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Original Article

Enhanced efficacy of bisoprolol and digoxin combination in elderly patients with atrial fibrillation

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Abstract: Objective: To investigate the effect of combining bisoprolol and digoxin on cardiac function in elderly patients with atrial fibrillation (AF). Methods: A retrospective analysis was conducted on the clinical records of 100 elderly AF patients treated at the Second Affiliated Hospital of Hainan Medical University from April 2020 to April 2023. Forty-six patients treated with digoxin alone were assigned to the control group, while the remaining 54 patients treated with bisoprolol in addition to digox comprised the study group. Outcome measures included cardiac function-associated indices (left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic diameter (LVESD) and left ventricular ejection fraction (LVEF)), ventricular rate at rest and during exercise, myocardial energy metabolism (plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) and creatine kinase (CK)), and psychological status prior to and post therapy, and the overall response rate and adverse reactions. Multiple logistic regression was performed to identify independent risk factors for an unfavorable prognosis. Results: After treatment, LVEDD and LVESD levels significantly dropped in both groups (P<0.01), and LVEF level increased significantly (P<0.001), especially in the study group (P<0.01). Ventricular rate at rest and during exercise also decreased significantly in both groups (P<0.001), with a more pronounced effect in the study group (P<0.001). NT-proBNP and CK levels greatly decreased in both groups (P<0.001), especially the study group (P<0.001). The study group presented a notably higher overall response rate compared to the control group (P=0.011), but no significant inter-group difference was observed in the total incidence of adverse reactions (P=0.547). Both groups showed significant reductions in SAS and SDS scores after treatment (P<0.05), with a more substantial improvement in the study group (P<0.05). Logistics regression analysis identified comorbid diabetes mellitus (P=0.025; OR=6.086; 95% CI=1.250-29.638), comorbid hypertension (P=0.007; OR=7.059; 95% CI=1.728-28.842), New York Heart Association classification (P=0.023; OR=0.197; 95% CI=0.049-0.800), and treatment modality (P=0.020; OR=5.911; 95% CI=1.326-26.338) as independent risk factors for unfavorable prognosis. Conclusion: In contrast to digoxin alone, combined application of bisoprolol and digoxin is more effective in treating elderly AF patients. The combined treatment can significantly improve LVEDD, LVESD, LVEF, and ventricular rate without increasing adverse reactions, making it a promising approach for clinical application.

Keywords: Bisoprolol, digoxin, atrial fibrillation, LVEDD, LVESD, LVEF, ultrasonic diagnosis

Introduction

Atrial fibrillation (AF) is a prevalent cardiovascular disorder frequently encountered in clinical settings, with multiple risk factors and comorbidities [1]. The elderly are the most affected group, with the incidence increasing with age [2]. The primary causes of AF include coronary heart disease, hypertension, rheumatic heart disease, and post-cardiac surgery - associated factors [1]. Symptoms of AF typically include palpitations, chest tightness, shortness of breath, and fatigue [1]. In severe cases, AF can lead to hemodynamic instability.

The exact etiology of AF remains unclear, but most studies suggest that its onset is associated with age, underlying conditions (such as hypertension and coronary heart disease), and unhealthy living and eating habits [3, 4]. AF significantly impacts patients' hemodynamics, often leading to complications such as left atrial failure, pulmonary congestion, pulmonary edema, and even death. As a result, active and

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effective treatment approaches are often needed [5].

Clinical treatment of AF primarily aims at controlling the ventricular rate, preventing thrombosis, and, in some patients, restoring rhythm. Antithrombotic and ventricular rate control are the cornerstone treatment for AF [6]. Bisoprolol, a relatively selective β-blocker, exerts its effects by inhibiting adrenergic stimulation of the atrioventricular node, thereby directly reducing atrioventricular conduction. Bisoprolol effectively controls the ventricular rate at rest and during exercise or other sympathetic stimuli in AF patients [7, 8]. Digoxin, on the other hand, controls the ventricular rate by inhibiting atrioventricular conduction, which prevents excessive impulses from passing through the atrioventricular node to the ventricles [9]. Despite the individual benefits of these treatments, there are few clinical studies investigating the combined use of bisoprolol and digoxin in elderly patients with AF.

Therefore, this study explored the effect of combining bisoprolol and digoxin in elderly patients with AF. The novelty of this study lies in its investigation of independent risk factors affecting the prognosis of AF patients. Our findings highlight the enhanced therapeutic efficacy of the combination therapy, demonstrating significant improvements in cardiac function indices and ventricular rates.

