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Renin–angiotensin–aldosterone system blockers for heart failure with reduced ejection fraction or left ventricular dysfunction: Network meta-analysis

Wuxiang Xie [a,*,1,2], Fanfan Zheng [b,1,2], Xiaoyu Song [c,2], Baoliang Zhong [d,2], Li Yan [e,2]

[a] Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China
[b] Brainnetome Center, Institute of Automation, Chinese Academy of Sciences, Beijing, China
[c] Department of Biostatistics, Columbia University, New York, USA
[d] Department of Psychiatry, University of Rochester Medical Center, New York, USA
[e] Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, UK

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ABSTRACT

Background: Renin–angiotensin–aldosterone system (RAAS) blockers are effective therapies for heart failure and reduced ejection fraction (HFrEF) or left ventricular dysfunction (LVD). We aimed to assess the efficacy and safety of RAAS blockers in these patients.
Methods: We searched MEDLINE, EMBASE, and Cochrane Library in May 2015. Twenty-one double-blind randomized controlled trials (RCTs) with 69,229 patients were included this network meta-analysis.
Results: Compared with placebo, an angiotensin receptor–neprilysin inhibitor (ARNI) had the highest probability of reducing all-cause mortality (odds ratio [OR] = 0.67, 95% credible interval [CrI]: 0.48–0.86), followed by an aldosterone receptor antagonist (ARA, OR = 0.74, 95% CrI: 0.62–0.88) and an angiotensin-converting enzyme inhibitor (ACEI, OR = 0.80, 95% CrI: 0.71–0.89). The most efficacious therapy for preventing heart failure hospitalization was ARNI (OR = 0.55, 95% CrI: 0.40–0.71), followed by combination therapy with an angiotensin II receptor blocker (ARB) plus an ACEI (OR = 0.61, 95% CrI: 0.49–0.75), then an ACEI alone (OR = 0.69, 95% CrI: 0.61–0.77). Sensitivity analysis restricted to nine RCTs with a high background use of ACEI and/or ARB (>80%) indicated that adding an ARA to current standard therapy significantly reduced mortality (OR = 0.73, 95% CrI: 0.51–0.95) and hospitalization risk (OR = 0.67, 95% CrI: 0.47–0.87), but did not significantly increase the discontinuation risk (OR = 1.29, 95% CrI: 0.83–2.31).
Conclusions: ARNI has the highest probability of being the most efficacious therapy for HFrEF in reducing death and hospitalization for heart failure. ARA has the most favorable benefit–risk profile as an adjunct to background ACEI and/or ARB therapy.

1. Introduction

Heart failure is a major public health issue, affecting more than 23 million people worldwide [1]. Despite the success of standard heart failure therapy, mortality remains unacceptably high. Approximately 50% of people diagnosed with heart failure will die within 5 years [2,3]. Heart failure ranks as the most frequent reason for hospitalization and re-hospitalization in older people, accounting for 5% of all hospital discharge diagnoses [2,4].

Blockade of the renin–angiotensin–aldosterone system (RAAS) has long been recognized as an effective treatment for patients with heart failure and reduced ejection fraction (HFrEF) [5], and angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB) and aldosterone receptor antagonists (ARA) are recommended by all major national and international guidelines [2,6]. Previous trials also demonstrated that the greatest relative and absolute benefits have been obtained with long-term ACEI or ARB therapy in patients with left ventricular dysfunction (LVD), signs or symptoms of heart failure, or both [2,6].

Recently, the ASTRONAUT [7] and PARADIGM-HF trials [8] examined the efficacy of two new classes of RAAS blocker in the treatment of HFrEF; a direct renin inhibitor (DRI) and an angiotensin receptor–neprilysin inhibitor (ARNI), respectively. Although the ASTRONAUT trial reported that aliskiren, administered as an adjunct to standard therapy, did not reduce death or heart failure re-hospitalization [7], the PARADIGM-HF trial reported that LCZ696, the first-in-class ARNI,

* Corresponding author at: Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, No. 2 Anzhen Street, Chaoyang District, 100029 Beijing, China.
E-mail address: xiewuxiang@163.com (W. Xie).
[1] Drs W. Xie and F. Zheng contributed equally to this work.
[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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proved superior to enalapril in reducing the risks of death and hospitalization for heart failure [8]. Given this new evidence, an overarching view of all available randomized controlled trials (RCTs) is urgently needed to inform the updating of current treatment guidelines. In this systematic review, we performed a standard pairwise meta-analysis of direct evidence as well as Bayesian network meta-analysis combining direct and indirect evidence comparing the relative efficacy and tolerability of all available RAAS therapies in patients with HFrEF or LVD.

2. Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. Ethics approval was not necessary for this study as only de-identified pooled data from individual studies were analyzed.

2.1. Data sources and search strategy

A systematic literature search was conducted on 20 May 2015 using MEDLINE via Web of Science, EMBASE and the Cochrane Library database for trials. We limited our search to RCTs conducted in humans. Details of our search strategy are provided in the Supplementary Appendix. Initially, titles alone were reviewed for suitability. The abstracts of suitable titles were obtained, and these were then reviewed for suitability for full-text retrieval. Data were then extracted from suitable full-text reports. Additional appropriate reports were added when discovered by citation tracking.

2.2. Study selection

Randomized controlled trials were eligible for inclusion if they met the following criteria: double-blind; mono versus placebo, mono versus mono, or dual versus mono RAAS therapy was tested in adults (aged ≥18 years) with HFrEF or LVD; and had a treatment duration of at least 6 months. As network meta-analysis requires a reasonably homogeneous sample [10], we did not include six RCTs conducted in patients with heart failure and preserved ejection fraction (HFpEF) [11–16].

2.3. Data extraction and quality assessment

Two authors (FZ and XS) independently extracted data using a predetermined data collection template. In the event of disagreement about study inclusion or interpretation of data, a third investigator (WX) was consulted, and consensus was reached by discussion.

The following data were recorded: publication characteristics, countries or regions of the study, study centers, patient characteristics, New York Heart Association (NYHA) functional class, left ventricular ejection fraction, sample size, duration of follow-up, blinding, intention-to-treat analysis, background therapy, interventions and dosages, and efficacy and safety outcomes. The primary outcome was all-cause death; the secondary outcomes were hospitalization for heart failure and discontinuation due to any adverse events.

Study quality was independently assessed by three reviewers (FZ, XS and LY), who used the Cochrane Collaboration's risk-of-bias method [17]. Supplementary Fig. S1 shows the risk of bias of the included trials.

2.4. Data synthesis and analysis

Network meta-analysis combines direct and indirect evidence for all relative treatment effects and provides estimates with maximum statistical power [18]. We fitted the models within a Bayesian framework using WinBUGS software (version 1.4.3) [19]. The models, the WinBUGS codes and R routines used in this study are open access and can be found online [20]. Convergence was assessed by running three Markov chains, and all results pertain to 100,000 Markov Chain Monte Carlo cycles after a 10,000 simulation burn-in phase. Relative effect sizes were calculated as odds ratios (ORs) with corresponding 95% credible intervals (CrIs). Model fit was assessed with deviance information criterion, a measure of model fitness that penalizes model complexity. We used surface under the cumulative ranking curve (SUCRA) probabilities to rank RAAS therapies: [18] SUCRA is a proportion, expressed as the percentage of efficacy of an intervention on the outcome that would be ranked first without uncertainty, which equals 100% when the treatment is certain to be the best and 0% when it is certain to be the worst [18]. The network results were assessed for consistency by comparing them with the results of pairwise meta-analyses. We also estimated inconsistency as the difference between direct and indirect estimates (called the inconsistency factor) and the corresponding 95% confidence interval (CI) for the inconsistency factor in each closed loop, by using R code "ifplot.fun", which can also be found online [20]. Inconsistent loops are those that present inconsistency factors with 95% CIs incompatible with zero. Pairwise meta-analyses were performed using STATA (version 11; Stata Corp, College Station, TX) within a random-effect (DerSimonian–Laird) framework that takes study heterogeneity into account to generate the pooled OR and 95% CI. The extent of variability across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic.

