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.
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). 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. However, adrenocorticotropic hormone, hyponatremia, and atrial natriuretic peptide have also been described in the regulation of aldosterone. The renin-angiotensin-aldosterone system controls the production of angiotensin II through sensing intravascular volume. Receptors within the afferent arteries of the juxtaglomerular apparatus sense a decrease in intravascular volume, stimulating the release of renin. 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.

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. Hyperkalemia has also been associated with aldosterone secretion. 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. While the exact mechanism by which potassium affects aldosterone levels remains elusive, there appears to be an association between elevated potassium and angiotensin II.

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. Aldosterone enhances sodium reabsorption in the distal tubules by increasing the number of Na⁺/Cl⁻ cotransporters in the luminal membrane. 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. 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. 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.

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 (AT₁) receptors may play a role. 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 AT₁ receptors stems from a study by Viridis et al. 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. 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. 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 AT₁ receptors.
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 (t1/2, 1.3–1.4 hours)40 and is metabolized to three active metabolites which prolong its activity (13.8–16.5 hours41 and 17–22 hours42). 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 (t1/2, 4–6 hours).43 Elimination occurs predominantly 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 (Cmax) 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/m².46 This reduction in dose was used to minimize the development of hyperkalemia. It has been reported that both the AUC and Cmax 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 Cmax 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
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. In RALES, spironolactone was associated with a 10% incidence of gynecomastia or mastodynia in men. Additionally, when patients receive doses higher than those used in RALES there is an even higher rate (52.2% of patients with doses $\geq 150$ mg) of development of gynecomastia.

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) and, more recently, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) 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. In RALES, spironolactone was associated with an even higher rate (52.2% of patients with doses $\geq 150$ mg) of development of gynecomastia. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) and, more recently, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) studies, the incidence of gynecomastia and other breast disorders was similar between eplerenone and placebo.

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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. 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 antagonist in 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. 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. All of the secondary endpoints showed significant benefits in favor of spironolactone over placebo at final analysis.

Table 1 Pharmacokinetic properties and clinical uses for spironolactone and eplerenone

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

<table>
<thead>
<tr>
<th>Trial design</th>
<th>EPHESUS</th>
<th>EMPHASIS-HF</th>
<th>RALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>Starting dose 25 mg/day (4 weeks)</td>
<td>Starting dose 25 mg/day (4 weeks)</td>
<td>Starting dose 25 mg/day (8 weeks)</td>
</tr>
<tr>
<td></td>
<td>Target dose 50 mg/day</td>
<td>Target dose 50 mg/day</td>
<td>Target dose 50 mg/day</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Mean: 16 months</td>
<td>Median: 21 months</td>
<td>Mean: 24 months</td>
</tr>
<tr>
<td>Patient population</td>
<td>Placebo (n = 3313)</td>
<td>Placebo (n = 1373)</td>
<td>Placebo (n = 841)</td>
</tr>
<tr>
<td></td>
<td>64 years</td>
<td>68.6 years</td>
<td>65 years</td>
</tr>
<tr>
<td></td>
<td>90% Caucasian</td>
<td>81.1% Caucasian</td>
<td>87% Caucasian</td>
</tr>
<tr>
<td></td>
<td>70% male</td>
<td>78.1% male</td>
<td>73% male</td>
</tr>
<tr>
<td></td>
<td>BP (mmHg)</td>
<td>BP (mmHg)</td>
<td>BP (mmHg)</td>
</tr>
<tr>
<td></td>
<td>Systolic 119</td>
<td>Systolic 124</td>
<td>Systolic 122</td>
</tr>
<tr>
<td></td>
<td>Diastolic 72</td>
<td>Diastolic 75</td>
<td>Diastolic 75</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>Placebo</td>
<td>Eplerenone</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>LVeF 33%</td>
<td>LVEF 33%</td>
<td>LVEF 26.1%</td>
</tr>
<tr>
<td></td>
<td>Scr 1.1 mg/dL</td>
<td>Scr 1.1 mg/dL</td>
<td>Scr 1.16 mg/dL</td>
</tr>
<tr>
<td></td>
<td>CrCl 79 mL/min</td>
<td>CrCl 78 mL/min</td>
<td>GFR 70.4 mL/min/1.73 m²</td>
</tr>
<tr>
<td></td>
<td>K 4.3 mmol/L</td>
<td>K 4.3 mmol/L</td>
<td>GFR &lt; 60.34%</td>
</tr>
<tr>
<td>Past medical history</td>
<td>Placebo</td>
<td>Eplerenone</td>
<td>Placebo</td>
</tr>
<tr>
<td>(% patients)</td>
<td>AMI 27</td>
<td>AMI 27</td>
<td>AMI 50.6</td>
</tr>
<tr>
<td></td>
<td>DM 32</td>
<td>DM 32</td>
<td>DM 29.1</td>
</tr>
<tr>
<td></td>
<td>HF 15</td>
<td>HF 14</td>
<td>Hospital HF 52.9</td>
</tr>
<tr>
<td>Heart failure cause</td>
<td>HTN 61</td>
<td>HTN 60</td>
<td>HTN 66.2</td>
</tr>
</tbody>
</table>

