



This is a repository copy of *The burden of hyperkalaemia in chronic kidney disease: a systematic literature review*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/226837/>

Version: Published Version

Article:

Floege, J., Frankel, A.H., Erickson, K.F. et al. (6 more authors) (2025) The burden of hyperkalaemia in chronic kidney disease: a systematic literature review. *Clinical Kidney Journal*, 18 (5). sfaf127. ISSN 2048-8505

<https://doi.org/10.1093/ckj/sfaf127>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

Takedown



If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

ORIGINAL ARTICLE

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

Jürgen Floege¹, Andrew H. Frankel², Kevin F. Erickson³, Ketevan Rtveladze⁴, Yogesh Punekar⁴, Jahangir Nabi Mir ⁵, Jessica Walters⁴, Alexandra Ehm⁶ and James Fotheringham ⁷

¹Division of Nephrology and Dept of Cardiology, RWTH Aachen University, Aachen, Germany, ²Imperial College Healthcare NHS Trust, London, UK, ³Baylor College of Medicine, TX, USA, ⁴IQVIA, London, UK, ⁵IQVIA, Gurugram, Haryana, India, ⁶Boehringer Ingelheim, Germany and ⁷School of Medicine and Population Health, University of Sheffield, Sheffield, UK

Correspondence to: Jahangir Nabi Mir; E-mail: jahangri.nabi@iqvia.com

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.

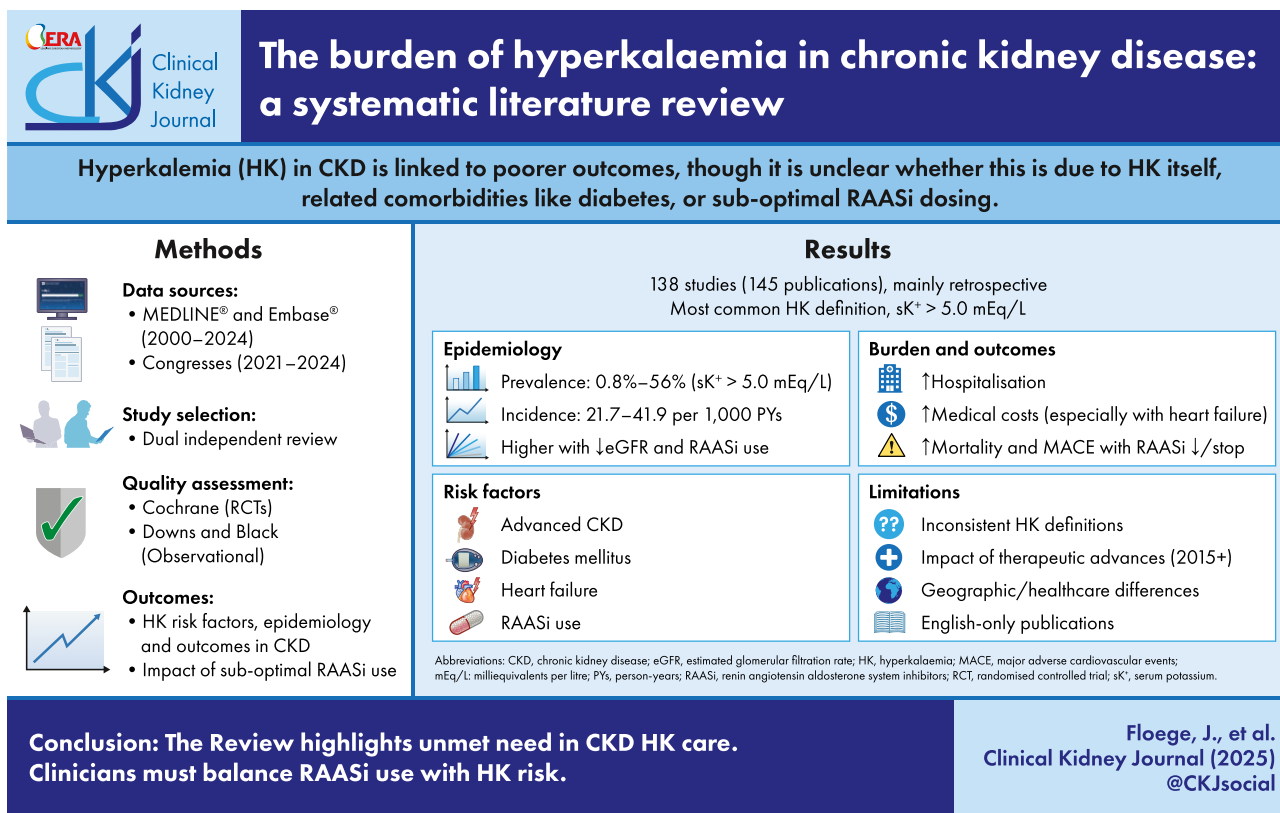
Results. A total of 138 studies described in 145 publications met the eligibility criteria. The published literature revealed varying prevalence of hyperkalaemia amongst inconsistent definitions and a significant increase in the prevalence and incidence of hyperkalaemia among patients with CKD, regardless 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.

Received: 27.2.2025; Editorial decision: 15.4.2025

© The Author(s) 2025. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

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 whether 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	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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	<p>Epidemiology:</p> <ul style="list-style-type: none"> Prevalence, incidence, epidemiology trends like risk factors (kidney failure, DM, adrenal disease), patient population size <p>Clinical burden:</p> <ul style="list-style-type: none"> 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 <p>Financial burden:</p> <ul style="list-style-type: none"> Direct costs (cost of dialysis, hospitalization cost, treatment cost, medical costs, etc.) Indirect costs (cost of caregiver cost, productivity loss etc.) <p>Humanistic burden:</p> <ul style="list-style-type: none"> HRQoL (SF-36, EQ-5D, KDQOL, FACIT-F), patient-reported outcomes and caregiver outcomes <p>Sub-optimal dosing:</p> <ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> RCTs, nRCTs and single arm trials Prospective and retrospective observational studies Cross-sectional and case-control study Cost of illness studies 	<ul style="list-style-type: none"> Case reports Case studies Editorials, notes, comments
Limits	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Exclude publications prior to 2000 and conference abstracts prior to 2021 Non-English literature

^aThe control group was relevant only for epidemiology and burden of illness review.

^bThe 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 $sK^+ \geq 5.5$ 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 from 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 1.73^2) [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.

FUNDING

This study was funded by Boehringer Ingelheim. The authors did not receive payment related to the development of the manuscript.

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 Trave. 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, Menarini, 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.

