



# Comparative efficacy and safety of mineralocorticoid receptor antagonists in heart failure: a network meta-analysis of randomized controlled trials

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## Abstract

The efficacy and safety of mineralocorticoid receptor antagonists (MRAs) in patients with heart failure (HF) are controversial. To explore the role of MRAs in HF patients with an ejection fraction of no more than 45%, we conducted a network meta-analysis of randomized controlled trials (RCTs). We systematically searched PubMed, Embase, the Cochrane Library, and Clinicaltrials. RCTs involving the efficacy and/or safety of the use of MRAs in patients with HF were included. Outputs are presented as the surface under the cumulative ranking area (SUCRA) probabilities. Thirteen RCTs involving a total of 13,597 participants were included. Finerenone 10 mg was associated with the lowest probability of achieving at cardiovascular mortality (SUCRA, 5.0%), followed by finerenone 7.5 mg (SUCRA, 31.6%). In reducing N-terminal pro-B-type natriuretic peptide, finerenone 15 mg and finerenone 7.5 mg ranked the best and second best (SUCRA 68.1% and 63.8%, respectively), followed by finerenone 10 mg (SUCRA 59.2%). Spironolactone and canrenone have a higher risk of hyperkalemia and renal deterioration. Regarding the prevention of worsening renal function, finerenone 7.5 mg (SUCRA 14.3%) was the best treatment, followed by finerenone 2.5 mg (SUCRA 16.3%) and finerenone 10 mg (SUCRA 25.6%). Compared with spironolactone and eplerenone, finerenone 10 mg was associated with low risk in the occurrence of cardiovascular mortality, hospitalization, and adverse events ( $P < 0.01$ ). This network meta-analysis is the first to find that finerenone 7.5–10 mg has the highest probability of being the optimal alternative among MRAs in the treatment of HF patients with an ejection fraction of no more than 45%.

**Keywords** Heart failure · Mineralocorticoid receptor antagonists · Hyperkalemia · Meta-analysis

## Introduction

Heart failure (HF) is a major public health problem that represents one of the leading causes of death worldwide [1, 2]. A variety of mechanisms are involved in the pathophysiological

development of HF, in which aldosterone plays an important role in mediating endothelial dysfunction, accelerating myocardial fibrosis, and subsequent cardiac remodeling [3, 4]. Although an angiotensin-converting enzyme inhibitor (ACEI) may reduce aldosterone for a short time, with chronic therapy, there is a rapid return of aldosterone to levels similar to those before ACEI therapy, described as “aldosterone breakthrough” [5]. In addition to ACEI, mineralocorticoid receptor antagonists (MRAs), which have shown effects on lowering aldosterone levels, may have potential benefits for HF patients [5].

Recently, steroidal MRAs, including spironolactone and eplerenone, have been shown to have beneficial effects in reducing cardiovascular mortality and hospitalizations in HF patients with an ejection fraction of no more than 35% [6–9]. Hence, steroidal MRA therapy is recommended in the American and European guidelines for the treatment of HF with reduced ejection fraction (HFrEF) patients [10, 11]. However, the high risk of adverse events associated with the use of steroidal MRAs including hyperkalemia and renal deterioration was the main cause for their suboptimal use in

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clinical practice, particularly in patients with chronic kidney disease (CKD) or type 2 diabetes mellitus [12–14].

As a novel nonsteroidal MRA, finerenone is characterized by higher selectivity towards the mineralocorticoid receptor (MR) and stronger MR-binding affinity than steroidal MRAs [15]. Moreover, basic trials revealed that finerenone was associated with decreasing levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and improving cardiac function via the binding mode of dihydropyridine-based L-type calcium channel blockers to antagonize the MR in chronic HF models [16, 17]. In recent years, clinical researchers have investigated the efficacy and safety of finerenone [18–21]. However, a debate continues as to whether finerenone is effective and the optimal dose that exerts beneficial effects with respect to decreasing plasma levels of NT-proBNP, the incidence of cardiovascular mortality, hospitalizations, hyperkalemia, worsening renal function, and adverse events in chronic HF patients [18–21].

Network meta-analysis (NMA) offers the potential to assess multiple therapeutic strategies simultaneously within a single framework and to rank treatments based on efficacy and safety [22]. In the current paper, we conducted an NMA of randomized controlled trials (RCTs) for the first time to explore the efficacy and safety of different doses of MRAs in HF patients with an ejection fraction of no more than 45%.

## Methods

### Data sources and search strategy

We conducted a systematic search of the period from January 1, 1999, to December 1, 2018, without any language restriction, using PubMed, Embase, the Cochrane Library, and Clinicaltrials. We searched studies with key words and Medical Subject Headings that covered “heart failure” or “systolic heart failure” or “heart failure with reduced ejection fraction” or “HF” or “SHF” or “HFREF” and “mineralocorticoid receptor antagonist”, or “MRA” or “aldosterone receptor antagonist” or “spironolactone” or “canrenone” or “eplerenone” or “finerenone” or “BAY 94-8862.” We also reviewed the corresponding reference list of each retrieved article to identify any relevant studies that may be neglected. The meta-analysis was conducted and reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23].

