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Drug Insight: eplerenone, a mineralocorticoid-receptor antagonist

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SUMMARY

Increasing recognition of the role of aldosterone in cardiovascular disease has been supported by a significant body of evidence from animal models. This evidence has been translated into clinical practice, and large-scale, randomized, placebo-controlled trials have confirmed the beneficial effects of mineralocorticoid blockade in patients with heart failure. As a consequence, there has been a resurgence in the use of mineralocorticoid-receptor antagonists in clinical practice that has prompted the search for a potent and specific antagonist without the sexual side effects of spironolactone. Eplerenone, a mineralocorticoid-receptor antagonist with minimal binding to the progesterone and androgen receptors, is now licensed for treatment of heart failure in Europe and heart failure and hypertension in the US; it has also been proposed as a treatment for a variety of cardiovascular conditions. This article reviews the current concepts of the actions of aldosterone at a cellular level. Recent findings regarding its role as a cardiovascular hormone, both in animal models and human studies, are discussed. We also describe the development of mineralocorticoid-receptor blockers following the isolation of aldosterone and discuss the subsequent search for a specific mineralocorticoid antagonist. In addition we detail the effects of eplerenone in a number of clinical situations and outline its potential future applications.

KEYWORDS aldosterone, cardiovascular, eplerenone, hypertension

REVIEW CRITERIA

We searched for original articles focusing on mineralocorticoid blockade in MEDLINE and PubMed published between 1960 and June 2007. The search terms we used were "eplerenone", "mineralocorticoid blockade", "aldosterone" and "spironolactone". All papers identified were English-language, full text papers. We also searched the references of identified articles for further papers.

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INTRODUCTION

The traditional perception of aldosterone as a hormone of the adrenal zona glomerulosa with actions limited to sodium and water homeostasis is now recognized as incomplete. Nonclassical actions of aldosterone in a variety of nonepithelial target tissues have been demonstrated;[1] rapid, nongenomic effects[2] have been identified, and the possibility of local renin–angiotensin–aldosterone systems (RAAS) has been suggested.[3] Increasing recognition of aldosterone as a key cardiovascular hormone has provoked interest in the therapeutic use of mineralocorticoid-receptor antagonism in a variety of clinical presentations. The adverse-effect profile of spironolactone has limited this approach; however, the highly selective mineralocorticoid-receptor blocker eplerenone has proven to be an effective intervention in randomized, controlled trials of heart failure and has been proposed as a promising treatment for other cardiovascular conditions.

This article provides an overview of the cellular actions of aldosterone and details recent findings about its role as a cardiovascular hormone. We then describe the development of mineralocorticoid-receptor blockers and detail the effects of eplerenone in a number of clinical situations. Finally, we outline potential future applications for mineralocorticoid-receptor blockade.

CELLULAR ACTIONS OF ALDOSTERONE

Aldosterone was originally identified as an important regulator of sodium and potassium homeostasis. It acts on classic mineralocorticoid receptors (Box 1) in the cortical collecting duct of the kidney to increase activity of the epithelial sodium channel, resulting in net reabsorption of sodium; electrical neutrality is maintained by loss of potassium from the renal cell to the tubular fluid. Secretion of aldosterone from the adrenal zona glomerulosa is regulated principally by angiotensin II and potassium.[4] Potassium is known to stimulate aldosterone synthesis, and sensitize its secretion in response to angiotensin II.

The concept of aldosterone as a hormone mainly involved in electrolyte homeostasis has now been widened to take account of the fact that mineralocorticoid receptors are found in a wide range of tissues, including adipose tissue,[5] vascular endothelial cells, cardiac myocytes and the brain.[6] The actions of aldosterone in regulating normal physiology are uncertain, but the pathophysiological consequences in circumstances of aldosterone excess are better understood, and include the generation of reactive oxygen species, proinflammatory effects and increased expression of cell adhesion molecules.[7,8]

The tissue specificity of aldosterone is determined in part by the presence of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which acts to convert cortisol to cortisone. In the absence of 11β-HSD2, cortisol, which binds with high affinity to the mineralocorticoid receptor, can bind to the receptor and prevent regulation by aldosterone. This mechanism might be of particular relevance to cardiac myocytes, where 11β-HSD2 is not co-localized with the receptor.[9] It has been suggested that whether cortisol will activate the receptor or simply bind to it might be determined by other factors, including the 'redox' state within the cell;[10] however, this hypothesis remains a matter of debate. Agents such as spironolactone or eplerenone will, nevertheless, act as antagonists to the receptor even when the circulating concentrations of aldosterone, its dominant ligand, are not substantially elevated.

