Chapter

Mineralocorticoid Receptor Antagonists in the Treatment of Coronary Artery Disease, Myocardial Infarction and Heart Failure

Carolin Zwadlo and Johann Bauersachs

Abstract

Affecting sodium reabsorption and potassium excretion in the kidney, mineralocorticoid receptor antagonists (MRA) were originally developed as antihypertensive drugs. After several large clinical trials, the concept of MR blockade has nowadays become a main treatment paradigm in heart failure with reduced ejection fraction (HFrEF) and for patients after myocardial infarction (MI) with left ventricular (LV) dysfunction. Recent analyses also point to a beneficial effect of early MRA treatment in patients with acute MI without LV dysfunction, however, there is no clear evidence yet. Although promising data from preclinical settings suggest that MRAs mediate favorable anti-atherogenic effects, clinical studies in patients with stable coronary artery disease (CAD) have not been able to detect differences of hard clinical outcomes. The concept might still be pursued using the most recent MRA, like the non-steroidal MR antagonist finerenone, and larger clinical trials need to be performed. Here, we review the current impact of MRA in patients with CAD and focus on the conflicting evidence of preclinical and clinical data in patients with stable CAD and preserved ejection fraction and summarize the current indications for MRA in these patients according to the guidelines.

Keywords: mineralocorticoid receptor antagonists (MRA), aldosterone, heart failure, myocardial infarction, spironolactone, eplerenone, finerenone

1. Introduction

Because of their effect on sodium reabsorption and potassium excretion in the kidney, mineralocorticoid receptor antagonists (MRA) were originally developed as antihypertensive drugs. Over the years, it became clear that their influence on the cardiovascular system is much broader than initially thought. Spironolactone was the first MRA to be developed. Later, eplerenone followed. Nowadays, mineralocorticoid receptor (MR) antagonism consists of the steroidal first- and second-generation MRAs spironolactone and eplerenone and the non-steroidal

third-generation MRAs, such as finerenone, the latter one not being in clinical use outside studies yet.

After several large clinical trials, the concept of MR blockade has become a main treatment paradigm with chronic heart failure with reduced ejection fraction (HFrEF) and for patients after myocardial infarction (MI) with left ventricular (LV) dysfunction. On the contrary, no general recommendation for immediate MR antagonism in patients without LV dysfunction is currently justified. Moreover, there are controversial data on the role of MRA in stable coronary artery disease (CAD), although high plasma aldosterone levels have been associated with increased mortality and ischemic events in patients with stable CAD with or without heart failure. Preclinical studies underline the anti-atherogenic and favorable vascular effects of spironolactone, eplerenone and finerenone via various mechanisms. These positive results, however, are largely limited to animal models and clinical studies could not confirm an improvement of markers of vascular health so far.

In the past, we have summarized the existing preclinical and clinical data on spironolactone and eplerenone in the treatment of CAD and its related complications [1]. Here, we review the impact of MRAs in these patients and supplement updated information on published clinical studies and especially the newly developed third-generation MRA, finerenone. We aim to shed light on the current conflicting evidence of preclinical and clinical data and summarize the indications for MR antagonism in patients with CAD and its complications.

2. Main part

2.1 Effects of aldosterone

The renin-angiotensin-aldosterone system (RAAS) regulates blood pressure and fluid and electrolyte balance under physiological and pathological conditions. Aldosterone is the final product of the RAAS. It is a steroid hormone produced by zona glomerulosa cells in the adrenal cortex. Traditionally, its action was thought to be restricted to sodium reabsorption and potassium excretion via activation of the cytosolic MR in epithelial cells of the distal colon, the renal nephron as well as salivary and sweat glands. However, over time it became clear that aldosterone's action is much broader than initially thought and MRs were identified in vascular endothelial and smooth muscle cells as well as in cardiomyocytes, endothelial cells, fibroblasts and macrophages in the heart [2].

Key evidence for the role of MR in the pathophysiology of cardiac diseases was derived from cell-specific overexpression and deletion studies. In mouse models of chronic pressure overload and myocardial infarction, deletion or inactivation of the MR gene attenuated left ventricular dilatation, cardiac hypertrophy and development of heart failure, whereas overexpression of the MR in cardiomyocytes induced ventricular remodeling, development of heart failure and pro-arrhythmogenic effects [3–7].

Aldosterone and glucocorticoids bind with similar affinity to MR. In the normal state, plasma glucocorticoid levels are more than 100 times higher that aldosterone levels and the majority of MRs in the heart is occupied by glucocorticoids. In patients with acute MI and chronic heart failure, not only circulating aldosterone levels but also aldosterone biosynthesis is enhanced. Moreover, the aldosterone-MR complex is more stable than the glucocorticoid-MR complex [8, 9]. Based on these findings, it is nowadays well accepted that aldosterone contributes to endothelial dysfunction, fibrinolytic disorders, inflammation, oxidative stress, fibrosis and

hypertrophy leading to or at least aggravating cardiovascular diseases (CVD) such as CAD and heart failure [10–13].

