Cardiovascular Innovations and Applications

RESEARCH ARTICLE

Comparison of the Safety and Efficacy of Warfarin Versus Rivaroxaban in Northern Chinese Patients with Different CHA2DS2-VASc Scores: A Retrospective Cohort Study

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Abstract

Purpose: This study was aimed at evaluating the safety and efficacy of warfarin versus rivaroxaban in patients with atrial fibrillation (AF) and different CHA2DS2-VASc score subgroups in northern China.
Methods: A retrospective cohort study was conducted to evaluate 387 patients with AF who received treatment at our institution between September 2018 and August 2019. The patients were divided into two groups receiving either warfarin (n = 194) or rivaroxaban (n = 193). Follow-up data were collected, including adherence, bleeding and ischemic stroke events.
Results: The group receiving rivaroxaban showed better adherence than the group receiving warfarin. In the warfarin-treated group, bleeding incidents declined with increasing scores. In the warfarin-treated group, patients with scores of 2–3 had greater adherence and fewer stroke occurrences. The events of bleeding and stroke did not significantly differ in patients in the rivaroxaban-treated group with different scores.
Conclusions: Compared with patients in the warfarin group with different CHA2DS2-VASc scores, those in the rivaroxaban group had greater compliance, and fewer bleeding and stroke events. Regardless of economic considerations, rivaroxaban is preferable for anticoagulative AF treatment in northern Chinese patients.

Keywords: Atrial fibrillation; Warfarin; Rivaroxaban; Ischemic stroke; CHA2DS2-VASc score

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Introduction

Atrial fibrillation (AF) is a common arrhythmia, and many independent risk factors that predispose individuals to a variety of complications, such as ischemic stroke (IS) have been reported; moreover, AF is a major cause of stroke [1–5]. Because of the cold weather, the incidence of AF, IS and other cardiovascular diseases is very high in northern China [6, 7]. Therefore, AF treatment has attracted substantial attention. Warfarin has been demonstrated to successfully prevent stroke in patients with AF [8–10]. However, the use of warfarin in patients is restricted because of the risk of bleeding incidents [11]. Numerous studies have shown that new oral anticoagulation agents (NOACs) are more effective than warfarin in preventing stroke in patients with non-valvular AF [12, 13]. The CHA2DS2-VASc score is generally used to evaluate the risk of IS in patients with AF. However, limited real-world evidence is available regarding the risk of IS according to CHA2DS2-VASc scores in northern Chinese patients [14]. In this retrospective, single-institution cohort study, we aimed to use real-world data to evaluate the incidence of bleeding and IS events in northern Chinese patients with AF treated with warfarin or rivaroxaban, according to their relative adherence and CHA2DS2-VASc scores.

Methods

Study Design and Patients

In our hospital database, we conducted a retrospective review of patients with non-valvular AF who were hospitalized at the Second Affiliated Hospital of Harbin Medical University (Harbin, China) between September 2018 and August 2019. Patients received oral anticoagulant therapy (216 patients received warfarin and 211 patients received rivaroxaban) for the prevention of IS. Patients taking anticoagulants for vein thrombosis treatment were excluded. According to physicians' recommendations, all patients received either rivaroxaban (15–20 mg/day) or warfarin (1.25–2.5 mg/day, INR: 2.0–3.0). The study protocol was approved by the Second Affiliated Hospital of Harbin Medical University (KY2020-195).

Safety and Efficacy Assessments

Bleeding incidents such as hemorrhinia, fundus hemorrhage, gingival bleeding and gastrointestinal bleeding were included in the safety outcomes. The efficacy outcome was identified according to thrombosis events. IS was defined as a focal neurological deficit for 24 h with no hemorrhage. Systemic embolism was defined as acute vascular occlusion. Bleeding and IS were diagnosed by physicians through radiological examination or vascular imaging. All medical records of the patients were evaluated by a physician.