Box 1 The mineralocorticoid receptor.

- Present in epithelial cells in renal collecting duct, colon and salivary glands
- Recently also shown to be present in nonepithelial tissue, for example cardiac myocytes and the brain
- Activation of mineralocorticoid receptors increases activity of epithelial sodium channels, causing increased sodium reabsorption. Potassium is lost to the luminal fluid, thereby maintaining electrical neutrality
- Both mineralocorticoids and glucocorticoids are potential ligands for the mineralocorticoid receptor
- 11β-Hydroxysteroid dehydrogenase type 2 (11β-HSD2) catalyses the reaction of cortisol to inactive cortisone. It is proposed that this protects the mineralocorticoid receptor from glucocorticoid activation in epithelial tissues where 11βHSD2 and the mineralocorticoid receptor are co-localized
- A mechanism that might offer further protection from illicit activation by cortisol is that glucocorticoids can simply occupy the mineralocorticoid receptor rather than activate it. It is proposed that this is dependent on the intracellular redox state

ALDOSTERONE—A KEY CARDIOVASCULAR HORMONE

The role of aldosterone in hypertension

Following the identification of aldosterone, it was recognized that primary excess of the hormone, due to secretion from adrenal adenomas, could result in hypertension characterized by hypokalemia—Conn's syndrome. This excess was felt to be a relatively rare occurrence, being identified in around 1–2% of patients with hypertension.

More recently, however, there has been recognition that inappropriate aldosterone production is a significant cause of hypertension. Between 10% and 15% of unselected hypertensive patients demonstrate dysregulation of aldosterone, identified by an abnormally high aldosterone : renin ratio.[11] In selected populations, such as those with resistant hypertension, the percentage of patients with evidence of primary aldosteronism is considerably higher (around 20%).[12] In these patients, aldosterone does not suppress normally in response to sodium-loading or volume expansion, but in only a minority is there a distinct solitary adrenal adenoma (possibly 4% of hypertensive patients).[13] The detrimental effects of aldosterone in these circumstances are underscored by findings that patients with primary aldosteronism have higher rates of left ventricular hypertrophy[14] and other adverse cardiovascular events[15] than patients with high blood pressure in whom aldosterone is not increased.

Finally, it is now clear that aldosterone is important in the determination of blood pressure not only in the context of primary aldosteronism but also in the normal population—variation within the normal range of aldosterone,[16] as well as the aldosterone : renin ratio,[17] correlates with future rises in blood pressure and rates of hypertension.

The role of aldosterone in heart failure

Aldosterone excess has also been implicated in the risk of poor outcomes in heart failure as well as of adverse events following myocardial infarction.[18–21] It is known that the degree of neurohumoral activation, and specifically of increased aldosterone concentrations in plasma, is associated with increased mortality; both SAVE[19] (the Survival and Ventricular Enlargement trial of treatment after myocardial infarction) and CONSENSUS[20] (Cooperative North Scandinavian Enalapril

Survival Study of treatment for heart failure) demonstrated that high aldosterone levels predict poor cardiovascular outcome. In addition, data published in 2007 have confirmed that this association of increased mortality is present in patients across all New York Heart Association (NYHA) classifications of heart failure.[21]

In the rat heart, excess aldosterone provokes myocardial fibrosis and remodeling, independently of blood pressure and angiotensin II levels.[22] Rocha *et al.*[23] provided elegant demonstrations of the detrimental effect of aldosterone on a range of cardiovascular tissues, including the heart and the kidney, in rat models; in many tissues there was markedly abnormal vascular damage, with perivascular inflammatory infiltration. It is of interest that the presence of aldosterone proved necessary, but not sufficient, for the development of vascular pathology; in these studies, the detrimental effects are observed in animals in the presence of both high-salt diet and excess aldosterone.[23–25]

Finally, the importance of mineralocorticoid-receptor activation on the development of advanced cardiovascular dysfunction is illustrated by clinical studies in patients with cardiac failure or myocardial infarction. A large number of studies have investigated the utility of inhibition of the renin–angiotensin system, but until recently the focus was primarily on angiotensin-converting enzyme (ACE) or blockade of the angiotensin II receptor. It is clear that these therapeutic targets are not always sufficient to permanently maintain suppression of the RAAS; pilot data from the RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) trial[26] demonstrated that even the combination of an ACE inhibitor and an angiotensin-receptor blocker does not chronically suppress aldosterone secretion—a phenomenon described as 'aldosterone escape' or 'aldosterone breakthrough'.

