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Heart failure: the role for mineralocorticoid receptor antagonists

Bertram Pitt

University of Michigan School of Medicine, Ann Arbor, MI, USA

In Memory of Dr Walter Schweizer, University of Basel: Gifted teacher, clinician, and mentor.

Summary

Mineralocorticoid receptor antagonists (MRA's) have been shown to be effective in patients with HFREF while their role in patients with HFPEF remains controversial. Despite a class one indication in both the ESC and AHA/ACC heart failure guidelines in patients with HFREF MRA's remain underused, in large part due to the fear of hyperkalaemia and renal dysfunction. While hyperkalaemia is a potential risk of MRA's, their use when potassium and renal function monitoring is properly carried out is minimal compared with their benefits in appropriate patients. New nonsteriodal MRA's and new potassium binding polymers currently under development hold the promise of further reducing the risks of hyperkalaemia while allowing higher doses of MRA's. They have been shown to overcome diuretic resistance and to potentially extend their benefits to patients with acute decompensated heart failure and those with chronic renal disease. While we await the results of studies with these new agents; application of current guidelines recommended therapies, including MRA's hold the best promise to further reduce cardiovascular mortality, hospitalisations for heart failure, and therefore, health care costs in patients with heart failure.

Key words: *aldosterone; mineralocorticoid receptor antagonists; heart failure; hyperkalaemia*

Introduction

Over the past two decades, evidence from randomized trials of angiotensin converting enzyme inhibitors (ACE-Is) or angiotensin blocking agents (ARBs), beta-adrenergic blocking agents (BBs), mineralocorticoid antagonists (MRAs), cardiac resynchronization therapy (CRT), automatic implantable cardiac defibrillators (AICD), cardiac transplantation, and left ventricular assist devices (LVADs) in patients with chronic heart failure (HF) and a reduced left ventricular ejection fraction (REF) has suggested a significant decrease in mortality and hospitalizations for heart failure [1]. However, although evidence for these therapeutic approaches is convincing, their application in various parts of the world is suboptimal. Limitations in economic resources understandably affect the usage of device therapy such as CRT, AICDs, LVADs and cardiac transplantation. Drug therapy, owing to its lower costs, is more widely available, but there remains a significant underuse, particularly of MRAs [2, 3]. The gap between the "real world" use of MRAs and the number of patients in whom they are thought to be appropriate in current guidelines [4, 5] represents one of the best opportunities to further reduce cardiovascular death, hospitalizations for heart failure, and therefore healthcare costs over the near term. The reasons for this underuse in large part reflect the fear of inducing serious hyperkalemia (HK) as well as a relative lack of understanding of the benefits of MRAs and the reasons underlying their benefits. This article will therefore briefly review the evidence supporting the role of MRAs in patients with chronic HFREF; as well as those with HF and a preserved left ventricular ejection fraction (HFPEF); the potential mechanisms accounting for these benefits; the dosage and choice of MRAs; their risks; and strategies to potentially reduce these risks in an attempt to reduce the gap in their usage and thereby further reduce cardiac mortality, hospitalizations for HF, and therefore potentially healthcare costs.

The use of MRAs in patients with chronic HFREF

In the 1980s and 1990s there was relatively little interest in the role of MRAs in patients with HF despite the fact that aldosterone was known to promote sodium retention, was thought important in the pathophysiology of HF, and the MRA spironolactone had been available for several decades. In large part the lack of interest in the use of spironolactone in patients with HF can be attributed to the fact that spironolactone was generic in many parts of the world and interest was focused on newer branded ACE-Is, ARBs, and BBs. The results of the RALES trial [6] in 1999 provided

