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REVIEW

Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure

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Clinical trials have demonstrated morbidity and mortality benefits of mineralocorticoid receptor antagonists (MRAs) in patients with heart failure. These studies have used either spironolactone or eplerenone as the MRA. It is generally believed that these two agents have the same effects, and the data from studies using one drug could be extrapolated for the other. National and international guidelines do not generally discriminate between spironolactone and eplerenone, but strongly recommend using an MRA for patients with heart failure due to LV systolic dysfunction and post-infarct LV systolic dysfunction. There are no major clinical trials directly comparing the efficacy of these two drugs. This article aims to compare the pharmacokinetics and pharmacodynamics of spironolactone and eplerenone, and to analyse the available data for their cardiovascular indications and adverse effects. We have also addressed the role of special circumstances including co-morbidities, concomitant drug therapy, cost, and licensing restrictions in choosing an appropriate MRA for a particular patient, thus combining an evidence-based approach with personalized medicine.

Keywords Aldosterone • Spironolactone • Eplerenone • Heart failure

Introduction

Mineralocorticoid receptor antagonists (MRAs) improve outcomes in patients with chronic heart failure (CHF) caused by LV systolic dysfunction (LVSD).[1–3] Eplerenone and spironolactone (or its metabolite, potassium canrenoate) are the currently licensed MRAs for clinical use. Clinical studies show the benefit of MRAs, but there are limited data on direct comparison of these MRAs. It is generally believed that the benefits of different MRAs represent a 'class effect'. National and international guidelines including those from the American Heart Association (AHA) and European Society of Cardiology (ESC) do not discriminate between spironolactone and eplerenone, but strongly recommend using these for patients with CHF and post-infarct LVSD.[4,5]

Spironolactone and eplerenone differ in their molecular structure, pharmacokinetics, and pharmacodynamics (*Table 1*). Spironolactone is a non-specific MRA and, due to its structural similarity to progesterone,[6] has affinity for progesterone, androgen, and glucocorticoid receptors. Eplerenone is chemically different,[7] and substitution of the 17-α-thioacetyl group of spironolactone with a carbomethoxy group in eplerenone provides greater selectivity for mineralocorticoid receptors (MRs) and minimal binding to progesterone and androgen receptors.[6] Spironolactone has substantially greater affinity for MRs than eplerenone, which is important to consider when comparing similar doses of these two drugs. Spironolactone and eplerenone differ in their metabolism and half-life.[6,8] Eplerenone produces more consistent inhibition of the rapid non-genomic effects of aldosterone (including coronary vasoconstriction, increased systemic vascular resistance, and potentiation of the vasoconstrictor effect of angiotensin II in coronary arteries) than spironolactone.[7,9] Based on these biochemical and pharmacological differences, this review aims to

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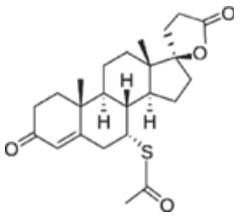
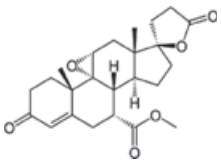
Table 1 Comparison of biochemical and pharmacological properties of spiranolactone and eplerenone

	Spironolactone	Eplerenone
Chemical structure		
Chemical formula	$C_{24}H_{32}O_4S$	$C_{24}H_{30}O_6$
Mode of action	Competitive MR antagonism	Competitive MR antagonism
MR affinity	High	10- to 20-fold lower
MR selectivity	Non-selective (also binds to glucocorticoid, progesterone, and androgen receptors)	Higher selectivity for MR
Inhibition of non-genomic MR effects	No	Yes
Onset/offset of action	Slow	Quicker
Bioavailability	60–90%	Absolute bioavailability unknown
Volume of distribution	Unknown	43–90 L
Protein binding	90% bound to plasma proteins	50% bound to plasma proteins
Metabolism	Hepatic metabolism to active metabolites	Hepatic metabolism by CYP3A4 to inactive metabolites
Half-life of drug	1–2 h	4–6 h
Active metabolites	Yes	No
Elimination half-life of drug and metabolites	10–35 h	4–6 h

MR, mineralocorticoid receptor.

compare systematically the available data to evaluate whether spironolactone and eplerenone can be substituted for each other for their cardiovascular indications.

