INPLASY PROTOCOL

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None declared.

Efficacy and safety of selective nonsteroidal mineralocorticoid receptor antagonist finerenone in chronic kidney disease: a systematic review and meta-analysis of randomized clinical trials

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Review question / Objective: **To assess the beneficial effect and safety of finerenone for patients with chronic kidney disease.**
Information sources: **Electronic databases: PubMed; Embase; The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; China National Knowledge Infrastructure (CNKI); Wanfang Data; Chinese Biomedical Literature Database (SinoMed) and China Science and Technology Journal database (VIP). If necessary, we will contact with authors.**

***(Co-first authors) Mingzhu Zhang and Wujisiguleng Bao contributed equally.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 September 2021 and was last updated on 07 September 2021 (registration number INPLASY202190020).

INTRODUCTION

Review question / Objective: **To assess the beneficial effect and safety of finerenone for patients with chronic kidney disease.**

Rationale: **Chronic kidney disease (CKD) has become a major public health problem due to its high incidence, poor prognosis and high cost of medical treatment, Patients with chronic kidney disease are characterized by a progressive decline in renal function as well as a high risk of cardiovascular disease. Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, reduced composite**

kidney and cardiovascular outcome in trials involving patients with chronic kidney disease. Recently, quite a few clinical studies have been conducted to compare finerenone and placebo. Our meta-analysis aimed to investigate the efficacy and safety of finerenone in chronic kidney disease.

Condition being studied: Chronic kidney disease (CKD) has become a major public health problem due to its high incidence, poor prognosis and high cost of medical treatment, Patients with chronic kidney disease are characterized by a progressive decline in renal function as well as a high risk of cardiovascular disease. A variety of factors are involved in the patho-physiological development of CKD, including aldosterone. Aldosterone, a mineralocorticoid hormone, is a downstream target of the activation of the renin-angiotensin system (RAS) that may have an impact on human kidneys due to its potential ability to increase proteinuria and decrease renal function. Current studies have revealed that aldosterone causes inflammation in various ways, including stimulating the formation of reactive oxygen species (ROS), endothelial exocytosis and adhesion, leading to fibrosis and remodeling in the heart and kidney. Finerenone is currently the most advanced third-generation nonsteroidal MRI drug. Preclinical studies have shown that finerenone has a higher selectivity than spironolactone, a better affinity than eplerenone and a lower risk of hyperkalemia. Recently, quite a few clinical studies have been conducted to compare finerenone and placebo. Thus, our meta-analysis aimed to investigate the efficacy and safety of finerenone in chronic kidney disease.

METHODS

Search strategy: Terms: finerenone; kerendia; BAY 94-8862; Renal Insufficiency, Chronic; Chronic Renal Insufficiencies; Renal Insufficiencies, Chronic; Chronic Renal Insufficiency; Kidney Insufficiency, Chronic; Chronic Kidney Insufficiency; Chronic Kidney Insufficiencies; Kidney Insufficiencies, Chronic; Chronic Kidney Diseases; Chronic Kidney Disease; Disease, Chronic Kidney; Diseases, Chronic Kidney; Kidney Disease, Chronic; Kidney Diseases, Chronic; Chronic Renal Diseases; Chronic Renal Disease; Disease, Chronic Renal; Diseases, Chronic Renal; Renal Disease, Chronic; Renal Diseases, Chronic; randomized controlled trial; controlled clinical trial; randomized; placebo; drug therapy; randomly; trial; groups; animals; humans. Electronic databases: PubMed; Embase; The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; China National Knowledge Infrastructure (CNKI); Wanfang Data; Chinese Biomedical Literature Database (SinoMed) and China Science and Technology Journal database (VIP).

Participant or population: Patients were adults (ĄÜ18 years old) with chronic kidney disease, regardless of race, gender or economic status will be included.

Intervention: Experimental intervention is finerenone, administered orally, taken either alone or in combination with other active treatment. Control intervention can be no treatment, placebo, or other active treatment.

Comparator: Control intervention can be no treatment, placebo, or other active treatment.

Study designs to be included: Randomized clinical trials (RCTs).

Eligibility criteria: Randomized clinical trials (RCTs) comparing finerenone with placebo or other active interventions will be included, regardless of language and publication status.

Information sources: Electronic databases: PubMed; Embase; The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; China National Knowledge Infrastructure (CNKI); Wanfang Data; Chinese Biomedical Literature Database (SinoMed) and China Science and Technology Journal database (VIP). If necessary, we will contact with authors.

Main outcome(s): 1) decrease in eGFR; 2) change in urinary albumin-to-creatinine ratio (UACR).

Additional outcome(s): 1) composite kidney outcome including the occurence of kidney failure, doubling of serum creatinine, eGFR decreasing by more than 40% or death and so on; 2) composite cardiovascular outcome including death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure; 3) hyperkalemia; 4) Adverse events.

Data management: Retrieved citations from the various search engines will be imported into EndNote and checked for duplicates. Two review authors will use a pre-piloted data extraction form to extract data on general information (study ID, study author and title); methodological information (study design, the number of groups, sequence generation, allocation sequence concealment, blinding, selective outcome reporting, baseline comparability); participant characteristics (diagnostic criteria, inclusion criteria, exclusion criteria, total number of intervention groups, number lost during follow-up, age, sex, country, setting and disease duration); intervention (the name of therapeutic drug, dosage and regimen, other treatments given, drug combination, duration of treatment), and outcome measures. We will record relevant data using a pre-defined data extraction form. We will resolve disagreements through discussion, and contact the corresponding trial author in case of unclear and missing data.

Quality assessment / Risk of bias analysis: We will use the Cochrane "Risk of bias"tool of Cochrane Handbook for Systematic Reviews of Interventions to evaluate each trial's methodological quality, and then recorded in the table. The key components in the tool were: sequence generation, allocation concealment, blinding of participants, personnel and outcomes assessors, incomplete outcome data, selective outcome reporting and other possible sources of bias. Any disagreements will resolve through discussion with a third author.

Strategy of data synthesis: We will use RevMan to analyze the data. We will use RR with 95% CIs and a random-effects model to pool their results in the meta-analyses if there are sufficient clinically similar studies available. For dichotomous outcomes, we will calculate the RR for each study and then aggregate the data. For continuous outcomes, if all the trials measured results on the same scale, we will pool MDs between the treatment arms at the end of the follow-up, otherwise we will pool SMDs. Where a meta-analysis is inappropriate, we will summarize data in tables.

Subgroup analysis: We will perform the following subgroup analyses for people with CKD to investigate heterogeneity: dosage regimen; stages of CKD; whether or not patients had diabetes.

Sensitivity analysis: We will conduct sensitivity analyses to explore the impact of losses to follow-up on the effect estimates for the primary outcomes and to exclude studies considered to be high risk of bias. For dichotomous outcomes, we will vary the event rate within the missing patients from intervention and control groups within plausible limits. For continuous data, we will perform sensitivity analyses using methods described by Ebrahim 2013 and Ebrahim 2014.

Language: No restriction.

Country(ies) involved: China.

Keywords: Finerenone; chronic kidney disease; meta-analysis; randomized clinical trials.

Dissemination plans: We plan to publish a systematic review and meta-analysis base on this protocol.

Contributions of each author:

Author 1 - Mingzhu Zhang - The author drafted the manuscript.
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Author 2 - Wujisiguleng Bao - The author provided statistical expertise.
Author 3 - Luying Sun - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
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