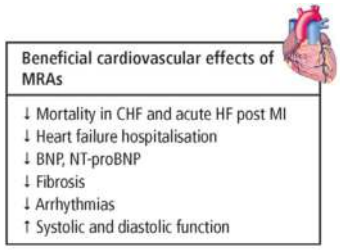
Presumably, the exact molecular mechanism of aldosterone's action is still not fully understood and appears to be more complex than initially thought. For example, aldosterone has been shown to promote the formation of venous thrombosis in normotensive rats via mechanisms involving primary hemostasis, fibrinolysis, nitric oxide and oxidative stress-dependent pathways but MR blockade was insufficient to reverse the effect. Notably, other receptors, such as the glucocorticoid receptor (GR) and angiotensin II receptor type 1 are involved [14, 15]. The effects of aldosterone are mediated via classic nuclear receptors (genomic actions of aldosterone) and cell-membrane receptors (non-genomic actions of aldosterone) with alternative pathways, including activation of protein kinases or secondary messenger signaling cascades [16, 17]. Indeed, in high, non-physiological plasma conditions, aldosterone can also act via GR [18] or the G protein-coupled estrogen receptor (GPR30). The latter one plays an important role in aldosterone-mediated regulation of endothelial cell growth and in aldosterone's endothelial-mediated regulation of vasoreactivity [19].

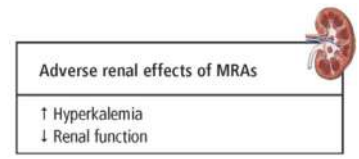
2.2 Development of MRAs

The development of MRAs begun during the 1950s. At that time, the main role of aldosterone was considered to be renal sodium and potassium excretion. Spironolactone, the first steroidal MRA, was primarily developed and used for the medical control of edema and ascites and control blood pressure, respectively. With the RALES trial, the perception of spironolactone changed; spironolactone, in addition to standard therapy, substantially reduced the risk of both morbidity and death among patients with severe heart failure [20]. With eplerenone, a second-generation steroidal MRA was developed. The advantage of eplerenone compared to spironolactone is mainly the higher selectivity for mineralocorticoid receptors, therefore avoiding hormonal side effects such as gynecomastia. Despite considerable efforts to ensure a broad application of this essential medication in this defined patient collective, many clinicians were reluctant to employ MRAs in their clinical practice due to potential side effects. These side effects included worsening of renal function, hyperkalemia and gynecomastia.

Interestingly, Vukadinović et al. performed a meta-analysis. The authors emphasize that non-MRA-related rises in potassium levels might be underestimated and should be rigorously explored before cessation of the evidence-based therapy with MRAs [21].

Nevertheless, the issue of hyperkalemia and worsening renal function triggered several pharmaceutical companies to develop novel MR-antagonizing compounds. These so-called third-generation MRAs, such as finerenone or canrenone, are non-steroidal compounds with both high selectivity and high potency to inhibit MR. The first compound of these novel MRAs undergoing clinical evaluation was finerenone, formerly known as BAY 94-8862. Finerenone is even more selective than eplerenone to the MR with very low affinity to androgen, glucocorticoid and progesterone receptor. In clear contrast to spironolactone and eplerenone, which have a higher tendency to concentrate in the kidney, finerenone displays a balanced distribution pattern into cardiac and kidney tissue of healthy rats [22, 23]. This suggests a more favorable balance between cardioprotection and renal side effects, especially in populations prone to hyperkalemia such as patients with chronic kidney disease or diabetes (**Figure 1**) [24, 25].





Generation	Class	Example	Affinity to MR	Selectivity	Adverse hormonal effects	Tissue distribution	Assumed risk for WRF/Hyperkalemia
I.	Steroidal	Spironolactone	High	Low	+	6-fold higher in kidney	High
II.	Steroidal	Eplerenone	Medium	Medium-High	-	3-fold higher in kidney	Medium
III.	Non-steroidal	Finerenone	High	High	-	Equal	Low

Figure 1.
Characteristics of three generations of mineralocorticoid receptor antagonists (MRAs).

To date, finerenone is under investigation in two large clinical trials (FIGARO-DKD: A Randomized, Double-Blind-Placebo-controlled, Multicenter, Event-driven Phase 3 Study to Investigate Efficacy and Safety of Finerenone on the Reduction of Cardiovascular Morbidity and Mortality in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease in Addition to Standard of Care (NCT02545049) and FIDELIO-DKD: A Randomized, Double-Blind, Placebo-controlled, Parallel-group, Multicenter, Event-driven Phase 3 Study to Investigate the Efficacy and Safety of Finerenone, in Addition to Standard of Care, on the Progression of Kidney Disease in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (NCT02540993)). The effect of canrenone compared to other therapies on cardiovascular mortality in patients with chronic heart failure and preserved systolic function is currently undertaken in the "COFFEE-IT" study: "CanrenOne eFFects on cardiovascular mortality in patiEnts with congEstIve hearT failure" (https://clinicaltrials.gov/ct2/show/NCT03263962).

2.3 MRAs in chronic systolic LV dysfunction (after ischemia)

For a long time, the strongest evidence for the clinical usefulness of MRAs existed for patients with chronic heart failure NYHA III and reduced ejection fraction. In 2012, the guidelines for diagnosis and treatment of acute and chronic heart failure by the European Society of Cardiology amended the recommendation of MRAs for all patients with symptoms of heart failure class II and worse according to the New York Heart Association (NYHA)-classification and an ejection fraction ≤35% [26]. Since then, the concept of MR blockade has become a main treatment paradigm in HFrEF.

