Discussion
Clinical evidence shows that increased serum potassium above the normal range in patients with CKD is associated with a higher mortality rate, especially in patients with advanced age and comorbidities (Figures 2). Hyperkalemia is common in patients with CKD due to multiple risk factors. Management strategies should be based on the degree and cause of hyperkalemia. Conventional treatments focus on intermittent management of hyperkalemia and may pose safety risks. New agents in the potassium binder class may allow for improved management of hyperkalemia.

Figure 2. All-Cause Mortality Associated with Serum Potassium Levels in Patients with CKD Not on Dialysis 36

Multivariable adjusted log hazard ratios (solid line) and 95% confidence intervals (dashed lines) of all-cause predialysis mortality associated with serum potassium levels in the entire study population (N=127).


References
**Introduction**

Hyperkalemia is a well-known complication of chronic kidney disease (CKD), since the kidneys are the main route for potassium excretion. Hyperkalemia is associated with increases in all-cause mortality and hospitalizations. Treatment with renin-angiotensin-aldosterone system inhibitors (RAASi) is often associated with increased risk of hyperkalemia in patients with CKD, which may lead to dose reduction or discontinuation. While the main therapeutic goal of treating hyperkalemia is to reduce potassium loss, there have been limited treatment options to accomplish this safely and effectively.

**Underlying Risk of Hyperkalemia in CKD**

Patients with CKD have a high risk of hyperkalemia, due in part to the effects of kidney dysfunction on potassium homeostasis. Research shows that hyperkalemia is also frequently seen in patients with cardiovascular disease (CVD) who are taking RAASi. Independent predictors of hyperkalemia include advanced age, CVD, diabetes, heart failure, and RAASi use. Therefore, patients with CVD treated with RAASi, especially at a higher dose or treatment with more than one RAASi, are at very high risk for hyperkalemia. As a result, hyperkalemia is the major barrier against the optimal use of RAASi in patients with CVD.5, 6

**Importance of RAAS Blockade in CKD**

To prevent CKD progression clinical practice guidelines suggest that an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) be used in diabetic adults with CKD and urinary albumin-creatinine ratio >30-200 mg/g (or equivalent), and recommend that an ACE-I or ARB be used in both diabetic and non-diabetic adults with CKD and urinary albumin-creatinine ratio >300 mg/g (or equivalent).1, 4 However, combination therapy with an ACE-I and ARB should not be used in non-diabetic patients and hypertension since studies show more adverse events, including severe hyperkalemia, kidney dysfunction, and hypertension, without any increase in benefits.4, 5, 10

Hyperkalemia and worsening kidney function can develop in some CKD patients after initiating an ACE-I or an ARB, particularly if RAASi can lower glomerular filtration rate and can decrease potassium secretion. Therefore, it is important to monitor serum potassium and estimated glomerular filtration rate (eGFR) within several weeks of starting a RAASi. Discontinuing these drugs is helpful in controlling or treating hyperkalemia, but the disadvantage to doing this is that it increases the risk for kidney disease progression and cardiovascular events.

**Diagnosis and Evaluation of Hyperkalemia**

The spectrum of hyperkalemia ranges from single episodes of hyperkalemia, sustained hyperkalemia, recurrent hyperkalemia, or severe cases that require dialysis, but what constitutes mild, moderate, or severe hyperkalemia is not consistently defined. Additionally, the cardiotoxic effects of a particular potassium concentration depend on the baseline value, the rate of increase in potassium concentration, as well as the acid base status, and serum calcium concentration.11 Pseudohyperkalemia must also be ruled out. Causes of pseudohyperkalemia include release of potassium from red blood cells in the test tube because of venipuncture trauma or prolonged storage before analysis, and very high platelet counts (>500,000 per microliter). Pseudohyperkalemia is never temporary and patients should consider separating SPS dosing from other medications taken by mouth at least 6 hours.

