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

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

Methods and Results—We assessed hyperkalemia and outcomes in African Americans (AAs; n=120) and non-AAs (n=1543; white 93%) with New York Heart Association (NYHA) class III or IV HF and left ventricular dysfunction who were randomized to spironolactone, titrated to 25 or 50 mg daily or placebo, in the Randomized Aldactone Evaluation Study (RALES). AA participants were significantly younger, less likely to have an ischemic HF pathogenesis, more likely to be NYHA functional class IV, and more likely to have a higher estimated glomerular filtration rate and heart rate, less hypertension, diabetes mellitus, or history of myocardial infarction compared with non-AA participants. Potassium increased with spironolactone in non-AAs (4.29±0.5–4.55±0.49 mmol/L) but not in AAs (4.32±0.54–4.31±0.49 mmol/L; race by treatment interaction, P=0.03) during the first month and remained higher throughout the trial. Compared with AAs, non-AAs were more likely to attain maximal spironolactone dose (13.9% versus 5.8%; P=0.04) and had higher rates of hyperkalemia (potassium>5.5 mmol/L; 9.7% versus 4.2%; P<0.046), as well as lower rates of hypokalemia (potassium<3.5 mmol/L; 5.6% versus 17.9%; P<0.001). After adjustment for differences in baseline characteristics and achieved study drug dose, spironolactone reduced the combined end point of death or hospitalization for HF in non-AAs (hazard ratio, 0.63; 95% confidence interval, 0.55–0.73) but not in AAs (hazard ratio, 1.07; 95% confidence interval, 0.67–1.71; P value for interaction=0.032).

Conclusions—AAs with HF exhibited less hyperkalemia and more hypokalemia with spironolactone compared with non-AAs and seemed to derive less clinical benefit. These hypothesis-generating findings suggest that safety and efficacy of mineralocorticoid receptor antagonists may differ by race. (Circ Heart Fail. 2013;6:970-976.)

Key Words: heart failure ■ pharmacology ■ potassium
of hyperkalemia in AAs compared with non-AAs 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 New York Heart Association (NYHA) functional class III or IV HF. Participants were enrolled if they had a left ventricular EF <35% while taking background angiotensin-converting enzyme 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. After 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 measurements 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. Use of oral potassium supplements was discouraged unless hypokalemia (defined as a serum potassium concentration of <3.5 mmol/L) developed. The protocol was approved by the institutional review boards of the participating sites. All participants provided written informed consent in accordance with established guidelines for the protection of human subjects.

Statistical Analyses

Incidence of hyperkalemia was defined as potassium level ≥5.5 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 χ² or Fisher tests for categorical variables.

We compared potassium levels at baseline and at 1 month after randomization by treatment assignment between AA and non-AA participants by unpaired t tests. To test the hypothesis that the population-averaged relationship between postbaseline 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 end point of death or HF hospitalization among AAs and non-AAs. Models were adjusted for the following covariates: sex, age, diabetes mellitus, hypertension, history of myocardial infarction, NYHA functional class, baseline potassium, estimated glomerular filtration rate (eGFR), maximal dose of study medication achieved, and baseline medications (diuretic, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ARB), β-blocker, digoxin, aspirin).

Time to hyperkalemia and hypokalemia between AAs and non-AAs was also assessed. Additionally, we performed formal interaction testing between race, treatment assignment, and the outcomes of hyperkalemia, hypokalemia, all-cause mortality, and the combined end point of death or HF hospitalization. Another model that included multiple treatment by covariate interaction terms for eGFR, age, gender, NYHA status, potassium level, and usage of angiotensin-converting enzyme inhibitor/ARB, digoxin, β-blocker, and loop diuretic at baseline was fit. Doses of study drug were recorded, and mean and maximal dose achieved were compared. A critical α 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

Of 1663 patients included in the RALES study, 120 (7%) were AAs and 1543 were non-AAs (white, Asian, or other). Baseline characteristics by race are shown in the Table. AA participants were significantly younger, less likely to have an ischemic HF pathogenesis, more likely to be NYHA functional class IV (but similar baseline EF), and more likely to have a higher eGFR and heart rate, less hypertension, diabetes mellitus, or history of myocardial infarction compared with non-AA participants. Moreover, fewer AA participants took β-blockers and aspirin and more took digoxin at study entry. More non-AA participants attained the maximal dose of study medication compared with AA participants (13.9% versus 5.8%; P=0.04), and mean doses of spironolactone were higher in non-AAs compared with AAs (26.4 versus 25.1 mg; 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 versus 4.25±0.44 mEq/L). If the participants developed hyperkalemia 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 χ² or Fisher tests for categorical variables.

