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Original article

Novel potassium binders to optimize RAASi therapy in heart failure: A systematic review and meta-analysis

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ABSTRACT

Aims: Hyperkalemia often occurs among heart failure (HF) patients, particularly when treated with renin-angiotensin-aldosterone system inhibitors (RAASi). Even modest potassium levels variations raise the risk of mortality and prompt patients to discontinue disease-modifying treatment, as RAASi. Novel potassium binders (NPB), patiromer and sodium zirconium cyclosilicate, are effective in reducing potassium levels and are approved for the treatment of hyperkalemia in HF, but whether their use results in a real optimization of HF treatment remains to be seen. The aim of the present meta-analysis was to assess the efficacy of NPB on the optimization of RAASi therapy in HF patients.

Methods and results: PubMed, Web of Science and Clinicaltrial.gov were searched without restrictions from inception to 06 August 2022 to identify valuable articles. The studies that met the inclusion criteria were analyzed. The prespecified primary outcome was the optimization of RAASi therapy in HF patients, defined as the proportion of patients on RAASi at the end of follow-up. Secondary outcomes were hyperkalemia events, reduction in potassium levels, and adverse drugs reactions. Six studies with a total of 1390 patients were included. NPB improved RAASi therapy optimization in HF by 14% (95% CI: 4–26%), decreased hyperkalemia events by 29% (95% CI: 55–92%), and reduced potassium levels by 0.31 mEq/L (95% CI: 0.18–0.44) compared to placebo, maintaining a good safety profile.

Conclusion: NPB are effective in allowing RAASi therapy optimization in patients affected by HF, in reducing hyperkalemia events and potassium levels.

Systematic Review registration: CRD42022351811 URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=351811

1. Introduction

Heart failure (HF) is a major cause of cardiovascular (CV) mortality and morbidity, resulting in more than one million hospitalizations per year. In patients affected by HF with reduced ejection fraction (HFrEF), a therapeutic approach based on the prescription of the four classes of disease-modifying drugs, as ACE inhibitors/Angiotensin Receptor-Neprilysin Inhibitors (ARNI), beta-blockers, mineralocorticoid receptor antagonists (MRA) and sodium-glucose co-transporter 2 (SGLT2) inhibitors, significantly impact on medium and long-term prognosis; similarly, the use of renin-angiotensin-aldosterone system inhibitors (RAASi) has a Class of Recommendation IIa in HF with mildly reduced EF (HFmrEF) in the most recent European Guidelines. Thus, the use of these drugs is essential in the majority of HF patients ad all the available measures need to be adopted to avoid lack of prescription or drugs discontinuation. One of the major issues concerning the use of RAASi is the occurrence of hyperkalemia [1], the most common electrolyte disorder in HF, particularly in patients with combined comorbid conditions, as chronic kidney disease and diabetes mellitus. Hyperkalemia, together with hypotension and worsening of renal function, is one of the

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main reasons of RAASi discontinuation, dose reduction, lack of titration over time, and treatment non-prescription [2]. Moreover, hyperkalemia is related to adverse prognosis in HF patients, event most likely related to RAASi withdrawal than to hyperkalemia negative effects [2]. The therapeutic approach to hyperkalemia has been very limited in the last years due to insufficient efficacy or lack of evidence of the available measures. However, the recent availability of novel potassium binders (NPB), as patiromer and sodium zirconium cyclosilicate (SZC), to chronically treat hyperkalemia is changing the path of HFrEF therapy, reducing the risks related to this electrolyte disorder and, especially, facilitating the optimization of disease-modifying treatment with a very low occurrence of side effects. The present systematic review and meta-analysis investigated the efficacy of NPB on optimization of RAASi therapy and on potassium levels and hyperkalemia events reduction in patients affected by HF, in order to clarify the importance of their use in the clinical practice.

2. Methods

The present meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines [3] (Supplementary Table I) and registered on PROSPERO (CRD42022351811).

2.1. Search strategy and study selection

PubMed, Web of Science and Clinicaltrials.gov were searched without any restrictions from inception to 06 August 2022. The search strategy is included in the Supplementary Materials. Two authors separately examined the titles and abstracts of all obtained publications to exclude clearly unrelated research. According to the inclusion criteria, the remaining articles were chosen for full-text examination. The final list of included studies was then reviewed by the authors, and any difference was addressed via discussion. Studies were included if satisfying the following criteria: [1] a comprehensive study design with rigorous criteria for inclusion and exclusion; [2] randomized-controlled trials; [3] a follow-up period of at least 28 days; [4] focused on HF patients.

2.2. Data extraction and quality assessment

The primary analyzed outcome was optimization of RAASi therapy in HF patients. We defined RAASi therapy optimization as the proportion of HF patients on RAASi (ACE inhibitors, angiotensin-receptor blockers, ARNI and/or MRA) compared to placebo at the end of the study.

The secondary outcomes were occurrence of hyperkalemia events, defined as a serum potassium level $\geq$5.5 mEq/L, and reduction of serum potassium levels.

