BERTRAM PITT, MD*
University of Michigan School of Medicine, Ann Arbor, MI; investigator in the RALES, EPHESUS, and 4E trials

SANJAY RAJAGOPALAN, MD
Mt. Sinai School of Medicine, New York, NY

Aldosterone receptor antagonists for heart failure: Current status, future indications

ABSTRACT

Many patients with heart failure should receive an aldosterone receptor antagonist, ie, either spironolactone (Aldactone) or the newer agent eplerenone (Inspra)—in addition to an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) or both, and a beta-blocker. We review the evidence and indications.

KEY POINTS

All patients with severe heart failure with systolic left ventricular (LV) dysfunction (LV ejection fraction ≤ 40%) should receive spironolactone or eplerenone unless these drugs are contraindicated because of hyperkalemia or renal dysfunction.

An aldosterone receptor antagonist should be started early in patients with heart failure and systolic LV dysfunction after a myocardial infarction (MI).

To avoid hyperkalemia with its cardiovascular risk, the glomerular filtration rate should be estimated before starting an aldosterone receptor antagonist, and the potassium level should be monitored frequently.

Whether these drugs help patients with mild heart failure, diastolic dysfunction, or asymptomatic systolic LV dysfunction is not proven, but they appear promising.

Aldosterone receptor antagonists are not advisable for patients with inferior or non-ST-segment elevation MI without signs of heart failure or systolic LV dysfunction.

THERAPY for heart failure has changed considerably over the last several years. Now, guidelines call for all patients with chronic heart failure with systolic left ventricular (LV) dysfunction or heart failure after myocardial infarction (MI) to receive an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker at target doses, unless these drugs are contraindicated or are not tolerated.

However, adherence remains poor, and even when the recommended drugs are used at target or maximally tolerated doses, the rates of cardiovascular death and hospitalization for heart failure remain high.

To try to further improve outcomes in patients with heart failure, clinical researchers have been testing ways to suppress the renin-angiotensin-aldosterone system more completely. One of the ways is to combine an ACE inhibitor with an angiotensin II type 1 receptor blocker (ARB), although this strategy has had inconsistent results (see below). Another way, and the focus of this paper, is to add one of the aldosterone receptor antagonists, ie, spironolactone (Aldactone) or eplerenone (Inspra).

SHOULD AN ARB BE ADDED TO AN ACE INHIBITOR?

In the renin-angiotensin-aldosterone cascade, ACE cleaves angiotensin I to make angiotensin II, which is a vasoconstrictor that also stimulates production of aldosterone. ACE inhibitors

*Dr. Pitt has indicated that he serves as a consultant for the Pfizer corporation.

block this pathway, but some angiotensin II is still produced via ACE-independent pathways.

Could we block angiotensin II more completely and improve patient outcomes by combining an ACE inhibitor with an ARB? Two studies tested this hypothesis, with different results.

The Valsartan Heart Failure Trial (Val-HeFT)[1] tested adding the ARB valsartan (160 mg twice daily) to an ACE inhibitor (captopril) in patients with advanced systolic LV dysfunction (mean LV ejection fraction 30%) and heart failure that was treated with standard therapy (beta-blockers, diuretics, and digoxin).

In patients who could not tolerate an ACE inhibitor or a beta-blocker, valsartan appeared to reduce the rates of cardiovascular mortality and hospitalization for heart failure, but it offered no additional mortality benefit in patients who were already receiving optimal therapy with both an ACE inhibitor and a beta-blocker.

The Candesartan in Heart Failure Assessment of Mortality and Morbidity (CHARM)-Added trial[2] tested adding the ARB candesartan (32 mg daily) to captopril and a beta-blocker in patients with New York Heart Association (NYHA) class II, III, or IV heart failure. Compared with placebo, candesartan reduced the rates of cardiovascular mortality and hospitalization for heart failure by 11% ($P = .01$).

