Incidence, Predictors, and Outcomes Related to Hypo- and Hyperkalemia in Patients With Severe Heart Failure Treated With a Mineralocorticoid Receptor Antagonist

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Background—Mineralocorticoid receptor antagonists reduce morbidity and mortality in patients with heart failure but can cause hyperkalemia, which contributes to reduced use of these drugs. Hypokalemia also leads to worse outcomes in patients with heart failure and may be attenuated by mineralocorticoid receptor antagonists.

Methods and Results—We assessed incidence and predictors of hyperkalemia (potassium ≥5.5 mmol/L) and hypokalemia (potassium <3.5 mmol/L) and the relationship to outcomes in 1663 patients with class III or IV heart failure and left ventricular ejection fraction <35% randomized to treatment with spironolactone 25 mg or placebo in the Randomized Aldactone Evaluation Study (RALES) trial. All-cause mortality rates and the influence of potassium levels on the effectiveness of spironolactone were assessed in a landmark analysis and in relation to time-varying potassium levels. After 1 month, mean potassium levels increased in the spironolactone group but not in the placebo group (4.54±0.49 versus 4.28±0.50 mmol/L; $P<0.001$) and remained elevated during the trial. Although the extremes of hypokalemia and hyperkalemia at 4 weeks were associated with increased risk of mortality in both treatment arms, participants in the spironolactone arm had lower mortality rates at all potassium levels throughout the duration of the trial. The treatment benefit of spironolactone was maintained at least until potassium exceeded 5.5 mmol/L.

Conclusions—With appropriate surveillance of potassium and creatinine, the use of spironolactone was associated with less hypokalemia and improved survival in patients with severe heart failure even in the setting of moderate hyperkalemia. (***Circ Heart Fail*. 2014;7:573-579.**)

Key Words: heart failure ■ pharmacology ■ potassium ■ spironolactone

Mineralocorticoid receptor antagonists (MRAs) have been shown to reduce morbidity and mortality in patients with mild to severe heart failure (HF) with reduced left ventricular ejection fraction and after acute myocardial infarction with HF symptoms or diabetes mellitus and reduced left ventricular ejection fraction.[1–3] Although the benefits of MRAs have been confirmed with multiple randomized, controlled studies, only a fraction of individuals with HF who are eligible for MRAs receives them.[4,5] This may be, in part, because of concerns of hyperkalemia known to occur with the use of these drugs, which seems to be more frequent in clinical practice than reported in previous clinical trials.[6]

Clinical Perspective on p 579

Hypokalemia is common among patients with HF, despite the use of inhibitors of the renin–angiotensin–aldosterone system.[7] Previous analyses in HF noted poorer outcomes in patients with potassium levels below 4.0 mmol/L,[8,9] and incident hypokalemia may be potentially attenuated by the use of MRAs. An analysis of the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study showed that clinical benefits with eplerenone remained even in those who developed hyperkalemia,[10] but whether elevations in potassium levels reduce the clinical benefit observed with MRAs in patients with severe HF is unknown.

We used data from the Randomized Aldactone Evaluation Study (RALES) to assess the incidence and predictors of hypokalemia and hyperkalemia, and hypothesized that hyperkalemia would not modify the efficacy of spironolactone in patients with severe HF.

Methods

Study Design and Patient Selection

RALES was a double-blind, randomized, placebo controlled trial designed to assess the effect of spironolactone treatment on all-cause mortality and cardiovascular hospitalizations in patients with New

