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Comparative effectiveness, safety, and costs of rivaroxaban and warfarin among morbidly obese patients with atrial fibrillation

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Background There are limited data regarding clinical outcomes and healthcare resource utilization of direct oral anticoagulants (DOACs) in patients with atrial fibrillation (AF) who are morbidly obese (body mass index >40 kg/m² or body weight >120 kg).

Methods Using data from 2 US healthcare claims databases, we identified patients initiating rivaroxaban or warfarin who had ≥1 medical claim with an AF diagnosis, a diagnostic code for morbid obesity (ICD-9: 278.01, V85.4%; ICD-10: E66.01%, E66.2%, Z68.4%), and a minimum continuous enrollment of 12 months before and 3 months after treatment initiation. Patients were excluded if they had mitral stenosis, a mechanical heart valve procedure, an organ/tissue transplant, or an oral anticoagulant prescription prior to the index date. Rivaroxaban and warfarin patients were 1:1 propensity score matched. Conditional logistic regression was used to compare ischemic stroke/systemic embolism and major bleeding risk. Generalized linear models were used to compare healthcare resource utilization and costs.

Results A total of 3563 matched pairs of morbidly obese AF patients treated with rivaroxaban or warfarin were identified. The majority (81.4%) of patients in the rivaroxaban cohort were receiving the 20 mg dose. The rivaroxaban and warfarin cohorts were well balanced after propensity score matching. The risks of ischemic stroke/systemic embolism and major bleeding were similar for rivaroxaban and warfarin users (stroke/systemic embolism: 1.5% vs 1.7%; odds ratio [OR]: 0.88; 95% confidence interval [CI]: 0.60, 1.28; P = .5028; major bleeding: 2.2% vs 2.7%; OR: 0.80; 95% CI: 0.59, 1.08; P = .1447). Total healthcare costs including medication costs per patient per year (PPPY) were significantly lower with rivaroxaban versus warfarin ($48,552 vs $52,418; P = .0025), which was primarily driven by lower hospitalization rate (50.2% vs 54.1%; P = .0008), shorter length of stay (7.5 vs 9.1 days; P = .0010), and less outpatient service utilization (86 vs 115 visits PPPY; P < .0001).

Conclusions Morbidly obese AF patients treated with rivaroxaban had comparable risk of ischemic stroke/systemic embolism and major bleeding as those treated with warfarin, but lower healthcare resource utilization and costs. (Am Heart J 2019;212:113-9.)

Obesity and morbid obesity are associated with a higher risk of developing atrial fibrillation (AF). Among obese patients, AF may be more severe and more persistent. The standard of care for long-term prevention of embolic events in patients with AF is oral anticoagulation. Warfarin and newer direct-acting oral anticoagulants (DOACs), such as rivaroxaban, have been shown to significantly reduce the risk of stroke in patients with AF. Rivaroxaban has also been associated with a reduction in intracranial hemorrhage compared with warfarin.

Pharmacokinetic parameters, including volume of distribution, half-life, and clearance, can be altered in obese patients, raising concerns about the potential effects of obesity on anticoagulant activity. Compared with patients with normal body weight, obese and morbidly obese patients receiving warfarin had a decreased initial response and longer time to achieve therapeutic international normalized ratio (INR) values (8 and 10 days, respectively,
Population pharmacokinetic and pharmacodynamic studies also indicate that high body weight does not have a clinically meaningful impact on rivaroxaban pharmacology.9 Unfortunately, no randomized controlled trials of DOACs have been conducted in large numbers of obese patients to determine the clinical effects of obesity on anticoagulant efficacy and safety; however, subgroup analyses of data from large phase 3 DOAC clinical trials suggest that the drugs are safe and efficacious in obese patients.14,15

In 2016, the Scientific and Standardization Committee (SSC) of the International Society of Thrombosis and Haemostasis (ISTH) reviewed the available data on DOAC use in obese patients and provided several guidance statements.8 The committee concluded that DOACs are safe and effective in obese patients with body mass index (BMI) ≤40 kg/m² or body weight ≤120 kg; however, limited data were available for patients with morbid obesity (BMI >40 kg/m² or body weight >120 kg), and the committee suggested that DOACs not be used in this population because of the potential for decreased drug exposures, reduced peak concentrations, and shorter half-lives, leading to potential underdosing. If DOACs are used in morbid obesity, specific pharmacokinetic monitoring was suggested, 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.