The safety outcomes were hypokalemia events, defined as a serum potassium level <3.5 mEq/L, severe hypokalemia events, defined as serum potassium level <3.0 mEq/L, gastrointestinal events, defined as either diarrhea, constipation, nausea or vomiting, hypomagnesemia for patiromer and edema for SZC.

The following information was gathered from each included study: baseline characteristics of studies (authors, publication year, journal, country), patients' characteristics (sample size, gender, age, comorbidities) and HF characteristics (NYHA class, NT-proBNP, HF etiology, serum potassium levels, hyperkalemia events at screening, HF therapy). To analyze the risk of bias, the GRADE tool and Cochrane Collaboration's tool were used [4] (Supplementary Table II). If necessary, two reviewers independently estimated means and measures of dispersion from figures in the reports using DigitizeIt, version 2.5 (Braunschweig, Germany). The final values were determined by averaging the opinions of independent reviewers.

2.3. Statistical analysis

STATA 17.0 (Stata Corp, College Station, TX, USA) was used. The Chi-square test and I^2 test were used to investigate heterogeneity, with $p \leq 0.10$ or I^2 >50% indicating considerable heterogeneity. Due to the limited number of studies involved and to better redistribute the weight between individual trials, a DerSimonian-Laird random effect model was used. Risk ratios (RR) and 95% confidence intervals (CI) were estimated for binary variables and weighted mean difference (WMD) and 95% CI were determined for the quantitative variables. In addition, sensitivity analysis and Egger's test were performed to assess the stability of estimates and publication bias of included papers. A two-tailed p-value of 0.05 was deemed significant. If necessary, recent methods [5–7] were used to convert data provided as sample size, median, first and third quartiles, or minimum and maximum to mean and its related standard error.

3. Results

3.1. Study characteristics

Of 1050 papers identified in the initial research, 52 were retrieved for a more detailed evaluation (Fig. 1). According to the inclusion criteria, 14 studies were rejected, while 32 were abstracts of trials already included. At the end, 6 trials were included, published between 2011 and 2022, totally comprising 1390 patients, and with a follow-up that varied from 1 to 12 months [8–13]. Table 1 provides a summary of the baseline characteristics of the included studies.

3.2. Primary outcome

Through the analysis of five studies, we examined the optimization of RAASi therapy in HF patients. Across the included studies, the use of NPB provided an optimization of RAASi therapy of 14% compared to placebo (RR: 1.14, 95% CI: 1.04–1.26) (Fig. 2), implying that on NBP a greater proportion of patients (+14%) was on RAASi at the end of the studies compared to placebo. Albeit no significant heterogeneity was found (I^2: 38.81%), we conducted a subgroup analysis according to follow-up duration (<3 months and $\geq$3 months) (Fig. 3) and type of NPB (Fig. 4), showing no significant between group difference ($p = 0.15$ and $p = 0.91$, respectively) and, thus, confirming the efficacy of NPB in the optimization of RAASi therapy net of other analyzed variables.

3.3. Secondary outcomes

As regards the occurrence of hyperkalemia, five studies estimated hyperkalemia events in patients with HF; across the included studies, the use of NPB reduced hyperkalemia events by 29% compared to placebo (RR: 0.71, 95% confidence interval: 0.55–0.92) (Fig. 5).

Similarly, five studies analyzed the reduction in mean potassium levels in patients with HF; across the included studies, mean potassium level was reduced by 0.31 mEq/L more than with placebo (95% confidence interval: 0.44–0.18) (Fig. 6).

3.4. Safety outcomes

Six studies examined the occurrence of hypokalemia events in patients with HF; the use of NPB was related with an increase in hypokalemia events by 52% compared to placebo (RR: 1.52, 95% confidence interval: 1.08–2.13) (Fig. 7).

No significant correlation was found between hypomagnesemia and the use of patiromer, between edema and the use of SZC (Supplementary Figure I), and between gastrointestinal adverse events or severe hypokalemia events and the use of NPB (Supplementary Figure II).

