Systematic Review and Meta-Analysis

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Serelaxin, recombinant human relaxin-2, for heart failure patients

A systematic review and meta-analysis

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Abstract

Background: Serelaxin, recombinant human relaxin-2, is a hormone with vasodilatory and end-organ protective effects. Recently, it has been licensed to treat acute decompensated heart failure. Here, a systematic review and meta-analysis on randomized controlled trials (RCTs) was performed to assess the effect of serelaxin on mortality and dyspnea improvement in patients with heart failure.

Methods: RCTs comparing serelaxin treatment to other heart failure treatments were searched in PubMed, Embase, Cochrane Library, and ClinicalTrials.gov. The main endpoints were mortality and dyspnea improvement. Pooled data were assessed by using a random effects model.

Results: A total of 451 studies were identified, of which 8 studies (8477 participants) were eligible and included in our analysis. Compared with other heart failure treatment group, serelaxin group had no effect on 30-day, 60-day, and 180-day mortality (OR, 0.79; 95% CI, 0.65–0.96). Compared with control group, there was no effect on dyspnea improvement.

Conclusion: Serelaxin treatment is irrelevant with the mortality, and it cannot improve dyspnea of heart failure patients.

Abbreviations: AHF = acute heart failure, NYHA = New York Heart Association, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials.

Keywords: heart failure, mortality, recombinant human relaxin-2, Serelaxin

1. Introduction

Acute heart failure (AHF) is a common and occasionally life-threatening disease. As the aging society, the burden of heart failure on health services is expected to rise, with increased healthcare expenditure and activity.[1] Additionally, the economic burden associated with the treatment of AHF has been further increased by an elevated rate of readmissions, which reaches 25% at 30 days and 30% at 60 to 90 days after discharge.[2] The major medical and economic burdens of this disease have created a large demand for systems-wide changes in health care delivery as well as new therapies with positive impacts on AHF mortality and readmissions.[3]

Serelaxin is a recombinant form of the pregnancy hormone relaxin-2, the hormone regulates maternal adaptations to improve arterial compliance, cardiac output, and renal blood flow.[4] Serelaxin has a unique mechanism of acting that could potentially address the complex pathophysiology of AHF through multiple pathways, possibly leading to organ protection.[5–7]

However, The RELAX-AHF-2 trial showed that short-term intravenous infusion of serelaxin did not reduce mortality compared with placebo in patients with AHF. Paradoxically, pre-RELAX-AHF trial suggested that the treatment of AHF with serelaxin could significantly reduce mortality compared with the control group.[8] RELAX-AHF trial also showed similar outcomes after serelaxin treatment.[9] A series of clinical trials have assessed indicators of dyspnea, which showed different results.

In order to clarify the conflicting opinions, we therefore performed a systematic review and meta-analysis on randomized controlled trials to investigate the role of serelaxin in mortality and dyspnea improvement in patients with AHF.

2. Methods

2.1. Literature research

Our meta-analysis was registered at International Prospective Register of Systematic Reviews (No.: CRD42017058860) and followed the PRISMA statement (Reporting Items for Systematic Reviews and Meta-Analyses).

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LY, LJC, and JS contributed equally to this work.

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A literature search of Web of Knowledge, Embase, ClinicalTrials.gov, and PubMed from Jan 1, 1950 to December 1, 2017 was conducted without language restrictions. A combination of the following keywords was used: "Serelaxin" and "Heart Failure." The complete search used for PubMed was as follows: (serelaxin protein, human [MeSH] OR serelaxin protein, human OR human relaxin-2 OR RLN2 protein, human OR relaxin H2, human OR relaxin-2 protein, human OR H2 relaxin, human OR Recombinant Proteins, human OR Recombinant Fusion Proteins, human) AND (Heart Failure [MeSH] OR Heart Failure OR Cardiac Failure OR Heart Decompensation OR Decompensation, Heart OR Heart Failure, Right-Sided OR Heart Failure, Right Sided OR Right-Sided Heart Failure OR Right Sided Heart Failure OR Heart Failure, Left-Sided OR Heart Failure, Left Sided OR Left-Sided Heart Failure OR Left Sided Heart Failure OR Myocardial Failure OR Congestive Heart Failure OR Heart Failure, Congestive). Additional studies were also obtained by manually screening the references list.

2.2. Eligibility criteria and data extraction

Studies were considered eligible if they met following inclusion criteria: randomized clinical trials in adults with heart failure; compared serelaxin to another treatment strategies; reported changes in mortality or dyspnea improvement during the trial. Studies were excluded if they were: only published in the abstract; not randomized controlled trial (RCT); the absence of intention to treatment data; or no treatment for patients with heart failure.

We compared serelaxin to any other treatment strategies regardless of previous treatment. The outcomes assessed were as follows: mortality at any time during the experiment, changes in dyspnea between baseline and the end of intervention.