REFERENCES

1. Palmer BF, Carrero JJ, Clegg DJ et al. Clinical management of hyperkalemia. *Mayo Clin Proc* 2021;96:744–62. <https://doi.org/10.1016/j.mayocp.2020.06.014>
2. Rosano GM, Tamargo J, Kjeldsen KP et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J Cardiovasc Pharmacother* 2018;4:180–8.
3. Humphrey T, Davids MR, Chothia M-Y et al. How common is hyperkalaemia? A systematic review and meta-analysis of the prevalence and incidence of hyperkalaemia reported in observational studies. *Clin Kidney J* 2022;15:727–37. <https://doi.org/10.1093/ckj/sfab243>
4. Ferreira JP, Zannad F, Butler J et al. Empagliflozin and serum potassium in heart failure: an analysis from EMPEROR-Pooled. *Eur Heart J* 2022;43:2984–93. <https://doi.org/10.1093/eurheartj/ehac306>
5. Lott C, Truhlář A, Alfonzo A et al. European Resuscitation Council Guidelines: cardiac arrest in special circumstances. *Resuscitation* 2021;161:152–219.
6. Lehnhardt A, Kemper MJ. Pathogenesis, diagnosis and management of hyperkalemia. *Pediatr Nephrol* 2011;26:377–84. <https://doi.org/10.1007/s00467-010-1699-3>

7. Elliott MJ, Ronksley PE, Clase CM et al. Management of patients with acute hyperkalemia. *Can Med Assoc J* 2010;182:1631–5. <https://doi.org/10.1503/cmaj.100461>
8. Clase CM, Carrero J-J, Ellison DH et al. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2020;97:42–61. <https://doi.org/10.1016/j.kint.2019.09.018>
9. Watanabe R. Hyperkalemia in chronic kidney disease. *Rev Assoc Med Bras* 2020;66:s31–6. <https://doi.org/10.1590/1806-9282.66.s1.31>
10. Douglas M, Rizzolo D, Kruger D. Hyperkalemia in adults: review of a common electrolyte imbalance. *Clin Rev* 2017;27:40–9.
11. Rowan C, Kovesdy C, Du Mond C et al. Comparison of potassium values before and after patiromer initiation among patients receiving chronic hemodialysis in the United States. *Nephrol Dial Transplant* 2017;32(Suppl 3):iii692–3.
12. Sarafidis PA, Blacklock R, Wood E et al. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. *Clin J Am Soc Nephrol* 2012;7:1234–41. <https://doi.org/10.2215/CJN.01150112>
13. Bjune T, Bøe TB, Kjellevoid SA et al. Hyperkalemia and the use of new potassium binders a single center experience from Vestfold Norway (the PotBind study). *Int J Nephrol Renovasc Dis* 2023;16:73–82.
14. Bianchi S, Regolisti G. Pivotal clinical trials, meta-analyses and current guidelines in the treatment of hyperkalemia. *Nephrol Dial Transplant* 2019;34:iii51–61. <https://doi.org/10.1093/ndt/gfz213>
15. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. *Nat Rev Nephrol* 2014;10:653–62. <https://doi.org/10.1038/nrneph.2014.168>
16. Santoro A, Perrone V, Giacomini E et al. Association between hyperkalemia, RAASi non-adherence and outcomes in chronic kidney disease. *J Nephrol* 2022;35:463–72. <https://doi.org/10.1007/s40620-021-01070-6>
17. Evans M, Palaka E, Furuland H et al. The value of maintaining normokalaemia and enabling RAASi therapy in chronic kidney disease. *BMC Nephrol* 2019;20:1–11. <https://doi.org/10.1186/s12882-019-1228-y>
18. Kuijvenhoven MA, Haak EA, Gombert-Handoko KB et al. Evaluation of the concurrent use of potassium-influencing drugs as risk factors for the development of hyperkalemia. *Int J Clin Pharm* 2013;35:1099–104. <https://doi.org/10.1007/s11096-013-9830-8>
19. Burton JO, Coats AJ, Kovesdy CP et al. An international Delphi consensus regarding best practice recommendations for hyperkalaemia across the cardiorenal spectrum. *Eur J Heart Fail* 2022;24:1467–77. <https://doi.org/10.1002/ehf.2612>
20. Higgins JP, Thomas J, Chandler J et al. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, England: John Wiley & Sons Ltd., 2019. <https://doi.org/10.1002/9781119536604>
21. Centre for Reviews and Dissemination (CRD). *Guidance for Undertaking Reviews in Health Care*. Systematic Reviews CRD. Layerthorpe, York: University of York, 2008. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf (27 April 2023, date last accessed).
22. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Int J Surg* 2021;88:105906. <https://doi.org/10.1016/j.ijsu.2021.105906>
23. National Institute for Health and Care Excellence (NICE). *Single Technology Appraisal: User Guide for Company Evidence Submission Template*. London, UK: The National Institute for Health and Care Excellence (NICE), 2015. <https://www.nice.org.uk/process/pmg24/chapter/clinical-effectiveness#quality-assessment-of-the-relevant-clinical-effectiveness-evidence> (27 April 2023, date last accessed).
24. Higgins JPT, Altman DG, Gøtzsche PC et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. <https://doi.org/10.1136/bmj.d5928>
25. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Commun Health* 1998;52:377–84. <https://doi.org/10.1136/jech.52.6.377>
26. Li X, Li B, Guo Y. Impact of hyperkalemia on hospitalization days in advanced chronic kidney disease patients with Type-2 diabetes mellitus: a prospective study. *Pakistan J Med Sci* 2023;39:885–90.
27. Wang J, Wang F. WCN23-1101 Instantaneous and persistent elevation of serum potassium and progression of chronic kidney disease, a single center-based cohort study. *Kidney Int Rep* 2023;8:S159. <https://doi.org/10.1016/j.ekir.2023.02.358>
28. Calabrese V, Cernaro V, Battaglia V et al. Correlation between hyperkalemia and the duration of several hospitalizations in patients with chronic kidney disease. *J Clin Med* 2022;11:244. <https://doi.org/10.3390/jcm11010244>
29. Zhang J, He X, Wu J. the impact of hyperkalemia on mortality and healthcare resource utilization among patients with chronic kidney disease: a matched cohort study in China. *Front Public Health* 2022;10:855395. <https://doi.org/10.3389/fpubh.2022.855395>
30. Sharma A, Alvarez PJ, Woods SD et al. Healthcare resource utilization and costs associated with hyperkalemia in a large managed care population. *J Pharm Health Serv Res* 2021;12:35–41. <https://doi.org/10.1093/jphsr/rmaa004>
31. Kohsaka S, Okami S, Kanda E et al. Cardiovascular and renal outcomes associated with hyperkalemia in chronic kidney disease: a hospital-based cohort study. *Mayo Clinic Proc* 2021;5:274–85.
32. Grandy S, Jackson J, Moon R et al. Health-related quality of life and lifestyle changes in patients with chronic kidney disease and hyperkalaemia: real-world data from the US, five European countries and China. *Int J Clin Pract* 2021;75:e14326. <https://doi.org/10.1111/ijcp.14326>
33. Sharma A, Alvarez PJ, Woods SD et al. A model to predict risk of hyperkalemia in patients with chronic kidney disease using a large administrative claims database. *Clinicoecon Outcomes Res* 2020;12:657–67. <https://doi.org/10.2147/CEOR.S267063>
34. Kanda E, Kashihara N, Kohsaka S et al. Clinical and economic burden of hyperkalemia: a nationwide hospital-based cohort study in Japan. *Kidney Medicine* 2020;2:742–52.e1. <https://doi.org/10.1016/j.xkme.2020.09.003>
35. Jimenez-Marrero S, Cainzos-Achirica M, Monterde D et al. Real-world epidemiology of potassium derangements among chronic cardiovascular, metabolic and renal conditions: a population-based analysis. *Clin Epidemiol* 2020;12:941–52. <https://doi.org/10.2147/CLEP.S253745>
36. Betts KA, Woolley JM, Mu F et al. Postdischarge health care costs and readmission in patients with

