Am J Transl Res 2025;17(8):6131-6140
www.ajtr.org /ISSN:1943-8141/AJTR0165747

Original Article

Amiodarone combined with metoprolol improves cardiac function in patients with coronary heart disease complicated by arrhythmia

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Received April 29, 2025; Accepted July 29, 2025; Epub August 15, 2025; Published August 30, 2025

Abstract: Objective: To evaluate the efficacy and safety of amiodarone combined with metoprolol for improving cardiac function in patients with coronary heart disease (CHD) complicated by arrhythmia. Methods: A retrospective analysis was conducted on 102 patients with CHD and arrhythmia treated at Zhuzhou Central Hospital from January 2018 to March 2021. Patients were divided into two groups: an amiodarone group (n = 48) and a combination group (amiodarone plus metoprolol, n = 54). Primary endpoints included therapeutic efficacy, time to clinical stability and cardioversion, QT dispersion (QTd), heart rate, hemodynamic indices (plasma fibrinogen, hematocrit, plasma viscosity), cardiac function indices (LVEDD, LVEF, LVESD), heart rate variability (HRV) indices (premature contractions, SDNN, SDNNI), myocardial biomarkers, and adverse events. Cardiovascular event rates were also compared using a 3-year follow-up. Results: The combination group showed a significantly higher efficacy rate ($P<0.05$), with faster clinical stabilization and cardioversion ($P<0.05$). Both groups improved post-treatment, but the combination group showed greater improvements in QTd, heart rate, hemodynamics, cardiac function, HRV indices, and myocardial markers (all $P<0.05$). Adverse events were significantly lower in the combination group ($P<0.001$), as was the incidence of cardiovascular events during follow-up ($P<0.05$). Conclusion: Amiodarone combined with metoprolol is a safe and effective strategy for managing CHD complicated by arrhythmia, providing superior improvements in cardiac function and HRV, with a lower rate of adverse events.

Keywords: Amiodarone, metoprolol, coronary heart disease with arrhythmia, heart function, safety

Introduction

Coronary heart disease (CHD), a common cardiovascular disorder especially in the elderly, is caused primarily by coronary artery stenosis and occlusion [1]. As a leading cause of global mortality, CHD is responsible for over 7 million deaths annually [2]. Ventricular arrhythmia, a severe complication of CHD, significantly increases myocardial oxygen consumption, exacerbating myocardial ischemia. This can enlarge the infarct size, induce chest pain or angina, impair cardiac function, and elevate mortality risk [3]. Effective management of CHD complicated by arrhythmia is therefore a clinical priority.

Amiodarone, a class III antiarrhythmic agent, exhibits broad-spectrum activity. It acts as a noncompetitive α- and β-adrenergic receptor antagonist and inhibits potassium and calcium channels, thereby prolonging cardiomyocyte action potential and slowing atrioventricular conduction to reduce heart rate (HR) - key mechanisms underlying its antiarrhythmic effect [4, 5]. However, amiodarone monotherapy in CHD with arrhythmia often yields suboptimal outcomes, with delayed sinus rhythm restoration, insufficient myocardial ischemia control, and a risk of adverse effects (e.g., pulmonary and hepatic toxicity, cardiac dysfunction, and thyroid disorders) due to its high iodine content [6-8].

Metoprolol, a class II antiarrhythmic β-blocker, reduces ventricular arrhythmias through β-adrenergic receptor blockade [9]. In elderly CHD patients with arrhythmia, metoprolol improves myocardial perfusion and reduces cardiovascular events such as sudden cardiac

https://doi.org/10.62347/TTLB6414

death [10]. Nevertheless, the efficacy and safety of combined amiodarone - metoprolol therapy for CHD with arrhythmia have not been sufficiently studied.

This study evaluated the clinical outcomes and safety of amiodarone combined with metoprolol in CHD patients with arrhythmia, aiming to support clinical decision-making and optimize treatment.

