https://doi.org/10.31925/farmacia.2024.5.23 **ORIGINAL ARTICLE**

THE EFFECT OF SACUBITRIL/VALSARTAN COMBINED WITH METOPROLOL SUCCINATE SUSTAINED-RELEASE TABLET ON CARDIAC FUNCTION IN PATIENTS WITH CORONARY HEART DISEASE AND HEART FAILURE

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Abstract

Coronary artery disease (CAD) with heart failure (HF) is a common clinical condition. This study aimed to assess the effects of sacubitril/valsartan combined with metoprolol succinate extended-release tablets on cardiac function (CF) in patients with CAD and HF. A retrospective analysis of patients admitted between January 2018 and December 2020 was conducted. Patients were divided into two groups: an observation (Obs) group treated with sacubitril/valsartan and metoprolol succinate, and a control (Ctrl) group treated with metoprolol succinate alone. ECG parameters, vascular endothelial function (VEF), CF indicators, oxidative stress markers and clinical efficacy (CE) were compared. The Obs group showed significant improvements in left ventricular ejection fraction (LVEF), reduced left ventricular end-diastolic diameter (LVEDD) and lower levels of angiotensin II, sVCAM-1 and sICAM-1. Plasma nitric oxide (NO) levels increased, and cardiac biomarkers like NT-proBNP and cardiac troponin I (cTnI) decreased in the Obs group. The 6-minute walk test (6MWT) and oxidative stress markers (SOD, GPx) also improved. Overall, the Obs group had better CF, VEF and CE, with no significant difference in adverse events between the two groups. Sacubitril/valsartan combined with metoprolol shows potential benefits in managing CAD and HF.

Rezumat

Boala coronariană (BC) asociată cu insuficiența cardiacă (IC) reprezintă o afecțiune clinică comună. Studiul a avut ca scop evaluarea efectelor combinației dintre sacubitril/valsartan și comprimatele cu eliberare prelungită de metoprolol succinat asupra funcției cardiace (FC) la pacienții cu BC și IC. A fost realizată o analiză retrospectivă ce a cuprins pacienți internați între ianuarie 2018 și decembrie 2020, ce au fost împărțiți în două grupuri: un grup de observație (Obs) tratat cu sacubitril/valsartan și metoprolol succinat și un grup de control (Ctrl) tratat doar cu metoprolol succinat. Au fost evaluați parametrii EKG, funcția endotelială vasculară (FEV), indicatorii funcției cardiace, markerii de stres oxidativ și eficacitatea clinică (EC), în cele două grupuri. Grupul Obs a prezentat îmbunătățiri semnificative ale fracției de ejecție a ventriculului stâng (FEVS), reducerea diametrului telediastolic al ventriculului stâng (DTDVS) și niveluri mai scăzute de angiotensină II, sVCAM-1 și sICAM-1. Nivelurile de oxid nitric (NO) plasmatic au crescut, iar biomarkerii cardiaci precum NT-proBNP și troponina cardiacă I (cTnI) au scăzut în grupul Obs. Testul de mers de 6 minute (6MWT) și markerii de stres oxidativ (SOD, GPx) au arătat, de asemenea, îmbunătățiri. În general, grupul Obs a avut o FC, FEV și EC mai bune, fără diferențe semnificative în evenimentele adverse între cele două grupuri. Combinația sacubitril/valsartan și metoprolol arată beneficii potențiale în gestionarea BC și IC.

Keywords: Sacubitril/Valsartan, Metoprolol Succinate Sustained-Release Tablet, coronary heart disease, heart failure, EKG

Introduction

Coronary artery disease (CAD) is a common cardiovascular disease (CVD) [1]. In patients with CAD, the myocardium often experiences ischemia and hypoxia, which can lead to complications such as myocardial infarction (MI), ventricular remodelling and heart failure (HF) [2]. HF refers to the dysfunction of the heart's pumping or relaxing function, resulting in venous congestion and inadequate arterial perfusion, leading to circulatory dysfunction. In patients with CAD and concomitant HF, the oxygen-carrying capacity of the blood is reduced and both the systolic and diastolic functions of the heart are significantly impaired, failing to meet the patient's basic needs [3, 4]. The electrocardiogram (ECG), as a simple and widely used diagnostic tool, plays a crucial role in the assessment of cardiac function in patients with CHD and HF. The duration of the QRS complex in the ECG reflects the depolarization function of the left and right ventricles. The ECG is a readily available and supervised method for the initial assessment of the condition in CAD patients with HF. The higher the New York Heart Association (NYHA) classification of

HF, the more severe the disease and the more severe the myocardial ischemia. ECG examination provides information about the patient's HF status through the duration of the QRS complex. As the HF condition worsens, the prognosis becomes worse [5, 6].

