The presence of heart failure or LV systolic dysfunction in the setting of acute myocardial infarction is associated with poor prognosis. Aldosterone is an important downstream mediator of the renin-angiotensin-aldosterone system which, in the post-acute myocardial infarction setting, promotes myocardial collagen deposition, myocardial fibrosis, apoptosis, endothelial dysfunction, ventricular remodeling, and heart failure, with attendant increased morbidity and mortality. Extending the findings from the Randomized Aldactone Evaluation Study (RALES) in chronic heart failure patients, the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) demonstrated that the selective aldosterone blocker eplerenone offered a significant survival benefit, attenuated the progression of heart failure, and prevented sudden cardiac death when used in addition to optimal medical therapy. The current evidence-based guidelines suggest that aldosterone blockade should be an integral component of heart failure therapy to improve outcomes in this high-risk population.

Key Words: Acute myocardial infarction • Apoptosis • Heart failure • Renin-angiotensin-aldosterone system • Ventricular remodeling

INTRODUCTION

Acute myocardial infarction remains a significant public health problem worldwide. Therapies for acute myocardial infarction (MI) continue to evolve, contributing to improved long-term survival benefits in patients with MI. Despite improved therapies and process of care, left ventricular (LV) systolic dysfunction (left ven-

tricular ejection fraction [LVEF] < 40%) and heart failure development are common sequelae of acute MI and continue to be associated with increased mortality. The renin-angiotensin-aldosterone system (RAAS) is upregulated in the setting of LV dysfunction or heart failure; thus, blocking RAAS has proven to be one of the most successful therapeutic strategies for improving outcomes in these patients. Pharmacologic inhibitors of this system that have proven value in improving outcomes in patients following acute MI include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and aldosterone antagonists. Significant improvement in morbidity and mortality was demonstrated with the addition of aldosterone blockers in the Randomized Aldactone Evaluation Study (RALES) and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). These studies highlighted the role of aldosterone blockade in ameliorating risk in patients with heart failure (Table 1). Aldosterone is the major mineralocorticoid hormone secreted by the adrenal cortex in response to angiotensin II
Table 1.

<table>
<thead>
<tr>
<th>Study, year</th>
<th>RALES Trial Pitt B et al., 1999</th>
</tr>
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<tbody>
<tr>
<td>Study design</td>
<td>Active therapeutic dosage</td>
</tr>
<tr>
<td>Multicenter, international randomised, double-blind placebo-controlled trial</td>
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<td></td>
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<tr>
<td>Baseline Information</td>
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<td>Age (years)</td>
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<tr>
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</tr>
<tr>
<td>Placebo group (N = 841)</td>
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<tr>
<td>Secondary end-points</td>
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<tr>
<td>Death from cardiac causes, hospitalization for cardiac causes</td>
<td></td>
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<tr>
<td>Combined incidence of death from cardiac causes or hospitalization for cardiac causes and a change in NYHA class</td>
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</tr>
<tr>
<td>Results</td>
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<tr>
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<tr>
<td>Secondary outcome: Death from cardiac causes or hospitalization for cardiac causes (combined end-points): 32% reduction (RR = 0.68, 95% confidence intervals: 0.59-0.78, p &lt; 0.001)</td>
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Study, year | EPHESUS Trial Pitt B et al., 2003 |
<table>
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<tr>
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<tr>
<td>Secondary end-points</td>
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</tr>
<tr>
<td>Death from cardiovascular event, including heart failure, recurrent acute myocardial infarction, stroke, or ventricular arrhythmia.</td>
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</tr>
<tr>
<td>Results</td>
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<tr>
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</tr>
<tr>
<td>Primary outcome: Cardiovascular death or hospitalization for cardiovascular events: 13% reduction (RR = 0.87, 95% confidence intervals: 0.79-0.95, p = 0.002)</td>
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<tr>
<td>Secondary outcome: Hospitalization for cardiovascular events: 13% reduction (RR = 0.85, 95% confidence intervals: 0.74-0.99, p = 0.002)</td>
<td></td>
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<tr>
<td>Secondary outcome: 41% improvement of NYHA in treatment group compared to 33% improvement in the placebo group, p &lt; 0.001 by Wilcoxon test</td>
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ACEI, angiotensin-converting enzyme inhibitors; BB, beta-blocker; LVEF, left ventricular ejection fraction; HF, heart failure; NYHA, New York Heart Association functional class; RR, relative risk.
stimulation, hyperkalemia, and corticotrophin (Figure 1). It is an essential neurohormonal mediator of the RAAS regulation of fluid and potassium balance. Additionally, aldosterone stimulates fibroblast growth and synthesis of fibrillar collagen and may play a role in cardiac and vascular fibrosis and ventricular remodeling. Aldosterone blockers are a class I recommendation for patients with chronic heart failure and for patients with LV systolic dysfunction or heart failure following MI in the current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines.