Titles and abstracts of studies were reviewed independently by 3 investigators (LY LJC, and YBZ). Studies that were in accordance with the inclusion criteria were retrieved for full-text assessment, with data extracted and analyzed. If there is a disagreement, a fourth investigator (JS) participated in the evaluation.

The primary data were extracted: name of first author, design, trial duration, year of publication, different interventions in study groups, sex, age, New York Heart Association (NYHA) classification, number of deaths during the trial, and the number of subjects whose dyspnea was improved during the trial. According to the PRISMA statement, 2 independent reviewers (LY and LJC) assessed risks of bias.

2.3. Statistical analysis

The effect of serelaxin treatment on mortality and dyspnea improvement was evaluated, and the odds ratio (OR) was calculated.

Pooled estimates of the mean differences in mortality and dyspnea improvement between intervention groups were assessed using a random-effects model (DerSimonian–Laird method) to adequately account for the additional uncertainty associated with inter-study variability in the effect of different antiheart failure drugs. Pooled estimates of the relative risk were calculated with a random-effects model for categorical outcomes.

The publication bias was assessed by constructing a funnel plot with the effect size of each trail against the standard error. The Cochran Q test was used to assess heterogeneity among studies. I^2 test was employed to assess the magnitude of the heterogeneity among studies. Moderate-to-high heterogeneity was indicated, if the values were greater than 50%. Review Manager 5.3 was used for all statistical analyses.

3. Results

A total of 451 studies were identified, according to the eligibility criteria, 8 studies (8477 participants) published between 2009 and 2017 were included in our analysis finally. The characteristics of these studies are represented in Table 1. All trials compared serelaxin with placebo among heart failure patients.

All 8 randomized controlled trials reported adequate randomization, none of which was terminated before the intervention

Table 1

Characteristics of the included studies.

Author	Year	Different interventions in study groups	Design	Duration of interventions, hours	Follow-up	Randomized patients (Serelaxin/Control)	Number of men	Mean age
John R Teerlink[8]	2009	Serelaxin vs placebo	DB-P	48	180 days	229 (168/61)	128 (55.9%)	70.3
John R Teerlink[9]	2013	Serelaxin vs placebo	DB-P	48	180 days	1161 (581/580)	725 (62.4%)	72
Piotr Ponikowski[10]	2013	Serelaxin vs placebo	DB-P	20	30 days	71 (34/37)	53 (74.6%)	68.6
Marion Dahlke[11]	2014	Serelaxin vs placebo	DB-P	48	10 days	40 (32/8)	15 (37.5%)	29.8
Adriaan A. Voors[12]	2014	Serelaxin vs placebo	DB-P	24	28 hours	65 (28/37)	58 (89.2%)	67.9
NaokiSato[13]	2015	Serelaxin vs placebo	DB-P	48	60 days	46 (31/15)	34 (73.9)	75.3
John R Teerlink	2016	Serelaxin vs placebo	DB-P	48	16 weeks	320 (212/108)	Not available	Not available
John R Teerlink[14]	2017	Serelaxin vs placebo	DB-P	48	180 days	6545 (3274/3271)	3927 (60%)	73.0

		NYHA classification, n (%)						
Author	Year	Class I	Class II	Class III	Class IV	Mean baseline dyspnea (%)	Mortality event (Nesiritide/Control)	
John R Teerlink[8]	2009	2 (4)/ 2 (3)	33 (19.6)/ 16 (26)	69 (41.1)/ 23 (38)	47 (30.0)/ 12 (20)	100	12	8
John R Teerlink[9]	2013	12 (3)/ 11 (3)	164 (38)/140 (33)	191 (44)/ 198 (47)	63 (14)/ 72 (17)	100	42	65
Piotr Ponikowski[10]	2013	N/A	N/A	14 (41.2)/ 20 (54.1)	20 (58.8)/ 17 (45.9)	Not available	2	2
Marion Dahlke[11]	2014	N/A	N/A	N/A	N/A	Not available	0	0
Adriaan A. Voors[12]	2014	N/A	17 (60.7)/26 (70.3)	11 (39.3)/ 11 (29.7)	N/A	Not available	0	0
Naoki Sato[13]	2015	1 (3.2)/1 (6.7)	6 (19.4)/ 1 (6.7)	3 (9.7)/ 6 (40.0)	2 (6.5)/ 3 (20.0)	100	0	0
John R Teerlink	2016	N/A	N/A	N/A	N/A	Not available	Not available	Not available
John R Teerlink[14]	2017	N/A	N/A	3011 (46%)	720 (11%)	Not available	285	291

DB-P = double-blind parallel, N/A = not available.

