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REVIEW

The efficacy and safety of new potassium binders on renin–angiotensin–aldosterone system inhibitor optimization in heart failure patients: a systematic review and meta-analysis

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Abstract

Guideline-directed medical therapy (GDMT) has improved outcomes in patients with heart failure, including the use of renin–angiotensin–aldosterone system inhibitors, which can hinder the excretion of potassium, resulting in hyperkalaemia. New potassium binders (NPBs) can prevent this adverse effect; however, the efficacy and safety of NPB for this indication have not been fully established. We conducted a systematic review and meta-analysis synthesizing randomized controlled trials (RCTs), which were retrieved by systematically searching PubMed, Web of Science, Scopus, and Cochrane through 26 April 2023. The risk of bias assessment was conducted, following Cochrane's updated Risk of Bias 2 assessment tool. We used the fixed-effects model to pool dichotomous data using risk ratio (RR) and continuous data using mean difference (MD), with a 95% confidence interval (CI) (PROSPERO ID: CRD42023426113). We included six RCTs with a total of 1432 patients. NPB was significantly associated with successful mineralocorticoid receptor antagonist (MRA) optimization [RR: 1.13 with 95% CI (1.02–1.25), $P = 0.02$], decreased patients with MRA at less than the target dose [RR: 0.72 with 95% CI (0.57–0.90), $P = 0.004$], and decreased hyperkalaemic episodes [RR: 0.42 with 95% CI (0.24–0.72), $P = 0.002$]. However, there was no difference between NPB and placebo regarding angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)/angiotensin receptor/neprilysin inhibitor (ANRi) optimization [RR: 1.02 with 95% CI (0.89–1.17), $P = 0.76$] and serum potassium change [MD: −0.31 with 95% CI (−0.61 to 0.00), $P = 0.05$], with an acceptable safety profile except for the increased incidence of hypokalaemia with NPB [RR: 1.57 with 95% CI (1.12–2.21), $P = 0.009$]. NPB has been shown to improve GDMT outcomes by enhancing MRA optimization and reducing hyperkalaemic episodes. However, there are limited data on the effects of NPB on ACEi/ARB/ANRi optimization. Future RCTs should investigate ACEi/ARB/ANRi optimization and conduct head-to-head comparisons of NPB (patiromer and sodium zirconium cyclosilicate).

Keywords New potassium binders; Patiromer; Heart failure; Hyperkalaemia; Review; Meta-analysis

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Introduction

Heart failure (HF) is a complex cardiovascular condition characterized by the heart's inability to pump blood to meet the body's metabolic demands adequately. It can be categorized into two main types, HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).[1] This chronic and progressive condition affects millions of people worldwide, and its prevalence is estimated to increase by 46% from 2012 to 2023.[2] HF is a severe disease that requires

the use of multiple medications to improve patient outcomes. Despite advances in HF management, it remains a major cause of hospitalization and mortality.

Guideline-directed medical therapy (GDMT) has been shown to improve outcomes in patients with HF, including the use of angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs), which are known as renin–angiotensin–aldosterone system inhibitors (RAASis). RAASis can hinder the excretion of potassium, resulting in elevated blood potassium levels, a condition known as hyperkalaemia. Hyperkalaemia is a common and serious complication of HF and is often caused by impaired renal function due to decreased renal blood flow or the use of nephrotoxic medications.[3] This electrolyte imbalance can restrict the optimal use of RAASis, which are key components of GDMT.

To address this limitation, new potassium binders (NPBs), including patiromer and sodium zirconium cyclosilicate (SZC), have emerged as a class of medications that can reduce serum potassium levels by binding to potassium in the gastrointestinal tract, thereby preventing its absorption. Recent studies have suggested that NPB may be effective in preventing hyperkalaemia in patients with HF receiving RAASi therapy, enabling the optimization of GDMT.[4–9] However, the efficacy and safety of NPB for this indication have not been fully established.

Accordingly, we have undertaken a systematic review and meta-analysis to evaluate the use of NPB for GDMT optimization in HF patients who developed hyperkalaemia while receiving RAASi therapy. This comprehensive analysis aims to provide important insights into the role of NPB in the management of HF and to inform clinical practice guidelines for the treatment of this condition. By assessing the available evidence, we can better understand the potential benefits and risks of utilizing NPB in this specific patient population, ultimately improving the care and outcomes for individuals with HF and hyperkalaemia.

Methodology

Protocol registration

This study was conducted under the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement,[10] and the Cochrane Handbook for Systematic Reviews and Meta-Analyses,[11] and prospectively registered in PROSPERO with ID: CRD42023426113.

Data sources and search strategy

A comprehensive search was conducted in major electronic databases such as MEDLINE (PubMed), Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL). The search was not limited by language or time restrictions. The details of the search strategy, including the keywords and the results of the search, can be found in Supporting Information, *Table S1*.

Eligibility criteria and study selection

Three reviewers (A.A., A.M.A., and I.G.) independently screened studies for inclusion based on pre-specified PICOS eligibility criteria: population (P): HF patients with current or a history of hyperkalaemia; intervention (I): NPB, including patiromer and SZC; comparator (C): placebo; outcome (O): the primary outcome was MRA optimization defined as patients with MRA at guidelines target dose, and the secondary outcomes included MRA at $<$50% of the target dose, hyperkalaemic episodes, ACEi/ARB/angiotensin receptor/neprilysin inhibitor (ANRi) optimization, change in serum potassium, and safety outcomes; and study design (S): randomized controlled trials (RCTs). Any conflict between the two reviewers was resolved by discussion and consensus; if a consensus could not be reached, a third reviewer (M.A.) was consulted to make the final decision.

The following were excluded: animal studies, pilot studies, case–control studies, case reports, case series, cohort studies, single-arm clinical trials, *in vitro* studies, book chapters, editorials, press articles, and conference abstracts.

Data extraction

Four reviewers (A.A., A.B., A.M.A., and I.G.) independently used a pre-designed extraction sheet to extract the following data: summary characteristics (study design, country, total participants, potassium binder intervention details, control, main inclusion criteria, follow-up duration, and primary outcome), baseline characteristics [number of participants in each group, age, gender, basal metabolic index (BMI), serum potassium, left ventricular ejection fraction (LVEF), glomerular filtration rate (GFR), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and comorbidities], and efficacy and safety outcomes data. Any conflict was resolved by discussion.

Risk of bias and quality assessment

Four reviewers (A.A., A.B., A.M.A., and I.G.) independently utilized the Cochrane Risk of Bias 2 (RoB2) tool[12] to assess the quality of the included studies. The domains evaluated included the risk of bias stemming from the randomization process, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of reported results. In the case of any disagreements, the

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reviewers engaged in discussions and reached a consensus. To appraise the quality of evidence, two reviewers (M.A. and B.A.) utilized the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.[13,14] The evaluation was carried out for each outcome, and the decisions made were justified and documented. Any discrepancies were settled through discussion.

