Update on Aldosterone Antagonists Use in Heart Failure With Reduced Left Ventricular Ejection Fraction Heart Failure Society of America Guidelines Committee

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ABSTRACT

Aldosterone antagonists (or mineralocorticoid receptor antagonists [MRAs]) are guideline-recommended therapy for patients with moderate to severe heart failure (HF) symptoms and reduced left ventricular ejection fraction (LVEF), and in postmyocardial infarction patients with HF. The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial evaluated the MRA eplerenone in patients with mild HF symptoms. Eplerenone reduced the risk of the primary endpoint of cardiovascular death or HF hospitalization (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.54–0.74, P < .001) and all-cause mortality (adjusted HR 0.76, 95% CI 0.62–0.93, P < .008) after a median of 21 months. Based on EMPHASIS-HF, an MRA is recommended for patients with New York Heart Association (NYHA) Class II–IV symptoms and reduced LVEF (<35%) on standard therapy (Strength of Evidence A). Patients with NYHA Class II symptoms should have another high-risk feature to be consistent with the EMPHASIS-HF population (age >55 years, QRS duration >130 msec [if LVEF between 31% and 35%], HF hospitalization within 6 months or elevated B-type natriuretic peptide level). Renal function and serum potassium should be closely monitored. Dose selection should consider renal function, baseline potassium, and concomitant drug interactions. The efficacy of eplerenone in patients with mild HF symptoms translates into a unique opportunity to reduce morbidity and mortality earlier in the course of the disease. (J Cardiac Fail 2012;18:265–281)

Key Words: Aldosterone antagonists, eplerenone, heart failure, spironolactone.

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Aldosterone receptor antagonists, also referred to as mineralocorticoid receptor antagonists (MRA), are currently guideline-recommended evidence-based therapy for select patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF). The contribution of aldosterone to the development and progression of HF is well-established (Table 1). Further, large randomized, controlled clinical trials of aldosterone receptor antagonists showed that spironolactone improved survival in patients with severe HF with depressed EF, and eplerenone reduced morbidity and mortality in postmyocardial infarction (MI) patients with HF and LV dysfunction. The Heart Failure Society of America (HFSA) and other national and international guidelines therefore recommend the use of aldosterone receptor antagonists in HF patients similar to the populations studied in the Randomized Aldactone Evaluation study (RALES) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trials (Table 2). These trials excluded patients with mild HF symptoms, rendering a knowledge gap regarding the efficacy and safety of aldosterone receptor antagonists in this specific population.

The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial was designed to address this knowledge gap. The data generated from this study necessitates a reexamination of the current guideline recommendations. The purpose of this article is to evaluate the existing and new evidence for aldosterone antagonism in patients across the spectrum of HF, and to provide suggestions for how clinicians may incorporate this evidence into their clinical practice. This document is not a formal guideline update, but rather a document to communicate latest results, cumulative evidence, highlight persistent knowledge gaps, and provide care recommendations related to aldosterone antagonism in HF in accordance with emerging evidence.

### Table 1. Pleiotropic Effects of Aldosterone in Heart Failure*

<table>
<thead>
<tr>
<th>Heart</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Myocyte hypertrophy</td>
<td>• Sodium and water retention</td>
</tr>
<tr>
<td>• Intersitial fibrosis</td>
<td>• Potassium and magnesium wasting</td>
</tr>
<tr>
<td>• Coronary atherosclerosis</td>
<td>• Glomerulosclerosis</td>
</tr>
<tr>
<td>• Decreased natriuretic peptide synthesis</td>
<td>• Tubulointerstitial fibrosis</td>
</tr>
<tr>
<td>• Reduced norepinephrine uptake</td>
<td>• Podocyte apoptosis and proteinuria</td>
</tr>
<tr>
<td>• Endothelial cell hypertrophy</td>
<td>• Vasomotor dysfunction</td>
</tr>
<tr>
<td>• Vascular smooth muscle cell hypertrophy</td>
<td>• Platelet aggregation</td>
</tr>
<tr>
<td>• Atherosclerosis</td>
<td>• Reduced nitric oxide bioavailability</td>
</tr>
</tbody>
</table>

*Oxidative stress and inflammation have been shown to play a pathophysiologic role in all systems.

### Pathophysiology of Aldosterone in HF

More than 50 years ago, Luetscher and Johnson first observed that adults and children with HF secrete a steroid hormone in the urine with sodium-retaining properties. Using selective venous sampling and liquid chromatography, Davis et al then identified this hormone as aldosterone and found that it was produced in excess in the adrenal gland in edematous states. Subsequent studies have shown that plasma aldosterone levels are elevated in patients with HF despite maximal renin-angiotensin system blockade (so-called aldosterone escape), correlate with disease severity, and predict mortality. These data suggested that aldosterone is not simply a biomarker of disease activity, but a potent mediator of ventricular and vascular remodeling and disease progression.

Elevated plasma concentrations of aldosterone are due to both increased adrenal production and decreased hepatic clearance. In patients with HF, major triggers of aldosterone release include angiotensin II (especially when intravascular volume is reduced with diuretic therapy), serum potassium concentration, and corticotropic. Additional stimuli that play a minor role in normal adults but are upregulated in HF include circulating arginine vasopressin, catecholamines, and endothelin. Aldosterone has pleiotropic effects on the heart, kidney, and the vasculature (Table 1). In the myocardium, aldosterone exerts growth-promoting and pro-fibrotic effects on myocytes and the interstitium, respectively. Transgenic mouse models demonstrate that cardiac-specific overexpression of 11ß-hydroxysteroid dehydrogenase type 2 with activation of mineralocorticoid receptors leads to concentric ventricular remodeling, myocardial fibrosis and premature death. This phenotype can be attenuated and survival enhanced with aldosterone receptor blockade. Reduction in dietary salt intake may also play a key role in limiting aldosterone-mediated cardiovascular damage.

Beyond the adrenal cortex, aldosterone is produced by vascular endothelial cells where it promotes inflammation and fibrosis leading to endothelial dysfunction. Relevant to patients with ischemic HF, stimulation of mineralocorticoid receptors in the coronary and peripheral arteries also exerts proatherogenic effects, which are accelerated by downregulation of the inhibitory enzyme 11ß-hydroxysteroid dehydrogenase type 2. Numerous studies in animals and humans have demonstrated salutary effects of aldosterone receptor blockade on vasomotor reactivity, baroreceptor responsiveness, and norepinephrine uptake. Myocardial injury can be attenuated by inhibiting the development of coronary inflammatory lesions. These experimental data provide an explanation for reduction in both HF and sudden death mortality demonstrated in RALES, EPHESUS, and EMPHASIS-HF.

