Brief Review

Mineralocorticoid Receptor Activation and Mineralocorticoid Receptor Antagonist Treatment in Cardiac and Renal Diseases

Johann Bauersachs, Frédéric Jaisser, Robert Toto

Cardiac and renal diseases remain major challenges for healthcare systems in developed countries and commonly coexist, with a disorder in the heart or kidney often leading to secondary dysfunction or injury in the other organ. Indeed, the term cardiorenal syndrome has been introduced to describe the broad spectrum of disease involving both the heart and kidneys.1

Aldosterone is a steroid hormone with mineralocorticoid activity, produced primarily in the glomerular zone of the adrenal cortex.2 Aldosterone fulfills its major physiological function of maintaining sodium and potassium balance and blood pressure control by binding to the mineralocorticoid receptor (MR) in the connecting tubule and cortical collecting duct in the kidneys, thereby increasing sodium reabsorption and potassium secretion. There is a growing body of evidence for a broader role of aldosterone and MR activation in the pathophysiology of cardiovascular and renal disease.3,4

This article focuses on our knowledge and understanding of the direct roles of aldosterone and MR activation in the heart and kidneys, including common pathophysiological mechanisms in both organs and implications for clinical use of MR antagonists (MRAs) in the treatment of cardiac and renal diseases.

MR Signaling in the Kidneys and Heart

MR expression has been demonstrated in vivo in vascular endothelial cells and vascular smooth muscle cells of interlobar arteries in mouse kidneys and ex vivo in cultured podocytes, mesangial cells, and renal fibroblasts.5 The MR is also expressed in multiple cell types in the heart, including cardiomyocytes, coronary endothelial and vascular smooth muscle cells, fibroblasts, and inflammatory cells, such as macrophages.5

Aldosterone and the glucocorticoid cortisol bind to the MR with similar affinities. Plasma concentrations of glucocorticoids are 100- to 1000-fold higher than those of aldosterone. Overstimulation of the MR is prevented by the coexpression of 11β-hydroxysteroid dehydrogenase type 2 (11-BHSD2). This enzyme converts cortisol into cortisone, which has a lower affinity for the MR. 11-BHSD2 activity has been demonstrated in both the kidneys and heart;6,7 however, expression of 11-BHSD2 varies in different cell types, with some cells, such as cardiomyocytes, having very low levels of 11-BHSD2. There is not yet consensus on whether aldosterone or cortisol activates the MR in these cells, but direct effects of aldosterone have still been observed, suggesting mechanisms yet to be determined fully may operate to allow the binding of aldosterone to the MR.8,9

Once aldosterone binds to the MR, the hormone–receptor complex dimerizes, migrates into the nucleus, and binds to a specific DNA sequence, triggering the transcription of target genes. It takes ≈1 hour for the classic genomic action of aldosterone to start to have a biological effect, with complete changes in gene expression not apparent for hours or days.10 A second, more rapid, nongenomic pathway, the effects of which are short-lived, has also been described, although the physiological and clinical relevance of this pathway remains to be established.11,12

The principal functional role of the MR in normal kidneys is to control sodium reabsorption and potassium secretion.3 The function of the MR in the healthy heart is not fully understood, but may include regulation of cardiomyocyte growth and cardiac electrophysiology.5,13

Key evidence for the role of the MR in the pathophysiology of cardiac and renal diseases has come from cell–specific overexpression and deletion studies. In mouse models of chronic pressure overload or myocardial infarction (MI), deletion or inactivation of the MR gene attenuated left ventricular dilatation, cardiac hypertrophy, and development of heart failure (HF), whereas overexpression of the MR in cardiomyocytes induced ventricular remodeling, development of HF, and proarrhythmic effects.14–17 Expression of both the MR and 11-BHSD2 is upregulated in rats post-MI and in response to a high-salt diet.18,19 In patients with congestive HF and in those with atrial fibrillation, myocardial MR expression is increased.20,21 Renal MR expression is increased in animal disease models, such as streptozotocin-induced type 1 diabetes mellitus and type 2 diabetes mellitus.22 In patients with renal failure, MR expression is increased 5-fold in those with high albuminuria compared with patients with no or moderate albuminuria.23
Direct deleterious effects of aldosterone in the heart include development of myocardial hypertrophy, ventricular remodeling, proarrhythmogenic effects, myocardial ischemia, reduced coronary blood flow, and myocardial injury; the effects of aldosterone on the kidneys include glomerular hypertrophy, glomerulosclerosis, proteinuria, reduced renal blood flow, and renal injury (Figure). Importantly, the aldosterone-induced damage to the heart and kidneys is largely independent of the systemic effects on blood pressure.

Inflammation and fibrosis seem to play central roles in the pathophysiology of both cardiac and renal aldosterone-induced injury. In response to treatment with aldosterone and salt, rat myocardium displays increased inflammation and upregulated expression of proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-1β, and transforming growth factor-β1 (TGF-β1). In the rat kidney, aldosterone increases the expression of intercellular adhesion molecule-1. These effects may be mediated by serum- and glucocorticoid-induced protein kinase-1 and transcription factors nuclear factor-κB and activator protein-1, the expression and activity of which, respectively, are stimulated by aldosterone/salt or angiotensin II/salt in animal heart and kidneys.

