

# Efficacy of urapidil for the treatment of patients with senile hypertension and acute heart failure

Yan-Zhong Xie, MM<sup>a</sup>, Jian-Ming Ni, MM<sup>a</sup>, Shan-Jing Zhang, MM<sup>a</sup>, Guo-Rong Ding, MM<sup>a,\*</sup>, Jun-Fei Feng, MM<sup>b,\*</sup>

## Abstract

**Background:** Previous clinical studies have reported that urapidil can effectively treat patients with senile hypertension (SH) and acute heart failure (AHF). However, no studies have systematically assessed the efficacy and safety of urapidil for patients with SH and AHF. Thus, this study will investigate the efficacy and safety of urapidil for SH and AHF.

**Methods:** In this study, we will search the following electronic databases from inception to the June 30, 2019: MEDLINE, EMBASE, Cochrane Library, Google scholar, Springer, WANGFANG, and China Knowledge Resource Integrated Database. We will search all these electronic databases without language limitations. We will also search grey records to avoid missing potential literature. In this study, only randomized controlled trials on assessing efficacy and safety of urapidil for SH and AHF will be considered. We will use RevMan 5.3 software and STATA 15.0 software to carry out statistical analysis.

**Results:** This study will evaluate the efficacy and safety of urapidil for SH and AHF by assessing all-cause mortality, change in body weight, urine output, change in serum sodium; and incidence of all adverse events.

**Conclusion:** This study will provide latest evidence of the efficacy and safety of urapidil for patients with SH and AHF.

**Dissemination and ethics:** This study will only analyze published data; therefore, no ethical approval is needed. The findings of this study will be published at peer-reviewed journals.

**Systematic review registration:** PROSPERO CRD42019139344.

**Abbreviations:** AHF = acute heart failure, RCTs = randomized controlled trials, SH = senile hypertension.

**Keywords:** acute heart failure, efficacy, safety, senile hypertension, urapidil

## 1. Introduction

Acute heart failure (AHF) is a very common disorder in the clinic practice of cardiovascular department.<sup>[1–2]</sup> It is characterized by an acute deterioration in cardiac function.<sup>[3–6]</sup> In addition, such severe disorder has been a major public health problem, and is also associated with high intervention and health care costs, as well as high risk of mortality and morbidity.<sup>[7–10]</sup> It has been estimated that its prevalence is about 4.2 million in China and 23 million globally.<sup>[11–13]</sup> Previous studies have reported that

patients with senile hypertension (SH) are more likely to suffer from AHF among elderly population.<sup>[14–19]</sup> Therefore, it is very important to manage patients with SH and AHF. Fortunately, urapidil has reported to treat patients with SH and AHF very well.<sup>[20–23]</sup> However, there is still no systematic study to assess the efficacy and safety in patients with SH and AHF. Therefore, this study will firstly explore the efficacy and safety of urapidil for the management of SH and AHF.

## 2. Methods

### 2.1. Objective

This study will systematically assess the efficacy and safety of urapidil for patients with SH and AHF.

### 2.2. Study registration

We have registered this study on PROSPERO (CRD42019139344). We have reported this study according to the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol.<sup>[24]</sup>

### 2.3. Criteria for considering studies for this study

**2.3.1. Types of studies.** We will include randomized controlled trials (RCTs) which have explored the efficacy and safety of urapidil for patients with SH and AHF.

**2.3.2. Types of participants.** All patients with SH and AHF will be included regardless the race, sex, and age.

This study is partly supported by Fuyang District Science and Technology Bureau Project (81403234).

The authors report no conflicts of interest.

<sup>a</sup>Department of Emergency,, <sup>b</sup>Department of Respiratory Medicine, Hangzhou Fuyang Hospital of Traditional Chinese Medicine, Hangzhou, China.