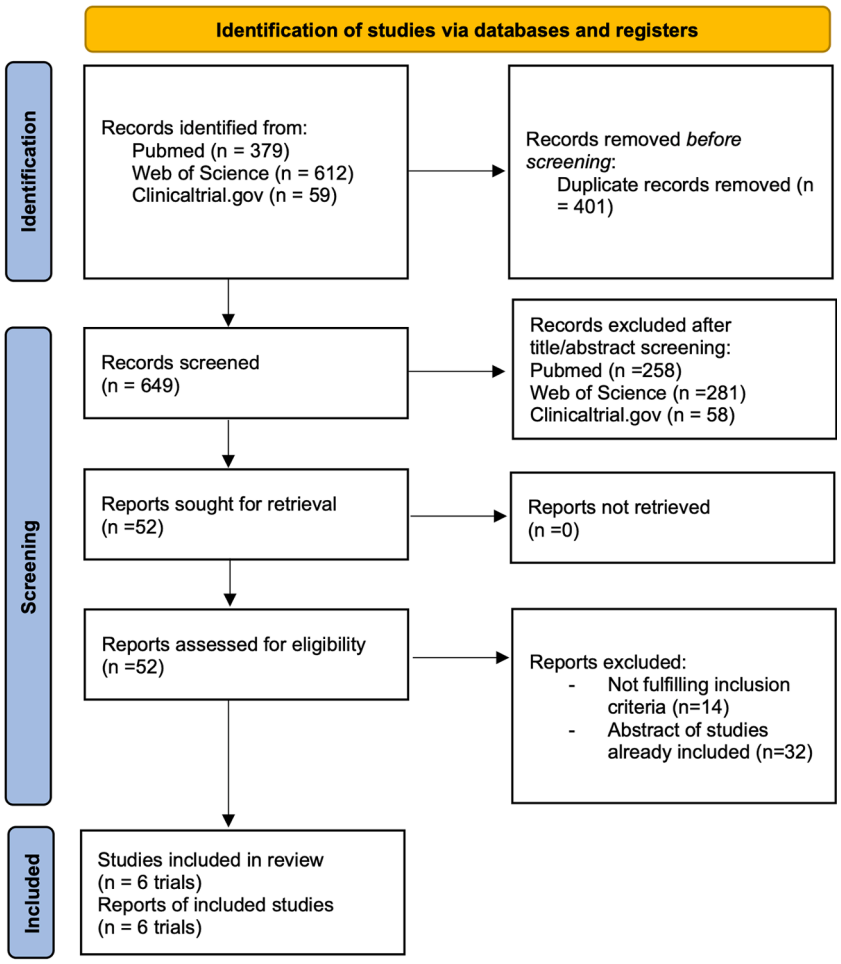

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews.
Caption: Study selection according to the pre-specified inclusion criteria.

3.5. Publication bias and sensitivity analysis

Publication bias for all outcomes was assessed (Supplementary Table III). Due to the low number of studies included in the present meta-analysis, we could not totally exclude publication bias, as suggested by the egger's test values and as reported in previous meta-analysis on the topic [14,15]. To evaluate the consistency of the findings, sensitivity analyses were conducted on all outcomes, that were stable showing a consistent effect regardless of any single study exclusion (Supplementary Figure III).

4. Discussion

The main finding of the current meta-analysis is that the use of NPB in patients with HF is associated with an optimization of RAASi therapy, conveyed by a 14% increase of patients receiving RAASi compared to placebo. In addition, NPB effectively reduce the occurrence of hyperkalemia and potassium levels.

Hyperkalemia occurs in up to 40% of patients with chronic HFrEF and in up to 73% of patients with advanced chronic kidney disease; it leads to more frequent hospitalizations and increases mortality rates, especially when stringent monitoring is not performed [2]. In these pathological conditions, one of the main causes of hyperkalemia is the concomitant use of drugs blocking the RAAS and occurrence of hyperkalemia often leads to withdrawal or de-escalation of RAASi.

Hyperkalemia is a negative prognostic marker in patients with HF. Although main trials, such as EMPHASIS-HF [16] and EPHESUS [17], demonstrated that a serum potassium level of 5.0 to 5.5 mEq/L does not offset the therapeutic benefits of HF treatment, recent studies reported that and how potassium levels correlate with short and long-term mortality. An analysis of the Swedish HF Registry showed that the relationship between potassium and mortality is u-shaped, with hypokalemia being associated with increased long-term mortality and hyperkalemia being associated with increased short-term mortality [18]. In a very informative work Thomsen et al. [19] showed, via a cohort study, that almost 4 out of 10 patients with HF develop hyperkalemia, whose risk is strongly associated with the degree of renal impairment and use of spironolactone, and whose incidence is associated with severe clinical outcomes and death. These results were also confirmed by Aldhal et al. [20], showing from the Danish National Registry that potassium levels within the lower (3.5–4.1 mEq/L) and upper (4.8–5.0 mEq/L) range are associated with a significant increased short-term risk of death in HF.

However, it is still unclear whether the negative association between potassium levels and adverse outcomes in HF represents a direct negative effect of the electrolyte disturbance itself or indirectly reflects the negative impact derived from inadequate use of HF disease-modifying drugs, as RAASi. An analysis of the ESC-HFA-EORP Heart Failure Long-Term Registry [21] performed on 9222 HF outpatients (60.6% with HFrEF), showed that, when adjusting for RAASi discontinuation, hyperkalemia was no longer associated with mortality, suggesting that the adverse effects of hyperkalemia might be explained by RAASi discontinuation and that hyperkalemia might be considered as a risk marker for a suboptimal HF treatment.

Table 1
Baseline characteristics of the included studies.