### Selection criteria

We collected all RCTs to compare the therapeutic effects of different MRAs in systolic HF patients with an ejection fraction  $\leq 45\%$  in this meta-analysis. Inclusion criteria of the studies were as follows: (a) HF patients with an ejection fraction of

no more than 45%, (b) study design was an RCT of the treatment group (MRAs) and control group, (c) studies with outcomes of “death from cardiac causes,” “hospitalization for cardiac causes,” “the number of patients with a decrease in plasma NT-proBNP level of  $> 30\%$ ,” “hyperkalemia,” “worsening renal function,” and/or “adverse event.”

The criteria for exclusion were as follows: (a) studies such as systemic reviews, comments, case reports, conference abstracts, and editorials; (b) subjects with a serum potassium level exceeding 5.5 mmol/l; and (c) articles that had no data on HF patients with an ejection fraction.

Included trials reported comparisons of nine interventions (placebo, spironolactone 25–50 mg, eplerenone 25–50 mg, the initial dose of finerenone with 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, canrenone 25–50 mg). NMA integrates data from direct comparisons of treatments within trials and from indirect comparisons of interventions assessed against a common comparator in separate trials to compare all investigated treatments.

### Data extraction and quality assessment

Two authors (Y-PP and S-W) extracted data and accessed quality independently in an electronic database. The investigators cross-checked the data and reached a consensus on any discrepancies through discussion. Disagreements were resolved through discussions or referral to a third author (W-QH). Reference lists of identified trials and review articles were manually scanned to identify related research references at the same time as indicated in Fig. 1.

The extracted data included the first author’s name, year of publication, kidney function, potassium level, sample size, doses of treatment, control, follow-up duration, the number of patients, the outcomes of cardiovascular mortality, hospitalizations, NT-proBNP level, hyperkalemia, worsening renal function, and adverse events.

### Risk of bias assessment

Two independent reviewers (Y-PP and S-W) assessed the methodological quality of included trials using a slightly adapted version of the risk of bias approach by using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) risk of bias tool including four sections: selection, performance, detection, attrition, reporting, and other biases. The publication bias assessment was performed via Deek’s funnel plot asymmetry.

### Statistical analysis

The data were abstracted and analyzed by R software using the “gemtc” package, STATA (version 14.0, Stata MP) and WinBUGS (version 1.4.3, MRC Biostatistics Unit,