Statistical analysis

The statistical analysis was conducted using the RevMan v5.3 software.[15] To combine the results of dichotomous outcomes, we used the risk ratio (RR), and for continuous outcomes, we used the mean difference (MD), both with a 95% confidence interval (CI), employing the fixed-effects model. We used the χ^2 and I^2 tests to evaluate heterogeneity, where the χ^2 test determines if heterogeneity exists and the I^2 test evaluates the extent of heterogeneity. As per the Cochrane Handbook (Chapter 9),[16] we considered an alpha level below 0.1 for the χ^2 test to denote significant heterogeneity, while the I^2 test was interpreted as follows: 0–40% indicated not significant, 30–60% indicated moderate heterogeneity, and 50–90% indicated substantial heterogeneity.

Meta-regression was conducted to explore the potential sources of heterogeneity in the included studies. The following variables were considered as potential covariates: LVEF, GFR, baseline potassium, and age. A random-effects model was used to estimate the meta-regression coefficients. Finally, trial sequential analysis (TSA) was performed to assess the reliability and conclusiveness of the meta-analysis findings. TSA incorporates both the information size and the cumulative *z* curve to determine if the available evidence is sufficient and robust. The required information size (RIS) was calculated based on the anticipated intervention effect, diversity-adjusted RIS (DARIS), and diversity-adjusted information size (DAIS). Monitoring boundaries were applied to control the risks of Type I and Type II errors. TSA was conducted using the Trial Sequential Analysis software.[17]

Results

Search results and study selection

After searching five electronic databases, we retrieved 1181 records, excluding 558 duplicates via Covidence. Then we screened 623 abstracts, leaving 31 full texts. After the full-text screening, we included six RCTs (*Figure 1*).

Characteristics of included studies

Six RCTs[4–9] with a total of 1432 patients were included in our analysis; 737 received NPB, and 695 received placebo. The summary and baseline characteristics are outlined in *Tables 1* and *2*.

Risk of bias and certainty of evidence

All the included studies showed an overall low risk of bias (*Figure 2*). Only OPAL-HK[4] showed a high risk of bias mainly due to the lack of double blinding. Certainty of evidence is outlined in a GRADE evidence profile (*Table 3*).

Efficacy outcomes

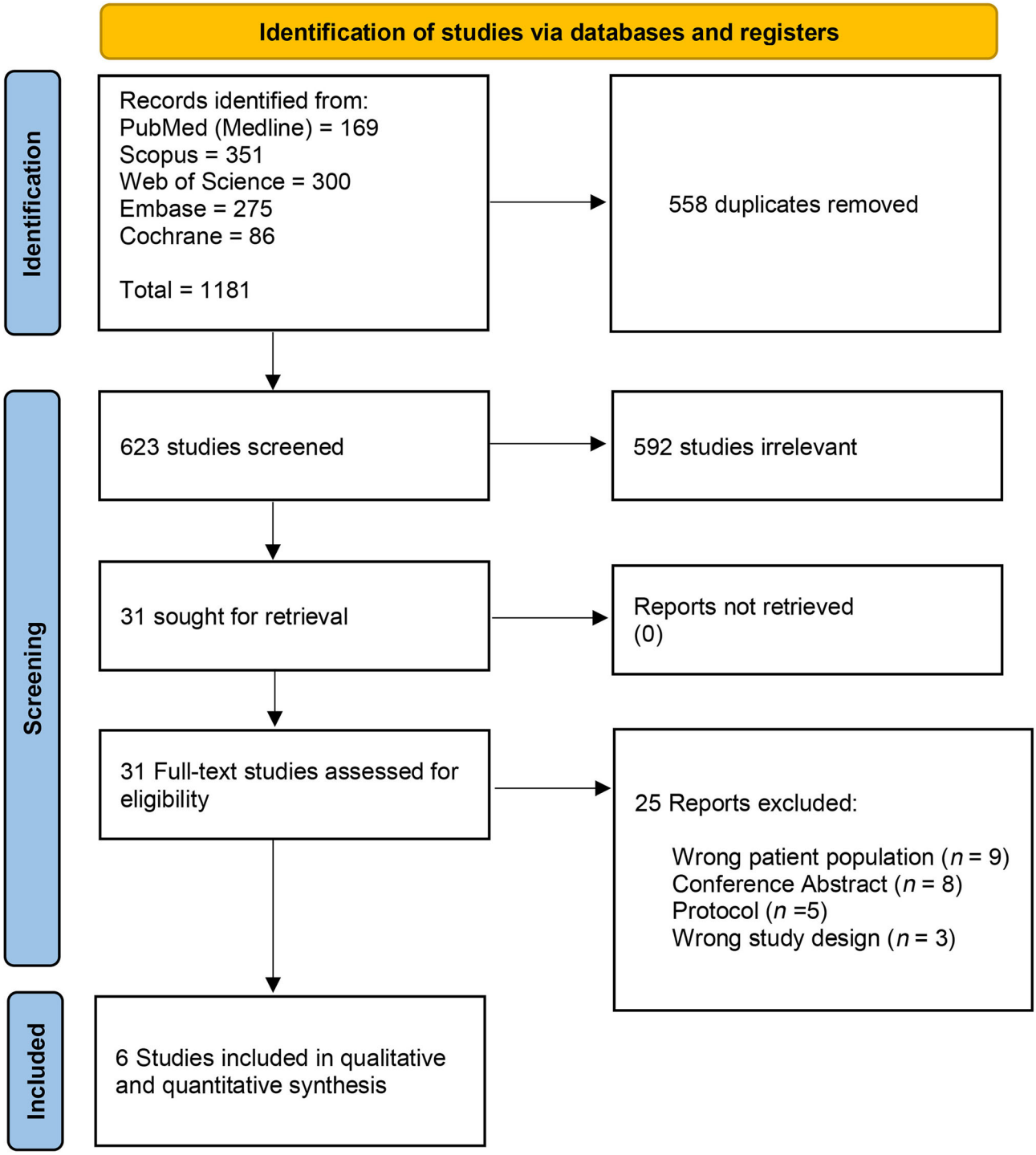
NPB was significantly associated with successful MRA optimization [RR: 1.13 with 95% CI (1.02–1.25), $P = 0.02$], decreased patients with MRA at less than the target dose [RR: 0.72 with 95% CI (0.57–0.90), $P = 0.004$], and decreased hyperkalaemic episodes [RR: 0.42 with 95% CI (0.24–0.72), $P = 0.002$]. However, there was no difference between NPB and placebo regarding ACEi/ARB/ANRi optimization [RR: 1.02 with 95% CI (0.89–1.17), $P = 0.76$] and serum potassium change [MD: −0.31 with 95% CI (−0.61 to 0.00), $P = 0.05$] (*Figure 3* and *Table 3*).