Trial name (registration number)	Year	Treatment	Patients, n	Inclusion criteria	Primary outcome	Age (±SD)	Female (%)	Baseline potassium levels (±SD)	Months of follow-up	Primary outcome result
PEARL-HF (NCT00868439)	2011	Patiromer	105	- ≥18 years of age - History of chronic HF - Indication to initiate spironolactone - K+ between 4.3 and 5.1 mEq/L - And at least one between: - eGFR <60 mL/min and receiving one or more HF therapies (ACEI, ARB, beta-blockers) - A documented history of hyperkalaemia that led to discontinuation of therapy with RAASi or beta-blocker within 6 months prior to the baseline visit	Mean change of serum K+ levels from baseline to the end of the study	67 (9.9)	60.5	4.7 (0.2)	1	−0.45 mEq/L ($p < 0.001$)
HARMONIZE (NCT02088073)	2015	SZC (10 mg group used as the treatment group)	44	- ≥18 years of age - Hyperkalaemia defined as K+≥5.1 mEq/L - History of chronic HF	Mean serum K+ levels between placebo and each treatment group during days 8 through 29 of the randomized phase	68 (10.7)	33.3	5.66 (0.3)	1	Patients in the 5 g, 10 g, and 15 g dose groups maintained lower serum potassium levels at 4.7 mEq/L (95% CI 4.5–4.9), 4.5 mEq/L (95% CI 4.3–4.6), and 4.4 mEq/L (95% CI 4.2–4.5), respectively ($p < 0.001$ for all doses)
OPAL-HK (NCT01810939)	2015	Patiromer	49	- 18–80 years of age - Stage 3 or 4 CKD - Hyperkalaemia, defined as K+ between 5.1 and 6.5 mEq/L - Had been receiving a stable dose of ≥1 RAASi for ≥ 28 days	Mean change in K+ levels from baseline to week 4	67.4 (8.6)	45	5.6 (0.6)	2	−1.06 ± 0.05 mEq/L (95% CI −1.16 to −0.95) ($p < 0.001$)
AMBER (NCT03071263)	2020	Patiromer	132	- ≥18 years of age - eGFR of 25–45 mL/min/1.73 m2 - K+ between 4.3 and 5.1 mEq/L - Resistant hypertension	Difference in the proportion of patients remaining on spironolactone at week 12.	70.1 (10.1)	48	4.71 (0.42)	3	between-group absolute difference 16.0% (95% CI 1.8–30.2) (p = 0.0504)
PRIORITIZE-HF (NCT03532009)	2021	SZC	182	- ≥18 years of age - History of chronic HF - EF ≤40% - Therapy with ACEI/ARB/ARNI, MRA and beta-blockers stable for ≥4 weeks - No MRA or a low dose of MRA (spironolactone, eplerenone, or canrenone) defined as less than or equal to 12.5 mg once a day or 25 mg every other day - Individuals with mild hyperkalaemia or at risk of developing hyperkalaemia, defined as: - eGFR 20–44 ml/min/1.73m2 and a K+ value between 4.0–5.5 mEq/L - eGFR 45–59 ml/min/1.73m2 and K+ value between 5.1–5.5 mEq/L - eGFR 45–59 ml/min/1.73m2 and K+ value between 4.0–5.0 mEq/L and a documented history of K+ > 5.0 mEq/L due to RAASi therapy	Percentage of patients receiving different categories of RAASi treatments at month 3	71.9 (8.5)	40.7	NA	3	RR 1.14 (95% CI 0.92–1.41) (p = 0.426)

(*continued on next page*)

Table 1 (*continued*)

Trial name (registration number)	Year	Treatment	Patients, n	Inclusion criteria	Primary outcome	Age (±SD)	Female (%)	Baseline potassium levels (±SD)	Months of follow-up	Primary outcome result
DIAMOND (NCT03888066)	2022	Patiromer	878	- ≥18 years of age - History of chronic HF - EF ≤40% - Hyperkalemia, defined as two K+ values >5.0mEq/l while receiving ACEI, ARB, ARNI and/or MRA. - Patients were also eligible if they were normokalemic but had a history of dose reduction or discontinuation of RAASi therapy due to hyperkalemia in the previous 12 months	Adjusted mean change in serum K+ levels from baseline	66.8 [10]	26.5	4.6 (0.3)	12	−0.10 mEq (95% CI −0.13, −0.07) ($p <$ 0.001)

ACEI, ACE inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; CKD, chronic kidney disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; MRA, mineralocorticoid receptor antagonists; RAASi, renin-angiotensin-aldosterone system inhibitors.; SZC, sodium zirconium cyclosilicate.

Thus, in HF patients the use of NPB is recommended by the most recent ESC [22] and AHA/ACC/HFSA [23] HF guidelines to control hyperkalemia and, consequently, to allow an adequate use of RAASi. Clinical trials on NPB have been conducted assessing as primary endpoint the effects on potassium levels. In the present meta-analysis we confirmed, as secondary outcome, this specific point, showing that NPB are effective in reducing serum potassium levels, specifically responsible of a decrease by 0.31 mEq/L more than placebo (95% confidence interval: 0.44–0.18). Moreover, we reported, still as secondary outcome, that NPB reduce hyperkalemia events [by 29% compared to placebo (RR: 0.71, 95% confidence interval: 0.55–0.92)], defined as a serum potassium level ≥5.5 mEq/L, an event rather frequent in HF patients on RAASi and/or with impaired renal function. However, in the studies included in the present meta-analysis, a specific outcome to assess the impact of NPB on the status of RAASi therapy during the follow-up was not always reported. Thus, we addressed this specific outcome, by adding to the data of studies assessing this outcome [8,11–13], data extracted from tables, figures and supplementary materials of studies not assessing this specific endpoint [9,10]. Our data showed a significant improvement in the primary endpoint of RAASi optimization compared to placebo (RR: 1.14, 95% confidence interval: 1.04–1.26) (Fig. 2), with no significant heterogeneity (I^2: 38.81%), or between group differences at the subgroup analysis (Figs. 3 and 4). Thus, the introduction of NPB in patients affected by HF with hyperkalemia or with a history of hyperkalemia allows to maintain a greater proportion of patients on RAASi therapy. Differently from a previous meta-analysis focusing on MRA therapy optimization [15], we focused on complete RAASi therapy and added recent trials analyzing similar endpoints.

