The Efficacy and Safety of Patiromer for Heart Failure Patients A Systematic Review and Meta-analysis

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Abstract

Purpose
To evaluate the efficacy and safety of patiromer, a novel potassium binder, in reducing the risk of hyperkalemia in patients with heart failure and optimizing the therapy of RAASi on them.

Design
Systematic review and meta-analyses.

Method
The authors conducted a systematic search in the Pubmed, Embase, Web of Science, and Cochrane Library for randomized controlled trials investigating efficacy and safety of patiromer in heart failure patients from inception to 31 January 2023 and updated on 25 March 2023. The primary outcome was the association between reduction of hyperkalemia and patiromer compared with placebo, and the secondary outcome was the association between optimization of RAASi therapy and patiromer.

Results
A total of four Randomized Controlled Trials (n=1163) were included in the study. Patiromer was found capable to reduce the risk of hyperkalemia in heart failure patients by 44% (RR 0.56, 95% CI 0.36 to 0.87; I^2= 61.9%), improving tolerance to standard doses of MRA in patients with heart failure (RR 1.15, 95% CI 1.02 to 1.30; I^2=49.4%), and decrease the proportion of all-cause discontinuation of RAASi (RR 0.49, 95%CI 0.25 to 0.98; I^2=48.4%). However, patiromer therapy was associated with an increased risk of hypokalemia (RR 1.51, 95% CI 1.07 to 2.12; I^2=0%), while no other statistically significant adverse events were observed.

Conclusion
Patiromer appears to have a considerable effect on reducing the incidence of hyperkalemia in heart failure patients and on optimizing the therapy of RAASi in those patients.

Introduction
Heart failure (HF) is a global pandemic, affecting up to 37.7 million people worldwide, with a prevalence of approximately 1–2% in the adult population in developed countries, rising to over 10% in people over 80 years of age[1]. In the case of HF, disturbances in potassium homeostasis are rather common[2]. According to a recent large observational study, 24.4% of heart failure patients experienced at least one hyperkalemia event within 1 year, and 10.2% reported moderate or severe hyperkalemia[3].
Studies have shown that hyperkalemia is associated with an increased risk of mortality and other adverse events in HF patients, including those with Heart Failure with reduced Ejection Fraction (HFrEF) and Heart Failure with preserved Ejection Fraction (HFpEF).\[4–9]\.

Renin-angiotensin-aldosterone system inhibitors (RAASi) are first-line therapies for preventing the progression of cardiovascular disease.\[10]\ However, these drugs often have to be reduced or discontinued due to the induction of hyperkalemia, which prevents some patients from benefiting from these therapies.\[11–13]\.

Patiromer is a Novel Potassium Binder (NPB) that can exchange potassium (K\(^+\)) for calcium (Ca\(^{2+}\)) in the gastrointestinal tract and can be used to improve control of serum potassium.\[14]\.

2022ACC/AHA/HFSA guidelines expounded that the effectiveness of patiromer to improve outcomes of heart failure patients by facilitating the continuation of RAASi therapy is uncertain. The Class of Recommendation (COR) was 2b, and the Level of Evidence (LOE) was B-R.\[10]\.

Several Randomized Controlled Trials (RCTs) had investigated and reported the effect of patiromer in lowering mean serum potassium levels, reducing the incidence of hyperkalemia, and optimizing RAASi therapy in HF patients. However, the reported outcomes remained inconclusive.

Recent meta-analysis reported the efficacy of NPBs, including patiromer and SZC, to optimize the RAASi therapy in HF patients.\[19]\ But there is currently no available meta-analysis specifically focused on patiromer as a single drug, assessing its efficacy of reducing the incidence of hyperkalemia, increasing the tolerance of standard dose of MRA and decreasing discontinuation of RAASi therapy in HF patients.

