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REVIEW

Aldosterone and aldosterone receptor antagonists in patients with chronic heart failure

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Abstract: Aldosterone is a mineralocorticoid hormone synthesized by the adrenal glands that has several regulatory functions to help the body maintain normal volume status and electrolyte balance. Studies have shown significantly higher levels of aldosterone secretion in patients with congestive heart failure compared with normal patients. Elevated levels of aldosterone have been shown to elevate blood pressure, cause left ventricular hypertrophy, and promote cardiac fibrosis. An appreciation of the true role of aldosterone in patients with chronic heart failure did not become apparent until the publication of the Randomized Aldactone Evaluation Study. Until recently, the use of aldosterone receptor antagonists has been limited to patients with severe heart failure and patients with heart failure following myocardial infarction. The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study added additional evidence to support the expanded use of aldosterone receptor antagonists in heart failure patients. The results of the EMPHASIS-HF trial showed that patients with mild-to-moderate (New York Heart Association Class II) heart failure had reductions in mortality and hospitalizations from the addition of eplerenone to optimal medical therapy. Evidence remains elusive about the exact mechanism by which aldosterone receptor antagonists improve heart failure morbidity and mortality. The benefits of aldosterone receptor antagonist use in heart failure must be weighed against the potential risk of complications, ie, hyperkalemia and, in the case of spironolactone, possible endocrine abnormalities, in particular gynecomastia. With appropriate monitoring, these risks can be minimized. We now have evidence that patients with mild-to-severe symptoms associated with systolic heart failure will benefit from the addition of an aldosterone receptor antagonist to the standard therapies of angiotensin-converting enzyme inhibitors and beta-blockers. This review will address the pharmacologic basis of aldosterone receptor antagonists in patients with heart failure and the clinical impact of this therapy.

Keywords: aldosterone receptor antagonists, eplerenone, spironolactone, systolic heart failure

Introduction

Heart failure is a common disorder, particularly among the elderly. It carries a heavy financial burden due to frequent hospitalizations. Pharmacologic therapy, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers are the cornerstone of therapy for the vast majority of patients. Diuretics are indicated for patients with signs or symptoms of congestion and digoxin is used for those patients remaining symptomatic despite optimal therapy with angiotensin-converting enzyme inhibitors and beta-blockers. Spironolactone, an aldosterone receptor antagonist, has been used for decades in the management of excess volume, although generally playing a minor role relative to the more potent loop diuretics.

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However, an appreciation of the true role of aldosterone in patients with chronic heart failure did not become apparent until the publication of the Randomized Aldactone Evaluation Study (RALES).[1] This review will address the pharmacologic basis of aldosterone receptor antagonists in patients with heart failure and the clinical impact of this therapy.

Overview of aldosterone

Aldosterone and the kidney

Aldosterone is a mineralocorticoid hormone synthesized by the adrenal glands that has several regulatory functions to help the body maintain normal volume status and electrolyte balance. Aldosterone secretion is controlled in part by angiotensin II and potassium levels.[2,3] However, adrenocorticotropic hormone, hyponatremia, and atrial natriuretic peptide have also been described in the regulation of aldosterone.[4] The renin-angiotensin-aldosterone system controls the production of angiotensin II through sensing intravascular volume. Receptors within the afferent arterioles of the juxtaglomerular apparatus sense a decrease in intravascular volume, stimulating the release of renin.[5] This causes the conversion of angiotensinogen to angiotensin I, which is further cleaved to angiotensin II by angiotensin-converting enzyme. Angiotensin II has multiple effects in the body, including systemic vasoconstriction, cardiac remodeling, and sodium and water retention through aldosterone secretion.[6]

Aldosterone is synthesized in the zona glomerulosa after angiotensin II binds to a G protein coupled receptor, prompting the release of secondary messengers. This process causes intracellular calcium concentrations to increase biosynthesis of aldosterone.[2,7,8] Hyperkalemia has also been associated with aldosterone secretion.[9] Studies by Himathongkam et al and Young et al provided evidence that as potassium levels rose above 3.5 mEq/L there was a linear increase in aldosterone levels.[10,11] While the exact mechanism of how potassium affects aldosterone levels remains elusive, there appears to be an association between elevated potassium and angiotensin II.[12]

Aldosterone works primarily to regulate the electrolyte balance as well as volume status through its effects on the distal tubules and collecting ducts of the kidneys by controlling sodium reabsorption and potassium excretion.[9] Aldosterone enhances sodium reabsorption in the distal tubules by increasing the number of Na^+/Cl^- cotransporters in the luminal membrane.[13] Within the collecting ducts, aldosterone increases the amount of sodium and potassium that is filtered across the apical membrane through increasing transporter proteins. Ultimately, elevated aldosterone levels affect Na^+/K^+-ATPase by increasing its activity and abundance, promoting sodium reabsorption and potassium secretion.[14,15] Thus the addition of an aldosterone receptor antagonist will help maintain adequate serum potassium concentrations.

