5%; OR: 0.66; 95% CI: 0.45, 0.98; $P = 0.0388$) (Table 4). The number of major bleeding events PPPY was similar for both groups (rivaroxaban, 0.02; warfarin, 0.03; $P = 0.0937$) and the mean time-to-first event was 82 days for rivaroxaban and 105 days for warfarin ($P = 0.0831$).

All-cause healthcare resources were used less frequently by patients receiving rivaroxaban compared with those receiving warfarin in the ITT analyses (Table 5). Specifically, hospitalizations (OR: 0.86, 95% CI: 0.77, 0.96; $P = 0.0057$) and outpatient visits (including INR monitoring; OR: 0.23, 95% CI: 0.10, 0.56; $P = 0.0012$), were significantly lower with rivaroxaban versus warfarin, respectively. Total medical costs PPPY were significantly lower by an average of $2829 (95% CI: −$5048, −$457; $P = 0.0201$) for rivaroxaban patients compared with warfarin patients ($34,824 vs $37,653) (Fig. 1). The difference in total medical cost in the ITT analysis was driven primarily by hospitalization costs ($15,552 vs $18,320, mean difference: −$2767, 95% CI: −$4849, −$364; $P = 0.0255$). On average, total healthcare costs (including medical and pharmacy costs) PPPY were numerically lower with rivaroxaban by $1531 (95% CI: −$3953, $1036; $P = 0.2370$) compared to warfarin, but this difference was not statistically significant ($43,034 vs $44,565).

3.2. On-treatment analysis

Among 2832 matched pairs of patients who were followed from treatment initiation to discontinuation, the risk of recurrent VTE was not significantly different between rivaroxaban (14.8%) and warfarin (13.4%), with an OR of 1.02 (95% CI: 0.87, 1.20; $P = 0.8343$) (Table 2). There were no significant differences between treatment cohorts for number of events PPPY (rivaroxaban, 0.34; warfarin, 0.32; $P = 0.6370$; Table 2). The time-to-first recurrent VTE was 30 days for each treatment.

There was no significant difference in the risk of major bleeding in the on-treatment analysis (rivaroxaban, 1.4%; warfarin, 1.8%, OR: 0.75, 95% CI: 0.47, 1.19, $P = 0.2266$; Table 4). The number of major bleeding events PPPY was also similar between groups (rivaroxaban, 0.03; warfarin, 0.04; $P = 0.3915$) and the mean time-to-first event was 69 days for rivaroxaban and 77 days for warfarin ($P = 0.3637$).

Similar to the ITT analysis, all-cause healthcare resource utilization was lower for patients receiving rivaroxaban compared with those receiving warfarin in the on-treatment analysis (Table 5), with significant differences for hospitalizations (OR: 0.87, 95% CI: 0.77, 0.98;

Table 4
Risk of major bleeding with rivaroxaban and warfarin.

	Rivaroxaban	Warfarin	Estimate[a] (95% CI)	*P* value
ITT analysis	n = 2890	n = 2890		
Follow-up time, months, mean (SD)	10.04 (3.01)	10.51 (2.77)	Mean difference: −0.47 (−0.61, −0.32)	< 0.0001
Risk of major bleeding,[b] n (%)	52 (1.8%)	73 (2.5%)	OR: 0.66 (0.45, 0.98)	0.0388
Number of major bleeding events (PPPY), mean (SD)	0.02 (0.18)	0.03 (0.22)	Mean difference: −0.01 (−0.02, 0.002)	0.0937
Time-to-first major bleeding event, days, mean (SD)	82 (88)	105 (93)	HR: 0.73 (0.51, 1.04)	0.0831
On-treatment analysis[c]	n = 2832	n = 2832		
Follow-up time, months, mean (SD)	6.04 (3.80)	6.43 (3.98)		
Risk of major bleeding,[b] n (%)	40 (1.4%)	50 (1.8%)	OR: 0.75 (0.47, 1.19)	0.2266
Number of major bleeding events (PPPY), mean (SD)	0.03 (0.37)	0.04 (0.44)	Mean difference: −0.01 (−0.02, 0.02)	0.3915
Time-to-first major bleeding event, days, mean (SD)	69 (83)	77 (79)	HR: 0.83 (0.54, 1.25)	0.3637

CI, confidence interval; HR: hazard ratio; ITT, intent-to-treat; OR, odds ratio; PPPY, per patient per year; SD, standard deviation.

