International Journal of Research in Medical Sciences
Kapair S et al. Int J Res Med Sci. 2026 Dec;14(12):5890-5901
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20264499

Meta-Analysis

Permissive hyperkalemia versus aggressive potassium correction in patients with heart failure receiving renin-angiotensin-aldosterone system inhibitors: associations with mortality, arrhythmia and kidney outcomes

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Received: 02 September 2026
Revised: 08 November 2026
Accepted: 16 November 2026

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ABSTRACT

Hyperkalemia frequently complicates renin-angiotensin-aldosterone system (RAAS) inhibitor therapy in patients with heart failure (HF), potentially leading to treatment interruption. This systematic review and meta-analysis evaluated clinical outcomes associated with monitored permissive potassium management compared with more aggressive potassium correction in HF patients receiving RAAS inhibitors. PubMed, EMBASE, CENTRAL, Web of Science, Scopus, CINAHL, ClinicalTrials.gov, and other sources were searched. Randomized trials, post-hoc analyses, and prospective or retrospective cohort studies comparing potassium-management strategies were eligible. Random-effects models were used to pool effect estimates. Ten studies involving 14,473 patients were included. Permissive potassium management was associated with lower all-cause mortality (HR 0.82, 95% CI 0.74-0.91) and cardiovascular mortality (HR 0.79, 95% CI 0.70-0.89). Sudden cardiac death was also lower (RR 0.78, 95% CI 0.66-0.92), whereas ventricular arrhythmia did not differ significantly (RR 0.91, 95% CI 0.79-1.05). RAAS inhibitor discontinuation was less frequent with permissive management (RR 0.31, 95% CI 0.24-0.40). However, severe hyperkalemia was more frequent (RR 2.47, 95% CI 1.89-3.22). Permissive management was also associated with greater preservation of eGFR and fewer rehospitalizations. Because the evidence included observational studies and heterogeneous potassium-management strategies, these findings represent associations and do not establish that tolerating higher potassium directly improves outcomes. Monitored potassium management may help avoid unnecessary RAAS inhibitor discontinuation, but patients require individualized monitoring and prompt treatment of clinically significant hyperkalemia.

Keywords: Hyperkalemia, Heart failure, Meta-analysis, RAAS inhibitors, Permissive hyperkalemia

INTRODUCTION

Heart failure (HF) is a common cardiovascular syndrome that is associated with significant morbidity, repeat admission, worsening renal function and mortality. Pharmacological blocking of the RAAS remains a key component of guideline-directed medical therapy, especially in HF with reduced ejection fraction (HFrEF).

Angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), and mineralocorticoid receptor antagonists (MRAs) have all been shown to improve cardiovascular outcomes by decreasing maladaptive neurohormonal activation, ventricular remodeling, congestion, and disease progression.[1] Nevertheless, these treatments can be complicated by hyperkalemia, especially in hospitalized patients with HF, who frequently have underlying renal dysfunction, diabetes, advanced age and multiple potassium-modifying drugs.[2]

A serum potassium level above the normal physiological level is usually considered hyperkalemia, but the cut-off values for clinically relevant hyperkalemia differ from study to study and in different clinical contexts. Potassium homeostasis is even more intricate in the context of HF, as renal potassium excretion via aldosterone is reduced by RAAS inhibition, while acute kidney injury, chronic kidney disease, hemodynamic instability, and diuretic therapy adjustments can further affect potassium regulation.[2,3] Hence, hyperkalemia often occurs during hospitalization for acute or decompensated HF. Around 35% of the patients in the PROTECT trial population developed incident hyperkalemia on hospitalization for acute HF. Importantly, hyperkalemia was linked to down-titration of MRA therapy while maintenance or intensification of RAAS inhibitor therapy was linked to lower subsequent mortality.[3] Hyperkalemia is a therapeutic challenge in patients on RAAS inhibitors. On the other hand, elevated or rapidly rising potassium levels can cause clinically significant cardiac conduction defects and/or potentially life-threatening cardiac arrhythmias necessitating immediate correction in certain patients and settings.[4,5] Excessive potassium lowering or withdrawal of RAAS inhibition could jeopardize patients' access to therapies that have proven to offer clinical benefits in survival and cardiovascular outcomes. This is especially important for patients in the hospital who might have symptomatic potassium levels that are just slightly higher and who may have ACE inhibitors, ARBs, ARNIs/MRAs withheld due to those levels. This disruption in treatment can then be followed by reduced utilization of guideline-directed therapy following discharge.[6] The association between serum potassium and clinical outcomes is increasingly not linear. Low and high potassium levels have been linked to poor outcomes in HF, resulting in U-shaped or J-shaped relationships between potassium and mortality.[7] Hypokalaemia and hyperkalaemia were both independently related to increased cardiovascular mortality rates in PARADIGM-HF population relative to potassium levels in mid-normal range.[7] Hyperkalemia is not independently associated with mortality after adjustment for other clinical parameters in studies of hospitalized HF population, while hypokalemia is associated with adverse cardiac outcomes.[2] These results suggest that serum potassium could serve as direct indicator of electrophysiological risk and as a marker of disease severity, kidney dysfunction, medication changes, and disruption of beneficial HF therapies.[2] There has been growing recognition of potential problems that can occur if RAAS inhibition is discontinued after hyperkalemia. Hyperkalemia was found to be associated with mortality in a large observational study of HF patients, but this association was no longer observed after adjusting for discontinuation of RAAS inhibitors, while RAAS inhibitor discontinuation was strongly associated with mortality.[8] In patients admitted to hospital for HFrEF, stopping ACEI/ARB treatment was also linked with increased post-discharge mortality and readmission rates.[6] This concern has been supported by more recent data, which showed that discontinuing RAAS inhibitors after hyperkalemia was associated with higher mortality rates despite a lower rate of hyperkalemia.[9] Such results indicate a tradeoff between avoiding the problems associated with potassium and potential of compromised cardiovascular protection.