We also undertook sensitivity analysis to compare the efficacy and safety of RAAS therapies added to background ACEI and/or ARB therapy. The sensitivity analysis was planned in advance, and was restricted to RCTs in which there was high background use of ACEI and/or ARB (>80%) among the participants. Comparison of a combination of an ARB and ACEI with an ACEI alone in two trials was considered as ARB versus placebo with 100% background use of ACEI [21,22].

3. Results

3.1. Study selection

Fig. 1 shows the study selection process according to the PRISMA statement. The initial search identified 3637 publications. The full text of 68 articles was reviewed in detail, and 47 were further excluded because of: treatment duration <6 months (n = 23), no outcomes of interest (n = 10), participants included patients with HFpEF (n = 6), duplicate trials (n = 5) or open-label trials (n = 3). Finally, 21 double-blind RCTs with 69,229 participants were included in our network meta-analysis [5,7,8,21–38].

3.2. Study characteristics

Supplementary Table S1 summarizes the characteristics of the 21 trials, of which 14 enrolled patients with HFrEF [5,7,8,21,24–30,33,36,38], six enrolled patients with heart failure and/or LVD after acute myocardial infarction [22,23,31,32,34,37], and one enrolled patients with LVD [35]. Supplementary Table S2 summarizes the RAAS therapies, dosages and outcomes used in these trials.

3.3. All-cause death

For the primary outcome, 21 trials were included in the network meta-analysis. The following RAAS therapies were tested in the trials: ACEI versus placebo (six trials with 13,016 patients); [5,23,34–37] ARB versus placebo (four trials with 9878 patients); [24,26,27,38] ARA versus placebo (four trials with 11,470 patients); [25,30,31,33] DRI versus placebo (one trial with 1615 patients); [7] ARB versus ACEI (five trials with 19,605 patients); [21,22,28,29,32] ARNI versus ACEI (one trial with 8399 patients); [8] a combination of ARB and ACEI versus ACEI (two trials with 10,235 patients); and [21,22] a combination of ARB with ACEI versus ARB (two trials with 10,453 patients) [21,22]. The network of RAAS therapies comparisons is shown in Fig. 2.