Our review focuses on the possible mechanisms involved in the benefit of aldosterone blockade in patients with heart failure and LV systolic dysfunction following MI. In addition, practical approaches and precautions will be discussed for the use of these agents to provide optimal evidence-based care.

**Aldosterone and cardiovascular pathophysiology in development of heart failure following acute myocardial infarction**

It is believed that aldosterone is produced in various tissues, including the myocardium, brain, and vascular tissue in addition to the adrenal cortex, and has paracrine actions beyond the kidney (Figure 1). Aldosterone may be a mediator of adverse vascular and myocardial remodeling and contributes to increased inhibition of nitric oxide synthesis, endothelial dysfunction and myocardial stiffness. Systemic and local cardiac activation of RAAS promotes hypertrophy of cardiac myocytes, marked increase in tissue aldosterone, increased perivascular interstitial fibrosis, and LV dilatation (Figure 2).

Following acute MI, increased activity of matrix metalloproteinases (MMPs) promotes the formation of new collagen that is poorly cross-linked while breaking down existing collagen. Poorly cross-linked collagen

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**Figure 1.** Aldosterone and the renin-angiotensin-aldosterone system (RAAS). Angiotensinogen from the liver is the precursor of angiotensin I and II following consecutive cleavage by renin and angiotensin-converting enzyme (ACE). Aldosterone is produced by the zona glomerulosa cells of the adrenal cortex in response to angiotensin II, hyperkalemia, and corticotrophin (ACTH). Aldosterone exerts its primary actions on the renal collecting tubules, but its paracrine activities are far flung and are upregulated in the post-myocardial infarction setting, with deleterious consequences. ACE: angiotensin converting enzyme; K⁺: potassium.
contributes to the side-to-side slippage of myocytes and thus purportedly contributes to LV remodeling after acute MI\textsuperscript{12} (Figure 2). Activation of adrenergic mediators and RAAS plays an important contributory role in the pathophysiology of post-MI LV remodeling. Increase in myocardial angiotensin II increases the production of reactive oxygen species and augments apoptosis via increased cytosolic calcium.\textsuperscript{12} Raised concentrations of circulating angiotensin II stimulates increased renal re-absorption of sodium and water subsequently leading to an increased volume load on the heart and augmenting stretch-induced abnormalities. Aldosterone is another important component of the RAAS and its production is partially mediated by angiotensin II via aldosterone synthase.\textsuperscript{13} The existence and upregulation of aldosterone synthase in the heart has been reported in rats with MI, suggesting local cardiac production of aldosterone in patients with MI.\textsuperscript{14} It has also been shown that plasma aldosterone is extracted by the heart following MI and correlates with increased LV end-diastolic volume index at one month.\textsuperscript{15} Furthermore, high plasma aldosterone levels were independently associated with adverse clinical outcomes including heart failure and mortality among patients referred for primary percutaneous intervention after acute myocardial infarction.\textsuperscript{16,17} The combination of fibrosis and increased cell death post-MI leads to a disorganized, poorly contracting myocardium\textsuperscript{18} and may represent mechanisms by which aldosterone promotes remodeling of the infarcted heart (Figure 2).

