

CKD progression: interpreting guidelines through the lens of recent data

CKD and RAASi optimisation

Chronic kidney disease (CKD) is a common disorder affecting over 3.5 million people in the United Kingdom. The number of CKD patients is expected to steadily increase in the upcoming years related to the rise in risk factors such as ageing, obesity, diabetes and hypertension. Besides extensive detrimental effects on patients' overall survival, health and quality of life, CKD presents a high economic burden for the healthcare system, with over half of the annual costs spent on the treatment of end-stage renal disease (ESRD). Therefore, every effort should be made to attenuate disease progression and delay the terminal stage as long as possible.

Existing and novel treatment options for preserving glomerular filtration rate

The globally accepted KDIGO guidelines define CKD as the presence of glomerular filtration rate GFR $<60\text{mL/min/1.73m}^2$ or the presence of markers of kidney damage, e.g. albuminuria, lasting more than three months. Albuminuria is a crucial and powerful independent predictor of renal disease progression but is also strongly associated with cardiovascular morbidity and mortality in CKD patients. It is a more sensitive marker of renal function than GFR and provides an earlier insight into nephron loss. Namely, in patients with type 2 diabetes (T2DM), an eGFR of 60mL/min/1.73m^2 is recorded when already 75% of the renal mass is lost, while microalbuminuria alerts to the loss of only 20% of the renal mass. Efficient proteinuria control, traditionally relying on renin-angiotensin-aldosterone system (RAAS) inhibition, proved potent in delaying ESRD. RAAS blockade was the first intervention that irrefutably conferred renal benefits in patients with diabetic kidney disease and remained the cornerstone of diabetic nephropathy treatment for over two decades. It eventually became an essential intervention in all CKD patients regardless of the underlying renal disease. In the recent years, new agents, such as sodium-glucose transporter protein 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP1) agonists and novel mineralocorticoid antagonists (MRA) have also emerged and already appear to be shaping the future of CKD management as promising strategies to attenuate renal function decline. SGLT2-inhibitors were also initially introduced as antidiabetic medications, but recent results suggest that they may also efficiently reduce GFR decline, risks of major adverse kidney and cardiovascular events and all-cause mortality even in the non-diabetic CKD population. They are therefore steadily securing their place in the protocols for CKD treatment in all patient cohorts. However, despite such tremendous advancements, there remained a residual risk for cardiovascular events in CKD patients with T2DM, thus imposing the need for other agents that could alleviate this burden. MRAs originally had limitations for use in patients with reduced renal function, but a novel class of nonsteroidal MRAs with a unique mode of action that is distinct from currently available steroidal MRAs exhibited efficacy in attenuating progressive kidney disease with negligible side effects, accompanied by the overall benefit of improving cardiovascular outcomes and mortality. Thus, it appears that even the novel treatment options are still relying on RAAS inhibition as the mainstay of kidney protection.



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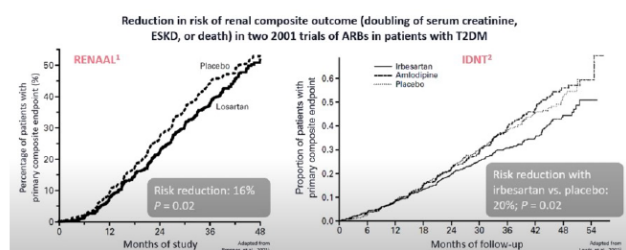


Figure 1.

Effect of RAAS inhibition on renal risk reduction in T2DM patients

RAAS inhibition in advanced CKD

The main objective of employing RAAS inhibitors in managing CKD is to attenuate the exponential decline of GFR from CKD stage 4. Namely, even though RAAS inhibition undoubtedly slows the progression of mild or moderate CKD some studies have suggested that their discontinuation in patients with advanced renal failure may increase estimated GFR or slow its decline. This hypothesis has been refuted in a recent study by Bhandari et al. thus encouraging the use of these agents even in the later stages of CKD. Nevertheless, there remains the major concern of hyperkalemia associated with RAAS inhibition, which is especially common in advanced CKD.