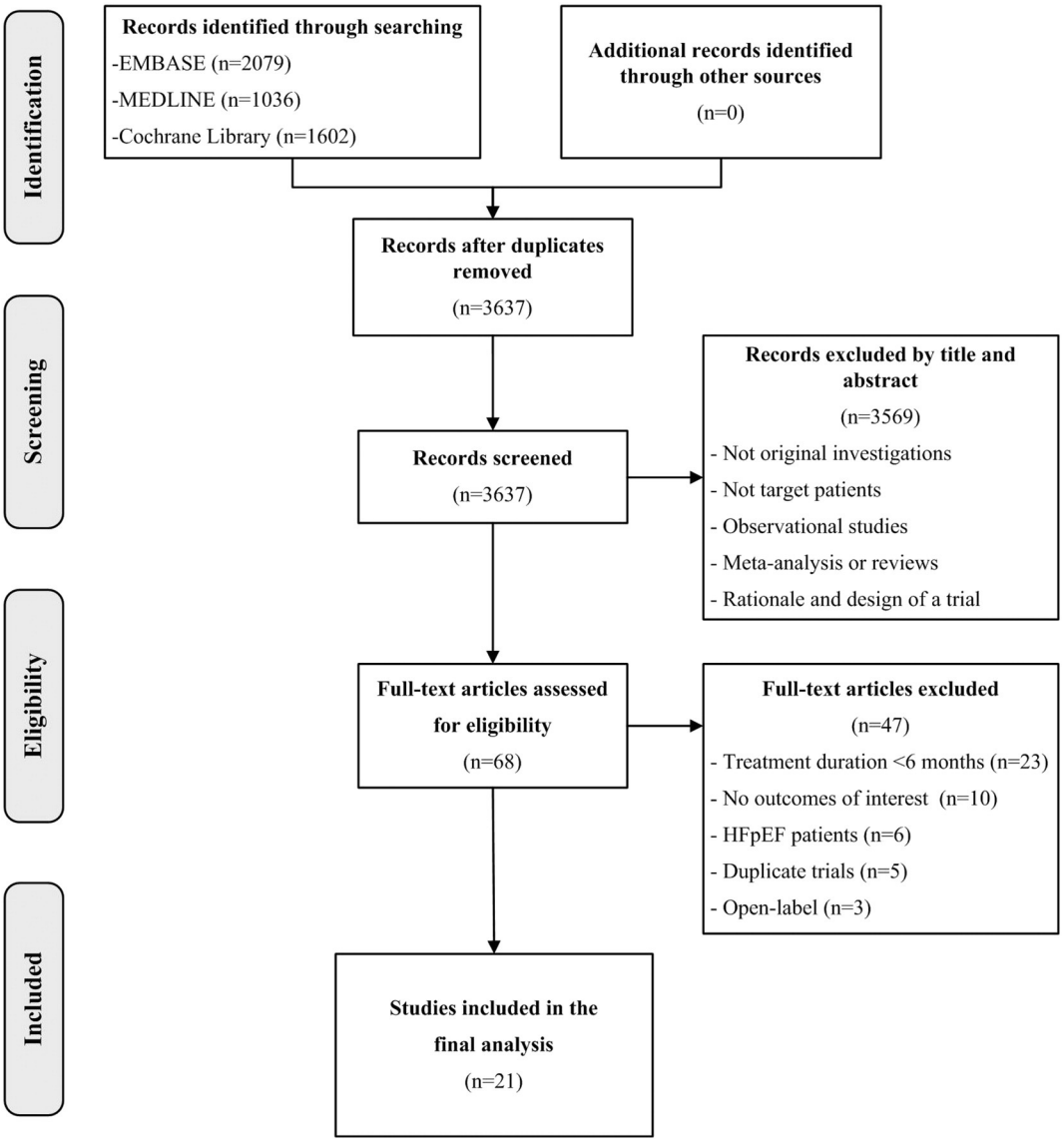

Fig. 1. Study selection flow diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. HFpEF indicates heart failure and preserved ejection fraction.

Network meta-analysis found that ACEI, ARB, ARA and ARNI all significantly reduced all-cause mortality compared with placebo (Table 1). In general, the results obtained from pairwise meta-analysis closely matched those of the network meta-analysis. The only discrepancy was observed in the comparison of ARB versus placebo, for which a comparable point estimator was obtained, but only the network meta-analysis yielded a significant result. Supplementary Fig. S2 reports the full results from six pairwise comparisons. Significant heterogeneity was identified in one pairwise meta-analysis of the four trials of ARB versus placebo ($I^2 = 62.1\%$, $P = 0.048$).

3.4. Heart failure hospitalization

For this outcome, 20 trials were included in the network meta-analysis. Both network meta-analysis and pairwise meta-analysis found that ACEI, ARB and ARA significantly reduced the risk of hospitalization for heart failure compared with placebo (Table 2). Furthermore, network meta-analysis indicated that ARNI was more efficacious than placebo, ARB, ACEI and DRI, and that ARB-ACEI combination therapy was better than placebo. Heterogeneity was evident in one of six pairwise meta-analyses, which compared ARA with placebo ($I^2 = 74.3\%$, $P = 0.009$; Supplementary Fig. S3).

3.5. Discontinuation due to any adverse events

For this outcome, 19 trials were included in the network meta-analysis, which found that ACEI, ARB, ARB-ACEI combination therapy, and ARNI, significantly increased the risk of discontinuation due to any adverse events compared with placebo (Table 3). There were significantly more discontinuations with ARB-ACEI combination therapy, and ACEI alone, than with ARB, ARA or DRI (Table 3). Pairwise meta-analysis also verified that both ACEI and ARB resulted in significantly more discontinuations than placebo, and that ARB-ACEI combination therapy, and ACEI alone, caused significantly more discontinuations than ARB. The direct comparison found that ARNI significantly reduced the risk of discontinuation compared with ACEI (OR = 0.85, 95% CI: 0.75–0.98), but this was not consistent with the network meta-analysis (OR = 0.89, 95% CrI: 0.58–1.30). Supplementary Fig. S4 shows that significant heterogeneity was identified in two of four pairwise meta-analyses (ARA versus placebo, and ARB versus ACEI).