It is worth noting that, patiromer and sodium zirconium cyclosilicate (SZC) have considerable distinctions in pharmacokinetic, pharmacodynamic, and safety profile respects, rendering them dissimilar. Despite that their pharmacologic mechanisms work similarly as exchanging cations for potassium in the gastrointestinal tract, binding potassium, and increasing its fecal excretion, the cations they exchange potassium for are totally different: patiromer for Ca\(^{2+}\), SZC for Na\(^+\).\[20]\ As a consequence, the incidence of edema would be much higher in patients under SZC therapy due to an increased absorption of Na\(^+\).\[21]\ Considering that HF patients are often volume overloaded, the net clinical benefit of lowering serum potassium with patiromer and SZC might not be equivalent. Considering the above factors, only studies that compare patiromer with placebo were included in this study.

Considering the factors mentioned above, we conducted a systematic review and meta-analysis of existing evidence from RCTs to quantitatively evaluate the potential of this drug.

**Methods**

We followed a guide on how to design, conduct, and publish a systematic review and meta-analysis. Reporting was done in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and
Meta-Analyses) guidelines[22]. We registered the protocol for this systematic review with PROSPERO (CRD42023395789).

Data sources and searches

The literature search was conducted in Pubmed, Embase, Web of Science, and Cochrane Library from inception to January 31 for potentially relevant studies, and the search was updated on 25 March 2023. Supplementary Appendix S1 provides full details of the search strategy.

Study selection

We considered studies eligible for inclusion if they: 1) were RCTs, 2) involved HF patients, 3) examined the effects of patiromer on reducing hyperkalemia or optimizing RAASi therapy, and 4) compared patiromer with placebo. The exclusion criteria were as follows: 1) animal experiments, or 2) repeated studies. Study selection was performed with two phases: primary screening of title and abstract, then full text review for potentially eligible articles. Two review authors (L.H. and Y.G.) independently evaluated eligibility, with discrepancies resolved by a third investigator (J. F.).

Data extraction

Two review authors (L.H. and Y.G.) independently extracted data from eligible studies. Extracted data included first author, publication year, country, setting of the run-in period, duration of follow-up, dose of patiromer, sample size, participant feature, and outcome variables of interest. The primary outcome was the association between the reduction of hyperkalemia and patiromer comparing with placebo. The secondary outcome was the association between optimization of RAASi therapy (including incidence of accepting standard dose of MRA and proportion of discontinuing of RAASi) and patiromer. The safety outcomes take Adverse Events (AE), Severe Adverse Events (SAE), AE leading to disconnection, all-cause death, hypokalemia, hypomagnesemia, gastrointestinal disorder, and headache into consideration.

Risk of bias and certainty of evidence assessment

The authors (C.L. and Z.Z.) independently performed the quality assessment and risk of bias using the Cochrane Risk of Bias Tool, and disagreements were resolved through the consensus method. Certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, which divides evidence into very low, low, moderate, and high levels.

Subgroup analyses
Subgroup analyses were performed on the following variables: blinding (single-blind or double-blind); run-in period (with or without run-in period); duration of run-in period (≤ 4 weeks or > 4 weeks); duration of follow-up duration (≤ 8 weeks or > 8 weeks); data source (from a RCT subgroup or a Specialized RCT); risk of bias (low or high); participant feature (with or without Hyperkemia).

Data synthesis and analyses

The statistical analyses were performed using Review Manager, version 5.3 (Cochrane Collaboration), and Stata, version 16.0 (College Station, Texas, USA). The heterogeneity across studies was quantified using the $I^2$ statistic (0–25% low heterogeneity, 25–50% moderate heterogeneity, 50–75% substantial heterogeneity, 75–100% high heterogeneity). Dichotomous data was analyzed using the Mantel–Haenszel method, and the pooled risk ratios (RR) and corresponding 95% confidence intervals (CI) were then calculated. Publication bias was assessed by Egger's method. We did not create a funnel plot because we included fewer than 10 trials.