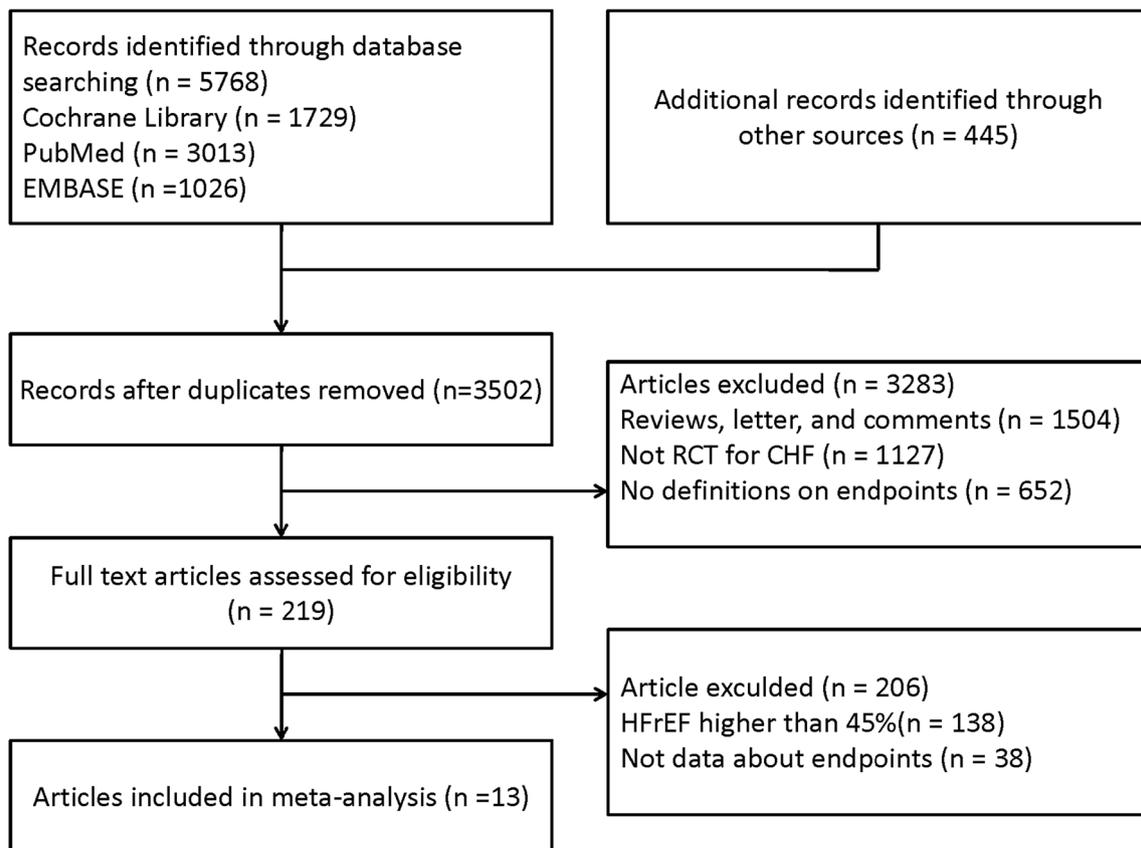


Fig. 1 PRISMA diagram of the study selection process for the meta-analysis

Cambridge, UK). The odds ratios (ORs) and their corresponding 95% confidence interval (CI) were used to compare different medications with respect to various clinical outcomes. Before conducting NMA, we conducted conventional pair-wise meta-analyses for treatments that were directly compared in RCTs by R software utilizing relative forest plots. An NMA was conducted in a Bayesian random-effects model assuming a binomial likelihood and was executed using the “gemtc” R package which recalls JAGS in R for Markov chain Monte Carlo (MCMC) sampling. For each analysis, we generated 5000 simulations for each of the two sets of different initial values and discarded the first 2000 simulations as the burn-in period. The stability of the results was obtained by sensitivity analyses by discarding each study sequentially. Convergence was checked using trace plots and the Brooks-Gelman-Rubin diagnostic [24]. To rank the treatments for an outcome, we used the surface under the cumulative ranking area (SUCRA) probabilities [25]. Thus, a larger SUCRA score might indicate a higher probability of the end point event. We also used loop-specific inconsistency (used in STATA) and the node-splitting approach (used in R with “gemtc” package) to assess the inconsistency that is the actual difference between direct and indirect comparisons [26]. Sensitivity analysis was conducted in R.

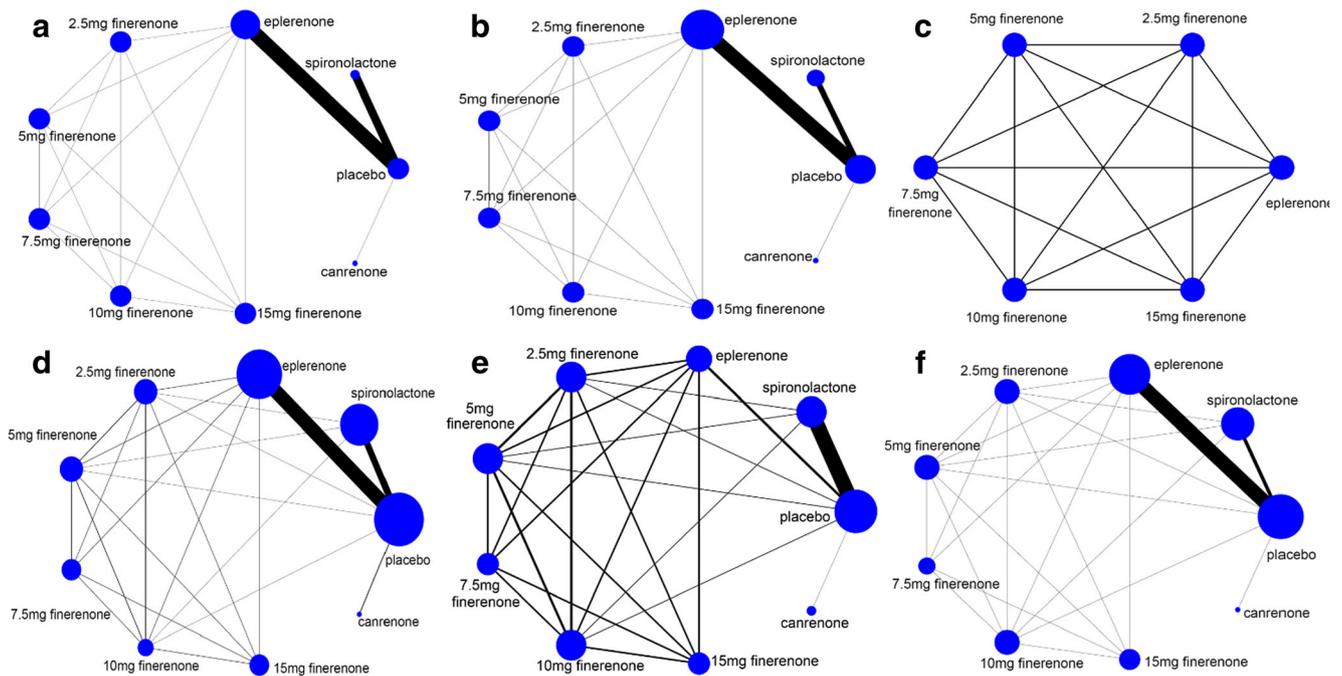
## Results

### Description of included studies

We identified 3502 unique records from our searches. Thirteen RCTs involving a total of 13,597 participants were eligible for this NMA. The selection process details are shown in Fig. 1. The trials included were issued from 1999 to 2018. Supplementary S1 summarizes the essential baseline characteristics of these studies. Of the 13 studies, all studies reported the end point event of hyperkalemia; 12 studies submitted data on hospitalizations for cardiovascular diseases, and 9 studies provided data on serious adverse events. The number of patients included in every study ranged from 16 to 6608, and the follow-up for patients ranged from 1 to 24 months. The risk of bias in studies contributing to the primary outcomes was generally low (Supplementary S2).