Follow-up and Outcomes

Clinical information on the participants in this study was collected from outpatient medical records, hospitalization medical records or telephone questionnaires. The median follow-up time was 11.2 months in the warfarin-treated group and 9.7 months in the rivaroxaban-treated group. During the follow-up visits, patients' clinical condition, medication compliance, bleeding incidents (such as hemorrhinia, fundus hemorrhage, gingival bleeding and gastrointestinal bleeding), risk of stroke and other adverse effects were evaluated. The results in the groups treated with rivaroxaban and warfarin were compared.

Statistical Analysis

The CHA2DS2-VASc score was used to evaluate stroke risk. Warfarin- and rivaroxaban-treated patients were further divided into three groups with CHA2DS2-VASc scores of 0–1, 2–3 and ≥4, according to a previous study [15]. Data are shown as mean ± SEM and were compared with independent-samples t-tests for continuous variables. Data are shown as percentages and were compared with the chi-square test for categorical variables. All statistical assessments were conducted in SPSS 20 (SPSS, USA). $P < 0.05$ was considered to indicate statistical significance.

Results

Study Population

A total of 427 patients with AF who received anticoagulant therapy with warfarin or rivaroxaban

were enrolled in the study. One group (216 participants) was treated with warfarin, and the other group (211 participants) was treated with rivaroxaban. A total of 40 participants were lost during the follow-up period: 22 in the warfarin-treated group and 18 in the rivaroxaban-treated group. The two groups were comparable in aspects including age, sex, hypertension, diabetes mellitus, previous stroke, cardiac function, CHA2DS2-VASc score and blood biochemical indexes (Table 1). The mean CHA2DS2-VASc scores were similar between the warfarin- and rivaroxaban-treated groups (2.75 ± 1.44 versus 2.90 ± 1.77, respectively). The median age was 61.75 ± 9.83 years and 64.90 ± 11.81 years in the warfarin-treated

and rivaroxaban-treated groups, respectively. Moreover, 55.2% and 58.0% of patients were male in the warfarin-treated and rivaroxaban-treated groups, respectively.

With bleeding events and stroke events as the dependent variables, and the baseline characteristics of the study population, such as age, hypertension and heart failure, as the independent variables, the statistically significant differences in the univariate analysis were subjected to multivariate logistic regression analysis (Tables 2 and 3). LDL-C was found to be an independent risk factor for stroke events (OR = 11.95, 95% confidence interval of the OR values: 1.144–124.804, $P = 0.0382$).

Table 1 Baseline Characteristics of the Study Population.

Characteristic	Warfarin (n = 194)	Rivaroxaban (n = 193)	P-value
Age (years)	61.75 ± 9.83	64.90 ± 11.81	0.005
Men (%)	107 (55.2%)	112 (58.0%)	0.568
Hypertension (%)	68 (35.1%)	95 (49.2%)	0.005
Diabetes mellitus (%)	30 (15.5%)	40 (20.7%)	0.179
Previous stroke/TIA (%)	31 (16.0%)	35 (18.1%)	0.573
Heart failure (%)	126 (64.9%)	45 (23.3%)	<0.001
Vascular disease (%)	87 (44.8%)	118 (61.1%)	0.001
CHA2DS2-VASc score (mean)	2.75 ± 1.44	2.90 ± 1.77	0.348
Smoking (%)	52 (26.8%)	35 (18.1%)	0.041
Alcohol use (%)	37 (19.1%)	24 (12.4%)	0.073
LDL-C (mmol/L)	2.59 ± 0.85	2.33 ± 0.73	0.001
HDL-C (mmol/L)	1.11 ± 0.32	1.09 ± 0.25	0.590
Total cholesterol (mmol/L)	4.20 ± 1.03	3.98 ± 0.87	0.033
Triglyceride (mmol/L)	1.55 ± 0.71	1.72 ± 1.16	0.089
Lipoprotein (a) (g/L)	1.12 ± 0.24	1.17 ± 0.26	0.062
Lipoprotein (b) (g/L)	0.90 ± 0.26	0.81 ± 0.23	0.001
Uric acid (μmol/L)	393.31 ± 137.17	342.82 ± 122.61	<0.001
Crcl (mL/min)	96.83 ± 46.51	90.49 ± 31.51	0.118
LAD (mm)	45.98 ± 9.98	40.16 ± 6.38	<0.001
LVEF (%)	55.34 ± 10.75	58.83 ± 8.20	0.001
CHA2DS2-VASc scores (%)			0.0028
0–1	37 (19.07)	49 (25.39)	
2–3	104 (53.61)	70 (36.27)	
≥4	53 (27.32)	74 (38.34)	
Bleeding (%)	30 (15.46)	26 (13.47)	0.5775
Stroke (%)	15 (7.73)	12 (6.22)	0.5588