Results

Literature search and study selection

In our initial and update searches, we identified 204 records after removing duplicates. After screening the title and abstract comments, the full text of 37 articles is reviewed. 4 studies were eligible for data extraction and quantitative analysis[15–18]. Figure 1 shows the flow of records through the review, Supplementary Appendix S2 includes a list of excluded studies with reasons. Table 1 summarizes the characteristics of the included articles.

The included studies were compiled from four databases which were published between 2012 and 2022. All of these studies were RCTs, one of which was single-blind and the others were double-blind. Three of the studies designed a "run-in period" or similar mechanism to screen the population for inclusion, whereby all eligible people were given a certain dose of RAASi and patiromer before entering the placebo-controlled phase; and titrated patiromer and RAASi doses based on serum K⁺. At the end of the run-in period, patients were randomly assigned to patiromer or placebo groups for further study; 2 studies included patients with normal serum potassium, 1 study included patients with hyperkalemia, and 1 study included patients with hyperkalemia or at risk of hyperkalemia.

Risk of bias

The risk of bias for the included trials is presented in Fig. 2. The description of the randomization process and allocation concealment was presented ambiguously in 2 RCTs[17, 18]. There was a single-blind study that may have introduced a performance bias[17]. However, since the primary outcome was detected by laboratory methods, the results of this meta-analysis are less likely to be influenced by the single-blind
study design. One study whose experimental design may have excluded patients who were insensitive to patiromer was considered to be at high risk of bias\cite{17}. Considering these studies were all sponsored by the pharmaceutical industry, they may contain uncertain risk of bias.

**Primary outcome**

The effect of patiromer on reducing the incidence of hyperkalemia in patients with HF was reported in 4 eligible studies. The random-effects model was used to assess the pooled results, which showed a 44% reduction in the overall risk of hyperkalemia in patients (RR 0.56, 95% CI 0.36 to 0.87; $I^2 = 61.9\%$) (Fig. 3). Pooled results carried substantial heterogeneity. We found evidence of publication bias through Egger's test (p = 0.035). In terms of the primary outcome, these findings were considered evidence with moderate proof power. Supplementary Table 6 summarizes the quality of evidence based on the GRADE framework.

**Secondary outcomes**

Secondary outcomes were assessed by a random-effects model. Compared with placebo, patients taking patiromer had better tolerance to standard doses of mineralocorticoid receptor antagonist (MRA) (RR 1.15, 95% CI 1.02 to 1.30; $I^2 = 49.4\%$) (Fig. 4), and the incidence of discontinuation of RAASi therapy decreased by 51% (RR 0.49, 95%CI 0.25 to 0.98; $I^2 = 48.4\%$) (Fig. 5). Egger's test showed that the former had no significant publication bias (p = 0.077), while the latter had statistically significant publication bias (p = 0.031). According to the GRADE framework, the overall quality of the evidence is high and moderate (Supplementary Table 6).

**Safety outcomes**

We examined the incidence of several safety outcomes, including total Adverse Events (AE), Serious Adverse Events (SAE), AE leading to disconnection, all cause death, hypokalemia, hypomagnesemia, gastrointestinal disorder and headache. The entire results for all safety outcomes are shown in Table 2.

Overall, the patiromer therapy was associated with an increased risk for hypokalemia (RR 1.47, 95% CI 1.04 to 2.07, $I^2 = 0\%$).

There was no evidence demonstrating other significant safety issue differences, such as SAEs, all-cause death or hypomagnesemia, between patiromer therapy and placebo.
Table 2
Meta-analysis for the risk of safety outcomes.