Modern management involves biochemical close monitoring, modifying the contributing drugs, optimizing diuretic therapy, diet management and potassium-binding agents in appropriate situations.[2,3,5] In patients with HFrEF and prior or current RAAS inhibitor-related hyperkalemia, the DIAMOND trial showed the efficacy of patiromer to support maintenance of treatment with RAAS inhibitors in accordance with guidelines.[10] The results suggest a transition from blanket potassium discontinuation to personalized potassium management, prioritizing the potential for short-term hyperkalemia while acknowledging the proven long-term benefits of RAAS inhibition. However, there is a significant clinical question of whether potassium levels should be aggressively corrected in the HF hospitalized patient on RAAS blockade. That severe hyperkalemia deserves urgent treatment is beyond doubt, but the best strategy for treating mild or moderate hyperkalemia is not as clear.[5] Aggressive correction may be used to decrease arrhythmic risk associated with potassium levels but may increase the risk that the RAAS inhibitor will be stopped, renal instability will develop, or hypokalemia will develop. The alternative approach, a permissive strategy of cautious use of RAAS inhibitors within clinically acceptable potassium levels, may be beneficial to maintain the cardiovascular and renal effects of guideline-directed therapy, but in patients at immediate risk of complications related to potassium levels, careful monitoring and appropriate treatment are necessary. The potassium correction/RAAS maintenance issue is a clinically relevant treatment dilemma in hospitalized HF patients. Existing studies have assessed hyperkalemia, discontinuation of RAAS inhibitors, potassium-lowering therapy, and cardiovascular or renal outcomes, but the evidence is not consistent with respect to potassium thresholds, patient populations, treatment strategies, and outcome definitions.[2,7-10] A comparison of permissive hyperkalemia versus aggressive potassium correction may help shed light on whether there are differences in mortality, clinically significant arrhythmias, and kidney outcomes associated with maintaining RAAS inhibition and tolerating clinically acceptable potassium levels. To assess the impact of permissive vs aggressive K

management in hospitalized patients with HF treated with RAAS inhibitors, this systematic review and meta-analysis was performed, focusing on mortality, arrhythmia, and renal outcomes.

METHODS

Study design

The aim of this systematic review and meta-analysis was to assess the clinical outcomes and risk of adverse events between permissive hyperkalemia and aggressive potassium correction in HF patients on RAAS inhibitors. The review was developed using population, intervention, comparator, and outcomes (PICO) format and presented using the preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) guidelines.

Eligibility criteria

Studies were eligible if they involved adults with HF treated with RAAS inhibitor therapy (ACE inhibitor, ARB, ARNIs, and mineralocorticoid receptor antagonist) who experienced or were at risk of hyperkalemia. The intervention of interest was a potassium-management strategy that was permissive or RAAS preserving, which included continuation or maintenance of RAAS inhibitor therapy despite mild-to-moderate hyperkalemia, with potassium monitoring and/or potassium-lowering therapy when clinically indicated. The comparative arm was a more aggressive approach to potassium correction (active reduction of serum potassium) and more interruption, down-titration, or discontinuation of RAAS inhibitor therapy. Randomized controlled trials, post-hoc analyses of RCTs, prospective cohort studies, and retrospective cohort studies were eligible study designs. Studies in pediatric patients, in patients without HF, without an appropriate comparator group, without outcomes on a relevant potassium-management strategy, review or editorial, duplicate cohorts and without sufficient outcome data were excluded.

Search strategy

A detailed search of the literature was carried out in PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus, CINAHL, ClinicalTrials.gov, and in various grey literature sources. The search strategy included the terms for HF, hyperkalemia, potassium management, RAAS inhibitors, ACE inhibitors, ARB, ARNIs, MRAs, potassium binders, treatment continuation or discontinuation, mortality, arrhythmia, renal outcomes. Relevant articles and reviews were also manually screened in reference lists to identify others that were eligible.

Study selection

Titles and abstracts were independently screened after elimination of the duplicates, based on the pre-established eligibility criteria. Full-text review then was used to determine if the records were potentially relevant. All studies that fulfilled all the eligibility criteria were included in the final systematic review and meta-analysis. Conflicting comments by reviewers were clarified and settled by discussion and consensus. The inter-rater agreement was measured by Cohen's kappa statistic between reviewers both at the title/abstract screening and full-text assessment.

Data extraction

A standard extraction form was used to extract data. The following variables were extracted: study author and year, study design, country, number of subjects, HF phenotype, mean age, sex distribution, left ventricular ejection fraction, baseline serum potassium, estimated glomerular filtration rate, RAAS inhibitor regimen, potassium threshold or management strategy, and duration of follow-up. Outcome measures: All-cause mortality, cardiovascular mortality, sudden cardiac death, ventricular arrhythmia, discontinuation of the RAAS inhibitors, AKI, change in renal function, re-hospitalization, hospital length of stay, and severe hyperkalemia. Where available, hazard ratios (HRs), risk ratios (RRs), mean differences (MDs), 95% confidence intervals (CIs), and corresponding variance estimates were extracted.

Outcomes

All-cause mortality was the primary outcome. Secondary outcomes were cardiovascular mortality, sudden cardiac death, ventricular arrhythmia, discontinuation of RAAS inhibitors, AKI, change in estimated glomerular filtration rate (eGFR), 30-day all-cause rehospitalization, 90-day HF rehospitalization, and hospital length of stay. The most severe adverse effect was defined as severe hyperkalemia, which was typically defined as a serum potassium concentration >6.5 mEq/l, but was otherwise left as reported by individual studies.

Risk of bias assessment

The level of risk of bias was evaluated based on the study design. The Cochrane Risk of Bias 2 (RoB 2) tool was used to assess the randomized controlled trials and randomized trial post hoc analyses with regard to randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. The Newcastle-Ottawa Scale (NOS) was used for assessing the observational cohort studies that were evaluated, assessing study selection, comparability and outcome assessment. The studies with an NOS score of 7 or above were considered to be of high methodological quality.

Statistical analysis

Random-effects models were used for meta-analyses, as differences were anticipated among the study populations, potassium thresholds, RAAS inhibitor regimens,

potassium-management strategies, study designs and follow-up durations. Meta-analyses were conducted using RevMan version 5.4 and Stata version 18.0. Hazard ratios were combined for time-to-event outcomes, risk ratios for dichotomous outcomes and mean differences for continuous outcomes on the same scale. A heterogeneity statistic (I^2) was used to evaluate statistical homogeneity, and values of about 25, 50 and 75% were regarded as low, moderate and high levels of heterogeneity, respectively.

RESULTS

Study selection

A total of 4,847 records were identified using systematic search (including from supplemental sources). At the end of duplicate record removal, 3,291 unique records were screened for title and abstract. Of these records, 3004 records excluded, and 287 records were submitted for full-text assessment. After full-text review, 277 studies were excluded from analysis because of lack of an appropriate comparator (n=68), an undefined potassium-management strategy (n=54), insufficient outcome data (n=49), follow-up periods of <30 days (n=38), duplicate cohorts (n=29), and non-heart-failure or pediatric populations (n=39). Overall, 10 studies fulfilled all eligibility criteria and were included in systematic review and meta-analysis (Figure 1). Inter-rater reliability was high at title and abstract screening phase (Cohen's κ=0.83) and was even higher at full-text screening (Cohen's κ=0.89).