The mechanisms behind aldosterone breakthrough are not well understood; it is recognized that angiotensin II levels rise over time in patients taking ACE inhibitors, and it might be that this provokes the rise in aldosterone. The rise in angiotensin II and aldosterone is not always seen simultaneously,[27] however, and increased levels of potassium, the dominant trophin of aldosterone, might be responsible for aldosterone breakthrough. Regardless of the mechanism, the breakthrough of aldosterone described in the observational data from the RESOLVD trial[26] prompted the evaluation of mineralocorticoid blockade as an alternative approach in cardiovascular therapy. The Randomised Aldactone Evaluation Study (RALES)[28] provided crucial evidence that spironolactone improved mortality in patients with left ventricular systolic dysfunction, leading to a re-evaluation of the perception of mineralocorticoid-receptor antagonists and their clinical applications.

DEVELOPMENT OF MINERALOCORTICOID-RECEPTOR ANTAGONISTS

The development of the first mineralocorticoid-receptor antagonists followed swiftly from the isolation of aldosterone by Sylvia and James Tait in 1953 (see Tait *et al.*[29]). Spironolactone was derived from a series of steroidal compounds (spirolactones) that exhibit anti-mineralocorticoid effects in animal models, and the patent was issued in 1961, only 8 years after the identification of aldosterone. Many molecules were evaluated (the manufacturers of spironolactone alone screened over 1,000 spirolactones in animals and several in humans) but it proved difficult to identify a well-tolerated candidate with potency greater than that of spironolactone.

Drawbacks of spironolactone

Initially licensed for the treatment of hypertension, primary hyperaldosteronism, peripheral edema and hypokalemia, spironolactone is relatively poorly tolerated. Problems with its administration relate mainly to its lack of specificity for the mineralocorticoid receptor; it also binds to progesterone receptors and androgen receptors. Menstrual irregularity in women and painful, sometimes unilateral, gynecomastia in men are commonly reported. In one large series, 13% of male patients reported gynecomastia.[30] In the same series, there was a mild elevation of mean plasma potassium levels (0.7 mmol/l in men and 0.5 mmol/l in women), but no occurrences of severe hyperkalemia were seen.

Despite these problems, spironolactone continued to be used in the treatment of resistant hypertension, nephrotic syndrome and in the management of ascites secondary to cirrhosis. In some countries, it remains widely used as an antihypertensive therapy; indeed, in a recent analysis of patients in ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), the addition of spironolactone proved of major benefit in lowering blood pressure in patients with resistant

hypertension.[31] This benefit has been confirmed in a number of further studies.[32,33] The adverse-event profile has, however, prompted the search for better-tolerated alternatives.

Eplerenone—a more specific antagonist

Initial investigations for more-specific, potent aldosterone antagonists produced a number of mineralocorticoid antagonists over the next 10-year period, including prorenone, a compound that demonstrated greater affinity for the mineralocorticoid receptor than did spironolactone.[34] It was not until 1987, however, that the addition of an epoxy group (Figure 1) to the compounds gave them a reduced affinity for the progesterone receptors and androgen receptors.[35] Clinical studies were undertaken with these compounds, but it was a further 15 years before eplerenone (epoxymexrenone) gained its license.

Eplerenone has an approximately 20-fold lower binding affinity for the mineralocorticoid receptor than spironolactone has *in vitro,* although this contrasts with *in vivo* studies where eplerenone has been demonstrated to have around 50% of the binding capacity of spironolactone.[36] Eplerenone differs significantly from spironolactone in its reduced affinity for the progesterone receptor and estrogen receptor (see Table 1), leading to a negligible sexual adverse-effect profile.[35] In common with spironolactone, the most significant potential adverse effects are electrolyte disturbances, specifically hyperkalemia. Careful monitoring of electrolytes is required during treatment with either agent, particularly when used in combination with other agents that have activity on the RAAS.