In clinical practice, treatment often includes angiotensin-converting enzyme inhibitors, beta-blockers, inotropic agents and aldosterone receptor antagonists to improve the condition and relieve the symptoms of patients with HF. However, long-term treatment outcomes remain suboptimal, with unresolved issues such as high readmission rates, increased mortality and reduced patient quality of life (QOL) [7, 8]. Sacubitril/valsartan and metoprolol succinate extended-release tablets are well-known medications used in the treatment of HF [9]. Metoprolol Succinate Sustained-Release Tablet is a beta-blocker commonly used in clinical practice to treat CHD with concomitant HF. It works by inhibiting sympathetic nervous system activity, promoting vasodilation, reducing myocardial oxygen consumption and improving heart rate control and blood pressure. It can also effectively dilate blood vessels and improve sodium excretion. However, its efficacy is limited when used as a single agent [10, 11]. Sacubitril/ valsartan is a novel drug for the treatment of heart failure and hypertension and is recommended in guidelines. In HF patients with a low ejection fraction (EF) of ≤ 40% and New York Heart Association (NYHA) functional class II-IV, sacubitril/valsartan is recommended to prevent cardiovascular mortality [12, 13]. The combination of sacubitril valsartan and metoprolol succinate delayed-release tablets, either alone or in combination, has shown significant success in the treatment of HF [14]. However, whether their combined use can lead to positive ECG improvements in patients with both CAD and HF has not been thoroughly studied.

This work investigated the effects of sacubitril/valsartan in combination with metoprolol succinate extended-release tablets on the ECG assessment of CF in patients with CHD and HF. The aim was to gain a more comprehensive understanding of the potential impact of this combination therapy on CF and patients' quality of life. This work aimed to provide further scientific evidence to support intervention in CHD patients with concomitant HF and to promote advances in CVD treatment.

Materials and Methods

A retrospective analysis of patients with CHD and HF hospitalised between January 2018 and December 2020 was performed. Patients were selected for the study according to the principles of balance based on admission order, age, disease duration and gender. They were divided into a control (Ctrl) group (n = 80) and an observation (Obs) group (n = 80) based on different treatment medications. The Obs group included 46 male and 34 female patients with a mean age of (65.28 ± 8.53) years. The disease duration ranged from 1 to 11 years with a mean of (6.81 ± 2.07) years. The Ctrl group consisted of 48 males and 32 females with a mean age of (63.76 ± 7.94) years and a disease duration ranging from 1 to 11 years (mean (6.74 ± 3.75) years). Two experienced cardiologists performed comprehensive laboratory tests, reviewed medical histories and diagnosed patients with CAD and HF. General information analysis showed that the patients had stable vital signs, no apparent contraindications and comparable baseline characteristics in terms of age, disease duration and gender between the two groups ($p < 0.05$). The study adhered to the guidelines of the World Medical Association's Declaration of Helsinki and was approved by the hospital ethics committee. All patients who met the inclusion criteria received the experimental protocol, gave informed consent and the research was conducted in accordance with ethical principles.

Inclusion criteria were: (1) patients confirmed by ECG and echocardiography; (2) patients with CAD and HF; (3) patients in long-term hospital care; (4) those with symptoms of HF, systolic blood pressure (SBP) ≥ 90 mmHg (1 mmHg = 0.133 kPa) and diastolic blood pressure (DBP) ≥ 90 mmHg; (5) those with adequate comprehension and communication skills; (6) patients with impaired vision or colour vision disorders; (7) those with CF classification (*i.e.*, New York Heart Association functional class) of ≥ II or above [15].

Patients with any of the following had to be excluded: (1) patients with concomitant other CVD; (2) those with incomplete medical records; (3) patients with abnormal heart or lung function; (4) patients who had received prior treatment; (5) patients with vascular oedema; (6) patients with concomitant CVD or auto-immune diseases; and (7) patients with chronic HF caused by other factors.

Treatment

The two groups of patients were advised to rest and to follow a low-fat, low-salt, low-spicy diet. Patients in the Ctrl group received metoprolol succinate extended-release tablets (AstraZeneca Pharmaceutical Co., Ltd., China) at 23.75 mg/day, three times daily. During treatment, medication adjustments could be made based on patient tolerability and response, with a maximum daily dose of 50 mg. Each treatment course lasted 4 weeks, and three consecutive treatment courses were administered. In the Obs group, patients were prescribed sacubitril/ valsartan sodium tablets (Novartis Pharmaceutical Co., Ltd., China) in addition to the treatment received in the Ctrl group. The initial dose was 100 mg/day, and during the first 2 to 4 weeks of treatment, the dose could be adjusted according to patient tolerance, with a possible increase to 200 mg/day. Each treatment course lasted 4 weeks and three consecutive treatment courses were administered.

Detection methods

Vascular endothelial functions (VEF). Plasma NO levels in both groups of patients were determined using a colorimetric assay. Plasma levels of calcitonin gene-related peptide (CGRP) and endothelin (ET) were measured by enzyme-linked immunosorbent assay (ELISA) before and after treatment (Jiangsu Jianglai Biotechnology Co., Ltd., China). Plasma angiotensin (AgII) was measured by ELISA, specifically enzyme-linked immunosorbent assay, before and after treatment (Shanghai Jiwei Biotechnology Co., Ltd., China).

