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RESISTANT HYPERTENSION (L DRAGER, SECTION EDITOR)

Eplerenone Versus Spironolactone in Resistant Hypertension: an Efficacy and/or Cost or Just a Men's Issue?

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Abstract

Purpose of Review To review comparative efficacy and tolerability data between the two main mineralocorticoid receptor antagonists (MRAs), spironolactone and eplerenone, in patients with resistant hypertension (HTN). The focus was whether spironolactone, being the classical non-selective agent that has been used for years, albeit with several anti-androgenic side effects, can be rivaled by eplerenone, an apparently weaker, but better tolerated, more selective MRA.

Recent Findings Evidence has accumulated that resistant HTN is generally volume-dependent, attributable to varying degrees of aldosterone excess with its attendant renal effects of sodium and fluid retention. Such aldosteronism may be due to an underestimated occurrence of primary aldosteronism; however, it more commonly occurs separately from it and independent from angiotensin II. The aldosterone-induced volume excess placed at the root of the development of resistant HTN in a large number of patients, together with the extrarenal deleterious effects of aldosterone, such as endothelial dysfunction, vascular remodeling and increased arterial stiffness, cardiac hypertrophy, and fibrosis can all be counterbalanced by the administration of MRAs. In the absence of a direct comparison between spironolactone and eplerenone, and in light of compelling evidence provided by the recently reported results of the PATHWAY-2 and ReHOT studies, spironolactone has been established as the most effective add-on anti-aldosterone therapy in resistant HTN. The data on use of eplerenone continue to emerge and are quite encouraging.

Summary Despite the lack of direct comparative data, the weight of evidence regarding efficacy is currently in favor of spironolactone. However, the data on the efficacy of eplerenone are promising but still being accumulated suggesting this agent as an alternative to spironolactone and certainly as the preferred choice for those not tolerating spironolactone, especially for patients developing anti-androgenic side effects like breast tenderness, gynecomastia/mastodynia, and/or sexual dysfunction. Both these agents appear to have several other pleiotropic effects that confer cardioprotection and renoprotection beyond their antihypertensive effect. Potassium levels and renal function need to be closely monitored during administration of these therapies. Future comparative studies may shed more light on these issues, while emerging newer agents may offer better and safer therapeutic options.

Keywords Hypertension · Resistant hypertension · Aldosterone · Aldosteronism · Spironolactone · Eplerenone · Mineralocorticoid receptor antagonist · Heart failure

This article is part of the Topical Collection on *Resistant Hypertension*

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Abbreviations

ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
BP	Blood pressure
CKD	Chronic kidney disease
CV	Cardiovascular
eGFR	Estimated glomerular filtration rate
HF	Heart failure
HTN	Hypertension
LV	Left ventricle(-ular)

LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
NYHA	New York Heart Association
PA	Primary aldosteronism
RAAS	Renin–angiotensin–aldosterone system
RAS	Renin–angiotensin system
RCT	Randomized controlled trial
SCD	Sudden cardiac death

Introduction

Spironolactone was the first mineralocorticoid receptor antagonist (MRA) available for the treatment of hypertension (HTN) and heart failure (HF) [1•]. Eplerenone was the second MRA that received Food and Drug Administration (FDA) approval 15 years ago for the same indications. Aldosterone, part of the renin–angiotensin–aldosterone system (RAAS), has been linked to HTN, cardiac hypertrophy, and cardiac and vascular fibrosis [2]. Despite treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), suppression of aldosterone is not complete due to non-angiotensin II regulators of aldosterone production, such as serum potassium.

Spironolactone is a non-selective MRA that has progestational and anti-androgenic adverse effects due to its nonspecific binding to various steroid receptors. Eplerenone is a more selective inhibitor of the mineralocorticoid receptor, with up to a 500-fold lower affinity for the androgen and progestin receptors that leads to fewer side effects [3]. Other non-steroidal MRAs (finerenone, apararenone, esaxerenone) are in clinical trials in patients with HTN, HF, chronic kidney disease (CKD), and liver disease [1•]. MRAs have proven efficacy in patients with resistant HTN, considered as one of the best pharmacologic options in this subgroup of patients [4, 5]. As detailed below, a milestone randomized controlled trial (RCT), the PATHWAY-2 study, demonstrated that spironolactone was the most effective drug added to a standard three-drug regimen in the treatment of resistant HTN [6••], while another more recent study (ReHOT) indicated that spironolactone is preferable as the fourth drug for the treatment of resistant HTN [7•].

Deleterious Effects of Aldosterone in Hypertensive Patients

Aldosterone excess has been commonly documented in patients with resistant HTN [8•, 9•, 10]. Furthermore, primary aldosteronism (PA) may be more common than what was previously thought, particularly in patients with resistant HTN [2]. The effectiveness of antihypertensive therapy with MRAs apparently attests to the plethora of observations indicating a significant role of aldosterone in contributing to resistant or difficult to treat HTN [11, 12, 13•, 14•, 15•]. Aldosterone excess occurring separately from PA and independent from angiotensin II may have several causes, including, but not limited to, obesity and/or sleep apnea [2, 16, 17].

Beyond sodium reabsorption in the distal nephron of the kidney, aldosterone exerts several other effects on the kidney, heart, and vasculature (Fig. 1) [18, 19]. Several studies have indicated an important role of aldosterone in the pathophysiological mechanism of target-organ damage encountered in hypertensive disease [18, 20]. Aldosterone has been implicated in left ventricular hypertrophy (LVH), renal injury, vascular disease [21–24], atrial (atrial fibrillation/flutter), and ventricular arrhythmias [25] and structural and functional changes of medium-sized arteries [26], as well as microcirculation injuries and endothelial dysfunction [27–29]. Hence, the impetus has emerged to counter these deleterious effects with use of MRAs in hypertensive patients.

MRAs in Hypertension

Spironolactone A longer experience with MRAs in HTN therapy exists for spironolactone, which has been used with or without a thiazide diuretic to treat mild to moderate HTN and more recently as add-on therapy for resistant HTN [30–34].

A meta-analysis of 5 crossover trials ($n = 137$) and of 1 RCT ($n = 42$) studying patients with primary HTN followed for 4–8 weeks of therapy found a reduction in systolic blood pressure (BP) of 20.09 mmHg ($p < 0.00001$) and a 6.75-mmHg ($p < 0.00001$) reduction in diastolic BP [35•]. There was no evidence of heterogeneity between the studies. It appeared that doses > 50 mg/day did not produce further reductions in either systolic BP or diastolic BP. One crossover study found that spironolactone 25 mg/day did not statistically significantly change systolic or diastolic BP compared to placebo. The authors concluded that spironolactone appears to lower BP compared to placebo at reasonable doses of 25 to 100 mg/day. There was no evidence of the effect of spironolactone on clinical outcomes in hypertensive patients.

Eplerenone Eplerenone has also been used effectively in managing patients with mild/moderate HTN [36, 37, 38•, 39]. The antihypertensive effect of eplerenone has been shown to be equal in black and white patients and even superior to an ARB in black patients [40]. According to a meta-analysis of 11 randomized clinical trials assessing eplerenone in > 3500 hypertensives with mild to moderate HTN, eplerenone is an effective antihypertensive agent when used alone or in combination with other medications [41•]. In doses of 25–100 mg

