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Efficacy and Safety of Direct Oral Anticoagulants in Patients With Atrial Fibrillation Combined With Hypertension: A Multicenter, Retrospective Cohort Study

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Abstract

Whether there are differences in direct oral anticoagulants efficacy and safety in patients with atrial fibrillation (AF) combined with hypertension is unclear. We therefore conducted a multicenter retrospective cohort study to assess the differences in the efficacy and safety of direct oral anticoagulants in patients with AF combined with hypertension. This multicenter retrospective cohort study was based on data from 15 centers in China and included 2086 patients with AF. We divided the patients into dabigatran and rivaroxaban groups according to their direct oral anticoagulants. Propensity score matching was used to balance the covariates between the groups. Due to our limited sample size, the number of cases of some clinical events with low incidence was small. During a mean follow-up period of 10 months, a total of 268 (12.9%) bleeding events occurred, including 27 (1.3%) major bleeding events and 241 (11.6%) minor bleeding events, and 45 (2.2%) thromboembolic events. In patients with AF combined with hypertension, rivaroxaban was associated with a higher major bleeding incidence than dabigatran (odds ratio [OR], 2.89 [95% confidence interval [CI, 1.22-6.87]; $P = .012$). In contrast, the risk of thromboembolism and minor bleeding was similar for rivaroxaban (OR, 0.55 [95%CI, 0.29-1.01]; $P = .069$) and dabigatran (OR, 0.82 [95%CI, 0.63-1.08]; $P = .150$). Based on the results of this study, in patients with AF and hypertension treated with direct oral anticoagulants, the incidence of thromboembolism and minor bleeding was not statistically different between dabigatran and rivaroxaban, but compared with rivaroxaban, dabigatran was associated with a lower risk of major bleeding.

Keywords

atrial fibrillation, bleeding, comorbidities, direct oral anticoagulant, hypertension, thromboembolism

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Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia.[1] From 1990 to 2010, the overall global incidence of AF increased by 27.7% and 35.8% in men and women, respectively, and the mortality associated with AF increased by a factor of 2 and 1.9, respectively.[2] Age is one of the main risk factors for AF, with the risk of AF doubling with every 10-year increase in age.[3] In recent years, with the increasing global trend of population aging, the increase in the elderly population will further increase the prevalence and incidence of AF.[4] AF is associated with an increased risk of stroke and thromboembolism, and AF–related stroke leads to higher mortality.[5] Therefore, stroke prevention through anticoagulation is key to the health management of patients with AF, and anticoagulation also reduces long-term cardiovascular events in patients.[6,7] The effectiveness of warfarin in preventing stroke and thromboembolism in patients with AF is well established, but warfarin requires coagulation monitoring.[8,9] In contrast, direct oral anticoagulants are more convenient to use and are a suitable alternative to warfarin, which makes them increasingly common in clinical practice.[10-12]

Patients with AF often have a combination of heart failure, hypertension, and diabetes, which contribute to the progression of AF by promoting atrial remodeling.[13,14] At the same time, these comorbidities can significantly impact the clinical outcome of patients with AF. A US health insurance analysis showed that patients with AF and diabetes had a significantly increased risk of ischemic stroke and myocardial infarction compared with patients with AF without diabetes.[15] In a study examining the efficacy of 4 direct oral anticoagulants in patients with nonvalvular AF, >80% of patients had hypertension as the most common comorbidity.[12] In addition, hypertension was included in the CHA_2DS_2-VASc score and the HAS-BLED score as an independent risk factor for stroke and bleeding.[16,17] Hypertension leads to an increase in stroke and systemic embolic events, increases the risk of bleeding, and reduces the quality of life in patients with AF.[17,18] Although several studies have compared the efficacy and safety of each direct oral anticoagulants in patients with AF, the stroke prevention effect of direct oral anticoagulants in patients with AF with hypertension and whether the risk of bleeding differs between direct oral anticoagulants is still unclear.[12,19] We conducted a multicenter study to evaluate the efficacy and safety of different direct oral anticoagulants in patients with AF with hypertension. Since apixaban has no indication for AF in China and edoxaban was available only in China in 2019, the direct oral anticoagulants in this study were rivaroxaban and dabigatran.

