POTASSIUM MANAGEMENT: OBSERVATIONS FROM A KDIGO CONTROVERSIES CONFERENCE

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Kidney Disease: Improving Global Outcomes

GLOBAL SCIENCE
LOCAL CHANGE
Controversies Conference Leadership

Co-chairs:
Catherine Clase (Canada)
Roberto Pecoits-Filho (Brazil)

Breakout Groups:
- **Potassium Homeostasis** - David Ellison (US) and Biff Palmer (US)
- **Potassium Intake & Epidemiology of Dyskalemias** – Juan-Jesus Carrero (Sweden) and Gregorio Obrador (Mexico)
- **Hypokalemia** – Morgan Grams (US) and Gregory Kline (Canada)
- **Chronic Hyperkalemia** – Meg Jardine (Australia) and Csaba Kovesdy (US)
- **Acute Hyperkalemia & Hyperkalemia in AKI** – Brenda Hemmelgarn (Canada) and Gregor Lindner (Switzerland)
Potassium Homeostasis in Man

- Most abundant cation in the human body
- $[K^{+}_{IC}]/[K^{+}_{EC}]$ gradient critical for normal cell function
  - especially in excitable tissues, e.g. skeletal muscle, myocardial muscle, neurons
- Mandates tight regulation of $K^{+}$ homeostasis overall challenge in light of considerable variation in daily dietary $K^{+}$ intake

Normal Range for Serum $[K^+]$

- Lower limit of normal: 3.5 mEq/L
- Upper limit of normal: 5.0 mEq/L
  - or 5.1 mEq/L?
  - or 5.5 mEq/L? (e.g., FDA Investigators Manual)
  - 5.3 mEq/L (my hospital)
  - others…?

- Important to consider “normal” not just in light of population distribution, but also relative to risks/outcomes

Dietary Intake of Potassium

<table>
<thead>
<tr>
<th>CKD*</th>
<th>Overall</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>w/o CKD</td>
<td>2081 (884)</td>
<td>1976 (1394-2586)</td>
<td>2306 (909)</td>
</tr>
<tr>
<td>w/ CKD</td>
<td>2054 (1197)</td>
<td>1754 (1322-2459)</td>
<td>2301 (1286)</td>
</tr>
</tbody>
</table>

Unweighted 24-hour urinary potassium excretion, in mg, NHANES 2014

*eGFR <60 mL/min/1.73m² or urinary ACR >30 mg/g.

Cogswell ME et al. *JAMA* 2018;319:1209.
No regulation of [K⁺] uptake from intestine. (?

Intestinal sensor, inhibits activity of the Na⁺/Cl⁻ cotransporter in the proximal distal convoluted tubule → increased Na⁺ delivery to distal nephron → increased K⁺ secretion

This occurs even prior to any changes in serum [K⁺]

In advanced CKD, increase in potassium excretion through feces, from ~5% normally to >20% in advanced CKD.
Shifting of $K^+$ Between EC and IC Compartments

Distribution of $K^+$ within the body is mainly driven by mechanisms that are
- Insulin-mediated
- Beta-adrenergic mediated
- (aldosterone-mediated)

Tightly controlled by multiple mechanisms, but mostly through regulation of the activity of the $\text{Na}^+/\text{K}^+-\text{ATPase}$ (predominantly skeletal muscle)

Important process for acute removal of $K^+$ from EC compartment after $K^+$ ingestion

Can be disrupted by changes in acid-base, tonicity

Mostly in the kidney through an intrinsic web of control mechanisms & feedback loops. Looking for detailed information?

Potassium Homeostasis in Man

Well regulated processes able to tightly maintain EC and IC potassium homeostasis despite high variability in $[K^+]$ intake

**Acute:** EC-IC shifts mediated by insulin-, beta-adrenergic-mechanisms (much less aldosterone)

**Chronic:** kidney regulates potassium homeostasis via potassium secretion in distal nephron – aldosterone is the major player and acts at several levels

Works exquisitely well as long as kidney function is mostly intact.
Potassium Homeostasis in Man

Decline in available glomeruli as CKD progresses leads to increasing difficulty in maintaining K⁺ homeostasis

Other factors become increasingly important as causes of hyperkalemia as kidney function declines

• Dietary intake
• Concurrent morbid conditions (diabetes, heart failure)
• Medications
  • Inhibitors of the renin-angiotensin-aldosterone system (RAASi)
  • Others
# Risk Factors for Hyperkalemia

*In CKD, hyperkalemia risk is inversely related to GFR and increases substantially below an eGFR <30 mL/min/1.73 m²*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
</tbody>
</table>
  - Inhibition of renin release from juxtaglomerular cells: β-blockers; calcineurin inhibitors: cyclosporine, tacrolimus; nonsteroidal anti-inflammatory drugs  
  - Inhibition of aldosterone release from the adrenal gland: heparin; ketoconazole  
  - Mineralcorticoid receptor blockade: spironolactone; eplerenone  
  - Blockade of epithelial sodium channel renal collecting duct: amiloride; triamterene; trimethoprim |
| Potassium intake | 
  - Supplementation, salt substitutes, certain herbs, and potassium-enriched foods in setting of impaired renal excretion |

