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ORIGINAL RESEARCH

Comparative Bleeding Risk of Brand Vs Generic Rivaroxaban in Elderly Inpatients with Atrial Fibrillation

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Video abstract

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Objective: Atrial fibrillation (AF) is the most common abnormal heart rhythm in elderly patients. Rivaroxaban has been widely used for stroke prevention. The anticoagulant response to rivaroxaban increases with age, which may make elderly patients susceptible to adverse outcomes resulting from small differences in bioavailability between generic and brand products.

Methods: We designed a cohort study of ≥65-year-old inpatients with AF. Sociodemographic and laboratory measures of qualified patients who received brand or generic rivaroxaban for at least 72 hours at the study hospital from January 2021 to June 2023 were collected retrospectively. The primary outcome was the incidence of bleeding.

Results: A total of 1008 qualifying patients were included for analysis, with 626 (62.1%) receiving brand rivaroxaban and 382 (37.9%) receiving generic rivaroxaban. After propensity score matching and weighting to account for confounders, the odds ratios comparing brand vs generic rivaroxaban (95% confidence intervals) for the bleeding was 1.15 (0.72–1.82). Results from subgroup analyses of patients with age ≥85, HAS-BLED score ≥ 3, containment of antiplatelet drugs, and female patients were consistent with the primary analysis.

Conclusion: It provides evidence regarding the clinical safety outcome of generic rivaroxaban in the elderly AF population that may be particularly susceptible to adverse outcomes resulting from small allowable differences in pharmacokinetics.

Keywords: bleeding, rivaroxaban, generic, brand, atrial fibrillation

Introduction

Generic medicine contains the same active substance(s) as brand/reference medicine and is bioequivalent to brand/reference medicine. Generally, generic medicine[1] is considered to be comparable to brand/reference medicine in dosage form, route of administration, and treatment characteristics. In the context of increasing global healthcare expenditure, generic medicine utilization is often encouraged as a cost-containment measure, which can be priced as low as 2–10% of pre-patent loss prices.[2] While the negative opinions about generic medicines by both professionals and the general public interfere with the acceptance of generic medicines in healthcare provision.[3]

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in elderly patients.[4] Rational anticoagulation for stroke prevention is one of the pillars of AF management.[5] Direct oral anticoagulants (DOACs) are now recommended as first-line therapy by up-to-date guidelines.[6,7] Rivaroxaban[8] is a direct factor Xa inhibitor, targeting free and clot-bound coagulation factor Xa and blocking the common coagulation pathway. Despite a better safety profile than warfarin,[9] as more patients are being treated with rivaroxaban, the absolute number of bleeding events increases.[10]

Advanced age[11] is a shared risk factor for both thromboembolic and bleeding events. Additionally, elderly patients frequently face challenges such as polypharmacy, poor medication adherence, impaired liver and kidney

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function, and increased risk of falls and undernutrition,[12–14] which make them more susceptible to suboptimal anticoagulation or excessive anticoagulation when receiving rivaroxaban treatment. Elderly subjects exhibited higher plasma concentrations, with mean AUC values being 41% higher in the elderly than in younger subjects.[15] When formulating an individualized anticoagulation regimen for elderly patients with AF, the consistency of safety and efficacy between brand and generic rivaroxaban has been a main clinical concern.

Given the wide use of rivaroxaban, it is important to assess whether small allowable differences in bioavailability between brand and generic versions are associated with differences in clinical outcomes in the real world. Currently, no studies have been conducted to compare the clinical outcomes between generic and brand rivaroxaban. To that end, we designed this study of 65 years or older inpatients with AF to compare clinical adverse outcomes between generic and brand rivaroxaban.