In the kidney, aldosterone has long been understood to promote reabsorption of sodium and water from tubular fluid, an effect that is regulated by the α-subunit of the
## Table 2. Aldosterone Antagonists in Heart Failure: Evidence From Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Population</th>
<th>Primary Endpoint</th>
<th>Mean Length of Follow-up (Months)</th>
<th>ACE inhibitor or ARB, %</th>
<th>β-blocker, %</th>
<th>All-cause Mortality, n (%) RR (95% CI)</th>
<th>Death or HF Hospitalization, n (%) RR (95% CI)</th>
<th>Serious Hyperkalemia, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES</td>
<td>822 S 841 P</td>
<td>NYHA Class III/IV (IV within 6 months prior) (SCr &gt; 2.5 mg/dL or serum potassium &gt; 5 mmol/L excluded)</td>
<td>All-cause mortality</td>
<td>24</td>
<td>95% S 94% P</td>
<td>11% S 10% P</td>
<td>284 (35) S 386 (46) P 0.7 (0.60–0.82), $P &lt; .001$</td>
<td>CV death or CV hospitalization ≥6 mmol/L 14 (2) S 10 (1) P, $P = .42$</td>
<td></td>
</tr>
<tr>
<td>EPHESUS</td>
<td>3319 E 3313 P</td>
<td>AMI, LVEF ≤40, and HF symptoms (SCr &gt; 2.5 mg/dL or serum potassium &gt; 5 mmol/L excluded)</td>
<td>Co-primary: Time to death from any cause or first CV hospitalization</td>
<td>16</td>
<td>86% E 87% P</td>
<td>75% E 75% P</td>
<td>478 (14.4) E 554 (16.7) P 0.85 (0.75–0.96), P = .008</td>
<td>CV death or CV hospitalization ≥6 mmol/L 180 (5.5) E 126 (3.9) P, P = .002</td>
<td></td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>1364 E 1373 P</td>
<td>NYHA Class II (NYHA III/IV, eGFR &lt; 30 mL/minute, serum potassium &gt; 5 mmol/L excluded)</td>
<td>CV death or first HF hospitalization (primary endpoint)</td>
<td>21 (median)</td>
<td>94% E 93% P</td>
<td>87% E 87% P</td>
<td>171 (12.5) E 213 (15.5) P 0.76 (0.62–0.93), P = .008</td>
<td>CV death or HF hospitalization &gt;6 mmol/L 33 (2.5) E 25 (1.9) P, P = .29</td>
<td></td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; AMI, acute MI; CV, cardiovascular; E, eplerenone; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; S, spironolactone; P, placebo; RALES, Randomized Aldactone Evaluation study; SCr, serum creatinine.
epithelial sodium channel. More recent data suggest that stimulation of mineralocorticoid receptors in the renal cortex can also contribute to ischemic injury, mesangial cell proliferation, and nephrosclerosis. In kidneys isolated from diabetic or spontaneously hypertensive rats, aldosterone activity is increased in glomeruli and proximal tubules, and is associated with podocyte apoptosis and proteinuria. Notably, these effects can be reversed with spironolactone or eplerenone. In addition, aldosterone can alter the intrarenal hemodynamics regulating glomerular filtration. As demonstrated in the myocardium, mechanisms of renal damage likely involve induction of reactive oxygen species and inflammatory molecules. Although the impact of aldosterone-mediated renal damage in HF remains unclear, the growing population of patients with coexistent cardiac and renal dysfunction (or cardiorenal syndrome) suggests that aldosterone antagonists may have renoprotective as well as cardioprotective effects.

Overview of Pharmacology

Aldosterone exerts its effects by binding to the mineralocorticoid receptor. In the United States, 2 pharmacologic agents competitively inhibit aldosterone at the mineralocorticoid receptor sites, spironolactone and eplerenone. Spironolactone is a nonselective MRA that is structurally similar to progesterone. In addition to its aldosterone-blocking effects, spironolactone inhibits the effects of dihydrotestosterone at the receptor site and increases the peripheral conversion of testosterone into estradiol. As a result, it is associated with antiandrogenic and progestogenic adverse effects including gynecomastia, impotence, and menstrual irregularities.

Eplerenone is a selective MRA, with a 100- to 1000-fold lower affinity for androgen, glucocorticoid, and progesterone receptors than spironolactone. As a result, eplerenone is not associated with the antiandrogenic side effects observed with spironolactone therapy. Some data also suggest that eplerenone may influence other steroid receptors to a lesser degree than spironolactone. In 1 study of 107 patients with mild HF, serum cortisol levels and hemoglobin A1c increased from baseline in patients treated with spironolactone and did not change in those treated with eplerenone. Whether these effects are clinically relevant is not known. Based on currently available data, the pharmacologic differences between spironolactone and eplerenone appear to be limited to tolerability (antiandrogenic or other steroid-related side effects) rather than clinical efficacy, as both drugs have been shown to improve outcomes in HF.

Eplerenone is extensively metabolized to inactive metabolites, whereas spironolactone is metabolized to the active metabolite canrenone. In the distal tubule, aldosterone promotes sodium reabsorption and potassium excretion. Aldosterone antagonists block potassium excretion in the renal distal tubule and collecting ducts, leading to the risk of hyperkalemia.

### Review of the Evidence

Several randomized controlled trials of aldosterone antagonists in patients with HF and reduced LVEF have been conducted to date (Table 2). A systematic review of these and other studies with aldosterone receptor antagonists included 10 trials that have specifically enrolled New York Heart Association (NYHA) Class II patients with reduced LVEF.

### NYHA Class III or IV

The RALES trial evaluated patients with NYHA Class III/IV symptoms, LVEF ≤35%, and background angiotensin-converting enzyme (ACE) inhibitor therapy. Patients with serum creatinine >2.5 mg/dL were excluded. Mean age of participants was 65 ± 12 years, 73% were male, 55% had ischemic cardiomyopathy, and mean LVEF was 25.6 ± 6.7%. While 95% of patients were on an ACE inhibitor, only 11% were treated with a β-blocker. The mean spironolactone dose achieved was 26 mg/day.

After a mean follow-up of 24 months, spironolactone reduced the primary endpoint of all cause mortality by 31% compared with standard therapy (relative risk [RR] 0.69, 95% confidence interval [CI] 0.58–0.82, \( P < .001 \)). HF hospitalizations, cardiovascular hospitalizations, and cardiac mortality rates were also lowered. Patients treated with a β-blocker at baseline derived a similar benefit from spironolactone as the overall population. The number needed to treat (NNT) with spironolactone for 2 years to save 1 life was 9 patients in this population with an annualized placebo mortality rate of \( \sim 27\% \).