[a] Odds ratio, difference in means, and hazard ratios were used for risk of major bleeding, number of major bleeding events, and time-to-first event, respectively. Statistical comparisons are comparing rivaroxaban to warfarin (reference group). The model was adjusted for index VTE type (DVT, PE, or both) and time between treatment initiation and VTE diagnosis (≤7 days vs > 7 days).

[b] A major bleeding event was defined using a validated claims-based algorithm developed by Cunningham et al. Risk of major bleeding was measured by estimating the proportion of at-risk patients who had ≥1 major bleeding event during follow-up.

[c] Patients were followed from treatment initiation to discontinuation (switching or adding another anticoagulant was censored in the on-treatment analysis).

Table 5
Healthcare resource utilization and length of stay associated with rivaroxaban and warfarin use in morbidly obese patients with VTE.

	VTE patients				Estimate[a] (95% CI)	*P* value
	Rivaroxaban		Warfarin			
ITT analysis	n = 2890		n = 2890			
Patients with ≥ 1 event of interest, n (%)						
Hospitalization	1015	35.1%	1115	38.6%	0.86 (0.77, 0.96)	0.0057
ER visit	1137	39.3%	1158	40.1%	0.97 (0.87, 1.08)	0.5678
Office visit	2867	99.2%	2861	99.0%	1.26 (0.73, 2.18)	0.4064
Outpatient visit	2864	99.1%	2884	99.8%	0.23 (0.10, 0.56)	0.0012
SNF/long-term care	142	4.9%	169	5.8%	0.83 (0.66, 1.05)	0.1115
Number of events of interest (PPPY), mean (SD)						
Hospitalization	0.87	1.95	1.01	2.39	−0.13 (−0.22, −0.04)	0.0064
ER visit	0.90	1.71	0.95	2.11	−0.05 (−0.13, 0.04)	0.2515
Office visit	15.84	11.36	20.04	14.07	−4.21 (−4.74, −3.66)	< 0.0001
Outpatient visit	92.97	108.37	111.98	106.20	−19.02 (−22.94, −14.92)	< 0.0001
Pharmacy fill	47.89	34.44	52.15	37.15	−4.28 (−5.91, −2.59)	< 0.0001
Length of hospital stay, mean (SD)						
Among all patients	4.22	13.41	5.11	15.27	−0.88 (−1.62, −0.14)	0.0197
Among patients with ≥1 hospitalization	12.03	20.45	13.24	22.30	−1.21 (−3.03, 0.62)	0.1943
On-treatment analysis	n = 2832		n = 2832			
Patients with ≥ 1 event of interest, n (%)						
Hospitalization	749	26.4%	829	29.3%	0.87 (0.77, 0.98)	0.0169
ER visit	890	31.4%	897	31.7%	0.99 (0.88, 1.11)	0.8395
Office visit	2720	96.0%	2743	96.9%	0.79 (0.60, 1.05)	0.1003
Outpatient visit	2733	96.5%	2809	99.2%	0.22 (0.14, 0.35)	< 0.0001
SNF/long-term care	92	3.2%	118	4.2%	0.77 (0.58, 1.02)	0.0654
Number of events of interest (PPPY), mean (SD)						
Hospitalization	0.90	2.53	1.05	2.92	−0.15 (−0.26, −0.02)	0.0223
ER visit	0.98	2.26	1.04	2.47	−0.06 (−0.17, 0.06)	0.3228
Office visit	17.57	12.71	23.66	16.97	−6.13 (−6.74, −5.51)	< 0.0001
Outpatient visit	98.43	115.61	126.85	120.23	−28.41 (−32.65, −23.99)	< 0.0001
Pharmacy fill	53.95	35.40	59.53	39.07	−5.62 (−7.23, −3.96)	< 0.0001
Length of hospital stay, mean (SD)						
Among all patients	2.37	7.86	3.14	10.53	−0.76 (−1.25, −0.28)	< 0.0001
Among patients with ≥1 hospitalization	8.98	13.21	10.72	17.25	−1.74 (−3.27, −0.21)	< 0.0001

CI, confidence interval; ER, emergency room; ITT, intent-to-treat; PPPY, per patient per year; SD, standard deviation; SNF, skilled nursing facility; VTE, venous thromboembolism.