- hyperkalemia-related hospitalizations. *Kidney Int Rep* 2020;5:1280–90. <https://doi.org/10.1016/j.ekir.2020.06.004>
37. Mu F, Betts KA, Woolley JM et al. Prevalence and economic burden of hyperkalemia in the United States Medicare population. *Curr Med Res Opin* 2020;36:1333–41. <https://doi.org/10.1080/03007995.2020.1775072>
 38. James G, Carrero JJ, Kumar S et al. Pos-328 The burden of hyperkalemia in patients with chronic kidney disease: a report from the DISCOVER CKD retrospective cohort. *Kidney Int Rep* 2021;6:S141–2. <https://doi.org/10.1016/j.ekir.2021.03.344>
 39. James G, Carrero JJ, Khezrian M et al. Pos-305 Hospitalizations and length of stay in patients with CKD with and without hyperkalemia: a report from the DISCOVER CKD retrospective cohort. *Kidney Int Rep* 2022;7:S136–7. <https://doi.org/10.1016/j.ekir.2022.01.325>
 40. Thomsen RW, Nicolaisen SK, Hasvold P et al. Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes—a Danish population-based cohort study. *Nephrol Dial Transplant* 2018;33:1610–20. <https://doi.org/10.1093/ndt/gfx312>
 41. Furuland H, McEwan P, Evans M et al. Serum potassium as a predictor of adverse clinical outcomes in patients with chronic kidney disease: New risk equations using the UK clinical practice research datalink. *BMC Nephrol* 2018;19:211. <https://doi.org/10.1186/s12882-018-1007-1>
 42. Neuenschwander JF, Silverstein AR, Teigland CL et al. The increased clinical and economic burden of hyperkalemia in Medicare patients admitted to long-term care settings. *Adv Ther* 2023;40:1204–23. <https://doi.org/10.1007/s12325-022-02420-x>
 43. Betts KA, Woolley JM, Mu F et al. The cost of hyperkalemia in the United States. *Kidney Int Rep* 2018;3:385–93. <https://doi.org/10.1016/j.ekir.2017.11.003>
 44. Luo J, Brunelli SM, Jensen DE et al. Association between serum potassium and outcomes in patients with reduced kidney function. *Clin J Am Soc Nephrol* 2016;11:90–100. <https://doi.org/10.2215/CJN.01730215>
 45. Nakhoul GN, Huang H, Arrigain S et al. Serum potassium, end-stage renal disease and mortality in chronic kidney disease. *Am J Nephrol* 2015;41:456–63. <https://doi.org/10.1159/000437151>
 46. Wang HH, Hung CC, Hwang DY et al. Hypokalemia, its contributing factors and renal outcomes in patients with chronic kidney disease. *PLoS One* 2013;8:e67140. <https://doi.org/10.1371/journal.pone.0067140>
 47. Hayes J, Kalantar-Zadeh K, Lu JL et al. Association of hypo- and hyperkalemia with disease progression and mortality in males with chronic kidney disease: the role of race. *Nephron Clin Pract* 2012;120:C8–16.
 48. Jain N, Kotla S, Little BB et al. Predictors of hyperkalemia and death in patients with cardiac and renal disease. *Am J Cardiol* 2012;109:1510–3. <https://doi.org/10.1016/j.amjcard.2012.01.367>
 49. Wagner S, Metzger M, Flamant M et al. Association of plasma potassium with mortality and end-stage kidney disease in patients with chronic kidney disease under nephrologist care—The NephroTest study. *BMC Nephrol* 2017;18:295. <https://doi.org/10.1186/s12882-017-0710-7>
 50. Collins AJ, Pitt B, Reaven N et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol* 2017;46:213–21. <https://doi.org/10.1159/000479802>
 51. Korgaonkar S, Tilea A, Gillespie BW et al. Serum potassium and outcomes in CKD: insights from the RRI-CKD cohort study. *Clin J Am Soc Nephrol* 2010;5:762–9. <https://doi.org/10.2215/CJN.05850809>
 52. Hwang J-C, Wang C-T, Chen C-A et al. Hypokalemia is associated with increased mortality rate in chronic hemodialysis patients. *Blood Purif* 2011;32:254–61. <https://doi.org/10.1159/000325226>
 53. Brookes EM, Snider J, Hart GK et al. Serum potassium abnormalities in chronic kidney disease: prevalence, patient characteristics and clinical outcomes. *Intern Med J* 2021;51:1906–18. <https://doi.org/10.1111/imj.14970>
 54. Shang G, Gao Y, Liu K et al. Serum potassium in elderly heart failure patients as a predictor of readmission within 1 year. *Heart Vessels* 2022;38:507–16.
 55. Jimenez-Marrero S, Cainzos-Achirica M, Monterde D et al. Impact on clinical outcomes and health costs of deranged potassium levels in patients with chronic cardiovascular, metabolic, and renal conditions. *Rev Esp Cardiol* 2021;74:312–20.
 56. Tanaka K, Saito H, Iwasaki T et al. Association between serum potassium levels and adverse outcomes in chronic kidney disease: the Fukushima CKD cohort study. *Clin Exp Nephrol* 2021;25:410–7. <https://doi.org/10.1007/s10157-020-02010-7>
 57. Li JF, Qu X, Gao Z et al. Association between dosing of spironolactone and outcomes in heart failure with preserved ejection fraction patients combined with chronic kidney disease—balance of efficacy and risk. *Front Pharmacol* 2023;14:1084442. <https://doi.org/10.3389/fphar.2023.1084442>
 58. Kanda E, Rastogi A, Murohara T et al. Clinical impact of suboptimal RAASi therapy following an episode of hyperkalemia. *BMC Nephrol* 2023;24:18. <https://doi.org/10.1186/s12882-022-03054-5>
 59. Lin DSH, Lin FJ, Lin YS et al. The effects of mineralocorticoid receptor antagonists on cardiovascular outcomes in patients with end-stage renal disease and heart failure. *Eur J Heart Fail* 2023;25:98–107. <https://doi.org/10.1002/ehf.2740>
 60. Tumlin JA, Kopyt NP, Wilson DJ. Safety and efficacy of maximally tolerated RAS therapy alone or in combination with spironolactone in diabetic kidney disease: effect on proteinuria and eGFR in the MRA-ACE trial. *J Am Soc Nephrol* 2022;33:677. <https://doi.org/10.1681/ASN.20223311S1677c>
 61. Sadjadi SA, McMillan JI, Jaipaul N et al. A comparative study of the prevalence of hyperkalemia with the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers. *Ther Clin Risk Manage* 2009;5:547–52.
 62. Khosla N, Kalaitzidis R, Bakris GL. Predictors of hyperkalemia risk following hypertension control with aldosterone blockade. *Am J Nephrol* 2009;30:418–24. <https://doi.org/10.1159/000237742>
 63. Weinberg JM, Appel LJ, Bakris G et al. Risk of hyperkalemia in nondiabetic patients with chronic kidney disease receiving antihypertensive therapy. *Arch Intern Med* 2009;169:1587–94. <https://doi.org/10.1001/archinternmed.2009.284>
 64. Knoll GA, Sahgal A, Nair RC et al. Renin-angiotensin system blockade and the risk of hyperkalemia in chronic hemodialysis patients. *Am J Med* 2002;112:110–4. [https://doi.org/10.1016/S0002-9343\(01\)01068-3](https://doi.org/10.1016/S0002-9343(01)01068-3)
 65. Hayashi K, Kumagai H, Saruta T. Effect of efonidipine and ACE inhibitors on proteinuria in human hypertension with renal impairment. *Am J Hypertens* 2003;16:116–22. [https://doi.org/10.1016/S0895-7061\(02\)03147-3](https://doi.org/10.1016/S0895-7061(02)03147-3)