the first convincing evidence that spironolactone in a dose of 12.5–50 mg/day in addition to standard therapy including an ACE-I could reduce total mortality as well as hospitalizations for HF in patients with chronic severe HFREF. Patients with a serum potassium (K^+) >5.0 meq/l and/or a serum creatinine >2.5 mg/dl were excluded. The RALES trial was stopped prematurely owing to a 30% significant benefit on total mortality, but many clinicians remained skeptical and did not apply this therapy, in part because when the RALES trial was initiated there was no evidence for the use of BBs in patients with chronic severe HFREF and only 10% of patients in RALES were on a BB at baseline. More importantly, several investigators, in particular Jurlink et al. [7] in Canada, pointed out a relatively high incidence of hospitalizations for HK, renal failure, and deaths due to HK after the results of RALES were reported and spironolactone began to be used more frequently in patients with HF. A critical review of the study by Jurlink et al. suggests however that in many instances physicians in Canada used higher doses of spironolactone than in RALES [6]; included older patients with concomitant chronic renal disease, the severity of which was not adequately reflected by determination of serum creatinine alone; and did not serially monitor serum K^+ and or adjust the dose of spironolactone accordingly.

The RALES study [6] was followed by the EPHESUS trial [8], in which patients with HFREF early (3–14 days) post myocardial infarction (MI) were randomized to the newer more selective MRA eplerenone 25–50 mg/day in addition to standard therapy. Patients in EPHESUS randomized to eplerenone had a significant reduction in the combined endpoint of cardiovascular mortality and hospitalizations for HF, as well as total mortality. Of particular interest was the finding that within 30 days of randomization to eplerenone (mean time of randomization post MI was 7 days) there was a significant reduction in total mortality, mainly due to a reduction in sudden cardiac death [9]. This is of especial importance since in the first month post MI there is a relatively high incidence of sudden cardiac death, which has not been reduced by the use of AICDs. In contrast to the RALES study [6], 85% of patients in EPHESUS [8] were on a BB and an analysis of the patients on "optimum" medical therapy including those who received an aspirin, reperfusion, a statin, an ACE-I or ARB, a BB, and a diuretic showed a reduction the co-primary endpoint of time to cardiovascular mortality or hospitalization for HF. These results in large part allayed the skepticism surrounding the results of RALES [6] due to the relatively low usage of BBs but did not reduce the fear in clinicians' minds of inducing HK with a MRA, despite the fact that the incidence of HK (serum K^+ >5.5 meq/l) in EPHESUS [8] was only 3%, and the fact that in both RALES [6] and EPHESUS [8] there was not a single death attributable to HK in patients randomized to a MRA.

The effectiveness of MRAs in patients with chronic HFREF is further substantiated by the results of EMPHASIS-HF [10], in which patients with HFREF and mild symptoms (New York Heart Association class II) who had a history of a cardiovascular hospitalization within the 6 months prior to randomization or an elevated brain natriuretic peptide (BNP) or N-terminal of BNP prohormone (NT-proBNP) randomized to eplerenone 25–50 mg/day in addition to standard therapy were found to have a significant reduction in time to cardiovascular mortality or hospitalizations for HF. Most importantly, patients randomized to eplerenone had a significant reduction in total mortality as well as total hospitalizations. Of particular interest was the safety of eplerenone. Although there was a 3% increase in the incidence of HK (serum K^+ >5.5 meq/l) there was no significant increase in the incidence of serious HK (serum K^+ ≥6.0 meq/l), discontinuation of eplerenone due to HK, hospitalizations for HK, or hospitalizations due to renal failure. In contrast, there was a significant reduction in the incidence of hypokalemia (serum K^+ <3.5 meq/l). Of interest in view of the previous study by Jurlink et al. [7] pointing out the risk of spironolactone for HK was the finding in high-risk subsets of patients in EMPHASIS-HF [11], including the very old (≥75 years of age), those with diabetes mellitus and or with chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2), that the overall effect on the primary endpoint (time to cardiovascular mortality or hospitalization for HF) was maintained without a significant difference in these subsets in the safety of eplerenone, in particular the incidence of hospitalization HK and or renal failure.

