INPLASY PROTOCOL

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

Renal Safety and Efficacy of Angiotensin Receptor-neprilysin Inhibitor : a meta-analysis of Randomized Controlled Trials

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Review question / Objective: **Angiotensin receptor-neprilysin inhibitor (ARNi) has been shown to improve cardiovascular outcomes in the PARADIGM-HF (Prospective Comparison of ARNi with angiotensin-converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) study. While the renal safety and efficacy of ARNi in clinical trials are still controversial.**
Condition being studied: **A large RCT (Prospective Comparison of ARNi With ACE Inhibitor to Determine Impact on Mortality and Morbidity in Heart Failure, PARADIGM-HF trial) with 8448 patients has demonstrated LCZ696 reduced the risk of death and hospital admission, while improving the quality of life and renal outcome in patients with HF, compared with enalapril. While, the United Kingdom Heart and Renal Protection (UK HARP)-III trial comparing the effects of LCZ696 versus irbesartan in the CKD population, have found that no clinical difference in eGFR during the follow-up time8. When facing the various results from individual clinical trials, we need to conduct a meta-analysis to increase the statistical power.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 April 2020 and was last updated on 19 April 2020 (registration number INPLASY202040115).

INTRODUCTION

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METHODS

Participant or population: Patients are treated with ARNi.

Intervention: Angiotensin receptor-neprilysin inhibitor.

Comparator: ACEI/ARB was used in the control group.

Study designs to be included: Randomized Controlled Trials.

Eligibility criteria: Patients were assigned to ARNi treatment; the clinical trial was RCTs; ACEI/ARB was used in the control group; trials reported renal outcomes; all publications were in English.

Information sources: We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to undertake this meta-analysis. We searched PubMed, EMBASE, the Cochrane Library, Web of Science, and ClinicalTrial.gov, We have searched all databases from their inception to the present. About other sources, we also searched the reference lists of relevant publications and contacted the authors if the results were unpublished.

Main outcome(s): Renal dysfunction, estimated glomerular filtration rate (eGFR) and elevated serum potassium, UACR. hyperkalemia and elevated serum creatinine.

Quality assessment / Risk of bias analysis: The risk bias of the RCTs were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions for random sequence generation, allocation concealment, blinding of participants and treatment providers, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias.

Strategy of data synthesis: The meta-analysis was performed in Review Manager software (version 5.3; Cochrane Collaboration, Oxford, UK). Dichotomous variables were expressed as event counts, and continuous variables were reported as mean ± SD, with risk ratio (RR) and 95% confidence interval (CI) values provided for dichotomous variables and mean difference and 95% CIs for continuous variables. Both fixed-effects (inverse-variance weighted) and random-effects (DerSimonian and Laird) Mantel-Haenszel (M-H) models were applied. The I2 statistic was used to analyze the heterogeneity, which was classified as follows: < 25% low, 25% to 50% moderate and > 50% high. When I2 > 50% and P < 0.1, random effects model was used. Statistical significance was met as P value was less than 0.05 in all included studies.

Subgroup analysis: The subgroup analysis was based on the follow-up time.

Sensibility analysis: The effect of each study on the overall effect size was assessed by sensitivityanalysis usingthe leave-one-out approach.

Language: English.

Country(ies) involved: China.

Keywords: Angiotensin receptor-neprilysin inhibitor, RAS inhibition, meta-analysis, renal efficacy.