Methods and data

Patient selection

With approval from the Medical Ethics Committee of the Second Affiliated Hospital of Hainan Medical University, the clinical records of 125 elderly AF patients treated at the Hospital from April 2020 to April 2023 were retrospectively analyzed. After screening, 100 patients met the inclusion criteria for this study.

Inclusion criteria: 1) Patients presented symptoms such as palpitation, dyspnea, fatigue, palpitation, and chest discomfort [10]; 2) A diagnosis of AF was confirmed based on electrocardiogram findings: (i) Rapid and irregular atrial contractions leading to an overall irregular heart rate; (ii) Disappearance of P waves and irregular QRS complexes in the ventricles due to the irregular atrial contractions; (iii) An overall increase in heart rate typical of atrial fibrillation; 3) Patients were classified as New York Heart Association (NYHA) Class II-III; 4) Patients were ≥60 years old; 5) No contraindications or allergies to the therapeutic drugs used in the study; 6) Complete clinical records available.

Exclusion criteria: 1) Presence of severe organ dysfunction (e.g., liver, kidney or lung failure); 2) Presence of serious cardiovascular or cerebrovascular diseases (e.g., myocardial infarction or acute myocarditis); 3) Poor patient compliance; 4) Use of antiarrhythmic drugs (e.g., amiodarone, propafenone, or calcium channel blockers) within two weeks prior to admission.

A total of 46 patients who received digoxin were assigned to the control group, while the remaining 54 treated by bisoprolol in addition to digoxin were included in the study group. Treatment decisions were made by healthcare professionals based on clinical judgment and individual patient needs. Patients or their legal guardians were provided with detailed information on treatment options, risks, and benefits. The screening and grouping process is illustrated in **Figure 1**.

Data collection

Clinical data and various indices were collected from the patients' electronic medical records and outpatient follow-up records, including age, sex, body mass index (BMI), disease duration, underlying comorbidities, NYHA classification, and place of residence.

Treatment protocols

All patients were given routine basic treatment, including anticoagulant therapy, water-electrolyte imbalance correction, diet control (sodium restriction), and physical activity limitation. Prior to treatment, the use of drugs other than those specified in this study, such as β-blockers, calcium channel antagonists, digitalis, and amiodarone, was prohibited. Drug use was adjusted strictly according to the instructions and the individual needs of the patients to ensure the scientific treatment and enhance the quality of the research.

In the control group, each patient was orally administered digoxin tablets (Shanghai Pharmaceuticals Sine, State Food and Drug Ad-