The role of MRAs in patients with HFPEF

Patients with HFPEF have a number of important differences in comparison with those with HFREF. In particular, they have a higher incidence of comorbidities, especially: hypertension, obesity, the metabolic syndrome, diabetes mellitus, sleep disorder breathing, atrial fibrillation, and CKD. They are generally older than those patients with HFREF and mainly female. Many of the important comorbidities associated with patients with HFPEF have been shown to be associated with an increase in serum aldosterone and or an increase in mineralocorticoid receptor (MR) expression. For example, patients with resistant hypertension have been found to have elevated levels of aldosterone and cortisol [12]. This is of importance since cortisol as well as aldosterone can occupy and activate the MR, especially under conditions associated with an increase in inflammatory cytokines and reactive oxygen species (ROS) [13, 14]. In patients with obesity and or the metabolic syndrome, aldosterone levels are elevated [15], in part as a result of factors released from the adipocyte that stimulate the adrenal production and release of aldosterone [16]. In preclinical models fed a high-fat diet, MR expression is increased [17]. Similarly, in HFPEF or diastolic HF MR expression is increased [18]. Furthermore, an increase in extracellular matrix formation, myocardial fibrosis, left ventricular hypertrophy, left atrial enlargement and diastolic dysfunction has been associated with the transition from hypertensive heart disease to HFPEF. MRAs have been shown to be effective in reducing left ventricular hypertrophy, left atrial enlargement, and diastolic dysfunction in patients with HFPEF [19–21]. However, although an increase in extracellular matrix formation and myocardial fibrosis appear to be an important component of the pathophysiology of HFPEF, recent studies have suggested that

an increase in myocardial stiffness due to an alteration in phosphorylation of the myocardial protein titin may play an important role in HFPEF, independent of an increase in extracellular matrix formation [22]. The increase in serum aldosterone and cortisol levels associated with HFPEF and several of its associated comorbidities as well as the increase in MR expression provides the background for the hypotheses that MRAs are effective in reducing cardiovascular events in patients with HFPEF. The recent NHLBI TOPCAT trial [23] evaluated the MRA spironolactone at a dose of 15–45 mg/day in patients with HFPEF treated with standard therapy including an ACE-I or ARB, BB, and a diuretic. A total of 3,345 patients from the Americas (Canada, USA, Brazil, and Argentina) and from Eastern Europe (Russia and the Republic of Georgia) were randomized into the study on the basis of symptoms of HF and either a history of hospitalization within the year prior to randomization, a major component of which was HF, or on the basis of an elevated BNP or NT-proBNP [24–26]. Patients randomized into the study had a mean age of 69 years (52% were female), had a mean left ventricular ejection fraction of 56%, and had their blood pressure relatively well controlled (mean BP 130/80 mm Hg) at baseline prior to randomization. As expected, they had a relatively high incidence of comorbidities including a history of hypertension in 92%, diabetes mellitus in a third, coronary artery disease in over half and atrial fibrillation in 35%, with a mean body mass index of 31 kg/m^2. At baseline 84% were on either an ACE-I or ARB, 78% on a BB, and 81% on a diuretic. After a mean follow-up of 3.3 years the primary endpoint – the combination of time to cardiovascular death, resuscitated cardiac arrest, and hospitalization for HF – was reduced insignificantly by 11%, although one of its components, time to hospitalization for HF, was reduced significantly, as was total hospitalizations for HF. Although the overall results were not significant, it was found that those entering the trial on the basis of an elevated BNP or NT-proBNP did have a significant reduction in the primary endpoint of 35% (interaction $p = 0.013$). However, it should be emphasized that this was only one of 22 subgroups that were prespecified and therefore the significance could be due to chance. Of particular interest was the retrospective finding that patients entering the trial from Russia and the Republic of Georgia had a placebo cardiovascular mortality rate of approximately 2%/year and a heart failure hospitalization rate of <1% a year, which is not compatible with prior epidemiologic studies or randomized studies of patients with HFPEF. Although there was no apparent benefit of spironolactone in these relatively low-risk patients from Russia and the Republic of Georgia, there was a significant reduction in the primary endpoint in those entering the trial from the Americas (Canada, USA, Brazil, and Argentina), who comprised approximately half of the patients. The p-value for treatment interaction was not significant between those patients entering from Russia and the Republic of Georgia and those from the Americas, but this was likely due to the relatively wide confidence intervals in the effectiveness of spironolactone in the low-risk patients entering from Russia and the Republic of Georgia. Although the reasons for the marked geographic heterogeneity in placebo event rates remains as yet unexplained, these results suggest the hypotheses that in patients who have a cardiovascular risk compatible with prior studies of patients with HFPEF spironolactone is safe and effective.

