Comparison of Safety and Efficacy of Warfarin Versus Rivaroxaban in Northern Chinese Patients With Different CHA2DS2-VASc Score

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Research

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Abstract

Purpose: Although many researches have indicated the anticoagulant effect of warfarin and rivaroxaban in atrial fibrillation (AF) patients, the comparison of these drugs on safety and efficacy in northern Chinese patients with different CHA2DS2-VASc Score is unclear. We aim to compare the safety and efficacy of warfarin versus rivaroxaban in northern Chinese AF patients with different CHA2DS2-VASc Score subgroups.

Methods: 387 AF patients were recruited in the study. Of these, one group patients (n=194) were receiving warfarin, and the other group patients (n=193) were receiving rivaroxaban. Follow-up data were collected for one year, which included adherence, bleeding and ischemic stroke (IS) events.

Results: There was better adherence in rivaroxaban-treated group than warfarin-treated group. The events of bleeding decreased with increased score in warfarin-treated group. Patients with score 2-3, had better adherence and less stroke events in warfarin-treated group. The events of bleeding and stroke was not significantly different in rivaroxaban-treated group at different score.

Conclusions: We found that there was better adherence and less bleeding and stroke events in rivaroxaban-treated group than warfarin-treated group with different CHA2DS2-VASc score. There is better choice for northern Chinese patients to select rivaroxaban in the anticoagulative treatment of AF, regardless of economic factors.

Introduction

Atrial fibrillation (AF), reported common cardiac arrhythmias, has high incidence in aging society [1, 2]. AF patients have high risk of death and various diseases, such as IS [3]. Due to the cold weather in northern China, the incidence of cardiovascular disease, such as AF and IS, is very high. Warfarin has been proven to effectively inhibit stroke events in patients with AF [4–6]. However, warfarin has a lot of restricted application in patients beacuse of bleeding events [7]. At present, new oral anticoagulation agents (NOACs) have been indicated to be better than warfarin for preventing of stroke in non-valvular AF patients [8, 9]. Rivaroxaban plays the anticoagulant role by inhibiting coagulation factor Xa. Although rivaroxaban and warfarin have similar risks of bleeding and stroke events, rivaroxaban is easy to use and does not require therapeutic monitoring.

Although warfarin and NOACs are effective anticoagulation therapy for preventing stroke in patients with AF [10], improved medication adherence of AF patients is important for treatment benefits. Previous study reported that NOACs may have higher adherence, because of less require routine monitoring with laboratory testing than warfarin [11–13]. However, the higher proportion of medical insurance payment for warfarin than rivaroxaban in northern China and using of warfarin can reduce medical costs. The current situation of adherence to medication in northern Chinese patients is unclear. In this way, studying adherence of northern Chinese patients may be beneficial to the safety and efficacy of oral anticoagulants in cold region.

The CHA2DS2-VASc score has been generally known to evaluate the risk of IS in AF patients, however, there has been limited real-world evidence about the risk of IS according to the scores in northern Chinese patients. In this study, we aim to use real-world data to evaluate the incidence of bleeding and IS events according to relative adherence and different CHA2DS2-VASc scores in northern Chinese AF patients who were treated by warfarin or rivaroxaban.

Methods

Study Subjects

We selected patients with non-valvular AF from September 2018 to August 2019 at the Second Affiliated Hospital, Harbin Medical University in our hospital's database. Patients received oral anticoagulant therapy (216 patients using warfarin and 211 patients using rivaroxaban) for prevention of IS. Patients who were taking anticoagulants for vein thrombosis treating were excluded. All patients were treated with warfarin (1.25–2.5 mg/d, INR: 2.0–3.0) or rivaroxaban (15–20 mg/d) according to physician's decision. The study protocols were approved by the Second Affiliated Hospital of the Harbin Medical University (KY2020-195).

Safety and Efficacy Assessments

The safety outcome included bleeding events such as hemorrhinia, fundus hemorrhage, gingival bleeding, and gastrointestinal bleeding. The efficacy outcome was identified with thrombosis events. The definition of IS was focal neurological deficit for 24 h but no hemorrhage. The definition of systemic embolism was acute vascular occlusion. Bleeding and IS was diagnosed by physician using radiological examination or vascular imaging. All medical records of the patients were evaluated by physician.