Methods

Study Design and Participants

This retrospective observational study was approved by the ethics review board of Jinhua Municipal Central Hospital ((2023) Ethics approval No. (03)); the process of patient consent was waived. Records that identified the subject of the study were kept confidential. This study was conducted according to the Declaration of Helsinki, ethical principles of medical research involving human subjects. The electronic medical records of patients who were treated with the brand (Bayer AG Co. Ltd., Germany) and generic (Guangdong Dongyangguang Pharmaceutical Co. Ltd., China) rivaroxaban between January 1, 2021, and June 30, 2023 were consecutively reviewed. Patients were classified into two exposure groups: generic group and brand group.

The inclusion criteria were: (1) age≥65 years, regardless of gender; (2) received brand or generic rivaroxaban for at least 3 days; (3) diagnosis of AF (identified by 12-lead electrocardiogram with no discernible repeating P waves and irregular RR intervals). The exclusion criteria were: (1) switching to other oral anticoagulants from rivaroxaban during hospitalization; (2) alternating between generic and brand rivaroxaban during hospitalization; (3) creatinine clearance < 30mL/min (calculated by the Cockcroft-Gault equation).

Outcomes

The primary outcome was bleeding events during hospitalization. Bleeding events were classified according to the criteria of a previous pivotal trial of rivaroxaban,[16] including major bleeding, clinically relevant non-major (CRNM) bleeding, and minor bleeding.

Covariates

We identified 50 potential confounders according to the electronic medical records. Specifically, the confounders that were collected from the medical records included: (i) patient demographics (age, sex, weight, BMI, educational level, current tobacco use, and current alcohol use, blood pressure); (ii) comorbid conditions, including hypertension, diabetes, cancer, heart failure, coronary heart disease, hyperthyroidism, hypothyroidism, vascular disease (including myocardial infarction, peripheral arterial disease or aortic plaque), and history of bleeding, thrombosis, gastrointestinal disorders; (iii) comedications, including concurrent use of proton pump inhibitors (PPIs), amiodarone, azole antifungal drugs, antiplatelet drugs, and nonsteroidal anti-inflammatory drugs (NSAIDs); (iv) coagulation features, including international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen (FIB), thrombin time (TT), D-Dimer (DD); (v) biochemical and blood routine indicators including, total bilirubin, albumin, creatinine, hemoglobin, platelet, creatinine clearance (CrCl); (vi) composite scores, including CHA2DS2-VASc (stroke and thromboembolism risk of assessment tool), HAS-BLED (bleeding risk assessment tool), and Child-Turcotte-Pugh (CTP, liver function evaluation tool).

Statistical Analysis

Patient characteristics were summarized using descriptive statistics in both exposure groups. Continuous variables are expressed as the median (interquartile range). Categorical variables are expressed as a number (%). Continuous variables

were analyzed using Mann–Whitney *U*-test, and proportions were compared using Pearson's chi-squared and Fisher's exact tests.

We performed a power analysis that concluded the inclusion of 382 patients at bleeding rates of 40% for generic rivaroxaban and 626 patients of 30% for brand rivaroxaban[17–19] would yield a statistical power of 90% at a significance level of alpha equal to 0.05 for a two-tailed analysis.

Characteristic variables were inspected for missing values and the proportion of missing data ranged from 0 to 25.1% (Figure S1). Missing data were imputed by multiple imputations by chained equations with the MICE package (https://github.com/amices/mice), in which predictive mean matching is embedded with the cases (k)=20.[20] Model estimates and standard errors were calculated with Rubin's rules.[21] A complete case analysis was also performed to assess the sensitivity of our imputation strategy.

Two propensity score (PS)-based methods were applied to reduce the effects of confounding using the MatchThem package (https://github.com/FarhadPishgar/MatchThem). The individual PS of being in each treatment group was calculated with an ordinary logistic regression model on all measured baseline covariates. Absolute standardized difference (ASD) of all baseline covariates was used to evaluate the balance between the two groups. When ASDs were ≤0.1 (10%) in all covariates, the two groups were well-balanced.[22]

The primary analysis used inverse probability of treatment weighting (IPTW). Univariate logistic regression analysis was performed to compare the rates of clinical events between the two groups. A secondary analysis was conducted by propensity-score matching (PSM). We matched generic and brand rivaroxaban recipients using a nearest-neighbor algorithm, within calipers of 0.05 units on the propensity score scale. Maximum absolute standardized mean differences and maximum Kolmogorov–Smirnov were calculated for each covariate in weighted and matched datasets to evaluate the balance.