Data are presented as mean ± standard deviation or proportions. TIA, transient ischemic attack; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Crcl, creatinine clearance; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

Table 2 Multivariate Logistic Regression Analysis of Bleeding Events.

Variate	β	Se	Wald χ^2	P value	OR (95% CI)
Group (two groups of drugs)	0.1461	0.3794	0.1482	0.7003	1.157 (0.55, 2.435)
Age	−0.0277	0.0184	2.2687	0.132	0.973 (0.938, 1.008)
Hypertension	0.3076	0.3502	0.7716	0.3797	1.36 (0.685, 2.702)
Heart failure	0.2867	0.4458	0.4134	0.5202	1.332 (0.556, 3.191)
Vascular disease	0.1073	0.3723	0.083	0.7732	1.113 (0.537, 2.309)
Smoking	−0.6193	0.4564	1.8413	0.1748	0.538 (0.22, 1.317)
LDL-C	−0.3421	0.5915	0.3346	0.563	0.71 (0.223, 2.264)
Total cholesterol	0.1978	0.4783	0.1711	0.6792	1.219 (0.477, 3.112)
Lipoprotein (b)	−0.2501	2.2003	0.0129	0.9095	0.779 (0.01, 58.113)
Uric acid	−0.00086	0.00155	0.3063	0.58	0.999 (0.996, 1.002)
LAD	0.0107	0.0245	0.1897	0.6632	1.011 (0.963, 1.06)
LVEF	0.00287	0.0213	0.018	0.8932	1.003 (0.962, 1.046)

Table 3 Multivariate Logistic Regression Analysis of Stroke Events.

Variate	β	Se	Wald χ^2	P	OR (95% CI)
Group (two groups of drugs)	−1.1389	0.5593	4.1459	0.0417	0.32 (0.107, 0.958)
Age	−0.00389	0.0278	0.0195	0.889	0.996 (0.943, 1.052)
Hypertension	0.6763	0.52	1.6917	0.1934	1.967 (0.71, 5.45)
Heart failure	−0.5405	0.6773	0.6369	0.4248	0.582 (0.154, 2.197)
Vascular disease	0.3792	0.5446	0.485	0.4862	1.461 (0.503, 4.248)
Smoking	−0.7727	0.6795	1.2935	0.2554	0.462 (0.122, 1.749)
LDL-C	2.4807	1.197	4.2951	0.0382	11.95 (1.144, 124.804)
Total cholesterol	−0.8983	0.8342	1.1598	0.2815	0.407 (0.079, 2.089)
Lipoprotein (b)	−4.9727	3.622	1.8849	0.1698	0.007 (0.001, 8.384)
Uric acid	−0.0009	0.00229	0.1542	0.6946	0.999 (0.995, 1.004)
LAD	−0.0176	0.0359	0.241	0.6235	0.983 (0.916, 1.054)
LVEF	−0.00248	0.034	0.0053	0.9418	0.998 (0.933, 1.066)

Adherence

As shown in Table 4, the adherence rate was 59.3% in the warfarin-treated group, which was lower than the 78.2% in the rivaroxaban-treated group (P < 0.001). The adherence rate of patients with moderate risk of stroke (score 2–3, 67.3%) was higher than those in patients with low or high risk of stroke in the warfarin-treated group (score 0–1, 51.4%; score ≥4, 49.1%). The adherence rates were similar in rivaroxaban-treated patients with different CHA2DS2-VASc scores (score 0–1, 79.6%; score

Table 4 Adherence to Warfarin and Rivaroxaban.

