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Original Article

ORIGINAL ARTICLE

The burden of hyperkalaemia in chronic kidney disease: a systematic literature review

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ABSTRACT

Background. The global epidemiology and burden of hyperkalaemia in patients with chronic kidney disease (CKD) are unclear due to the inconsistent definitions of hyperkalaemia. The combination of adverse effects and interaction between comorbidity and pharmacotherapies, such as renin–angiotensin–aldosterone system inhibitors (RAASi), justify a systematic understanding of this common complication of CKD.

Methods. This systematic literature review aimed to identify and descriptively summarize the evidence on hyperkalaemia risk factors and associated characteristics in adult CKD patients, including the effects of sub-optimal RAASi. Medline® and Embase® databases were searched from January 2000 to April 2024, with additional hand searching. Publications were screened by two independent reviewers. Data were extracted by one reviewer and verified by another reviewer; study quality assessment was also conducted.

Results. A total of 138 studies described in 145 publications met the eligibility criteria. The published literature revealed varying prevalence of hyperkalaemia amongst inconsistent definitions and a significant increase in the prevalence and incidence of hyperkalaemia among patients with CKD, regardless of RAASi treatment. Hyperkalaemia was associated with adverse outcomes and increased hospital resource use. Additionally, studies pointed to negative health and economic outcomes due to sub-optimal RAASi dosing in CKD patients with hyperkalaemia, as well as in those with CKD and comorbid heart failure.

Conclusions. This review expands on current research, offering a new perspective specifically focused on CKD patients and wider clinical and economic outcomes. Identification of wider clinical and economic consequences of hyperkalaemia in CKD patients, and the interplay between these risks and the risks of sub-optimal RAASi dosing, justify the need for future research. Clinicians should exercise caution when managing this condition in this complex patient group.

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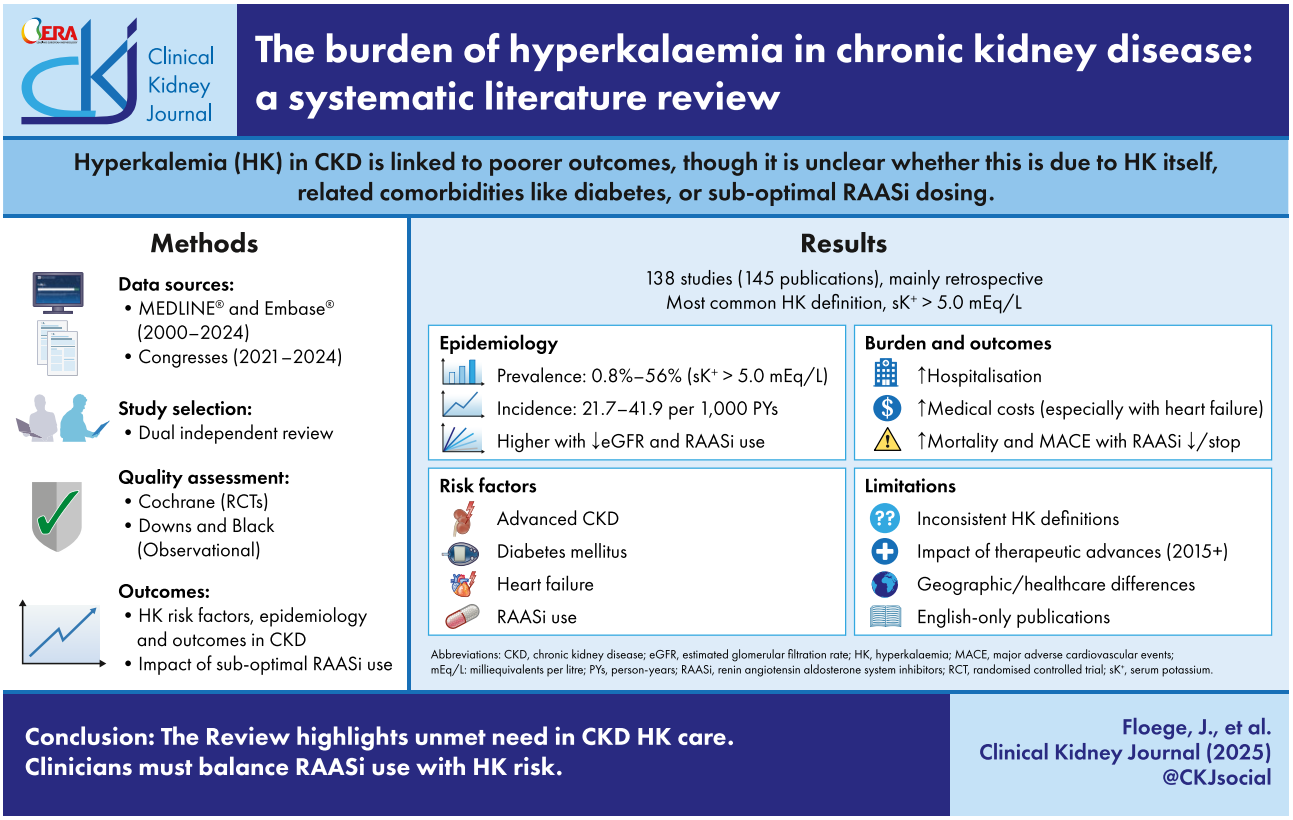
GRAPHICAL ABSTRACT