Our research was performed according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidance[23] (Table S1). We considered a 2-sided P value of <0.05 to be statistically significant. The statistical analyses were performed with the use of R software, version 4.3.2 (R Project for Statistical Computing).

Subgroup Analyses

The following subgroups were specified to further evaluate the comparative outcomes of generic and brand rivaroxaban: (i) patients at high risk for bleeding, defined as HAS-BLED score of 3 or higher; and (ii) extremely elderly patients aged over 85 years old; and (iii) patients with concomitant antiplatelet use, and (iv) female patients.

Results

Between January 1, 2021 and June 30, 2023, a total of 3466 patients were identified. Following the exclusion of 2438 patients, 1008 qualifying patients were included for analysis, with 626 (62.1%) receiving brand rivaroxaban and 382 (37.9%) receiving generic rivaroxaban. The flow diagram of this study is shown in Figure 1.

The demographic and clinical characteristics of the patients are summarized in Table 1. The median age in both groups was 79 years and the proportion of female patients was lower than that of males (45.2% females and 54.8% males in total), with a balanced distribution between brand and generic groups. The generic group had a lower proportion with thrombotic history (25.7% vs 35.0%). Smoking prevalence and proportion with CHA2DS2-VASc ≥3 was higher among the brand group. The generic group was noted to be healthier with a lower prevalence of several comorbid conditions, including heart failure (33.8% vs 40.6%), and coronary heart disease (34.6% vs 42.5%), compared with the brand group. The most common dosing strategy was 10 mg once daily (62.2%), followed by 15 mg once daily (27.1%). The median treatment course was 6 (IQR 4–8) days in the brand group and 5 (IQR 4–8) days in the generic group. The proportion of concomitant use of amiodarone (16.3% vs 11.5%) and antiplatelet drugs (23.6% vs 15.2%) in the brand group were greater than that of the generic group. After propensity score adjustments, the number of variables with ASD greater than 0.1 decreased from 15 to 2. (Table S2).

Among the 1008 patients included in the analysis, bleeding events developed in 140 patients (13.9%); a total of 117 (11.6%) patients with minor bleeding, 17 (1.7%) with clinically relevant non-major bleeding, and 6 (0.6%) with major bleeding (Table 2). In the crude unadjusted analysis, patients who received generic rivaroxaban were more likely to suffer bleeding events than

