CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will consider the use of aldosterone receptor antagonists in patients with congestive heart failure with minimal symptoms

VIJAIGANESH NAGARAJAN, MD
Department of Hospital Medicine, Cleveland Clinic

MOHAMMED CHAMSI-PASHA, MD
Department of Internal Medicine, Cleveland Clinic

W. H. WILSON TANG, MD
Director of Cardiomyopathy Program and Research Director, Section of Heart Failure and Cardiac Transplantation Medicine, Cleveland Clinic; Associate Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University

The role of aldosterone receptor antagonists in the management of heart failure: An update

ABSTRACT

The aldosterone receptor antagonists (ARAs) spironolactone (Aldactone) and eplerenone (Inspra) have become part of standard medical therapy for heart failure, having shown clinical efficacy in randomized trials in patients with advanced symptomatic systolic heart failure, postinfarction heart failure with cardiac dysfunction, and systolic heart failure with mild symptoms. The benefits include a lower rate of death. Yet to be answered is whether the two drugs are clinically equivalent; another question is whether they may benefit everyone with symptomatic heart failure, including diastolic heart failure.

KEY POINTS

Although caution is advised in starting ARAs, these drugs are commonly underused in heart failure.

Aldosterone "escape" can blunt the effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. This is the rationale for also using ARAs.

The major trials of ARAs in heart failure to date have been the Randomized Aldactone Evaluation Study (RALES), the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF).

Close monitoring is essential when starting an ARA, as severe hyperkalemia and renal insufficiency can occur.

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Over the past 30 years, the focus of treating heart failure has shifted from managing symptoms to prolonging lives. When the neurohormonal hypothesis (ie, the concept that neurohormonal dysregulation and not merely hemodynamic changes are responsible for the onset and progression of heart failure) was introduced, it brought a dramatic change that included new classes of drugs that interfere with the renin-angiotensin-aldosterone system, ie, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and, most recently, aldosterone receptor antagonists (ARAs) (FIGURE 1).

Evidence supporting the use of the ARAs spironolactone (Aldactone) and eplerenone (Inspra) in heart failure has been growing, as has evidence of their usefulness in treating diabetes and chronic renal disease. Still, these drugs must be used cautiously, as they can cause hyperkalemia.

This paper will review the clinical use of ARAs in symptomatic systolic heart failure, their side effects, the findings and implications of recent trials, and controversies in this area, notably whether there is any evidence favoring the use of one drug over another.

ALDOSTERONE IN HEART FAILURE

Aldosterone, a hormone secreted by the zona glomerulosa of the adrenal gland, was first isolated by Simpson and Tait more than half a century ago.[1] Later, it was found to promote reabsorption of sodium and excretion of potassium in the kidneys and hence was categorized as a mineralocorticoid hormone.