66. Adelborg K, Nicolaisen SK, Hasvold P et al. Predictors for repeated hyperkalemia and potassium trajectories in high-risk patients—A population-based cohort study. *PLoS One* 2019;14:e0218739. <https://doi.org/10.1371/journal.pone.0218739>
67. Sengul E, Sahin T, Sevin E et al. Effect of spironolactone on urinary protein excretion in patients with chronic kidney disease. *Ren Fail* 2009;31:928–32. <https://doi.org/10.3109/08860220903216121>
68. Abolghasmi R, Taziki O. Efficacy of low dose spironolactone in chronic kidney disease with resistant hypertension. *Saudi J Kidney Dis Transplant* 2011;22:75–8.
69. Frohlich H, Nelges C, Tager T et al. Long-term changes of renal function in relation to ace inhibitor/angiotensin receptor blocker dosing in patients with heart failure and chronic kidney disease. *Am Heart J* 2016;178:28–36. <https://doi.org/10.1016/j.ahj.2016.03.024>
70. Eschaliel R, McMurray JJV, Swedberg K et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (eplerenone in mild patients hospitalization and survival study in heart failure). *J Am Coll Cardiol* 2013;62:1585–93. <https://doi.org/10.1016/j.jacc.2013.04.086>
71. Polson M, Lord TC, Kangethe A et al. Clinical and economic impact of hyperkalemia in patients with chronic kidney disease and heart failure. *J Manag Care Spec Pharm* 2017;23:S2–9.
72. Wetmore JB, Yan H, Horne L et al. Risk of hyperkalemia from renin-angiotensin-aldosterone system inhibitors and factors associated with treatment discontinuities in a real-world population. *Nephrol Dial Transplant* 2021;36:826–39. <https://doi.org/10.1093/ndt/gfz263>
73. Yang A, Shi M, Lau ESH et al. Clinical outcomes following discontinuation of renin-angiotensin-system inhibitors in patients with type 2 diabetes and advanced chronic kidney disease: a prospective cohort study. *eClinicalMedicine* 2023;55:101751. <https://doi.org/10.1016/j.eclim.2022.101751>
74. Buckallew AR, Teller KB, Watson R et al. Evaluation of the safety and tolerability of spironolactone in patients with heart failure and chronic kidney disease. *Eur J Clin Pharmacol* 2021;77:955–60. <https://doi.org/10.1007/s00228-020-03069-7>
75. De Rosa ML, Cardace P, Rossi M et al. Evaluation of long-term efficacy and tolerability of irbesartan in elderly hypertensive patients with renal impairment in an open-label study. *Curr Ther Res* 2002;63:201–15. [https://doi.org/10.1016/S0011-393X\(02\)80027-3](https://doi.org/10.1016/S0011-393X(02)80027-3)
76. Ren H, Leon SJ, Whitlock R et al. Prescription patterns of sodium and calcium polystyrene sulfonate in patients with hyperkalemia and chronic kidney disease receiving RAAS inhibitors. *Clin Kidney J* 2022;15:1713–9. <https://doi.org/10.1093/ckj/sfac077>
77. Riccio E, Capuano I, Buonanno P et al. RAAS inhibitor prescription and hyperkalemia event in patients with chronic kidney disease: a single-center retrospective study. *Front Cardiovasc Med* 2022;9:824095. <https://doi.org/10.3389/fcvm.2022.824095>
78. Uchida HA, Nakajima H, Hashimoto M et al. Efficacy and safety of esaxerenone in hypertensive patients with diabetic kidney disease: a multicenter, open-label, prospective study. *Adv Ther* 2022;39:5158–75.
79. Tang SCW, Chan KW, Ip DKM et al. Direct Renin Inhibition in Non-diabetic chronic Kidney disease (DRINK): a prospective randomized trial. *Nephrol Dial Transplant* 2021;36:1648–56. <https://doi.org/10.1093/ndt/gfaa085>
80. Bakris G, Pergola PE, Delgado B et al. Effect of KBP-5074 on blood pressure in advanced chronic kidney disease: results of the BLOCK-CKD study. *Hypertension* 2021;78:74–81. <https://doi.org/10.1161/HYPERTENSIONAHA.121.17073>
81. Einhorn LM, Zhan M, Hsu VD et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009;169:1156–62. <https://doi.org/10.1001/archinternmed.2009.132>
82. Johnson ES, Weinstein JR, Thorp ML et al. Predicting the risk of hyperkalemia in patients with chronic kidney disease starting lisinopril. *Pharmacoepidemiol Drug Saf* 2010;19:266–72. <https://doi.org/10.1002/pds.1923>
83. Raebel MA, Ross C, Xu S et al. Diabetes and drug-associated hyperkalemia: effect of potassium monitoring. *J Gen Intern Med* 2010;25:326–33. <https://doi.org/10.1007/s11606-009-1228-x>
84. Frimodt-Moller M, Hoj Nielsen A, Strandgaard S et al. Feasibility of combined treatment with enalapril and candesartan in advanced chronic kidney disease. *Nephrol Dial Transplant* 2010;25:842–7. <https://doi.org/10.1093/ndt/gfp547>
85. Taheri S, Mortazavi M, Pourmoghadas A et al. A prospective double-blind randomized placebo-controlled clinical trial to evaluate the safety and efficacy of spironolactone in patients with advanced congestive heart failure on continuous ambulatory peritoneal dialysis. *Saudi J Kidney Dis Transpl* 2012;23:507–12.
86. Espinel E, Joven J, Gil I et al. Risk of hyperkalemia in patients with moderate chronic kidney disease initiating angiotensin converting enzyme inhibitors or angiotensin receptor blockers: a randomized study. *BMC Res Notes* 2013;6:306. <https://doi.org/10.1186/1756-0500-6-306>
87. Boesby L, Elung-Jensen T, Klausen TW et al. Moderate antiproteinuric effect of add-on aldosterone blockade with eplerenone in non-diabetic chronic kidney disease: a randomized cross-over study. *PLoS One* 2011;6:e26904. <https://doi.org/10.1371/journal.pone.0026904>
88. Edwards NC, Steeds RP, Chue CD et al. The safety and tolerability of spironolactone in patients with mild to moderate chronic kidney disease. *Brit J Clin Pharmacol* 2012;73:447–54. <https://doi.org/10.1111/j.1365-2125.2011.04102.x>
89. Tseng WC, Liu JS, Hung SC et al. Effect of spironolactone on the risks of mortality and hospitalization for heart failure in pre-dialysis advanced chronic kidney disease: a nationwide population-based study. *Int J Cardiol* 2017;238:72–8. <https://doi.org/10.1016/j.ijcard.2017.03.080>
90. Ando K, Ohtsu H, Uchida S et al. Anti-albuminuric effect of the aldosterone blocker eplerenone in non-diabetic hypertensive patients with albuminuria: a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2014;2:944–53. [https://doi.org/10.1016/S2213-8587\(14\)70194-9](https://doi.org/10.1016/S2213-8587(14)70194-9)
91. Maddirala S, Khan A, Vincent A et al. Effect of angiotensin converting enzyme inhibitors and angiotensin receptor blockers on serum potassium levels and renal function in ambulatory outpatients: risk factors analysis. *Am J Med Sci* 2008;336:330–5. <https://doi.org/10.1097/MAJ.0b013e3181836ac7>
92. Rysava R, Tesar V, Merta M. Effect of telmisartan on blood pressure control and kidney function in