Two large clinical trials have firmly established the role of MRAs in chronic heart failure: the Randomized Aldactone Evaluation Study (RALES) and the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF). Death from all causes and specifically cardiac death as well as hospitalization due to heart failure were decreased proving the efficacy of MRAs in patients with severely reduced LV function [20, 27]. Although the underlying pathophysiology is complex, the clinical effects of MRAs in these patients are thought to be mainly related to the improvement of LV remodeling with a reduction in collagen synthesis and myocardial fibrosis, seen as a decrease in LV size and hypertrophy and improved LV function [28].

With the development of the third-generation MRAs, such as finerenone, there came the necessity for further clinical trials. In rats with deoxycorticosterone acetate-(DOCA)/salt-induced heart and kidney injury as well as in a chronic myocardial infarction rat model, finerenone had proved to reduce cardiac hypertrophy, NT-proBNP and proteinuria more efficiently than eplerenone when directly comparing equinatriuretic doses [29]. Similarly, in a mouse model of pressure overload-induced heart failure treatment with finerenone compared to head-to-head with eplerenone resulted in a more pronounced prevention of myocardial hypertrophy [30].

ARTS (MinerAlocortocoid Receptor antagonist Tolerability Study) was the first randomized, controlled, phase II trial to test the safety and tolerability (Part A) of oral finerenone, at that time still under the name BAY 94-8862, in comparison with placebo and spironolactone (Part B). Finerenone was associated with significantly less increases in serum potassium concentration and fewer incidences of hyperkalemia (5.3 and 12.7%, respectively). Moreover, it decreased the levels of BNP, NT-proBNP and albuminuria at least as much as spironolactone. Adverse events related to the substance were infrequent and mostly mild. The authors concluded that in patients with HFrEF and moderate CKD, finerenone in various concentrations was at least as effective as spironolactone in decreasing biomarkers of hemodynamic stress and was associated with lower incidences of hyperkalemia [31, 32]. After these promising results, ARTS-HF (MinerAlocortocoid Receptor antagonist Tolerability Study-Heart Failure), a randomized, double-blind, phase IIb multicenter study was initiated to evaluate oral doses of finerenone given in patients with worsening heart failure and reduced ejection fraction and chronic kidney disease and/or diabetes mellitus. The trial showed a comparable efficacy between all dosage groups of finerenone and eplerenone in the primary endpoint, the decrease of >30% in plasma NT-proBNP from baseline to day 90 [33]. Similar results were obtained in the relatively small ARTS-HF Japan trial, conducted in Japan with the same regime as described for ARTS-HF [34]. Overall, finerenone showed a promising safety and efficacy profile in the so far conducted trials. However, patient numbers are too small to draw any fundamental conclusions. With FINESSE-HF, a multicenter, randomized, double-blind, double-dummy, parallel-group, active-controlled study to evaluate the efficacy and safety of finerenone compared to eplerenone on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction after recent heart failure. Decompensation and additional risk factors was supposed to launch. However, the trial prematurely ended in May 2016 (https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-002168-17/HU#D). To date, finerenone holds its promise of a novel MRA with greater selectivity, greater potency and fewer side effects. However, further clinical trials with enough power are needed in patients.

Currently, two clinical trials are evaluating the efficacy and safety of finerenone in patients with type 2 diabetes mellitus and diabetic kidney disease: the FIGARO-DKD and FIDELIO-DKD trial. Both trials evaluate whether oral finerenone compared to placebo is effective and safe in addition to standard of care. The primary outcome measures are, however, different. FIGARO-DKD evaluates the time of the first occurrence of the composite endpoint of cardiovascular death and non-fatal cardiovascular events (myocardial infarction, stroke or hospitalization for heart failure) in a follow-up of up to 53 months. The study is still recruiting and a total enrollment of 6400 participants with primary completion in January 2020 is estimated (https://clinicaltrials.gov/ct2/show/NCT02545049). FIDELIO-DKD aims to investigate the time of the first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of estimated glomerular filtration rate (eGFR) ≥40% from baseline over at least 4 weeks and renal death in a follow-up of up to

48 months. A total of 4800 participants and a study completion date of October 2019 is estimated (https://clinicaltrials.gov/ct2/show/NCT02540993).

2.4 MRAs early post infarction

Several preclinical animal studies with coronary artery disease and/or with heart failure have provided substantial evidence that activation of MR plays a pivotal role in cardiac healing and remodeling after myocardial ischemia. These studies suggested that cardiomyocyte-specific deletion of the MR gene attenuates LV dilatation, hypertrophy, fibrosis and heart failure, whereas cardiomyocyte-specific MR overexpression induced adverse remodeling and pro-arrhythmogenic effects [3, 7]. Moreover, administration of MRAs early after MI reduced the expansion of the healing infarct, attenuated early left ventricular dilatation and dysfunction and had more beneficial effects on survival, early cardiac dilatation and functional decline [3, 7, 35–38]. Indeed, after an acute MI, not only circulating aldosterone levels are increased but also the myocardium distant from the infarct zone shows enhanced activation of aldosterone synthesis [36].