There is a need for studies that specifically examine outcomes of anticoagulation therapy among morbidly obese patients. Thus, to understand the impact of morbid obesity on real-world outcomes of anticoagulation among AF patients, US healthcare claims data were analyzed to compare the effectiveness, safety, and healthcare resource utilization and costs of a DOAC (rivaroxaban) and warfarin in this population.

Materials and methods
Study design

This retrospective cohort study combined data from the Truven MarketScan Commercial Claims and Encounters and Medicare Supplemental databases from December 1, 2010 to December 31, 2016. The MarketScan Commercial Claims and Encounters database includes approximately 138 million unique de-identified persons insured by employer-sponsored plans. The database contains inpatient admission records, outpatient services, prescription drugs, enrollment status, and costs of medical services and drugs. The Medicare Supplemental database includes health claims for Medicare-eligible active and retired employees and their dependents from employer-sponsored supplemental plans and contains person-specific clinical utilization, cost, and enrollment across inpatient, outpatient, prescription drug, and carve-out services.

Study population

Adult patients were eligible if they had ≥1 pharmacy claim for rivaroxaban or warfarin between December 1, 2011 and September 30, 2016. The first pharmacy claim date for rivaroxaban or warfarin was the index date. Patients were also required to have: (1) ≥1 medical claim with an AF diagnosis (International Classification of Diseases, Ninth Revision [ICD-9]: 427.31; ICD, Tenth Revision [ICD-10]: 148.0%, 148.2%, 148.91%) during the 12 months prior to or on the index date, (2) a minimum continuous health plan enrollment period of 12 months before and 3 months following the index date, and (3) ≥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%) during the 12-month baseline period through 3 months after the index date. Patients were excluded if they had mitral stenosis (ICD-9: 394.0%, 394.2%, 396.0%, 396.1%, 746.5%, 996.02, 996.71; ICD-10: 105.0%, 105.2%, 108.0%, 134.2%, Q23.2%, T82.0%, T82.827%, T82.837%, T82.847%, T82.857%, T82.867%, T82.879%, T82.9X%), a mechanical heart valve procedure (Current Procedural Terminology [CPT]: 33405, 33420, 33422, 33425, 33426, 33427, 33430, 92987), an organ/tissue transplant (ICD-9: V42.2%, V58.44; ICD-10: Z94.4%, Z48.8%), or an oral anticoagulant prescription prior to the index date.

Data analysis

Demographic variables, including age, gender, and insurance type (commercial or Medicare) were evaluated on the index date, and baseline characteristics, including Quan-Charlson Comorbidity Index (QCI) score,16 individual comorbid conditions (identified via ICD-9 or ICD-10 codes for the disease condition of interest; see Supplemental Table 1), and medication use, were measured during the 12-month baseline period. The modified CHA2DS2-VASc and HAS-BLED scores were measured at baseline to provide information about the risks of stroke and major bleeding in the patient cohorts. Modifications to estimate the CHA2DS2-VASc and HAS-BLED scores were measured at baseline to provide information about the risks of stroke and major bleeding in the patient cohorts. Modifications to estimate the CHA2DS2-VASc and HAS-BLED scores were measured at baseline to provide information about the risks of stroke and major bleeding in the patient cohorts. A modified HAS-BLED score of ≥3 indicated a high risk of major bleeding.18 The frequency and proportion of patients who had ≥1 prescription medication and mean (standard deviation [SD]) number of different pharmacy prescriptions used also were reported.

All-cause healthcare resource utilization and costs incurred during the 12-month baseline period and follow-up period were reported for each treatment
cohort. All-cause healthcare resource utilization included the frequency and proportion of patients who had ≥1 visit and the mean (SD) number of visits for inpatient hospitalization (including mean [SD] length of stay), emergency room (ER), physician office, outpatient services, skilled nursing facility (SNF), and pharmacy prescription(s). All costs were inflated to 2016 US dollars and reported as total medical cost (ie, costs for inpatient hospitalization, ER, physician office, outpatient services, and SNF/long-term care), and total pharmacy prescription cost. The mean number of INR measurements per patient per year (PPPY) was identified based on CPT code 85610 during the follow-up period and was reported for the warfarin cohort to evaluate whether warfarin patients were being routinely monitored. Limited data on anti-FXa measurement were available in the databases (0.3% of rivaroxaban patients had an anti-FXa test); thus, no analysis of the measurement of rivaroxaban’s anticoagulant activity using anti-FXa was conducted.