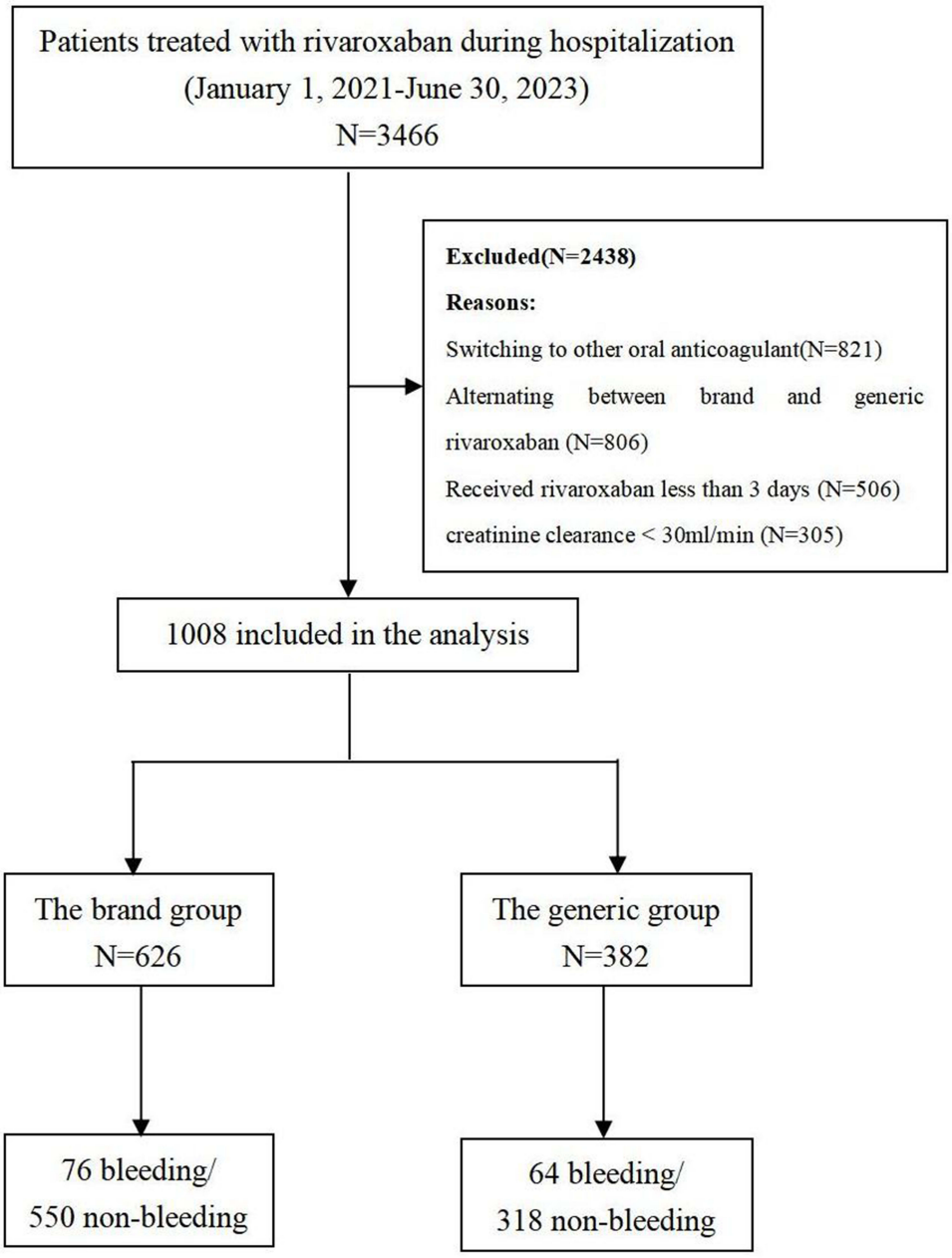

Figure 1 The flow diagram of study.

patients who received brand rivaroxaban (odds ratio, 1.46; 95% CI, 1.02 to 2.09) (Figure 2). In the primary multivariable analysis with IPTW according to the propensity score, there was no significant association between generic rivaroxaban use and the bleeding events (odds ratio, 1.15; 95% CI, 0.72 to 1.82) (Figure 2). Additional multivariable analyses with PSM yielded similar results (odds ratio, 1.04; 95% CI, 0.62 to 1.72) (Figure 2). The result of the complete case analysis was consistent with the primary analysis (Table S3).

Among subgroups of patients older than 85 years (odds ratio, 1.46; 95% CI, 0.55 to 3.86), containment of antiplatelet drugs (odds ratio, 0.73; 95% CI, 0.22 to 2.37), and with high bleeding risk (odds ratio, 0.98; 95% CI, 0.29 to 2.37), and female patients (odds ratio, 1.42; 95% CI, 0.69 to 2.94), the result for bleeding events was consistent with the primary analysis indicating no differences in rates between brand and generic groups (Figure 2).

