Potassium Handling with Dual Renin-Angiotensin System Inhibition in Diabetic Nephropathy

Peter N. Van Buren,*† Beverley Adams-Huet,† Mark Nguyen,* Christopher Molina,* and Robert D. Toto*†

Summary

Background and objectives Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the cornerstones of pharmacologic therapy in diabetic nephropathy. Mineralocorticoid receptor blockers reduce proteinuria as single agents or add-on therapy to other renin-angiotensin-aldosterone system-inhibiting drugs in these patients. The long-term benefits and ultimate role of mineralocorticoid receptor blockers in diabetic nephropathy remain unknown. A clinical trial previously showed that the kalemic effect of spironolactone is higher than losartan when added to lisinopril in patients with diabetic nephropathy. The purpose of this study was to investigate if renal potassium handling was primarily responsible for that observation.

Design, setting, participants, & measurements In a blinded, randomized, three-arm placebo-controlled clinical trial, 80 participants with diabetic nephropathy taking lisinopril (80 mg) were randomized to spironolactone (25 mg daily), losartan (100 mg daily), or placebo (trial dates from July of 2003 to December of 2006). Serum potassium, aldosterone, and 24-hour urine sodium, potassium, and creatinine were measured over 48 weeks. Differences were analyzed with repeated measures mixed models.

Results Mean follow-up serum potassium was 5.0 mEq/L for spironolactone, 4.7 mEq/L for losartan (P=0.05 versus spironolactone), and 4.5 mEq/L for placebo (P<0.001 versus spironolactone; P=0.03 versus losartan). The difference in serum potassium was 0.23 mEq/L for losartan versus placebo (P=0.02), 0.43 mEq/L for spironolactone versus placebo (P<0.001), and 0.2 mEq/L for spironolactone versus losartan (P=0.05). Serum and urine potassium excretion and secretion rates were similar between groups throughout the study.

Conclusion Spironolactone raised serum potassium more than losartan in patients with diabetic nephropathy receiving lisinopril, despite similar renal sodium and potassium excretion. This finding suggests that extrarenal potassium homeostasis contributes to hyperkalemia in these patients. A better understanding of extrarenal potassium homeostasis will provide an opportunity to use this drug more safely in patients with diabetic nephropathy as well as other patient populations.

Introduction

Diabetic nephropathy is the leading cause of ESRD in the United States. Inhibiting the renin-angiotensin-aldosterone system (RAAS) slows this progression (1–4). The incidence of ESRD remains unacceptably high, however, even among patients receiving RAAS inhibition. Various regimens combining RAAS-inhibiting drugs have been investigated to further slow the progression of diabetic nephropathy.

Combinations include an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB), a direct renin inhibitor (DRI) and an ACE inhibitor or ARB, and ACE inhibitors and mineralocorticoid receptor blockers (MRBs). All strategies reduce proteinuria compared with single-agent therapy (5–11), but hyperkalemia is a risk (12,13). Regimens including an ACE inhibitor and ARB or either drug and DRI are not recommended not only because of the risk of hyperkalemia but also because of renal failure and hypotension, which were seen in large clinical trials (14,15).

MRBs reduce proteinuria in diabetic nephropathy but have yet to be evaluated in a long-term outcome trial in this population. Although potential benefits from MRBs exist, additional understanding of the exact mechanism responsible for their kalemic effect may provide insight for preventing and managing this complication.

In this secondary analysis of a randomized trial, we explored effects of different RAAS-inhibiting combinations on serum potassium in patients with diabetic nephropathy. The purpose was to determine how factors known to modify serum potassium levels were influenced by combination therapy with lisinopril and spironolactone compared with therapy with lisinopril and losartan or lisinopril and placebo. We hypothesized that between-group differences in serum
potassium might be accounted for by differences in renal potassium handling.

Materials and Methods

Study Design

This study was a secondary analysis of a prospective, randomized, double-blind, placebo-controlled clinical trial (ClinicalTrials.gov NCT00381134) with previously published results (9).