Patients and methods

Case selection

This retrospective study included 102 CHD patients complicated by arrhythmia who were admitted to Zhuzhou Central Hospital between January 2018 and March 2021. Patients were divided into two groups based on treatment strategy: the amiodarone monotherapy group (n = 48) and the combination group receiving amiodarone plus metoprolol (n = 54).

Inclusion criteria were: (1) diagnosis of CHD and arrhythmia based on established guidelines; (2) no contraindications or known allergies to the study drugs.

Exclusion criteria were: (1) severe hepatic or renal impairment; (2) atrioventricular block; (3) cognitive or psychiatric disorders; (4) poor treatment compliance.

This study was approved by the Ethics Committee of Zhuzhou Central Hospital and conducted in accordance with the Declaration of Helsinki. All treatments were selected by physicians in consultation with patients, with full disclosure of risks and benefits.

Treatment protocols

All patients received standard care including low-flow oxygen, aspirin, nitrates, statins, and ACE inhibitors.

The amiodarone group received oral amiodarone (Sanofi Hangzhou; 0.2 g/tablet, National Drug Code H19993254): 200 mg three times daily in Week 1, twice daily in Week 2, and once daily in Week 3 onward.

The combination group received the same amiodarone regimen plus metoprolol tartrate sustained-release tablets (Southwest Pharmaceutical; 25 mg/tablet, Code H20033190), starting at 6.25 mg/day for 1-2 weeks, titrated up to 25 mg twice daily based on tolerance. Treatment lasted for two months. All assessments were conducted at baseline and two months post-treatment.

Data collection and outcome measurement

Primary outcomes: Therapeutic efficacy: Markedly effective: restoration of sinus rhythm, ≥2-grade improvement in cardiac function, symptom resolution, and >90% reduction of ventricular arrhythmia.

Effective: ≥1-grade improvement in cardiac function, symptom relief, and >50% reduction of arrhythmia.

Ineffective: no significant improvement in the above indicators.

Total effective rate = [(markedly effective + effective cases)/total cases] × 100%.

Cardiac function indicators: Left ventricular end-systolic diameter (LVESD), end-diastolic diameter (LVEDD), and ejection fraction (LVEF) were measured by echocardiography before and after treatment.

Secondary outcomes: Time to clinical stability and cardioversion, determined from treatment initiation to vital sign stabilization or sustained sinus rhythm for ≥24 hours.

QT dispersion (QTd) and HR before and after treatment.

Hemodynamic indicators, including plasma fibrinogen, hematocrit, and plasma specific viscosity, assessed using an Innocor™ hemodynamic detector.

Heart rate variability (HRV) indices, including premature contractions, standard deviation of normal-to-normal (SDNN) and the SDNN interval (SDNNI), measured by 24-hour Holter electrocardiogram recordings.

Myocardial injury markers, including brain natriuretic peptide (BNP), creatine kinase-MB (CK-MB), and cardiac troponin I (cTnI), before and after treatment.

Adverse events, such as hepatic dysfunction, hypsotension, bradycardia, and gastrointestinal discomfort.

Table 1. Comparison of basic patient information

Factor	Amiodarone group (n = 48)	Combination group (n = 54)	t/χ^2	P
Gender			0.035	0.852
Male	24 (50.00)	28 (51.85)		
Female	24 (50.00)	26 (48.15)		
Age (years)			0.021	0.885
≤71	18 (37.50)	21 (38.89)		
>71	30 (62.50)	33 (61.11)		
BMI (kg/m^2)			0.002	0.963
≤23	26 (54.17)	29 (53.70)		
>23	22 (45.83)	25 (46.30)		
Course of disease (days)	7.58±2.10	7.54±2.12	0.095	0.924
History of Smoking			0.059	0.808
YES	30 (62.50)	35 (64.81)		
NO	18 (37.50)	19 (35.19)		
Hypertension			0.027	0.870
YES	25 (52.08)	29 (53.70)		
NO	23 (47.92)	25 (46.30)		
Heart function classification			0.032	0.859
Grade III	33 (68.75)	38 (70.37)		
Grade IV	15 (31.25)	16 (29.63)		

Long-term cardiovascular events over a 3-year follow-up by outpatient visits, phone calls, and WeChat. Events included cardiac death, non-fatal myocardial infarction, hospitalization for unstable angina, heart failure, and malignant arrhythmia.