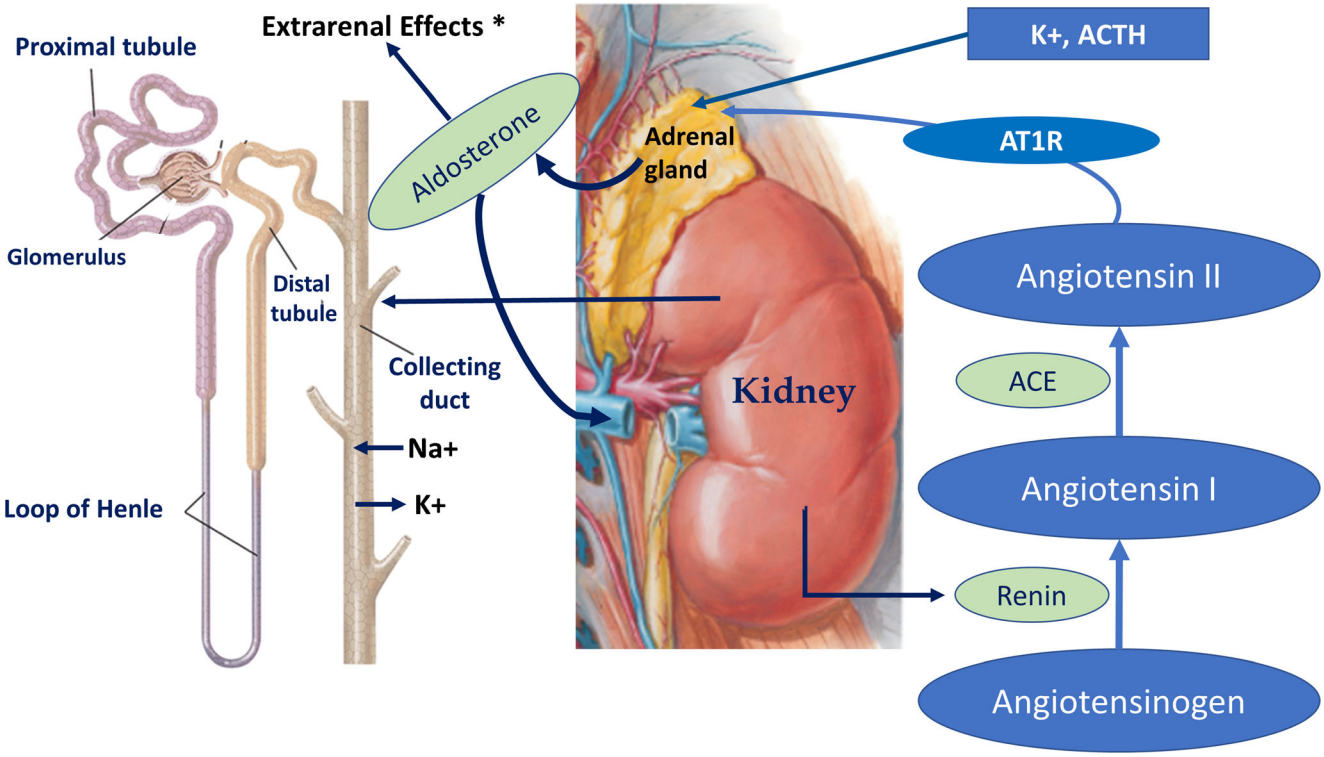

Fig. 1 Production and effects of aldosterone. Aldosterone is produced in the zona glomerulosa of the adrenal cortex in response to angiotensin II, increased serum potassium, and corticotropin (ACTH). It regulates total body sodium (Na+) and potassium (K+) balance by binding and activating mineralocorticoid receptors in the distal collecting duct of the kidney. However, aldosterone exerts additional extrarenal effects on vascular tissue and the heart (*). These effects may culminate in end-organ damage via inflammation, vascular and cardiac fibrosis, left ventricular hypertrophy, endothelial dysfunction, and oxidative stress. Similar to the angiotensin II, the renal and extrarenal effects of aldosterone may contribute to the control of systemic blood pressure and are directly implicated in the development of resistant hypertension. ACTH = adrenocorticotropin hormone; ACE = angiotensin-converting enzyme; AT1R = angiotensin II type-1 receptor.
*Extrarenal effects: in the *heart* (pro-arrhythmia/electrical ionic remodeling, tissue inflammation/cardiac anatomical remodeling and fibrosis, cardiac hypertrophy, oxidative stress), the *vascular tissue* (endothelial dysfunction, vascular smooth cell muscle cell proliferation, arterial stiffness, vascular inflammation and injury), and the *adipose tissue* (local activation of RAAS, insulin resistance, metabolic syndrome, inflammation, oxidative stress)

daily, eplerenone monotherapy results in a dose-dependent reduction in clinic BP. As compared to placebo, eplerenone reduces significantly BP from baseline; a 100-mg daily dose of eplerenone has a BP lowering effect that is 50–75% that of spironolactone. Eplerenone seems to supersede the antihypertensive effect of losartan, and its efficacy is comparable to the effect of amlodipine while eplerenone is better tolerated.

A meta-analysis and review of the effects of eplerenone monotherapy (25–400 mg/day) versus placebo for primary HTN in 1437 adult patients participating in 5 RCTs, with treatment durations ranging from 8 to 16 weeks, showed a reduction in systolic BP of 9.21 mmHg and of diastolic BP of 4.18 mmHg (moderate quality evidence) [42•]. Overall, there did not appear to be a clinically important dose response in lowering systolic or diastolic BP at eplerenone doses of 50 to 400 mg daily. With only 3 of the 5 studies reporting adverse events, there did not appear to be any differences in the number of patients who withdrew due to adverse events or the number of patients with at least one adverse event in the eplerenone group compared with placebo.

An RCT (EVALUATE study) [43] showed that the addition of low-dose (50 mg/d) eplerenone to renin–angiotensin system (RAS) inhibitors in 170 hypertensive patients with non-diabetic CKD and albuminuria may have renoprotective effects compared to controls (n = 166) through reduction of albuminuria in this cohort, without serious safety concerns. Although mean serum potassium concentration was higher in the eplerenone group than the placebo group, severe hyperkalemia (5.5 mmol/L) was not recorded in either group.

MRAs in Resistant Hypertension

Resistant HTN is defined as uncontrolled elevated BP (> 140/90 mmHg) in a patient despite the concurrent use of three antihypertensive drug classes, usually including a calcium channel blocker, a blocker of the RAS (ACE inhibitor or ARB), and a diuretic. The global prevalence of true resistant HTN remains high (~ 10%) after excluding causes of pseudo-

resistant HTN including white-coat HTN with the use of ambulatory BP measurement [44••]. The burden of resistant HTN is higher in CKD (~ 20%), renal transplant (~ 55%) and elderly (~ 12%) patients. Thus, there is a dire need for effective treatments for resistant HTN, considering the disastrous complications of the disease.

Aldosterone excess and evidence of intravascular volume expansion have been noted in patients with resistant HTN, supporting a relationship of aldosteronism and poor BP control in these patients and suggesting a role of MRAs in their management [4, 9•, 10, 45]. The phenomenon of aldosterone excess or "escape" observed in PA, has also been noted in patients with resistant HTN after treatment with drugs that block the RAS, and despite its presence, MRAs have been shown to reduce BP and improve endothelial and diastolic function and left ventricular (LV) hypertrophy (LVH) in these patients [46].

A meta-analysis was conducted with the inclusion of 15 studies (3 RCTs, 1 non-RCT, and 11 single-arm studies) reporting on the effects of use of MRAs in 1204 patients with resistant HTN over a follow-up period of 1.4–10.3 months; 12 studies used spironolactone, 1 study used eplerenone, and 2 studies used both eplerenone and spironolactone [13•]. Spironolactone was used at doses of 12.5–100 mg and eplerenone at 50–100 mg. In comparative studies, MRAs reduced systolic BP by 24.26 mmHg ($p = 0.002$) and diastolic BP by 7.79 mmHg ($p = 0.0001$). Similarly, MRAs reduced systolic BP by 22.74 mmHg ($p < 0.00001$) and diastolic BP by 10.49 mmHg ($p < 0.00001$) in single-arm studies. MRAs resulted in significant change in serum electrolytes in single-arm studies but not in comparative studies. Significantly, more adverse events were noted in single-arm studies but not in comparative studies. The authors concluded that MRAs are safe and effective in patients with resistant HTN.

Spironolactone

Several small studies including a post hoc analysis of the ASCOT trial showed significant benefit of spironolactone use in lowering BP in patients with resistant HTN (with or without PA) when added to multidrug regimens that include a diuretic, an ACE inhibitor or an ARB, and a calcium channel blocker [14•, 32–34, 47–49]. The most frequent adverse events include gynecomastia or breast discomfort and hyperkalemia.

In 2015, a landmark RCT, the PATHWAY-2 study, examined the role of spironolactone in 314 patients with resistant HTN who completed treatment cycles with spironolactone, doxazosin, bisoprolol, and placebo [6••]. The study showed that spironolactone (25–50 mg/day) was superior to other drugs and the most effective add-on drug, when added to a regimen comprising an ACE inhibitor/ARB, plus a calcium channel blocker, plus a thiazide-like diuretic, for the treatment of resistant HTN. The authors concluded that the superiority of spironolactone supports a primary role of sodium retention in resistant HTN. There were only 6 (2.1%) of the 285 patients who received spironolactone, in whom serum potassium exceeded 6 mmol/L on one occasion. The same group subsequently reported the results of three substudies showing that resistant HTN is a salt-retaining state, most likely due to inappropriate aldosterone secretion and the antihypertensive effect of spironolactone is largely due to its aldosterone antagonism and its resultant natriuretic and diuretic effects [50•]. A clinically important corollary finding of this investigation was that amiloride appeared as effective as spironolactone as a fourth drug for treating resistant hypertension [50•].

A meta-analysis (2016) of 5 RCTs involving 553 patients with resistant HTN showed that, compared with control therapies, additional spironolactone treatment significantly decreased 24-h ambulatory systolic, diastolic, daytime systolic, night-time systolic, and night-time diastolic BP, as well as office systolic and diastolic BP (all $ps < 0.001$) [51•]. However, serum potassium might be slightly elevated by additional spironolactone ($p = 0.011$). The authors concluded that spironolactone combined with triple-drug therapy may be an effective and relatively safe strategy for the management of patients with resistant HTN.

Another meta-analysis (2017) of 5 RCTs comprising 662 patients with resistant HTN, including the PATHWAY-2 study, showed that spironolactone reduced office systolic BP by 15.73 mmHg ($p < 0.00001$) and diastolic BP by 6.21 mmHg ($p < 0.00001$) compared with the placebo group [15•]. The pooled changes of 24 h ambulatory or home systolic and diastolic BP of − 8.7 mmHg ($p < 0.00001$) and − 4.12 mmHg ($p < 0.00001$) favored spironolactone. In comparison with alternative drugs including beta blocker, candesartan, or alpha methyldopa, spironolactone reduced home systolic BP by 4.5 mmHg ($p < 0.00001$). The authors concluded that addition of spironolactone is beneficial in patients with resistant HTN.