[a] Odds ratio was used for categorical variables, and difference in means was used for continuous variables.

$P = 0.0169$) and outpatient visits (including INR monitoring; OR: 0.22, 95% CI: 0.14, 0.35; $P < 0.0001$). Total medical costs PPPY were significantly lower by an average of $4787 (95% CI: −$7038, −$2380; $P = 0.0002$) for rivaroxaban patients compared with warfarin patients ($34,712 vs $39,508) and the major contributor was a significant difference in hospitalization costs ($14,655 vs $18,655, mean difference: −$4001, 95% CI: −$6053, −$1615; $P = 0.0017$) (Fig. 2). In the on-treatment analysis, average total healthcare costs PPPY were lower with rivaroxaban with a mean differnce of $2641 (95% CI: −$5123, −$14; $P = 0.0489$) compared to warfarin ($44,474 vs $47,123).

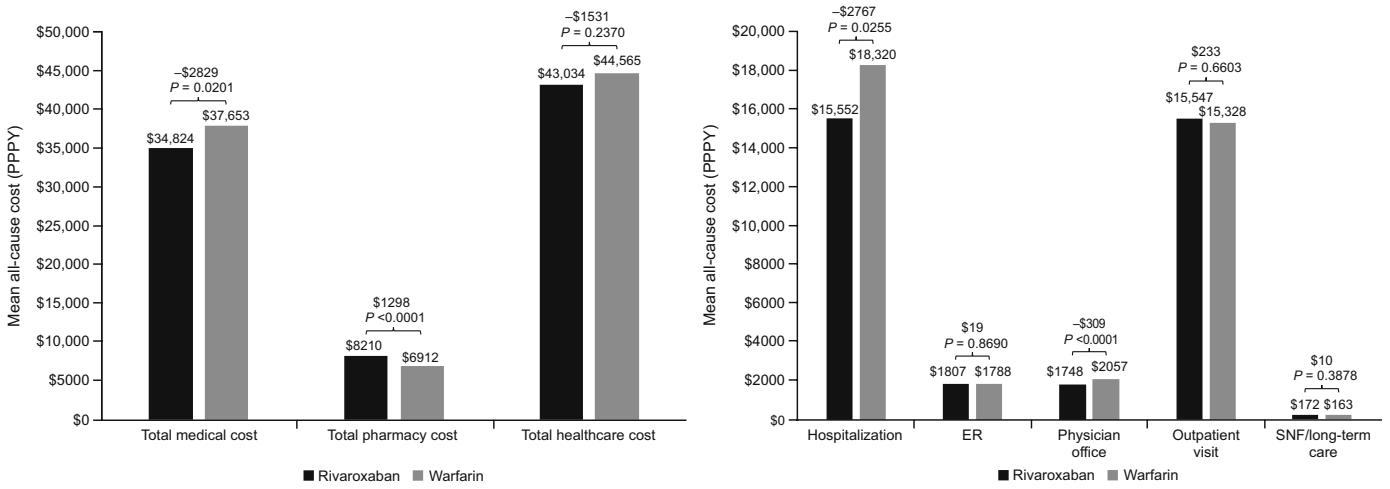

Fig. 1. ITT analysis: all-cause costs (PPPY) for A) total medical and pharmacy expenditures and B) individual components of medical costs associated with rivaroxaban and warfarin use in morbidly obese patients with VTE.