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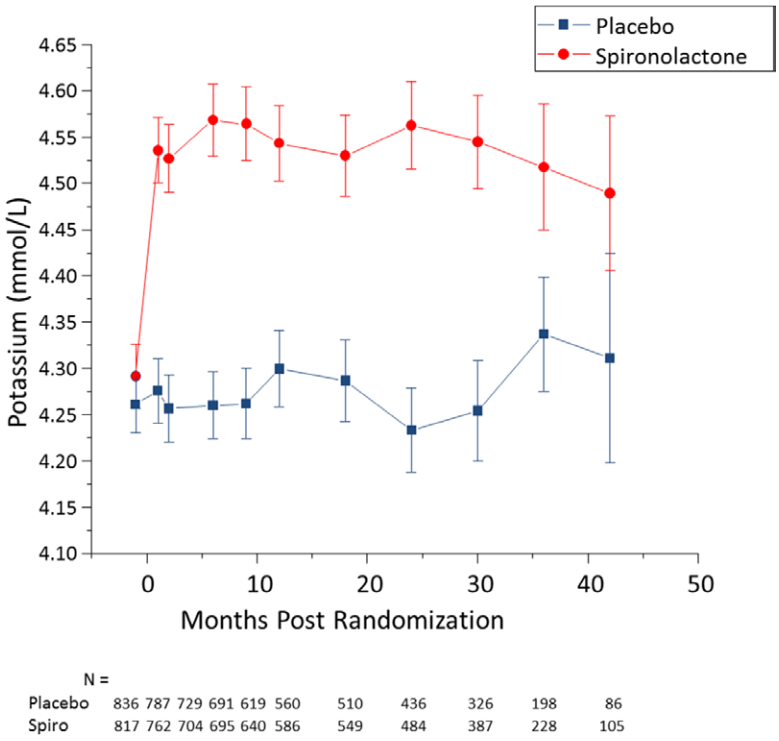

Figure 1. Potassium levels during the study by treatment. After randomization, potassium values were on average 0.25 mEq/L higher in the spironolactone group when compared with those in the placebo group (P<0.001 for comparison between groups). Number of participants by treatment assignment at each time point is shown below the graph.

York Heart Association class III or IV HF.[1] RALES began recruitment in March 1995 and follow-up ended in December 1999, with participants from 195 centers in 15 countries. Participants were enrolled if they had a left ventricular ejection fraction <35% while taking background angiotensin-converting enzyme (ACE) inhibitors and diuretics. As the trial was conducted before the development of treatment guidelines endorsing routine β-blocker therapy in patients with HF and reduced ejection fraction, β-blocker treatment was not mandated per protocol. Patients with primary valvular disease, congenital heart disease, unstable angina, liver failure, listing for cardiac transplant, active cancer, or any other life-threatening disease were excluded as were those with serum creatinine >2.5 mg/dL or potassium >5.0 mmol/L. Participants were randomized to receive spironolactone 25 mg or placebo daily. After 8 weeks, investigators were permitted to increase the dose to 50 mg daily for participants with persistent HF signs and symptoms without evidence of hyperkalemia (serum potassium concentration, ≥5.5 mmol/L). The use of potassium-sparing diuretics was not permitted. Oral potassium supplement use was discouraged unless hypokalemia (defined as a serum potassium concentration of <3.5 mmol/L) developed. Serum potassium and creatinine were measured at 4, 8, and 12 weeks during the titration phase and every 3 months thereafter during the study. If the participants developed hyperkalemia at any time, investigators were given discretion to reduce the dose to 25 mg every other day but were encouraged to adjust concomitant medications first. The protocol was approved at each participating site by an ethics committee or institutional review board. All participants provided written informed consent in accordance with established guidelines for the protection of human subjects.

Statistical Analyses

Hyperkalemia was defined as potassium level ≥5.5 mmol/L and severe hyperkalemia as potassium level ≥6.0 mmol/L at any study visit. Hypokalemia was defined as potassium level <3.5 mmol/L at any study visit, whereas borderline hypokalemia was defined as potassium level between 3.5 and 3.9 mmol/L. To identify potential differences, baseline characteristics were compared (within allocated treatment groups) between participants who experienced moderate hyperkalemia