### NYHA Class II

The EMPHASIS-HF trial was a randomized, double-blind, placebo controlled trial of eplerenone or placebo in addition to standard therapy in 2737 patients >55 years old with NYHA Class II HF and LVEF ≤35%. Patients with an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m² or serum potassium >5.0 mmol/L were excluded. Additionally, patients had to be enrolled within 6 months of a cardiac hospitalization or have an elevated BNP level >250 pg/mL or N terminal B-type natriuretic peptide >500 pg/mL (men) or >750 pg/mL (women). Patients with an LVEF between 31% and 35% were additionally required to have QRS duration of ≥130 ms. Patients enrolled in EMPHASIS-HF had a mean age of 68.7 ± 7.7 years, 78% were male, 69% had an ischemic cardiomyopathy, and mean LVEF was 26.2 ± 4.6%. The majority of patients received either an ACE-inhibitor or angiotensin receptor blocker (ARB) (94%), and β-blocker (87%). Eplerenone reduced the risk of the primary endpoint of cardiovascular death or HF hospitalization (hazard ratio [HR] 0.63, 95% CI 0.54–0.74, \( P < .001 \)) and all-cause mortality (adjusted HR 0.76, 95% CI 0.62–0.93, \( P < .008 \)) after a median of 21 months of follow-up. Additional reductions were observed in all-cause, cardiac, and HF...

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**Table 2:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>LVEF</th>
<th>Primary Endpoint</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES</td>
<td>NYHA Class III/IV</td>
<td>≤35%</td>
<td>All-cause mortality</td>
<td>0.69 (0.58–0.82)</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>NYHA Class II</td>
<td>≤35%</td>
<td>All-cause mortality</td>
<td>0.63 (0.54–0.74)</td>
</tr>
</tbody>
</table>
hospitalizations. These findings were consistent across all presupervised subgroups including those with the presence of an implantable cardioverter defibrillator, cardiac re-synchronization therapy, a prolonged QRS duration, or LVEF above 30%. Overall, the NNT with eplerenone to postpone 1 death per year of follow-up was 51 patients (95% CI 32–180) in this population with an annualized placebo mortality rate of 7.1%.

The anti-remodelling effect of canrenone in patients with mild chronic heart failure (AREA IN-CHF) trial was a randomized, double-blind, placebo-controlled trial of 467 patients with NYHA Class II HF symptoms and LVEF ≤45% on optimal background therapy, who were randomized to canrenone (the active metabolite of spironolactone; not available in North America) or placebo.35 Patients enrolled had a mean age of 62 ± 9.5 years, 84% were male, 51% had an ischemic cardiomyopathy, and mean LVEF was 40% ± 8.6%. Ninety-six percent were on an ACE inhibitor or ARB, and 81% were on a β-blocker. The mean dose of canrenone achieved was 44 mg/day. The primary endpoint of reduction in left ventricular end diastolic volume at 12 months was not significantly different between the 2 groups. However, LVEF improvement was higher in the canrenone arm as compared with placebo (canrenone 39.9 ± 8.6 to 45.1 ± 9.6 vs. placebo 39.7 ± 8.6 to 42.9 ± 9.7; P = .04). After 12 months, the canrenone group had a nonsignificant reduction in all-cause mortality compared with placebo (2.8% vs. 5.4%, P = .17). Additionally, the composite of cardiac death or hospitalization was significantly lowered with canrenone (7.9% vs. 15.1%, P = .02).35

Post-MI HF

In EPHERUS, patients 3 to 14 days post-MI with LVEF ≤40 and HF signs (pulmonary rales, pulmonary venous congestion, or S3) were randomized to eplerenone or placebo. Post-MI patients with diabetes and LVEF ≤40 were not required to have HF signs or symptoms. Mean age of the patients was 64 ± 1 year, 70% were men, and mean LVEF was 33 ± 6%. Most patients received background therapy with an ACE inhibitor or ARB (86%) and β-blocker (75%). The mean dose of eplerenone achieved was 43 mg/day. After a mean follow-up of 16 months, eplerenone reduced the coprimary endpoints of all-cause mortality by 15% (RR 0.85, 95% CI 0.75–0.96) and cardiovascular death or cardiovascular hospitalization by 13% (RR 0.87, 95% CI 0.72–0.94). All-cause death or all-cause hospitalization (RR 0.92, 95% CI 0.86–0.98) and cardiovascular death (RR 0.83, 95% CI 0.72–0.94) were also reduced.8 In the diabetes cohort who were not required to have HF signs and symptoms, eplerenone reduced the relative risk of the composite endpoint of cardiovascular mortality or any hospitalization by 17% (RR 0.83, 95% CI 0.71–0.98; P = .031).36 Findings were consistent across multiple presupervised subgroups. The estimated NNT to save 1 life per year was 50, and the NNT was 33 to prevent 1 cardiovascular death or one cardiovascular hospitalization in this population with an annualized mortality of 13.6%.8

Impact of New Evidence on Guideline Recommendations/Clinical Practice

The impact of the new evidence on guideline recommendations is summarized in Table 3.

Role of Eplerenone and Spironolactone

The European Society of Cardiology, American College of Cardiology Foundation (ACCF)/American Heart Association (AHA), and HFSA all recommend the administration of a low-dose aldosterone antagonist (spironolactone 12.5 to 25 mg or eplerenone 25 mg daily) in patients with an LVEF ≤35% and NYHA Class III—IV symptoms in the absence of significant renal dysfunction or hyperkalemia.1,5,10 The ACCF/AHA also recommends eplerenone in patients after an acute MI with clinical HF signs and symptoms and a LVEF <40%.10 The HFSA suggests health care providers should consider using eplerenone in this clinical scenario.1

On the basis of data from the RALES,7 EPHERUS,8 and more recently EMPHASIS-HF11 trials, there are 3 clinical scenarios where aldosterone antagonism in the absence of significant renal dysfunction or hyperkalemia may be used: 1) LVEF ≤35% and NYHA Class III—IV symptoms; 2) post-MI with signs and symptoms of acute HF and LVEF ≤40%, or post-MI patients with diabetes and LVEF ≤40% (regardless of HF symptoms); and 3) LVEF ≤30% (or if LVEF >30 to 35 then QRS >130 ms should also be present), NYHA Class II symptoms and another high risk feature (eg, age >55 years, HF hospitalization within the previous 6 months [or if no hospitalization, BNP >250 pg/mL, NT-proBNP >500 pg/mL (men) or >750 pg/mL (women)]. Renal function and electrolytes should be evaluated before therapy initiation. Recommendations for dosing and monitoring are shown in Table 4.