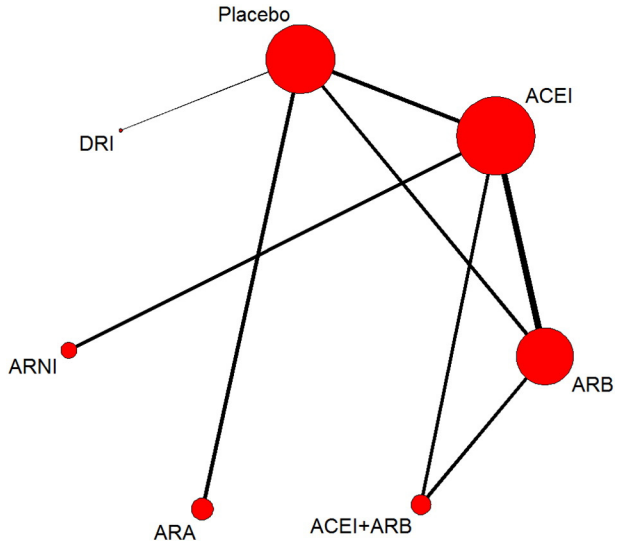

Fig. 2. Network of treatment comparisons for all-cause death. The size of the node corresponds to the total sample size of the treatment from all included trials. Directly comparable treatments are linked with a line, the thickness of which corresponds to the total sample size for assessing the comparison. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARA, aldosterone receptor antagonist; ARNI, angiotensin receptor–neprilysin inhibitor; DRI, direct renin inhibitor.

3.6. SUCRA probability and inconsistency factor

Table 4 shows the mean values of SUCRA probabilities that provided the hierarchies for the efficacy and safety of the RAAS therapies: ARNI was the most efficacious in preventing death, with a 92.8% SUCRA probability. Furthermore, ARNI also had a 76.2% probability of being the best therapy for reducing mortality (Supplementary Fig. S5). The second and third best therapies were ARA and ACEI, respectively. The most efficacious therapy for preventing heart failure hospitalization was ARNI, followed by ARB-ACEI combination therapy, then ACEI alone. The combination of ARB with ACEI had the highest probability of being associated with the highest discontinuation rate, followed by ACEI then ARNI. Supplementary Figs. S5–S7 show the ranking probability of each therapy for all outcomes.

No inconsistent loop was identified in the analyses of the inconsistency factor (Supplementary Fig. S8).

3.7. Sensitivity analysis

Sensitivity analysis included nine RCTs enrolling 30,878 patients in which there was a high background use of ACEI and/or ARB (>80%) [7,21,22,25,26,30,31,33,38]. Supplementary Tables S3–S6 and Supplementary Figs. S9–S15 show the full results of the sensitivity analysis. Most importantly, both network and pairwise meta-analyses demonstrated that adding an ARA to current standard therapy significantly reduced mortality and the risk of hospitalization for heart failure, but did not significantly increase the risk of discontinuation. Pairwise meta-analyses found that ARB significantly reduced the risk of hospitalization, but significantly increased the risk of discontinuation. Among the three RAAS therapies, ARA had the best benefit–risk profile when added to standard therapy (Table S6).

4. Discussion

Our network meta-analysis provides evidence-based hierarchies for the efficacy and safety of long-term RAAS therapies for patients with HFrEF or LVD. It overcomes a major limitation of conventional pairwise meta-analysis by combining direct and indirect evidence of the efficacy of treatment strategies. Our main findings were that ARNI had the highest probability of being the best therapy for preventing death and hospitalization for heart failure, and that ARA displayed the best benefit–risk profile when added to background ACEI and/or ARB therapy. As far as we are aware, this is the first network meta-analysis to evaluate and provide evidence-based hierarchies for the long-term efficacy and safety of all available RAAS therapies for patients with HFrEF or LVD.