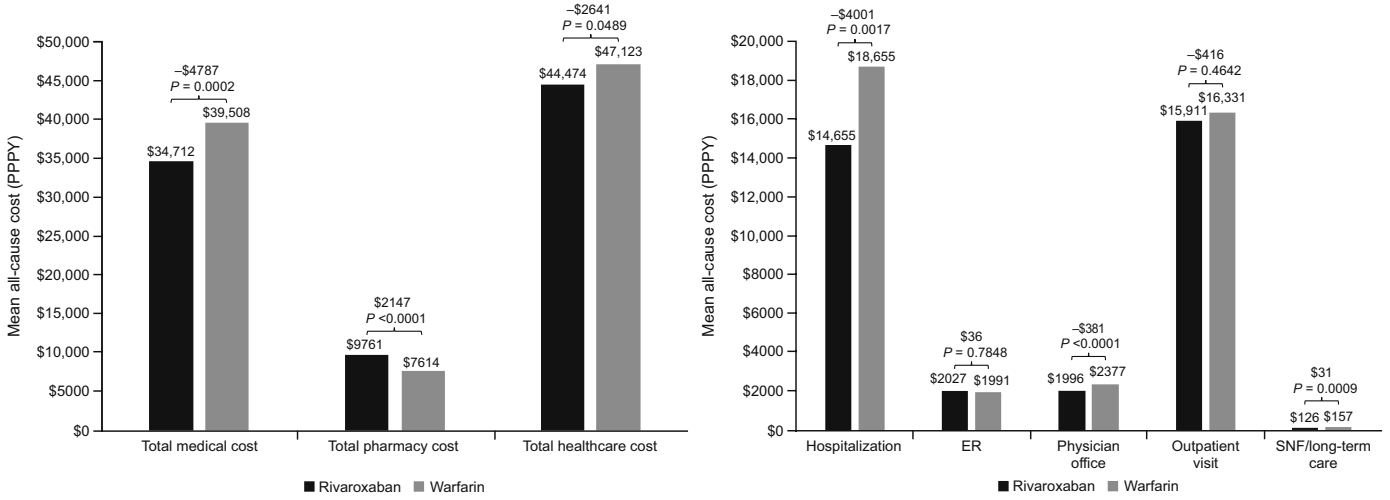

Fig. 2. On-treatment analysis: all-cause costs (PPPY) for A) total medical and pharmacy expenditures and B) individual components of medical costs associated with rivaroxaban and warfarin use in morbidly obese patients with VTE.

4. Discussion

The present study is the largest of its kind using a real-world database of healthcare claims comparing clinical outcomes of rivaroxaban and warfarin for the treatment of VTE in morbidly obese patients. We found that patients with morbid obesity initiating and continuing rivaroxaban or warfarin had similar risks of recurrent VTE and major bleeding. As < 1% of rivaroxaban-treated patients had an anti-FXa test, these outcomes provide reassurance for clinicians that patients with morbid obesity treated with rivaroxaban for VTE have similar outcomes to standard warfarin, without the need for routine anti-FXa measurement as suggested by the 2016 ISTH Guidance statement [12].

The results of this claims database analysis are consistent with data from randomized clinical trials, EINSTEIN DVT and EINSTEIN PE, which found that fixed-dose rivaroxaban compared with enoxaparin/VKA was not associated with an increased risk of recurrent VTE or major bleeding in patients with high body weight [2]. Additionally, the multicenter, noninterventional XALIA study found no significant differences in rates of recurrent VTE or major bleeding among patient subgroups based on body weight with rivaroxaban versus standard anticoagulation therapy for treatment of VTE in routine clinical practice [11]. The Dresden non-vitamin K antagonists oral anticoagulants (NOAC) registry examined prospectively collected data to evaluate the impact of BMI on cardiovascular events, major bleeding, and all-cause mortality [10]. Overall, rates of all clinical outcomes were lowest among overweight and obese patients compared with normal-weight patients, which suggested that elevated BMI was not associated with a lack of DOAC effectiveness or safety.