Our results were homogenous in MRA optimization ($I^2 = 0\%$, $P = 0.41$), MRA at less than the target dose ($I^2 = 0\%$, $P = 0.55$), and ACEi/ARB/ANRi optimization ($I^2 = 0\%$, $P = 0.9$). However, it was heterogeneous in hyperkalaemic episodes ($I^2 = 77\%$, $P = 0.002$) and serum potassium change ($I^2 = 90\%$, $P = 0.0001$). Heterogeneity was not resolved by sensitivity analysis in hyperkalaemia. However, in serum potassium change analysis, after excluding Anker *et al.*, heterogeneity was resolved and decreased from $I^2 = 90\%$ to $I^2 = 36\%$ (Supporting Information, *Table S2*).

Safety outcomes

There was no difference between NPB and placebo regarding all-cause mortality [RR: 1.22 with 95% CI (0.68–2.21), $P = 0.51$], any adverse events [RR: 1.04 with 95% CI (0.88–1.23), $P = 0.64$], any serious adverse events [RR: 0.96 with 95% CI (0.71–1.31), $P = 0.81$], any adverse event leading to drug discontinuation [RR: 0.90 with 95% CI (0.49–1.65), $P = 0.74$], and gastrointestinal disorders [RR: 1.97 with 95% CI (0.59–6.57), $P = 0.27$]. However, NPBs were significantly associated with the incidence of hypokalaemia [RR: 1.57 with 95% CI (1.12–2.21), $P = 0.009$] (*Figure 4* and *Table 3*).

Figure 1 PRISMA flow chart of the screening process.



Our results were homogenous in all-cause mortality (I^2 = 0%, P = 0.66), any adverse events (I^2 = 42%, P = 0.13), any serious adverse events (I^2 = 0%, P = 0.55), any adverse event leading to drug discontinuation (I^2 = 0%, P = 0.72), and hypokalaemia (I^2 = 0%, P = 0.45). However, it was heterogeneous in gastrointestinal disorders (I^2 = 87%, P = 0.00001) and heterogeneity was not resolved by sensitivity analysis (Supporting Information, *Table S2*).

Table 1 Summary characteristics of the included RCTs

Study ID	Study design	Sample size	NPB		Frequency of administration	Treatment duration	Primary outcome	Follow-up duration
			Drug	Dose				
Anker *et al.*, 2015 (HARMONIZE)[8]	Double-blind, multicentre RCT	87	SZC	5 g (n = 18), 10 g (n = 18), or 15 g (n = 25)	Once daily	4 weeks	Mean potassium change	4 weeks
Butler *et al.*, 2022 (DIAMOND)[9]	Double-blind, multicentre RCT	878	Patiromer	8.4 g	Up to three t imes daily	27 weeks	Mean potassium change	27 weeks
Pitt *et al.*, 2011 (PEARL-HF)[5]	Double-blind, multicentre RCT	104	Patiromer	15 g	Twice daily	4 weeks	Mean potassium change	4 weeks
Pitt *et al.*, 2015 (OPAL-HK)[4]	Single-blind, multicentre RCT	49	Patiromer	8.4–52.4 g/day titrated according to severity of hyperkalaemia		8 weeks	Mean potassium change	2 weeks
Rossignol *et al.*, 2020 (AMBER)[6]	Double-blind, multicentre RCT	132	Patiromer	4.2 g	Once daily	12 weeks	MRA optimization	12 weeks
Tardif *et al.*, 2022 (PRIORITIZE-HF)[7]	Double-blind, multicentre RCT	182	SZC	5 g	Once daily	12 weeks	MRA optimization	12 weeks

MRA, mineralocorticoid receptor antagonist; NPB, new potassium binder; RCT, randomized controlled trial; SZC, sodium zirconium cyclosilicate.

Meta-regression analysis

LVEF showed a significant effect (β = −0.105, P = 0.0094) when tested as a moderator for hyperkalaemia (Supporting Information, *Table S3* and *Figure S1*). However, none of the rest models showed a significant association as shown in Supporting Information, *Table S3* and *Figures S2–S18*. Also, heterogeneity in hyperkalaemia was resolved in a meta-regression model based on LVEF (Supporting Information, *Figure S19*).

Trial sequential analysis

The TSA results revealed that the available evidence surpassed the RIS and reached the trial sequential monitoring boundary, indicating robust conclusions. These findings strongly suggest that NPB can significantly reduce the incidence of hyperkalaemia and improve MRA optimization in HF patients (*Figure 5*).

Discussion

Our meta-analysis, involving six RCTs with a total of 1432 patients, found that NPB improved MRA optimization, reduced patients receiving suboptimal MRA, and the incidence of hyperkalaemia episodes compared with placebo. NPB also showed potential risks of hypokalaemia without any increase in the rates of other adverse events. This indicates that the use of NPB was effective in decreasing hyperkalaemia in patients with HF. However, there were no significant differences in ACEi/ARB/ANRi optimization and serum potassium change between the two groups.

The 2021 European Society of Cardiology, the 2021 American College of Cardiology expert consensus decision pathway, and the 2020/2021 Kidney Disease: Improving Global Outcomes clinical practice guidelines have all recognized the efficacy of NPB in managing hyperkalaemia in patients with HF and/or chronic kidney disease.[18–20] These guidelines recommend the use of NPB to facilitate the initiation and optimization of guideline-directed RAASi therapy. The implementation of GDMT in HF patients is often suboptimal, particularly when it comes to MRA.[21,22] This challenge may be attributed to the increased risk of hyperkalaemia associated with MRA.[23,24] Hyperkalaemia has been linked to MRA discontinuation and dose reduction[25,26] and has been identified as a predictor of receiving <50% of the target dose.[27] Sequentially, discontinuing or not starting RAASi is associated with a significant risk of 1 year mortality (~41%) and HF readmission (potentially exceeding 64%).[28] Scicchitano *et al*. reported a notable 75% mortality rate in HFrEF patients who stopped MRA over 65 months.[29] This challenging effect