Kidney biopsies from patients with high albuminuria show significant increases in the expression of serum- and glucocorticoid-induced protein kinase-1 and the inflammatory mediators macrophage chemoattractant protein-1, TGF-β, and...
interleukin-6 compared with those from patients with no or moderate albuminuria. Administration of aldosterone/salt in rats increases myocardial collagen synthesis and content, fibrosis, and profibrotic factors, including connective tissue growth factor, TGF-β, plasminogen activator inhibitor-1, matrix metalloproteinase-2, and tumor necrosis factor-α. Renal fibrosis occurs in hypertensive transgenic rats with elevated serum aldosterone and proteinuria, and aldosterone is known to increase the renal expression of the fibrotic proteins osteopontin, fibrinogen, collagen type 1, plasminogen activator inhibitor-1, and connective tissue growth factor.

Oxidative stress is a well-recognized trigger for inflammation and contributes to the development of fibrosis. In several animal models, increased in angiotensin II and aldosterone enhance oxidative stress in the heart, as is evident from increased nicotinamide adenine dinucleotide phosphate oxidase activity, expression of nicotinamide adenine dinucleotide phosphate oxidase components, and reactive oxygen species formation. Increased oxidative stress, inflammation, and fibrosis are evident in several animal models of cardiac and renal diseases (eg, rats post-MI, dogs with HF, and uninephrectomized diabetic rats). Oxidative stress, inflammation, and fibrosis in the animal heart and kidneys are thought to be caused by an aldosterone-mediated decrease in the bioavailability of nitric oxide.

The requirement for a high-salt environment for aldosterone-mediated injury is common to both the cardiac and renal effects and was first observed almost 40 years ago. A high-salt diet may stimulate oxidative stress, which then promotes activation of the MR. Thus, there may be a synergism between activation of the MR and oxidative stress, although the mechanisms for this are yet to be fully elucidated. Cross-talk and interactions between the MR and the angiotensin receptor 1 have also been proposed to contribute to end-organ damage in both the heart and kidneys.

Although the data from expression studies and investigations into the effects of aldosterone infusions have provided valuable insights into MR signaling, perhaps the most compelling evidence for the pathophysiological role of MR activation has come from the demonstration of the protective effects of the currently available MRAs, spironolactone, and eplerenone, in models of cardiac and renal diseases (Figure; also Table S1 in the online-only Data Supplement). Treatment with an MRA attenuates or prevents cardiac hypertrophy and the development of HF in several experimental models of heart disease (Table S1). MRAs also improve glomerulosclerosis, attenuate proteinuria, and reduce glomerular hypertrophy and renal injury in multiple animal models of kidney disease (Table S1). MRAs suppress overactivation of the MR in rat models of hypertension and post-MI and in uninephrectomized diabetic rats (Table S1). MRA treatment in animal heart and kidneys, and in animal models of cardiac and renal disease, prevents or reduces inflammation, fibrosis, and expression of markers of oxidative stress induced by aldosterone/salt (Figure; Table S1). Treatment with spironolactone significantly attenuates the increases in cardiac expression of proinflammatory and profibrotic mediators, such as serum- and glucocorticoid-induced protein kinase-1, TGF-β, connective tissue growth factor, matrix metalloproteinase-2, interleukin-1β, and nicotinamide adenine dinucleotide phosphate oxidase components that are induced with aldosterone/salt. Reductions in renal expression of proinflammatory and profibrotic mediators, including TGF-β, connective tissue growth factor, and cytokines, have also been demonstrated with eplerenone in spontaneously hypertensive rats.

In addition to these effects on inflammation and fibrosis, MRA treatment attenuates apoptosis and endothelial dysfunction and improves coronary and renal blood flow in animal models of cardiac and renal disease (Table S1). Improvements in endothelial function and blood flow with MRAs are associated with increases in endothelial nitric oxide synthase in both rat kidneys and hearts. Further benefits of MRAs include inhibition of electric remodeling and prevention of arrhythmogenic activity caused by aldosterone or disease states in mice, rat, and dog models and attenuation of podocyte injury in rat models of hypertension and diabetes mellitus (Table S1).

The beneficial effects of MRAs in preventing or attenuating cardiac and renal diseases in animal models are largely independent of the systemic hemodynamic changes, suggesting they are a result of blocking the direct deleterious effects of MR activation in the heart and kidneys.

Clinical Evidence: MRAs in Cardiac and Renal Diseases

Cardiac Disease

In 3 landmark randomized controlled trials, MRA treatment in patients with HF and reduced left ventricular ejection fraction (LVEF) significantly reduced mortality and morbidity (Table S2). In the Randomized Aldactone Evaluation Study (RALES), spironolactone significantly reduced death from all causes, the frequency of hospitalization for worsening HF, and the severity of HF symptoms compared with placebo in patients with severe HF receiving standard therapy (Table S2). The reduction in mortality with spironolactone was attributed to a lower risk of death from progressive HF and of sudden death from cardiac causes. The Eplerenone Post-Myocardial Heart Failure Efficacy and Survival Study (EPHESUS) demonstrated significant reductions in death from any cause and in the rate of deaths or hospitalization from cardiovascular causes with eplerenone versus placebo in patients with HF and reduced LVEF post-MI (Table S2). More recently, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) reported significant benefits of eplerenone on mortality and cardiovascular morbidity compared with placebo in patients with mild HF and reduced LVEF already receiving recommended therapy (Table S2).