Statistical analysis

SPSS version 19.0 (IBM, USA) was used for data analysis. Sample size was calculated using PASS software, with $\alpha = 0.05$ (two-sided) and power = 80%. Categorical variables were expressed as counts and percentages and analyzed using the χ^2 test. Continuous variables were presented as mean ± SD. Paired t-tests were used for within-group comparisons, and independent t-tests for between-group comparisons. LSD/t post hoc tests were applied when appropriate. A *P* value <0.05 was considered significant.

Results

Comparison of general characteristics

No significant differences were observed between the two groups regarding baseline characteristics, including gender, age, BMI, disease duration, smoking history, hypertension, or cardiac function classification (all P>0.05; **Table 1**).

Comparison of therapeutic efficacy

The total effective rate in the combination group was significantly higher than that of the amiodarone group (96.30% vs. 77.08%, P<0.05; **Table 2**). Specifically, 31 patients (57.41%) in the combination group achieved marked improvement, 21 (38.89%) were effective, and 2 (3.70%) were ineffective. In contrast, the amiodarone group had 22 (45.83%) markedly effective, 15 (31.25%) effective, and 11 (22.92%) ineffective cases.

Comparison of cardiac function

Before treatment, LVESD, LVEDD, and LVEF did not differ significantly between groups (all P>0.05). After treatment, both groups showed significant improvements (all P<0.05). The combination group demonstrated lower LVESD and LVEDD, and higher LVEF than the standard group (P<0.05; **Figure 1**).

Comparison of time to clinical stability and cardioversion

Patients in the combination group achieved clinical stability and cardioversion more rapidly

Table 2. Comparison of therapeutic efficacy

Therapeutic efficacy	Amiodarone group (n = 48)	Combination group (n = 54)	χ^2	P
Markedly Effective	22 (45.83)	31 (57.41)	-	-
Effective	15 (31.25)	21 (38.89)	-	-
Ineffective	11 (22.92)	2 (3.70)	-	-
Effective Rate	37 (77.08)	52 (96.30)	8.435	0.004