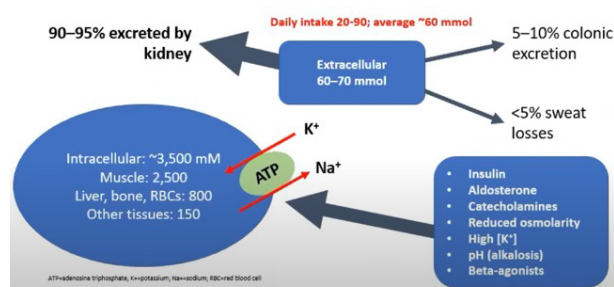


Figure 2.
Potassium homeostasis

Potassium is the most abundant intracellular cation with about 98% of the total pool confined to the intracellular compartment, whereas only 2% is located in the extracellular fluids where it ranges from 3.5 to 5 mEq/L (depending on the local laboratory reference range). Serum potassium levels are affected by the shifts between the intracellular and extracellular space in addition to the total body balance. Potassium is predominantly removed by urine (90%) and to a much lesser extent by faeces (10%). In healthy persons the ingested potassium load does not result in a significant increase in serum potassium as a large cellular storage reservoir (including muscles, liver and bones) buffers plasma potassium upon its intake.

Serum potassium exhibits a U-shaped association with all-cause mortality in CKD, diabetic and heart failure patients, with a significant rise in death rate for every 0.1 mEq/L change in serum potassium <4.0 mEq/L and ≥5.0 mEq/L. Therefore, in practice, RAAS inhibitors are often down-titrated or even discontinued following a hyperkalemia episode, even though cessation of this treatment is also associated with an increased risk for cardiovascular events, hospitalizations and death. This leaves physicians with a conundrum of the best management approach to RAASi-related hyperkalemia.

A hyperkalemic emergency is typically managed by stabilizing the cardiomyocyte membrane with intravenous calcium, shifting potassium intracellularly with insulin-glucose, sodium-bicarbonate

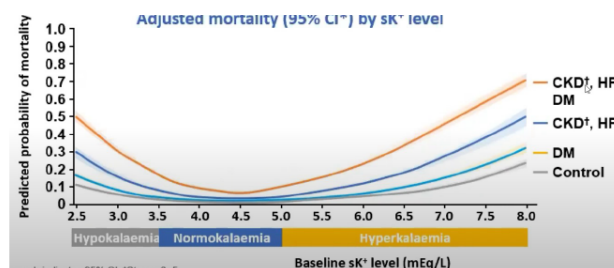


Figure 3.

Relationship between all-cause mortality and serum potassium level in at-risk populations (adapted from Collins, 2017)

and beta-adrenergic agonists, and removing it from the body with loop diuretics. Long-term control of chronic RAASi-related hyperkalemia relies on adequate diet and provoked potassium removal with loop diuretics and gastrointestinal cation exchangers which can increase potassium faecal excretion from the average 6 mmol/day to as high as 40 mmol/day. The novel potassium binders, sodium-zirconium cyclosilicate (SZC) and patiromer, are very efficient and generally well tolerated, as confirmed in several large randomized studies. A minor concern related to sodium load from SZC in heart failure patients has yet to be substantiated, while patiromer is already included in the National Institute for Health and Care Excellence guidelines for treating hyperkalemia as a very useful option for patients on RAAS inhibitors.

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KEY POINTS

- 1 Slowing of eGFR and decreasing cardiovascular events are the key outcomes in CKD patients
- 2 RAAS inhibition remains the cornerstone of CKD treatment, regardless of the presence of diabetes and hypertension
- 3 Novel therapies, such as SGLT2 inhibitors and GLP1-agonists, still leave a significant treatment gap in terms of curtailing the risk for cardiovascular events
- 4 Novel MRAs appear to attenuate eGFR decline, but may sometimes be associated with hyperkalemia
- 5 Different approaches are available for efficient control of hyperkalemia and should be vigorously employed to retain the beneficial effects of RAAS inhibition in the CKD population

Further readings

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