Aldosterone and the cardiovascular system

Hypoperfusion causes release of renin and ultimately leads to increased aldosterone levels, which increase intravascular volume and preload. However, in heart failure, the problem of hypoperfusion is not related to a low volume status but to a decrease in stroke volume. The compensatory mechanism of the kidneys to increase intravascular volume increases the workload on an already failing heart. Studies have shown significantly higher levels of aldosterone secretion in patients with congestive heart failure compared with normal patients.[16–18] While aldosterone has been shown to be an integral part of maintaining fluid and electrolyte balance, it is also known to cause damage to the cardiovascular system. Similar to angiotensin II, too much aldosterone can worsen certain conditions. Elevated levels of aldosterone have repeatedly been shown to elevate blood pressure, cause left ventricular hypertrophy, and promote cardiac fibrosis.[19–22]

Aldosterone synthase is mediated by angiotensin II. There are also mineralocorticoid receptors present in the heart and aldosterone is produced by the diseased myocardium. While the exact mechanism by which cardiac fibrosis is promoted remains controversial, several animal models suggest that an increase in angiotensin type 1 (AT_1) receptors may play a role.[23,24] Binding of angiotensin II will lead to higher secretion of aldosterone. The idea of the ability of angiotensin II to work in pathways that do not require AT_1 receptors stems from a study by Viridis et al.[25] They were able to demonstrate in rats that structural and functional damage caused by angiotensin II was partially corrected with the use of spironolactone. Harda et al demonstrated that aldosterone causes an upregulation of angiotensin-converting enzyme mRNA expression, leading to increased levels of angiotensin II.[26] The initiation of this process leads to a situation that feeds itself. Angiotensin II will cause an increase in the circulating aldosterone, which produces upregulation of angiotensin-converting enzyme activity, leading to increased levels of angiotensin II.[25,27] Several investigators have looked at the interaction between angiotensin II and aldosterone in vascular smooth muscle animal models. Based on their findings, there is a possibility that synergism exists between angiotensin II and aldosterone, as well as an interaction between mineralocorticoid receptors and AT_1 receptors.[28–30]

The first report that nonrenal effects of aldosterone existed was in animal models which showed the action of aldosterone to occur within minutes, now termed "nongenomic".[31] Chai et al were the first to demonstrate nongenomic actions of aldosterone in the human heart.[31] These findings were followed by studies showing that aldosterone had deleterious effects on contractility and metabolic functions of the ischemic heart, increased systemic vascular resistance, and increased the vasoconstrictive action of angiotensin II in the coronary arteries.[32–34]

Another mechanism for the elevated aldosterone concentrations seen in heart failure relates to decreased metabolic clearance by the liver. Due to the hypoperfusion seen with a failing heart, aldosterone clearance is not complete within one passage through the liver, as occurs in normal subjects.[35] The inability to clear aldosterone properly can lead to significantly higher aldosterone plasma concentrations.[35,36] There are also studies showing that the development of cardiovascular disease may be independent of angiotensin II, based on correlations between aldosterone and cardiovascular morbidity and mortality.[37,38] Patients with excess aldosterone secretion due to primary aldosteronism have an increased cardiovascular risk compared with patients having primary hypertension.[2,3,39]

Aldosterone receptor antagonists

Aldosterone receptor antagonists compete with aldosterone to bind at the mineralocorticoid receptor. They were originally developed in an effort to counteract the effects of aldosterone, specifically aldosterone-related potassium excretion. Spironolactone was considered a potassium-sparing diuretic, but later studies have demonstrated nonrenal benefits. The location of the mineralocorticoid receptor (kidney, heart/blood vessels) has an impact on the effect manifested through binding. Prior to the randomized trials looking at specific aldosterone receptor antagonists in heart failure, there were compelling data showing beneficial effects on preventing cardiac fibrosis in animal models.[19,22,35]