Soluble vascular cell adhesion molecule (VCAM-1) and soluble intercellular adhesion molecule (ICAM-1) levels were determined by sandwich ELISA using double antibodies. ELISA kits were purchased from Shanghai Enzyme-Linked Biotechnology Co., Ltd, China. Patients were required to fast early in the morning and provide a 5 mL venous blood sample, which was then placed in a sample room. After clotting, the samples were centrifuged at 2,000 rpm for 10 minutes, and the supernatant was collected and stored at -20°C for later use. The sVCAM-1 and sICAM-1 assay kits were purchased from Shenzhen Jingmei Corporation, China and the procedures were strictly followed according to the instructions.

Cardiac function (CF) indicators. Ultrasound echocardiography was performed using the Vivid 7 colour Doppler ultrasound diagnostic device (GE, USA). This diagnostic device was used to perform echocardiographic examinations on the patients, measuring parameters such as left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF) and left ventricular end-systolic diameter (LVESD).

NT-BNP, cTnI and 6MWT. N-terminal pro-brain natriuretic peptide (NT-BNP) and cardiac troponin I (cTnI) levels were measured before and after 12 months of treatment. Patients were examined in the fasting state and a 5 mL venous blood sample was taken for centrifugation at 300 rpm for 10 minutes for serum separation. cTnI was measured by ELISA kits (Shanghai Enzyme-Linked Biotechnology Co., Ltd, China), while NT-BNP was determined by an electrochemical chemiluminescence method.

The 6MWT was used to assess the distance a patient could walk on a flat, unobstructed surface in 6 minutes. Patients started at a designated point, walked as far as they could and then returned to the starting point, recording the distance covered during the 6-minute period. Patients who walked a distance of 426 - 550, 150 - 425 and < 150 meters were classified as having mild, moderate and severe CF impairment, respectively.

Oxidative stress parameters. Oxidative stress markers were used to assess intracellular oxidative stress, which reflects the balance between oxidative damage and antioxidant defence. Blood samples were taken to determine the levels of glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) using colorimetric assays with reagents purchased from Jiangsu Jianglai Biotechnology Co., Ltd., China, ELISA (Shanghai Enzyme-Linked Biotechnology Co., Ltd, China) and the barbituric acid method, respectively.

ECG indicators. A 12-lead ECG analysis was performed to measure the QTI three times in all patients. The average QTI was calculated to mitigate the influence of HR correction. The corrected QTI (QTIc) was computed using QTIc = QTI/RR. This resulted in the calculation of QTc dispersion (QTcd) by subtracting the shortest and longest QTIc. Values affected by T-wave endpoint ambiguity or poor lead quality were omitted, ensuring that at least 5 leads were utilised for QT measurement. Using the number of leads helped correct QTcd to avoid the influence of maximum or minimum QT values.

For P-wave dispersion (PD) assessment, patients were in a supine position with synchronised 12-lead ECG recording. The measurements were taken during a stable baseline with clear and undistorted images of cardiac cycles. Efforts were made to minimize the interference from muscle electrical activity and artifacts. Three P-waves were measured within each lead, and the difference between the widest P-wave (P_{max}) and the narrowest P-wave (P_{min}) was calculated to obtain PD. Finally, the average PD value was determined.

Clinical efficacy (CE) evaluation. The treatment outcomes of all patients in various groups were assessed based on their CF classification. Effective results were categorised as marked improvement: HF symptoms remarkably improved or nearly disappeared, and CF classification increased by 2 or more levels; effective: HF symptoms showed some degree of improvement, but were not completely resolved, and CF classification increased by 1 level; and ineffective: HF symptoms did not remarkably improve and CF classification remained unchanged.

Adverse Event (AE) evaluation. AE rates of patients after varying treatments were compared between groups.

Statistical analysis

Quantitative experimental results were expressed as mean ± standard deviation. Data were processed using SPSS 22.0. Normality and variance tests were performed on general data, disease duration, CF indicators and LVEF indicators. Data that followed a normal distribution and had homogeneity of variance were presented as mean ± standard deviation. Categorical data were compared using the chi-squared test. Before and after intervention comparisons for indicators were performed using the t-test and count data were presented as percentages (n, %). A value of $p < 0.05$ indicates statistically significant differences.