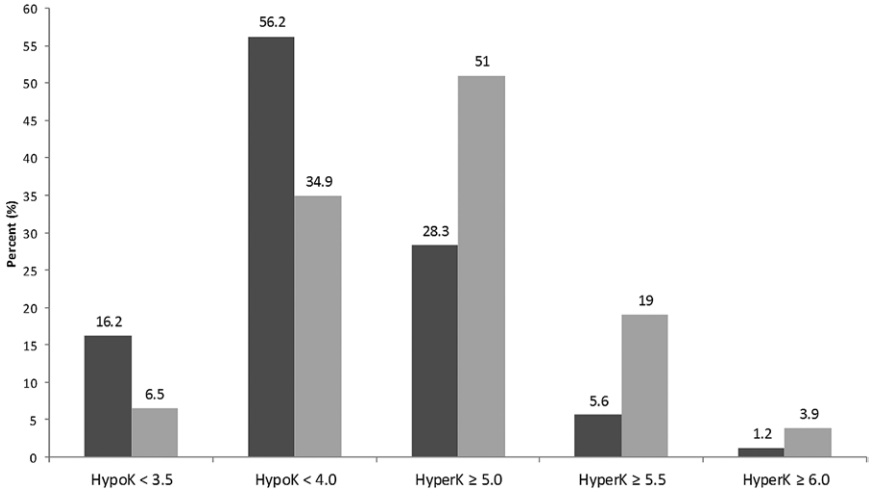

Figure 2. Percentage of participants experiencing any hypokalemic or hyperkalemic event during follow-up, by treatment group. The bins are not mutually exclusive and an individual patient could experience both events. Hyperkalemia was more common among those in the spironolactone group, and hypokalemia was more common in the placebo group. Light gray, spironolactone group and dark gray, placebo group.

(defined as potassium ≥ 5.5 mmol/L) at any postbaseline visit versus those that did not develop hyperkalemia, as well as between participants who experienced hypokalemia at any postbaseline visit (defined as potassium <3.5 mmol/L) versus those that did not. Between-group assessments were performed using *t* tests for continuous variables, and χ^2 or Fisher exact tests, as appropriate, for categorical variables.

We compared potassium levels at baseline and at each visit after randomization by treatment assignment with 2-sample *t* tests. Cox proportional hazards regression models were used to examine associations between baseline characteristics and time to postbaseline moderate hyperkalemia (potassium ≥ 5.5 mmol/L) and hypokalemia (potassium <3.5 mmol/L), adjusting for treatment assignment and the following covariates chosen a priori based on clinical knowledge of factors known to affect potassium homeostasis and clinical outcome in this population: age, sex, race, diabetes mellitus, hypertension, history of myocardial infarction, diabetes mellitus, New York Heart Association functional class, baseline potassium, estimated glomerular filtration rate (eGFR), systolic and diastolic blood pressure, and baseline medications (diuretic, ACE inhibitor or angiotensin receptor blocker [ARB], β-blocker, digoxin, and aspirin). Mortality rates were assessed among spironolactone participants after experiencing any hypokalemic (<3.5 mmol/L) event, participants experiencing potassium levels between 3.5 and 4.0 mmol/L at any time, any mild, moderate, or severe hyperkalemic (between 5.0 and 5.4, 5.5, and 5.9 or ≥6.0 mmol/L) event at any time, and patients who were normokalemic (4.0–4.9 mmol/L) throughout the study. Treatment-specific Poisson regression models were used to conduct a landmark analysis at visit 2 (4 weeks), estimating via quadratic spline models the rate of subsequent death based on potassium levels observed at that visit. Finally, a Cox proportional hazards model was constructed to examine the relationship between mortality among spironolactone participants and maximum postbaseline potassium level, treated as a time-varying covariate using a flexible cubic model when compared with a referent group of placebo patients with serum potassium <5.0 mEq/L, adjusting for age, diabetes mellitus, baseline eGFR and eGFR as a time-varying covariate, and baseline potassium. A *P* value of <0.05 was considered statistically significant. All analyses were conducted at Brigham and Women's Hospital with the original trial data set using STATA, version 11 (StataCorp LP, College Station, TX).

