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Original Article

Comparison of clinical effects and costs among dabigatran etexilate, rivaroxaban and warfarin in elderly patients with atrial fibrillation

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Abstract: Objective: To analyze the clinical effects and economic costs between Warfarin and novel oral anticoagulants in elderly patients with atrial fibrillation (AF). Methods: This is a retrospective study. A total of 680 elderly AF patients receiving oral anticoagulants for the first time were selected as subjects and assigned into Group A, B and C. Patients in group A, B and C were given dabigatran etexilate, rivaroxaban and warfarin, respectively. Patients were followed up for 2 years. This study compared indicators of left ventricular diastolic function such as left ventricular posterior wall in end-diastole (LVPWd), minimum peak velocity in early diastole phase and maximum peak velocity in late diastole phase, indicators of myocardial ischemia including creatine kinase isoenzyme, lactate dehydrogenase (LDH) and myoglobin, as well as other outcomes including adverse events incidences and treatment costs, among the three groups. Results: After treatment, LVPWd was found to be obviously lower in group A and group B than that in group C, while the minimum peak velocity in early diastole phase was markedly more in group A and B than that in group C (all $P<0.05$). In addition, the concentrations of myoglobin and LDH were significantly reduced in group A and B than those in group C (all $P<0.05$). The occurrence rate of adverse events was significantly lower in group A and B than that in group C ($P<0.05$). Moreover, treatment cost was markedly less in group A and B than that in group C ($P<0.05$). Conclusion: Compared with warfarin, dabigatran etexilate and rivaroxaban not only have the ability to inhibit the myocardial ischemia indicators and improve left ventricular diastolic function while reducing the incidence of adverse events, but they also offer certain cost-effectiveness advantages for elderly patients with AF.

Keywords: Atrial fibrillation, rivaroxaban, warfarin, dabigatran etexilate, cost-effective, clinical effects

Introduction

Atrial fibrillation is a common cardiac arrhythmia with an incidence of approximately 1% [1]. Previous studies showed that the incidence of atrial fibrillation was positively correlated with age [2]. Patients with atrial fibrillation are prone to have complications with thromboembolism and stroke, which is a prime cause of death for these patients. Some studies reported that in non-atrial fibrillation patients the incidence of stroke was only 1/5 of that in atrial fibrillation patients, and the disability rate and the mortality following stroke in non-atrial fibrillation patients were also markedly lower than those in atrial fibrillation patients [3, 4]. Relevant study showed that about 20% of stroke diseases in clinic were closely associated with atrial fibrillation, and 90% of thrombus in non-valvular atrial fibrillation patients originated from the left atrial appendage [5]. With the increased aging of the population, risk factors for atrial fibrillation have also been increasing. Atrial fibrillation is more common in the elderly, and in addition to stroke, it could also lead to progressive heart failure and cardiac arrest. Studies showed that among people over 80 years old in China, the prevalence rate of atrial fibrillation could reach about 7.5%, and the incidence of stroke in such patients could go as high as

32.8% [6]. Therefore, elderly patients with atrial fibrillation exhibit high rates of disability and mortality.

For the treatment of atrial fibrillation, it had been considered that anticoagulation was more important than rhythm management, so anticoagulation therapy is currently the preferred method for atrial fibrillation therapy. In recent years, effective results have also been achieved in the terms of the prevention of embolic events. Warfarin, as the traditional treatment drug, was widely used in clinical practice with definite therapeutic effects. However, the application of Warfarin is associated with several limitations, including a slow onset time, the need for frequent and ongoing monitoring of the international normalized ratio (INR) and susceptibility to drug and food interactions, which decrease patient compliance [7]. Patients over 65 years old often have multiple comorbidities and multi-drug resistance, leading to increased scores on both the CHA2DS2-VASc and the HAS-BLED scales. As a result, these patients are at higher risk of cerebral hemorrhage and stroke. At present, both dabigatran etexilate and rivaroxaban are the most cutting-edge oral anticoagulant drugs used in clinic. They have been proven to be effective in terms of preventing systemic embolism and stroke in non-valvular atrial fibrillation patients [8, 9]. Although both novel oral anticoagulants and Warfarin have been confirmed to have good efficacy in many clinical studies, there is no research regarding whether the novel oral anticoagulants are more cost-effective than Warfarin for the treatment of elderly patients with atrial fibrillation. In this context, we conducted a study on the outcomes of 680 elderly patients with atrial fibrillation who received oral anticoagulants for the first time, and investigated the clinical therapeutic effects and economic costs. The findings of this study aimed to provide clinical evidence for the treatment of atrial fibrillation with anticoagulants in elderly patients.