Order of Therapy

ACE inhibitors and β-blockers form the foundation of effective HF therapy.1 After optimization of these agents, clinicians may choose to initiate therapy with an ARB, an aldosterone antagonist, or the combination of hydralazine and isosorbide dinitrate. Specific recommendations for adding a third agent are included in the 2010 HFSA guidelines. The EMPHASIS-HF trial results justify a reexamination of the evidence-based approach to selecting add-on therapy in patients with mild HF.

Background Therapy

In EMPHASIS-HF, the majority of patients were treated with an ACE inhibitor or ARB and β-blocker. The magnitude of benefit for eplerenone was smaller in the subgroup of patients not receiving a β-blocker at baseline, but there was no statistical evidence of heterogeneity.11 A similar
<table>
<thead>
<tr>
<th>Existing Recommendation (2010 Guideline)</th>
<th>Summary of Potential Change</th>
<th>Potential Change Related to New Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.14. Administration of an aldosterone antagonist is recommended for patients with NYHA Class IV (or Class III, previously Class IV) HF from reduced LVEF (&lt;35%) while receiving standard therapy, including diuretics (Strength of Evidence A).</td>
<td>Expand to include NYHA Class II</td>
<td>7.14. Administration of an aldosterone antagonist is recommended for patients with NYHA Class II*-IV HF from reduced LVEF (&lt;35%) while receiving standard therapy, including ACE inhibitor (or ARB if ACE inhibitor is not tolerated) and β-blocker (Strength of Evidence A).</td>
</tr>
<tr>
<td>7.15. Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical HF signs and symptoms or history of diabetes mellitus, and an LVEF &lt;40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker (Strength of Evidence A).</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>7.16. Aldosterone antagonists are not recommended when creatinine is &gt;2.5 mg/dL (or creatinine clearance is &lt;30 mL/min) or serum potassium is &gt;5.0 mmol/L or in conjunction with other potassium-sparing diuretics (Strength of Evidence A).</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>7.17. It is recommended that serum potassium concentration be monitored frequently following initiation or change in an aldosterone antagonist. Monitoring should reflect protocols followed in clinical trials (Strength of Evidence A).</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>7.18. In the absence of persistent hypokalemia (&lt;4.0 mmol/L), supplemental potassium is not recommended in patients taking an aldosterone antagonist (Strength of Evidence A).</td>
<td>Change to Strength of Evidence A</td>
<td>7.21 Additional pharmacologic therapy should be considered in patients with HF and reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and β-blocker. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure, and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia (Strength of Evidence C).</td>
</tr>
<tr>
<td>7.21. Additional pharmacologic therapy should be considered in patients with HF and reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and β-blocker. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure, and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia (Strength of Evidence C).</td>
<td>Change to “mild to moderate HF”</td>
<td>7.21(a). The addition of an aldosterone antagonist is recommended in the following clinical scenarios:</td>
</tr>
<tr>
<td>• Addition of an aldosterone antagonist:</td>
<td>Change to “may be considered”</td>
<td>• for severe HF (Strength of Evidence A)</td>
</tr>
<tr>
<td>• for severe HF (Strength of Evidence A)</td>
<td>Move statement regarding triple combination to a stand-alone recommendation highlight importance</td>
<td>• for mild to moderate HF (NYHA Class II*-III) (Strength of Evidence A)</td>
</tr>
<tr>
<td>• for moderate HF (Strength of Evidence C)</td>
<td>No change</td>
<td>7.22 (b). The addition of an ARB may be considered in patients who do not meet criteria for or who do not tolerate an aldosterone receptor antagonist (Strength of Evidence A)</td>
</tr>
<tr>
<td>• Addition of an ARB (Strength of Evidence A)</td>
<td>No change</td>
<td>7.22 (c). The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia or renal impairment (Strength of Evidence A).</td>
</tr>
<tr>
<td>7.22. Additional pharmacological therapy should be considered in patients with HF and reduced LVEF who are unable to tolerate a β-blocker and have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure, and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended due to the high risk of hyperkalemia (Strength of Evidence C).</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>• Addition of an ARB (Strength of Evidence C)</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>• Addition of an aldosterone antagonist</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>• for severe HF (Strength of Evidence C)</td>
<td>Change to include mild heart failure</td>
<td>For mild° to moderate HF (Strength of Evidence C)</td>
</tr>
<tr>
<td>• for moderate HF (Strength of Evidence C)</td>
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</tbody>
</table>

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

°For NYHA Class II, high-risk modifiers should also be present: LVEF ≤30% (if LVEF >30-35, then QRS >130 ms should also be present), age >55 years, HF hospitalization within 6 months (if no hospitalization within 6 months then BNP > 250 pg/mL or NT-proBNP > 500 pg/mL [men] or 750 pg/mL [women] should be present).
result with regard to ARB add-on therapy was observed in the subgroup of patients not receiving a β-blocker in the CHARM-Added trial. These data suggest that ACE-inhibitors and β-blockers should be initiated and optimized as clinically appropriate before initiating therapy with an aldosterone receptor antagonist or ARB.

Add-on Therapy

In the CHARM-Added trial, candesartan, added to background ACE inhibitor and β-blocker therapy, decreased the risk of cardiovascular death or HF hospitalization (the primary endpoint) by 15%, but it did not significantly reduce all-cause mortality (Table 5). In EMPHASIS-HF, eplerenone reduced the risk of cardiovascular death or HF hospitalization (the primary endpoint) by 37%, and it also decreased the risk of all-cause mortality by 24% (Table 5). Both the magnitude of benefit on the composite endpoint and the statistical certainty around the result were greater for eplerenone than for candesartan.

The combination of hydralazine and isosorbide dinitrate is another option for add-on therapy. The majority of evidence supports this therapy for African American patients with HF, but it may be considered in non-African Americans as well. The combination of hydralazine and isosorbide dinitrate is more relevant to the moderate to severe HF population, because few patients (0.2%) in African-American Heart Failure Trial (A-HeFT) had NYHA Class II symptoms. Thus, in African Americans, aldosterone antagonists may be used as add-on therapy in NYHA Class II patients after ACE inhibitors and β-blockers, followed by hydralazine and isosorbide dinitrate in patients who remain symptomatic. However, it should be noted that only 2.7% of patients in EMPHASIS-HF were African American. A retrospective analysis of A-HeFT suggested the morbidity and mortality benefit of spironolactone in African Americans was limited to those randomized to receive hydralazine and isosorbide dinitrate (39% of A-HeFT patients were treated with spironolactone), but these data require further evaluation in a prospective study.