Table 1 Demographics and Clinical Characteristics in Patients Treated with Brand and Generic Rivaroxaban

Variables	Total (n=1008)	Brand Group (n=626)	Generic Group (n=382)	ASD
Personal characteristics				
Gender (female) n(%)	456 (45.2)	283 (45.2)	173 (45.3)	0.002
Age, years, (median [IQR])	79.00 [73.00, 85.00]	79.00 [74.00, 85.00]	79.00 [73.00, 85.00]	0.09
Weight, kg, (median [IQR])	60.00 [51.00, 70.00]	60.00 [52.00, 70.00]	61.00 [51.00, 69.00]	0.023
BMI, kg/m^2 (median [IQR])	22.99 [20.42, 25.71]	22.89 [20.28, 25.71]	23.18 [20.76, 25.78]	0.038
Educational_level[a] (high) n(%)	128 (12.7)	85 (13.6)	43 (11.3)	0.07
Systolic_pressure (median [IQR])	139.00 [126.00, 156.00]	139.00 [126.00, 156.00]	139.00 [127.00, 154.00]	0.024
Current_tobacco_use (yes) n(%)	114 (11.3)	81 (12.9)	33 (8.6)	0.139
Current_alcohol_use (yes) n(%)	99 (9.8)	67 (10.7)	32 (8.4)	0.079
History_of_digestive_diseases (yes) n(%)	182 (18.1)	115 (18.4)	67 (17.5)	0.022
Bleeding_history (yes) n(%)	43 (4.3)	26 (4.2)	17 (4.5)	0.015
Thrombotic_history (yes) n(%)	317 (31.4)	219 (35.0)	98 (25.7)	0.204
CHA2DS2VASc (≥3) n(%)	842 (83.5)	534 (85.3)	308 (80.6)	0.168
HAS_BLED (≥3) n(%)	221 (21.9)	144 (23.0)	77 (20.2)	0.058
Comorbid conditions				
Hypertension (yes) n(%)	702 (69.6)	442 (70.6)	260 (68.1)	0.055
Diabetes (yes) n(%)	243 (24.1)	151 (24.1)	92 (24.1)	0.001
Cancer (yes) n(%)	87 (8.6)	48 (7.7)	39 (10.2)	0.089
Heart_failure (yes) n(%)	383 (38.0)	254 (40.6)	129 (33.8)	0.141
Coronary_heart_disease (yes) n(%)	398 (39.5)	266 (42.5)	132 (34.6)	0.164
Hyperthyroidism (yes) n(%)	14 (1.4)	6 (1.0)	8 (2.1)	0.093
Hypothyroidism (yes) n(%)	52 (5.2)	38 (6.1)	14 (3.7)	0.112
Vascular_disease (yes) n(%)	246 (24.4)	138 (22.0)	108 (28.3)	0.144
Laboratory tests (median [IQR])				
Total_bilirubin, μmol/L	14.80 [11.40, 20.25]	14.40 [11.30, 19.50]	15.45 [11.43, 20.80]	0.039
Albumin, g/L	36.00 [33.10, 39.00]	35.90 [33.30, 39.20]	36.00 [33.10, 38.80]	0.068
Platelet, 10^9/L	168.00 [129.00, 211.00]	167.50 [131.00, 208.25]	169.00 [128.00, 215.00]	0.042
Hemoglobin, g/L	124.00 [109.00, 137.00]	124.00 [109.00, 137.25]	123.00 [106.00, 136.00]	0.047
INR	1.12 [1.03, 1.28]	1.14 [1.04, 1.29]	1.11 [1.02, 1.25]	0.096
CTP score	5.00 [3.00, 6.00]	5.00 [4.00, 6.00]	4.00 [3.00, 5.00]	0.789
CrCl, mL/min	45.07 [31.37, 58.14]	44.83 [31.92, 58.24]	45.53 [31.06, 57.57]	0.034
APTT, s	31.90 [29.30, 35.20]	31.85 [29.20, 35.10]	31.90 [29.60, 35.30]	0.129
FIB, g/L	3.35 [2.84, 3.96]	3.31 [2.82, 3.93]	3.43 [2.87, 3.99]	0.12

(*Continued*)

Table 1 (Continued).