Material and methods

General information

This is a retrospective study. Through the electronic medical record system, a total of 680 elderly patients with atrial fibrillation who received oral anticoagulant drugs for the first time were selected as subjects. All the patients in the study were admitted to the outpatient and/or inpatient departments of Zhoushan Hospital of Zhejiang University from July 1, 2019 to June 30, 2020. The eligible patients were assigned into three groups: group A, group B and group C, according to the treatment regimens. Inclusion criteria: ① Patients were diagnosed with atrial fibrillation disease according to the American Guidelines for the Management of Atrial Fibrillation (2013) [10], and were treatment-naïve. ② Patients were over 75 years old. ③ Patients were diagnosed with atrial fibrillation by electrocardiography and other examinations. ④ Patients had a score of more than 2 points in CHA2DS2-VASc scale. ⑤ Patients had complete case records and finished the treatment without any changes in the treatment drugs. Exclusion criteria: ① Patients had valvular atrial fibrillation. ② Patients had coagulation disorders. ③ Patients were accompanied with severe hepatorenal dysfunction and a glomerular filtration rate of less than 30 ml/min/1.73 m^2. ④ Patients had severe digestive system disease such as peptic ulcer. ⑤ Patients were combined with tumors. ⑥ Patients had incomplete medical records, including current and past medical history. This trial was authorized by the Ethics Committee of China Coast Guard Hospital of the People's Armed Police Force (Ethics approval number: 202032).

Data collection

General data of eligible patients, including age, sex, CHA2DS2-VASc scores, drinking and smoking history, hypertension, diabetes, hyperlipidemia and renal insufficiency were collected from the medical records.

The follow-up data, which was comprised of left ventricular diastolic function (left ventricular posterior wall in end-diastole, minimum peak velocity in early diastole phase, maximum peak velocity in late diastole phase), myocardial ischemia (creatine kinase isoenzyme, lactate dehydrogenase, myoglobin), incidence of adverse events and treatment costs were also collected. We manually reviewed and checked the printed medical records to validate the accuracy of the data.

Treatment methods

Patients in group A received treatment of oral dabigatran etexilate, 2 times per day, 1 capsule per time. The capsules were from Boehringer

Table 1. Comparison of general information between the two groups

Baseline characteristics	Group A N=226 No. (%)	Group B N=227 No. (%)	Group C N=227 No. (%)	F/χ^2 value	*P* value
Age (years)	77.32±0.53	77.36±0.57	77.38±0.59	0.665	0.515
Sex (n)					
Male	132 (58.4%)	135 (59.5%)	129 (56.8%)	0.330	0.848
Female	94 (41.6%)	92 (40.5%)	98 (43.2%)		
CHA2DS2-VASc scores	3.16±0.22	3.14±0.21	3.18±0.24	1.815	0.164
Drinking and smoking history (n)	92 (40.7%)	96 (42.3%)	91 (40.1%)	0.242	0.886
Hypertension (n)	143 (63.3%)	145 (63.9%)	141 (62.1%)	0.156	0.925
Diabetes (n)	138 (61.1%)	139 (61.2%)	135 (59.5%)	0.179	0.914
Hyperlipidemia (n)	129 (57.1%)	125 (55.1%)	131 (57.7%)	1.948	0.378
Renal insufficiency (n)	2 (0.9%)	1 (0.4%)	3 (1.3%)	1.007	0.604

Ingelheim Pharma GmbH & Co. KG (Approval number: H20130163; Specification: 110 mg × 10 capsules). Patients in group B received treatment of rivaroxaban, once per day at 15 mg per time. The oral rivaroxaban tablets were from Bayer Healthcare Co., Ltd (Approval number: H20140132; Specification: 10 mg × 5 tablets). Patients in group C were given warfarin treatment. Oral warfarin sodium tablets were from Shanghai Xinyi Pharmaceutical Co., Ltd (Approval number: H31022123; Specification: 2.5 mg × 60 tablets). The starting dose was 2.5 mg per time, once per day. Then, the dose of warfarin was adjusted according to their INR. The INR value was examined every day and controlled between 2 and 3. All the patients were suggested to take their medicine with warm water.

Observed indicators

The primary outcomes in this study were left ventricular diastolic function and treatment cost. The secondary outcomes were indicators for evaluating myocardial ischemia and incidence of clinical adverse events.