**Hyperkalemia and worsening kidney function can develop in some CKD patients after initiating an ACE-I or an ARB, particularly if RAASi can lower glomerular filtration rate and can decrease potassium secretion. Therefore, it is important to monitor serum potassium and estimated glomerular filtration rate within several weeks of starting a RAASi. Discontinuing these drugs is helpful in controlling or treating hyperkalemia, but the disadvantage to doing this is that it increases the risk for kidney disease progression and cardiovascular events.**

**The cause of hyperkalemia has to be determined to prevent future episodes. Figure 1 shows an etiologic workup of hyperkalemia based on GFR and aldosterone levels.**

**Benefits and Risks of Conventional Management**

**Non-Emergent Treatment**

Clinicians should individualize therapeutic strategies by considering the degree and cause of hyperkalemia. The non-emergent treatment can be divided into four mechanisms of action: (1) restriction – diet, supplements, herbs; (2) excretion – thiazide or loop diuretics, euvolemic (or hypovolemic) furosemide; (3) removal – dialysis; and (4) redistribution – sodium bicarbonate (does not affect total body potassium levels).12

**Potassium Restriction**

Potassium restriction can be achieved by reducing potassium-rich foods such as fruits and vegetables are part of a heart-healthy diet, and the serum potassium level. Many potassium-rich foods such as potatoes, bananas, and dried fruits contain high potassium levels. The most effective method to reduce dietary potassium intake is to choose foods that are low in potassium. Foods such as fruits, vegetables, and lean meats are generally lower in potassium than high-potassium foods such as potatoes, bananas, and dried fruits. Patients with limited GFR.

**Sodium Bicarbonate Infusion**

Sodium bicarbonate infusion can shift potassium from the extracellular to intracellular space by increasing blood pH. The onset of action is 5–10 minutes and the duration of effect is about 2 hours.14 In general, the efficacy of bicarbonate on hyperkalemia is controversial, and some studies suggest a lack of efficacy.15, 16 This therapy only has a moderate effect on hemodialysis patients when given as a long infusion, and the sodium load may worsen pre-existing hypertension and heart failure.16

**Emergency Treatment**

The life-threatening nature of severe hyperkalemia requires immediate attention, which entails acute medical interventions and occasionally hemodialysis.17 Details regarding emergency treatment are described elsewhere.

**Novel Treatment Options for the Management of Hyperkalemia**

New potassium-lowering medications may provide renewed opportunities for improved management of hyperkalemia. A sodium-free, non-absorbed potassium binder for the treatment of hyperkalemia was recently approved by the FDA. A second potassium binder agent, which is an insoluble, non-absorbed cation exchanger, is currently under clinical investigation.18

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**Figure 1. Diagnostic Algorithm in Hyperkalemia**

<table>
<thead>
<tr>
<th>GFR &gt;15mL/min/1.73m²</th>
<th>GFR &lt;15mL/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>High potassium load</td>
<td>Decreased renal potassium excretion</td>
</tr>
<tr>
<td>+ Acute renal failure</td>
<td>+ Increased potassium load</td>
</tr>
<tr>
<td>+ Potassium-rich diet</td>
<td>+ Supplementation (oral)/Potassium-rich diet</td>
</tr>
<tr>
<td>+ Tumor lysis/hemolysis</td>
<td>+ Electrolyte imbalance</td>
</tr>
<tr>
<td>+ Diabetes</td>
<td>+ Hypokalemia</td>
</tr>
</tbody>
</table>

**Figure 2. Management of Hyperkalemia**

<table>
<thead>
<tr>
<th>GFR &gt;15mL/min/1.73m²</th>
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<tbody>
<tr>
<td>+ Post renal transplant</td>
<td>+ Oral potassium binder</td>
</tr>
<tr>
<td>+ Diuretic unresponsiveness</td>
<td>+ Sodium bicarbonate</td>
</tr>
<tr>
<td>+ Acute kidney injury</td>
<td>+ Dialysis</td>
</tr>
<tr>
<td>+ FNA type I/type 2</td>
<td>+ Type 1/2 RTA</td>
</tr>
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Introduction

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Underlying Risk of Hyperkalemia in CKD

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Importance of RAAS Blockade in CKD

To prevent CKD progression clinical practice guidelines suggest that an angiotensin converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) be used in diabetic adults with CKD and urinary albumin-creatinine ratio 30-300 mg/g (or equivalent), and recommend that an ACE-I or ARB be used in both diabetic and non-diabetic adults with CKD and urinary albumin-creatinine ratio >300 mg/g (or equivalent). 5, 6 However, combination therapy with an ACE-I and ARB should not be used in non-diabetic patients with CKD and hypertension since studies show more adverse events, including severe hyperkalemia, kidney dysfunction, and hypertension, without any increase in benefits. 7, 8, 9, 10

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Mild to moderate hyperkalemia is usually asymptomatic. Patients with moderate to severe hyperkalemia may complain of palpitations, nausea, muscle weakness, or paresthesia. However, moderate and especially severe hyperkalemia can lead to cardiac arrhythmias and conduction abnormalities, and may be fatal.

