ejpmr, 2020,7(9), 101-111

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

THE HEART FAILURE CASCADE AND THE ROLE OF MINERALOCORTICOID RECEPTOR ANTAGONISTS

Dr. Anish Desai[1]* and Dr. Sunaina Anand[2]

[1]Director, IntelliMed Healthcare Solutions.
[2]Medical Affairs Executive, IntelliMed Healthcare Solutions

***Corresponding Author: Dr. Anish Desai**

Director, IntelliMed Healthcare Solutions.

Article Received on 25/06/2020 **Article Revised on 15/07/2020** **Article Accepted on 05/08/2020**

ABSTRACT

The guidelines on heart failure with reduced ejection fraction (HFrEF) have also recommended the use of Mineralocorticoid receptor antagonists (MRAs) despite treatment with an angiotensin-converting enzyme inhibitors (ACEI) and a beta-blocker in symptomatic patients with ejection fraction ≤35%, to reduce mortality and HF-related hospitalization. However, the use of MRAs is suboptimal. The current review aims to summarize the vast body of clinical evidence and mechanism behind the efficacy and safety of MRAs (Spironolactone, Eplerenone, Esaxerenone, Finerenone) in an attempt to increase their use in guideline eligible patients with HF. It will also provide the basis for understanding potential new opportunities for their use in patients with HF complicated with diabetes mellitus or renal impairment.

KEYWORDS: Aldosterone, Guidelines, Heart failure, Ejection fraction, Mineralocorticoid receptor antagonists (MRAs).

1. INTRODUCTION

1.1 Epidemiology of HF in India

Epidemiology of HF in India is in transition phase due to the increased aged population, life expectancy, and chronic conditions lead to raised cardiovascular risk factors and mortality. In 2010, Huffman et al estimated the prevalence of Heart Failure in India to be around 1.3 – 4.6 million with an annual incidence of 4.9- 18 million.[1] In 2016, Chaturvedi et al assessed the epidemiology of breathlessness amongst a rural and tertiary care hospital based population and found that 1 % of a rural population was suffering from breathlessness of which 9% were diagnosed with HF leading to a prevalence of 1.2 cases/1000 patients. They have estimated the prevalence of HF in India around 1 % (approximately 8 – 10 million).[2]

Table 1: Epidemiology of Indian Heart Failure patients across the registries.[3,6]

	Asian Sudden Cardiac Death in Heart Failure (Asian-HF)	Trivandrum heart failure registry (thfr)	International congestive heart failure (inter-chf)	Medanta hf registry
Aetiology	Ischemic (37.3%)	Ischemic Heart disease (72%) Dilated Cardiomyopathy (13%) Rheumatic Heart Disease (8%)	Ischemic Heart Disease (46%) Hypertensive Heart disease (14%) Valvular Heart Disease (12%) Idiopathic Dilated Cardiomyopathy (11%)	Coronary artery disease (77.8%) Rheumatic Heart Disease 4.8%
Mean Age (Years)	57.8	61.2	56	59±12
Patients on guideline– based medical therapy	ACEI: 45.4% ARB: 33.8% BB: 67.3% Diuretics: 79.6% MRAs: 61.3%	ACEI: 38.6% ARB: 10.1% BB: 58.2% Diuretics: 81.2% MRAs: 45.9%	ACEI: 51% ARB: 17% - BB: 57% Loop diuretics: 81% MRAs: 47%	BB: 81.8% ACEI/ARBs: 65.8 % Digoxin: Ivabradine: 19.8% Loop diuretics: 79.4 %

ARB/ ACEI: Angiotensin receptor blocker/ Angiotensin converting enzyme inhibitor BB: Beta blocker.

1.2 Heart Failure Cascade and Pathophysiology

Among the HF patients, plasma levels of aldosterone may increase as high as 60 times (300 ng/dL) of the normal value. The aldosterone works through the renin-angiotensin-aldosterone system (RAAS), thereby provokes myocardial hypertrophy and remodeling, fibrosis and. However, if chronically activated, RAAS promotes critical structural changes in every component of the cardiovascular system, including the heart, and the large and small vessels.

In brief, angiotensin II (ATII) produced in response to low cardiac output, which acts through the AT1 receptor, is an important stimulus for the adrenal release of aldosterone. It stimulates the reabsorption of sodium and the excretion of potassium in the renal distal tubule. An increase in aldosterone and activation of the MR in the renal tubular epithelial cells results in sodium retention and potassium loss, with a resultant increase in plasma volume and predisposition to heart failure in patients with left ventricular systolic dysfunction, as well as those with diastolic dysfunction. Once the MR is activated there is also an increase in sodium channel expression (eNAc) and predisposition to further sodium retention and plasma volume expansion. In the renal tubule, aldosterone is the major activator of the MR. Activation of the nonepithelial MR has a number of important effects that contribute to the adverse effects of MR activation in the renal tubule and vascular wall, including a decrease in antioxidant reserves, activation of inflammatory cytokines, activation of the nuclear factor kappa light-chain-enhancer of activated B cells (NF-kappaB) and activator protein-1 (AP-1) signaling pathways, apoptosis, myocardial and vascular hypertrophy and fibrosis. Importantly, heart failure is associated with an upregulation of MR on the macrophage and infiltration of these cells into the myocardium leading to myocardial fibrosis. Furthermore, Aldosterone induces arrhythmias due to its effect on calcium exchange in cardiomyocytes, activation of the sympathetic nervous system, reduction of baroreceptor sensitivity, and activation of myocyte apoptosis. Thus, activation of the RAAS leads to a series of renal and extrarenal effects of aldosterone including cardiac hypertrophy, cardiac remodeling, and myocardial fibrosis which may lead to sudden cardiac death.[7,8]

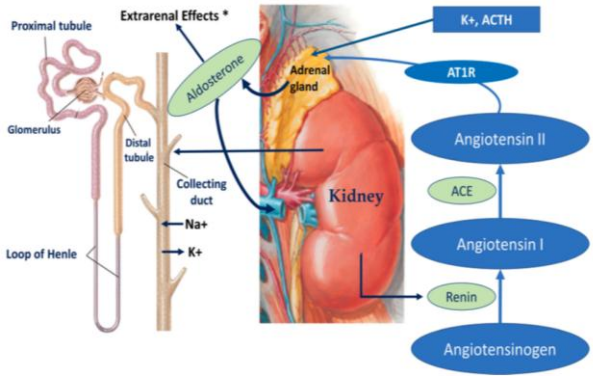

Figure 1: The schematic representation of renin angiotensin aldosterone system (RAAS).