Combination Add-on Therapy

In EMPHASIS-HF, a very small number of patients (n = 85) were treated with background combination of beta-blocker, ACE-inhibitor, and ARB. In this subgroup, the direction of eplerenone’s effect on the primary endpoint was similar to the overall result. However, the confidence interval was wide and conclusions about the safety and efficacy of this 4-drug combination cannot be drawn from this subgroup analysis. The triple combination of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended because of the high risk of hyperkalemia, although this recommendation is based primarily on expert opinion rather than prospective clinical trial data.
Individualization of Therapy

Although the totality of evidence is in favor of an aldosterone receptor antagonist as first-line add-on therapy, an ARB may be preferable in some clinical situations. Patients with renal impairment or serum potassium levels outside the recommended range for an aldosterone antagonist (eGFR < 30 mL/min/1.73 m² or potassium > 5 mmol/L) may be able to tolerate an ARB. In a pooled analysis of trials (eGFR < 10 mL/min), ARBs were as effective as spironolactone in reducing CV death or HF hospitalization (HR 0.86, 95% CI 0.71–1.05; P = .022). ARBs are also associated with lower rates of CV death or composite morbidity (HR 0.82, 95% CI 0.70–0.96; P = .003). Even in patients with eGFR ≥ 30 mL/min/1.73 m² and serum potassium ≤ 5.5 mmol/L, ARBs may be preferred as first-line add-on therapy, as they are associated with lower CV death or hospitalization due to HF compared to spironolactone (HR 0.85, 95% CI 0.74–0.97; P < .001). ARB should be directly compared with spironolactone; both were randomized controlled trials and their characteristics were similar. ARBs and spironolactone should continue to be used with caution in patients with renal impairment and hyperkalemia that still exist with ARB therapy.

Recommended Clinical Approach

After ACE inhibitor and β-blocker therapy, the 2010 HHS guideline recommendation supports the consideration of an ARB (Level II) as add-on therapy for patients who are not candidates or who do not tolerate aldosterone blockade (Table 1).

Are Spirodotone and Eplerenone Interchangeable?

Few studies have evaluated the class effect of spironolactone and eplerenone. One 8-week, multicenter, double-blind, placebo-controlled trial in parallel groups demonstrated that the primary endpoint was change in diastolic blood pressure, with no significant difference between the two groups (Table 2). The decrease in diastolic blood pressure in the spironolactone group was greater than that in the eplerenone group, but it was still lower than the reduction observed in patients receiving eplerenone 100 mg. It is not clear whether eplerenone 100 mg was lower than that of patients receiving spironolactone 100 mg. Thus, the effectiveness of spironolactone 50 mg, 100 mg, or 400 mg versus eplerenone 25 mg, 50 mg, or 100 mg twice daily in parallel groups has not been compared. It is possible that eplerenone may be less potent than spironolactone. However, the resulting increase in diastolic blood pressure among patients receiving eplerenone 100 mg was lower than that of patients receiving spironolactone 100 mg. Thus, eplerenone 100 mg is preferred over spironolactone 100 mg for patients who are not candidates or who do not tolerate aldosterone blockade (Table 1).

Table 5. Comparison of Evidence Supporting Add-on Therapy

<table>
<thead>
<tr>
<th>Add-on drug class</th>
<th>Val-HeFT</th>
<th>CHARM-Overall</th>
<th>CHARM-Added</th>
<th>A-HeFT</th>
<th>EMPHASIS-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), years</td>
<td>62 (11)</td>
<td>66 (11)</td>
<td>64 (11)</td>
<td>57 (12)</td>
<td>69 (8)</td>
</tr>
<tr>
<td>Mean LVEF (SD), %</td>
<td>26.6 (7.3)</td>
<td>38.8 (14.9)</td>
<td>28.7 (5.3)</td>
<td>24%</td>
<td>27 (4)</td>
</tr>
<tr>
<td>NYHA Class II, %</td>
<td>62.1%</td>
<td>44–45%</td>
<td>24%</td>
<td>2%</td>
<td>100%</td>
</tr>
<tr>
<td>Background therapy</td>
<td>ACEI</td>
<td>ARB</td>
<td>ARB</td>
<td>Hydralazine isosorbide dinitrate (BiDil)</td>
<td>Eplerenone</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>92.6%</td>
<td>41%</td>
<td>100%</td>
<td>69%</td>
<td>77–78%</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>34.5%</td>
<td>55%</td>
<td>74%</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td>Mortality, n</td>
<td>495 (19.7%)</td>
<td>1398 (37%)</td>
<td>377 (30%)</td>
<td>32 (6.2%)</td>
<td>171 (12.5%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>148 (19.4%)</td>
<td>1541 (41%)</td>
<td>118 (32%)</td>
<td>54 (102%)</td>
<td>213 (15.5%)</td>
</tr>
<tr>
<td>CV death or HF hospitalization</td>
<td>RR 1.02 (0.88–1.18), P = .8</td>
<td>HR 0.9 (0.82–0.99), P = .032</td>
<td>HR 0.8 (0.77–0.91), P = .001</td>
<td>HR 0.83 (0.75–0.90), P = .010</td>
<td>HR 0.63 (0.54–0.74), P &lt; .001</td>
</tr>
</tbody>
</table>

A-HeFT, African-American Heart Failure Trial; C, candesartan; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure; HF, heart failure; H/I, hydralazine/isosorbide dinitrate; P, placebo; V, valsartan; Val-HeFT, Valsartan Heart Failure Trial.
use in patients with HF and post-MI left ventricular systolic dysfunction. The eplerenone trials have included more patients (9369 eplerenone vs. 1663 spironolactone), and the mean eplerenone doses were higher than the spironolactone doses (43.5 mg/day and 39 mg/day vs. 26 mg/day).

Whether or not the 2 aldosterone antagonists can be interchanged is not known, particularly for a population in which spironolactone has not been studied. Pharmacologic differences and the lack of efficacy data make the substitution of one for the other problematic. Recent studies of other drugs suggest that class effects are not universal. For example, differential effects between statins, thiazolidinediones, and β-blockers have been well studied and documented. The substantial difference in cost between the 2 drugs makes the issue of using spironolactone instead of eplerenone even more clinically relevant. The cost of generic eplerenone ranges from $1.34 to $2.59 for a 25-mg dose, whereas a 25-mg dose of Inspra™ ranges from $3.32 to $5.02. In contrast, generic spironolactone is available at large retail chain pharmacies for $3.32 to $5.02. In contrast, generic spironolactone is available at large retail chain pharmacies for $3.32 to $5.02.