### Exploration of network structure, heterogeneity, and consistency

A network plot of treatment comparisons for Bayesian NMA is shown in Fig. 2. There are six interventions for NT-proBNP and nine interventions for death and hospitalization from cardiac causes, hyperkalemia, worsening renal function, and



**Fig. 2** Network plot of treatment comparisons for Bayesian NMA. Lines represent trials comparing 2 classes of drug or drugs for **a** death due to cardiac causes, **b** hospitalization due to cardiac causes, **c** a 30% reduction in NT-proBNP, **d** hyperkalemia, **e** worsening renal function, and **f** adverse

events. The size of the nodes (blue circles) corresponds to the sample size of the interventions. Comparisons are linked with a line, of which the thickness corresponds to the number of trials that assessed the comparison

adverse events. The size of the nodes (blue circles) corresponds to the sample size of the interventions. The comparisons are linked by a straight line, of which the thickness corresponds to the number of trials that assessed the comparison. As shown in the network plot, the number of interventions varied in different subjects.

First, 50,000 iterations were increased to obtain satisfactory convergence as shown in the diagnostics and trace plots (Supplementary S3). In the pairwise meta-analysis and NMA, statistical heterogeneity was mild-to-moderate in networks for hyperkalemia, hospitalizations for cardiovascular diseases, and adverse events, as shown in Supplementary S4. Treatment from direct and network indirect evidence in general did not demonstrate evidence of statistical inconsistency (Supplementary S5). However, the results for inconsistency were imprecise; therefore, the possibility of inconsistency could not be excluded.

## The primary outcome

### Death and hospitalization for cardiac causes

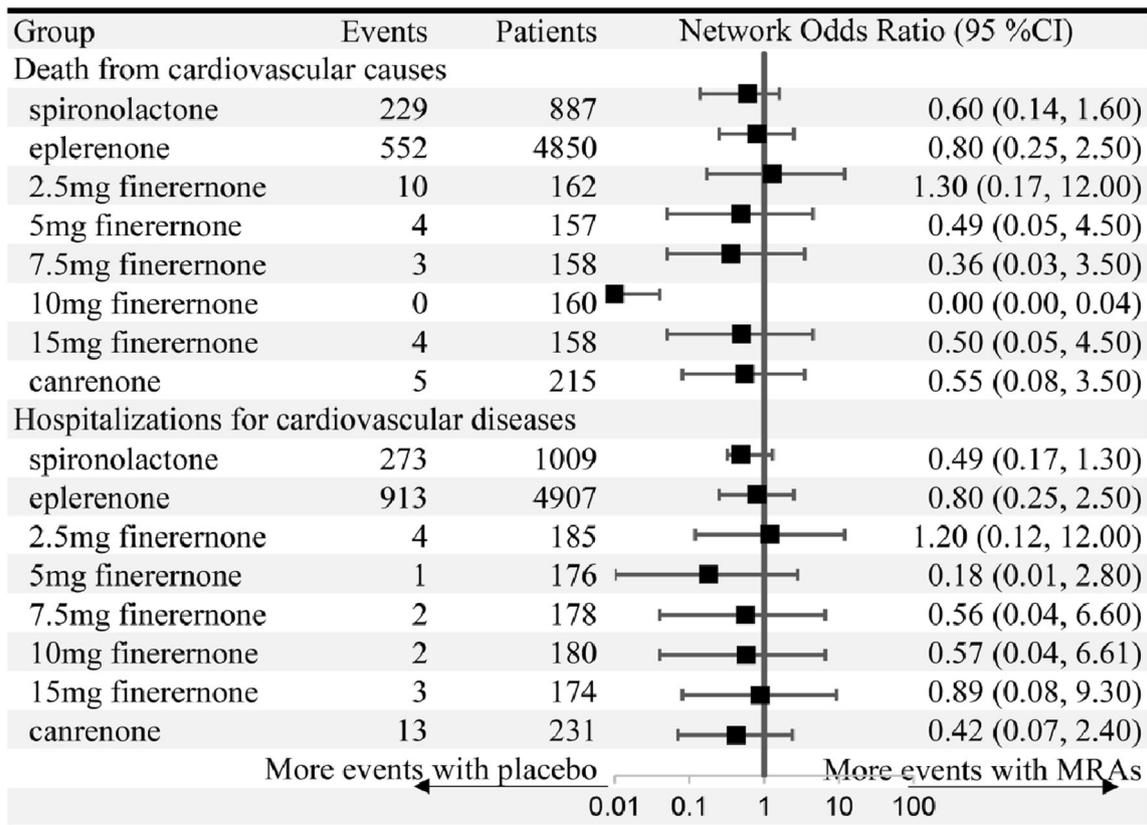
We performed a series of pairwise and network meta-analysis to summarize the results of trials directly and indirectly comparing the same classes of MRAs. Data for network comparisons of estimates for the primary outcomes of death from cardiac causes and hospitalization for cardiovascular diseases are presented in Fig. 3. In NMA, there were no significant

differences among all interventions in the occurrence of death from cardiac causes, or hospitalization for cardiovascular diseases, except for finerenone 10 mg vs. placebo (OR of  $1.3^{e-10}$ , 95% CI  $1.7^{e-26}$ –0.04). Finerenone 10 mg was superior to spironolactone and eplerenone in reducing cardiovascular mortality and cardiovascular hospitalization by pairwise meta-analysis ( $P < 0.01$ ), as depicted in Table 1.