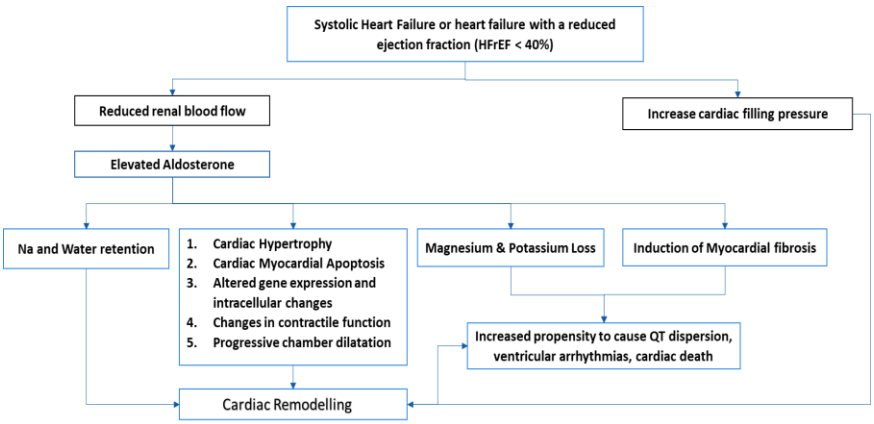

Figure 2: Schematic representation of cardiac remodeling.

1.3 Underlying mechanisms of the effect of MRAs

Spironolactone, one of the MRA, found to prevent the aldosterone-mediated collagen synthesis.[9] The MRA in post-infarct HF improves left ventricular (LV) diastolic and systolic functions, and reduce fibrosis, and myocardial norepinephrine content.[10] In preclinical studies, eplerenone found to inhibit superoxide formation and enhances nitric oxide-dependent relaxation. The research so far supports that MRA prevents the deleterious effect of aldosterone on CVS.[11]

The Belgian RALES, a sub study of RALES found that after administration of spironolactone in congestive heart failure (CHF) the circulating natriuretic peptides were decreased and aldosterone and angiotensin II were elevated. The levels of circulating natriuretic peptides are inversely proportional to the severity of left ventricular dysfunction and important in the prognostication of HF.[12] The beneficial effect of spironolactone in CHF patients is also due to the extra-renal effect of spironolactone in the form of decreased level of cardiac fibrosis synthesis markers and increased levels of collagen synthesis markers.[13] It is also supported by the

EPHESUS sub study, by reporting that diuretic effect of eplerenone is independently associated with 11% to 19% beneficial clinical outcomes in CHF patients. The results reinforces the MR pathway for cardioprotective effect is independent of diuretic and potassium-sparing effect i.e. extra-renal effect.[14] However, the potential evidence demonstrating the clinical effect of MRAs on remodeling does not exist and advanced research is expected in this domain. This and other mechanisms responsible for MRAs clinical effect such as in heart failure patients with preserved ejection fraction need to explore to develop hypotheses for further study.[15]

2. Mineralocorticoid receptor antagonists

2.1 Spironolactone (Steroidal Non-Selective)

The data on spironolactone was submitted to FDA in September 1959 with intend to get approval for the management of edematous conditions, primary aldosteronism, and essential hypertension. The extra-diuretic application of spironolactone is use in heart failure patients.[16] The application has been approved after the RALES landmark trial, through which Pitt et al. demonstrated beneficial effect on reducing the mortality in severe HF patients when administered even at a low dose along with standard of care drugs. However, major risks are associated with its use. First, as a non-selective aldosterone blocker and structural similarity to androgen and progesterone it may cause painful gynecomastia and, impotence, and menstrual irregularities respectively. About 10% of patients after chronic treatment come across gynecomastia or breast pain.[17] It also causes potentially life-threatening risk of hyperkalemia when given with other RAAS blockers. In normal patients its plasma half-life is 1.4 hour, however, it may increase 5-fold in CHF patients with hepatic congestion. The peak clinical response of spironolactone is observed 48 h after dosing. It is metabolized in liver completely to form active metabolites. Additionally, Because of high side effects, other selective MRA are used commonly than spironolactone.[16]

2.2 Eplerenone (Steroidal Selective)

It is a selective antagonist of aldosterone receptors derived from spironolactone. As it has a lower affinity towards progesterone and androgen receptors, it shows lower side effects compared to spironolactone. It get metabolized completely without any active metabolites, hence, serves as ideal pharmacokinetic–pharmacodynamics profile in MRAs.[16] Cook et al. after sequential dosing of 100 mg (the approved dose of eplerenone in the U.S. for hypertension) determined a half-life of 4 h in steady state.[18] Thosar et al. found short half-life of only 2.9 h after a single oral dose of 50 mg in healthy subjects.[16] Despite, a short half-life, eplerenone is effective in reducing mortality when administered once daily to HF patients.[19,20]

The clinical activity of eplerenone is evaluated in coronary artery disease patients through a variety of clinical trials. In a randomized clinical trial, eplerenone (25 mg, daily) did not improve endothelial cell function compared to placebo.[21] The EWISE trial showed similar findings, that low-dose eplerenone did not improve endothelial cell and vascular function and also coronary diameters and reserved flow.[22] However, some other clinical trials demonstrated the clinical efficacy of eplerenone on left ventricular remodeling following myocardial infarction.[19,23] The therapeutic effect of eplerenone has also been evaluated in diabetes mellitus patients and improved coronary circulation, blood pressure, and endothelial cell function were observed after a 4-week treatment.[24]