\*Correspondence: Guo-Rong Ding, Department of Emergency, Hangzhou Fuyang Hospital of Traditional Chinese Medicine, No. 4 Beimen Road, Fuyang District, Hangzhou 311400, China (e-mail: Guorongding1980@outlook.com); Jun-Fei Feng, Department of Respiratory Medicine, Hangzhou Fuyang Hospital of Traditional Chinese Medicine, No. 4 Beimen Road, Fuyang District, Hangzhou 311400, China (e-mail: junfei2000@hotmail.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Xie YZ, Ni JM, Zhang SJ, Ding GR, Feng JF. Efficacy of urapidil for the treatment of patients with senile hypertension and acute heart failure. *Medicine* 2019;98:41(e17352).

Received: 3 September 2019 / Accepted: 3 September 2019

<http://dx.doi.org/10.1097/MD.00000000000017352>

**2.3.3. Types of interventions.** Patients in the experimental group can receive any forms of urapidil.

Patient in the control group can receive any interventions, except urapidil.

**2.3.4. Type of outcome measurements.** The primary outcome consists of all-cause mortality. The secondary outcomes comprise of change in body weight, urine output, change in serum sodium; and incidence of all adverse events.

## 2.4. Search methods for identification of studies

**2.4.1. Electronic searches.** For this study, we will search the following electronic databases from inception to the June 30, 2019: Cochrane Library, MEDLINE, EMBASE, Google scholar, Springer, WANGFANG, and China Knowledge Resource Integrated Database without language restrictions. Details of the search strategy for Cochrane Library are showed in the Table 1. We will also use identical search strategies to other electronic databases.

**2.4.2. Search for other resources.** We will also check unpublished studies, dissertations, and reference lists of obtained reviews in this study.

## 2.5. Data collection and analysis

**2.5.1. Selection of studies.** Two independent authors will check titles and abstracts of all records according to the pre-designed eligibility. A third experienced author will be invited to solve disagreements between 2 authors by discussion. Initially, all searched studies will be checked if they meet the primary inclusion criteria. Then, all irrelevant studies will be excluded, and remaining studies will be read by full-texts. The process of study selection will be reported in the diagram chart in Figure 1.

**2.5.2. Data extraction and management.** Two authors will independently extract and summarize details of eligible studies by using previous designed data extraction form. A third author will help to solve any disagreements between 2 authors. The following information will be extracted.

- (1) Study characteristics, such as title, author, published year, etc;
- (2) Patient characteristics, such as race, age, gender, etc;

- (3) Study design and methods, such as sample size, randomization, blinding, etc;
- (4) Intervention details, such as treatments, comparators, duration, etc;
- (5) Outcome measurements, such as primary, secondary outcomes, safety, etc.

**2.5.3. Dealing with missing data.** We will attempt to obtain any missing or insufficient data by contacting primary authors. If we cannot require those additional data, only available data will be analyzed in this study.

**2.5.4. Assessment of risk of bias.** Two independent authors will evaluate the risk of bias for the included studies. We will use Cochrane risk of bias tool. Any divisions between 2 authors will be solved by a third author through discussion. It has seven criteria, each 1 is further judged with low risk of bias, unclear risk of bias and high risk of bias.

## 2.6. Statistical analysis

**2.6.1. Measurement of treatment effect.** For each trial with dichotomous outcomes, we will calculate as odd ratio or risk ratio and 95% confidence intervals. Where outcomes for continuous outcomes, we will calculate as mean difference or standardized mean difference and 95% confidence intervals.

**2.6.2. Assessment of heterogeneity.** We will apply  $I^2$  statistic to check heterogeneity among trials.  $I^2 \leq 50\%$  indicates reasonable heterogeneity, and a fixed-effect model will be applied.  $I^2 > 50\%$  indicates substantial heterogeneity, and a random-effect model will be used.

**2.6.3. Data synthesis.** When the reasonable heterogeneity is obtained, meta-analysis will be carried out. When the substantial heterogeneity is identified, subgroup analysis will be performed to check any reasons that may lead to such high heterogeneity. If significant heterogeneity is still obtained after subgroup analysis, we will not pool the data and will only report narrative summary.