Follow-up and Outcomes

Follow-up data were obtained at 1, 3, 6 and 12 months. The patients' clinical status, mediation adherence, bleeding events (hemorrhinia, fundus hemorrhage, gingival bleeding, and gastrointestinal bleeding), stroke occurrence, and other side effects were assessed during the follow-up visits. The follow-up outcomes of warfarin and rivaroxaban -treated group was compared.

Statistical Analysis

We used CHA2DS2-VASc score to evaluate stroke risk. Warfarin and rivaroxaban -treated patients were further divided into three groups with CHA2DS2-VASc score 0–1, score 2–3 and score ≥ 4 according to the previous study [14]. Data were shown mean and ± standard deviation and were compared with independent-samples t test for continuous variables. Data were shown percentage and were compared using the chi-square test for categorical variables. All statistical assessments were conducted with SPSS 20 (SPSS, USA). $P < 0.05$ was accepted for statistical significance.

Results

Study Population

427 AF patients who received anticoagulant therapy with warfarin or rivaroxaban were enrolled in the study. One group (216 participants) were treated with warfarin, the other group (211 participants) were treated with rivaroxaban. However, 40 participants were lost during the follow-up period: 22 in warfarin-treated group and 18 in rivaroxaban-treated group. The two group were comparable in age, gender, hypertension, diabetes mellitus, previous stroke, cardiac function, CHA2DS2-VASc score, and blood biochemical indexes et al. The results showed in Table 1.

Table 1
Baseline characteristics of 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
Smoker (%)	52 (26.8%)	35 (18.1%)	0.041
Alcohol user (%)	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

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.

Adherence

Adherence rate was 59.3% in warfarin-treated group, which was lower than rivaroxaban-treated group (78.2%, $P < 0.001$). The adherence rate of moderate-risk stroke patients (score 2–3, 67.3%) was higher than patients with low or high-risk stroke in warfarin-treated group (score 0–1, 51.4% and score ≥ 4,

49.1%). The adherence rates were similar in rivaroxaban-treated patients with different CHA2DS2-VASc scores (score 0–1, 79.6%; score 2–3, 75.7%; score ≥ 4, 79.7%). There was lower adherence of warfarin-treated group than rivaroxaban-treated group with score 0–1 and score ≥ 4 ($P < 0.01$ for all comparisons). The results showed in Table 2.

Table 2
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 year, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, sex category.

Safety and Efficacy Outcomes

The safety and efficacy outcomes of two groups during the follow-up period were showed in Fig. 1. Bleeding events were more in warfarin-treated group (36, 18.6%) than rivaroxaban-treated group (29, 15.0%), but there was no statistical difference (Fig. 1A). There was 36 patients occurred bleeding in the warfarin group, which included hemorrhinia (12, 33.3%), fundus hemorrhage (4, 11.1%), gingival bleeding (16, 44.4%), and gastrointestinal bleeding (4, 11.1%) (Fig. 1C). There was 29 patients occurred bleeding in the rivaroxaban group, which included hemorrhinia (3, 10.3%), fundus hemorrhage (5, 17.2%), gingival bleeding (17, 58.6%), and gastrointestinal bleeding (4, 13.8%) (Fig. 1D). The cumulative incidence of IS events in the warfarin and rivaroxaban groups was 8.8% (17/194) and 6.7% (13/193), respectively (Fig. 1B). There was no statistical difference in the two treatment groups.

Risks of Bleeding and IS based on CHA2DS2-VASc Scores

To evaluate the safety and efficacy of warfarin versus rivaroxaban in AF patients at different CHA2DS2-VASc scores, we classified the AF patients to three groups: CHA2DS2-VASc score 0–1, score 2–3, and score ≥ 4, which have treated with warfarin or rivaroxaban. Bleeding events tended to be more in warfarin-treated group than rivaroxaban-treated group at score 0–1 and score 2–3, but the difference was no significance (Fig. 2A). Furthermore, in warfarin-treated group, patients with score 0–1 have more bleeding events than patients with score 2–3 and score ≥ 4 (Fig. 2B) ($P < 0.05$). In rivaroxaban-treated group, bleeding was not significantly different between patients with different scores (Fig. 2C).