Currently, there are two aldosterone receptor antagonists that act at mineralocorticoid receptors, ie, spironolactone and eplerenone. Spironolactone and eplerenone are structurally similar compounds devised to block aldosterone at the mineralocorticoid receptor. Spironolactone has structural elements similar to progesterone, resulting in progestogenic and antiandrogenic adverse effects.[35] Eplerenone is a derivative of spironolactone and designed to avoid side effects that occur as a result of the interaction between spironolactone and testosterone and progesterone receptors.[3] By substituting the 17 α-thoacetyl group, eplerenone has increased selectivity for the aldosterone receptor over other steroid receptors.[3] While in vitro studies have shown a significantly greater affinity for spironolactone at aldosterone receptors, eplerenone was seen to inhibit aldosterone binding at a much lower in vivo dosage.[34]

The pharmacokinetic profiles between the two drugs differ (see Table 1). Spironolactone has a shorter half-life ($t_{1/2}$1.3–1.4 hours)[40] and is metabolized to three active metabolites which prolong its activity (13.8–16.5 hours[41] and 17–22 hours[42]). The active metabolites of spironolactone are excreted by the kidney, so spironolactone requires close monitoring if given to patients with renal insufficiency. Eplerenone undergoes rapid metabolism by the liver to inactive metabolites ($t_{1/2}$ 4–6 hours).[43] Elimination occurs predominately through the kidneys for both agents (eplerenone 67% and spironolactone 47%–51%); however, a higher percentage of spironolactone (35%–41%) is eliminated through the feces compared with eplerenone (32%).[43–45]

These elimination properties have an important role in determining appropriate doses for patients with renal and/or hepatic dysfunction. Extra caution needs to be exercised in patient with renal dysfunction because failure to eliminate the aldosterone receptor antagonist leads to accumulation of drug, causing increased serum potassium concentrations. Both the area under the curve (AUC) and peak plasma concentration (C_{max}) of eplerenone are increased with renal insufficiency.[3]

In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), patients were given a lower dose (25 mg on alternative days) if they had a glomerular filtration rate <30 mL/min/m^2.[46] This reduction in dose was used to minimize the development of hyperkalemia. It has been reported that both the AUC and C_{max} of eplerenone are increased in the presence of renal insufficiency.[2] Caution should initially be exercised in patients receiving both spironolactone and eplerenone when hepatic insufficiency is present. The AUC and C_{max} of eplerenone were increased by 3.6% and 42%, respectively, when normal patients were compared with patients classified as having Child–Pugh Class B hepatic impairment.[3] Accumulation was not seen with canrenone, a major metabolite of spironolactone in a study by Jackson et al.[47] However, the elimination half-life was increased from the reported range of 13.5–24 hours to 50 hours (range 32–105 hours) in five patients with chronic liver disease, indicating a possible prolongation of the effect of spironolactone.[47]

Table 1 Pharmacokinetic properties and clinical uses for spironolactone and eplerenone[34,40,43,44]

	Spironolactone	Eplerenone
Pharmacokinetic properties		
Absorption	73% bioavailable (↑ by food)	69% bioavailable
Distribution	90% protein bound	50% protein bound
Metabolism	Liver and kidney (active metabolites)	Liver (3A4) (inactive metabolites)
Excretion	Renal (47%–51%)	Renal (67%)
	Feces (35%–41%)	Feces (32%)
Elimination half-life ($t_{1/2}$)	Parent compound: 1.3–1.4 hours	4–6 hours
	Active metabolites: 13.8–22 hours	
Clinical uses		
Hypertension	50–100 mg/day (single or divided doses) adjust in 2 weeks	50 mg once or twice daily
Heart failure	25 mg/day increased to 50 mg/day after 8 weeks (as tolerated)	25 mg/day increased to 50 mg/day after 1 month (as tolerated)
Primary hyperaldosteronism	400 mg/day	
Edematous conditions associated with cirrhosis and nephrotic syndrome	100 mg/day (range 25–200 mg)	
Hypokalemia	25–100 mg/day	

Adverse effects

One limitation of spironolactone use is associated with its action on androgen and progesterone receptors. Unlike eplerenone, which is more selective for mineralocorticoid receptors, spironolactone has both dose-dependent and duration-dependent sexual side effects that decreases tolerability.[48] In RALES, spironolactone was associated with a 10% incidence of gynecomastia or mastodynia in men.[1] Additionally, when patients receive doses higher than those used in RALES there is an even higher rate (52.2% of patients with doses ≥150 mg) of development of gynecomastia.[48,49] In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[50] and, more recently, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)[46] studies, the incidence of gynecomastia and other breast disorders was similar between eplerenone and placebo.

