Race Influences the Safety and Efficacy of Spironolactone in Severe Heart Failure

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Abstract

Background—The incidence of hyperkalemia due to mineralocorticoid receptor antagonists (MRAs) may vary by race, but whether race influences efficacy of MRAs in heart failure (HF) is unknown.

Methods and Results—We assessed hyperkalemia and outcomes in African Americans (AA, N=120) and non-African Americans (non-AA N=1543; Caucasian 93%) with NYHA class III or IV HF and LV dysfunction randomized to spironolactone, titrated to 25mg or 50 mg daily or placebo in the Randomized Aldactone Evaluation Study (RALES). AA participants were significantly younger, more likely to have an ischemic HF etiology, more likely to be NYHA FC IV, have a higher eGFR and heart rate, less hypertension, diabetes, or history of myocardial infarction compared to non-AA participants. Potassium increased with spironolactone in non-AA (4.29±0.5 to 4.55±0.49 mmol/L), but not in AA (4.32±0.54 to 4.31±0.49 mmol/L; race by treatment interaction, p=0.03) during the first month and remained higher throughout the trial. Compared to AA, non-AA were more likely to attain maximal spironolactone dose (13.9% vs. 5.8%, p=0.04) and had higher rates of hyperkalemia (potassium >5.5 mmol/L, 9.7% vs. 4.2%, p<0.046), as well as lower rates of hypokalemia (potassium <3.5 mmol/L, 5.6% vs. 17.9%, p<0.001). After adjustment for differences in baseline characteristics and achieved study drug dose, spironolactone reduced the combined endpoint of death or hospitalization for HF in non-AA (HR 0.63, 95% CI 0.55-0.73), but not in AA (HR 1.07, 95% CI 0.67-1.71; p-interaction=0.038).

Conclusions—AA with heart failure exhibited less hyperkalemia and more hypokalemia with spironolactone compared to non-AA, and appeared to derive less clinical benefit. These hypothesis-generating findings suggest that safety and efficacy of MRAs may differ by race.

Key Words: heart failure, pharmacology, potassium
Addition of mineralocorticoid receptor antagonists (MRAs) to standard medical therapies reduces morbidity and mortality in a broad spectrum of patients with heart failure.1-3 Current HF treatment guidelines recommend the use of MRAs in patients with reduced left ventricular ejection fraction (LVEF) and moderately severe to severe symptoms of HF, and in patients after acute myocardial infarction with concomitant symptoms of HF and reduced LVEF.4,5

Hyperkalemia is a known adverse effect from MRAs. Rates of hyperkalemia are higher in routine clinical practice than previously reported in clinical trials, perhaps due to less stringent standards for monitoring.6,7 Accordingly, fear of hyperkalemia has led to underuse of this potentially life-saving therapy.8,9

Previous studies have shown that the incidence of hyperkalemia in patients treated with MRAs may vary by race with African Americans exhibiting less hyperkalemia than non-African Americans.10,11 Several medical therapies for HF may also have differential effects by race, as evidenced in post-hoc analyses of the V-HeFT trials,12 in which the combination of hydralazine and isosorbide dinitrate was more beneficial in African Americans than in the non-African American population. These findings provided the rationale for the A-HeFT trial, which demonstrated a 43% reduction in the all-cause mortality with this combination compared to placebo in the African American population.13 Whether race influences the efficacy of MRAs in patients with HF, however, is unknown.

We utilized data from the Randomized Aldactone Evaluation Study (RALES) to examine differences in the incidence of hyperkalemia in African Americans (AA) compared with non-African Americans (non-AA), and hypothesized that race would modify the efficacy of spironolactone in patients with HF.
Methods