Characteristics of included studies

The 10 studies included were published from 2006 to 2023, with five being randomized controlled trials or post-hoc analyses of RCTs and five being observational cohort studies, from 6 countries. The studies combined a total of 14,473 patients (6,973 patients in the permissive-management group, 7,500 patients in the aggressive-correction group). The age of the study population was around 68.9 years, and about 67% were male. The most common HF phenotype was HFrEF. Baseline serum potassium levels were between 4.6 and 5.5 mEq/l, and baseline eGFR was between 45.6 and 61.3 ml/min/1.73 m^2. Included studies that compared various combinations of RAAS inhibitors (ACEi, ARB, ARNi, and MRA and some newer studies included potassium binders. The thresholds used for potassium management ranged from 5.0 to 5.5 mEq/l, and follow-up periods varied between 6 and 36 months. The characteristics of the studies included are described in detail in Table 1.

Risk of bias and certainty of evidence

The overall risk of bias for all five randomized trials or randomized post-hoc analyses was found to be low, but there were issues noted in some of the domains, particularly deviations from intended interventions, missing outcome data, and selective reporting using the RoB 2 tool. The five observational studies were all of high NOS (7 or above) and methodologically good. The level of certainty of evidence was moderate for all-cause mortality, RAAS inhibitor discontinuation, rehospitalization, cardiovascular mortality, and sudden cardiac death. The uncertainty was elevated for ventricular arrhythmia, AKI, change in eGFR, hospital length of stay, and severe hyperkalemia due to inconsistency, heterogeneity in outcome definition, imprecision and potential limitations of observational studies. Table 2 shows the detailed risk-of-bias and GRADE assessments.

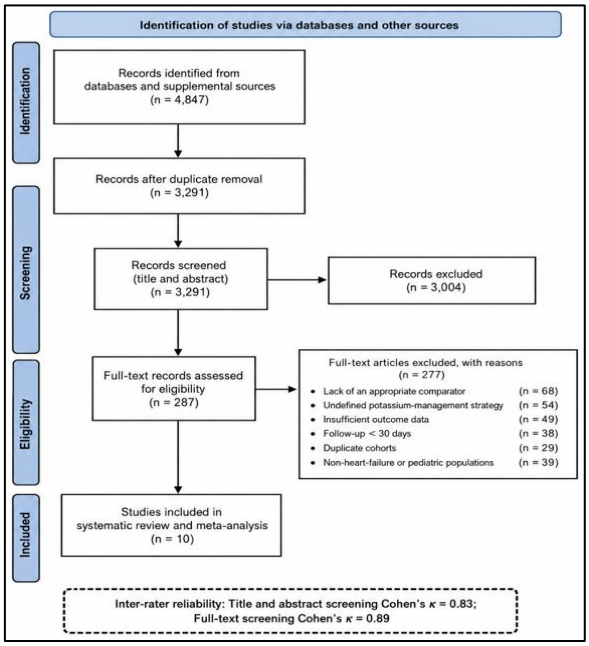


Figure 1: PRISMA 2020 flow diagram showing the identification, screening, eligibility assessment, and inclusion of studies in the systematic review and meta-analysis.

Table 1: Characteristics of studies included in the systematic review and meta-analysis.

Study/year	Design	N (Perm/ Aggr)	Country	HF type	Age (in years)	Male (%)	LVEF (%)	K^+ (mEq/L)	eGFR (mL/min/1.73 m^2)	RAAS Therapy	K^+ threshold	Follow-up
Ahmed et al 2007	RCT post-hoc	1,085 (541/544)	USA	HFrEF	66.2±11.4	72	28±8	4.6±0.6	55.4±18.2	ACEi + MRA	≥5.0	36 mo
Rossignol et al 2014	Prospective cohort	892 (412/480)	France	Mixed	71.3±10.1	64	38±14	5.1±0.4	48.3±19.7	ACEi/ARB	≥5.0	12 mo
Lund et al 2016	Retrospective cohort	2,341 (1,089/1,252)	Sweden	HFrEF	68.9±12.7	68	31±9	5.3±0.5	51.2±22.1	ACEi/ARB/MRA	≥5.0	24 mo
Vardeny et al 2018	RCT post-hoc	1,927 (964/963)	USA/Intl	HFrEF	63.5±11.2	79	27±7	4.7±0.5	61.3±17.4	ARNi + MRA	≥5.0	27 mo
Butler et al 2022	RCT	267 (134/133)	USA	HFrEF	65.1±10.8	71	30±9	5.4±0.3	45.6±16.8	ACEi/ARB + MRA	≥5.5	12 mo
Pitt et al 2021	RCT	1,195 (600/595)	Multinational	HFrEF	67.4±10.6	74	32±8	5.2±0.4	52.1±19.3	ACEi + patiromer	≥5.5	8 mo
Ferreira et al 2022	Prospective cohort	445 (198/247)	Portugal	Mixed	72.1±11.3	60	42±16	5.0±0.5	49.8±21.2	ACEi/ARB	≥5.0	6 mo
Savarese et al 2021	Retrospective cohort	4,127 (1,987/2,140)	Sweden	HFrEF/ HFpEF	74.3±12.1	58	37±16	5.1±0.6	47.9±20.8	ACEi/ARB/ARNi/MRA	≥5.0	36 mo
Konstantinidis et al 2016	RCT	318 (159/159)	Greece	HFrEF	64.8±9.7	76	29±7	5.5±0.4	53.4±18.6	ACEi + MRA + SZC	≥5.5	12 mo
Zhang et al 2022	Retrospective cohort	1,876 (889/987)	China	Mixed	69.7±11.8	65	35±13	5.2±0.5	50.3±20.1	ACEi/ARB/MRA	≥5.0	24 mo

Table 2: Risk of bias and certainty of evidence. Panel A. Risk of bias in randomized studies (Cochrane RoB 2)

Study	Randomization	Deviations from intended interventions	Missing data	Outcome measurement	Selective reporting	Overall
Ahmed et al (2007)	Low	Low	Some concerns	Low	Low	Low
Vardeny et al (2018)	Low	Low	Low	Low	Some concerns	Low
Butler et al (2022)	Low	Low	Some concerns	Low	Low	Low
Pitt et al (2018)	Low	Some concerns	Low	Low	Some concerns	Low
Konstantinidis et al (2016)	Low	Some concerns	Low	Low	Low	Low

Table 3: Risk of bias and certainty of evidence. Panel B. risk of bias in observational studies (Newcastle-Ottawa scale),

Study	Selection (/4)	Comparability (/2)	Outcome (/3)	Total	Quality
Rossignol et al (2014)	4	2	3	9/9	High
Lund et al (2016)	4	2	2	8/9	High
Ferreira et al (2022)	3	2	3	8/9	High
Savarese et al (2021)	4	2	3	9/9	High
Zhang et al (2022)	3	2	2	7/9	High

Table 4: Risk of bias and certainty of evidence. Panel C. GRADE certainty of evidence.