Results

Baseline potassium levels were similar between spironolactone and placebo groups (4.29±0.5 versus 4.26±0.44 mmol/L; *P*=0.19). Starting at 1 month after randomization and throughout the trial, mean potassium levels remained higher in the spironolactone group when compared with individuals randomized to placebo (Figure 1; *P*<0.001 for comparison between treatment groups at all comparison times). Participants randomized to spironolactone had a higher risk for hyperkalemia when compared with those randomized to placebo (unadjusted hazard ratio, 3.57; 95% confidence interval, 2.58–4.95 and adjusted hazard ratio, 3.9; 95% confidence interval, 2.78–5.45) and had a lower risk for hypokalemia (unadjusted hazard ratio, 0.38; 95% confidence interval, 0.26–0.49 and adjusted hazard ratio, 0.36; 95% confidence interval, 0.26–0.49; Figure 2). Baseline characteristics within assigned treatment groups by hyperkalemia and hypokalemia status during the trial are shown in Tables 1 and 2. Among

Table 1. Baseline Characteristics by Hyperkalemia Status (Defined as Potassium ≥5.5 mmol/L) at Any Postbaseline Visit

	Placebo			Spironolactone		
	No Hyperkalemia During Trial n=794	Hyperkalemia During Trial n=47	*P* Value	No Hyperkalemia During Trial n=666	Hyperkalemia During Trial n=156	*P* Value
Age, y (SD)	65.0 (11.8)	68.6 (10.5)	0.04	64.5 (12.3)	68.8 (9.6)	<0.001
Female sex, %	26.7	31.9	0.43	26.1	28.8	0.49
White race, %	86.2	93.6	0.14	85.4	91.7	0.04
Ischemic cause, %	54.2	48.9	0.48	54.1	60.9	0.12
NYHA class						
NYHA III	69.0	70.2	0.86	72.8	68.6	0.29
NYHA IV	30.6	29.8	0.91	26.6	31.4	0.22
Diabetes mellitus, %	22.7	31.9	0.14	18.2	34.0	< 0.001
Myocardial infarction, %	29.2	23.4	0.39	27.3	30.1	0.48
Hypertension, %	23.7	21.3	0.71	23.1	25.0	0.62
eGFR, mL/min per 1.73 m^2 (SD)	64.8 (23.0)	58.6 (19.7)	0.07	67.0 (23.8)	58.2 (18.3)	<0.001
EF (SD)	25.1 (6.8)	25.9 (6.4)	0.45	25.7 (6.7)	25.1 (6.4)	0.29
Blood pressure, mm Hg (SD)	121.3 (19.5)/ 74.4 (11.3)	127.4 (21.0)/ 75.4 (11.3)	0.03/0.57	122.2 (20.2)/ 74.6 (12.3)	125.4 (22.0)/ 75.0 (10.3)	0.08/0.73
Pulse, bpm (SD)	81.1 (14.5)	78.9 (14.4)	0.30	80.6 (14.1)	81.2 (12.4)	0.65
Potassium, mmol/L (SD)	4.3 (0.4)	4.4 (0.5)	0.04	4.3 (0.5)	4.5 (0.5)	<0.001
Medications						
β-Blockers, %	10.2	10.6	0.92	11.1	7.0	0.13
ACEi or ARB, %	95.1	97.9	0.38	95.0	99.4	0.015
Loop diuretic, %	90.6	87.2	0.45	90.8	87.8	0.25
Digoxin, %	71.9	72.3	0.95	75.5	69.2	0.10
ASA, %	36.9	48.9	0.10	33.5	39.7	0.14

ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ASA, aspirin; EF, ejection fraction; eGFR, estimated glomerular filtration rate; and NYHA, New York Heart Association.

Table 2. Baseline Characteristics by Hypokalemia Status (Defined as Potassium <3.5 mmol/L) at Any Postbaseline Visit