(Continued)
Table 2 (Continued)

<table>
<thead>
<tr>
<th>EPHEUS</th>
<th>EMPHASIS-HF</th>
<th>RALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications taken at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(%) patients</td>
<td>Placebo</td>
<td>Eplerenone</td>
</tr>
<tr>
<td>Diuretic</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>87</td>
<td>86</td>
</tr>
<tr>
<td>ASA</td>
<td>89</td>
<td>88</td>
</tr>
<tr>
<td>β-blocker</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Statins 47</td>
<td>Statins 47</td>
<td></td>
</tr>
</tbody>
</table>

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

Exclusion criteria
- K-sparing diuretic
- SCr >2.5 mg/dL
- K >5 mmol/L before randomization

Study drug dose adjustments
- If K >5.5 mmol/L dose reduced or discontinued until K <5.5
- Baseline = 48 hours after first dose
- 1,45 + scheduled visits and within
- 1 week of dose change

Primary endpoint
- Time to death from any cause
- Time to death from CV cause or hospitalization for CV event

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

Secondary endpoints
- Death from CV cause
- Death from any cause or hospitalization for any reason

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

Death from CV causes
- Hospitalization for HF or death from any cause
- Death from any cause
- Death from CV causes
- Hospitalization for any reason

Hospitalization for HF

NYHA Class IV HF within 6 months and NYHA III/IV at time of randomization

K-sparing diuretic, Operable valvular heart disease, UA, other life-threatening disease

Previous heart transplant or waiting

Receiving ACEi + loop diuretic LVEF ≤ 35% within 6 months before enrollment

NYHA Class IV HF within 6 months and NYHA III/IV at time of randomization

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

AMi, NYHA Class III/IV HF

K >5 mmol/L, GFR < 30 mL/min/1.73 m²

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

Deaths: 284 (35%) spironolactone vs 386 (46%) Placebo
- Kaplan–Meier estimates: RR: 0.70; P < 0.001
- NNT to prevent 1 death = 9

Death from CV causes
- Hospitalization for HF or death from any cause
- Death from any cause
- Death from CV causes
- Hospitalization for any reason

Hospitalization for HF

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Death from CV causes
- Hospitalization for HF or death from any cause
- Death from any cause
- Death from CV causes
- Hospitalization for any reason

Hospitalization for HF
Aldosterone receptor antagonists in HF

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. 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%). 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. 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; \( P = 0.002 \)). Secondary endpoints included reduced death from cardiovascular causes (RR: 0.83; \( P = 0.005 \), which was primarily

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Secondary endpoint results

- Death from CV causes: RR: 0.83 (\( P < 0.005 \))
- Hospitalization for CV or hospitalization for any reason: RR: 0.76 (\( P = 0.008 \))
- NYHA class change (spironolactone) compared with placebo (30.0%, RR: 0.87; \( P = 0.008 \)). 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; \( P = 0.002 \)). Secondary endpoints included reduced death from cardiovascular causes (RR: 0.83; \( P = 0.005 \), which was primarily

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- Death from CV causes: RR: 0.83 (\( P < 0.005 \))
- Hospitalization for CV or hospitalization for any reason: RR: 0.76 (\( P = 0.008 \))
- NYHA class change (spironolactone) compared with placebo (30.0%, RR: 0.87; \( P = 0.008 \)). 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; \( P = 0.002 \)). Secondary endpoints included reduced death from cardiovascular causes (RR: 0.83; \( P = 0.005 \), which was primarily

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Secondary endpoint results

- Death from CV causes: RR: 0.83 (\( P < 0.005 \))
- Hospitalization for CV or hospitalization for any reason: RR: 0.76 (\( P = 0.008 \))
- NYHA class change (spironolactone) compared with placebo (30.0%, RR: 0.87; \( P = 0.008 \)). 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; \( P = 0.002 \)). Secondary endpoints included reduced death from cardiovascular causes (RR: 0.83; \( P = 0.005 \), which was primarily

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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 sud-
den cardiac death in patients receiving an aldosterone recep-
tor 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 $\leq$35% to either epler-
enone or placebo.$^{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 aldos-
teron 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 guide-
lines 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 recomenda-
tion 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 
dressed 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.\(^5\) 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.\(^5\) 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, EMPHASIS-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.\(^5\) 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/angiotensin 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.

**References**