IS events were more in warfarin-treated group than rivaroxaban-treated group at score 0–1 and score ≥ 4, but the difference was no statistical significance (Fig. 2D). Furthermore, in warfarin-treated group, patients with score ≥ 4 have more IS events than patients with score 2–3 (Fig. 2E) ($P < 0.01$). In

rivaroxaban-treated group, IS events was not significantly different between patients with different scores (Fig. 2F).

To further study type of bleeding with CHA2DS2-VASc score, we divided the bleeding into four subgroups: hemorrhinia, fundus hemorrhage, gingival bleeding, and gastrointestinal bleeding, which have induced by warfarin or rivaroxaban (Fig. 3). Only hemorrhinia was more in the warfarin-treated group than the rivaroxaban-treated group with score 0–1 (Fig. 3A) ($P < 0.05$). The incidence rate of fundus hemorrhage, gingival bleeding, and gastrointestinal bleeding was not significantly different in warfarin or rivaroxaban-treated group with different scores (Fig. 3B-D).

Hospitalization

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

Discussion

Our study is a retrospective research to compare safety and efficacy of warfarin versus rivaroxaban in northern Chinese AF patients with different CHA2DS2-VASc Scores. The findings of our study were including: (1) There was better adherence in the rivaroxaban-treated group than the warfarin-treated group; (2) Bleeding events decreased with the increased score in warfarin-treated group. Patients with score 2–3, had better adherence and less stroke events in warfarin-treated group; (3) The events of bleeding and stroke was not significantly different in rivaroxaban-treated group at different score.

The risks of bleeding events were relatively high in our present study. Previous study indicated that warfarin and rivaroxaban have similar risks of major bleeding [15–17]. The previous study also found that 10.1% and 16.4% patients occurred major bleeding in the NOACs and warfarin group, respectively [18]. Our study found that bleeding events was less in rivaroxaban-treated group (15.0%) than warfarin-treated group (18.6%), but there was no significant difference. Bleeding events in warfarin-treated group were more than in rivaroxaban-treated group with score 0–1 and score 2–3, but the difference was no significance (Fig. 2A). Furthermore, warfarin-treated group with score 0–1 have higher bleeding risk than group with score 2–3 and score ≥ 4 (Fig. 2B) ($P < 0.05$). These result indicated that AF patients with score 0–1 might be induced bleeding by warfarin. The result was not consistent with previous findings [19]. They found that the high rates for bleeding events happened in the patients at score ≥ 5.

In the present study, incidence rate of IS was high. Previous studies found that there was similar stroke rates in NOACs and warfarin-treated group [20–22]. In our study, IS risk in warfarin-treated group was higher than that in rivaroxaban-treated group with score 0–1 and score ≥ 4, but the difference was no significance (Fig. 2D). Furthermore, in warfarin-treated group, patients with score 2–3 have less IS events

than patients with score 0–1 and score ≥ 4 (Fig. 2E) ($P < 0.01$). These results may be induced because of the higher adherence to treatment with warfarin in patients with score 2–3 (Table 2).

Oral anticoagulants are usually used for preventing thrombosis in AF patients, before the onset of symptoms, so AF patient is not especially vulnerable to adherence. The application of warfarin requires regular monitoring, which may be another reason for nonadherence. Many studies indicated that patients who were treated by warfarin, many difficulties to maintain adherence for long term [23, 24]. Our findings indicated low adherence rate to warfarin, which was consistent with previous study [25]. The important advantage of rivaroxaban is freedom from monitoring. Previous study indicated NOACs improved adherence [12], which is consistent with our data indicated that adherence to rivaroxaban was higher than warfarin. There were several limitations in our study: (1) Our data and analysis were retrospective. (2) The follow-up time was relatively short. (3) The number of AF patients for analysis and statistics were relatively small. (4) There was no reasons for nonadherence were explored in our present study.