Aldosterone inhibition has been shown to reduce post-infarction collagen synthesis and progressive LV dilation in patients with MI and heart failure.\textsuperscript{19} Aldosterone inhibition by spironolactone reduces the plasma level of procollagen type III amino-terminal peptide (PIIINP), an indirect marker of myocardial collagen

\textbf{Figure 2.} Post-myocardial infarction aldosterone pathophysiology. In the post-myocardial infarction (MI) setting, aldosterone’s actions extend to the fibroblast, the cardiac myocyte, and the endothelium, triggering a cascade that influences ventricular and arterial remodeling, cardiac myocyte electrical stability, and atherothrombotic events — that can result increased cardiovascular morbidity and mortality. Aldosterone antagonists can block several of these maladaptive responses, with measurable positive clinical impact. ACE: angiotensin-converting enzyme; K, potassium; LV: left ventricle; K, potassium; NADPH: nicotinamide adenine dinucleotide phosphate; NE: norepinephrine.

\textit{Acta Cardiol Sin} 2010;26:203–15

206
turnover, in patients with heart failure. High levels of plasma PIIINP, in relation to ventricular fibrosis, were reportedly associated with poor LV function, remodeling, and prognosis. Suppression of such markers immediately following acute MI was also observed to be associated with further prevention of ventricular remodeling. Zannad et al, in a substudy of RALES, emphasized this importance by demonstrating that the beneficial effects of aldosterone blockade with spironolactone in RALES may be secondary to its ability to suppress cardiac collagen synthesis.

Some remodeling after myocardial infarction is independent of angiotensin-II blockade, probably because of persistent cardiac aldosterone synthesis. Blockade of the RAAS with ACEIs and ARBs have been shown to incompletely suppress aldosterone levels over the long-term, termed as aldosterone escape. Aldosterone escape happens even with the use of higher doses of ACEIs or ARBs or their use in combination. Although the mechanisms of aldosterone escape are poorly understood, this phenomenon could be secondary to continued production of aldosterone from angiotensin independent pathways such as cardiac myocytes, due to production from alternate chymase pathway, or by direct stimulation by endothelin. Additive benefit in LV remodeling was also reported when eplerenone was added to ACEIs in post-MI animal model. Given the significant role of aldosterone in post-MI pathophysiology, its blockade with agents such as spironolactone or eplerenone beyond ACE inhibition is essential for continued benefit.