	Placebo			Spironolactone		
	No Hypokalemia During Trial n=705	Hypokalemia During Trial n=136	*P* Value	No Hypokalemia During Trial n=769	Hypokalemia During Trial n=53	*P* Value
Age, y (SD)	65.5 (11.7)	63.6 (11.9)	0.08	65.3 (12.0)	64.7 (12.3)	0.69
Female sex, %	25.1	36.8	0.005	26.7	26.4	0.97
White race, %	87.1	83.8	0.31	87.3	77.4	0.04
Ischemic cause, %	54.3	52.2	0.66	55.4	54.7	0.92
NYHA class						
NYHA III	70.9	59.6	0.009	72.6	64.2	0.19
NYHA IV	28.8	39.7	0.011	26.9	35.9	0.16
Diabetes mellitus, %	24.0	19.1	0.22	20.8	26.4	0.33
Myocardial infarction, %	29.2	27.2	0.64	28.0	26.4	0.81
Hypertension, %	24.4	19.1	0.18	23.4	24.5	0.85
eGFR, mL/min per 1.73 m^2 (SD)	64.3 (22.9)	65.3 (22.5)	0.66	65.0 (23.0)	69.5 (24.1)	0.18
EF (SD)	25.3 (6.8)	24.7 (6.5)	0.39	25.6 (6.6)	24.9 (7.4)	0.42
Blood pressure, mm Hg (SD)	121.7 (19.7)/ 74.1 (11.1)	121.2 (19.2)/ 76.5 (11.8)	0.77/0.02	123.0 (20.2)/ 74.8 (11.9)	120.4 (25.0)/ 73.6 (12.5)	0.38/0.50
Pulse, bpm (SD)	80.9 (14.6)	81.4 (14.3)	0.74	80.7 (13.6)	81.8 (16.6)	0.56
Potassium, mmol/L (SD)	4.3 (0.4)	4.0 (0.5)	<0.001	4.3 (0.5)	4.0 (0.5)	<0.001
Medications						
β-Blockers, %	10.9	6.6	0.13	10.4	9.4	0.82
ACEi or ARB, %	95.9	91.9	0.05	96.0	94.3	0.56
Loop diuretic, %	91.1	86.8	0.12	90.2	90.6	0.94
Digoxin, %	71.1	76.5	0.20	74.4	73.6	0.90
ASA, %	37.9	36.0	0.68	33.7	49.1	0.02

ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; EF, ejection fraction; eGFR, estimated glomerular filtration rate; and NYHA, New York Heart Association.

those randomized to spironolactone, those who attained study drug dose of 25 mg had a 13.5% risk of hyperkalemia, whereas patients who attained a study dose of 50 mg had a 41.4% risk of hyperkalemia. Within the spironolactone group, mortality was similar in those who achieved the 50- and 25-mg dose.

Aside from treatment assignment, factors that were associated with hyperkalemia in multivariable models included study drug dose, age, worse New York Heart Association functional class, history of diabetes mellitus, higher baseline potassium levels, lower eGFR, and background therapy with ACE inhibitors or ARBs and β-blockers (Table 3). For hypokalemia, black race, worse New York Heart Association functional class, higher diastolic blood pressure, and baseline potassium levels were associated with potassium concentrations below 3.5 mmol/L (Table 4). Background use of ACE inhibitors or ARBs and assignment to spironolactone were associated with reduced risk for hypokalemia.

Table 3. Predictors of Hyperkalemia (Defined as Potassium ≥5.5 mmol/L)

Variables	Univariate HR (95% CI)	Multivariable HR (95% CI)	Multivariable |Z| Score
Spironolactone	3.57 (2.57–4.95)	3.20 (2.26–4.47)	6.6
Dose of spironolactone (per 12.5 mg daily)	1.06 (1.05–1.07)	1.04 (1.03–1.05)	6.3
Baseline potassium value (per 1 mmol/L)	2.31 (1.73–3.09)	1.94 (1.47–2.57)	4.7
NYHA functional class	1.26 (0.94–1.69)	1.51 (1.11–2.05)	2.6
Baseline eGFR (per 1 mL/min per 1.73 m^2)	0.98 (0.97–0.99)	0.99 (0.98–1.0)	2.5
History of diabetes mellitus	1.88 (1.41–2.52)	1.47 (1.09–2.0)	2.5
Baseline use of ACE inhibitors or ARBs	4.81 (1.20–19.38)	5.96 (1.47–24.2)	2.5
Baseline use of β-blockers	0.67 (0.40–1.12)	0.53 (0.31–0.90)	2.4
Age (per 1 y)	1.03 (1.02—1.05)	1.02 (1.0–1.03)	2.2
Baseline systolic BP (per 10 mm Hg)	1.07 (1.00–1.15)	1.09 (1.0–1.2)	1.9

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; and NYHA, New York Heart Association.

