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The Effectiveness of Eplerenone vs Spironolactone on Left Ventricular Systolic Function, Hospitalization and Cardiovascular Death in Patients With Chronic Heart Failure–HFrEF

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ABSTRACT

Background: Heart failure remains one of the most prevalent clinical syndromes associated with significant morbidity and mortality. According to current guidelines, the prescription of a MRA is recommended to reduce the risk of HF hospitalization and death in all patients with symptomatic heart failure and no contraindications for this therapy. **Objective:** The aim of our study was to determine the efficacy of eplerenone vs. spironolactone on left ventricular systolic function by measuring left ventricle ejection fraction (LVEF) in patients with chronic heart failure, especially their effect on preventing hospitalization, reducing mortality, and improving clinical status among patients with chronic HF. **Methods:** From June 2021 to June 2022, the study was a randomized, prospective clinical trial single blind study. A total of 142 patients of chronic heart failure with reduced ejection fraction were selected by random sampling. Each patient was randomly allocated into either of the two groups and was continued receiving treatment with either spironolactone (Spiron-HF group) or eplerenone (Epler-HF group). Patients in Epler-HF group were compared with an arm of the same size and matched by age and gender patients in Spiron-HF group for management of chronic HFrEF. Each patient was evaluated clinically, biochemically, and echocardiographically at the beginning of treatment (baseline) after 6 months and at the end of 12th month. Echocardiography was performed to find out change in left ventricular systolic function. **Results:** After 12 months of treatment, significant improvement of left ventricular ejection fraction was observed in eplerenone treated arm (37.9 ± 3.8 ± 4.6 in Spiron-HF group versus 40.1 ± 5.7 in Epler-HF group; P < 0.05). A significant reduction in left ventricular end-systolic volume (6.3 ± 2.5ml in Spiron-HF versus 17.8± 4.4ml in Epler-HF group; P < 0.05) and left ventricular systolic diameter volume (2.7 ± 0.5ml in Spiron-HF versus 6.7 ± 0.2ml in Epler-HF group; P < 0.05), occurred after 12 months of treatment. Left ventricular global longitudinal strain (LV GLS) was significantly improved in Epler-HF group compared with Spiron-HF group (0.6 ± 0.4 versus 3.4 ± 0.9; P < 0.05). There were no significant differences observed in reduction of left ventricular end-diastolic volume (2.2 ± 0.5 ml versus 4.7 ± 1.1ml; P =0.103) and left ventricular diastolic diameter (1.2 ± 0.6 versus 1.7 ± 0.3; P=0.082) in both arms. The effects of both MRA agents spironolactone and eplerenone on the primary composite outcome, each of the individual mortality and hospital admission outcomes are shown in Figure 1 and 2**.** Patients of the Epler-HF group showed statistically significant lower cardiovascular mortality (HR 0.53; 95% CI 0.34–0.82; p= 0.007) and all-cause mortality (HR 0.64; 95% CI 0.44–0.93; p= 0.022) than patients of the Spiron-HF group. The statistical analysis did not show a statistically significant difference between Epler -HF and Spiron-HF study groups regarding the risk of the primary composite outcome; cardiovascular death or hospitalization due to HF (Hazard Ratio (HR) eplerenone vs. spironolactone = 0.95; 95% Confidence Interval (CI) 0.73– 1.27; p= 0.675). **Conclusion:** Our study has demonstrated favorable effects of eplerenone on cardiac remodeling parameters and reduction of cardiovascular mortality and all-cause mortality compared with spironolactone in the treatment of HFrEF. The ability of eplerenone to effectively block the mineralocorticoid receptor while minimizing side effects and a significant reduction in the risk of hospitalization and cardiovascular death confirms its key role in the treatment of patients with chronic HFrEF.

Keywords: Chronic heart failure, Heart failure with reduced ejection fraction, Eplerenone, Spironolactone, Left ventricular systolic function.