The renin-angiotensin-aldosterone system and drugs that block it

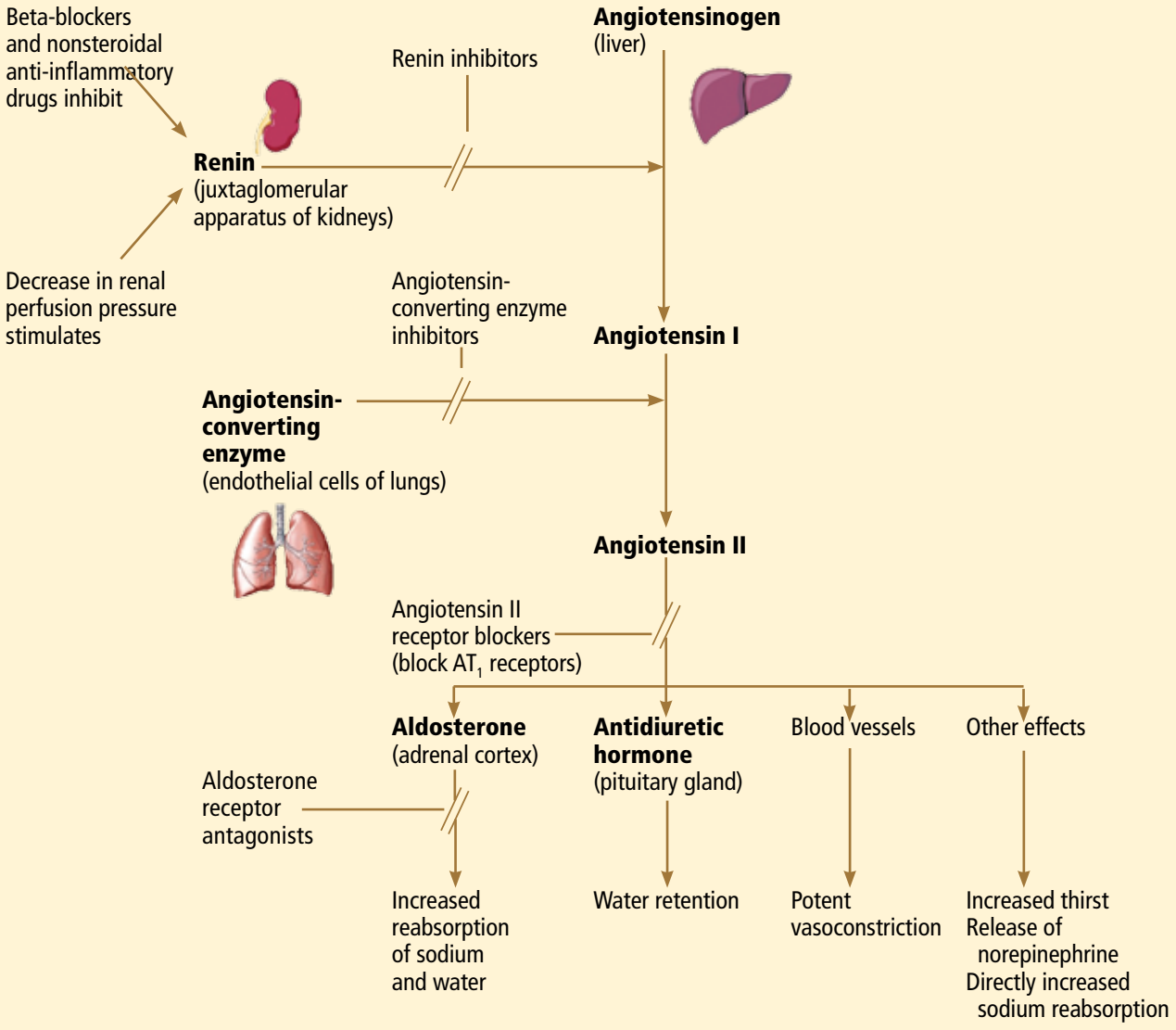

FIGURE 1

Release of aldosterone is stimulated by decreased renal perfusion via angiotensin II, hyperkalemia, and possibly adrenocorticotropic hormone.[2] Aldosterone exerts its effects by binding to mineralocorticoid receptors in renal epithelial cells.

Aldosterone has several deleterious effects on the failing heart, primarily sodium and fluid retention, but also endothelial dysfunction, left ventricular hypertrophy, and myocardial fibrosis.[2,3] Plasma aldosterone levels can be markedly elevated in patients with heart failure, likely due to activation of the renin-angiotensin-aldosterone system. Elevated aldosterone and angiotensin II levels have been associated with higher mortality rates.[4]

ALDOSTERONE 'ESCAPE' BLUNTS THE EFFECT OF ACE INHIBITORS AND ARBs

ACE inhibitors and ARBs have become standards of care for patients with systolic heart failure, and for many years, it was believed that these drugs suppressed aldosterone levels

sufficiently. But elevated aldosterone levels have been noted in up to 38% of patients on chronic ACE inhibitor therapy.[5] In one study, patients on dual blockade, ie, on both an ACE inhibitor and an ARB, had significantly lower aldosterone levels at 17 weeks of therapy, but not at 43 weeks.[6] This phenomenon is known as "aldosterone escape."