Keywords: CKD, epidemiology, health and economic outcomes, hyperkalaemia, RAASi, sub-optimal dosing

KEY LEARNING POINTS

What was known:

- The global epidemiology of hyperkalaemia varies across different populations, definitions, healthcare settings, diseases and pharmacotherapies.
- The definition of hyperkalaemia is not well defined within clinical guidelines and current literature, with prevalence and incidence varying according to definition/threshold used.
- As new chronic kidney disease (CKD) pharmacotherapies emerge, and with increasing observation of multimorbid patients, this systematic literature review aimed to provide a contemporary assessment of epidemiology and burden specifically within adult CKD patients, due to their increased risk of hyperkalaemia and related events.

This study adds:

- There is an increased prevalence/incidence of hyperkalaemia in adult CKD patients, which is linked to adverse outcomes and increased hospital resource use.
- Modifying renin–angiotensin–aldosterone system inhibitors (RAASi) dose to lower serum potassium may have detrimental consequences on clinical outcomes of CKD patients, particularly in those with comorbid conditions like heart failure.
- There is substantial evidence of negative health and economic outcomes due to sub-optimal RAASi dosing in CKD patients with hyperkalaemia, particularly for those with CKD and comorbid conditions.

Potential impact:

- Treatments currently available for CKD patients with or at risk of chronic hyperkalaemia are still limited, presenting a specific unmet need, and careful consideration by clinicians is required when managing these multimorbid patients.

INTRODUCTION

Although there is no clear definition for hyperkalaemia in guidelines and current literature, it is typically defined as serum potassium (sK^+) levels exceeding the upper limit of the normal reference range, which is generally greater than 5.0 or 5.5 milliequivalents (mEq)/litre (L), though this may vary slightly between laboratories [1–4]. In clinical practice, hyperkalaemia is often classified by severity as mild (sK^+ level 5.5–5.9 mEq/L), moderate (sK^+ level 6.0–6.4 mEq/L) or severe (sK^+ level ≥6.5 mEq/L) [5]. While these thresholds provide a framework for classification, the clinical relevance of elevated sK^+ levels depends on the broader context, including weather the sample was obtained during routine monitoring or in response to clinical symptoms [6–8].

Hyperkalaemia often occurs in patients with acute kidney injury or chronic kidney disease (CKD) due to several factors. These include impaired renal excretion of K^+ due to low estimated glomerular filtration rate (eGFR), shift of intracellular K^+ to the extracellular space and in conjunction with a maintained dietary K^+ intake [3]. Diabetes mellitus (DM) and cardiovascular disease (CVD) [including heart failure (HF)] are also known risk factors for hyperkalaemia [9]. Additionally, patients with CKD and CVD often receive treatments that affect K^+ excretion, potentially leading to hyperkalaemia. These treatments include renin–angiotensin–aldosterone system inhibitors (RAASi) such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin-receptor blockers (ARBs) and, increasingly, mineralocorticoid receptor antagonists (MRAs) [10–12].