Hyperlalemia is a significant adverse event and one of the most common concerns associated with the use of MRAs. The reported incidence of serious hyperkalemia in the landmark MRA HF trials was between 2% and 11.8%. Subanalyses of the HF trials have provided support for preclinical data on the role of aldosterone/MR activation in the pathophysiology of cardiac disease. In RALES, spironolactone decreased from baseline serum levels of procollagen type
1 carboxy-terminal peptide, procollagen type 1 aminoterminal propeptide, and procollagen type III aminoterminal peptide, all of which are markers of cardiac fibrosis (Table S2). Similarly, in a subgroup analysis of EPHEREUS, levels of collagen biomarkers were significantly lower in the eplerenone group than in the placebo group (Table S2).

The safety and tolerability of a novel nonsteroidal MRA, finerenone, were investigated in patients with HF with reduced LVEF and mild or moderate chronic kidney disease (CKD) in the phase 2 Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS; Table S2). Finerenone was at least as effective as spironolactone in decreasing levels of serum brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), which are biomarkers of hemodynamic stress, and was associated with a lower incidence of hyperkalemia and worsening renal function.52 There was a significant decrease in blood pressure from baseline in patients receiving spironolactone, but not in those receiving finerenone or placebo.

Additional small-scale clinical studies have reported the benefits of MRA treatment on left ventricular modeling, diastolic function, and New York Heart Association class in patients with HF and reduced LVEF.4

The efficacy of MRAs in the treatment of patients with HF and preserved LVEF has also been investigated. The Aldosterone Receptor Blockade in Diastolic Heart Failure trial reported significant improvements in diastolic function and significant reductions in left ventricular mass index with spironolactone compared with placebo in patients with chronic HF, preserved LVEF, and echocardiographic evidence of diastolic dysfunction, although there were no significant differences in maximal exercise capacity, HF symptoms, or quality of life between the 2 groups (Table S2). The Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial investigated the efficacy of spironolactone in reducing mortality and morbidity in patients with HF and LVEF of ≥45% (Table S2). Spironolactone did not significantly reduce the number of patients who reached the primary composite end point of cardiovascular death, hospitalization for HF, or aborted cardiac arrest (non-significant reduction of 11%), but did significantly reduce the risk of hospitalization for HF compared with placebo.

The proven benefits of the addition of an MRA to standard therapy on long-term mortality and morbidity in patients with HF and a reduced LVEF is in contrast to the lack of clear evidence for the protective effects of adding an angiotensin receptor blocker (ARB) to angiotensin-converting enzyme (ACE) inhibitor therapy on such outcomes in these patients.53 There is also evidence of the benefits of MRAs in patients with other types of cardiac disease (Table S2). Eplerenone significantly reduced left ventricular mass and lowered systolic and diastolic blood pressure from baseline in patients with left ventricular hypertrophy and hypertension (Table S2). In patients with resistant hypertension, the addition of an MRA to standard therapy afforded significant reductions in blood pressure and left ventricular mass, which were independent of plasma aldosterone levels (Table S2). In patients with a first anterior MI, addition of spironolactone significantly improved LVEF, suppressed left ventricular end-diastolic volume index, and reduced markers of fibrosis compared with ACE inhibitor therapy alone (Table S2).

In the recent Role of Eplerenone in Acute Myocardial Infarction–Double-Blind, Early Treatment Initiation, Randomized, placebo-controlled, multi-center study (REMINERDER), eplerenone provided a significant reduction in the composite end point of cardiovascular mortality and morbidity and elevated BNP/NT-proBNP levels versus placebo in patients with acute ST-elevation MI and no history of HF (Table S2).

Renal Disease

Numerous small-scale clinical studies have demonstrated reductions in proteinuria or albuminuria with the addition of MRAs to ACE inhibitor/ARB therapy in patients with CKD and diabetic nephropathy (Table S3). In the majority of studies, these beneficial effects were independent of changes in blood pressure. An analysis of 8 studies reported a 23% to 61% reduction in albuminuria in patients with diabetic nephropathy with the addition of an MRA compared with standard treatment alone.54 Not unexpectedly, MRAs were associated with increases in mean serum potassium and incident hyperkalemia. In a prospective randomized open-label study in patients with CKD already receiving ACE inhibitors or ARBs, spironolactone slowed the decrease in estimated glomerular filtration rate, and therefore the progression of CKD, in addition to reducing proteinuria, compared with controls (Table S3). In patients with nondiabetic nephropathy, the addition of spironolactone reduced markers of tubular injury and fibrosis compared with ACE inhibitor and ARB therapy alone, supporting the preclinical findings of the effects of aldosterone/MR activation on the pathophysiology of renal disease (Table S3).

In ARTS, which assessed the effects of finerenone in patients with HF with reduced LVEF and mild or moderate CKD, the novel MRA was associated with similar reductions in the urinary albumin-to-creatinine ratio from baseline, significantly smaller decreases in estimated glomerular filtration rate from baseline and significantly lower incidences of worsening renal function, renal impairment, and renal dysfunction compared with spironolactone (Table S3). Although the mean increase in serum potassium concentration from baseline was significantly greater with some doses of finerenone than with placebo, these increases were significantly smaller than those in the spironolactone group.52

The efficacy and safety of MRAs in the treatment of patients with end-stage renal disease are now being explored (Table S3). Safety data on the use of MRAs in patients with end-stage renal disease undergoing hemodialysis suggest that the risk of hyperkalemia with low-dose MRAs is significantly lower than previously thought, and MRA treatment with close laboratory monitoring is a favorable treatment option in these patients.2 A recent randomized controlled trial in patients with oliguria undergoing hemodialysis demonstrated substantial reductions in cardiovascular and cerebrovascular mortality and morbidity with spironolactone compared with controls, providing a strong rationale for further investigations in large-scale clinical trials (Table S3).