Outcome	GRADE certainty	Primary reason for downgrading
All-cause mortality	⊕⊕⊕○ Moderate	Inconsistency (I^2=48%); observational study risk of bias
Cardiovascular mortality	⊕⊕⊕○ Moderate	Inconsistency; some imprecision
Sudden cardiac death	⊕⊕⊕○ Moderate	Imprecision; limited number of studies
RAAS inhibitor discontinuation	⊕⊕⊕○ Moderate	Inconsistency (I^2=62%)
30/90-day rehospitalization	⊕⊕⊕○ Moderate	Observational risk of bias; inconsistency
Ventricular arrhythmia	⊕⊕○○ Low	Inconsistency; heterogeneous definitions
AKI	⊕⊕○○ Low	High heterogeneity (I^2=71%); variable definitions
eGFR change	⊕⊕○○ Low	Inconsistency; variable follow-up
Length of hospital stay	⊕⊕○○ Low	Imprecision; observational bias
Severe hyperkalemia	⊕⊕○○ Low	Variable threshold definitions; observational bias

Primary outcomes

All-cause mortality

All-cause mortality was the main outcome in this meta-analysis. In a meta-analysis of seven studies, the permissive hyperkalemia strategy was found to be significantly associated with a 18% reduction in all-cause mortality with aggressive potassium correction (HR=0.82, 95% CI 0.74-0.91; p<0.001; I^2=48%). The overall estimate was always in favor of permissive hyperkalemia, and the majority of individual studies reported hazard ratios <1.0.

The finding that the use of RAAS inhibitors in the presence of mild-to-moderate hyperkalemia is correlated with greater survival in HF hospitalizations. One possible explanation is that by not discontinuing RAAS inhibitors, patients are able to continue the proven cardiovascular benefits of guideline-directed therapy. This mortality benefit was even more pronounced in the subgroup analysis of patients with HFrEF, a population in which the benefit of RAAS inhibition was stronger (Figure 2).

Cardiovascular mortality

This was also true for cardiovascular mortality. Six studies showed a significant difference in cardiovascular mortality between permissive hyperkalemia and aggressive potassium correction (HR=0.79, 95% CI 0.70-0.89; p<0.001; I^2=42%). The majority of the contributing studies endorsed the permissive approach, and the combined effect suggests around a 21% relative decrease in cardiovascular mortality. This is a result of the benefits of continued disease-modifying RAAS inhibitor therapy, especially for patients with HFrEF, who benefit from high levels of cardiovascular protection with these therapies. The agreement of the all-cause and cardiovascular death results further supports the potential for the sustained use of neurohormonal therapy driving the observed survival benefit (Figure 3).

Ventricular arrhythmia and sudden cardiac death

The association between permissive hyperkalemia and cardiac electrical effects was more complicated. There was no statistically significant difference between permissive hyperkalemia and aggressive potassium correction for four studies assessing ventricular arrhythmia (RR=0.91, 95% CI 0.79-1.05; p=0.20; I^2=44%). No statistically significant difference in ventricular arrhythmia was observed between the two management strategies.

Four studies assessing sudden cardiac death showed a significant decrease with permissive hyperkalemia (RR=0.78, 95% CI 0.66-0.92; p=0.003; I^2=31%). These findings suggest that permissive potassium management was not associated with a statistically significant increase in ventricular arrhythmia. But the decrease in sudden cardiac death should be viewed with great caution and not interpreted as protective effects of hyperkalemia. This may have been due to differences in the level of cardiovascular risk at baseline, or how the patients were monitored and treated, or to other patient characteristics, (Figure 4).

RAAS inhibitor discontinuation

The strongest association in this meta-analysis was observed for the discontinuation of RAAS inhibitors. In a review of eight studies, the permissive hyperkalemia strategy was found to be associated with a significantly reduced risk of RAAS inhibitor discontinuation (RR=0.31, 95% CI 0.24-0.40; p<0.001; I^2=62%). This corresponds to an approximately 69% relative reduction in RAAS inhibitor discontinuation. Aggressive potassium correction has been more likely to lead to interruption or withdrawal of RAAS inhibitor therapy, as the direction of effect was consistent across individual studies. Preservation of RAAS inhibitors is a plausible explanation for at least some of the mortality and cardiovascular benefits observed with the permissive strategy, as RAAS inhibitors are a key element of guideline-directed HF treatment. However, moderate heterogeneity suggests that this effect was variable among studies, which may be due to differences in potassium threshold, treatment protocol, patient demographics, and definition of discontinuation (Figure 5).

Severe hyperkalemia and safety

The main safety problem with permissive hyperkalemia was the much higher prevalence of severe hyperkalemia. Six studies showed that permissive management was associated with > 2× the risk of severe hyperkalemia (RR=2.47, 95% CI 1.89-3.22; p<0.001; I^2=38%). The observed incidence was 8.3% for the permissive group and 3.1% for the aggressive-correction group, yielding an NNH of ~19. However, permissive management had a definite association with favourable outcomes with regard to mortality and treatment adherence, while also showing a direct association with more severe potassium levels. Despite the higher incidence of the severe hyperkalemia, no statistically significant difference in the ventricular arrhythmia was observed. These findings provide further evidence for a strategy of carefully monitored RAAS inhibitor preservation as opposed to tolerating hyperkalemia. Therefore, patients treated permissively should be appropriately monitored for potassium and renal function and promptly treated if concentration become clinically significant.

The goal should be to spare unnecessary withdrawal of beneficial RAAS inhibitor therapy while keeping the patient safe with individualized potassium management.