Traditionally, long-term management of hyperkalaemia has focused on prevention through a low dietary K^+ intake, adequate diuretic therapy and addressing metabolic acidosis [13, 14]. Discontinuation or dose-modification of medications that may precipitate hyperkalaemia, such as RAASi might be needed [15]. However, sub-optimal RAASi dosing or halting RAASi in patients with CKD can lead to increased risk of cardiovascular events [hazard ratio (HR) 1.45] and all-cause death (HR 2.26) and even worse outcomes in populations with HF and DM [16, 17]. Mortality rates of patients on sub-optimal RAASi doses are nearly double compared with those on maximum RAASi doses [18]. Recently, contemporary potassium-lowering agents have shown a favourable safety profile and can reduce the risk of hyperkalaemia, allowing patients to continue RAASi treatment [13, 14]. Guidelines for managing diabetes (2020) and blood pressure (2021) in CKD recommend treating hyperkalaemia with K^+-lowering therapies before RAASi down-titration [19].

A recent (2022) published systematic literature review (SLR) and meta-analysis sought to provide a comprehensive overview of the epidemiology of hyperkalaemia across different populations, definitions, healthcare settings, diseases and pharmacotherapies, given this lack of extensive current literature [3]. As new CKD pharmacotherapies emerge, and with increasing observation of multimorbid patients, our SLR aimed to provide a contemporary assessment specifically within adult CKD patients, due to their increased risk of hyperkalaemia and related events. While hyperkalaemia has been linked to poorer outcomes, it remains unclear whether these outcomes are directly due to hyperkalaemia itself, related comorbid conditions such as DM, or consequent sub-optimal RAASi dosing. Findings from this SLR in CKD patients were therefore qualitatively summarized to (i) describe the risk factors and global epidemiology of hyperkalaemia; (ii) identify the clinical, humanistic and economic burden of hyperkalaemia; and (iii) describe how RAASi use is associated with hyperkalaemia, the consequent impact of hyperkalaemia on RAASi use, and examine the sub-optimal dosing effect of RAASi on clinical and economic outcomes. The findings of this SLR are intended to provide healthcare practitioners with evidence-based insights for managing pharmacotherapy in CKD patients with hyperkalaemia, thereby enhancing clinical decision-making.

MATERIALS AND METHODS

The SLR was conducted according to the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [20], the general principles of the Centre for Reviews and Dissemination (CRD, University of York) guidance [21] for undertaking reviews in health care, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22] and the methods for systematic reviews as specified by National Institute for Health and Care Excellence (NICE) [23]. The SLR was registered with the International Prospective Register of Systematic Reviews (PROSPERO; www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023440088). To gather evidence reflecting the current practice standards, searches in Medline® and Embase® were conducted from January 2000 to April 2024 and to identify relevant studies not available through electronic databases, abstracts from relevant conferences published from January 2021 through April 2024 were hand-searched. For further information see the supplementary materials (Supplementary data, Tables S1–S9).

The SLR eligibility criteria, determined using the PICOS (population, intervention, comparator, outcomes and study design) framework [20], is outlined in Table 1.

Study selection

Titles and abstracts were independently reviewed by two researchers against the pre-defined eligibility criteria using the PICOS framework. Publications selected as potentially relevant from abstract review were retained and full text publications were independently assessed by two reviewers, with discrepancies resolved by consulting a third reviewer and on reaching consensus.

Data extraction and study quality assessment

Data extraction from the full text studies identified by the searches was conducted by one researcher and quality checked by another independent researcher. The methodological quality of the randomized controlled trials (RCTs) was assessed using the Cochrane Collaboration tool for assessing the risk of bias [24]. The Downs and Black checklist [25] was used to assess the risk of bias in non-randomized/observational studies. The complete list of extracted data (Supplementary data, Table S10) and the quality assessment checklist, along with the results (Supplementary data, Table S11, Figs S9 and S10), are detailed in the supplementary materials.

RESULTS

A total of 138 studies, described in 144 publications [16, 26–146, 147–168] met the PICOS criteria. The PRISMA flow diagrams, per research question are presented in Supplementary data, Figs S1 and S2 of the supplementary materials; a full list of the included studies is presented in Supplementary data, Tables S13 and S14 of the supplementary materials.

Table 1: SLR eligibility criteria.