Methods

Study Design

From January 2016 to December 2020, we conducted retrospective multicenter enrollment at 15 centers in China (Table S1). Figure S1 shows the distribution of multicenter hospitals. This study was approved by the Ethics Committee of Fujian Medical University Union Hospital (registration no. ChiCTR2000031909, 2020/04/14). Due to the retrospective nature of this study, the review board waived the informed consent. The inclusion criteria for this study were as follows: (1) ≥18 years of age, (2) diagnosis of AF, (3) taking a direct oral anticoagulant (DOAC) for ≥3 months, and (4) diagnosis of hypertension. Exclusion criteria were as follows: (1) patients with valvular AF, (2) warfarin administration after discharge, (3) uncontrolled hypertension, and (4) follow-up <90 days or insufficient data. We selectively excluded common comorbidities of AF other than hypertension, such as heart failure and diabetes, to eliminate confusion arising from other comorbidities. A total of 3043 patients with nonvalvular AF treated with DOACs and combined with hypertension met the inclusion criteria and were eligible to participate in this study. The flowchart of the study population selection is displayed in Figure 1. See Table S6 for the definition of a clinical event. We also explored the efficacy and safety of dabigatran and rivaroxaban in patients with AF without hypertension.

Data Collection and Study Outcomes

Researchers at each hospital reviewed the selected patients' hospital records through the electronic medical record system and recorded patient demographic characteristics, lifestyle, laboratory data, comorbid disease information, and medication use information. We have training for all data collectors before collecting data. Data from each center are quality controlled, aggregated and collated by 1 person, and reconciled by another. We collected information on whether patients experienced adverse events after using DOACs through follow-up. Follow-up was conducted by 4 trained medical personnel. Before the follow-up, we standardized the follow-up questions and strictly defined each clinical event. The information we collected at each follow-up included whether the patient continued anticoagulation, the dose of DOAC, the drugs used in combination, comorbidities, whether bleeding or thrombotic events occurred, and the site and timing of these adverse events. The follow-up period was defined from the date of DOAC treatment until the date of discontinuation of DOAC treatment or the end date of the study period.

The primary outcomes in this study were major bleeding, minor bleeding, and thromboembolism. The International Society on Thrombosis and Haemostasis

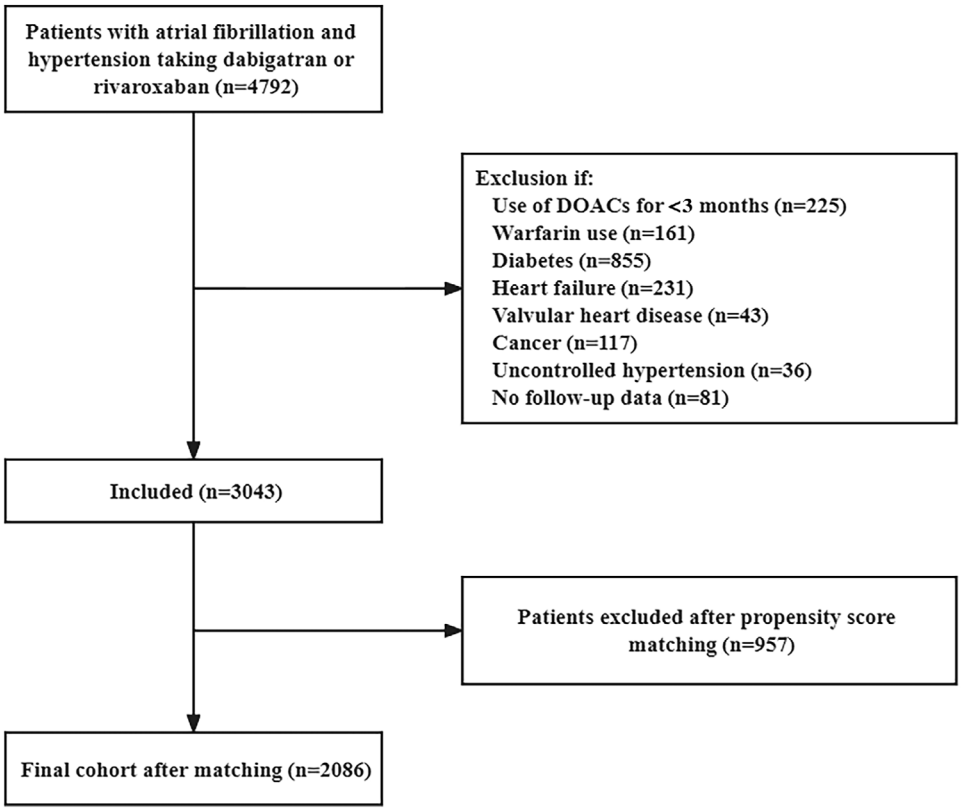

Figure 1. The flowchart of the study population selection. DOACs, direct oral anticoagulants.