Clinical Implications

The effectiveness of MRAs in some patients with cardiac disease, particularly HF, has been proven in clinical trials. Future challenges will be to assess the mortality and morbidity benefits of MRAs in a wider population of patients with cardiac disease.
disease, including high-risk patients with concomitant renal disease. Initial clinical findings suggest the potential efficacy of MRAs in the treatment of patients with CKD and diabetic nephropathy, but robust safety data, data on morbidity and mortality, and data on hard clinical outcomes assessing disease progression, such as loss of renal function and progression to end-stage renal disease, are still lacking and remain important goals for future clinical trials.

Hyperkalemia is a significant concern with MRAs and has limited the use of these agents in some populations with HF. It has also dampened enthusiasm for the development of MRAs as treatments for renal disease because hyperkalemia is a common complication of CKD.63 A higher incidence of hyperkalemia has been documented with MRAs in clinical practice than in the landmark HF clinical trials (incidences of 2%−11.8%), and increases in hyperkalemia-associated hospitalizations and deaths have been reported since publication of the first trial, RALES.56 Other studies, however, have described similar rates of hyperkalemia to those reported in the 3 landmark clinical trials and no significant increases in hyperkalemia-related hospitalizations and deaths in clinical practice following the RALES study.57 Indeed, the clinical relevance of reported increases in the risk of hyperkalemia warrants close examination. In RALES, the median potassium concentration in the spironolactone group was only 0.3 mmol/L greater than in the placebo group.51 In addition, it is important to note that in all 3 landmark HF trials, the overall beneficial effects of the MRAs on mortality and morbidity were consistent, regardless of serum potassium levels and worsening renal function, and were independent of the diuretic effects of the MRAs.68–70 Furthermore, although hyperkalemia is the most common concern, the risk of hypokalemia also merits consideration. There is some evidence of an association between hypokalemia and increased mortality and morbidity, even in patients with CKD.62 In both EPHESUS and EMPHASIS-HF, the incidence of serious hypokalemia was lower in the MRA group than in the placebo group.49,50 Thus, when assessing the risks associated with MRAs, all of the effects on potassium levels and associated implications should be examined, particularly among patients with HF. The effects of MRAs on potassium metabolism have been proposed to underlie some of the benefits demonstrated in HF trials.64 Subanalyses of the landmark MRA trials in patients with HF, however, suggest that the benefits of MRA treatment are largely independent of their effects on potassium levels, and hyperkalemia remains the primary concern limiting the use of MRAs in patients with HF/CKD in clinical practice.55–61 An increase in serum potassium levels can also occur during treatment with ACE inhibitors and ARBs and, by stimulating aldosterone synthesis and release from the adrenal glands, may contribute to aldosterone breakthrough, a phenomenon well-documented with chronic use of these therapies.64 The risk of hyperkalemia may be minimized by routine monitoring of serum potassium and renal function and avoidance of concomitant drugs and foods associated with potassium retention. A novel potassium-binding polymer, RLY5016, prevented hyperkalemia in patients with chronic HF receiving spironolactone and may have a role in preventing this complication, although further studies are required, particularly in patients with CKD.65 Additional preventive oral therapies are also under investigation.66 Novel MRAs with a more favorable safety profile than those of spironolactone and eplerenone may also significantly reduce the risk of hyperkalemia.

Additional drawbacks of available MRAs, most notably the antiandrogenic effects associated with spironolactone, have also contributed to underuse in clinical practice and the drive to discover the next generation of MRAs. The novel, nonsteroidal MRA finerenone has shown greater selectivity than spironolactone and greater potency for the MR than eplerenone (Table S4).67 Finerenone may also have greater selectivity for cardiovascular tissue than for renal tissue and, therefore, a potentially improved cardiac-to-renal activity ratio compared with available MRAs.67 The findings from ARTS that finerenone is at least as effective as spironolactone in reducing biomarkers of hemodynamic stress and is associated with lower incidences of hyperkalemia and renal adverse events than spironolactone in patients with HF, reduced LVEF, and moderate CKD provide support for this more favorable balance of cardiac and renal effects.52,60

Conclusions

Direct deleterious effects of aldosterone and MR activation, via mechanisms involving oxidative stress, inflammation, and fibrosis, occur in both the heart and kidneys. Clinical data support the findings of experimental studies and have shown that MRAs block these mechanisms and subsequent cardiac and renal injury independently of systemic hemodynamic changes. Such effects of MRAs are likely to play a major role in the proven benefits of these agents on mortality, morbidity, and disease progression in multiple types of cardiac disease and in the initial findings of similar benefits in renal disease. Ongoing and future clinical trials are merited to explore the potential of MRAs further in more patient populations with cardiac and renal disease. Hyperkalemia remains a concern with MRAs but may be addressed, in part, by novel MRAs, such as finerenone, which have shown a potentially more favorable cardiac-to-renalin activity ratio.

Acknowledgments

J. Bauersachs and F. Jaisser get support from the FP7-funded COST ADMIRE network (BM1301). Editorial support was provided by Dr Charlotte Cookson and Dr Emma Moorhouse of Oxford PharmaGenesis™ Ltd.