Study Population

Participants were all enrolled in a randomized trial testing the hypothesis that, compared with placebo, addition of ARB or MRB to lisinopril (80 mg daily) would reduce albuminuria by 30%. Inclusion criteria were age >18 years, diabetes melitus, seated systolic BP ≥ 130 mmHg or treated systolic BP < 130 mmHg and a history of hypertension, and a urinary albumin-to-creatinine ratio (UACR) > 300 mg/g, despite ACE inhibition > 3 months. Exclusion criteria were serum creatinine > 3.0 mg/dl in women and > 4.0 mg/dl in men; secondary hypertension; baseline serum potassium > 5.5 mEq/L; hemoglobin A1c > 11%; recent stroke, myocardial infarction, or coronary revascularization; congestive heart failure; and anticipated need for renal replacement therapy within 1 year. The protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center–Dallas, and procedures fully adhered to the Declaration of Helsinki. All participants provided written informed consent.

Study Procedures

Screening and Run-In Visits. Screening visits, including BP measurement, serum chemistry, and spot urine collection for albumin and creatinine, were conducted on 235 participants, with 128 patients eligible for run-in. At the first run-in visit, participants started lisinopril at 20–40 mg daily. All other RAAS-inhibiting drugs were discontinued. A dietician prescribed a 2 g sodium, 0.8 mEq/kg potassium, and 0.8 g/kg protein diet. During the 4- to 8-week run-in period, lisinopril was increased to 80 mg daily. Each visit included BP measurement, serum potassium and creatinine, and spot UACR. Additional antihypertensives, excluding other RAAS-inhibiting drugs or calcium channel blockers, were prescribed to achieve systolic BP < 130 mmHg. Participants were ineligible to proceed if serum potassium was persistently > 5.5 mEq/L despite dietary and diuretic adjustment, albuminuria regressed, or systolic BP was persistently < 100 mmHg after antihypertensive dose reduction and/or repeat measurement. After the final run-in, participants were admitted to our Clinical and Translational Research Center (CTRC) for measurements of 24-hour ambulatory BP and urine albumin, urea, creatinine, sodium, and potassium.

Randomization and Follow-Up. After CTRC measurements, participants were randomly assigned in a double-blind manner to losartan (50 mg), spironolactone (12.5 mg), or placebo. After 1 week, titrations were made to losartan (100 mg) and spironolactone (25 mg). Every 4 weeks, office BP and serum chemistries were obtained. Every 12 weeks, 24-hour ambulatory BP and urine sodium, potassium, creatinine, and albumin were measured. At weeks 24 and 48, a 4-hour water-loaded clearance study was performed in the CTRC with measurement of an overnight supine aldosterone level. We calculated the 24-hour creatinine clearance, fractional excretion of potassium, and potassium excretion rate. After 48 weeks, study drugs were discontinued.

Study Measurements

BP. Clinic BP was measured by certified staff according to the American Heart Association. Ambulatory measurements were obtained with a Spacelabs 90207 monitor every 30 minutes during the daytime and every 1 hour at night.

Laboratory Measurements. Serum and urine chemistries were assayed in the CTRC Laboratory on a Beckman Model CX-9 Analyzer. Urine albumin was quantified by immunoprecipitation (DiaSorin, Stillwater, MN), with a within-assay coefficient of variation range of 1.7%–2.8% and a between-assay coefficient of variation range of 2.4%–4.2%.

Calculations. Fractional excretion of potassium was calculated from the 24-hour urine sample as the ratio of the product of the urine potassium concentration multiplied by serum creatinine concentration to the product of the serum potassium concentration multiplied by urine creatinine concentration (expressed as a percent). Urine potassium secretion was calculated from the clearance study as the difference between the urine potassium excretion and the filtered load of potassium as follows: (urine potassium concentration × urine flow rate)/(creatinine clearance × serum potassium concentration); it was expressed in microequivalents per minute.

Statistical Analyses

Normally distributed data are expressed as means and SDs, and skewed data are expressed as geometric means and 95% confidence intervals. The primary outcome variable in this analysis was serum potassium. A mixed model repeated measures analysis compared serum potassium between treatment groups with the covariance pattern specified using Akaikie information criterion. This model included the treatment effect, time, and randomization values as covariates, whereas participants were random effects. Similar models were individually used to compare between-group differences in plasma aldosterone and systolic BP as well as 24-hour measurements of urinary creatinine clearance, potassium excretion, and sodium excretion and UACR. These variables were then included as independent variables in an adjusted model using change in serum potassium as the primary outcome variable. Mixed models were used to compare between-group changes in fractional excretion rate of potassium and potassium secretion rate. We conducted a logistic regression analysis on occurrence of hyperkalemia (serum potassium ≥ 6.0 mEq/L) using demographics and urine/serum chemistries as predictor variables. Statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