We ranked the comparative effects of different doses of MRAs against placebo with SUCRA probabilities shown in Fig. 4. The NMA suggested that finerenone, 10 mg once daily, was associated with the lowest probability of achieving at cardiovascular mortality (SUCRA 5.0%), followed by finerenone 7.5 mg (SUCRA 31.6%), finerenone 15 mg (SUCRA 42.5%), finerenone 5 mg (SUCRA 43.1%), and canrenone (SUCRA 43.4%) (Fig. 4). However, canrenone was associated with the lowest probability of hospitalization for cardiac causes (SUCRA 24.1%), followed by finerenone 5 mg (SUCRA 24.4%), spironolactone (SUCRA 40.0%), finerenone 10 mg (SUCRA 45.6%), and finerenone 7.5 mg (SUCRA 46.5%) (Supplementary S6). Hospitalization for cardiac causes was reported in nine studies (12,938 participants), but because data were scant for some treatments, it was difficult to draw clear conclusions.

### NT-proBNP

According to these comprehensive comparisons, finerenone 2.5 mg, 7.5 mg, 10 mg, and 15 mg were



**Fig. 3** Data of network comparisons with estimates for the primary outcomes of death and hospitalization for cardiac causes

slightly superior to eplerenone for the effective number of cases with a 30% reduction in NT-proBNP (Fig. 5). Finerenone 15 mg and finerenone 7.5 mg ranked the best and second (SUCRA of 68.1% and 63.8%, respectively), followed by finerenone 10 mg (SUCRA of 59.2%). Finerenone 5 mg was ranked the least effective treatment in reducing NT-proBNP (Supplementary S6). The efficacy of finerenone in reducing NT-proBNP levels and the safety outcomes of hyperkalemia appeared to be dose-dependent.

## The safety outcomes

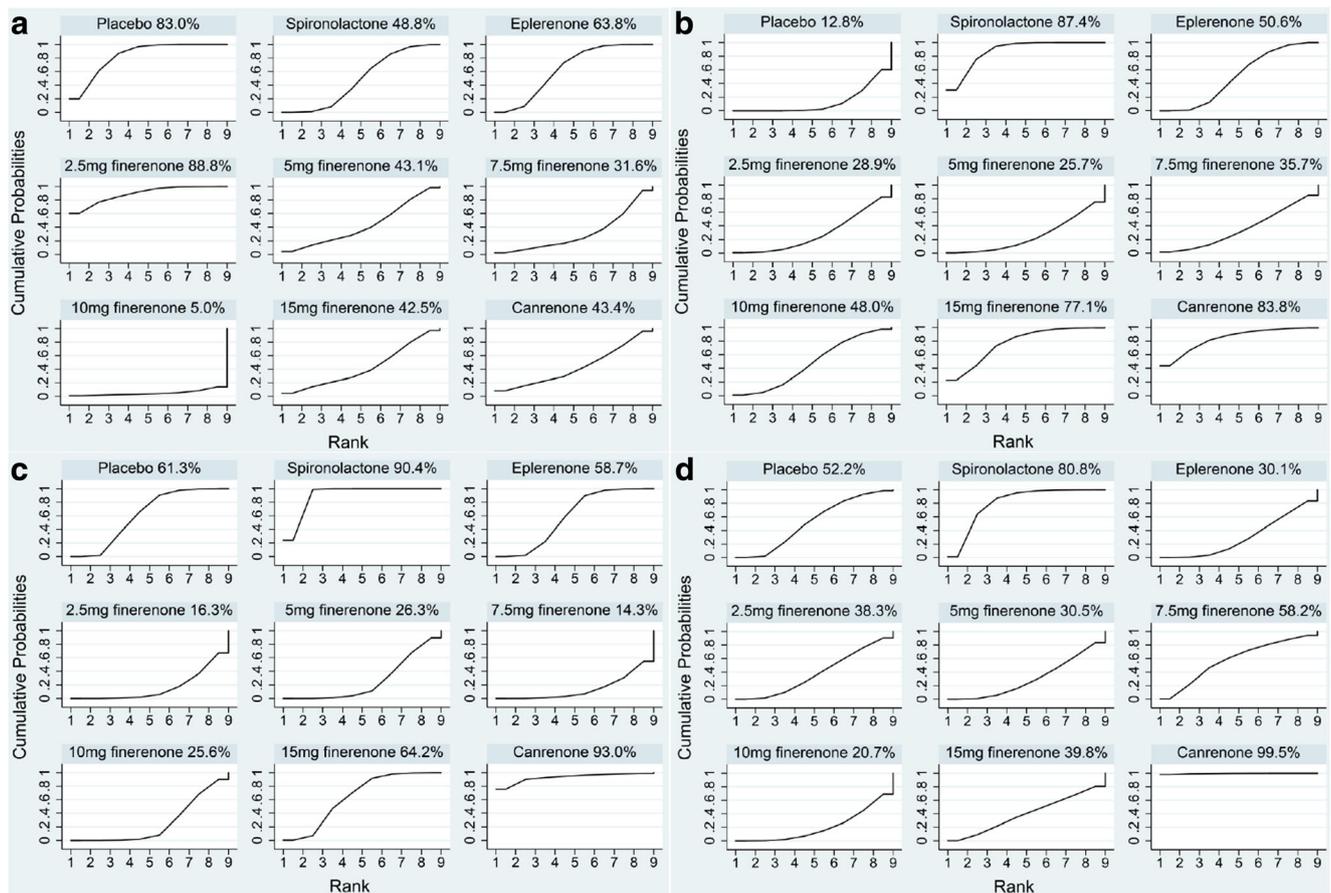
### Hyperkalemia

Spironolactone, eplerenone, finerenone 15 mg, and canrenone were associated with significantly increased risks of hyperkalemia (OR of 3.60, 95% CI 2.30–7.40; 1.80, 95% CI 1.20–3.00; 3.00, 95% CI 1.00–9.40; and 3.30, 95% CI 1.20–10.00, respectively) compared with placebo. The incidence of hyperkalemia induced by finerenone 2.5–10 mg was