(1) Left ventricular diastolic function: All patients underwent cardiac color ultrasound examination before treatment and at the end of two-year follow-up. The items included the minimum peak velocity in early diastole phase, the maximum peak velocity in late diastole phase, and the thickness of left ventricular posterior wall in end diastole. (2) Indicators for evaluating myocardial ischemia: 3 ml of fast peripheral venous blood was collected from each patient in the early morning before treatment and at the end of two-year follow-up, respectively. Then, the serum was isolated for detection after centrifugation (15 min, 3500 r/min), and the albumin cobalt binding test was used to detect the levels of myoglobin. The concentrations of creatine kinase isoenzyme and lactate dehydrogenase were examined using enzyme-linked immunosorbent assay. (3) The incidence of clinical adverse events such as stroke, gastrointestinal bleeding, intracranial hemorrhage and thromboembolism during the treatment process were recorded and compared among groups. (4) At the end of follow-up, the direct treatment costs included drugs, medical examination and hospitalization expense for the clinical accident, indirect treatment costs such as traffic and nutriments, as well as the sum were calculated for comparison.

Statistical methods

SPSS 19.0 software was employed for analyzing the data. The measured data were presented in form of mean ± standard deviation (SD). The inter-group comparison was conducted by one-way ANOVA analysis followed by LSD-t test. The intra-group before-after comparison was performed by paired sample t test. The enumeration data were presented in the form of [n (%)], and χ^2 test was used for the pairwise comparison. $P<0.05$ was considered as statistical significance.

Results

Comparison of general information

As shown in **Table 1**, no marked differences were observed in terms of sex, age, history of drinking and smoking, hypertension, diabetes,

Table 2. Comparison of left ventricular diastolic function among group A, B and C (Mean ± SD)

Groups	Cases	The thickness of left ventricular posterior wall in end diastole (mm)		The maximum peak velocity in late diastole phase (cm/s)		The minimum peak velocity in early diastole phase (cm/s)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A	226	12.48±2.02	10.51±1.12*,#	69.70±8.32	62.45±6.75*	51.82±6.34	65.67±8.76*,#
Group B	227	12.51±2.05	10.43±1.04*,#	68.79±9.11	62.31±6.56*	50.94±5.76	65.78±8.85*,#
Group C	227	12.84±1.88	11.33±1.87*	69.65±8.41	64.54±6.79*	51.73±6.29	61.43±7.40*
F value		1.903	98.649	2.252	0.304	2.503	8.731
P value		0.386	0.000	0.324	0.859	0.286	0.013

Note: Compared with those prior therapy, *P<0.05; Compared with those after therapy in group C, #P<0.05.

Table 3. Comparison of indicators for myocardial ischemia among groups (Mean ± SD)

Groups	Cases	Myoglobin (ng/mL)		Lactate dehydrogenase (U/L)		Creatine kinase isoenzyme (μg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A	226	250.85±5.25	83.11±4.28*,#	89.43±16.75	36.01±5.09*,#	1.85±0.34	1.26±0.23*
Group B	227	251.42±5.37	82.33±4.27*,#	88.49±15.84	35.14±5.18*,#	1.79±0.36	1.25±0.24*
Group C	227	251.47±5.48	117.74±5.16*	87.95±16.34	43.50±8.60*	1.81±0.35	1.36±1.25*
F value		0.414	11.037	0.704	86.049	0.735	1.563
P value		0.813	0.004	0.703	0.000	0.693	0.458

Note: Compared with those prior treatment, *P<0.05; Compared with those post treatment in group C, #P<0.05.

hyperlipidemia, renal insufficiency and CHA-2DS2-VASc score among the three groups, so they were comparable (all P>0.05).

Comparison of left ventricular diastolic function among groups

As seen in **Table 2**, no obvious differences in the minimum peak velocity in early diastole phase, the maximum peak velocity in late diastole phase, the thickness of left ventricular posterior wall in end diastole were observed before treatment among the three groups (all P>0.05). After treatment no statistical differences in the maximum peak velocities in late diastole phase was obtained among the three groups (P>0.05). However, in all 3 groups, the thickness of the posterior wall of the left ventricle in end diastole and the maximum peak velocity in the late diastole phase were markedly less than those prior treatment, and the minimum peak velocity in the early diastole was markedly more than that prior treatment. Furthermore, compared with group C, group A and B had decreased thickness of left ventricular posterior wall in end diastole and increased minimum peak velocity in the early diastole, with statistically significant differences (all P<0.05).

