

## Original Research Article

# Investigation of the efficacy of beta-blockers and renin-angiotensin-aldosterone system inhibitors in chronic heart failure with preserved ejection fraction

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### Abstract

**Purpose:** To investigate the clinical effectiveness of beta-blockers (BBs) and renin-angiotensin-aldosterone system (RAAS) inhibitors in chronic heart failure with preserved ejection fraction (HFpEF).

**Methods:** 100 patients with HFpEF admitted to The Third Affiliated Hospital of Qiqihar Medical University, China, between April and June 2023 were stratified into five groups. Beta-blocker (BB) group received bisoprolol, angiotensin-converting enzyme inhibitor (ACEI) group received benazepril hydrochloride, angiotensin II receptor blocker (ARB) group received candesartan, angiotensin receptor neprilysin inhibitor (ARNI) group received sacubitril valsartan, and mineralocorticoid receptor antagonist (MRA) group received spironolactone. Differences in clinical effectiveness, six-minute walking distance (6MWD), cardiac functionality, quality of life, and survival rate were compared among the groups.

**Results:** Beta-blocker group showed the highest efficacy. After treatment, all groups except MRA showed significant improvement in 6MWD. Also, ACEI, ARB, and ARNI groups exhibited significantly longer 6 MWD than MRA group ( $p < 0.05$ ). Left ventricular ejection fraction levels showed significant improvement in the ACEI, ARNI, and MRA groups ( $p < 0.05$ ), while pulmonary artery pressure (PAP) decreased in the BB, ACEI, ARNI, and MRA groups ( $p < 0.05$ ). After treatment, the Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores of BB, ACEI, ARB, and ARNI groups were significantly lower than before treatment ( $p < 0.05$ ). All five groups significantly exhibited decline in NT-proBNP levels after treatment ( $p < 0.05$ ). However, at 18-month follow-up, there was no significant difference in survival rates among the groups ( $p > 0.05$ ).

**Conclusion:** Beta-blockers (BBs) and RAAS inhibitors show promising activity in HFpEF, bisoprolol enhances cardiac function, benazepril improves symptoms, candesartan aids exercise and sacubitril valsartan elevates cardiac class. However, none of these drugs significantly improves clinical outcomes.

**Keywords:** Beta-blocker, Renin-Angiotensin-Aldosterone System inhibitor, Heart failure with preserved ejection fraction, Efficacy, Cardiac function

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## INTRODUCTION

Heart failure remains a prevalent condition among geriatric populations. The 2019 China

Cardiovascular Disease Report revealed approximately 4.5 million heart failure sufferers in China and nearly 23 million globally. The burgeoning demographic of the aging society

further escalates these figures, rendering heart failure a paramount public health issue of international concern [1,2].

Heart failure patients typically present with dyspnea, physical activity limitations, and fluid retention. Heart failure with preserved ejection fraction (HFpEF) constitutes the most prevalent type of heart failure in the elderly, accounting for approximately 50 % of all cases [3]. Incidence of acute decompensation in HFpEF parallels that of heart failure with reduced ejection fraction (HfrEF). However, HFpEF patients exhibit heightened morbidity, mortality, and rehospitalization rates compared to HfrEF patients, and correspondingly, a diminished quality of life [4,5]. Despite the substantial impact of HFpEF on health and economic domains, optimal pharmacological treatment strategies remain undefined. Considerable progress has been achieved in China regarding the prevention and control of heart failure over the past few years through the publication and regular updating of various heart failure guidelines and expert consensus. Beta-blockers (BB) and renin-angiotensin-aldosterone system (RAAS) inhibitors represent the gold standard in acute and chronic heart failure management. However, these pre-eminent guidelines offer no specific treatment recommendations concerning their utilization [6]. It was pointed out that the concomitant use of angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA) might marginally reduce hospitalization rates in HFpEF patients [7]. In addition, the European Society of Cardiology accentuated that angiotensin receptor neprilysin inhibitors (ARNI) and BBs, when combined, prove more efficacious than single agents in the management of HFpEF [8].