Since the publication of the CONSENSUS trial in 1987 [5], LCZ696 is the first drug proven to be superior to enalapril [8], and therefore appears to have the potential to substantially improve the outcomes of patients with HFrEF should it become part of routine clinical practice. The point estimators of the OR calculated by our network meta-analysis were comparable with those reported by the PARADIGM-HF investigators, but the 95% CrIs in our network meta-analyses were wider. This is not surprising, since the network meta-analysis included only one trial investigating ARNI, hereby leading to a larger 95% CrI than the 95% CI obtained from a direct comparison. Ranking probabilities of the six RAAS therapies indicated that ARNI had the highest probability of being the best therapy for reducing all-cause mortality and the risk of hospitalization. Our findings are consistent with a recent putative placebo analysis, which reported similarly large effects of LCZ696 on all-cause mortality and heart failure hospitalization [39]. The latest Canadian guidelines for the treatment of heart failure have already conditionally recommended that in patients with HFrEF should be treated with LCZ696 in place of an ACEI or an ARB [40]. However, other major national and international guidelines have not updated yet. We believe this study will provide additional evidence beyond PARADIGM-HF trial for guideline task forces. Besides, it should be noted that ARNI had the third highest probability of being associated with the highest discontinuation rate. The top three most frequent adverse events of LCZ696 were elevated serum potassium concentration, hypotension and cough [8]. More RCTs are needed to confirm the efficacy and safety of LCZ696, and answer the major question—to what extent should LCZ696 replace ACEIs in the treatment of patients with HFrEF?

Table 1
Results for all-cause death, from network meta-analysis (upper diagonal part) and pairwise meta-analysis (lower diagonal part).

Treatment	Placebo	ACEI	ARB	ARB + ACEI	ARA	ARNI	DRI
Placebo	1.00	**0.80 (0.71–0.89)***	**0.86 (0.75–0.97)**	0.85 (0.68–1.12)	**0.74 (0.62–0.88)**	**0.67 (0.48–0.86)**	0.97 (0.67–1.34)
ACEI	**0.79 (0.71–0.87)**	1.00	1.08 (0.94–1.21)	1.27 (0.87–1.87)	0.93 (0.75–1.14)	**0.84 (0.71–0.99)**	1.23 (0.83–1.73)
ARB	0.87 (0.73–1.04)	1.07 (0.94–1.21)	1.00	1.00 (0.80–1.27)	0.87 (0.69–1.05)	0.78 (0.57–1.02)	1.14 (0.76–1.61)
ARB + ACEI	—	1.34 (0.57–3.19)	1.07 (0.74–1.54)	1.00	0.88 (0.62–1.14)	0.79 (0.54–1.06)	1.16 (0.71–1.70)
ARA	**0.74 (0.62–0.88)**	—	—	—	1.00	0.91 (0.64–1.22)	1.33 (0.85–1.97)
ARNI	—	**0.83 (0.74–0.92)**	—	—	—	1.00	1.49 (0.92–2.25)
DRI	0.97 (0.75–1.24)	—	—	—	—	—	1.00

Each cell gives an odds ratio (OR) and 95% credible interval (CrI) or confidence interval (CI). In the upper diagonal part, the OR (95% CrI) compares the column condition with the row condition, and in the lower diagonal part, this OR (95% CI) compares the row condition with the column condition.
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARA, aldosterone receptor antagonist; ARNI, angiotensin receptor–neprilysin inhibitor; DRI, direct renin inhibitor.
* Significant results are in bold.

Table 2
Results for heart failure hospitalization, from network meta-analysis (upper diagonal part) and pairwise meta-analysis (lower diagonal part).

Treatment	Placebo	ACEI	ARB	ARB + ACEI	ARA	ARNI	DRI
Placebo	1.00	**0.69 (0.61–0.77)***	**0.71 (0.63–0.81)**	**0.61 (0.49–0.75)**	**0.70 (0.57–0.82)**	**0.55 (0.40–0.71)**	0.94 (0.67–1.28)
ACEI	**0.67 (0.61–0.74)**	1.00	1.04 (0.92–1.20)	0.90 (0.72–1.10)	1.02 (0.81–1.24)	**0.80 (0.67–0.96)**	1.38 (0.97–1.93)
ARB	**0.72 (0.64–0.82)**	1.03 (0.89–1.19)	1.00	0.86 (0.69–1.06)	0.98 (0.78–1.20)	**0.77 (0.56–0.99)**	1.33 (0.91–1.84)
ARB + ACEI	—	0.96 (0.63–1.48)	0.87 (0.74–1.02)	1.00	1.15 (0.85–1.50)	0.90 (0.64–1.24)	1.55 (1.00–2.25)
ARA	**0.67 (0.53–0.86)**	—	—	—	1.00	0.79 (0.55–1.07)	1.37 (0.94–1.94)
ARNI	—	**0.79 (0.70–0.90)**	—	—	—	1.00	**1.76 (1.13–2.71)**
DRI	0.93 (0.74–1.15)	—	—	—	—	—	1.00