Similar findings were reported by another meta-analysis (2017) of 5 studies (2 RCTs and 3 non-RCTs) comprising 755 patients comparing data between the use of MRAs (spironolactone) and use of other fourth-line agents including bisoprolol, doxazosin, and furosemide and additional blockade of the RAAS [52•]. Spironolactone reduced BP by 7.4 mmHg in RCTs and by 11.9 mmHg in non-RCTs more than the active comparator. The authors concluded that MRAs reduce BP more effectively than other fourth-line agents in resistant HTN. Finally, the efficacy of add-on spironolactone as fourth-line therapy in patients with resistant HTN was evaluated in 869 patients participating in 4 trials (the PATHWAY-2 study included) with a mean follow-up of 12 ± 3 weeks [53]. The reduction of systolic and diastolic BP in patients treated with spironolactone was greater than placebo (weighted mean differences [WMD] for systolic BP − 16.67 mmHg, $p < 0.01$; for diastolic BP − 6.11 mmHg, $p < 0.001$). The rates of serious

adverse effects or patient withdrawals from the trials tended to be higher in patients treated with spironolactone than placebo (WMD for odds ratio 2.11, $p = 0.05$).

Recently (2018), the ReHOT study results were reported indicating that clonidine was not superior to spironolactone as a fourth-drug therapy in patients with resistant HTN [7•]. Specifically, 187 patients with resistant HTN were randomized to an additional 12-week treatment with spironolactone ($n = 95$; dose, 12.5–50 mg qd) or clonidine ($n = 92$; dose, 0.1–0.3 mg bid). The clonidine group presented similar rates of achieving the primary end point of BP control during office and 24-h ambulatory BP monitoring (20.5% vs 20.8%, $p =$ ns). Secondary end point analysis showed similar office BP (33.3% vs 29.3%) and ambulatory BP monitoring (44% vs 46.2%) control. However, spironolactone conferred greater decrease in 24-h systolic and diastolic BP and diastolic daytime ambulatory BP than clonidine. The authors concluded that considering easier posology and greater decrease in secondary end points, spironolactone is preferable as the fourth drug for the treatment of resistant HTN [7•]. Importantly, there was an overall low rate of side effects reported for both drugs, albeit for a very short follow-up period of 12 weeks. No case of gynecomastia was reported in the spironolactone group, while clonidine produced a higher frequency of somnolence. There were no differences observed in the heart rate between the two drugs, while patients randomized to spironolactone had a slight increase in the creatinine levels compared with clonidine (1.12 ± 0.38 vs 0.98 ± 0.35 mg/dL; $p = 0.01$) and a higher percentage of hyperkalemia (14.3% vs 2.6%; $p = 0.01$).

In *summary*, several studies including the pivotal PATHWAY-2 study and the recent ReHOT study [6••, 7•] showed significant benefit of spironolactone use in lowering BP in patients with resistant HTN (with or without PA) when added to multidrug regimens, with hyperkalemia and gynecomastia/mastodynia being the most frequent adverse events; the latter mainly observed during longer follow-up periods [49, 54•].

Eplerenone

Although eplerenone has proven efficacy in the treatment of HTN [40, 55, 56], as well as in patients with myocardial infarction (MI) associated with reduced systolic LV function and in patients with HF [57••], there are fewer data with eplerenone in the treatment of resistant HTN [11, 12, 58]. An early study assessed eplerenone in 341 hypertensive patients whose BP was not controlled despite ACE inhibitor or ARB [11]. Patients were randomized to 50 mg eplerenone (increasing to 100 mg if required) once daily or placebo for 8 weeks. At week 8, mean seated diastolic BP was significantly reduced from week 0 among patients receiving eplerenone/ARB (-12.7 ± 0.81 mmHg) compared with those receiving placebo/ARB (-9.3 ± 0.83 mmHg). Systolic BP levels were also significantly lower at week 8 for eplerenone/ACE inhibitor (-13.4 ± 1.35 mmHg) and eplerenone/ARB (-16.0 ± 1.37 mmHg) patients, respectively, compared with placebo/ACE inhibitor (-7.5 ± 1.31 mmHg) and placebo/ARB patients (-9.2 ± 1.41 mmHg). Adverse events were generally non-severe and not significantly different between eplerenone and placebo. The authors concluded that selective aldosterone blockade with eplerenone may be useful add-on therapy in hypertensive patients inadequately controlled on ACE inhibitor or ARB alone.

Eplerenone demonstrated substantial efficacy and was well tolerated with modest changes in plasma potassium in a study comprising 52 patients with resistant HTN, in whom a mean number of antihypertensive agents of 3.7 ± 0.8 (range, 3–7 drugs) had failed to achieve BP control [12]. Serum aldosterone and plasma renin activity did not predict BP responses to eplerenone in this population.

Add-on therapy with eplerenone in 117 patients with uncontrolled HTN (mean age of 50.5 ± 6.6 years) decreased office BP from 149/91 to 142/87 mmHg ($p < 0.001$) and ambulatory BP from 141/87 to 132/83 mmHg after 3 months of treatment ($p < 0.001$) [58]. Treatment resulted in a small rise in serum potassium and creatinine. Among 37 patients with a history of resistant HTN and a supine plasma aldosterone level ≥ 360 pmol/L who were randomized to eplerenone ($n = 19$) versus placebo ($n = 18$), eplerenone significantly reduced resistance to concomitant antihypertensive medication, without the development of hyperkalemia [59]. The authors of this small study suggest that among patients with resistant HTN, it may be useful to measure plasma aldosterone with the aim to add an MRA, such as eplerenone, in those with elevated aldosterone levels.

In another small study of 57 drug-resistant hypertensive patients with home BP $\geq 135/85$ mmHg, randomized to either an eplerenone ($n = 35$) or a control group ($n = 22$) and followed for 12 weeks, home morning (148 ± 15 vs 140 ± 15 mmHg) and evening systolic BP (137 ± 16 vs 130 ± 16 mmHg) were significantly lowered in the eplerenone group compared with baseline (both $p < 0.05$) [60]. BP reductions in the eplerenone group were most pronounced for ambulatory awake systolic BP ($P = 0.04$), awake diastolic BP ($p = 0.004$), and 24-h diastolic BP ($p = 0.02$). Flow-mediated vasodilation was also significantly improved in the eplerenone group. The authors concluded that in patients with drug-resistant HTN, add-on use of eplerenone was effective in lowering BP, especially home and ambulatory awake BP.

In addition to its antihypertensive effect, eplerenone has also been shown to decrease LV mass in patients with resistant HTN, a much desirable corollary effect of antihypertensive treatment [61]. When combined with a RAS blocker, this effect in LVH regression may be enhanced [38•]. Nevertheless, spironolactone has also been shown to reverse LVH in patients with resistant HTN and hyperaldosteronism [62].

In *summary*, the data of eplerenone use in resistant HTN are encouraging but currently appear to trail those reported with the use of spironolactone. However, for patients developing anti-androgenic side effects from spironolactone, eplerenone is efficacious and better tolerated and thus a good alternative.

Eplerenone vs Spironolactone Studies of head-to-head comparison of the two MRAs, spironolactone and eplerenone, in patients with HTN are not available. However, comparative data have been reported between these two agents in patients with HF.

In a recent study, among patients hospitalized for HF, 90 treated with eplerenone (34 ± 15 mg) were compared with 90 treated with spironolactone (27 ± 8 mg) [63•]. During follow-up (mean 1.6 years), primary endpoints of cardiovascular (CV) death and hospitalization occurred in 27 patients in the eplerenone group (30%) and 25 patients in the spironolactone group (27.8%). Serial changes in LV ejection fraction (LVEF), serum brain natriuretic peptide, systolic BP, and estimated glomerular filtration rate did not differ significantly between groups. Although gynecomastia in men was common in the spironolactone group ($p = 0.018$), the discontinuation rates due to adverse events were similar in the two groups. Subgroup analyses suggested that eplerenone was associated with a lower hazard rate of the primary endpoint in female patients (interaction, $p = 0.076$). The authors concluded that among patients with HF, eplerenone and spironolactone have similar impacts on CV outcomes and safety.

An old review of 16 HF studies (10 with spironolactone, 3 with canrenone and 3 with eplerenone) indicated a significant reduction of mortality with all aldosterone antagonists, but eplerenone (relative risk [RR], 0.85; $p = 0.0007$) was outperformed by spironolactone and canrenone (RR, 0.74; $p < 0.0001$) [64]. The risk of gynecomastia was lower, albeit not significantly, in the eplerenone group.

Spironolactone and eplerenone differ in their pharmacokinetic properties (Table 1) [65]. Spironolactone is metabolized in the liver into two active metabolites, 7a-thiomethylspironolactone and canrenone, which account for its long half-life (> 12 h in healthy individuals, 24 h in HF patients, and up to 58 h in patients with liver cirrhosis). On the other hand, eplerenone does not have active metabolites, its half-life is shorter at 3–4 h, and it is directly metabolized in the liver by the cytochrome P450 member, CYP3A4, explaining why other drugs that affect CYP3A4 function can change its blood concentration (Table 1).

There are also other pharmacological differences between these two agents [66]. Eplerenone does not affect metabolic parameters, glucose and cortisol, while spironolactone may raise plasma glycated hemoglobin (HbA1c) and cortisol levels and reduce plasma adiponectin levels in patients with HF. Spironolactone may also worsen endothelial function and heart rate variability in patients with diabetes, possibly due to the worsening of glycemic control and increase in plasma angiotensin II conferred by spironolactone [67]. Based on these results, it appears that eplerenone may be the MRA of choice in patients with diabetes and probably in those with visceral obesity and the metabolic syndrome who are at risk of developing diabetes. Another factor to consider is that spironolactone due to its longer half-life may be associated with a higher incidence of hyperkalemia and renal dysfunction [68••, 69].