2.3 Esaxerenone: (Non-steroidal Selective)

Esaxerenone is a non-steroid, novel, selective antagonist of MR. Esaxerenone has high binding potential to MRA compared to spironolactone and a 1000-fold higher selectivity for MR.[25] Preclinically esaxerenone showed the antihypertensive effect at a lower dose (0.5mg/kg) compared to spironolactone and eplerenone. It also found reducing proteinuria and renal hypertrophy.[26] It is under phase 3 pivotal trial for the treatment of essential hypertension in Japanese patients.[16] Ito et al. in phase 2 testing of esaxerenone in essential hypertension found dose dependent reduction in sitting systolic and diastolic pressure without dose dependent increase in serum potassium level. The results suggests that esaxerenone at doses 1.25, 2.5, or 5 mg/day is safe and effective.[27] In the dose escalation study, when esaxerenone at low dose (1.25 mg) with RAAS antagonists showed antihypertensive and antialbuminuric effects and a low risk of hyperkalemia in Japanese hypertensive patients with type 2 diabetes and albuminuria.[28]

2.4 Finerenone

Finerenone is also a novel, non-steroidal selective antagonist of MR. It is as potent as spironolactone and 500- fold selective MRA compared to eplerenone.[29] In the recent phase 2 trial (ARTS-HF Japan), the effects of finerenone and eplerenone were compared in HFrEF patients with chronic kidney disease and/or diabetes mellitus. The primary end outcome of > 30% increase in NT-proBNP was achieved by both finerenone and eplerenone, however, finerenone was more tolerated than eplerenone. However, study unable to come to any conclusion due to small sample size.[30] The similar results were also observed in the ARTS HF study in patients with worsening heart failure and reduced ejection fraction and chronic kidney disease and/or diabetes mellitus. However, reduced clinical effects were observed in finerenone 10→20 mg group, it warranted further study.[31] In another randomized controlled study of finerenone versus placebo (ARTS DN Japan), finerenone in addition to other RAAS inhibitors showed reduced albuminuria without worsening the kidney function in Japanese type 2 diabetes mellitus and diabetic nephropathy patients.[32]

3. Complications/challenges associated with MRAs

3.1 Dose response and the balance between efficacy and safety

The subgroup analysis of EPHESUS showed that eplerenone at 25 to 50 mg/d dosage with standard therapy improves cardiac outcomes in post–acute myocardial infarction patients with HF and left ventricular systolic dysfunction without the risk of hyperkalemia (≥6.0 mEq/L), provided regular monitoring of serum potassium is mandatory.[33] However, dose-dependent change in serum potassium levels was observed after MRAs in both hypertensive and heart failure patients.[34,37]

3.2 Hyperkalemia

One of the major complications of MRAs is hyperkalemia due to its tendency to retain potassium. The rate of hyperkalemia after MRAs treatment is as high as 10%.[10] Although, no death attributable to hyperkalaemia was reported in RALES, EPHESUS, or EMPHASIS-HF studies.[19,20,34] However, the subsequent pharmacovigilance studies published after RALES study found increase in the reporting of hyperkalemia in CHF patients treated with spironolactone.[38,39] The severe hyperkalemia may precipitate potential destabilization of cardiomyocytes and unstable ventricular arrhythmias.[11,20] Discontinuing the therapy in case of kidney injury may also require. However, the incidence of hyperkalemia is low for non-steroidal MRAs, such as finerenone, due to the high selectivity and potency towards MRs, without compromising beneficial effects in CVS diseases.[40] The ESC guidelines contraindicated the use of MRAs in patients with impaired renal function and serum potassium levels >5.0 mmol/L.[41]

3.3 Gynecomastia

Another major complication of spironolactone is gynecomastia due to cross-reaction with androgen receptors. However, the complication gets resolved after discontinuation of the drug.[17] Of note, eplerenone and non-steroid MRA have the highest specificity towards MRs and did not show androgen receptor-related complications.

Table 2: Characteristics of mineralocorticoid receptor antagonist.

Type of MRA	MRA	Affinity to MR	Selectivity	Cross-reactivity to androgen receptor	Hyperkalemia
Steroid	Spironolactone	High	Low	High	High
Steroid	Eplerenone	Medium	Medium	Low	Medium
Non-steroid	Finerenone	High	High	Low	Low

3.4 Renal Impairment

The reported rate of worsening renal function is about 8.9% after MRA treatment, however the varied definitions are used across the trails. The eplerenone showed lower rate of estimated glomerular filtration rate (eGFR) within the first month of treatment (adjusted difference, 21.3+0.4 mL/min/1.73 m2) compared to placebo. However, the multivariate analyses showed various other prognosticators for early worsening renal function (20% decrease in eGFR in 1 month) in addition to eplerenone female sex, age ≥65 years, LVEF,35%, smoking, and baseline use of loop diuretics or antiarrhythmics.[42] The Belgian Rales substudy demonstrated the renal safety of 25 mg daily dose of spironolactone in CHF patients.[43] It is also supported by RALES sub study by Vardeny et al. They found that worsening of renal function was found only in patients with baseline worse renal function and the optimal effect was found in those with reduced eGFR. Although, the net benefit of spironolactone therapy is remained in patients with worse renal function.[44] As MRAs are associated with significant reductions in proteinuria without changes in renal function, suggests the long term renal safety of MRAs as like ACE-inhibitors. However, the hypothesis required further research.[42]

3.5 New onset diabetes and HbA1c changes

Some studies of spironolactone showed increased cortisol and HbA1c levels in diabetic patients along with angiotensin II.[45] Few randomized controlled studies showed that eplerenone or spironolactone had similar clinical effect in both diabetic and non-diabetic patients.

Similarly, cardiovascular mortality or hospitalization (primary endpoint) was found reduced compared to placebo [35.8% eplerenone vs. 40.9% placebo, P = 0.031] in diabetic patients treated with eplerenone in EPHESUS sub-study. Additionally, no changes were observed in the glycaemic control in diabetic patients.[46] The RALES study reported the similar results. They reported no difference in the mortality rate after spironolactone compared with placebo in both diabetic and non-diabetic patients.[17]

4. Clinical Evidence/Guideline recommendations of MRA

4.1 Effect of MRAs in heart failure with reduced ejection fraction (HFrEF)

MRAs inhibit the deleterious effect of aldosterone on the CVS system after chronic HF with left ventricular dysfunction. Various clinical studies including the landmark randomized trials proved the efficacy and safety by reducing the rate of death and hospitalization of MRAs in HFrEF. The summary results of these landmark randomized trials are given in Table 3.