Results

Patient Characteristics

Baseline characteristics of 80 randomized participants are in Table 1. Most participants were African American or Hispanic. There were no differences in antihypertensive or diuretic use.
Changes in Serum Potassium throughout the Study

Between-group differences were not significant. There were 4.0 (3.1 to 5.2), 4.1 (2.9 to 5.6), and 4.0 (2.7 to 6.1) ng/dl for placebo; 3.4 (2.4 to 4.9), 4.0 (2.9 to 5.5), and 2.8 (2.1 to 3.7) ng/dl for losartan; and 5.0 (3.7 to 6.7), 6.2 (4.5 to 8.5), and 4.9 (3.4 to 7.1) ng/dl for spironolactone, respectively. The between-group differences were not significant ($P=0.78$).

**Table 1. Baseline characteristics of participants at randomization**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo ($n=27$)</th>
<th>Losartan ($n=26$)</th>
<th>Spironolactone ($n=27$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>44</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>African American (%)</td>
<td>37</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>44</td>
<td>46</td>
<td>63</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>49.3 (±8.8)</td>
<td>52.3 (±9.1)</td>
<td>51.7 (±9.3)</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>14.4 (±9.6)</td>
<td>17.0 (±7.7)</td>
<td>17.0 (±9.1)</td>
</tr>
<tr>
<td>24-h ambulatory systolic BP (mmHg)</td>
<td>138 (±15)</td>
<td>143 (±15)</td>
<td>135 (±11)</td>
</tr>
<tr>
<td>24-h ambulatory diastolic BP (mmHg)</td>
<td>75 (±9)</td>
<td>75 (±9)</td>
<td>71 (±9)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.4 (±0.7)</td>
<td>1.7 (±0.7)</td>
<td>1.8 (±0.9)</td>
</tr>
<tr>
<td>Urine albumin to creatinine ratio (mg/g)</td>
<td>917 (633 to 1329)</td>
<td>897 (611 to 1316)</td>
<td>1094 (758 to 1579)</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>8.1 (±1.3)</td>
<td>7.6 (±1.3)</td>
<td>7.4 (±1.6)</td>
</tr>
</tbody>
</table>

**Antihypertensive regimens at randomization**

- Diuretic (%)
  - Placebo: 85.5
  - Losartan: 88.5
  - Spironolactone: 96.3
- β-Blocker
  - Placebo: 70.4
  - Losartan: 63.4
  - Spironolactone: 77.8
- α-Blocker
  - Placebo: 29.6
  - Losartan: 30.8
  - Spironolactone: 25.9
- Central adrenergic antagonist
  - Placebo: 7.4
  - Losartan: 11.5
  - Spironolactone: 11.1
- Vasodilator
  - Placebo: 3.7
  - Losartan: 0
  - Spironolactone: 0
- Three or more drugs (%)
  - Placebo: 59
  - Losartan: 65
  - Spironolactone: 48

**Data**

- Data are listed as mean (SD) or geometric mean (95% confidence interval).
- There were no statistically significant between-group differences.

**Serum Potassium**

Mean randomization serum potassium levels were 4.5 (±0.7), 4.5 (±0.4), and 4.5 (±0.7) mEq/L for placebo, losartan, and spironolactone groups, respectively. There were 838 measurements obtained during the study. The mean during the trial was 4.5 mEq/L (±0.38) for placebo, 4.7 mEq/L (±0.33) for losartan ($P=0.03$ versus placebo), and 5.0 mEq/L (±0.51) for the spironolactone group ($P<0.001$ versus placebo; $P=0.05$ versus losartan). The course of these potassium levels over time was previously published (9).

**Twenty-Four-Hour Urine Chemistry**

No significant between-group differences existed in repeated measures analyses of urine sodium, potassium, or creatinine clearance (complete data shown in Table 2). No between-group difference existed in the change in fractional excretion of potassium (complete data shown in Table 3). Within the spironolactone group, the potassium secretion rate was different between weeks 24 (244 μEq/min; 192 to 309) and 48 (203 μEq/min; 154 to 266; $P=0.01$). However, no between-group differences existed for the three treatment groups throughout the duration of the entire study (complete data shown in Table 3).