Statistical analysis

Comparable rivaroxaban and warfarin cohorts were created at a 1:1 ratio using propensity score-matching techniques. A logistic regression model calculated propensity scores for each patient based on independent variables (Supplemental Table I) of demographic and baseline characteristics and a dependent variable of whether the patient initiated rivaroxaban or warfarin treatment. The primary outcome compared between treatment cohorts was the composite risk of ischemic stroke and systemic embolism, calculated as the proportion of patients with an ischemic stroke and systemic embolism (defined as hospitalization or ER visit with a primary diagnosis of ischemic stroke and systemic embolism, respectively, during the follow-up period) divided by the total number of patients in the treatment cohort. The mean (SD) number of ischemic stroke/systemic embolism events PPPY and the time to first event (from 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 during the follow-up period, and risk, number of events, and time-to-event measures were calculated as per the primary outcome. Multivariable regression models compared outcomes between propensity score–matched treatment cohorts. Odds ratios (OR), 95% confidence intervals (CI), and P values were calculated. All statistical analyses were conducted using SAS Enterprise Guide 7 (Cary, NC).

Funding

This study was funded by Janssen Scientific Affairs, LLC. Programming support was provided by Kamal Kant Mangla of Mu Sigma Business Solutions Pvt. Ltd. (Bengaluru, India). Medical writing support was provided...
Table II. Risk of ischemic stroke/systemic embolism and major bleeding with rivaroxaban and warfarin

<table>
<thead>
<tr>
<th>Estimate* (95% CI)</th>
<th>Rivaroxaban (n = 3563)</th>
<th>Warfarin (n = 3563)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time, months, mean (SD)</td>
<td>10.27 (2.89)</td>
<td>10.56 (2.70)</td>
<td>−0.29 (−0.42, −0.16)</td>
</tr>
<tr>
<td>Composite risk of ischemic stroke/systemic embolism</td>
<td>52 (1.5%)</td>
<td>59 (1.7%)</td>
<td>0.88 (0.60, 1.28)</td>
</tr>
<tr>
<td>Number of composite events (PPPY), mean (SD)</td>
<td>0.001 (0.046)</td>
<td>0.002 (0.048)</td>
<td>−0.01 (−0.02, 0.01)</td>
</tr>
<tr>
<td>Time to first composite event, days, mean (SD)</td>
<td>111.87 (107.01)</td>
<td>125.90 (105.64)</td>
<td>0.90 (0.62, 1.30)</td>
</tr>
<tr>
<td>Risk of major bleeding, n (%)</td>
<td>77 (2.2)</td>
<td>96 (2.7)</td>
<td>0.80 (0.59, 1.10)</td>
</tr>
<tr>
<td>Number of major bleeding events (PPPY), mean (SD)</td>
<td>0.03 (0.20)</td>
<td>0.03 (0.22)</td>
<td>−0.01 (−0.01, 0.01)</td>
</tr>
<tr>
<td>Time to first major bleeding event, days, mean (SD)</td>
<td>127.99 (97.72)</td>
<td>147.56 (110.65)</td>
<td>0.82 (0.61, 1.10)</td>
</tr>
</tbody>
</table>

CI, confidence interval; PPPY, per patient per year; SD, standard deviation.

*Odds ratio, difference in means and hazard ratios were used for ischemic stroke/systemic embolism risk, risk of major bleeding, number of ischemic stroke/systemic embolism and major bleeding events, and time to first event, respectively. Statistical comparisons are comparing rivaroxaban to warfarin (reference group).

†An ischemic stroke event and systemic embolism event were defined as a hospitalization or emergency room visit with a primary diagnosis of ischemic stroke and systemic embolism, respectively, during follow-up. Risk of ischemic stroke/systemic embolism was measured by estimating the proportion of at-risk patients who had 1 ischemic stroke/systemic embolism event during follow-up.

‡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.

by Ashley O’Dunne, PhD, of MedErgy (Yardley, PA, USA), which was funded by Janssen Scientific Affairs, LLC (Titusville, NJ, USA).

Results

Across the 2 databases, 267,467 adult patients met entry criteria with ≥1 pharmacy claim for rivaroxaban or warfarin, ≥1 medical claim for a diagnosis of AF, and 12 months of continuous plan enrollment prior to the index date. Patients were excluded for oral anticoagulant use between study start and index date (n = 144,340) and for mitral stenosis, mechanical heart valve procedure, or transplants (n = 9261). Of the 103,837 with continuous use between study start and index date (n = 144,340) and 12 months of continuous plan enrollment prior to the index date, 9474 (9%) patients. Demographic and baseline characteristics for patients before propensity score matching are shown in Table I. The majority (81.4%) of patients in the rivaroxaban cohort were receiving the 20 mg dose. Patients receiving warfarin were older, were more likely to be female, and had higher risk scores and more comorbidities and pharmacy prescriptions compared with those receiving rivaroxaban. Significant differences between treatment cohorts were found for all characteristics, except the presence of hypertension and hyperlipidemia. Propensity score matching was successful for 3563 matched pairs of patients with AF and morbid obesity who initiated treatment with either rivaroxaban or warfarin (Table I). The mean follow-up time was 10.3 months and 10.6 months for rivaroxaban and warfarin, respectively.