IN VIVO ACTIONS OF EPLERENONE

Preclinical studies in experimental animals

There are sufficient preclinical data to raise expectations that treatment with eplerenone will have beneficial effects on cardiovascular function.

Rocha *et al.*[7] highlighted this effect in a model of hypertension using uni-nephrectomized, salt-loaded rats treated with aldosterone for 2 weeks. This model features vascular inflammatory lesions resulting in myocardial ischemia and necrosis, with increased expression of proinflammatory molecules. These changes were substantially attenuated by treatment with eplerenone. In this study, blood pressure was lower in the eplerenone-treated animals; thus, the beneficial effects of eplerenone might have been mediated by a reduction in blood pressure. Further investigations by the same group, however, demonstrated a beneficial effect of mineralocorticoid blockade without significant differences in blood pressure reduction.[24] In this study, myocardial injury was induced in rats treated with angiotensin II and L-NAME (NG-nitro-L-arginine methyl ester, an inhibitor of nitric oxide synthesis): reversal of myocardial necrosis was observed in animals where exposure to aldosterone was removed either by adrenalectomy or treatment with eplerenone, independently of blood pressure.

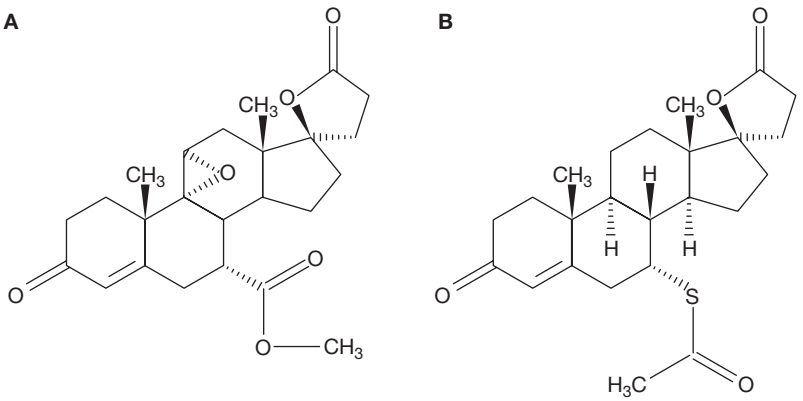

Figure 1 Structures of mineralocorticoid-receptor antagonists. (**A**) Eplerenone. (**B**) Spironolactone.

Eplerenone also ameliorates vascular stiffness and fibronectin accumulation in a rat model of hypertension (uni-nephrectomized, salt-loaded Sprague Dawley® [Harlan Holdings, Inc., Wilmington, DE] rats treated with aldosterone),[37] as well as inhibiting the development of experimental atherosclerosis in a number of models of heart failure.[38–40] Left ventricular fibrosis and endothelial dysfunction are reduced in eplerenone-treated, salt-loaded SHRSPs (stroke-prone, spontaneously hypertensive rats) but not in animals treated with hydralazine (a vasodilating antihypertensive).[41] The rise in blood pressure was attenuated by eplerenone in the salt-loaded rats, with little effect on control SHRSPs and SHRSPs with low salt levels, again highlighting the central role of sodium in the pathogenesis of cardiovascular damage.

Finally, aldosterone has been implicated in the pathogenesis of renovascular end-organ damage independent of blood pressure and angiotensin II levels. Rocha *et al.*[42] demonstrated that infusion of aldosterone reversed the protective effect of the ACE inhibitor captopril in

Table 1 Relative binding affinities for spironolactone and eplerenone.

Drug	Affinity for the mineralocorticoid receptor (aldosterone =1)	Affinity for the androgen receptor (methyltrienolone =1)	Affinity for the progesterone receptor (progesterone =1)
Spironolactone	1.1×10^{-1}	9.1×10^{-3}	7.0×10^{-3}
Eplerenone	5.1×10^{-3}	7.6×10^{-6}	$<5.0 \times 10^{-5}$

Table 2 Proposed effects of mineralocorticoid blockade.