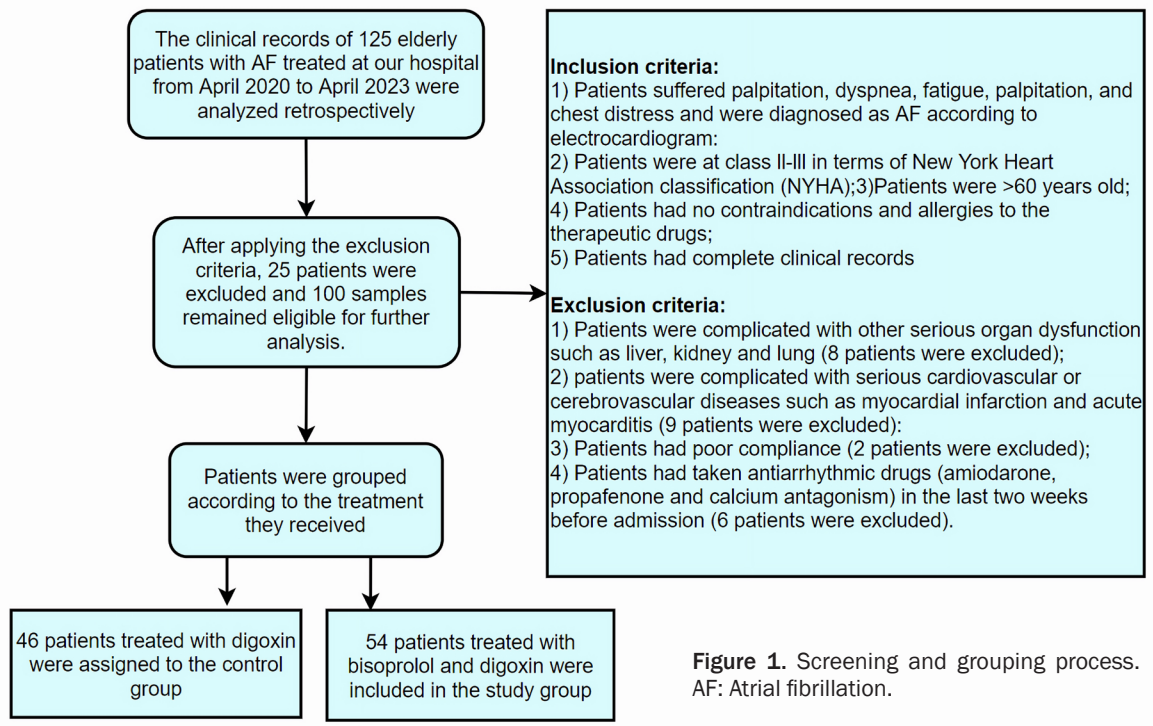

Figure 1. Screening and grouping process. AF: Atrial fibrillation.

ministration (SFDA) approval No. H31020678; 0.25 mg) with an initial dose of 0.125 mg once daily. Patient reactions were closely monitored during treatment. If serious symptoms occurred, the dosage was appropriately increased to 0.25 mg once daily.

In addition to the treatment used in the control group, the study group received bisoprolol fumarate tablets (Beijing HEALSO Pharmaceutical Co., Ltd., SFDA approval number: H10970082, 5 mg), with an initial dose of 2.5 mg once daily. If ventricular rate control was inadequate, the dose was increased to 5 mg once daily. The dosage and administration of digoxin were the same as those of the control group.

Both groups received continuous therapy for 4 months. Before and after treatment, patients in both groups received comprehensive nursing interventions, including medication guidance, health education, psychological counselling, dietary management, and lifestyle guidance, to enhance treatment outcomes and promote healthy recovery.

Outcome measures

Primary outcome measures: (1) Treatment efficacy: The improvement of NYHA classification was used to evaluate and compare the efficacy of the two groups. Markedly effective: After treatment, the NYHA classification improved by 2 classes, and the heart rhythm was normal; Effective: After treatment, the NYHA classification improved by 1 class, and symptoms were relieved; Ineffective: After treatment, the NYHA classification did not change, and symptoms either remained the same or worsened. Overall response rate = (number of markedly effective cases + number of effective cases)/total number of cases × 100%. (2) Cardiac function indices: Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic diameter (LVESD), were measured one day before treatment and after 4 months of treatment using a color Doppler ultrasonic diagnostic apparatus (Siemens, German). (3) Independent risk factors for unfavorable prognosis: Patients were grouped based on treatment efficacy, and independent risk factors for unfavorable prognosis were identified through multiple logistics regression analysis.

Secondary outcome measures: (1) Clinical data: Baseline clinical data of the patients were analyzed. (2) Ventricular rate: The ventricular rate at rest and during exercise was monitored and recorded one day before treatment and after 4 months of treatment. (3) Adverse reactions: Adverse reactions during treatment were statistically analyzed, including bradycardia,

Table 1. Comparison of baseline data between the two groups

Factors	Study group (n=54)	Control group (n=46)	χ^2	*P* value
Age			0.718	0.397
≥65 years old	35	26		
<65 years old	19	20		
Sex			1.413	0.235
Male	40	29		
Female	14	17		
BMI			0.190	0.663
≥23 kg/m^2	20	19		
<23 kg/m^2	34	27		
Course of disease			2.390	0.122
≥1 years	21	25		
<1 year	33	21		
Comorbid diabetes mellitus			1.140	0.286
Yes	10	5		
No	44	41		
Comorbid hypertension			0.447	0.504
Yes	11	7		
No	43	39		
NYHA classification			0.143	0.705
Class II	18	17		
Class III	36	29		
Place of residence			1.448	0.229
Rural area	39	28		
Urban area	15	18		

Notes: BMI: Body Mass Index; NYHA: New York Heart Association classification.

hypotension, and gastrointestinal dysfunction. (4) Myocardial energy metabolism: Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) and creatine kinase (CK) levels were measured by chemiluminescence immunoassay and automatic biochemical analyzer, respectively, one day before treatment and after 4 months of treatment. (5) Assessment of anxiety and depression: The Self-Rating Anxiety Scale (SAS) and the Self-Rating Depression Scale (SDS) were used to assess anxiety and depression levels before and after 4 months of treatment [11].