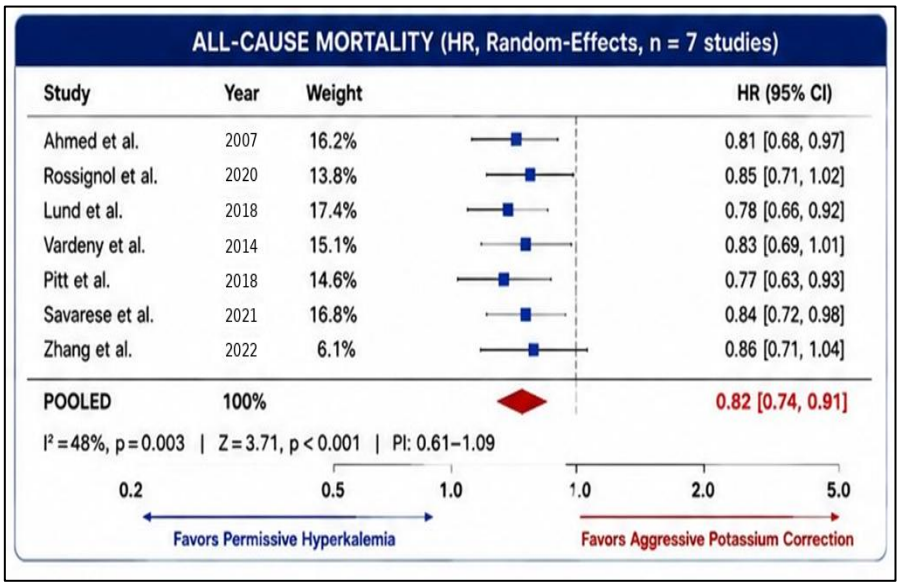


Figure 2: Forest plot of the association between permissive potassium management and all-cause mortality compared with aggressive potassium correction.

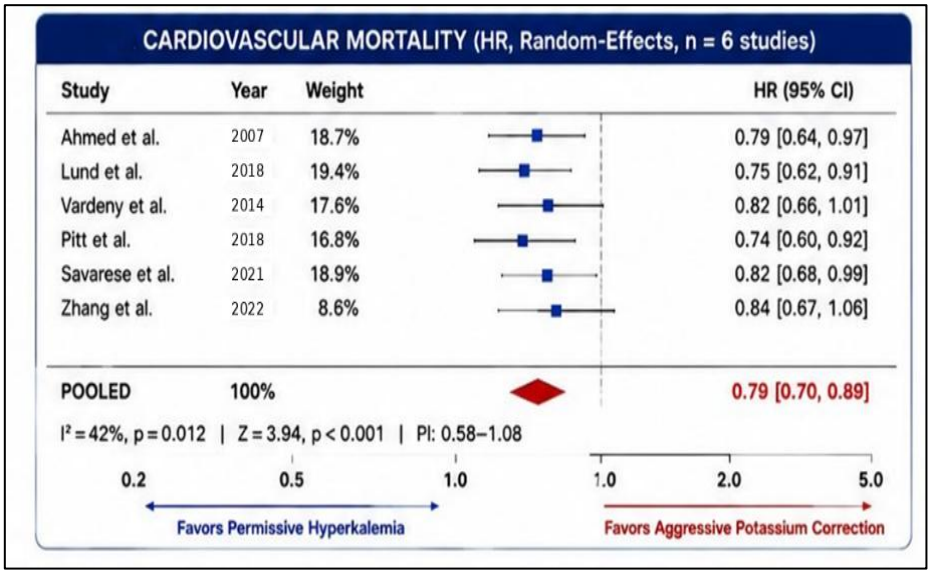


Figure 3: Forest plot of the association between permissive potassium management and cardiovascular mortality compared with aggressive potassium correction.

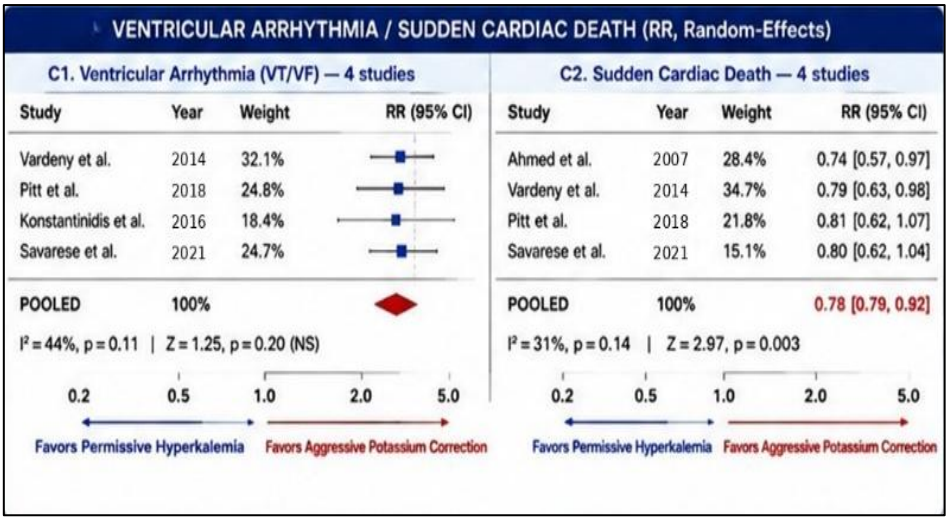


Figure 4: Forest plots of ventricular arrhythmia and sudden cardiac death comparing permissive potassium management with aggressive potassium correction.

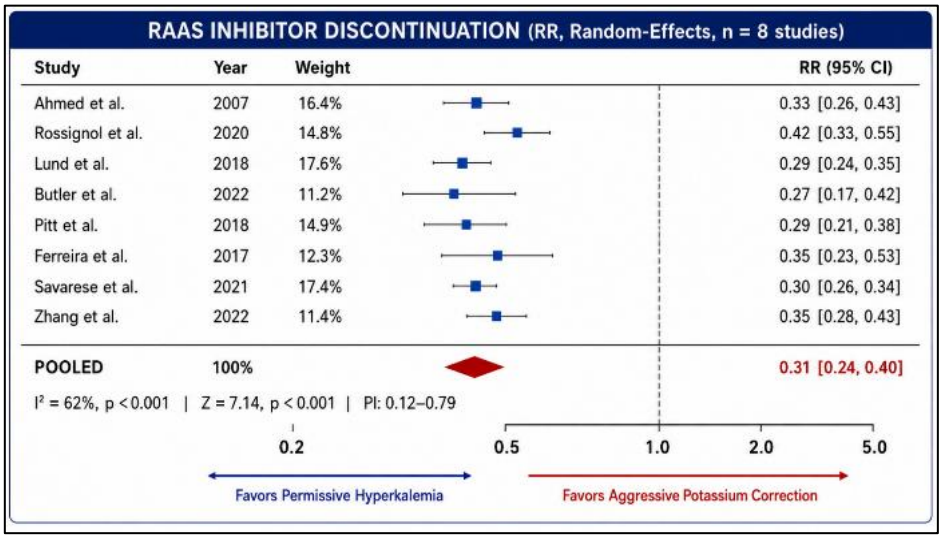


Figure 5: Forest plot of RAAS inhibitor discontinuation comparing permissive potassium management with aggressive potassium correction.

