Angiotensin Receptor Blockers and Aldosterone Antagonists in Chronic Heart Failure

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Synopsis

Prognosis in congestive heart failure is directly linked to neurohormonal activation. Angiotensin II through the activation of the renin angiotensin aldosterone system has been the principal focus of therapy over the last two decades. New agents that target selective blockade of the angiotensin II receptor have been introduced in clinical trials for the treatment of heart failure. Aldosterone has been identified as a critically important neurohormone with direct detrimental effects on the myocardium. Aldosterone antagonists have been utilized in clinical trials to improve mortality in patients with chronic heart failure.

Congestive heart failure has emerged as a major public health issue for the new millennium. Currently there are approximately five million patients with this diagnosis in the United States. The prevalence increases with age and mortality and morbidity remain high despite significant advances in pharmacologic therapy. Congestive heart failure symptoms can occur in the presence of systolic dysfunction usually documented by a decrease in ejection fraction or can present with impaired diastolic function occasionally labeled as heart failure with preserved systolic function of the left ventricle. Over the last two decades we have learned that neurohormonal activation primarily mediated through the renin angiotensin aldosterone system, as well as, the sympathetic nervous system is a key determinant in the progression of chronic heart failure. Considerable effort in the form of large scale clinical trials have helped define the current recommendations for pharmacologic treatment of symptomatic patients with heart failure due to left ventricular systolic dysfunction. Diuretics as a drug class appear to be important in symptom relief in congestive heart failure from any etiology. Digitalis appears to be beneficial in many patients again in providing symptomatic benefit. However, it is only until recently where our full comprehension of the role of neurohormonal activation has led to the conclusion that patients with symptomatic heart failure should be treated with agents to decrease angiotensin II, as well as, with beta blocking agents to slow the progression of the disease.

Role of angiotensin II

The renin-angiotensin aldosterone system has been studied extensively in chronic congestive heart failure. Angiotensin II has been the initial focus for modification with pharmacologic therapy. It is clear that neurohormonal activation occurs early in the development of chronic heart failure, particularly heart failure due to a compromise in left ventricular systolic function [1]. Angiotensin II is responsible for a number of pathophysiologic effects on the cardiovascular system including vasoconstriction, abnormal cell growth and the release of aldosterone. These effects are mediated through activation of the angiotensin II Type I receptor (AT1). All of these pathophysiologic effects are detrimental in chronic heart failure. The abnormal cell growth stimulation results in significant remodeling of the left ventricle and this can be altered using agents that block the effects of angiotensin II [2]. Recently there have been increasing evidence that in heart failure, activation of the renin-angiotensin aldosterone system occurs systemically and also local activation of this system may occur at the myocardial cell level. A complex interaction with other factors may upregulate the tissue or local renin angiotensin aldosterone system particularly cytokines, adrenogenic peptide and endothelin [3].

The cardiac hypertrophy that is mediated by angiotensin II plays a critical role in the remodeling process of the left ventricle and the progression of chronic heart failure. The ability of various agents to block the effects of angiotensin II have been shown to have a positive effect on clinical outcomes in patients with chronic heart failure [4].

Angiotensin receptor blockers
Based on these trials, angiotensin converting enzyme inhibitors (ACE) which simultaneously decrease the conversion of angiotensin I to angiotensin II as well as prevent the breakdown of bradykinin, are indicated in all patients who manifest congestive heart failure with left ventricular systolic dysfunction. However, it became clear that angiotensin II suppression is not complete with the administration of chronic ACE inhibitors. This has led to the development of a new class of drugs which interferes with the action of angiotensin II at the AT1 receptor level. The agents developed were known as angiotensin II receptor blockers (ARB's) as they are selective for the AT1 receptor. It appears that this receptor is responsible for the adverse vasoconstrictor and cellular growth abnormalities mediated by angiotensin II. By selectively blocking this receptor with an ARB, angiotensin II activity is shunted to other receptors particularly the AT2 receptor which appears to mediate vasodilation and decreased cell growth [6]. Additionally, bradykinin which accumulates with the use of ACE inhibitors seems to mediate two important side effects of this class of compounds, that is, cough and angioedema. These side effects would be reduced if angiotensin converting enzyme remains intact and angiotensin II blockade is maintained at the receptor level. However, it also appears that the accumulation of bradykinin results in an increased availability of nitric oxide, which may play a critical role in congestive heart failure and may be one of the potential benefits of the ACE inhibitors.