Statistical analysis

SPSS 20.0 (IBM Corp, Armonk, NY, USA) was adopted for statistical analyses, and GraphPad 8 (GraphPad Software, Inc., San Diego CA, USA) was used for data visualization. Measurement data were normally distributed and described as mean ± standard deviation (SD). Inter-group/intro-group comparisons were conducted using the independent-samples t-test and paired t-test, respectively. Categorical data were presented as cases (%), analyzed using the chi-square test, and reported as χ^2. Multiple logistics regression was used to identify independent risk factors for poor prognosis. A *P*-value of <0.05 was statistically significant.

Results

Comparison of baseline data

There were no significant differences between the control and study groups in terms of sex, age, course of disease, body mass index (BMI), and other baseline characteristics (P>0.05, **Table 1**).

Comparison of cardiac function-associated indices

Before treatment, the two groups were comparable in terms of LVEDD, LVESD and LVEF (P>0.05). However, after treatment, LVEDD and

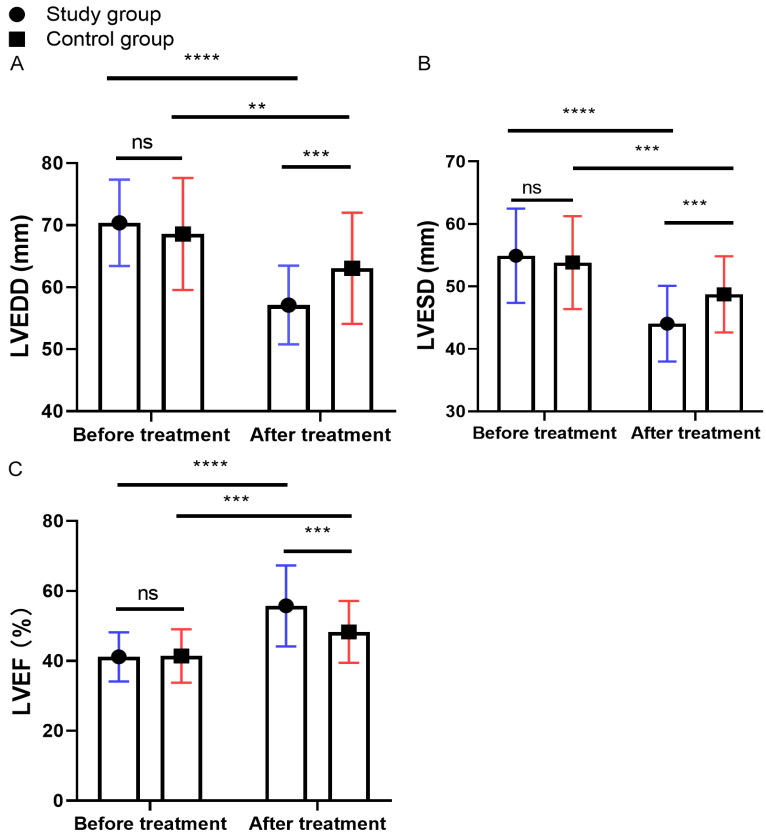

Figure 2. Comparison of cardiac function-associated indices between the two groups before and after treatment. A: Comparison of LVEDD level between the two groups before and after treatment; B: Comparison of LVESD level between the two groups before and after treatment; C: Comparison of LVEF level between the two groups before and after treatment. Notes: nsP>0.05; **P<0.01; ***P<0.001; ****P<0.0001. LVEDD: Left ventricular end-diastolic diameter; LVESD; Left ventricular end-stage systole diameter; LVEF: Left ventricular ejection fraction.