Sources of Funding

Editorial work (by Dr Charlotte Cookson and Dr Emma Moorhouse of Oxford PharmaGenesis™ Ltd) was funded by Bayer Pharma AG. Bayer Pharma AG had no role in developing or reviewing the scope or content of the article.

Disclosures

J. Bauersachs has received research support and honoraria for lectures from Bayer and Pfizer. F. Jaisser has received research support from Bayer. R. Toto has served as a consultant for Amgen, BoehringerIngelheim, ZS Pharma, Celgene, and Stealth Peptides, and has received research funding from Ardelyx.

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Hypertension. 2015;65:257-263; originally published online November 3, 2014;
doi: 10.1161/HYPERTENSIONAHA.114.04488

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
http://hyper.ahajournals.org/content/65/2/257

Data Supplement (unedited) at:
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MINERALOCORTICOID RECEPTOR ANTAGONIST TREATMENT IN
CARDIAC AND RENAL DISEASES

Johann Bauersachs, Frédéric Jaisser, Robert Toto

1Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany;
2Centre de Recherche des Cordeliers, Paris, France; 3University of Texas Southwestern Medical
Center, Dallas, TX, USA

Short title: Mineralocorticoid receptor activation in disease

Corresponding author: Prof. Dr med. Johann Bauersachs, Department of Cardiology and
Angiology, Centre for Internal Medicine, Hannover Medical School, Carl-Neuberg-Str. 1, 30625
Hanover, Germany. Tel: 0511 532-3841; Fax: 0511 532-5412; E-mail: bauersachs.johann@mh-
hannover.de

ONLINE SUPPLEMENT
References


Supplementary Tables

Table S1. Preclinical evidence of the beneficial effects of MRAs in the heart and kidneys.

<table>
<thead>
<tr>
<th>Effect of MRA</th>
<th>Animal models of cardiac disease</th>
<th>Animal models of renal disease</th>
</tr>
</thead>
</table>
| ↓ MR expression | - Dahl salt-sensitive rats fed a high-salt diet\(^1\)  
- Rats post-MI\(^2\) | - Uninephrectomized diabetic rats\(^3\) |
| ↓ markers of oxidative stress (e.g. suppression of increase in NADPH activity) | - Transgenic rats with increases in tissue angiotensin II and circulating aldosterone\(^4\)  
- Angiotensin II receptor knockout mice treated with aldosterone/high-salt diet\(^5\)  
- Dahl salt-sensitive rats fed high-salt diet\(^1\)  
- Mice with chronic pressure overload\(^6\)  
- Rats post-MI\(^7\)  
- Neonatal rat model of diabetes mellitus\(^8\) | - Cultured MR-expressing podocytes\(^9\)  
- Rats treated with aldosterone\(^10\)  
- Hypertensive and diabetic rats\(^11, 12\) |
| ↓ pro-inflammatory and pro-fibrotic mediators (e.g. CTGF, TGF-β, osteopontin) | - Transgenic mice over-expressing 11-BHSD in cardiomyocytes\(^13\)  
- Transgenic rats with increases in tissue angiotensin II and circulating aldosterone\(^4\)  
- Angiotensin II receptor knockout mice treated with aldosterone/high-salt diet\(^5\)  
- Dahl salt-sensitive rats fed high-salt diet\(^1, 14\)  
- Rats treated with aldosterone/high-salt diet\(^15, 16\)  
- Mice with chronic pressure overload\(^6\)  
- Two rat models of hypertension: two kidney/one clip model of renovascular hypertension and continuous administration of aldosterone\(^17\)  
- Rats post-MI\(^18\)  
- Mice post-MI\(^19\) | - Rats treated with aldosterone/high-salt diet\(^10, 23\)  
- Dahl salt-sensitive hypertensive rats\(^24\)  
- SHRs\(^25\)  
- Rats treated with L-NAME alone or in combination with angiotensin II and high-salt diet\(^26, 27\)  
- Uninephrectomized diabetic rats\(^3\)  
- Uninephrectomized rats treated with aldosterone\(^28\)  
- Uninephrectomized mice treated with aldosterone\(^29\)  
- Uninephrectomized rats treated with salt solution and DOCA\(^30\)  
- Streptozotocin-treated SHRs\(^31\) |
<table>
<thead>
<tr>
<th>Effect</th>
<th>Models/Cell Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ apoptosis</td>
<td>Dogs with HF(^{20,21}), Neonatal rat model of diabetes mellitus(^{8}), Uninephrectomized rats receiving high-salt diet(^{22})</td>
</tr>
<tr>
<td></td>
<td>OLETF rats(^{32})</td>
</tr>
<tr>
<td>↓ endothelial dysfunction/vasoconstriction</td>
<td>Cultured rat cardiomyocytes(^{2}), Rats post-MI(^{2}), Mice with chronic pressure overload(^{6})</td>
</tr>
<tr>
<td></td>
<td>Isolated podocytes exposed to aldosterone(^{33}), Rat mesangial cells treated with aldosterone and glucose(^{34}), Streptozotocin-treated rats(^{35})</td>
</tr>
<tr>
<td></td>
<td>Mice with cardiomyocyte-specific over-expression of human MR(^{36}), Dahl salt-sensitive hypertensive rats(^{24}), Rats with cyclosporine nephrotoxicity(^{37})</td>
</tr>
<tr>
<td>Prevention of cardiac hypertrophy and HF</td>
<td>Transgenic mice over-expressing 11-BHSD in cardiomyocytes(^{13})</td>
</tr>
<tr>
<td></td>
<td>Aldosterone synthase knockout mice treated with angiotensin II/high-salt diet(^{38})</td>
</tr>
<tr>
<td></td>
<td>Dahl salt-sensitive rats fed high-salt diet(^{1,14}), Mice with chronic pressure overload(^{6})</td>
</tr>
<tr>
<td></td>
<td>Rats post-MI(^{18,39}), Mice post-MI(^{19}), SHRs(^{40}), Neonatal rat model of diabetes mellitus(^{8})</td>
</tr>
<tr>
<td>↓ electrical remodeling and arrhythmogenic activity</td>
<td>Transgenic mouse model with conditional cardiac-specific overexpression of the human MR(^{41})</td>
</tr>
<tr>
<td></td>
<td>Male Wistar rats treated chronically with aldosterone(^{42}), Dogs subjected to rapid ventricular pacing(^{43})</td>
</tr>
</tbody>
</table>
Improved podocyte injury, glomerulosclerosis, proteinuria and glomerular hypertrophy