Characteristic	Warfarin (n = 194)	Rivaroxaban (n = 193)	P value
All	115 (59.3%)	151 (78.2%)	<0.001
CHA2DS2-VASc score 0 or 1	19 (51.4%)	39 (79.6%)	0.006
CHA2DS2-VASc score 2 or 3	70 (67.3%)	53 (75.7%)	0.232
CHA2DS2-VASc score ≥4	26 (49.1%)	59 (79.7%)	<0.001

CHA2DS2-VASc, risk based on the presence of congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease and sex.

2–3, 75.7%; score ≥4, 79.7%). Lower adherence was observed in patients with scores of 0–1 and ≥4 in the warfarin-treated group than the rivaroxaban-treated group (P < 0.01 for all comparisons).

Safety and Efficacy Outcomes

The safety and efficacy outcomes of the two groups during the follow-up period are shown in Figure 1. More bleeding events were observed in the warfarin-treated group (36, 18.6%) than the rivaroxaban-treated group (29, 15.0%), but a statistical difference was not observed (Figure 1A). A total of 36 patients experienced bleeding in the warfarin group, including hemorrhinia (12, 33.3%), fundus hemorrhage (4, 11.1%), gingival bleeding (16, 44.4%) and gastrointestinal bleeding (4, 11.1%) (Figure 1C). Moreover, 29 patients experienced bleeding in the rivaroxaban group, including hemorrhinia (3, 10.3%), fundus hemorrhage (5, 17.2%), gingival bleeding (17, 58.6%) and gastrointestinal bleeding (4, 13.8%) (Figure 1D). The cumulative incidence of IS events in the warfarin and rivaroxaban groups was 8.8% (17/194) and 6.7% (13/193), respectively (Figure 1B). No statistical difference was observed between treatment groups.

Risks of Bleeding and IS According to CHA2DS2-VASc Score

To evaluate the safety and efficacy of warfarin versus rivaroxaban in patients with AF with different CHA2DS2-VASc scores, we classified the patients with AF into three groups with CHA2DS2-VASc scores of 0–1, 2–3 and ≥4, who were treated with warfarin or rivaroxaban. More bleeding events were observed in the warfarin-treated group than the rivaroxaban-treated group among patients with scores of 0–1 and 2–3, but the difference was not significant (Figure 2A). Furthermore, in the warfarin- or rivaroxaban-treated group, bleeding did not significantly differ among patients with different scores (Figure 2B–C).

More IS events were observed among patients with scores of 0–1 and ≥4 in the warfarin-treated group than the rivaroxaban-treated group, but the difference was not statistically significant (Figure 2D). Furthermore, in the warfarin-treated group, patients
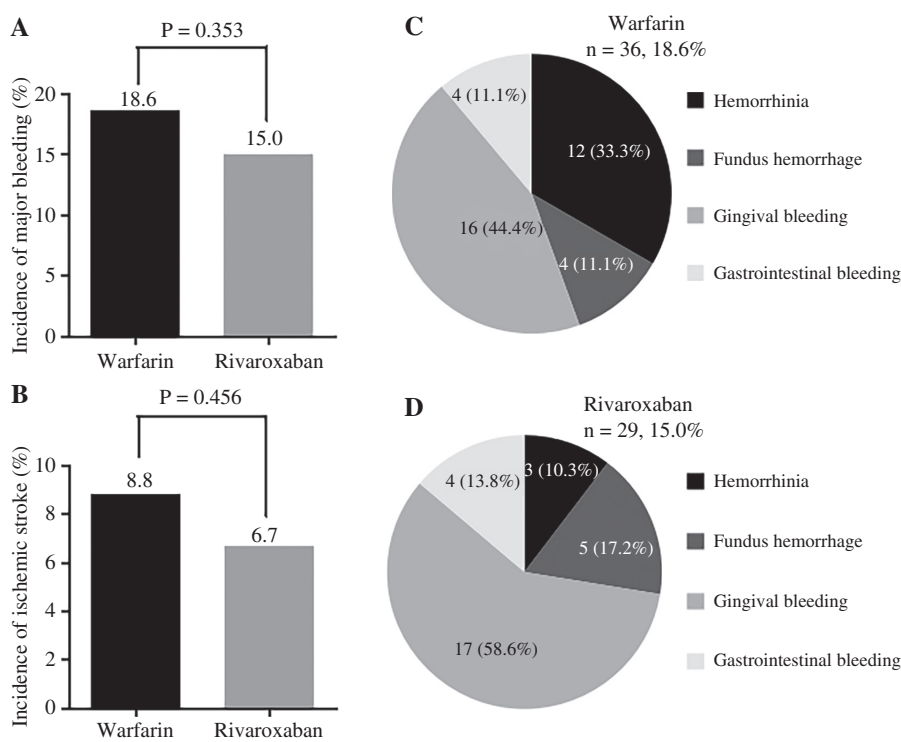