Results and Discussion

VEF

Figure 1A showed no visible difference in plasma NO levels in all patients before treatment ($p > 0.05$). However, the post-treatment NO levels in the Obs

group were higher than those in the Ctrl group ($p < 0.05$). As shown in Figure 1B, AgII did not show much difference before treatment ($p > 0.05$). The post-treatment AgII levels in the Obs group were shifted downwards in contrast to those in the Ctrl group ($p < 0.05$). Figure 1C compares the changes in VCAM-1 before and after different treatments. It showed no visible difference in pre-VCAM-1 ($p > 0.05$) and higher post-VCAM-1 in the Obs group ($p < 0.05$). Furthermore, ICAM-1 showed similar results with the other three indicators before the patients were treated, meaning that no obvious change was observed ($p > 0.05$). However, after treatment, ICAM-1 was significantly down-regulated in the Obs group, showing a remarkable difference from that in the Ctrl group ($p < 0.05$).

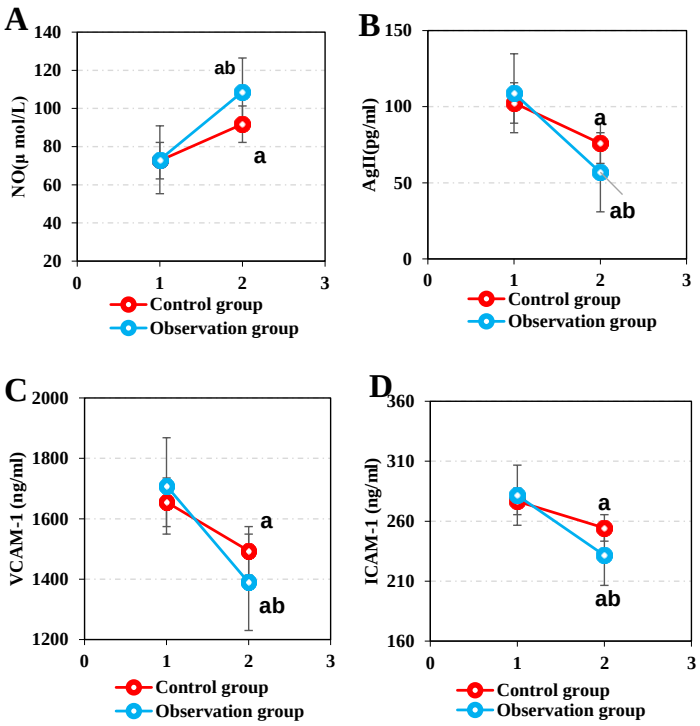

Figure 1.

Changes in VEF-related indicators: A: NO; B: AgII; C: VCAM-1; D: ICAM-1

([a] $p < 0.05$ compared with pre-treatment value; [b] $p < 0.05$ compared with Ctrl group)

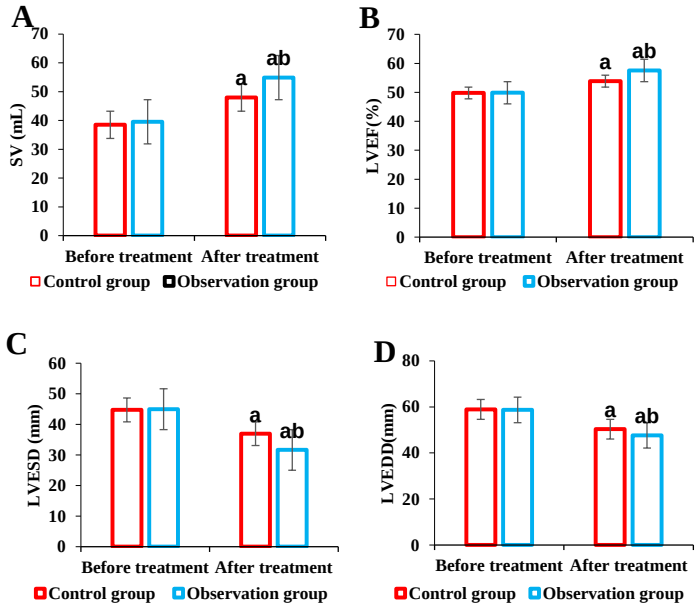

Figure 2.

Changes in CF-relevant indicators: A: SV; B: LVEF; C: LVESD; D: LVEDD

([a] $p < 0.05$ compared with pre-treatment value; [b] $p < 0.05$ compared with Ctrl group)

Changes in CF-relevant parameters

Figure 2 shows that CF-relevant indicators did not differ significantly in patients before treatment ($p > 0.05$). However, significant differences were observed when comparing treatment outcomes with pre-treatment status ($p < 0.05$). In particular, patients in the Obs group showed significant improvements in SV, LVEF, LVESD and LVEDD after treatment, which were clearly different from those in the Ctrl group ($p < 0.05$).

Changes in NT-BNP, cTnI and 6MWT

Figure 3 compares the changes in NT-BNP, cTnI and 6MWT. All three indicators were similar before treatment ($p > 0.05$). The Obs group had significantly lower NT-BNP and cTnI levels ($p < 0.05$) but better 6MWT results ($p < 0.05$) compared to the Ctrl group, as shown in Figures 3A, 3B and 3C, respectively.