Organ or system affected	Proposed effects
Heart	Prevents interstitial fibrosis and remodeling Reduces left ventricular hypertrophy Reduces sudden cardiac death Improves myocardial perfusion
Blood vessels	Improves endothelial function Attenuates inflammatory lesions and ischemia
Blood pressure	Reduces systolic and diastolic pressure
Kidney	Reduces proteinuria and reduces histological damage

saline-drinking SHRSPs and, although blood pressure was similar in all animals, typical lesions of malignant nephrosclerosis were observed only in aldosterone-treated animals. Specific mineralocorticoid blockade by eplerenone effectively reduces histological damage as well as protein loss in a variety of animal models.[25,43,44] The putative benefits of mineralocorticoid blockade are summarized in Table 2.

Clinical studies

Actions of eplerenone in hypertension

Eplerenone is a well-tolerated antihypertensive with an incidence of adverse events similar to placebo and no reports of gynecomastia or menstrual irregularity.[45,46] The doses used in clinical trials have generally been between 25 and 200 mg, although one study has used doses up to 400 mg with few adverse effects.[46] The incidence of hyperkalemia in the setting of clinical trials is similar to that seen with spironolactone, and only modest rises in potassium levels are usually noted.

This situation should, however, be compared with 'real life' clinical practice. The use of mineralocorticoid-receptor blockers increased substantially following the publication of trial data; along with this, an increase in the rate of complications of therapy, including hyperkalemia, was observed.[47] It is worth noting that trial patients constitute a carefully selected cohort, and patients with risk factors for adverse events such as hyperkalemia (e.g. patients with chronic renal failure or advancing age) can be excluded. In clinical practice, the increased risk of therapy to these types of patients should be carefully considered, and regular laboratory monitoring is required.

A comparison of the effect on blood pressure reduction has shown that eplerenone is a slightly less potent agent than spironolactone; 100 mg of eplerenone produces 75% of the blood pressure reduction seen with the equivalent dose of spironolactone.[46] Eplerenone is as effective as other antihypertensive agents when compared with monotherapy using a calcium channel blocker (amlodipine),[48] an ACE inhibitor (enalapril)[49] or an angiotensin-II-receptor blocker (losartan).[50,51] In black, hypertensive patients[51] and hypertensive patients with low renin levels[50]—subgroups that tend to respond relatively poorly to inhibition of ACE or angiotensin II—it has been suggested that eplerenone has greater efficacy than the comparator agent losartan, although this has not been a consistent finding.[52] Addition of eplerenone to an ACE inhibitor or an angiotensin II antagonist has, nevertheless, been shown to provide added antihypertensive benefit in patients whose condition was not controlled by monotherapy.[53]

Given the evidence that aldosterone has deleterious effects on heart and kidney, the consequence of antagonism of the mineralocorticoid receptor on end-organ function is of particular interest. The 4E (eplerenone, enalapril, and eplerenone plus enalapril) trial[54] has provided clinical data to support the hypothesis that blockade of the mineralocorticoid receptor with eplerenone is an effective method of reducing end-organ damage. This study was a 9-month, randomized, double-blind trial in patients with hypertension and left ventricular hypertrophy. Monotherapy with either eplerenone or enalapril, or the combination of both, demonstrated equal efficacy in relation to reduction of diastolic blood pressure; for systolic blood pressure,

enalapril and eplerenone in combination were more effective than either agent alone. Left ventricular mass was decreased in the group receiving combination therapy to a greater extent than with eplerenone alone. The smallest difference in left ventricular mass was seen in the enalapril-only group, although comparison between this and eplerenone alone did not reach statistical significance. The reduction in left ventricular mass did not, however, correlate with blood pressure reduction.

A significant confounding effect in this study was seen as a result of the use of add-on therapy to achieve equivalent blood pressure reductions, with more patients in the enalapril group requiring add-on antihypertensive drugs (hydrochlorothiazide and amlodipine). Analysis of the data when those requiring add-on therapy were removed did not, however, suggest any difference between enalapril and eplerenone in reducing left ventricular mass when blood pressure reduction was equivalent. This study confirms that eplerenone is as effective as enalapril in reducing the target-organ damage associated with hypertension and suggests that more-complete blockade of the RAAS with two agents provides more-effective protection. It does not, however, suggest that eplerenone has a uniquely beneficial effect on cardiac function. It must be noted that this was a relatively short-term study, and it is possible that longer-term therapy might be required to demonstrate specific benefit in relation to cardiac mass from blockade of the mineralocorticoid receptor.