Conclusions

According to the results of the safety and efficacy clinical profile for warfarin and rivaroxaban in northern Chinese AF patients at different CHA2DS2-VASc Scores, we found that better adherence and lower bleeding and thrombosis events in rivaroxaban-treated group than warfarin-treated group with different CHA2DS2-VASc score. There was better choice for northern Chinese patients to select rivaroxaban in the anticoagulative treatment of AF, regardless of economic factors.

Declarations

Ethics approval consent to participate

This study was reviewed by the Second Affiliated Hospital of the Harbin Medical University (KY2020-195). Informed consent was not applicable.

Consent for publication

All authors have given their consent for the manuscript to be published.

Availability of data and materials

The datasets generated and/or analysed during this study are available from the corresponding author on reasonable request.

Competing interests

There was no conflicts of interest to declare.

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Authors' contributions

Conception and design: Shiwei Xu, Zengxiang Dong. Data analysis and interpretation: Yuanyuan Guo, Xianghui Li. Manuscript writing: Zengxiang Dong, Xin Hai. Final approval of manuscript: Zengxiang Dong, Xin Hai.

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Figures

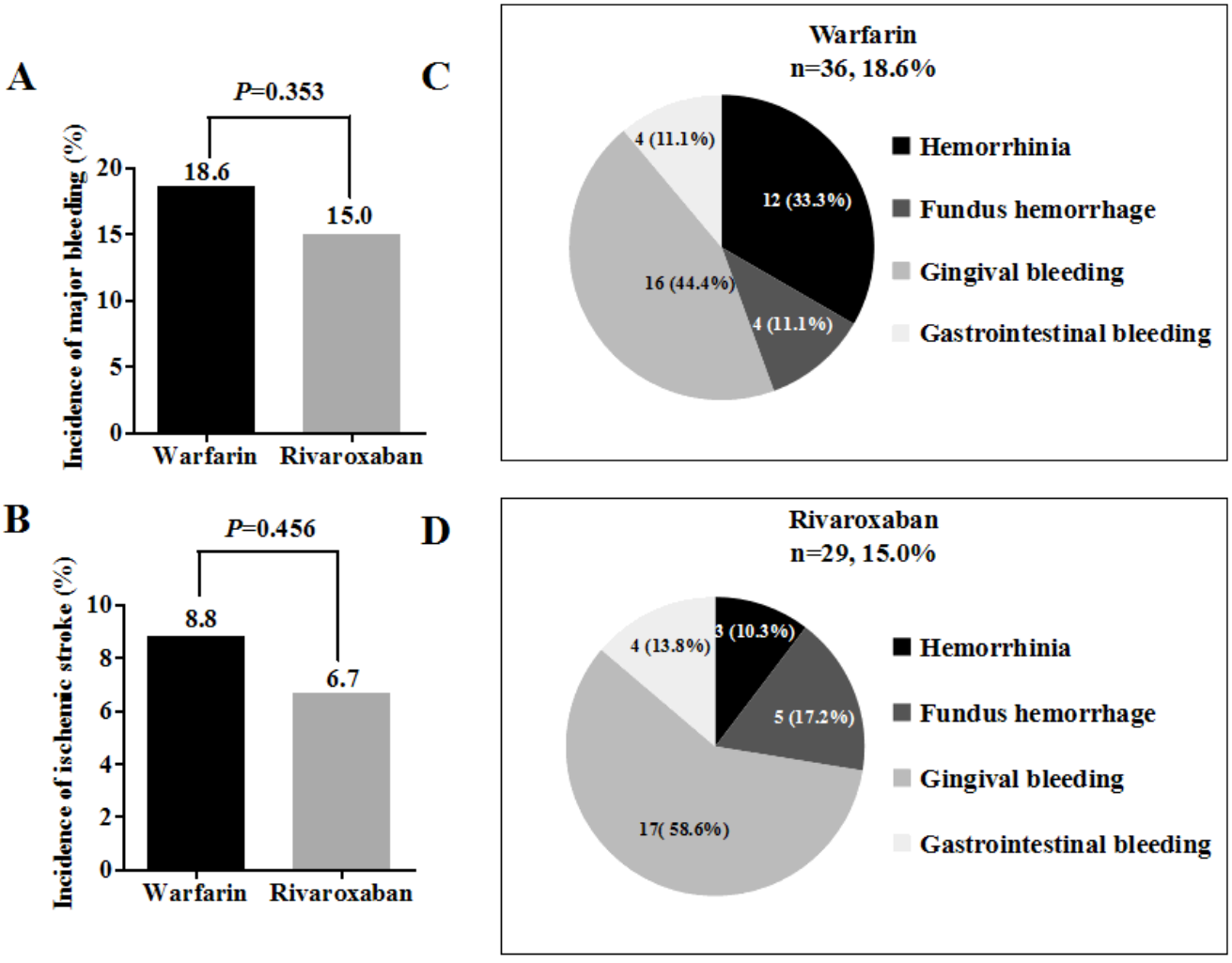

Figure 1

The efficacy and safety outcomes according to warfarin or rivaroxaban treatment. (A) The bleeding events incurred with warfarin or rivaroxaban treatment. (B) Ischemic stroke with warfarin or rivaroxaban treatment. Sites of bleeding with warfarin (C) or rivaroxaban (D).