PICOS	Inclusion criteria	Exclusion criteria
Population	• Adults with CKD + hyperkalaemia versus CKD + normokalaemia/hypokalaemia[a] • Adults with CKD + chronic HF + hyperkalaemia versus CKD normokalaemia/hypokalaemia[a] • Adults with CKD + HT + hyperkalaemia versus CKD + normokalaemia/hypokalaemia[a] • Adults with CKD + DM + hyperkalaemia versus CKD + normokalaemia/hypokalaemia[a] • Aged 18 years of age	• Patients with indications other than CKD • Patients with kidney damage due to trauma • Children and paediatric populations • Animal studies
Intervention/comparator	Not applicable	No applicable
Outcomes	Epidemiology: • Prevalence, incidence, epidemiology trends like risk factors (kidney failure, DM, adrenal disease), patient population size Clinical burden: • Time to ESRD, time to acute kidney injury, time to CV death, time to renal death, time to all-cause mortality, time to non-fatal MI, time to non-fatal stroke • Hospitalization rate, length of stay, requirement of dialysis Financial burden: • Direct costs (cost of dialysis, hospitalization cost, treatment cost, medical costs, etc.) • Indirect costs (cost of caregiver cost, productivity loss etc.) Humanistic burden: • HRQoL (SF-36, EQ-5D, KDQOL, FACIT-F), patient-reported outcomes and caregiver outcomes Sub-optimal dosing: • Prevalence and incidence of RAASi-associated hyperkalaemia • Proportion of patients with RAASi discontinuation • Proportion of patients with RAASi sub-optimal dosing/dose modification • Impact of RAASi sub-optimal dosing/dose modification on clinical/economic or humanistic outcome	Any outcomes not listed in the inclusion criteria
Study design(s)	• RCTs, nRCTs and single arm trials • Prospective and retrospective observational studies • Cross-sectional and case–control study • Cost of illness studies	• Case reports • Case studies • Editorials, notes, comments
Limits	• Timeframe: full-texts 2000 to current; conference abstracts 2021, 2022, 2023 and 2024 • Geography: no restrictions: the regional differences will be reported where data is available • Language: English only[b]	• Exclude publications prior to 2000 and conference abstracts prior to 2021 • Non-English literature

[a]The control group was relevant only for epidemiology and burden of illness review.
[b]The majority of abstracts/full text were in English.
CV, cardiovascular; EQ-5D, EuroQol 5 dimensions; FACIT-F, Functional assessment of chronic illness therapy—fatigue; HRQoL, health-related quality of life; HT, hypertension; KDQOL, Kidney disease and quality of life; MI, myocardial infarction; nRCTs, non-randomized controlled trials; SF-36, Short form-36.

Most of the studies ($n = 87$) were retrospective observational, followed by 33 RCTs. Most of these studies were based in the USA ($n = 35$) or were multinational ($n = 17$). Across the studies, 38 different definitions or thresholds of hyperkalaemia were applied, with some studies using more than one. The most frequently employed criteria were sK^+ >5.0 mEq/L in 27 studies, followed by sK^+ >5.5 mEq/L in 23 studies and sK^+ ≥5.5 mEq/L in 22 studies. Among the studies that provided information on CKD stages, there was significant variation in the distribution of disease severity (Supplementary data, Table S14). All extracted results are tabulated in the supplementary materials (Supplementary data, Tables S15–S25).

Risk factors for hyperkalaemia

The studies included in this review identified CKD stage and eGFR category as the most significant risk factors for hyperkalaemia in CKD patients, along with comorbidities such as DM and HF. Additionally, this SLR highlighted that one of the most critical risk factors of hyperkalaemia in CKD patients was the

prescription of RAASi [29], including MRAs. For example, the HR by multivariate analysis was 7.00 for ACEi vs calcium channel blocker use [95% confidence interval (CI) 2.29–21.39; $P < .001$], 2.85 for ACEi vs beta-blocker (β-blocker) use (95% CI 1.5–5.42; $P = .001$) [63] and 7.71 for aliskiren use (95% CI 1.14–52.3; $P = .04$) [79].