1. BACKGROUND

The current global prevalence of heart failure is estimated at 64.34 million cases and 9.91 million years of disability as a result (1). Heart failure remains one of the most prevalent clinical syndromes associated with significant morbidity and mortality. Mineralocorticoid receptor antagonists (MRA) play a central role in the therapeutic scheme recommended for patients with heart failure and reduced left ventricular ejection fraction (HFrEF). According to current ESC and ACC guidelines, the prescription of a MRA is recommended to reduce the risk of HF hospitalization and death in all patients with symptomatic HFrEF and no contraindications for this therapy (2, 3). A class I recommendation is given indistinctly to spironolactone and eplerenone; however, there are substantial differences between these two drugs regarding their pharmacokinetics and metabolism. MRAs can be selective (e.g., eplerenone) or nonselective (e.g., spironolactone). Eplerenone was synthesized through chemical modification of spironolactone in order to enhance binding of mineralocorticoid receptors while reducing off-target binding to progesterone or androgen receptors. Spironolactone is structurally like progesterone and binds to progesterone, androgen and mineralocorticoid receptors. Eplerenone is a selective mineralocorticoid receptor antagonist, so it lacks the anti-androgenic side effects of spironolactone. Eplerenone is associated with lower rates of impotence, gynecomastia or breast pain in comparison to spironolactone.

2. OBJECTIVE

The aim of our study was to determine the efficacy of eplerenone vs. spironolactone on left ventricular systolic function by measuring left ventricle ejection fraction (LVEF) in patients with chronic heart failure with reduced ejection fraction, especially their effect on preventing hospitalization, reducing mortality, and improving clinical status among patients with chronic HF. In this study we evaluate the primary composite end-point cardiovascular death or hospitalization due to worsening of HF.

3. PATIENTS AND METHODS

A prospective study of 142 patients with chronic heart failure with reduced ejection fraction (HFrEF) was conducted from June 2021 to June 2022. The inclusion criteria for participating in the study were as follows: adult patients age ≥18 years with chronic HF, New York Heart Association (NYHA) functional class II/III/IV classification symptoms despite standard optimal medical therapy, left ventricle ejection fraction (LVEF) of ≤40%, N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥ 600 pg/ml depend on the value of LVEF, HF hospitalization within 12 months, estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2. The exclusion criteria were a history of hypersensitivity or intolerance to MRA, RAAS inhibitors and SGLT2, eGFR <30 mL/min/1.73 m^2, acute coronary syndrome stroke, or transient ischemic attack (TIA) within <3 months, recent coronary revascularization, severe valvular heart disease, acute decompensated HF, implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) within 3 months.

We randomized 142 patients with HFrEF into two groups of similar size (n = 71), each taking a standard optimal medical therapy for HFrEF according to the guidelines for chronic HF treatment. The first group represents patients treated with MRA Eplerenone, β-blockers, RAAS inhibitors, angiotensin receptor-nephrilysin (ARNI), SGLT2 and digoxin, This group is named Epler-HF. A second group of patients were treated MRA Spironolactone, β-blockers, RAAS inhibitors, angiotensin receptor-nephrilysin (ARNI), SGLT2 and digoxin, This group is named Spiron-HF. during the follow up period of 12-months.

At baseline, we conducted complete medical histories, physical examinations, electrocardiograms, transthoracic echocardiograms, blood analysis, renal function, and NT-pro-BNP tests for all participants. Simpson's method was used to estimate left ventricle ejection fraction (LVEF) from the apical four (A4C) and apical two (A2C) chamber views. The echocardiograms were performed with a phased-array echocardiography xMATRIX array transducer with PureWave crystal technology X51, Epiq 7 Philips ultrasound machine. These measurements were conducted in accordance with the latest cardiac chamber quantification guidelines.

To assess the effectiveness of both mineralocorticoid receptor antagonists (eplerenone and spironolactone). On the initial visit, at the third and sixth months, and at the end of the follow-up after 12 months in both arms, we assessed NYHA class, NT-pro-BNP, left ventricle ejection fraction (LVEF), cardiac remodeling parameters: left ventricle mass index (LVMi), left ventricle end diastolic volume index (LVEDVi), left ventricle end systolic volume index (LVESVi), left ventricular global longitudinal strain (LV GLS), left atrial volume index (LAVi) and functional mitral regurgitation ≥ II grade. The composite outcome cardiovascular death or hospitalization due to worsening HF was selected as the primary endpoint of the study. Secondary endpoints were cardiovascular death, hospitalization due to HF or all-cause death. Cardiovascular deaths were those caused by refractory HF, cerebrovascular disease, malignant arrhythmia, arterial or venous thromboembolism, complications of a cardiovascular procedure and unexplained sudden deaths. SAS StatView 5.0® software was used for all statistical analyses.

