Need to Revisit Heart Failure Treatment Guidelines for Hyperkalemia Management During the Use of Mineralocorticoid Receptor Antagonists

Javed Butler, MD MPH MBA[1], Shilpa Vijayakumar, MD[1], Bertram Pitt, MD[2]

[1] Division of Cardiology, Department of Medicine, Stony Brook University, Stony Brook, NY

[2] Division of Cardiology, Department of Medicine, University of Michigan, Ann Arbor, MI

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Address for Correspondence: Javed Butler MD MPH, Division of Cardiology, Stony Brook University, Health Sciences Center, T-16, Room 080, SUNY at Stony Brook, NY 11794, USA. Email: javed.butler@stonybrookmedicine.edu. Tel: 631 444 1066. Fax: 631 444 1054

Mineralocorticoid receptor antagonists (MRA) have greatly impacted the management of patients with heart failure (HF). Both the European Society of Cardiology (ESC) and the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) practice guidelines now give a class I recommendation for patients with HF and reduced ejection fraction (HFrEF) across the symptom spectrum with relatively preserved renal function to reduce mortality and morbidity risk, and a class II recommendation for those with HF and preserved ejection fraction (HFpEF) to decrease risk of hospitalization.[1]

Important clinical trials have shaped the evidence behind these recommendations. In patients with HFrEF, MRAs have been studied by three major outcomes trials: the Randomized Aldactone Evaluation Study (RALES)[2], the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[3], and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)[4]. The RALES trial evaluated spironolactone in patients with New York Heart Association (NYHA) class III and IV symptoms. Two subsequent studies, EPHESUS and EMPHASIS-HF, evaluated eplerenone in HF patients in the days following acute myocardial infarction and in patients with mild symptoms (NYHA functional class II), respectively. All three studies demonstrated significant risk reduction for morbidity and cardiovascular mortality with MRA therapy in addition to standard care. In patients with HFpEF, one key trial, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT),[5] found no reduction in risk of cardiovascular mortality but did show a reduced risk for HF-related hospitalization in the spironolactone group as compared to placebo; additionally there were major concerns raised regarding the trial conduct and regional differences in this trial.

Notably, all four randomized clinical trials excluded patients with serum potassium levels >5 mmol/L and patients with renal impairment, as measured by either serum creatinine >221 µmol/L (2.5 mg/dL) or estimated glomerular filtration rate <30 mL/min (**Table 1**). These exclusion criteria were selected to curb the potential for harm related to an increased risk of hyperkalemia in patients with

HF, a risk that is further heightened by other comorbid diseases like chronic kidney disease (CKD) and background pharmacologic therapies including beta-blockers and those modulating angiotensin II.[6, 7] The clinical implications of this risk were fully realized by a report by Juurlink et al.[8] that demonstrated an increase in both prescription of spironolactone and of hyperkalemia-associated morbidity and mortality following publication of RALES. Based on these concerns, both the ESC and the ACC/AHA/HFSA guidelines advise caution in initiating MRA therapy, limiting it to patients with serum potassium levels of <5 mmol/L and in those with relatively preserved renal function.

While there is clarity in terms of the eligibility criteria for clinical trials with MRAs with regards to initiating therapy in clinical practice, the management of patients who develop hyperkalemia subsequent to the initiation of therapy remains uncertain and inconsistent. Current ESC as well as ACC/AHA/HFSA guidance recommend continuation of MRAs with serum potassium levels ≤5.5 mmol/L. If serum potassium >5.5 mmol/L, current recommendation is to halve the dose and closely monitor blood chemistry. If serum potassium is >6.0 mmol/L, cessation of MRA therapy is advised (**Table 2**).[1, 9, 10]

Since this guidance was first issued, subsequent studies have deepened our understanding of the risks associated with hyperkalemia in low risk patients as well as those with various comorbidities (**Figure 1)**. Secondary analyses of RALES and EMPHASIS-HF trials showed that despite serum potassium levels >5.5 mmol/L, MRAs maintained their benefits, implicitly suggesting that perhaps the benefit of therapy was greater than the risks of mild hyperkalemia.[11, 12] Recently, a growing body of observational evidence demonstrate a U-shaped relationship between potassium levels and mortality in patients with various morbidities including HF, hypertension, and myocardial infarction, where those with either hypo- or hyperkalemia fare worse. It is unclear as to how much of the outcomes are related to hyperkalemia itself, how much to progression of underlying disease due to sub-optimal therapy related to hyperkalemia, and how much to the underlying comorbidity burden that puts individuals at risk for hyperkalemia.