Table 3: Randomized controlled trials of MRAs in heart failure with reduced ejection fraction (HFrEF).

Study	RALES	EPHESUS	EMPHASIS-HF
Year	1999	2003	2011
Primary end point	All cause death	All-cause or cardiovascular death, hospitalization for heart failure	cardiovascular death, hospitalization for heart failure
Number of patients	1663	6642	2737
Mean age, Years± SD	65 ± 12	64 ± 12	68.7 ± 7.7
Inclusion Criteria	Severe CHF	Post-MI (within 3–14 days), CHF	Mild CHF, <55 years
	NYHA III-IV	NYHA I-IV	NYHA II
	Ejection Fraction <35%	Ejection Fraction <40%	Ejection Fraction <35%
MRA	Spironolactone	Eplerenone	Eplerenone
Dose, Mg/day	25–50	25–50	25–50
Other medical therapy	ACE-I, loop diuretic, diagitalis, vasodilators	ACE-I/ARB, ß-blocker, diuretic, coronary reperfusion therapy	ACE-I/ARB, ß-blocker, diuretic
Follow-up, Months	24	16	21
End point result, HR (95% CI) P-value	All cause death: 284 vs 386 (placebo), 0.70 (0.60–0.82), <0.001	All cause death: 478 vs 554 (placebo), 0.85 (0.75 - 0.96), 0.008	All cause death: 171 vs 213 (placebo), 0.76 (0.62–0.93), 0.008
	Cardiac death: 226 vs 314 (placebo), 0.69 (0.58–0.82), <0.001	Cardiac death: 407 vs 483 (placebo), 0.83 (0.72 - 0.94) 0.005	Cardiac death: 249 vs 356 (placebo), 0.63 (0.54–0.74), <0.001
	Hospitalization for heart failure: 215/413 vs 300/663 (placebo), 0.65 (0.54–0.77), <0.001	Hospitalization for heart failure: 345 vs 391 (placebo), 0.85 (0.74–0.99), 0.03	Hospitalization for heart failure: 270 vs 376 (placebo), 0.65 (0.55–0.76), <0.001

MI: Myocardial infarction; CHF: Chronic heart failure; ARB/ ACEI: Angiotensin receptor blocker/ Angiotensin converting enzyme inhibitor

4.1.1 Spironolactone

The RALES study was conducted between 1995 and 1996 in 1663 patients with severe heart failure with an EF <35% and were on angiotensin-converting–enzyme inhibitor, a loop diuretic, and digoxin therapy. They compared 25 mg of spironolactone daily with a placebo in the context of the primary endpoint of death from all causes. The rate of death was significantly reduced (P<0.001) in the spironolactone group compared to the placebo. Along with the frequency of hospitalization was also decreased considerably (P<0.001) in the spironolactone group compared to placebo. However, the rate of gynecomastia or breast pain was also significantly higher (P<0.001) in the spironolactone group. Besides, the NYHA functional class was improved after the treatment. Also, the incidence of hyperkalemia after the treatment of spironolactone was 2% and was statistically similar (P = 0.42) with the placebo group.[17] The post-hoc analysis suggested that the spironolactone did not increase the risk of mortality (adjusted hazard ratio, 0.84) and HF-related hospitalization (adjusted hazard ratio, 1.18).[47]

4.1.2 Eplerenone

The second landmark study, the Eplerenone Post-myocardial infarction Heart failure Efficacy and Survival Study (EPHESUS), was based upon the hypothesis that eplerenone may prevent LV remodeling after acute myocardial infarction as aldosterone stimulates MRs to increase cardiac collagen synthesis and fibroblast proliferation. The study evaluated the effect of eplerenone in addition to standard medical therapy against standard medical therapy only in the randomized controlled setting. The primary endpoints of the study were death from any cause and death from cardiovascular causes or hospitalization for heart failure, acute myocardial infarction, stroke, or ventricular arrhythmia. After 16 months of mean follow-up, death due to any cause and cardiovascular death was lowered (P=0.008) in the eplerenone group compared to standard medical therapy only. However, the other primary endpoint death from cardiovascular causes or hospitalization for cardiovascular events was significantly (P=0.002) lowered in the eplerenone group compared to standard medical therapy only. However, eplerenone was found associated with significant safety concerns. In the eplerenone group, severe hyperkalemia was 5.5% compared to 3.9% in standard medical therapy only group (P= 0.002), on the contrary, the incidence of hypokalemia was 8.4% in the eplerenone group compared to 13.1 in the in standard medical therapy only group (P<0.001). The results suggest that eplerenone enhances the efficacy of standard medical therapy with moderate safety concerns. Besides, it has been confirmed that MRAs are not associated with the risk of hypokalemia, however, steroidal MRA, here eplerenone, is moderately associated with the risk of severe hyperkalemia.[19]

4.2 Effect of MRAs in heart failure with preserved ejection fraction (HFpEF)

The heart failure patients with ejection fraction >50%, have different etiologies, demographics, co-morbidities, and response to therapies than HFrEF. In patients with HFpEF, death, and hospitalization are mainly due to the non-cardiovascular causes and distinguishing between cardiovascular and non-cardiovascular morbidities and managing them differently proved beneficial. However, no convincing treatment to reduce mortality and morbidity has not been established. Additionally, many of these patients are elderly, symptomatic, and have a poor quality of life. Hence, the management of these patients mainly involves alleviating the symptoms and improving overall well-being.[41] A small randomized trial in hypertensive patients with HFpEF, spironolactone proved to improve LV relaxation and filling patterns compared to placebo.[50] Additionally, the Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial showed improved diastolic function in patients with HFpEF.[51]

4.2.1 TOPCAT (Treatment of preserved cardiac function with an aldosterone antagonist)

The TOPCAT is a large (n=3445) randomized, blinded, controlled trial powered to detect morbidity and mortality evaluated the effect spironolactone (up to 30 mg) vs placebo in HFpEF patients over 3.3 years. The primary outcome of the study (composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure) occurred in 18.6 % (320 of 1722) of patients treated with spironolactone vs 20.4% (351 of 1723) patients on placebo (p= 0.14). Also, the rate of death and hospitalization due to non-cardiovascular causes was similar in both groups, except, hospitalization for heart failure was significantly lower in the spironolactone group than in the placebo group (12% vs 14%, P=0.04). Additionally, increase in the serum creatinine levels and a doubling of the rate of hyperkalemia (18.7% in spironolactone group vs. 9.1% in placebo group) was observed in the spironolactone group.[52] The results of the study demonstrated potential of MRAs in the treatment of HFpEF due to the lower rate of hospitalization and mortality after MRAs. However, further research is necessitated to support the use of MRAs in the treatment of HFpEF.