We compared potassium levels at baseline and at 1 month after randomization by treatment assignment between AA and non-AA participants by unpaired t tests. To test the hypothesis that the population-averaged relationship between postbaseline 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 end point of death or HF hospitalization among AAs and non-AAs. Models were adjusted for the following covariates: sex, age, diabetes mellitus, hypertension, history of myocardial infarction, NYHA functional class, baseline potassium, estimated glomerular filtration rate (eGFR), maximal dose of study medication achieved, and baseline medications (diuretic, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ARB), β-blocker, digoxin, aspirin).

Time to hyperkalemia and hypokalemia between AAs and non-AAs was also assessed. Additionally, we performed formal interaction testing between race, treatment assignment, and the outcomes of hyperkalemia, hypokalemia, all-cause mortality, and the combined end point of death or HF hospitalization. Another model that included multiple treatment by covariate interaction terms for eGFR, age, gender, NYHA status, potassium level, and usage of angiotensin-converting enzyme inhibitor/ARB, digoxin, β-blocker, and loop diuretic at baseline was fit. Doses of study drug were recorded, and mean and maximal dose achieved were compared. A critical α P value of <0.05 was considered statistically significant. All analyses were conducted using Stata, version 11 (StataCorp LP, College Station, TX).

Table. Baseline Characteristics by Race

<table>
<thead>
<tr>
<th>Value</th>
<th>African Americans (n=120)</th>
<th>Non-African Americans (n=1543)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.8±12.5</td>
<td>66.1±11.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>34%</td>
<td>26%</td>
<td>0.06</td>
</tr>
<tr>
<td>Non-ischemic pathogenesis</td>
<td>81%</td>
<td>43%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class</td>
<td>57%</td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>NYHA III</td>
<td>43%</td>
<td>28%</td>
<td>0.004</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>11%</td>
<td>23%</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7%</td>
<td>30%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14%</td>
<td>24%</td>
<td>0.012</td>
</tr>
<tr>
<td>Hypertension</td>
<td>84.1±30</td>
<td>63.3±22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR&lt;60</td>
<td>17%</td>
<td>50%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF</td>
<td>26.1±6.7</td>
<td>25.3±6.7</td>
<td>0.25</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>120.0±20.9/76.9±12.3</td>
<td>122.4±20.0/74.4±11.5</td>
<td>0.20/0.02</td>
</tr>
<tr>
<td>Pulse</td>
<td>85.6±14.8</td>
<td>80.5±14.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.31±0.46</td>
<td>4.27±0.47</td>
<td>0.41</td>
</tr>
<tr>
<td>Medications</td>
<td>2.5%</td>
<td>10.9%</td>
<td>0.004</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>97%</td>
<td>95%</td>
<td>0.53</td>
</tr>
<tr>
<td>ACEi or ARB</td>
<td>93%</td>
<td>90%</td>
<td>0.25</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>94%</td>
<td>72%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASA</td>
<td>21%</td>
<td>37%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, aspirin; EF, ejection fraction; eGFR, estimated glomerular filtration rate; and NYHA, New York Heart Association.
mmol/L; \( P=0.51 \)). At 1 month after randomization (visit 1), potassium levels increased significantly from baseline in non-AAs taking spironolactone (4.30±0.38 versus 4.55±0.49; \( P<0.0001 \)) but not in AAs assigned to spironolactone (4.25±0.4 versus 4.31±0.49 mmol/L; \( P=0.91 \); between group comparison \( P<0.001 \); Figure 1). Potassium levels at 1 month postrandomization were similar between AAs and non-AAs taking placebo (\( P=0.97 \)). Mean doses of spironolactone at 1 month were similar between groups (25.5 mg among AAs versus 26.1 mg in non-AAs; \( P=0.45 \)). Differences in potassium concentrations between AAs and non-AAs persisted throughout the trial. Controlling for baseline potassium values and study medication dose (mean and maximum achieved dose), it was found that spironolactone was associated with an overall increase in postbaseline potassium values (mean increase, 0.28 mmol/L; \( P<0.001 \)). AA participants experienced a significantly smaller potassium increase associated with treatment (0.13 versus 0.29 mmol/L for AAs versus non-AAs; \( P=0.03 \)), and there were no significant differences between AA and non-AA participants taking placebo (\( P=0.38 \)).

