Analysing the impact of a guideline for the use of new potassium binders for treatment of chronic hyperkalaemia to maximise inhibition of renin–angiotensin–aldosterone system (RAAS) within the general nephrology clinic?

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Research article

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Abstract

Background Renin–angiotensin–aldosterone system (RAAS) inhibitors provide significant cardiorenal benefits with improved long-term outcomes for patients. This is most significant for patients receiving maximal RAAS inhibition, but some patients are unable to tolerate this therapy because of hyperkalaemia. Recently published National Institute for Health and Care Excellence (NICE) technology appraisal guidance recommended using sodium zirconium cyclosilicate (SZC) and patiromer for patients with chronic kidney disease (CKD) stage 3b to 5 or heart failure with reduced ejection fraction, who are not taking an optimised dosage of RAAS inhibitor because of hyperkalaemia. Objective Determine the impact of a locally produced guideline on effective implementation of NICE recommendation for use of SZC or patiromer to help maximise inhibition of the renin–angiotensin–aldosterone system within the general nephrology clinic. Methods A local guideline to practically support the implementation of recommendations made by NICE in the chronic use of new potassium binders was produced. One hundred sequential patients in a general nephrology clinic with non-immune chronic kidney disease (CKD 3 to 5) had their electronic records reviewed. Those with an indication for RAAS inhibition were identified. Results Of the 100 consecutive patients audited, 46 were female and 54 were male. The mean age of these patients was 64 and the mean estimated glomerular filtration rate (eGFR) was 33. Sixty-eight patients had an indication for being on RAAS inhibition with only 10 on maximal doses. Of the remaining 58 patients, 26 (45%) were limited by hyperkalaemia. Of these 26 patients, 12 of these patients (46%) had hyperkalaemia associated with an episode of acute kidney injury (AKI). Therefore, 14% of patients attending a general nephrology clinic were identified suitable for SZC and patiromer. Conclusions A significant proportion (14%) of unselected patients attending a general nephrology clinic were not on optimum RAAS inhibition due to hyperkalaemia. These patients would meet the criteria established within a working guideline for the implementation of the chronic use of SZC or patiromer and are likely to attain prognostic long-term benefit by using these new potassium binders to maximise RAAS inhibition. This analysis has implications for renal centres across the UK.

Background

Renin–angiotensin–aldosterone system (RAAS) inhibitors are widely used medications globally providing significant benefits including slowing deterioration of kidney function in patients with diabetic or proteinuric kidney disease [1, 2], improved outcomes for patients with heart failure with reduced ejection fraction [3] and patients with ischaemic heart or cerebral vascular disease [4]. Patients receiving maximal RAAS inhibition achieved the greatest response [2, 5], but some patients are unable to tolerate this because of hyperkalaemia.

Hyperkalaemia can be a potentially life-threatening complication of chronic kidney disease (CKD) associated with an increased risk of major cardiovascular events and mortality [6]. The management of CKD requires a careful balance of the beneficial effects of specific treatments like RAAS inhibitors which
may further exacerbate the occurrence of hyperkalaemia. RAAS inhibitors, which slow CKD progression and improve cardiovascular outcomes, are often routinely discontinued if hyperkalaemia persists [7]. These measures deprive CKD patients from therapies which they could otherwise benefit from, as patients on submaximal or discontinued RAAS inhibition experience worse outcomes [8].

Until now, the long-term pharmacological management of hyperkalaemia in patients with CKD has depended upon low potassium diets, sodium polystyrene sulfonate (SPS), which is a resin that exchanges potassium for sodium within the gastrointestinal tract [9], and the optimisation of metabolic acidosis in patients with more advanced CKD [10]. Using SPS continues to be controversial from its safety and efficacy profile and remains poorly adhered to from its gastrointestinal side effects [11]. Poor compliance to low potassium diets is likewise a challenge [12]. With newly approved potassium-binding agents; like sodium zirconium cyclosilicate (SZC) which is a highly selective non-polymer compound exchanging potassium for sodium and hydrogen ions [13], and patiromer which is a sodium-free non-absorbed cation-exchange polymer [14]; there is potential to better manage hyperkalaemia in patients enabling them to benefit from maximal RAAS inhibition.

