

# Efficacy and safety of spironolactone for the treatment of patients with acute heart failure

## A protocol for systematic review

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### Abstract

**Background:** This study will investigate the efficacy and safety of spironolactone for the treatment of acute heart failure (AHF).

**Methods:** The following electronic databases will be retrieved in PUBMED, EMBASE, Cochrane Library, Web of Science, CINAHL, CBM, CNKI, and VIP database from inception through present. Two researchers will independently screen and assess the obtained literatures and extract outcome data. All study methodological quality will be assessed using Cochrane risk of bias tool, and all statistical analysis will be performed by RevMan 5.3 software. Additionally, we will undertake a narrative synthesis if it is possible.

**Results:** This study will summarize most recent evidence to investigate the efficacy and safety of spironolactone for the treatment of AHF.

**Conclusion:** This study will seek to assess the efficacy and safety of spironolactone for treating AHF.

**Systematic review registration:** INPLASY202070053.

**Abbreviations:** AHF = acute heart failure, CIs = confidence intervals, RCTs = randomized controlled trials.

**Keywords:** acute heart failure, efficacy, safety, spironolactone

## 1. Introduction

Acute heart failure (AHF) is a major public health issue.<sup>[1,2]</sup> It is a characterized by a rapid onset or acute worsening of symptoms (dyspnoea, orthopnoea, lower limb swelling) and signs (elevated jugular venous pressure, pulmonary congestion).<sup>[3–5]</sup> It is resulted from a structural and/or functional cardiac abnormality.<sup>[6,7]</sup> It is reported that AHF is associated with more than 26 million hospitalizations annually around the world.<sup>[8–10]</sup> Its annual mortality rate after AHF hospitalization is still about 20% to 30%, and there is still high potential risk of subsequent hospitalization.<sup>[11]</sup>

Management of AHF relies on rapid recognition of its symptoms and signs.<sup>[12,13]</sup> Previous studies reported that spironolactone can benefit patients with AHF.<sup>[14–24]</sup> However, no systematic review specifically assesses the efficacy and safety of spironolactone alone for the treatment of patients with AHF. Thus, this systematic review will investigate the efficacy and safety of spironolactone for the treatment of AHF.

## 2. Methods

### 2.1. Study registration

We registered this study through INPLASY202070053. We report it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol statement guidelines.<sup>[2,5]</sup>

### 2.2. Ethics and dissemination

It is not necessary to supply ethical approval, since this study only harvest data from published study. We will publish this study on a peer-reviewed journal or a conference meeting.

### 2.3. Study eligibility criteria

**2.3.1. Types of studies.** This study will identify all potential randomized controlled trials (RCTs) on efficacy and safety of spironolactone in treating AHF, in spite of language and publication time.

**2.3.2. Types of participants.** All patients who were diagnosed as AHF will be included in this study, irrespective gender, age, economic status, and other information.

### 2.3.3. Types of interventions

**2.3.3.1. Experimental interventions.** We will include any forms of spironolactone in treating patients with AHF.

*This study is supported by Yan'an Diabetes Prevention Research and Technology Innovation Team (2015CXTD-09). The funder did not involve this study.*

*The authors have no conflicts of interests to disclose.*

*Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.*

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*How to cite this article: Feng Yi, Lu M. Efficacy and safety of spironolactone for the treatment of patients with acute heart failure: a protocol for systematic review. *Medicine* 2020;99:43(e22590).*

*Received: 3 September 2020 / Accepted: 8 September 2020*

*<http://dx.doi.org/10.1097/MD.00000000000022590>*

**Table 1**  
**Specific description of search strategy of PUBMED.**

Number	Search terms
1	heart failure
2	congestive heart failure
3	coronary artery disease
4	heart attack
5	heart decompensation
6	myocardial failure
7	acute
8	Or 1–7
9	spironolactone
10	Aldactone
11	potassium-sparing diuretic
12	generic drug
13	Or 9–12
14	randomized
15	randomly
16	random
17	allocation
18	concealment
19	placebo
20	blind
21	control trial
22	clinical trial
23	Or 14–22
24	8 and 13 and 23

**2.3.3.2. Control interventions.** We will consider any therapies in treating AHF. However, we will exclude combined treatments with spironolactone.