- hypertensive, proteinuric patients with chronic kidney disease. *Blood Press Monit* 2005;10:207–13. <https://doi.org/10.1097/01.mbp.0000172708.97534.15>
93. Pitt B, Filippatos G, Agarwal R et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;385:2252–63. <https://doi.org/10.1056/NEJMoa2110956>
 94. Bakris GL, Agarwal R, Anker SD et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;383:2219–29. <https://doi.org/10.1056/NEJMoa2025845>
 95. Agarwal R, Joseph A, Anker SD et al. Hyperkalemia risk with finerenone: results from the FIDELIO-DKD trial. *J Am Soc Nephrol* 2022;33:225–37. <https://doi.org/10.1681/ASN.2021070942>
 96. Zhang H. Effect of finerenone on CKD outcomes in type 2 diabetes: a Chinese subgroup analysis of the FIDELIO-DKD study. *Kidney week. J Am Soc Nephrol* 2022;33:678.
 97. Filippatos G, Anker SD, Agarwal R et al. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. *Circulation* 2021;143:540–52. <https://doi.org/10.1161/CIRCULATIONAHA.120.051898>
 98. Rossing P, Filippatos G, Agarwal R et al. Finerenone in predominantly advanced CKD and type 2 diabetes with or without sodium-glucose cotransporter-2 inhibitor therapy. *Kidney Int Rep* 2022;7:36–45. <https://doi.org/10.1016/j.ekir.2021.10.008>
 99. Rossing P, Burgess E, Agarwal R et al. Finerenone in patients with chronic kidney disease and type 2 diabetes according to baseline hba1c and insulin use: an analysis from the FIDELIO-DKD study. *Diabetes Care* 2022;45:e888–97. <https://doi.org/10.2337/dc21-1944>
 100. Zhang H, Xie J, Hao C et al. Finerenone in patients with chronic kidney disease and type 2 diabetes: the FIDELIO-DKD subgroup from China. *Kidney Dis* 2023;9:498–506. <https://doi.org/10.1159/000531997>
 101. Fang G, Annis IE, Farley JF et al. Incidence of and risk factors for severe adverse events in elderly patients taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers after an acute myocardial infarction. *Pharmacotherapy* 2018;38:29–41. <https://doi.org/10.1002/phar.2051>
 102. Silvarino R, Rios P, Baldovinos G et al. Is chronic kidney disease progression influenced by the type of renin-angiotensin-system blocker used? *Nephron* 2019;143:100–7. <https://doi.org/10.1159/000500925>
 103. Linde C, Bakhai A, Furuland H et al. Real-world associations of renin-angiotensin-aldosterone system inhibitor dose, hyperkalemia, and adverse clinical outcomes in a cohort of patients with new-onset chronic kidney disease or heart failure in the United Kingdom. *J Am Heart Assoc* 2019;8:e012655. <https://doi.org/10.1161/JAHA.119.012655>
 104. Iskandar H, Hidayat, WU, Hersunaryati YA et al. A retrospective study on the potential drug interaction between angiotensin converting enzyme inhibitor or angiotensin receptor antagonist and other drugs in end-stage chronic renal failure patients. *Int Res J Pharmacy* 2012;3:86–9.
 105. Kashihara N, Kohsaka S, Kanda E et al. Hyperkalemia in real-world patients under continuous medical care in Japan. *Kidney Int Rep* 2019;4:1248–60. <https://doi.org/10.1016/j.ekir.2019.05.018>
 106. Saito Y, Yamamoto H, Nakajima H et al. Incidence of and risk factors for newly diagnosed hyperkalemia after hospital discharge in non-dialysis-dependent CKD patients treated with RAS inhibitors. *PLoS One* 2017;12:e0184402. <https://doi.org/10.1371/journal.pone.0184402>
 107. Pitt B, Kober L, Ponikowski P et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur Heart J* 2013;34:2453–63. <https://doi.org/10.1093/eurheartj/ehd187>
 108. Persson F, Lewis JB, Lewis EJ et al. Impact of baseline renal function on the efficacy and safety of Aliskiren added to losartan in patients with type 2 diabetes and nephropathy. *Diabetes Care* 2010;33:2304–9. <https://doi.org/10.2337/dc10-0833>
 109. Gwoo S, Kim YN, Shin HS et al. Predictors of hyperkalemia risk after hypertension control with aldosterone blockade according to the presence or absence of chronic kidney disease. *Nephron Clin Pract* 2014;128:381–6. <https://doi.org/10.1159/000369138>
 110. Vukusich A, Kunstmann S, Varela C et al. A randomized, double-blind, placebo-controlled trial of spironolactone on carotid intima-media thickness in nondiabetic hemodialysis patients. *Clin J Am Soc Nephrol* 2010;5:1380–7. <https://doi.org/10.2215/CJN.09421209>
 111. Walsh M, Manns B, Garg AX et al. The safety of eplerenone in hemodialysis patients: a noninferiority randomized controlled trial. *Clin J Am Soc Nephrol* 2015;10:1602–8. <https://doi.org/10.2215/CJN.12371214>
 112. An J, Niu F, Sim JJ. Cardiovascular and kidney outcomes of spironolactone or eplerenone in combination with ACEI/ARBs in patients with diabetic kidney disease. *Pharmacotherapy* 2021;41:998–1008. <https://doi.org/10.1002/phar.2633>
 113. Qu X, Yao H, Chen C et al. Spironolactone improves the all-cause mortality and re-hospitalization rates in acute myocardial infarction with chronic kidney disease patients. *Front Pharmacol* 2021;12:632978. <https://doi.org/10.3389/fphar.2021.632978>
 114. Edwards NC, Price AM, Mehta S et al. Effects of spironolactone and chlorthalidone on cardiovascular structure and function in chronic kidney disease: a randomized, open-label trial. *Clin J Am Soc Nephrol* 2021;16:1491–501. <https://doi.org/10.2215/CJN.01930221>
 115. Straburzynska-Migaj E, Senni M, Wachter R et al. Initiation of sacubitril/valsartan in patients with renal impairment early after acute decompensated heart failure in the TRAN-SITION study. *Eur J Heart Fail* 2021;23:46.
 116. Ruilope LM, Aldigier JC, Ponticelli C et al. Safety of the combination of valsartan and benazepril in patients with chronic renal disease. *J Hypertens* 2000;18:89–95. <https://doi.org/10.1097/00004872-200018010-00013>
 117. De Rosa ML, De Cristofaro A, Rossi M et al. Irbesartan effects on renal function in patients with renal impairment and hypertension: a drug-withdrawal study. *J Cardiovasc Pharmacol* 2001;38:482–9. <https://doi.org/10.1097/00005344-200109000-00017>
 118. Hammer F, Malzahn U, Donhauser J et al. A randomized controlled trial of the effect of spironolactone on left ventricular mass in hemodialysis patients. *Kidney Int* 2019;95:983–91. <https://doi.org/10.1016/j.kint.2018.11.025>
 119. Charytan DM, Himmelfarb J, Ikizler TA et al. Safety and cardiovascular efficacy of spironolactone in dialysis-dependent ESRD (SPin-D): a randomized, placebo-controlled, multiple dosage trial. *Kidney Int* 2019;95:973–82. <https://doi.org/10.1016/j.kint.2018.08.034>