Table 2 Baseline characteristics of the participants

Study ID	Serum potassium, mean (SD)		Age (years), mean (SD)		eGFR, mean (SD)		SBP, mean (SD)	
	NPB	Placebo	NPB	Placebo	NPB	Placebo	NPB	Placebo
Anker *et al.*, 2015 (HARMONIZE)[8]	5 g 4.42, 10 g 4.36, 15 g 4.37	4.53	5 g 69.2 (32.9), 10 g 66.6 (31.3), 15 g 62 (36.1)	65.3 (29)	NA	NA	NA	NA
Butler *et al.*, 2022 (DIAMOND)[9]	4.6 (0.3)	4.6 (0.3)	66.6 (10.0)	67.1 (9.9)	62.6 (22.6)	63.5 (21.4)	125 (12)	124 (13)
Pitt *et al.*, 2011 (PEARL-HF)[5]	4.69 (0.1)	4.65 (0.1)	68 (9)	68 (11)	84 (35)	78 (32)	128 (13)	128 (12)
Pitt *et al.*, 2015 (OPAL-HK)[4]	4.52	4.56	72.9 (11.2)	76.5 (8.3)	32.8 (3.11)	39.1 (3.76)	NA	NA
Rossignol *et al.*, 2020 (AMBER)[6]	4.73 (0.42)	4.70 (0.42)	70.9 (10.4)	69.4 (9.9)	34.6 (6.1)	37.3 (8.3)	143.2 (6.4)	145.1 (6.8)
Tardif *et al.*, 2022 (PRIORITIZE-HF)[7]	4.85 (0.37)	4.87 (0.33)	72.9 (8.8)	71.0 (8.1)	40.0 (11.0)	42.7 (11.5)	NA	NA

AF, atrial fibrillation; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; LVEF, left ventricular ejection fraction; NA, not available; NPB, new potassium binder; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

Table 2 (continued)

Study ID	LVEF, mean (SD)		Comorbidities, *N* (%)							
			DM		HTN		CKD		AF	
	NPB	Placebo	NPB	Placebo	NPB	Placebo	NPB	Placebo	NPB	Placebo
Anker *et al.*, 2015 (HARMONIZE)[8]	NA	NA	5 g 13 (72.2), 10 g 16 (88.9), 15 g 17 (68.0)	18 (69.2)	NA	NA	5 g 12 (66.7), 10 g 15 (83.3), 15 g 18 (72.0)	19 (73.1)	NA	NA
Butler *et al.*, 2022 (DIAMOND)[9]	33.5 (5.8)	33.5 (5.7)	182 (41.5)	174 (39.6)	406 (92.5)	396 (90.2)	439 (100)	439 (100)	160 (36.4)	181 (41.2)
Pitt *et al.*, 2011 (PEARL-HF)[5]	40 (12)	41 (12)	15 (27)	18 (37)	NA	NA	27 (50)	30 (63)	NA	NA
Pitt *et al.*, 2015 (OPAL-HK)[4]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rossignol *et al.*, 2020 (AMBER)[6]	48 (11)	50 (8)	24 (38)	33 (48)	63 (100)	69 (100)	NA	NA	9 (14)	12 (17)
Tardif *et al.*, 2022 (PRIORITIZE-HF)[7]	33.8 (5.8)	33.9 (6.1)	40 (43.5)	42 (46.7)	86 (93.5)	85 (94.4)	NA	NA	42 (45.7)	42 (46.7)

Table 2 (continued)

Study ID	NYHA class, *N* (%)							
	I		II		III		IV	
	NPB	Placebo	NPB	Placebo	NPB	Placebo	NPB	Placebo
Anker *et al.*, 2015 (HARMONIZE)[8]	NA	NA	NA	NA	NA	NA	NA	NA
Butler *et al.*, 2022 (DIAMOND)[9]	10 (2.3)	4 (0.9)	221 (50.3)	251 (57.4)	208 (47.4)	178 (40.7)	0	4 (0.9)
Pitt *et al.*, 2011 (PEARL-HF)[5]	2 (4)	1 (2)	29 (53)	28 (57)	24 (44)	20 (41)	0	0
Pitt *et al.*, 2015 (OPAL-HK)[4]	NA	NA	NA	NA	NA	NA	NA	NA
Rossignol *et al.*, 2020 (AMBER)[6]	11 (18)	11 (16)	41 (65)	55 (80)	11 (18)	3 (4)	0	0
Tardif *et al.*, 2022 (PRIORITIZE-HF)[7]	NA	NA	61 (66.3)	57 (63.3)	31 (33.7)	33 (36.7)	NA	NA

AF, atrial fibrillation; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; LVEF, left ventricular ejection fraction; NA, not available; NPB, new potassium binder; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

can be managed by adding NPB to aid in continuing and reaching RAASi target doses as higher plasma potassium levels are also associated with increased risks of all-cause mortality, cardiovascular death, HF-related death, and sudden cardiac death, even when considering other influencing factors.[29]

In our meta-analysis, NPBs significantly reduced suboptimal MRA doses and optimized MRA dosage. However, no effect was observed on ACEi/ARB/ANRi optimization. ACEi/ARB/ANRi optimization was reported by only two trials; hence, this outcome is underpowered. Furthermore, Tardif *et al*. implied that trial investigators (who were blinded from the treatment allocation) may have been concerned with renal function, hyperkalaemia, or hypotension related to initiation or up-titration of ACEi/ARB/ANRi.[7] This can explain the lack of benefit upon ACEi/ARB/ANRi optimization in the context of the current underpowered available data for this outcome.

Furthermore, our analysis revealed a significant reduction in the incidence of hyperkalaemia. Hyperkalaemia, defined as a serum potassium level exceeding 5.0 mmol/L,[30] is a common occurrence in patients with HF. Its reported incidences range between 3.1% and 16.6%.[31] This electrolyte imbalance poses a significant risk to a patient's health and is associated with a worsened prognosis, particularly in HF patients.[32,33] NPB works by binding to potassium in the gastrointestinal tract and preventing its absorption. Patiromer exchanges calcium ions for potassium ions in the colon, promoting potassium excretion through faeces. SZC selectively traps potassium ions in exchange for sodium and hydrogen ions in the gut. Both binders effectively lower serum potassium levels, helping manage hyperkalaemia and optimize treatment outcomes, particularly in conditions like HF.[34] Additionally, both patiromer and SZC were found to be safe in the treatment of hyperkalaemia,[35] which has been supported in our analysis.

Our analysis revealed no significant effect of NPB on all-cause mortality. Although mitigating RAASi discontinuation or the negative effects of hyperkalaemia can improve hard cardiovascular outcomes over the long term,[9] our analysis revealed no significant effect of NPB on all-cause mortality. Butler *et al*. attributed this effect to a lack of sufficient power to detect significant differences in hard cardiovascular outcomes.[9] Furthermore, most of the included trials were more underpowered and with less follow-up duration[4–8] compared with DIAMOND,[9] which can justify the lack of NPB effect on all-cause mortality. Additionally, Tardif *et al*. found no significant differences in hospitalization rates between SZC and placebo,[7] and Butler *et al*. found no substantial difference in cardiovascular hospitalization, HF exacerbation, cardiovascular death, or overall mortality.[9] Nevertheless, Butler *et al*. reported that patiromer significantly reduced hyperkalaemia-related morbidity.[9] Finally, NPB might have the potential to mitigate the adverse effects and mortality associated with hyperkalaemia in HF patients. Further large-scale RCTs are still necessary to explore the effect on hard outcomes.