The stimulation of the MR by aldosterone occurs through a genomic pathway, resulting in transcription and translation of effector proteins. These effects take hours to days to generate a biological effect. It has been shown that aldosterone can actually induce a wide range of effects through membrane receptors other than traditional MR-dependent in epithelial (such as kidney) and non-epithelial tissue (such as vasculature and heart) in a nongenomic manner. Regulation via classic genomic pathway by activating nuclear receptor directly bound to a hormone response element (HRE) and other non-HRE related pathways have been described more recently in non-epithelial cells (Figure 3). These nongenomic effects of aldosterone can occur within minutes of aldosterone exposure, unlike the genomic pathway, which demonstrates a lag time and some have been observed to occur via activation of the pertussis toxin-sensitive heterotrimeric G proteins via Akt-signaling.
Figure 3. Aldosterone signaling in the primary epithelial cells (A) and cardiomyocytes (B). Left Panel of A: Aldosterone signaling in the primary epithelial cell of the collecting duct via the classical genomic pathway. Aldosterone regulates sodium excretion through mineralocorticoid receptor (MR)-dependent genomic effects in the distal nephron of the kidney. Aldosterone binds to the inactive cytosolic MR of the target cell, resulting in a ligand-activated MR that is translocated to the nucleus. Here, it binds to hormone-response elements (HRE) within the regulatory region of target gene promoters. MR induces serum- and glucocorticoid-inducible kinase-1 (Sgk-1) gene expression and triggers a cascade involving epithelial sodium channel (ENaC). This results in sodium and water absorption with concomitant potassium excretion, leading to volume expansion and hypertension. Sgk-1 phosphorylates Nedd4-2, a ubiquitin-protein ligase that targets ENaC for degradation. In response to aldosterone, corticosteroid hormone-induced factor (CHIF), a small transmembrane protein, enhances Na,K-ATPase activity and affinity for sodium. Similarly, aldosterone is necessary for the expression of small modulatory G protein (Ras) which promotes increased Na⁺ transport. Right Panel of A: Rapid signaling through nongenomic MR-dependent and MR-independent mechanisms. Nongenomic aldosterone actions have been described for an increasing number of epithelial and nonepithelial cell types. MR-dependent mechanisms can proceed through HRE-independent processes that generally involve rapid activation of second messenger pathways. MR-independent pathways may be mediated via transmembrane receptors distinct from the cytosolic MR. These may involve rapid flux of cytosolic calcium (Ca²⁺) and dose-dependent phosphorylation (P) via protein kinases downstream. B, aldosterone-dependent pathways via MR as well as an MR-independent cellular signaling pathway exist within cardiac myocytes and fibroblasts. Through such genomic and non-genomic pathways, aldosterone stimulates elastogenesis and degradation of the extracellular matrix. A: aldosterone; Akt: a serine-threonine protein kinase encoded by the Akt gene; c-Src: cellular sarcoma family of proto-oncogenic tyrosine kinases; ET-1: endothelin-1 isoform; Gα, Gβ, and Gγ: three main G-protein-mediated signaling pathways; GPCR: G-protein coupled receptor (transmembrane); HRE: hormone-responsive element; IGF-1: insulin-like growth factor 1; IRS-1: insulin receptor substrate 1; MMPs: matrix metalloproteinases; MR: mineralocorticoid receptor; PI 3-kinase: phosphatidylinositol 3-kinase; PTK: protein tyrosine kinases; TGF-β1: transforming growth factor beta 1.
pathway. Instead, involvement of amiloride-sensitive epithelial sodium channel (ENaC), representing the principle rate-limiting step controlling for sodium flux (nuclear actions), and some other rapid, non-genomic (non-nuclear actions) pathways were observed in the collecting duct of distal renal tubules (Figure 3). Which biological effects of aldosterone are mediated through a genomic or a non-genomic pathway in these different tissues is not completely understood. The non-genomic effects of aldosterone are thought to be mediated by membrane receptors other than the traditional MR and do not involve transcription or protein synthesis.

**BENEFICIAL EFFECTS AND CLINICAL APPLICATIONS OF ALDOSTERONE BLOCKADE**

A mortality benefit of aldosterone blockade was demonstrated in two landmark trials, EPHESUS and RALES (Table 1). In RALES, the aldosterone blocker spironolactone was added to standard therapy in selected patients with symptomatic chronic heart failure (New York Heart Association class III-IV; mean LVEF, 25.6% ± 7%) who remained symptomatic despite optimal medical treatment. The dosage of spironolactone used was low, at 25 mg/day, and could be increased to 50 mg/day if there was progression of heart failure or decreased to 25 mg/day if hyperkalemia developed. Addition of spironolactone reduced mortality by 30% (p < 0.001), primarily due to a 29% (p = 0.02) reduction in sudden cardiac deaths and a 35% reduction in hospitalization for heart failure (p < 0.001). The reduction in mortality and hospitalization for heart failure were observed after two to three months of treatment and persisted throughout the study (mean follow-up, 24 months).

In contrast, the EPHESUS study was conducted in patients with acute MI complicated by evidence of LV systolic dysfunction (LVEF < 40%) and signs of heart failure (presence of pulmonary rales or congestion) or the presence of a third heart sound. In the EPHESUS trial the addition of eplerenone, a selective aldosterone blocker, resulted in a 15% (p = 0.008) reduction in total mortality, a 17% (p = 0.005) reduction in cardiovascular mortality and reduced mortality within one month, predominantly due to a 21% (p = 0.02) reduction in sudden cardiac death in patients already receiving optimal adjunctive therapy including coronary reperfusion, aspirin, statins, ACEI or ARB, and β-blocker.