Several secondary analyses of the TOPCAT study, to identify markers of prognosis in HFpEF and to identify subgroups of HFpEF patients who may benefit by MRAs have been conducted. Results of such secondary analyses have highlighted the association of hypo or hyperkalemia, increase in LAV, frailty, baseline heart rate, changes in heart rate, physical activity, diastolic blood pressure, serum chloride homeostasis, with clinical outcomes.[53,59]

5. Future Indications for MRAs

5. 1 Post- ST-segment elevation myocardial infarction

Hyashi et al. evaluated MRAs (intravenous canrenone followed by oral spironolactone for 6 month) in first anterior ST-segment elevation myocardial infarction (STEMI) patients without early HF.[60] MRAs were found safe and have reduced ventricular remodeling, myocardial fibrosis, and inflammatory cytokine activation when given post-MI. The MRAs not only blocks aldosterone and cortisol mediated MR activation, but also improves nitric oxide availability, reduces ventricular arrhythmias, and lowers risk of sudden cardiac death.

5.2 Diabetic kidney disease

Studies demonstrated the positive clinical outcomes of MRAs when given in combination with standard regimen in patients with type 2 diabetes with nephropathy but it is limited by hyperkalemia. Finerenone have shown promising data in the phase 2 testing in patients with type 2 diabetes mellitus and/or chronic kidney disease with/without HF. It is now under phase 3 testing for patients with type 2 diabetes mellitus and DKD.[61]

5.3 Pediatric heart failure

Although there is scarcity of evidence base treatment for pediatric HF, spironolactone is used in pediatric HF at a dose between 1 mg/kg/day and 2 mg/kg/day due to unavailability of experience of eplerenone in pediatric patients.[62]

6. Future research

Future research in this area is mainly focused on novel MRAs and synthesis inhibition of aldosterone. The novel non-steroidal MRAs being developed are expected to offer higher efficacy and safety than spironolactone or eplerenone. BAY94-8662 found to have more selectivity and specificity than eplerenone. It was found safe and tolerable in patients with chronic heart failure and mild chronic kidney disease and similarly efficacious as spironolactone in a phase 2 study.[63]

The MRAs inhibits MRs effectively, however, the higher serum aldosterone and renin levels in patients may have deleterious effect irrespective of MR antagonism. Hence, aldosterone synthase inhibitors may effective over MRAs by preventing both genomic and non-genomic pathways.[64,65] FAD286 found a dose-dependent effect on the reduction of urine and plasma aldosterone in spontaneously hypertensive rats. However, it found to have an additive effect with spironolactone by increasing hyperkalemia and hydration, underlies the potential adverse effect of combination therapy. The lack of selectivity of FAD286 has several limitations for its therapeutic use.[66,67]

Another, aldosterone synthase inhibitor, LC1699, inhibits aldosterone synthase by selectively inhibiting CY11B2 and lower effect on cortisol synthesis. It is an aldosterone synthase inhibitor tested clinically. The

phase 1 study showed dose-dependent safety and tolerability below 3 mg once daily dose. However, above 3 mg once daily dose lose its specificity.[68] In phase 2 studies, it showed safety and tolerability below 1 mg once daily dose, reduced aldosterone synthesis effectively, and corrects hypokalemia in primary hyperaldosteronism patients.

The ATHENA trial sponsored by National Heart, Lung, and Blood Institute (NHLBI) will evaluate clinical outcomes of 100 mg/day spironolactone in patients with acute decompensated HF.[69] The ALCHEMIST trial is designed to evaluate cardiovascular events after spironolactone vs. placebo in HF patients with chronic haemodialysis.[70] Additionally, the FIDELIO trial is being conducted in patients with diabetic nephropathy and the FIGARO trial in patients with renal disease at increased risk for cardiovascular events evaluating effect of finerenone in these patient population. Another novel approach is use of new potassium lowering drugs such as patiromer or sodium zirconium cyclosilicate (ZS9). They are especially effective in the treatment of patients with compromised renal function and at risk of developing hyperkalemia. In such patients patiromer or sodium zirconium cyclosilicate (ZS9 have been shown to be effective in lowering serum potassium to normokalaemic levels.[71,72]

CONCLUSION

The MRAs are potential in reducing morbidity and mortality in chronic HFrEF patients with moderate to high severity and in selective patients with chronic HFpEF. The guidelines on HFrEF have also recommended the use of MRAs (despite treatment with an ACEI and a beta-blocker) in symptomatic patients with ejection fraction ≤35%, to reduce mortality and HF-related hospitalization. However, the use of MRAs is suboptimal due to fear of hyperkalemia, such cases steroidal MRAs can be replaced non-steroidal MRAs or can be used in conjunction with novel potassium lowering agents (such as patiromer and ZS9). The novel approaches will enable the use of MRAs in HF patients complicated with diabetes mellitus or renal impairments. However, to broaden the patient segments likely benefitted from MRAs, researches targeting the exclusion criteria of previous clinical trials in HFrEF patients, homogenous HFpEF patients and patient segments are needed.