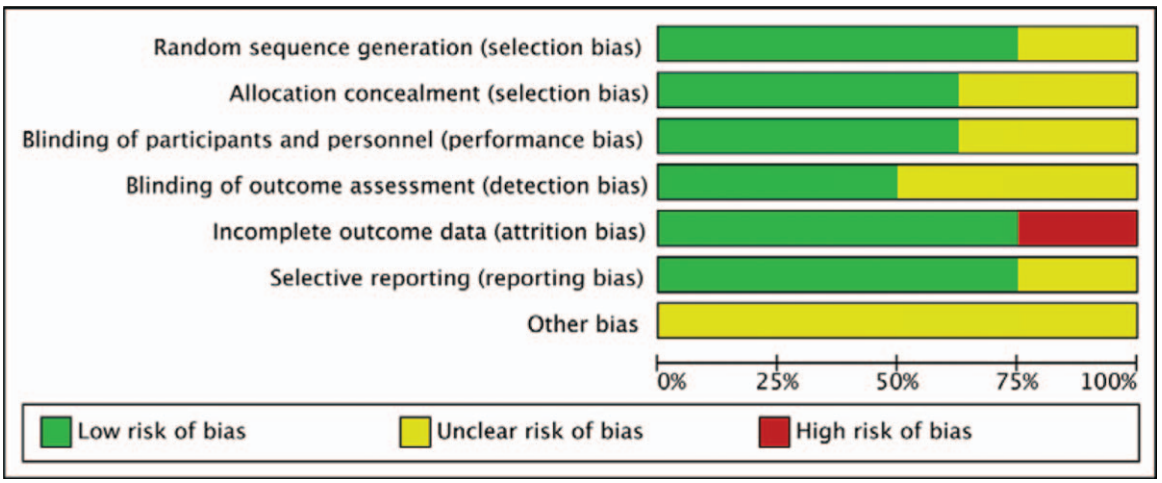

Figure 1. 30-day mortality.

was completed. Around 7 studies were conducted in multiple centers, and only 1 study was carried out at a single center. Whether participants and outcome assessors were marked to treatment allocation was specified in all studies. Risks of bias are shown in Figures 1 and 2. About 30-day mortality was evaluated in 4 trials (n = 1337) shown in Figure 3, 60-day mortality was reported in 3 trials (n = 1436) shown in Figure 4, and 180-day mortality was reported in 3 trials (n = 7935) shown in Figure 5. Dyspnea was reported in 3 trials (n = 1436) shown in Figure 6. Dosage of serelaxin ranged from 10 to 250 μg/kg per day, and the duration of interventions lasted from 20 to 48 hours. Compared with control group, results of the 30-day (OR, 0.66; 95% CI, 0.33–1.32), 60-day (OR, 0.64; 95% CI, 0.37–1.10) and 180-day mortality (OR, 0.75; 95% CI, 0.52–1.09) suggested that there was no significant difference. Compared with control group, there was no significant difference in dyspnea in serelaxin group (OR, 1.41; 95% CI, 1.00–1.98). The heterogeneity of 8 studies was assessed, with I^2 of 0% to 59%. No publication bias was found in all the analyses.

Serelaxin treatment is not related to either the long-term or short-term mortality, and cannot improve dyspnea in patients with heart failure. Meanwhile, serelaxin is well tolerated and safe in patients with AHF, and no serious drug-related adverse events have been reported yet. Nevertheless, further testing and approval is required for serelaxin.

4. Discussion

Compared with other heart failure treatments, serelaxin did not significantly decrease mortality, with no remarkable improvement in dyspnea. These data suggested that serelaxin, as a therapeutic strategy, did not improve the mortality of heart failure patients. AHF is a common reason for hospitalization or death, and it places a heavy economic burden on society.[15] The prevalence of AHF is difficult to assess, according to a recent statistic, there are about 1% to 12% AHF globally.[16] At present, no AHF therapy receives Level I and Class A recommendation from guidelines,[17,18] highlighting the lack of robust evidence from randomized studies. Unfortunately, the treatments of AHF have not make much progress in the last 4 decades.[19] Serelaxin has been proved to have beneficial clinical and hemodynamic effects without serious adverse effects in many randomized controlled trials.

Several RCTs on serelaxin treatment for AHF have been performed since 2017, after analyzed the short-term and long-

Figure 2. 60-day mortality.

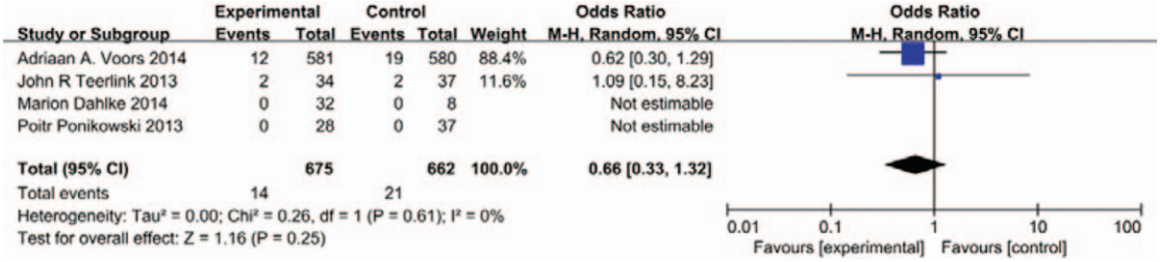

Figure 3. 180-day mortality.

