Novel Approaches to Understanding Risks and Management of Hyperkalemia

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Important Disclosures

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There are 4 main objectives that I’d like to cover with you today:

• First, to review the definition, prevalence, and risk of hyperkalemia in certain populations
• Second, to review why RAASi are recommended in treatment guidelines
• Third, to understand how hyperkalemia can be a barrier to implementing guideline-recommended therapies for chronic kidney disease and heart failure
• And finally, to describe current approaches for managing hyperkalemia
• The definition of hyperkalemia, or elevated serum potassium, can vary across clinical studies and from setting to setting (e.g., different laboratories and different hospitals).

• The normal serum potassium range is typically considered to fall within 3.8 to 5.0 mEq/L; however, this can vary.

• In published studies, the cutoff for hyperkalemia is typically 5.0, 5.5, or 6.0 mEq/L.
Hyperkalemia Is A Serious Chronic Risk in CKD and HF Patients

- Hyperkalemia:
  - Varying definitions
  - Most common is >5.0 mEq/L
  - May present as an asymptomatic condition
  - Has serious risks that may include:
    - Life-threatening cardiac arrhythmias\(^1\)
    - Sudden cardiac death\(^3\)-\(^5\)

- Most commonly affects patients with CKD, with or without diabetes or heart failure particularly if receiving RAASi therapy\(^2\), \(^6\)-\(^8\)

- Treatment with RAASi reduces adverse CV outcomes and slows progression to ESRD\(^9\)-\(^12\)
  - But, RAASi can raise serum K\(^+\) levels\(^9\)-\(^11\)

Based on analysis of 1.63 million persons aged 5+ years with potassium values on 2 dates (2008-2012), with >1 K⁺ value between 2.5 and 10 mEq/L during 2008-2012.

Control population composed of patients ≥65 years without CKD stages 2-5, heart failure, diabetes, or ESRD.

Hyperkalemia defined as highest reported potassium value ≥5.1 in 2008-2012.
- HCUPnet is a free, online query system based on data from the Healthcare Cost and Utilization Project (HCUP).

- It provides access to health statistics and information on hospital inpatient and emergency department utilization.

- In 2011, nearly 70,000 emergency department visits were related to hyperkalemia; of these, approximately 45,000 were for Medicare members.

- Nearly 40,000 hospitalizations were also reported for patients with hyperkalemia; of these, nearly 30,000 were for Medicare members.

- These hospitalizations for Medicare admissions equaled nearly $700 million in costs and the average length of stay was 3.2 days.

- Based on these data, hyperkalemia represents a burden on our health care system.
• These data highlight that in a younger or elderly population with cardiovascular comorbidities, there is a significant increase in mortality risk at serum potassium levels below 4.1 mEq/L and above 5.0 mEq/L. These data were consistent in patients between 45 and 64 years of age and greater than or equal to 65 years of age.

• Confidence limits around these curves were extremely tight, as represented by the shaded area around the blue and orange lines.

• These increases remained after adjustment for patient comorbidities.
Limitations of RAASi utilization due to Hyperkalemia
The Use of ARBs Delays the Progression of Chronic Kidney Disease

Primary Renal Endpoint: Death, Progression to Dialysis, or Doubling of Serum Creatinine\textsuperscript{1,2}

**IDNT**
Irbesartan Diabetic Nephropathy Trial (proteinuria $\geq 900$ mg/day and serum creatinine range 1.0-3.0 mg/dL)\textsuperscript{1}
20% lower risk ($P=0.02$) of primary renal endpoint with ARB\textsuperscript{2}
- **32.6%** irbesartan group
- **39.0%** placebo group

**RENAAL**
The Reduction in Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (proteinuria $\geq 500$ mg/day, and serum creatinine between 1.3 and 3.0 mg/dL)\textsuperscript{2}
16% lower risk ($P=0.02$) of primary renal endpoint with ARB\textsuperscript{2}
- **43.5%** losartan group
- **47.1%** placebo group

ARBs: angiotensin II receptor blockers; NIDDM: non-insulin-dependent diabetes mellitus.

- The use of ARBs delays the progression of chronic kidney disease defined as death, progression to dialysis, or a doubling of the serum creatinine.
- These data are one of the reasons why guidelines recommend ARBs as the cornerstone therapy for patients with diabetic nephropathy.
• Despite this careful patient selection and monitoring, rates of hyperkalemia were 18.6% with irbesartan using a >6.0 mEq/L cutoff and 10.8% with losartan using >5.5 mEq/L as a cutoff.