Despite similarities between treatment groups, the VTE recurrence risk of approximately 16% in both groups in this analysis was higher than rates reported in clinical trials and observational studies, as well as previous small outcome studies in morbid obesity [10,11]. VTE is often a chronic condition, with annual recurrence rates of 5% to 10% [17,18]. The risk is highest in the 6 to 12 months after stopping anticoagulant therapy. A specific explanation for the observed rate in the current study may be due to an increased risk of VTE in obese individuals [17,19]. In a cohort study of 1107 patients followed for 46 months after a first VTE and withdrawal of anticoagulant therapy, the frequency of recurrent VTE at 4 years was 9.3% among patients with a normal BMI and 17.5% among obese patients (BMI ≥ 30 kg/m^2) [3]. The adjusted HR of recurrence was 1.6 (95% CI: 1.1–2.4; $P = 0.02$) for obese individuals compared with those of normal body weight. The population attributable risk of recurrent VTE corresponding to excess body weight was 26.8%. Other studies have shown a 2-fold or greater increase in the risk of VTE in obese patients [20–22]. Thus, obesity is an important risk factor for recurrent VTE and should be considered along

with other risk factors when evaluating the need for anticoagulant therapy [23].

In this analysis, ER claims were included to capture patients who were treated and released because many patients with DVT and low-risk PE can be treated as outpatients [24]. Sensitivity analyses showed a 50% reduction in rate of recurrent VTE when only patients with a primary inpatient diagnosis of VTE were included. Furthermore, by restricting the recurrent VTE definition to a primary inpatient diagnosis and a primary imaging code during follow-up, the rate of recurrent VTE was further reduced (≤3%) and consistent with rates reported in randomized clinical trials. ER coding may be limited by differences in dataset availability and lack of specificity. An analysis of Medicare data identified differences in ER events based on provider versus facility claims, including overcounting ER events for patients who may have emergency services outside the ER [25]. Additionally, as more patients with VTE are evaluated for outpatient therapy, coding may be less specific in the ER. For example, diagnostic coding in the ER represents a snapshot in time and may change as new information is collected on a patient's clinical course, medical history, and various investigations [26].

Another factor in the risk of recurrent VTE is persistence of anticoagulant therapy. A systematic review of 12 observational studies found the estimated persistence for 3, 6, and 12 months of therapy was 83%, 62%, and 31%, respectively [27]. Only 2 studies reported risk of VTE recurrence: patients who discontinued warfarin treatment within 3 months had a 45% increased risk compared with those who discontinued at or after 3 months and patients who were nonpersistent or discontinued within 12 months had a 48% increased risk compared with those who were persistent for 12 months. These data indicate that persistence of anticoagulant is suboptimal, worsens over time, and contributes to an increased risk of recurrent VTE. However, our data reassuringly suggests that comparable VTE recurrence rates of rivaroxaban versus warfarin exist across our primary outcome and subsequent sensitivity analyses.

To the authors' best knowledge, this is also the first study to assess healthcare resource utilization and costs between a DOAC such as rivaroxaban and warfarin in morbidly obese patients. Treatment with rivaroxaban was associated with significantly lower healthcare resource utilization, particularly for hospitalizations and outpatient visits, whether we used the ITT or on-treatment analysis. One contributing factor, particularly for outpatient visits, may be the lack of routine monitoring of the anticoagulant effect of rivaroxaban. In contrast, patients receiving warfarin had an average of 14 claims annually for INR monitoring, which is consistent with that found in real-world practice settings for warfarin monitoring [28]. Another contributing factor in lower healthcare utilization may have been the reduction in major bleeding with rivaroxaban when compared to warfarin as noted in ≥1 of our analyses (ITT), with numerically fewer major bleeding events with rivaroxaban in the on-treatment analysis that did not reach statistical significance. This observation of an improved safety profile of DOACs over warfarin has been consistently shown in the pivotal trials [6,29,30]. As a result of difference in healthcare resource utilization, total medical costs were significantly lower by nearly $3000 in the ITT analysis and by nearly $4800 in the on-treatment analysis for rivaroxaban patients compared with warfarin patients. When pharmacy costs were added to medical costs, total healthcare costs remained numerically lower for rivaroxaban versus warfarin but the difference was no longer statistically significant in the ITT analysis. In the on-treatment analysis, total healthcare costs were $2600 lower with rivaroxaban versus warfarin ($P = 0.049$). Rivaroxaban has previously been shown to be cost-effective compared to enoxaparin and vitamin K antagonist therapy with a savings of $2448 per patient based on the EINSTEIN trials [31].