Figure 2 Quality assessment of the risk of bias in the included trials. The upper panel presents a schematic representation of risks (low = green, unclear = yellow, and high = red) for specific types of biases of each of the studies in the review. The lower panel presents risks (low = red, unclear = yellow, and high = red) for the subtypes of biases of the combination of studies included in this review.

Although the NPB mechanism of action may lead to gastrointestinal adverse events such as diarrhoea, constipation, nausea or vomiting, and electrolyte imbalances, including hypomagnesaemia,[34] our study did not find any significant difference in the risk of gastrointestinal disorders. However, NPB was significantly associated with an increased incidence of hypokalaemia, which may be because most patients can be additionally on loop or thiazide diuretics for hypertension management. In the included RCTs, most patients who experienced hypokalaemia had serum potassium levels ranging from 3.0 to 3.5 mEq/L. None of the patients in PRIORITIZE-HF had serum potassium levels below 3.0 mEq/L, indicating severe hypokalaemia.[7] However, in DIAMOND, one patient in each treatment arm had severe hypokalaemia, but they did not provide a specific definition for severe hypokalaemia.[9]

Moreover, dyskalaemia, which encompasses both hypokalaemia and hyperkalaemia, is prevalent in patients with HF due to the underlying HF condition itself, associated comorbidities, and the medications used for HF management. A recent large observational study revealed that within 1 year, 24.4% of patients encountered at least one hyperkalaemia event, with 10.2% reporting moderate to severe hyperkalaemia.[36] Also, 20.3% of patients experienced at least one episode of hypokalaemia, while 3.7% of them encountered severe hypokalaemia.[36] This indicates that dyskalaemia is a normal phenomenon in HF patients, and as long as NPB does not significantly increase severe hypokalaemia, they can be considered safe with a recommendation to monitor serum potassium level.

Multiple previous meta-analyses investigated NPB for HF. Carvalho *et al*. and Montagnani *et al*. are in line with our findings regarding MRA optimization.[37,38] Also, Carvalho *et al*. showed the same findings regarding all other outcomes,[38] with Montagnani *et al*. focusing on MRA optimization only.[37] However, none of them reported pooled analysis on ACEi/ARB/ANRi optimization. Also, our review is the first to provide certainty of evidence assessment, following GRADE guidelines, and TSA, assessing the reliability and conclusiveness of our findings. Therefore, our review adds to the available

Table 3 GRADE evidence profile

Certainty assessment						
Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence
MRA optimization (50 mg/day) 1290 (4 RCTs)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕○ Moderate
MRA at less than the target dose 1290 (4 RCTs)	Not serious	Not serious	Not serious	Very serious[b]	None	⊕⊕○○ Low
Hyperkalaemia (serum potassium >5.5 mEq/L) 1248 (5 RCTs)	Not serious	Very serious[c]	Not serious	Serious[a]	None	⊕○○○ Very low
ACEi/ARB/ANRi optimization 1054 (2 RCTs)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕○ Moderate
Serum potassium change (at the latest endpoint) 1060 (3 RCTs)	Not serious	Very serious[c]	Not serious	Serious[a]	None	⊕○○○ Very low
All-cause mortality 1240 (4 RCTs)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕○ Moderate
Any adverse events 1431 (6 RCTs)	Not serious	Serious[d]	Not serious	Serious[a]	None	⊕⊕○○ Low
Any serious adverse events 1431 (6 RCTs)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕○ Moderate
Any adverse event leading to drug discontinuation 1250 (5 RCTs)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕○ Moderate
Gastrointestinal disorders 1821 (6 RCTs)	Not serious	Very serious[c]	Not serious	Very serious[a]	None	⊕○○○ Very low
Hypokalaemia 1431 (6 RCTs)	Not serious	Very serious[c]	Not serious	Not serious	None	⊕⊕○○ Low

ACEi, angiotensin-converting enzyme inhibitor; ANRi, angiotensin receptor/neprilysin inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference; MRA, mineralocorticoid receptor antagonist; RCTs, randomized controlled trials; RR, risk ratio.
[a]Confidence interval does not exclude the risk of appreciable benefit/harm.
[1b]Confidence interval does not exclude the risk of appreciable benefit/harm, and the number of events is <300 events.
[2c]$I^2 > 75\%$.
[3d]$I^2 > 50\%$.

Table 3 (continued)

Certainty assessment	Summary of findings				
	Study event rates (%)			Anticipated absolute effects	
Participants (studies) follow-up	With (comparison)	With (intervention)	Relative effect (95% CI)	Risk with (comparison)	Risk difference with (intervention)
MRA optimization (50 mg/day) 1290 (4 RCTs)	321/644 (49.8%)	364/646 (56.3%)	RR 1.13 (1.02–1.25)	498 per 1000	65 more per 1000 (from 10 more to 125 more)
MRA at less than the target dose 1290 (4 RCTs)	145/644 (22.5%)	104/646 (16.1%)	RR 0.72 (0.57–0.90)	225 per 1000	63 fewer per 1000 (from 97 fewer to 23 fewer)
Hyperkalaemia (serum potassium >5.5 mEq/L) 1248 (5 RCTs)	166/604 (27.5%)	102/644 (15.8%)	RR 0.42 (0.24–0.72)	275 per 1000	159 fewer per 1000 (from 209 fewer to 77 fewer)
ACEi/ARB/ANRi optimization 1054 (2 RCTs)	225/526 (42.8%)	230/528 (43.6%)	RR 1.02 (0.89–1.17)	428 per 1000	9 more per 1000 (from 47 fewer to 73 more)
Serum potassium change (at the latest endpoint) 1060 (3 RCTs)	509	551	—	The mean serum potassium change (at the latest endpoint) was 0	MD 0.31 lower (0.61 lower to 0)
All-cause mortality 1240 (4 RCTs)	19/620 (3.1%)	23/620 (3.7%)	RR 1.22 (0.68–2.21)	31 per 1000	7 more per 1000 (from 10 fewer to 37 more)
Any adverse events 1431 (6 RCTs)	443/695 (63.7%)	469/736 (63.7%)	RR 1.04 (0.88–1.23)	637 per 1000	25 more per 1000 (from 76 fewer to 147 more)
Any serious adverse events 1431 (6 RCTs)	74/695 (10.6%)	70/736 (9.5%)	RR 0.96 (0.71–1.31)	106 per 1000	4 fewer per 1000 (from 31 fewer to 33 more)
Any adverse event leading to drug discontinuation 1250 (5 RCTs)	22/605 (3.6%)	20/645 (3.1%)	RR 0.90 (0.49–1.65)	36 per 1000	4 fewer per 1000 (from 19 fewer to 24 more)
Gastrointestinal disorders 1821 (6 RCTs)	46/1085 (4.2%)	65/736 (8.8%)	RR 1.97 (0.59–6.57)	42 per 1000	41 more per 1000 (from 17 fewer to 236 more)
Hypokalaemia 1431 (6 RCTs)	46/695 (6.6%)	83/736 (11.3%)	RR 1.57 (1.12–2.21)	66 per 1000	38 more per 1000 (from 8 more to 80 more)

