REVIEW ARTICLE

Reappraising the Role of Eplerenone in the Management of Heart Failure

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ABSTRACT

Background: In India, the prevalence of heart failure (HF) is increasing at 1.2/1,000 people according to a study in northern India, and the mortality rate at 1 year (INTERnational Congestive Heart Failure [INTER-CHF]) is 37%. Due to the diverse phenotypes of HF, nonadherence to guideline-directed medical therapy (GDMT), resistance to uptitration of medication and underuse of mineralocorticoid receptor antagonists (MRAs), such as eplerenone, a uniform management approach may not be feasible. This review is aimed at assessing the burden of HF, reasons for underutilization of MRAs in treatment, evaluating the evidence and reappraising the disease-modifying role of eplerenone in HF management. **Methods:** An electronic database search was performed to identify relevant literature. **Results:** The review details various studies that demonstrate the role of MRA eplerenone as a disease-modifying agent in patients with mild-to-moderate hypertension and those with acute myocardial infarction (MI) complicated by left ventricular dysfunction and HF. It also outlines different patient profiles for eplerenone use and ways to handle minor side-effects. **Conclusions:** Eplerenone shows a promising effect in selectively blocking aldosterone receptors to suppress fibrosis and reverse cardiac remodeling.

Keywords: Heart failure, eplerenone, disease-modifying agent, biomarkers

Heart failure (HF) has emerged as a major global health concern, with an estimated worldwide prevalence of more than 37.7 million and its burden is projected to rise by 25% by the year 2030.[1] In India, the burden of HF is equally concerning, with post-admission mortality of 20% to 30%.[2] Interestingly, Indian patients experience HF at a much younger age than those in the West and show a different male-to-female ratio as shown in Table 1. HF prognosis in Indian patients is worse than those in the West. The Trivandrum Heart Failure Registry (THFR) observed almost twice the mortality at 8.4% compared to the 4% observed by the Acute Decompensated Heart Failure National Registry (ADHERE) in the US. Also, the INTERnational Congestive Heart Failure (INTER-CHF) study reported higher 1-year mortality in India at 37%.[1]

In Indian patients, medication adherence ranges from 25% to 50%, which is coupled with low tolerance of guideline-based medication along with limited access to devices such as implantable cardioverter-defibrillators (ICD), cardiac resynchronization therapy (CRT) devices and left ventricular assist devices (LVAD).[2]

Table 1. Lower Mean Age and Male-Female Ratio for Indians Compared to the West[1]

Name of the study	Country	Mean age of HF in years	Male: female ratio
Acute Decompensated Heart Failure National Registry (ADHERE)	USA	72.4	~ 50:50
Trivandrum Heart Failure Registry (THFR)	India	61.2	69:31
Medanta Registry	India	58.9	83:17
INTERnational Congestive Heart Failure (INTER-CHF)	Indian subset	56	62:38

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Of the therapeutic options, mineralocorticoid receptor antagonists (MRAs) are associated with improved outcomes in heart failure with reduced ejection fraction (HFrEF).[3] They are also given a class I, level of recommendation A by the 2016 European Society of Cardiology (ESC) guidelines for prevention of HF hospitalization and death in patients with HFrEF, who have persistent symptoms despite treatment with an angiotensin-converting enzyme (ACE) inhibitor and a β-blocker and have a left ventricular ejection fraction (LVEF) below 35%.[4] Despite this, MRAs remain underutilized.[3] There is considerable difference between optimal, evidence-based, guideline-recommended care and what is delivered in practice, which is referred to as "care gap".[5] Hence, this review is aimed at understanding the current scenario in the management of HF, assessing the reasons for underutilization of MRAs, particularly eplerenone and evaluating the evidence to possibly reappraise the role of eplerenone.

METHODS

To reach the above-mentioned objective, we performed a literature search using electronic databases such as PubMed/MEDLINE and identified articles that fulfilled the criteria for HF, MRAs, cardiovascular diseases (CVDs), eplerenone, spironolactone, underuse, efficacy, safety, prevalence, diagnosis and management from the year 2000 to 2020, published in scientific literature in English language, limited to clinical and human data. The reviewed articles included systematic reviews, meta-analysis, randomized-controlled trials, review articles and clinical practice guidelines.

