A 63-year-old woman is evaluated after a recent hospitalization for an acute myocardial infarction. She reports fatigue and exertional dyspnea after ambulating 25 m. Her left ventricular (LV) ejection fraction is 38%, and her medications include aspirin, clopidogrel, a loop diuretic, an angiotensin-converting enzyme inhibitor (ACE-I), and a β-adrenergic receptor antagonist. On physical examination, her blood pressure is 144/92 mm Hg, and her heart rate is 72 bpm. Her jugular venous pressure is 9 cm water, and bilateral inspiratory rales and 1+ peripheral edema are noted. The patient’s serum K⁺ is 4.5 mEq/L and creatinine is 1.2 mg/dL. She is diagnosed with hypertension and moderate congestive heart failure (CHF) with LV systolic dysfunction.

Overview
Despite evidence from clinical trials demonstrating a morbidity and mortality advantage for selected patients treated with aldosterone receptor antagonists, these drugs are underused in clinical practice. The Randomized Aldactone Evaluation Study (RALES) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) established that spironolactone and eplerenone, respectively, increased survival in patients with severe CHF symptoms from LV systolic dysfunction occurring with minimal exertion or at rest (New York Heart Association [NYHA] class III or IV) or CHF after an acute myocardial infarction.1–3 As a result of these studies, aldosterone receptor antagonists were given an American Heart Association/American College of Cardiology class I recommendation for use, yet only 32% of eligible patients are routinely prescribed these drugs.4,5 This trend likely reflects clinicians’ persisting concerns over reports linking increased community-based spironolactone use with drug-induced deaths and hospitalizations.6 This association is drawn largely from population-based observational data demonstrating a temporal (and not causal) relationship between increased prescription rates of spironolactone and increased rates of hospital admission for the treatment of hyperkalemia and subsequent in-hospital deaths. Given that aldosterone receptor antagonists are often used in combination with other cardiovascular medications, reservations about polypharmacy may also contribute to low prescription rates. Nevertheless, aldosterone receptor antagonist underutilization in patients for whom clinical trial data support their use occurs today despite sound evidence that these drugs are safe when prescribed and monitored appropriately. Moreover, recent scientific advances have elucidated further the relationship between hyperaldosteronism and cardiovascular dysfunction and may expand the spectrum of patients who stand to benefit from this pharmacotherapy. These advances have also resulted in the reconsideration of aldosterone receptor antagonists for the treatment of conventional cardiovascular diseases for which these agents are underused, particularly essential hypertension.

Pathophysiology
Aldosterone Synthesis
Aldosterone is synthesized by the adrenal glands to preserve intravascular sodium, potassium, and water homeostasis (Figure 1). Aldosterone binds to mineralocorticoid receptors in the kidney, colon, and sweat glands and induces sodium (and water) reabsorption with concomitant potassium excretion. Patho-
Cardiovascular Actions of Aldosterone

The pathobiological effects of hyperaldosteronism on the cardiovascular system extend beyond increased intravascular fluid retention and volume overload. Hyperaldosteronism causes endothelial dysfunction and impairs vascular reactivity, in part, by decreasing vascular antioxidant capacity, increasing oxidant stress, and limiting bioavailable nitric oxide. Hyperaldosteronism also activates inflammation, alters fibrinolysis by increasing plasminogen activator inhibitor-1 expression, and promotes tissue fibrosis. Other adverse effects attributed to hyperaldosteronism that may influence cardiovascular function include sympathetic nervous system activation, decreased baroreceptor sensitivity, increased electrolyte excretion (K⁺, Mg²⁺), and cardiomyocyte apoptosis (Figure 1). Thus, in addition to modulating volume status, some of the clinical benefit of aldosterone receptor antagonists comes from abrogating these adverse effects to limit target organ dysfunction.

Clinical Pharmacology

Current guidelines suggest that patients with a clinical indication for an aldosterone receptor antagonist initiate therapy only if they have a baseline serum K⁺ <5.0 mEq/L and a serum creatinine ≥2.5 mg/dL for men or ≥2.0 mg/dL for women. Serum K⁺ and creatinine levels are monitored 4 weeks after the start of treatment or after 1 week in those patients with an increased risk of severe hyperkalemia (≥6.0 mEq/L) such as patients with diabetes mellitus or decreased renal function with a glomerular filtration rate <60 mL/min. Potassium supplements should be discontinued, and combination therapy with other drugs that cause hyperkalemia such as ACE-I and nonsteroidal antiinflammatory drugs should prompt enhanced electrolyte surveillance. Specifically, serum K⁺ levels should be reassessed within 2 weeks after a change in the prescribed dose of a medication that increases the risk for hyperkalemia when coadministered with an aldosterone receptor antagonist or if there is a change in the patient’s clinical status that influences serum electrolyte levels or fluid balance (eg, vomiting, diarrhea, or worsening CHF). Furthermore, although formal guidelines to advise clinicians on the long-term frequency of K⁺ and creatinine monitoring do not exist, protocols advise K⁺ and creatinine every 3 to 6 months for individuals at low risk for hyperkalemia and monthly for those individuals at high risk.