Studies in patients with hypertension have documented that ARB's produce a similar blood pressure lowering and protective effect in patients with hypertension as do ACE inhibitors. However, few studies have been done in heart failure. One of the critically important benefits of ACE inhibition in patients with hypertension has been LVH regression. Since left ventricular hypertrophy is closely tied to clinical outcomes, this has been looked at as an important benefit. Recently there had been encouraging evidence that the ARB's can also produce regression of left ventricular hypertrophy in patients with hypertension [7-9].

Preliminary studies in patients with heart failure using ARB's have documented the positive effects on symptoms, tolerability and hemodynamics in patients with heart failure [10-12]. This led to the design of a large scale clinical trial called the Evaluation of Losartan in the Elderly Study, ELITE. This was a multi-center randomized, double-blind, positive controlled trial of over 700 patients 65 years or older with mild to severe congestive heart failure symptoms and ejection fractions less than 40%. Patients were randomized to losartan titrated to 50 mg daily or captopril titrated to 50 mg three times daily for a total study duration of 48 weeks. The primary end point in this study was the deterioration of renal function measured by changes in serum creatinine. The study was monitored by a data safety monitoring board so hospitalizations and mortality were also tracked.

The study results were interesting in that the primary end point results were identical in both patient groups. This provided additional data concerning the safety and tolerability of this class of drugs in patients with congestive heart failure. However, when the secondary end point of death and/or admission to the hospital for heart failure were analyzed a risk reduction of 32% with an insignificant P value was noted favoring the patients randomized to losartan. This risk reduction appeared to be due to a decrease in all cause mortality resulting in a risk reduction of 46% which was statistically significant. However, this trial was not powered for mortality and the number of events was quite small. Sub-studies from this clinical trial demonstrated a similar reduction in left ventricular remodeling by both losartan and captopril [14]. However, this clinical trial did not demonstrate from a statistical and design standpoint the superiority of an ARB, losartan over an ACE inhibitor, captopril in patients with mild to severe heart failure.

Consequently, a long term mortality trial was developed called ELITE II and was undertaken with a larger number of patients [15]. This again was a multi-center study designed to confirm whether losartan was superior to captopril in heart failure. The patients were elderly, this time ages 60 and older, with mild to severe congestive heart failure symptoms and an ejection fraction of 40%. Over 3000 patients were recruited for this trial and were randomized to receive losartan 50 mg daily versus captopril 50 mg three times daily. The primary end point was all cause mortality. The secondary end points were sudden cardiac death or resuscitated cardiac arrest. The follow-up in this trial was 555 days. This study demonstrated a similar mortality rate in both groups although there was a non-significant decrease in mortality in the captopril assigned patients (hazard ratio of 1.13; CI 0.95-1.35; P=0.16) (Table 1). Similarly, there was no significant difference in the end point of sudden death or resuscitated arrests (hazard ratio of 1.25; CI 0.98-1.60; P=0.08). However, there was significantly fewer patients assigned to losartan who discontinued study treatment because of adverse effects. The trial raised several questions but primarily established that angiotensin II receptor blockers are not superior to angiotensin converting enzyme inhibitors in patients with congestive heart failure. The potential mechanisms of action of ARB's suggest a beneficial effect over angiotensin converting inhibitors which needs to be re-evaluated. One of the pivotal questions revolves around bradykinin accumulation and the effect that this has on nitric oxide release in heart failure patients.
Preliminary studies in animal models of heart failure have suggested that a more beneficial blockade of angiotensin II can be accomplished by combining the effects of an angiotensin converting enzyme inhibitor and an ARB. In an experimental pig model of non-ischemic cardiomyopathy induced by pacing, left ventricular systolic work was increased using a combination of agents compared to either one alone [16]. These types of observations have led to the design of several clinical trials to ascertain whether a combination of an ARB and an angiotensin converting inhibitor might be beneficial in improving clinical outcomes in patients with congestive heart failure. The first of these studies was a complicated efficacy trial which utilized candesartan and enalapril alone and in combination in various doses in patients with mild to moderate heart failure who were then subsequently randomized to placebo versus a beta blocker [17]. This trial enrolled over 700 patients but was not designed as a mortality trial. The primary end points were the six minute walk test, neurohormonal levels and quality of life. These were similar in all patient groups. An oversight committee did review mortality and/or hospitalizations and while most of these numbers were relatively small there were no significant differences among the three randomized groups. A sub-study, which looked at left ventricular remodeling, however, did seem to indicate an improvement in ventricular size with the combination of the ARB and the angiotensin converting enzyme inhibitor.