4. RESULTS

Out of 142 patients with chronic HFrEF were prospectively enrolled from June 2021 to Juned 2022 year. The baseline characteristics of the randomized patients are shown in Table 1. A median age of 65.7 ± 7.1 years, 69% of patients were male, 65% had arterial hypertension, 42% had diabetes mellitus, 35% had ischemic heart disease, 27% had atrial fibrillation, 35% had chronic kidney disease, 11% had a stroke, 21% had peripheral artery disease, and 16% had chronic obstructive pulmonary

Items	All (N = 142)	Epler-HF Group (N = 71)	Spiron-HF Group (N = 71)	P value
Medical history				
Age (years)	65.7 ± 7.1	65.8 ± 7.2	65.7 ± 7.1	0.797
Male gender (%)	69	68	69	0.840
Body Mass Index (kg/m^2)	26.6 ± 4.8	26.5 ± 4.3	26.8 ± 4.2	0.621
Arterial Hypertension (%)	65	64.5	64.8	0.841
Diabetes mellitus (%)	42	41.4	42.2	0.876
Ischemic heart disease (%)	35	35.1	34.5	0.874
Atrial fibrillation (%)	27	26,1	27,2	0.765
Chronic kidney disease (%)	35	34.8	34.7	0.972
Stroke (%)	11	11,3	10,9	0.838
Peripheral artery disease (%)	21	20,2	21,4	0.647
Dyslipidemia (%)	61	61,4	60,9	0.881
COPD (%)	16	17,1	15,6	0.633
Implantable defibrillator ICD (%)	11	11.9	10.8	0,802
Cardiac Resynch. Therapy CRT (%)	13	12.8	13.3	0.772
NYHA Class (%)				
I	8	7,0	8,7	0.745
II	49	50,3	48.6	
III	37	37.2	36.8	
IV	6	6.9	5.7	
Systolic BP (mm Hg)	114 ± 9	114 ± 12	115 ± 6	0.835
Diastolic BP (mmHg)	67.7 ± 7.7	68.1 ± 8.2	67.3 ± 7.2	0.862
Laboratory tests				
NT-pro-BNP (pg/mL)	4403 ± 3233	4430 ± 3275	4376 ± 31923	0.842
Potassium (mmol/l)	4.5 ± 0.7	4.7 ± 0.5	4.3 ± 0.9	0.773
Blood glucose (mmol/L)	6.7 ± 1.5	6.8 ± 1.8	6.7 ± 1.3	0.826
Creatinine (µmol/L)	106 ± 37	108 ± 38	104 ± 36	0.773
eGFR (ml/min/m^2)	75 ± 27	76 ± 24	75 ± 31	0.826
Medical therapy				
Beta-blockers (%)	89	88.5	89.3	0.795
RAAS inhibitors (%)	75	77	74	0.872
ARNI (%)	15	15,6	14,9	0.798
Loop diuretics (%)	92	92.1	91.9	0.765
Digoxin (%)	29	29,8	28.8	0.773
SGLT2 inhibitors (%)	26	26,4	26,1	0.883

Table 1. Baseline demographic and clinical characteristics of patients with chronic HFrEF treated with mineralocorticoid antagonists spironolactone and eplerenone.. COPD: Chronic Obstructive Pulmonary Disease. RAAS inhibitors: Renin-Angiotensin-Aldosterone System inhibitors. BP: Blood Pressure. NT-pro-BNP: N-terminal pro-B-type natriuretic peptide. eGFR: estimated glomerular filtration ratio. NYHA: New York Heart Association Class. ARNI: Angiotensin receptor-nephrilysin inhibitors.

disease. The eGFR was 75 mL/min/1.73 m^2, the NT-pro-BNP was 4234 ± 2965 pg/mL. The ischemic etiology of heart failure was 35%. NYHA Classes: I in 8%, II in 49%, III 37% and IV in 6% of patients. Other patient characteristics and medications at baseline were similar between treatment groups. The proportion of medical therapy with beta-blockers, RAAS inhibitors, ARNI, loop diuretics, SGLT2 inhibitors, digoxin, CRT or ICD, systolic and diastolic BP and other laboratory tests are shown in Table 1.