Spiromolactone

Spiromolactone is a nonselective aldosterone receptor antagonist that is metabolized extensively in the liver to its active metabolites (the Table). The plasma half-life of the drug is ≈1.4 hours, although in CHF patients with hepatic congestion, this duration may increase 5-fold. A maximal drug response is seen 48 hours after the first dose.

![Figure 1](http://circ.ahajournals.org/Download/56x139.png)

**Figure 1.** The effect of impaired LV function on aldosterone synthesis. A, A decrease in cardiac output as a result of LV systolic dysfunction is perceived as a decrease in efferent renal blood flow. B, This stimulates renin secretion from the juxtaglomerular apparatus. C, In the peripheral circulation, renin cleaves angiotensinogen to angiotensin I (AT I), which is converted to angiotensin II (AT II) by ACE in the pulmonary artery vasculature (D). E, Angiotensin II stimulates zona glomerulosa cells in the adrenal cortex to secrete aldosterone. Extraadrenal synthesis of aldosterone occurs in vascular, adipose, and myocardial tissue (inset). Elevated plasma levels of aldosterone have a number of adverse effects on the cardiovascular system. NO indicates nitric oxide. (Heart images reproduced with permission from U-Write patient education, © 1998 William Frid, dba U-Write; kidney and glomerulus images reproduced with permission from Bill Canelet; blood vessel images reproduced with permission from John MacNeil; adrenal gland image reproduced with permission from McGill Molson Medical Informatics Project, McGill University; adipose image reproduced with permission from Steve Moskowitz, Advanced Medical Graphics.)
Spironolactone is structurally similar to progesterone, thereby allowing sex-steroid receptor cross-reactivity. This phenomenon accounts for the antiprogestin and antiandrogen effects observed in some patients treated with spironolactone. Spironolactone is dosed between 25 and 200 mg/d for CHF and 50 and 100 mg/d for hypertension, with dose titration recommended at 4- to 6-week intervals until the desired clinical effect is achieved.11

Eplerenone

Eplerenone is a selective aldosterone receptor antagonist derived from spironolactone but with limited affinity for the progesterone and androgen receptors and therefore lacks sex-related adverse side effects (the Table). Eplerenone is metabolized by cytochrome P450 (isoenzyme CYP3A4); inhibitors of CYP3A4, including ketoconazole, itraconazole, ribonavir, and clarithromycin, are associated with significant increases in peak eplerenone levels, whereas inducers of CYP3A4 such as St John’s wort decrease levels by 30%. Eplerenone has a plasma half-life of 4 to 6 hours, and steady-state drug levels are usually achieved 48 hours after the first dose. Eplerenone is dosed 25 mg/d and uptitrated for clinical response to a target concentration of 50 mg/d or a maximum concentration of 50 mg twice a day if necessary.11

Side Effects

Spironolactone and eplerenone have different side effect profiles that may influence the selection of one agent in preference to the other, although both drugs share hyperkalemia as a serious side effect. Aldosterone receptor antagonism influences serum K⁺ levels by impairing aldosterone-mediated effects on K⁺ homeostasis in the principal cells of the kidney. Activation of the aldosterone receptor stimulates the apical Na⁺-K⁺-ATPase pump and luminal K⁺ channel activity to promote luminal K⁺ excretion into the late distal convoluted tubules and the distal collecting ducts. Therefore, antagonism of the aldosterone receptor decreases luminal K⁺ excretion, thereby increasing the possibility of clinically significant hyperkalemia; when severe, hyperkalemia may precipitate cardiomyocyte membrane potential destabilization and unstable ventricular arrhythmias.12 Although serious hyperkalemia occurred in only 2% of spironolactone-treated patients in RALES, rates as high as 10% in the community have been reported.1,6,13 Factors contributing to this discrepancy, however, may include inappropriate patient selection for therapy and suboptimal serum electrolyte monitoring.14 The risk of serious hyperkalemia is minimized by identification of appropriate clinical