• These rates of hyperkalemia were 2 to 3 times higher than seen with placebo.
### Randomized Trials With Built-in Design Features to Minimize Risk of Hyperkalemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Exclusion Criteria Related to Hyperkalemia Risk</th>
<th>Monitoring</th>
<th>Hyperkalemia Treatment</th>
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</table>
| RENAAL¹ | - K⁺ levels >5.5 mEq/L  
- Chronic use of NSAIDs  
- Serum creatinine >3.0 mg/dL | - Week 1  
- Month 1  
- Month 3  
- 3-month intervals over study duration | Not described |
| IDNT² | - K⁺ levels outside of “normal range”  
- Serum creatinine >3.0 mg/dL | - Month 3  
- 3-month intervals over study duration | - Serum K⁺ >6.0 mEq/L required corrective measures and the possible discontinuation of study drug  
- Attempts were made to keep patients on the highest dose of study drug that avoided further episodes of hyperkalemia* |

*Measures included the use of loop diuretics, mineralocorticoids, or potassium exchange resins.

NSAID: nonsteroidal anti-inflammatory drug.


- It is important to note that these 2 pivotal trials built in design features within their protocols to minimize the risk of hyperkalemia.
- RENAAL excluded patients with serum potassium levels >5.5 mEq/L, patients using NSAIDs, and patients with a serum creatinine >3.0 mg/dL. Similarly, IDNT excluded patients with elevated serum potassium and patients with serum creatinine >3.0 mg/dL.
- In addition, close monitoring of these patients was conducted at 3-month intervals.
- IDNT also incorporated measures to treat hyperkalemia over 6.0 mEq/L to try to keep patients in the study.
This study provides a snapshot of the key studies of RAAS inhibitors in patients with heart failure.

<table>
<thead>
<tr>
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<th>Post-MI Low EF</th>
<th>Mild-Mod CHF Low EF</th>
<th>CHF Severe HF</th>
<th>CHF Preserved EF</th>
</tr>
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<tbody>
<tr>
<td>ACEI&lt;sup&gt;1&lt;/sup&gt;</td>
<td>AIRE SAVE</td>
<td>SOLVD</td>
<td>CONSENSUS</td>
<td>PEP-CHF (perindopril)</td>
</tr>
<tr>
<td>MRA</td>
<td>EPHESIS&lt;sup&gt;1&lt;/sup&gt; (epilrenone)</td>
<td>EPHASIS&lt;sup&gt;1&lt;/sup&gt; (epilrenone)</td>
<td>RALE&lt;sup&gt;1&lt;/sup&gt; (spironolactone)</td>
<td>TOPCAT&lt;sup&gt;2&lt;/sup&gt; (spironolactone)</td>
</tr>
<tr>
<td>ARB&lt;sup&gt;1&lt;/sup&gt;</td>
<td>OPTIMAAL VALIANT</td>
<td>ELITE-II HEALL VAL-HeFT CHARM</td>
<td></td>
<td>CHARM-Preserved I-PRESERVE</td>
</tr>
<tr>
<td>ARNI&lt;sup&gt;3&lt;/sup&gt;</td>
<td>PARADIGM-HF (LCZ-696)</td>
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I think we all know from clinical practice that hyperkalemia is a major reason for either not starting or discontinuing RAASi therapy in patients with CKD.

Surprisingly, there is little published information on how frequently patients are not receiving RAASi therapy because of hyperkalemia.

In this retrospective review of 279 patients with stages 3-5 CKD, a baseline eGFR of 33 mL/min/1.73 m², and a baseline serum potassium of 4.7 mEq/L, hyperkalemia was a common reason for not starting RAASi therapy and the number 1 reason for discontinuing RAASi therapy.
The guidelines are consistent when providing recommendations related to prescribing RAASi to patients at risk for hyperkalemia.

The K/DOQI, NICE, the Heart Failure Society of America, and the American College of Cardiology/American Heart Association all recommend avoiding RAASi therapy in patients with serum potassium >5.0 mEq/L.

In addition, the European Society of Cardiology and K/DOQI guidelines both recommend discontinuing or lowering the dose of RAASi if serum potassium levels rise above 5.5 mEq/L.

And finally, the NICE guidelines from the United Kingdom recommend stopping RAASi if hyperkalemia >6.0 mEq/L develops.
This slide is a schematic of various treatment options for hyperkalemia.

On the far left are the key agents used in the emergency department for hyperkalemia.

Calcium gluconate salt is commonly given, especially in the presence of ECG changes to stabilize cell membranes. The effect of the infusion starts in 1–3 minutes and lasts 30–60 minutes.

Insulin works by pushing potassium from the serum into the cells.

Insulin works within 10–20 minutes and lasts for 4–6 hours. Dextrose should be given with insulin, unless the serum glucose is above 250 mg/dL, because of the risk of developing hypoglycemia due to insulin therapy.

Effects of nebulized beta2-agonists start at about 30 min and last for 2–6 h.