Uncertainty remains about adding an ARB to an ACE inhibitor in heart failure

Comment. In view of the discrepant results in the Val-HeFT and CHARM-Added trials, considerable uncertainty remains as to the effectiveness of adding an ARB to an ACE inhibitor in heart failure. Hence, this strategy has not yet been given a class I recommendation (evidence, general agreement, or both, that the treatment is beneficial, useful, and effective) in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for heart failure.[3]

THEORETICAL BENEFITS OF ALDOSTERONE RECEPTOR ANTAGONISTS

Aldosterone not only tells the kidneys to retain more salt and water, it has several independent deleterious effects in the blood vessels and myocardium.[4] Conversely, blocking its receptor with spironolactone or eplerenone has pleiotropic beneficial effects, improving endothelial function and reducing inflammation, collagen synthesis, and thrombosis.[5]

Another reason for using these drugs is that aldosterone synthesis is determined not only by angiotensin II but also by other mediators such as potassium, adrenocorticotropic hormone, and cytokines.[6] Thus, although ACE inhibitors and ARBs reduce aldosterone levels in the short term, they consistently fail to do so over the long term.[7]

Yet another factor that may underlie some of the beneficial effects of spironolactone and eplerenone is that they raise serum potassium levels, which may have independent beneficial effects on the vasculature.[5]

CLINICAL TRIALS OF ALDOSTERONE RECEPTOR ANTAGONISTS

RALES: Spironolactone is beneficial in severe chronic heart failure with systolic LV dysfunction

In the Randomized Aldactone Evaluation study (RALES),[8] spironolactone was added to standard therapy in patients with severe heart failure (NYHA class III or IV) and systolic LV dysfunction.

The dosage of spironolactone was low: 25 mg/day, which could be increased to 50 mg once daily if the patient showed signs and symptoms of progression of heart failure, or reduced to 25 mg every other day if hyperkalemia developed. Approximately 15% of the patients were maintained on 25 mg every other day, 70% on 25 mg/day, and 15% on 50 mg/day.

The trial was stopped early, after a mean follow-up of 24 months, when spironolactone reduced the mortality rate by 30%, owing to a reduction both in death due to progressive heart failure and in sudden cardiac death. This effect was consistent in both men and women, irrespective of the cause of heart failure (ischemic vs nonischemic), and regardless of baseline therapy with an ACE inhibitor, beta-blocker, or both.

Only 10% to 11% of patients in RALES were taking a beta-blocker, as this study was started before definitive data from the Carvedilol Prospective Randomized Cumulative Survival

TABLE 1

Management of patients with MI with ST-segment elevation

Immediately

Give aspirin, clopidogrel, or both

Consider for percutaneous coronary intervention or thrombolysis

In the first 24 hours

Start a beta-blocker in all patients without contraindications and continue indefinitely

Start an angiotensin-converting enzyme (ACE) inhibitor in all patients without contraindications and continue indefinitely

Start an angiotensin II receptor blocker (ARB) in patients who cannot tolerate an ACE inhibitor and in those with either clinical or radiologic signs of heart failure or a left ventricular ejection fraction of < 40%

As soon as feasible

Start an aldosterone receptor antagonist if the patient has all of the following:

- Either heart failure or diabetes
- Left ventricular ejection fraction ≤ 40%
- Already receiving therapeutic doses of an ACE inhibitor
- Adequate renal function (serum creatinine ≤ 2.5 mg/dL in men or ≤ 2.0 mg/dL in women)
- Serum potassium ≤ 5.0 mmol/L

ADAPTED FROM ANTMAN EM, ANBE DT, ARMSTRONG PW, ET AL. ACC/AHA GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION; A REPORT OF THE AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION TASK FORCE ON PRACTICE GUIDELINES (COMMITTEE TO REVISE THE 1999 GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION). J AM COLL CARDIOL 2004; 44:E1–E211.