### Key Pharmacological Properties of Spironolactone and Eplerenone

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Spironolactone</th>
<th>Eplerenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical indication</td>
<td>Severe (NYHA class III–IV) CHF with LV systolic dysfunction Essential hypertension</td>
<td>Severe (NYHA class III–IV) CHF after myocardial infarction Essential hypertension</td>
</tr>
<tr>
<td>Receptor binding affinity (aldosterone = 1)</td>
<td>1.1×10⁻¹</td>
<td>5.1×10⁻³</td>
</tr>
<tr>
<td>Sex-steroid receptor cross-reactivity</td>
<td>Yes</td>
<td>Minimal</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic</td>
<td>Cytochrome P450, isoenzyme CYP3A4</td>
</tr>
<tr>
<td>Conversion to metabolites for effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>1.4</td>
<td>4–6</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal and bile</td>
<td>Renal and GI</td>
</tr>
<tr>
<td>Administration</td>
<td>With food to maximize absorption</td>
<td>With or without food</td>
</tr>
<tr>
<td>Recommended dose, mg/d</td>
<td>Hypertension, 50–100; CHF, 25–200</td>
<td>Hypertension, 50–100; CHF, 25–50</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Potentiate hyperkalem</td>
<td>Potentiate hyperkalem</td>
</tr>
<tr>
<td></td>
<td>ACE-I</td>
<td>ACE-I</td>
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<tr>
<td></td>
<td>NSAIDs</td>
<td>NSAIDs</td>
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<tr>
<td></td>
<td>Potentiate hypotension</td>
<td>CYP3A4 inhibitors increase eplerenone:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>itraconazole, ribonavir, clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Narcotics</td>
<td>CYP3A4 inducers decrease eplerenone:</td>
</tr>
<tr>
<td></td>
<td>Increase digoxin levels</td>
<td>St John’s wort</td>
</tr>
<tr>
<td>Side effects</td>
<td>Hyperkalemia</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Gynecomastia, breast tenderness</td>
<td>Abdominal pain, diarrhea</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysmenorrhea, amenorrhea</td>
<td></td>
</tr>
</tbody>
</table>

GI indicates gastrointestinal; NSAIDs, nonsteroidal antiinflammatory drugs.
indications for drug therapy, routine serum K⁺ and renal function monitoring, and avoidance of concurrent pharmacotherapies associated with hyperkalemia. Dose adjustments; drug holidays; review of over-the-counter medications, vitamins, and diet and dietary supplements containing high levels of K⁺; and increased monitoring should be evaluated on an individualized basis. For example, daily spironolactone therapy should be decreased in dose by 50% when serum K⁺ is 5.5 to 5.9 mEq/L and discontinued when K⁺ ≥6.0 mEq/L until levels are <5.5 mEq/L.¹⁰

The incidence of spironolactone-associated breast tenderness and gynecomastia reported in clinical trials is 6.9% to 10% for men and typically occurs at doses ≥50 mg/d. Generally, these side effects resolve with drug cessation. Spironolactone may also lower testosterone levels, and drug use is associated with erectile dysfunction and menstrual irregularities; when present, these side effects increase rates of medication noncompliance.¹¹

Clinical Populations Proven to Benefit From Aldosterone Antagonist Therapy

Congestive Heart Failure

Nearly one third of patients with LV systolic dysfunction have clinically important aldosterone levels despite serological evidence of complete ACE inhibition.¹⁵ This phenomenon, termed aldosterone breakthrough, may explain the beneficial effects of aldosterone receptor antagonists when added to ACE-I in patients with symptomatic CHF. In NYHA class III to IV patients with LV systolic dysfunction, spironolactone (25 mg/d) decreased mortality in the RALES trial by 30% over 24 months when added to an ACE-I and loop diuretic therapy.¹ Similarly, in patients with symptomatic CHF from an acute myocardial infarction (LV ejection fraction = 33%), the addition of eplerenone (25 to 50 mg/d) to standard therapy decreased all-cause mortality by 15% and sudden cardiac death by 21%.² The survival advantage with eplerenone treatment was seen as early as 30 days after initiation of therapy.¹⁶ These findings are in line with reports that hyperaldosteronemia discovered at presentation for an acute STElevation myocardial infarction is an independent prognostic marker for future CHF, ventricular arrhythmia, and cardiac death.¹⁷

Aldosterone antagonists also improve LV structural remodeling and performance by increasing LV ejection fraction and decreasing LV end-diastolic and end-systolic volumes when measured echocardiographically. These favorable effects on cardiac physiology may explain improvements in peak oxygen consumption, reductions in CHF-associated hospitalizations, and shorter hospital stay durations attributed to aldosterone antagonists when used in combination with standard therapy.¹⁸,¹⁹