In 2012, a cohort study demonstrated patients with serum potassium >5 mmol/L as well as those with even high-normal potassium levels had worse outcomes, with an ideal serum potassium level ranging between 3.5-4.5 mmol/L.[13] Subsequent data from the Danish National registry further

attested to the U-shaped correlation between potassium level and mortality risk. In 2015, a study in patients receiving loop diuretics after their first episode of myocardial infarction identified a higher risk of mortality with serum potassium levels outside 3.9-4.5 mmol/L.[14] Another report examined 44,799 hypertensive patients, and found that serum potassium levels outside 4.1-4.7 mmol/L were associated with higher mortality.[15] Recently, another study analyzed 19,549 patients with HF receiving treatment with both loop diuretics and angiotensin converting enzyme inhibitors or angiotensin-II receptor blockers and found potassium <3.5 mmol/L and >5 mmol/L to be associated with higher mortality. Levels of potassium even within the lower (3.5-4.1 mmol/L) and upper (4.8-5.0 mmol/L) normal range were associated with higher 90-day mortality risk.[16]

Another study by Núñez et al. monitored potassium levels during follow-up encounters in patients after HF hospitalization and found similar U-shaped risk. Interestingly, persistently elevated potassium levels were associated with higher mortality risk, and normalization of these imbalances was independently associated with lowered mortality risk.[17] A recent report by Collins et al. also demonstrated a U-shaped association between serum potassium and mortality risk, but noted that this mortality risk was significantly greater in those with comorbid HF, CKD or diabetes mellitus (DM).[18] These reports propose that better outcomes are associated with a more limited range of potassium levels than previously believed, even extending into a presumed normal range. It is important to note that some studies do not demonstrate the same heightened mortality risk with increased serum potassium levels. For example, Hoss et al. analyzed a cohort of 6073 patients with chronic HF and found those with "high-normal" potassium levels (in the range of 5.0-5.5 mmol/L) to have better outcomes.[19] Data regarding the safety of hyperkalemia is further limited in patients with acute HF. Tromp et al. analyzed combined data from two large cohorts and noted a linear association between potassium levels at admission and mortality, an association that was no longer apparent after multivariate adjustment.[20] Another study by Khan et al. found no association between in-hospital changes in potassium and mortality or hospitalization for HF.[21] In patients with acute HF, some data analyses find a decrease in serum potassium levels during hospitalization of >15% to be associated with higher mortality risk.[22]

Although data remains limited, it still calls into question the current recommendation that MRA dose be halved with potassium levels >5.5 mmol/L and stopped only with levels >6.0 mmol/L since allowing patients with HF, CKD, DM, and especially those > 65 years of age with these comorbidities to remain at a serum potassium > 5.0 mmol/l if not on a MRA places them at increased risk of death. These data further support the need for closer long-term monitoring of serum potassium throughout MRA therapy, perhaps more frequently in those at increased risk of hyperkalemia than the current recommendations of every 4 months. Caution should also be exercised in patients with levels >5.5 mmol/L who are on an MRA, including those taking beta-blockers or angiotensin II modulators and every attempt should be made to keep serum potassium levels ≤5 mmol/L in those patients not on a MRA. Finally, better therapies for long-term management of hyperkalemia to optimize HF management are urgently needed.[23]

HF is a challenging chronic illness and suspending life-saving therapies puts this susceptible population at increased risk. MRAs are already underutilized in HFrEF. However, while appropriate use should be encouraged, clear guidelines to manage these patients on therapy also need to be developed and updated in light of these new data. In patients already initiated on MRA therapy, the challenge becomes attaining a fine balance between optimization of medications to prevent disease progression and minimizing risk of hyperkalemia-related adverse events. We must be cautious not to cause iatrogenic harm. Accruing evidence has questioned the safety not only of serum potassium levels >5 mmol/L but even potassium levels on the higher end of "normal," especially in patients with HF, CKD and DM. The increased mortality risk associated with a high serum potassium level reflects multiple risks including ventricular fibrillation and other conduction abnormalities, comorbidity burden, and underutilization of optimal medical therapy. Of note, at any particular serum potassium level, other factors including an underlying pathophysiology, rate of change in potassium level, pH, and calcium concentration will all influence complication and mortality risk.