The composite risk of ischemic stroke and systemic embolism was not significantly different between patients receiving rivaroxaban (1.5%) and those receiving warfarin (1.7%; OR: 0.88, 95% CI: 0.60, 1.28; P = .5028; Table II). The number of ischemic stroke/systemic embolism events PPPY was also similar between groups (rivaroxaban, 0.001; warfarin, 0.002; P = .3592). The time to first composite event was 111.9 days with rivaroxaban compared with 125.9 days with warfarin, a difference that was not significant (P = .5690).

Similarly, the risk of major bleeding was not significantly different between treatment cohorts (rivaroxaban, 2.2%; warfarin, 2.7%, OR: 0.80, 95% CI: 0.59, 1.08; P = .1447; Table II). The number of major bleeding events was the same for both groups (0.03; P = .2570) and the time to first event was 128.0 days for rivaroxaban and 147.6 days for warfarin (P = .1878).

Despite similar effectiveness and safety, rivaroxaban patients had an average of $3890 lower total healthcare costs PPPY than warfarin patients ($48,552 vs $52,418, 95% CI: −$6260, −$1398; P = .0025; Figure 1). The differences in cost were mainly driven by a lower hospitalization rate (50.2% vs 54.1%, OR: 0.85, 95% CI: 0.78, 0.94; P = .0008), shorter length of stay (7.5 vs 9.1 days, difference in mean: −1.61, 95% CI: −2.57, −0.65; P = .0010), and less outpatient service utilization (86 vs 115 visits, difference in mean: −28.81, 95% CI: −32.06, −25.53; P < .0001) PPPY with rivaroxaban compared with warfarin, respectively (Table III). The average number of INR events PPPY for warfarin users was 11 (SD, 11.4).

Discussion

The results of this study indicate that AF patients with morbid obesity initiating rivaroxaban or warfarin had similar risks of ischemic stroke/systemic embolism and major bleeding in clinical practice. These results are consistent with the ROCKET-AF clinical trial findings that demonstrated comparable efficacy and safety of rivaroxaban versus warfarin in patients with diverse body weights. In the current database analysis, risks of stroke/systemic embolism (1.5% and 1.7%) and major bleeding (2.2% and 2.7%) were slightly lower than those reported in the clinical trial. Interestingly, a lower risk of stroke and mortality has been observed with increasing
BMI in AF patients. This “obesity paradox” was most evident in cohorts from randomized controlled trials. Lower mortality rates with increasing BMI category were also observed in the GARFIELD AF registry and the ORBIT-AF registry. Proietti and colleagues also reviewed the obesity paradox data in AF patients and found that the difference in adverse outcomes, stroke or systemic embolic event, was not apparent in observational studies after statistical adjustment for associated comorbidities in obese patients because of more intense risk factor management and improved outcomes. Our data suggest that morbidly obese patients with AF who

**Figure 1**

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 AF. AF, atrial fibrillation; ER, emergency room; PPPY, per patient per year; SNF, skilled nursing facility.
Table III. Healthcare resource utilization and length of stay associated with rivaroxaban and warfarin use in morbidly obese patients with AF