REFERENCES

1. Huffman MD, Prabhakaran D. Heart failure: epidemiology and prevention in India. The National medical journal of India, 2010; 23(5): 283-8.
2. Chaturvedi V, Parakh N, Seth S, Bhargava B, Ramakrishnan S, Roy A, Saxena A, Gupta N, Misra P, Rai S, Anand K, Pandav C, Sharma R, Prasad S. Heart failure in India: The INDUS (INDia Ukieri Study) study. Journal of the Practice of Cardiovascular Sciences, 2016; 2(1): 28-35.
3. Chopra VK, Mittal S, Bansal M, Singh B, Trehan N. Clinical profile and one-year survival of patients with heart failure with reduced ejection fraction: The largest report from India. Indian heart journal, 2019; 71(3): 242-8.
4. Sanjay G, Jeemon P, Agarwal A, Viswanathan S, Sreedharan M, Vijayaraghavan G, Bahuleyan CG, Biju R, Nair T, Prathapkumar N, Krishnakumar G, Rajalekshmi N, Suresh K, Park LP, Huffman MD, Harikrishnan S. In-Hospital and Three-Year Outcomes of Heart Failure Patients in South India: The Trivandrum Heart Failure Registry. Journal of cardiac failure, 2018; 24(12): 842-8.
5. Lam CS, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto B, Ling LH, Richards AM. Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. European journal of heart failure, 2013; 15(8): 928-36.
6. Dokainish H, Teo K, Zhu J, Roy A, AlHabib KF, ElSayed A, Palileo-Villaneuva L, Lopez-Jaramillo P, Karaye K, Yusoff K, Orlandini A, Sliwa K, Mondo C, Lanas F, Prabhakaran D, Badr A, Elmaghawry M, Damasceno A, Tibazarwa K, Belley-Cote E, Balasubramanian K, Islam S, Yacoub MH, Huffman MD, Harkness K, Grinvalds A, McKelvie R, Bangdiwala SI, Yusuf S. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. The Lancet Global health, 2017; 5(7): 665-72.
7. Zannad F, Gattis Stough W, Rossignol P, Bauersachs J, McMurray JJ, Swedberg K, Struthers AD, Voors AA, Ruilope LM, Bakris GL, O'Connor CM, Gheorghiade M, Mentz RJ, Cohen-Solal A, Maggioni AP, Beygui F, Filippatos GS, Massy ZA, Pathak A, Pina IL, Sabbah HN, Sica DA, Tavazzi L, Pitt B. Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integrating evidence into clinical practice. European heart journal, 2012; 33(22): 2782-95.
8. Pitt B. Heart failure: the role for mineralocorticoid receptor antagonists. Swiss medical weekly, 2014; 144: 13959.
9. Brilla C.G. Aldosterone and myocardial fibrosis in heart failure. Herz, 2000; 25: 299–306.
10. Cittadini A., Monti M.G., Isgaard J., Casaburi C., Strömer H., Di Gianni A. Aldosterone receptor blockade improves left ventricular remodeling and increases ventricular fibrillation threshold in experimental heart failure. Cardiovasc Res, 2003; 58: 555–564.
11. Schafer A., Fraccarollo D., Hildemann S.K., Tas P., Ertl G., Bauersachs J. Addition of the selective aldosterone receptor antagonist eplerenone to ACE inhibition in heart failure: effect on endothelial dysfunction. Cardiovasc Res, 2003; 58: 655–662.
12. Rousseau MF, Gurne O, Duprez D, Van Mieghem W, Robert A, Ahn S, Galanti L, Ketelslegers JM. Beneficial neurohormonal profile of spironolactone

in severe congestive heart failure: results from the RALES neurohormonal substudy. Journal of the American College of Cardiology, 2002; 40(9): 1596-601.
13. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). Rales Investigators. Circulation, 2000; 102(22): 2700-6.
14. Rossignol P, Menard J, Fay R, Gustafsson F, Pitt B, Zannad F. Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) substudy. Journal of the American College of Cardiology, 2011; 58(19): 1958-66.
15. Zannad F, Gattis Stough W, Rossignol P, Bauersachs J, McMurray JJ, Swedberg K, Struthers AD, Voors AA, Ruilope LM, Bakris GL, O'Connor CM, Gheorghiade M, Mentz RJ, Cohen-Solal A, Maggioni AP, Beygui F, Filippatos GS, Massy ZA, Pathak A, Pina IL, Sabbah HN, Sica DA, Tavazzi L, Pitt B. Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integrating evidence into clinical practice. European heart journal, 2012; 33(22): 2782-95.
16. Kolkhof P, Barfacker L. 30 YEARS OF THE MINERALOCORTICOID RECEPTOR: Mineralocorticoid receptor antagonists: 60 years of research and development. The Journal of endocrinology, 2017; 234(1): 125-40.
17. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. The New England journal of medicine, 1999; 341(10): 709-17.
18. Cook CS, Berry LM, Bible RH, Hribar JD, Hajdu E, Liu NW. Pharmacokinetics and metabolism of [14C]eplerenone after oral administration to humans. Drug metabolism and disposition: the biological fate of chemicals, 2003; 31(11): 1448-55.
19. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. The New England journal of medicine, 2003; 348(14): 1309-21.
20. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. The New England journal of medicine, 2011; 364(1): 11-21.
21. Sudano I, Naegele M, Roas S, Periat D, Frank M, Kouroedov A, Noll G, Luscher TF, Enseleit F, Ruschitzka F, Flammer AJ. Vascular Effects of Eplerenone in Coronary Artery Disease With Preserved Ejection Fraction: A Double-Blind, Randomized, Placebo-Controlled Trial. Clinical cardiology, 2016; 39(5): 285-90.
22. Bavry AA, Handberg EM, Huo T, Lerman A, Quyyumi AA, Shufelt C, Sharaf B, Merz CN, Cooper-DeHoff RM, Sopko G, Pepine CJ. Aldosterone inhibition and coronary endothelial function in women without obstructive coronary artery disease: an ancillary study of the national heart, lung, and blood institute-sponsored women's ischemia syndrome evaluation. American heart journal, 2014; 167(6): 826-32.
23. Schneider A, Schwab J, Karg MV, Kalizki T, Reinold A, Schneider MP, Schmieder RE, Schmidt BM. Low-dose eplerenone decreases left ventricular mass in treatment-resistant hypertension. Journal of hypertension, 2017; 35(5): 1086-92.
24. Joffe HV, Kwong RY, Gerhard-Herman MD, Rice C, Feldman K, Adler GK. Beneficial effects of eplerenone versus hydrochlorothiazide on coronary circulatory function in patients with diabetes mellitus. The Journal of clinical endocrinology and metabolism, 2007; 92(7): 2552-8.
25. Arai K, Homma T, Morikawa Y, Ubukata N, Tsuruoka H, Aoki K, Ishikawa H, Mizuno M, Sada T. Pharmacological profile of CS-3150, a novel, highly potent and selective non-steroidal mineralocorticoid receptor antagonist. European journal of pharmacology, 2015; 761: 226-34.
26. Arai K, Tsuruoka H, Homma T. CS-3150, a novel non-steroidal mineralocorticoid receptor antagonist, prevents hypertension and cardiorenal injury in Dahl salt-sensitive hypertensive rats. European journal of pharmacology, 2015; 769: 266-73.
27. Ito S, Itoh H, Rakugi H, Okuda Y, Yamakawa S. Efficacy and safety of esaxerenone (CS-3150) for the treatment of essential hypertension: a phase 2 randomized, placebo-controlled, double-blind study. Journal of human hypertension, 2019; 33(7): 542-51.
28. Itoh H, Ito S, Rakugi H, Okuda Y, Nishioka S. Efficacy and safety of dosage-escalation of low-dosage esaxerenone added to a RAS inhibitor in hypertensive patients with type 2 diabetes and albuminuria: a single-arm, open-label study. Hypertension research: official journal of the Japanese Society of Hypertension, 2019; 42(10): 1572-81.
29. Gueret A, Harouki N, Favre J, Galmiche G, Nicol L, Henry JP, Besnier M, Thuillez C, Richard V, Kolkhof P, Mulder P, Jaisser F, Ouvrard-Pascaud A. Vascular Smooth Muscle Mineralocorticoid Receptor Contributes to Coronary and Left Ventricular Dysfunction After Myocardial Infarction. Hypertension, 2016; 67(4): 717-23.
30. Sato N, Ajioka M, Yamada T, Kato M, Myoishi M, Yamada T, Kim SY, Nowack C, Kolkhof P, Shiga T. A Randomized Controlled Study of Finerenone vs. Eplerenone in Japanese Patients With Worsening Chronic Heart Failure and Diabetes and/or Chronic