This research was carried out to systematically appraise the impact of BB, angiotensin-converting enzyme inhibitors (ACEI), ARB, ARNI, and MRA on cardiac function, exercise capacity, survival, and quality of life in HFpEF patients through the establishment of controlled subgroups. The purpose was to investigate the efficacy and safety of BB and RAAS inhibitors in HFpEF, thereby contributing potential resolutions to the impasse surrounding HFpEF management.

## METHODS

### Study population and design

The research involved 100 patients diagnosed with HFpEF admitted to the Department of Cardiology at the Third Affiliated Hospital of Qiqihar Medical College, China between April

and June 2023. The patients were allocated randomly into 5 groups: BB, ACEI, ARB, ARNI, and MRA groups, each comprising 20 individuals. The study protocol received institutional Ethics Committee approval (no. 2023LL-61) and followed the guidelines of the Declaration of Helsinki [9].

### Inclusion criteria

Left Ventricular Ejection Fraction (LVEF)  $\geq$  50 %, New York Heart Association (NYHA) [10] functional classes I-IV, and objective proof of HF, as indicated by one or more of the subsequent parameters: previous HF hospitalization with imaging confirmation of pulmonary congestion, increased left ventricular end-diastolic pressure or pulmonary capillary wedge pressure during resting ( $\geq$  15 mm Hg) or exercise ( $\geq$  25 mm Hg), elevated N-terminal prohormone of brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP) levels ( $>$  200 pg/mL), or evidence of diastolic dysfunction on echocardiography, indicated by an E/E' ratio  $\geq$  15 or left atrial enlargement. Additional criteria included HF history exceeding two months, no contraindications for current drugs, an age range of 18 to 80 years, and voluntary participation.

### Exclusion criteria

Acute myocardial infarction, severe heart failure, cardiac function up to grade IV, concomitant serious physical illnesses such as severe liver and kidney insufficiency, severe malnutrition, malignancy, mental disorders, pregnancy or lactation, and the presence of primary diseases from other systems.

### Treatment protocol

All five groups received conventional lifestyle interventions including low salt, low fat, light diet, regular rest, moderate activity, and smoking cessation. Specific medications administered to each group were as follows:

**BB group:** Bisoprolol (Salutas Pharma GmbH), at starting dose of 1.25 mg/day, adjusted every 1-2 weeks, with a maximal dosage increased to 5 mg once daily.

**ACEI group:** Benazepril hydrochloride tablets (manufacturer: Chengdu Dior Pharmaceutical Group Co., Ltd.), 10 mg/day.

**ARB group:** Candesartan (Tianjin Pharmaceutical Research Institute Co., Ltd.), starting dose of 4mg/day, adjusted every 1-2 weeks, with a maximal dosage increased to 8 mg once daily.

**ARNI group:** Sakubatril Valsartan (Novartis Pharma Schweiz AG), starting dose of 100 mg twice daily, adjusted every 1-2 weeks, with a maximal dosage increased to 200 mg twice daily.

**MRA group:** Spironolactone (Hainan Haishen Tongzhou Pharmaceutical Co., Ltd.), 25 mg/day. The dose was adjusted according to patient tolerance.

Each treatment regimen was designed to last for eight weeks divided into two four-week courses.

**Evaluation of parameters/indices**

**Clinical efficacy**

This was classified into three categories based on the change in NYHA assessment: significant improvement (NYHA grade decrease  $\geq 2$ ), improvement (NYHA grade decrease 1), and no significant change.

**Six-Minute Walking Distance (6MWD)**

The maximum distance patients could walk within six minutes was recorded.

**Cardiac Function**

A total of 5 mL fasting blood samples were collected from the elbow vein of patients in the morning, and centrifuged at 3000 r/min for 5 min. Left ventricular ejection fraction (LVEF) and pulmonary artery pressure (PAP) were assessed via echocardiography, and serum NT-proBNP levels were investigated using immunofluorescence assay (Elabscience Co., Ltd).

**Quality of Life**

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) [11] was utilized to

assess patients' quality of life, with higher scores indicating worse conditions.

**Survival rate**

The survival rate was determined over a total of 18 months from hospital admission, with follow-up conducted every two weeks during the medication period and every three months thereafter.