Several mechanisms might explain this phenomenon. Angiotensin II, a potent inducer of aldosterone, is "reactivated" during long-term ACE inhibitor therapy. Interestingly, patients progress toward aldosterone escape regardless of whether the ACE inhibitor dose is low or high.[7] There is evidence that some aldosterone is produced by endothelial cells and vascular smooth muscle in the heart and blood vessels,[8] but ACE inhibitors and ARBs suppress only the aldosterone secreted by the adrenal glands.

Regardless of the mechanism, aldosterone escape can blunt the effects of ACE inhibitors and ARBs, reducing their favorable effects on the risk of death in heart failure patients. This is the rationale for also using ARAs.

ARAs IN HEART FAILURE

Aldosterone acts by regulating gene expression after binding to mineralocorticoid receptors. These receptors are found not only in epithelial tissue in the kidneys and glands, but also in nonepithelial tissues such as cardiomyocytes, vessel walls, and the hippocampus of the brain.[9] The nonepithelial effects were first demonstrated 2 decades ago by Brilla et al,[10] who noted that chronically elevated aldosterone levels in rats promoted cardiac fibroblast growth, collagen accumulation, and, hence, ventricular remodeling.

The hypertensive effect of aldosterone may also be mediated through mineralocorticoid receptors in the brain. Gomez-Sanchez et al[11] found that infusing aldosterone into the cerebral ventricles caused significant hypertension. A selective mineralocorticoid antagonist inhibited this effect when infused into the cerebral ventricles but not when given systemically.

In 1959, Cella and Kagawa created spironolactone, a nonselective ARA, by combining elements of progesterone for its antimineralocorticoid effect and elements of digitoxin for its cardiotonic effect.[12] Although spironolactone is very effective in treating hypertension and heart failure, its use is limited by progestational and antiandrogenic side effects. This led, in 1987, to the invention by de Gasparo et al of a newer molecule, a selective ARA now called eplerenone.[13] Although eplerenone may be somewhat less potent than spironolactone in blocking mineralocorticoid receptors, no significant difference in efficacy has been noted in randomized clinical trials, and its antiandrogenic action is negligible.[12]

Although these drugs target aldosterone receptors, newer drugs may target different aspects of mineralocorticoid activities, and thus the term "mineralocorticoid receptor antagonist" has been proposed.

TRIALS OF ARAs IN HEART FAILURE

An online data supplement that accompanies this paper at http://www.ccjm.org/content/79/9/631/suppl/DC2 provides a detailed comparison of the three major trials of ARAs in patients with heart failure.

The Randomized Aldactone Evaluation Study (RALES)

Aldosterone has several deleterious effects on the failing heart

The first major clinical trial of an ARA was the Randomized Aldactone Evaluation Study (RALES),[14] a randomized, double-blind, controlled comparison of spironolactone and placebo.

The 1,663 patients in the trial all had severe heart failure (New York Heart Association class [NYHA] III and ambulatory class IV symptoms) and a left ventricular ejection fraction of 35% or less. Most were on an ACE inhibitor, a loop diuretic, and digoxin, but only 10% of patients in both groups were on a beta-blocker. Patients with chronic renal failure (serum creatinine > 2.5 mg/dL) or hyperkalemia (potassium > 5.0 mmol/L) were excluded.

RALES was halted early when an interim analysis at a mean follow-up of 24 months showed that significantly fewer patients were dying in the spironolactone group; their all-cause mortality rate was 30% lower (relative risk [RR] 0.70, 95% confidence interval [CI] 0.60–0.82, $P < .001$), and their cardiac mortality rate was 31% lower (RR 0.69, 95% CI 0.58–0.82, $P < .001$). This was concordant

with a lower risk of both sudden cardiac death and death from progressive heart failure. The risk of hospitalization for cardiac causes was also 30% lower for patients in the spironolactone group, who also experienced significant symptom improvement.