Mineralocorticoid receptor antagonists for systemic hypertension

Mineralocorticoid receptor antagonists are effective in reducing blood pressure (BP) when used as monotherapy[10,11] or in combination regimens.[11–13] MRAs have been shown to be as effective as ACE inhibitors or ARBs in lowering BP.[14] Furthermore, it has also been suggested that MRAs can reduce BP as effectively as calcium channel blockers and, additionally, may have a more potent effect on reducing microalbuminuria.[15] Eplerenone has been shown to be better tolerated than the widely used calcium channel blocker amlodipine, with comparable reductions in systolic BP.[16] MRAs have also been shown to prevent end-organ damage in both pre-clinical[17] and clinical studies.[18,19] Furthermore, in the EPHESUS trial, eplerenone-associated reduction in all-cause mortality was significantly greater in those with a history of systemic hypertension.[2] The use of MRAs as anti-hypertensive agents, however, remains low. Current guidelines consider MRAs as fourth-line therapy for essential hypertension (except for patients with hypertension secondary to hyperalodsteronism, where it is first line),[20] which effectively limits their use to resistant hypertension only. Further large-scale studies showing efficacy, safety, and end-organ protection are warranted before MRAs can be moved higher up in the treatment algorithm for essential hypertension.[21]

The two MRAs have been directly compared in a few trials of systemic hypertension. A multicentre, double-blind, placebo-controlled trial in >400 patients with mild to moderate essential hypertension evaluated the efficacy, safety, and tolerability of the two MRAs over an 8-week treatment period and found that the magnitude of reduction in BP with eplerenone (100 mg daily) was 25% less than that with a similar dose of spironolactone, suggesting that spironolactone may have a more potent effect on BP.[22] The antihypertensive effect of spironolactone has also been shown to be greater than that of eplerenone in systemic hypertension associated with primary aldosteronism; a multicentre, double-blind, parallel-group, randomized, controlled trial showed that spironolactone (75–225 mg once daily) had almost a two-fold greater BP-lowering effect than eplerenone (100–300 mg once daily).[23] Another randomized, open-label, blinded-endpoint study compared spironolactone (25 mg twice a day) and eplerenone (25 mg twice a day) in patients with idiopathic hyperaldosteronism, and found that an equal proportion of patients achieved normal BP in both groups.[24] However, the BP-lowering effect of spironolactone was greater than that of equal doses of eplerenone.[24] The more potent and prolonged effect of spironolactone in lowering BP may be due to the longer half-life of its active metabolites, as compared with eplerenone.[6,8]

These data suggest that spironolactone is more effective than eplerenone when used at the same doses and, although there is no dose equivalence between the two drugs, spironolactone could be

used as first-choice MRA in the treatment of essential or secondary hypertension. However, if patients develop spironolactone-related adverse effects, then it may be worth switching to eplerenone, probably at a higher dose.

Mineralocorticoid receptor antagonists for heart failure

National and international guidelines recommend MRAs for patients with CHF caused by LVSD,[4,5] based on morbidity and mortality benefits seen in three landmark trials (RALES, EPHESUS, and EMPHASIS-HF).[1–3] These trials are not, however, directly comparable due to considerable differences in patient populations and trial design.[25] The RALES trial consisted of patients with advanced CHF, the EPHESUS trial included patients with LVSD after acute myocardial infarction (AMI), and the EMPHASIS-HF trial enrolled CHF patients with mild (NYHA II) symptoms.[1–3] Baseline drug therapy, especially the use of beta-blockers and ACE inhibitors, also differed markedly among these trials and could partially account for the observed differences in mortality reduction in these trials. Based on these differences, caution is warranted in directly comparing the results of these trials. Chatterjee *et al.* have recently carried out an 'indirect pooled analysis' of 13 studies using spironolactone (or canrenone) and eplerenone, and suggested that eplerenone was outperformed by other MRAs (15% vs. 26% reduction in all-cause mortality and 17% vs. 25% reduction in cardiac mortality).[26] However, this comparison is misleading for a variety of reasons. This analysis included some small trials with <100 subjects or short follow-up of 2–3 months duration, which may not be relevant to measure mortality or safety endpoints. Without these limitations, only three studies (EPHESUS, EMPHASIS-HF, and RALES) drove the results. However, these three trials cannot be directly compared due to differences in trial population and design (*Table 2*). We believe that available data have to be analysed at patient and trial level to decide on evidence-based use of the two MRAs. We will compare the use of these drugs for different forms of heart failure separately.