Recently published National Institute for Health and Care Excellence (NICE) technology appraisal guidance has recommended using SZC or patiromer for out-patients with persistent hyperkalaemia and chronic kidney disease (CKD) stage 3b to 5 or heart failure with reduced ejection fraction, who are not taking an optimised dosage of RAAS inhibitor because of hyperkalaemia [13]. This recommendation provides both an opportunity and a challenge to both nephrologists and cardiologists. It is now possible to provide patients on insufficient dosages of RAAS inhibitors a means of achieving an improved outcome by maximising this dose but a challenge to ensure that the NICE recommendation is implemented safely and effectively across the nephrology in cardiology outpatient environment. It is important to determine the proportion of patients who would benefit from SZC or Patiromer and meet the inclusion criteria of any guideline produced to operationalise the NICE recommendation. This report supports a strategy to identify patients who would benefit from these newer potassium binding agents with the implementation of a new locally produced guideline (see appendix) for the management of people on submaximal doses of RAAS inhibitors because of hyperkalaemia.

**Methods**

A guideline was produced locally by collaborative multidisciplinary and multi-professional discussion to safely operationalise the implementation of the NICE recommendations relating to the chronic use of SZC and patiromer. To support the implementation of this guideline a clinical audit was conducted of general nephrology patients in one of the largest renal and transplant centres within the United Kingdom.
The audit was approved and registered with the Imperial College Healthcare NHS Trust Clinical Governance Department. The data was recorded anonymously within an excel spreadsheet which was stored on an online hard drive within the secure hospital trust network in accordance with data protection standards.

One hundred unselected sequential patients in a general nephrology clinic with non-immune and non-dialysis chronic kidney disease patients (stages 2 to 5) had their electronic records reviewed, identifying those with an indication for RAAS inhibition.

These indications included:

1. CKD with proteinuria (urine PCR >100mg/mmol)
2. CKD due to diabetes mellitus
3. Heart failure with reduced ejection fraction (HFrEF)
4. CKD in combination with either ischaemic heart or cerebrovascular disease

Maximal RAAS inhibition was defined as the maximum dose for each of the RAAS inhibitors as advised by the summary of product characteristics (SmPC) document in relation to heart failure treatment and renal disease. e.g. Losartan 100mg, Irbesartan 300mg, Ramipril 10mg etc. If these patients were not on maximal RAAS inhibition, then a documented reason was searched for. If no reason was documented, the patient’s results were assessed to identify hyperkalaemia, defined as a documented serum potassium level of >6.0mmol/litre or persistently > 5.5mmol/litre, which was defined as at least two historical episodes of > 5.5mmol/litre.

Where hyperkalaemia had occurred acutely it was only documented as a contra-indication for RAAS inhibition if it occurred without an associated episode of acute kidney injury (AKI). This was determined by assessing the patient’s renal profile in line with the KDIGO (Kidney Disease Improving Global Guidelines) clinical practice guidelines for AKI [15]. In cases where hyperkalaemia limited dosage of RAAS inhibition it was determined whether these patients had received measures to reduce hyperkalaemia including optimisation of metabolic acidosis by examining the patient’s drug history and venous bicarbonate.
Dietary advice is given to all patients in the clinic whose serum potassium levels are above 5.2(mmol/L). Those CKD patients with evidence of chronic metabolic acidosis with serum bicarbonate levels <22(mmol/L) are initiated on oral sodium bicarbonate therapy. The aim to maintain serum bicarbonate levels >22(mmol/L) in such patients. None of these patients are on sodium polystyrene sulfonate (SPS) as it is not a measure used in this clinic to lower potassium levels in CKD.

Results

Data was collected and analysed for 100 consecutive patients. 46 were female and 54 were male with the mean age of these patients being 64. The mean estimated glomerular filtration rate (eGFR) was 33(ml/min/1.73m²) with the lowest eGFR recorded being 7(ml/min/1.73m²) and highest 90(ml/min/1.73m²). Figure 1 shows the number of patients in each CKD stage.

68 patients had at least one of the four (as defined in the methods section) predetermined indications for being on RAAS inhibition with a total of 91 indications from the entire patient group as illustrated in Table 1. Only 10 (15%) patients were on a maximal dose. Of these patients who were on maximum treatment doses 7 were on Irbesartan 300mg, 2 were on Ramipril 10mg with 1 patient on Perindopril 8mg.