Study Design and Patient Selection

RALES was a double blind, randomized, placebo controlled trial that was designed to assess the efficacy of spironolactone on prevention of all-cause mortality and cardiac-related hospitalizations in patients with NYHA Functional Class (FC) III or IV HF. Participants were enrolled if they had a LVEF < 35% while taking background angiotensin converting enzyme (ACE) inhibitors and diuretics. 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 mmol/L. Participants were randomized to receive spironolactone 25 mg or placebo daily. Following 8 weeks, the dose could be increased to 50 mg daily for participants with signs and symptoms of progression of HF without evidence of hyperkalemia (serum potassium concentration ≥ 5.5 mEq/L). 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. Serum potassium and creatinine were measured at 4, 8, and 12 weeks during the titration phase, and every 3 months thereafter during the study, and were available in 1658 of the 1663 patients enrolled in the study. Concomitant treatment with digoxin and vasodilators was allowed, and the use of potassium-sparing diuretics was not permitted. Oral potassium supplement use was discouraged unless hypokalemia (defined as a serum potassium concentration of less than 3.5 mmol per liter) developed. The protocol was approved participating sites’ institutional review boards. All participants provided written informed consent in accordance with established guidelines for the protection of human subjects.
**Statistical Analyses**

Incidence hyperkalemia was defined as a potassium level \( \geq 5.5 \text{ mmol/L} \) at any visit during study follow up. Race was self-identified by study participants at the time of enrollment. Baseline demographics between AA and non-AA participants were compared to identify potential differences. Between-group assessments were performed using t-tests for continuous variables, and Chi-Square or Fisher’s exact tests, as appropriate, for categorical variables.

We compared potassium levels at baseline and at one month following randomization by treatment assignment between AA and non-AA participants by un-paired t-tests. In order to test the hypothesis that the population-averaged relationship between post-baseline potassium values and treatment was not modified by race, we fit a generalized estimating equations model for repeated measures, allowing for within-patient correlation, and controlling for baseline potassium value. Cox proportional hazards regression models were used to examine associations between treatment assignment and all-cause mortality and the combined endpoint of death or HF hospitalization among AA and non-AA. Models were adjusted for the following covariates: age, sex, diabetes, hypertension, history of MI, NYHA FC, baseline potassium, eGFR, maximal dose of study medication achieved, and baseline medications (diuretic, ACE inhibitor or ARB, beta-blocker, digoxin, aspirin). Times to hyperkalemia and hypokalemia between AA and non-AA were also assessed. Additionally, we performed formal interaction testing between race, treatment assignment, and the outcomes of hyperkalemia, hypokalemia, all-cause mortality, and the combined endpoint of death or HF hospitalization. Another model was fit which included multiple treatment by covariate interaction terms for eGFR, age, gender, NYHA status, potassium level, and usage of ACE inhibitor/ARB, digoxin, beta-blocker, and loop diuretic at baseline. Doses of study drug were recorded, and mean and maximal dose achieved were
compared. A critical alpha probability (p) value of <0.05 was considered statistically significant. All analyses were conducted using Stata, version 11 (StataCorp LP, College Station, TX).

**Results**

**Baseline Patient Demographics**

Out of 1663 patients included in the RALES study, 120 (7%) were AA, and 1543 were non-AA (Caucasian, Asian, or Other). Baseline characteristics by race are shown in the Table. AA participants were significantly younger, more likely to have an ischemic HF etiology, more likely to be NYHA FC IV (but similar baseline ejection fraction), have a higher eGFR and heart rate, less hypertension, diabetes, or history of myocardial infarction compared to non-AA participants. Moreover, fewer AA participants took beta-blockers and aspirin, and more took digoxin at study entry. More non-AA attained the maximal dose of study medication compared to AA participants (13.9% vs. 5.8%, p = 0.04), and mean doses of spironolactone were higher in non-AA compared to AA (26.4mg versus 25.1mg, p=0.004). Adherence, assessed by pill counts, was not different between AA and non-AA participants.

**Baseline and Changes in Potassium over Time**

Baseline potassium concentrations were comparable between AA and non-AA participants (4.30 ± 0.38 mmol/L versus 4.25 ± 0.44 mmol/L, p=0.51). At one month following randomization (visit 1), potassium levels increased significantly from baseline in non-AA taking spironolactone (4.30 ± 0.38 vs. 4.55 ± 0.49, p < 0.0001), but not in AAs assigned to spironolactone (4.25 ± 0.4 vs. 4.31 ± 0.49 mmol/L, p = 0.91; between group comparison p<0.001 Figure 1). Potassium levels at one month post-randomization were similar between AA and non-AA taking placebo (p=0.97). Mean doses of spironolactone at one month were similar between groups (25.5mg
among AA vs. 26.1mg in non-AA, p=0.45). Differences in potassium concentrations between AA and non-AA persisted throughout the trial. Controlling for baseline potassium values, study medication dose (mean and maximum achieved dose), spironolactone was associated with an overall increase in post-baseline potassium values (mean increase 0.28 mmol/L [p<0.001]). AA participants experienced a significantly smaller potassium increase associated with treatment (0.13 vs 0.29 mmol/L for AA vs non-AA, p-interaction = 0.03), and there were no significant differences between AA and non-AA participants taking placebo (p=0.38).