**Plasma Aldosterone**

Plasma aldosterone values (geometric mean and 95% confidence interval) at randomization, week 24, and week 48 were 4.0 (3.1 to 5.2), 4.1 (2.9 to 5.6), and 4.0 (2.7 to 6.1) ng/dl for placebo; 3.4 (2.4 to 4.9), 4.0 (2.9 to 5.5), and 2.8 (2.1 to 3.7) ng/dl for losartan; and 5.0 (3.7 to 6.7), 6.2 (4.5 to 8.5), and 4.9 (3.4 to 7.1) ng/dl for spironolactone, respectively. The between-group differences were not significant ($P=0.78$).

**Changes in Serum Potassium throughout the Study**

Between-group differences in serum potassium throughout the study are shown in Table 4. In unadjusted analyses, there were significant increases in potassium for spironolactone compared with both losartan and placebo. There was also a significant increase in serum potassium in the losartan group compared with placebo. In models adjusting for pre- or postrandomization measurements of systolic BP and plasma aldosterone as well as 24-hour urine sodium excretion, potassium excretion, UACR, and creatinine clearance, serum potassium was significantly higher in the spironolactone group and losartan group compared with placebo. The results were unchanged when accounting for available data on baseline urine pH and serum bicarbonate (data not shown).

**Hyperkalemia**

Hyperkalemia (serum potassium≥6.0 mEq/L) occurred in 7.4%, 38.5%, and 51.9% of participants in the placebo, losartan, and spironolactone groups, respectively. All episodes were managed with kayexalate, although two participants in the spironolactone group discontinued the drug because of recurrent hyperkalemia. Significant predictors of hyperkalemia while controlling for treatment included (1) baseline serum potassium (odds ratio [OR], 1.3; 95% confidence interval [95% CI], 1.1 to 1.5 per 0.1 mEq/L increase), (2) baseline creatinine clearance (OR, 0.7; 95% CI, 0.5 to 0.95 per 10 ml/min increase), and (3) urinary potassium (OR, 0.5; 95% CI, 0.2 to 0.9 per 10 mEq increase). Serum potassium>4.5 mEq/L was a significant risk for developing hyperkalemia in the spironolactone group (OR, 13.8; 95% CI, 2.1 to 92), and there was a non-significant risk for estimated GFR<45 ml/min per 1.73 m² (OR, 4.3; 95% CI, 0.8 to 22.9). Among participants in all groups, baseline serum bicarbonate and urine pH levels were 24.6 (±2.9) and 5.6 (±0.5) among those participants who developed hyperkalemia. Serum potassium and 26.2 (±2.6, $P=0.02$) and 5.7 (±0.4, $P=0.08$) for those participants who did not develop hyperkalemia, respectively.
In patients with diabetic nephropathy receiving maximum doses of lisinopril, the addition of spironolactone increases serum potassium to a greater extent than losartan. Consequently, there are more episodes of hyperkalemia with spironolactone compared with the other dual RAAS-inhibiting regimens. Our data indicate that the differences in serum potassium cannot be explained by modification of renal potassium excretion alone. These findings came from a randomized trial accounting for potentially confounding variables.

Pharmacologic RAAS inhibition slows the diabetic nephropathy progression (1–4,16), but hyperkalemia remains a limitation (12,13). The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial was not powered to conclusively show increased hyperkalemia and renal failure among patients with diabetes or microalbuminuria receiving combination therapy (15,17). The Diabetes in Nephropathy study, specifically designed to test the ACE inhibitor and ARB strategy in patients with diabetic nephropathy (18), was recently stopped for safety concerns. The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints was recently terminated, because individuals with diabetic nephropathy experienced more hyperkalemia and hypotension on a DRI-based combination compared with ACE inhibitor or ARB alone (14). However, the long-term effects of MRB in diabetic nephropathy as combination- or single-agent RAAS inhibition remain unexplored. As a potential option for managing diabetic nephropathy, understanding the mechanisms of hyperkalemia from their use is critical.