Of the remaining 58 patients who were not currently on maximal RAAS inhibition therapy, 26 (45%) were limited by hyperkalaemia and whilst a small number of patients were limited by allergies, intolerances and reluctance, the majority of remaining patients had no documented or obvious reason to explain why they were not initiated on RAAS inhibition. Of the 26 patients who were documented as being limited by hyperkalaemia, 12 of these patients (46%) had hyperkalaemia associated to an episode of AKI which was neither chronic nor persistent in nature. 19 of these 26 patients (73%) were on regular oral sodium bicarbonate treatment to help reduce serum potassium levels and correct chronic metabolic acidosis secondary to their CKD.

As a result, 14% of patients attending a general nephrology clinic were identified suitable for SZC or patiromer. The data has been summarised into a table as shown in Table 2.

Discussion

Chronic kidney disease (CKD), heart failure and diabetes mellitus encompass the leading risk factors in the development of chronic hyperkalaemia which puts patients at increased risk of mortality and morbidity [16]. The occurrence of hyperkalaemia often precludes patients benefiting from maximal doses of RAAS inhibition and is itself linked to worsening clinical outcomes [8]. NICE have approved the use of
sodium zirconium cyclosilicate and patiromer in both the acute and, more recently, the chronic management of hyperkalaemia. The use of these agents for the chronic management of hyperkalaemia could prove pivotal in the treatment for such patient groups. The indication is additional to the use of sodium zirconium cyclosilicate and patiromer in the management of acute hyperkalaemia.

Outpatient studies evaluating the use of these newer potassium binding agents within selected chronic kidney disease patient groups experiencing hyperkalaemia has demonstrated the correction and maintenance of normokalaemia [17] as well as the ability to maintain or increase the dose of RAAS inhibition in a significant proportion of patients [18]. These findings were predominantly in those patients with moderate to severe CKD, where 75% were CKD stage 3 or 4, and this mirrors the patient group reported on within this general nephrology clinic.

Current therapeutic options available for managing chronic hyperkalaemia are suboptimal [19] and the introduction of new potassium binding agents provides a new clinical opportunity. In order to implement the effective use of new potassium binders, Imperial College Healthcare NHS Trust have developed a new cross departmental guideline to ensure the optimal use of these agents to maximise the inhibition of RAAS in the patient groups who are likely to benefit from this. This audit collected data from unselected patients within a single general nephrology clinic in one trust, fundamentally finding that 14% of patients could benefit from chronic use of sodium zirconium cyclosilicate or patiromer to better manage their underlying chronic kidney disease, diabetes mellitus and heart failure.

When considering diabetes, hyperkalaemia is probably contributed to by the syndrome of hyporeninaemic hypoaldosteronism, resulting from mild-to-moderate renal impairment [19]. Such patients typically present with asymptomatic hyperkalaemia, commonly occurring in elderly diabetics particularly those on SGLT-2 inhibitor and RAAS inhibitor therapy in the context of impaired renal function [20]. It is important to always consider concomitant medication in case these may be aggravating the hyperkalaemia.

This audit is limited to hospital outpatients and fails to consider the impact on the large number of patients within primary care and in the community with chronic kidney disease, diabetes mellitus and heart failure. General practitioners face many barriers in managing heart failure patients in the community who tend to be frail, elderly with polypharmacy and multiple co-morbidities adding to their risk for hyperkalaemia. The lack of awareness of the diagnosis of heart failure is likely to act as a further barrier to effective treatment [21]. But with growing numbers of heart failure patients seen in community cardiology clinics by general practitioners with a special interest, there is better scope for the potential use of these therapeutic agents to maximise the beneficial effects of RAAS inhibition [22].
Many patients with CKD receive suboptimal treatment due to difficulties with regular monitoring or even because they are undiagnosed, given that CKD remains largely asymptomatic. Without regularly screening diminishing renal function may go undetected, leaving a significant percentage of the population with CKD undiagnosed [23]. This illustrates the potential wider reaching impact which these newer potassium binding agents can have in the management of these chronic conditions in primary care and within the community.

Within this study patients who experienced hyperkalaemia associated with an episode of acute kidney injury (AKI), defined earlier in the methodology, were excluded as being not suitable for sodium zirconium cyclosilicate or patiromer. It is however not clear whether these episodes of acute kidney injury occurred in response to medications such as RAAS inhibitors or due to other reversible causes such as sepsis and hypovolaemia [15]. Potentially re-challenging such patients in controlled environments with monitoring of their renal profiles to assess for a recurring AKI could help determine their suitability for these newer potassium binding agents going forward.