defines major bleeding as occurring in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or intrapericardial, myofascial compartment syndrome) or a decrease in hemoglobin level of at least 2 g/dL or transfusion of at least 2 units of red blood cells.[20] Minor bleeding events were defined as those not fulfilling the criteria of major or clinically relevant nonmajor bleeding. Thromboembolism includes ischemic stroke and systemic embolism. Systemic embolism was defined as acute vascular occlusion of a limb or organ documented by imaging, surgery, or autopsy.[21]

Statistical Analysis

Propensity score matching was used to control for unbalanced confounders, and the propensity score was used for 1:1 matching of prescribed dabigatran with those prescribed rivaroxaban. With baseline characteristics as independent variables (Table 1) and whether patients received dabigatran or rivaroxaban as dependent variables, a logistic regression model was used to calculate the propensity score for each patient. Nearest-neighbor matching without replacement was performed by using a caliper of 0.05 on the propensity score scale.[22] Since the propensity-matched data set is a resampling from a sample representing the total, and the hypothesis test corresponds to the total where the sample is located. In addition, the reduced sample size of the propensity-matched data would have resulted in a larger P value. Therefore, standardized differences rather than statistical tests were used to assess the balance of covariates within the matched cohort. A standardized difference ≤ 0.1 indicates adequate balance between groups.[23] If a covariate is unbalanced, we will check whether including it in the regression affects the results.

Continuous variables were tested for normality and described by mean $\pm$ standard deviation if they conformed to a normal distribution or median (interquartile range) if they did not conform to a normal distribution. Categorical variables are presented as frequencies and percentages. Categorical variables were analyzed using the chi-square test and either Fisher's exact test or Yates's correction for continuity. Odds ratios (ORs), 95% confidence intervals (CIs), and P value were calculated. A 2-tailed test with a P-value $<.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 25 software (IBM Corporation, Armonk, NY).

Results

Baseline Characteristics

A total of 3043 patients with AF and hypertension taking dabigatran (n = 1786) and rivaroxaban

Table 1. Baseline Characteristics of Patients With Nonvalvular Atrial Fibrillation Combined With Hypertension After Propensity Score Matching.

	Dabigatran (n = 1043)	Rivaroxaban (n = 1043)	Standardized Difference
Age, y, mean (SD)	65.3 (9.9)	65.3 (9.8)	0.004
Sex, female, n (%)	458 (43.9)	441 (42.3)	0.034
SBP, mm Hg, mean (SD)	158.6 (19.8)	155.1 (21.6)	0.031
DBP, mm Hg, mean (SD)	91.7 (17.3)	89.0 (15.2)	0.068
Smoking, n (%)	614 (58.9)	632 (60.6)	0.034
Alcohol, n (%)	773 (74.1)	761 (73.0)	0.025
BMI, mean (SD)	25.2 (3.3)	25.0 (3.3)	0.054
Laboratories			
TBIL, μmol/L, mean (SD)	15.2 (4.8)	15.2 (7.3)	0.011
ALT, IU/L, mean (SD)	25.1 (19.4)	24.5 (20.8)	0.025
AST, IU/L, mean (SD)	36.1 (29.5)	34.9 (25.1)	0.040
ALP, IU/L, mean (SD)	81.9 (17.2)	80.9 (21.8)	0.042
CrCl, mL/min, mean (SD)	75.9 (16.4)	77.1 (17.6)	0.065
Combined medication, n (%)			
Antiplatelet drugs	299 (28.7)	302 (29.0)	0.007
PPI	730 (70.0)	752 (72.1)	0.047
Statins	503 (48.2)	490 (47.0)	0.023
Amiodarone	179 (17.2)	179 (17.2)	<0.001
H_2 blockers	312 (29.9)	323 (31.0)	0.027
Digoxin	105 (10.1)	100 (9.6)	0.020
ACEI	241 (23.1)	229 (22.0)	0.030
ARB	299 (28.7)	299 (28.7)	<0.001
Beta blockers	666 (63.9)	682 (65.4)	0.028
Diltiazem	108 (10.4)	123 (11.8)	0.049
CCB	403 (38.6)	379 (36.3)	0.048
CHA_2DS_2-VASc, mean (SD)	2.2 (0.9)	2.2 (1.0)	0.008
CHA_2DS_2-VASc ≥2, n (%)	767 (73.5)	770 (73.8)	0.007
HAS-BLED, mean (SD)	1.8 (0.7)	1.8 (0.7)	0.012
HAS-BLED ≥ 3, n (%)	123 (11.8)	136 (13.0)	0.032

