Changing the Landscape of CKD Progression

George L. Bakris, MD, F.A.S.N, F.A.S.H.
Professor of Medicine
Director, ASH Comprehensive Hypertension Center
The University of Chicago Medicine
Chicago, IL 60637
Conflicts of Interest

- National Clinical Trial Principal Investigator Studies - Bayer, Relypsa (direct funding to University of Chicago)
- Consultant/Advisor - Takeda, AbbVie, CVRx, Janssen, Eli Lilly/Boeringher-Ingelheim, Medtronic, Novartis, GSK, Bayer
- Editor, Am J Nephrology ; Editor in Chief, Hypertension-UpToDate
- Special Government Employee-FDA and CMS
Biggest Causes of End Stage Kidney Disease in the World

- Diabetes
- Hypertension
- IgA Nephropathy
- Polycystic Kidney Disease
Global Burden of Hypertension*  
2025 Projection

**Year 2000**
- 26.4% of world adult population had hypertension
- Total of 972 million adults
- Highest prevalence is in established market economies (e.g., North America, Europe)

**Year 2025**
- 29.2% of world adult population will have hypertension
- Total of 1.56 billion adults (60% ↑ overall; 24% ↑ in developed nations, 80% ↑ in developing nations)
- Highest prevalence will be in economically developing continents (e.g., Asia, Africa) will account for 75% of world’s hypertensive patients

*defined by a BP>140/90 mm Hg; >130/80 mm Hg in diabetes and renal impairment*  

Egan B et al. JAMA 2010;303:2043-2050
Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958–2010

Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 Years or older

Obesity (BMI ≥30 kg/m²)

1994

2000

2010

Diabetes

1994

2000

2010

Prevalence estimates of diabetes, 2025

SOURCE: DIABETES ATLAS THIRD EDITION, © INTERNATIONAL DIABETES FEDERATION, 2006

4.05 13.21 16.14
4.63 7.81 7.56
3.55 0.19 0.35
0.45

Incident counts & adjusted rates, by race

Figure 2.5 (Volume 2)

Incident ESRD patients; rates adjusted for age & gender.

USRDS 2010 ADR
What Do We Know About Nephropathy Progression
17 Year Follow-Up from VA Hypertension Clinics on ESRD

## Studies With Primary Renal Endpoints That Show Differences in Outcome: \( \text{min} = 2.5 \text{ year F/U} \)

### Nondiabetic

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD, N Engl J Med, 1993</td>
<td>40*</td>
</tr>
<tr>
<td>AIPRI, N Engl J Med, 1996</td>
<td>52</td>
</tr>
<tr>
<td>REIN, Lancet, 1997</td>
<td>56*</td>
</tr>
<tr>
<td>AASK, JAMA, 2002</td>
<td>46*</td>
</tr>
<tr>
<td>Hou, NEJM, 2006</td>
<td>27</td>
</tr>
</tbody>
</table>

### Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril Trial, N Engl J Med, 1993</td>
<td>68</td>
</tr>
<tr>
<td>Hannadouche et.al B Med J, 1994</td>
<td>51</td>
</tr>
<tr>
<td>Bakris et.al Kidney Int., 1996</td>
<td>59</td>
</tr>
<tr>
<td>Bakris et.al Hypertension, 1997</td>
<td>62</td>
</tr>
<tr>
<td>IDNT, N Engl J Med, 2001</td>
<td>51</td>
</tr>
<tr>
<td>RENAAAL, N Engl J Med, 2001</td>
<td>49</td>
</tr>
<tr>
<td>ABCD, Diabetes Care (Suppl), 2000</td>
<td>87</td>
</tr>
</tbody>
</table>

* Signifies GFR measured using iothalamate or iohexol
Composite Ranking for Relative Risks by glomerular filtration rate (GFR) and Albuminuria (Kidney Disease: Improving Global Outcomes (KDIGO) 2009)