Table 2 Differences in RALES, EPHESUS, and EMPHASIS-HF trials

	RALES	EPHESUS	EMPHASIS-HF
Patient number	1663	6632	2737
Drug	Spironolactone	Eplerenone	Eplerenone
Mean drug dose (mg)	26	44	39
NYHA class	III–IV	I–IV	II
LVEF (%)	26	33	26
Ischaemic aetiology (%)	55	100	70
ACE inhibitor/ARB (%)	95	86	94
Beta-blockers (%)	11	75	87
Diuretics (%)	100	60	84
Years of recruitment	1995–96	1999–2001	2006–10
Mean follow-up (months)	24	16	21
Mortality in placebo group at 1 year (%)	27	14	7

Chronic heart failure due to left ventricular systolic dysfunction

RALES and EMPHASIS-HF have evaluated the efficacy of the two MRAs in CHF due to LVSD, showing that both drugs were effective in reducing mortality. In RALES, spironolactone produced a 30% relative reduction in mortality during an average follow-up of 24 months.[1] In EMPHASIS-HF, there was a 24% reduction in cardiovascular death and a 42% reduction in hospitalization for heart failure.[3] Based on individual trial design, it could be suggested to use spironolactone for advanced CHF and eplerenone for CHF with mild symptoms. However, it is counterintuitive to believe that these drugs will be effective in patients with only severe or mild symptoms, respectively. It may be tempting to think that either of these two drugs could be used in CHF due to LVSD. One possible limitation to this 'class effect' reasoning is the concern about dosing. In the 'real world', spironolactone is being used overwhelmingly, even in mild to moderate CHF, at doses used in the RALES trials. Several observational studies, inherently of less value than prospective randomized trials, have raised concerns that MRAs (mainly spironolactone) may not be as effective and safe as suggested by the results of the three main randomized trials.[27] This could possibly be due to off-label usage in higher risk groups, inappropriate dosing, or lack of careful monitoring, factors which are seldom seen in the settings of a clinical trial. Based on good evidence-based practice, one can expect the benefit–risk ratio shown in individual trials only when using the same drugs and dosages as used in corresponding trials. Therefore, until further data are available, it might be prudent to use the MRA and dosing regimens proven to be safe and effective in the major randomized trials, i.e. spironolactone 12.5–50 mg/day in patients with severe CHF due to LVSD and eplerenone 25–50 mg/day in patients with CHF due to LVSD and mild symptoms. Indeed, this approach has been adopted in some of the guidelines.[28,29]

Left ventricular systolic dysfuntion after myocardial infarction

Both spironolactone and eplerenone have been shown to improve LV pressure recovery following ischaemia and reperfusion in pre-clinical studies.[30] Spironolactone has not been studied in clinical trials for this indication. In the landmark EPHESUS trial, a mean dose of 43 mg of eplerenone produced 15% reduction in all-cause mortality, 17% reduction in cardiovascular mortality, and 21% reduction in sudden cardiac death (SCD).[2]