Currently two studies are underway which are designed as mortality and morbidity trials with large numbers of patients to answer the question as to whether or not an angiotensin receptor blocker when added to an ACE inhibitor will have an important contribution to clinical outcomes in chronic congestive heart failure [18, 19]. The results of one of these trials, The Valsartan Heart Failure Trial (Val-HeFT) was presented at the American Heart Association (November 2000) [20]. In this trial 5010 patients were randomized to valsartan or placebo. All subjects had chronic heart failure (NYHA II-IV) with ejection fraction of < 40%, and were treated with ACE inhibitors, diuretics and digoxin. Only a small number of patients were taking beta blockers. The results of this study indicated no significant reduction in mortality but a reduction in combined morbidity-mortality (Table II). This would seem to indicate a potential benefit of combining ACE inhibitors with angiotensin receptor blockers in chronic heart failure. Confirmatory trials (i.e., CHARM) will help to establish this benefit.

**TABLE I**

<table>
<thead>
<tr>
<th></th>
<th>Losartan</th>
<th>Captopril</th>
<th>Hazards Ratio</th>
<th>CI</th>
<th>P</th>
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<tbody>
<tr>
<td>All Cause Mortality</td>
<td>280/1579 (17.7%)</td>
<td>250/1574 (15.9%)</td>
<td>1.13</td>
<td>0.95-1.35</td>
<td>0.16</td>
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<td>Total Mortality or Hospitalization</td>
<td>752/1578 (47.7%)</td>
<td>707/1574 (44.9%)</td>
<td>1.07</td>
<td>0.97-1.19</td>
<td>0.18</td>
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**TABLE II**

<table>
<thead>
<tr>
<th></th>
<th>Valsartan</th>
<th>Placebo</th>
<th>Hazards Ratio</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause Mortality</td>
<td>495/2511 (19.7%)</td>
<td>484/2499 (19.4%)</td>
<td>1.02</td>
<td>0.90-1.15</td>
<td>0.80</td>
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<td>All Cause Mortality and Morbidity</td>
<td>732/2511 (28.9%)</td>
<td>801/2499 (32.1%)</td>
<td>1.07</td>
<td>0.79-0.96</td>
<td>0.009</td>
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Role of aldosterone

About half a century ago, the urinary extracts, from patients with Congestive Heart Failure (CHF) were found to contain a substance with sodium retaining activity. These patients also had elevated levels of this substance in their plasma. Subsequently named aldosterone, this substance was later isolated, purified and further characterized as the primary mediator for the salt and water retention characteristic of congestive heart failure [21].

The activity of Renin-Angiotensin-Aldosterone System (RAAS) is increased in most patients with CHF. Plasma levels of aldosterone may reach 20 times the normal level in patients with CHF [22]. Several pathophysiological mechanisms contribute to this elevated level. Even though CHF is a state of excess total body sodium and water, the underfilling of another compartment, the so-called effective blood volume, is a strong stimulus for renin secretion. Renin through an enzymatic cascade produces Angiotensin II, which stimulates the secretion of aldosterone from the adrenal cortex. The increase in aldosterone levels is also accounted for, in part, by the decrease in hepatic clearance of the hormone [23].

Aldosterone was originally thought to be important in the pathophysiology of heart failure only because of its ability to increase sodium retention and potassium loss. This effect of aldosterone is mediated by its action on the cells of the distal collecting ducts of the kidney. However, the past several years’ research has shown that aldosterone causes myocardial and vascular fibrosis, direct vascular damage, and baroreceptor dysfunction.
and prevents the uptake of norepinephrine by the myocardium.

The effect of aldosterone on remodeling stems from its growth promoting activity on non-epithelial cells. Sustained increase in circulating aldosterone levels, together with dietary sodium loading are accompanied by proliferation of fibroblasts and induction of perivascular and interstitial fibrosis [24]. This fibrosis, both at sites of injury and at sites remote from the injury, is the cause of subsequent vascular re-modeling of the atria, ventricles, and great vessels. This fibrosis may have a role in the reduction of systolic function, increasing ventricular stiffness, and thereby impairing diastolic dysfunction and possibly generating heterogeneous intra cardiac conduction defects with the potential for serious reentrant arrhythmias. This fibrosis can be prevented by treatment with spironolactone [25].