<table>
<thead>
<tr>
<th>Safety outcome</th>
<th>No. of studies (patients)</th>
<th>RR</th>
<th>$I^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>4(1136)</td>
<td>1.01(0.93, 1.09)</td>
<td>51%</td>
<td>0.78</td>
</tr>
<tr>
<td>Any SAE</td>
<td>4(1136)</td>
<td>0.87(0.63, 1.22)</td>
<td>0</td>
<td>0.43</td>
</tr>
<tr>
<td>AE leading to disconnection</td>
<td>4(1136)</td>
<td>1.24(0.72, 2.14)</td>
<td>44%</td>
<td>0.45</td>
</tr>
<tr>
<td>All-cause death</td>
<td>4(1136)</td>
<td>1.13(0.64, 2.02)</td>
<td>0</td>
<td>0.67</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4(1136)</td>
<td>1.51(1.07, 2.12)</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>4(1136)</td>
<td>1.39(0.83, 2.33)</td>
<td>71%</td>
<td>0.21</td>
</tr>
<tr>
<td>Headache</td>
<td>2(181)</td>
<td>0.37(0.10, 1.34)</td>
<td>0</td>
<td>0.13</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>4(1136)</td>
<td>1.40(0.95, 2.06)</td>
<td>47%</td>
<td>0.09</td>
</tr>
<tr>
<td>Constipation</td>
<td>2(927)</td>
<td>2.23(0.82, 6.02)</td>
<td>0</td>
<td>0.11</td>
</tr>
<tr>
<td>Nausea</td>
<td>2(927)</td>
<td>1.38(0.41, 4.60)</td>
<td>0</td>
<td>0.61</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3(1059)</td>
<td>1.21(0.67, 2.18)</td>
<td>0</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Sensitive analyses

We performed leave-out analyses to explore the sources of heterogeneity. The heterogeneity of the primary outcome was mainly driven by the study by Pitt et al.[17] If this study was excluded, the $I^2$ in the adjusted analysis would be reduced to 25.4% (RR 0.68, 95%CI 0.52 to 0.90; $I^2 = 25.4$%). The source of heterogeneity may be related to the design of the trail and participant feature.

According to the design of the study by Pitt et al. [17], the patients carrying HF, renal failure and hyperkalemia at the same time were included. These patients would take a certain dose of patiromer in the run-in period, and if they would gain normal serum potassium at the end of the run-in period, they would be eligible to enter the follow-up period, which randomly divided eligible patients into placebo group or patiromer group. Therefore, patients who were insensitive to patiromer would be screened out after the run-in period, while sensitive patients would be enrolled in the follow-up period. This conjecture also consisted with the result that the study by Pitt et al. presented the highest RR value[17].

The study by Butler et al.[16] drove the main heterogeneity of the first part of the secondary outcomes, which is the tolerance to standard dose MRA, and if this study is excluded, heterogeneity would be reduced from 49.4–0% in adjusted analysis (RR 1.25, 95% CI 1.08 to 1.45; $I^2 = 0$%). Longer follow-up period may contribute to higher heterogeneity, and in the subsequent subgroup analyses, we adjusted the relevant factors.
After excluding studies one by one, we found that the main source of heterogeneity in the second part of the secondary outcomes, which is the proportion of discontinuing of RAASi, was the study by Pitt et al. [17] After removing this trial, $I^2$ decreased to 0% (RR 0.58, 95% CI 0.38 to 0.89; $I^2 = 0\%$). By comparing the research characteristics, it was supposed that the heterogeneity is related to the design of the study by Pitt et al. above-mentioned which screened out patients insensitive to patiromer before entering the randomized controlled period. In addition, the study by Butler[16] and the study by Rossignol[15] reported the rate of patients who discontinued MRA, while the study by Pitt[17] reported the rate of patients who discontinued various types of RAASi, which might also be a source of heterogeneity.

**Subgroup Analyses**

To investigate the subgroup differences in the outcomes, we conducted subgroup analyses according to the characteristics of eligible studies, including blinding, run-in period, participant feature and risk of bias.