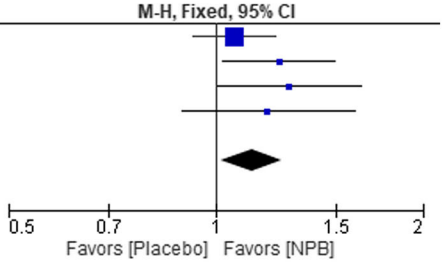
ACEi, angiotensin-converting enzyme inhibitor; ANRi, angiotensin receptor/neprilysin inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference; MRA, mineralocorticoid receptor antagonist; RCTs, randomized controlled trials; RR, risk ratio.
[a]Confidence interval does not exclude the risk of appreciable benefit/harm.
[b]Confidence interval does not exclude the risk of appreciable benefit/harm, and the number of events is <300 events.
[c]$I^2 > 75\%$.
[d]$I^2 > 50\%$.

Figure 3 Forest plots of the efficacy outcomes. (A) Mineralocorticoid receptor antagonist (MRA) optimization, (B) MRA at less than the target dose, (C) hyperkalaemia (potassium >5.5 mEq/L), (D) angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor/neprilysin inhibitor optimization, and (E) serum potassium change. CI, confidence interval; M-H, Mantel–Haenszel; NPB, new potassium binder.

(A)

Study or Subgroup	NPB Events	NPB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Butler et al. 2022 (DIAMOND)	216	439	203	439	63.1%	1.06 [0.93, 1.22]
Pitt et al. 2011 (the PEARL-HF)	50	55	36	49	11.8%	1.24 [1.03, 1.49]
Rossignol et al. 2020 (AMBER)	48	63	41	69	12.2%	1.28 [1.01, 1.63]
Tardif et al. 2022 (PRIORITIZE-HF)	50	89	41	87	12.9%	1.19 [0.89, 1.59]
Total (95% CI)		**646**		**644**	**100.0%**	**1.13 [1.02, 1.25]**
Total events	364		321			

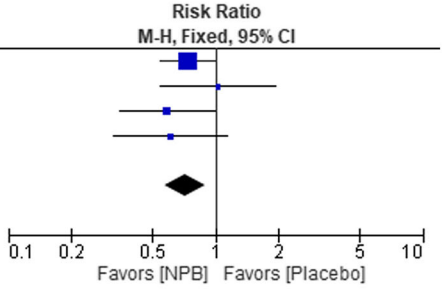
Heterogeneity: Chi² = 2.87, df = 3 (*P* = 0.41); I² = 0%
Test for overall effect: Z = 2.33 (*P* = 0.02)



(B)

Study or Subgroup	NPB Events	NPB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Butler et al. 2022 (DIAMOND)	61	439	83	439	57.4%	0.73 [0.54, 0.99]
Pitt et al. 2011 (the PEARL-HF)	15	55	13	49	9.5%	1.03 [0.54, 1.94]
Rossignol et al. 2020 (AMBER)	15	63	28	69	18.5%	0.59 [0.35, 0.99]
Tardif et al. 2022 (PRIORITIZE-HF)	13	89	21	87	14.7%	0.61 [0.32, 1.13]
Total (95% CI)		**646**		**644**	**100.0%**	**0.72 [0.57, 0.90]**
Total events	104		145			

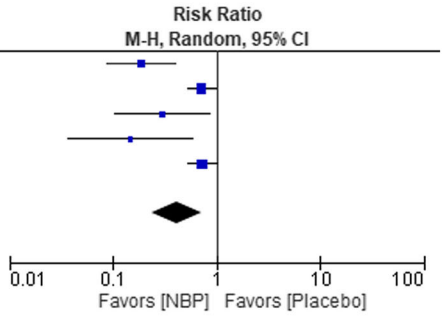
Heterogeneity: Chi² = 2.10, df = 3 (*P* = 0.55); I² = 0%
Test for overall effect: Z = 2.89 (*P* = 0.004)



(C)

Study or Subgroup	NPB Events	NPB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Anker et al. 2015 (HARMONIZE)	7	61	16	26	19.4%	0.19 [0.09, 0.40]
Butler et al. 2022 (DIAMOND)	61	439	85	439	28.4%	0.72 [0.53, 0.97]
Pitt et al. 2011 (the PEARL-HF)	4	55	12	49	14.2%	0.30 [0.10, 0.86]
Pitt et al. 2015 (OPAL-HK)	2	26	11	21	10.3%	0.15 [0.04, 0.59]
Rossignol et al. 2020 (AMBER)	28	63	42	69	27.8%	0.73 [0.52, 1.02]
Total (95% CI)		**644**		**604**	**100.0%**	**0.42 [0.24, 0.72]**
Total events	102		166			

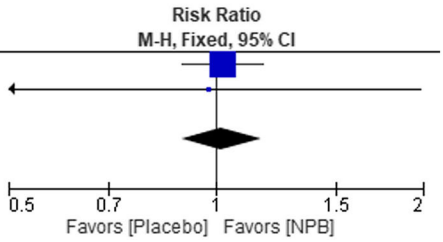
Heterogeneity: Tau² = 0.25; Chi² = 17.55, df = 4 (*P* = 0.002); I² = 77%
Test for overall effect: Z = 3.15 (*P* = 0.002)



(D)

Study or Subgroup	NPB Events	NPB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Butler et al. 2022 (DIAMOND)	217	439	212	439	94.2%	1.02 [0.89, 1.17]
Tardif et al. 2022 (PRIORITIZE-HF)	13	89	13	87	5.8%	0.98 [0.48, 1.99]
Total (95% CI)		**528**		**526**	**100.0%**	**1.02 [0.89, 1.17]**
Total events	230		225			

Heterogeneity: Chi² = 0.02, df = 1 (*P* = 0.90); I² = 0%
Test for overall effect: Z = 0.30 (*P* = 0.76)



(E)