Figure 1 Efficacy and Safety Outcomes According to Warfarin or Rivaroxaban Treatment.
(A) Bleeding events after warfarin or rivaroxaban treatment. (B) Ischemic stroke with warfarin or rivaroxaban treatment. Sites of bleeding with warfarin (C) or rivaroxaban (D).
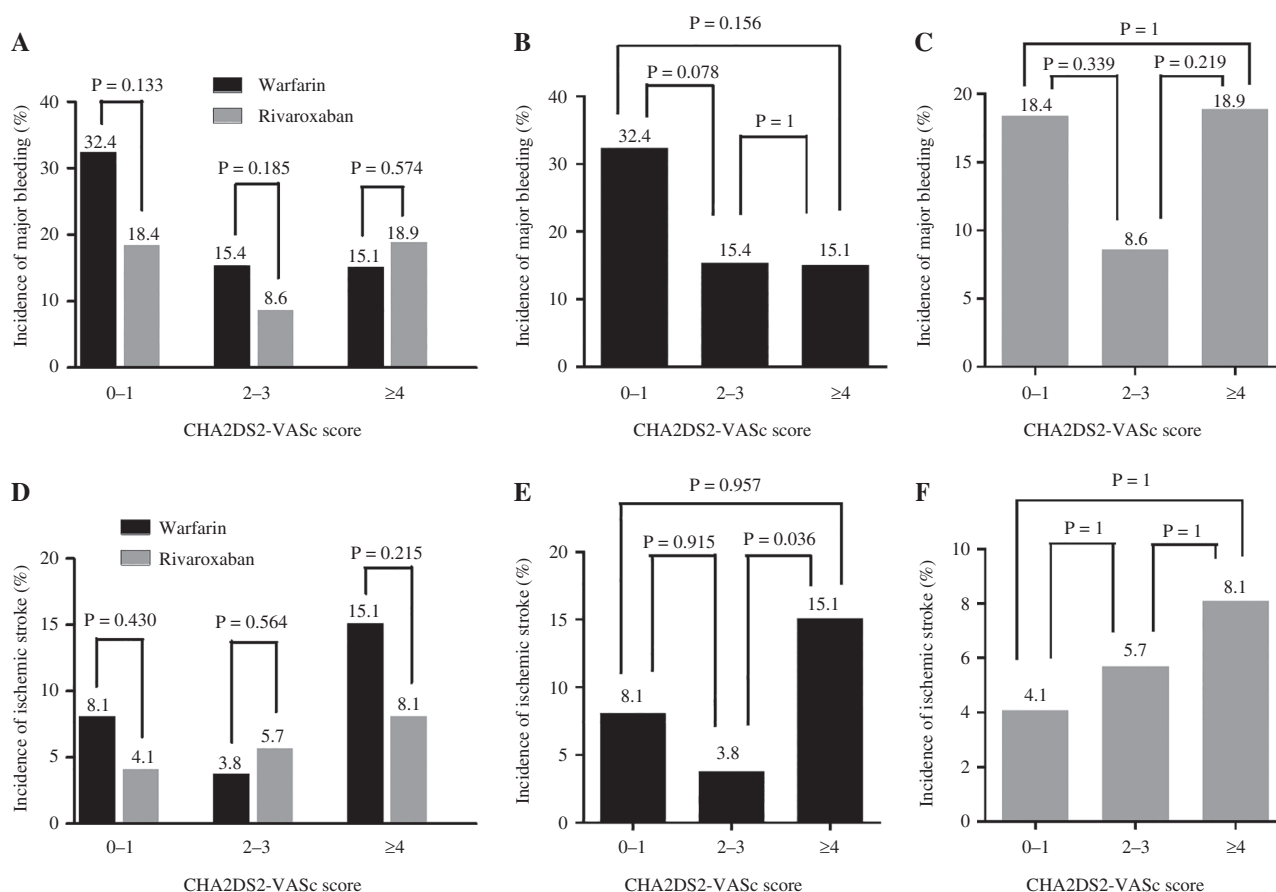
Figure 2 Incidence Rates of Bleeding and Ischemic Stroke According to CHA2DS2-VASc Score.
(A) Bleeding after warfarin and rivaroxaban treatment, according to CHA2DS2-VASc score. Bleeding after warfarin (B) or rivaroxaban (C) treatment, according to CHA2DS2-VASc score. (D) IS after warfarin or rivaroxaban treatment, according to CHA2DS2-VASc score. IS after warfarin (E) or rivaroxaban (F) treatment, according to CHA2DS2-VASc score.