Rates of hyperkalemia (serum potassium ≥ 5.5mmol/L) were higher among non-AA participants assigned to spironolactone compared to AA participants (16.6% versus 5.4%, p<0.001, Figure 2). There were no statistically significant differences in hyperkalemia among AA randomized to spironolactone compared to placebo (5.4% versus 3.0%, p=0.54). In comparison, non-AA participants taking spironolactone had a statistically higher frequency of hyperkalemia compared to placebo (16.6% versus 4.8%, p<0.001). Conversely, hypokalemia (serum potassium < 3.5mmol/L) was more frequent among AA participants taking spironolactone compared to non-AA (19.6% versus 6.1%, p<0.001, Figure 2), and we observed a significant race by treatment interaction for time to hypokalemia (p-interaction=0.032).

Study Outcomes

In the placebo group, overall rates of mortality and the combined endpoint of death or HF hospitalization were similar in AAs and non-AAs (Figure 3). In non-AA participants, spironolactone was associated with a 30% reduction in the risk for all-cause mortality (adjusted HR 0.70, 95% CI 0.59, 0.82), and a 36% reduction in the risk for the composite outcome of death or hospitalization for HF (adjusted HR 0.64, 95% CI 0.55, 0.74) (Figure 4). By contrast, in the AA participants spironolactone use was associated with no effect on mortality (adjusted HR
0.87, 95% CI 0.47, 1.59), or death or hospitalizations for HF (adjusted HR 1.18, 95% CI 0.72, 1.94) (Figure 4). There was a significant race by treatment interaction for the outcome of death or hospitalizations for HF (p-interaction=0.032), but not for mortality. Even after adjusting for multiple treatment by covariate interactions to assess for the effect of baseline covariate imbalances between AA and non-AA individuals, there remained a significant interaction between race and treatment on the composite of death or hospitalizations for HF (p-interaction=0.030). Of note, Blood pressure changes in response to spironolactone at visit 2 and over the course of the trial were similar between AA and non-AA.

Discussion
In this analysis of patients with moderately severe to severe HF with reduced ejection fraction randomized to a mineralocorticoid receptor antagonist or placebo, self-identified AA patients developed less hyperkalemia but higher rates of hypokalemia while taking spironolactone compared to similarly treated non-AA patients. Despite a similar initial study drug dose, potassium concentrations increased substantially in non-AA individuals assigned to spironolactone within a month following randomization, while potassium levels in AA participants did not change significantly. However, AA participants appeared to derive less clinical benefit from an MRA.

Differences in potassium response to spironolactone among AA and non-AA participants were evident early in the study and persisted throughout the trial. Non-AA participant potassium levels increased, on average, by 0.25mmol/L while taking spironolactone compared to those taking placebo. Changes in potassium concentrations were minimal in AA participants. In addition, there were lower rates of hyperkalemia and higher rates of hypokalemia among AA.
Our findings are consistent with two other analyses that also reported less pronounced changes in serum potassium in AA patients with HF taking spironolactone compared to non-AA.\textsuperscript{10,11}

Patients with heart failure may be at higher risk for hyperkalemia from renin-angiotensin-aldosterone system blockers, due to inherently diminished renal perfusion, reducing delivery of sodium at distal tubule sites, which results in decreased potassium excretion.\textsuperscript{14} Several risk factors are known to further augment the risk for hyperkalemia in those with heart failure, including renal dysfunction, diabetes, and use of concomitant medications that enhance potassium levels such as ACE inhibitors or ARBs and beta adrenergic blockers.\textsuperscript{15} In the RALES study, AA participants had higher calculated eGFRs and less diabetes, in addition to a lower frequency of beta blocker use, and lower mean doses of study medication. These differences in the two groups may have contributed to different rates of hyperkalemia and hypokalemia observed between them. We attempted to control for baseline differences between groups in our analyses. In addition, there was a statistically significant, but numerically small (mean difference of 1.3 mg) difference in spironolactone dose between groups. This small dose difference would not be expected to result in the profound potassium differences observed, but the fact that less AA achieved maximum dose of spironolactone could have also impacted potassium levels.