The Echocardiographic parameters at baseline and at the end of the follow up period of 12 months in both groups are shown in Table 2 After 12 months of treatment, significant improvement of left ventricular ejection fraction was observed in eplerenone treated arm (37.9 ± 3.8 ± 4.6 in Spiron-HF group versus 40.1 ± 5.7 in Epler-HF group; P < 0.05). A significant reduction in left ventricular end-systolic volume (6.3 ± 2.5ml in Spiron-HF versus 17.8± 4.4ml in Epler-HF group; P < 0.05) and left ventricular systolic diameter volume (2.7 ± 0.5ml in Spiron-HF versus 6.7 ± 0.2ml in Epler-HF group; P < 0.05), occurred after 12 months of treatment. Left ventricular global longitudinal strain (LV GLS) was significantly improved in Epler-HF group compared with Spiron-HF group (0.6 ± 0.4 versus 3.4 ± 0.9; P < 0.05). There were no significant differences observed in reduction of left ventricular end-diastolic volume (2.2 ± 0.5 ml versus 4.7 ± 1.1ml; P =0.103) and left ventricular diastolic diameter (1.2 ± 0.6 versus 1.7 ± 0.3; P=0.082) in both arms.

The effects of both MRA agents spironolactone and eplerenone on the primary composite outcome, each of the individual mortality and hospital admission outcomes are shown in Figure 1 and 2. Patients of the Epler-

LV function parameters	Spiron – HF group		Mean of Difference	Epler-HF group		Mean of Difference	P value
	Baseline	After 12 months		Baseline	After 12 months		
LVIDd (mm)	61.7 ± 8.1	60.5 ± 7.5	1.2 ± 0.6	62.6 ± 5.2	60.9 ± 4.9	1.7 ± 0.3	0.082
LVIDs (mm)	51.3 ± 4.6	48.6 ± 4.1	2.7 ± 0.5	51.9 ± 4.9	45.2 ± 5.1	6.7 ± 0.2	0.002
LVEDVi (mL/m2)	188.7 ± 36.9	186.5 ± 36.4	2.2 ± 0.5	196.8 ± 35.6	192.1 ± 34.5	4.7 ± 1.1	0.103
LVESVi (mL/m2)	124.8 ± 18.4	118.5 ± 15.9	6.3 ± 2.5	130.7 ± 9.6	112.9 ± 5.2	17.8± 4.4	0.007
LVEF (%)	34.6 ± 2.6	37.9 ± 3.8	3.3 ± 1.2	33.6 ± 3.4	40.1 ± 5.7	6.5 ± 2.3	0.001
LV GLS (%)	12.5 ± 2.4	13.1 ± 2.8	0.6 ± 0.4	12.2 ± 2.1	15.6 ± 3.0	3.4 ± 0.9	0.005

Table 2. Changes in echocardiographic left ventricular function parameters in both groups after 12 months of treatment. LVIDd: Left ventricular internal diameter in diastole, LVIDs: Left ventricular internal diameter in systole, LVEDVi: left ventricular end-diastolic volume index, LVESVi: left ventricular end-systolic volume index, LVEF: left ventricular ejection fraction, LV GLS: left ventricular global longitudinal strain.

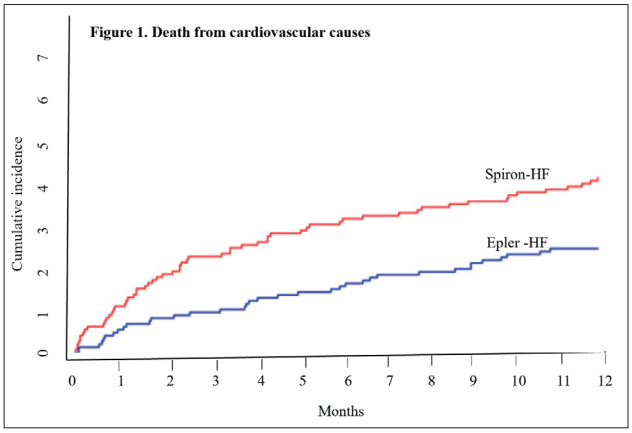

Figure 1. Cumulative estimates of cardiovascular mortality in both groups.

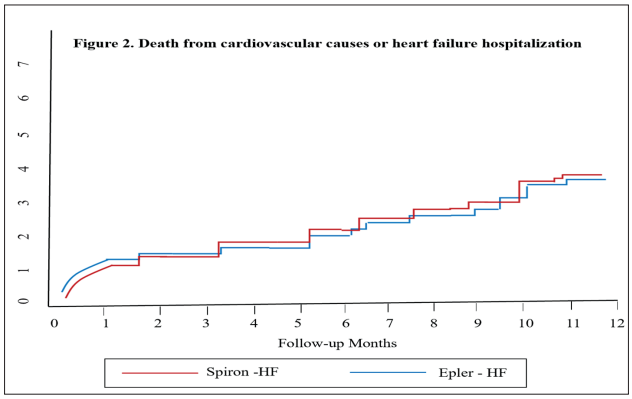

Figure 2. Cumulative incidence of the primary end-point death from cardiovascular causes or hospitalization due to heart failure in both groups.