The recommendations for aldosterone antagonist use in NYHA Class III/IV HF and post-MI HF are unaffected by the new data generated in EMPHASIS-HF. Thus, clinical practitioners should follow the recommendations in the current guideline. However, it should be noted that in an analysis of a large quality improvement registry, only 32.5% of 12,565 eligible patients hospitalized for acute decompensated heart failure (those meeting guideline criteria without contraindications) received an aldosterone antagonist at the time of hospital discharge. Focused efforts to reduce this treatment gap are warranted, although the safety of initiating MRAs during a heart failure admission has not been tested.

Safety: Monitoring and Follow-up

As with all medical therapy, there are risks to be considered with aldosterone receptor antagonists, especially in conjunction with other medications that block the renin-angiotensin system, alter volume status, or influence potassium levels. The principal risks of aldosterone receptor antagonists are hyperkalemia, renal dysfunction, and gynecomastia.

Hyperkalemia

Hyperkalemia resulting from aldosterone receptor antagonism has been extensively studied in single-center case-control or cohort studies, and within the context of clinical trials. In a systematic review including 19 randomized controlled trials (n = 10,807 patients), the rate of serious hyperkalemia was 5.9% in the aldosterone antagonist arm and 3% in the placebo arm. Subsequently, in EMPHASIS-HF, the rate of serum potassium concentration > 5.5 mmol/L was 11.8% in the eplerenone group and 7.2% in the placebo group (P < .001). Serum potassium > 6.0 mmol/L was observed in 2.5% of the eplerenone group, and 1.9% of the placebo group (P = .29). Wei et al conducted an analysis of spironolactone use in a large nonrandomized cohort of HF patients and reported a 2.9% incidence of hyperkalemia (> 6 mmol/L); patients with higher baseline creatinine or potassium levels were at a higher risk.

It is important to recognize that the risks of hyperkalemia among patients enrolled in the major randomized controlled trials were limited by the study eligibility criteria. In general, these patients had baseline serum creatinine of < 2.5 mg/dL (< 221 umol/L), serum potassium concentration of < 5 mmol/L, and were largely already on a maximally tolerated dose of an ACE inhibitor or ARB. Patients also underwent frequent laboratory assessment at the time of study drug initiation or titration, and in the setting of other illnesses (eg, influenza, diarrhea) or medications (eg, nonsteroidal anti-inflammatory drugs) that could increase the risk for hyperkalemia or renal impairment. In the analysis of a community-based population, an increased frequency of potassium and serum creatinine...
monitoring may have contributed to the lower incidence of serious hyperkalemia.\textsuperscript{51}

When initiating an aldosterone antagonist, the following patient characteristics should be considered: NYHA Class II–IV symptoms, serum potassium concentration <5.0 mmol/L, and eGFR >30 mL/min/1.73 m\textsuperscript{2}. Concomitant use of potassium sparing diuretics should be avoided. The frequency of serum creatinine and potassium monitoring is between 72 hours and 1 week after initiation or up titration of aldosterone antagonists, then monthly for the first 3 months, followed by every 3 to 4 months thereafter, or at any time a concurrent disease or other medication could influence potassium homeostasis (Table 4).

**Renal Impairment**

Renal dysfunction associated with these drugs is more difficult to quantify because the cohort and randomized trials have used varying definitions. Within randomized trials, the overall rate of renal failure (using the definitions from within each trial) was 8.9\% in the aldosterone antagonist arm and 1.6\% in the placebo arm.\textsuperscript{34} However, in the EMPHASIS-HF trial, this adverse event was not significantly different between the eplerenone and placebo groups (2.8\% and 3.0\%, respectively).\textsuperscript{11}

**Gynecomastia**

Gynecomastia is an uncommon side effect of spironolactone, and when present, is due to its activity as an androgen receptor blocker, inhibiting the effects of dihydrotestosterone at the receptor site and increasing the peripheral conversion of testosterone to estradiol.\textsuperscript{29} The incidence of gynecomastia in clinical trials of spironolactone was 4\% (compared with 0.6\% of controls).\textsuperscript{34} but it was higher if breast tenderness was included. Eplerenone is a selective aldosterone receptor antagonist that has a reduced affinity for endocrine receptors. In clinical trials, the incidence of gynecomastia with eplerenone was similar to placebo.

**Drug Interactions**

**Pharmacokinetic**

Eplerenone is a substrate of the cytochrome P-450 3A4 isoenzyme.\textsuperscript{54,55} Thus, the serum concentration of eplerenone is affected by concomitant use of CYP 3A4 inhibitors or inducers (Table 6). Concomitant use of a CYP 3A4 inhibitor inhibits eplerenone metabolism, thereby increasing eplerenone serum concentrations, enhancing the risk for hyperkalemia. Drugs that are potent inhibitors of CYP 3A4 (ketocazole) increase the eplerenone area under the curve (AUC) by 5-fold and should be avoided in patients treated with eplerenone.\textsuperscript{54–57} Erythromycin is a moderate inhibitor of CYP 3A4, and concomitant administration with eplerenone resulted in a 2- to 3-fold increase in eplerenone AUC. Moderate to weak inhibitors of CYP 3A4 should be used cautiously, and more frequent monitoring of serum potassium and creatinine should be implemented. A lower eplerenone dose is recommended if these drugs are used concomitantly. Although grapefruit juice is typically considered a potent inhibitor of CYP 3A4, it has been shown to increase eplerenone AUC only to a minor degree (25\%).\textsuperscript{54} Patients should be educated to maintain consistency in their dietary intake of grapefruit juice. Starfruit is a tropical fruit that is also a potent inhibitor of CYP 3A4, and although there are no published studies documenting an interaction between ingestion of starfruit and eplerenone, avoidance may be warranted on the basis of its potent inhibitory properties.\textsuperscript{58} Inducers of the CYP3A4 isoenzyme may lower eplerenone levels, but the clinical relevance of this interaction has not been established.