<table>
<thead>
<tr>
<th>GFR stages, description and range (ml/min per 1.73 m²)</th>
<th>Albuminuria stages, description and range (mg/g)</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 High and optimal</td>
<td>Optimal and high-normal</td>
<td>&gt;105</td>
<td>90–104</td>
<td></td>
</tr>
<tr>
<td>G2 Mild</td>
<td>High</td>
<td>75–89</td>
<td>60–74</td>
<td></td>
</tr>
<tr>
<td>G3a Mild-moderate</td>
<td>Very high and nephrotic</td>
<td>45–59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3b Moderate-severe</td>
<td></td>
<td>30–44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G4 Severe</td>
<td></td>
<td>15–29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5 Kidney failure</td>
<td></td>
<td>&lt;15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Levey AS et al. Kidney Int 2010; doi: 10.1038/ki.2010.483
Relationship Between Achieved BP and Decline in Kidney Function from Primary Renal Endpoint Trials

Nondiabetes

REIN. *Lancet.* 1997
AASK. *JAMA.* 2002
Parsa A et al. NEJM 2013

Diabetes

IDNT. NEJM. 2001
RENAAL. NEJM. 2001
ABCD. *Diabetes Care (Suppl).* 2000

Update from Kalaitzidis R and Bakris GL In: *Handbook of Chronic Kidney Disease* Daugirdas J (Ed.) 2011
Between-Group Comparisons of the eGFR Slope and Proportion of Patients Free from a Primary Outcome Event in the CRIC Study

A Patients with Diabetes

B Patients without Diabetes

C Patients with Diabetes

D Patients without Diabetes

Microalbuminuria (High Albuminuria)

Indicates continuous variable for CV/CKD risk

Inflammation; ↑CV Risk and Vascular Dysfunction

Macroalbuminuria (Very High Albuminuria)

Higher CV Risk and Presence of CKD and Vascular Dysfunction
Clinical Trials and Renal Outcomes Based on Proteinuria Reduction (Retrospective Analysis)

Increased Time to Dialysis
- (30-35% proteinuria reduction)
- Captopril NEJM, 1993
- AASK Trial-JAMA, 2001
- RENAAL- NEJM, 2001
- IDNT- NEJM, 2001

No Change in Time to Dialysis
- (NO proteinuria reduction)
- DHPCCB arm-IDNT
- DHPCCB arm-AASK

Hart P & Bakris GL Managing Hypertension in the Diabetic Patient.
IN: Egan BM, Basile JN, and Lackland DT (eds.) *Hot Topics in Hypertension*
Prospective Trials Demonstrating Further Significant Reductions in Proteinuria Translating into Worse Renal Outcomes

- VA NEPHRON-D
- ALTITUDE
What is the Goal BP and Initial Therapy in Kidney Disease or Diabetes to Reduce CV Risk?

<table>
<thead>
<tr>
<th>Group</th>
<th>Goal BP (mmHg)</th>
<th>Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA (2015)</td>
<td>&lt;140/90</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>KDIGO/KDOQI (NKF) (2012)</td>
<td>&lt;140/90</td>
<td>ACE Inhibitor/ARB</td>
</tr>
<tr>
<td>2014 Expert Panel</td>
<td>&lt;140/90</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>KDOQI (NKF) (2004)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>JNC 7 (2003)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Am. Diabetes Assoc (2003)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Canadian HTN Soc. (2002)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Am. Diabetes Assoc (2002)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Natl. Kidney Foundation (2000)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor*</td>
</tr>
<tr>
<td>British HTN Soc. (1999)</td>
<td>&lt;140/80</td>
<td>ACE Inhibitor</td>
</tr>
<tr>
<td>WHO/ISH (1999)</td>
<td>&lt;130/85</td>
<td>ACE Inhibitor</td>
</tr>
<tr>
<td>JNC VI (1997)</td>
<td>&lt;130/85</td>
<td>ACE Inhibitor</td>
</tr>
</tbody>
</table>
Three Randomized Trials of BP Control on CKD Progression In Non-Diabetic CKD