120. Haynes R, Judge PK, Staplin N et al. Effects of sacubitril/valsartan versus irbesartan in patients with chronic kidney disease: a randomized double-blind trial. *Circulation* 2018;138:1505–14. <https://doi.org/10.1161/CIRCULATIONAHA.118.034818>
121. Lee J-H, Kwon YE, Park JT et al. The effect of renin-angiotensin system blockade on renal protection in chronic kidney disease patients with hyperkalemia. *J Renin Angiotensin Aldosterone Syst* 2014;15:491–7. <https://doi.org/10.1177/1470320313507122>
122. Agrawal A, Kamila S, Reddy S et al. Effect of telmisartan on kidney function in patients with chronic kidney disease: an observational study. *J Drug Assess* 2016;5:24–28. <https://doi.org/10.1080/21556660.2016.1252380>
123. Woo K-T, Choong H-L, Wong K-S et al. A retrospective aliskiren and losartan study in non-diabetic chronic kidney disease. *World J Nephrol* 2013;2:129–35.
124. Yildirim T, Arici M, Piskinpasa S et al. Major barriers against renin-angiotensin-aldosterone system blocker use in chronic kidney disease stages 3-5 in clinical practice: a safety concern? *Ren Fail* 2012;34:1095–9. <https://doi.org/10.3109/0886022X.2012.717478>
125. Pisoni R, Acelajado MC, Cartmill FR et al. Long-term effects of aldosterone blockade in resistant hypertension associated with chronic kidney disease. *J Hum Hypertens* 2012;26:502–6. <https://doi.org/10.1038/jhh.2011.60>
126. Hirai T, Yamaga R, Fujita A et al. Low body mass index is a risk factor for hyperkalaemia associated with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers treatments. *J Clin Pharm Ther* 2018;43:829–35. <https://doi.org/10.1111/jcpt.12720>
127. Jun M, Jardine MJ, Perkovic V et al. Hyperkalemia and renin-angiotensin aldosterone system inhibitor therapy in chronic kidney disease: a general practice-based, observational study. *PLoS One* 2019;14:e0213192. <https://doi.org/10.1371/journal.pone.0213192>
128. Belmar Vega L, Galabia ER, Bada da Silva J et al. Epidemiology of hyperkalemia in chronic kidney disease. *Nefrologia* 2019;39:277–86. <https://doi.org/10.1016/j.nefro.2018.11.011>
129. Beldhuis IE, Myhre PL, Claggett B et al. Efficacy and safety of spironolactone in patients with HFpEF and chronic kidney disease. *JACC Heart Fail* 2019;7:25–32.
130. Heshka J, Ruzicka M, Hiremath S et al. Spironolactone for difficult to control hypertension in chronic kidney disease: an analysis of safety and efficacy. *J Am Soc Hypertens* 2010;4:295–301. <https://doi.org/10.1016/j.jash.2010.09.006>
131. Johnson M, Morrison FJ, McMahon G et al. Outcomes in patients with cardiometabolic disease who develop hyperkalemia while treated with a renin-angiotensin-aldosterone system inhibitor. *Am Heart J* 2023;258:49–59. <https://doi.org/10.1016/j.ahj.2023.01.002>
132. Provenzano M, Puchades MJ, Garofalo C et al. Albuminuria-lowering effect of dapagliflozin, eplerenone, and their combination in patients with chronic kidney disease: a randomized cross-over clinical trial. *J Am Soc Nephrol* 2022;33:1569–80. <https://doi.org/10.1681/ASN.2022020207>
133. Leon SJ, Whitlock R, Rigatto C et al. Hyperkalemia-related discontinuation of renin-angiotensin-aldosterone system inhibitors and clinical outcomes in CKD: a population-based cohort study. *Am J Kidney Dis* 2022;80:164–73.e1. <https://doi.org/10.1053/j.ajkd.2022.01.002>
134. Salik JR, Golas SB, McCoy TH. A comparative study assessing the incidence and degree of hyperkalemia in patients on angiotensin-converting enzyme inhibitors versus angiotensin-receptor blockers. *J Hum Hypertens* 2022;36:485–7. <https://doi.org/10.1038/s41371-021-00625-1>
135. Tokunaga M, Kabashima N, Serino R et al. Renoprotective effects of telmisartan in patients with advanced chronic kidney disease. *Clin Nephrol* 2010;73:139–46. <https://doi.org/10.5414/CNP73139>
136. Bhandari S, Mehta S, Khwaja A et al. Renin-angiotensin system inhibition in advanced chronic kidney disease. *N Engl J Med* 2022;387:2021–32. <https://doi.org/10.1056/NEJMoa2210639>
137. Fu EL, Evans M, Clase CM et al. Stopping renin-angiotensin system inhibitors in patients with advanced CKD and risk of adverse outcomes: a nationwide study. *J Am Soc Nephrol* 2021;32:424. <https://doi.org/10.1681/ASN.2020050682>
138. Ahmed AK, Kamath NS, El Kossi M et al. The impact of stopping inhibitors of the renin-angiotensin system in patients with advanced chronic kidney disease. *Nephrol Dial Transplant* 2010;25:3977–82. <https://doi.org/10.1093/ndt/gfp511>
139. Parmar S, Ali M, Lopez T et al. WCN24-2118 Hyperkalaemia in patients with chronic kidney disease and heart failure. *Kidney Int Rep* 2024;9:S327–8. <https://doi.org/10.1016/j.ekir.2024.02.633>
140. Sevamontree C, Jintajirapan S, Phakdeekitcharoen P et al. The prevalence and risk factors of hyperkalemia in the outpatient setting. *Int J Nephrol* 2024;2024:1–9. <https://doi.org/10.1155/2024/5694131>
141. Valdivielso JM, Carriazo S, Martin M et al. Gender-specific risk factors and outcomes of hyperkalemia in CKD patients: smoking as a driver of hyperkalemia in men. *Clin Kidney J* 2024;17:sfad212. <https://doi.org/10.1093/ckj/sfad212>
142. Gülçiçek S, Seyahi N. Hyperkalemia: a cause of non-adherence to renin-angiotensin-aldosterone system inhibitors in chronic kidney disease: a retrospective study. *Istanbul Med J* 2023;24:404–11. <https://doi.org/10.4274/imj.galenos.2023.55889>
143. Zhou J, Jin X, Zhou J et al. Clinical outcomes by serum potassium levels for patients hospitalized for heart failure: Secondary analysis of data from the China National Heart Failure Registry. *Clin Cardiol* 2023;46:1345–52. <https://doi.org/10.1002/clc.24114>
144. Qadir A, Ullah Z, Khalil MD et al. Frequency of hyperkalaemia in non-dialysis dependent chronic kidney disease (CKD) patients. *Medical Forum Monthly* 2023;34.
145. de Rooij EN, de Fijter JW, Le Cessie S et al. Serum potassium and risk of death or kidney replacement therapy in older people with CKD stages 4-5: eight-year follow-up. *Am J Kidney Dis* 2023;82:257–66.e1. <https://doi.org/10.1053/j.ajkd.2023.03.008>
146. Perez-Navarro LM, Valdez-Ortiz R, Reyna-Blanco J. Prevalence and factors associated with hyperkalemia in outpatients with CKD. *J Am Soc Nephrol* 2023;34:397. <https://doi.org/10.1681/ASN.20233411S1397a>
147. Bakris GL, Agiro A, Greatsinger A et al. REVOLUTIONIZE III: consequences of recurrent hyperkalemia on healthcare resource utilization and cost. *J Am Soc Nephrol* 2023;34:190–1. <https://doi.org/10.1681/ASN.20233411S1190d>
148. Gaol DL, Nilasari D, Halim DS et al. WCN24-2258 Serum potassium profile and associated factors in hemodialysis patients: single center study. *Kidney Int Rep* 2024;9:S8. <https://doi.org/10.1016/j.ekir.2024.02.028>
149. Rastogi A, Pollack C, Lesen E et al. Association between reduced RAASi therapy and progression to ESKD in