Spironolactone is a potent inhibitor of P-glycoprotein.\textsuperscript{59} Digoxin is a substrate for P-glycoprotein transport, and spironolactone can reduce the renal clearance of digoxin. This interaction is sometimes difficult to quantify since spironolactone can also cross react with some digoxin assays and give falsely elevated digoxin concentrations. The need to reduce digoxin dose when used concomitantly with spironolactone has been documented in the literature, but it may not be necessary in all patients.\textsuperscript{60}

**Pharmacodynamics**

Concomitant use of other agents that block potassium excretion or otherwise raise serum potassium levels should be avoided, with the exception of an ACE inhibitor or ARB. Thus, concomitant use of potassium-sparing diuretics (amiloride, triamterene), nonsteroidal anti-inflammatory drugs, pentamidine, and drospirenone (antimineralocorticoid activity similar to spironolactone) should be avoided. Potassium supplements are commonly used among patients receiving loop diuretics. In many patients, potassium supplementation will not be needed when aldosterone receptor antagonists are used; however, some patients may still require oral potassium replacement to avoid hypokalemia and should be monitored closely.

**Dietary Considerations**

Patients should be educated to avoid using potassium containing salt substitutes (eg, Nu-Salt\textsuperscript{TM}, No Salt\textsuperscript{TM}). In patients with a history of hyperkalemia, avoidance of high potassium-containing foods may be reasonable. Patients should be screened for the use of nutraceuticals, over-the-counter vitamins, or other dietary sources of potassium.

**Knowledge Gaps/Research Needs**

**HF With Preserved Ejection Fraction**

HF with preserved ejection fraction (HFPEF) accounts for approximately half of the overall HF burden in the community.\textsuperscript{61} Over the past 2 decades, the prevalence growth rate for HFPEF has exceeded that of HF with reduced EF.\textsuperscript{62} This trend may be related to the aging of the population and the age-related changes in cardiac structure and
Table 6. Potential Interactions With Aldosterone Receptor Antagonists

<table>
<thead>
<tr>
<th>Potent inhibitors of CYP3A4 Avoid concomitant use</th>
<th>Moderate to weak inhibitors of CYP3A4 Avoid concomitant use, or if medically necessary to use concomitantly, reduce aldosterone antagonist dose and increase monitoring</th>
<th>Potent inhibitors of P-glycoprotein substrates Suggested actions</th>
<th>Pharmacodynamic interactions with other drugs that raise serum potassium If medically necessary to use concomitantly, reduce aldosterone antagonist dose and increase monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Fluconazole</td>
<td>Eplerenone dose and increase monitoring</td>
<td>Potassium-sparing diuretics</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Saquinavir</td>
<td>Avoid concomitant use</td>
<td>Potassium-sparing diuretics</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Itraconazole</td>
<td>If medically necessary to use concomitantly,</td>
<td>NSAI ds</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Clarithromycin</td>
<td>reduce aldosterone antagonist dose and increase</td>
<td>Pentamidine</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Imatinib</td>
<td>monitoring</td>
<td>Drospirenone</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Nefazodone</td>
<td></td>
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<tr>
<td>Nelfinavir</td>
<td>Nelfinavir</td>
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<tr>
<td>Ritonavir</td>
<td>Ritonavir</td>
<td></td>
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</tr>
<tr>
<td>Conivaptan</td>
<td>Conivaptan</td>
<td></td>
<td></td>
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<tr>
<td>Grapefruit Juice</td>
<td>Grapefruit Juice</td>
<td></td>
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</tr>
<tr>
<td>Telithromycin</td>
<td>Telithromycin</td>
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<tr>
<td>Conivaptan</td>
<td>Conivaptan</td>
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</tr>
<tr>
<td>Delavirdine</td>
<td>Delavirdine</td>
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</tbody>
</table>

- *These interactions have the potential to influence the P-glycoprotein substrate’s systemic exposure. These interactions do not increase the systemic exposure of spironolactone, and therefore would not be expected to enhance the risk of hyperkalemia associated with spironolactone.

Adapted from references 56,57,59

IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs.

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function. No interventions tested to date have been shown to reduce all-cause mortality in this patient population. Patients with HFPEF have a mortality and morbidity burden that is comparable to patients with HF and reduced EF. The RALES, EMPHASIS-HF, and EPHESUS trials of aldosterone antagonists in HF were exclusively conducted in patients with reduced EF. Extracellular matrix fibrosis plays a major role in ventricular stiffness and relaxation, and in turn the development of HF. Aldosterone promotes myocardial fibrosis, enhances ventricular stiffness, and worsens diastolic function. Hypertension potentiates diastolic dysfunction by enhancing myocyte hypertrophy and interstitial fibrosis. Therefore, evaluating aldosterone antagonists in patients with HFPEF is important. Indeed, early data are promising in this respect, and a large scale randomized controlled trial of spironolactone versus placebo, the Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone antagonist (ie, TOPCAT) in patients with HFPEF is ongoing.

LVF 35% to 45%

The LVF inclusion criteria in the RALES trial was <35%. In EMPHASIS-HF, it was <30% or 30% to 35% with a QRS duration of >130 ms, and in the EPHESUS trial it was <40%. Although it may appear mostly semantic, the LVF cutoff ranges for inclusion in clinical trials have significant impact on the subsequent drug or device approval by the Food and Drug Administration, and in turn, on practice guidelines and quality and performance measures. Most trials with HF and systolic dysfunction have included patients with LVF <40%, but this criterion has not been uniform. For example, all studies with cardiac resynchronization therapy and implantable cardioverter defibrillators for primary prevention included patients with LVF <35%, making this cutoff an approved indication for these devices. Similarly, there has been no uniform definition of HFPEF. The CHARM preserved EF arm included patients with LVF 40%, whereas I-PRESERVE included patients with LVF >45%, and Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study included patients with LVF 40% to 50%. Data for aldosterone antagonism are lacking in patients with LVF between 35% and 45%. This is compounded by the fact that there is modest inter- and intra-observer variability in LVF assessment. If the TOPCAT trial is positive, it is likely, though not certain, that there will be a low threshold to use aldosterone antagonists in HF across the spectrum, including patients with LVF between 35% and 45%. This supposition is based on an extension of pathophysiologic logic because of consistent positive trials among patients with LVF ≤35 and >45%. If, however, the TOPCAT trial is negative or neutral, uncertainty will remain regarding the efficacy of using these agents in patients with LVF 35% to 45%.

The totality of evidence supports the efficacy of aldosterone receptor antagonists in all symptomatic heart failure patients, from patients with NYHA Class IV through NYHA Class II symptoms and the EMPHASIS-HF enrollment qualifiers (LVEF ≤30% [if LVEF > 30 to 35, then also QRS > 130 ms], age > 55 years, HF hospitalization within 6 months [if no hospitalization within 6 months, then BNP > 250 pg/mL or NT-proBNP > 500 pg/mL [men] or 750 pg/mL [women]). It may be reasonable to consider aldosterone antagonists in patients with low LVF and NYHA Class II symptoms who do not have the EMPHASIS-HF enrollment qualifiers, but a gap in the evidence currently exists for this patient population.