A review of 72 articles reporting on the effects of MRAs on glycemia indicated that spironolactone may have a potential negative effect on glucose regulation mainly observed in HF and diabetes trials, while a neutral or positive effect was detected in diseases characterized by hyperandrogenism, and inconclusive for hypertension [70•]. Meta-analysis of 12 RCTs evaluating spironolactone's impact on HbA1c in diabetic patients showed that spironolactone had a nonsignificant effect in parallel-group studies, but significantly increased HbA1c in crossover studies. Eplerenone did not seem to influence glycemia, while limited data indicated that canrenone may exert a neutral or beneficial effect.

Spironolactone is a non-selective MRA with moderate affinity for both progesterone and androgen receptors, which also explains its progestogenic and anti-androgenic side effects, such as gynecomastia, mastodynia (breast pain) or nipple tenderness, erectile dysfunction, and menstrual irregularities [3, 65]. Eplerenone has ~ 500-fold lower affinity for androgen and progestin receptors than spironolactone, which accounts for a considerable decrease in the progestogenic and/or anti-androgenic adverse effects [3]. The higher cost of the newer MRA agent, eplerenone, has been considered an important drawback for its use. However, cost-efficacy studies have shown it to be cost-effective, at least for its use in patients with HF [71•, 72•].

In *summary*, head-to-head comparisons between these two MRA agents, spironolactone and eplerenone, are lacking for hypertensive patients. In patients with HF, these agents have equivalent efficacy, while the adverse-effect profile favors eplerenone. The two agents have differences in pharmacologic and pharmacokinetic properties that need to be taken into consideration during selection, such as the longer half-life (due to active metabolites) of spironolactone or the drug–drug interactions of eplerenone (see Table 1 for details). Furthermore, a more favorable metabolic profile of eplerenone in patients with diabetes or the metabolic syndrome should also be taken into consideration during drug selection.

Primary Aldosteronism Primary aldosteronism (PA) is the most common endocrine cause of resistant HTN. Although older studies reported a low incidence of PA in hypertensive patients (< 1%), newer data based on cross-sectional and prospective studies report PA in > 5% and possibly > 10% of

Table 1 Mineralocorticoid receptor antagonists used in hypertension: comparative data

Variable	Spironolactone	Eplerenone
Absorption	↑ bioavailability by food	Not affected by food
Plasma protein binding	> 90%	~ 50%
MR affinity	High	10–20-fold lower
MR selectivity	Non-selective	High
Half-life	1–2 h/10–35 h (active metabolites)	4–6 h
Metabolism	Liver (non-CYP-dependent)	Liver (CYP 3A4)[c]
Active metabolites	7a-Thiomethylspironolactone/canrenone	None
Mild/moderate HTN (efficacy)	++	++
Resistant HTN (efficacy)	+++	++
Dosing	25–100 mg/day	50 mg qd–50 mg bid
Anti-androgenic SE[a]	++++	+
Metabolic SE[b]	++	–
Hyperkalemia	+++	++
WRF	++	+

N.B.: MRAs may enhance the hyperkalemic effect of ACE inhibitors/ARBs

CYP cytochrome P, *HTN* hypertension, *MR* mineralocorticoid receptor, *SE* side-effects, *WRF* worsening renal function

[a] Loss of libido, gynecomastia/mastodynia, and menstrual irregularities

[b] Worsening glycemic control (increase of HbA1c and cortisol, decrease of adiponectin)

[c] Caution for drug–drug interactions with cytochrome (CYP 3A4) inducers (e.g., carbamazepine, rifampicin, phenytoin, phenobarbital, pioglitazone, enzalutamide) which decrease eplerenone levels or inhibitors (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir, amiodarone, verapamil, diltiazem) which increase eplerenone levels

hypertensive patients, both in general and in specialty settings [73••, 74]. In the absence of a suppression test, the triad of spontaneous hypokalemia, completely suppressed renin, and plasma aldosterone of > 20 ng/dL (550 pmol/L) suffices for the diagnosis of PA. Otherwise, in patients with a positive aldosterone/renin ratio (ARR) (ARR cut-off of 3.7 ng/dL/mIU/L), a proper confirmatory test (saline suppression test, fludrocortisone suppression test, or captopril challenge test [CCT]) will be required to confirm a diagnosis of PA. Importantly, hypokalemia is not considered the sine qua non of PA, as it is encountered in only 9–37% of patients, with normokalemic HTN constituting the most common presentation of the disease; hypokalemia probably characterizes only the more severe cases. Adrenal imaging with computed tomography or adrenal vein sampling will be able to localize the disease.

There is a higher risk of complications associated with PA compared to primary HTN, such as stroke, MI, atrial fibrillation (AF), CKD, LVH, metabolic syndrome, and obstructive sleep apnea [74]. This disease is treatable, either by adrenal resection when unilateral or with use of MRAs when bilateral. Spironolactone has been considered the standard medical treatment [54•]; however, eplerenone, although a weaker MRA, has a more favorable side effect profile [59, 75]. Due to its shorter half-life, eplerenone should be given twice daily for optimal effect. An RCT comprising 141 patients indicated that the antihypertensive effect of spironolactone was significantly greater than that of eplerenone in HTN associated with primary aldosteronism, albeit with increased incidence of male gynecomastia or female mastodynia (21% vs 0–4.5%) [54•].

MRA Dosing Once daily dosing of spironolactone (25–100 mg/day) for the treatment of HTN usually suffices due to its long half-life and its active metabolites (e.g., 7a-thiomethylspironolactone and canrenone) [31, 76]. In patients with cirrhosis or renal failure, spironolactone may need to be administered at an alternate-day schedule [77]. Hyperkalemia remains a dose-limiting side effect and/or a reason for discontinuation of the drug, especially in patients with renal failure [78]. Thus, in patients receiving the drug, other risk factors for hyperkalemia should be taken into consideration, prescriptions of other medications that contribute to hyperkalemia should be minimized, and renal function and potassium levels should be closely monitored.

With regard to eplerenone, although in patients with heart failure this drug may be administered at a dose of 25 mg/day, in patients with HTN, the initial starting dose of eplerenone is 50 mg/day, increased to 50 mg bid (and not 100 mg once daily) if BP is inadequately controlled with the starting dose, as the antihypertensive effect of eplerenone is a bit greater when it is administered twice daily, probably related to its lack

of active metabolites and a relatively short duration of action [36, 79]. Although < 5% of eplerenone is excreted unchanged in the urine and thus renal dysfunction has little effect on eplerenone pharmacokinetics, dose adjustment of eplerenone may still be needed in renal failure when considering the potential development of hyperkalemia [80].

MRAs in Heart Failure

Aldosterone blockade with use of either MRA agent, spironolactone or eplerenone, has been shown to confer a mortality benefit in three landmark trials, RALES, EPHESUS, and EMPHASIS-HF [57••, 81••, 82•]. In RALES, spironolactone was added to standard therapy in selected patients with chronic heart failure (New York Heart Association [NYHA] class III–IV symptoms; mean LVEF, 25.6% ± 7%) who remained symptomatic despite optimal medical treatment [81••]. Addition of spironolactone (25–50 mg qd) reduced mortality by 30% ($p < 0.001$), primarily due to a 29% ($p = 0.02$) reduction in sudden cardiac deaths and a 35% reduction in hospitalization for heart failure ($p < 0.001$). Gynecomastia or mastodynia was reported in 10% of men treated with spironolactone vs 1% of men in the placebo group ($p < 0.001$) over a mean follow-up period of 2 years. The incidence of serious hyperkalemia was minimal (2% vs 1%) [81••].

In the EPHESUS study [57••], comprising patients with acute MI and evidence of LV systolic dysfunction (LVEF < 40%) and signs of HF, the addition of eplerenone to optimal medical therapy resulted in a 15% ($p = 0.008$) reduction in total mortality over a mean of 16 months, a 17% ($p = 0.005$) reduction in CV mortality, and a 21% ($p = 0.02$) reduction in sudden cardiac death. At 30 days after randomization, eplerenone reduced the risk of all-cause mortality by 31% ($p = 0.004$), the risk of CV mortality by 32% ($p = 0.003$) and the risk of sudden cardiac death by 37% ($p = 0.051$) [83••].

In EMPHASIS-HF, the effects of eplerenone (up to 50 mg/day) were evaluated in patients with chronic systolic HF (LVEF ≤ 35%) and mild symptoms (NYHA class II) [82•]. At a median of 21 months, death from CV causes or hospitalization for HF occurred in 18.3% of patients in the eplerenone group as compared with 25.9% in the placebo group (hazard ratio [HR], 0.63; $p < 0.001$); death occurred in 12.5% vs 15.5%, respectively (HR, 0.76; $p = 0.008$); and CV death occurred in 10.8% and 13.5%, respectively (HR, 0.76; $p = 0.01$). Hospitalizations for HF were also reduced with eplerenone. A serum potassium level exceeding 5.5 mmol/L occurred in 11.8% vs 7.2%, respectively ($p < 0.001$).