HF group showed statistically significant lower cardiovascular mortality (HR 0.53; 95% CI 0.34–0.82; p= 0.007) and all-cause mortality (HR 0.64; 95% CI 0.44–0.93; p= 0.022) than patients of the Spiron-HF group (Figure 1). The statistical analysis did not show a statistically significant difference between Epler -HF and Spiron-HF study groups regarding the risk of the primary composite outcome; cardiovascular death or hospitalization due to HF (Hazard Ratio (HR) eplerenone vs. spironolactone = 0.95; 95% Confidence Interval (CI) 0.73-1.27; p= 0.675 (Figure 2).

Tolerability and adverse events

The study medication both with MRA was stopped in 2 patients (2,8%) in the Epler-HF arm and 5 (7,0%) in Spiron-HF group. The most common adverse events of interest were those related to gynecomastia, hyperkalemia and renal impairment. In Spiron-HF group, hyperkalaemia occurred in 14,2%, gynecomastia occurred in 11.2% of patients, dizziness in 10.6%, mastalgia in 6.1%. In Epler-HF group hyperkalaemia occurred in 2,8%, dizziness occurred in 3.5% of patients, none of patients observed developed mastalgia, gynecomastia.

5. DISCUSSION

Heart failure is still one of the leading causes of hospitalization and mortality worldwide despite current established treatments. The prevalence of chronic heart failure (CHF) is up to 1-2% of the adult population in developed countries, rising to >10% after the age of 70. Heart failure with reduced ejection fraction (HFrEF) remains a prevalent clinical syndrome associated with significant morbidity and mortality. Despite significant advances in heart failure with reduced ejection fraction pharmacotherapy, 5-year mortality remains 50%. The primary goals of treatment include improving functional capacity, quality of life, preventing hospital admissions, and reducing mortality. (1, 3, 18).

A primary objective of the study was to compare left ventricular systolic function between chronic HFrEF patients treated with spironolactone and eplerenone. In the present study, the baseline characteristics of the two treatment arms were the same; therefore, the effectiveness of spironolactone and eplerenone is clearly comparable.

Our study demonstrates that eplerenone improves cardiac performance to a greater extent than spironolactone during the 12 months treatment of patients with chronic HFrEF. When compared with the spironolactone arm, the Epler-HF group showed larger increases in LV ejection fraction and LV systolic dimensions (volume and diameter) at rest. In contrast, no significant difference was found in left ventricular diastolic dimensions (LVIDd and LVEDV) between the 2 groups. But both drugs improved symptoms, exercise tolerance, and quality of life to a similar extent.

Most previous studies that evaluated the hemodynamic response after 6 to 12 months of MRA therapy have reported benefits. These include improvements in the left ventricle ejection fraction and reduced cardiac volumes. (13,19-22) Our findings are consistent with

most of these studies, as measures of left ventricular end-diastolic volume, left ventricular end-systolic volume, and LV ejection fraction tend to improve in both arms but more with eplerenone, although the reductions in end-diastolic volume did not reach statistical significance. The Eplerenone Neurohormonal Efficacy and Survival Trial (EPHESUS) in 6200 patients with LV dysfunction (ejection fraction <40%) after a recent myocardial infarction, has evaluated the effects of the addition of eplerenone (25 to 50 mg/d) to standard therapy. The published results indicate that addition of eplerenone significantly reduced all cause and cardiovascular mortality (6).

In current practice guidelines, treatment with a MRA, either spironolactone or eplerenone, is indicated to reduce the risk of HF hospitalization or death in symptomatic patients with HFrEF. This is a class I level A recommendation. Both drugs have demonstrated consistent reductions in mortality and morbidity (1,2,3) in different subsets of patients with HFrEF; however, a well-powered, head-to-head randomized comparison between them is still lacking. Indirect pooled analyses of placebo-controlled randomized clinical trials suggested that spironolactone might outperform eplerenone in terms of mortality reduction (8, 12). However, this conclusion may be misleading (8), given the existence of significant variations regarding the baseline risk and background therapy of patients with HFrEF included in different studies. Globally, spironolactone was studied in sicker, less optimally treated patients than eplerenone; it is intuitive that the benefit of MRA in this setting might be superior (19, 23, 24).