HF Prevention: Asymptomatic LV Dysfunction and Stage B HF

One in 5 Americans will be over the age 65 by 2030. The incidence and prevalence of HF is highest in the elderly. If the current epidemiologic trends continue, then by 2030 the prevalence of HF will increase by 25%, as opposed to the estimated 16.6% and 9.9% rise in coronary heart disease and hypertension prevalence, respectively. The economic impact will be a rise in direct and indirect cost of care to $95 billion annually. These trends underscore the importance of furthering HF prevention efforts. Subclinical changes in cardiac structure and function, including LV hypertrophy, enlargement, wall motion abnormalities, diastolic dysfunction, or reduced EF, and left atrial enlargement, often precede the development of Stage C HF. In cohort studies, LV changes have been strongly associated with increased HF risk after adjustment for clinical characteristics. Prevalence of asymptomatic left ventricular dysfunction (ALVD) is up to 16% in some populations. Patients with ALVD represent a group with a distinct opportunity to reduce incident HF. Patients with ALVD have half the mortality rate (5% annualized) of those with overt HF; however, the risk of death is 5 to 8 times higher than a normal age-matched population. In the SOLVD Prevention Study, patients with untreated ALVD developed overt HF at a 10% annual rate, with a further 8% annual risk of death or hospitalization for HF.

Both ACE inhibitors and β-blockers reduce the risk of new-onset HF in patients with ALVD. Considering the role of the renin angiotensin aldosterone system in LV dysfunction, it is possible that individuals with ALVD may benefit from aldosterone antagonists. However, this hypothesis needs to be tested. Similarly, to further prevention efforts, the ACCF/AHA guidelines include LV hypertrophy in their criteria for Stage B HF. Stage B HF is associated with adverse outcomes among men. If the TOPCAT trial is positive, new questions will emerge as to whether aldosterone antagonists could be used to prevent HF in patients with certain Stage B clinical characteristics.

Niche HF

HF is a syndrome composed of various etiologies that all present with a common set of symptoms and signs. Although many patients with nonischemic cardiomyopathy
may not have an identifiable underlying etiology, a distinct minority have specific causes (eg, amyloidosis, hypertrophic cardiomyopathy, sarcoidosis). These conditions are not common and patients with these diseases are typically either excluded from trials or represent a distinct minority of patients enrolled. The use of typical HF drugs in these clinical scenarios, including aldosterone antagonists, may be chosen based on a clinical and pathophysiologic rationale; however, definitive data do not exist.

**In-hospital Initiation and Continuation**

Use of aldosterone antagonists is associated with renal dysfunction and hyperkalemia, especially in conjunction with the use of agents that effect renal function or potassium levels. Of significant concern is the co-administration of aldosterone antagonist therapy with an ACE inhibitor, ARB, diuretic, or potassium supplementation.52 Recently, Albert et al assessed data from the AHA Get with the Guidelines database and showed a substantial gap in aldosterone antagonist prescription in eligible patients with acute HF at discharge.49 In-hospital initiation of medications has been shown to be 1 of the best predictors of long term adherence.86,87 Concerns with in-hospital initiation of HF medications have also been raised previously, for example, with β-blocker therapy. However, in several observational studies, in-hospital initiation of β-blockers was not only safe (once patients were diuresed), but it was associated with improved outcomes.87,88 These observational data led to a randomized control trial of β-blocker initiation at the time of discharge among patients with acute HF that confirmed the earlier positive observational data.89

Currently, there are no randomized trials of in-hospital initiation of aldosterone antagonists. Data from Get with the Guidelines are encouraging in this respect. However, in the absence of randomized trials, the safety of this approach should not be assumed, and it is prudent to only start this therapy in patients who have been reliable in terms of close medical follow-up.

Another related issue is the continuation of aldosterone antagonists when patients present with acute HF. Acute HF may be associated with significantly altered renal function because of the primary cause of acute HF (high systemic vascular resistance, high central venous pressure, or low cardiac output), treatment (diuretics), or to in-hospital procedures using radiocontrast.90 Close to one third of acute HF patients develop worsening renal function.91 Thus, the continuation of aldosterone antagonists needs to be individualized based on the clinical scenario. If these agents are stopped due to renal concerns, it is important to consider the safety of restarting them after renal function stabilizes.

**Duration of Therapy in the Setting of Normalized LVEF**

One common issue for all HF medications is whether to discontinue their use if the LVEF normalizes over time. Reverse remodeling and substantial improvement in LVEF was uncommon before use of β-blocker therapy. However, ACE inhibitors, β-blockers, and cardiac resynchronization therapy promote reverse remodeling leading to a substantial minority of patients who normalize their LVEF on therapy,92 especially those with a nonischemic etiology.93 As a result, clinicians are faced with a dilemma of how long multidrug therapy should be continued. Although there are no specific data to help guide this issue, it may be reasonable to discontinue single-therapies gradually on a trial basis for patients with distinct etiologies (eg, peripartum cardiomyopathy) provided they can be closely monitored.

**Conclusion**

In earlier trials, aldosterone receptor antagonists, or MRAs, demonstrated clinically meaningful improvements in rehospitalizations and survival and are now an established, though underused, part of the standard therapy of selected patients with HF or post-MI LV dysfunction. The results of the EMPHASIS-HF trial have filled a prominent knowledge gap and support the addition of an MRA to standard therapy in selected patients with mild HF with reduced EF. Although formal revisions to established guidelines will follow, these data suggest that clinicians should strongly consider the expansion of their use of MRAs to patients similar to those enrolled in EMPHASIS-HF and should continue to use these life-saving agents in patients where current guidelines already have recommended their use. Large-scale clinical trials are currently enrolling patients to address additional knowledge gaps regarding MRA therapy in patients with HF as well as other potential therapeutic targets. Clinicians should strongly consider the addition of an ARB or MRA for patients with symptomatic HF already on an ACE inhibitor and β-blocker. In most situations, an MRA will be an appropriate addition, proven to provide additional reductions in morbidity and mortality.

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<table>
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<th>Name</th>
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<th>Speaker’s Bureau</th>
<th>Research Grants</th>
<th>Equity Interests/ Stock/Stock Options</th>
<th>Equity Interests</th>
<th>Royalty Income</th>
<th>Non-Royalty Payments</th>
<th>Other Financial Benefit</th>
<th>Intellectual Property Rights</th>
<th>Fellowship Support</th>
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References


six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study). Am J Cardiol 2001;87:1051–7.