In asymptomatic or mildly symptomatic patients with LV systolic dysfunction, the efficacy of aldosterone receptor antagonists is not fully established. Therapy with canrenone, a spironolactone metabolite that is not available for therapeutic use in the United States, however, modestly improves LV ejection fraction in NYHA class II CHF patients, leading to a reduction in cardiac death and hospitalization rates.²⁰ Further data evaluating eplerenone in this patient subgroup are forthcoming from the Effect of Eplerenone in Chronic Systolic Heart Failure (EMPHASIS-HF) trial. Evidence to support aldosterone receptor antagonist use in symptomatic CHF patients with preserved LV systolic function (ie, impaired diastolic relaxation) is derived primarily from small patient cohorts. Nevertheless, spironolactone therapy (over 6 months) promotes favorable LV remodeling by reducing posterior LV wall thickness and improving LV relaxation and filling patterns compared with placebo in patients with impaired diastolic relaxation.²¹ Adequately powered prospective, randomized clinical studies to assess the utility of aldosterone receptor antagonists in patients with CHF and impaired diastolic relaxation such as the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial are ongoing. At this time, however, there are insufficient clinical data to recommend the use of aldosterone antagonist therapy for the treatment of diastolic dysfunction.

Hypertension

Circulating aldosterone levels positively correlate with incident, resistant, and obesity- and obstructive sleep apnea–related hypertension.²²–²⁵ The relationship between aldosterone and incident hypertension was shown in the Framingham Offspring Study in which over 4 years there was a 17% increased risk for developing hypertension per quartile increase in plasma aldosterone levels.²³ Among patients with resistant hypertension (ie, hypertension requiring ≥3 different antihypertensive medications at pharmacologically effective doses), the prevalence of primary hyperaldosteronism is between 17% to 23%.²⁴,²⁵ Interestingly, the majority of patients with primary hyperaldosteronism and hypertension had a normal serum potassium at the time of diagnosis, indicating that hypokalemia is a late manifestation of aldosterone excess.²⁶ Furthermore, patients with hypertension and primary hyperaldosteronism had higher rates of atrial fibrillation, myocardial infarction, and stroke compared with hypertensive patients matched for elevations in blood pressure.²⁷

Individual studies have shown that spironolactone and eplerenone are each efficacious in reducing blood pressure; however, there have been a limited number of head-to-head comparison studies designed to establish drug superiority.²⁸ In a small study of patients with resistant hypertension, 6 months of spironolactone added to diuretic and ACE-I therapy reduced systolic and diastolic blood pressures by 25 and 12 mm Hg, respectively, and the magnitude of the response was not predicted by the plasma aldosterone level.²⁹ Similar conclusions from a substudy of 1411 patients with resis-
tant hypertension participating in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) support the use of spironolactone as add-on therapy to conventional regimens requiring at least 2 antihypertensive medications (eg, amlopidine plus perindopril or atenolol plus bendroflumethiazide). In mildly hypertensive self-described black patients, another group at increased risk for hypertension-associated cardiovascular complications, eplerenone is superior to angiotensin receptor blocker monotherapy, but has not been sufficiently compared with other antihypertensive drugs in this population.

In hypertensive patients, aldosterone receptor antagonists decrease blood pressure to limit end-organ damage. Eplerenone improves arterial compliance and reduces vascular stiffness by decreasing the collagen-to-elastin ratio. Both spironolactone and eplerenone have been shown to decrease LV mass with a reduction in the prevalence of hypertrophy in treated patients from 30% to 7%.

Chronic Kidney Disease
Hyperaldosteronism is associated with renal injury and the development of chronic kidney disease in patients with hypertension, diabetes mellitus, and obesity. By some estimates, up to 85% of patients with primary hyperaldosteronism have evidence of proteinuria. Albuminuria occurs to a greater extent in patients with aldosterone-mediated hypertension than in those with idiopathic hypertension, and in normotensive individuals, there is an association between proteinuria and aldosterone levels.

The administration of an ACE-I or angiotensin receptor blocker decreases proteinuria in patients at high risk for renal damage (eg, diabetes mellitus) but does not fully halt the progression of renal disease. One meta-analysis of 11 studies found that the addition of spironolactone or eplerenone to an ACE-I or angiotensin receptor blocker, however, significantly decreased 24-hour urinary protein excretion beyond single-agent therapy alone. Although this finding may be attributed to improved blood pressure control, in contrast to ACE-I drugs, aldosterone receptor antagonists do not mediate efferent renal arterial pressure and thus do not induce nephrotoxicity. Overall, data linking aldosterone receptor antagonists with renal function improvement are, to date, derived mainly from numerous small studies limited by brief follow-up periods. The long-term effect of these drugs on renal disease–associated outcomes is under investigation.

Clinical Follow-Up
In the case vignette patient, hypertension and impaired LV systolic function with NYHA class III CHF symptoms are both clinical indications for aldosterone receptor antagonist therapy (Figure 2). Her serum K+ and renal function are acceptable to initiate treatment. Spironolactone 25 mg/d was prescribed, and as a consequence of concurrent ACE-I use, laboratory surveillance was scheduled at 1 week and monthly thereafter. Six weeks later, the patient’s blood pressure was at goal, and a subjective improvement in exercise capacity was reported.

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None.

References


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