**2.6.4. Subgroup analysis.** In this study, subgroup analysis will be performed in accordance with the different treatments, controls, and outcomes.

**Table 1**

### Search strategy for Cochrane Library database.

Number	Search terms
1	Mesh descriptor: (heart failure) explode all trees
2	((acute* or (congestive heart failure*) or (cardiac failure*) or (heart decompensation*) or (myocardial failure*) or (right-sided heart failure*) or (left sided heart failure*)):ti, ab, kw
3	Or 1–2
4	MeSH descriptor: (hypertension) explode all trees
5	MeSH descriptor: (blood pressure) explode all trees
6	((diastolic blood pressure*) or (systolic blood pressure*) or (DBP*) or (SBP*) or (blood pressure*) or (hypertension*)):ti, ab, kw
7	Or 4–6
8	MeSH descriptor: (Urapidil) explode all trees
9	((urapidil*) or (antihypertensive drug*) or ( $\alpha$ 1-adrenoceptor antagonist*) or (5-HT1A receptor agonist*) or ( $\alpha$ 2-adrenoceptor agonist*)):ti, ab, kw
10	Or 8–9
11	MeSH descriptor: (randomized controlled trial) explode all trees
12	((controlled trial*) or (clinical trial*) or (randomly*) or (random*) or (blind*) or (placebo*) or (sham*) or (control*)):ti, ab, kw
13	Or 11-12
14	3 and 7 and 10and 13