Both aldosterone blockers, spironolactone and eplerenone, are approved for use in the United States in patients with heart failure and LV systolic dysfunction or in patients following MI and with symptomatic heart failure. Eplerenone has greater selectivity for the MR and has a lower affinity for androgen receptors compared to spironolactone. Due to the lower affinity for the androgen receptors, the incidence of gynecomastia and impotence among men in the eplerenone group was no greater than that in the placebo group.

**Clinical application and patient selection**

The results from the EPHESUS trial provided a strong rationale for routine incorporation of aldosterone blocker in the management of patients following acute myocardial infarction without significant renal dysfunction or hyperkalemia, who are receiving an ACEI or ARB, have an LVEF ≤ 40%, and have either symptomatic heart failure or diabetes. The ACC/AHA guidelines for patients with acute MI include a class IA recommendation for long-term aldosterone blockade in this population. In RALES, spironolactone was initiated at a dose of 25 mg/day and then increased to 50 mg/day after 8 weeks if the patient showed signs or symptoms of progressive heart failure without hyperkalemia or renal insufficiency. In the EPHESUS trial, eplerenone therapy was also begun at 25 mg/day and increased to a maximum dose of 50 mg/day after 4 weeks. The significant beneficial effects of eplerenone were seen as early as thirty days post randomization, although patients were not titrated to the target dose of 50 mg/day until after thirty days, a 32% risk reduction in cardiovascular mortality and a 36% risk reduction in sudden cardiac deaths were observed with the use of eplerenone by 30 days. This is particularly noteworthy as the risk for sudden death is highest during the first thirty days after MI among patients with LV dysfunction, heart failure or both.

This underscores the importance of early initiation of aldosterone blockade in patients following MI and with heart failure. Although eplerenone’s target dose specified in the EPHESUS trial was 50 mg/day, a recent study by Banas et al. showed that patients unable to achieve the specified target dose in the EPHESUS trial
experienced significant reductions in the endpoints with a dose of 25 mg/day or even 25 mg every other day.

Although eplerenone and spironolactone both block the binding of aldosterone to the MR and spironolactone is less expensive than eplerenone, they are different drug molecules and may not be completely interchangeable. As discussed above, eplerenone has fewer endocrine-related adverse effects due to its lower affinity for androgen receptors. The potency of the dose of eplerenone (25-50 mg/day) in EPHESUS, with respect to aldosterone blockade, may be relatively less than the dose of spironolactone (25-50 mg/day) in RALES. This may lead to increased risk of hypotension or hypokalemia with use of spironolactone at starting doses of 25 mg/day in these patients. Regardless of the choice of aldosterone blocker, current evidence-based guidelines coupled with the results from the EPHESUS trial provide a strong rationale for the routine incorporation of these agents in management of patients with acute MI complicated with heart failure and LV systolic dysfunction. These agents should be used in conjunction with optimal conventional therapy for patients with acute MI and heart failure including coronary reperfusion, aspirin, statins, ACEIs or ARBs, and a β-blocker.

For evidence-based therapies to have a wider applicability, it is desirable that they must be cost-effective. A recent cost-effective analysis by Weintraub et al. demonstrated that the use of eplerenone compared to placebo in EPHESUS resulted in an incremental cost-effectiveness ratio of $13,718 per quality-adjusted life-year gained. This was well below the common benchmark ceiling ratio of $50,000 per life-year gained and suggested that eplerenone use compared with placebo in the treatment of heart failure after acute myocardial infarction is effective in reducing mortality and is cost-effective in increasing years of life by commonly used criteria.

**Further challenges and directions**

It is possible although still unproven that the addition of aldosterone receptor blockers will be beneficial in patients with asymptomatic LV systolic dysfunction following MI or in patients with preserved systolic function heart failure. The ongoing NHLBI-sponsored Treatment of Preserved Cardiac function heart failure with an Aldosterone anTagonist (TOPCAT) trial will determine whether the additional of spironolactone to standard therapy will benefit patients with heart failure and normal ejection fraction. Although suppression of aldosterone seems like a logical therapeutic extension in this population at the present time, this strategy cannot be recommended because of lack of data from randomized control trials. Patients with high-risk MI with heart failure or LV systolic dysfunction are at high risk for sudden cardiac death. Implantable cardioverter-defibrillators are effective in reducing long-term mortality in chronic heart failure patients with severe LV systolic dysfunction, but are ineffective in reducing total mortality when used early post MI. Thus a combination approach of aldosterone blockade with implantable cardioverter defibrillators for more effective prevention of sudden cardiac deaths in patients with persistent severe LV systolic dysfunction post-MI seems intriguing which will need evaluation in a prospective randomized trial.