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

**Study Outcomes**

In the placebo group, overall rates of mortality and the combined end point 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 hazard ratio, 0.70; 95% confidence interval, 0.59–0.82) and a 36% reduction in the risk for the composite outcome of death or hospitalization for HF (adjusted hazard ratio, 0.64; 95% confidence interval, 0.55–0.74; Figure 4). By contrast, in the AA participants, spironolactone use was associated with no effect on mortality (adjusted hazard ratio, 0.87; 95% confidence interval, 0.47–1.59) or death or hospitalizations for HF (adjusted hazard ratio, 1.18; 95% confidence interval, 0.72–1.94; Figure 4). There was a significant race by treatment interaction for the outcome of death or hospitalizations for HF (\( P=0.032 \)) 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 (\( P=0.030 \)). Of note,
β as angiotensin-converting enzyme inhibitors or ARBs and concomitant medications that enhance potassium levels such as hydralazine and isosorbide dinitrate or placebo in A-HeFT study. 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 uncertain, but several mechanisms have been postulated. First, adherence has previously been shown to be lower among AA patients in general,17,18 and reduced adherence may negatively affect outcomes19 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 2 groups is unlikely to explain these differences in outcomes. Whether AA patients respond less favorably to neurohormonal inhibition compared with non-AA patients is controversial. A post

Discussion
In this analysis of patients with moderately severe to severe HF with reduced EF who were randomized to a MRA or placebo, self-identified AA patients developed less hyperkalemia but higher rates of hypokalemia while taking spironolactone compared with 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 after randomization, whereas potassium levels in AA participants did not change significantly. However, AA participants seemed 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. Potassium levels of non-AA participants increased, on average, by 0.25 mmol/L while taking spironolactone compared with 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 AAs. Our findings are consistent with 2 other analyses that also reported less pronounced changes in serum potassium in AA patients with HF who were taking spironolactone compared with non-AA patients.10,11

Patients with HF may be at higher risk for hyperkalemia from renin-angiotensin-aldosterone system blockers because of inherently diminished renal perfusion, reducing delivery of sodium at distal tubule sites, which results in decreased potassium excretion.14 Several risk factors are known to further augment the risk for hyperkalemia in those patients with HF, including renal dysfunction, diabetes mellitus, and use of concomitant medications that enhance potassium levels such as angiotensin-converting enzyme inhibitors or ARBs and β-adrenergic blockers.15 In the RALES study, AA participants had higher calculated eGFRs and less diabetes mellitus, in addition to a lower frequency of β-blocker use and lower mean doses of study medication. These differences in the 2 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 few AAs achieved maximum dose of spironolactone could have also affected potassium levels.

We found that spironolactone was less effective in reducing death or HF hospitalization in AAs than in non-AAs. There are no previous 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 a post hoc analysis of A-HeFT study, in which AA patients were randomized to a fixed dose combination of hydralazine and isosorbide dinitrate 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.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 fixed dose combination of hydralazine and isosorbide dinitrate group but not in the placebo group, suggesting a synergistic effect of the MRA with fixed dose combination of hydralazine and isosorbide dinitrate. Although 39% of A-HeFT study participants were taking spironolactone, this treatment was not randomized; thus, these observations may be confounded.