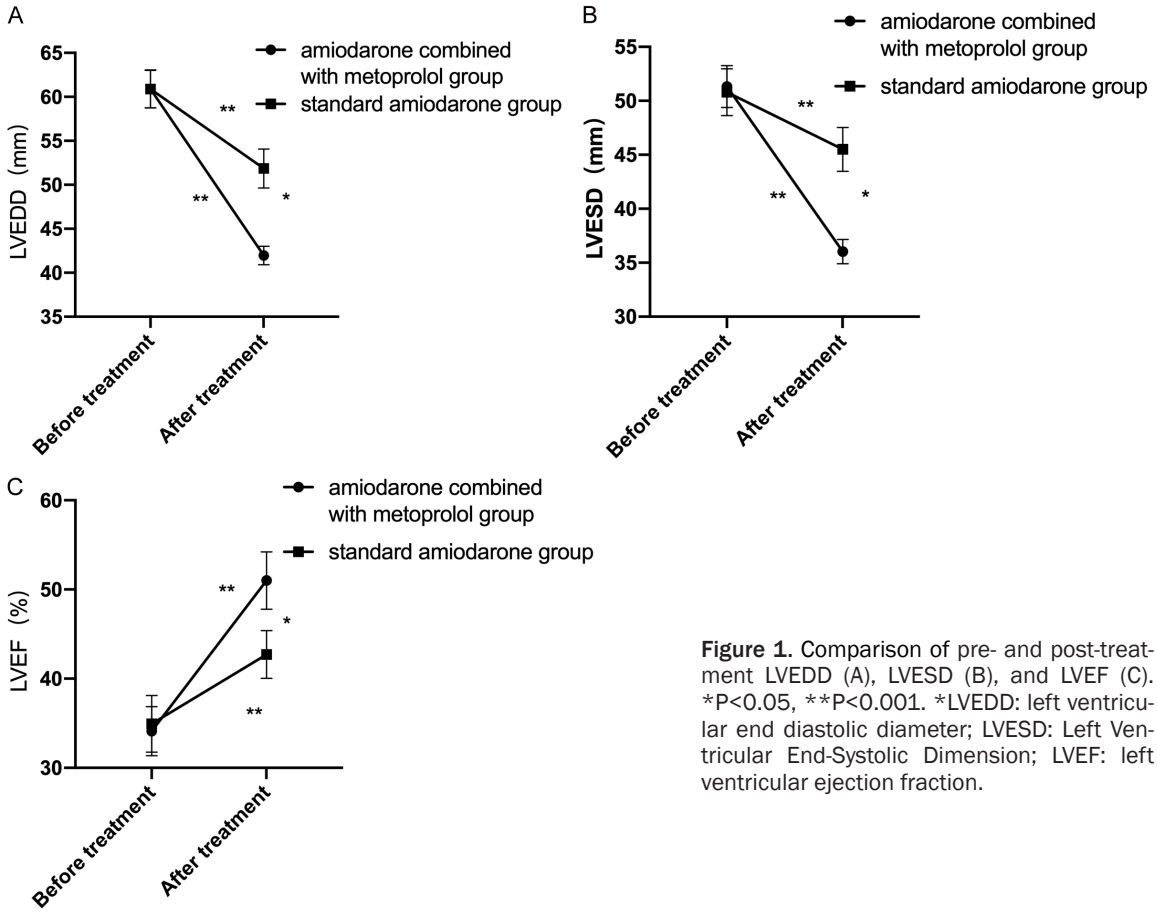

Figure 1. Comparison of pre- and post-treatment LVEDD (A), LVESD (B), and LVEF (C). *P<0.05, **P<0.001. *LVEDD: left ventricular end diastolic diameter; LVESD: Left Ventricular End-Systolic Dimension; LVEF: left ventricular ejection fraction.

Table 3. Comparison of time to clinical stability and cardioversion (d)

Variable	Amiodarone group (n = 48)	Combination group (n = 54)	t	P
Time to clinical stability	3.25±0.43	2.03±0.34	15.98	<0.001
Time to cardioversion	3.18±0.38	2.18±0.32	14.42	<0.001

than those in the standard group (both P< 0.001; **Table 3**), suggesting faster symptom relief and rhythm control with combination therapy.

Comparison of QTd and HR

Baseline QTd and HR were comparable between groups (both P>0.05). Post-treatment, both indices significantly improved in both groups, with greater improvements in the combination group (both P<0.05; **Figure 2**).

Comparison of hemodynamic indicators

No significant pre-treatment differences were observed in plasma fibrinogen, hematocrit, or plasma specific viscosity (all P>0.05). These