In the field of cardiology, it's worth highlighting the current relevance of hyperkalemia in HF. This significance is further underscored by the recent release of a contemporary meta-analysis focused on this very topic [24]. A noteworthy improvement in the present manuscript, as compared to this recent meta-analysis, lies in its enhanced methodology. Specifically, the present manuscript has introduced a sub-analysis based on distinct follow-up periods; additionally, the inclusion of a larger cohort of patients for several outcomes has allowed more accurate estimations, improving the overall precision of the findings. Moreover, the manuscript explores a range of different and more clinically severe cut-off points for potassium levels, adding depth to the findings.

Regarding the safety analysis, NPB administration significantly increased total hypokalemia events, with no effects on severe hypokalemia; moreover, other dreaded adverse events that can occur with the use of NPB were not more likely to occur in patients on NPB compared to placebo, as gastrointestinal events, hypomagnesemia with the use of patiromer, and edema with the use of SZC. Thus, NPB are safe other than effective, also in a frail population, as represented by HF patients.

4.1. Limitations

Our meta-analysis suffers of some limitation. First, the small number of studies included led to a potential publication bias and high heterogeneity in the secondary outcomes that we cannot explain through meta-regression or subgroup analysis. While this is a limitation, the stability of the results assessed in the sensitivity analysis adds validity and strength to our study. In addition, this meta-analysis is not based on individual patient data and the included studies follow-up was limited. Moreover, it was not possible to perform a distinct subgroup analysis according to the presence of chronic kidney disease, in order to detect the impact of renal function on the primary outcome, since an eGFR ≤60 mL/min/1.73 m^2 was an inclusion criteria for the AMBER and PRIORITIZE-HF trials, and the percentage of patients with an eGFR ≤60 mL/min/1.73 m^2 was very high in the OPAL-HF (91%) and HARMONIZE (72.2%) trials; thus, a comparison among patients with or without renal dysfunction would have been not balanced. Last, it should be noted that both the PRIORITIZE-HF and DIAMOND trials were affected by the COVID-19 pandemic: the PRIORITIZE-HF was prematurely terminated due to the

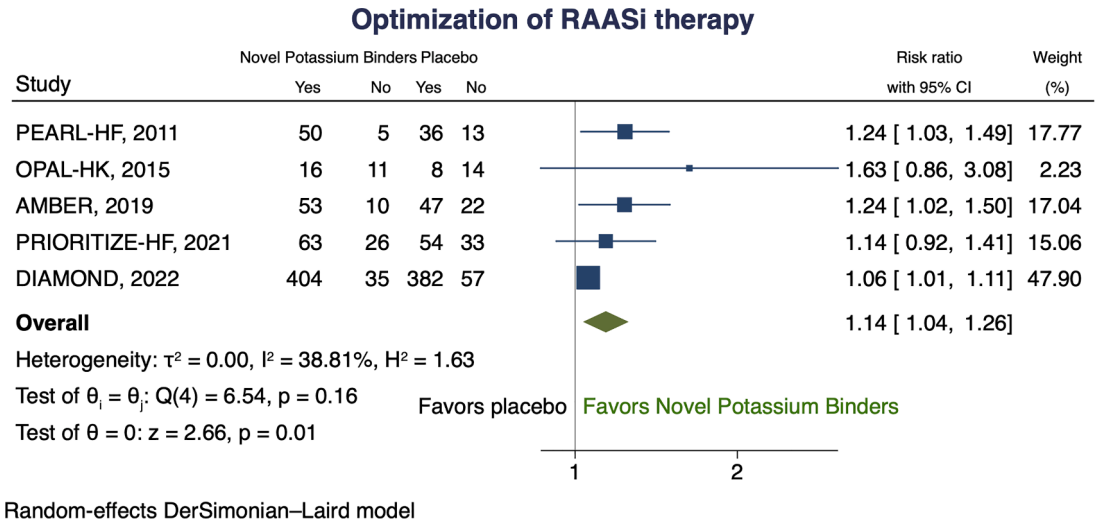

Fig. 2. Optimization of RAASi therapy.
Caption: Solid squares represent mean differences in trials and have a size proportional to the weight of the difference. The 95% confidence intervals (CI) for individual trials are denoted by lines and those for the pooled effect by a diamond.
RAASi, renin-angiotensin-aldosterone system inhibitors.