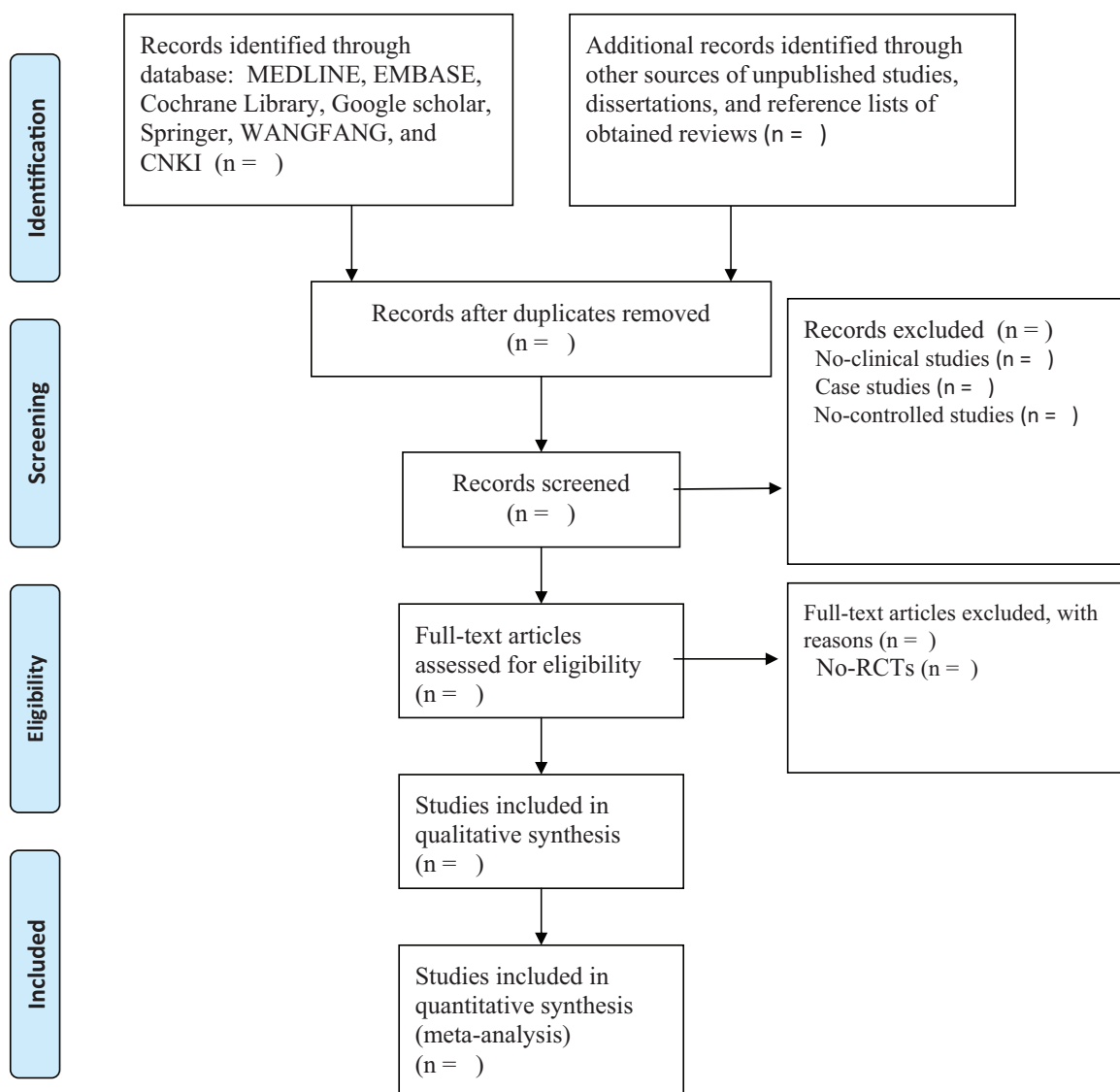


Figure 1. Process of study selection.

**2.6.5. Sensitivity analysis.** We will carry out sensitivity analysis to check the robustness and stability of outcome results by removing low methodological quality studies.

**2.6.6. Reporting bias.** We will check reporting bias using funnel plot and Egger test<sup>[25]</sup> when more than 10 trials are entered in this study.

### 3. Discussion

Previous studies have reported that urapidil is used for the treatment of patients with SH and AHF.<sup>[20–23]</sup> However, no systematic review has explored the efficacy and safety of urapidil for treating SH and AHF. Thus, this study will demonstrate that urapidil administration is as effective in patients with SH and AHF. In this study, we will search all relevant studies without language limitations, and all potentials studies related to the urapidil for treating SH and AHF will be considered. The results of this study will summarize update evidence on the efficacy and

safety of urapidil for treating SH and AHF. It may also provide helpful evidence for patients, clinician, and health policy-makers.