The results of subgroup analyses of the primary outcome are shown in Table 3 and Supplementary Fig. 6. In subgroup analyses of the primary outcome, there were significant differences between subgroups in blinding ($P = 0.02$), risk of bias ($P = 0.02$), and duration of the follow-up period ($P = 0.006$). Coincidentally, the blinding subgroups contain exactly the same trails as the subgroups of risk of bias. As the primary outcome was detected by laboratory methods, the results of this meta-analysis are unlikely to have been influenced by the single-blind study design.

It was mentioned in the previous sensitivity analysis that the study by Pitt et al. [17]may be a major source of heterogeneity due to the study design which might introduce the risk of bias, thus we adjusted the risk of bias in the subgroup analyses, and there appeared a statistically significant difference between the subgroups. There were statistical differences between subgroups in the duration of follow-up period, while $I^2$ decreased to 0% inside each subgroup.

These discoveries revealed a possible trend: there was a difference between the long-term and short-term effects of patiromer in reducing the incidence of hyperkalemia in patients with HF.

The first part of results of subgroup analyses of the secondary outcomes were presented in Table 4 and Supplementary Fig. 7, while the second part in Table 5 and Supplementary Fig. 8. There was no statistically significant difference between the subgroups for the secondary outcomes.

**Table 3** Subgroup analyses of association between patiromer and incidence of hyperkalemia according to study characteristics.
Table 4 Subgroup analyses of association between patiromer and tolerance of standard dose of MRA according to study characteristics.

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>No. of studies</th>
<th>I² (%)</th>
<th>P for within groups</th>
<th>P for subgroup difference</th>
<th>Risk Ratio (95%CI)</th>
<th>Risk Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>4</td>
<td>63</td>
<td>-</td>
<td>-</td>
<td>0.65(0.51 to 0.79)</td>
<td></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>blinding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>single</td>
<td>1</td>
<td>-</td>
<td>0.005</td>
<td>0.02</td>
<td>0.14(0.03 to 0.54)</td>
<td></td>
</tr>
<tr>
<td>double</td>
<td>3</td>
<td>23</td>
<td>0.0009</td>
<td>0.68</td>
<td>0.68(0.54 to 0.85)</td>
<td></td>
</tr>
<tr>
<td><strong>run-in period setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without</td>
<td>1</td>
<td>-</td>
<td>0.03</td>
<td>0.14</td>
<td>0.29(0.10 to 0.85)</td>
<td></td>
</tr>
<tr>
<td>with</td>
<td>3</td>
<td>64</td>
<td>0.0004</td>
<td>0.67</td>
<td>0.67(0.53 to 0.83)</td>
<td></td>
</tr>
<tr>
<td><strong>duration of run-in period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4 weeks</td>
<td>2</td>
<td>83</td>
<td>0.001</td>
<td>0.36</td>
<td>0.58(0.42 to 0.81)</td>
<td></td>
</tr>
<tr>
<td>&gt; 4 weeks</td>
<td>1</td>
<td>-</td>
<td>0.03</td>
<td>0.72</td>
<td>0.72(0.53 to 0.97)</td>
<td></td>
</tr>
<tr>
<td><strong>duration of follow-up period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8 weeks</td>
<td>2</td>
<td>0</td>
<td>0.0003</td>
<td>0.006</td>
<td>0.21(0.09 to 0.49)</td>
<td></td>
</tr>
<tr>
<td>&gt; 8 weeks</td>
<td>2</td>
<td>0</td>
<td>0.006</td>
<td>0.72</td>
<td>0.72(0.57 to 0.91)</td>
<td></td>
</tr>
<tr>
<td><strong>data source</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>specialized RCT</td>
<td>2</td>
<td>59</td>
<td>0.085</td>
<td>0.57</td>
<td>0.66(0.50 to 0.88)</td>
<td></td>
</tr>
<tr>
<td>subgroup data</td>
<td>2</td>
<td>83</td>
<td>0.001</td>
<td>0.58</td>
<td>0.58(0.42 to 0.81)</td>
<td></td>
</tr>
<tr>
<td><strong>risk of bias</strong></td>
<td></td>
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<tr>
<td>low</td>
<td>3</td>
<td>23</td>
<td>0.0009</td>
<td>0.02</td>
<td>0.68(0.55 to 0.85)</td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>1</td>
<td>-</td>
<td>0.005</td>
<td>0.14</td>
<td>0.14(0.03 to 0.54)</td>
<td></td>
</tr>
<tr>
<td><strong>Participant feature</strong></td>
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<td></td>
</tr>
<tr>
<td>hyperkalemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without</td>
<td>2</td>
<td>63</td>
<td>0.005</td>
<td>0.92</td>
<td>0.62(0.45 to 0.86)</td>
<td></td>
</tr>
<tr>
<td>with</td>
<td>2</td>
<td>81</td>
<td>0.002</td>
<td>0.64</td>
<td>0.64(0.48 to 0.85)</td>
<td></td>
</tr>
</tbody>
</table>
Table 5 Subgroup analyses of association between patiromer and incidence of discontinuation of RAASi therapy according to study characteristics.