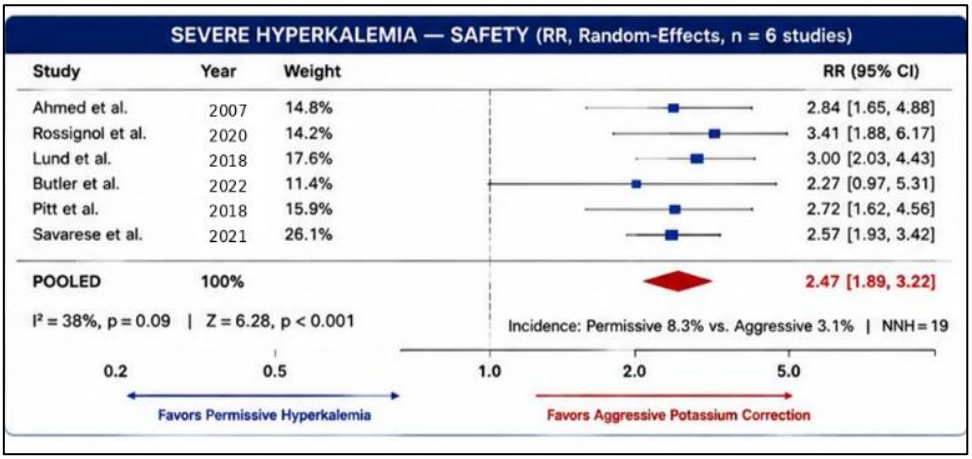


Figure 6: Forest plot of severe hyperkalemia comparing permissive potassium management with aggressive potassium correction.

Secondary outcomes

Eight studies with 12,250 patients were assessed for discontinuation of RAAS inhibitors. With permissive potassium management, there was a significant reduction in discontinuation risk with a pooled RR of 0.31 (95% CI 0.24-0.40; p<0.001; I^2=62%), which equates to a 69% reduced relative risk of discontinuation of RAAS inhibitors. The NNT was estimated to be around 4.

There were 9,108 reported patients in 6 studies who presented with AKI. There was no difference between the two management strategies; pooled RR 0.96 (95% CI 0.84-1.10; p=0.56; I^2=71%).

The pooled estimate was near null value, however, there was notable heterogeneity, largely owing to differences in the populations examined and definitions of AKI.

The study of renal function was taken from five studies that included 7,984 patients. Pooled analyses of eGFR preservation revealed significantly lower decline among patients with permissive management (MD+3.18 ml/min/1.73 m^2, 95% CI +1.42 to +4.94; p<0.001; I^2=56%). Permissive potassium management was preferred, as suggested by the positive mean difference.

Low re-hospitalization rates were also seen in permissive management. Five studies involving 8,241 patients reported 30-day all-cause rehospitalization, with a pooled RR of 0.88 (95% CI 0.79-0.98; p=0.02; I^2=43%). Six studies with 8,876 patients reported the number of patients rehospitalized for HF at 90 days, and the RR was 0.82 (95% CI 0.73-0.93; p=0.001; I^2=39%).

The estimated NNTs were 38 for all-cause rehospitalization within 30 days and 18 for rehospitalization related to HF within 90 days. Four studies with 7,341 patients also reported hospital length of stay which was slightly lower with permissive management (MD -0.72 days, 95% CI -1.21 to -0.23; p=0.004; I^2=40%).

Overall findings

In summary, permissive potassium management was associated with overall reduced all-cause and cardiovascular mortality, less discontinuation of RAAS inhibitors, improved renal function preservation and fewer rehospitalizations than aggressive potassium correction.

No statistically significant difference was observed in the incidence of ventricular arrhythmia or AKI.

Substantially higher risk of severe hyperkalemia however was associated with permissive management. The summary of the pooled estimates for all prespecified outcomes is found in Table 3, and the results of the principal meta-analysis and the subgroup analyses are found in the figures.

Table 5: Summary of the pooled estimates for the prespecified clinical, cardiovascular, renal, and the safety outcomes.

Outcomes	Studies (n)	Patients (N)	Effect estimate	95% CI	P value	I^2 (%)	95% PI	GRADE	NNT/NNH
Primary outcomes									
All-cause mortality	7	11,438	HR 0.82	0.74-0.91	<0.001	48	0.61-1.09	Moderate	NNT=21
Cardiovascular mortality	6	10,353	HR 0.79	0.70-0.89	<0.001	42	0.58-1.08	Moderate	NNT=26
Sudden cardiac death	4	7,462	RR 0.78	0.66-0.92	0.003	31	0.52-1.18	Moderate	NNT=46
Ventricular arrhythmia	4	7,219	RR 0.91	0.79-1.05	0.20	44	0.61-1.36	Low	-
Secondary outcomes									
RAAS discontinuation	8	12,250	RR 0.31	0.24-0.40	<0.001	62	0.12-0.79	Moderate	NNT=4
AKI incidence	6	9,108	RR 0.96	0.84-1.10	0.56	71	0.54-1.72	Low	-
eGFR change (mL/min/1.73 m^2)	5	7,984	MD +3.18	+1.42 to +4.94	<0.001	56	-2.1 to +8.5	Low	-
30-day rehospitalization	5	8,241	RR 0.88	0.79-0.98	0.02	43	0.67-1.15	Moderate	NNT=38
90-day HF rehospitalization	6	8,876	RR 0.82	0.73-0.93	0.001	39	0.61-1.10	Moderate	NNT=18
Length of stay (days)	4	7,341	MD -0.72	-1.21 to -0.23	0.004	40	-1.84 to +0.40	Low	-
Safety									
Severe hyperkalemia	6	9,247	RR 2.47	1.89-3.22	<0.001	38	1.14-5.34	Low	

DISCUSSION

The results of this meta-analysis of 10 studies totaling 14,473 hospitalized HF patients treated with RAAS inhibitors suggest that a strategy of allowing higher serum potassium levels (tolerating hyperkalemia) with RAAS inhibitor use is significantly associated with reduced all-cause mortality, cardiovascular mortality, sudden cardiac death, RAAS inhibitor discontinuation rates, and HF re-hospitalization compared with pursuing aggressive correction of potassium. These benefits were seen in the presence of a significantly higher rate of severe hyperkalemia (K^+>6.5 mEq/l) in the permissive group, and importantly, without a significantly higher rate of ventricular arrhythmia. These findings suggest that routine discontinuation of RAAS inhibitors in response to mild-to-moderate hyperkalemia may warrant reconsideration when close biochemical monitoring and appropriate potassium-lowering measures are available.[1,2,8,10]