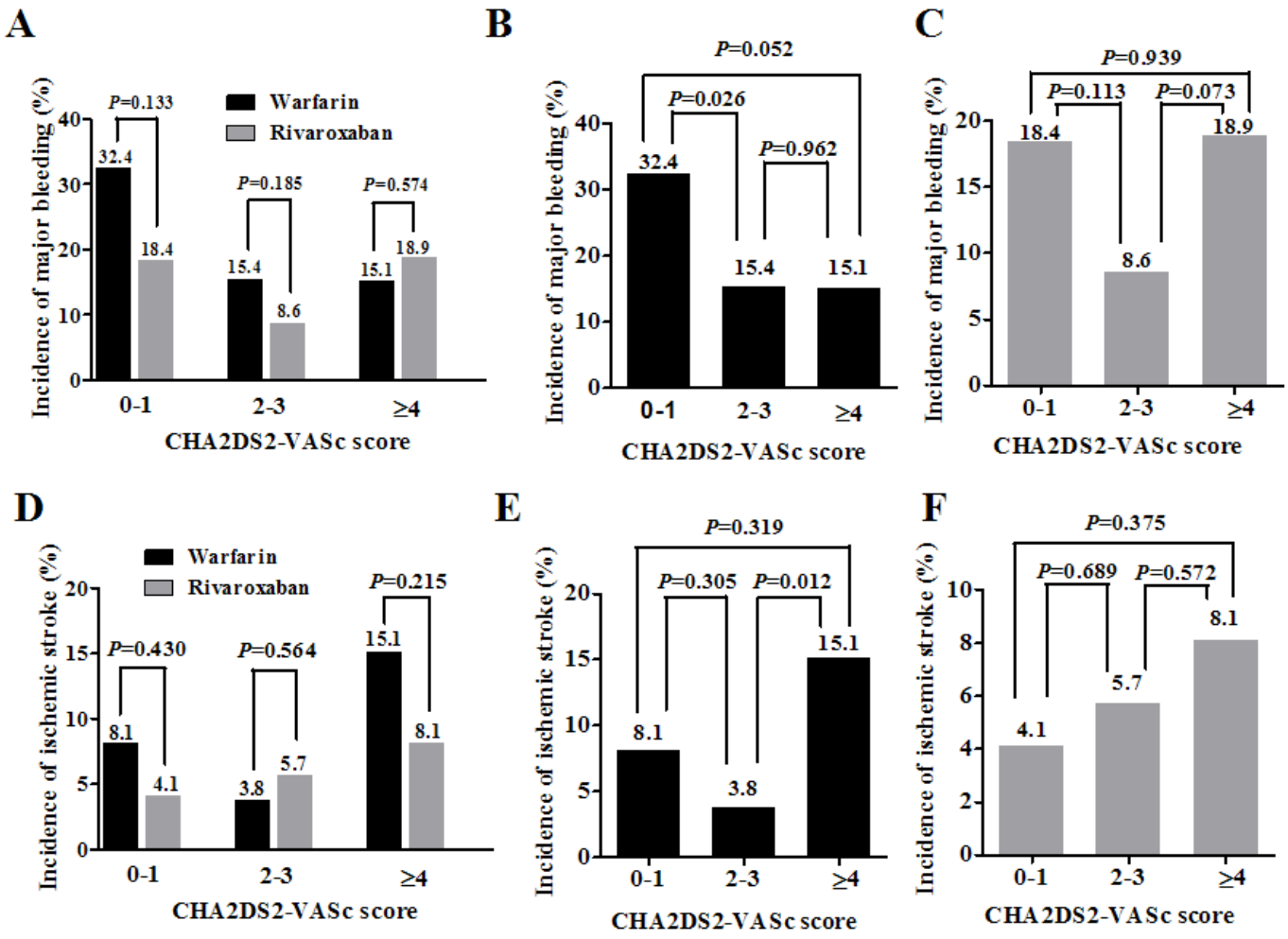

Figure 2

The incidence rate of bleeding and ischemic stroke according to CHA2DS2-VASc Scores. (A) The bleeding with warfarin and rivaroxaban treatment according to score. The bleeding with warfarin (B) or rivaroxaban (C) treatment according to score. (D) IS with warfarin or rivaroxaban treatment according to score. IS with warfarin (E) or rivaroxaban (F) treatment according to CHA2DS2-VASc Scores.