Table 4. Predictors of Hypokalemia (Defined as Potassium <3.5 mmol/L)

Variable	Univariate HR (95% CI)	Multivariable HR (95% CI)	Multivariable |Z| Score
Baseline potassium value (per 1 mmol/L)	0.26 (0.19–0.37)	0.26 (0.18–0.36)	8.0
Spironolactone	0.38 (0.26–0.49)	0.36 (0.26–0.50)	6.1
Black race	2.1 (1.34–3.2)	1.97 (1.22–3.18)	2.8
NYHA functional class	1.77 (1.32–2.38)	1.46 (1.07–1.97)	2.4
Diastolic blood pressure (per 10 mm Hg)	1.05 (0.93–1.19)	1.21 (1.01–1.45)	2.1
Use of ACEi or ARB	0.53 (0.31–0.92)	0.55 (0.31–0.96)	2.1
Female sex	1.4 (1.04–1.9)	1.23 (0.88–1.67)	1.2

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio; and NYHA, New York Heart Association.

In a landmark analysis, we observed a u-shaped relationship between potassium levels at 4 weeks after randomization and subsequent rates of mortality in both treatment arms such that subsequent rates of death were highest in patients with the lowest (<3.5 mmol/L) and highest (>6.0 mmol/L) 4-week potassium values. Nevertheless, across the spectrum, the benefit of spironolactone relative to placebo was maintained, with higher mortality rates in the placebo group than in the spironolactone group at any given level of 4-week potassium value (Figure 3).

The relationship between time-varying highest potassium value and the treatment effect of spironolactone was assessed by comparing all treated patients to a referent placebo group who never experience hyperkalemia (K≥5.0 mmol/L), adjusting for age, eGFR (baseline and time varying), baseline potassium, and diabetes mellitus (Figure 4). The treatment benefit of spironolactone was maintained at least until potassium exceeded 5.5 mmol/L although this benefit lost statistical significance as potassium value neared 6.0 mmol/L.

Discussion

We found that in patients with severe HF enrolled in RALES, potassium levels rose within 4 weeks of randomization to spironolactone and remained elevated for the duration of the trial. Although both hypokalemia, which was more likely in the placebo group, and hyperkalemia, which was more likely in the spironolactone group, were associated with higher mortality, patients randomized to spironolactone derived benefit at least until potassium levels exceeded 5.5 mmol/L. These findings suggest that spironolactone maintained its beneficial effects in most patients with severe HF exhibiting modest elevations in potassium.

The occurrence of hyperkalemia with the use of MRAs is widely recognized, and HF treatment guidelines recommend initiation of an MRA only if baseline serum potassium is <5.0 mmol/L and when the eGFR exceeds 30 mL/min per 1.73 m^2 and further advise on frequent monitoring of serum potassium and renal function.[11] Despite distinct criteria for the use and clear monitoring recommendations for MRAs,[11] these medications are vastly underused in patients with HF, at least in part, because of concerns of hyperkalemia.

In RALES, although potassium levels remained higher in the spironolactone group when compared with those in the placebo for the duration of the trial, the greatest change in potassium occurred within the first 4 weeks after initiation of spironolactone. This finding underscores the importance of early monitoring of potassium after initiation of an MRA because elevations occur quickly. We found that throughout the trial, participants in the spironolactone group exhibited lower mortality when compared with those taking placebo even in the

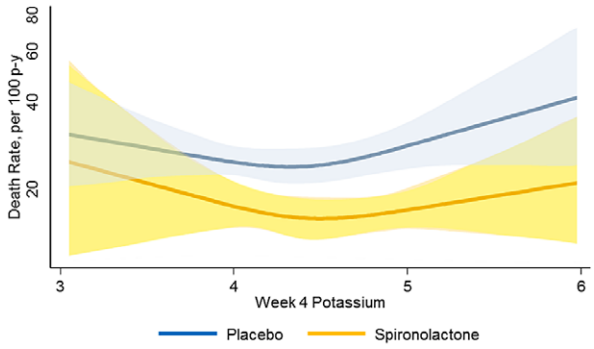

Figure 3. Rates of death after visit 2 (4 weeks) by treatment, based on serum potassium levels at visit 2. Mortality rates were higher in participants randomized to placebo when compared with those taking spironolactone at all potassium levels. *P*<0.0001 for comparison between spironolactone and placebo. Shaded areas represent 95% confidence intervals.