The choice of MRAs in patients with HF

Both spironolactone and eplerenone are effective MRAs and have been shown to reduce total mortality in patients with HFREF [6, 8, 10]. There are, however, several differences [27] that may suggest one or the other in certain indications and or in individual circumstances. Spironolactone is more tightly bound to the MR than eplerenone and therefore more effective on a mg/mg basis. Approximately 25 mg of spironolactone is equivalent to 50 mg of eplerenone. Spironolactone has a longer half-life than Eplerenone owing to its metabolite canreoanate. This has potential advantages and disadvantages. The longer plasma half-life of spironolactone would be an advantage in patients who are noncompliant and tend to miss doses of their medication. On the other hand it could be a disadvantage if a patient developed hyperkalemia, in which case the longer plasma half-life of spironolactone could increase the risk of hyperkalemia and its consequences. Spironolactone, however, is not as specific for the MR as eplerenone and affects androgen and prostagen receptors. This accounts for the relatively increased incidence of side effects such as breast pain, gynechomastia, and impotence in males, as well as menstrual abnormalities and hirsutism in premenstrual females, associated with spironolactone but not eplerenone. A small direct comparative trial of spironolactone and eplerenone in patients with diabetes mellitus and HF [28] has shown that spironolactone but not eplerenone increases glycated hemoglobin (HbA_{1c}) and cortisol levels while reducing adiponectin levels. Spironolactone has also been shown to worsen endothelial function in patients with diabetes mellitus associated with an increase in HbA_{1c} levels [29], whereas in patients with HF without diabetes mellitus it improves endothelial function [30]. The difference between spironolactone and eplerenone in patients with diabetes mellitus has been attributed to the relative lack of specificity for the MR of spironolactone. It should, however, be emphasized that there have been no large-scale outcome studies comparing spironolactone with eplerenone and both have been shown to reduce mortality in patients with HFREF and diabetes (spironolactone in RALES [6] and Eplerenone in EPHESUS [8] and EMPHASIS-HF [10]. It should also be emphasized that, although both spironolactone and eplerenone are generic in the USA (although not as yet in some other parts of the world), spironolactone is considerably less expensive than eplerenone owing to the greater complexity in the production of eplerenone. Many clinicians have extrapolated the benefits of eplerenone 25–50 mg/day in EPHESUS [8] in patients with HFREF post MI and EMPHASIS-HF [10] in patients with chronic mild HFREF to spironolactone and have used the dosing strategy of spironolactone that was shown to be effective in RALES [6] of 12.5–50 mg day in situations such as HFREF and mild symptoms, in which eplerenone has been shown to be effective in reducing total mortality and well tolerated. However, as mentioned