This study analyzed claims from 2 large databases and included geographically diverse patients that included > 40% of morbidly obese VTE patients who were treated with rivaroxaban, which suggests that this was a relevant subgroup to analyze; however, our results are likely more generalizable to a population of insured morbidly obese VTE patients and not the entire US population. The study is limited by the potential for inherent coding errors and inconsistencies in administrative claims data. These coding limitations may include the exact timing of VTE recurrence and treatment discontinuation. Based on previous studies about VTE recurrence [27,32], we expect that most events occur after treatment discontinuation. Selection bias was reduced with the use of propensity score matching, which took into account a wide range of potential measurable confounders, but residual confounding could not be excluded due to potential unmeasured confounders that were not included when matching our 2 cohorts. Longitudinal analysis of outcomes was accomplished by requiring ≥ 15 months of continuous health plan enrollment. The use of ITT and on-treatment analyses allowed consideration of continued anticoagulant use, with consistent results among both the ITT and on-treatment groups, although a claim for dispensed medication does not confirm that the medication was taken as prescribed. In addition, data regarding INR and time in therapeutic range for patients receiving warfarin were not available in the databases. The identification of morbid obesity by using diagnostic codes has been associated with substantial underreporting in administrative databases [13]. Although addition of height and body weight information would have been optimal to define morbid obesity, we were not able to do this in our analysis due to lack of uniform availability of these variables. However, the claims codes used in this study have previously been shown to have high specificity [13,33]. Martin and colleagues found obesity coding was accurate with specificity of 98% and positive predictive value of 66% when it was coded in the database, and obesity coding could be used to identify a cohort for follow-up or outcome studies [13]. A recent study by Ammann and colleagues also confirmed high specificity (99%) of BMI-related codes for morbid obesity using the Optum Integrated Claims-Clinical Database [33]. Our study defined major bleeding using a validated claims-based algorithm [14]. Furthermore, a systematic review by Tamariz and colleagues demonstrated that the use of codes for both DVT and PE were associated with high positive predictive values for identifying a VTE event (65%–95%), which supports the accuracy of these codes for identifying VTE events in claims databases [34]. Finally, a prespecified exploratory analysis of morbidly obese patients who had undergone bariatric surgery was not possible due to very low patient counts (156 rivaroxaban and 267 warfarin patients).

To conclude, especially in light of perceptions that DOACs may be less effective due to relative underdosing in patients with increasing body weight, our data provide important information for morbidly obese patients with VTE. The risks of recurrent VTE and major bleeding were similar and suggest comparable efficacy of rivaroxaban as compared with warfarin in this population without routine laboratory measurement. Treatment with rivaroxaban was associated with less all-cause healthcare resource utilization and reduced total medical costs, although total healthcare costs were not significantly different between groups. Further large prospective studies specifically in morbidly obese patients are needed in VTE treatment comparing outcomes of DOACs to warfarin.

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Author contributions

A.C. Spyropoulos contributed to the concept and design, interpretation of data, and critical writing and revising the intellectual content. V. Ashton contributed to the concept and design, interpretation of data, and critical writing and revising the intellectual content. Y. Chen contributed to the analysis of data and critical writing and revising the intellectual content. B. Wu contributed to the analysis of data and critical writing and revising the intellectual content. E.D. Peterson contributed to the concept and design, interpretation of data, and

critical writing and revising the intellectual content. All authors gave final approval of the version to be published.

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Declaration of competing interest

A.C. Spyropoulos: Consultant/Advisory Board; Janssen Scientific Affairs, LLC.

V. Ashton: Employment; Janssen Scientific Affairs, LLC.

Y. Chen: Employment; Janssen Scientific Affairs, LLC.

B. Wu: Employment; Janssen Scientific Affairs, LLC.

E.D. Peterson: Consultant/Advisory Board; Janssen Scientific Affairs, LLC.

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