(COPERNICUS) trial became available, which showed a significant benefit of the beta-blocker carvedilol in patients with severe heart failure with systolic LV dysfunction.[9] Interestingly, the reduction in total mortality with spironolactone in RALES was even greater for patients on a beta-blocker than for those not on a beta-blocker, although the difference between subgroups was not statistically significant.[5,8]

On the basis of the RALES data, aldosterone receptor antagonists are now class I recommendations for patients with severe heart failure (NYHA class III or IV) in the ACC/AHA guidelines[3] and those of the European Society of Cardiology.[10]

Less evidence in mild heart failure

We have no data on mortality and morbidity from large randomized trials of aldosterone receptor antagonists in patients with mild heart failure (NYHA class I or II). However, several small randomized trials[11–15] found these drugs beneficial in terms of a variety of surrogate end points, including LV ejection fraction, exercise tolerance, collagen synthesis, QT dispersion, and endothelial function in patients with mild heart failure, many of whom were receiving both an ACE inhibitor and a beta-blocker.

Although no definitive recommendation for the use of an aldosterone receptor antagonist in patients with class I or II heart failure can be made at this time, if mild heart failure is progressing despite the use of an ACE inhibitor (or ARB), beta-blocker, diuretic, and digoxin, we would carefully consider adding an aldosterone receptor antagonist, using a dosing strategy based on renal function and serum potassium.

EPHESUS: Eplerenone is beneficial after MI with LV dysfunction

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival study (EPHESUS)[16] compared the effects of eplerenone and placebo on top of standard therapy in 6,632 patients with acute MI complicated by systolic LV dysfunction. More than 86% of the patients were receiving an ACE inhibitor or ARB, and 75% were on a

It seems reasonable to start eplerenone as early as feasible after an MI

beta-blocker. Seventy-five percent of the patients had an anterior infarction; the mean ejection fraction at randomization was 33%. Patients with diabetes did not need to have heart failure to be enrolled, in view of their higher risk.

Eplerenone was started at 25 mg daily and was titrated to 50 mg daily. The mean time from onset of the MI to randomization was 7.3 days.

Over a mean follow-up of 16 months, eplerenone reduced the total mortality rate by 15% (P = .008), cardiovascular death and hospitalizations by 13% (P = .002), cardiovascular death by 17% (P = .005), and sudden cardiac death by 21% (P = .03).

On the basis of these results, aldosterone receptor antagonists carry a class I recommendation in the ACC/AHA guidelines for patients after an MI with systolic LV dysfunction and heart failure (TABLE 1).[17]

In this situation, eplerenone may also be a cost-effective strategy for increasing years of life by commonly used criteria.[18]

When should eplerenone be started after an MI?

Eplerenone 50 mg is equivalent to spironolactone 25 mg

In EPHESUS, eplerenone was started between 3 and 14 days (mean 7.3 days) after the MI.[16] The death rate in the first 30 days, especially due to sudden cardiac death, was relatively high—4.6% in the placebo group and 3.2% in the eplerenone group (a 31% risk reduction with eplerenone, P = .004). The benefit of eplerenone was evident early, with a significant reduction in death from cardiovascular causes of 32% (P = .003) and a 36% reduction in episodes of sudden cardiac death by 30 days.[19] Therefore, it is reasonable to give this drug as early as feasible after an MI.

WHICH ALDOSTERONE RECEPTOR ANTAGONIST TO USE?

Eplerenone is similar to spironolactone in that it blocks the mineralocorticoid receptor, a member of the steroid receptor family. (Other members include the progesterone and androgen receptors.) Unlike spironolactone, however, eplerenone does not cause side effects such as gynecomastia, breast pain, impotence, or menstrual irregularities.[20] These side effects of spironolactone are due to its nonselectivity and interaction with other steroid receptors such as the progesterone and androgen receptors.

On the other hand, spironolactone is cheaper than eplerenone: the average wholesale price is $13.80 for a 30-day supply of generic spironolactone 25 mg, compared with $113.40 for eplerenone 25 mg.