above, spironolactone is more tightly bound to the MR and has a longer plasma half-life than Eplerenone. Substituting 25–50 mg of spironolactone for 25–50 mg of eplerenone in patients with HFREF post MI or chronic mild HFREF may therefore have a different safety profile than noted in EPHESUS [8] and EMPHASIS-HF [10], and could be associated with a higher incidence of hyperkalemia than noted in these trials. The excellent safety profile of eplerenone has recently been confirmed in the REMINDER trial [24], in which patients with an acute ST-elevation MI (STEMI) were randomized to eplerenone starting at a dose of 25 mg/day on day 1 or placebo post MI with subsequent up-titration of study drug to 50 mg/day at 1 month if the serum K^+ remained <5.0 meq/l. Given the importance of healthcare costs, the lower cost of spironolactone is, however, clearly an advantage. However, the failure to use an MRA in patients in whom they are appropriate according to current guidelines due to the fear of hyperkalemia and in particular eplerenone in patients who do not tolerate spironolactone may in the long run be far more costly than the cost differential between eplerenone and spironolactone. One might consider the use eplerenone 25–50 mg/day in patients with diabetes mellitus and or CKD, as well as in young male patients for the reasons outlined above. If, however, cost is an important factor spironolactone at a dose of 12.5–25 mg should be used initially and eplerenone substituted in those patients in whom spironolactone is not tolerated. It should, however, be emphasized that the dosing strategy for spironolactone in RALES [6] has not been adequately tested in patients with HFREF and mild symptoms, and its effectiveness and particularly its safety are therefore uncertain. Without further direct large scale comparative trials clinicians of necessity are forced to use their individual judgment based upon their assessment of the available data.

Risk of HK in patients with HFREF and HFPEF

The increased incidence of HK in patients with HFREF in the large-scale randomized studies RALES [6], EPHESUS [8], and EMPHASIS-HF [10], although of concern, has been associated with a reduction of total mortality. In TOPCAT [24], in patients with HFPEF there was a 9.6% increase in hyperkalemia (serum K^+ >5.5 mmol/l), but, as in patients with HFREF, there were not any deaths attributable to HK. It should, however, be emphasized that patients in these large-scale randomized trials were carefully selected and patients with a baseline serum K^+ >5.0 mmol/l, a serum creatinine >2.5 mg/dl, and/or an eGFR <30 ml/min/1.73 m^2 were excluded, serum K^+ was serially monitored and the dose of the MR adjusted accordingly. In general, in patients with normal renal function the risk of HK is relatively low and serum K^+ can be monitored after the first month during routine follow-up visits. However, if the patient begins to take an agent that interferes with the renal excretion of K^+ such as a nonsteroidal anti-inflammatory drug or if they have an episode of diarrhea or vomiting, serum K^+ should be immediately rechecked and closely monitored until the situation stabilizes. In patients with chronic renal disease and/or diabetes mellitus, especially those with an eGFR <45 ml/min/1.73 m^2, serum K^+ should be more closely monitored, for example, at baseline, at 3 days, 1 week, 2 weeks, 4 weeks, and 1 to 3 monthly thereafter. In patients with HF, and especially those with CKD, one should be hesitant to prescribe a MRA if the patient is unwilling or unable to undergo serial K^+ monitoring despite their proven benefits on mortality. Although there is clearly a risk of HK and its consequences, including renal failure and death, when using a MRA, the recent experience with eplerenone 25–50 mg /day in EMPHASIS-HF, in which there was a significant reduction in total mortality and total hospitalizations, is reassuring. Despite a significant increase in the incidence of HK there was no increase in the incidence of serious HK, discontinuation from eplerenone due to HK, increase in hospitalization for HK, increase in hospitalization for renal failure, and not a single death attributable to HK. Thus if patients are carefully selected as outlined in the major randomized trials and K^+ serially monitored, even in patients with CKD and or DM there is a significant reduction in mortality with only minimal risk. The increased risk of HK and its serious consequences reported from observational studies can in part be attributed to the failure of clinicians to monitor serum K^+ and to adjust the dose of the MRA accordingly. However, as mentioned above, despite careful selection of patients and serial monitoring of serum K^+ there are individuals who will develop HK. The recent introduction of an orally effective K^+ polymer patiromer (RLY 5016), which removes K^+ from the blood and binds it in the colon, holds promise for the use of renin-angiotensin-aldosteroine system (RAAS) inhibitors especially MRAs in patients who develop HK while on therapy. In the Pearl-HF study [31] in patients with chronic HF who either had discontinued a RAAS inhibitor or BB because of HK or who had CKD (eGFR <60 ml/min/1.73 m^2) and were given spironolactone 50 mg day in addition to their standard HF therapy which could include an ACE-I or ARB and a BB, there was a significant reduction in the incidence of HK in patients randomized to patiromer. The incidence of side effects, mainly gastrointestinal, associated with the use of patiromer was relatively low. Recent studies in patients with hyperkalemia have shown its effectiveness and tolerability over a year [32, 33]. It should be emphasized that Patiromer has not as yet been approved for use by US Food and Drug Administration or European Medicines Agency.