**Statistical analysis**

Statistic Package for Social Science (SPSS version 22.0 software, IBM, Armonk, NY, USA) was employed for data analysis. Categorical variables were presented as percentages and analyzed using chi-square test. Continuous variables were presented as mean  $\pm$  standard deviation (SD) and were analyzed using student t-test. Survival rates among the groups were compared using Kaplan-Meier survival curves.  $P < 0.05$  was considered statistically significant.

**RESULTS**

**Baseline clinical characteristics**

Differences in baseline characteristics including gender, mean age, average disease duration, and underlying comorbidities, across the five patient groups were not statistically significant ( $p > 0.05$ ). This suggests that the groups were well-matched at baseline, allowing for a reliable comparison of treatment outcomes (Table 1).

**Clinical efficacy**

The BB group demonstrated the highest overall efficacy, with a total effective rate of 100 % (20/20), surpassing ACEI group at 75 % (15/20), ARB group at 70 % (14/20), and ARNI group at 90 % (16/20), and this difference was statistically significant ( $p < 0.05$ ; Table 2).

**Table 1:** Comparison of baseline clinical characteristics (mean  $\pm$  SD) (N = 20)

Group	Male/ female	Mean age (years)	Mean disease duration (months)	Primary disease		
				Hypertension (case)	Diabetes (case)	Rheumatic heart disease (case)
BB	13/7	56.98 $\pm$ 6.32	3.23 $\pm$ 0.65	6	3	1
ACEI	15/5	56.08 $\pm$ 10.56	3.16 $\pm$ 0.81	9	5	0
ARB	14/6	55.93 $\pm$ 12.55	2.96 $\pm$ 1.11	10	4	1
ARNI	12/8	59.68 $\pm$ 13.56	3.63 $\pm$ 1.56	9	4	0
MARs	11/9	53.26 $\pm$ 6.98	3.05 $\pm$ 0.81	11	3	0
T-value	1.221	0.698	0.771	1.015	1.665	0.696
P-value	0.365	0.551	0.663	0.636	0.214	0.563

**Table 2:** Comparison of clinical efficacy of patients in five groups (N = 20) (N (%))

Group	Apparent effect	Excellent	Ineffective	Effective
BB	6 (30.00)	14 (70.00)	0 (0.00)	20 (100.00)
ACEI	3 (15.00)	12 (60.00)	5 (25.00)	15 (75.00) <sup>a</sup>
ARB	2 (10.00)	12 (60.00)	6 (30.00)	14 (70.00) <sup>a</sup>
ARNI	6 (30.00)	10 (50.00)	4 (20.00)	16 (90.00) <sup>a</sup>
MARs	1 (5.00)	14 (70.00)	5 (25.00)	15 (75.00) <sup>a</sup>
$\chi^2$	-	-	-	6.302
P-value	-	-	-	0.038

<sup>a</sup>P < 0.05 vs, BB group

**Table 3:** Comparison of 6-minute walking distance among patients in five groups (N = 20, mean ± SD)

Group	Before treatment	After treatment
BB	350.11±36.59	426.53±41.51 <sup>ab</sup>
ACEI	341.59±45.69	421.11±56.36 <sup>ab</sup>
ARB	330.56±56.98	386.98±64.15 <sup>ab</sup>
ARNI	351.69±91.11	421.56±59.63 <sup>ab</sup>
MARs	323.69±50.18	340.15±43.65
T-value	0.888	9.548
P-value	0.474	<0.001

<sup>a</sup>P < 0.05 vs. pre-treatment, <sup>b</sup>p < 0.05 vs. MARs group

**Table 4:** Differences in cardiac function before and after treatment in the five groups (N = 20, mean ± SD)

Group	LVEF (%)		PAP (mmHg)	
	Before treatment	After treatment	Before treatment	After treatment
BB	37.51±2.96	38.49±3.65	35.16±3.65	25.11±3.96 <sup>ab</sup>
ACEI	36.95±3.81	40.41±4.81 <sup>a</sup>	34.98±4.11	26.98±3.51 <sup>ab</sup>
ARB	35.98±4.11	38.41±5.16	35.07±5.18	32.81±3.69
ARNI	37.56±4.11	48.96±3.65 <sup>ab</sup>	34.26±4.19	24.01±3.65 <sup>ab</sup>
MARs	36.98±5.62	47.98±4.15 <sup>ab</sup>	36.51±4.98	23.98±4.15 <sup>ab</sup>
T-value	0.986	12.541	0.441	9.568
P-value	0.441	0.000	0.639	0.000