with scores ≥ 4 had more IS events than patients with scores of 2–3 (Figure 2E) (P < 0.05). In the rivaroxaban-treated group, IS events did not significantly differ among patients with different scores (Figure 2F).

To further study the type of bleeding according to the CHA2DS2-VASc scores, we divided the bleeding patients into four subgroups with hemorrhinia, fundus hemorrhage, gingival bleeding or gastrointestinal bleeding induced by warfarin or rivaroxaban (Figure 3). Only hemorrhinia was greater in the warfarin-treated group than the rivaroxaban-treated group, among patients with scores of 0–1 (Figure 3A, P = 0.018). The incidence rates of fundus hemorrhage, gingival bleeding and gastrointestinal bleeding did not significantly differ between the warfarin- and rivaroxaban-treated groups, among patients with different scores (Figure 3B–D).

Hospitalization

A total of 99 patients were hospitalized in the follow-up period. The incidence rates of hospitalization were 23.2% (45/194) in the warfarin-treated group and 28.0% (54/193) in the rivaroxaban-treated group (Figure 4A). The incidence rates of hospitalization did not significantly differ in the warfarin- or rivaroxaban-treated groups, among patients with different scores (Figure 4B).

Discussion

AF, which is among the most prevalent and dangerous clinical arrhythmias, poses a substantial risk to human health [1]. Oral anticoagulant drugs currently play an important role in the anticoagulant treatment of patients with AF [16]. Warfarin is a classical anticoagulant that is the most widely used in clinical