In the clinical setting, Hayashi et al. demonstrated in 2003 that in patients with their first anterior STEMI and no evidence of early heart failure, intravenous canrenone followed by oral spironolactone for 6 months beginning day one post-MI was safe and associated with a significant reduction in ventricular remodeling, myocardial fibrosis and inflammatory cytokine activation [39]. In the same year, the well-planned and executed Eplerenone Post-acute myocardial infarction Heart failure Efficacy and Survival Study (EPHESUS) demonstrated MR blockade to substantially improve morbidity and mortality among patients with moderate to severe heart failure and LV dysfunction after MI [40]. More than 3000 patients with an ejection fraction $<40\%$ received either 50 mg eplerenone or placebo on a daily basis, starting 3–14 days after MI. In comparison to the placebo-group, all-cause mortality, cardiovascular mortality and sudden cardiac death were decreased by 15, 17 and 21%, respectively, in the eplerenone group.

Although EPHESUS had clearly established the clinical efficacy of MRAs in patients with heart failure after an acute MI, the value of MRAs after MI without concomitant heart failure needed to be determined. Moreover, EPHESUS suggested that an early initiation of eplerenone treatment had significant beneficial effects compared to later initiation [41]. The REMINDER trial (Role of Eplerenone in acute Myocardial Infarction-Double-blind, Early treatment initiation, Randomized, placebo-controlled, multi-center study) evaluated the potential benefit of early administered eplerenone on cardiovascular morbidity and mortality after STEMI. In this randomized, placebo-controlled, double-blind trial, 1012 patients with acute STEMI and without a history of heart failure were randomized to receive either eplerenone (25–50 mg once daily) or placebo in addition to standard therapy. Treatment was initiated within 24 hours after onset of symptoms. The primary endpoint was the composite of CV mortality, re-hospitalization or extended initial hospital stay, due to diagnosis of heart failure, sustained ventricular tachycardia or fibrillation, ejection fraction $\leq 40\%$ or elevated BNP/NT-proBNP at 1 month or more after randomization. The trial showed that the addition of eplerenone during the acute phase of STEMI was safe and well tolerated. It reduced the primary endpoint over a mean 13 months follow-up mostly because of significantly lower natriuretic peptide levels [42].

Similarly, the ALBATROSS trial (Aldosterone Lethal effects Blocked in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at 6 months follow-up) randomized patients admitted for STEMI and non-STEMI to test whether administration of MRAs within 72 hours after onset of

symptoms improves cardiovascular outcome regardless of heart failure and treatment strategy. In total, 1603 patients were included an received an MRA regime with a single 200 mg intravenous bolus of potassium canrenoate followed by 25 mg oral spironolactone once daily for 6 months in addition to standard therapy or standard therapy alone. The primary outcome of the study was the composite of death, resuscitated cardiac arrest, significant ventricular arrhythmia, indication for implantable defibrillator, or new or worsening heart failure at 6-month follow-up. Key secondary/safety outcomes included death and other individual components of the primary outcome and rates of hyperkalemia at 6 months [43]. However, the study failed to show the benefit of early MRA use in addition to standard therapy in patients admitted for MI, and was intensively discussed among experts. In the overall opinion, both ALBATROSS and REMINDER are undersized to detect a difference in rates of hard clinical outcomes [43, 44]. Beygui et al. therefore conducted a pre-specific meta-analysis and pooled individual patient-level data of the STEMI subgroup of the ALBATROSS and the total population of the REMINDER trial. Their analysis showed reduced rates of death in the MRA-treated group compared to standard therapy. Although the authors underline that this specific subgroup analysis should be considered "exploratory," it suggests a consistent effect of the early MRA-treatment in patients with STEMI [45]. However, under these circumstances, additional studies are needed to clarify the role of early use of MRAs in patients with MI without heart failure.

2.5 MRAs in stable coronary artery disease

A large number of preclinical studies indicate that aldosterone is an important stimulus for vascular disease, with inflammation and fibrosis being the key players, [3–6] and MRAs are able to inhibit atherosclerosis progression in different animal models [46–49]. Treatment with aldosterone results in increased inflammation and upregulated expression of proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-1β and transforming growth factor-β1 in rat myocardium. Additionally, it leads to an increase in 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 [7]. Oxidative stress is well-recognized to trigger inflammation and to contribute to the development of fibrosis [7]. Furthermore, MR activation stimulates apoptosis and causes vasoconstriction and reduced blood flow in the animal heart and MRA treatment reverses these effects [7]. Especially finerenone can significantly reduce apoptosis of endothelial cells and simultaneously attenuate smooth muscle cells proliferation, resulting in accelerated endothelial healing and reduced neointima formation of the injured vessels [50]. Over the years, several clinical studies in patients with coronary artery disease pinpointed the association of high aldosterone levels with an increased risk of cardiovascular death and all-cause-mortality [51], the occurrence of an ischemic event [52] or the progression of carotid artery plaques [53]. Although clear evidence exists that there is a strong relationship between aldosterone and the progression of chronic CAD, up to now no large clinical trial has specifically evaluated the effect of MRAs on the amelioration of plaque formation. Vukusich et al. executed a randomized, double-blind, placebo-controlled trial to assess the effectiveness of spironolactone in preventing progression of carotid intima-media thickness (CIMT) in non-diabetic hemodialysis patients. Over a period of 24 months, 53 patients received either 50 mg spironolactone or placebo thrice weekly after dialysis. CIMT measurements revealed a progression in the placebo-group whereas in the spironolactone-treated patients, CIMT significantly decreased [54]. Another clinical trial is currently