RESULTS

Lesser-known Markers of Heart Failure

Of the various biomarkers available for HF diagnosis, B-type natriuretic peptide (BNP) and N-terminal (NT)-pro hormone BNP (NT-proBNP) are widely used in clinical practice. However, although the negative predictive value of BNP/NT-proBNP is very high (0.94-0.98), the positive predictive value is low (0.64-0.67), which makes them a good tool to rule out HF, but a poor tool to help establish the diagnosis. Newer biomarkers such as suppressor of tumorigenicity (ST2) and galectin-3 show promising role in HF diagnosis. Their usage in Indian setting is still lagging due to high cost and availability issues.[1]

MRA: An Underutilized Drug Class?

In a US based national sample, out of >12,000 hospitalized patients of HF, only one-third received MRA prescription at discharge, depicting the underutilization of MRAs. As per a survey done amongst health care professionals, 51% were unfamiliar with eplerenone and 6% did not know about spironolactone. Focus-group analysis identified 8 barriers to MRA use in 3 categories: patient-related barriers (concerns about polypharmacy and comorbidities, adverse effects, perceived patient nonadherence), provider-related barriers (unclear roles and responsibilities, coordination and transitions of care, lack of experience or familiarity with MRAs) and system-based barriers (system overload and provider time constraints, lack of systematic follow-up procedures).[6]

As per a study by Savarese et al from the Swedish HF Registry in patients with HFrEF (ejection fraction [EF] <40%), New York Heart Association (NYHA) class II-IV and HF duration ≥6 months, characteristics independently associated with MRA nonuse in descending order of magnitude were: lower creatinine clearance (<60 mL/min), absence of need for diuretics, no CRT/ICD, raised blood pressure (BP), no digoxin use, higher EF, outpatient setting, older age, lower income, ischemic heart disease, male sex, follow-up in primary as against specialty care, lower NYHA class and no diagnosis of hypertension. Their decreased usage was not related to elevated potassium but to impaired renal function, even at creatinine clearance range of 30-59.9 mL/min, where MRAs are not contraindicated. Moreover, the underuse is associated with nonspecialist care, milder HF and nonusage of other HF therapy.[3]

Further, in guideline-eligible patients with HFrEF, the relative underuse of MRAs has largely been accredited to the fear that it will cause hyperkalemia and/or renal insufficiency, particularly in patients having diabetes mellitus (DM) and/or chronic kidney disease (CKD). Contradictory to the perceived fear, observations from a subgroup study of the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial showed that eplerenone reduces all-cause mortality and hospitalizations in patients with HFrEF including those with DM and/or CKD.[7]

Eplerenone: Reappraising the Role in HF Management

Eplerenone as a disease-modifying agent

Aldosterone is a key factor in hypertension, congestive heart failure (CHF), ventricular arrhythmias, myocardial hypertrophy, renal dysfunction and increased mortality. Evidence, thus suggests that selective aldosterone blockade can help in lowering the incidence of cardiovascular damage.[8] Also, HF activates the renin-angiotensin system (RAS), which leads to rise in aldosterone and BP, and

stimulates vasoconstriction, fibrosis and left ventricular hypertrophy (LVH). Therefore, most of the therapies work by blocking this pathway.[9]

Although most patients are treated with ACE inhibitors, angiotensin receptor blockers (ARBs) and β-blockers, trials have shown clinical superiority of three more drug classes, i.e., MRAs, sodium-glucose cotransporter 2 (SGLT2) inhibitors and angiotensin receptor-neprilysin inhibitors (ARNIs) compared to placebo in increasing the life expectancy in patients with HFrEF.[10]

Being a selective aldosterone blocker, eplerenone selectively targets aldosterone receptors and thus minimizes the risk of adverse hormonal effects. Additionally, it is better tolerated than spironolactone in patients with hypertension.[8] According to a meta-analysis by Li et al, there may be beneficial effects of MRA treatment on the reversal of cardiac remodeling and improvement of left ventricular function.[11]

Furthermore, in late stage of CHF, there is immunoregulation, which activates T-lymphocytes (Tregs) proliferation via the up-regulation of Kv1.3 potassium channel (regulating T-lymphocytes activation). This stimulates cardiac fibrosis by primarily secreting the fibrogenic cytokine transforming growth factor beta (TGF-β). Eplerenone's high affinity to Kv1.3 channel allows it to antagonize the Kv1.3 channels directly, thereby suppressing Tregs proliferation, which in turn can have an immunoregulatory role in CHF by preventing cardiac fibrosis.[12]

Evidence analysis

Numerous studies have illustrated the positive role of eplerenone in HF management.