We found that spironolactone was less effective in reducing death or HF hospitalization in AAs than in non-AA. There are no prior randomized data analyzing the effect of spironolactone on clinical outcomes by race, and most large randomized trials with MRAs have too few AAs to elucidate outcomes by self-reported race. In an post hoc analysis of A-HeFT study, in which AA patients were randomized to a fixed dose combination of hydralazine and isosorbide dinitrate (FDC-H/I) or placebo in addition to standard therapy, spironolactone use was not associated with a reduction in all-cause mortality, mortality or first HF hospitalization, or
first HF hospitalization in the overall sample.\textsuperscript{16} However, when the analysis was done within each randomized treatment group, spironolactone use was associated with a 59\% reduction in all-cause mortality in the FDC-H/I group but not in the placebo group, suggesting a synergistic effect of the MRA with FDC-H/I. Although 39\% of A-HeFT study participants were taking spironolactone, this treatment was not randomized, thus, these observations may be confounded.

The mechanisms underlying differences by race in potassium and clinical responses to spironolactone are unclear, but several mechanisms have been postulated. First, adherence has previously been shown to be lower among AA patients in general\textsuperscript{17,18} and reduced adherence may negatively affect outcomes,\textsuperscript{19} although adherence as assessed by pill count was not different by race in the RALES study. Moreover, the minimal difference in dose of spironolactone between the two groups is unlikely to explain these differences in outcomes. Whether AA patients respond less favorably to neurohormonal inhibition compared to non-AA is controversial. A post-hoc analysis of the SOLVD (Studies on Left Ventricular Dysfunction) trial demonstrated less blood pressure lowering with enalapril in AA compared to non-AA, and higher rates of hospitalizations.\textsuperscript{20} In the ALLHAT study, AA exhibited higher relative risk for incident coronary heart disease, stroke, and heart failure while taking lisinopril compared to non-AA, however formal testing for race and treatment interaction in predicting HF was not significant.\textsuperscript{21} With beta adrenergic receptor blockers, one analysis found an attenuated effect on death or hospitalization among AA with heart failure,\textsuperscript{22} while other analyses suggested similar benefits between AA and non-AA.\textsuperscript{23,24} Discrepancies in study findings may be related to unclear environmental or genetic contributors, or to instability in point estimates of efficacy related to small numbers of AA patients enrolled in the large scale clinical trials.
Mineralocorticoid receptor antagonists (MRAs) lead to increased serum potassium concentrations by interfering with aldosterone’s activity at the mineralocorticoid receptor, thus reducing renal excretion of potassium via the Na+/K+-ATPase.25 Mineralocorticoid receptors are also present in cardiac tissue, where they are believed to modulate cardiac responses, such as anti-fibrotic effects, to MRAs.26 Differences in the mineralocorticoid receptor, also referred to as the nuclear receptor superfamily 3, group C, member 2 (NR3C2), could potentially contribute to racial differences in MRA response. For example, a single nucleotide polymorphism located in the NR3C2 gene, c.-2C>G (rs2070951), occurs more commonly in Caucasians compared to AAs (prevalence of 45% versus 20-30%) and results in altered receptor activity.27 More pronounced potassium elevations in response to spironolactone have been reported among NR3C2 -2G allele carriers.28 It is possible that clinical outcomes may also be associated with genetic variants of the mineralocorticoid receptor that might vary by race. Whether NR3C2 genotype also impacts clinical outcomes with MRAs and contributes to racial differences in MRA response is unknown and unfortunately cannot be evaluated in RALES because genetic samples are not available.