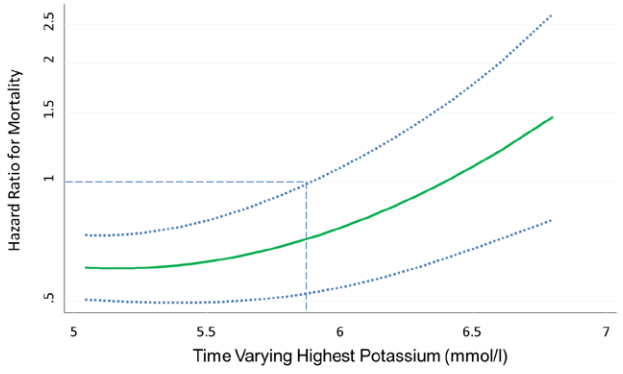

Figure 4. Hazard ratio (95% confidence interval) for mortality for participants in the spironolactone group based on time-varying maximum potassium level when compared with a referent participant on placebo who never experienced potassium levels ≥5.0 mEq/L, adjusting for age, estimated glomerular filtration rate, baseline potassium, and diabetes mellitus. The confidence intervals were obtained from a fit of time-updated Cox proportional hazards model, estimating the hazard ratio associated with given values of maximum potassium among patients treated with spironolactone when compared with placebo patients whose maximum potassium was <5.0, with remaining covariates set to their mean observed values. The treatment benefit of spironolactone seems to be maintained at least until potassium value exceeds 5.5 mEq/L. Dotted lines represent the 95% confidence intervals.

setting of moderate hyperkalemia. A previous analysis of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) in patients after myocardial infarction with left ventricular dysfunction showed that an early rise in potassium levels at 1 month with eplerenone was associated with better cardiovascular outcomes.[12] In the EMPHASIS-HF study, a recent analysis showed that the survival benefits of eplerenone were maintained in the setting of hyperkalemia.[10] Our results are concordant with findings from EPHESUS and EMPHASIS-HF and extend the notion that patients with modest elevations in potassium with MRAs will still derive benefit even in the setting of severe HF. These findings argue against the practice of some clinicians to discontinue an MRA after mild elevations in potassium.

In the current analysis, we observed a higher risk of hyperkalemia associated with lower eGFR and diabetes mellitus in univariate and multivariable models, as has previously been shown,[13,14] in addition to baseline potassium levels. Despite an increased risk of hyperkalemia, patients with renal dysfunction have been shown to derive benefit from MRAs in the closely monitored RALES and EMPHASIS-HF trials.[10,15,16] Higher study medication doses were also associated with an increased risk for hyperkalemia. Specifically, ≤40% of participants taking spironolactone 50 mg daily exhibited hyperkalemia, whereas 13.5% of those taking a spironolactone dose of 25 mg had hyperkalemia. These data suggest that hyperkalemia related to spironolactone may be dose related, and limiting the maximum dose to 25 mg daily may reduce this risk.

Some of the benefits of spironolactone in RALES may have been secondary to lowering the risk of hypokalemia, which was substantially less in participants randomized to spironolactone. Similar reductions in hypokalemia were observed in EPHESUS and EMPHASIS-HF with eplerenone.[2,17] Hypokalemia is common in patients with HF, in part, because of elevated aldosterone levels from neurohormonal activation, as well as from the use of diuretics. Aldosterone stimulates exchange of sodium and potassium in distal renal tubules, leading to excretion of potassium in the urine. Low potassium levels amplify the risk for sudden cardiac death through accelerating depolarization, increasing automaticity, and lengthening the action potential.[7,18,19] Potassium levels <4 mmol/L were associated with increased mortality in the DIG (Digitalis Investigation Group) trial.[8,20]