Kidney Disease. Circulation journal : official journal of the Japanese Circulation Society, 2016; 80(5): 1113-22.
31. Filippatos G, Anker SD, Bohm M, Gheorghiade M, Kober L, Krum H, Maggioni AP, Ponikowski P, Voors AA, Zannad F, Kim SY, Nowack C, Palombo G, Kolkhof P, Kimmeskamp-Kirschbaum N, Pieper A, Pitt B. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. European heart journal, 2016; 37(27): 2105-14.
32. Katayama S, Yamada D, Nakayama M, Yamada T, Myoishi M, Kato M, Nowack C, Kolkhof P, Yamasaki Y. A randomized controlled study of finerenone versus placebo in Japanese patients with type 2 diabetes mellitus and diabetic nephropathy. Journal of diabetes and its complications, 2017; 31(4): 758-65.
33. Pitt B, Bakris G, Ruilope LM, DiCarlo L, Mukherjee R. Serum potassium and clinical outcomes in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). Circulation, 2008; 118(16): 1643-50.
34. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). The American journal of cardiology, 1996; 78(8): 902-7.
35. Weinberger MH, Roniker B, Krause SL, Weiss RJ. Eplerenone, a selective aldosterone blocker, in mild-to-moderate hypertension. American journal of hypertension, 2002; 15(8): 709-16.
36. Levy DG, Rocha R, Funder JW. Distinguishing the Antihypertensive and Electrolyte Effects of Eplerenone. The Journal of Clinical Endocrinology & Metabolism, 2004; 89(6): 2736-40.
37. Sica DA. Pharmacokinetics and pharmacodynamics of mineralocorticoid blocking agents and their effects on potassium homeostasis. Heart failure reviews, 2005; 10(1): 23-9.
38. Hauben M, Reich L, Gerrits CM. Reports of hyperkalemia after publication of RALES--a pharmacovigilance study. Pharmacoepidemiology and drug safety, 2006; 15(11): 775-83.
39. Hauben M, Reich L, Gerrits CM, Madigan D. Detection of spironolactone-associated hyperkalaemia following the Randomized Aldactone Evaluation Study (RALES). Drug safety, 2007; 30(12): 1143-9.
40. Zwadlo C, Bauersachs J. Mineralocorticoid Receptor Antagonists in the Treatment of Coronary Artery Disease, Myocardial Infarction and Heart Failure. In: Harvey B, Jaisser F, editors. Aldosterone-Mineralocorticoid Receptor - Cell Biology to Translational Medicine: InTechOpen, 2019.
41. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal, 2016; 37(27): 2129-200.
42. Zannad F, Gattis Stough W, Rossignol P, Bauersachs J, McMurray JJ, Swedberg K, Struthers AD, Voors AA, Ruilope LM, Bakris GL, O'Connor CM, Gheorghiade M, Mentz RJ, Cohen-Solal A, Maggioni AP, Beygui F, Filippatos GS, Massy ZA, Pathak A, Pina IL, Sabbah HN, Sica DA, Tavazzi L, Pitt B. Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integrating evidence into clinical practice. European heart journal, 2012; 33(22): 2782-95.
43. ousseau MF, Olivier G, Ahn SA. Effect of Spironolactone on Renal Function in Severe Congestive Heart Failure. Results from the Belgian Rales Substudy. Journal of cardiac failure, 2007; 16(6).
44. Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, Solomon SD. Influence of baseline and worsening renal function on efficacy of spironolactone in patients With severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). Journal of the American College of Cardiology, 2012; 60(20): 2082-9.
45. Nagai Y, Miyata K, Sun GP, Rahman M, Kimura S, Miyatake A, Kiyomoto H, Kohno M, Abe Y, Yoshizumi M, Nishiyama A. Aldosterone stimulates collagen gene expression and synthesis via activation of ERK1/2 in rat renal fibroblasts. Hypertension (Dallas, Tex : 1979), 2005; 46(4): 1039-45.
46. O'Keefe JH, Abuissa H, Pitt B. Eplerenone improves prognosis in postmyocardial infarction diabetic patients with heart failure: results from EPHESUS. Diabetes, obesity & metabolism, 2008; 10(6): 492-7.
47. Vardeny O., Cavallari L.H., Claggett B., Desai A.S., Anand I., Rossignol P. Race influences the safety and efficacy of spironolactone in severe heart failure. Circ Heart Fail, 2013; 6: 970–976.
48. Collier T.J., Pocock S.J., McMurray J.J., Zannad F., Krum H., van Veldhuisen D.J. The impact of eplerenone at different levels of risk in patients with systolic heart failure and mild symptoms: insight from a novel risk score for prognosis derived from the EMPHASIS-HF trial. Eur Heart J, 2013; 34: 2823–2829.
49. Writing Committee Members, Yancy C.W., Jessup M., Bozkurt B., Butler J., Casey D.E., Jr., Drazner M.H. ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association