<sup>a</sup>P < 0.05 vs. pre-treatment, <sup>b</sup>p < 0.05 vs. ARB group

### Six-minute walking distance

All groups revealed no significant differences in 6MWD prior to treatment ( $p > 0.05$ ). However, post-treatment analysis revealed a significant improvement in 6MWD in all groups, except for MRA group ( $p < 0.05$ ). The 6MWD in the BB, ACEI, ARB, and ARNI groups significantly exceeded that of MRA group after treatment ( $p < 0.05$ ) (Table 3).

### Cardiac function

Before treatment, all the groups showed no statistically significant differences in LVEF and PAP ( $p > 0.05$ ). After treatment, LVEF levels significantly increased in the ACEI, ARNI, and MRA groups, and PAP significantly decreased in the BB, ACEI, ARNI, and MRA groups ( $p < 0.05$ ) (Table 4).

### Quality of life assessment

Pre-treatment scores on the MLHFQ demonstrated no significant difference among

groups ( $p > 0.05$ ). However, scores after treatment showed a significant decrease compared to scores before treatment in all groups, except MRA group ( $p < 0.05$ ) (Figure 1).

There was no statistically significant difference ( $p > 0.05$ ) in MLHFQ scores among the groups before treatment.

Also, the scores were significantly lower ( $p < 0.05$ ) after treatment compared to before treatment, except for the MARs group.

### NT-proBNP levels

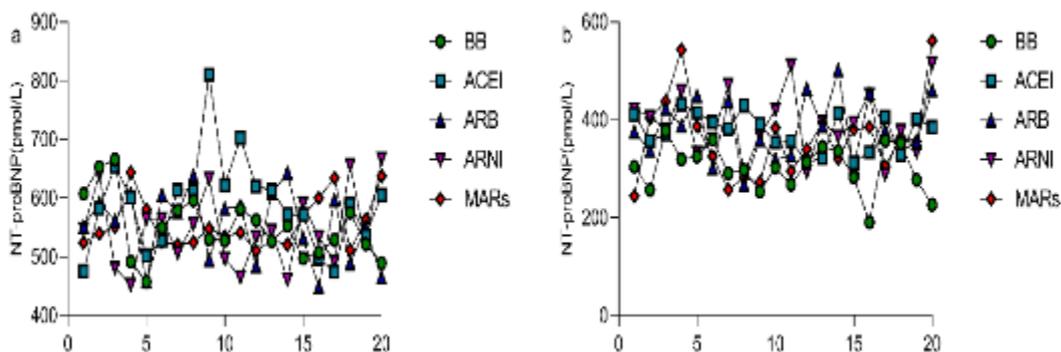
At baseline, no significant difference in NT-proBNP levels across the groups ( $p > 0.05$ ). All groups exhibited a significant decline in post-treatment NT-proBNP levels in contrast to baseline ( $p < 0.05$ ; Figure 2).

### Survival rates

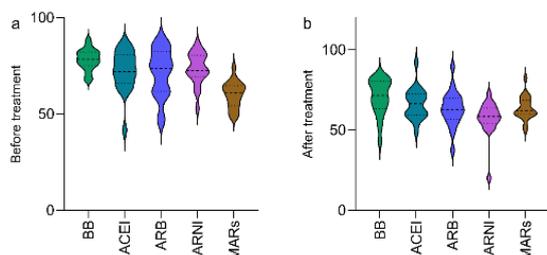
The 18-month follow-up period revealed that incidence of composite endpoint (cardiac death

and/or HF readmission) was 20 % in BB group, 20 % in ACEI group, 15 % in ARB group, 25 % in ARNI group, and 25 % in MRA group. Also, there

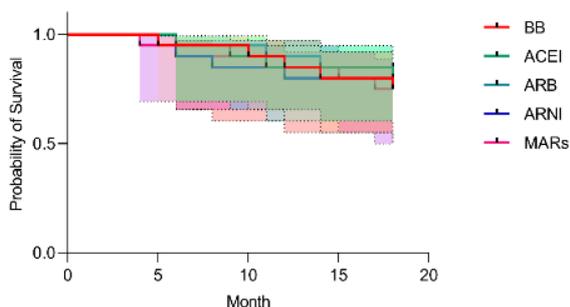
was no statistical significance in survival rates among the groups ( $p > 0.05$ ; Figure 3).