A recent exploratory study of patients enrolled in EPHESUS and EMPHASIS-HF trials identified groups with worst event-free survival characterized by older age, lower body mass index, worse renal function, higher baseline potassium levels, high prevalence of anemia, diabetes mellitus, previous revascularization and higher rates of eplerenone discontinuation, and hyperkalemia during follow-up [84].

MRA Pleiotropic Effects/Additional CV Protection

Regression of LVH and Cardiac Fibrosis A BP-independent reduction of cardiac fibrosis has been observed with use of MRAs. Treatment with spironolactone in a subgroup of the RALES population was shown to lead to a decrease in the serum levels of markers for collagen synthesis and cardiac fibrosis [85]. It was suggested that limitation of the excessive extracellular matrix turnover may be one of the various extrarenal mechanisms contributing to the beneficial effect of spironolactone in patients with HF. In patients with LVH, treatment with spironolactone for 6 months decreased LV fibrosis [86]. It was suggested that MRAs may alter myocardial ultrasonic texture with regression of LV fibrosis, at least partly via enhanced collagen degradation. As already mentioned, studies have shown that MRA therapy may lead to a decrease in LV mass and regression of LVH in patients with resistant HTN [38•, 61]. It has also been suggested that eplerenone might affect atrial fibrosis in patients with HTN and thus might favorably influence AF [87].

Improvement in Endothelial Dysfunction There is evidence that MRA therapy may lead to improvement in endothelial dysfunction noted in patients with HTN or heart failure with potential vascular protection and improved outcomes compared to other therapies (e.g., beta blocker therapy) [29, 88, 89]. In hypertensive patients, BP control for 1 year with atenolol was associated with increased wall stiffness of resistance arteries, whereas eplerenone treatment was associated with reduced stiffness, decreased collagen/elastin ratio, and a reduction in circulating inflammatory mediators [88]. Another study indicated that eplerenone beneficially affected markers of arterial stiffness and wave reflection, independently of BP lowering, in 51 patients with resistant HTN randomized to add-on eplerenone (50 mg) or placebo for 6 months [90]. A strong association has been shown between aldosterone excess and impaired endothelial function in patients with resistant HTN as reflected by comparatively lower flow-mediated arterial vasodilation in those with hyperaldosteronism; 3 months of treatment with spironolactone significantly increased brachial artery flow-mediated dilation independently of BP change [29]. In another study, in patients with heart failure, spironolactone improved endothelial dysfunction, increased nitric oxide (NO) bioactivity, and inhibited vascular angiotensin (Ang) I/Ang II conversion [89]. Experimental studies have indicated that adipocytes may release secretory

products that stimulate aldosterone release from the adrenal glands, while they themselves may serve as a direct source of aldosterone contributing to perivascular inflammation, endothelial dysfunction, and vascular stiffness; aldosterone blockade with use of MRAs improved arterial endothelial dysfunction [91]. These findings suggest that aldosterone-induced endothelial dysfunction and vascular stiffness, particularly in obese individuals, may contribute to the development of resistant HTN. As mentioned, clinical studies have demonstrated that aldosterone blockade improves vascular function in hypertensive patients [29, 88].

Renoprotection/Anti-albuminuric Effect With similar decreases in BP, superior anti-albuminuric effects of dual therapy with eplerenone and ACE inhibition as compared to ACE inhibition alone have been noted in patients with diabetic nephropathy without producing significant increases in hyperkalemia [92]. In another study (RCT), eplerenone reduced microalbuminuria to a greater extent than amlodipine (52% vs 10%) in an older patient group of 269 patients ($p = 0.04$) [37]. A systematic review of 15 studies evaluating MRAs as additive therapy to conventional RAS blockade in patients with CKD further confirmed these findings by indicating significant decreases in proteinuria without adverse effects of hyperkalemia and impaired renal function [93]. Nevertheless, caution and close monitoring is advised in such patients (see discussion below). Furthermore, there can be an initial reduction in estimated glomerular filtration rate (eGFR) when MRA treatment is initiated.

Anti-arrhythmic Efficacy/Reduction of Death and Sudden Death A meta-analysis of 14 studies (5 RCTs and 9 observational cohort studies) comprising 5332 patients of whom 45% received an MRA (spironolactone or eplerenone) showed that fewer (8.5%) patients treated with MRAs developed AF, compared to patients without MRA treatment (18.6%) (odds ratio [OR] 0.48, $p < 0.001$) [94•].

According to a meta-analysis of 7 trials comprising 8635 patients, MRAs reduced the risk of sudden cardiac death (SCD) in patients with HF by 21% (relative risk [RR], 0.79) [95•]. MRAs significantly reduced the episodes of ventricular premature complexes (mean difference 705 ± 646 episodes per 24 h) and the risk of ventricular tachycardia by 72% (RR, 0.28; 95% CI, 0.10–0.77). The authors concluded that the additional administration of MRAs in patients with HF or coronary artery disease shows a benefit in reducing the risk of SCD and may also be effective for reducing episodes of ventricular premature complexes and ventricular tachycardia.

As mentioned, MRAs have been shown to significantly reduce total and sudden death mortality in patients with chronic HF (spironolactone) and in patients with LV dysfunction or HF (eplerenone) as demonstrated in the two landmark trials, EPHESUS and RALES [57••, 81••]. Furthermore, individual patient data from another 2 RCTs (ALBATROSS and REMINDER) studying the benefit of aldosterone blockade in MI irrespective or in absence of HF were analyzed in patients allocated (1:1) to two MRA regimens ($n = 1118$) vs placebo ($n = 1123$) (an intravenous bolus of potassium canrenoate (200 mg) followed by oral spironolactone at 25 mg qd versus standard therapy or oral eplerenone of 25–50 mg versus placebo) [96•]. After a median of ~ 6 months, the primary (all-cause-death) and secondary outcomes (composite of all-cause death or resuscitated sudden death) occurred in 5 (0.4%) and 17 (1.5%) patients (adjusted HR 0.31, $p = 0.03$) and 6 (0.5%) and 22 (2%) patients (HR 0.26, $p = 0.004$) in the MRA and control groups, respectively. There were also trends towards lower rates of CV death ($p = 0.06$) and ventricular fibrillation ($p = 0.08$) in the MRA group. Rates of hyperkalemia > 5.5 mmol/L were significantly higher among patients treated with MRA (3.3% vs 1.8%; $p = 0.03$), while rates of more severe hyperkalemia > 6 mmol/L (1% vs 0.4%) and acute renal failure (2.3% vs 1.6%) were not significantly different between the two groups ($p = 0.1$). The authors concluded that compared with standard therapy, MRA regimens are associated with a reduction of death and death or resuscitated sudden death in MI.

Risk of Hyperkalemia

A subanalysis of the EMPHASIS-HF, which enrolled patients ≥ 55 years old with HF and reduced ejection fraction (HF-REF), in NYHA functional class II and with an eGFR > 30 ml/min/1.73 m^2 and serum potassium < 5.0 mmol/l, examined the safety and efficacy of eplerenone in patients at high risk for hyperkalemia or worsening renal function (WRF) [97•]. Patients at high risk of hyperkalemia or WRF were patients ≥ 75 years of age, with diabetes, with eGFR < 60 ml/min/1.73 m^2, and with systolic BP < median of 123 mmHg). In all high-risk subgroups, patients treated with eplerenone had an increased risk of potassium > 5.5 mmol/l, but not of potassium > 6.0 mmol/l, and of hospitalization for hyperkalemia or discontinuation of study medication due to adverse events. Eplerenone was effective in reducing the primary composite endpoint (hospitalization for HF or CV mortality) in all subgroups. The authors concluded that in patients with chronic HF-REF, in NYHA functional class II, and meeting specific inclusion and exclusion criteria, including an eGFR > 30 ml/min/1.73 m^2 and potassium < 5.0 mmol/l, eplerenone was both efficacious and safe when carefully monitored, even in subgroups at high risk of developing hyperkalemia or WRF.

A meta-analysis of 7 RCTs reporting hyperkalemia on MRAs in 16,065 patients after MI or with chronic HF, hyperkalemia was more frequently observed on MRA (9.3%) vs placebo (4.3%) (risk ratio 2.17, $p < 0.0001$) [68••].

Truly MRA-related hyperkalemia was 54%, whereas 46% were non-MRA related. In trials using eplerenone, hyperkalemia was documented in 5% on eplerenone and in 2.6% on placebo ($p < 0.0001$). In spironolactone trials, hyperkalemia was documented in 17.5% and in 7.5% of patients on placebo ($p = 0.0001$). The authors concluded that in clinical trials, 54% of hyperkalemia cases were specifically related to the MRA treatment and 46% to other reasons; therefore, non-MRA-related rises in potassium levels might be underestimated and should be further explored before stopping MRAs.

Caution is advised when using MRAs for BP control in patients with advanced chronic kidney disease (CKD) (stage 3) with a serum potassium of > 4.5 mEq/L for safety reasons [98]. Predictors of hyperkalemia may include a baseline eGFR of ≥ 45 ml/min/1.73 m^2 in whom serum potassium is >4.5 mEq/L on appropriately dosed diuretics. Contributing risks in this subgroup may be a systolic BP reduction of > 15 mmHg associated with an eGFR fall of > 30% [98]. Other investigators have indicated that CKD, basal hyperkalemia, reduction in eGFR, and diabetes are predictive of a hyperkalemia risk following MRA use [99]. They also suggest that the greatest risk is observed during the first month after initiating MRA treatment and thus they advise strict monitoring over the first month of treatment followed by standard surveillance thereafter. Nevertheless, use of MRAs in patients with end-stage renal disease has been shown beneficial with a low (1.9%) incidence of hyperkalemia requiring drug discontinuation [100].