These data support the need for reevaluation of guidelines, which currently suggest that serum potassium levels of up to 5.5 mmol/L can be monitored without intervention in patients with HF. Normokalemia may be a narrower range than previously recognized in patients with HF. Changes in guidelines are common as new data emerge, e.g. serum digoxin concentrations were considered

to be safe up to 2 ng/mL. However, subsequent data showed risk of digoxin-associated mortality at lower levels, leading to new guidelines recommendation to keep digoxin concentration <1.2 ng/mL.[24] Similar revision for MRA therapy and hyperkalemia is warranted. Emerging data calls for narrower ranges of acceptable potassium levels during MRA therapy in patients with HF, especially those with concomitant CKD and or DM > 65 years of age. Perhaps revised, more explicit guidelines for monitoring and intervening during MRA therapy for patients with HF will increase the safety of these agents and thus the utilization of this life-saving therapy.

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Table 1: Eligibility criteria and management of hyperkalemia in randomized trials

Clinical Trial	Exclusion Criteria	Dose Adjustments for Serum Potassium (K) (mmol/L)
RALES[2]	Scr > 221 µmol/L (2.5 mg/dL), serum K > 5 mmol/L	If K ≥ 5.5, decrease dose to 25 mg every other day (although investigator encouraged to initially adjust doses of concomitant medications) If K ≥ 6.0, withhold study medication
EPHESUS[3]	Scr > 221 µmol/L (2.5 mg/dL), serum K > 5 mmol/L	If K ≥ 5.5, decrease dose by 25 mg (and withhold if on lowest dose of 25 mg daily) If K ≥ 6.0, discontinue until K < 5.5
EMPHASIS-HF[4]	eGFR < 30 mL/min, serum K > 5 mmol/L	For eGFR ≥ 50 mL/min: If K ≥ 5.5, decrease dose to 25 mg; If K ≥ 6.0, withhold dose, re-check K within 72 hours and resume if K < 5.0 For eGFR 30-49 mL/min: If K ≥ 5.5, withhold dose and re-check within 72 hours and resume if K < 5.0; If K ≥ 6.0, withhold and recheck K within 72 hours and resume if K < 5.0
TOPCAT[5]	eGFR < 30 mL/min, Scr ≥ 221 µmol/L (2.5 mg/dL), serum K ≥ 5.5 mmol/L in past 6 months, serum K ≥ 5 mmol/L in past 2 weeks	If K ≥ 5.5, reduce drug by 15 mg (no uptitration beyond this level for remainder of study) If K ≥ 6.0, permanently discontinue study drug

Abbreviations: eGFR, estimated glomerular filtration rate; K, potassium; MRA, mineralocorticoid receptor antagonist; Scr, serum creatinine

Table 2: Current guidelines for the initiation, monitoring, and management of hyperkalemia on MRA therapy.

Organization	Initiation of MRA	Monitoring	Intervention
ACC/AHA/HFSA[9, 10]	Serum K < 5.0 mmol/L Scr < 221 µmol/L (2.5 mg/dL) in men, Scr < 176.8 µmol/L (2.0 mg/dL) in women (or eGFR > 30 mL/min)	Monitor Scr and serum K 72 hours-1 week after initiation or dose increase of MRA, then monthly for first 3 months, then 3-4 months thereafter	If K 5.5-5.9 mmol/L, halve dose (or take every other day if at lowest dose) If K > 6.0 mmol/L, hold and reassess after 72 hours until K < 5.0 mmol/L
ESC[1]	Serum K < 5.0 mmol/L Scr < 221 µmol/L (2.5 mg/dL) (or eGFR > 30 mL/min)	Monitor blood chemistry 1 and 4 weeks after initiation/uptitration and at 8 and 12 weeks and 6, 9 and 12 months. Thereafter, monitor every 4 months.	If K > 5.5 mmol/L or Scr > 221 µmol/L (2.5 mg/dL), halve dose and monitor blood chemistry closely If K > 6.0 mmol/L or Scr > 309.4 µmol/L (3.5 mg/dL), stop MRA therapy immediately

Abbreviations: eGFR, estimated glomerular filtration rate; K, potassium; Scr, serum creatinine; MRA, mineralocorticoid receptor antagonist; WRF, worsening renal function

Figure 1