Task Force on Practice Guidelines. Circulation, 2013; 128: 240–319.
50. Grandi A.M., Imperiale D., Santillo R. Aldosterone antagonist improves diastolic function in essential hypertension. Hypertension, 2002; 40: 647–652.
51. Edelmann F., Wachter R., Schmidt A.G. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA, 2013; 309: 781–791.
52. Shah S.J., Heitner J.F., Sweitzer N.K. Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. Circ Heart Fail, 2013; 6: 184–192.
53. Beldhuis IE, Myhre PL, Claggett B, Damman K, Fang JC, Lewis EF, O'Meara E, Pitt B, Shah SJ, Voors AA, Pfeffer MA, Solomon SD, Desai AS. Efficacy and Safety of Spironolactone in Patients With HFpEF and Chronic Kidney Disease. JACC Heart failure, 2019; 7(1): 25-32.
54. Grodin JL, Philips S, Mullens W, Nijst P, Martens P, Fang JC, Drazner MH, Tang WHW, Pandey A. Prognostic implications of plasma volume status estimates in heart failure with preserved ejection fraction: insights from TOPCAT. European journal of heart failure, 2019; 21(5): 634-42.
55. Kapelios CJ, Murrow JR, Nuhrenberg TG, Montoro Lopez MN. Effect of mineralocorticoid receptor antagonists on cardiac function in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis of randomized controlled trials. Heart failure reviews, 2019; 24(3): 367-77.
56. Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex Differences in Outcomes and Responses to Spironolactone in Heart Failure With Preserved Ejection Fraction: A Secondary Analysis of TOPCAT Trial. JACC Heart failure, 2019; 7(3): 228-38.
57. Selvaraj S, Claggett B, Shah SJ, Anand IS, Rouleau JL, Desai AS, Lewis EF, Vaduganathan M, Wang SY, Pitt B, Sweitzer NK, Pfeffer MA, Solomon SD. Utility of the Cardiovascular Physical Examination and Impact of Spironolactone in Heart Failure With Preserved Ejection Fraction. Circulation Heart failure, 2019; 12(7): 006125.
58. Kosmala W, Przewlocka-Kosmala M, Marwick TH. Association of Active and Passive Components of LV Diastolic Filling With Exercise Intolerance in Heart Failure With Preserved Ejection Fraction: Mechanistic Insights From Spironolactone Response. JACC Cardiovascular imaging, 2019; 12(5): 784-94.
59. Neefs J, van den Berg NWE, Krul SPJ, Boekholdt SM, de Groot JR. Effect of Spironolactone on Atrial Fibrillation in Patients with Heart Failure with Preserved Ejection Fraction: Post-Hoc Analysis of the Randomized, Placebo-Controlled TOPCAT Trial. American journal of cardiovascular drugs : drugs, devices, and other interventions, 2019.
60. Hayashi M, Tsutamoto T, Wada A, Tsutsui T, Ishii C, Ohno K, Fujii M, Taniguchi A, Hamatani T, Nozato Y, Kataoka K, Morigami N, Ohnishi M, Kinoshita M, Horie M. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. Circulation, 2003; 107(20): 2559-65.
61. Pitt B. MRAs in Patients With AMI Without Early Evidence of Heart Failure: Time for Reappraisal? Journal of the American College of Cardiology, 2016; 67(16): 1928-30.
62. Dojki FK, Bakris G. Nonsteroidal mineralocorticoid antagonists in diabetic kidney disease. Current opinion in nephrology and hypertension, 2017; 26(5): 368-74.
63. Jayaprasad N. Heart Failure in Children. Heart Views, 2016; 17(3): 92–99.
64. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, Nowack C, Kolkhof P, Kim SY, Zannad F. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. European heart journal, 2013; 34(31): 2453-63.
65. Amar L, Azizi M, Menard J, Peyrard S, Plouin PF. Sequential comparison of aldosterone synthase inhibition and mineralocorticoid blockade in patients with primary aldosteronism. Journal of hypertension, 2013; 31(3): 624-9.
66. Hargovan M, Ferro A. Aldosterone synthase inhibitors in hypertension: current status and future possibilities. JRSM cardiovascular disease, 2014; 3: 2048004014522440.
67. Menard J, Gonzalez MF, Guyene TT, Bissery A. Investigation of aldosterone-synthase inhibition in rats. Journal of hypertension, 2006; 24(6): 1147-55.
68. Cooper LB, Hammill BG, Peterson ED, Pitt B, Maciejewski ML, Curtis LH, Hernandez AF. Consistency of Laboratory Monitoring During Initiation of Mineralocorticoid Receptor Antagonist Therapy in Patients With Heart Failure. Jama, 2015; 314(18): 1973-5.
69. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, Mann DL, Margulies KB, McNulty SE, Mentz RJ, Redfield MM. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. JAMA cardiology, 2017; 2(9): 950-8.
70. Hammer F, Malzahn U, Donhauser J, Betz C, Schneider MP, Grupp C, Pollak N, Störk S, Wanner C, Krane V, Berweck S. A randomized controlled trial of the effect of spironolactone on left ventricular mass in hemodialysis patients. Kidney international, 2019; 95(4): 983-91.
71. Pitt B, Bakris GL, Bushinsky DA, Garza D, Mayo MR, Stasiv Y, Christ-Schmidt H, Berman L, Weir

MR. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. European journal of heart failure, 2015; 17(10): 1057-65.
72. Rafique Z, Peacock WF, LoVecchio F, Levy PD. Sodium zirconium cyclosilicate (ZS-9) for the treatment of hyperkalemia. Expert opinion on pharmacotherapy, 2015; 16(11): 1727-34.