At least in post-MI patients, it has been suggested that spironolactone be used initially and be switched to eplerenone if it causes these side effects. Without a comparative trial, it is difficult to be sure that this is a correct strategy, and there could be considerations other than those dictated by pharmacodynamics that could determine nonequivalence. For instance, if a patient suffers an event after stopping spironolactone because of a side effect, then it would have been far cheaper to give eplerenone in the first place. Clearly, the choice of agent must be individualized on the basis of patient and economic variables.

We would choose eplerenone 25 mg/day, increased to 50 mg if it is tolerated well and if potassium levels remain acceptable. If cost is a factor, spironolactone would be acceptable, starting at 25 mg every other day and increasing to 25 mg/day.

HYPERKALEMIA WITH ALDOSTERONE RECEPTOR ANTAGONISTS

Pathophysiologic basis of hyperkalemia

ACE inhibitors and ARBs decrease urinary excretion of potassium by reducing or blocking angiotensin II-mediated adrenal production of aldosterone[21]; aldosterone receptor antagonists decrease potassium excretion by preventing aldosterone from binding to its receptor.

In addition, three different abnormalities may be present to varying degrees in patients with systolic LV dysfunction that may contribute to decreased potassium excretion and hyperkalemia, ie:

- **Decreased distal tubular delivery of sodium.** The amount of sodium delivered to the distal tubule is a major factor that determines net potassium reabsorption, as the sodium-potassium exchange pump reabsorbs sodium in lieu of potassium. In severe heart failure,

TABLE 2

Risk factors for hyperkalemia with aldosterone receptor antagonists

Advanced age

Baseline hyperkalemia

Chronic kidney disease or low glomerular filtration rate, or both

Diabetes

Drug therapy

- Nonsteroidal anti-inflammatory drugs (both cyclo-oxygenase [COX]-1 and COX-2 inhibitors)
- Beta-blockers
- Cyclosporine, tacrolimus
- Potassium-sparing diuretics (amiloride, triamterene)
- Potassium supplements

when renal perfusion is markedly reduced and sodium is avidly reabsorbed in the proximal tubule, very little sodium is presented to the distal tubule.

- **Decreased aldosterone activity independent of drug use** in states such as normal aging and diabetes mellitus (hyporeninemic hypoaldosteronism).
- **Dysfunction of the cortical collecting tubule.** The distal tubule may be damaged in diabetes, tubulointerstitial disease, renal transplantation, obstructive uropathy, or amyloidosis. Some of these conditions may also be associated with hyporeninemic hypoaldosteronism and may further compound increases in serum potassium.

Decrease the spironolactone or eplerenone if potassium increases to 5.5 mmol/L

TABLE 2 lists risk factors for hyperkalemia and representative variables that all prescribing physicians should be aware of when adding spironolactone or eplerenone, especially on top of ACE inhibitors and beta-blockers.

Risk of hyperkalemia may be higher in the real world than in trials

In both RALES and EPHESUS, fewer than 2% of the more than 4,000 patients who received spironolactone or eplerenone developed severe hyperkalemia (serum potassium concentration ≥ 6.0 mmol/L), and nobody died of it.[9,16]

After the RALES data were published, however, several reports suggested that combining an aldosterone receptor antagonist with an ACE inhibitor or beta-blocker, or both, actually causes serious hyperkalemia fairly often, with a consequent increase in the risk of renal failure, need for hemodialysis, and death.[22]

Juurlink et al[23] analyzed all the prescriptions written for spironolactone in Ontario, Canada, and found that use of this drug increased fourfold after publication of the RALES data, but the rates of hospitalization for hyperkalemia and associated in-hospital deaths increased threefold.