Finally, a potassium-sparing effect defined by a serum potassium increase of 0.11 mmol/L after one month independently contributed to the mortality and morbidity benefit of eplerenone in HF patients post myocardial infarction in EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival study).29 This small serum potassium elevation associated with a MRA was consistent with that reported in a review of the use of RAAS inhibitors in a broad spectrum of clinical studies.30 Although hyperkalemia is generally the aspect of potassium homeostasis that is discussed in the context of MRAs, hypokalemia is also clinically important. Some data suggest that hypokalemia in patients with HF may be associated with increased mortality.31-33 In the present study, it was shown that AA exhibited
lower serum potassium concentrations while taking spironolactone and more frequent hypokalemia. Altogether, it may therefore also be proposed that the lower serum potassium levels observed in AA compared to non AA participants may have contributed to the poorer outcomes.

Some limitations of this study should be noted. This was a post-hoc analysis of the RALES study and hence the results should be interpreted with caution. In particular, the number of AA was small therefore point estimates noted are not definitive. However, serum potassium results are consistent with those from previous analyses. Beta blocker usage in the RALES study was low, and beta blockers are known to reduce mortality in HF and also enhance the risk for hyperkalemia. As such, it is unclear whether the magnitude of differences observed in hyperkalemia rates, or in rates of mortality or death and hospitalization from HF, would be similarly observed with contemporary HF therapy. Baseline characteristics of AA in the RALES study differed from those of AA enrolled in A-HeFT study, including baseline renal function and higher incidence of ischemic etiology. As such, results from these analyses cannot be extrapolated to all AA. Furthermore, our findings are in the setting of low dose spironolactone and we cannot exclude the possibility that higher spironolactone doses may confer enhanced clinical benefits and negate any differences by race. We believe this question requires further investigation. The differential effect of spironolactone on changes in potassium by race appeared to be concordant with the effect of spironolactone on outcomes. However, we cannot determine whether potassium changes simply represent a marker of response to spironolactone or whether these changes may have played a role in the differential outcomes observed. Lastly, we cannot exclude the possibility that drug interactions occurred as a result of differences in unidentified
medication use between AA and non-AA, and it is possible that these drug interactions could have affected the efficacy of spironolactone.

In summary, we found that among patients with advanced HF, those of African American heritage exhibited lower serum potassium levels with spironolactone compared to non-African Americans, and appeared to derive less clinical benefit. While limited by a small number of African American participants and power, these hypothesis generating findings raise the possibility that safety and efficacy of MRAs may differ by heritage, and suggests the need for further prospective investigation.

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Disclosures

None.

References


29. Rossignol P, Menard J, Fay R, Gustafsson F, Pitt B, Zannad F. Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an EPHESUS (Eplerenone Post-


Table. Baseline Characteristics by Race

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<th>African Americans</th>
<th>Non-African Americans</th>
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<td></td>
<td>N=120</td>
<td>N=1543</td>
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<td>Age</td>
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Figure Legends

Figure 1. Potassium levels (mmol/L) during the study by treatment and race. AA = African American, non-AA = non-African American, PL = placebo.

Figure 2. Percentage of Patients experiencing any hypokalemic (K < 3.5) or Hyperkalemic (K > 5.5) event during follow-up, by race and treatment group. African Americans demonstrated less hyperkalemia among those randomized to spironolactone (black bars), but more hypokalemia on spironolactone compared to non-African Americans (race x treatment p-interaction = 0.032 for time to hypokalemia). * indicates p<0.001 for comparisons between African American and non-African Americans.

Figure 3. Kaplan-Meier curves showing similar placebo event rates for all-cause mortality (Panel A) and the composite of death or hospitalization for HF (Panel B) in non-African Americans (black line) and African Americans (dashed) in the RALES study.

Figure 4. Kaplan-Meier curves showing all-cause mortality (top panel) and death or hospitalization for HF (bottom panel) for participants in the spironolactone group (black) and placebo group (dashed) among non-African Americans (left panel) and African Americans (right panel). The combined endpoint of death or hospitalization for HF were reduced in non-AA Americans randomized to spironolactone, but not in AA participants taking spironolactone (death or HF hospitalization), adjusted p-interaction = 0.034.
A. All-Cause Mortality

B. Death or Hospitalization for HF
A. Mortality, Non-AA

HR 0.69 (95% CI 0.59, 0.81)

B. Mortality, AA

HR 0.91 (95% CI 0.52, 1.60)

C. Death or Hospitalizations for HF, Non-AA

HR 0.63 (95% CI 0.55, 0.73)

D. Death or Hospitalizations for HF, AA

HR 1.07 (95% CI 0.67, 1.71)
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