**RISK OF HYPERKALEMIA FROM ALDOSTERONE RECEPTOR BLOCKERS**

Both eplerenone and spironolactone may cause hyperkalemia, and aldosterone blockade is contraindicated if the serum potassium level is greater than 5.5 mEq/L at initiation or if the estimated glomerular filtration rate is less than 30 mL/min. Aldosterone facilitates sodium-potassium exchange by the cells of the cortical collecting tubule, and its blockade decreases potassium excretion. Aldosterone blockers may also reduce glomerular filtration rate and sodium delivery to distal nephrons, further impairing sodium potassium exchange and potassium excretion. Advancing age and diabetes mellitus are associated with decreased aldosterone activity (hyporeninemic hypoaldosteronism state) and a higher risk of renal impairment in which may predispose them to develop hyperkalemia. The patients on spironolactone in the RALES trial experienced 1% absolute increase in the risk of developing serious hyperkalemia (2% in spironolactone group compared to 1% in placebo group; statistically not significant). Patients who developed serious hyperkalemia were also more likely to have a baseline potassium level greater than 5.5 mEq/L. Similarly in the EPHESUS trial, a similar increased risk of serious hyperkalemia was found in the eplerenone group (5.5% in the eplerenone group compared to 3.9%...
in the placebo group, *p* = 0.002). A recent report, however, indicated that with standard eplerenone therapy of 25-50 mg/day in post-MI patients, no excess risk of hyperkalemia (≥ 6.0 mEq/L) was seen when serum potassium level was periodically monitored.44

In the EPHESUS and the RALES trial, the reported incidence of hyperkalemia was considerably low and no deaths were attributed to hyperkalemia, however, the use of spironolactone in clinical practice has been associated with a relatively high incidence of serious hyperkalemia resulting in renal failure, need for dialysis, and death.45 Higher rates of hyperkalemia in clinical practice observed after the publication of RALES could be attributed to patients being older than those entered into RALES or EPHESUS, having higher pre-treatment creatinine levels, perhaps not having had serial potassium monitoring with dose adjustment for serum potassium > 5.5 mmol/l or discontinuation for serum potassium > 6.0 mmol/l. Another possibility may be due to higher doses of spironolactone exposure in clinical practice than in RALES trial as larger doses of spironolactone may induce marked diuresis, volume depletion, and renal impairment.41 Serum creatinine poorly reflects renal function and is not, by itself, an accurate index of glomerular filtration rate. Urinary creatinine excretion is lower in patients with chronic kidney disease, and can lead to systematic overestimation of glomerular filtration rate if used as the sole estimate of renal function. Thus over-reliance on creatinine levels in clinical practice to estimate renal function increases the risk of serious hyperkalemia when using aldosterone blockers. Other risk factors for hyperkalemia in patients receiving aldosterone blockers include the concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 enzyme inhibitors (both suppress renin release), volume depletion status, concomitant usage of β-blockers (blocks the action of renin), heparin preparations (imparts aldosterone secretion), ACEI or ARBs (blocks the action of angiotensin II), cyclosporine and other potassium sparing diuretics (amiloride, triamterene).27

**ALDOSTERONE BLOCKER THERAPY: IMPORTANT ISSUES IN PATIENT CARE**

Appropriate patient selection, timing of aldosterone blocker initiation, history of hyperkalemia or prevailing hyperkalemia, renal function and current medication use are all important factors to be considered in avoiding serious hyperkalemia from aldosterone blockade and affording optimal care to the post MI patient (Figure 4). Careful attention should be paid to elderly patients, those with a history of diabetes mellitus, and patients on potassium supplements, ACEIs or ARBs before initiating therapy with aldosterone blockers.