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>No. of studies</th>
<th>I² (%)</th>
<th>P for within groups</th>
<th>P for subgroup difference</th>
<th>Risk Ratio (95%CI)</th>
<th>Risk Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>total</td>
<td>3</td>
<td>51</td>
<td>-</td>
<td>-</td>
<td>1.10(1.05,1.16)</td>
<td></td>
</tr>
<tr>
<td>study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>run-in period setting</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without</td>
<td>1</td>
<td>-</td>
<td>0.03</td>
<td>0.21</td>
<td>1.24(1.03,1.49)</td>
<td></td>
</tr>
<tr>
<td>with</td>
<td>2</td>
<td>55</td>
<td>0.003</td>
<td>1.06(1.03,1.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>duration of run-in period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4 weeks</td>
<td>1</td>
<td>-</td>
<td>0.04</td>
<td>0.15</td>
<td>1.28(1.01,1.63)</td>
<td></td>
</tr>
<tr>
<td>&gt; 4 weeks</td>
<td>1</td>
<td>-</td>
<td>0.02</td>
<td>1.07(1.01,1.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>duration of follow-up period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8 weeks</td>
<td>1</td>
<td>-</td>
<td>0.03</td>
<td>0.21</td>
<td>1.24(1.03,1.49)</td>
<td></td>
</tr>
<tr>
<td>&gt; 8 weeks</td>
<td>2</td>
<td>55</td>
<td>0.003</td>
<td>1.09(1.03,1.15)</td>
<td></td>
<td></td>
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<tr>
<td>data source</td>
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<td>specialized RCT</td>
<td>2</td>
<td>53</td>
<td>0.003</td>
<td>0.18</td>
<td>1.05(1.03,1.15)</td>
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<tr>
<td>subgroup data</td>
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<td>-</td>
<td>0.04</td>
<td>1.28(1.01,1.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant feature</td>
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<td></td>
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<tr>
<td>hyperkalemia</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>without</td>
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<td>0.05</td>
<td>1.26(1.08,1.47)</td>
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<tr>
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<td>-</td>
<td>0.02</td>
<td>1.00(1.01,1.13)</td>
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</table>
Discussion

Principal findings

In the present meta-analysis of 4 studies enrolling 1136 patients with HF, patiromer therapy resulted in a potential reduction on incidence of hyperkalemia. In addition, patiromer therapy was also associated with optimization of RAASi therapy (including increasing proportion of tolerance of standard-dose MRA and reducing ratio of RAASi discontinuation). Compared to placebo, the incidence of hypokalemia was significantly higher under patiromer therapy. Our study demonstrated that the incidence of other AEs under patiromer therapy was generally similar comparing using placebo.