recruiting patients to study the effect of spironolactone on vascular atherosclerotic burden. The "Mineralocorticoid Receptor Antagonism Clinical Evaluation in atherosclerosis Trial" (NCT02169089) is a phase IV trial that aims to evaluate the efficacy of spironolactone in decelerating the worsening of atherosclerotic disease in the aorta in patients with type 2 diabetes and a previous history of CAD. The patients are randomized to spironolactone (12.5–25 mg daily) versus placebo. The primary endpoint is the atheroma volume evaluated via magnetic resonance imaging (MRI) pictures of the aortic wall before and after therapy (https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-002168-17/HU#D). In another clinical approach, Garg et al. measured the effect of spironolactone on cardiovascular function in patients with diabetes and used the coronary flow reserve as a marker for coronary microvascular function. A total of 64 participants with well-controlled diabetes who were on chronic ACE-therapy were randomized to 25 mg spironolactone, 12.5 mg hydrochlorothiazide or placebo for 6 months. The spironolactone-treated patients showed a significant improvement in coronary microvascular function [55].

Endothelial dysfunction plays an important role in the pathogenesis of CAD and is a well-established marker for cardiovascular risk and prognosis [56]. Accordingly, MR blockade has been shown to improve endothelial dysfunction in patients with HFrEF [57]. Bavry et al. designed a double-blind, parallel-group, repeated measures study in women with symptoms and signs of ischemia and coronary endothelial dysfunction but no significant CAD already receiving ACE-inhibitor or angiotensin receptor blockers. Patients received either eplerenone (25 mg daily for 4 weeks, then uptitrated to 50 mg daily for 12 weeks) or placebo. The primary outcome was percent change in coronary diameter to acetylcholine and secondary in flow reserve to adenosine at 16 weeks. A total of 41 women completed the treatment period, but there was no significant difference between treatment groups [58]. Similarly, Sudano et al. randomized CAD patients with preserved ejection fraction to receive daily eplerenone (25 mg) or placebo and assessed endothelial cell function after 4 weeks of treatment. Based on brachial artery dilatation, the investigators did not find any differences in the endothelial cell function between the groups [59].

In contrast to the firmly established benefit of MR blockade in HFrEF and patients with LV-dysfunction after MI, the role of MRAs with stable CAD with preserved ejection fraction remains a matter of debate. The variety of small studies with different approaches and endpoints is not sufficient to give a general recommendation. Larger, prospective, randomized trials are needed further evaluating the role of MR blockade in stable CAD.

3. Conclusion

It has long been clear that the effects of aldosterone are more diverse than originally thought. High aldosterone plasma levels early after STEMI or NSTEMI or in patients with heart failure are associated with increased cardiovascular morbidity and mortality. Clinical trials have firmly established that MR blocking therapy provides considerable improvements in cardiovascular mortality and morbidity in patients with severe heart failure (RALES and ARTS-HF), LV dysfunction after acute MI (EPHESUS), as well as in patients with less symptomatic chronic heart failure (EMPHASIS-HF) (**Table 1**). With REMINDER and ALBATROSS, there is conflicting data on the role of MRAs in patients after MI without LV-dysfunction. However, one has to keep in mind that ALBATROSS and REMINDER were both underpowered and group analysis showed that patients with STEMI might benefit from treatment. As with stable CAD and preserved ejection fraction, the role of MR

Study	RALES	EPHESUS	EMPHASIS-HF	REMINDER	ALBATROSS	ARTS	ARTS-HF	ARTS-HF Japan	FIGARO-DKD	FIDELIO-DKD
Year	1999	2003	2011	2014	2016	2013	2015	2016	Recruiting	Active, not recruiting
Primary end-point	Mortality	All-cause or CV mortality, hosp. for CHF	CV death, hosp. for CHF	Mortality, hosp. for CHF	Death, worsened CHF, arrhythmias	Part A: safety and tolerability; Part B: change in serum potassium	decrease in NT-proBNP >30%	decrease in NT-proBNP >30%	CV death and no-fatal CV events	Onset of kidney failure, decrease of eGFR
No. of patients	1663	6642	2737	506	1603	65 (Part A) +393 (Part B)	1066	72	6400 (estimated)	4800 (estimated)
Inclusion criteria	Severe CHF	Post-MI (within 3–14 days), CHF or diabetes	Mild CHF, <55 years	STEMI	STEMI or high risk non-STEMI, ≥18 years	HFrEF and mild (Part A)/ moderate (Part B) chronic kidney disease	Worsening CHF, treatment with diuretics; eGFR ≥30 ml/min/m^2	Worsening CHF, treatment with diuretics; eGFR ≥30 ml/min/m^2	Type 2 Diabetes mellitus, Diabetic Kidney Disease, pretreatment with ACE-I	Type 2 Diabetes mellitus, Diabetic Kidney Disease, pretreatment with ACE-I
	NYHA III-IV	NYHA I-IV	NYHA II	n.a.	n.a.	NYHA II-III	n.a.	n.a.	n.a.	n.a.
	EF <35%	EF <40%	EF <35%	EF >40%	n.a.	EF ≤40%	EF ≤40%	EF ≤40%	n.a.	n.a.
Major exclusion criteria	P-creatinine >220 μm, P-K >5.0	P-creatinine >220 μm, P-K >5.0	eGFR < 30 ml/min/m^2, P-K >5.0	eGFR < 30 ml/min/m^2, P-creatinine ≥220 μm	P-creatinine >220 μm and/ or Creatinine clearance < 30 ml/m	worsening HF requiring hospitalization/ treatment with diuretucs	*de novo* HF, acute inflammation, ACS/ stroke 3 months prior	*de novo* HF, acute inflammation, ACS/stroke 3 months prior	HFrEF, NYHA II-IV, Dialysis	HFrEF, NYHA II-IV, Dialysis
Mean age (years ± SD)	65 ± 12	64 ± 12	68.7 ± 7.7	58.5 ± 10.8	58		69.2 – 72.5 ± 9.7 – 10.6 (different treatment groups)	65.9 – 78.2 (different treatment groups)		