Finally, for patients at high risk for hyperkalemia and in order to continue availing of the beneficial effects of MRAs, use of a novel potassium binding polymer, *patiromer*, has been shown to prevent hyperkalemia in this clinical testing and thus facilitate MRA therapy [101]. Newer MRA agents (e.g., finerenone) are also currently being evaluated that may prove safer in CKD patients with possibly lower rates of hyperkalemia [102•].

Guidelines

The NICE (National Institute for Health and Care Excellence) guidelines (2016 update) on the management of primary HTN in adults recommend adding spironolactone (25 mg qd) in patients with resistant HTN if the blood potassium level is ≤ 4.5 mmol/L while using particular caution in people with a reduced eGFR for risk of hyperkalemia [103••].

The American guidelines on HTN (2017) advise among other recommendations the addition of an MRA in patients with resistant HTN [104••]. In the text, they state that considerable evidence indicates that the addition of spironolactone to multidrug regimens provides substantial BP reduction compared with placebo or other active drugs. They make particular mention of the PATHWAY-2 RCT which demonstrated the superiority of spironolactone over alpha and beta blockers.

The recent (2018) European (ESC/ESH) guidelines recommend for the treatment of resistant HTN the addition of low-dose spironolactone to existing treatment or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride, a higher-dose thiazide/thiazide-like diuretic, or a loop diuretic [105••].

A most recent (2018) scientific statement from the American Heart Association (AHA) on resistant HTN advises among other interventions the addition of an MRA (spironolactone or eplerenone) for the management of resistant HTN [106••].

Finally, in patients with primary aldosteronism, regarded as the most common endocrine cause of resistant HTN, when due to bilateral adrenal disease or in patients with unilateral disease who are unwilling or unable to undergo surgery, the 2016 Endocrine Society clinical practice guidelines (sponsored by the AHA and ESH among several societies) recommend medical treatment with an MRA (strong recommendation/quality of evidence [QOE]: low); with spironolactone as the primary agent, and eplerenone as an alternative (weak recommendation/QOE: very low) [73••].

Conclusions

Several studies have provided evidence that resistant HTN can be attributed to persistent fluid retention secondary to varying degrees of aldosterone excess. Such aldosteronism, either due to an underestimated occurrence of primary aldosteronism (PA) but more commonly occurring separately from PA and independent from angiotensin II, may well explain the favorable response of patients with resistant HTN to MRA therapy.

In the absence of a direct comparison, and in light of the compelling evidence provided by the PATHWAY-2 and ReHOT studies, spironolactone has been established as the most effective add-on MRA agent in patients with resistant HTN. The data on use of eplerenone are encouraging that this agent may be an alternative to spironolactone and certainly the preferred choice for those not tolerating spironolactone, especially for patients developing or prone to develop anti-androgenic side effects like breast tenderness, gynecomastia/mastodynia, and/or sexual dysfunction. These side effects, particularly gynecomastia, are most bothersome for men and this may be a good reason to opt for eplerenone, even as first choice, for this patient population. In addition, eplerenone has a more favorable metabolic profile in patients with diabetes, obesity or the metabolic syndrome that needs to be taken into consideration during drug selection. Nevertheless, the weight of evidence regarding efficacy in the management of resistant HTN is currently in favor of spironolactone, although data on the efficacy of eplerenone are still being accumulated. Hence,

for now, the selection of a particular MRA agent for resistant HTN is an efficacy and possibly a cost issue and not just a men's issue regarding the anti-androgenic effects. Furthermore, the pleiotropic effects of both these MRA agents with cardioprotection and renoprotection beyond the anti-hypertensive effect are very appealing and promising for our clinical decision-making strategies. Newer MRA agents are in the pipeline that may broaden our choices in our therapeutic armamentarium for the hypertensive and/or HF and post-MI patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Kolkhof P, Barfacker L. 30 years of the mineralocorticoid receptor: mineralocorticoid receptor antagonists: 60 years of research and development. J Endocrinol. 2017;234(1):T125–t40. **An important review of the history of the various generations of MRAs.**
2. Calhoun DA. Aldosteronism and hypertension. Clin J Am Soc Nephrol. 2006;1(5):1039–45.
3. Garthwaite SM, McMahon EG. The evolution of aldosterone antagonists. Mol Cell Endocrinol. 2004;217(1–2):27–31.
4. Yugar-Toledo JC, Modolo R, de Faria AP, Moreno H. Managing resistant hypertension: focus on mineralocorticoid-receptor antagonists. Vasc Health Risk Manag. 2017;13:403–11.
5. Epstein M, Duprez DA. Resistant hypertension and the pivotal role for mineralocorticoid receptor antagonists: a clinical update 2016. Am J Med. 2016;129(7):661–6.
6.•• Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, cross-over trial. Lancet. 2015;386(10008):2059–68. **A pivotal trial establishing the role of spironolactone in the treatment of resistant hypertension.**
7.• Krieger EM, Drager LF, Giorgi DMA, Pereira AC, Barreto-Filho JAS, Nogueira AR, et al. Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: the ReHOT randomized study (resistant hypertension optimal treatment). Hypertension. 2018;71(4):681–90. **An important trial suggesting spironolactone as the preferable fourth agent for resistant hypertension.**
8.• Pimenta E, Gaddam KK, Pratt-Ubunama MN, Nishizaka MK, Cofield SS, Oparil S, et al. Aldosterone excess and resistance to 24-h blood pressure control. J Hypertens. 2007;25(10):2131–7. **Important prospective study suggesting a role of aldosterone excess in resistant hypertension.**
9.• Gaddam KK, Nishizaka MK, Pratt-Ubunama MN, Pimenta E, Aban I, Oparil S, et al. Characterization of resistant hypertension: association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. Arch Intern Med. 2008;168(11):1159–64. **An important prospective study suggesting a role of intravascular volume expansion in resistane hypertension.**
10. Martins LC, Figueiredo VN, Quinaglia T, Boer-Martins L, Yugar-Toledo JC, Martin JF, et al. Characteristics of resistant hypertension: ageing, body mass index, hyperaldosteronism, cardiac hypertrophy and vascular stiffness. J Hum Hypertens. 2011;25(9):532–8.
11. Krum H, Nolly H, Workman D, He W, Roniker B, Krause S, et al. Efficacy of eplerenone added to renin-angiotensin blockade in hypertensive patients. Hypertension. 2002;40(2):117–23.
12. Calhoun DA, White WB. Effectiveness of the selective aldosterone blocker, eplerenone, in patients with resistant hypertension. J Am Soc Hypertens. 2008;2(6):462–8.
13.• Dahal K, Kunwar S, Rijal J, Alqatahni F, Panta R, Ishak N, et al. The effects of aldosterone antagonists in patients with resistant hypertension: a meta-analysis of randomized and nonrandomized studies. Am J Hypertens. 2015;28(11):1376–85. **A meta-analysis showing that MRAs are safe and effective therapy in patients with resistant hypertension.**
14.• Guo H, Xiao Q. Clinical efficacy of spironolactone for resistant hypertension: a meta analysis from randomized controlled clinical trials. Int J Clin Exp Med. 2015;8(5):7270–8. **A meta-analysis on the efficacy of spironolactone in resistant hypertension.**
15.• Liu L, Xu B, Ju Y. Addition of spironolactone in patients with resistant hypertension: a meta-analysis of randomized controlled trials. Clin Exp Hypertens. 2017;39(3):257–63. **A meta-analysis on the benefit of spironolactone in patients with resistant hypertension.**
16. Clark D 3rd, Ahmed MI, Calhoun DA. Resistant hypertension and aldosterone: an update. Can J Cardiol. 2012;28(3):318–25.
17. Zhang WD, Zhang JW, Wu KF, Chen X, Wang YP, Zhou LH, et al. Effect of aldosterone antagonists on obstructive sleep apnea in patients with resistant hypertension: a systematic review and meta-analysis. J Hum Hypertens. 2017;31(12):855–6.
18. Briet M, Schiffrin EL. Aldosterone: effects on the kidney and cardiovascular system. Nat Rev Nephrol. 2010;6(5):261–73.
19. Nguyen Dinh Cat A, Jaisser F. Extrarenal effects of aldosterone. Curr Opin Nephrol Hypertens. 2012;21(2):147–56.
20. Mackenzie SM, Connell J. Hypertension and the expanding role of aldosterone. Curr Hypertens Rep. 2006;8(3):255–61.
21. Duprez DA, Bauwens FR, De Buyzere ML, De Backer TL, Kaufman JM, Van Hoecke J, et al. Influence of arterial blood pressure and aldosterone on left ventricular hypertrophy in moderate essential hypertension. Am J Cardiol. 1993;71(3):17a–20a.
22. Rocha R, Funder JW. The pathophysiology of aldosterone in the cardiovascular system. Ann N Y Acad Sci. 2002;970:89–100.
23. Blasi ER, Rocha R, Rudolph AE, Blomme EA, Polly ML, McMahon EG. Aldosterone/salt induces renal inflammation and fibrosis in hypertensive rats. Kidney Int. 2003;63(5):1791–800.
24. Matsumura K, Fujii K, Oniki H, Oka M, Iida M. Role of aldosterone in left ventricular hypertrophy in hypertension. Am J Hypertens. 2006;19(1):13–8.
25. Dartsch T, Fischer R, Gapelyuk A, Weiergraeber M, Ladage D, Schneider T, et al. Aldosterone induces electrical remodeling independent of hypertension. Int J Cardiol. 2013;164(2):170–8.