ACEI, angiotensin-converting enzyme inhibitors; ALP, alkaline phosphatase (normal range: 45-135 U/L); ALT, alanine aminotransferase (normal range: 0-40 U/L); ARB, angiotensin receptor blocker; AST, aspartate aminotransferase (normal range: 0-40 U/L); BMI, body mass index; CCB, calcium antagonists; CHA_2DS_2-VASc; congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65-74 years, sex category (female); CrCl, creatinine clearance (normal range: 80-120 mL/min); DBP, diastolic blood pressure (normal range: 60-89 mm Hg); HAS-BLED, uncontrolled hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; PPI, proton pump inhibitors; SBP, systolic blood pressure (normal range: 90-139 mm Hg); TBIL, total bilirubin (normal range: 3.4-17.1 μmol/L).

(n = 1257) were included. Before propensity score matching, patients in the dabigatran group were younger and had higher CHA_2DS_2-VASc scores than patients in the rivaroxaban group. Detailed demographic and baseline characteristics are shown in Table S2. After a 1:1 propensity score matching, we retained 1043 patients on dabigatran and 1043 patients on rivaroxaban, and all differences in baseline characteristics were balanced (standardized differences <0.1) (Table 1). A total of 210 patients with AF without hypertension who received dabigatran or rivaroxaban were successfully matched. Detailed baseline information is provided in Table S4.

Efficacy Outcomes

During a mean follow-up period of 10 months, 45 (2.2%) thromboembolic events occurred in patients with AF and hypertension. The specific thromboembolic events of patients with nonvalvular AF in different DOAC groups are shown in Table 2. In patients with nonvalvular AF and hypertension, the event rates for thromboembolism were 1.5% in the rivaroxaban group and 2.8% in the dabigatran group, respectively, with no significant difference between the 2 groups (OR, 0.55 [95%CI, 0.29-1.01]; $P = .069$) (Table 2 and Figure 2).

A total of 12 (2.9%) thromboembolic events occurred in patients with AF without hypertension. The event rates for thrombotic outcomes in the dabigatran and rivaroxaban groups were 2.4% and 3.3%, respectively, with no significant difference between the 2 groups (OR, 1.41 [95%CI, 0.44-4.53]; $P = .558$) (Table S5).

Safety Outcomes

During the follow-up period, a total of 268 (12.9%) bleeding events occurred in patients with AF and hypertension, including 27 (1.3%) major bleeding events and 241 (11.6%) minor bleeding events. The specific

Table 2. Principal Outcomes of Patients With Nonvalvular Atrial Fibrillation Combined With Hypertension.