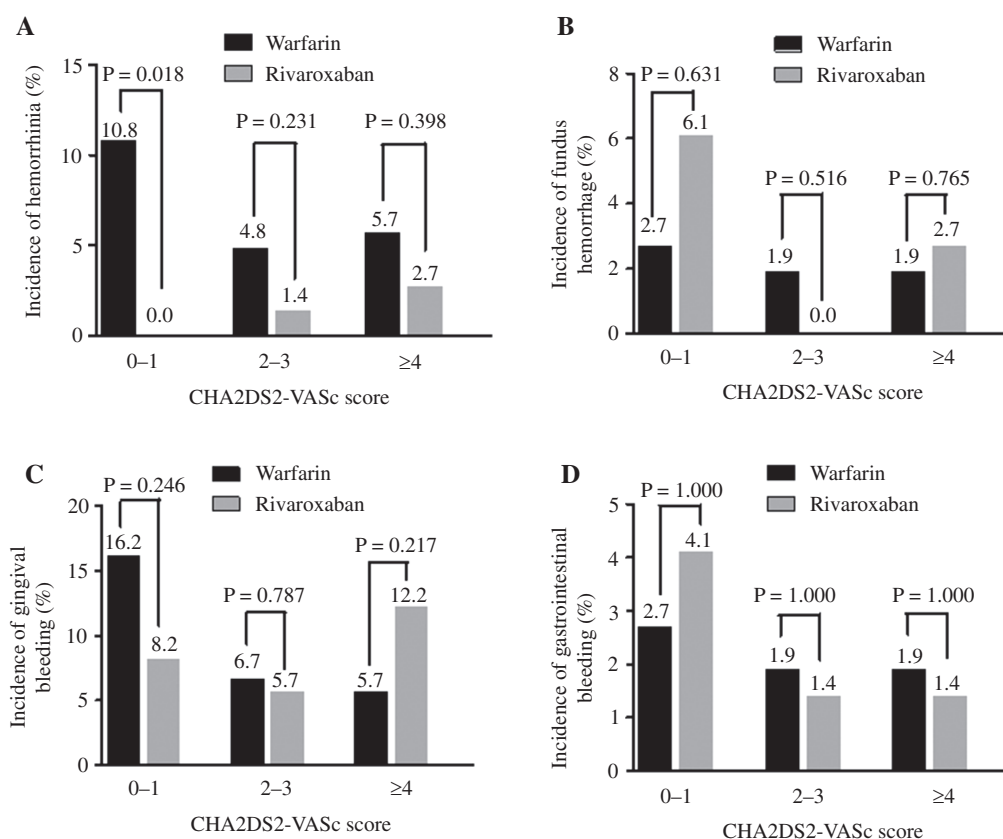
Figure 3 Subgroups of Bleeding after Warfarin and Rivaroxaban Treatment, According to CHA2DS2-VASc Score. (A) Hemorrhinia, (B) fundus hemorrhage, (C) gingival bleeding and (D) gastrointestinal bleeding.
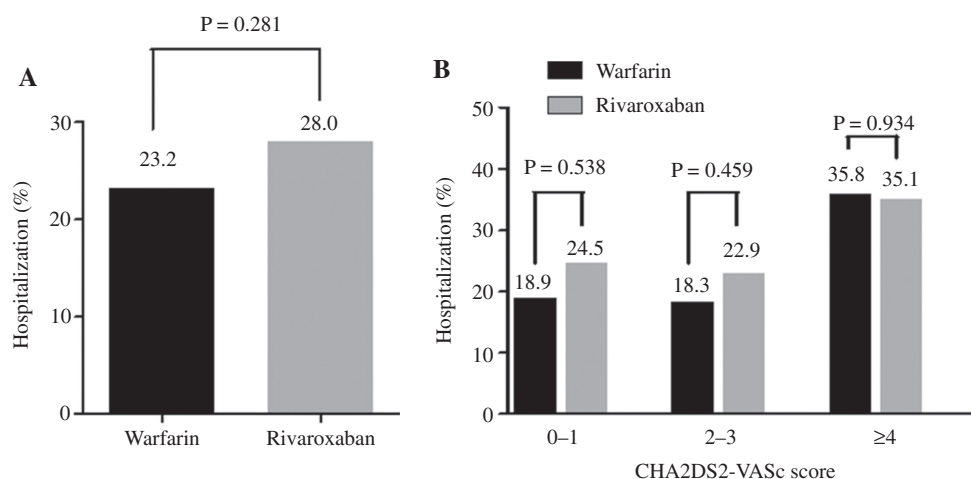

Figure 4 Incidence Rate of Hospitalization. (A) Incidence rate of hospitalization after warfarin and rivaroxaban treatment. (B) Incidence rate of hospitalization, according to CHA2DS2-VASc score.

practice. It is a coumarin anticoagulant that has anticoagulant and antiplatelet aggregation functions through competing with the action of vitamin K in the liver, inhibiting the synthesis of clotting factors in liver cells and decreasing of the thrombin-induced platelet aggregation reaction [17]. Although warfarin has high anticoagulant efficiency, the effective dose of warfarin varies among individuals, thus requiring frequent blood monitoring of patients to adjust the effective dose of warfarin, as well as cumbersome

treatment procedures, and effects of food or drug interactions that can significantly decrease clinical benefit [18]. Rivaroxaban is a new anticoagulant that directly inhibits factor Xa, blocks endogenous and exogenous clotting pathways and inhibits thrombin production and thrombosis. Rivaroxaban is a dose-dependent inhibitor of factor Xa activity, and it has the advantages of being safe, effective and convenient for the prevention and treatment of thromboembolic diseases [19].