26. Martinez-Aguayo A, Carvajal CA, Campino C, Aglony M, Bolte L, Garcia H, et al. Primary aldosteronism and its impact on the generation of arterial hypertension, endothelial injury and oxidative stress. J Pediatr Endocrinol Metab. 2010;23(4):323–30.
27. Schiffrin EL. Effects of aldosterone on the vasculature. Hypertension. 2006;47(3):312–8.
28. Schmidt BM, Oehmer S, Delles C, Bratke R, Schneider MP, Klingbeil A, et al. Rapid nongenomic effects of aldosterone on human forearm vasculature. Hypertension. 2003;42(2):156–60.
29. Nishizaka MK, Zaman MA, Green SA, Renfroe KY, Calhoun DA. Impaired endothelium-dependent flow-mediated vasodilation in hypertensive subjects with hyperaldosteronism. Circulation. 2004;109(23):2857–61.
30. Schrijver G, Weinberger MH. Hydrochlorothiazide and spironolactone in hypertension. Clin Pharmacol Ther. 1979;25(1):33–42.
31. Ludbrook A, Dynon M, Mendelsohn FA, Louis WJ. Comparison of a single-dose and twice-a-day spironolactone therapy in mild hypertension. Med J Aust. 1980;1(3):124–5.
32. de Souza F, Muxfeldt E, Fiszman R, Salles G. Efficacy of spironolactone therapy in patients with true resistant hypertension. Hypertension. 2010;55(1):147–52.
33. Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. Am J Hypertens. 2003;16(11 Pt 1):925–30.
34. Chapman N, Dobson J, Wilson S, Dahlof B, Sever PS, Wedel H, et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension. 2007;49(4):839–45.
35.• Batterink J, Stabler SN, Tejani AM, Fowkes CT. Spironolactone for hypertension. Cochrane Database Syst Rev. 2010;8: Cd008169. **A meta-analysis on the role of spironolactone in the treatment of hypertension pointing to reasonable dosing of 25–100 mg/day.**
36. Weinberger MH, Roniker B, Krause SL, Weiss RJ. Eplerenone, a selective aldosterone blocker, in mild-to-moderate hypertension. Am J Hypertens. 2002;15(8):709–16.
37. White WB, Duprez D, St Hillaire R, Krause S, Roniker B, Kuse-Hamilton J, et al. Effects of the selective aldosterone blocker eplerenone versus the calcium antagonist amlodipine in systolic hypertension. Hypertension. 2003;41(5):1021–6.
38.• Pitt B, Reichek N, Willenbrock R, Zannad F, Phillips RA, Roniker B, et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. Circulation. 2003;108(15):1831–8. **An important study demonstrating the efficacy of eplerenone in LVH regression and blood pressure control.**
39. White WB, Carr AA, Krause S, Jordan R, Roniker B, Oigman W. Assessment of the novel selective aldosterone blocker eplerenone using ambulatory and clinical blood pressure in patients with systemic hypertension. Am J Cardiol. 2003;92(1):38–42.
40. Flack JM, Oparil S, Pratt JH, Roniker B, Garthwaite S, Kleiman JH, et al. Efficacy and tolerability of eplerenone and losartan in hypertensive black and white patients. J Am Coll Cardiol. 2003;41(7):1148–55.
41.• Pelliccia F, Patti G, Rosano G, Greco C, Gaudio C. Efficacy and safety of eplerenone in the management of mild to moderate arterial hypertension: systematic review and meta-analysis. Int J Cardiol. 2014;177(1):219–28. **A meta-analysis demonstrating the efficacy and safety of eplerenone in treating hypertension.**
42.• Tam TS, Wu MH, Masson SC, Tsang MP, Stabler SN, Kinkade A, et al. Eplerenone for hypertension. Cochrane Database Syst Rev. 2017;2:Cd008996. **A meta-analysis on the role of eplerenone in the treatment of hypertension pointing to effective dosing of 50 mg/day.**
43. Ando K, Ohtsu H, Uchida S, Kaname S, Arakawa Y, Fujita T. Anti-albuminuric effect of the aldosterone blocker eplerenone in non-diabetic hypertensive patients with albuminuria: a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2014;2(12):944–53.
44.•• Noubiap JJ, Nansseu JR, Nyaga UF, Sime PS, Francis I, Bigna JJ. Global prevalence of resistant hypertension: a meta-analysis of data from 3.2 million patients. Heart. 2019;105(2):98–105. **A meta-analysis of a large pooled sample of hypertensive patients indicating high global prevalence of resistant hypertension.**
45. de Faria AP, Demacq C, Figueiredo VN, Moraes CH, Santos RC, Sabbatini AR, et al. Hypoadiponectinemia and aldosterone excess are associated with lack of blood pressure control in subjects with resistant hypertension. Hypertens Res. 2013;36(12):1067–72.
46. Ubaid-Girioli S, Adriana de Souza L, Yugar-Toledo JC, Martins LC, Ferreira-Melo S, Coelho OR, et al. Aldosterone excess or escape: treating resistant hypertension. J Clin Hypertens (Greenwich). 2009;11(5):245–52.
47. Vaclavik J, Sedlak R, Plachy M, Navratil K, Plasek J, Jarkovsky J, et al. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. Hypertension. 2011;57(6):1069–75.
48. Oxlund CS, Henriksen JE, Tarnow L, Schousboe K, Gram J, Jacobsen IA. Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial. J Hypertens. 2013;31(10): 2094–102.
49. Engbaek M, Hjerrild M, Hallas J, Jacobsen IA. The effect of low-dose spironolactone on resistant hypertension. J Am Soc Hypertens. 2010;4(6):290–4.
50.• Williams B, MacDonald TM, Morant SV, Webb DJ, Sever P, McInnes GT, et al. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. Lancet Diabetes Endocrinol. 2018;6(6):464–75. **An analysis of the PATHWAY-2 substudies indicating that resistant hypertension is a salt-retaining state due to inappropriate aldosterone secretion.**
51.• Wang C, Xiong B, Huang J. Efficacy and safety of spironolactone in patients with resistant hypertension: a meta-analysis of randomised controlled trials. Heart Lung Circ. 2016;25(10): 1021–30. **A meta-analysis on the efficacy and safety of spironolactone in resistant hypertension.**
52.• Sinnott SJ, Tomlinson LA, Root AA, Mathur R, Mansfield KE, Smeeth L, et al. Comparative effectiveness of fourth-line anti-hypertensive agents in resistant hypertension: a systematic review and meta-analysis. Eur J Prev Cardiol. 2017;24(3):228–38. **A meta-analysis on the comparative effectiveness of MRAs in resistant hypertension.**
53. Zhao D, Liu H, Dong P, Zhao J. A meta-analysis of add-on use of spironolactone in patients with resistant hypertension. Int J Cardiol. 2017;233:113–7.
54.• Parthasarathy HK, Menard J, White WB, Young WF Jr, Williams GH, Williams B, et al. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. J Hypertens. 2011;29(5):980–90. **An important comparative RCT of spironolactone vs eplerenone.**
55. Weinberger MH, White WB, Ruilope LM, MacDonald TM, Davidson RC, Roniker B, et al. Effects of eplerenone versus losartan in patients with low-renin hypertension. Am Heart J. 2005;150(3):426–33.
56. Jansen PM, Danser AH, Imholz BP, van den Meiracker AH. Aldosterone-receptor antagonism in hypertension. J Hypertens. 2009;27(4):680–91.

57.•• Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348(14):1309–21. **A pivotal trial of eplerenone in patients with left ventricular dysfunction after myocardial infarction.**

58. Jansen PM, Frenkel WJ, van den Born BJ, de Bruijne EL, Deinum J, Kerstens MN, et al. Determinants of blood pressure reduction by eplerenone in uncontrolled hypertension. J Hypertens. 2013;31(2):404–13.

59. Spence JD, Bogiatzi C, Kuk M, Dresser GK, Hackam DG. Effects of eplerenone on resistance to antihypertensive medication in patients with primary or secondary hyperaldosteronism. J Transl Int Med. 2017;5(2):93–9.

60. Eguchi K, Kabutoya T, Hoshide S, Ishikawa S, Kario K. Add-on use of eplerenone is effective for lowering home and ambulatory blood pressure in drug-resistant hypertension. J Clin Hypertens (Greenwich). 2016;18(12):1250–7.

61. Schneider A, Schwab J, Karg MV, Kalizki T, Reinold A, Schneider MP, et al. Low-dose eplerenone decreases left ventricular mass in treatment-resistant hypertension. J Hypertens. 2017;35(5):1086–92.

62. Gaddam K, Corros C, Pimenta E, Ahmed M, Denney T, Aban I, et al. Rapid reversal of left ventricular hypertrophy and intracardiac volume overload in patients with resistant hypertension and hyperaldosteronism: a prospective clinical study. Hypertension. 2010;55(5):1137–42.