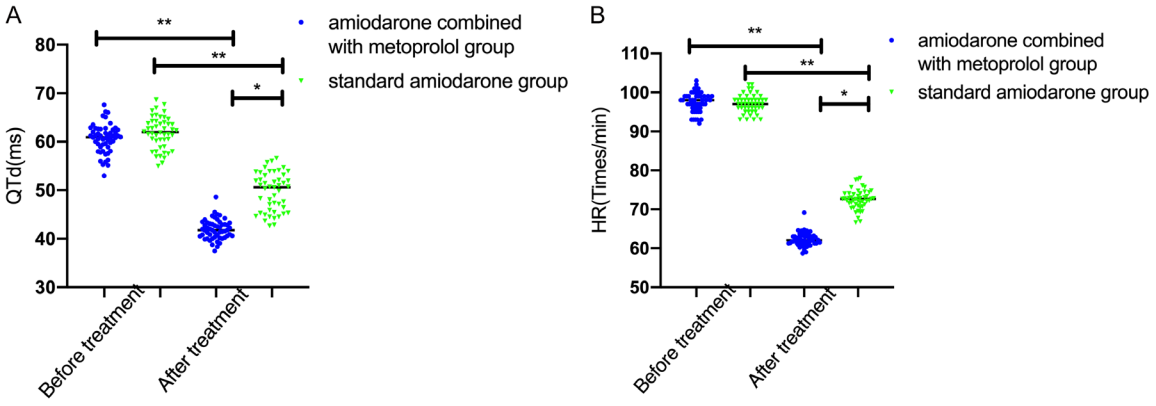

Figure 2. Comparison of pre- and post-treatment QTd (A) and HR (B) in both groups. *P<0.05. **P<0.001. *QTd: Qualifying Time Deposit; HR: Heart Rate.

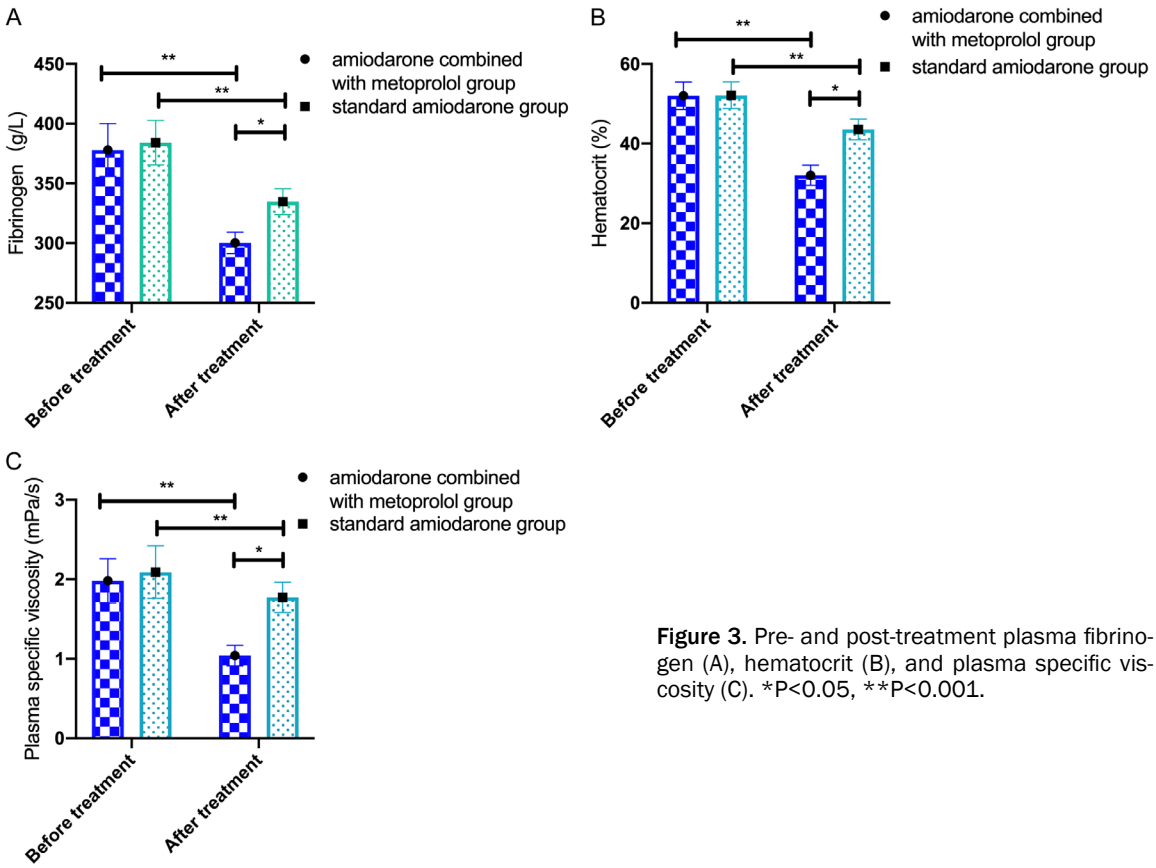

Figure 3. Pre- and post-treatment plasma fibrinogen (A), hematocrit (B), and plasma specific viscosity (C). *P<0.05, **P<0.001.