Adapted from Palmer BF and Clegg DL. *JAMA*. 2015;314:2405
# Risk Factors for Hyperkalemia

Table 2. Incidence of Hyperkalemia (Per 100 Patient-Months) Among Patients With and Without Chronic Kidney Disease (CKD) and/or Renin-Angiotensin-Aldosterone System (RAAS) Blocker Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Potassium (\geq 5.5) mEq/L (Inclusive)</th>
<th>Potassium (5.5 \text{ and } &lt; 6.0) mEq/L</th>
<th>Potassium (\geq 6.0) mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of potassium events</td>
<td>66,259</td>
<td>44,907</td>
<td>21,352</td>
</tr>
<tr>
<td>Total No. of patient-months</td>
<td>1,581,299</td>
<td>1,581,299</td>
<td>1,581,299</td>
</tr>
<tr>
<td>RAAS blocker treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>29,023</td>
<td>19,371</td>
<td>9,652</td>
</tr>
<tr>
<td>No. of patient-months</td>
<td>317,701</td>
<td>317,701</td>
<td>317,701</td>
</tr>
<tr>
<td>Adjusted rate (95% CI)(^{a,b})</td>
<td>7.67 (7.57-7.78)</td>
<td>5.06 (4.97-5.14)</td>
<td>2.60 (2.54-2.66)</td>
</tr>
<tr>
<td>No CKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>15,302</td>
<td>10,714</td>
<td>4,588</td>
</tr>
<tr>
<td>No. of patient-months</td>
<td>577,747</td>
<td>577,747</td>
<td>577,747</td>
</tr>
<tr>
<td>Adjusted rate (95% CI)(^{a,b})</td>
<td>2.30 (2.26-2.33)</td>
<td>1.63 (1.59-1.66)</td>
<td>0.67 (0.65-0.69)</td>
</tr>
<tr>
<td>No RAAS blocker treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>12,709</td>
<td>8,506</td>
<td>4,203</td>
</tr>
<tr>
<td>No. of patient-months</td>
<td>146,884</td>
<td>146,884</td>
<td>146,884</td>
</tr>
<tr>
<td>Adjusted rate (95% CI)(^{a,b})</td>
<td>8.22 (8.07-8.37)</td>
<td>5.43 (5.31-5.56)</td>
<td>2.76 (2.68-2.85)</td>
</tr>
<tr>
<td>No CKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>9,225</td>
<td>6,316</td>
<td>2,909</td>
</tr>
<tr>
<td>No. of patient-months</td>
<td>538,967</td>
<td>538,967</td>
<td>538,967</td>
</tr>
<tr>
<td>Adjusted rate (95% CI)(^{a,b})</td>
<td>1.77 (1.73-1.81)</td>
<td>1.24 (1.21-1.27)</td>
<td>0.53 (0.51-0.55)</td>
</tr>
</tbody>
</table>

Consequences of Hyperkalemia

Next-day Mortality

Consequences of Hyperkalemia


All-Cause Mortality (ESRD-censored)
Consequences of Hyperkalemia

Death or Cardiovascular Event

Korgaronkar S, et al. CJASN 2010;5:762
Consequences of Hyperkalemia

Mortality

- Adjusted HR vs Potassium, mmol/L
  - Non-African Americans
  - African Americans

ESRD

- Adjusted HR vs Potassium, mmol/L
  - Non-African Americans
  - African Americans

Chen Y et al. AJKD 2017;70:244
## Consequences of Hyperkalemia

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Outcome</th>
<th>Hyperkalemia Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAAL</td>
<td>CKD, DM (Diabetic Nephropathy)</td>
<td>22% risk reduction</td>
<td>38% &gt;5.0mEq/L, 23% &gt;5.5 mEq/l</td>
</tr>
<tr>
<td>IDNT</td>
<td>CKD, DM (Diabetic Nephropathy)</td>
<td>20% risk reduction</td>
<td>18.6% &gt;6.0mEq/L</td>
</tr>
<tr>
<td>RALES</td>
<td>Moderate−Severe HF</td>
<td>30% risk reduction</td>
<td>2% in RALES, 13% &gt;5.5 mEq/L (25 mg in RALES pilot)</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>HF post-MI</td>
<td>15% risk reduction</td>
<td>16% &gt;5.5mEq/L, 5% &gt;6.0mEq/L</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>Mild HF</td>
<td>37% risk reduction</td>
<td>12% &gt;5.5mEq/L</td>
</tr>
</tbody>
</table>
Consequences of Hyperkalemia