63.• Yamamoto M, Seo Y, Ishizu T, Nishi I, Hamada-Harimura Y, Machino-Ohtsuka T, et al. Comparison of effects of aldosterone receptor antagonists spironolactone and eplerenone on cardiovascular outcomes and safety in patients with acute decompensated heart failure. Heart Vessels. 2018. https://doi.org/10.1007/s00380-018-1250-1. **A comparative trial of spironolactone and eplerenone in patients with heart failure.**

64. Chatterjee S, Moeller C, Shah N, Bolorunduro O, Lichstein E, Moskovits N, et al. Eplerenone is not superior to older and less expensive aldosterone antagonists. Am J Med. 2012;125(8):817–25.

65. Sica DA. Pharmacokinetics and pharmacodynamics of mineralocorticoid blocking agents and their effects on potassium homeostasis. Heart Fail Rev. 2005;10(1):23–9.

66. Lainscak M, Pelliccia F, Rosano G, Vitale C, Schiariti M, Greco C, et al. Safety profile of mineralocorticoid receptor antagonists: spironolactone and eplerenone. Int J Cardiol. 2015;200:25–9.

67. Davies JI, Band M, Morris A, Struthers AD. Spironolactone impairs endothelial function and heart rate variability in patients with type 2 diabetes. Diabetologia. 2004;47(10):1687–94.

68.•• Vukadinovic D, Lavall D, Vukadinovic AN, Pitt B, Wagenpfeil S, Bohm M. True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: a meta-analysis. Am Heart J. 2017;188:99–108. **A meta-analysis on MRA-related hyperkalemia but also raising the issue of non-MRA-related hyperkalemia.**

69. Tang WH, Parameswaran AC, Maroo AP, Francis GS. Aldosterone receptor antagonists in the medical management of chronic heart failure. Mayo Clin Proc. 2005;80(12):1623–30.

70.• Korol S, Mottet F, Perreault S, Baker WL, White M, de Denus S. A systematic review and meta-analysis of the impact of mineralocorticoid receptor antagonists on glucose homeostasis. Medicine (Baltimore). 2017;96(48):e8719. **A meta-analysis on the impact of MRAs on glycemia.**

71.• Ademi Z, Pasupathi K, Krum H, Liew D. Cost effectiveness of eplerenone in patients with chronic heart failure. Am J Cardiovasc Drugs. 2014;14(3):209–16. **A cost-effectiveness analysis of eplerenone in heart failure.**

72.• Lee D, Wilson K, Akehurst R, Cowie MR, Zannad F, Krum H, et al. Cost-effectiveness of eplerenone in patients with systolic heart failure and mild symptoms. Heart. 2014;100(21):1681–7. **A cost-effectiveness analysis of eplerenone in the EMPHASIS-HF trial.**

73.•• Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(5):1889–916. **Endocrine Society Guidelines on the management of primary aldosteronism.**

74. Kline GA, Prebtani APH, Leung AA, Schiffrin EL. Primary aldosteronism: a common cause of resistant hypertension. CMAJ. 2017;189(22):E773–e8.

75. Karashima S, Yoneda T, Kometani M, Ohe M, Mori S, Sawamura T, et al. Comparison of eplerenone and spironolactone for the treatment of primary aldosteronism. Hypertens Res. 2016;39(3):133–7.

76. Bell GM, Fananapazir L, Anderton JL. Comparison of single and divided daily dose spironolactone in the control of hypertension. Br J Clin Pharmacol. 1981;12(4):585–8.

77. Sungaila I, Bartle WR, Walker SE, DeAngelis C, Uetrecht J, Pappas C, et al. Spironolactone pharmacokinetics and pharmacodynamics in patients with cirrhotic ascites. Gastroenterology. 1992;102(5):1680–5.

78. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med. 2004;351(6):543–51.

79. Craft J. Eplerenone (Inspra), a new aldosterone antagonist for the treatment of systemic hypertension and heart failure. Proc (Bayl Univ Med Cent). 2004;17(2):217–20.

80. Ravis WR, Reid S, Sica DA, Tolbert DS. Pharmacokinetics of eplerenone after single and multiple dosing in subjects with and without renal impairment. J Clin Pharmacol. 2005;45(7):810–21.

81.•• Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. N Engl J Med. 1999;341(10):709–17. **A landmark trial on the effect of spironolactone on morbidity and mortality in patients with heart failure.**

82.• Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364(1):11–21. **A pivotal trial of eplerenone in heart failure patients.**

83.•• Pitt B, White H, Nicolau J, Martinez F, Gheorghiade M, Aschermann M, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. J Am Coll Cardiol. 2005;46(3):425–31. **A pivotal trial of eplerenone in heart failure patients after myocardial infarction.**

84. Ferreira JP, Duarte K, McMurray JJV, Pitt B, van Veldhuisen DJ, Vincent J, et al. Data-driven approach to identify subgroups of heart failure with reduced ejection fraction patients with different prognoses and aldosterone antagonist response patterns. Circ Heart Fail. 2018;11(7):e004926.

85. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). Rales Investig Circ. 2000;102(22):2700–6.

86. Nishikawa N, Yamamoto K, Sakata Y, Mano T, Yoshida J, Umekawa S, et al. Long-term effect of spironolactone on cardiac structure as assessed by analysis of ultrasonic radio-frequency signals in patients with ventricular hypertrophy. Circ J. 2005;69(11):1394–400.

87. Kawasaki M, Yamada T, Okuyama Y, Morita T, Furukawa Y, Tamaki S, et al. Eplerenone might affect atrial fibrosis in patients with hypertension. Pacing Clin Electrophysiol. 2017;40(10):1096–102.
88. Savoia C, Touyz RM, Amiri F, Schiffrin EL. Selective mineralocorticoid receptor blocker eplerenone reduces resistance artery stiffness in hypertensive patients. Hypertension. 2008;51(2):432–9.
89. 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):594–7.
90. Kalizki T, Schmidt BMW, Raff U, Reinold A, Schwarz TK, Schneider MP, et al. Low dose-eplerenone treatment decreases aortic stiffness in patients with resistant hypertension. J Clin Hypertens. 2017;19(7):669–76.
91. Briones AM, Nguyen Dinh Cat A, Callera GE, Yogi A, Burger D, He Y, et al. Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: implications in diabetes mellitus-associated obesity and vascular dysfunction. Hypertension. 2012;59(5):1069–78.
92. Epstein M, Williams GH, Weinberger M, Lewin A, Krause S, Mukherjee R, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clin J Am Soc Nephrol. 2006;1(5):940–51.
93. Bomback AS, Kshirsagar AV, Amamoo MA, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. Am J Kidney Dis. 2008;51(2):199–211.
94.• Neefs J, van den Berg NW, Limpens J, Berger WR, Boekholdt SM, Sanders P, et al. Aldosterone pathway blockade to prevent atrial fibrillation: a systematic review and meta-analysis. Int J Cardiol. 2017;231:155–61. **A meta-analysis on the effects of MRAs on atrial fibrillation.**
95.• Wei J, Ni J, Huang D, Chen M, Yan S, Peng Y. The effect of aldosterone antagonists for ventricular arrhythmia: a meta-analysis. Clin Cardiol. 2010;33(9):572–7. **A meta-analysis on the effects of MRAs on ventricular arrhythmias.**
96.• Beygui F, Van Belle E, Ecollan P, Machecourt J, Hamm CW, Lopez De Sa E, et al. Individual participant data analysis of two trials on aldosterone blockade in myocardial infarction. Heart. 2018;104(22):1843–9. **An important analysis of data on the effect of MRAs on total and sudden death mortality after a myocardial infarction.**
97.• Eschalier R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). J Am Coll Cardiol. 2013;62(17):1585–93. **A subgroup analysis of the EMPHASIS-HF trial on the effect of eplerenone in patients prone to hyperkalemia.**
98. Khosla N, Kalaitzidis R, Bakris GL. Predictors of hyperkalemia risk following hypertension control with aldosterone blockade. Am J Nephrol. 2009;30(5):418–24.
99. Gwoo S, Kim YN, Shin HS, Jung YS, Rim H. Predictors of hyperkalemia risk after hypertension control with aldosterone blockade according to the presence or absence of chronic kidney disease. Nephron Clin Pract. 2014;128(3–4):381–6.
100. Matsumoto Y, Mori Y, Kageyama S, Arihara K, Sugiyama T, Ohmura H, et al. Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. J Am Coll Cardiol. 2014;63(6):528–36.
101. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J. 2011;32(7):820–8.
102.• Pei H, Wang W, Zhao D, Wang L, Su GH, Zhao Z. The use of a novel non-steroidal mineralocorticoid receptor antagonist finerenone for the treatment of chronic heart failure: a systematic review and meta-analysis. Medicine (Baltimore). 2018;97(16):e0254. **Data on the new MRA, finerenone.**
103.•• NICE. Hypertension in adults: diagnosis and management. 2016. https://www.nice.org.uk/guidance/cg127. **British guidelines on hypertension**. Accessed 29 Oct 2018
104.•• Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19):e127–248. **New (2018) American guidelines on hypertension.**
105.•• Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–104. **New (2018) European guidelines on hypertension.**
106.•• Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension. 2018;72(5):e53–90. **New (2018) scientific statement from the American Heart Association on resistant hypertension.**