values declined significantly in both groups after treatment, with more marked reductions in the combination group (all P<0.05; **Figure 3**).

Comparison of HRV

Both groups exhibited reduced premature contractions and increased SDNN and SDNNI after treatment (both P<0.05). The combination group showed significantly greater improvements in all three HRV metrics (P<0.05; **Figure 4**).

Comparison of myocardial markers

Baseline levels of BNP, cTnI, and CK-MB did not differ significantly between groups (all P>0.05). Following treatment, all three markers

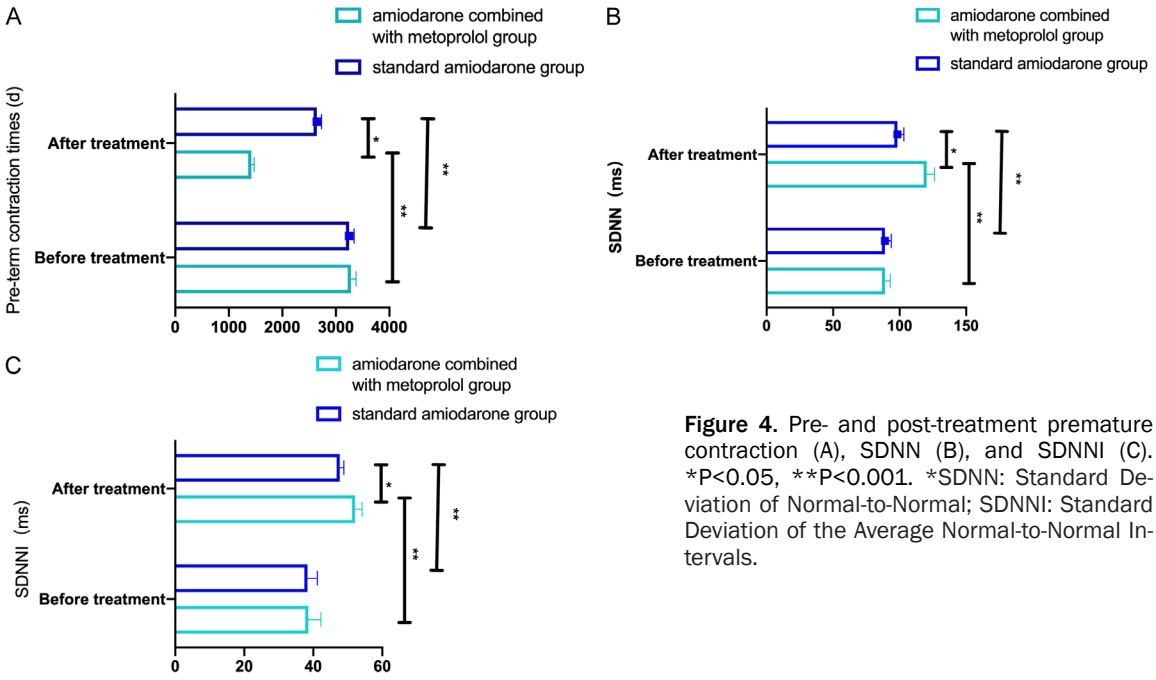

Figure 4. Pre- and post-treatment premature contraction (A), SDNN (B), and SDNNI (C). *P<0.05, **P<0.001. *SDNN: Standard Deviation of Normal-to-Normal; SDNNI: Standard Deviation of the Average Normal-to-Normal Intervals.