Comparison of myocardial ischemia indicators among groups

As shown in **Table 3**, there were no statistical differences in concentrations of creatine kinase isoenzyme, lactate dehydrogenase and myoglobin among the three groups before treatment (all P>0.05). After treatment, the concentrations of myoglobin, creatine kinase isoenzyme and lactate dehydrogenase were significantly decreased (all P<0.05). Moreover, the levels of myoglobin and lactate dehydrogenase after treatment in group A and group B were less than those in group C, and significant differences were observed (all P<0.05).

Comparison of the incidence of adverse events among three groups

As shown in **Table 4**, in group A, there was 1 case with stroke, 1 case with intracranial hemorrhage and 1 case with thromboembolism. The incidence of adverse events was 1.32%. In group B, there was 1 case with stroke, 2 cases with intracranial hemorrhage and 1 case with thromboembolism. The incidence of adverse events was 1.76%. In group C, there were 6 cases with stroke, 16 cases with intracranial hemorrhage, 3 cases with gastrointestinal

Table 4. Comparison of the incidence rate of adverse events among three groups [n (%)]

Groups	Cases	Stroke	Intracranial hemorrhage	Gastrointestinal bleeding	Thromboembolism	The incidence rate of adverse events
Group A	226	1 (0.44)*	1 (0.44)*	0 (0.00)*	1 (0.44)*	3 (1.32)*
Group B	227	1 (0.44)*	2 (0.88)*	0 (0.00)*	1 (0.44)*	4 (1.76)*
Group C	227	6 (2.64)	16 (7.06)	3 (1.32)	6 (2.64)	31 (13.66)
χ^2 value		6.305	20.942	3.100	6.305	42.083
P value		0.043	0.000	0.212	0.043	<0.001

Note: Compared with those in group C, *P<0.05.

Table 5. Comparison of treatment costs among three groups ($\bar{x}\pm s$, Ten thousand Yuan)

Groups	Cases	Drug cost	Cost of medical examination	Hospitalization expense for clinical accident	Traffic cost	Nutriment cost	Total cost
Group A	226	4.15±0.14*	0.42±0.09	0.53±0.09*	0.14±0.06*	0.39±0.17*	5.63±0.25*
Group B	227	4.23±0.16*	0.41±0.09	0.52±0.08*	0.13±0.05*	0.37±0.16*	5.66±0.27*
Group C	227	0.65±0.12	0.43±0.10	4.57±0.11	0.36±0.08	0.58±0.21	6.59±0.34
F value		18.446	3.410	23.799	51.377	19.048	23.900
P value		<0.001	0.182	<0.001	<0.001	<0.001	<0.001

Note: Compared with those in group C, *P<0.05.

bleeding and 6 cases with thromboembolism. The incidence of adverse events was 13.66%. No statistical difference was observed in the incidence of adverse events between group A and group B (P>0.05). However, the incidence of adverse events was lower in group A and group B than that in group C, with a statistically significant difference (all P<0.05).

Comparison of treatment costs among three groups

As shown in **Table 5**, no statistical differences were found between group A and B in drug costs, medical examination expense, hospitalization costs for clinical accidents, traffic costs, nutriment costs, as well as the total cost. While compared with those in group C, the drug costs, hospitalization costs for clinical accidents, traffic costs, nutriment costs, and the total cost in group A and B were significantly reduced, with statistical differences found (all P<0.05).

Discussion

Atrial fibrillation is a prevalent cardiovascular disease seen in clinical practice. The onset of atrial fibrillation is often accompanied by atrial systolic dysfunction, which can lead to blood stasis in the cardiac atrium and the development of thrombus. If the thrombus detaches and flows into the bloodstream, it can cause arterial embolism [11]. The risk of ischemic stroke in atrial fibrillation patients is 4 to 5 times that in the general population. Elderly patients with atrial fibrillation have a higher risk of complications including stroke and bleeding, as a result of many underlying diseases. Correspondingly, they are often subjected to increased treatment costs [12]. Warfarin, a traditional anticoagulant, is effective in the treatment of atrial fibrillation. However, its use is limited by several shortcomings such as a narrow therapeutic window, large individual differences, and the need for frequent monitoring of coagulation function, which restrict its wide application in clinic [13]. Additionally, elderly patients with atrial fibrillation often lack understanding of anticoagulation therapy for stroke prevention and have poor medication compliance, leading to unfavorable monitoring of blood coagulation and large fluctuations in INR. These factors lead to a markedly increased rate of revisits due to bleeding. In contrast, the novel oral anticoagulants have a stability and do not require monitoring of blood coagulation indicators during treatment. The anticoagulant efficacy is comparable to or even better than that of warfarin. The novel anticoagulants also showed lower incidence of complications such as bleeding and stroke, which could significantly reduce the number of hospital visits, the hospitalization rate, and medical costs [14].