The mechanisms by which mineralocorticoid-receptor antagonists such as eplerenone provide cardiovascular protection in patients with heart failure are not completely understood. Activation of the mineralocorticoid receptor by both aldosterone and cortisol plays an influential role in the pathophysiology of heart failure, and mineralocorticoid receptors are overexpressed in the failing heart (8, 12, 18).

A large multicentre cohort-based study failed to demonstrate a substantial survival benefit of spironolactone in real-world Swedish patients with HF, with side effects providing the most probable reason for this result (25). No significant difference between spironolactone and eplerenone was found about the risk of the composite end-point cardiovascular death or HF hospitalization or the incidence of side effects in a real-world, single-center study based on a propensity-score matched cohort of 180 Japanese patients with acutely decompensated HF, regardless of LVEF (26). Another multicentre, real-life, propensity-score matched, Italian study showed no significant differences between MRA-treated and MRA-untreated patients with HFrEF (27).

Real-world comparison of spironolactone and eplerenone in chronic HF populations with EF EF <40% and NYHA I–IV found that spironolactone was not associated with reduced all-cause mortality. The significant reduction in cardiovascular mortality and all-cause mortality observed in the Eplerenone group was the most relevant finding of the study (38).

Sexual side effects like dysmenorrhea in women and gynaecomastia in men are relatively frequent with spironolactone but rarely seen with eplerenone and may constitute a barrier to treatment adherence in a real-world setting. Moreover, the incidence of hyperkalaemia appears to be lower in patients treated with eplerenone than in patients treated with spironolactone (30), a fact that might be explained by the longer half-life of the first drug (8). The safety profile of eplerenone appears to have some advantages over spironolactone that may increase the effectiveness of treatment in daily clinical practice. Spironolactone is less specific than eplerenone for the mineralocorticoid receptor, and is associated with gynecomastia, impotence, and loss of libido, and therefore lack of adherence. Spironolactone is associated with adverse metabolic effects and anabolic deficiency, which is in turn associated with reduced survival, and has active metabolites with long half-lives, increasing the risk of hyperkalaemia (23, 29, 31). Despite significant differences in adverse drug reactions observed between arms, Spiron-HF patients receiving spironolactone experienced more adverse side effects than Epler-HF patients. A study of the adverse effects of the medication shows that hyperkalaemia occurred in 14,2% of Spiron-HF participants, gynecomastia in 11.2%, dizziness in 10.6%, and mastalgia in 6.1%, whereas hyperkalaemia occurred in 2,8% of Epler-HF participants, dizziness occurred in 3.5% of patients, and none of the patients developed mastalgia or gynecomastia.

Systematic review and meta-analysis of 15 trials with 1632 patients evaluated the use of MRAs compared to placebo or no treatment for HF. MRA use in patients with heart failure was associated with a significant reduction in adverse cardiovascular outcomes: cardiovascular death, all-cause mortality, and cardiac hospitalizations. The conclusion of this systematic review was that MRAs reduce the risk of adverse cardiac events in HFrEF but not in patients with heart failure with preserved ejection fraction (HFpEF). This meta-analysis has provided evidence that MRAs should not be used in HFpEF. MRA usage in HFpEF is associated with a risk of hyperkalaemia and/or gynecomastia without reducing the risk of cardiac events (39-42).

6. CONCLUSION

Clinical trials have established the incremental benefits of aldosterone antagonist therapy in patients with HFrEF, such that aldosterone antagonists were designated as class I, "useful and recommended," within the ESC and ACC Chronic HF Guidelines. Our study has demonstrated that eplerenone have favorable changes on cardiac remodeling parameters (LVEF and LV systolic dimension (volume and diameter) in patients with HFrEF. In our study, eplerenone use in patients with chronic HFrEF has demonstrated statistically significant lower cardiovascular mortality and all-cause mortality than patients treated with spironolactone. The ability of eplerenone to effectively block the mineralocorticoid re-

ceptor while minimizing side effects and a significant reduction in the risk of hospitalization and cardiovascular death confirms its key role in the treatment of patients with chronic HFrEF.

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- **Conflict of interest**: The authors declare that they have no conflict of interest.
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