Intravenous bicarbonate has no role in the acute treatment of hyperkalemia and is much less effective when hyperkalemia is not related to metabolic acidosis. In patients with metabolic acidosis, a delayed drop in plasma potassium concentration can be seen after 4–6 hours of isotonic bicarbonate infusion.

Dialysis and loop diuretics are also therapies to eliminate potassium from the body. However, the amount of potassium removed is variable and the time to start dialysis prevents use in an emergent setting.

When loop diuretics are given IV, urine flow usually increases within minutes and persists for approximately 4 to 6 hours. Close monitoring of the patient’s volume status and other electrolyte concentrations is required.

Kayexalate, or sodium polystyrene sulfonate, has a warning related to intestinal necrosis and a precaution related to sodium load. The effect of SPS on plasma potassium concentration is slow; the full effect may take up to 24 hours and usually requires repeated
doses up to four times a day.

- Therefore, putting patients on a difficult-to-adhere-to low potassium diet or stopping or reducing renoprotective RAASi therapy is often the only option.
Kayexalate (sodium polystyrene sulfonate) is the only approved product for the treatment of hyperkalemia.

- It was approved by the FDA in 1958.
- At the time of approval, less robust data were required to demonstrate efficacy than for current products.
- In addition, in 2009 and 2011 the FDA added additional gastrointestinal safety warnings and precautions to the label.

<table>
<thead>
<tr>
<th>PROPERTY</th>
<th>Kayexalate</th>
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<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Potassium binder that is ingested and exchanges sodium for potassium in the GI tract to reduce serum potassium levels</td>
</tr>
<tr>
<td>Safety and Tolerability</td>
<td>Intestinal necrosis warning, GI side effects</td>
</tr>
<tr>
<td>Design/Active Pharmaceutical Ingredient</td>
<td>Bulk gel material, nonuniform size, and fine, brown, clay-like consistency</td>
</tr>
<tr>
<td>Counterion</td>
<td>NaCl-loaded, about 1/3 is delivered to the body</td>
</tr>
<tr>
<td>Efficacy Data</td>
<td>Efficacy and safety not studied in large, systematic, long-term trials</td>
</tr>
<tr>
<td>Dosing</td>
<td>Average daily adult dose is 15g-60g/day</td>
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• Since Kayexalate uses sodium to exchange for potassium in the gastrointestinal tract, there is a precaution in the label related to sodium load.

• This is important because certain patients cannot tolerate even a small increase in sodium load.
A low potassium diet is extremely difficult to adhere to, since many foods are rich in potassium.

Trying to adhere to a low potassium diet can be challenging for patients and caregivers.

In addition, the DASH Diet, which can reduce blood pressure and delay progression of kidney disease, is rich in high-potassium food.

Hence, due to the risk of hyperkalemia, we advise our patients to avoid many of the healthy foods included in the DASH diet. Since they already have so many dietary restrictions this may impact their quality of life.
Limitations of Long-Term Hyperkalemia Management Strategies

<table>
<thead>
<tr>
<th>Treatment focuses on diet changes, removal of therapies that increase serum K⁺, and Kayexalate</th>
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<tr>
<td><strong>RAASi reduction</strong></td>
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<tr>
<td>Limiting the dose or discontinuing treatment of drugs known to be effective in these populations¹</td>
</tr>
<tr>
<td><strong>Kayexalate</strong></td>
</tr>
<tr>
<td>Warnings related to serious gastrointestinal adverse events²</td>
</tr>
<tr>
<td>Precaution related to sodium²</td>
</tr>
<tr>
<td><strong>Dietary K⁺ restriction of 50-75 mEq/day¹</strong></td>
</tr>
<tr>
<td>Potassium is common ingredient in many foods³</td>
</tr>
<tr>
<td>Restricts consumption of healthy foods (such as the DASH diet)³</td>
</tr>
<tr>
<td>Low K⁺ diet often expensive³</td>
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</tbody>
</table>


- In summary, long-term management of hyperkalemia has numerous limitations.
- Reducing RAASi may impact the delay in disease progression.
- Kayexalate has serious GI warnings and sodium load precautions that can limit its use.
- A low potassium diet is difficult to implement and contrary to a healthy diet of fruits and vegetables.
Hyperkalemia is highly prevalent in patients with CKD and/or heart failure.

- As the kidney is the primary route for potassium elimination, CKD is associated with chronic risk of hyperkalemia.
- The use of RAASi to preserve kidney function in CKD further increases this risk.

Hyperkalemia contributes to ED visits, hospitalizations, and health care costs.

Hyperkalemia is associated with increased mortality.

Current treatment options including low-potassium diets and sodium polystyrene sulfonate have significant limitations.

Down-titration or discontinuation of RAASi is a common consequence of hyperkalemia.