**Table 1** Pairwise meta-analysis to summarize the results of trials directly comparing finerenone 10 mg with spironolactone and eplerenone

Outcome	Finerenone 10 mg vs. spironolactone, OR (95% CI), <i>P</i> value	Finerenone 10 mg vs. eplerenone, OR (95% CI), <i>P</i> value
Death from cardiovascular causes	0.01 (0.00, 0.14), <i>P</i> = 0.0009	0.02 (0.00, 0.39), <i>P</i> = 0.009
Hospitalizations for cardiovascular diseases	0.03 (0.01, 0.12), <i>P</i> < 0.00001	0.05 (0.01, 0.20), <i>P</i> < 0.0001
30% reduction in NT-proBNP	NA	1.33 (0.81, 2.17), <i>P</i> = 0.26
Hyperkalemia	0.23 (0.13, 0.39), <i>P</i> < 0.00001	0.77 (0.45, 1.32), <i>P</i> = 0.34
Worsening renal function	0.28 (0.17, 0.47), <i>P</i> < 0.00001	2.82 (1.59, 5.00), <i>P</i> = 0.0004
Adverse events	0.21 (0.16, 0.28), <i>P</i> < 0.00001	0.33 (0.26, 0.42), <i>P</i> < 0.00001

OR, odds ratio; 95% CI, 95% confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NA, not applicable



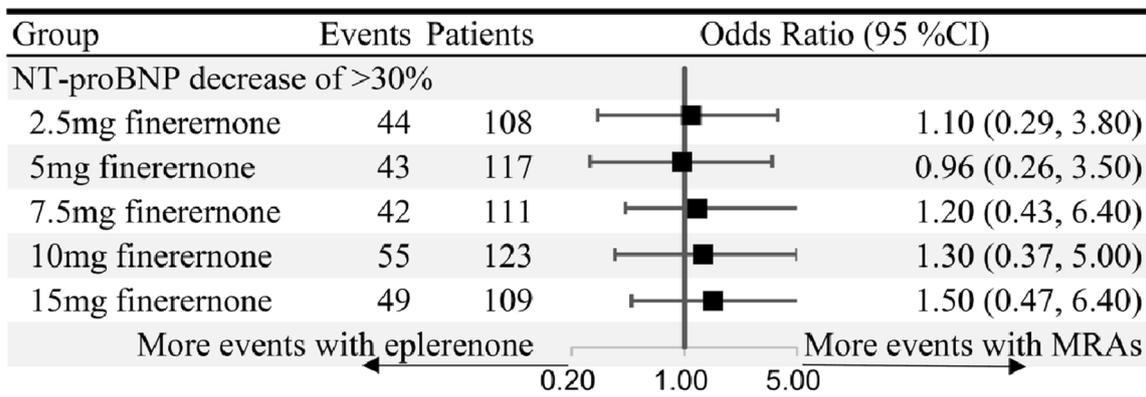
**Fig. 4** Rankings of SUCRA for the efficacy of treatments to induce end points in heart failure. **a** Death for cardiac causes, **b** hyperkalemia, **c** worsening renal function, and **d** adverse events of heart failure. The graphs display the distribution of probabilities of treatment ranking from best to worst for each outcome. Ranking indicates the probability

that drug class is first “best,” second “best,” etc. For example, the ranking suggests that finerenone 2.5 mg posed the highest risk for incurring death for cardiac causes (worst), while finerenone 10 mg incurred the lowest probability of cardiovascular mortality (best)

significantly lower than that induced by steroidal MRAs. These NMA results are illustrated in Fig. 6. Compared to spironolactone, finerenone 10 mg was associated with a lower risk of hyperkalemia ( $P < 0.00001$ ), as shown in Table 1.

Spironolactone had the highest probability of being ranked first with respect to hyperkalemia (SUCRA

87.4%), whereas canrenone had the second highest probability (SUCRA 83.8%); finerenone 15 mg and eplerenone showed similar probabilities of being ranked first for hyperkalemia, with all values above 50% (SUCRA 77.1%, 50.6%, respectively), as depicted in Fig. 4 and Supplementary S6.