	Dabigatran (n = 1043)		Rivaroxaban (n = 1043)		
	Incident Number (n)	Incidence Rate (%/n)	Incident Number (n)	Incidence Rate (%/n)	*P* value
Thromboembolism					
All	29	2.8	16	1.5	.069
Age <65	12	2.7	8	1.7	.316
Age ≥65	17	2.9	8	1.4	.083
Male	15	2.6	9	1.5	.191
Female	14	3.1	7	1.6	.145
BMI <25	15	2.9	9	1.5	.127
BMI ≥25	14	2.7	7	1.5	.214
Major bleeding					
All	7	0.7	20	1.9	.012
Age <65	2	0.5	8	1.7	.128
Age ≥65	5	0.8	12	2.1	0.089
Male	5	0.9	13	2.2	.109
Female	2	0.4	7	1.6	.083
BMI < 25	5	1.0	9	1.5	.390
BMI ≥ 25	2	0.4	11	2.4	.006
Minor bleeding					
All	131	12.6	110	10.6	.150
Age < 65	61	13.7	56	12.0	.454
Age ≥ 65	70	11.7	54	9.4	.698
Male	70	12.0	57	9.5	.164
Female	61	13.3	53	12.0	.558
BMI < 25	80	15.3	69	11.8	.084
BMI ≥ 25	51	9.8	41	9.0	.663

BMI, body mass index.

bleeding events of patients with nonvalvular AF in different direct oral anticoagulants groups are shown in Table 2. The event rates of minor bleeding in the dabigatran and rivaroxaban groups were 12.6% and 10.6%, respectively; the event rates of major bleeding in the dabigatran and rivaroxaban groups were 0.7% and 1.9%, respectively (Table 2). The risk of minor bleeding was not statistically different between the rivaroxaban and dabigatran groups (OR, 0.82 [95%CI, 0.63-1.08]; $P = .150$). However, the incidence of major bleeding was significantly higher in patients using rivaroxaban than those using dabigatran (OR, 2.89 [95%CI, 1.22-6.87]; $P = .012$) (Figure 2).

A total of 51 (12.1%) bleeding events occurred in patients with AF without hypertension, including 6 major bleeding events (1.4%) and 45 minor bleeding events (10.7%). The event rates for minor bleeding outcomes were 11.4% and 10.0% in the dabigatran and rivaroxaban groups, respectively; the event rates for major bleeding outcomes were 1.9% and 1.0% in the dabigatran and rivaroxaban groups, respectively (Table 2). There was no statistical difference in the risk of minor bleeding (OR, 0.86 [95%CI, 0.46-1.60]; $P = .636$) and major bleeding (OR, 0.50 [95%CI, 0.09-2.73]; $P = .685$) between the dabigatran and rivaroxaban groups (Table S5).

Subgroup Analyses

Subgroup analysis was performed for age <65 years, age ≥65 years, male, female, body mass index (BMI) <25, and BMI ≥25 subgroups. Among patients with BMI ≥25, the event rates for major bleeding were 0.4% and 2.4% in the dabigatran and rivaroxaban groups, respectively (Table 2). The incidence of major bleeding was significantly higher with rivaroxaban compared with dabigatran (OR, 6.40 [95%CI, 1.41-29.04]; $P = .006$) (Figure 2). In the subgroups of age <65 years, age ≥65 years, male, female, and BMI <25, no significant differences in the efficacy and safety outcomes of dabigatran and rivaroxaban were observed. The specific data and OR values can be viewed in Table 2 and Figure 2.

We also compared the clinical outcomes of patients on dabigatran or rivaroxaban separately by age, sex, and BMI. Among patients on dabigatran, the event rates of minor bleeding were 15.3% and 9.8% for BMI <25 and BMI ≥25, respectively (Table S3). The incidence of minor bleeding was significantly higher in patients with BMI <25 than in those with BMI ≥25 (Figure S2). No significant differences were observed between age <65 years and age ≥65 years and between men and women. In patients on rivaroxaban, no significant differences were observed between different ages, sexes, or BMIs.