Figure 3. Kaplan-Meier curves showing similar placebo event rates for all-cause mortality (A) and the composite of death or hospitalization for heart failure (HF; B) in non-African Americans (non-AA; black line) and African Americans (AA; dashed) in the Randomized Aldactone Evaluation Study (RALES).
hoc analysis of the Studies on Left Ventricular Dysfunction (SOLVD) trial demonstrated less blood pressure lowering with enalapril in AAs compared with non-AAs and higher rates of hospitalizations. In the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study, AAs exhibited higher relative risk for incident coronary heart disease, stroke, and HF while taking lisinopril compared with non-AAs; however, formal testing for race and treatment interaction in predicting HF was not significant. With β-adrenergic receptor blockers, 1 analysis found an attenuated effect on death or hospitalization among AAs with HF, whereas other analyses suggested similar benefits between AAs and non-AAs. 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.

MRAs lead to increased serum potassium concentrations by interfering with the activity of aldosterone at the mineralocorticoid receptor, thus reducing renal excretion of potassium via the Na+/K+-ATPase. Mineralocorticoid receptors are also present in cardiac tissue in which they are thought to modulate cardiac responses, such as antifibrotic effects, to MRAs. 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 whites compared with AAs (prevalence of 45% versus 20%–30%) and results in altered receptor activity. More pronounced potassium elevations in response to spironolactone have been reported among NR3C2-2G allele carriers. 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 affects clinical outcomes with MRAs and contributes to racial differences in MRA response is unknown, and unfortunately this 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 1 month independently contributed to the mortality and morbidity benefit of eplerenone in patients with HF after myocardial infarction in Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival study (EPHESUS). This small serum potassium elevation associated with a MRA was consistent with that reported in a review of the use of renin-angiotensin-aldosterone system inhibitors in a broad spectrum of clinical studies. 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.\(^1\) In the present study, it was shown that AAs 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 participants compared with 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 AAs 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 AAs in the RALES study differed from those of AAs enrolled in the A-HeFT study, including baseline renal function. As results from these analyses cannot be extrapolated to all AAs. 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 think that this question requires further investigation. The differential effect of spironolactone on changes in potassium by race seemed 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. Finally, we cannot exclude the possibility that drug interactions occurred as a result of differences in the use of unidentified medications between AAs and non-AAs, 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 AA heritage exhibited lower serum potassium levels with spironolactone compared with non-AAs and seemed to derive less clinical benefit. Although limited by a small number of AA participants and power, these hypothesis-generating findings raise the possibility that safety and efficacy of MRAs may differ by heritage and suggest the need for further prospective investigation.

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The RALES Trial was funded by Searle (Skokie, IL). No additional funding was provided for these analyses.

Disclosures
None.

References
CLINICAL PERSPECTIVE

In this post hoc analysis of the Randomized Aldactone Evaluation Study (RALES), we assessed hyperkalemia and clinical outcomes among African American (AA) participants (n=120) versus non-AA participants (n=1543) randomized to spironolactone or placebo for the treatment of moderate to severe heart failure. Baseline potassium was similar between AA and non-AA groups. After 1 month, potassium levels rose significantly in non-AA participants randomized to spironolactone but not in AA individuals, and levels remained elevated among non-AA throughout the trial, with a significant race by treatment interaction for change in potassium levels (P=0.03). Compared with AA, non-AA had higher rates of hyperkalemia and lower rates of hypokalemia. Moreover, in non-AA participants, spironolactone was associated with a 30% reduction in the risk for all-cause mortality and a 36% reduction in the risk for the composite outcome of death or hospitalization for heart failure. By contrast, in AA participants, spironolactone use was associated with no effect on mortality or death or hospitalizations for heart failure, with a significant race by treatment interaction for the combined outcome of death or hospitalizations for heart failure (P=0.038). These hypothesis-generating findings suggest that while AA exhibit less hyperkalemia when taking spironolactone, they may also derive less clinical benefit. Future prospective studies should assess the role of mineralocorticoid receptor antagonists in AA patients with heart failure.
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