- In Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), eplerenone along with optimal medical therapy was shown to reduce mortality as compared to placebo. A reduction in both primary endpoint and secondary endpoint was observed with eplerenone – mortality among patients due to any cause (relative risk [RR] 0.85; 95% confidence interval [CI] 0.75-0.96; p = 0.008), death from cardiovascular causes or hospitalization (RR 0.87; 95% CI, 0.79-0.95; p = 0.02), death from any cause or any hospitalization (RR 0.92; 95% CI, 0.86-0.98; p = 0.02), and rate of sudden cardiac deaths (RR 0.79; 95% CI, 0.64-0.97; p = 0.03).[13]
- As per EMPHASIS-HF trial, mortality with placebo was higher than with eplerenone, i.e., 15.5% vs. 12.5%, respectively (hazard ratio [HR], 0.76; 95% CI 0.62-0.93; p = 0.008); percentage hospitalizations for any cause (HR = 0.77; 95% CI, 0.67-0.88; p <0.001) and for HF (HR = 0.58; 95% CI, 0.47-0.70; p <0.001) were lower with eplerenone compared to placebo.[14]

  None of the deaths in the EPHESUS and EMPHASIS trials were due to hyperkalemia. Moreover, add-on eplerenone therapy has shown to reduce LVH in patients with resistant hypertension.[13,14]
- A cross-trial analysis evaluated the treatment effects of comprehensive disease-modifying pharmacological therapy (ARNI, β-blocker, MRA and SGLT2 inhibitor) versus conventional therapy (ACE inhibitor or ARB and β-blocker) in chronic HFrEF patients. The study made indirect comparisons of three vital trials: EMPHASIS-HF, Prospective Comparison of ARNI with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF), and Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF); the control group was of the EMPHASIS-HF trial (ACE inhibitor or ARB and β-blocker). The HR for primary endpoint of cardiovascular death or hospital admission for HF was (0.38 [95% CI 0.30-0.47]); HRs were also favorable for cardiovascular death alone (0.50 [95% CI 0.37-0.67]), hospital admission for HF alone (0.32 [0.24-0.43]) and for all-cause mortality (0.53 [0.40-0.70]).[10]

  These results support the use of MRAs in high-risk subgroups, i.e., the population likely to have the most beneficial effect from disease-modifying therapies.
- In another study by Udelson et al, eplerenone showed greater reductions in markers of collagen turnover, i.e., amino-terminal propeptide of type I procollagen (PINP) and BNP (P values 0.01 and 0.04, respectively) compared to placebo in patients with mild-to-moderate HF symptoms and left ventricular systolic dysfunction (LVSD), as can be observed from Table 2.[15]
- In another multicenter, open-label, uncontrolled trial by Burgess et al in patients with mild-to-moderate essential hypertension, 74.4% patients in the intent-to-treat population achieved BP control during treatment with eplerenone of which 44.8% had received eplerenone monotherapy and 30.0% had received eplerenone plus another antihypertensive agent over a period of 14 months.[8]

Efficacy of Eplerenone

For patients with CKD (eGFR <60 mL/min/1.73 m^2) and DM

- A decrease was observed in incident potassium >6.0 mmol/L, 8 (1.9) in eplerenone patients versus 25 (2.74) patients on placebo, p = 0.01.[16]

Table 2. Changes in Markers of Collagen Turnover and BNP with Eplerenone Treatment from Baseline to 36 Weeks[15]

Markers	Baseline (Mean ± SE)		Δ Week 36 (Mean ± SE)		P* value
	Eplerenone	Placebo	Eplerenone	Placebo	
PIIINP (µg/L)	4.9 (0.16)	4.5 (0.15)	−0.5 (0.17)	−0.1 (0.18)	0.28
PINP (µg/L)	42.7 (2.31)	44.0 (1.66)	−6.7 (2.04)	−2.4 (1.46)	0.01
BNP (pg/mL)	248.3 (34.65)	197.5 (20.79)	−73.7 (31.55)	18.2 (25.40)	0.04

SE = Standard error; PIIINP = Amino-terminal propeptide of type III procollagen; PINP = Propeptide of type I procollagen; BNP = Brain natriuretic peptide.

