International Journal of Cardiology 205 (2016) 65–71

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

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

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ARTICLE INFO

Article history:
Received 3 September 2015
Received in revised form 6 December 2015
Accepted 12 December 2015
Available online 15 December 2015

Keywords:
Renin–angiotensin–aldosterone system
Network meta-analysis
Heart failure and reduced ejection fraction
Left ventricular dysfunction

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.

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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,

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http://dx.doi.org/10.1016/j.ijcard.2015.12.010
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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.

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