If hyperkalemia is more common in the real world than in clinical trials such as RALES and EPHESUS, several reasons might explain this discrepancy:

- The trials excluded patients at higher risk of hyperkalemia (TABLE 2), who might receive spironolactone or eplerenone in real-world situations.
- Most physicians in practice use the serum creatinine concentration rather than the glomerular filtration rate (GFR) to assess renal function, even though serum creatinine is less accurate.
- Some physicians may fail to monitor serum potassium levels after starting the drug. In trials such as RALES, potassium was measured at baseline, 1 week, 1 month, and then every 3 to 6 months thereafter. The dosage should be reduced if serum potassium increases to 5.5 mmol/L or more.
- Some physicians may not pay attention to concomitant therapy that may influence potassium levels (TABLE 2).

Avoiding hyperkalemia with aldosterone receptor antagonists

TABLE 3 outlines an approach for reducing the risk of hyperkalemia when starting treatment with aldosterone receptor antagonists.

Eplerenone may pose a lower risk of hyperkalemia than spironolactone, if only because you can give a lower effective dose of eplerenone. The smallest available tablet of both drugs is 25 mg, but eplerenone 50 mg is approximately equal to spironolactone 25 mg.

We must emphasize, however, that not all patients with moderate renal dysfunction (GFR 30–60 mL/minute) and heart failure will tolerate an aldosterone receptor antago-

TABLE 3

Preventing hyperkalemia when prescribing aldosterone receptor antagonists

Stop drugs that interfere with potassium excretion, as well as potassium supplements and cyclo-oxygenase [COX]-1 and COX-2 inhibitors (which interfere with renin synthesis)

Be aware of the risk of hyperkalemia (eg, in older or diabetic patients)

Assess the glomerular filtration rate (GFR)
GFR = 186 × serum creatinine (in mg/dL)$^{-1.154}$ × age (in years)$^{-0.203}$ × 0.742 (if female) × 1.21 (if black)
(On-line calculator at **www.kidney.org/professionals/kdoqi/gfr_page.cfm**)

If GFR is ≥ 60 mL/minute
- Start spironolactone at 25 mg/day or eplerenone at 50 mg/day, and check potassium levels in 1 week
- If potassium increases to > 5.0 mmol/L, reduce the dosage of the drug and/or increase loop diuretic dosage; recheck potassium levels in 1 week
- If potassium levels are < 5.0, recheck potassium levels in 1 month and then in 3 to 6 months

If GFR is 30–60 mL/minute
- Start spironolactone at 25 mg every other day and titrate upward to 25 mg daily after 1 month if serum potassium is ≤ 5.0 mmol/L
- If eplerenone is used, the initial dose should be 25 mg/day
- Prescribe thiazide or loop diuretics if necessary for potassium excretion
- If potassium increases to > 5.5 mmol/L, discontinue the drug
- If potassium increases to ≥ 5.0 but is ≤ 5.5, try increasing the dosage of loop diuretic (in patients with heart failure); recheck potassium in < 7 days
- If potassium is < 5.0, the dose can be increased after 1 month in patients with potassium ≤ 5.0 mmol/L; recheck potassium frequently

Do not use spironolactone or eplerenone if GFR is < 30 mL/minute or baseline potassium is > 5.0 mmol/L

Prescribe thiazide or loop diuretics if necessary for potassium excretion

This approach assumes that the patient is already on stable doses of an angiotensin-converting enzyme inhibitor (or angiotensin II receptor blocker) and a beta-blocker.

nist, and that some of them will need to stop taking the drug because of hyperkalemia. The goal should not be to completely avoid hyperkalemia but to lower the cardiovascular risk in as many of these high-risk patients with heart failure and renal dysfunction as possible.

In patients with relatively normal renal function (GFR ≥ 60 mL/minute), spironolactone can be started at 25 mg daily or eplerenone at 25 to 50 mg daily with monitoring of serum potassium at 1 week, 1 month, and every 3 to 6 months thereafter, as was done in RALES and EPHESUS. However, in patients with a GFR of 30 to 60 mL/minute, more frequent potassium monitoring may be desirable.