Mechanisms associated with the beneficial effects of MRAs in patients with HF

Our understanding of the mechanisms associated with the beneficial effects of MRAs in patients with HF continues to evolve. In brief, angiotensin II (ATII), through the AT1 receptor, is an important stimulus for the adrenal release of aldosterone. Other stimuli such as adrenocorticotropic hormone (ACTH), sodium and potassium are also of importance as evidenced by the finding in the angiotensinogen knock-out mouse, in which ATII is not present, that the release of aldosterone from the adrenal gland can be stimulated by modulation of serum sodium [34]. It should also be emphasized that, although ATII is an important stimu-

lus for the production of aldosterone, once it is released from the adrenal gland aldosterone activates the MR resulting in an up-regulation of tissue ACE and the AT1 receptor [35], thereby creating a vicious cycle. ACE-Is and or AT1 receptor antagonists reduce aldosterone levels over time, but there is an increase in aldosterone levels over time ("aldosterone escape") often above baseline levels prior to ACE inhibition [36]. Therefore, to block the RAAS optimally it is necessary to prevent activation of the AT1 receptor and the MR. An increase in aldosterone and activation of the MR in the renal tubular epithelial cells results in sodium retention and potassium loss, with a resultant increase in plasma volume and predisposition to heart failure in patients with left ventricular systolic dysfunction, as well as those with diastolic dysfunction. Once the MR is activated there is also an increase in sodium channel expression (eNAc) [37] such that there is a predisposition to further sodium retention and plasma volume expansion. An increase in aldosterone levels has also been associated with an increase in salt taste [38, 39], thus potentially explaining the observation that patients with acute decompensated HF treated with high-dose loop diuretics, which while reducing plasma volume stimulate the release of aldosterone, are often readmitted with HF soon after hospital discharge as a result of dietary indiscretion involving an increased intake of salty foods.

MRs have also been found in the myocardium, vascular wall, brain, monocyte, colon, retinae, and the skin. In the renal tubule, aldosterone is the major activator of the MR. Cortisol, however, has a greater affinity for the MR than aldosterone, but, due the abundance of the enzyme 11-beta-hydroxysteroid dehydrogenase 2 in the renal epithelial cells, cortisol is metabolized to corticosterone, which cannot activate the MR. In patients with heart failure this enzyme is down-regulated such that cortisol rather than aldosterone may activate the MR [40]. In patients with heart failure an increase in both aldosterone and cortisol levels has been shown to be associated with an increase in cardiovascular death and hospitalizations for heart failure [41, 42]. In nonepithelial tissues such as the myocyte this enzyme is absent or minimally expressed. Under normal circumstances cortisol, as a result of its greater affinity, may occupy the MR but activates it only during conditions associated with an increase in oxidative stress. Activation of these nonepithelial MRs has a number of important effects that contribute to the adverse effects of MR activation in the renal tubule and vascular wall, including a decrease in antioxidant reserves, activation of inflammatory cytokines, activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) and activator protein-1 (AP-1) signaling pathways, apoptosis, myocardial and vascular hypertrophy and fibrosis [37, 43, 44–48]. Importantly, heart failure is associated with an up-regulation of MRs on the macrophage and infiltration of these cells into the myocardium. The importance of the macrophage MR can be seen from experiments in which the macrophage MR is knocked out, in which case the adverse effects of aldosterone on the myocardium are negated independent of macrophage traffic into the myocardium [49]. Similarly, knock out of galectin-3 protects against aldosterone-induced myocardial, renal, and hepatic fibrosis [50]. Activation of the MR is also associated with endothelial dysfunction, an increase in norepinephrine release from sympathetic nerve terminals, and ventricular and atrial arrhythmias. The increase in ventricular arrhythmias and sudden cardiac death associated with MR activation is in part due to an increase in calcium channel expression and tissue depletion of potassium and magnesium [51]. Aldosterone has been associated with an increase in insulin resistance and aldosterone levels have been shown to be elevated in patients with visceral obesity and the metabolic syndrome [15]. Aldosterone increases brown fat but blocks thermogenesis of this tissue, resulting in deregulation of brown fat as well as causing an increase in inflammatory cytokines and macrophage invasion into white fat tissue, thus resulting in adipocyte dysfunction [52]. These effects on the adipocyte may be particularly important in causing target-organ damage in patients with HFPEF, in whom visceral obesity and the metabolic syndrome are increasingly frequent.