Each cell gives an odds ratio (OR) and 95% credible interval (CrI) or confidence interval (CI). In the upper diagonal part, the OR (95% CrI) compares the column condition with the row condition, and in the lower diagonal part, this OR (95% CI) compares the row condition with the column condition.
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARA, aldosterone receptor antagonist; ARNI, angiotensin receptor–neprilysin inhibitor; DRI, direct renin inhibitor.
* Significant results are in bold.

The latest American College of Cardiology Foundation/American Heart Association guideline recommends "Addition of an ARB may be considered in persistently symptomatic patients with HFrEF who are already being treated with an ACEI and a beta-blocker in whom an aldosterone antagonist is not indicated or tolerated (Class: IIa, Level: A)" [2]. Similarly, the latest European Society of Cardiology guideline recommends "ARB is recommended to reduce the risk of HF hospitalization in patients with an EF ≤40% and persisting symptoms (NYHA class II–IV) despite treatment with an ACEI and a beta-blocker who are unable to tolerate a mineralocorticoid receptor antagonist (Class: I, Level: A)" [6]. These recommendations are corroborated by our sensitivity analysis. We propose that an ARA should be the first-choice recommendation in patients with HFrEF who remain symptomatic despite optimal treatment with an ACEI.

Among the six RAAS therapies, our findings suggest that DRI was the least effective therapy for reducing death and hospitalization, but was the therapy associated with the lowest discontinuation rate. Aliskiren, a first-in-class orally active DRI approved for the treatment of hypertension, has demonstrated favorable neurohumoral effects in heart failure, and is reportedly well tolerated [41]. However, the ASTRONAUT trial failed to show a beneficial effect of aliskiren on mortality and the risk of hospitalization for heart failure in 1615 patients with HFrEF [7]. In view of the limited sample size and patient-years of exposure in the ASTRONAUT trial, it is still too early to draw firm conclusions about the efficacy of aliskiren. The ATMOSPHERE trial, an ongoing long-term study of 7041 patients with HFrEF that is comparing aliskiren and enalapril alone and in combination, will provide further insights [42].

During the last decades, treatment of patients with HFrEF has improved dramatically with the introduction of RAAS therapies, yet RAAS inhibitors fail to show a benefit in patients with HFpEF, which has the similarity in outcomes and neurohormonal activation as HFrEF [43–44]. We identified six double-blind RCTs that examined the efficacy of RAAS therapies in patients with HFpEF (summarized in Supplementary Tables S7 and S8) [11–16]. Our pairwise meta-analyses showed that neither ACEI, ARB nor ARA significantly reduced all-cause mortality or the risk of hospitalization for heart failure (Supplementary Figs. S16 and S17). Choosing the most effective pharmacological treatment for HFpEF remains problematic: a better characterization of the patients and better pathophysiological insight are urgently needed to improve the outcome of patients with HFpEF [43–44].

Compared with previous studies, a major strength of our analysis is the inclusion of a large number of high-quality RCTs that together had 69,229 participants, making it the largest evaluation of the efficacy and safety of RAAS therapies to date. Furthermore, the Bayesian network meta-analysis makes indirect comparisons of the multiple treatment options available, a particular advantage when there are few trials directly comparing different RAAS therapies. We have provided evidence-based hierarchies for the long-term efficacy and safety of all available RAAS therapies for patients with HFrEF or LVD, but our study also has some limitations. First, the pooled ORs were calculated using trial-level rather than individual-level data. Individual patient information would have added further insights into the analysis. Second, it is possible that some trials, for example those not published in English, may not have been included, which could have led to selection bias. We diligently searched the accessible literature on relevant studies, and the trials included represent the major accessible published literature on RAAS therapies in patients with heart failure. We believe that the possibility of selection bias was minimized by the relatively large number of studies available in English. In addition, previous studies have demonstrated that excluding studies published in languages other than English generally has little effect on summary effect estimates [45,46]. Third, not all included trials reported the results of hospitalization for heart failure or discontinuation due to any adverse events, which may affect the accuracy of our findings. Fourth, significant heterogeneity was identified in four pairwise meta-analyses, which may have led to bias in the estimators derived from network meta-analyses. In addition, the background use of beta blockers is very different between 1990s and 2000s, from 0% to 100% (Supplementary

Table 3
Results for discontinuation due to any adverse events, from network meta-analysis (upper diagonal part) and pairwise meta-analysis (lower diagonal part).