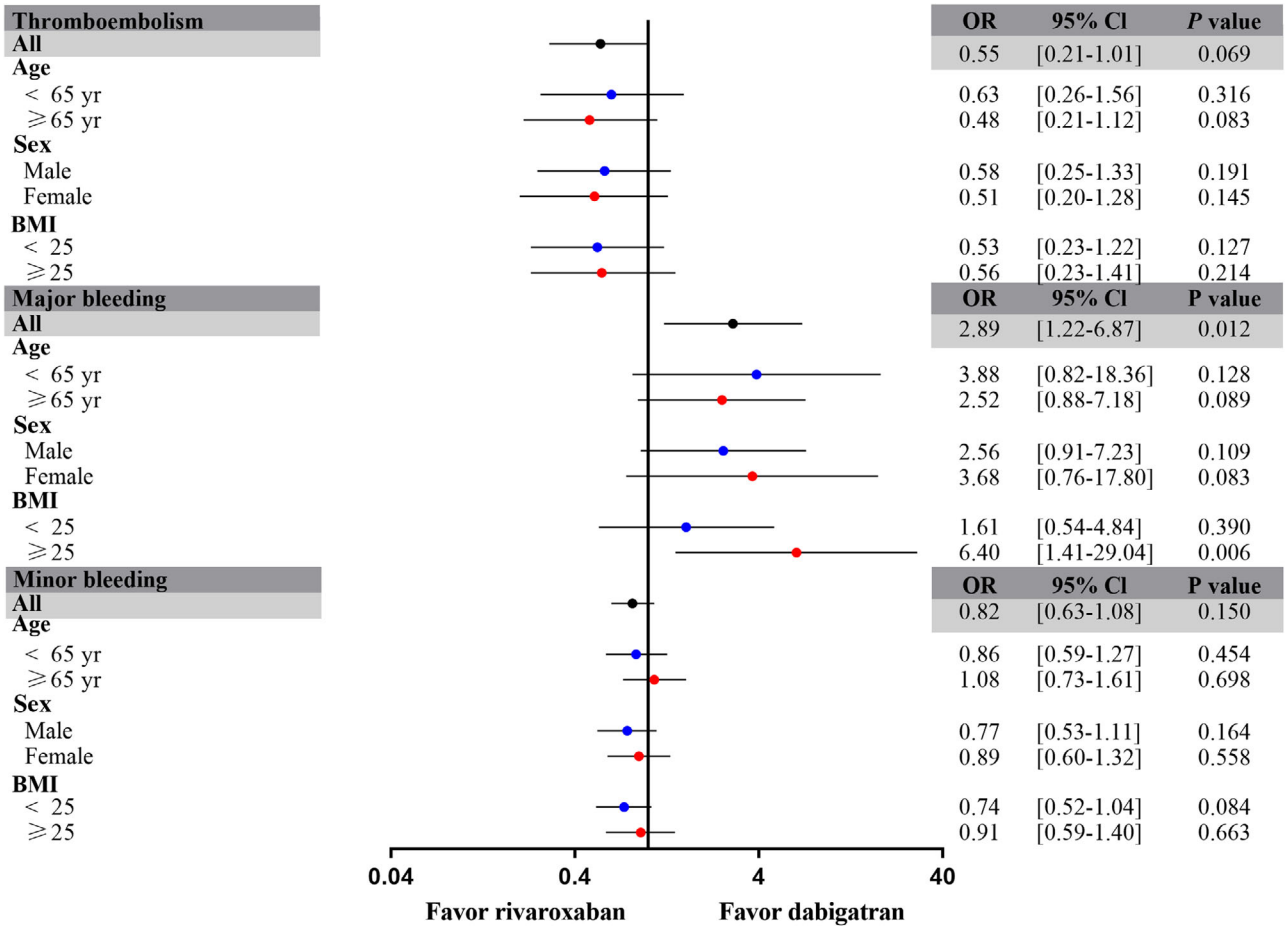

Figure 2. Forest plot of OR for dabigatran versus rivaroxaban. BMI, body mass index; CI, confidence interval; OR, odds ratio.

The specific data and OR values can be viewed in Table S3 and Figure S2.

Discussion

This study was based on a multicenter retrospective cohort from 15 hospitals in China and aimed to investigate the safety and efficacy of dabigatran and rivaroxaban in patients with AF and hypertension. The main findings of our study are as follows: (1) In patients with AF and combined hypertension, dabigatran may be associated with a lower incidence of major bleeding compared to rivaroxaban; (2) risks of thromboembolism and minor bleeding are similar for dabigatran and rivaroxaban; (3) in patients with AF without hypertension, there was no significant difference in the risk of thromboembolism, major bleeding, and minor bleeding between dabigatran and rivaroxaban.