Study	RALES	EPHESUS	EMPHASIS-HF	REMINDER	ALBATROSS	ARTS	ARTS-HF	ARTS-HF Japan	FIGARO-DKD	FIDELIO-DKD
Medical therapy	ACE-I, diuretic	ACE-I/ ARB, ß-blocker, diuretic	ACE-I/ARB, ß-blocker, diuretic	ACE-I/ARB, ß-blocker	ACE-I/ARB, ß-blocker	ACE-I/ARB, ß-blocker, diuretic	ACE-I/ARB, ß-blocker, diuretic	ACE-I/ARB, ß-blocker, diuretic	ACE-I	ACE-I
MRA	Spironolactone	Eplerenone	Eplerenone	Eplerenone	Bolus of K+ canreonate, then spironolactone	Finerenone versus Spironolactone versus Placebo	Finerenone versus Eplerenone	Finerenone versus Eplerenone	Finerenone	Finerenone
Dose (mg/ day)	25–50	25–50	25–50	Up to 50	25	2.5–10 (Finerenone); up to 50 mg (Spironolactone)	2.5–20 (Finerenone); up to 50 mg (Eplerenone)	2.5–20 (Finerenone); up to 50 (Eplerenone)	10 and 20 mg	10 and 20 mg
Mean daily dose (mg/day)	26	43	39	88.6% received high dose	25	%	%	%		
Follow-up	24 months	16 months	21 months	18 months	6 months	1 month	90 days	90 days	53 months	48 months
End-point	−30% all-cause mortality	−15% all-cause mortality	−34% all-cause mortality	composite clinical endpoint: eplerenone 1.8%, placebo 3.2%	primary outcome: spironolactone 11.8%, placebo 12.2%	Part A: safety and tolerabilty confirmed; Part B: lower incidences of hyperkalaemia	37.2% eplerenone; 30.9–38.8% finerenone	23.1% eplerenone; 15.4–45.5% finerenone		
	−31% cardiovasc. mortality	−17% cardiovasc. mortality	−37% cardiovasc. mortality							
	−33% hosp. for HF	−23% hosp. for HF	−42% hosp. for HF							

Table 1.
Trials of mineralocorticoid receptor antagonists in the context of myocardial infarction and heart failure: demographics and outcome.

blockade in this highly inhomogeneous patient collective is still unclear and remains a matter of debate. The variety of small studies with different approaches and endpoints is not sufficient to give a general recommendation. Larger, prospective, randomized trials are urgently needed.

Regarding drug safety and side effects: when contraindications such as co-medication with potassium-sparing diuretics are respected and renal function and potassium levels are closely monitored, application of spironolactone and eplerenone is relatively safe and patients with mild to moderate renal insufficiency gain similar reductions in mortality and hospitalization as heart failure patients with normal renal function. Nevertheless, there are always cases in which deterioration of the kidney function or hyperkalemia requires the discontinuation of the medication. Especially with the development of the non-steroidal third-generation MRAs, such as finerenone, with both high selectivity and high potency to inhibit MR, we might be able to fulfill the hope of achieving cardiovascular benefit without or at least with fewer renal side effects than spironolactone and eplerenone (**Figure 1**).

Without any question, MRAs are nowadays one of the mainstays of current pharmacotherapy for cardiovascular diseases and are clearly indicated in patients with chronic heart failure (NYHA class II–IV and and/or an ejection fraction ≤35%) as well as in patients with evidence of heart failure/LV dysfunction early after an acute MI. On the contrary, no general recommendation for immediate MR antagonism is currently justified in patients without LV dysfunction after MI. An adequately powered prospective randomized trial evaluating the safety and efficacy of MRA administration early post-MI in patients without heart failure/LV dysfunction is still needed to finally answer that question.

Acknowledgements

This publication is based upon work from the EU COST Action ADMIRE BM1301 in Aldosterone and Mineralocorticoid Receptor Physiology and Pathophysiology www.admirecosteu.com.