Epidemiology of hyperkalaemia

A total of 33 studies [26–29, 31–35, 38, 41, 42, 44–56, 139–146] were reviewed to determine the prevalence of hyperkalaemia and hypokalaemia/normokalaemia among CKD patients. Prevalence differed depending on the hyperkalaemia definition used. The prevalence rate of the most commonly used threshold of hyperkalaemia (sK^+ >5.0 mEq/L) varied significantly between studies due to the differing stages of disease and multimorbid patients, ranging from 0.8% in a subgroup of patients with stage 1 CKD not on renal replacement therapy (N = 118 patients) in Taiwan between November 2002 and July 2010 [46], to 56.0% in a subgroup of patients with stage 5 CKD (N = 421 patients) in Mexico between February 2019 and August 2022 [146]. In addition, the overall prevalence of hyperkalaemia varied considerably by region, with studies from the USA reporting rates ranging from 1.1% [44] to 20.1% [48], China from 3.8% [29] to 44.4% [26], and Japan showing higher rates ranging from 10.6% [56] to 57.6% [31]. Studies form the European region, including the UK, Italy, Spain and France, reported CKD prevalence estimates ranging from 0.7% [41] to 33.6% [141]. Additional data from Australia [53], Taiwan [46, 52], Thailand [140], Turkey [142], Mexico [146] and Pakistan [144] further highlighted the geographic variation, likely reflecting differences in CKD stage distribution, comorbidity profiles, and hyperkalaemia definitions across studies (Supplementary data, Table S16).

Further, in the nine studies [31, 34, 46, 50, 53, 56, 140, 141, 146] reporting prevalence of hyperkalaemia among different stages of CKD, the overall prevalence of hyperkalaemia was observed to increase with declining kidney function [31].

Seven additional studies [16, 61, 66, 105, 128, 131, 141] have reported the increasing prevalence of RAASi associated hyperkalaemia in CKD patients. For example, a Spanish study of patients with stage 3–5 CKD (non-dialyzed), DM and/or HF between 1971 and 2017, reported the prevalence rate of hyperkalaemia for patients taking RAASi and for patients not taking RAASi. In the analysis of patients with different CKD stages and comorbidities such as DM and HF, the prevalence rate was higher among CKD patients taking RAASi vs patients not taking RAASi [128].

The prevalence rates of hyperkalaemia in CKD patients were found to vary for those on ARBs vs ACEi, with one US study of stage 1–5 CKD patients reporting higher hyperkalaemia prevalence among patients taking ARBs (31% vs 20.4%, for ARBs vs ACEi) [61] and a Danish study reporting higher prevalence in CKD patients taking ACEi (17.2% vs 34.3%, for ARBs vs ACEi) [66]; both studies defined hyperkalaemia at sK^+ >5.0 mEq/L.

Two studies [47, 55] have reported the incidence of hyperkalaemia and hypokalaemia/normokalaemia among CKD patients. In a US study with moderate and advanced non-dialysis-dependent CKD (N = 1227 patients, 86% stage 3 or 4), the incidence rate of hyperkalaemia (sK^+ >5.3 mEq/L) was 21.7 cases per 1000 person-years [vs 9.7 cases of hypokalaemia (defined as sK^+ <3.6 mEq/L) per 1000 person-years] [47]. A higher incidence was reported in a Spanish study of patients with CKD (N = 1129 patients): 41.9 cases per 1000 person-years of hyperkalaemia (defined as sK^+ >5.0 mEq/L) [vs 18.9 cases of hypokalaemia (sK^+ <3.5 mEq/L) per 1000 person-years] [55].

An additional 69 studies [57, 59, 60, 62–65, 67–70, 72–74, 77–86, 88, 90, 91, 93, 94, 101, 102, 104–116, 118–121, 123, 125–127, 129, 130, 132, 134, 135, 150–153, 155, 158, 160–163, 165, 168] reported the incidence of RAASi-associated hyperkalaemia in CKD patients. Supplementary data, Figs S3 and S4 show the trend of increased hyperkalaemia incidence and incidence rate with declining kidney function, as well as the increased hyperkalaemia incidence with RAASi use. Notably, a trend of increased incidence of hyperkalaemia with MRA use was reported in 15 studies (from 19 publications [70, 80, 83, 85, 88, 93–95, 97–100, 107, 114, 118, 119, 129, 132, 153], all of which compared patients on an MRA with those on placebo/non-MRA).