*P value is associated with the change from baseline to Week 36 EDVi and the ANCOVA model with treatment group and baseline value as the only factors.

- There was no increase in serum potassium >6.0 mmol/L, 17 (3.8) in eplerenone versus 8 (2.1) on placebo, p = 0.16 in patients with DM; no more patients discontinued eplerenone due to hyperkalemia in diabetes compared to no-diabetes patients (interaction p = 0.12).[16]
- In CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) and DM patients, fewer of them in eplerenone group (16.1% and 15.1%, respectively) discontinued treatment due to an adverse event or any other reason as compared to higher percentage discontinuation (22.3% and 18.1%, respectively) in the placebo group.[16]

For patients with below median systolic BP (<123 mmHg)

- Incidence of potassium >5.5 mmol/L in patients with a systolic BP <123 mmHg in eplerenone group was higher than the placebo group; however, there was no increase in serum potassium >6.0 mmol/L.[16]
- Also, there was no increase in the incidence of serum potassium >5.5 nor >6.0 mmol/L in patients in the lowest quartile of baseline systolic BP (<110 mmHg) and in patients between lowest quartile and median (between 110 and 123 mmHg) in the eplerenone group.[16]

Side Effects: Are All MRAs the Same?

As far as class effect is concerned, both spironolactone and eplerenone have been shown to manifest common adverse events like hyperkalemia and gynecomastia. However, spironolactone, a nonselective MRA having structural similarities with progesterone, leads to side effects like loss of libido, menstrual irregularities and gynecomastia in addition to hyperkalemia. On the other hand, eplerenone, a second-generation MRA that binds selectively to the mineralocorticoid receptor with minimum binding to progesterone and androgen receptors causes fewer incidences of sexual adverse events.[17] From the EPHESUS trial; it was evident that deaths were not related to hyperkalemia unlike the normal perception. This emphasizes the need for proper dose titration of eplerenone. Risk of hyperkalemia could be reduced using Cockcroft-Gault formula to estimate creatinine clearance, excluding patients with moderate-to-severe renal insufficiency, treating mild renal insufficiency with loop diuretics, and adherence to 25 to 50 mg/day dosage of eplerenone.[13]

An analysis of the EPHESUS trial comparing spironolactone's and eplerenone's pharmacological properties showed an increase in level of glycated hemoglobin (HbA1c) by spironolactone, but no increase in HbA1c and cortisol with eplerenone. On one hand, spironolactone improves endothelial function in patients with HF, but it fails to do so in those with DM whereas eplerenone does. This indicates that eplerenone can be the MRA of choice in patients with DM and/or CKD.[18]

Managing Hyperkalemia Concerns

Various treatment options exist for managing severe hyperkalemia encountered during eplerenone use.

- Sodium polystyrene sulfonate (SPS) can be used in patients >50 years of age for long-term lowering of serum potassium levels.[19]
- Patiromer, a potassium binder is approved by the US Food and Drug Administration (FDA) for use in patients >50 years of age. As per a randomized, multicenter, open-label 52-week trial in patients having HF and CKD, type 2 diabetes and hypertension, patiromer decreased serum potassium mean level to ≤5.0 mEq/L and maintained this level for about a year.[19]
- Sodium zirconium cyclosilicate (ZS-9), a sodium-potassium cation exchanger is >125 times more selective for potassium than SPS *in vitro*. Efficacy of ZS-9 has been demonstrated in the Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) phase-III trial.[19]

Efficacy of Eplerenone Across Patient Populations in the Management of HF

Patients with mild symptoms of HF

Analysis of EMPHASIS-HF trial for first and repeat hospitalizations, with focus on HF hospitalizations showed that first hospitalizations were more in the placebo group as compared to eplerenone (277 vs. 186). Repeat HF hospitalizations (excluding the first) gave a rate ratio for the eplerenone group, of 0.52 (95% CI, 0.33-0.82; p = 0.004) in comparison with placebo. The analysis revealed that in systolic HF with only mild symptoms, hospital admission of patients due to worsening HF is common and repeat admission is frequent. Eplerenone not only reduces the risk of first admission, but also lowers the possibility of second and subsequent admissions.[20]