- MDRD (Modification of Dietary Protein in Renal Disease)
- REIN-2 (Ramipril Efficacy in Nephropathy)
- AASK (African American Study of Kidney Disease)
- None support BP <130/80 mmHg
Does Hyperkalemia Limit the Use of RAAS Inhibitor Therapy?
Hyperkalemia Rates in IDNT and RENAAL

**IDNT**
Hyperkalemia: In IDNT (proteinuria ≥900 mg/day, and serum creatinine ranging from 1.0-3.0 mg/dL), the percent of patients with hyperkalemia (>6 mEq/L) was 18.6% in the irbesartan group versus 6.0% in the placebo group.

**RENAAL**
Results at month 6, 22.8% patients in the losartan group and 5.1% patients in the placebo group had serum potassium ≥5.5 mmol/l, (p<0.001).

## Lower Doses of ACEi/ARB Are NOT Effective in Slowing CKD Progression

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>N</th>
<th>OUTCOME (vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RENAAL</strong>₁</td>
<td>1513</td>
<td><strong>Losartan 100 mg (~ 80 % of active patients):</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25% ↓RR doubling of SC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28% ↓RR in progression to ESRD</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Losartan 50 mg (~ 20 % of active patients):</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No proven renoprotective effect</td>
</tr>
</tbody>
</table>

₁ T2DM with HTN + macroalbuminuria + mean eGFR ~ 43

| **IDNT**² | 1715| **Irbesartan 300 mg:**                                                             |
|           |     | 33% ↓RR doubling of SC                                                             |
|           |     | 28% ↓RR in progression to ESRD                                                      |

² T2DM with HTN + macroalbuminuria + mean eGFR ~ 41

| **IRMA 2**³ | 611 | **Irbesartan 300 mg:**                                                             |
|             |     | 70 % ↓RR of progression to macroalbuminuria                                        |
|             |     | **Irbesartan 150 mg:**                                                            |
|             |     | No statistically significant effect in ↓RR of progression to macroalbuminuria      |

³ T2DM with HTN, microalbuminuria (20-200 ug/min UAE rate); <1.5 mg/dl SC

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RAASi Use Falls From 43%–47% 8 Quarters Before ESRD to 33%–37% in the Quarter Following Initiation of ESRD

ACEi/ARB/renin inhibitor use in Part D enrollees in the transition to ESRD, 2011

ICD-9-CM codes

- 585.1 Chronic kidney disease, Stage 1
- 585.2 Chronic kidney disease, Stage 2 (mild)
- 585.3 Chronic kidney disease, Stage 3 (moderate)
- 585.4 Chronic kidney disease, Stage 4 (severe)
- 585.5 Chronic kidney disease, Stage 5 (excludes 585.6: Stage 5, requiring chronic dialysis.)*

Chronic kidney disease, unknown/unspecific

*In USRDS analyses, patients with ICD-9-CM code 585.6 & with no ESRD 2728 form or other indication of ESRD are considered to have code 585.5; see Appendix A for details.

CKD stage estimates are from a single measurement. For clinical case definition, abnormalities should be present ≥ 3 months.
## Odd Ratio of Hyperkalemia Development following Aldosterone Antagonism in Nephropathy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline eGFR ≤45 ml/min/1.73m² + serum potassium &gt;4.5 mEq/L</td>
<td>8.71 (2.89-24.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline eGFR ≤45 ml/min/1.73m² + &gt;30% reduction in eGFR</td>
<td>7.76 (2.13-29.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline eGFR ≤45 ml/min/1.73m²</td>
<td>2.97 (1.14-21.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline eGFR ≤45 ml/min/1.73m² + &gt;15 mmHg in systolic BP</td>
<td>3.98 (0.89-27.1)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Adjusted Mortality in Patients with CKD 3-5 vs Controls