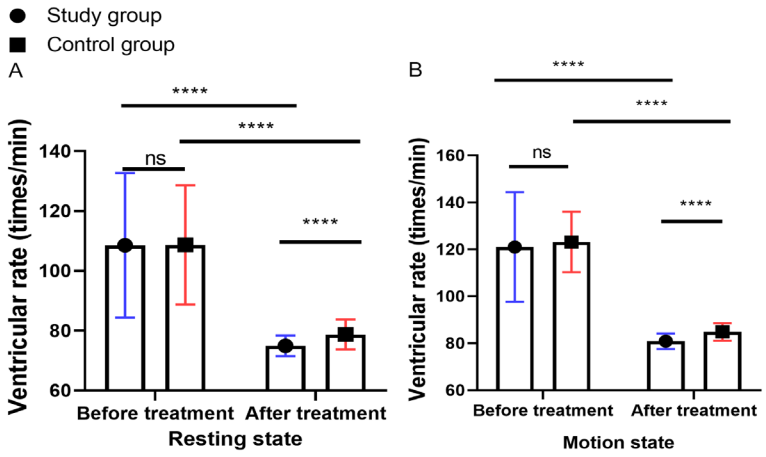

Figure 3. Comparison of ventricular rate between the two groups before and after treatment. A: Comparison of ventricular rate at rest between the two groups before and after treatment; B: Comparison of ventricular rate during exercise between the two groups before and after treatment. Notes: nsP>0.05; ****P<0.0001.

LVESD significantly decreased while LVEF significantly elevated in both groups (P<0.01). The study group showed significantly lower LVEDD and LVESD levels and a significantly higher LVEF compared to the control group (all P<0.01, **Figure 2**).

Comparison of ventricular rate

Before therapy, no significant inter-group difference was found in the ventricular rate at rest and during exercise (P>0.05). After treatment, the ventricular rate at rest and during exercise dropped significantly in both groups (P<0.0001), with a more pronounced reduction in the study group (P<0.0001, **Figure 3**).

Comparison of myocardial energy metabolism

Before treatment, NT-proBNP and CK levels were similar between the two groups (P>0.05); whereas after treatment, both NT-proBNP and CK levels decreased significantly in both groups (P<0.05), with the study group showing a more substantial reduction (P<0.05, **Table 2**).

Comparison of efficacy

A significantly higher overall response rate was observed in the study group compared to the control group (P=0.011, **Table 3**).

Comparison of adverse reactions

No notable inter-group difference was observed regarding the total incidence of adverse reactions (P=0.547, **Table 4**).

Table 2. Comparison of myocardial energy metabolism between the two groups before and after treatment

	NT-proBNP (ng/L)		CK (U/L)	
	Before treatment	After treatment	Before treatment	After treatment
Study group (n=54)	2279.23±385.39	515.06±92.96[a]	157.21±35,67	89.76±15.29[a]
Control group (n=46)	2275.86±389.04	1014.37±188.27[a]	159.64±28.85	116.76±21.73[a]
t	0.043	17.190	0.371	7.263
P value	0.966	<0.001	0.712	<0.001

Notes: NT-proBNP: N-terminal pro-B-type natriuretic peptide; CK: Creatine kinase. [a]P<0.0001, compared with before treatment values.

Table 3. Comparison of treatment efficacy between the two groups [n (%)]

Group	Markedly effective	Effective	Ineffective	Overall response
Study group (n=54)	30 (55.56)	20 (37.03)	4 (7.41)	50 (92.59)
Control group (n=46)	15 (32.61)	19 (41.30)	12 (26.09)	34 (73.91)
χ^2	5.285	0.190	6.449	6.449
P value	0.022	0.663	0.011	0.011

Table 4. Incidence of adverse reactions in the two groups [n (%)]

Group	Bradycardia	Decreased blood pressure	Gastrointestinal dysfunction	Total adverse reaction
Study group (n=54)	2 (3.70)	1 (1.85)	1 (1.85)	4 (7.40)
Control group (n=46)	1 (2.17)	2 (4.35)	2 (4.35)	5 (10.87)
χ^2	0.199	0.532	0.532	0.364
P value	0.655	0.466	0.466	0.547

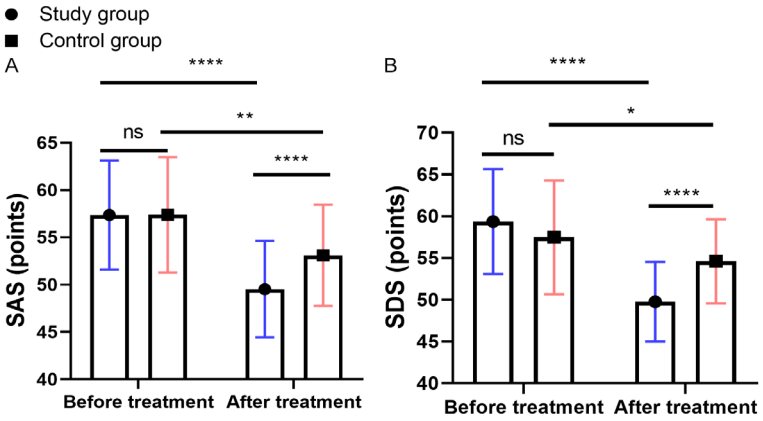

Figure 4. Comparison of psychological status between the two groups. A: Comparison of SAS scores between the two groups before and after treatment; B: Comparison of SDS scores between the two groups before and after treatment. Notes: nsP>0.05; **P<0.01; ****P<0.0001. SAS: Self-rating Anxiety Scale; SDS: Self-rating Depression Scale.