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n = 3563)</th>
<th>Warfarin (n = 3563)</th>
<th>Estimate* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause healthcare resource utilization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with ≥ 1 event of interest, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient hospitalization</td>
<td>1787 (50.2)</td>
<td>1929 (54.1)</td>
<td>0.85 (0.78, 0.94)</td>
<td>.0008</td>
</tr>
<tr>
<td>ER visit</td>
<td>1011 (28.4)</td>
<td>1149 (32.2)</td>
<td>0.83 (0.75, 0.92)</td>
<td>.0004</td>
</tr>
<tr>
<td>Office visit</td>
<td>3484 (97.8)</td>
<td>3485 (97.8)</td>
<td>0.99 (0.72, 1.36)</td>
<td>.9351</td>
</tr>
<tr>
<td>Outpatient visit</td>
<td>3549 (99.6)</td>
<td>3547 (99.6)</td>
<td>1.14 (0.56, 2.34)</td>
<td>.7152</td>
</tr>
<tr>
<td>SNF/long-term care</td>
<td>286 (8.0)</td>
<td>344 (9.7)</td>
<td>0.81 (0.68, 0.96)</td>
<td>.0131</td>
</tr>
<tr>
<td>Number of events of interest (PPPY), mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient hospitalization</td>
<td>1.48 (2.76)</td>
<td>1.90 (3.81)</td>
<td>−0.41 (−0.52, −0.29)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ER visit</td>
<td>0.52 (1.12)</td>
<td>0.63 (1.53)</td>
<td>−0.11 (−0.16, −0.06)</td>
<td>.0001</td>
</tr>
<tr>
<td>Office visit</td>
<td>15.50 (10.87)</td>
<td>19.21 (14.03)</td>
<td>−3.72 (−4.21, −3.21)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Outpatient visit</td>
<td>86.01 (78.53)</td>
<td>114.82 (130.66)</td>
<td>−28.81 (−32.06, −25.43)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pharmacy fill</td>
<td>60.73 (36.35)</td>
<td>64.14 (37.83)</td>
<td>−3.42 (−4.99, −1.81)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Length of hospital stay, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among all patients</td>
<td>7.45 (19.52)</td>
<td>9.06 (21.76)</td>
<td>−1.61 (−2.57, −0.65)</td>
<td>.0010</td>
</tr>
<tr>
<td>Among patients with ≥1 hospitalization</td>
<td>14.85 (25.49)</td>
<td>16.74 (27.32)</td>
<td>−1.88 (−3.59, −0.18)</td>
<td>.0302</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CI, confidence interval; ER, emergency room; PPPY, per patient per year; SD, standard deviation; SNF, skilled nursing facility.
* Odds ratio was used for categorical variables, and difference in means was used for continuous variables.

were matched for comorbidities and underlying risks can achieve similarly effective anticoagulation with rivaroxaban as with warfarin. These data are valuable because they provide real-world outcomes for the morbidly obese population with AF.

While providing similar effectiveness and safety, treatment with rivaroxaban was associated with significantly lower healthcare resource utilization and costs than warfarin in this patient population. Routine monitoring of the anticoagulant effect of rivaroxaban using specialized coagulation assays, such as anti-FXa, was not routinely done, which may contribute to the large difference in outpatient visits between treatment groups. Patients receiving warfarin had an average of 11 claims annually for INR monitoring. This nearly monthly INR monitoring is consistent with the frequency of INR monitoring found in real-world practice settings for warfarin monitoring.21

In addition to fewer outpatient visits, rivaroxaban treatment also resulted in a significantly lower hospitalization rate and shorter length of hospital stay. Laliberté and colleagues compared healthcare costs between AF patients regardless of body weight or BMI using rivaroxaban and a matched sample of patients using warfarin and found that (similar to results of the current study in morbidly obese AF patients) all-cause hospitalization and outpatient costs were significantly lower for AF patients treated with rivaroxaban compared to those treated with warfarin.22 Treatment with rivaroxaban appears to result in less interaction with healthcare systems, either on an inpatient or outpatient basis, 22 which is consistent with the current study findings.

This study has several strengths, including the availability of a large dataset of obese patients with geographically diverse claims data to increase the generalizability of the data and its analyses. Propensity score matching reduced selection biases from measured confounders, such as comorbidities, and improved the internal validity of the estimates. At least 15 months of continuous health plan enrollment in this retrospective study enabled researchers to better understand the population characteristics and longitudinally evaluate outcomes during the follow-up period without interruption. Study limitations include the use of administrative claims data that, in general, are subject to potential coding errors and inconsistencies. The presence of a claim for a dispensed prescription does not indicate that the medication was consumed or that it was taken as prescribed. Also, the use of diagnosis codes to identify obesity may underestimate this patient population, as height and weight are not available in claims data to confirm BMI status. Martin and colleagues assessed the validity of obesity coding in an administrative database and found substantial underreporting.23 However, once obesity was coded, it was done accurately and could be used to identify a cohort for follow-up or outcomes studies.23 The addition of height and body weight information into routine administrative data coding could eliminate inconsistencies between clinician observation and patient reporting and improve data resources for population-based studies.25

These real-world data add to the clinical and pharmacologic data supporting the use of rivaroxaban in morbidly obese patients with AF. The risks of ischemic stroke/systemic embolism and major bleeding were comparable with rivaroxaban and warfarin in this patient population. In addition to similar outcomes, healthcare
costs were significantly lower with rivaroxaban as a result of fewer inpatient and outpatient visits compared with warfarin.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.02.001.

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Declaration of interests

E. D. Peterson: 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.

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

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Previous Presentation


References