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CKD 3–5</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>74.3</td>
<td></td>
</tr>
<tr>
<td>CKD Stage 3a</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>CKD Stage 3b</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>CKD Stage 4</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>CKD Stage 5</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

N=700,000

Management of Hyperkalemia

- Low Potassium Diet
- Polystrene Binding resins
- Newer compounds
Systematic Review of Necrosis Case Reports of SPS-Related GI Adverse Events

- Review included search of Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), bibliographies of identified articles, and websites of relevant drug agencies and professional associations

- 58 cases were identified in 30 reports
  - Necrosis was reported in patients given Kayexalate with (n=41) and without sorbitol (n=17)

- Mortality due to gastrointestinal injury was reported in 33% of these cases

- Cases of necrosis treated without sorbitol were more likely to be receiving chronic SPS (41%) than cases without (0%)

**Histopathology of SPS-Related GI Injury**

Necrosis (62%), Ulceration (48%), Perforation (9%), and SPS Crystals (90%)¹


* Circumferential wall thickening and pericolonic stranding on CT scan²*

* Angulated basophilic crystals, a typical appearance of Kayexalate²*

Fragments of colonic mucosa have miniaturized crypts with leakage of RBCs and fibrin into the surrounding lamina propria²**

* IV and oral contrast, a focal region of large bowel in the proximal transverse colon, near the hepatic flexure.

** a few normal-sized crypts are present at the bottom center for comparison.
Serum Potassium Over Time: Treatment Phase. Values are observed mean from central laboratory. I bars indicate standard errors.

Weir M et al. NEJM Jan 2015
Time to First Recurrent Hyperkalemia: Withdrawal Phase

A. Time to First Serum Potassium $\geq 5.5$ mmol/l

<table>
<thead>
<tr>
<th>Week of Withdrawal Phase</th>
<th>Placebo</th>
<th>Patiromer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>1</td>
<td>46</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>32</td>
</tr>
</tbody>
</table>

Weir M et.al. NEJM Jan 2015
Forest Plot of the Primary Efficacy End Point by Subgroups: Withdrawal Phase. Difference between placebo and Patiromer in median change in serum potassium from the start of the Withdrawal to Week 4 of the Withdrawal Phase.

Weir M et al. NEJM Jan 2015
Patient Disposition by Assigned Strata (Mild or Moderate Hyperkalemia) Over 52 Weeks

Patients Enrolled (N = 324)

Patients Randomized to Starting Dose of Patiromer (N = 306)*

<table>
<thead>
<tr>
<th>Mild Hyperkalemia Serum K⁺ &gt;5.0 - 5.5 mEq/L n=222</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Treated 2/222 (1%)</td>
</tr>
<tr>
<td>Treated 220/222 (99%)</td>
</tr>
<tr>
<td>Discontinued 65/222 (29%)</td>
</tr>
<tr>
<td>Completed 157/222 (71%)†</td>
</tr>
</tbody>
</table>

Most Frequent Reasons for Premature Discontinuation‡
- Withdrawal of consent, n=23 (10%)
- Adverse events, n=13 (6%)
- Noncompliance, n=10 (5%)
- Death, n=5 (2%)
- High serum K⁺, n=3 (1%)
- Low serum K⁺, n=3 (1%)

<table>
<thead>
<tr>
<th>Moderate Hyperkalemia Serum K⁺ &gt;5.5 - &lt;6.0 mEq/L n=84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated 84/84 (100%)</td>
</tr>
<tr>
<td>Discontinued 30/84 (36%)</td>
</tr>
<tr>
<td>Completed 54/84 (64%)†</td>
</tr>
</tbody>
</table>

Most Frequent Reasons for Premature Discontinuation‡
- Withdrawal of consent, n=8 (10%)
- Adverse events, n=6 (7%)
- High serum K⁺, n=4 (5%)
- Low serum K⁺, n=4 (5%)
- Death, n=3 (4%)
- Abnormal renal function, n=2 (2%)

*Eighteen patients from Cohorts 1 and 2 who were enrolled in the trial failed the run-in and were not eligible for randomization.
†Ten patients with mild hyperkalemia and 4 patients with moderate hyperkalemia completed the 8-wk Treatment Phase before the protocol amendment that added the 44-wk Maintenance Phase.
‡Reasons were assigned by study investigators; in the adverse event category, events leading to discontinuations in 5 patients were fatal adverse events.