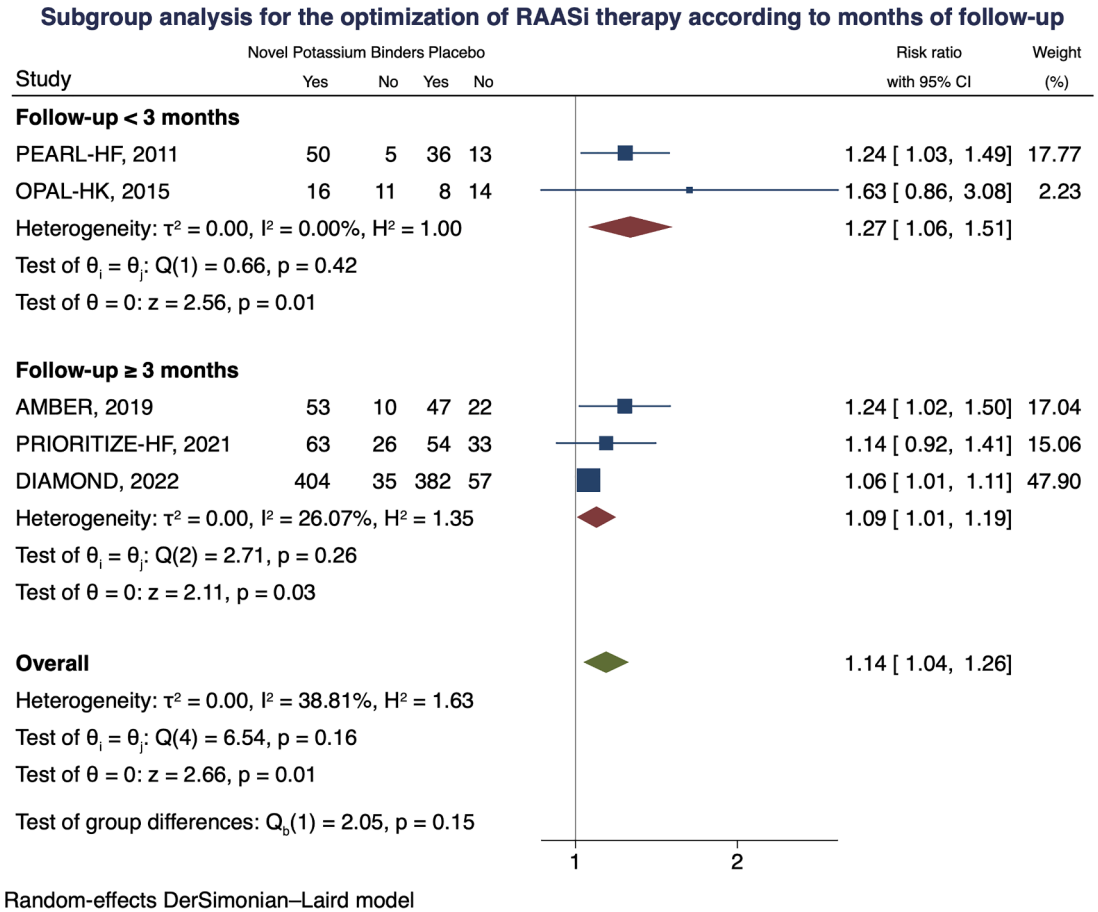

Fig. 3. Subgroup analysis for the optimization of RAASi therapy according to months of follow-up
Caption: Solid squares represent mean differences in trials and have a size proportional to the weight of the difference. The 95% confidence intervals (CI) for individual trials are denoted by lines and those for the pooled effect by a diamond.
RAASi, renin-angiotensin-aldosterone system inhibitors.

COVID-19 pandemic resulting in a reduced sample size and in a high premature treatment discontinuation rate, while the DIAMOND trial, originally designed as a cardiovascular outcome trial, was then thwarted by difficulties in enrolling and following patients during the pandemic; therefore, the original clinical endpoint was abandoned, and the primary endpoint was revised to the mean change in serum potassium