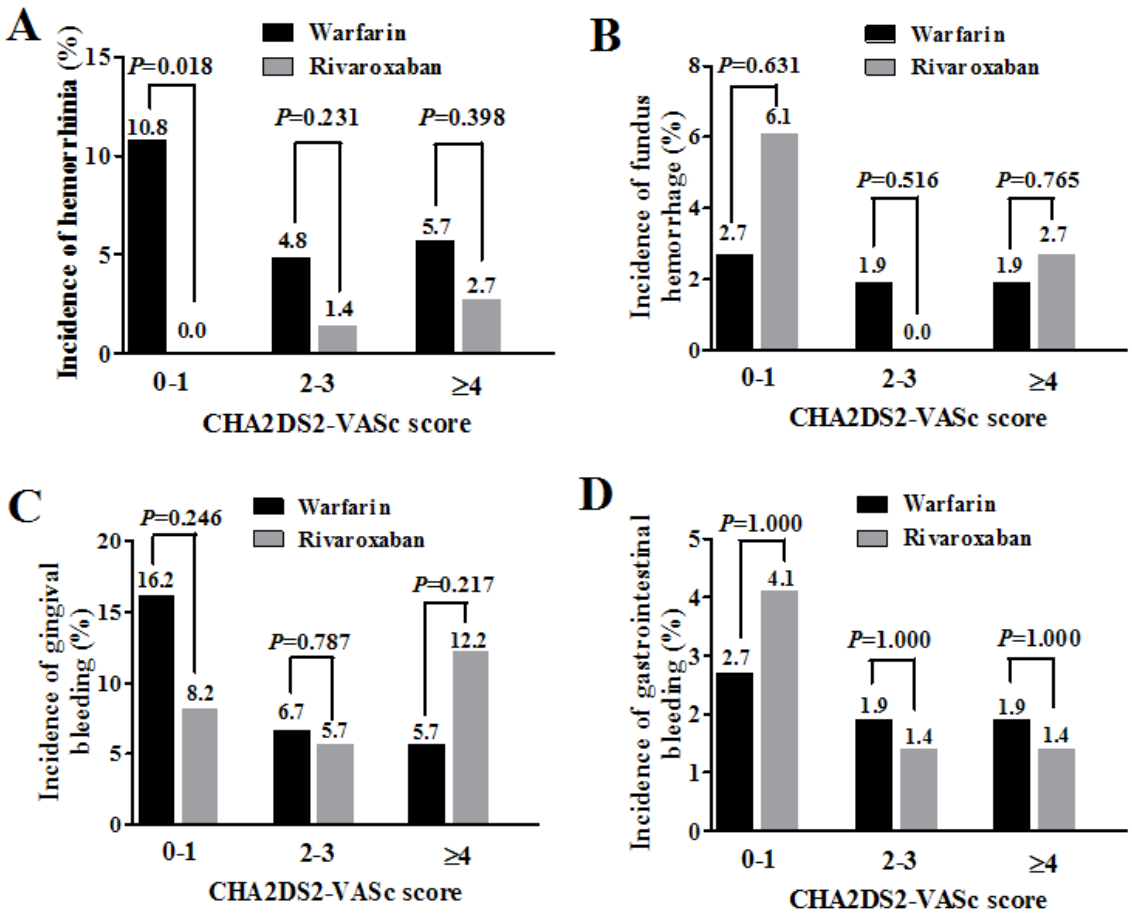

Figure 3

The subgroups of bleeding with warfarin and rivaroxaban treatment according to CHA2DS2-VASc Scores. (A) Hemorrhinia, (B) fundus hemorrhage, (C) gingival bleeding, and (D) gastrointestinal bleeding.