Low risk of hypotension in patients with heart failure

Clinicians may hesitate to add an aldosterone receptor antagonist to the regimen for fear of causing hypotension. Many patients with chronic heart failure and systolic LV dysfunction or with heart failure and systolic LV dysfunction after an MI have a systolic blood pressure of 100 mm Hg or less due to their LV dysfunction or to use of an ACE inhibitor or ARB and a beta-blocker.

Although hypotension may occur after adding a beta-blocker to an ACE inhibitor, or an ARB to an ACE inhibitor, this does not seem to be the case when adding spironolactone or eplerenone. In both RALES and EPHESUS there was no significant decrease in blood pressure when adding these drugs to an ACE inhibitor or a beta-blocker, or both.

Can other MI patients benefit from these drugs?

Although EPHESUS included post-MI patients with systolic LV dysfunction and heart failure symptoms (except for diabetic patients), the signs of heart failure in most post-MI patients (including those in EPHESUS) were transient and often disappeared

after the administration of a diuretic.

Furthermore, Hayashi et al[24] found that patients randomized to receive spironolactone one day after having a first anterior MI (immediately after undergoing primary angioplasty) had less ventricular remodeling and collagen synthesis at 30 days, without any significant adverse effects. In this study, the baseline LV ejection fraction was approximately 47%, and patients were not required to have evidence of heart failure.

Thus, perhaps an aldosterone receptor antagonist could be given to patients with an anterior MI regardless of LV ejection fraction or signs of heart failure. A definitive recommendation for these drugs in all patients with an anterior MI regardless of LV ejection fraction or signs of heart failure will, however, require confirmation by a large-scale prospective randomized study in which rates of death and hospitalization for heart failure are evaluated.

We advise against giving these drugs to patients with an inferior MI or MI without ST-segment elevation who have no signs of heart failure or systolic LV dysfunction at this time.

FUTURE INDICATIONS FOR ALDOSTERONE RECEPTOR ANTAGONISTS

Perhaps the most important role of these drugs in heart failure will be not in therapy but in prevention

Asymptomatic systolic LV dysfunction

Although asymptomatic systolic LV dysfunction seems like a logical extension of the indications for aldosterone receptor antagonists, we cannot recommend this strategy at present, since there are no data from randomized controlled trials to support it. However, the effect of these drugs on a variety of surrogates of benefit in patients with mild systolic LV dysfunction, as outlined previously, is promising and suggests a potential benefit in these patients.

In theory, these drugs may also help in preventing and treating heart failure associated with primary valvular disease such as mitral regurgitation, aortic regurgitation, or aortic stenosis in view of their effects on collagen, ventricular hypertrophy, and ventricular remodeling.

Diastolic dysfunction

Preliminary studies have suggested that aldosterone receptor antagonists improve diastolic function[25] and reduce LV hypertrophy.[26] Therefore, they may in theory help patients with heart failure with diastolic dysfunction, in which systolic LV function is preserved (LV ejection fraction > 40%). The Trial of Aldosterone Antagonist Therapy in Adults With Preserved Ejection Fraction Congestive Heart Failure (TOPCAT), a large-scale prospective randomized study organized by the National Heart, Lung, and Blood Institute, is assessing the effect of spironolactone on rates of death and hospitalization for heart failure in patients with diastolic dysfunction treated with standard therapy.

On the other hand, the CHARM-Preserved study[27] found equivocal results when an ARB was added in patients with heart failure and diastolic dysfunction. We would therefore suggest that an aldosterone receptor antagonist not be used in this situation until the results and the risk-benefit ratio of this strategy is determined in this trial.

Aldosterone receptor antagonists may pose more risk and offer less benefit for patients with heart failure with diastolic dysfunction than for those with systolic dysfunction. For example, in patients with diastolic dysfunction, the effect of these drugs on ventricular remodeling may not be as important. Further, these patients are often older than those with systolic dysfunction, and they have a higher incidence of hypertension, diabetes mellitus, and renal dysfunction, predisposing them to hyperkalemia.