Variables	Total (n=1008)	Brand Group (n=626)	Generic Group (n=382)	ASD
TT, s	15.70 [14.80, 16.60]	15.80 [14.80, 16.70]	15.70 [14.80, 16.60]	0.075
DD, μg/L	602.50 [296.00, 1188.75]	563.00 [291.25, 1185.00]	643.00 [316.25, 1204.25]	0.027
In-hospital treatment				
Dosing_regimen (%)				0.249
10mg qd	619 (62.2)	401 (64.1)	226 (59.2)	
15mg qd	273 (27.1)	152 (24.3)	121 (31.7)	
20mg qd	51 (5.1)	33 (5.3)	18 (4.7)	
5mg qd	23 (2.3)	19 (3.0)	4 (1.0)	
2.5mg bid	19 (1.9)	13 (2.1)	6 (1.6)	
15mg bid	7 (0.7)	4 (0.6)	3 (0.8)	
10mg bid	5 (0.5)	3 (0.5)	2 (0.5)	
7.5mg qd	2 (0.2)	0 (0.0)	2 (0.5)	
2mg qd	1 (0.1)	1 (0.2)	0 (0.0)	
Course /days (median [IQR])	6 [4, 8]	6 [4, 8]	5 [4, 8]	0.143
Co-medication				
Concomitant use of PPIs n(%)	436 (43.3)	265 (42.3)	171 (44.8)	0.049
Concomitant use of amiodarone n(%)	146 (14.5)	102 (16.3)	44 (11.5)	0.138
Concomitant use of AAD n(%)	10 (1.0)	9 (1.4)	1 (0.3)	0.128
Concomitant use of anti-platelet drugs n(%)	206 (20.4)	148 (23.6)	58 (15.2)	0.215
Concomitant use of NSAIDs n(%)	67 (6.6)	38 (6.1)	29 (7.6)	0.06

Note: [a]High school and above is defined as high level of educational attainment.
Abbreviations: ASD, absolute standardized difference; BMI, body mass index; IQR, interquartile range; INR, international normalized ratio; CTP, child-turcotte-pugh; CrCl, creatinine clearance; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen; DD, D-dimer; qd, once daily; bid, twice daily; PPIs, proton pump inhibitors; AAD, azole antifungal drugs; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2 The Incidence, Severity and Sites of Bleeding Events

Variables	Total (n=1008)	Brand Group (n=626)	Generic Group (n=382)
Bleeding_events (%)			
No	868 (86.1)	550 (87.9)	318 (83.2)
Yes	140 (13.9)	76 (12.1)	64 (16.8)
Bleeding_severity (%)			
\	868 (86.1)	550 (87.9)	318 (83.2)
Minor	117 (11.6)	61 (9.7)	56 (14.7)
CRNM	17 (1.7)	11 (1.8)	6 (1.6)
Major	6 (0.6)	4 (0.6)	2 (0.5)

(*Continued*)

Table 2 (Continued).

Variables	Total (n=1008)	Brand Group (n=626)	Generic Group (n=382)
Bleeding_site (%)			
\	868 (86.1)	550 (87.9)	318 (83.2)
Gastrointestinal bleeding	62 (6.2)	37 (5.9)	25 (6.5)
Hematuresis	58 (5.8)	28 (4.5)	30 (7.9)
Subcutaneous hemorrhage	7 (0.7)	2 (0.3)	5 (1.3)
Other sites	6 (0.6)	4 (0.6)	2 (0.5)
Epistaxis	4 (0.4)	3 (0.5)	1 (0.3)
Intracranial hemorrhage	3 (0.3)	2 (0.3)	1 (0.3)

Abbreviation: CRNM, clinically relevant non-major.