Treatment	Placebo	ACEI	ARB	ARB + ACEI	ARA	ARNI	DRI
Placebo	1.00	**2.08 (1.74–2.49)***	**1.28 (1.04–1.55)**	**2.31 (1.48–3.38)**	1.11 (0.86–1.49)	**1.85 (1.15–2.90)**	1.10 (0.67–1.70)
ACEI	**1.96 (1.73–2.22)**	1.00	**0.62 (0.50–0.73)**	1.11 (0.76–1.60)	**0.54 (0.39–0.75)**	0.89 (0.58–1.30)	**0.53 (0.31–0.84)**
ARB	**1.33 (1.16–1.52)**	**0.59 (0.48–0.74)**	1.00	**1.82 (1.23–2.59)**	0.88 (0.63–1.26)	1.45 (0.92–2.27)	0.87 (0.51–1.42)
ARB + ACEI	—	**1.19 (1.03–1.37)**	**1.62 (1.38–1.89)**	1.00	**0.50 (0.31–0.84)**	0.82 (0.47–1.38)	**0.49 (0.26–0.88)**
ARA	1.18 (0.82–1.72)	—	—	—	1.00	1.69 (0.93–2.82)	1.01 (0.55–1.62)
ARNI	—	**0.85 (0.75–0.98)**	—	—	—	1.00	0.63 (0.32–1.12)
DRI	1.06 (0.83–1.35)	—	—	—	—	—	1.00

Each cell gives an odds ratio (OR) and 95% credible interval (CrI) or confidence interval (CI). In the upper diagonal part, the OR (95% CrI) compares the column condition with the row condition, and in the lower diagonal part, this OR (95% CI) compares the row condition with the column condition.
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARA, aldosterone receptor antagonist; ARNI, angiotensin receptor–neprilysin inhibitor; DRI, direct renin inhibitor.
* Significant results are in bold.

Table 4
Surface under the cumulative ranking curve (SUCRA) probabilities of renin–angiotensin–aldosterone system blockers on efficacy and safety outcomes.

	All-cause death		Heart failure hospitalization		Discontinuation due to any adverse events	
Treatment	SUCRA	Median rank*	SUCRA	Median rank	SUCRA	Median rank
Placebo	0.085	7	0.050	7	0.893	1
ACEI	0.625	3	0.569	3	0.159	6
ARB	0.395	5	0.446	5	0.562	4
ARB + ACEI	0.452	4	0.806	2	0.079	7
ARA	0.778	2	0.534	4	0.749	3
ARNI	0.928	1	0.945	1	0.292	5
DRI	0.237	6	0.150	6	0.766	2

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARA, aldosterone receptor antagonist; ARNI, angiotensin receptor–neprilysin inhibitor; DRI, direct renin inhibitor; CrI, credible interval.

* Ranking SUCRA probabilities in order: being the best treatment, the second best, the third best, and so on, among the therapies.

Table S1), which might lead to confounding. However, given that all the 21 included studies in our meta-analysis are randomized controlled trials, which results in balanced background usage of beta blockers between groups at baseline in each trial, we consider that the confounding effect from beta blocker usage on our results might be limited to a certain degree. Last, only one RCT using ARNI is included in the analysis, which may undermine the strength of our conclusion.

In conclusion, our network meta-analysis found that ARNI has the highest probability of being the most efficacious therapy for HFrEF in reducing death and hospitalization for heart failure, but more RCTs are needed to confirm its efficacy and safety. Furthermore, we conclude that ARA has the most favorable benefit–risk profile when administered as an adjunct to background ACEI and/or ARB therapy.

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.12.010.

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