The potential for developing hyperkalemia relates directly to the mechanism of action of either aldosterone receptor antagonist. Previous studies looking at aldosterone receptor antagonists in essential hypertension have noted a dose-related increase in serum potassium concentrations.[49,51] In RALES, the median increase in serum potassium due to spironolactone was 0.3 mmol/L when given with angiotensin-converting enzyme inhibitors and loop diuretics.[1] In the EPHESUS and EMPHASIS-HF trials, potassium levels increased from baseline by 0.3 mmol/L and 0.16 mmol/L, respectively.[46,50] The effect of eplerenone on potassium levels in the two trials was similar to the results published by Weinberger et al, who reported changes up to 0.36 mmol/L on doses of 400 mg/day.[51]

Efficacy of aldosterone blockade in heart failure patients

The deleterious effects of the renin-angiotensin-aldosterone system on the cardiovascular system, including left ventricular remodeling, vasoconstriction/hypertension, and ventricular hypertrophy have been known for many years. Aldosterone, as described earlier, has many effects on the cardiovascular system, and the benefits of adding an aldosterone receptor antagonist to a heart failure regimen are seen in the RALES, EPHESUS, and EMPHASIS-HF trials.[1,46,50] While each trial was directed at a specific heart failure patient population, the results were similar in demonstrating overwhelming benefit with the addition of an aldosterone receptor antagonist to patients with heart failure. A comparison of the three trials can be seen in Table 2.

RALES was the first trial investigating the use of an aldosterone receptor antagonistin heart failure patients and was conducted in 1995–1998. The trial was designed to determine the effect of spironolactone on death from any cause (primary endpoint) in patients with New York Heart Association Class III/IV symptoms of heart failure. After the fifth interim analysis, the beneficial effect of spironolactone exceeded the predetermined "z-value" and the trial was stopped for complete analysis after a mean follow-up of 24 months.[1] A total of 1663 patients were enrolled. Data were analyzed using the intention-to-treat principle. The primary endpoint occurred in 284 patients receiving spironolactone and 386 patients receiving placebo. Kaplan–Meier analysis estimated a relative risk of 0.70 ($P < 0.001$) in favor of spironolactone.[1] All of the secondary endpoints showed significant benefits in favor of spironolactone over placebo at final analysis.

Table 2 Major aldosterone receptor antagonist trials in patients with heart failure.

	EPHESUS		EMPHASIS-HF		RALES	
Trial design	Randomized, double-blind, placebo-controlled		Randomized, double-blind, placebo-controlled		Randomized, double-blind, placebo-controlled	
Dosing	Starting dose 25 mg/day (4 weeks) Target dose 50 mg/day		Starting dose 25 mg/day (4 weeks) 25 mg every other day (if GFR $<$ 30 mL/min/m^2) Target dose 50 mg/day		Starting dose 25 mg/day (8 weeks) Target dose 50 mg/day	
Follow-up	Mean: 16 months		Median: 21 months		Mean: 24 months	
Patient population	Placebo (n = 3313) 64 years 90% Caucasian 70% male BP (mmHg) Systolic 119 Diastolic 72	Eplerenone (n = 3319) 64 years 90% Caucasian 72% male BP (mmHg) Systolic 119 Diastolic 72	Placebo (n = 1373) 68.6 years 83.1% Caucasian 78.1% male BP (mmHg) Systolic 124 Diastolic 75	Eplerenone (n = 1364) 68.7 years 82.6% Caucasian 77.3% male BP (mmHg) Systolic 124 Diastolic 75	Placebo (n = 841) 65 years 87% Caucasian 73% male BP (mmHg) Systolic 122 Diastolic 75 NYHA II: 0.4% III: 69% IV: 31%	Spironolactone (n = 822) 65 years 87% Caucasian 73% male BP (mmHg) Systolic 123 Diastolic 75 NYHA II: 0.5% III: 72% IV: 27%
Baseline characteristics	Placebo LVEF 33% SCr 1.1 mg/dL CrC l 79 mL/min K 4.3 mmol/L	Eplerenone LVEF 33% SCr 1.1 mg/dL CrCl 78 mL/min K 4.3 mmol/L	Placebo LVEF 26.1% QRS 122 msec SCr 1.16 mg/dL GFR 70.4 mL/min/ 1.73 m^2 GFR $<$ 60 34.5% K 4.3 mmol/L	Eplerenone LVEF 26.2% QRS 121 msec SCr 1.14 mg/dL GFR 71.2 mL/min/ 1.73 m^2 GFR $<$ 60 32.2% K 4.3 mmol/L	Placebo LVEF 25.2%	Spironolactone LVEF 25.6%
Past medical history (% patients)	Placebo AMI 27 DM 32 HF 15 HTN 61	Eplerenone AMI 27 DM 32 HF 14 HTN 60	Placebo AMI 50.6 DM 29.1 Hospital HF 52.9 HTN 66.2 AP 43.6 PCI 21.6 CABG 18.9	Eplerenone AMI 50.3 DM 33.7 Hospital HF 52.3 HTN 66.7 AP 43.3 PCI 22.0 CABG 18.8	Not reported	
Heart failure cause	Recent MI complicated by LVED and signs of HF Recent MI complicated by diabetes with LVED		Placebo Ischemic 68.1% Non-I 31.8% Unknown 0.1%	Eplerenone Ischemic 69.7% Non-I 30.1% Unknown 0.2%	Placebo Ischemic 54% Non-I 46%	Spironolactone Ischemic 55% Non-I 45%