Although lack of clinical data does not mean that spironolactone has no effect in post-infarct LVSD, the evidence-based approach suggests that eplerenone, and not spironolactone, should be recommended for post-infarct LVSD patients, as suggested by the National Institute for Health and Clinical Excellence (NICE), UK. Furthermore, patients with MI are frequently treated with PCIs, and eplerenone (but not spironolactone) may also prevent in-stent restenosis.[31] Spironolactone was shown to inhibit post-angioplasty restenosis in rabbits.[32] However, these results could not be reproduced in a porcine coronary angioplasty model[31] or in a clinical trial.[33] However, eplerenone has shown promising results in many pre-clinical models.[31,34,35] This differential effect of eplerenone

could possibly be due to substantial (65%) reduction in collagen content in the neointima and media, which spironolactone has not been shown to reduce.[31] Furthermore, whilst eplerenone is selective for MRs, spironolactone may also block progesterone receptors (progesterone has been shown to have antiatherosclerotic and antirestenotic properties by inhibiting foam cell formation).[36] The efficacy of eplerenone for this indication has not been formally tested in a clinical trial. However, in the EPHESUS trial, 24% of patients received PCI as a treatment for AMI and, although there was no statistically significant interaction, the magnitude of beneficial effects of eplerenone, as compared with placebo, was greater in PCI-treated patients compared with patients who did not have PCI.[2] There are currently two ongoing trials to test MRAs in an AMI population: ALBATROSS (NCT-01059136) and REMINDER (NCT-01176968) testing spironolactone and eplerenone, respectively. Both agents will be administered within 24 h of an AMI. These trials may help understand potential similarities and differences between the two MRAs.

Prevention of sudden cardiac death in heart failure

Mineralocorticoid receptor antagonists, in addition to standard therapy, reduced the incidence of SCD in the RALES, EPHESUS, and EMPHASIS-HF trials.[1–3] Spironolactone has been shown to improve electrophysiological parameters such as QT interval dispersion.[37] Furthermore, spironolactone, in combination with ACE inhibitors, reduced arrhythmias in post-MI patients.[38] MRAs acutely improve cardiac vagal control, irrespective of any diuretic effects, which may partially explain their beneficial effects.[39] Wei *et al.* performed a meta-analysis of MRA trials to evaluate their role in the prevention of SCD in heart failure patients.[40] This meta-analysis included seven trials with a total of 8635 patients. All eplerenone data were derived from the EPHESUS trial. The majority of the spironolactone data came from the RALES trial, whilst the other five trials (all with spironolactone) contributed only 340 patients in this meta-analysis. Both MRAs significantly reduced the risk of SCD, ventricular tachycardia, and episodes of ventricular premature complexes (*Table 3*).[40]

In summary, both drugs have a potential, and similar, role in prevention of ventricular arrhythmias and SCD in CHF patients. Hence, this indication does not affect the choice of which MRA should be used. Thus, the choice continues to be based on the severity of symptoms and the circumstances of heart failure (post-infarct or not).

Heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction (HF-PEF) or diastolic heart failure (DHF) is pathophysiologically different from heart failure due to LVSD.[41] Hence, the data from studies evaluating the effects on patients with heart failure due to LVSD should not be directly extrapolated to diastolic dysfunction.

Mineralocorticoid receptor activation leads to LV hypertrophy and collagen deposition, which reduces compliance.[42] Eplerenone has been shown to attenuate collagen turnover in patients with DHF[43,44] and to improve the echocardiographic measures of diastolic function.[44] There was, however, no significant improvement in 6 min walk distance.[44] Furthermore, any benefit of eplerenone on morbidity and mortality in HF-PEF remains to be demonstrated.

Table 3 Mineralocorticoid receptor antagonists for prevention of sudden cardiac death

	Spironolactone	Eplerenone
Dose (mg/day)	25	25–50
Patient number	1663	6632
NYHA class	III or IV	II
LVEF	<35%	<40%
Follow-up	24	16
VA hospitalization	Spironolactone 2.8% vs. control 2.8%, $P = 0.9$	Eplerenone 1.6% vs. control 1.6%, $P = 0.8$
Sudden cardiac death	Spironolactone 10% vs. control 13%, $P = 0.02$	Eplerenone 4.9% vs. control 6.1%, $P = 0.03$

VA, ventricular arrhythmias.