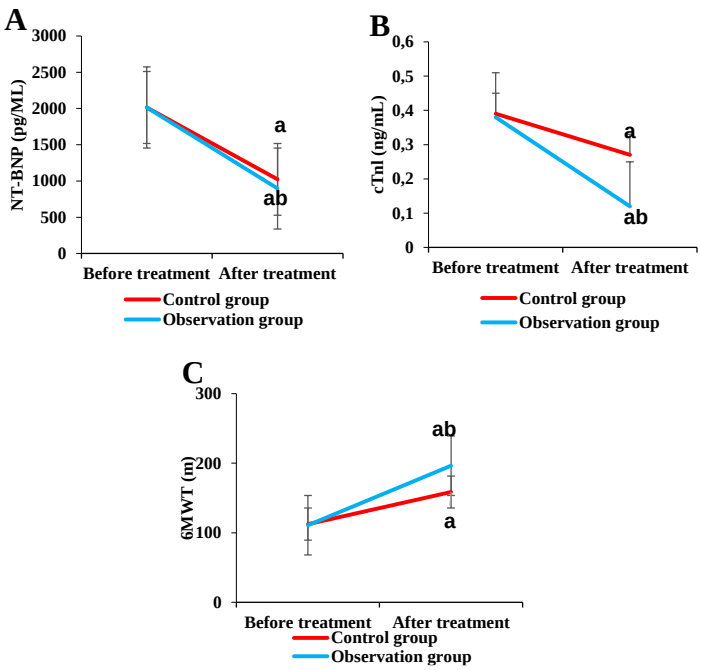

Figure 3.

Variations in laboratory parameters: A: NT-BNP; B: cTnl; C: 6MWT

([a] $p < 0.05$ compared with pre-treatment value; [b] $p < 0.05$ compared with Ctrl group)

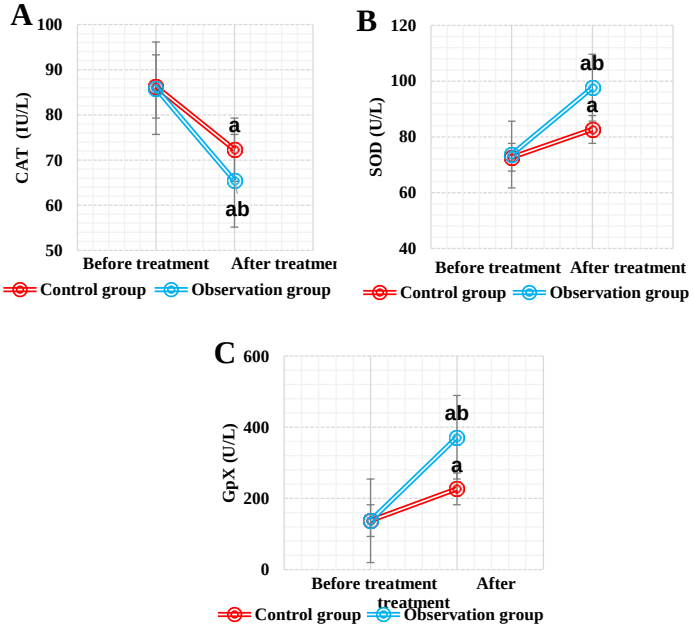

Figure 4.

Alternations in oxidative stress indexes: A: CAT; B: SOD; C: GPx

([a] $p < 0.05$ compared with pre-treatment value; [b] $p < 0.05$ compared with Ctrl group)

Oxidative stress indexes

Figure 4 shows the changes in oxidative stress indices, which indicated no visible differences in CAT, SOD and GPx levels before treatment for patients in different groups ($p < 0.05$). As shown in Figures 4A, 4B and 4C, the levels of CAT, SOD and GPx changed significantly after the intervention in the patients, with obviously lower CAT but higher SOD and GPx, respectively. All comparisons here showed strong differences for patients in the Ctrl and Obs groups, so $p < 0.05$ is indicated for them.

ECG parameters

Notable findings are shown in Figure 5. Figure 5A shows that the Obs group had a significantly lower QTcd ($p < 0.05$). In addition, before treatment, both groups had PD values greater than 40 ms, and no visible difference was observed between them ($p > 0.05$), as shown in Figure 5B. However, the Obs group showed a significant decrease in PD after treatment compared to the Ctrl group ($p < 0.05$).