Burden of hyperkalaemia

Twelve studies [26, 28, 29, 31, 34, 38, 40, 42, 44, 55, 71, 147] reported the health outcomes of hyperkalaemia, focusing on hospitalization numbers, rates and length of stay. Compared with CKD patients with normokalaemia, those with hyperkalaemia (including stage 1–5 CKD and CKD concomitant with end-stage renal disease (ESRD) or HF] had an average number of 0.8–1.9 vs 0.3–1.4 hospitalizations during 1 year of follow-up period [29, 34, 42, 147]. Four studies [26, 28, 29, 34] also noted that CKD patients with hyperkalaemia had longer hospital stays compared with those without hyperkalaemia.

Nine studies [29, 30, 34, 36, 37, 42, 43, 71, 147] estimated the economic burden of hyperkalaemia, all focusing on direct healthcare costs. The total healthcare costs (pharmacy and medical) per patient per year in a US study were estimated 1-year post-index date, revealing that hyperkalaemic patients (including at least two sK^+ readings >5.0 mEq/L on different dates) used more healthcare resources and therefore were considerably more costly (ranging from $10 687 to $67 758) than normokalaemic patients (sK^+ 3.8–5.0 mEq/L) (ranging from $6417 to $58 969), regardless of the CKD stage (stage 1 to 5; stage 5 with and without dialysis) [30]. Similar results of substantial costs associated with hyperkalaemia were reported consistently in four other studies in an overall CKD population analysis [37, 43, 71, 147].

Hyperkalaemia can become a medical emergency requiring hospitalization, increasing the economic burden [169]. Addressing this specifically, the total all-cause healthcare costs (medical and pharmacy) during 1 year post-discharge in a US study were almost twice as high in CKD patients with hospitalizations related to hyperkalaemia (sK^+ >5.0 mEq/L) compared with CKD patients with hospitalizations but without evidence of hyperkalaemia (sK^+ <5.0 mEq/L) [36]. These findings were further corroborated by two detailed analysis in China and Japan [34, 46].

Patients with CKD who develop hyperkalaemia due to RAASi treatment may need to reduce their dosage (sub-optimal dosing) or stop the treatment altogether. An additional 16 studies [58, 69, 76, 77, 84, 95, 103, 114, 121, 125, 127, 133, 142, 149, 154, 157] on CKD patients with sub-optimal RAASi dosing due to hyperkalaemia and 44 studies [16, 57, 58, 60, 70, 75–80, 84–88, 92–94, 103, 107, 111, 113, 114, 116–120, 122, 124, 125, 127, 129, 130, 133, 142, 149, 155, 157, 159, 165, 166, 167] on those who discontinued RAASi for the same reason were identified. A trend of down-titration was observed across these studies, with a UK study showing that the highest proportions of sub-optimal dosing and discontinuation were among patients on higher RAASi doses compared with lower doses, across three hyperkalaemia thresholds (sK^+ 5 mEq/L, sK^+ 5.5 mEq/L, sK^+ 6 mEq/L) [103].

Despite the association between RAASi and hyperkalaemia, this does not always result in more frequent dose reductions in

patients with CKD. An Australian study of patients with stage 3–5 CKD ($N = 20\,184$ patients) after 3.9 years of follow-up reported the proportion of patients with sub-optimal RAASi dosing decreasing from stage 3a (10.7%) to stage 5 (5.4%), despite an increased incidence of hyperkalaemia in the later stages of the disease [127].

RAASi discontinuation compared with RAASi continuation was associated with a greater absolute 5-year risk of mortality (54.5% vs 40.9%) and major adverse cardiovascular events (59.5% vs 47.6%) in patients with advanced CKD (eGFR <30 mL/min per $1.73\,m^2$) [137], and lower mean eGFR (12.6 vs 13.3 mL/min/1.73 m^2) [136]. These risks were observed greatest amongst the most advanced CKD patients investigated [137]. The mean number of inpatient visits was generally higher amongst patients with sub-optimal dosing as compared with optimal dosing [71]. Finally, the median medical costs for patients with CKD and a diagnosis of hyperkalaemia in the USA were significantly higher for patients with optimal RAASi dosing as compared with sub-optimal dosing ($12 671 vs $9065, respectively) [71]. However, for the subgroup of patients with CKD and HF and a diagnosis of hyperkalaemia who received RAASi at an optimal dose, the overall median medical cost were lower than the same patients who received sub-optimal dosing ($27 075 vs $28 293) [71]. See Supplementary data, Figs S5 to S8 for graphical visualizations of sub-optimal RAASi dosing findings.