A few studies have assessed the effect of spironolactone on diastolic dysfunction. Spironolactone (25 mg/day) in combination with ACE inhibitors improved myocardial function, reduced LV hypertrophy, and reduced markers of collagen turnover in patients with metabolic syndrome and already receiving ACE inhibitors.[45] Aldo-DHF randomized 422 patients with DHF (NYHA II/III, EF ≥50% and echocardiographic evidence of diastolic dysfunction) to receive either spironolactone (25 mg/day) or placebo for a period of 12 months and revealed no improvement in exercise capacity or quality of life, despite improved biochemical and echocardiographic features in the spironolactone group.[46] TOPCAT is a large ($n = 3445$) multicentre, randomized, double-blind, placebo-controlled trial of spironolactone in patients with DHF.[47] The trial results were presented at AHA Scientific Sessions, November 18, 2013. During an average follow-up of 3.3 years, there was no difference in the primary endpoints (the rate of cardiovascular mortality, aborted cardiac arrest, or heart failure hospitalization) between the spironolactone and placebo groups (18.6% vs. 20.4%; HR 0.89, 95% CI 0.77–1.04). The rate of heart failure hospitalization was, however, significantly reduced in the spironolactone group (12% vs. 14.2%, HR 0.83, 95% CI 0.69–0.99).

In summary, for HF-PEF there is no current indication for either agent. However, spironolactone can potentially be used for reduction in heart failure hospitalisation in this challenging group of patients with limited therapeutic options.

Right heart failure and pulmonary arterial hypertension

Plasma aldosterone levels have been shown to correlate with progression of pulmonary arterial hypertension (PAH).[48] Conversely, MR blockade reduces the proliferation of pulmonary arterial smooth muscle cells.[49] Both spironolactone and eplerenone have

been shown to prevent or reverse pulmonary vascular remodelling and improve cardiopulmonary haemodynamics in murine models of PAH.[50]

To date, no studies have evaluated the role of MRAs in patients with PAH and right heart failure. The use of MRAs in the treatment of PAH and right heart failure is, therefore, not licensed at the moment (except as part of diuretic therapy), due to lack of clinical evidence. However, the pre-clinical data appear promising and clinical trials are warranted.

Other potential factors in choosing a mineralocorticoid receptor antagonist

Gender

Spironolactone can produce endocrine sexual side effects. It can interfere with 17-hydroxylase activity (causing a decrease in testosterone synthesis) and peripheral metabolism of testosterone (causing changes in the testosterone to oestradiol ratio), resulting in gynaecomastia,[51] which is reported in 10–20% of the men taking spironolactone.[1,13] Hypertensive trials have directly compared spironolactone and eplerenone, and suggest that eplerenone causes fewer endocrine side effects, including gynaecomastia.[22–24] As a significant proportion of men are likely to be affected with this side effect, it is reasonable to offer eplerenone as an alternative long-term therapy in male patients affected by gynaecomastia on spironolactone or who elect not to be given spironolactone for fear of developing that complication. In female patients, spironolactone is likely to be better tolerated than in male patients and should remain as first-line therapy. However, it must be kept in mind that women receiving spironolactone can also develop mastodynia and menstrual irregularities,[22,23] and may require switching to eplerenone, a manoeuvre that usually ameliorates these symptoms.[24]

Heart failure with diabetes mellitus

Spironolactone and eplerenone are equally effective in CHF patients with or without diabetes.[52] However, spironolactone has been shown to impair endothelial function, as measured by acetylcholine-mediated vasodilatation, in patients with type 2 diabetes, possibly due to the worsening of glycaemic control and an increase in plasma angiotensin II.[53] In contrast, eplerenone could improve coronary circulatory function (adenosine-stimulated myocardial perfusion reserve) and endothelial function in diabetic patients already receiving ACE inhibitors.[54] Furthermore, spironolactone can increase HbA_{1c} (glycated haemoglobin) levels in patients with type 2 diabetes with or without nephropathy or poorly controlled hypertension.[53,55] In a study of 107 patients with mild CHF, spironolactone increased HbA_{1c} and cortisol levels and reduced adiponectin levels over 4 months, findings which might be expected to herald an increased risk of developing diabetes.[56] However, eplerenone has no such effects, suggesting the possibility of a differential effect, depending on the selectivity of MR blockade.[56] Therefore, it could be argued that eplerenone is the preferred MRA for diabetics. However, it must be noted that there are opposing reports on the relationship of HbA_{1c} levels and outcomes in patients with CHF.[57,58] Therefore, caution is warranted in interpreting the differences between eplerenone and spironolactone in patients with diabetes in the absence of direct comparative outcome trials.