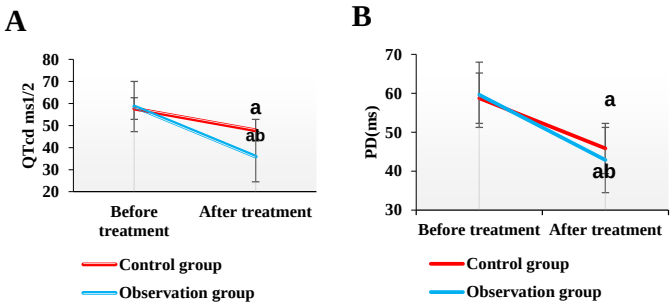

Figure 5.
Comparison of ECG parameters: A: QTcd; B: PD
([a] $p < 0.05$ compared with pre-treatment value;
[b] $p < 0.05$ compared with Ctrl group)

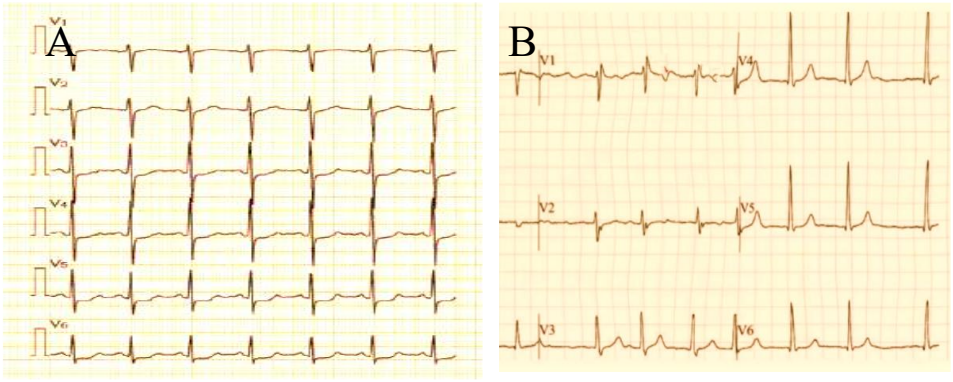

Figure 6.
Level of ECG of patients

Figure 6 below compares the changes in ECC parameters. As shown in Figure 6A, there was evidence of ST segment depression greater than 0.05 mV in a 67-year-old male patient. This significant ST-segment depression suggested myocardial ischemia. The reliability of myocardial ischemia was relatively reduced when the ST segment was inferior. Figure 6B shows a 68-year-old female patient with atrial fibrillation associated with CHD. ECG lead V1 showed rSr with T-wave inversion and there was clear evidence of delayed terminal conduction in the near field of lead V3.

Changes in CE

Comparing the two groups after 12 months of treatment in terms of the total clinical effectiveness rate (TER), the results were summarised as follows (Figure 7). In the Ctrl group, 42 cases (52.5%) were classified as clearly effective, 26 cases (32.5%) as effective and 12 cases (15.0%) as ineffective, giving a TER of 85.0%. In the Obs group, 48 cases (60.0%) were classified as highly effective, 27 cases (33.75%) as effective and 5 cases (6.25%) as ineffective, giving a TER of 93.75%.

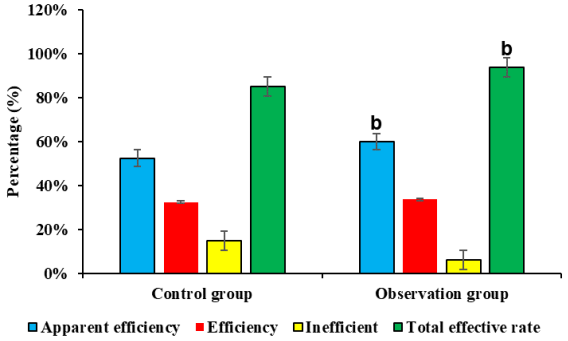

Figure 7.
CE of patients after varying treatments
([b] $p < 0.05$ compared with Ctrl group)

AE rate

AAEs were observed in the Ctrl group as follows: 1 case (1.25%) of hyperkalaemia, 3 cases (3.75%) of somnolence, 1 case (1.25%) of vascular neurogenic oedema, 3 cases (3.75%) of hypotension, 2 cases (2.5%) of renal dysfunction and 1 case (1.25%) of gastrointestinal reaction. In contrast, in the Obs group there were 2 cases (2.5%) of hyperkalaemia, 2 cases (2.5%) of somnolence, 2 cases (2.5%) of vascular neurogenic oedema, 1 case (1.25%) of hypotension, 1

case (1.25%) of renal dysfunction and 3 cases (3.75%) of gastrointestinal reactions. These observations did not indicate any visible differences in terms of AEs in patients treated with different methods ($p > 0.05$) (Figure 8).

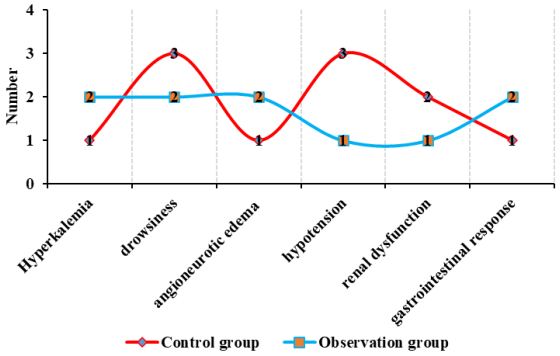

Figure 8.
Statistical results of AEs in various groups.