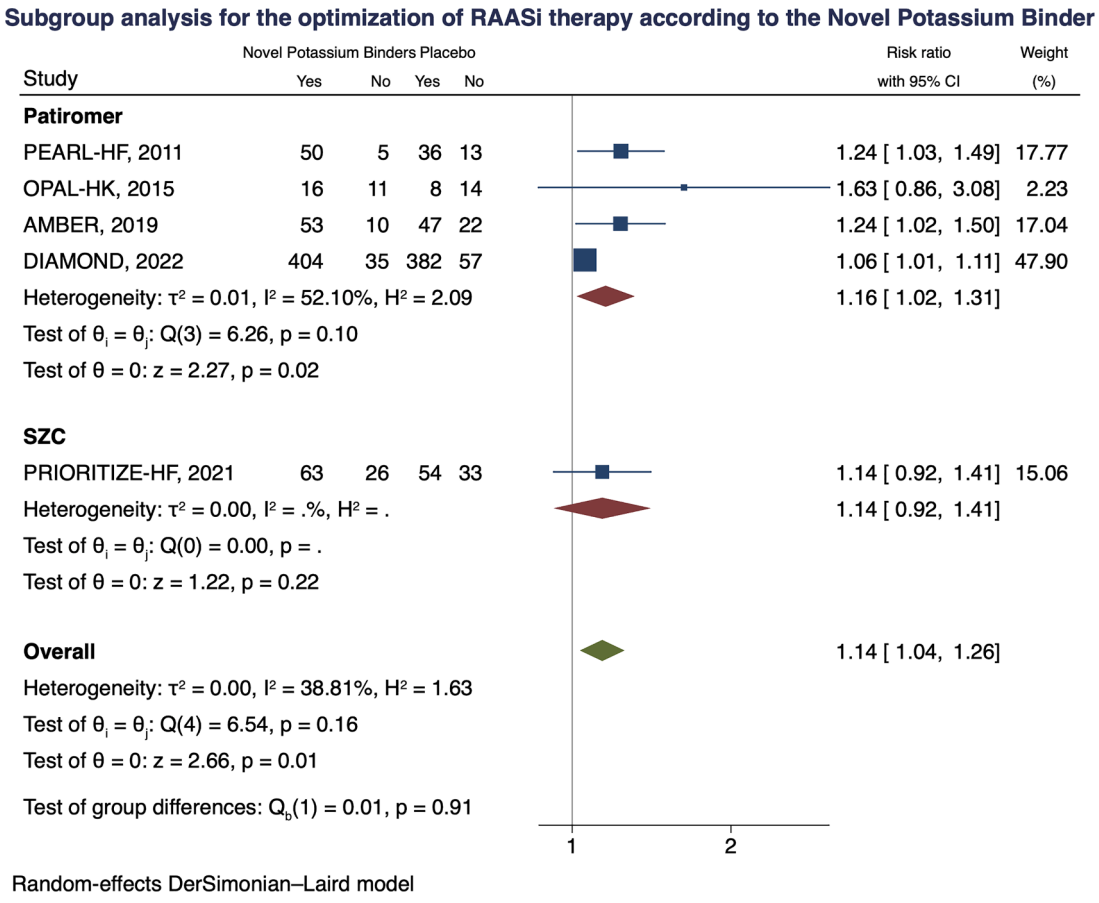

Fig. 4. Subgroup analysis for the optimization of RAASi therapy according to type of novel potassium binder.
Caption: Solid squares represent mean differences in trials and have a size proportional to the weight of the difference. The 95% confidence intervals (CI) for individual trials are denoted by lines and those for the pooled effect by a diamond.
RAASi, renin-angiotensin-aldosterone system inhibitors; SZC: sodium zirconium cyclosilicate.

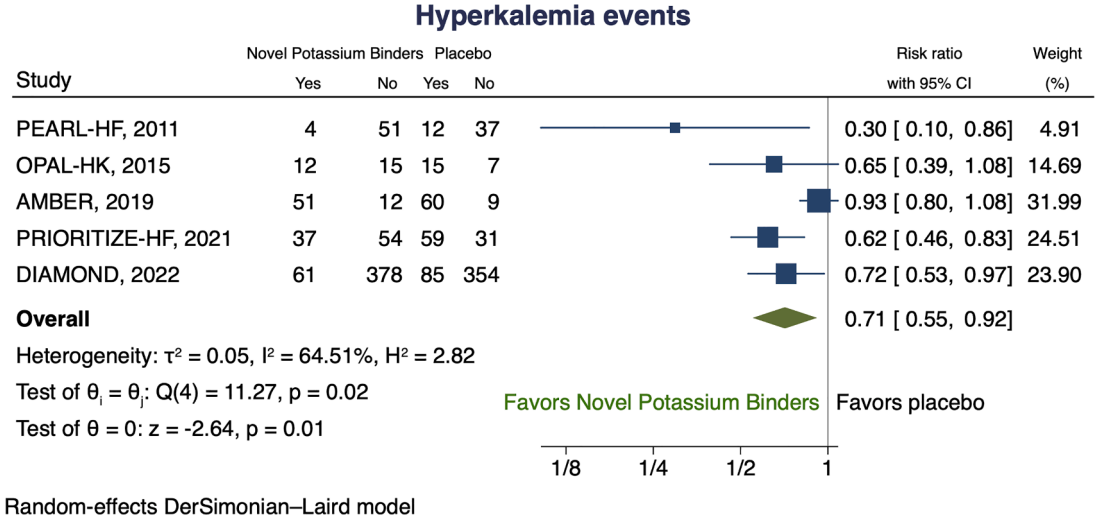

Fig. 5. Reduction in hyperkalemia events.
Caption: Solid squares represent mean differences in trials and have a size proportional to the weight of the difference. The 95% confidence intervals (CI) for individual trials are denoted by lines and those for the pooled effect by a diamond.

levels from baseline.