Comparison with other studies

In recent years, several clinical trials have reported the effects of patiromer in lowering serum potassium, reducing the incidence of hyperkalemia, and optimizing RAASi therapy in patients with HF.
A previous meta-analysis based on 3 studies concluded that NPBs could optimize RAASi therapy in patients with HF (RR 1.25, 1.08to1.45)[19]. However, this study included only 3 studies, with a lack of heterogeneity, limited follow-up period (1–3 months), and small numbers of events and patients, which were believed, hindered the drawing of valid conclusions[23]. Besides, they performed subgroups of the types of potassium binders only, which we believe may, to some extent, omitted some outcomes with clinical value.

Our study has several advantages over previous meta-analysis. Firstly, we comprehensively and systematically studied the effect of patiromer on reducing the incidence of hyperkalemia and optimizing RAASi therapy in HF patients, obtaining pooled results of higher accuracy by excluding confounding factors such as different types of NPBs and various outcomes. Secondly, we are confident that our results are reliable because the included studies were all RCTs, only one of which had a high risk of bias; despite of the high heterogeneity of the pooled results, the sources of heterogeneity were all reasonably justified in sensitive analyses and subgroup analyses, and the pooled results remained stable without directional changes after excluding studies that primarily drove heterogeneity.

**Underlying mechanisms**

Pathophysiology mechanisms

The renin-angiotensin system plays an important role in potassium metabolism in patients with HF. Commonly, according to pathophysiological mechanisms, patients with HF have lower cardiac output compared to normal persons, which results in renal hypoperfusion, which activates the renin-angiotensin system, thereby promoting potassium excretion by stimulating aldosterone synthesis[24]. However, the application of RAASi, including ACEi, ARB and MRA, inhibits the synthesis or action of aldosterone, resulting in a reduction in potassium excretion. The Inhibition would be especially more apparent under the circumstance of combination therapy[20, 21]; In addition, high serum potassium can directly inhibit RAAS[25], resulting in a tendency to further elevate serum potassium.

Accumulating evidence supports the link between disturbances in potassium metabolism and adverse clinical outcomes in patients with HF. Several studies reported a U-shaped association between serum potassium and adverse clinical outcomes in patients with HF[4, 26–28], which is, the incidence of adverse clinical outcomes in patients with HF was relatively low in a narrow range of serum potassium.

It is worth noticing that in the observational study by Cooper et al., after covariate adjustment, hyperkalemia was found associated only with the rising of short-term but not long-term mortality[4]. Elucidating this causal relationship is of particular clinical importance, because it remains unclear whether treatment targeting hyperkalemia can increase the long-term survival rate of patients with HF.

Although it is uncertain whether hyperkalemia is a risk factor or a sign of increased risk for adverse clinical outcomes in patients with HF, certain mechanisms that may increase such risk should be paid
attention to.

Hyperkalemia has a grand effect on cardiac electrophysiology, including a decrease in myocardial resting membrane potential, increased cardiac depolarization, myocardial excitability, cardiac instability and conduction system abnormalities, which could ultimately lead to arrhythmias, and even progress to ventricular fibrillation and asystole[29, 30].

Even if it is indeterminacy whether therapies targeting hyperkalemia themselves could directly improve clinical outcomes, such therapies may make it possible for patients with HF to tolerate higher doses of RAASi, thus providing indirect clinical benefits[21].

**Drug mechanisms**

Patiromer is a type of non-absorbable, low expansion ratio, cross-linked polymer, composed of beads with a diameter of about 118um, with fine fluidity and appropriate viscosity, and is stable in physiological environments.

Its main mechanism is to exchange Ca\(^{2+}\) for K\(^{+}\) in the digestive tract (mainly in the colon, where the concentration of K\(^{+}\) is the highest) and promote the excretion of K\(^{+}\) from the feces [ag, ah]. Compared with Sodium polystyrene sulfonate (SPS), patiromer carries physical properties such as limited water absorption and low expansion ratio, so the digestive tract reactions it may cause is relatively low. Another advantage of patiromer is that its exchange ion is Ca\(^{2+}\) instead of Na\(^{+}\), so it may be more applicable in patients with high volume load, such as HF, severe hypertension and edema. At physiological pH, each gram of patiromer can bind 8.5-8.8mEq K\(^{+}\) in vitro, which is much higher than SPS and other resins[21].