Table 4 Comparison of adverse events in spironolactone and eplerenone chronic heart failure with left ventricular systolic dysfunction trials

	Spironolactone	Eplerenone
Main trial	RALES	EMPHASIS-HF
Mean drug dose (mg)	26	39
Gynaecomastia (%)	9	0.5
Breast pain (%)	2	0.5
Adverse event (%)	82	72
Serious hyperkalaemia ($K^+ > 6$ mmol)	1.2% in placebo and 1.7% in spironolactone group ($P < 0.001$)	1.9% in placebo and 2.5% in eplerenone group ($P = 0.3$)
Discontinuation due to adverse event	3% higher than placebo group	2.4% less than placebo group

Hyperkalaemia

Both drugs can cause hyperkalaemia, and the incidence of serious hyperkalaemia is likely to be higher in real life than in clinical trials.[1,2,59] There are no direct comparative data to differentiate between the two agents in terms of risk of hyperkalaemia. However, the available evidence suggests that the risk of hyperkalaemia may be lower with eplerenone (*Table 4*). In view of the greater affinity of spironolactone for MRs, as well as its longer half-life, the risk of hyperkalaemia may be greater with 25 mg of spironolactone than with 25 mg of eplerenone, the starting doses of these drugs in the landmark trials. Furthermore, if hyperkalaemia develops with MRA treatment, it is likely to take a longer time to obtain normokalaemia with spironolactone in view of its longer half-life.

Other co-morbidities

Spironolactone is also used for non-cardiac indications including hyperaldosteronism, cirrhosis with ascites and portal hypertension, and nephrotic syndrome. There have been no major placebo-controlled, randomized trials comparing the relative efficacy of the two drugs in the management of these conditions and, until more data become available, it is reasonable to start with spironolactone in these co-morbid conditions and switch to eplerenone if side effects are limiting.

Concomitant therapy

Caution is warranted for patients on multiple drugs to avoid potential drug interaction and altered metabolism of drugs.[25] Eplerenone is metabolized primarily by cytochrome P450 3A4 (CYP3A4); therefore, it should be avoided in patients receiving

potent inhibitors of this enzyme, such as ketoconazole (may induce a five-fold increase in eplerenone levels). Closer monitoring may be needed when eplerenone is used with less potent inhibitors of CYP3A4, such as verapamil, erythromycin, fluconazole, and protease inhibitors. Conversely, the CYP3A4 inducer, St John's Wort, may reduce eplerenone levels by 30%.

Licensing restrictions

The licensing restrictions may have implications on which agent can be prescribed in different geographical and ethnic groups. Spironolactone is widely licensed for treatment of hypertension and heart failure. In Europe and Canada, eplerenone is indicated for patients with CHF and post-infarct LVSD, but not for the treatment of essential hypertension.[60] In the USA, eplerenone is indicated for all these conditions, whilst in some Asian countries eplerenone is indicated only for hypertension.[22,61,62]

Cost implications

Treatment with an MRA is cost-effective for the management of CHF due to LVSD.[63] In the absence of a randomized controlled trial, it is difficult to establish the cost benefit of one agent over the other. Although spironolactone is substantially cheaper, eplerenone causes fewer side effects and may potentially be more cost-effective in the management of post-infarct LVSD.[64] The incremental cost-effectiveness ratio of eplerenone, compared with that of standard care alone (and not spironolactone), is £4457 and £7893 for each additional quality-adjusted life year (QALY) when 2-year and lifetime treatment duration is assumed, respectively.[64] These figures are well below the £20 000 threshold accepted as good value by NICE, UK. The results of these health economic analyses are based on higher relative effectiveness estimated for eplerenone compared with spironolactone from the meta-regression. However, if a 'class effect' is considered more plausible than the results of an evidence synthesis model, spironolactone is the most cost-effective treatment.