(*Continued*)

Table 2 (*Continued*)

	EPHESUS		EMPHASIS-HF		RALES	
Medications taken at baseline (% patients)	Placebo Diuretic 61 ACEi/ARB 87 ASA 89 β-blocker 75 Statins 47	Eplerenone Diuretic 60 ACEi/ARB 86 ASA 88 β-blocker 75 Statins 47	Placebo Diuretic 85.7 ACEi/ARB 92.9 ACEi 76.8 ARB 19.4 β-blocker 86.9 Digoxin 27.5 Lipid-lowering 62.3 Antithrombotic 88.4	Eplerenone Diuretic 84.3 ACEi/ARB 94 ACEi 78.3 ARB 19.1 β-blocker 86.6 Digoxin 26.6 Lipid-lowering 62.8 Antithrombotic 88.3	Placebo Loop 100 ACEi 94 Digoxin 72 ASA 37 β-blocker 10	Spironolactone Loop 100 ACEi 95 Digoxin 75 ASA 36 β-blocker 11
Inclusion criteria	3–14 days postinfarction EF <40% and signs of HF or EF <40% and presence of diabetes Optimal medical therapy as well as coronary reperfusion		Age >55 years with NYHA Class II symptoms EF <30% or >30%–35% with QRS > 130 msec ACEi and/or ARB and a β-blocker at recommended or maximum tolerated dose Randomized within 6 months of CV hospitalization or BNP > 250 pg/mL (or n-terminal pro-BNP > 500 in men and 750 women)*		NYHA Class IV HF within 6 months and NYHA III/IV at time of randomization HF diagnosis ≥6 weeks before enrollment Receiving ACEi + loop diuretic LVEF ≤ 35% within 6 months before enrollment	
Exclusion criteria	K-sparing diuretic SCr >2.5 mg/dL K >5 mmol/L before randomization		K-sparing diuretic AMI, NYHA Class III/IV HF K >5 mmol/L, GFR < 30 mL/min/1.73 m^2		K sparing diuretic, Operable valvular heart disease, UA, other life-threatening disease Previous heart transplant or waiting SCr > 2.5 mg/dL K >5.0 mmol/L	
Study drug dose adjustments	If K >5.5 mmol/L dose reduced or discontinued until K <5.5 Baseline = 48 hours after first dose 1,4,5 + scheduled visits and within 1 week of dose change		Evaluated every 4 mo Adjusted if K between 5.5–5.9 withheld if >6 Remeasure at 72 hours restart once K <5.0 mmol/L		Every 4 weeks (×12 weeks) then every 3 months (1 year) then 6 months until end of study K also measured at 9 weeks, could dose adjust if hyperkalemia SCr > 4 or severe hyperkalemia hold med	
Primary endpoint	Time to death from any cause Time to death from CV cause or hospitalization for CV event		Death from CV cause and first hospitalization for HF		Death from any cause	
Primary endpoint results	Deaths: 478 (14.4%) eplerenone vs 554 (16.7%) placebo Kaplan–Meier estimates: RR: 0.85; $P = 0.008$ CV death/hospitalization: 885 eplerenone vs 993 placebo Kaplan–Meier estimates: RR: 0.876; $P = 0.002$ NNT to prevent 1 death = 43		Combined endpoint: 249 (18.3%) eplerenone vs 356 (25.9%) placebo Kaplan–Meier estimates: HR: 0.63; $P < 0.001$ NNT to prevent death/hospitalization = 13		Deaths: 284 (35%) spironolactone vs 386 (46%) Placebo Kaplan–Meier estimates: RR: 0.70; $P < 0.001$ NNT to prevent 1 death = 9	
Secondary endpoints	Death from CV cause Death from any cause or hospitalization for any reason		Hospitalization for HF or death from any cause Death from any cause Death from CV causes Hospitalization for any reason Hospitalization for HF		Death from CV causes Hospital for CV causes Death from CV or hospital causes Change in NYHA class	