Table 4. Comparison of myocardial markers

Index	Timing	Amiodarone group (n = 48)	Combination group (n = 54)	t	P
BNP (pg/ml)	Before treatment	497.59±18.26	500.04±21.92	0.689	0.544
	After treatment	192.31±11.37	149.74±8.8	21.27	<0.001
cTnI (ug/L)	Before treatment	0.86±0.1	0.84±0.1	1.008	0.316
	After treatment	0.33±0.06	0.16±0.03	18.40	<0.001
CK-MB (U/L)	Before treatment	66.74±4.9	67.17±5.27	0.425	0.672
	After treatment	36.13±4.43	17.65±2.3	26.86	<0.001

*BNP: Brain Natriuretic Peptide; cTnI: cardiac troponin I; CK-MB: Creatine Kinase-Myocardial Band.

Table 5. Comparison of adverse reaction rate [n, (%)]

Adverse Reaction	Amiodarone group n = 48	Combination group n = 54	χ^2	P
Abnormal liver function	3 (6.25)	2 (3.70)	-	-
Hypotension	4 (8.33)	1 (1.85)	-	-
Sinus bradycardia	4 (8.33)	0	-	-
Gastrointestinal discomfort	4 (8.33)	1 (1.85)	-	-
Total adverse reaction rate	15 (31.25)	4 (7.41)	11.26	<0.001

were significantly lower in the combination group than in the amiodarone group (all P<0.05; **Table 4**).

Comparison of adverse events

The incidence of adverse reactions was significantly lower in the combination group compared to the standard group (7.41% vs. 31.25%, P<0.001; **Table 5**).

Comparison of long-term cardiovascular events

Within 3 years of follow-up, the incidence of major cardiovascular events was significantly lower in the combination group (14.81%) than in the amiodarone group (41.67%, all P<0.05; **Tables 6**, **7**). Events included cardiac death, non-fatal myocardial infarction, and hospitalizations due to angina, heart failure, or malignant arrhythmias.

Table 6. Comparison of cardiovascular adverse events [n, (%)]

Cardiovascular adverse event	Amiodarone group n = 48	Combination group n = 54	X^2	P
Cardiac death	5 (10.42)	1 (1.85)	-	-
Non fatal myocardial infarction	3 (6.25)	2 (3.70)	-	-
Hospitalization due to unstable angina	4 (8.33)	2 (3.70)	-	-
Hospitalization due to heart failure	4 (8.33)	1 (1.85)	-	-
Hospitalization due to malignant arrhythmia	4 (8.33)	2 (3.70)	-	-
Total incidence rate	20 (41.67)	8 (14.81)	9.200	0.002

Table 7. Comparison of adverse cardiovascular events within 3 years after treatment

Annual cardiovascular adverse event	Amiodarone group n = 48	Combination group n = 54	X^2	P
The first year	5 (10.42)	1 (1.85)	-	-
second year	6 (12.50)	3 (5.56)	-	-
The third year	9 (18.75)	4 (7.41)	-	-
Total incidence rate	20 (41.67)	8 (14.81)	9.200	0.002

Table 8. Single factor analysis

Factor	Good prognosis group (n = 74)	Poor prognosis group (n = 28)	X^2	P
Age			9.374	0.002
≤71 (n = 39)	35 (47.30)	4 (14.29)		
>71 (n = 63)	39 (52.70)	24 (85.71)		
Smoking history			0.151	0.697
Yes (n = 65)	48 (64.86)	17 (60.71)		
No (n = 37)	26 (35.14)	11 (39.29)		
Heart function classification			71.18	<0.001
Grade III (n = 71)	69 (93.24)	2 (7.14)		
Grade IV (n = 31)	5 (6.76)	26 (92.86)		
Treatment Plan			23.15	<0.001
Amiodarone combined with metoprolol (n = 54)	50 (67.67)	4 (14.29)		
Amiodarone (n = 48)	24 (32.43)	24 (85.71)		