Potential future use of MRAs in patients with HF

Acute decompensated heart failure

MRAs have been shown to be effective in reducing total mortality along with standard therapy including an ACE-I or ARB, BB, and diuretics in patients with chronic HFREF and in patient s with HFREF early post MI, but they have not been systematically studied in patients with acute decompensated HF (ADHF). The mortality and incidence of recurrent hospitalizations for HF in patients with ADHF remains unacceptably high. Whereas high-dose spironolactone 100–200 mg/day has been shown to overcome diuretic resistance in a small pilot study in patients with ADHF [53–55] and 400 mg is often used to treat ascites in patients with hepatic cirrhosis, the safety of these doses in patients with ADHF, many of whom have transient and or chronic renal dysfunction, remains uncertain.

Potential new MRAs

Although both spironolactone and eplerenone have been proven to be effective in reducing total mortality in patients with chronic HFREF, their use remains suboptimal, in large part owing to the fear of inducing hyperkalemia and/or renal failure. New nonsteriodal MRAs are currently under development that hold the promise for effectively antagonizing the MR with a lower incidence of hyperkalemia than spironolactone and eplerenone. For example, the nonsteroidal MRA finerenone (BAY 94–8662) has been shown to have an affinity for the MR similar to spironolactone and specificity for the MR similar to eplerenone [56]. Importantly, the biodistribution of spironolactone and eplerenone is such that their level in the kidney is approximately 10-fold that in the myocardium, whereas the biodistribution of finerenone is approximately equal between the kidney and the heart, thus potentially providing relatively greater cardiac specificity with a consequent lower incidence of hyperkalemia. A recent study (ARTS) [57] in patients with HFREF and CKD comparing several doses of finerenone with placebo and spironolactone found that finerenone was

as effective as spironolactone in reducing BNP or NT-proBNP and albuminuria, but was associated with a lower increase in serum K^+ and incidence of hyperkalemia. Finerenone was, however, less effective in reducing systemic blood pressure, possibly because of its failure to cross the blood-brain barrier in comparison with spironolactone. Further studies of finerenone are currently underway comparing it to Eplerenone in patients with HFREF + CKD as well as in patients with diabetic nephropathy [58, 59]. It should, however, be emphasized that the nonsteroidal MRAs are still in a relatively early stage of development and have not as yet been proven to be safe and effective in patients with HF and/or CKD.

Conclusion

Newer strategies such as gene and stem cell therapy, newer drugs targeting specific signaling pathways, greater use of LVADs as destination therapy, and techniques such as sympathetic renal denervation hold promise for patients with chronic HFREF/HFPEF over the long term. While we await the results of further advances and large-scale studies with these new and exciting advances a better understanding and application of current medical therapy including ACE-Is or ARBs, BBs, and especially MRAs as outlined in current guidelines holds the best promise to further reduce cardiovascular mortality, hospitalizations for HF, and therefore healthcare costs over the near term in patients with chronic HF.

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Correspondence: *Professor Bertram Pitt, MD, University of Michigan School of Medicine, 1500 E. Medical Ctr. Dr., Ann Arbor, MI 48109 USA, bpitt[at]umich.edu*

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