**Figure 2:** Differences in NT-proBNP levels before and after treatment in the five groups. (a) NT-proBNP levels before treatment ( $p > 0.05$ ), (b) NT-proBNP levels after treatment.  $P < 0.05$  vs. before treatment



**Figure 1:** Differences in quality of life between the five groups. (a) The MLHFQ scores before treatment.  $P > 0.05$  vs. BB group. (b) The MLHFQ scores after treatment in all four groups.  $P < 0.05$  vs before treatment



**Figure 3:** Comparison of follow-up survival rates among the five groups.  $P > 0.05$  vs. before treatment

## DISCUSSION

Heart failure with preserved ejection fraction (HfpEF) manifests as diminished left ventricular compliance owing to hindered active myocardial relaxation while maintaining normal left ventricular contractility. It leads to a reduction in passive filling or dilatation capacity, diminished left ventricular filling, heightened filling pressures, and eventually, symptoms of pulmonary or systemic circulation stagnation [12]. Recent

research on HfpEF suggested an ever-growing prevalence rate [2]. Also, a longitudinal observation of 662 patients hospitalized due to an initial episode of heart failure revealed that only half of them had an ejection fraction  $> 50\%$ , and amongst those over the age of 75 suffering from heart failure, 61 % presented HfpEF [13].

Similar studies conducted domestically indicate that  $> 50\%$  of adult heart failure patients aged 35 to 74 years in China have HfpEF and tend to face poor prognosis [14]. While the pathogenesis of HfpEF remains uncertain, various factors play a role in its progression. These factors include endothelial dysfunction, variable temporal insufficiency, and impaired heart rate recovery. Additionally, dysfunctional vascular coupling, impaired vascular diastolic reserve, abnormal ventricular vascular recovery, postcapillary pulmonary hypertension, autonomic dysfunction, upregulation of the RAAS, and sympathetic nervous system may all be involved in the development of HfpEF [15]. These complex pathophysiological mechanisms reconfirm the heterogeneity of HfpEF, complicating early differential diagnosis.

The increasing prevalence of HfpEF, its association with high morbidity and mortality, and the paucity of evidence-based treatment pose significant challenges to physicians in the absence of dedicated heart failure management guidelines. This research was carried out to investigate the effect of BB, ACEI, ARB, ARNI, and MRAs on cardiac function, exercise capacity, survival, and quality of life in HfpEF patients by establishing controlled subgroups. These findings revealed that patients in BB group demonstrated the most significant improvement in cardiac function, compared to the other groups. Beta-blockers (BB) are ubiquitously used

in HfpEF treatment due to the high prevalence of comorbid conditions like systemic hypertension, atrial fibrillation, and coronary artery disease. Despite their widespread use in HfpEF, there are still few large-scale randomized controlled trials investigating these agents. A 21-month follow-up of HfpEF patients revealed that nebivolol significantly benefited patients in the EF > 35 % group when categorized into two groups (EF ≤ 35 % and EF > 35%); however, it failed to offer decisive evidence on the use of vasodilatory β-blockers in HfpEF [16]. A study involving 40 patients with LVEF ≥ 45 % who were administered carvedilol and a placebo, and after one-year follow-up, revealed that carvedilol reduced patients' BNP levels, improved NYHA functional class, and increased exercise capacity compared to placebo treatment [17]. These results are in tandem with these present findings, suggesting that BB confers vasodilatory effects by promoting nitric oxide production and enhancing patients' endothelial function. Long-term use of these drugs significantly improves patients' cardiac function and exercise capacity.