Among Patients on RAASi at Maximum Dose

- Maintained Dose
- Down-titrated Dose
- Discontinued

<table>
<thead>
<tr>
<th>Percent of Hyperkalemia Events</th>
<th>Mild Hyperkalemia (Potassium 5.1-5.4 mEq/L)</th>
<th>Moderate-to-Severe Hyperkalemia (Potassium ≥5.5 mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintained Dose</td>
<td>52%</td>
<td>41%</td>
</tr>
<tr>
<td>Down-titrated Dose</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>Discontinued</td>
<td>16%</td>
<td>47%</td>
</tr>
</tbody>
</table>

- 23,556 events
- 11,608 events

Among Patients on RAASi at Submaximum Dose

<table>
<thead>
<tr>
<th>Percent of Hyperkalemia Events</th>
<th>Mild Hyperkalemia (Potassium 5.1-5.4 mEq/L)</th>
<th>Moderate-to-Severe Hyperkalemia (Potassium ≥5.5 mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintained Dose</td>
<td>61%</td>
<td>24%</td>
</tr>
<tr>
<td>Discontinued</td>
<td>47%</td>
<td>27%</td>
</tr>
</tbody>
</table>

- 85,567 events
- 43,170 events

Consequences of Hyperkalemia

% of Patients Who Experienced Adverse Outcomes or Mortality by Prior RAASi Dose

Consequences of Hyperkalemia

- Hyperkalemia is the #1 reason why recommended RAASi treatments are discontinued.
- As a result, patients may not reap the full potential of these therapies on reducing risks of clinical outcomes important to them.
- Strategies are needed to better manage hyperkalemia in these patients and maintain RAASi therapy longer.
- Whether an intervention that allows prolonged RAASi treatment actually improves patient outcomes is currently theoretical and must be established through rigorous trials.
Management (Treatment) of Hyperkalemia

Need to distinguish between acute treatment and chronic treatment/management

**Acute:**
- Cell membrane “stabilization”
- Reduction of Serum $[K^+]$
  - Redistribution into cells
  - Elimination from the body

**Chronic:**
- Dietary interventions
- Risk factor exposure management
- Decreased uptake through GI tract
- Increased excretion (GI, kidney)
Acute Management (Treatment) of Hyperkalemia

Acute redistribution of [K+] to intracellular space:
• Beta$_2$-receptor agonists
• Insuline (+glucose)
• Sodium bicarbonate

Acute Removal:
• Kidney: Diuretics
• GI tract: Potassium binders (sodium polystyrene sulfonate)
• Extracorporeal: hemodialysis, peritoneal dialysis

KDIGO
“Our review (2010), which updates a prior Cochrane systematic review (2005) has highlighted the paucity of evidence to determine the most effective therapy for acute management of hyperkalemia”.
“We included seven studies (241 participants) in this review (2015).“
“Meta-analysis of these seven included studies was not possible due to heterogeneity of the treatments and because many of the studies did not provide sufficient statistical information with their results.“
“Allocation and blinding methodology was poorly described in most studies.“
Acute Management (Treatment) of Hyperkalemia

SYSTEMATIC REVIEW

Continued…

“Evidence for the acute pharmacological management of hyperkalaemia is limited, with no clinical studies demonstrating a reduction in adverse patient outcomes.“

“Of the studied agents, salbutamol via any route and IV insulin-dextrose appear to be most effective at reducing serum potassium.“

“There is limited evidence to support the use of other interventions, such as IV sodium bicarbonate or aminophylline.“

“The effectiveness of potassium binding resins and IV calcium salts has not been tested in RCTs and requires further study before firm recommendations for clinical practice can be made.“
Acute Management (Treatment) of Hyperkalemia

SYSTEMATIC REVIEW

RESEARCH ARTICLE

Optimal Dose and Method of Administration of Intravenous Insulin in the Management of Emergency Hyperkalemia: A Systematic Review

Ziv Hareli1,2,3, Kamel S. Kamel1,2,3*

“The limited data available in the literature shows no statistically significant difference between the different regimens of insulin used to acutely lower serum K+ concentration”.
Acute Management (Treatment) of Hyperkalemia

Novel potassium binders

- Patiromer
- Sodium circonium cyclosilicate (ZS-9)

Not sufficient evidence to come to a reasonably firm conclusion regarding the utility in acute management of hyperkalemia. Although:

Kosiborod M, et al. JAMA 2014;312:2223-33
Summary

Hyperkalemia is common in patients with CKD and its risk increases with reduced kidney function.

In parallel, other precipitating factors gain importance:

- Dietary potassium intake
- Other pharmacotherapies

Hyperkalemia associates with short- and long-term risks of undesired outcomes:

- Death, cardiovascular events, hospitalization, others

Hyperkalemia contributes to discontinuation of RAASi therapies.
Thank You