Study or Subgroup	NPB Mean	NPB SD	NPB Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Anker et al. 2015 (HARMONIZE)	4.6	0.38	61	5.2	0.5	26	31.7%	-0.60 [-0.81, -0.39]
Butler et al. 2022 (DIAMOND)	0.03	0.4	439	0.13	0.4	439	37.2%	-0.10 [-0.15, -0.05]
Tardif et al. 2022 (PRIORITIZE-HF)	-0.27	0.62	51	-0.02	0.52	44	31.1%	-0.25 [-0.48, -0.02]
Total (95% CI)			**551**			**509**	**100.0%**	**-0.31 [-0.61, 0.00]**

Heterogeneity: Tau² = 0.06; Chi² = 20.69, df = 2 (*P* < 0.0001); I² = 90%
Test for overall effect: Z = 1.96 (*P* = 0.05)

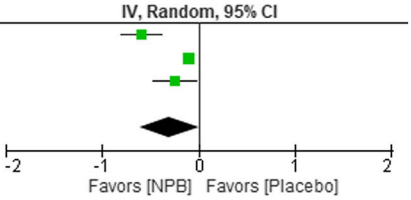


Figure 4 Forest plots of the safety outcomes. AE, adverse event; CI, confidence interval; M-H, Mantel–Haenszel; NPB, new potassium binder.

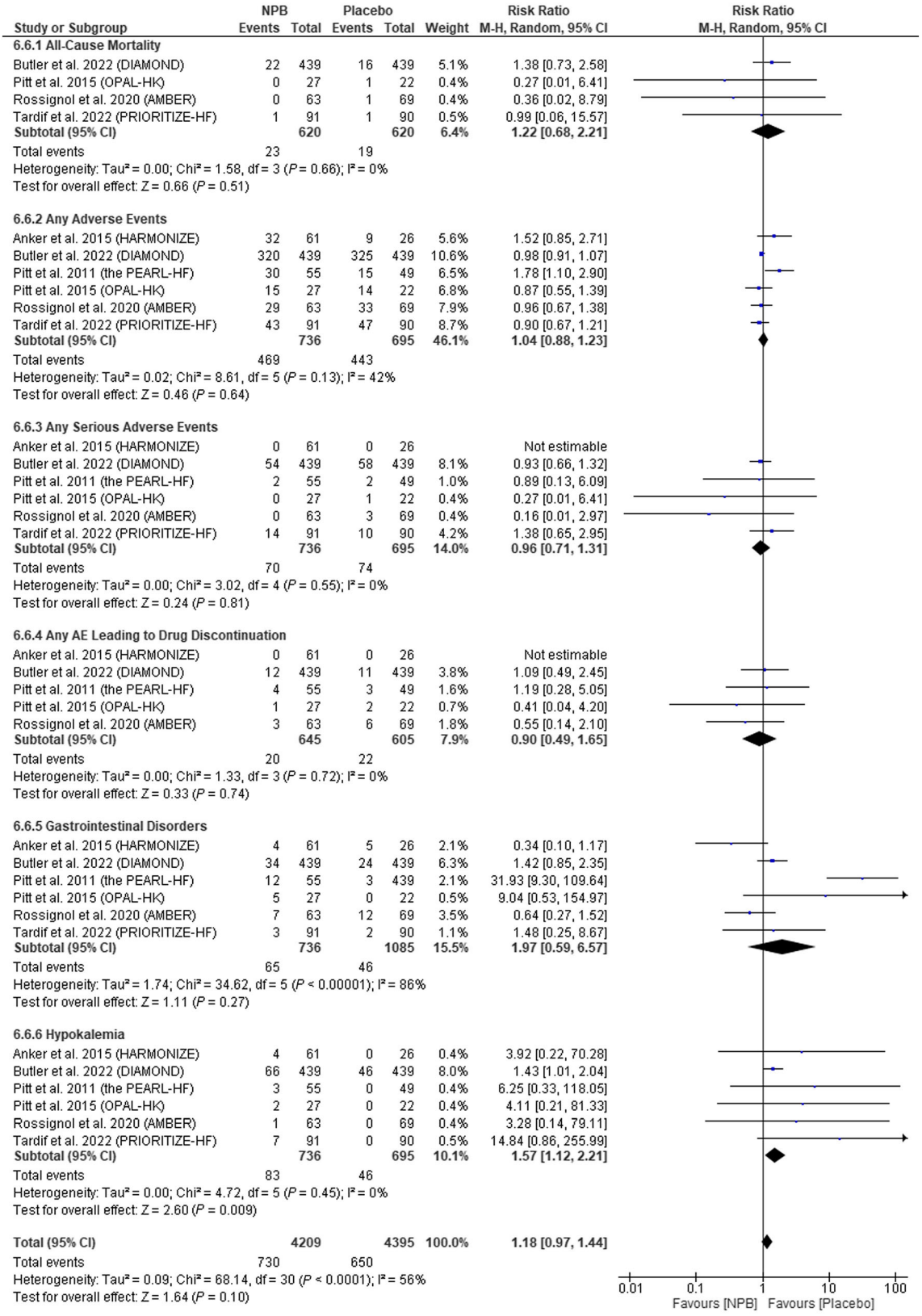
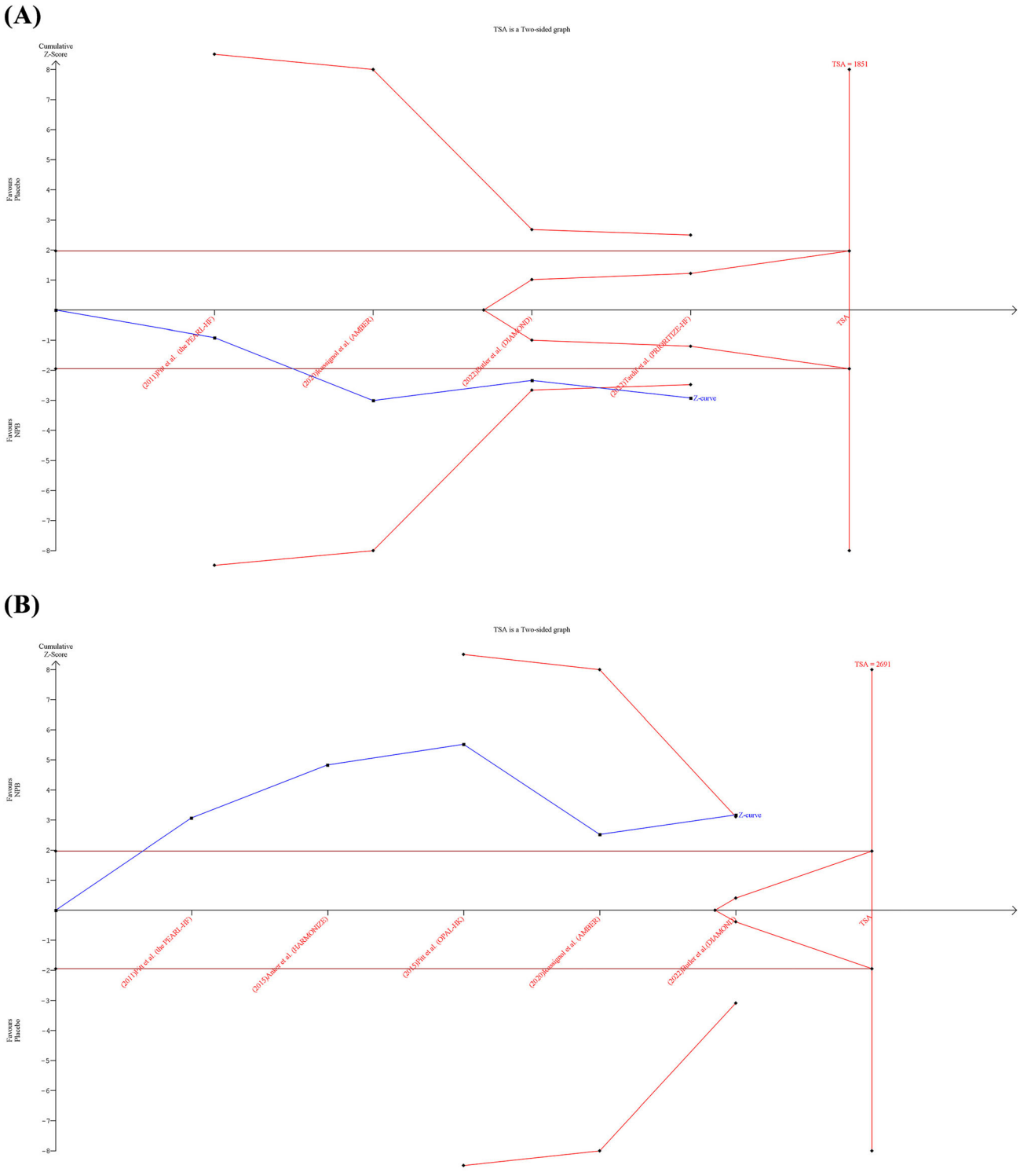