Gynecomastia and breast pain occurred in about 10% of patients in the spironolactone group, and adverse effects leading to study drug discontinuation occurred in 2%.[14]

Trials of aldosterone receptor antagonists

For a detailed comparison of the three major trials of aldosterone receptor antagonists (RALES, EPHESUS, and EMPHASIS-RF) go to http://www.ccjm.org/content/79/9/631/suppl/DC2

The Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)

The next landmark trial of an ARA was the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).[15] A total of 6,632 patients were randomized to receive eplerenone or placebo in this multicenter, double-blind trial. To be enrolled, patients had to have acute myocardial infarction, a left ventricular ejection fraction of 40% or less, and either clinical signs of heart failure 3 to 14 days after the infarction or a history of diabetes mellitus. Patients were excluded if they had chronic kidney disease (defined as a serum creatinine > 2.5 mg/dL or an estimated glomerular filtration rate < 30 mL/min/1.73 m^2) or hyperkalemia (a serum potassium > 5.0 mmol/L). All the patients received optimal medical therapy and reperfusion therapy, if warranted.

RALES was halted early because significantly fewer patients were dying in the spironolactone group

This event-driven trial was stopped when 1,012 deaths had occurred. During a mean follow-up of 16 months, there was a 15% lower rate of all-cause mortality in the eplerenone group (RR 0.85, 95% CI 0.75–0.96, *P* = .008) and a 13% lower rate of cardiovascular mortality (RR 0.83, 95% CI 0.72–0.94, *P* = .005). The reduction in the cardiovascular mortality rate was attributed to a 21% reduction in the rate of sudden cardiac deaths. The rate of heart failure hospitalization was also lower in the eplerenone group.

Serious hyperkalemia occurred significantly more frequently in the eplerenone group (5.5% vs 3.9%, *P* = .002), but similar rates of gynecomastia were observed. The incidence of hyperkalemia was higher in patients with a creatinine clearance less than 50 mL/min.

Further analyses revealed a 31% lower rate of all-cause mortality (95% CI 0.54–0.89, *P* = .004) and a 32% lower rate of cardiovascular mortality (95% CI 0.53–0.88, *P* = .003) at 30 days after randomization in the eplerenone group.[16] Importantly, 25% of all deaths in the EPHESUS study during the 16-month follow-up period occurred in the first 30 days after randomization. The Kaplan-Meier survival curves showed separation as early as 5 days after randomization. Hence, the 30-day mortality results from EPHESUS further indicated that starting eplerenone early may be particularly beneficial.

The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)

After RALES and EPHESUS, a gap remained in our knowledge, ie, how to use ARAs in patients with mild heart failure, who account for most cases. This led to the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial, which expanded the indications for ARAs to patients with chronic systolic heart failure with mild symptoms.[17]

In this double-blind trial, 2,737 patients with NYHA class II heart failure with a left ventricular ejection fraction of 35% or less were randomized to receive oral eplerenone 25 mg or placebo once daily. All patients were already on a beta-blocker; they were also all on an ACE inhibitor, an ARB, or both at the recommended or maximal tolerated dose. Patients with a glomerular filtration rate between 30 and 49 mL/min were started on alternate-day dosing, and those with glomerular filtration rates below 30 mL/min were excluded.

To ensure that the event rate was high enough to give this trial sufficient power:

- Only patients age 55 years or older were included
- Patients with a left ventricular ejection fraction greater than 30% were enrolled only if the QRS duration was greater than 130 ms

(only 3.5% of patients in both groups were enrolled based on this criterion)
- Patients either had to have been hospitalized for cardiovascular reasons in the 6 months before randomization or had to have elevated natriuretic peptides (B-type natriuretic peptide [BNP] level > 250 pg/mL or N-terminal pro-BNP > 500 pg/mL in men and > 750 pg/mL in women).