Actions of eplerenone in nephropathy

As discussed above, animal models have identified aldosterone as a potential causative agent in the pathogenesis of end-organ renal damage. Additionally, mineralocorticoid blockade with eplerenone attenuates the histological damage ascribed to aldosterone in a number of animal models. Observational data show that there is a correlation between aldosterone levels and the extent of proteinurea in patients with diabetic nephropathy, and limited, uncontrolled studies by Sato *et al.*[55] have suggested that treatment with spironolactone of patients in this circumstance reduces protein loss.

Although not the primary outcome measurement, early clinical trials of eplerenone in hypertension demonstrated that eplerenone treatment was associated with a consistent improvement in proteinuria. In particular, patients with baseline microalbuminuria demonstrated a greater reduction in protein excretion than was seen in patients on comparator drugs. For example, when compared with amlodipine, eplerenone reduced albumin excretion (in patients who had detectable albumin at baseline) by 52%, compared with 10% for amlodipine ($P = 0.04$).[48]

A similar beneficial effect of eplerenone was seen in a comparison of eplerenone and enalapril in a smaller cohort of patients.[49] The superiority of combined ACE inhibition and mineralocorticoid blockade was demonstrated in the 4E study, with a reduction of albumin excretion in the enalapril plus eplerenone group (52.6%) compared with enalapril (37.4%; $P = 0.038$) or eplerenone (24.9%; $P = 0.001$) alone.[54] Finally, data from Epstein *et al.*[56] corroborated these results, demonstrating the superior antialbuminuric effects of dual therapy with eplerenone and ACE inhibition as compared with ACE inhibition alone in patients with diabetic nephropathy.

Actions of eplerenone in heart failure and ischemic heart disease

The role of mineralocorticoid blockade in heart failure is now generally accepted after the RALES study, which demonstrated a 30% reduction in mortality in patients with severe heart failure (NYHA class III or IV) given spironolactone in addition to usual therapy.[28] The requirement for a more selective mineralocorticoid-receptor antagonist was, however, confirmed in this trial, in which around 10% of male participants complained of gynecomastia or breast pain even at the relatively low mean daily dose of 26 mg. It is noteworthy that there were few instances of other adverse effects such as severe hyperkalemia in this study. The results demonstrated that antagonism of the mineralocorticoid receptor was a safe and effective therapy and stimulated the development of additional approaches to mineralocorticoid-receptor antagonism in advanced cardiac disease.

The Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[57] enrolled patients with acute myocardial infarction complicated by left ventricular dysfunction, treated with standard medical therapy, and compared the addition of either placebo or eplerenone. This study again showed beneficial effects of blocking the mineralocorticoid receptor, with a 23% reduction in the risk of readmission with heart failure and a fall in total mortality and cardiovascular

mortality (relative risk reduction of 15% and 13% respectively). In comparison with the RALES study, the incidence of gynecomastia and impotence was similar in the active and placebo groups. The dose of eplerenone used started at 25 mg and was titrated to 50 mg, doses that had only a minor effect on blood pressure.

It is indeed of interest, and somewhat surprising, that there is an apparent discrepancy between the dose of the drug required to lower blood pressure and the dose that causes significant cardiovascular benefit in advanced disease; this might raise the possibility that different mechanisms mediate the cardiac benefit and the antihypertensive effect.

It is possible that the beneficial effects of mineralocorticoid blockade in these studies reflect changes to cardiac structure. Animal models of heart failure have demonstrated altered remodeling in groups treated with eplerenone. In dogs with heart failure, adverse morphological changes were prevented by eplerenone treatment, with beneficial effects also observed at a cellular level: namely, reduced interstitial fibrosis, reduced myocyte hypertrophy and increased capillary density.[58] Further analysis of the RALES study examined markers of collagen synthesis and, indeed, demonstrated not only that mineralocorticoid blockade was associated with reduced serum markers of cardiac fibrosis, but also that patients who received benefit from spironolactone therapy were those with higher levels of these markers at baseline.[59]