### Table 2. Measurements of urinary sodium excretion, potassium excretion, and 24-hour creatinine clearance at randomization and throughout the trial

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Placebo</th>
<th>Losartan</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 0</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>27</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Urine Na (mEq/d)</td>
<td>193 (82)</td>
<td>220 (77)</td>
<td>219 (127)</td>
</tr>
<tr>
<td>Urine K (mEq/d)</td>
<td>56 (18)</td>
<td>63 (15)</td>
<td>58 (19)</td>
</tr>
<tr>
<td>Urinary creatinine clearance (ml/min)</td>
<td>73 (59.6 to 89.4)</td>
<td>64.8 (53 to 79.2)</td>
<td>51.4 (40.1 to 65.8)</td>
</tr>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>22</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Urine Na (mEq/d)</td>
<td>223 (120)</td>
<td>206 (86)</td>
<td>220 (97)</td>
</tr>
<tr>
<td>Urine K (mEq/d)</td>
<td>59 (23)</td>
<td>58 (16)</td>
<td>54 (17)</td>
</tr>
<tr>
<td>Urinary creatinine clearance (ml/min)</td>
<td>67.5 (54.4 to 83.8)</td>
<td>60.5 (49.6 to 73.7)</td>
<td>48.1 (36.2 to 64.0)</td>
</tr>
<tr>
<td><strong>Week 48</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>21</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Urine Na (mEq/d)</td>
<td>196 (107)</td>
<td>213 (104)</td>
<td>221 (101)</td>
</tr>
<tr>
<td>Urine K (mEq/d)</td>
<td>53 (22)</td>
<td>52 (16)</td>
<td>55 (22)</td>
</tr>
<tr>
<td>Urinary creatinine clearance (ml/min)</td>
<td>64.3 (49.6 to 83.4)</td>
<td>54.1 (40.5 to 72.2)</td>
<td>51.6 (39.6 to 67.4)</td>
</tr>
</tbody>
</table>

Data are listed as mean (SD) or geometric mean (95% confidence interval). All treatment comparisons are not significant for repeated measures analysis (urine Na, P=0.28; urine K, P=0.11; creatinine clearance, P=0.80).

### Table 3. Fractional excretion of potassium and potassium secretion rates during the trial

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Placebo</th>
<th>Losartan</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 0</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>26</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>FEK (%)</td>
<td>15.8 (12.4 to 20.2)</td>
<td>17.2 (13.9 to 21.4)</td>
<td>17.1 (13.7 to 21.4)</td>
</tr>
<tr>
<td>K secretion rate ((\mu\text{Eq/min}))</td>
<td>265 (199 to 352)</td>
<td>263 (206 to 335)</td>
<td>213 (169 to 269)</td>
</tr>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>FEK (%)</td>
<td>14.9 (11.4 to 19.5)</td>
<td>16.5 (12.5 to 21.9)</td>
<td>14.8 (11.7 to 18.6)</td>
</tr>
<tr>
<td>K secretion rate ((\mu\text{Eq/min}))</td>
<td>258 (191 to 348)</td>
<td>258 (192 to 346)</td>
<td>244 (192 to 309)</td>
</tr>
<tr>
<td><strong>Week 48</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>FEK (%)</td>
<td>14.3 (11 to 18.6)</td>
<td>15.1 (11.9 to 19.1)</td>
<td>15.8 (12.4 to 20)</td>
</tr>
<tr>
<td>K secretion rate ((\mu\text{Eq/min}))</td>
<td>247 (181 to 337)</td>
<td>248 (192 to 32)</td>
<td>203 (154 to 266) a</td>
</tr>
</tbody>
</table>

Data are listed as geometric mean and 95% confidence interval. Repeated measures analysis: fractional excretion of potassium, P=0.64 for treatment, P=0.80 for week, P=0.50 for treatment week interaction; potassium secretion rate, P=0.80 for treatment, P=0.20 for treatment week interaction. FEK, fractional excretion of potassium.

aSpironolactone K secretion rate, P=0.01 for week 24 versus week 48.

**Discussion**

In patients with diabetic nephropathy receiving maximum doses of lisinopril, the addition of spironolactone increases serum potassium to a greater extent than losartan. Consequently, there are more episodes of hyperkalemia with spironolactone compared with the other dual RAAS-inhibiting regimens. Our data indicate that the differences in serum potassium cannot be explained by modification of renal potassium excretion alone. These findings came from a randomized trial accounting for potentially confounding variables.