DISCUSSION

This SLR highlights the complex relationship between the presence of hyperkalaemia and outcomes. Findings, including the most contemporary literature, confirmed that the prevalence of hyperkalaemia in CKD depends on the definition of the condition, i.e. the sK^+ threshold applied, as previously described [3, 170]. The data collected suggest that the prevalence of hyperkalaemia increases with declining kidney function, in agreement with hyperkalaemia being a well-established consequence of advancing CKD [170]. These findings closely reflect the prevalence findings described previously [171]. Similarly, as expected [45, 170, 171], other underlying conditions such as DM and HF contributed to higher sK^+ concentration.

RAASi medications for CKD are among the key determinants of elevated sK^+ concentration [170, 171], and hyperkalaemia has previously been proven prevalent in patients treated with these therapies [3]. Supporting this, the SLR identified evidence of increased prevalence and incidence of hyperkalaemia among patients with CKD treated with RAASi, including ACEi, ARBs and MRAs. Despite this observation, all these agents have previously been shown to reduce the incidence of endpoints important to stakeholders [172].

The results of this SLR show that CKD patients with hyperkalaemia, with or without comorbidities, experience higher absolute numbers and hospitalization rates, as well as longer hospitalization periods compared with CKD patients with normokalaemia. It should be noted that not all studies reported the cause of hospitalization or whether it was directly due to hyperkalaemia; when specified, it included kidney function/cardiac diagnosis or it was stated as related to hyperkalaemia. In the presence of other comorbidities, CKD patients with hyperkalaemia are likely to have worse outcomes as previously suggested [173], although in the present analysis few studies focused on hyperkalaemic patients with CKD and relevant comorbidities. Evidence describing multimorbid populations would be more relevant to the populations treated in clinical practice.

It has been reported in the literature that the annual mortality rate for patients with CKD and hyperkalaemia was more than double compared with patients with CKD without hyperkalaemia [174]. Other concordant studies strongly associated hyperkalaemia and increased mortality [170]. The present SLR observed similar findings, with generally worse health outcomes and an increased clinical burden among hyperkalaemic CKD patients. However, no published study could firmly resolve the question whether worse outcomes directly relate to hyperkalaemia or worse underlying or associated medical conditions, thus all studies remain at the level of an association with no evidence for causality.

From this analysis, it was also concluded that hyperkalaemia is associated with substantial additional healthcare expenditure, including medical and pharmacy expenses, both for the patient and healthcare systems globally. Inpatient care during hyperkalaemia-related hospitalization was a main driver of these costs among patients with hyperkalaemia and concomitant CKD or/and another comorbidity (e.g. HF). These results are consistent with previous reviews evaluating hyperkalaemia-related costs [175]. Regarding humanistic burden elements, only a single study was eligible for inclusion in this SLR and further research to evidence any quality-of-life burden here is needed.

Among the current strategies to improve sK^+ concentration and its observed burden are dose reductions or halting of RAASi treatment. Sub-optimal dosing and treatment discontinuation was observed at higher rates in patients receiving high doses of RAASi [103, 113], however the percentage varied by CKD stage [77, 127]. The finding suggests the adverse outcomes from hyperkalaemia and the adverse outcomes from sub-optimal dosing both place CKD patients at higher risk of negative health outcomes. Furthermore, increasing hyperkalaemia incidence does not always lead to sub-optimal RAASi dosing [127, 142]. Whilst it is highly likely that the increasing incidence of hyperkalaemia is caused by the increasing severity of CKD, and thus why RAASi use increases, it might be assumed that the risk of adverse clinical outcomes from RAASi sub-optimal dosing in those with severe CKD outweighs the dangers of hyperkalaemia in these patients. Our SLR findings on the clinical impact of sub-optimal dosing support this observation. It is imperative that the impact and balance between the risks are explored in further research.