Bakris GL. et.al. JAMA in review
Mean Patiromer Dose and LSM (±SD) Change from Baseline in Serum Potassium by Starting Dose at Weeks 4 and 8.

**From Baseline to Week 4**

<table>
<thead>
<tr>
<th>Stratum 1</th>
<th>Stratum 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 74</td>
<td>74</td>
</tr>
<tr>
<td>Δ LSM (mEq/L)</td>
<td>Δ LSM (mEq/L)</td>
</tr>
<tr>
<td>-0.35</td>
<td>-0.51</td>
</tr>
<tr>
<td>-0.55</td>
<td>-0.87</td>
</tr>
<tr>
<td>-0.97</td>
<td>-0.92</td>
</tr>
</tbody>
</table>

Overall change in mean (±SD) serum potassium: +0.47±0.039 mEq/L.

**From Baseline to Week 8**

<table>
<thead>
<tr>
<th>Stratum 1</th>
<th>Stratum 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 74</td>
<td>74</td>
</tr>
<tr>
<td>Δ LSM (mEq/L)</td>
<td>Δ LSM (mEq/L)</td>
</tr>
<tr>
<td>-0.37</td>
<td>-0.47</td>
</tr>
<tr>
<td>-0.54</td>
<td>-0.88</td>
</tr>
<tr>
<td>-0.95</td>
<td>-0.91</td>
</tr>
</tbody>
</table>

Overall change in mean (±SD) serum potassium: +0.92±0.075 mEq/L.

---

* Allowing for titration.

†P<0.001 versus baseline

Stratum 1, mild hyperkalemia (serum potassium >5.0 to 5.5 mEq/L). Stratum 2, moderate hyperkalemia (serum potassium >5.5 to <6.0 mEq/L).

Bakris GL. et.al. JAMA in review
Change from Baseline in Mean (±SE) Serum Potassium (mEq/L) to Week-52 (Treatment and Maintenance Phases) and Post-Treatment Follow-up Period in Patients with Mild or Moderate Hyperkalemia

Bakris GL. et.al. JAMA in review
## Most Common Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Event*</th>
<th>Mild hyperkalemia</th>
<th>Moderate hyperkalemia</th>
<th>Overall N=304</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=220</td>
<td>n=84</td>
<td></td>
</tr>
<tr>
<td>Worsening of CKD</td>
<td>14 (6.4%)</td>
<td>14 (16.7%)</td>
<td>28 (9.2%)</td>
</tr>
<tr>
<td>Hypomagnesemia†</td>
<td>15 (6.8%)</td>
<td>11 (13.1%)</td>
<td>26 (8.6%)</td>
</tr>
<tr>
<td>Worsening of HTN</td>
<td>14 (6.4%)</td>
<td>10 (11.9%)</td>
<td>24 (7.9%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>11 (5.0%)</td>
<td>8 (9.5%)</td>
<td>19 (6.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (5.5%)</td>
<td>5 (6.0%)</td>
<td>17 (5.6%)</td>
</tr>
<tr>
<td>Hypoglycemia†</td>
<td>4 (1.8%)</td>
<td>6 (7.1%)</td>
<td>10 (3.3%)</td>
</tr>
</tbody>
</table>

*Bakris GL. et.al. JAMA in review*
Sodium Zirconium Cyclosilicate in Hyperkalemia

David K. Packham, M.B., B.S., M.D., Henrik S. Rasmussen, M.D., Ph.D., Philip T. Lavin, Ph.D., Mohamed A. El-Shahawy, M.D., M.P.H., Simon D. Roger, M.D., Geoffrey Block, M.D., Wajeh Qunibi, M.D., Pablo Pergola, M.D., Ph.D., and Bhupinder Singh, M.D.