**Fig. 5** Data of network comparisons between eplerenone and finerenone for efficacy of treatments to induce a 30% reduction in NT-proBNP in heart failure patients

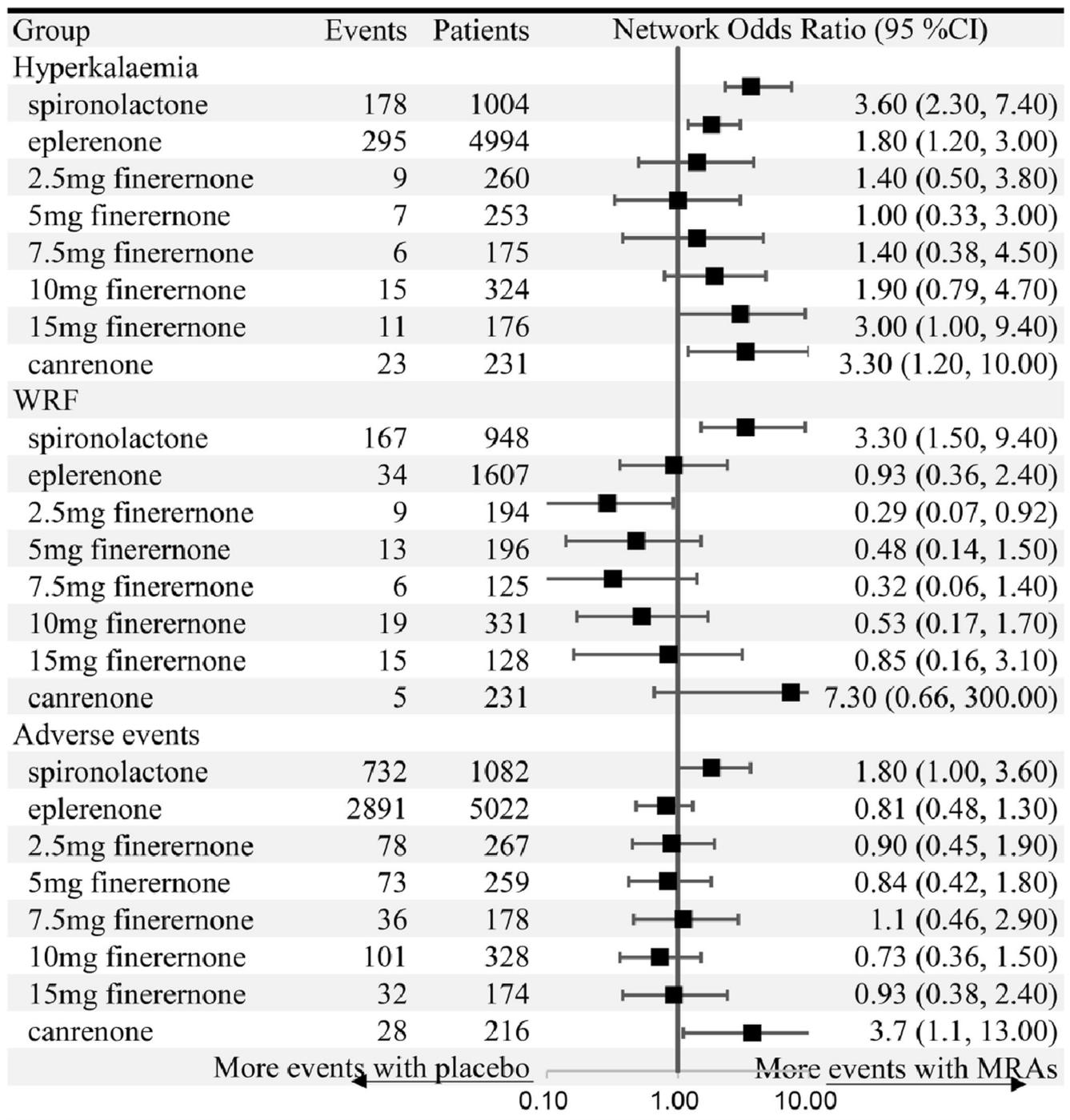


Fig. 6 Data of network comparisons with estimates for the safety outcomes of hyperkalemia, worsening renal function, and adverse events

### Worsening renal function

Compared to placebo, spironolactone displayed the highest risks for renal deterioration (OR 3.30, 95% CI 1.50–9.40). There was no evidence that finerenone 2.5–15 mg and eplerenone showed different effects on worsening renal function compared with placebo (Fig. 6).

Regarding the prevention of worsening renal function, finerenone 7.5 mg (SUCRA 14.3%) was the best treatment, followed by finerenone 2.5 mg (SUCRA 16.3%) and finerenone 10 mg (SUCRA 25.6%). Canrenone and spironolactone were the least effective in preventing the progression of renal deterioration (SUCRA 93.0% and 90.4%, respectively) (Fig. 4).

## Adverse events

There were no significant differences among all interventions in the occurrence of adverse events, apart from spironolactone and canrenone vs. placebo (OR of 1.8, 95% CI 1.00–3.60, and 3.70, 95% CI 1.10–13.00, respectively) (Fig. 6). For adverse events, canrenone (SUCRA 99.5%) and spironolactone (SUCRA 80.8%) were ranked highly, whereas finerenone 10 mg had the lowest rank (SUCRA 20.7%), as illustrated in Fig. 4. Finerenone 10 mg was associated with a low risk of adverse events compared with spironolactone and eplerenone by pairwise meta-analysis (OR of 0.21, 95% CI 0.16–0.28,  $P < 0.00001$ , and 0.33, 95% CI 0.26–0.42,  $P < 0.00001$ , respectively, Table 1).

## Sensitivity analysis and publication bias

A sensitivity analysis was conducted to examine the impact of studies according to the treatment effects on the safety outcomes of hyperkalemia, hospitalizations for cardiovascular diseases, and adverse events. We performed a subgroup analysis in HFrEF patients with an ejection fraction less than 40%, and there was no significant difference compared with the group with an ejection fraction less than 45% (Supplementary S7). No significant publication bias was detected in the funnel plot (Supplementary S8).