The cause of hyperkalemia has to be determined to prevent future episodes. Figure 1 shows an etiologic workup of hyperkalemia based on GFR and aldosterone levels.

Non-Emergent Treatment

Clinicians should individualize therapeutic strategies by considering the degree and cause of hyperkalemia. Non-emergent treatment can be divided into four mechanisms of action: (1) restriction – diet, supplements, herbs; (2) excretion – thiazide or loop diuretics, cation exchange resins; (3) removal – dialysis; and (4) redistribution – sodium bicarbonate (does not affect total body potassium levels). 13

Potassium Restriction

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<tbody>
<tr>
<td>GFR &lt;60 ml/min/1.73m²</td>
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<tr>
<td>Increased potassium load</td>
</tr>
<tr>
<td>Acute renal failure</td>
</tr>
<tr>
<td>Renin normal</td>
</tr>
<tr>
<td>Aldosterone low</td>
</tr>
<tr>
<td>Sodium polystyrene sulphonate (SPS)</td>
</tr>
<tr>
<td>Potassium &gt;5.5 mmol/l</td>
</tr>
</tbody>
</table>

**Hyperkalemia, hypokalemia, hyporeninemia as:** Intestinal nephrosis, pseudohyperkalemia, urinary tract tumor, hemolysis

**Primary hyperaldosteronism as:** Congenital adrenal hyperplasia, Dpgle, Addison/congential adrenal hyperplasia

<table>
<thead>
<tr>
<th>Hyperkalemia</th>
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</tr>
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<td>Solute-free, non-absorbed potassium binder for the treatment of hyperkalemia</td>
<td>Sodium polystyrene sulphonate (SPS)</td>
</tr>
</tbody>
</table>

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1. Potassium-rich diet
2. Electrolyte solution
3. Hypokalemia
4. Decreased renal potassium-excretion
5. Increased urinary potassium excretion
6. Hypoaldosteronism
7. Hyporeninemic
8. Congenital adrenal hyperplasia
9. Addison's/congenital adrenal hypoplasia
10. Obstructive uropathy
11. Elective/etiologic workup:
   1. Comprehensive laboratory workup
   2. Review of medications
   3. Electrocardiogram (ECG)
   4. Assessment of hydration status
   5. Tumor lysis/hemolysis

---

**Management of Hyperkalemia:**

1. Assess serum potassium level
2. Identify the cause of hyperkalemia
3. Initiate appropriate treatment
4. Monitor for response and side effects

---

<table>
<thead>
<tr>
<th>Emergency diagnostic workup:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Assessment of cardiac function, kidneys, and urinary tract</td>
</tr>
<tr>
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</tr>
<tr>
<td>3. Electrocardiogram (ECG)</td>
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</tbody>
</table>

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**Potassium Restriction:**

1. Dietary potassium restriction
2. Diuretics
3. Cation exchange resins
4. Sodium bicarbonate

---

**Potassium Redistribution:**

1. Potassium binding agents
2. Dialysis

---

**Emergency Treatment:**

1. Sodium bicarbonate infusion
2. Dialysis
Discussion
Clinical evidence shows that increased serum potassium above the normal range in patients with CKD is associated with a higher mortality rate, especially in patients with advanced age and comorbidities (Figures 2, 3). Hyperkalemia is common in patients with CKD due to multiple risk factors. Management strategies should be based on the degree and cause of hyperkalemia. Conventional treatments focus on intermittent management of hyperkalemia and may pose safety risks. New agents in the potassium binder class may allow for improved management of hyperkalemia.

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Multivariable adjusted log hazards (solid line) and 95% confidence intervals (dashed lines) of all-cause predialysis mortality associated with serum potassium levels in the entire study population (n=1,273).


References

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