Author details

Carolin Zwadlo and Johann Bauersachs*
Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany

*Address all correspondence to: bauersachs.johann@mh-hannover.de

References

[1] Zwadlo C, Bauersachs J. Mineralocorticoid receptor antagonists for therapy of coronary artery disease and related complications. Current Opinion in Pharmacology. 2013;**13**(2):280-286

[2] Messaoudi S et al. Aldosterone, mineralocorticoid receptor, and heart failure. Molecular and Cellular Endocrinology. 2012;**350**(2):266-272

[3] Fraccarollo D et al. Deletion of cardiomyocyte mineralocorticoid receptor ameliorates adverse remodeling after myocardial infarction. Circulation. 2011;**123**(4):400-408

[4] Lother A et al. Ablation of mineralocorticoid receptors in myocytes but not in fibroblasts preserves cardiac function. Hypertension. 2011;**57**(4): 746-754

[5] de Resende MM, Kauser K, Mill JG. Regulation of cardiac and renal mineralocorticoid receptor expression by captopril following myocardial infarction in rats. Life Sciences. 2006; **78**(26):3066-3073

[6] Ouvrard-Pascaud A et al. Conditional mineralocorticoid receptor expression in the heart leads to life-threatening arrhythmias. Circulation. 2005;**111**(23): 3025-3033

[7] Bauersachs J, Jaisser F, Toto R. Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. Hypertension. 2015; **65**(2):257-263

[8] Farman N, Rafestin-Oblin ME. Multiple aspects of mineralocorticoid selectivity. American Journal of Physiology. Renal Physiology. 2001; **280**(2):F181-F192

[9] Guder G et al. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. Circulation. 2007;**115**(13): 1754-1761

[10] Farquharson CA, Struthers AD. Aldosterone induces acute endothelial dysfunction in vivo in humans: Evidence for an aldosterone-induced vasculopathy. Clinical Science (London, England). 2002;**103**(4):425-431

[11] Brown NJ et al. Aldosterone modulates plasminogen activator inhibitor-1 and glomerulosclerosis in vivo. Kidney International. 2000; **58**(3):1219-1227

[12] Iglarz M et al. Involvement of oxidative stress in the profibrotic action of aldosterone. Interaction with the renin-angiotension system. American Journal of Hypertension. 2004;**17**(7): 597-603

[13] Sun Y et al. Aldosterone-induced inflammation in the rat heart: Role of oxidative stress. The American Journal of Pathology. 2002;**161**(5):1773-1781

[14] Gromotowicz A et al. Study of the mechanisms of aldosterone prothrombotic effect in rats. Journal of the Renin-Angiotensin-Aldosterone System. 2011;**12**(4):430-439

[15] Gromotowicz-Poplawska A et al. The acute prothrombotic effect of aldosterone in rats is partially mediated via angiotensin II receptor type 1. Thrombosis Research. 2016;**138**:114-120

[16] Dooley R, Harvey BJ, Thomas W. Non-genomic actions of aldosterone: From receptors and signals to membrane targets. Molecular and Cellular Endocrinology. 2012;**350**(2): 223-234

[17] Krug AW et al. Cell membrane-associated mineralocorticoid receptors?

New evidence. Hypertension. 2011; **57**(6):1019-1025

[18] Rossier MF, Python M, Maturana AD. Contribution of mineralocorticoid and glucocorticoid receptors to the chronotropic and hypertrophic actions of aldosterone in neonatal rat ventricular myocytes. Endocrinology. 2010;**151**(6):2777-2787

[19] Gros R et al. Aldosterone mediates its rapid effects in vascular endothelial cells through GPER activation. American Journal of Physiology. Cell Physiology. 2013;**304**(6):C532-C540

[20] Pitt B et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone evaluation study investigators. The New England Journal of Medicine. 1999; **341**(10):709-717

[21] Vukadinovic D et al. True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: A meta-analysis. American Heart Journal. 2017;**188**:99-108

[22] Kolkhof P, Borden SA. Molecular pharmacology of the mineralocorticoid receptor: Prospects for novel therapeutics. Molecular and Cellular Endocrinology. 2012;**350**(2):310-317

[23] Barfacker L et al. Discovery of BAY 94-8862: A nonsteroidal antagonist of the mineralocorticoid receptor for the treatment of cardiorenal diseases. ChemMedChem. 2012;7(8):1385-1403

[24] Bauersachs J. The ARTS of third-generation mineralocorticoid receptor antagonists: Achieving cardiovascular benefit with minimized renal side effects? European Heart Journal. 2013; **34**(31):2426-2428

[25] Kolkhof P, Barfacker L. 30 years of the mineralocorticoid receptor: Mineralocorticoid receptor antagonists: 60 years of research and development. The Journal of Endocrinology. 2017; **234**(1):T125-T140

[26] McMurray JJ et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. European Heart Journal. 2012; **33**(14):1787-1847

[27] Zannad F et al. Eplerenone in patients with systolic heart failure and mild symptoms. The New England Journal of Medicine. 2011;**364**(1):11-21

[28] Chan AK et al. Aldosterone receptor antagonism induces reverse remodeling when added to angiotensin receptor blockade in chronic heart failure. Journal of the American College of Cardiology. 2007;**50**(7):591-596

[29] Kolkhof P et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. Journal of Cardiovascular Pharmacology. 2014; **64**(1):69-78

[30] Grune J et al. Steroidal and nonsteroidal mineralocorticoid receptor antagonists cause differential cardiac gene expression in pressure overload-induced cardiac hypertrophy. Journal of Cardiovascular Pharmacology. 2016; **67**(5):402-411

[31] Pitt B et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: A randomized, double-blind trial. European Heart Journal. 2013;**34**(31): 2453-2463

[32] Pitt B et al. Rationale and design of ARTS: A randomized, double-blind

study of BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease. European Journal of Heart Failure. 2012; **14**(6):668-675