In an earlier study, the role of spironolactone in improving myocardial diastolic function and exercise capacity in HfpEF patients was investigated, and the result revealed that spironolactone significantly ameliorated left ventricular (LV) diastolic dysfunction, LV remodeling, and NT-proBNP levels, but did not enhance quality of life or exercise capacity [18]. However, another study revealed that HfpEF patients on spironolactone presented a reduced risk of adverse cardiovascular outcomes and the use of low-dose spironolactone (≤ 40 mg) displayed its optimal efficacy and safety profile [19]. Some scholars reported an improvement in cardiac structure/function in patients using spironolactone, but no enhancement in exercise capacity [20]. All of the above studies suggest that spironolactone is effective in improving clinical symptoms in HfpEF patients. The Chinese Medical Association also proposed spironolactone as a class lib treatment for HfpEF in 2018 [14]. Thus, the use of spironolactone in the treatment of HFPEF holds promise.

Dysregulation of RAAS is implicated in the initiation and development of HfpEF. Previous studies revealed that after 12 months of perindopril administration, endothelial function improved as assessed by photoplethysmographic pulse wave and capillaroscopy. This was evidenced by an increase in occlusion index from 1.45 to 1.8, an increase in displacement from 7.1 to 9.2 ms, a reduction in muscle macrovascular stiffness, and

a decline in the arterial stiffness index from 8.8 to 7.45 [21]. The effect of candesartan in HfpEF patients was investigated in previous research, randomizing 3023 heart failure patients with HfpEF to either 32 mg/day candesartan or a placebo group. The primary outcome was cardiovascular death or hospitalization for heart failure with mean patient follow-up of 36.6 months. Although primary outcome was not improved, the candesartan group had fewer patients with at least one heart failure hospitalization [22]. Although ARBs did not significantly impact clinical outcomes in patients with HfpEF, these drugs were able to decrease the number of hospitalizations for heart failure patients with a positive effect. Sacubitril valsartan, an ARNI, is a 1:1 mixture of angiotensin receptor blocker ARB and neprilysin (NEP) inhibitor sacubitril. It carries the dual function of inhibiting the RAAS system and amplifying the natriuretic peptide system, exerting diuretic, natriuretic, and cardiac preload and afterload-improving effects [23]. A randomized controlled trial at phase III conducted in 2022 included 4822 patients with HfpEF ≥ 45 % and demonstrated that ARNI was superior to conventional RAAS inhibitors in improving cardiac and renal function as well as reversing cardiac remodeling in HfpEF patients, with no significant difference in improving adverse prognosis such as mortality and hospitalization rates [24]. In contrast, in a 24-week randomized, double-blind, parallel-group clinical trial of 2572 patients screened at 40 centers across 32 countries, it was observed that sacubitril valsartan, when compared to conventional renin-angiotensin system inhibitors or placebo, significantly reduced NT-proBNP levels at 12 weeks of treatment [25]. As a result, ARNI drugs were superior to conventional RAAS inhibitors in enhancing cardiac and renal function and reversing cardiac remodeling in HfpEF patients with no significant difference in improving adverse prognoses such as mortality and hospitalization rates.

### Limitations of this study

Although this research compared the intervention value of different types of drugs for HfpEF patients, there were also shortcomings such as small number of cases and relatively simple source of patients in each group, which to some extent influenced the research findings. It is therefore proposed to carry out a large-sample, multi-center prospective randomized controlled trial in order to investigate the impacts of these drugs on HfpEF patients more precisely.

## CONCLUSION

Both  $\beta$ -blockers and renin-angiotensin-aldosterone system inhibitors demonstrate therapeutic effectiveness in HfpEF patients. Specifically, bisoprolol exerts a superior activity in enhancing cardiac function and significantly improves exercise capacity. Benazepril hydrochloride effectively improves clinical symptoms and exercise capacity. Candesartan enhances exercise function, albeit, slightly less effective in improving cardiac function. Sacubitril valsartan augment cardiac function grading. Spironolactone improves cardiac function and ameliorates left ventricular diastolic dysfunction. However, none of these drugs significantly improve clinical outcomes.

## DECLARATIONS

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### Funding

None provided.

### Ethical approval

None provided.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Conflict of Interest

No conflict of interest associated with this work.

### Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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