Cost-effectiveness analysis of the EMPHASIS-HF trial was recently presented at the ESC Conference, showing that eplerenone is cost-effective in CHF patients with mild symptoms, by improving quality of life and reducing hospitalization (John McMurray, ESC 2012). In addition to standard care, eplerenone prescription increased lifetime direct costs by £3822 for the UK, and €7239 for Spain, with additional quality-adjusted life expectancy of 1.22 QALYs (UK, discount rate 3.5%) and 1.33 years (Spain, discount rate 3%). Mean lifetime costs were £3140 per QALY in the UK, €4312 per QALY in Greece, and €5442 per QALY in Spain. Probabilistic sensitivity analysis suggested a 100% likelihood of eplerenone being regarded as cost-effective at a willingness to pay threshold of £20 000 per QALY (UK) or €30 000 per QALY (Spain). Therefore, by currently accepted standards of value for money, the addition of eplerenone to optimal medical therapy for patients with CHF and mild symptoms is likely to be cost-effective.

Future directions

Head-to-head trial to evaluate side effects

It would be difficult, if not impossible, to conduct a head-to-head trial of these two drugs, due to the reasons already outlined. However, as both drugs appear effective for many cardiovascular indications and the main factor in decision-making relates to side effect profile, it should be possible to conduct a small-scale trial focusing on side effects, and not the efficacy, of these two drugs.

Personalized medicine

In the absence of direct comparative evidence, it should remain perfectly acceptable (and preferable) to recommend one agent or the other based on an individual patient's profile, including gender, co-morbidities, etc. This approach allows combining evidence-based with personalzed medicine.

Non-steroidal mineralocorticoid receptor antagonists

Both spironolactone and eplerenone are steroidal compounds. There are a few non-steroidal MRAs at various stages of development.[65,66] It would be interesting to see if these compounds

Table 5 A suggested approach to select mineralocorticoid receptor antagonists for cardiovascular indications

Indication	First-line MRA	Selection of MRA
Hypertension	Spironolactone	Consider gender (eplerenone for male patients)[a] and licensing restrictions
Chronic heart failure and LVSD	Either	Consider eplerenone for mild heart failure and male patients and spironolactone for females or those with severe heart failure
LVSD post-MI	Eplerenone	
Diastolic heart failure	Potentially spironolactone	Consider eplerenone for male patients and switch to eplerenone for all patients with side effects
PAH/RHF	Neither	Convincing pre-clinical data merit clinical trials

LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; PAH, pulmonary arterial hypertension; RHF, right heart failure.

[a]There are limited data supporting a gender-based approach in selecting MRAs and it could be argued to give eplerenone to male patients only if/when sexual side effects occur.

show similar efficacy, but have fewer side effects. Being non-steroidal, it is envisaged that these compounds will have fewer endocrine side effects. It is also being suggested that these compounds may have higher affinity for cardiac MRs, rather than renal MRs, and, therefore, potentially less tendency for hyperkalaemia. BAY 94-8862 (Bayer Pharma, Germany) is currently being tested in ARTS (minerAlocorticoid Receptor antagonist Tolerability Study; NCT01345656) trial, and the results of this study will be of major interest.[66]

Summary

There is a paucity of direct comparative data for spironolactone and eplerenone. It may not be appropriate to compare trials using spironolactone or eplerenone in heart failure directly due to vast differences in patient population and trial design. Choice of a specific agent could be based on clinical indications (such as the nature of heart failure), individual patient factors (such as gender, co-morbidities, occurrence of side effects), geographical licensing restriction, and community-level cost–benefit analysis. Based on the data available, we have suggested a simple approach to select a particular MRA for various cardiovascular indications (*Table 5*). Further comparative studies and cost–benefit analyses are warranted.

Conflict of interest: B.P. has received honoraria from Pfizer and serves on the advisory boards for Pfizer and Novartis. A.A.M. was advisor to NICE (UK) for CHF guidelines and heart failure Quality Standards, and is a member of the NICE group on Acute Heart Failure NICE guidelines. F.Z. has received honoraria from Pfizer, Novartis, Roche, Servier, AstraZeneca, and Takeda. All other authors have no conflicts of interest to declare.

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