Our study performed a retrospective analysis to compare the safety and efficacy of warfarin versus rivaroxaban in northern Chinese patients with AF with different CHA2DS2-VASc scores. The following conclusions were drawn from the present study: (1) Adherence was better in the rivaroxaban-treated group than the warfarin-treated group. (2) Bleeding events decreased with increased scores in the warfarin-treated group: patients with scores of 2–3 had relatively better adherence and fewer stroke events in the warfarin-treated group. (3) The events of bleeding and stroke did not significantly differ among patients with different scores in the rivaroxaban-treated group.

In our current investigation, the risks of bleeding events were relatively high. Previous studies have indicated that warfarin and rivaroxaban pose similar risks of major bleeding [20–22]. A previous study has also reported significant bleeding in 10.1% and 16.4% of patients in the warfarin and NOAC groups, respectively [23]. Our study indicated fewer bleeding events in the rivaroxaban-treated group (15.0%) than the warfarin-treated group (18.6%), but no significant difference was observed. More bleeding events were observed in the warfarin-treated group than the rivaroxaban-treated group, among patients with scores of 0–1 and 2–3, but the difference was not significant (Figure 2A). Furthermore, patients in the warfarin-treated group with scores of 0–1 had higher bleeding risk than those with scores of 2–3 and ≥4, but the difference also was not significant (Figure 2B). These results indicated that patients with AF with scores of 0–1 might experience bleeding induced by warfarin. This result is not consistent with previous findings [24] indicating high rates of bleeding events in patients with scores ≥5.

In the present study, the incidence rate of IS was high. Previous studies have found similar stroke rates between the NOAC and warfarin-treated

groups [25–27]. In our study, the IS risk in the warfarin-treated group was higher than that in the rivaroxaban-treated group, among patients with scores of 0–1 and ≥4, but the difference was not significant (Figure 2D). Furthermore, in the warfarin-treated group, patients with scores of 2–3 had fewer IS events than patients with scores of 0–1 and ≥4 (Figure 2E). These results might have been due to the relatively higher adherence to treatment with warfarin in patients with scores of 2–3 (Table 4).

Oral anticoagulants are usually used for preventing thrombosis in patients with AF before the onset of symptoms; consequently, adherence to oral anticoagulants in patients with AF is poor. One reason why patients do not adhere to their prescription regimens is that regular monitoring is necessary when warfarin is used. Numerous studies have suggested that long-term adherence to warfarin therapy is quite challenging for patients [28, 29]. Our findings, which were in line with earlier research, showed a low incidence of warfarin adherence [30]. The drug limitations of VKA and the significant benefits of fixed dosages are overcome to some extent by NOACs. Our data, which indicated higher adherence to rivaroxaban than warfarin, are similar to those from previous studies indicating high adherence to NOACs [31]. This study has several limitations, as follows: (1) retrospective data and analysis were used; (2) the follow-up time was relatively short; (3) the number of patients with AF in the analysis was relatively small; (4) the causes of nonadherence were not assessed; and (5) Cox regression models were not used, owing to the lack of an accurate time point for bleeding and stroke. In future studies, survival analyses with large cohorts should be conducted to supplement and validate the current findings.

Conclusions

According to the results of the safety and efficacy clinical profiles for warfarin and rivaroxaban among northern Chinese patients with AF with different CHA2DS2-VASc scores, better adherence and lower bleeding and thrombosis events were observed in the rivaroxaban-treated group than the warfarin-treated group. Thus, rivaroxaban is a better choice for northern Chinese patients receiving anticoagulative treatment for AF, regardless of economic factors.

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