For both RALES and EPHESUS, patients were excluded if serum creatinine levels exceeded 2.5 mg per dL, but few patients were actually enrolled with serum creatinine levels above 1.5 mg per dL. Since serum creatinine is not an accurate index of renal function, we recommend estimating the glomerular filtration rate using the four-component Modification of Diet in Renal Disease (MDRD) study equation incorporating age, race, sex, and serum creatinine level before initiating aldosterone blockade.46 For the MDRD equation: Estimated glomerular filtration rate (mL/min per 1.73 m²) = 186 × (plasma creatinine [mg/dL])⁻¹.¹¹⁵⁴ × (age [years])⁻⁰.²⁰³ × (0.₇₄₂ [if female]) × (1.₂¹₀ [if African American]).

Serum potassium should be measured and aldosterone blockers should not be administered to patients with baseline serum potassium in excess of 5.0 mEq/L or estimated glomerular filtration rate less than 30 mL/min per 1.73 m², particularly in the presence of insulin-requiring diabetes mellitus. Careful assessment of the volume status is essential, and hypovolemia and hyperkalemia should be corrected before aldosterone blockade is initiated. Nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 enzyme inhibitors and potassium supplementation should be avoided, and patients should be counseled to avoid high potassium-containing foods.8,9 An initial dose of spironolactone 12.5 mg or eplerenone 25 mg is recommended, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg if appropriate (Figure 4).8

Although both eplerenone and spironolactone have a relatively weak diuretic effect, they may act synergistically with other diuretics to cause fluid depletion, further increasing the risk of renal dysfunction and hyperkalemia. Close monitoring of serum potassium is required; potassium levels and estimated glomerular filtration rate should be rechecked within 3 days and again at 1 week after initiation of aldosterone blockers. Subse-
quent monitoring should be dictated by the general clinical stability of renal function and fluid status but should occur at least monthly for the first 3 months and every 3 months thereafter. Any changes to the drug dose or addition or change to the ACEIs and ARBs’ dosage must prompt further monitoring of the potassium levels and renal function and should occur one week after any changes are made. The development of potassium levels in excess of 5.5 mEq/L, hypotension or worsening renal impairment should generally trigger either discontinuation or at least a 50% dose reduction of the aldosterone blocker, and a review of concomitant medications, such

Figure 4. Aldosterone blocker therapy. treatment with aldosterone receptor antagonists requires careful patient selection and assessment prior to initiating therapy. Careful attention to drug dosage, renal function, and close monitoring of patient’s overall clinical status are important, especially because of the need to minimize the risk of hyperkalemia. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; COX-2: cyclooxygenase-2; CRI: chronic renal insufficiency; K⁺, potassium; NSAID, non-steroidal anti-inflammatory drugs.
as ACEIs or ARBs, potassium supplements and non-steroidal anti-inflammatory medications is warranted. During hypovolemic states such as diarrhea, vomiting and excessive diuretic use, therapy with aldosterone blocker should be stopped until resolution.

CONCLUSION

Heart failure and LV systolic dysfunction complicating acute myocardial infarction are associated with substantial morbidity and mortality. Blockade of aldosterone with eplerenone or spironolactone inhibits post-myocardial infarction collagen deposition, myocardial fibrosis, apoptosis, ventricular remodeling and endothelial dysfunction. The results from landmark clinical trials have demonstrated substantial survival benefits of aldosterone blockers and their role in the primary prevention of sudden cardiac death. Early and aggressive adjunctive treatment with aldosterone blockers offers significant incremental benefit for reducing mortality and morbidity above and beyond standard proven therapies for post-myocardial infarction heart failure and, as such, should be incorporated into critical pathways for the care of these patients. Although hyperkalemia is potentially a serious threat, with appropriate patient selection and close monitoring, the benefits of aldosterone blockade in mitigating adverse outcomes should far outweigh its potential risks.

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