## Discussion

We grouped all MRAs together: spironolactone, the first generation MRA with high affinity and low selectivity; eplerenone, which is designed to avoid side effects due to its high selectivity; canrenone, a common active metabolite of spironolactone; and finerenone, a novel nonsteroidal MRA with high selectivity and high affinity for the MR. No studies have directly or simultaneously compared spironolactone, eplerenone, and canrenone, or finerenone. Our NMA is the first to provide a unified hierarchy of evidence for all MRAs in adults who have HF with an ejection fraction of no more than 45%, overcoming the absence of comparative data in head-to-head trials. Our study shows that the use of spironolactone and canrenone in patients with HF has a high risk of hyperkalemia. Finerenone also shows a dose-response model for hyperkalemia and a 30% reduction in BNP, but not in terms of hospitalizations and adverse events.

In the Randomized Aldactone Evaluation Study (RALES) [27] and the Eplerenone in Mild Patients: Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) [6] study, steroidal MRAs reduced the risk of all-cause mortality and hospitalization for cardiac causes among systolic HF patients. Spironolactone also ameliorated the symptoms of heart failure, as measured in accordance with changes in the New York

Heart Association (NYHA) functional class. However, MRAs remain underutilized, in large part owing to the risk of inducing treatment-associated severe adverse events including renal deterioration and hyperkalemia. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) [28], the rate of serious hyperkalemia ( $\geq 6.0$  mmol/l) was 5.5% in the eplerenone group and 3.9% in the placebo group ( $P = 0.002$ ), but it did not alter the cardiovascular benefit of eplerenone. The anti-remodeling effect of canrenone in patients with mild chronic heart failure (AREA IN-CHF) study [29] found that in patients with NYHA class II HF, the addition of canrenone on the top of optimal treatment improved left ventricular function, plasma BNP, hemodynamic conditions, and clinical symptoms, but discontinuation due to increased potassium occurred in 13 patients taking canrenone and in three taking placebo ( $P = 0.06$ ). These drugs differ predominantly in their side effects because hyperkalemia and worsening of kidney function may be the main side effects of using MRAs [30, 31], particularly when inhibitors of the renin angiotensin system (RAS) are given to systolic HF patients with concomitant kidney dysfunction.

Therefore, the mechanism of MRAs leading to side effects in the treatment of heart failure, especially hyperkalemia, remains to be further explored. Aldosterone exerts its effects on water homeostasis by transcriptional regulation of  $\text{Na}^+\text{-K}^+\text{-ATPase}$ , epithelial  $\text{Na}^+$  channel ( $\text{ENa}^+\text{C}$ ), and serum-glucocorticoid-regulated kinase 1 (Sgk1) [32, 33]. By analyzing its radioactivity after oral administration in rodents, the concentrations of spironolactone and eplerenone in the kidney are at least sixfold and threefold higher, respectively, than in the heart [17]. In contrast, finerenone is distributed equally into cardiac and renal tissues in rats [16, 17]. Those observations may in part explain the lower incidence of hyperkalemia with finerenone than spironolactone. Furthermore, preclinical studies have demonstrated that finerenone has more pronounced cardiac and renal anti-remodeling effects than steroidal MRA [34–36].

In clinical trials, the efficacy and safety of finerenone did not disappoint us. The aims of the ARTS are to evaluate the safety and tolerability of finerenone in patients with systolic HF and mild-to-moderate CKD [16]. Finerenone 5 to 10 mg/day was at least as effective as spironolactone 25 or 50 mg/day in reducing BNP, NT-proBNP, and albuminuria, with lower rates of renal impairment and hyperkalemia ( $P = 0.048$ ), and the majority of finerenone treatment-associated adverse events were mild [17]. The ARTS-HF study demonstrated that the incidence of the clinical composite end point was lower in subjects treated with all finerenone doses than in those treated with eplerenone, and the finerenone 10-mg group showed a much lower probability of each event. The changes in serum potassium levels were similar between groups [19, 37]. Comprehensive analysis from three clinical phase II trials [17, 19, 37] suggested that finerenone will provide an

alternative therapy option for patients with HF especially in those who are at high risk of hyperkalemia.

Our study has some potential limitations. First, due to limited data, we could not perform a subgroup analysis of all-cause mortality caused by MRAs in HF patients with concomitant kidney dysfunction. Second, some trial heterogeneity requires further exploration of the source of heterogeneity. Third, HF was defined poorly without the NYHA functional class. There were two studies that did not report the NYHA class. There is only one study of canrenone, and three for finerenone. Fifth, we did not control for the dose of spironolactone or eplerenone in our analyses; in some studies, we included clinicians who could titrate finerenone doses for individual participants.

## Conclusion

In conclusion, our results show that compared with spironolactone and eplerenone, finerenone 10 mg was associated with low risk in the occurrence of cardiovascular mortality, hospitalization, and adverse events ( $P < 0.01$ ). This network meta-analysis is the first to find that finerenone 7.5–10 mg has the highest probability of being the best choice among MRAs in the treatment of HF patients with an ejection fraction of no more than 45%.

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**Author contributions** Y-PP and S-W performed the meta-analysis; C-X, ZH-D, and X-XX were responsible for the statistical analysis; W-T and X-GS provided editing assistance; and W-QH prepared the manuscript. All authors have reviewed and agreed to this information before submission.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** Not required.

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