- Aldosterone synthase knockout mice treated with angiotensin II and salt
- Dahl salt-sensitive hypertensive rats
- Rats treated with L-NAME, angiotensin II and salt
- Uninephrectomized diabetic rats
- Streptozotocin-treated rats
- Streptozotocin-treated SHRs
- Rats with subtotal nephrectomy
- OLETF rats

11-BHSD, 11β-hydroxysteroid dehydrogenase; CTGF, connective tissue growth factor; DOCA, deoxycorticosterone acetate; HF, heart failure; L-NAME, L-NG-nitro-L-arginine methyl ester; MI, myocardial infarction; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; NADPH, nicotinamide adenine dinucleotide phosphate; OLETF rats, Otsuka Long-Evans Tokushima Fatty rats; SHRs, spontaneously hypertensive rats; TGF-β, transforming growth factor-β.
**Table S2.** Clinical evidence of the beneficial effects of MRAs on mortality, morbidity and markers of cardiac injury in patients with cardiac disease.

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Patient group</th>
<th>N</th>
<th>Duration of treatment/ follow-up</th>
<th>MRA</th>
<th>Endpoint/outcome</th>
<th>Effects of MRAs vs placebo/control</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES[^48^]</td>
<td>Patients with severe HF and LVEF (\leq 35%) receiving an ACE inhibitor, loop diuretic and, in most cases, digoxin</td>
<td>822</td>
<td>24 months</td>
<td>Spironolactone</td>
<td>Death from all causes (primary endpoint)</td>
<td>(\downarrow 30% \ (p &lt; 0.001))</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospitalization for worsening HF</td>
<td>(\downarrow 35% \ (p &lt; 0.001))</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Symptoms of HF</td>
<td>Significant improvement (p &lt; 0.001)</td>
</tr>
<tr>
<td>Subgroup analysis of RALES[^49^]</td>
<td>As above</td>
<td>261</td>
<td>6 months</td>
<td>Spironolactone</td>
<td>Changes in serum procollagen type I carboxy-terminal peptide, procollagen type I aminoterminal peptide and PIIINP from baseline</td>
<td>(\downarrow ) from baseline in the spironolactone group but not in the placebo group</td>
</tr>
<tr>
<td>EPHESUS[^50^]</td>
<td>Patients with LVEF (&lt; 40%) and HF following MI receiving optimal medical therapy</td>
<td>6632</td>
<td>16 months</td>
<td>Eplerenone</td>
<td>Death from any cause (primary endpoint)</td>
<td>(\downarrow 15% \ (p = 0.008))</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death from CV cause or hospitalization for CV events (primary</td>
<td>(\downarrow 13% \ (p = 0.002))</td>
</tr>
</tbody>
</table>
Subgroup analysis of EPHESUS<sup>51</sup>

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Duration</th>
<th>Treatment</th>
<th>Biomarker</th>
<th>Change in Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>As above</td>
<td>467 9 months</td>
<td>Eplerenone</td>
<td>Levels of collagen biomarkers</td>
<td>↓ levels of procollagen type I aminoterminal propeptide and PIIINP; these differences were significant from 6 months</td>
<td></td>
</tr>
<tr>
<td>AREA IN-CHF&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Patients with HF (NYHA class II) and LVEF ≤ 45% receiving optimal medical therapy</td>
<td>467 12 months</td>
<td>Canrenone (active metabolite of spironolactone)</td>
<td>Change in echocardiographic LV end-diastolic volume (primary endpoint)</td>
<td>↓ from baseline similar in both groups</td>
</tr>
</tbody>
</table>