Aldosterone also promotes potassium and magnesium depletion by its action on renal tubules. This state is potentially arrhythmogenic. Aldosterone blockade augments intracellular magnesium levels and reduces diuretic induced urinary magnesium [26]. Aldosterone may also increase the vulnerability to serious re-entrant arrhythmias through inhibition of cardiac norepinephrine uptake, augmentation of sympathetic activity, inhibition of parasympathetic traffic and impairment of baroreceptor-mediated heart-rate variability. Aldosterone has also been shown to be arrhythmogenic directly. In a recent study, aldosterone was shown to cause a dose dependent increase in ventricular ectopy after coronary ligation. This effect of aldosterone was more pronounced than the effect of epinephrine. The rapid onset of this effect suggests that the mechanism is unlikely to be electrolyte depletion [27].

Aldosterone is known to potentiate the effects of norepinephrine. In isolated blood vessels, aldosterone potentiates the pressor effects of norepinephrine. This effect is also enhanced by inhibition of neuronal and possibly extra-neuronal re-uptake of norepinephrine [28]. Poor myocardial catecholamine uptake has been shown to be a strong prognostic marker for overall mortality in CHF secondary to both idiopathic dilated and ischemic cardiomyopathy. I-MIBG scintigraphy has been shown in CHF to detect alterations in cardiac adrenergic activity with treatment. Spironolactone increases cardiac neuronal uptake of I-MIBG in-vivo [29].

ACEI mediated reduction of aldosterone levels are weak, variable and unsustained, whether or not angiotensin II levels remain suppressed. Up to 40% of patients on ACEI have persistently elevated concentrations of serum aldosterone via breakthrough generation of angiotensin II [30]. This transient suppression and the subsequent ‘escape’ phenomenon are accounted for by several ways. [31].

Aldosterone secretion may also proceed independent of angiotensin dependent mechanisms [32]. Aldosterone secretion is also modulated by other secretagogues, the most important being serum potassium. This mechanism comes to play in patients with diuretic induced kaliuresis treated with oral potassium supplementation. Changes in serum potassium concentrations by 0.1 mmol/L have been shown to change aldosterone secretion.

Moreover, extra adrenal production of aldosterone has been identified in non-classic sites like blood vessels and heart [33,34] and this has local autocrine and paracrine effects. These effects mediate most of the remodeling and arrhythmogenic effects of aldosterone. Hence, to counteract the effects of the residual aldosterone in circulation, and the local aldosterone, it makes sense to add an aldosterone receptor blocker to the armamentarium of therapies designed to decrease the mortality and morbidity associated with heart failure.

Clinical trials with aldosterone antagonists

Despite the belief that treatment with an aldosterone receptor blocker in conjunction with an ACE I was relatively contraindicated because of the potential for serious hyperkalemia [35], addition of an aldosterone receptor blocker (Spironolactone) to standard therapy was found to be well-tolerated. Barr et al [29] looked at the effects of the addition of a 50-mg (and if tolerated a 100-mg) dose of spironolactone to standard therapy with an ACEI and a loop diuretic, in 42 patients with NYHA class II - III ischemic cardiomyopathy. Four of 28 patients developed significant hyperkalemia and elevation of plasma creatinine and two of them needed discontinuation of the drug. No significant changes in body weight were seen.

In a pilot study of 214 patients, the Randomized Aldactone Evaluation Study (RALES) investigators [36], concluded that doses of 12.5 and 25 mg were relatively safe (provided serum potassium levels are monitored) and effective in blocking the effects of aldosterone, while reducing the potential for hypokalemia in patients with heart failure. Doses of 50 and 75 mg were found to be associated with a higher incidence of serious hyperkalemia.