### Author contributions

**Conceptualization:** Yan-Zhong Xie, Jian-Ming Ni, Shan-Jing Zhang, Guo-Rong Ding.

**Data curation:** Yan-Zhong Xie, Jian-Ming Ni, Guo-Rong Ding.

**Formal analysis:** Yan-Zhong Xie, Jian-Ming Ni, Shan-Jing Zhang.

**Investigation:** Guo-Rong Ding.

**Methodology:** Yan-Zhong Xie, Jian-Ming Ni, Shan-Jing Zhang.

**Project administration:** Guo-Rong Ding.

**Resources:** Yan-Zhong Xie, Jian-Ming Ni, Shan-Jing Zhang.

**Software:** Yan-Zhong Xie, Jian-Ming Ni, Shan-Jing Zhang.

**Supervision:** Guo-Rong Ding.

**Validation:** Yan-Zhong Xie, Jian-Ming Ni, Shan-Jing Zhang, Guo-Rong Ding.

**Visualization:** Yan-Zhong Xie, Jian-Ming Ni, Guo-Rong Ding.

**Writing – original draft:** Yan-Zhong Xie, Jian-Ming Ni, Shan-Jing Zhang, Guo-Rong Ding.

**Writing – review & editing:** Yan-Zhong Xie, Jian-Ming Ni, Shan-Jing Zhang, Guo-Rong Ding.

## References

- [1] Arrigo M, Ruschitzka F, Flammer AJ. Acute heart failure. *Ther Umsch* 2018;75:155–60.
- [2] Øerlinskaite K, Javanainen T, Cinotti R, et al. Acute heart failure management. *Korean Circ J* 2018;48:463–80.
- [3] Rayner-Hartley E, Virani S, Toma M. Update on the management of acute heart failure. *Curr Opin Cardiol* 2018;33:225–31.
- [4] Sabbah HN. Pathophysiology of acute heart failure syndrome: a knowledge gap. *Heart Fail Rev* 2017;22:621–39.
- [5] Mentz RJ, O'Connor CM. Pathophysiology and clinical evaluation of acute heart failure. *Nat Rev Cardiol* 2016;13:28–35.
- [6] Goldsmith SR. A new approach to treatment of acute heart failure. *J Cardiol* 2016;67:395–8.
- [7] Teixeira A, Arrigo M, Tolppanen H, et al. Management of acute heart failure in elderly patients. *Arch Cardiovasc Dis* 2016;109:422–30.
- [8] Viau DM, Sala-Mercado JA, Spranger MD, et al. The pathophysiology of hypertensive acute heart failure. *Heart* 2015;101:1861–7.
- [9] Farmakis D, Parissis J, Lekakis J, et al. Acute heart failure: Epidemiology, risk factors, and prevention. *Rev Esp Cardiol (Engl Ed)* 2015;68:245–8.
- [10] Montes-Santiago J, Arévalo Lorido JC, Cerqueiro González JM. Epidemiology of acute heart failure. *Med Clin (Barc)* 2014;142(Suppl 1):3–8.
- [11] Zsilinszka R, Mentz RJ, DeVore AD, et al. Acute heart failure: alternatives to hospitalization. *JACC Heart Fail* 2017;5:329–36.
- [12] He J, Gu D, Wu X, et al. Major causes of death among men and women in China. *N Engl J Med* 2005;353:1124–34.
- [13] Roger VL. Epidemiology of heart failure. *Circ Res* 2013;113:646–59.
- [14] Sztrymf B, Souza R, Bertoletti L, et al. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *Eur Respir J* 2010;35:1286–93.
- [15] Lobo Martínez P, Oulego Erroz I, Gautreux Minaya S, et al. Treatment of acute heart failure using levosimendan for a patient with dilated cardiomyopathy, chronic renal failure, and hypertension. *Pediatr Cardiol* 2011;32:1012–6.
- [16] Felsőci M, Parenica J, Spinar J, et al. Does previous hypertension affect outcome in acute heart failure? *Eur J Intern Med* 2011;22:591–6.
- [17] Ellenga Mbolla BF, Gombet TR, Atipo-Ibara BI, et al. Impact of severe hypertension in acute heart failure in Brazzaville (Congo). *Med Sante Trop* 2012;22:98–9.
- [18] Jamerson KA, Agodoa L. Hypertension as an emerging risk factor for acute heart failure in Africa: comment on “the causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries”. *Arch Intern Med* 2012;172:1395–6.
- [19] Felsőci M, Parenica J, Spinar J, et al. Impact of antecedent hypertension on outcomes in patients hospitalized with severe forms of acute heart failure. *Acta Cardiol* 2012;67:515–23.
- [20] Yang W, Zhou YJ, Fu Y, et al. Efficacy and safety of intravenous urapidil for older hypertensive patients with acute heart failure: a multicenter randomized controlled trial. *Yonsei Med J* 2017;58:105–13.
- [21] Alijotas-Reig J, Bove-Farre I, de Cabo-Frances F, et al. Effectiveness and safety of prehospital urapidil for hypertensive emergencies. *Am J Emerg Med* 2001;19:130–3.
- [22] Hirschl MM, Binder M, Bur A, et al. Safety and efficacy of urapidil and sodium nitroprusside in the treatment of hypertensive emergencies. *Intensive Care Med* 1997;23:885–8.
- [23] Yang W, Zhou YJ, Fu Y, et al. A multicenter, randomized, trial comparing urapidil and nitroglycerin in multifactor heart failure in the elderly. *Am J Med Sci* 2015;350:109–15.
- [24] Shamseer L, Moher D, Clarke M, et al. PRISMA-P Group Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- [25] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.