Control of hypertension and regression of LV hypertrophy

Perhaps the most important role of aldosterone receptor antagonists in heart failure will not be in therapy but rather in prevention. Spironolactone and eplerenone have been shown to reverse LV hypertrophy in patients with essential hypertension, which is a major risk factor for the development of heart failure and cardiovascular death.[28,29] They have also been shown to be particularly effective in patients with refractory hypertension.

Nishizaka and colleagues[30] found that in patients with essential hypertension resistant to three or more antihypertensive drugs (usually including a diuretic, an ACE inhibitor or

ARB, and a calcium channel blocker or beta-blocker), adding spironolactone 12.5 to 25 mg daily lowered blood pressure by a mean of 22/11 mm Hg, regardless of their aldosterone-renin ratio.

Atherosclerosis and acute coronary syndromes

There is emerging evidence that an aldosterone receptor antagonist alone or in combination with an ACE inhibitor or ARB could help prevent atherosclerosis from progressing.

In a study in lipid-fed rabbits,[31] eplerenone improved endothelial function by decreasing the generation of reactive oxygen species through a mechanism dependent on nicotinamide adenine dinucleotide phosphate (NADPH). These changes in vascular tone appear to favorably modulate atherosclerosis.

In a study in eplerenone-treated mice,[32] atherosclerotic lesion area in the aorta was significantly reduced by 35% compared with untreated mice.

Aldosterone regulates synthesis of plasminogen activator-inhibitor 1 (PAI-1) in cell cultures and in vivo, and spironolactone has been shown to alter the balance between PAI-1 and tissue plasminogen activator.[33,34]

In view of these data and the effects of eplerenone on restenosis,[35] aldosterone receptor antagonists may potentially be beneficial in patients with acute coronary syndromes.[36]

REFERENCES

1. **Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators.** A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001; 345:1667–1675.
2. **McMurray JJ, Ostergren J, Swedberg K, et al; CHARM Investigators and Committees.** Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003; 362:767–771.
3. **Hunt SA, Baker DW, Chin MH, et al; American College of Cardiology; American Heart Association.** ACC/AHA guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and management of heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005; 112:e154–235.
4. **Young MJ, Funder JW.** Mineralocorticoid receptors and pathophysiological roles for aldosterone in the cardiovascular system. J Hypertens 2002; 20:1465–1468.
5. **Pitt B, Stier CT Jr, Rajagopalan S.** Mineralocorticoid receptor blockade: new insights into the mechanism of action in patients with cardiovascular disease. J Renin Angiotensin Aldosterone Syst 2003; 4:164–168.
6. **Rajagopalan S, Pitt B.** Aldosterone antagonists in the treatment of hypertension and target organ damage. Curr Hypertens Rep 2001; 3:240–248.
7. **McKelvie RS, Yusuf S, Pericak D, et al.** Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. Circulation 1999; 100:1056–1064.
8. **Pitt B, Zannad F, Remme WJ, et al.** The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341:709–717.
9. **Krum H, Roecker EB, Mohacsi P, et al; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group.** Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. JAMA 2003; 289:712–718.
10. **Swedberg K, Cleland J, Dargie H, et al; Task Force for the Diagnosis and Treatment of Chronic heart Failure of the European Society of Cardiology.** Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic heart Failure of the European Society of Cardiology. Eur Heart J 2005; 26:1115–1140.
11. **Cicoira M, Zanolla L, Rossi A, et al.** Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol 2002; 40:304–310.
12. **Zannad F, Alla F, Dousset B, Perez A, Pitt B.** Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the Randomized Aldactone Evaluation Study (RALES). RALES Investigators. Circulation 2000; 102:2700–2706.
13. **MacFadyen RJ, Barr CS, Struthers AD.** Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. Cardiovasc Res 1997; 35:30–34.
14. **Yee KM, Pringle SD, Struthers AD.** Circadian variation in the effects of aldosterone blockade on heart rate variability and QT dispersion in congestive heart failure. J Am Coll Cardiol 2001; 37:1800–1807.
15. **Farquharson CA, Struthers AD.** Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. Circulation 2000; 101:594–597.
16. **Pitt B, Remme W, Zannad F, et al.** Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003; 348:1309–1321.
17. **Antman EM, Anbe DT, Armstrong PW, et al.** ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). J Am Coll Cardiol 2004; 44:E1–E211.
18. **Weintraub WS, Zhang Z, Mahoney EM, et al.** Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure. Circulation 2005; 111: 1106–1113
19. **Pitt B, White H, Martinez F, et al; EPHESUS Investigators.** Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. J Am Coll Cardiol 2005; 46:425–431.
20. **Delyani JA.** Mineralocorticoid receptor antagonists: the evolution of utility and pharmacology. Kidney Int 2000; 57:1408–1411.