The study was stopped early at a median follow-up of 21 months after an interim analysis showed a significantly lower rate of the primary composite end point (death from a cardiovascular cause or hospitalization for heart failure) in the eplerenone group: 18.3% vs 25.9% (hazard ratio [HR] 0.63, 95% CI 0.54–0.74, $P < .001$). The rates of all-cause mortality were 12.5% vs 15.5% (HR 0.76, 95% CI 0.62–0.93, $P = .008$), and the rates of cardiovascular mortality were 10.8% vs 13.5% (HR 0.76, 95% CI 0.61–0.94, $P = .01$). Kaplan-Meier curves for all-cause mortality showed significant separation only after 1 year, which was not the case in EPHESUS and RALES. But the curves for hospitalization separated within a few weeks after randomization.

The incidence of hyperkalemia (serum potassium level > 5.5 mmol/L) was significantly higher in the eplerenone group (11.8% vs 7.2%, $P < .001$), but there was no statistically significant difference between groups when potassium levels above 6 mmol/L were considered (2.5% vs 1.9%, $P = .29$). This is despite one-third of patients having an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2. Breast symptoms were very rare, occurring in 1% or fewer patients in both groups. The discontinuation rate of the study drug was similar in both groups.

HOW DO ARAs PREVENT DEATH?

Multiple studies show that spironolactone and eplerenone lower blood pressure in a dose-related manner.[18] These drugs reduce fluid volume and pulmonary congestion, which could have been the primary mechanism for the reduction in heart failure hospitalizations in the EMPHASIS-HF trial. But other mechanisms might explain the reduction in cardiovascular mortality rates in the trials summarized above.

TABLE 1

Aldosterone receptor antagonists: side effects and the risk of hyperkalemia

MAJOR ADVERSE EFFECTS

Electrolyte abnormalities
- Hyperkalemia
- Hyponatremia
- Hyperchloremic metabolic acidosis

Decline in glomerular filtration rate (GFR)

Antiandrogenic effects (dose-related, negligible with eplerenone)
- Gynecomastia
- Breast tenderness
- Impotence

Upper gastrointestinal side effects

RISK FACTORS FOR HYPERKALEMIA

Chronic kidney disease (risk inversely proportional to the GFR)
Concomitant use of an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker
Concomitant use of other drugs that could cause hyperkalemia, eg, nonsteroidal anti-inflammatory drugs, potassium-sparing diuretics
Older age
Diabetes
Prerenal failure (due to volume depletion)
Diarrhea
Renovascular disease

Transcardiac extraction of aldosterone was increased in a study of patients with heart failure.[19] The transcardiac gradient of plasma aldosterone correlated with levels of procollagen III N-terminal propeptide, a biochemical marker of myocardial fibrosis. This suggests that aldosterone could be a stimulant of myocardial fibrosis. Spironolactone inhibited the transcardiac extraction of aldosterone in the same study.[19]

In another study,[20] spironolactone significantly suppressed elevation of procollagen III N-terminal propeptide after myocardial infarction. It was also demonstrated that spironolactone prevented left ventricular remodeling after infarction, even in patients receiving an ACE inhibitor. Similar results, ie, decreased left ventricular myocardial fibrosis and remodeling, were noted in another trial in which eplerenone was added to an ARB.[21]

Myocardial fibrosis is a known substrate for ventricular arrhythmias. In a randomized study in 35 patients, spironolactone decreased

the incidence of ventricular arrhythmias.[22] This finding correlates with the decreased incidence of sudden cardiac death in the RALES and EPHESUS trials.

ADVERSE EFFECTS OF ARAs

Hyperkalemia, hyperkalemia, hyperkalemia

Potassium excretion is physiologically regulated by the serum aldosterone concentration and by the delivery of sodium to the distal nephron. Aldosterone increases potassium excretion. As a result of decreased renal perfusion that occurs with heart failure, sodium is intensely reabsorbed in the proximal tubule, and very little sodium reaches the distal nephron. When aldosterone receptors are blocked by ARAs, the risk of hyperkalemia increases.[23]

Other electrolyte abnormalities associated with ARAs are hyponatremia and hyperchloremic metabolic acidosis (TABLE 1). There could be a reversible decline in the glomerular filtration rate as well.[24] Of note, most patients with chronic systolic heart failure in the RALES and EMPHASIS-HF trials were already receiving a diuretic; thus, the adverse effect profile of ARAs in otherwise euvolemic (or even hypovolemic) patients is not well appreciated.