- hyperkalemic CKD patients. *J Am Soc Nephrol* 2023;34:379. <https://doi.org/10.1681/ASN.20233411S1379b>
150. Marup FH, Peters C, Nielsen S et al. Potassium levels and eGFR do not predict severe hyperkalemia following spironolactone introduction in patients with CKD at high risk of hyperkalemia. *Nephrol Dial Transplant* 2023;38:i668–9. https://doi.org/10.1093/ndt/gfad063c_3068
 151. Zhou Q, Yu W, Shao X et al. Efficacy and safety of sacubitril/valsartan in patients with stage 3B–5 CKD and hypertension. *Nephrol Dial Transplant* 2023;38:i665–7. https://doi.org/10.1093/ndt/gfad063c_5705
 152. Rajak K, Halder A, Khanal R et al. Renal dysfunction associated with finerenone—a pharmacovigilance analysis. *J Am Coll Cardiol* 2023;81:583. [https://doi.org/10.1016/S0735-1097\(23\)01027-6](https://doi.org/10.1016/S0735-1097(23)01027-6)
 153. Bornstein SR, de Zeeuw D, Heerspink HJ et al. Aldosterone synthase inhibitor (BI 690517) therapy for people with diabetes and albuminuric chronic kidney disease: a multicentre, randomized, double-blind, placebo-controlled, phase I trial. *Diabetes Obes Metab* 2024;26:2128–38. <https://doi.org/10.1111/dom.15518>
 154. Jiménez-Marrero S, Cainzos-Achirica M, Monterde D et al. Serum potassium abnormalities, renin-angiotensin-aldosterone system inhibitor discontinuation, and clinical outcomes in patients with chronic cardiovascular, metabolic, and renal conditions: a population-based analysis. *Eur J Inter Med* 2024;125:89–97. <https://doi.org/10.1016/j.ejim.2024.03.021>
 155. García-Prieto A, Verdalles Ú, de José AP et al. Renin-angiotensin-aldosterone system blockers effect in chronic kidney disease progression in hypertensive elderly patients without proteinuria: PROERCAN trial. *Hipertens Riesgo Vasc* 2024;41:95–103. <https://doi.org/10.1016/j.hipert.2023.11.005>
 156. An J, Zhou H, Ni L et al. Discontinuation of renin-angiotensin-aldosterone system inhibitors secondary to hyperkalemia translates into higher cardiorenal outcomes. *Am J Nephrol* 2023;54:258–67. <https://doi.org/10.1159/000531102>
 157. Agiro A, AN A, Cook EE et al. Real-world modifications of renin-angiotensin-aldosterone system inhibitors in patients with hyperkalemia initiating sodium zirconium cyclosilicate therapy: the OPTIMIZE I study. *Adv Ther* 2023;40:2886–901. <https://doi.org/10.1007/s12325-023-02518-w>
 158. Gregg LP, Richardson P, Herrera MA et al. Documented adverse drug reactions and discontinuation of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in chronic kidney disease. *Am J Nephrol* 2023;54:126–35. <https://doi.org/10.1159/000530988>
 159. Chinnadurai R, Rengarajan S, Budden JJ et al. Maintaining renin-angiotensin-aldosterone system inhibitor treatment with patiomer in hyperkalaemic chronic kidney disease patients: comparison of a propensity-matched real-world population with AMETHYST-DN. *Am J Nephrol* 2023;54:408–15. <https://doi.org/10.1159/000533753>
 160. Nicholas SB, Correa-Rotter R, Desai N et al. Interim results from FINE-REAL: a prospective study providing insights into the use of finerenone in routine clinical settings. *J Am Soc Nephrol* 2023;34:857. <https://doi.org/10.1681/ASN.20233411S1857a>
 161. McFarland KL, Sheridan EA. A retrospective analysis of sacubitril/valsartan in heart failure and chronic kidney disease. *J Pharm Technol* 2023;39:117–22. <https://doi.org/10.1177/87551225231168543>
 162. Ding Y, Wan L, Z-c Z et al. Effects of sacubitril-valsartan in patients undergoing maintenance dialysis. *Ren Fail* 2023;45:2222841. <https://doi.org/10.1080/0886022X.2023.2222841>
 163. Jariwala P, Pramod G. Effect of finerenone on heart failure outcomes in type 2 diabetes with chronic kidney disease: an early Indian experience. *Indian Heart J* 2023;75:S49. <https://doi.org/10.1016/j.ihj.2023.11.105>
 164. Svensson M, Kim K, Cars T et al. EE268 healthcare costs and all-cause mortality following a hyperkalemia event and reduction of RAASi therapy in Sweden. *Value Health* 2023;26:S103. <https://doi.org/10.1016/j.jval.2023.09.535>
 165. Tuttle KR, Hauske SJ, Canziani ME et al. Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease: a randomised, controlled, phase 2 trial. *Lancet* 2024;403:379–90. [https://doi.org/10.1016/S0140-6736\(23\)02408-X](https://doi.org/10.1016/S0140-6736(23)02408-X)
 166. Guney I, Selcuk NY, Altintepe L et al. Antifibrotic effects of aldosterone receptor blocker (spironolactone) in patients with chronic kidney disease. *Ren Fail* 2009;31:779–84. <https://doi.org/10.3109/08860220903150312>
 167. Edwards NC, Steeds RP, Stewart PM et al. Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. *J Am Coll Cardiol* 2009;54:505–12. <https://doi.org/10.1016/j.jacc.2009.03.066>
 168. Obertynska O. The risks and benefits of spironolactone use in heart failure with a reduced left ventricular ejection fraction and chronic kidney disease. *Eur Heart J* 2021;42:895. <https://doi.org/10.1093/eurheartj/ehab724.0895>
 169. An JN, Lee JP, Jeon HJ et al. Severe hyperkalemia requiring hospitalization: predictors of mortality. *Crit Care* 2012;16:1–14. <https://doi.org/10.1186/cc11872>
 170. Gilligan S, Raphael KL. Hyperkalemia and hypokalemia in CKD: prevalence, risk factors, and clinical outcomes. *Adv Chronic Kidney Dis* 2017;24:315–8. <https://doi.org/10.1053/j.ackd.2017.06.004>
 171. Kovesdy CP. Updates in hyperkalemia: outcomes and therapeutic strategies. *Rev Endocr Metab Disord* 2017;18:41–7. <https://doi.org/10.1007/s11154-016-9384-x>
 172. Matus Gonzalez A, Evangelidis N, Howell M et al. Outcomes for clinical trials involving adults with chronic kidney disease: a multinational Delphi survey involving patients, caregivers and health professionals. *Nephrol Dial Transplant* 2024;gfae010.
 173. Perazella MA. Drug-induced hyperkalemia: old culprits and new offenders. *Am J Med* 2000;109:307–14. [https://doi.org/10.1016/S0002-9343\(00\)00496-4](https://doi.org/10.1016/S0002-9343(00)00496-4)
 174. Fitch K, Woolley JM, Engel T et al. The clinical and economic burden of hyperkalemia on medicare and commercial payers. *Am Health Drug Benefits* 2017;10:202.
 175. Evans M, Lewis RD, Morgan AR et al. A narrative review of chronic kidney disease in clinical practice: current challenges and future perspectives. *Adv Ther* 2022;39:33–43. <https://doi.org/10.1007/s12325-021-01927-z>