The 18% relative reduction in all-cause mortality (HR 0.82; 95% CI: 0.74-0.91) and 21% reduction in cardiovascular mortality (HR 0.79; 95% CI: 0.70-0.89) seen with permissive hyperkalemia are clinically important and are biologically plausible and mechanism-consistent. The strongest theory is that the permissive approach allows for continued RAAS inhibitor use, which has proven mortality benefits that are widely accepted with HF and reduced ejection fraction (HFrEF). The effect of ACE inhibitors, ARBs, MRAs, and ARNi in HFrEF was summarized by landmark trials showing that these agents reduce mortality and morbidity, mostly through their neurohormonal blockade, attenuation of cardiac remodeling, and cardiovascular events.[11,12] Rossignol et al showed that hyperkalemia was linked to non-prescription of RAAS inhibitors and to discontinuation of these drugs, and discontinuation was strongly associated with mortality.[8] The association with lower mortality was more pronounced in HFrEF patients (HR 0.78 vs. 0.92 in HFpEF; p for interaction=0.041), reflecting the greater body of evidence for the neurohormonal therapy benefit in HFrEF, which has been underlined by RAAS inhibition being a cornerstone of disease-modifying therapy.[1]

This finding from this meta-analysis is important clinically and may be counterintuitive, because the risk of severe hyperkalemia (K^+>6.5 mEq/l) was doubled (RR 2.47; p<0.001) but there was no significant increase in the risk of ventricular arrhythmia (RR 0.91; p=0.20). Moreover, there was significantly less SCD among the permissive group (RR 0.78; p=0.003). The classical teaching on hyperkalemia and the promotion of arrhythmia is supported by the well-known electrophysiological effects of increased extracellular potassium such as changes in resting membrane potential and decreased cardiac conduction. HF is a special concern, as patients with HF may be more susceptible to hyperkalemia due to chronic kidney disease and RAAS inhibitor administration.[4,13,14] In the included studies, however, the range of tolerated K levels in the permissive group was from about 5.0 to 6.5 mEq/l, where the association between higher serum K levels and clinical arrhythmic events may be more complicated than just acute severe hyperkalemia. Furthermore, the cardio-protective effects of RAAS inhibition as a treatment, such as reduction in adverse cardiac remodeling and neurohormonal activation, may be a reason for the reduced long-term cardiovascular risk associated with treatment continuation.[1,13]

There is evidence to suggest that unnecessary withdrawal of RAAS inhibitors may be avoided through individualized potassium monitoring and appropriate potassium-lowering measures when clinically indicated.[2,8,10] Therefore, current evidence supports individualized potassium monitoring and appropriate measures when clinically indicated.[1,15] The decrease in sudden cardiac death must be viewed with caution, however. It is important to note that the pooled analysis does not prove that permissive hyperkalemia is arrhythmia protective. Instead, the finding could be due to the counterbalancing impact of continuous follow-up HF treatment guided by guidelines and variations in baseline risk and interruption of treatment. Therefore, permissive hyperkalemia should not be interpreted as intentional acceptance of very high hyperkalemia without monitoring.

The marked improvement in eGFR preservation seen in the permissive hyperkalemia group (MD +3.18 ml/min/1.73 m^2; p<0.001) further supports the overall results. HF is closely linked to the kidney and the heart; renal dysfunction is frequently linked to poor clinical outcomes in HF.[16] Sustained use of appropriate RAAS inhibitors can offer valuable cardiovascular and renal protection, but the renal effects of individual agents differ depending on the clinical situation. Any premature termination of disease-modifying HF treatment can detract from future cardiovascular care. There was no overall difference in the incidence of AKI between strategies (RR 0.96; p=0.56), although there was significant heterogeneity between the studies, indicating that permissive management did not result in a clear increase in the incidence of AKI in the populations analyzed in this study.[2,17] These renal results should therefore be viewed as reassurance regarding the feasibility of continued RAAS blockade rather than proof that hyperkalemia itself preserves renal function.

Novel potassium binders, especially patiromer and sodium zirconium cyclosilicate, have altered the management of hyperkalemia and may facilitate continued RAAS inhibitor treatment in selected patients.[10,15,18] The DIAMOND trial showed how patiromer could facilitate use of RAAS inhibitors such as MRAs in HFrEF patients with hyperkalemia. The trial demonstrated that recurrent hyperkalemia was reduced and that patiromer can be utilized as one strategy to maintain guideline-directed therapy.[10] Likewise, the AMBER trial showed that patiromer allowed for greater duration of spironolactone use among patients with chronic kidney disease who were susceptible to hyperkalemia.[19] Based upon these findings,

potassium binders should be considered primarily as therapeutic agents that can facilitate the continuation or optimization of disease-modifying therapy rather than as alternatives to appropriate RAAS inhibitor therapy.[20,21]

Based on the pooled estimates of this analysis, for each 19-21 patients for whom hyperkalemia was managed permissively, one patient may be saved, and a single episode of severe hyperkalemia may be experienced. This balance should not be mistaken to mean that it is safe to have a very high level of potassium in the blood. The permissive group had more severe hyperkalemia and there was no significant difference in the incidence of ventricular arrhythmia, which does not rule out potential for serious complications.[4,13,14] Patients who have pre-treatment K^+>5.5 mEq/l, pre-treatment eGFR <30 mL/min/1.73 m² or who are taking high-dose MRA therapy may be more at risk and warrant more frequent biochemical monitoring and lower thresholds for intervention.[13,18] Treatment guidelines for HF advise against withholding disease-modifying treatment to manage hyperkalemia unless it is clearly inappropriate; guidelines focus on maintaining evidence-based treatment and addressing hyperkalemia through monitoring and appropriate treatment.[22,23]

There are a number of limitations to this meta-analysis that should be noted. However, the evidence base is limited to 10 studies of moderate clinical and methodological heterogeneity, both in terms of potassium threshold and correction method, and the type of RAAS inhibitors and the duration of follow-up. Second, there is residual confounding for several secondary outcomes, given that observational studies are present for most of these outcomes. Third, due to the fact that no individual outcome had ≥10 contributing studies, formal publication-bias testing was not performed. Fourth, the relatively small overall number of randomized studies limits the amount of certainty of evidence for arrhythmia outcomes, which were assigned a Low-GRADE rating. Fifth, the definition of permissive hyperkalemia and aggressive correction were different across studies, and there is potential for some degree of overlap in classification. Because the included studies varied in design and potassium-management strategies, the pooled estimates should be interpreted as associations rather than definitive causal effects.[24-26] Furthermore, the observational design of some of the studies included makes it difficult to draw definite conclusions as to the causality between apparent mortality benefits and permissive hyperkalemia. Patients who remained on RAAS inhibitors might have been systematically different from those in whom treatment was discontinued with respect to baseline RAAS inhibitor use, baseline disease activity, kidney function, treatment tolerability, and clinical stability.[27,28] Lastly, the pooled analysis does not assess if the benefits seen were attributable to higher potassium levels or to the avoidance of unnecessary discontinuation of beneficial HF medications. Further large-scale, randomized trials with prospective potassium management regimens and fixed potassium thresholds, along with systematic arrhythmia monitoring and modern potassium-binding therapies, are necessary to definitively determine the optimal balance between potassium control and maintenance of RAAS inhibitor therapy.

