Novel Approaches to Understanding Risks and Management of Hyperkalemia

[Name]
[Date]

[Conference Name 2015]
Important Disclosures

• This program is sponsored and paid for by Relypsa, Inc.
• The presenter is an active consultant for and receiving payment from Relypsa, Inc.
• This program is not CME accredited and may not be used for CME accreditation.
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 (eg, 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. The upper limit of normal in published studies is typically 5.0, 5.5, or 6.0 mEq/L.
In the general population, hyperkalemia is rare (0%-6% of population).

In hospitalized patients, the incidence of hyperkalemia is slightly increased (1%-10%).

In contrast, in patients with chronic kidney disease, hyperkalemia ranges between 5% and 50%.

Certain factors can increase the risk of hyperkalemia including older age, heart failure, comorbid diabetes, and the use of multiple medications that impact the excretion of potassium.

Renin-angiotensin-aldosterone system inhibitors (RAASi) are some of the key medications associated with hyperkalemia in these patients.

The most clinically relevant impact of hyperkalemia is on the heart, but there can be neuromuscular manifestations including diarrhea, abdominal pain, myalgia, and paralysis.
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.
Hyperkalemia Contributes to ED Visits, Hospitalizations, and Health Care Costs

- In 2011, the estimated total annual hospital charges for Medicare admissions with hyperkalemia as primary diagnosis were ~$697 million
- Average Medicare LOS was 3.2 days; mean charges of $24,085 per stay
- One-third were discharged to another short-term hospital, institution, or home health care

ED: emergency department, LOS: length of stay


- 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. This effect was even more pronounced in patients >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.
**ARBs Reduced Composite Endpoint in Diabetic Nephropathy**

**Primary Renal Endpoint: Death, Progression to Dialysis, or Doubling of Serum Creatinine**¹,²

**IDNT**
Irbesartan Diabetic Nephropathy Trial (proteinuria ≥900 mg/day and serum creatinine range 1.0-3.0 mg/dL)³
- 20% lower risk (P=0.02) of primary renal endpoint with ARB²
  - 32.6% irbesartan group
  - 39.0% placebo group

**RENAAL**
The Reduction in Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (proteinuria ≥500 mg/day, and serum creatinine between 1.3 and 3.0 mg/dL)²
- 16% lower risk (P=0.02) of primary renal endpoint with ARB²
  - 43.5% losartan group
  - 47.1% placebo group

---

- 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.
RAASi Have Been Extensively Studied in Patients With Heart Failure (HF) and Post-Myocardial Infarction (MI)

<table>
<thead>
<tr>
<th></th>
<th>Post-MI Low EF</th>
<th>Mild-Mod CHF Low EF</th>
<th>CHF Severe HF</th>
<th>CHF Preserved EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI(^1)</td>
<td>AIRE SAVE</td>
<td>SOLVD</td>
<td>CONSENSUS</td>
<td>PEP-CHF (perindopril)</td>
</tr>
<tr>
<td>MRA</td>
<td>EPHESUS(^1)</td>
<td>EMPHASIS(^1)</td>
<td>RALES(^1)</td>
<td>TOPCAT(^2)</td>
</tr>
<tr>
<td></td>
<td>(eplereonone)</td>
<td>(eplereonone)</td>
<td>(spironolactone)</td>
<td>(spironolactone)</td>
</tr>
<tr>
<td>ARB(^1)</td>
<td>OPTIMAAL VALIANT</td>
<td>ELITE-II HEALL VAL-HeFT CHARM</td>
<td>CHARM-Preserved I-PRESERVE</td>
<td></td>
</tr>
<tr>
<td>ARNI(^3)</td>
<td>PARADIGM-HF (LCZ-696)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


- This study provides a snapshot of the key studies of RAAS inhibitors in patients with heart failure.
• RAASi clinical trial populations are carefully selected to exclude patients at high risk for hyperkalemia.
• That is why the incidence of hyperkalemia in "real-world" practice far exceeds that observed in clinical trials.
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 definition of hyperkalemia, or elevated serum potassium, can vary across clinical studies and from physician to physician. The normal serum potassium range is typically considered between 3.8 and 5.0 mEq/L; however, this can vary. A common definition is >5.0 mEq/L.

Hyperkalemia can cause depolarization of the cell membrane, which can lead to muscle weakness and/or life-threatening cardiac arrhythmias.

Hyperkalemia commonly affects patients with CKD, with or without diabetes or heart failure, particularly if they are receiving RAASI therapy.

Treatment with RAASI reduces adverse cardiovascular outcomes and slows progression to ESRD; however, RAASI can raise serum potassium levels.
This study is a schematic of various treatment options for hyperkalemia.

On the far left are the key agents used in the emergency department for hyperkalemia: insulin and beta-adrenoreceptor antagonists. These agents work by pushing potassium from serum into the cells.

Calcium gluconate salt is commonly given, especially in the presence of ECG changes to stabilize cell membranes.

Dialysis, loop diuretics, and sodium bicarbonate are also therapies to eliminate potassium from the body, although I will tell you in a moment why sodium bicarbonate may not be a good option for certain patients.

Finally, for longer-term options to manage persistent hyperkalemia, we are left with few options.

Kayexalate, or sodium polystyrene sulfonate, has a warning related to intestinal necrosis and a precaution related to sodium load; and long-term ongoing use of SPS has not been systematically studied.

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.
• 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 loads.
Low $K^+$ Diet Is Restrictive and Adherence May Be Difficult

- Foods rich in potassium content are pervasive
- Consequently, strictly adhering to a low potassium diet can be challenging for patients and caregivers
- A low potassium diet is counter to the DASH (Dietary Approaches to Stop Hypertension) diet
  - DASH Diet is recommended by the National Kidney Foundation (NKF) and the American Heart Association (AHA)
  - DASH Diet is a recognized treatment for hypertension, heart disease, and kidney disease and can slow both kidney and heart disease progression
  - However, DASH Diet is rich in high $K^+$ foods

- 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 kidney progression, is rich in high-potassium food.
- Hence, hyperkalemia forces us to tell our patients to avoid many healthy foods, which also has a significant impact on the patient’s quality of life.
In summary, long-term management of hyperkalemia has numerous limitations.

A low potassium diet is difficult to implement and contrary to a healthy diet of fruits and vegetables.

Reducing RAASi is stopping the very medications that can delay disease progression.

Kayexalate has serious GI warnings and sodium load precautions that can limit its use.

---

**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>
</tr>
</thead>
<tbody>
<tr>
<td>RAASi reduction</td>
</tr>
<tr>
<td>Kayexalate</td>
</tr>
<tr>
<td>• Precaution related to sodium²</td>
</tr>
<tr>
<td>Dietary K⁺ restriction of 50-75 mEq/day¹</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>
</tr>
</tbody>
</table>

---

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.
Questions