[33] Filippatos G et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. European Heart Journal. 2016;**37**(27): 2105-2114

[34] Sato N et al. A randomized controlled study of Finerenone vs. eplerenone in Japanese patients with worsening chronic heart failure and diabetes and/or chronic kidney disease. Circulation Journal. 2016;**80**(5): 1113-1122

[35] Bauersachs J, Fraccarollo D. Mineralocorticoid receptor-dependent adverse Remodeling after myocardial infarction mediated by uNGALant activation of NFkappaB. Hypertension. 2017;**70**(6):1080-1081

[36] Silvestre JS et al. Activation of cardiac aldosterone production in rat myocardial infarction: Effect of angiotensin II receptor blockade and role in cardiac fibrosis. Circulation. 1999;**99**(20):2694-2701

[37] Fraccarollo D et al. Immediate mineralocorticoid receptor blockade improves myocardial infarct healing by modulation of the inflammatory response. Hypertension. 2008;**51**(4): 905-914

[38] Fraccarollo D et al. Efficacy of mineralocorticoid receptor antagonism in the acute myocardial infarction phase: Eplerenone versus spironolactone. ESC Heart Failure. 2015;**2**(3):150-158

[39] Hayashi M et al. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. Circulation. 2003;**107**(20):2559-2565

[40] Pitt B et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. The New England Journal of Medicine. 2003; **348**(14):1309-1321

[41] Adamopoulos C et al. Timing of eplerenone initiation and outcomes in patients with heart failure after acute myocardial infarction complicated by left ventricular systolic dysfunction: Insights from the EPHESUS trial. European Journal of Heart Failure. 2009;**11**(11):1099-1105

[42] Montalescot G et al. Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: The randomized double-blind Reminder study. European Heart Journal. 2014; **35**(34):2295-2302

[43] Beygui F et al. Early aldosterone blockade in acute myocardial infarction: The ALBATROSS randomized clinical trial. Journal of the American College of Cardiology. 2016;**67**(16):1917-1927

[44] Pitt B. MRAs in patients with AMI without early evidence of heart failure: Time for reappraisal? Journal of the American College of Cardiology. 2016; **67**(16):1928-1930

[45] Beygui F et al. Individual participant data analysis of two trials on aldosterone blockade in myocardial infarction. Heart. Nov 2018;**104**(22):1843-1849. DOI: 10.1136/heartjnl-2018-312950. Epub 2018 Apr 25

[46] Rajagopalan S et al. Mineralocorticoid receptor antagonism in experimental atherosclerosis. Circulation. 2002;**105**(18):2212-2216

[47] Keidar S et al. Effect of eplerenone, a selective aldosterone blocker, on blood pressure, serum and macrophage oxidative stress, and atherosclerosis in apolipoprotein E-deficient mice. Journal of Cardiovascular Pharmacology. 2003; **41**(6):955-963

[48] Suzuki J et al. Eplerenone with valsartan effectively reduces atherosclerotic lesion by attenuation of oxidative stress and inflammation. Arteriosclerosis, Thrombosis, and Vascular Biology. 2006;**26**(4):917-921

[49] Dutzmann J, Bauersachs J, Sedding DG. Evidence for the use of mineralocorticoid receptor antagonists in the treatment of coronary artery disease and post-angioplasty restenosis. Vascular Pharmacology. 2017

[50] Dutzmann J et al. The novel mineralocorticoid receptor antagonist finerenone attenuates neointima formation after vascular injury. PLoS One. 2017;**12**(9):e0184888

[51] Tomaschitz A et al. Plasma aldosterone levels are associated with increased cardiovascular mortality: The Ludwigshafen risk and cardiovascular health (LURIC) study. European Heart Journal. 2010;**31**(10):1237-1247

[52] Ivanes F et al. Aldosterone, mortality, and acute ischaemic events in coronary artery disease patients outside the setting of acute myocardial infarction or heart failure. European Heart Journal. 2012;**33**(2):191-202

[53] de Rita O, Hackam DG, Spence JD. Effects of aldosterone on human atherosclerosis: Plasma aldosterone and progression of carotid plaque. The Canadian Journal of Cardiology. 2012; **28**(6):706-711

[54] Vukusich A et al. A randomized, double-blind, placebo-controlled trial of spironolactone on carotid intima-media thickness in nondiabetic hemodialysis patients. Clinical Journal of the American Society of Nephrology. 2010; **5**(8):1380-1387

[55] Garg R et al. Mineralocorticoid receptor blockade improves coronary microvascular function in individuals with type 2 diabetes. Diabetes. 2015; **64**(1):236-242

[56] Gutierrez E et al. Endothelial dysfunction over the course of coronary artery disease. European Heart Journal. 2013;**34**(41):3175-3181

[57] Farquharson CA, Struthers AD. Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. Circulation. 2000;**101**(6): 594-597

[58] Bavry AA et al. Aldosterone inhibition and coronary endothelial function in women without obstructive coronary artery disease: An ancillary study of the national heart, lung, and blood institute-sponsored women's ischemia syndrome evaluation. American Heart Journal. 2014;**167**(6): 826-832

[59] Sudano I et al. Vascular effects of eplerenone in coronary artery disease with preserved ejection fraction: A double-blind, randomized, placebo-controlled trial. Clinical Cardiology. 2016;**39**(5):285-290