[Click here for Prescribing Information](#)




This is a promotional advertisement intended for UK HCPs only, produced and funded by MEDICE UK

Vafseo® is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis¹

> A once-daily oral treatment for anaemia associated with CKD in patients receiving dialysis¹

Vafseo® is now recommended by NICE, within its marketing authorisation, as an option for treating symptomatic anaemia caused by CKD in adults having maintenance dialysis²



Contact MEDICE UK now to be put in touch with your regional Vafseo® Key Account Manager

Contact Us

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Adverse events should be reported. Reporting forms and information can be found at <https://yellowcard.mhra.gov.uk/> or search for MHRA Yellow Card in Google Play or Apple App Store. Adverse events should also be reported to Medice UK Ltd, 0204 582 2845, medicalinformation@medice.co.uk

MEDICE UK makes no warranties or representations of any kind as to the accuracy, completeness, reliability or usefulness of any information contained in third party sites and shall have no liability for any loss or damage of any kind that may arise from your use of such content or information. Inclusion of any third-party link does not imply an endorsement or recommendation by MEDICE UK.

Abbreviations: CKD, chronic kidney disease; HCP, healthcare professional; NICE, National Institute of Health and Care Excellence. **References:** 1. Vafseo 300 mg film-coated tablets Summary of Product Characteristics (SmPC). Available at: <https://www.medicines.org.uk/emc/product/15856/ampc> (Accessed March 2025). 2. NICE Guidance TA1035. Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease. Available at: <https://www.nice.org.uk/guidance/ta1035> (Accessed March 2025).



UK-VAF-2024-1863-v2
March 2025