Various techniques are used to diagnose HF, such as left ventricular volume index, central venous pressure measurement, assessment of local wall motion, coronary artery calcium scoring, intracardiac electrocardiogram mapping and myocardial perfusion imaging. These techniques are technically demanding, costly and complex. In contrast, ECG provides a simple, non-invasive method for routine cardiac assessment that is more convenient and faster than central venous pressure measurement and intracardiac electrocardiogram mapping [16, 17]. In this work, ECG detected low QRS voltage in different limb leads in patients with different degrees of heart failure. With worsening heart failure, the voltage showed a decreasing trend, mainly in the high lateral wall and inferior wall. In severe heart failure, there were no significant differences in voltage between the different leads. In patients with heart failure, there was a significant increase in QTcd, which contributes to electro cardiac instability and the risk of arrhythmia or sudden cardiac death. In this study, the Obs group had significantly lower QTcd, suggesting that combination therapy can reduce QT dispersion. Heart failure leads to a decline in cardiac contractile and diastolic function, increased atrial pressure, changes in atrial structure and function and uneven propagation of sinus impulses in different parts of the atrium. This can lead to arrhythmias such as tachycardia, bradycardia, atrioventricular block, ST-T segment changes and sinus-atrial block [18]. Koide *et al.* [19] suggested that PD can predict the occurrence of atrial fibrillation with good predictive value, while Ocak *et al.* [20, 21] suggested that PD can prevent the recurrence of atrial fibrillation. Furthermore, this work showed that the sensitivity of QTcd elevation and ST-SC increased with disease severity. Prior to treatment, all patients had PD greater than 40 ms, indicating the presence of heterogeneity in different parts of the atrium leading to arrhythmia. After the procedure, the PD in the Obs group was much lower than in the Ctrl group, indicating a better improvement in atrial function in the Obs group. This suggests that sacubitril/valsartan in combination with metoprolol succinate extended-release tablets has a beneficial role in the treatment and prevention of atrial fibrillation or other atrial arrhythmias, improving cardiac electrophysiological properties and improving cardiac function. The results of this work are consistent with those of Zhong *et al.* [21] and Chang *et al.* [22], suggesting that sacubitril/valsartan may reduce the incidence of arrhythmias. In addition, metoprolol succinate has a relatively high selectivity for β-receptors, allowing it to reduce sympathetic nervous system activity by inhibiting β1-receptor activity in the heart. This reduces the workload on the heart and relieves cardiac stress. Ding *et al.* (2022) [23] demonstrated that sacubitril/valsartan in combination with metoprolol succinate delayed-release tablets can improve CF, LVEF, reduce OSS and improve coagulation parameters. In addition, this combination therapy may improve left ventricular remodelling and has demonstrated good safety.

NO plays a role in vasodilation in the blood vessels, helping to maintain a relaxed state of the blood vessels and thereby reducing blood pressure [24]. In this study, NO levels were significantly increased in the Obs group after treatment, with a visible difference compared to the Ctrl group ($p < 0.05$). This suggests that patients in the combination therapy group had better blood pressure regulation and vascular function than those in the monotherapy group. In patients with CHD and HF, the reduced pumping capacity of the heart leads to reduced oxygen delivery to the tissues and organs of the body, stimulating the kidneys to release renin [25]. Angiotensin II receptor antagonists attenuate the effects of angiotensin II to reduce cardiac workload and improve the condition of HF patients [26]. This work also showed that AgII levels after treatment were significantly lower in the Obs group compared to the Ctrl group. This suggests that combination therapy contributes to the improvement of clinical symptoms in patients and enhances the reduction of plasma AgII levels. This has a positive impact on improving the quality of life of CHF patients. VCAM-1 is typically expressed on the surface of endothelial cells, especially vascular endothelial cells [27]. ICAM-1 is also expressed on endothelial cells and is involved in cell adhesion. Some studies have suggested that increased ICAM-1 expression after cerebral ischaemia may promote granulocyte aggregation in the ischaemic area, leading to microcirculatory failure [28, 29]. In addition, this work showed that both VCAM-1 and ICAM-1 were significantly lower in the Obs group compared to the Ctrl group. This suggests that combination therapy can reduce the distribution of adhesion molecules in CHF patients and effectively improve endothelial cell function.