Many clinical studies have reported that compared with warfarin, novel oral anticoagulants for atrial fibrillation have higher safety profiles while maintaining effective treatment outcomes, significantly reducing the incidence of major bleeding events, cardiovascular events and overall mortality [15, 16]. Nashid Farhan et al. [17] followed up non-valvular atrial fibrillation patients for two years and found that oral low-dose dabigatran etexilate (110 mg, twice per day) was similar to warfarin in preventing thromboembolic events in atrial fibrillation patients and could reduce incidences of major bleeding and intracranial hemorrhage. In this study, the elderly patients received the same dose of dabigatran etexilate, and the results revealed that the concentrations of myoglobin, lactate dehydrogenase, and creatine kinase isoenzyme were comparable to those in patients treated with rivaroxaban. The concentrations of myoglobin, creatine kinase isoenzyme and lactate dehydrogenase after treatment in both of groups were obviously less than those prior treatment. Also, the posttreatment concentrations of myoglobin and lactate dehydrogenase were lower in patients who received novel oral anticoagulants than those in patients treated with warfarin. It is suggested that dabigatran etexilate and rivaroxaban, as novel oral anticoagulants, can significantly improve myocardial ischemia in patients. This may be due to the rapid action of the novel oral anticoagulants, which can effectively reduce the levels of creatine kinase isoenzyme and lactate dehydrogenase, thereby inhibiting the production of myoglobin and relieving the myocardial ischemia [18].

Moreover, our results also showed that in contrast to those before treatment, the thickness of the left ventricular posterior wall in end diastole and the maximum peak velocity in late diastole phase were significantly reduced, and the minimum peak velocity in early diastole phase obviously increased in patients who receive dabigatran etexilate and rivaroxaban. Moreover, compared with patients treated with Warfarin, patients who received dabigatran etexilate showed decreased thickness of the left ventricular posterior wall in end diastole and increased minimum peak velocity in early diastole phase. It is suggested that dabigatran etexilate and rivaroxaban can significantly improve left ventricular diastolic function, which may be because the left ventricular diastolic dysfunction was one of the manifestations of myocardial ischemia in patients. Since myocardial ischemia was effectively relieved, left ventricular diastolic function was improved accordingly.

In addition, due to the relatively high price for novel oral anticoagulants in China (dabigatran etexilate 110 mg, 16.6 yuan/tablet, 996 yuan per month; rivaroxaban 10 mg, 27.6 yuan/tablet, 1656 yuan per month), the use of novel oral anticoagulants was limited. However, many pharmacoeconomic studies showed that in the term of stroke prevention in atrial fibrillation patients, new oral anticoagulants were considered to be more cost-effective than warfarin [19]. This study also revealed that the incidence of adverse events in elderly patients treated with dabigatran etexilate (1.32%) and rivaroxaban (1.76%) were markedly lower than that in patients receiving Warfarin (14.53%). The drug costs, hospitalization expense for the clinical accidents, traffic costs, nutrition costs and the total cost in patients treated with dabigatran etexilate and rivaroxaban were markedly less than those in patients who received Warfarin. It is indicated that the incidence of adverse events and the treatment-related cost were lower in patients who received novel drugs, with certain cost-effectiveness advantages. The reason for this may be that they have a stable dose-related anticoagulant effect, which is less affected by food and other drugs, so the patients do not require routine monitoring of coagulation function during the treatment process, which can increase the patient compliance and reduce the incidence of adverse events [20]. From the perspective of the price of the drug itself, the novel oral anticoagulants are more expensive. However, from the perspective of reducing complications, they can significantly reduce the costs because of fewer complications such as major bleeding [21], less hospitalization expense for the clinical accident, less traffic and nutrition costs, etc.

In conclusion, dabigatran etexilate and rivaroxaban, as novel oral anticoagulants, are better in the term of protecting the heart in elderly patients with atrial fibrillation in contrast to Warfarin. These novel oral anticoagulants can not only effectively improve left ventricular diastolic function, but also alleviate the symptoms

of myocardial ischemia. In additional, these novel oral anticoagulants could also effectively reduce the incidence of adverse events and treatment costs, with certain cost-effectiveness advantages. So, they are worthy of clinical application. However, there are some limitations about this study because this is a single-center study, with small sample size, no subgroups comparison, no long-term follow-up results, and no reports of the related mechanism. In the future, a multicenter controlled long-term follow-up study with larger sample size is required for further confirmation.

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Disclosure of conflict of interest

None.

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