On the basis of this information, the Randomized Aldactone Evaluation Study (RALES) was conducted [37]. In a double blind fashion, 1663 patients with severe heart failure (NYHA class III b & IV) and left ventricular
ejection fraction less than 35% were randomized to 25 mg spironolactone versus placebo. All patients were already being treated with ACEI, loop diuretics, and in most case, digoxin. After a mean follow up of 24 months, a 30 percent reduction in the risk of death and a 35 percent reduction in the frequency of hospitalization was noted in the spironolactone group (Table III). The reductions in risk of death and hospitalization were observed after 2 to 3 months of treatment and persisted throughout the study. The reduction in risk of death with spironolactone treatment was due to significant reductions in the risk of both death from progressive heart failure and sudden death from cardiac causes. A significant improvement in symptoms as assessed by functional class was also observed. These results are consistent with the current understanding of the effects of aldosterone in patients with heart failure.

<table>
<thead>
<tr>
<th>Spironolactone</th>
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<tbody>
<tr>
<td>All Cause Mortality</td>
<td>284/822</td>
</tr>
<tr>
<td>(35%)</td>
<td>(46%)</td>
</tr>
<tr>
<td>Hazards Ratio</td>
<td>0.70</td>
</tr>
<tr>
<td>CI</td>
<td>0.60-0.82</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
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Gynecomastia or breast pain was reported in 10 percent of the men. This percentage is similar to the numbers observed in patients taking doses less than 50-mg for treatment of hypertension. The use of a selective aldosterone receptor antagonist such as eplerenone which has a lower affinity for androgen and progesterone receptors than does spironolactone, may minimize the risk of gynecomastia.

The incidence of serious hyperkalemia was noted to be minimal in both groups. Only two percent of the subjects in the spironolactone group had serious hyperkalemia and the difference between the groups was not significant.

The fact that an aldosterone receptor blocker reduces morbidity and mortality among patients already on an ACE I emphasizes the ineffective suppression of aldosterone production by standard doses of an ACEI. The reduction in death observed in the RALES study does not appear to be entirely due to effects on sodium or potassium loss. Instead, it suggests a cardioprotective effect. No significant hemodynamic differences were observed between the groups. In the RALES pilot study [37] the 25-mg dose had no apparent diuretic effect. There was no change in body weight, sodium retention score or urinary sodium. The reduction in hospitalizations and death may be explained in part by the prevention of myocardial and vascular fibrosis by spironolactone. This prevention of remodeling may be instrumental in preventing progressive heart failure and reducing the risk of sudden death from cardiac causes. The other effects observed, norepinephrine uptake and baroreceptor function modulation may also play a role.

The patients studied in the RALES trial were at higher risk than those in recent studies with bisoprolol or Metoprolol XL. However, only a small fraction of the patients were receiving a beta-blocker and the reduction in risk of death did not differ in these groups. Therefore, studies are needed to examine the tolerability and effectiveness of the concomitant use of beta-blockers and spironolactone in such high-risk populations. Also, an algorithm for the concomitant versus separate initiation of both of these drugs needs to be studied. Similarly, the effect of spironolactone on morbidity and mortality in patients with lesser degrees of heart failure and, in asymptomatic patients with left ventricular dysfunction, needs to be studied. The current role of aldosterone receptor antagonists in patients with diastolic cardiac failure - which may account for 40% of community based cases of heart failure needs evaluation.

A recent clinical trial was published utilizing a selective aldosterone antagonist (eplerenone) in patients following an acute myocardial infarction with signs and symptoms of heart failure and left ventricular systolic dysfunction. [38] In this trial, a total of 6,632 patients were entered. The primary endpoint was all-cause mortality and death from cardiovascular causes or hospitalization for a cardiovascular event, which included heart failure, recurrent myocardial infarction, stroke, or ventricular arrhythmia. Mortality was reduced 15% (p = 0.008), and cardiovascular death or hospitalization for cardiovascular events was reduced 13% (p = 0.002). Importantly, there was also reduction in the rate of sudden death from cardiac causes (21% reduction, p = 0.03). Serious hyperkalemia was slightly increased in the eplerenone group, but other side effects that were noted with the nonselective aldosterone antagonist, spironolactone, in other trials were not present.

In summary, several new mechanisms for the beneficial effect of aldosterone antagonism in heart failure have been identified. The favorable effect of spironolactone on outcomes is in addition to those of ACEI. Hence, the standard-of-care, for treatment of patients with moderate to severe heart failure should be broadened to include an aldosterone receptor antagonist. When properly monitored, this therapeutic approach should reduce the risk of death among patients with this common and serious disorder. However, several practical questions need to be answered and the potential beneficial role among other subgroups of patients, needs to be explored.
References


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Lab. Gador contributed to the Congress