Secondary endpoint results	• Death from CV causes: RR: 0.83 ($P = 0.005$) SCD ($P = 0.03$) • Death from any cause or hospitalization for any reason RR: 0.79 ($P = 0.03$)	• Hospitalization for HF or death from any cause: HR: 0.65 ($P < 0.001$) • Death from any cause: HR: 0.76 ($P = 0.008$) • Death from CV causes HR: 0.76 ($P = 0.01$) • Hospitalization for any reason R: 0.77 ($P < 0.001$) • Hospitalization for HF HR: 0.58 ($P < 0.001$)	• Death from CV causes: RR: 0.69 ($P < 0.001$) • Hospital for CV causes RR: 0.7 ($P < 0.001$) Worsening HF ($P < 0.001$) • Death from CV or hospital causes RR: 0.68 ($P < 0.001$) • NYHA class change (spironolactone) Improved 41% Unchanged 21% Worsened 38%
Safety (1 year)	SCr increase (mg/dL) 0.02 (placebo) vs 0.06 (eplerenone) K increase mmol/L 0.2 (placebo) vs 0.3 (eplerenone) K >6 3.9% placebo vs 5.5% eplerenone ($P = 0.02$) Higher incidence of hyperkalemia with CrCl < 50 mL/min	SCr increase (mg/dL) 0.04 (placebo) vs 0.09 (eplerenone) K increase (mmol/L) 0.05 (placebo) vs 0.16 (eplerenone) K >6 1.9% placebo vs 2.5% eplerenone ($P = 0.29$)	SCr increase (mg/dL) 0.05–0.1 (spironolactone) K increased mmol/L 0.3 (spironolactone) K >6 1% placebo vs 2% spironolactone ($P = 0.42$) Gynecomastia 1% placebo vs 10% spironolactone ($P < 0.001$)

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ADE, adverse drug event; AMI, acute myocardial infarction; AP, angina pectoris; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; ASA, aspirin; β, Beta; BNP, brain natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; CrCl, creatinine clearance; CV, cardiovascular; DM, diabetes mellitus; GFR, glomerular filtration rate; HF, heart failure; HR, hazards ratio; HTN, hypertension; K, potassium; LVED, left ventricular ejection dysfunction; Non-I, non-ischemic; NNT, number needed to treat; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RR, relative risk; SCr, serum creatinine; UA, unstable angina.

A safety analysis revealed that 214 and 200 patients, in the spironolactone and placebo groups, respectively, dropped out of the study. Reasons for discontinuing were lack of response, adverse events, or for administrative reasons.[1] Serum creatinine increased by 0.05–0.1 mg/dL and potassium levels rose by 0.3 mmol/L compared with the placebo arm. There was a statistically significant difference between the spironolactone and placebo groups regarding the development of gynecomastia or breast pain (10% vs 1%) which may have contributed to the discontinuation rates with spironolactone when compared with placebo due to an adverse event (8% vs 5%).[1] Overall, RALES showed significant benefits of adding spironolactone to patients with moderate-to-severe symptoms of heart failure on what was considered optimal drug therapy (angiotensin-converting enzyme inhibitor/loop diuretic/digoxin) at the time. However, only 10% of the patients in RALES were receiving a beta-blocker at baseline and there is no mention of the use of devices that may affect outcomes (implantable cardioverter defibrillators or cardiac resynchronization therapy) or whether revascularization therapy was used in patients with ischemia.