21. **Palmer BF.** Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med 2004; 351:585–592.
22. **Schepkens H, Vanholder R, Billiouw JM, Lameire N.** Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. Am J Med 2001; 110:438–441.
23. **Juurlink DN, Mamdani MM, Lee DS, et al.** Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004; 351:543–551.
24. **Hayashi M, Tsutamoto T, Wada A, et al.** Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. Circulation 2003; 107:2559–2565.
25. **Grandi AM, Imperiale D, Santillo R, et al.** Aldosterone antagonist improves diastolic function in essential hypertension. Hypertension 2002; 40:647–652.
26. **Pitt B, Reichek N, Metscher B, et al.** Efficacy and safety of eplerenone, enalapril, and eplerenone/enalapril combination therapy for essential hypertension and left ventricular hypertrophy: The 4E Study [abstract]. In: American College of Cardiology, Atlanta, GA; 2002.
27. **Yusuf S, Pfeffer MA, Swedberg K, et al.** Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003; 362:772–776.
28. **Sato A, Suzuki Y, Saruta T.** Effects of spironolactone and angiotensin-converting enzyme inhibitor on left ventricular hypertrophy in patients with essential hypertension. Hypertens Res 1999; 22:17–22.
29. **Pitt B, Reichek N, Willenbrock R, et al.** Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. Circulation 2003; 108:1831–1838.
30. **Nishizaka MK, Zaman MA, Calhoun DA.** Efficacy of low-dose spironolactone in subjects with resistant hypertension. Am J Hypertens 2003; 16:925–930.
31. **Rajagopalan S, Duquaine D, King S, Pitt B, Patel P.** Mineralocorticoid receptor antagonism in experimental atherosclerosis. Circulation 2002; 105:2212–2216.
32. **Keidar S, Hayek T, Kaplan M, et al.** Effect of eplerenone, a selective aldosterone blocker, on blood pressure, serum and macrophage oxidative stress, and atherosclerosis in apolipoprotein E-deficient mice. J Cardiovasc Pharmacol 2003; 41:955–963.
33. **Brown NJ, Kim KS, Chen YQ, et al.** Synergistic effect of adrenal steroids and angiotensin II on plasminogen activator inhibitor-1 production. J Clin Endocrinol Metab 2000; 85:336–344.
34. **Sawathiparnich P, Kumar S, Vaughan DE, Brown NJ.** Spironolactone abolishes the relationship between aldosterone and plasminogen activator inhibitor-1 in humans. J Clin Endocrinol Metab 2002; 87:448–452.
35. **Ward MR, Kanellakis P, Ramsey D, Funder J, Bobik A.** Eplerenone suppresses constrictive remodeling and collagen accumulation after angioplasty in porcine coronary arteries. Circulation 2001; 104:467–472.
36. **Meier DJ, Pitt B, Rajagopalan S.** Eplerenone: will it have a role in the treatment of acute coronary syndromes? Curr Cardiol Rep 2004; 6:259–263.

ADDRESS: *Sanjay Rajagopalan, MD, One Gustave Levy Place, Box 1030, New York, NY 10029; e-mail sanjay.Rajagopalan@mssm.edu.*