In both EPHESUS and RALES, a reduction in sudden cardiac death in the treatment arm contributed significantly to the reduced mortality. Although the mechanisms behind this reduction are unclear, eplerenone has been reported to reduce cardiac arrhythmia in preclinical experiments.[60,61] It might be that a small increase in potassium levels in patients treated with eplerenone helps to avoid life-threatening, hypokalemia-associated arrhythmia. It is noteworthy that treatment with the potassium-sparing agent amiloride leads to a reduction in both Q–T interval and extra systoles, but does not produce the other beneficial effects of mineralocorticoid blockade on heart rate variability, endothelial dysfunction or myocardial fibrosis,[62] and it seems likely, therefore, that a simple change in serum potassium is not the only explanation for the observed fall in mortality.

Finally, it has also been suggested that myocardial perfusion might be improved with eplerenone. A study published in 2007 measured myocardial perfusion reserve, using cardiac MRI following adenosine stimulation, in 16 patients with diabetes. Patients were established on ACE-inhibitor therapy and randomized to receive either eplerenone or hydrochlorothiazide. Mineralocorticoid-receptor blockade was associated with significantly higher myocardial perfusion reserve (median 1.57 versus 1.30; $P = 0.03$).[63]

FUTURE DIRECTIONS

It is clear that mineralocorticoid-receptor blockade is an important additional therapeutic option in patients with hypertension, particularly those with aldosterone excess, those who are resistant to conventional therapy, or those with end-organ damage. Experiments using animal models have raised the possibility of additional cardiovascular benefit (e.g. improved endothelial function, reduced inflammation and improved vascular compliance); however, at present, there is limited evidence to confirm these findings in humans. Current data suggest the favorable adverse-effect profile will allow eplerenone to be used safely in a wide group of patients, although at present the drug does not have a license for treatment of hypertension in Europe; this would be an important step before its widespread use.

By contrast, there is unequivocal evidence of benefit in heart failure syndromes. It is clear that eplerenone offers a safe and effective additional therapy in a large cohort of patients and it seems reasonable to assume that the benefits in advanced heart failure will be equivalent to those from spironolactone, although no formal comparison has been made.

Current guidelines suggest that mineralocorticoid blockade should be considered in patients with NYHA class III or IV heart failure and left ventricular systolic dysfunction. Additionally, patients who have suffered a myocardial infarction and have left ventricular systolic dysfunction and signs of heart failure, or who have diabetes, should also be considered for treatment.[64] Preliminary data from the REMODEL (Reversal of Cardiac Remodeling with Eplerenone) trial suggest that eplerenone does not improve left ventricular remodeling in mild-to-moderate chronic heart failure,[65] but ongoing clinical trials might extend the use of mineralocorticoid blockade to patients with mild-to-moderate heart failure (EMPHASIS-HF [Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure]), as well

as to patients with heart failure and preserved systolic function (TOPCAT [Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist]).

Finally, there are currently no data regarding the role of eplerenone in the treatment of cirrhosis and nephrotic syndrome, although it is likely that the drug would provide benefit. Such studies, to identify a better-tolerated option than spironolactone, are clearly needed.

CONCLUSIONS

Mineralocorticoid-receptor blockade has significant beneficial effects both in animal studies and in clinical practice. The evolution of highly selective mineralocorticoid-receptor blockers has coincided with the increased understanding of the widespread deleterious actions of mineralocorticoid activation in the cardiovascular system.

Blockade of this component of the RAAS holds significant promise as an effective intervention and could provide a more targeted approach, intercepting the cascade of events that contribute to the end-organ damage seen in many conditions. With the exception of the EPHESUS study, however, there are no outcome data with eplerenone, and these are now required before its use can be more widely extended.

KEY POINTS

- There is increasing evidence that aldosterone has a key role in cardiovascular pathology
- Experimental data suggest that mineralocorticoid blockade is beneficial in models of hypertension, nephropathy and heart failure
- Mineralocorticoid blockade has proved a valuable therapeutic option in clinical studies of heart failure and after myocardial infarction
- Few data exist regarding outcomes in large cohorts of patients in other cardiovascular conditions (e.g. nephropathy, hypertension) and these are required, as well as confirmatory studies in heart failure, to establish the role of eplerenone in clinical practice

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