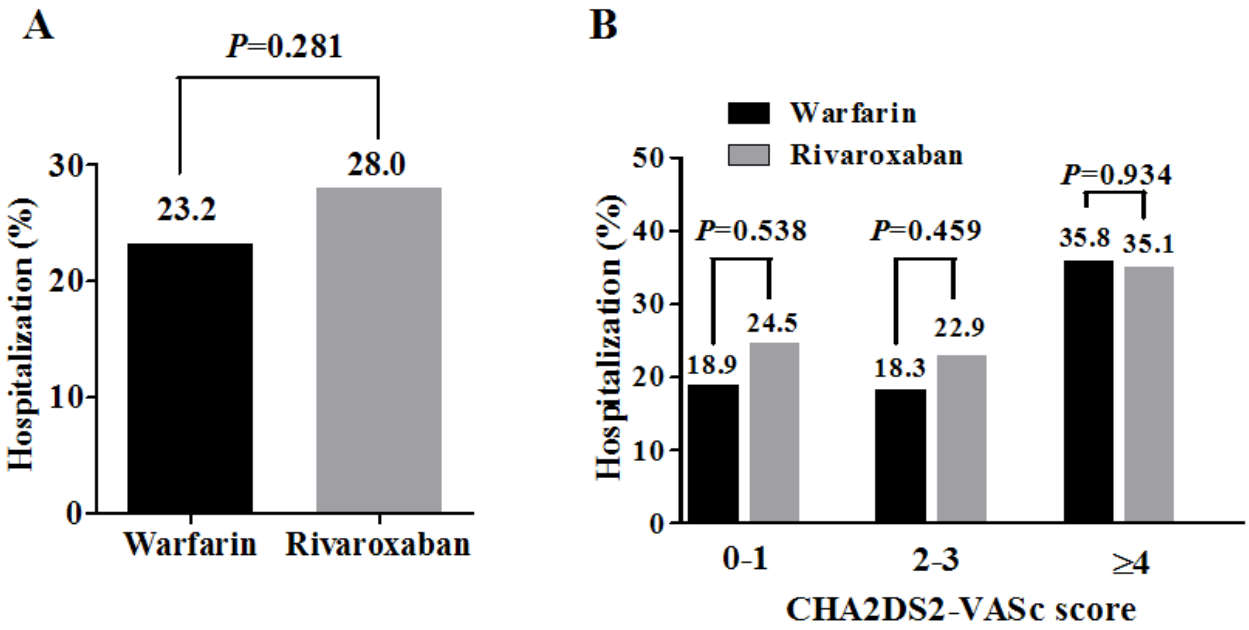

Figure 4

The incidence rate of hospitalization. (A) The incidence rate of hospitalization with warfarin and rivaroxaban treatment. (B) The incidence rate of hospitalization according to CHA2DS2-VASc Scores.