Figure 5 Trial sequential analysis (TSA). (A) Mineralocorticoid receptor antagonist optimization and (B) hyperkalaemia (potassium >5.5 mEq/L). NPB, new potassium binder.



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body of evidence by investigating ACEi/ARB/ANRi optimization and the thorough assessment of certainty of evidence and TSA.

Limitations

There are a few limitations in our study. First, the follow-up periods of the included studies ranged from 4 to 27 weeks, which may be relatively short for analysing hard cardiovascular endpoints, and the lack of significant results could be attributed to insufficient statistical power, especially in the serum potassium change, which included only three RCTs with a different point of assessment. Second, included trials excluded patients with severe hyperkalaemia, potassium-related electrocardiographic changes, and acute cardiovascular events, which restricts the generalizability of our findings to the entire population of HF patients at risk for hyperkalaemia. Third, the analysis in our study involved the examination of two NPBs with varying doses across the included studies. However, we considered these two drugs to be sufficiently similar in terms of their mechanism of action, consistent safety profile, and effectiveness across different studies. Fourth, it is important to note that adverse outcomes are infrequent events, and the lack of significant differences between the groups may be attributed to the limited statistical power of our analysis, and there is lack of direct comparisons between the two NPBs. Fifth, the DIAMOND trial[9] was prematurely halted due to the impact of the COVID-19 pandemic, and as a result, the study experienced a reduction in the number of participants and a higher rate of premature discontinuation of treatment. Sixth, the renal function can significantly affect our findings and we could not provide a meta-regression analysis based on creatinine clearance due to the lack of data. Finally, all our meta-regression models included data from $<$10 studies; thus, their findings are not reliable and should be interpreted with caution.

Implications for future practice and research

The emergence of NPB has improved the outcomes of patients on HF treatment by tackling the adverse effects of hyperkalaemia. NPBs allow patients to maximize the benefits of GDMT usage, especially MRA. Guidelines recommending the addition of NPB to HF management are in line with our analysis.[18–20] However, regular monitoring of serum potassium levels and appropriate adjustment of NPB doses can be instrumental in preventing hypokalaemia.[4] For future research, we suggest further investigating the optimization of ACEi/ARB/ANRi, conducting head-to-head studies comparing NPB, and investigating the effect of adjuvant administration of NPB with other cardiovascular drugs especially diuretics.

Conclusion

NPBs (patiromer and SZC) can successfully improve GDMT outcomes by enhancing MRA optimization and decreasing hyperkalaemic episodes, with an increased incidence of hypokalaemia, requiring regular monitoring of serum potassium levels. However, data regarding the NPB effect on ACEi/ARB/ANRi optimization remain scarce. Therefore, future RCTs should further investigate ACEi/ARB/ANRi optimization and conduct a head-to-head comparison of NPB.

Conflict of interest

None declared.

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We received no funding for this study.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1: Search strategy.
Table S2: Sensitivity Analysis.
Table S3: Meta-regression analysis.
Figure S1: meta-regression analysis model for hyperkalemia based on LVEF.
Figure S2: meta-regression analysis model for hyperkalemia based on GFR.
Figure S3: meta-regression analysis model for hyperkalemia based on baseline potassium level.
Figure S4: meta-regression analysis model for hyperkalemia based on mean age.
Figure S5: meta-regression analysis model for serum potassium change based on baseline potassium level.
Figure S6: meta-regression analysis model for serum potassium change based mean age.
Figure S7: meta-regression analysis model for hypokalemia based on LVEF.
Figure S8: meta-regression analysis model for hypokalemia based on GFR.
Figure S9: meta-regression analysis model for hypokalemia based on baseline potassium level.
Figure S10: meta-regression analysis model for hypokalemia based on mean age.
Figure S11: meta-regression analysis model for MRA optimization based on LVEF.

Figure S12: meta-regression analysis model for MRA optimization based on GFR.
Figure S13: meta-regression analysis model for MRA optimization based on baseline potassium level.
Figure S14: meta-regression analysis model for MRA optimization based on mean age.
Figure S15: meta-regression analysis model for All-Cause Mortality based on LVEF.
Figure S16: meta-regression analysis model for All-Cause Mortality based on GFR.
Figure S17: meta-regression analysis model for All-Cause Mortality based on baseline potassium level.
Figure S18: meta-regression analysis model for All-Cause Mortality based on mean age.
Figure S19: meta-regression analysis model for hyperkalemia based on LVEF.

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