Introduction

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Potassium is the most abundant intracellular cation and is essential for normal cellular function. Hyperkalaemia is defined as a potassium level ≥5.0 mmol/L and is common in patients with heart failure, renal failure, and diabetes.

Derangements of potassium regulation often lead to life-threatening neuromuscular, gastrointestinal, and cardiac abnormalities if left untreated.

Understanding hyperkalaemia and improving strategies to treat it and/or prevent it needs a clear understanding of potassium haemostasis in disease states, and of its association with diet and with drugs interfering with potassium haemostasis such as the renin-angiotensin-aldosterone system inhibitors (RAASi). Epidemiology of hyperkalaemia has received much attention. However, most reports suffer from definition issues, are based on single or limited number of potassium measurements, usually missing the dynamics of fast or slow potassium changes and are confounded by a number of co-variates difficult to adjust for. As a result, the reported association between hyperkalaemia and mortality is not consistent and varies in trial and real-world data. Importantly, hyperkalaemia and more so, concern about hyperkalaemia in daily practice is one of the most frequent cause of discontinuation or failure to initiate or up-titrate life-saving RAASI therapy to guideline recommended dosages. This creates a typical double whammy situation where hyperkalaemia may directly impact negatively clinical outcomes, but also indirectly as the result of depriving patients from optimal RAASI therapy.

In an emergency, serious hyperkalaemia is poorly defined. Treatment efficacy is questionable and strategies are not evidence-based, dialysis being the ultimate treatment. The role of potassium binders in the emergency setting is unclear. Recent and ongoing studies with the newest agents will likely provide better evidence based guidelines.

Chronic hyperkalaemia has been primarily managed by dietary restrictions and cessation or modification of inciting agents, with alternative options being increased potassium excretion in the kidney through diuretic therapy, and potassium elimination in the gastrointestinal tract with sodium polystyrene sulfonate (SPS). This drug has poor palatability exposing to poor adherence, and also significant safety issues which might have been an issue had this drug been submitted to the current strict regulatory requirements for drug approval.

Patiromer and sodium zirconium cyclosilicate are new potassium binders with some similar yet several different pharmacological properties. These are developed in a specific chapter of this compendium. Both agents have been shown in randomized trials to significantly reduce serum potassium in patients with hyperkalaemia, including in patients on RAASI. Additional research should focus on their long-term effects/safety profiles and drug-drug interactions. Head-to-head comparison to SPS and cost-effectiveness studies may help better guide implementation and reimbursement. Indeed, these new agents may likely help long-term management of hyperkalaemia that SPS, because of tolerability issues, has been unable to achieve.

In cardiology and nephrology, education about hyperkalaemia is much needed. Clinicians should know that hyperkalaemia is predictable, reversible, manageable, and preventable. They should learn how to identify risk situations, how to educate patients about diet and drugs interfering with potassium homeostasis, and how to monitor potassium levels more intensively in risk situations.

Clinicians face the challenge of finding a balance between optimizing life-saving RAASI therapy and minimizing hyperkalaemia-associated risk. They should learn how to manage dosages of life saving RAASI drugs without necessarily discontinuing them definitively. Actually, the clinical benefits of RAASI drugs appear to be preserved in patients even when these agents cause mild or moderate hyperkalaemia.

Potassium binders allow the maintenance (or increase) of RAASI doses maintaining serum potassium in the safe zone. Whether this may result in improved outcome should be investigated in appropriate trials.

Similarly, future trials need to focus on use of these agents to improve outcomes in Stages 4 and 5 chronic kidney disease (CKD).

The recent availability of the potassium binders patiromer and sodium zirconium cyclosilicate (SZC) may lead to a paradigm shift both in the treatment of hyperkalaemia and in enabling RAASI maintenance.

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