Comparison of psychological status

Before therapy, no significant inter-group difference was observed in terms of SAS and SDS scores (P>0.05). After therapy, both groups showed significant reductions in SAS and SDS scores (P< 0.05), with the study group demonstrating a more pronounced improvement (P< 0.05, **Figure 4**).

Univariate analysis of factors associated with efficacy outcomes

Patients were re-grouped based on their efficacy outcomes. Those with markedly effective or effective outcomes were assigned to the favorable prognosis group (n= 84) while the remaining patients were assigned to the unfavorable prognosis group (n=16). Univariate analysis revealed that age, course of disease, comorbid diabetes mellitus, comorbid hypertension, NYHA classification, and treatment protocol were associated with patient prognosis (**Table 5**).

Table 5. Univariate analysis of factors associated with treatment outcomes

Factors	Favorable prognosis group (n=84)	Unfavorable prognosis group (n=16)	χ^2	*P* value
Age			4.422	0.036
≥65 years old	55	6		
<65 years old	29	10		
Sex			1.448	0.229
Male	60	9		
Female	24	7		
BMI			0.481	0.488
≥23 kg/m^2	34	5		
<23 kg/m^2	50	11		
Course of disease			5.694	0.017
≥1 years	43	3		
<1 year	41	13		
Comorbid diabetes mellitus			12.351	0.001
Yes	8	7		
No	76	9		
Comorbid hypertension			18.881	<0.001
Yes	9	9		
No	75	7		
NYHA classification			6.332	0.012
Class II	25	10		
Class III	59	6		
Place of residence			0.0264	0.871
Rural area	56	11		
Urban area	28	5		
Treatment			6.449	0.011
Monotherapy	34	12		
Combine therapy	50	4		

Notes: BMI: Body mass index; NYHA: New York Heart Association classification.

Table 6. Assignment table

Factors	Assignment	
	0	1
Age	<65 years old	≥65 years old
Course of disease	<1 year	≥1 year
Comorbid diabetes mellitus	No	Yes
Comorbid hypertension	No	Yes
NYHA classification	Class II	Class III
Treatment	Multi-treatment	Monotherapy
Prognosis	Favorable prognosis	Unfavorable prognosis

Notes: NYHA: New York Heart Association classification.

Multivariate analysis of factors affecting efficacy outcomes

The variables found to be significantly different in the univariate analysis (**Table 6**) were further analyzed using multivariate logistic regression, which identified comorbid diabetes mellitus (P=0.025; OR=6.086; 95% CI=1.250-29.638), comorbid hypertension (P=0.007; OR=7.059; 95% CI=1.728-28.842), NYHA classification (P=0.023; OR=0.197; 95% CI=0.049-0.800) and treatment protocol (P=0.020; OR=5.911; 95% CI=1.326-26.338) as independent risk factors influencing patient prognosis (**Table 7**).

Discussion

Atrial fibrillation (AF) is increasingly prevalent in the young population due to lifestyle and work-related pressures [12, 13]. In the elderly patients, drug therapy remains the first-line treat-

Table 7. Multivariate analysis of factors independently affecting treatment outcomes

	B	S.E,	Wals	df	Sig.	Exp (B)	95% CI. of EXP(B)	
							Lower limit	Upper limit
Age	-1.029	0.727	2.003	1	0.157	0.358	0.086	1.486
Course of disease	-1.283	0.874	2.157	1	0.142	0.277	0.050	1.536
Comorbid diabetes mellitus	1.806	0.808	4.999	1	0.025	6.086	1.250	29.638
Comorbid hypertension	1.954	0.718	7.406	1	0.007	7.059	1.728	28.842
NYHA classification	-1.624	0.715	5.159	1	0.023	0.197	0.049	0.800
Treatment	1.777	0.762	5.432	1	0.020	5.911	1.326	26.338

Notes: NYHA: New York Heart Association classification.

ment for AF [13-15]. Digoxin is effective in managing AF in the elderly [16], but its standalone use has certain limitations [17]. Bisoprolol, with its higher selectivity and affinity for β 1 receptor compared to β 2 receptor, offers fewer side effects and a higher safety profile [18, 19]. This study aimed to investigate the effects of combined use of bisoprolol and digoxin on elderly AF patients, focusing on ultrasound-related indices.