Patients with MI and mid-range ejection fraction

A large percentage of patients with a recent myocardial infarction (MI) have an EF of 40% or greater irrespective of the presence or absence of signs and symptoms of HF. An analysis of the EPHESUS trial to evaluate the characteristics, event-rates and the effect of eplerenone in patients with mid-range EF (EF between 40% and 50%), compared to those with EF <40%, showed reduction in hospitalization and mortality in patients with MI and mid-range EF with eplerenone equivalent to patients having EF <40%. These findings should be taken into consideration during therapeutic decisions.[21]

Patients with resistant hypertension and obstructive sleep apnea

In patients with obstructive sleep apnea and resistant hypertension, eplerenone when added to standard antihypertensive therapy showed significant reduction (p < 0.001) in the night-time BP parameters for the treatment group including improved night BP fall from 4.6% to 8.9%. Further, the number of nondipper patients decreased by 45.1%. A significant decrease in LVH and in the apnea-hypopnea index was also seen. The potential benefit of eplerenone in treatment of patients with resistant hypertension is evidently seen in this study.[22]

Post-STEMI in patients without history of HF

In a randomized, placebo-controlled, double-blind trial, Montalescot et al studied outcomes in ST-elevation myocardial infarction (STEMI) patients. Critical parameters such as re-hospitalization/extended initial hospital stay for HF; BNP > threshold (≥1 month post randomization); cardiovascular death, HF and arrhythmia (combined) were lesser in eplerenone group compared to placebo.[23]

Post-AMI in diabetic patients with CHF

In a post-hoc analysis on diabetic group of EPHESUS trial, with LVSD and signs of CHF following acute MI (AMI), use of eplerenone in a mean dose of 43 mg/day for 3 to 14 days following AMI led to reduced mortality from cardiovascular causes or hospitalization for cardiovascular events.[24]

Patients with bilateral idiopathic hyperaldosteronism

A parallel-group, Prospective, Randomized, Open-label, Blinded-Endpoint (PROBE) study by Karagiannis et al showed a rapid decrease in mean systolic BP with eplerenone from baseline to Week 8 to Week 12 to Week 16. Relative systolic BP decrease from baseline to Week 16 in eplerenone was 29.3 ± 2.7% versus 27.0 ± 3.6% with spironolactone (p < 0.05). However, baseline systolic BP decreased considerably in both groups by the end of the study (i.e., at Week 24) (29.5 ± 3.4% with spironolactone and 30.2 ± 3.4% with eplerenone, p = 0.559).[25]

Patients with chronic heart failure

Plasma adiponectin levels are shown to have negative correlation with insulin resistance, so they might predict cardiovascular events in chronic HF patients. HbA1c levels are reported to be an independent risk factor for mortality in diabetic and nondiabetic patients, and cortisol levels are an independent predictor of cardiac events in chronic HF patients. Randomization of 107 mild chronic HF patients receiving standard therapy to eplerenone (50 mg/d) or spironolactone (25 mg/d) showed that plasma adiponectin levels were significantly decreased (12.6 ± 1.4-11.2 ± 1.3 μg/mL, p < 0.0001) with spironolactone, whereas HbA1c and cortisol levels were significantly increased (5.61 ± 0.1-5.8 ± 0.1%, p < 0.0001, 11.3 ± 0.8-14.7 ± 1.3 μg/dL, p = 0.003, respectively). In contrast, in patients receiving eplerenone (n = 73), plasma levels of adiponectin, HbA1c and cortisol did not change. These findings indicated that the metabolic effect of eplerenone differed from that of spironolactone and that eplerenone had a superior metabolic effect, especially on HbA1c in chronic HF patients.[26]

CONCLUSION

Management of HF is challenging, and suboptimal use of guideline-directed medical therapy (GDMT) predisposes a patient to increased morbidity and mortality. MRAs, a

cornerstone of HFrEF management, have been clinically underutilized in HF patients despite strong favorable evidence from randomized controlled trials. Amongst the MRAs, eplerenone has shown beneficial effects in suppressing post-AMI collagen turnover changes, thereby preventing cardiac remodeling and the deleterious effects of aldosterone in patients with HFrEF. Various trials have confirmed the efficacy, safety and tolerability of eplerenone as a disease-modifying agent. Eplerenone significantly reduces mortality, risk of hospitalization and improves the quality of life in HFrEF patients, which calls for the optimal use of MRAs, specifically eplerenone to improve patient outcomes in HF.

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