Discussion

In this observational study of 1008 AF inpatients 65 years or older, we did not identify substantial differences in bleeding events between those who were on brand or generic rivaroxaban. Further, no meaningful differences in various subgroups based on bleeding risk or age, suggesting equivalent safety outcomes between brand and generic rivaroxaban in older inpatients with AF. Results from our study add to the literature indicating therapeutic equivalence of brand and generic rivaroxaban. To the best of our knowledge, this is the first analysis to assess the safety of brand vs generic rivaroxaban in AF patients.

The most common adverse effect of rivaroxaban is bleeding-related events, which is the most important reason for patients to withdraw rivaroxaban.[24] These events can range from minor bruising or nosebleeds to more severe internal bleeding or hemorrhagic strokes. According to the data of previous clinical trial,[16] the incidence of major and clinically relevant nonmajor bleeding was 14.9% per year. The brand and generic versions of rivaroxaban might have slight differences in their inactive ingredients or formulation, which can affect their bioavailability or overall efficacy. This variation, although usually within acceptable limits, can lead to differences in how patients respond to rivaroxaban, which may induce more bleeding events in patients with generic rivaroxaban.

Several empirical studies[25,26] have provided largely consistent results regarding the safety and effectiveness of generic vs brand warfarin products. No significant differences were found in the rates of hospitalizations for bleeding or cerebral thromboembolism before and after the implementation of the generic warfarin substitution policy, based on a large ecological investigation from Canada.[27] There were no similar studies performed to assess the clinical equivalence between brand and generic rivaroxaban. Clinical studies and post-marketing surveillance are essential to gather data on the safety outcome between brand and generic rivaroxaban.

There were significant interactions[28,29] between age and treatment with rivaroxaban for the bleeding, with higher risks of bleeding observed with rivaroxaban (vs warfarin) in the elderly population. The anticoagulant response to rivaroxaban is exaggerated with advancing age.[30] Taken together, high use and potential for excessive anticoagulation make elderly AF patients more susceptible to adverse outcomes resulting from small allowable differences in the bioavailability of the generic rivaroxaban.

There are several strengths in our study. First, the use of electronic medical records allowed for accurate exposure classification into brand or generic rivaroxaban. Next, we incorporated and accounted for important confounding variables, including renal function, hepatic function, co-medication, as well as basic coagulation features. Further, the use of propensity score-based confounding adjustment reduced the likelihood that our findings were due to bias.