This may reduce the likelihood of related vascular complications and improve prognosis. Stroke volume is the amount of blood that the heart can pump out with each heartbeat [30]. In addition, this work showed that patients in the Obs group had a significantly higher SV after treatment, showing an observable difference from those in the Ctrl group, indicating an improvement in the heart's pumping function. A higher LVEF usually indicates better heart function. In this case, the treated patients in the Obs group had a significantly increased LVEF, indicating an improvement in left ventricular pumping function. LVESD can assess the size of the left ventricle. In patients with HF, the left ventricle is typically enlarged. In the Obs group, LVESD decreased significantly after treatment, suggesting that such treatment may help to reduce cardiac workload. LVEDD is used to assess the diastolic capacity of the left ventricle. In the Obs group, LVEDD decreased significantly after the intervention, indicating better diastolic capacity in the left ventricle. The heart can relax better when it is filling. A study by Du *et al*. [31] showed that valsartan can significantly improve LVEF, LVEDD, NT-proBNP and CF and improve the clinical symptoms and CF of patients. Valsartan can increase serum APN levels, decrease MMP-9 and BNP levels, and have a beneficial effect on cardiac electrophysiological properties. Valsartan has a protective effect on the VEF in patients with hypertension and HF. According to Li *et al*. [32], valsartan can improve endothelial function in HF patients while improving VEF. In this paper, the treated patients in the Obs group showed significant improvements in SV, LVEF, LVESD and LVEDD. This suggests that the CF of patients in the Obs group improved after being treated with combination therapy. Cardiac pumping function improved, left ventricular size decreased and diastolic capacity improved, indicating relief of patients' condition. These improvements may alleviate HF symptoms, improve patients' quality of life and reduce the potential for CVD-related events.

NT-BNP can be used to assess the severity and prognosis of HF. In patients with HF, the heart may be damaged to varying degrees, leading to increased cardiac workload and myocardial wall stress, resulting in increased release of NT-BNP [33]. Mishra *et al*. [34] stated that both BNP and NT-proBNP are important predictive indicators of stable CHD MACE. Assessment of NT-BNP can evaluate whether sacubitril/valsartan in combination with metoprolol succinate extended-release tablet therapy can reduce cardiac workload and thereby improve the condition of HF patients [35]. Wolsk *et al*. [36] also suggested that BNP and NT-proBNP are strong predictive factors for cardiovascular outcomes other than HF and death. They are also predictive factors for myocardial infarction and stroke. The results of this paper showed that NT-BNP levels were significantly reduced in the Obs group after treatment. This indicates a significant physiological response to treatment with sacubitril/valsartan and metoprolol succinate delayed-release tablets, demonstrating efficacy. cTnI can be used to assess the extent of myocardial damage. In CAD with HF, myocardial cells may be damaged to varying degrees, resulting in elevated cTnI levels. Zhao *et al*. [37] indicated that improvement in hs-CRP, brain natriuretic peptide, myoglobin and LVDD levels can improve the grading of HF and consequently improve HF. Árnadóttir *et al*. [38] suggested that most patients with high cardiac troponin T (> 99%) do not have structural heart disease, but 30% of them may benefit from prophylactic drug treatment. In this study, the post-treatment cTnI levels in the Obs group were significantly lower than those in the Ctrl group. This suggests that treatment with sacubitril/valsartan in combination with metoprolol succinate extended-release tablets has a significant effect on cTnI in patients with CHD, further indicating the efficacy of the treatment. The 6MWT can be used to assess rehabilitation progress and ensure that patients gradually increase their exercise levels during the recovery period. This study showed that the Obs group had significantly higher 6MWT scores after treatment compared to the Ctrl group, indicating that the combination therapy significantly improved patients' exercise capacity and physical tolerance. In cardiovascular patients, increasing CAT activity may reduce oxidative stress and help reduce the risk of CHD and atherosclerosis [39, 40]. SOD is an antioxidant enzyme that is primarily responsible for neutralizing and eliminating superoxide radicals. SOD helps to reduce the concentration of superoxide radicals, thereby reducing oxidative stress and alleviating oxidative damage to the cardiovascular system. GPx helps to reduce oxidative stress in cardiovascular patients by reducing oxidative damage to the vascular endothelium [41]. The results of this work reflected that the post-treatment levels of CAT, SOD and GPx in the Obs group differed significantly from those in the Ctrl group. This suggests that sacubitril/valsartan in combination with metoprolol succinate delayed-release tablet effectively degrades brain peptidase in patients, reduces their stress-induced damage and lowers their oxidative stress levels. Furthermore, the observations in this work were consistent with the results reported by Ding *et al*. [42]. This work suggested that there was no difference in complications between patients in different groups. This may be due to differences in individual patients' tolerance to medication due to different physical constitutions.

Conclusions

This work demonstrated that the combination of sacubitril/valsartan and metoprolol succinate extended-release tablet showed potential ECG improvement in patients with CHD and HF compared to the use of metoprolol succinate extended-release tablet alone.

While ensuring safe treatment, this combination significantly improved CF, VEF, oxidative stress levels and ECG-related parameters, providing greater therapeutic efficacy that contributed to the improvement in CF. ECG parameters helped clinicians to assess CF and rhythm in patients with CHD and HF. Timely identification of ECG abnormalities may aid in pro-active disease intervention. Future research can delve deeper into the analysis of ECG ST-SC, T-wave changes, R-wave amplitudes and other indicators to provide a more systematic understanding of the effects of this combination treatment on patients with CHD and HF.

Conflict of interest

The authors declare no conflict of interest.

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