Several limitations of this study should be noted. The RALES study was completed before widespread use of β-blockers for HF, and the percentage of participants taking these medications was low. As such, pharmacotherapy in RALES participants may not reflect contemporary HF treatment fully, which would also include hydralazine and isosorbide dinitrate for blacks and implantable cardiac defibrillators. Nevertheless, the percentage of patients developing hyperkalemia in RALES was numerically, but not statistically, lower in the patients taking β-blockers when compared with those not taking β-blockers although the number of participants taking β-blockers was small. In addition, similar results were also shown in the EPHESUS and EMPHASIS-HF studies in which the majority of participants were taking β-blockers. Serious hyperkalemia has been rare in clinical trials of MRAs, and its occurrence in clinical practice is reported more frequently, potentially because of less stringent monitoring and more strict inclusion criteria in clinical trials when compared with clinical practice.[6,21,22] Thus, results from this analysis may not be generalizable to nonclinical trial settings. Measurements of serum potassium were not blinded; hence, adjustments in ACE inhibitor or ARB doses could have occurred in the placebo group as a result of rising potassium levels, which could have affected clinical outcomes. We could not adjust for all potential confounding factors to hyperkalemia in our statistical models, such as dietary potassium intake, the use of over the counter potassium supplements, nonsteroidal anti-inflammatory drugs, or herbal preparation usage. A few of the potassium groups in our time-varying analyses, such as the percentage of participants with potassium ≥6.0 mmol/L, had small numbers; as such mortality rates reported should be interpreted with caution.

In summary, we found that patients with advanced HF randomized to spironolactone experienced more hyperkalemia and less hypokalemia when compared with patients randomized to placebo. The benefit of spironolactone was maintained even in the setting of moderate hyperkalemia, and clinical outcomes with spironolactone were superior to placebo when potassium levels remained <6.0 mmol/L. Although it is clinically prudent to monitor potassium levels in patients receiving spironolactone, especially those at highest risk, these data suggest that limiting spironolactone dose to 25 mg daily may reduce the risk of hyperkalemia and argue against automatic discontinuation of MRAs when potassium concentrations rise >5.0 mmol/L. Finally, because serum potassium changes were most pronounced during the first few months of treatment with spironolactone, strict monitoring of electrolytes is crucial immediately after the initiation of an MRA in clinical practice.

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Disclosures

Dr Pitt serves as a consultant for Pfizer, Bayer, and Relypsa. Dr Zannad serves as a consultant for Pfizer and Bayer. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

In this post hoc analysis of the Randomized Aldactone Evaluation Study (RALES), we assessed incidence and predictors of hypokalemia and hyperkalemia and examined whether elevations in potassium levels reduced the clinical benefit observed with spironolactone in patients with severe heart failure. Mean potassium levels were higher among those randomized to spironolactone when compared with individuals taking placebo starting at 1 month after randomization; these differences persisted for the duration of the trial. Participants randomized to spironolactone exhibited more hyperkalemia and less hypokalemia when compared with those in the placebo group. Factors associated with hyperkalemia included higher study drug dose, age, worse New York Heart Association functional class, history of diabetes mellitus, higher baseline potassium levels, and lower estimated glomerular filtration rate, whereas predictors of hypokalemia included black race, worse New York Heart Association functional class, higher diastolic blood pressure, and lower baseline potassium levels. In a landmark analysis of potassium level at 4 weeks after randomization, mortality rates were highest in those with potassium levels <3.5 mmol/L and levels >6.0 mmol/L in both treatment groups. Nonetheless, mortality rates were higher in the placebo group when compared with those in the spironolactone regardless of potassium level. In a time-varying analysis, the treatment benefit of spironolactone seemed to be maintained until potassium exceeded 5.5 mmol/L. Although these data underscore the importance of early monitoring of potassium levels after the initiation with mineralocorticoid receptor antagonists, they suggest that benefits of spironolactone may be maintained even in the setting of moderate hyperkalemia and argue against automatic discontinuation of MRAs if potassium rises >5.0 mmol/L.