N Engl J Med
Volume 372(3):222-231
January 15, 2015
Study Design.

Primary End Point (initial phase)
Exponential rate of change in serum potassium over 48 hr

N=754

Patients with normokalemia on morning of day 3 may proceed to maintenance phase

Secondary End Point (maintenance phase)
Exponential rate of change in serum potassium over 12-day treatment interval

### Characteristics of the Patients at Baseline.

**Table 1. Characteristics of the Patients at Baseline.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=158)</th>
<th>Placebo (N=154)</th>
<th>Placebo (N=151)</th>
<th>Placebo (N=157)</th>
<th>Placebo (N=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>65.6±12.2</td>
<td>65.4±13.1</td>
<td>65.9±11.7</td>
<td>65.2±11.9</td>
<td>66.2±12.2</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>98 (62.0)</td>
<td>83 (53.9)</td>
<td>91 (64.5)</td>
<td>96 (61.1)</td>
<td>80 (55.9)</td>
</tr>
<tr>
<td>Race — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>136 (86.1)</td>
<td>131 (85.1)</td>
<td>125 (88.7)</td>
<td>132 (84.1)</td>
<td>120 (83.9)</td>
</tr>
<tr>
<td>Black</td>
<td>17 (10.8)</td>
<td>20 (13.0)</td>
<td>11 (7.8)</td>
<td>20 (12.7)</td>
<td>19 (13.3)</td>
</tr>
<tr>
<td>Baseline serum potassium — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0—5.3 mmol/liter</td>
<td>95 (60.1)</td>
<td>76 (49.4)</td>
<td>72 (51.1)</td>
<td>90 (57.3)</td>
<td>94 (65.7)</td>
</tr>
<tr>
<td>5.4—5.5 mmol/liter</td>
<td>22 (13.9)</td>
<td>38 (24.7)</td>
<td>29 (20.6)</td>
<td>36 (22.9)</td>
<td>27 (18.9)</td>
</tr>
<tr>
<td>5.6—6.5 mmol/liter</td>
<td>41 (25.9)</td>
<td>40 (26.0)</td>
<td>40 (28.4)</td>
<td>31 (19.7)</td>
<td>22 (15.4)</td>
</tr>
<tr>
<td>Medical history — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>96 (60.8)</td>
<td>102 (66.2)</td>
<td>89 (63.1)</td>
<td>93 (59.2)</td>
<td>83 (58.0)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>66 (41.8)</td>
<td>57 (37.0)</td>
<td>54 (38.3)</td>
<td>64 (40.8)</td>
<td>59 (41.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>96 (60.8)</td>
<td>94 (61.0)</td>
<td>84 (59.6)</td>
<td>96 (61.1)</td>
<td>81 (56.6)</td>
</tr>
<tr>
<td>Use of RAAS inhibitor — no. (%)</td>
<td>101 (63.9)</td>
<td>109 (70.8)</td>
<td>97 (68.8)</td>
<td>99 (63.1)</td>
<td>96 (67.1)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. There were no significant differences among the groups at baseline, except for the serum potassium level (P=0.03 for the overall comparison among the five study groups). RAAS denotes renin–angiotensin–aldosterone system.

† Race was self-reported.
Potassium Levels during the Study.

A

![Graph A showing serum potassium levels over time for different dose groups.]

B

![Graph B comparing serum potassium levels on drug vs. placebo over days.]

C

![Graph C comparing serum potassium levels on drug vs. placebo over days.]