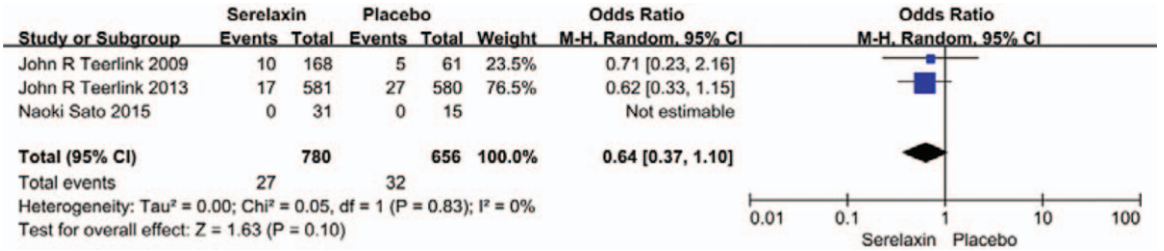

Figure 4. Dyspnea improvement.

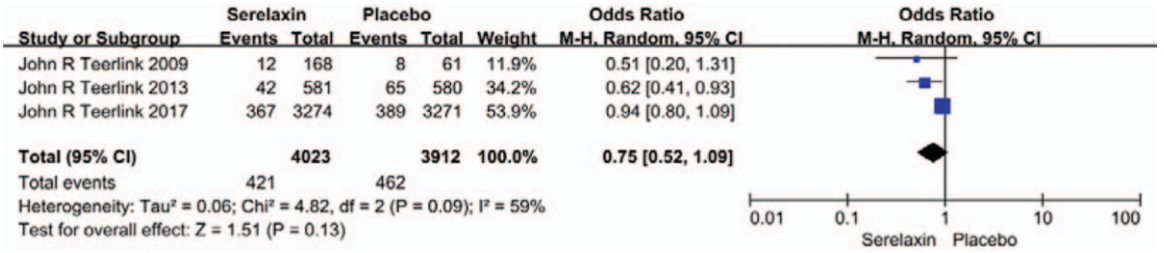

Figure 5. Risk of bias summary.

term follow-up results, we firstly revealed that there was no reduction in mortality of heart failure patients treated by serelaxin. Short-term, long-term mortality, and hospital readmission rates are major indicators to assess the therapeutic effects.[20] Unfortunately, our results indicated that serelaxin would not be considered as first-line therapy of AHF, for it failed to reduce the mortality of AHF. In conclusion, all the currently available RCTs of serelaxin treatment of AHF were included in our study, and our results revealed that serelaxin failed to reduce the mortality of patients with AHF.

There are also some limitations in this analysis. Firstly, the long-term durability of this treatment was unknown. Secondly, although most research was published in high-impact journals, there was still potential risk of bias, such as open-label design. Thirdly, safety, long-term durability, and side effects of serelaxin are still unclearly. Finally, there are still too less treatment efficacy

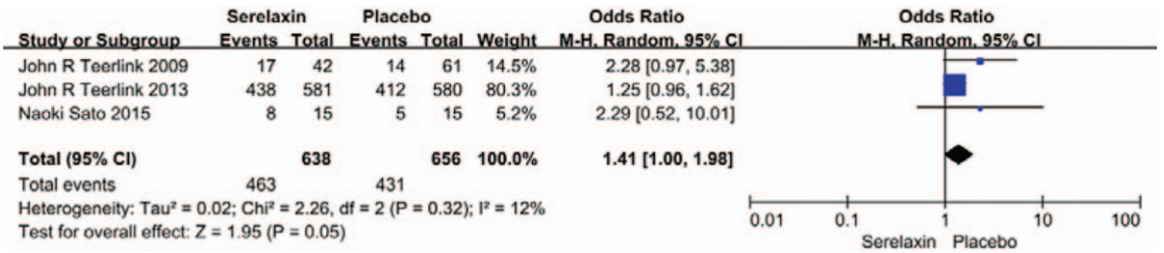

Figure 6. Risk of bias graph.

indicators, and more clinical indicators remain to be explored in the future.

Author contributions

Contributor ship statement: FZY, YBZ, LY, and LJC designed the study. LJC, JS, LY, and JS collected and analyzed the data, LJC wrote the manuscript with input from all authors, and YBZ and JS discussed the results and agreed the final vision. LY, LJC, JS, and YBZ supervised the project.

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