30-day results from EPHESUS indicated that starting eplerenone early may be particularly beneficial

Failure to closely monitor electrolyte levels increases the risk of hyperkalemia and renal failure, so there is a need for regular follow-up visits for patients taking an ARA.[25] This was made clear when a population-based analysis from Canada compared the rates of hyperkalemia-related hospitalization and death before and after the RALES trial was published. The prescription rate for spironolactone increased threefold, but the rate of hyperkalemia-related hospitalization increased fourfold and the rate of death increased sixfold.[26]

Although caution is recommended when starting a patient on an ARA, a recent trial conducted in 167 cardiology practices noted that ARAs were the most underused drugs for heart failure. In this study, an ARA was prescribed to only 35% of eligible patients. The prescription rate was not significantly higher even in dedicated heart failure clinics.[27] Possible reasons suggested by the authors were drug side effects, the need for closer monitoring of laboratory values, and a lack of knowledge.

A population-based analysis from the United Kingdom found a significant increase over time in spironolactone prescriptions after the release of the RALES trial results, but there was no increase in the rate of serious hyperkalemia (serum potassium > 6 mmol/L) or hyperkalemia-related hospitalization.[28] The authors suggested that careful monitoring could prevent hyperkalemia-related complications. They also observed that 75% of patients who had spironolactone-associated hyperkalemia were over 65 years old. Hence, we recommend closer monitoring when starting an elderly patient on an ARA.

Breast, gastrointestinal symptoms

The nonselective ARA spironolactone is associated with antiandrogenic side effects. In a smaller study in patients with resistant hypertension, Nishizaka et al noted that low-dose spironolactone (up to 50 mg/day) was associated with breast tenderness in about 10%.[29] Breast symptoms with spironolactone are dose-related, and the incidence can be as high as 50% when the drug is used in dosages of 150 mg/day or higher.[30]

In one population-based case-control study, spironolactone was associated with a 2.7 times higher risk of gastrointestinal side effects (bleeding or ulcer).[31]

ARAs IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

The concept of diastolic heart failure or "heart failure with preserved ejection fraction" has been growing. A significant proportion of patients with a diagnosis of heart failure have preserved left ventricular ejection fraction (≥ 50%) and diastolic dysfunction.

Despite multiple trials, no treatment has been shown to lower the mortality rate in heart failure with preserved ejection fraction.[32,33] A recently published randomized controlled trial in 44 patients with this condition showed reduction in serum biochemical markers of collagen turnover and improvement in diastolic function with ARAs, but there was no difference in exercise capacity.[34] A larger double-blind randomized control trial, Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF), is under way to evaluate the effects of ARAs on exercise capacity and diastolic function in patients with heart failure

with preserved ejection fraction.[35]

In January 2012, the Trial of Aldosterone Antagonist Therapy in Adults With Preserved Ejection Fraction Congestive Heart Failure (TOPCAT) completed enrollment of 3,445 patients to study the effect of ARAs in reducing the composite end point of cardiovascular mortality, aborted cardiac arrest, and heart failure hospitalization. Long-term follow-up of this event-driven study is currently under way.

ARAs IN DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE

Under physiologic conditions, the serum aldosterone level is regulated by volume status through the renin-angiotensin system. But in patients with chronic kidney disease, the serum aldosterone level could be elevated without renin-angiotensin system stimulation.[36]

High aldosterone levels were associated with proteinuria and glomerulosclerosis in rats.[37] In a study in 83 patients, aldosterone receptor blockade was shown to decrease proteinuria and possibly to retard the progression of chronic kidney disease. In this trial, baseline serum aldosterone levels correlated with proteinuria.[38] Animal studies suggest that adipocyte-derived factors may stimulate aldosterone, which may be relevant in patients who have both chronic kidney disease and metabolic syndrome.[39]