Of the patient group with hyperkalaemia limiting maximisation of RAAS inhibition, 73% were on regular oral sodium bicarbonate treatment to help manage their metabolic acidosis and reduce serum potassium levels. This has been proven to have a beneficial effect on hyperkalaemia in both short and long-term studies [24]. However, there was insufficient effect of this manoeuvre in the reported patients to enable an initiation or up-titration in RAAS inhibitor therapy. Studies report beneficial outcomes with sodium bicarbonate therapy in CKD patients who are at increased risk of hyperkalaemia including those on RAAS inhibition [24]. Further to this, sodium zirconium cyclosilicate has been shown to increase sodium bicarbonate levels [25] which could further assist in the correction of the metabolic acidosis within CKD.

A limitation of the data is whether the patients identified in this clinic would tolerate the new potassium binders. Patiromer can cause abdominal pain and gastrointestinal side effects, whilst sodium zirconium cyclosilicate can result in fluid retention and oedema [13, 14]. An ideal study would be to demonstrate whether the introduction of these agents to patients who are identified as needing the drug within clinics are successfully treated, to better understand its impact.

**Conclusion**

Chronic hyperkalaemia is a major treatment obstacle in chronic kidney disease, diabetes mellitus and heart failure where patients are often unable to benefit from maximal dose of RAAS inhibitors shown to improve long-term clinical outcomes. The recently approved potassium binding agents by NICE in the
form of sodium zirconium cyclosilicate and patiromer with enhanced safety and efficacy profiles are significant advancements in the management of chronic hyperkalaemia, particularly in the outpatient setting as this audit has demonstrated. Nephrologists and cardiologists need to ensure that the opportunities provided by these new potassium binders are offered to patients who fulfil the criteria for their use as recommended by NICE and that this is implemented yet safely. Further studies are needed to fully appreciate the impact of these potassium binders in improving long-term clinical outcomes, through optimising RAAS inhibition amongst suitable patient groups, in the fields of cardiovascular and cardiorenal medicine.

**List Of Abbreviations**

AKI: Acute kidney injury

CKD: Chronic kidney disease

eGFR: Estimated glomerular filtration rate

HFrEF: Heart failure with reduced ejection fraction

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

RAAS: Renin–angiotensin–aldosterone system

SGLT-2: Sodium-glucose co-transporter-2

SmPC: Summary of product characteristics

SZC: Sodium zirconium cyclosilicate

KDIGO: Kidney Disease Improving Global Guidelines

uPCR: Urine protein/creatinine ratio

**Declarations**

All manuscripts must contain the following sections under the heading 'Declarations':

Ethics approval and consent to participate

This clinical audit was approved and registered with the Imperial College Healthcare NHS Trust Clinical Governance Department with registration reference number REN_017 under the directorate of Renal. The need for consent was waived by obtaining our trust clinical governance approval for the audit and all data was collated anonymously.
Consent for Publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Author Contributions

Both AF and PP made substantial contributions in the conception and design of this work, data collection and interpretation as well as drafting of this manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Depicting the total number of patients meeting the specific indications for RAAS inhibitor treatment; considering that several patients had >1 indication documented.

| INDICATIONS FOR RAAS INHIBITION                                           | TOTAL NUMBER |
|--------------------------------------------------------------------------|--------------|
| CKD – Proteinuria (defined as historical PCR >100 or ACR >70)             | 37           |
| CKD – Diabetes Mellitus                                                  | 28           |
| Cerebrovascular Disease / Ischaemic Heart Disease (Myocardial Infarction) | 21           |
| Heart Failure with reduced Ejection Fraction (HFrEF)                     | 5            |

Table 2. Illustrating the breakdown of patient numbers within specific criterion.

| PATIENT CRITERION                                                                 | PATIENT NUMBER |
|----------------------------------------------------------------------------------|----------------|
| Number with RAAS indication                                                       | 68             |
| Number on maximal dose of RAAS inhibitor                                          | 10             |
| Limited by hyperkalaemia                                                          | 26             |
| Receiving bicarbonate for hyperkalaemia                                            | 19             |
| Hyperkalaemia with AKI                                                            | 12             |
| **Hyperkalaemia suitable for SZC / Patiromer**                                   | **14**         |
Figures

**Figure 1**

Bar graph depicting the distribution of CKD stages of the 100 patients analysed in this audit.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- PatiromerandSZCchronicusev1.0FINALMar20.pdf