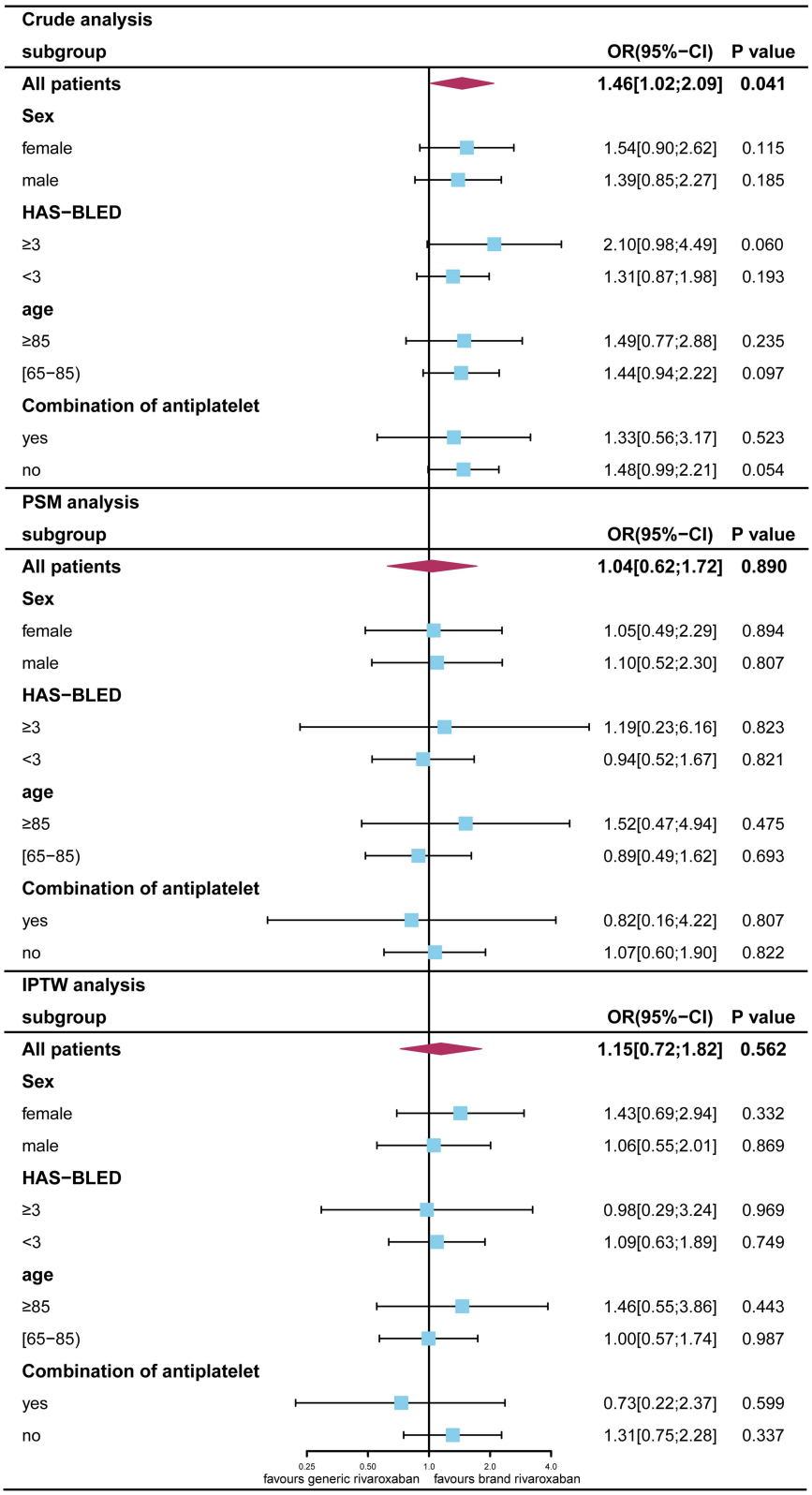

Figure 2 Comparing the bleeding risk of brand and generic rivaroxaban.
Abbreviations: OR, odds ratios; CI, confidence intervals; PSM, propensity-score matching; IPTW, inverse probability of treatment weighting.

Limitation

There were several limitations in this study. Firstly, there were inevitable biases in the nature of single-center retrospective design, such as the unbalanced distribution of several variables and the relatively low number of patients. We were limited in our ability to detect small differences between groups. Although PS adjustments were applied to adjust for the unbalanced covariates, multicenter prospective studies with larger sample sizes are still needed to verify the results. Secondly, only safety profile during hospitalization was considered. Medication compliance during hospitalization was generally good, with a low incidence of missed or incorrect dosages. Further research is required to assess whether the results could be generalized to outpatients. Thirdly, residual confounding cannot be ruled out. Limited to the feature of PS adjustment, the differences in unmeasured variables remained.

Conclusion

Comparable safety was observed between brand and generic rivaroxaban in a cohort of AF inpatients of 79 years of age on average. These results provide evidence regarding the clinical safety outcomes of generic rivaroxaban in this population that may be particularly susceptible to adverse outcomes resulting from small allowable differences in pharmacokinetics.

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Disclosure

The authors have no conflicts of interest to declare.

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