Our results showed that in patients with AF and hypertension, rivaroxaban was associated with a higher risk of major bleeding compared with dabigatran. Our findings are similar to the results of previous studies that did not specifically study patients with AF combined with hypertension.[24] This may be due to the large proportion of combined hypertension in patients with AF, which affects the total population outcome. A bleeding score model developed for patients with AF on oral anticoagulants also indicated that hypertension was a risk factor for bleeding in patients with AF on oral anticoagulants.[25] Meanwhile, when comparing the outcomes of patients taking dabigatran or rivaroxaban in different age, sex, and BMI categories, respectively, to investigate whether age, sex, and BMI have an impact on the effectiveness and safety of dabigatran or rivaroxaban, we found that age, sex, and BMI were not statistically significantly associated with minor bleeding, major bleeding, or thromboembolism in patients on rivaroxaban. The similar efficacy and safety of rivaroxaban across age, sex and BMI subgroups may be related to its pharmacokinetics and pharmacodynamics. A previous study of the population pharmacokinetics of rivaroxaban noted that age and BMI had little effect on the pharmacokinetics of rivaroxaban.[26] A randomized, single-blind, placebo-controlled, parallel-group study found no effect of age or sex on the pharmacokinetics and pharmacodynamics of rivaroxaban.[27] In patients

on dabigatran, although age and sex were not statistically significantly associated with clinical outcomes, minor bleeding was significantly lower in patients with a BMI ≥25 compared with those with a BMI <25. A higher incidence of minor bleeding in patients with obesity may be due to changes in the pharmacokinetics of dabigatran in different BMI populations. A subgroup analysis of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study showed that dabigatran has a different pharmacokinetic profile in patients with different body weights.[28] The trial showed that compared with patients weighing <50 kg, dabigatran plasma concentrations were 21% lower in patients weighing 50-100 kg and 53% lower in patients weighing ≥100 kg. The study also showed that bleeding events were proportional to the plasma concentration of dabigatran. Therefore, we hypothesize that it may be that lower dabigatran plasma concentrations in patients with obesity result in a relatively lower incidence of minor bleeding compared with normal-weight patients. The lower plasma concentration of dabigatran with weight gain may also account for the relatively lower incidence of major bleeding compared with the stable blood levels of rivaroxaban. Before our study, we were unaware of any other studies comparing the efficacy and safety of dabigatran and rivaroxaban in patients with AF combined with hypertension. Our study complements the existing studies on the efficacy and safety of DOACs.

We also observed that the choice of DOAC prescription was related to the underlying characteristics of the patients. Before propensity score matching, dabigatran was used in younger patients with AF with higher creatinine clearance, which may be because the high renal excretion rate of dabigatran (80%) leads to the accumulation of dabigatran in patients with renal insufficiency, which increases the risk of bleeding in patients.[29] Doctors prefer rivaroxaban when prescribing to patients with AF and low creatinine clearance. The proportion of patients at high stroke risk (CHA_2DS_2 score ≥2) was higher in the dabigatran group than in the rivaroxaban group, which may be because dabigatran demonstrated a substantial advantage in stroke prevention in the RE-LY study.[21]

There are some strengths to our study. The patients included in our study were from 15 centers in different provinces of China, which cover the vast majority of China. The number of cases included in the cohort was >2000, making our data and results representative. Our study also has several limitations. First, although we performed propensity score matching, which can help us effectively balance confounders for measured variables, it still fails to balance confounders for unmeasured variables. Second, our study is a retrospective cohort study, and compared with randomized clinical trials, some data will inevitably be missing, and patients will be lost to follow-up. Finally, due to our limited sample size, the number of cases of some clinical events with low incidence was small, and we hope that future studies with larger samples will refine our results.

Conclusion

In patients with AF and hypertension treated with DOACs, the incidence of thromboembolism and minor bleeding was not statistically different between dabigatran and rivaroxaban. We also found a lower incidence of major bleeding with dabigatran compared with rivaroxaban.

Authors' Contributions

J.Z. initiated the study. X.C., W.Z., N.H., H.D., P.G., X.H., X.D., R.L., Q.Z., X.L., and Y.L. collected and entered the data. M.L. and T.W. performed data collation. C.G. and M.Z. performed data extraction and analyses. C.G. drafted the first version of the manuscript. C.G., W.X., X.L., and Z.Z. critically reviewed the manuscript and revised it. C.G. and W.X. worked on data validation. C.G. and W.X. performed the graphical revisions. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Data Availability Statement

All data relevant to the study are included in the article as supplementary information.

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