Table 9. Multivariate analysis

Factor	B	S.E.	Wals	P	Exp (B)	95% C.I.	
						Lower limit	Upper limit
Age	-0.105	0.756	0.019	0.889	0.900	0.205	3.960
Heart function classification	2.691	0.664	16.419	0.000	14.751	4.013	5.241
Treatment Plan	2.186	0.803	7.414	0.006	8.901	1.845	2.941

Prognostic factor analysis

Based on the occurrence of cardiovascular events, patients were categorized into good (n = 74) and poor (n = 28) prognosis groups. Univariate analysis identified age, cardiac function grade, and treatment strategy as influencing factors (**Table 8**). Multivariate logistic regression revealed that cardiac function grade and treatment strategy were independent predictors of prognosis (**Table 9**).

Discussion

Amiodarone reduces heart rate (HR) by inhibiting potassium and calcium channels, suppress-

ing sinoatrial node automaticity, and decreasing ventricular myocardial excitability [14-16]. However, clinical studies have shown that amiodarone monotherapy often fails to achieve rapid and effective sinus rhythm restoration in CHD patients with concomitant arrhythmia [6-8, 11-13]. Additionally, its effects on alleviating myocardial ischemia are limited, and it carries risks of serious adverse events, including pulmonary and hepatic toxicity, cardiac dysfunction, and thyroid abnormalities [17].

In contrast, metoprolol has demonstrated significant therapeutic value for the treatment of myocardial infarction and heart failure by effectively regulating HR-related measurements in CHD patients [9]. Its cardioprotective effects are mediated through suppression of circulating catecholamines and inhibition of calcium influx, thereby reducing myocardial oxygen demand and enhancing antiarrhythmic efficacy [18, 19]. When used in combination with amiodarone, metoprolol appears to synergistically improve outcomes by enhancing atrioventricular conduction and stabilizing cardiac electrophysiology [20].

Our study compared amiodarone monotherapy with combined amiodarone - metoprolol therapy in CHD patients with arrhythmia. The combination group showed significantly higher efficacy, with faster time to clinical stability and cardioversion, indicating more rapid restoration of sinus rhythm. Post-treatment assessments revealed greater improvements in HR and QTd in the combination group, supporting the superiority of the combined regimen.

Echocardiographic indices - LVEF, LVESD, and LVEDD - are key indicators of cardiac function. LVEF reflects left ventricular systolic performance and correlates positively with overall cardiac function, particularly in arrhythmia patients [21]. Elevated LVESD and LVEDD typically indicate impaired ventricular contractility [22]. In this study, patients receiving combination therapy had significantly higher LVEF and lower LVESD and LVEDD values, consistent with prior findings with metoprolol's favorable effects on ventricular remodeling and function [23].

HRV indicators such as SDNN and SDNNI reflect autonomic nervous system regulation. Lower values suggest impaired cardiac autonomic function, a known contributor to arrhythmia progression [24, 25]. Metoprolol exerts antiarrhythmic effects by attenuating calcium influx, reducing cardiomyocyte automaticity, modulating conduction velocity, and prolonging atrioventricular conduction time [26, 27]. Our data showed that combination therapy significantly improved SDNN and SDNNI while reducing premature contractions, indicating enhanced autonomic regulation and rhythm control.

Moreover, the incidence of adverse events was significantly lower in the combination group, highlighting the favorable safety profile of the combined regimen.

In conclusion, the combination of amiodarone and metoprolol is a safe and effective strategy for treating CHD patients with arrhythmia. It improves cardiac function, enhances HRV, reduces premature contractions, and minimizes adverse effects. Nonetheless, this study has limitations. First, the potential for more effective drug combinations requires further investigation. Second, the limited sample size may reduce the generalizability of our findings. Future large-scale, multicenter studies are warranted to validate these results and support evidence-based treatment decisions for patients with CHD complicated by arrhythmia.

Disclosure of conflict of interest

None.

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