5. Conclusions

NPB administration allows optimization of RAASi therapy in patients affected by HF, supporting a potential favorable effect on prognosis by

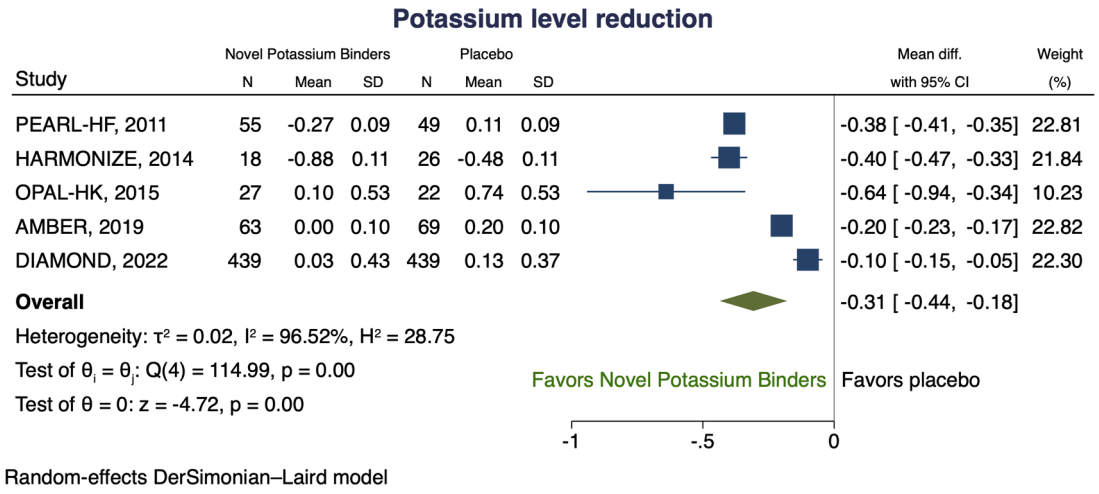

Fig. 6. Mean potassium level reduction.
Caption: Solid squares represent mean differences in trials and have a size proportional to the weight of the difference. The 95% confidence intervals (CI) for individual trials are denoted by lines and those for the pooled effect by a diamond.

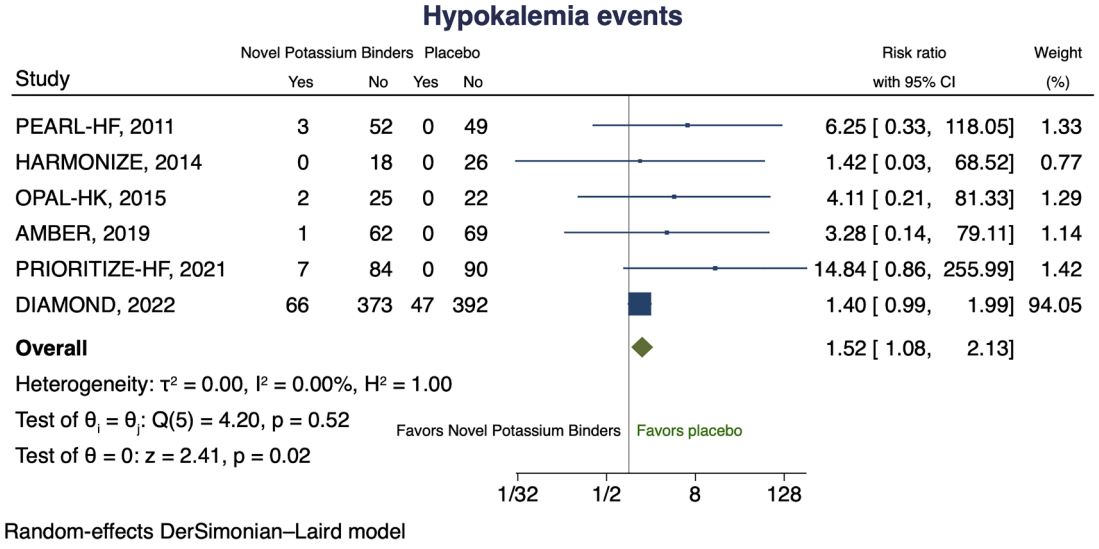

Fig. 7. Hypokalemia events.
Caption: Solid squares represent mean differences in trials and have a size proportional to the weight of the difference. The 95% confidence intervals (CI) for individual trials are denoted by lines and those for the pooled mean differences by empty diamonds.

reducing potassium levels and hyperkalemia events. Outcome trials are now needed to assess whether NBP therapy improves clinical outcome in HF patients.

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CRediT authorship contribution statement

Stefania Paolillo: Conceptualization, Writing – review & editing. **Christian Basile:** Data curation, Formal analysis, Methodology, Investigation, Visualization. **Simona Dell'Aversana:** Conceptualization. **Immacolata Esposito:** Conceptualization. **Alfonsina Chirico:** Writing – original draft. **Angela Colella:** Writing – original draft. **Gennaro Esposito:** Writing – original draft. **Mariafrancesca Di Santo:** Visualization. **Maria Francesca Fierro:** Writing – original draft. **Francesca Carbone:** Data curation, Formal analysis, Methodology, Investigation. **Federica Marzano:** Writing – review & editing. **Chiara Amato:** Data curation, Formal analysis, Methodology, Investigation. **Paola Gargiulo:** Writing – review & editing. **Pasquale Perrone Filardi:** Writing – review & editing.

Declaration of Competing Interest

None.

Data availability

No new data were generated or analyzed in support of this research.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.08.022.

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