- Changes in LVEF: ↑ significantly greater in canrenone group than in placebo group (p < 0.04)
- BNP concentration: ↓ from baseline to 6 months significantly greater in canrenone group than in placebo group (p < 0.0001)
- All-cause mortality: No significant difference between two groups
- Cardiac hospitalization: ↓ significantly greater in canrenone group than in placebo group (p = 0.01)
- Hospitalization for worsening HF: ↓ significantly greater in canrenone group than in placebo group (p = 0.02)
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Follow-Up</th>
<th>Intervention</th>
<th>Primary Endpoint</th>
<th>Result (%) (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPHASIS-HF&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Patients with mild HF (NYHA class II) and LVEF $\leq$ 35% receiving recommended therapy</td>
<td>2737 21 months</td>
<td>Eplerenone</td>
<td>Composite of death from CV causes and hospitalization for HF (primary endpoint)</td>
<td>↓ 37% ($p &lt; 0.001$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death from any cause</td>
<td>↓ 24% ($p = 0.008$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death from CV causes</td>
<td>↓ 24% ($p = 0.01$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospitalizations for HF</td>
<td>↓ 42% ($p &lt; 0.001$)</td>
</tr>
<tr>
<td>Aldo-DHF&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Ambulatory patients with NYHA class II or III HF with preserved LVEF of $\geq$ 50% and echocardiographic evidence of diastolic dysfunction</td>
<td>422 12 months</td>
<td>Spironolactone</td>
<td>Changes in diastolic function on echocardiography (primary endpoint)</td>
<td>Significant improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maximal exercise capacity (primary endpoint)</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left ventricular mass index</td>
<td>Significant reduction ($p = 0.009$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF symptoms and QoL</td>
<td>No significant difference</td>
</tr>
<tr>
<td>TOPCAT&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Patients with symptomatic HF and LVEF $\geq$ 45%</td>
<td>3445 3.3 years</td>
<td>Spironolactone</td>
<td>Composite of death from CV causes, aborted cardiac arrest, or hospitalization due</td>
<td>↓ 11% ($p = 0.14$)</td>
</tr>
<tr>
<td>Study</td>
<td>Patients with HF and LVEF ≤ 40% and mild-to-moderate CKD (eGFR 30–60 mL/min/1.73 m²)</td>
<td>ARTS 55</td>
<td>392</td>
<td>4 weeks</td>
<td>Spironolactone and finerenone</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------</td>
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<td>---------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>REMINDER 56</td>
<td>Patients with acute STEMI without a history of HF receiving standard therapy</td>
<td>1012</td>
<td>10.5 months</td>
<td>Eplerenone</td>
<td>Composite of CV mortality, re-hospitalization or extended initial hospital stay due to diagnosis of HF, sustained ventricular tachycardia or fibrillation, LVEF ≤ 40% or elevated BNP/NT-proBNP levels (primary endpoint)</td>
</tr>
</tbody>
</table>

Patients with first event

134 1 month Spironolactone Left ventricular Significant improvement in
<table>
<thead>
<tr>
<th>Patients with left ventricular hypertrophy and hypertension&lt;sup&gt;58&lt;/sup&gt;</th>
<th>202</th>
<th>9 months</th>
<th>Eplerenone</th>
<th>Change in left ventricular mass, as assessed by MRI (primary endpoint)</th>
<th>Significant reduction from baseline; reduction was even greater with the combination of eplerenone and enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with resistant hypertension receiving anti-hypertensive therapies&lt;sup&gt;59&lt;/sup&gt;</td>
<td>175</td>
<td>7 months</td>
<td>Spironolactone</td>
<td>Ambulatory BP</td>
<td>Addition of spironolactone to existing therapies significantly reduced systolic and diastolic BP compared with baseline</td>
</tr>
<tr>
<td>Patients with resistant hypertension with and without hyperaldosteronism&lt;sup&gt;6&lt;/sup&gt;</td>
<td>108</td>
<td>6 months</td>
<td>Spironolactone</td>
<td>BP, ventricular and atrial volumes, left ventricular mass and BNP levels</td>
<td>Spironolactone was associated with significant decreases from baseline in systolic BP, right and left ventricular end diastolic volumes, left atrial</td>
</tr>
<tr>
<td>anterior MI treated with ACE inhibitor and study drug just after revascularization&lt;sup&gt;57&lt;/sup&gt;</td>
<td>modeling</td>
<td>LVEF and suppression of the left ventricular end-diastolic volume index with spironolactone compared with ACE inhibitor alone (p values of 0.012 and 0.002, respectively)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemical marker of fibrosis (plasma PIIINP level)</td>
<td>Significant reduction (p = 0.002)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
volume, left ventricular mass, and BNP in patients with high aldosterone levels, and decreases in BP and left ventricular mass without changes in ventricular or atrial volumes or plasma BNP in patients with normal aldosterone levels.

Aldo-DHF, ALDOsterone receptor blockade in Diastolic Heart Failure; ACE, angiotensin-converting enzyme; AREA IN-CHF, Anti-remodeling Effect Of Aldosterone Receptors Blockade With Canrenone In Chronic Mild Heart Failure; ARTS, mineralocorticoid Receptor antagonist Tolerability Study; BNP, brain natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure trial; EPHESUS, Eplerenone Post-myocardial Heart failure Efficacy and Survival Study; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PIIINP, procollagen type III aminoterminal peptide; QoL, quality of life; RALES, Randomized ALdactone Evaluation Study; STEMI, ST elevation myocardial infarction; TOPCAT, Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist trial.
Table S3. Clinical evidence of the beneficial effects of MRAs on mortality and morbidity and markers of renal injury in patients with renal disease.