Vitro drug–drug interaction studies showed the binding rate of patiromer with multiple types of drug cannot be ignored[21]. Based on the vitro data, FDA recommended such types of drug should be taken at least 6 hours before or after patiromer[31, 32].

**limitations of this study**

We acknowledge the presence of limitations in our study. Firstly, Long-term conclusions could not be drawn due to the limited duration of the follow-up periods in three of the trials. In this regard, the duration of the follow-up period of the study by Butler et al. was several times longer than that of other studies, and the duration of follow-up period subgroups of the primary outcome reflected statistically significant differences.

Secondly, because few RCTs provided HF indicators, including LVEF, BNP etc., before and after patiromer therapy, the consolidation of relevant data was limited, which made it of high difficulty to assess the benefits of patiromer in reducing potassium and optimizing RAASi therapy.
Thirdly, some subgroup analyses with clinical value, such as the evaluation of patiromer efficacy in HF patients with or without chronic kidney disease were hindered due to limitations of the number of included studies and participant features.

Fourthly, due to the population included in the RCTs with chronic kidney disease is of non-negligible proportion, more caution is needed in generalizing the results of this study to the entire population of HF patients.

However, despite the study designs, data materials, follow-up periods, and study qualities varied and the limitations that existed, the relatively stable study results indicate that our findings were statistically reliable.

Therefore, we need additional data from postmarketing surveillance to assess the long-term effects of patiromer and the incidence of rare AEs. We expect the quality of the evidence to be improved with future updates and more high-quality studies.

**Conclusion**

Our systematic review and meta-analysis showed that patiromer has considerable effect on reducing the incidence of hyperkalemia and optimizing RAASI therapy in patients with HF. Subgroup analyses indicated that comparing the long-term and short-term effects of patiromer, in terms of reducing the incidence of hyperkalemia in HF population, the two present differently; but on the outcome of optimizing RAASI therapy, there was no significant difference.

For the HF patients receiving patiromer therapy, the only AE, presently observed, of statistically significant differences, compared with placebo, was hypokalemia, since there is currently no evidence that other AEs of statistically significant differences exist. Regular monitoring on serum K⁺ in patients taking patiromer is necessary, considering that hypokalemia is an independent risk factor for adverse clinical events in patients with heart failure[4].

Sufficient RCTs are needed in the future to assess the long-term effects and potential harms of patiromer to improve clinical outcomes in HF patients with, or at risk of hyperkalemia.

**Declarations**

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**Competing Interests** The authors have no relevant financial or non-financial interests to disclose.

**Author Contributions** All authors contributed to the study conception and design. Data search were performed by Zhipeng Zhang and Chunmiao Luo. Study selection and Data extraction were performed by
Yu Gao and Linlin Hou. Data analyses and visualization was performed by Yuhui Wang. The first draft of the manuscript was written by Yuhui Wang and reviewed by Jun Feng.

**Ethical Approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Consent for Participate** Not required.

**Consent for publication** All authors have read and approved the submission of the manuscript; the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.

**Data Availability and Material** The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

**Code Availability** Not applicable.

**References**


**Tables**

Table 1 is available in the Supplementary Files section.
Figure 1

The flow diagram for the study search process.
Figure 2

Risk of bias for the included trials.

Figure 3

Meta-analysis for the risk of hyperkalemia. The size of the box is proportional to the weight of the study in the meta-analysis. RR, risk ratio; CI, confidence interval.
Figure 4

Meta-analysis for tolerance to standard doses of MRA.

Figure 5

Meta-analysis for incidence of discontinuation of RAASi therapy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- SupplementaryMaterial.doc