RALES was followed by the EPHESUS and EMPHASIS-HF trials, which investigated eplerenone in two different heart failure patient populations. The EPHESUS trial was published in 2003 and investigated eplerenone 25 mg daily in a placebo-controlled, randomized, double-blind, event-driven trial.[50] Patients (6642 total analyzed) were included if they were status post (3–14 days) acute myocardial infarction complicated by left ventricular dysfunction, denoted by left ventricular ejection fraction ≤40%, and heart failure symptoms or diabetes with left ventricular dysfunction and no heart failure symptoms. Patients were receiving usual medical therapy for acute myocardial infarction complicated by left ventricular dysfunction, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (86%), beta-blockers (75%), statins (47%), aspirin (89%), and diuretics (60%) at baseline. There were two primary endpoints, ie, time to death from any cause and time to death from cardiovascular causes or first hospitalization for a cardiovascular event. There were 1012 deaths in the trial with eplerenone (14.4%) showing a significant benefit vs placebo (16.7%) in mortality (relative risk [RR]: 0.85; $P = 0.008$). The time to cardiovascular death or hospitalization related to a cardiovascular event also favored the patients receiving eplerenone (26.7%) compared with placebo (30.0%, RR: 0.87; $P = 0.002$).[50] Secondary endpoints included reduced death from cardiovascular causes (RR: 0.83; $P = 0.005$), which was primarily

due to the prevention of sudden cardiac death (RR: 0.79; $P = 0.03$), and decreased hospitalization for cardiovascular events (RR:0.87; $P = 0.03$), largely attributed to decreasing hospitalization for heart failure (RR: 0.77; $P = 0.002$) in the eplerenone group. A significantly higher percentage of patients were on beta-blockers in this trial compared with RALES (75% vs 11%).[46,50] However, both trials showed a decrease in sudden cardiac death in patients receiving an aldosterone receptor antagonist compared with placebo. While the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial showed morbidity and mortality benefits of beta-blockade following an acute myocardial infarction,[52] the decrease in sudden cardiac death in the EPHESUS trial demonstrated an additive benefit of an aldosterone receptor antagonist in patients receiving beta-blockers.

Serious hyperkalemia (serum potassium >6 mmol/L) occurred more frequently with eplerenone (5.5%) than with placebo (3.9%), particularly in those patients with a baseline creatinine clearance of <50 mL/min. Serious hypokalemia (serum potassium <3.5 mmol/L) occurred more frequently with placebo (13.1%) than with eplerenone (8.4%).[50] As opposed to RALES, which reported a significant increase in gynecomastia with spironolactone, the EPHESUS trial showed no difference between eplerenone and placebo in the development of gynecomastia, breast pain, or impotence.[50] Unlike RALES, 75% of patients in EPHESUS were receiving beta-blockers. However, as with RALES, there is no mention of the use of device or revascularization therapy. Although not specifically designed to look at smaller subgroups, it is interesting to note that in some subgroups, eplerenone did not demonstrate a mortality benefit; however the confidence intervals are wide, and it would be inappropriate to assume that these differences are meaningful. Although some improvement seen in the eplerenone group could be due to natural recovery following an acute myocardial infarction, it would be expected this would have also occurred in patients receiving placebo.

The second major trial involving eplerenone, EMPHASIS-HF, randomly assigned 2737 patients with mild-to-moderate heart failure (New York Heart Association Class II) with an ejection fraction ≤35% to either eplerenone or placebo.[46] Table 2 gives specific inclusion and exclusion criteria for the EMPHASIS-HF trial. The primary outcome was a composite of death from a cardiovascular cause or hospitalization for heart failure. After a follow-up period of 21 months, the primary endpoint was reached in 18.3% of the patients receiving eplerenone vs 25.9% in the placebo group (hazards ratio 0.63; $P < 0.001$). Secondary endpoints, including all-cause mortality, cardiovascular mortality, hospitalization for heart failure, cardiovascular causes, or any reason, all showed benefits of eplerenone over placebo. In this trial, 13% of patients had an implantable cardioverter defibrillator, 2.2% had cardiac resynchronization therapy, and 6.3% had both at baseline. In terms of adverse events, the EMPHASIS-HF trial had results that were similar to the EPHESUS trial. Hyperkalemia occurred more frequently in the eplerenone group (8%) when compared with placebo (3.7%, $P < 0.001$). Hypokalemia was noted more often in patients receiving placebo (2.2%) vs eplerenone (1.2%). A limitation of the EMPHASIS-HF trial is the exclusion of a substantial number of patients with New York Heart Association Class II symptoms but an ejection fraction >30%.[53]

The RALES, EPHESUS, and EMPHASIS-HF trials have provided clear and consistent evidence that adding an aldosterone receptor antagonist to patients with various degrees of heart failure results in statistically and clinically significant beneficial effects. A direct comparison between the three trials is not appropriate because the drugs were evaluated in different patient populations. However, due to its selectivity for the mineralocorticoid receptor, eplerenone appears to offer a more favorable side effect profile when compared with spironolactone.