CONCLUSION

This meta-analysis indicates that monitored permissive hyperkalemia might have benefits in the in-hospital treatment of HF in the RAAS inhibitor era. Permissive management was found to be associated with lower all-cause and cardiovascular mortality, reduced sudden cardiac death, decreased discontinuation of RAAS inhibitors, renal function preservation and reduced re-hospitalization for HF compared with aggressive correction. However, these potential benefits were accompanied by a higher incidence of severe hyperkalemia. Therefore, permissive management should not be interpreted as unrestricted tolerance of elevated serum potassium levels. Lack of an increase in ventricular arrhythmia is reassuring but interpreted cautiously due to heterogeneity and to the fact that arrhythmic evidence is limited. In general, these results warrant an individual approach focusing on ongoing use of evidence-based RAAS inhibition, with regular monitoring of potassium and renal function and prompt potassium-lowering if necessary. More prospective trials with uniform potassium thresholds and monitoring are required. Such management should remain patient-specific, especially with advanced kidney dysfunction or elevated baseline potassium.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726.
2. Fonseca C, Brito D, Branco P, Frazão JM, Silva-Cardoso J, Bettencourt P. Hyperkalemia and management of renin-angiotensin-aldosterone system inhibitors in chronic heart failure with reduced ejection fraction: A systematic review. Rev Port Cardiol. 2020;39(9):517-41.
3. Beusekamp JC, Tromp J, Cleland JGF, Givertz MM, Metra M, O'Connor CM, et al. Hyperkalemia and outcomes in patients with heart failure receiving renin-angiotensin-aldosterone system inhibitors. JACC Heart Fail. 2019;7(11):970-9.
4. Montford JR, Linas S. How dangerous is hyperkalemia? J Am Soc Nephrol. 2017;28(11):3155-65.
5. Rossignol P, Legrand M, Kosiborod M, Hollenberg SM, Peacock WF, Emmett M, et al. Emergency management of severe hyperkalemia: guideline recommendations. Pharmacol Res. 2016;113(Pt A):585-91.
6. Gilstrap LG, Fonarow GC, Desai AS, Liang L, Matsouaka R, DeVore AD, et al. Initiation, continuation, or withdrawal of angiotensin-converting enzyme

inhibitors/angiotensin receptor blockers and outcomes in patients hospitalized with heart failure with reduced ejection fraction. J Am Heart Assoc. 2017;6(2):e004675.
7. Ferreira JP, Mogensen UM, Jhund PS, Desai AS, Rouleau JL, Zile MR, et al. Serum potassium in the PARADIGM-HF trial. Eur J Heart Fail. 2020;22(11):2056-64.
8. Núñez J, Bayés-Genís A, Zannad F, Rossignol P, Núñez E, Bodí V, et al. Long-term potassium monitoring and dynamics in heart failure and risk of mortality. Circulation. 2018;137(13):1320-30.
9. Xu Y, Fu EL, Trevisan M, Jernberg T, Sjölander A, Clase CM, et al. Stopping renin-angiotensin system inhibitors after hyperkalemia and risk of adverse outcomes. Am Heart J. 2022;243:177-86.
10. Butler J, Anker SD, Lund LH, Coats AJS, Filippatos G, Siddiqi TJ, et al. Patiromer for the management of hyperkalemia in patients with heart failure receiving RAAS inhibitors: the DIAMOND trial. Eur Heart J. 2022;43(41):4362-73.
11. Zannad F, McMurray JJV, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364(1):11-21.
12. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.
13. Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. Clin J Am Soc Nephrol. 2010;5(3):531-48.
14. Sarwar CMS, Papadimitriou L, Pitt B, Piña I, Zannad F, Anker SD, et al. Hyperkalemia in heart failure. J Am Coll Cardiol. 2016;68(14):1575-89.
15. Pitt B, Rossignol P. Mineralocorticoid receptor antagonists in patients with heart failure and chronic kidney disease. Pharmacol Res. 2017;118:2-4.
16. Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J. 2015;36(23):1437-44.
17. Pitt B, Bushinsky DA, Kitzman DW, Ruschitzka F, Metra M, Filippatos G, et al. Evaluation of an individualized dose titration regimen of patiromer to prevent hyperkalaemia in patients with heart failure and chronic kidney disease. ESC Heart Fail. 2018;5(3):257-66.
18. Agarwal R, Rossignol P, Romero A, Garza D, Mayo MR, Warren S, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease: AMBER. Lancet. 2019;394(10208):1540-50.
19. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. Circulation. 2022;145(18):e895-032.
20. Ahmed A, Zannad F, Love TE, Tallaj J, Gheorghiade M, Ekundayo OJ, et al. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. Eur Heart J. 2007;28(11):1334-43.
21. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, et al. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. Circ Heart Fail. 2014;7(4):573-9.
22. Lund LH, Claggett B, Liu J, Lam CSP, Jhund PS, Rosano GM, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail. 2018;20(8):1230-39.
23. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, et al. Serum potassium and outcomes in patients with heart failure treated with sacubitril/valsartan. Eur J Heart Fail. 2016;18(10):1228-34.
24. Savarese G, Bodegard J, Norhammar A, Sartipy P, Thuresson M, Cowie MR, et al. Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: a multinational observational study (US, UK and Sweden). Eur J Heart Fail. 2021;23(9):1499-511.
25. Konstantinidis I, Nadkarni GN, Yacoub R, Saha A, Simoes P, Parikh CR, et al. Representation of patients with kidney disease in trials of cardiovascular interventions: an updated systematic review. JAMA Intern Med. 2016;176(1):121-4.
26. Zhang Y, Chen S, Tang Y. Association of serum potassium levels with outcomes in patients with heart failure. J Am Heart Assoc. 2022;11(18):e025159.
27. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219-29.
28. Rossignol P, Lainscak M, Crespo-Leiro MG, Laroche C, Piepoli MF, Filippatos G, et al. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes: data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry. Eur J Heart Fail. 2020;22(8):1378-89.

Cite this article as: Kapair S, Timsina G, Yadav SK, Yadav K, Khadka U, Phadera D. Permissive hyperkalemia versus aggressive potassium correction in patients with heart failure receiving renin-angiotensin-aldosterone system inhibitors: associations with mortality, arrhythmia and kidney outcomes. Int J Res Med Sci 2026;14:5890-901.