Echocardiographic indices are often used alongside other clinical assessment to diagnose and monitor heart diseases [20, 21]. Key indices like LVEDD, LVESD and LVEF are essential for evaluating cardiac function [22]. LVEDD reflects the size of the ventricle during diastole, and its increase may indicate cardiac enlargement, impaired myocardial relaxation, or congestive heart failure [23]. LVESD reflects ventricular size during systole, helping assess left ventricular systolic function and wall motion [24]. LVEF measures the percentage of blood ejected by the left ventricle during each contraction, with normal values usually above 50%. Low LVEF is associated with left ventricular dysfunction in patients with myocardial injury, heart valve disease, or cardiomyopathy [25]. In this study, after treatment, LVEDD and LVESD decreased significantly in both groups, while LVEF increased significantly. The study group showed notably lower LVEDD and LVESD levels and a notably higher LVEF compared to the control group. These results suggest that bisoprolol, when combined with digoxin, improves cardiac function in elderly AF patients. AF patients often experience symptoms such as palpitations, shortness of breath, and fatigue, which are caused by rapid or irregular ventricular rates that impair the heart's ability to pump blood effectively. Controlling the ventricular rate alleviates these symptoms and improves the quality of life [26, 27]. In this study, both groups showed significant reductions in ventricular rate at rest and during exercise, with the study group showing greater improvement. This suggests that the addition of bisoprolol can effectively control ventricular rate in elderly AF patients, regardless of the patient's state. The mechanism may involve bisoprolol inhibiting atrioventricular conduction, which reduces the transmission of impulses through the atrioventricular node [7]. NT-proBNP and CK are common markers of myocardial energy metabolism. This study demonstrated that after treatment with bisoprolol combined with digoxin, NT-proBNP and CK levels greatly decreased, surpassing the effects of digoxin monotherapy. This indicates that the combination therapy reduces myocardial energy consumption, potentially delaying disease progression. In addition, the study found that the study group had a significantly higher overall response rate compared to the control group, with no significant difference in the incidence of adverse reactions. These findings suggest that the combined therapy improves therapeutic effect for elderly AF patients without increasing adverse reactions, making it both safe and reliable. Yazdi et al. [28] found that β-blocker and digoxin didn't greatly influence risk during the first hospitalization within 90 days for heart failure patients, supporting the results of this study. Moreover, the study observed a significant decrease in SAS and SDS scores for both groups, with the study group showing a more marked improvement. This suggests that both treatments positively impact psychological well-being, with the combined treatment providing more effective in alleviating anxiety and depression.

Moreover, the analysis of prognostic factors identified comorbid diabetes mellitus, comor-

bid hypertension, NYHA classification, and treatment as independent risk factors affecting patient prognosis. Maclean et al. [29] revealed that low-dose oral bisoprolol administered to patients with acute non-ST elevation myocardial infarction within 4 h of admission can reduce the occurrence of inpatient major adverse cardiovascular events, aligning with the results of this study.

Despite these promising findings, there are several limitations to this study. First, the sample size is relatively small, which may introduce bias and affect the generalizability of the conclusion. Second, the long-term prognosis of the two groups remains unknown, so further research is needed to evaluate the prolonged effects of bisoprolol combined with digoxin on elderly patients with AF. Moreover, we did not explore the impact of varying drug dosages, which could provide valuable insights. Lastly, as this was a retrospective study, we were unable to control the treatment protocols followed by patients, which may lead to selection bias and confounding factors.

In conclusion, the combination therapy of bisoprolol and digoxin demonstrates superior efficacy in treating elderly patients with AF compared to digoxin monotherapy. This combination results in significant improvements in various parameters, including LVEDD, LVESD, and LVEF. Additionally, it effectively controls ventricular rate both at rest and during exercise. Importantly, this combined therapy does not increase the incidence of adverse reactions. Considering these positive outcomes, the combination therapy of bisoprolol and digoxin holds promising potential and deserves wider clinical adoption.

Disclosure of conflict of interest

None.

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