The most recent Heart Failure Society of America guidelines in 2010 recommend starting an aldosterone receptor antagonist in patients with New York Heart Association Class IV heart failure with reduced left ventricular ejection fraction (35%) and considering one in patients post-MI with signs of heart failure or a history of diabetes mellitus and a left ventricular ejection fraction <40%.[54] It is highly likely that the guidelines will be revised to expand the recommendation to patients with mild symptoms, given the results of the EMPHASIS-HF study.

The exact mechanism by which eplerenone improves morbidity and mortality is unclear. A major consideration for improved outcomes concerns the effect of the drug on the reversal of cardiac remodeling. While this was not specifically addressed in any of the aldosterone receptor antagonist trials, there are data showing an improvement in left ventricular ejection fraction of 3.1% when using an aldosterone receptor antagonist.[55] The ability of aldosterone blockade to improve left ventricular ejection fraction was also seen in the Italian study known as AREA-IN-CHF (antiremodeling effect of canrenone in patients with mild chronic heart failure).[56] In this trial, canrenone provided slightly more improvement in left ventricular ejection fraction in New York Heart Association

Class II heart failure compared with placebo. In contrast with these findings, the Reversal of Cardiac Remodeling with Eplerenone (REMODEL) trial, which had a similar study design to that of EMPHASIS-HF, showed no improvement in left ventricular remodeling or function, or in quality of life.[57] It is important to note that there were only 216 patients with stable heart failure (left ventricular ejection fraction <35% and New York Heart Association Class II/III), on optimal therapy (96% on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and 95% on beta-blockers), and these patients were only observed for 36 weeks as opposed to the 21-month follow-up in the EMPHASIS-HF trial.

There are no studies that directly compare spironolactone and eplerenone. Spironolactone has been available for decades, and usually costs less than eplerenone. Eplerenone is more selective for the mineralocorticoid receptor and, as such, adverse effects, eg, gynecomastia, occur less often. Testosterone may protect the heart from apoptosis and, as such, the protective effect of testosterone may be diminished with spironolactone as compared with eplerenone.[58] It is not known if the antiandrogen effect of spironolactone has any effect on testicular or prostate cancer. The majority of patients in the major studies of aldosterone receptor antagonists (EPHESUS, EMPAHSIS-HF, and RALES) have been male Caucasians. Additional studies with more diverse patients and patients with heart failure and a preserved ejection fraction will provide additional needed data.

Hyperkalemia from the use of an aldosterone receptor antagonist can lead to serious adverse consequences, including muscle weakness/paralysis, cardiac conduction abnormalities, and cardiac arrhythmias. Electrocardiographic changes due to hyperkalemia initially present as peaked T waves with a shortened QT interval. As the serum potassium increases the PR interval and the QRS duration lengthens, the P wave may disappear and eventually the QRS develops into a sine wave. Electrocardiographic changes are more likely to occur with the rapid onset of hyperkalemia and in the presence of hypocalcemia, hyponatremia, and acidemia.[59] It is essential to monitor serum potassium concentrations frequently in order to avoid potentially life-threatening adverse effects of aldosterone receptor antagonists.

Conclusion

Aldosterone is a mineralocorticoid produced in the adrenals, myocardium, brain, and blood vessels. The effects of aldosterone on fluid and electrolyte balance (renin-angiotensin-aldosterone system) have been known for many years. Newer data support the concept that aldosterone can have direct effects on the cardiovascular system. There is increased evidence suggesting synergism between angiotensin II and aldosterone, making the addition of an aldosterone receptor antagonist to current optimal therapy (angiotensin-converting enzyme inhibitor/angiotens in receptor blocker, diuretic, β-blocker) a strong consideration. The selective nature of eplerenone makes it an appealing choice when the use of an aldosterone receptor antagonist is warranted. Eplerenone has shown significant benefits for use in two specific heart failure patient populations, ie, acute myocardial infarction with symptoms of heart failure and reduced left ventricular ejection fraction (≤30%–35%) and mild-to-moderate heart failure (New York Heart Association Class II). Overall, eplerenone confers reduced morbidity and mortality in patients with heart failure based on the EPHESUS and EMPHASIS-HF trials and should be strongly considered in all patients with symptoms of systolic dysfunction, and particularly in those who require potassium supplementation.

Disclosure

The authors report no conflicts of interest in this work.

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