# Adverse Events during Initial Phase and Maintenance Phase.

<table>
<thead>
<tr>
<th>Adverse Events in Initial Phase</th>
<th>Placebo</th>
<th>ZS-9, 1.25 g</th>
<th>ZS-9, 2.5 g</th>
<th>ZS-9, 5 g</th>
<th>ZS-9, 10 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>158</td>
<td>154</td>
<td>141</td>
<td>157</td>
<td>143</td>
</tr>
<tr>
<td>Adverse event — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>17 (10.8)</td>
<td>25 (16.2)</td>
<td>13 (9.2)</td>
<td>22 (14.0)</td>
<td>17 (11.9)</td>
</tr>
<tr>
<td>Gastrointestinal disorder†</td>
<td>8 (5.1)</td>
<td>7 (4.5)</td>
<td>3 (2.1)</td>
<td>6 (3.8)</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>Cardiac disorder‡</td>
<td>0</td>
<td>1 (0.6)</td>
<td>0</td>
<td>3 (1.9)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>3 (1.9)</td>
<td>0</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Events in Maintenance Phase</th>
<th>ZS-9, 1.25 g</th>
<th>ZS-9, 2.5 g</th>
<th>Placebo</th>
<th>ZS-9, 1.25 g</th>
<th>ZS-9, 2.5 g</th>
<th>Placebo</th>
<th>ZS-9, 5 g</th>
<th>Placebo</th>
<th>ZS-9, 10 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>46</td>
<td>50</td>
<td>41</td>
<td>49</td>
<td>54</td>
<td>68</td>
<td>65</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>Adverse event — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>10 (21.7)</td>
<td>12 (24.0)</td>
<td>13 (31.7)</td>
<td>14 (28.6)</td>
<td>9 (19.6)</td>
<td>11 (20.4)</td>
<td>16 (23.5)</td>
<td>14 (21.5)</td>
<td>15 (24.6)</td>
</tr>
<tr>
<td>Gastrointestinal disorder†</td>
<td>4 (8.7)</td>
<td>2 (4.0)</td>
<td>1 (2.4)</td>
<td>0</td>
<td>2 (4.3)</td>
<td>4 (7.4)</td>
<td>5 (7.4)</td>
<td>5 (7.7)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disorder‡</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.9)</td>
<td>1 (1.5)</td>
<td>2 (3.1)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (4.3)</td>
<td>1 (2.0)</td>
<td>2 (4.9)</td>
<td>1 (2.0)</td>
<td>0</td>
<td>1 (1.9)</td>
<td>1 (1.5)</td>
<td>3 (4.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Patients in the ZS-9 group who had a serum potassium level of 3.5 to 4.9 mmol per liter at 48 hours during the initial phase of the study were randomly assigned to receive either their original ZS-9 dose or placebo once daily before breakfast on days 3 to 14 during the maintenance phase. Patients in the placebo group in the initial phase were randomly assigned to receive either 1.25 g or 2.5 g of ZS-9 in the maintenance phase.

† Gastrointestinal disorders included diarrhea, constipation, nausea, vomiting, abdominal pain, abdominal distention, dyspepsia, flatulence, gastric ulcers, gastritis, and frequent bowel movements.

‡ Cardiac disorders included atrial fibrillation, atrial flutter, bradycardia, palpitations, sinus tachycardia, ventricular extrasystole, left-sided bundle-branch block, congestive cardiac failure, cardiovascular disorder, diastolic dysfunction, and the long-QT syndrome.
Summary

- No data supporting additional benefit on CKD outcomes, regardless of strategy in patients with normo or microalbuminuria-over BP control and in normotensive patients apart maybe from glycemic control.
- No data to support advantage on CKD outcome in elderly without proteinuria.
- Only place where there is definitive data for RAAS to slow diabetic nephropathy is in advanced proteinuric disease.
Summary

• New therapies to reduce serum potassium in stage 3b and higher CKD will provide opportunities for better patient management and testing of hypotheses regarding RAS therapy and CKD outcomes.