Pharmacologic RAAS inhibition slows the diabetic nephropathy progression (1–4,16), but hyperkalemia remains a limitation (12,13). The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial was not powered to conclusively show increased hyperkalemia and renal failure among patients with diabetes or microalbuminuria receiving combination therapy (15,17). The Diabetes in Nephropathy study, specifically designed to test the ACE inhibitor and ARB strategy in patients with diabetic nephropathy (18), was recently stopped for safety concerns. The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints was recently terminated, because individuals with diabetic nephropathy experienced more hyperkalemia and hypotension on a DRI-based combination compared with ACE inhibitor or ARB alone (14). However, the long-term effects of MRB in diabetic nephropathy as combination- or single-agent RAAS inhibition remain unexplored. As a potential option for managing diabetic nephropathy, understanding the mechanisms of hyperkalemia from their use is critical.
Similar to other combinations, short-term administration of combination RAAS inhibition including MRBs reduces proteinuria in patients with kidney disease (7,8,19,20), although potassium increases and medically manageable hyperkalemia remain risks associated with this intervention. No prior study has directly compared the effects of add-on therapy with an MRB versus ARB in patients with diabetic nephropathy already receiving maximal ACE inhibition. In this analysis of a randomized placebo-controlled trial, serum potassium and the incidence of hyperkalemia were highest in participants taking spironolactone compared with losartan or placebo. Prior studies show that reduced baseline GFR predicts the development of hyperkalemia independent of treatment. No prior study has directly compared the effects of add-on therapy with an MRB versus ARB in patients with diabetic nephropathy already receiving maximal ACE inhibition.

Identifying risk factors for hyperkalemia may allow for better selection of patients to use dual RAAS inhibition. Baseline serum potassium, urine potassium, and creatinine clearance predicted hyperkalemia independent of treatment group. A prior study specifically identified baseline serum potassium >4.5 mEq/L and estimated GFR <45 mL/min per 1.73 m² as hyperkalemia predictors (>5.5 mEq/L) in CKD stages 2 and 3 patients receiving spironolactone and another RAAS-inhibiting drug (32). This serum potassium was predictive of hyperkalemia (>6.0 mEq/L), and this GFR was a nonsignificant predictor in our study.

| Table 4. Differences in serum potassium between treatment groups throughout the study |
|---------------------------------------------|------------------|------------------|
| **Statistical Model**                        | **Losartan Versus Placebo** | **Spironolactone Versus Placebo** | **Spironolactone Versus Losartan** |
| Unadjusted                                  | 0.23 (0.04 to 0.42), P=0.02 | 0.43 (0.23 to 0.62), P<0.001 | 0.2 (0.0 to 0.39), P=0.05 |
| Adjusted for randomization variables*       | 0.22 (0.02 to 0.42), P=0.03 | 0.37 (0.15 to 0.59), P=0.001 | 0.15 (−0.05 to 0.36), P=0.14 |
| Adjusted for postrandomization variables*   | 0.25 (0.03 to 0.46), P=0.03 | 0.42 (0.21 to 0.64), P<0.001 | 0.17 (−0.03 to 0.46), P=0.16 |

*Variables include systolic BP plasma aldosterone, 24-hour urinary creatinine clearance, 24-hour urinary excretion of sodium and potassium, and 24-hour urine albumin to creatinine ratio. Differences are linear model least squares means estimates and 95% confidence intervals.
Although hyperkalemia was medically managed in our study, in rare cases, dual RAA inhibition carries the potential risk of hyperkalemia that may require hemodialysis or cause cardiac arrest. Consequently, it is critical to monitor potassium on these regimens. Importantly, the ARB and DRI combination did not cause any hyperkalemia in one study done in diabetic patients with stages 1 and 2 CKD (33), supporting that this strategy is better tolerated in diabetic patients with only mildly reduced kidney function.

One limitation was exclusion of patients with severe renal disease and persistent hyperkalemia during run-in. Progression of CKD increases the hyperkalemia risk (34), and therefore, the hyperkalemia incidence and potassium levels may have been higher with these individuals included. In our results, higher serum potassium with spironolactone versus losartan was of borderline statistical significance. The original trial was powered for proteinuria changes. Finally, our population demographic makes it difficult to generalize in populations with more Caucasians.

The addition of spironolactone increases serum potassium more than losartan when added to the maximum dose of lisinopril in patients with diabetic nephropathy. There is evidence that extrarenal potassium homeostasis is involved in this effect. Combination therapies using ACE inhibitors and ARB or DRI plus either ACE inhibitors or ARBs are not recommended in diabetic nephropathy. MRBs effectively reduce proteinuria in patients with diabetic nephropathy, but long-term outcomes with this strategy have not been adequately assessed in clinical trials. Identifying specific mechanisms responsible for hyperkalemia may provide an opportunity to find more effective and safer uses of MRB to improve outcomes in diabetic nephropathy.

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**Disclosures**

None.

**References**


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