The impact of ARAs in patients with diabetes mellitus is often overlooked. In EPHESUS, diabetes mellitus was an inclusion criterion even in the absence of heart failure signs and symptoms in the postinfarction setting of impaired left ventricular ejection fraction.[15]

In patients with diabetic nephropathy, there is growing evidence that ARAs can decrease proteinuria, even if the serum aldosterone level is normal. For example, in a study in 20 patients with diabetic nephropathy, spironolactone reduced proteinuria by 32%. This reduction was independent of serum aldosterone levels.[40]

In diabetic rats, hyperglycemia was noted to cause podocyte injury through mineralocorticoid receptor-mediated production of reactive oxygen species, independently of serum aldosterone levels. Spironolactone decreased the production of reactive oxygen species, thereby potentially reducing proteinuria.[41]

RECOMMENDATIONS ARE BEING REVISED

The most recent joint guidelines of the American Heart Association and the American College of Cardiology for the management of heart failure[42] were published in 2009, which was before the EMPHASIS-HF results. An update is expected soon. In the 2009 version, ARAs received a class I recommendation for patients with moderately severe to severe symptoms, decreased ejection fraction, normal renal function, and normal potassium levels. The guidelines also said that the risks of ARAs may outweigh their benefits if regular monitoring is not possible.

The recommended starting dosage is 12.5 mg/day of spironolactone or 25 mg/day of eplerenone; the dose can be doubled, if tolerated.

Close monitoring is recommended, ie, measuring serum potassium and renal function 3 and 7 days after starting therapy and then monthly for the first 3 months. Closer monitoring is needed if an ACE inhibitor or an ARB is added later. In elderly patients, the glomerular filtration rate is preferred over the serum creatinine level, and ARA therapy is not advisable if the glomerular filtration rate is less than 30 mL/min/1.73 m^2.

Avoid concomitant use of the following:

- Potassium supplements (unless persistent hypokalemia is present)
- Nonsteroidal anti-inflammatory drugs
- An ACE inhibitor and an ARB in combination
- A high dose of an ACE inhibitor or ARB.

Conditions that can lead to dehydration (eg, diarrhea, excessive use of diuretics) or acute illness should warrant reduction (or even withholding) of ARAs. When to discontinue ARA therapy is not well described, nor is the safety of starting ARAs in the hospital. However, it is clear that many patients who are potentially eligible for ARAs are not prescribed them.[43]

The guidelines are currently being revised, and will likely incorporate the new data from EMPHASIS-HF to extend to a broader population. The benefits of ARAs can be met only if the risks are minimized.

EMPHASIS-HF expanded the indications for ARAs to patients with chronic systolic heart failure with mild symptoms

WHICH ARA IS BETTER?

The pharmacologic differences between the two ARAs have been described earlier, and guidelines have advocated evidence-based use of ARAs for their respective indications. There have been no large-scale, head-to-head comparisons of spironolactone and eplerenone in the heart failure population, and in clinical practice the drugs are prescribed interchangeably in most patients.

A double-blind randomized controlled trial in 141 patients with hypertension and primary hyperaldosteronism found that spironolactone lowered diastolic blood pressure more, but it also caused antiandrogenic effects more often.[44]

There is some evidence to suggest that eplerenone has a better metabolic profile than spironolactone. The data came from a small randomized controlled trial in 107 stable outpatients with mild heart failure.[45] Patients who were prescribed spironolactone had a higher cortisol level and hemoglobin A_{1c} level 4 months after starting treatment. This effect was not seen in patients who were on eplerenone. However, these findings need to be confirmed in larger trials.

While the differences between the two drugs remain to be determined, the most important differences in clinical practice are selectivity for receptors (and hence their antiandrogenic side effects) and price. Even though it is available as a generic drug, eplerenone still costs at least three times more than spironolactone for the same dosage and indication.

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***ADDRESS**: W.H. Wilson Tang, MD, Department of Cardiovascular Medicine, J3-4, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail tangw@ccf.org.*