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Patient group</th>
<th>N</th>
<th>Duration of treatment/ follow-up</th>
<th>MRA</th>
<th>Endpoint/outcome</th>
<th>Effects of MRAs vs placebo/control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oligoanuric patients undergoing hemodialysis&lt;sup&gt;6f&lt;/sup&gt;</td>
<td>157</td>
<td>3 years</td>
<td>Spironolactone</td>
<td>Composite of death from CCV events and hospitalization due to CCV events</td>
<td>↓ 62% (p = 0.016)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death from all causes</td>
<td>↓ 64% (p = 0.003)</td>
</tr>
<tr>
<td>ARTS&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Patients with HF and LVEF ≤ 40% and mild-to-moderate CKD (eGFR 30–60 mL/min/1.73 m²)</td>
<td>392</td>
<td>4 weeks</td>
<td>Spironolactone and finerenone</td>
<td>UACR</td>
<td>↓ UACR from baseline with finerenone and spironolactone, while there was an increase from baseline with placebo; the reduction in UACR was similar with finerenone and spironolactone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>eGFR</td>
<td>↓ eGFR from baseline with finerenone and spironolactone, while there was a small increase from baseline with placebo; the decrease in eGFR was significantly smaller with finerenone than with spironolactone (p = 0.0002–0.0133 for different dose groups)</td>
</tr>
</tbody>
</table>
WRF

Reported as an AE in 38% of patients receiving spironolactone, 1.5–10.4% of patients treated with finerenone and 9.2% of those receiving placebo.

Incidences of renal failure and renal impairment were also significantly lower with finerenone than with spironolactone.

Patients with CKD receiving ACE inhibitors and/or ARBs: 

<table>
<thead>
<tr>
<th>165</th>
<th>1 year</th>
<th>Spironolactone</th>
<th>Proteinuria and eGFR</th>
</tr>
</thead>
</table>

Significantly reduced proteinuria ($p < 0.001$) from baseline; while there was no change in patients receiving ACE inhibitors and ARBs alone.

By the end of 1 year, the monthly rate of the decrease in eGFR from baseline was lower in patients treated with spironolactone than in controls.

Patients with non-diabetic nephropathy and proteinuria > 0.5 mg/day receiving an ACE inhibitor and ARB:

<table>
<thead>
<tr>
<th>32</th>
<th>1 year</th>
<th>Spironolactone</th>
<th>Proteinuria</th>
<th>Urinary type IV</th>
</tr>
</thead>
</table>

↓ 58% in urinary protein level from baseline with spironolactone compared with no change in the control group ($p < 0.05$)

↓ 40% from baseline with
<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with chronic non-diabetic proteinuric renal disease receiving an ACE inhibitor and ARB in combination&lt;sup&gt;63&lt;/sup&gt;</td>
<td>18 2 months</td>
<td>Spironolactone</td>
<td>24-hour urine protein excretion (primary endpoint)</td>
<td>Significantly reduced with spironolactone compared with ACE inhibitor and ARB alone without any change in BP (&lt;em&gt;p&lt;/em&gt; = 0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urine excretion of N-acetyl-β-d-glucosaminidase (marker of tubular injury) and PIINP (marker of fibrosis)</td>
<td>Significant decrease in both markers with spironolactone compared with the ACE inhibitor and ARB alone</td>
</tr>
<tr>
<td>Patients with diabetes mellitus and UACR ≥ 300 mg/g receiving an ACE inhibitor or ARB&lt;sup&gt;65&lt;/sup&gt;</td>
<td>81 48 weeks</td>
<td>Spironolactone</td>
<td>UACR</td>
<td>34.0% greater fall in spironolactone group than in placebo group (&lt;em&gt;p&lt;/em&gt; = 0.007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.8% greater fall in losartan group than in placebo group (&lt;em&gt;p&lt;/em&gt; = 0.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BP</td>
<td>Decreased significantly in all three groups, but decreases were not significantly different between groups</td>
</tr>
</tbody>
</table>
| Patients with diabetes mellitus and UACR ≥ 50 mg/g receiving enalapril<sup>66</sup> | 268 | 12 weeks | Eplerenone | Percentage change from baseline in UACR and incidence of hyperkalemia (primary endpoints) | Significantly greater reductions in UACR from baseline (<em>p</em> < 0.001 for both eplerenone groups vs placebo)  
No significant difference in the incidences of sustained and severe hyperkalemia |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with proteinuric nephropathy, diabetic nephropathy and idiopathic glomerulonephritis (multiple small-scale studies)&lt;sup&gt;67, 68&lt;/sup&gt;</td>
<td>8–59 in each study</td>
<td>1–12 months in each study</td>
<td>Albuminuria/proteinuria</td>
<td>Decrease in proteinuria/albuminuria in all studies</td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARTS, mineralocorticoid Receptor antagonist Tolerability Study; BP, blood pressure; CCV, cardiovascular and cerebrovascular; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; UACR, urinary albumin-to-creatinine ratio; WRF, worsening renal function.
<table>
<thead>
<tr>
<th>Generation of MRA</th>
<th>Compound</th>
<th>Chemical class</th>
<th>Potency</th>
<th>Selectivity</th>
<th>Tissue distribution, kidneys vs heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Spironolactone</td>
<td>Steroidal</td>
<td>High</td>
<td>Low</td>
<td>At least six-fold higher in the kidneys than in the heart</td>
</tr>
<tr>
<td>II</td>
<td>Eplerenone</td>
<td>Steroidal</td>
<td>Low</td>
<td>Medium–high</td>
<td>Approximately three-fold higher in the kidneys than in the heart</td>
</tr>
<tr>
<td>III/IV</td>
<td>Finerenone</td>
<td>Non-steroidal</td>
<td>High</td>
<td>High</td>
<td>Balanced/equal (?)</td>
</tr>
</tbody>
</table>

MRA, mineralocorticoid receptor antagonist.