Consequences of sub-optimal RAASi dosing or discontinuation in CKD patients often leads to adverse clinical outcomes due to the increased risk of cardiorenal events [16, 58, 71, 73, 103, 121, 136–138, 149, 156, 157, 164]. However, in one study, sub-optimal RAASi dosing in patients with CKD and hyperkalaemia was associated with better clinical and economic outcomes compared with optimal dosing in the same patients [71]. The latter observation is likely due to the occurrence of hyperkalaemic events when RAASi therapies are prescribed at their maximum recommended doses, which have a high clinical and economic burden as already identified in this SLR and by previous research, as well as patients on optimal RAASi doses likely having comorbid conditions that are costly to manage. Moreover, the study also found that sub-optimal RAASi dosing in patients with CKD and hyperkalaemia and comorbid HF was associated with worse economic outcomes when compared with optimal dosing, confirming that there is a high cost of comorbid conditions like HF when RAASi is not used optimally. This highlights the importance of sK^+ monitoring amongst CKD patients treated with RAASi, and the much-needed research into alternative approaches for hyperkalaemia management in CKD, particularly at advanced stages of disease.

LIMITATIONS

The included studies varied greatly in terms of patient populations, settings, study design, sample size and hyperkalaemia definitions used; therefore, results are not always comparable across the studies. Moreover, most studies reporting the epidemiology of RAASi associated hyperkalaemia in CKD patients also reported rates for varying subgroups of CKD patients, differing by CKD stages and comorbidities. As these are also risk factors for hyperkalaemia in CKD patients, the differing epidemiology of hyperkalaemia attributed to RAASi between studies in this SLR should be interpreted with caution.

It is worth acknowledging that hyperkalaemia itself may be an indicator of poor health rather than the cause of adverse outcomes observed in this review; this should be investigated in future research. Moreover, therapeutic developments for hyperkalaemia since 2015 may have influenced the epidemiology of hyperkalaemia, although the impact of these advances remains unclear and warrants further research.

Finally, heterogeneity in reported hyperkalaemia prevalence may reflect geographic and healthcare system-related factors, such as differences in diet and cuisine, access to dietary counselling or dietetics services, availability, and affordability of medications associated with hyperkalaemia, and healthcare delivery models (e.g. public vs insurance-based systems). Finally, the restriction of the search to English-language publications may have further limited the ability to capture such regional differences in hyperkalaemia epidemiology.

Further studies are needed to explore the impact of these factors, assess the role of novel therapies and better understand the causal relationship between hyperkalaemia and clinical outcomes.

CONCLUSIONS

This SLR including the most contemporary literature highlights evidence that hyperkalaemia, with increasing prevalence in advancing CKD, is associated with adverse health outcomes and the additional use of hospital resources. Therefore, measures that could maintain sK^+ concentration within the normal range may decrease the prevalence/incidence and hence the total burden of hyperkalaemia. However, some measures that lower sK^+ in response to hyperkalaemia by modifying medications dose will have potential detrimental consequences in CKD outcomes, particularly in patients with comorbid conditions like HF. This emphasizes that the treatments currently available for CKD patients with or at risk of chronic hyperkalaemia are still limited, presenting a specific unmet need, and careful consideration by clinicians is required when managing these multimorbid patients [171, 174].

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

The authors meet criteria for authorship as recommended by the ICMJE. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations. J. Floege, K.R., Y.P., J.N.M. and A.E. were involved in the conception and design. K.R., Y.P., J.N.M. and J.W. were involved in data collection, analysis of data, writing the draft manuscript, revising the manuscript and final approval. J. Floege, J. Fotheringham, A.H.F., K.F.E. and A.E. were involved in reviewing the analysis, reviewing the manuscript and final approval. All authors contributed to the interpretation of the data and critically revised the manuscript, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

CONFLICT OF INTEREST STATEMENT

J. Floege has received consultancy and/or lecture honoraria from AstraZeneca, Bayer, Biogen, Boehringer Ingelheim, CSL Vifor, GSK, Novartis, Otsuka, Roche, Stadapharm and Travere. J. Fotheringham has conducted research for AstraZeneca and CSL Vifor. A.H.F. has received research grants, prepared educational materials, and attended drug advisory boards from/for Boehringer Ingelheim, Lilly, AstraZeneca, Menarani, Bayer and Apacor. K.F.E. has received consulting fees from Boehringer Ingelheim. K.R., Y.P. and J.N.M. are employees of IQVIA, which received funds from Boehringer Ingelheim for the conduct of this work.

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