**2.3.4. Type of outcome measurements.** Outcomes are all-cause mortality, clinical congestion score, urine output, weight change, quality of life, and safety.

#### 2.4. Search strategy and data management

**2.4.1. Search strategy.** This study will search all potential studies in PUBMED, EMBASE, Cochrane Library, Web of Science, CINAHL, CBM, CNKI, and VIP database from initial through present. A specific description of search strategy of PUBMED is built in Table 1. We will modify similar search strategies and will apply them to other electronic databases. Additional searches will be conducted from any associated sources, such as conference proceedings, thesis, dissertations, and reference lists of relevant reviews.

**2.4.2. Study selection.** We will examine titles/abstracts of searched studies, and will exclude all duplications and irrelevant studies. After eliminating those studies, we will check full papers of remaining potential studies based on all eligibility criteria. Two independent researchers will undertake selection of study. Disagreements between both of them will be figured out by another experienced researcher through discussion. We will present results of study selection in a flow diagram.

**2.4.3. Data extraction and management.** Two researchers will independently extract main data from several aspects: author, time of publication, country, study design, study setting, sample size, gender, age, diagnostic criteria, inclusion and exclusion criteria, treatment details, comparators, frequency, dosage,

outcomes, and adverse events. We will solve any disagreements between 2 researchers with the help of another researcher.

**2.4.4. Dealing with missing data.** We will contact primary trial authors to request any insufficient, unclear or missing data. If we can not receive those data, we will analyze available data using intention-to-treat analysis.

#### 2.5. Study quality assessment

Two researchers will appraise study quality using Cochrane risk of bias tool via 7 domains. If any different views occur, another experienced researcher will help to solve them through discussion.

#### 2.6. Strategy for statistical analysis

This study will utilize RevMan 5.3 software to perform data analysis. The dichotomous data will be presented as risk ratio and 95% confidence intervals (CIs), and continuous data will be estimated as mean difference or standardized mean difference and 95% CIs. The statistical heterogeneity across eligible trials is examined by  $I^2$  test. If there is few heterogeneity ( $I^2 \leq 50\%$ ) among sufficient eligible studies on the same outcome, data will be pooled using a fixed-effect model, and meta-analysis will be performed. If there is obvious statistical heterogeneity across included studies ( $I^2 > 50\%$ ), its sources will be identified using subgroup analysis. If we can not examine sources of obvious heterogeneity, we will perform descriptive analysis instead of meta-analysis.

#### 2.7. Additional analysis

We will explore source of obvious heterogeneity based on the study information, patient characteristics, study quality and outcomes.

We will employ sensitivity analysis to test robustness of merged outcome results by excluding studies with high risk of bias.

We will examine reporting bias using funnel plot and Eggers regression test if at least 10 studies are included.<sup>[26,27]</sup>

### 3. Discussion

This is the first systematic review to yield high quality evidence on the efficacy and safety of spironolactone for the treatment of AHF. We will search both electronic databases and other literature sources to avoid missing potential studies. Two researchers will independently carry out study selection, study quality assessment, and data collection. Any division will be solved by a third researcher through discussion. The results of this study will inform helpful information to notify the management of spironolactone for AHF. Its findings may provide solid data and robust evidence of spironolactone for AHF for both clinical practice and patients.

#### Author contributions

**Conceptualization:** Yan-lin Feng, Min Lu.

**Data curation:** Yan-lin Feng, Min Lu.

**Formal analysis:** Yan-lin Feng, Min Lu.

**Investigation:** Min Lu.

**Methodology:** Yan-lin Feng.

**Project administration:** Min Lu.

**Resources:** Yan-lin Feng.

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**Supervision:** Min Lu.

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**Visualization:** Yan-lin Feng, Min Lu.

**Writing – original draft:** Yan-lin Feng, Min Lu.

**Writing – review & editing:** Yan-lin Feng, Min Lu.

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