Systematic Review and Meta-Analysis

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The efficacy and safety of soluble guanylate cyclase stimulators in patients with heart failure

A systematic review and meta-analysis

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Abstract

Background: Several randomized controlled trials (RCTs) have been investigated the benefits of soluble guanylate cyclase (sGC) stimulators in the treatment of heart failure, but a comprehensive evaluation is lacking. We performed a meta-analysis to evaluate the efficacy and safety of oral sGC stimulators (vericiguat and riociguat) in patients with heart failure.

Methods: Studies were searched and screened in PubMed, Embase, and Cochrane Library. Eligible RCTs were included that reported mortality, the change of EuroQol Group 5-Dmensional Self-report Questionnaire (EQ-5D) US index, N-terminal pro-B-type natriuretic peptide (NT-proBNP), or serious adverse events (SAEs). Relative risk or weight mean difference (WMD) was estimated using fixed effect model or random effect model. Analysis of sensitivity and publication bias was conducted.

Results: Five trials with a total of 1200 patients were included. sGC stimulators had no impact on the mortality (1.25; 95% confidence interval 0.50–3.11) and significantly improved EQ-5D US index (0.04; 95% confidence interval 0.020–0.05). Furthermore, in comparison with control group, NT-proBNP was statistically decreased in riociguat group (−0.78; 95% confidence interval −1.01 to −0.47), but not in vericiguat group (0.04, 95% confidence interval −0.18 to 0.25). There were not obverse differences in SAEs between sGC stimulators and control groups (0.90; 95% confidence interval 0.72–1.12).

Conclusion: Our meta-analysis suggests that sGC stimulators could improve the quality of life in patients with heart failure with good tolerance and safety, but their long-term benefits need to be observed in the future. sGC stimulators are likely to be promising add-on strategies for the treatment of heart failure.

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitors, ARB = angiotensin II receptor blockers, C = control group, CCB = calcium channel blocker, cGMP = cyclic guanosine monophosphate, CI = confidence interval, DILATE = acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure, DM = diabetic mellitus, eGFR = estimated glomerular filtration rate, EQ-5D = EuroQol Group 5-Dmensional Self-report Questionnaire, HF = heart failure, HFpEF = HF with preserved ejection fraction, HFrEF = HF with reduced ejection fraction, LVEF = left ventricular ejection fraction, MRA = mineralocorticoid receptor antagonist, NA = not available, NO = nitric oxide, NT-proBNP = N-terminal pro-B-type natriuretic peptide, NYHA = New York Heart Association, PAH-CHD = The patients with persistent/recurrent pulmonary arterial hypertension after correction of congenital heart disease, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCTs = randomized controlled trials, RR = relative risk, SAEs = serious adverse events, SD = standard deviation, sGC = soluble guanylate cyclase, SOCRATES-PRESERVED = soluble guanylate cyclase stimulator in heart failure patients with preserved ejection fraction, SOCRATES-REDUCED = soluble guanylate cyclase stimulator in heart failure patients with reduced ejection fraction, T = treatment group, WMD = weight mean difference.

Keywords: heart failure, riociguat, soluble guanylate cyclase stimulators, vericiguat

1. Introduction

Heart failure (HF) is a severe syndrome that increases the rate of mortality and hospital readmission.[1] Although traditional pharmacologic interventions are applied to postpone the phase and improve clinical symptoms of HF, some patients still have poor quality of life as well as even worse prognosis. Novel pharmacologic therapies are particularly important in the setting of worsening chronic heart failure. The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway plays an important role in cardiovascular diseases, including vessels constriction, tissue fibrosis, oxidative stress, and inflammation.[2–4] Thus, targeting this signaling pathway can be a favorable approach for the treatment of HF.

The novel sGC stimulators have potential benefits for normal cardiac and vascular function through binding to the heme-containing sGC and triggering cGMP production, enhancing the affinity of sGC at even very low levels of NO.[5,6] It has been proved that sGC stimulators can be used in the treatment of pulmonary arterial hypertension by decreasing pulmonary pressures and improving hemodynamics.[7,8] Some theoretical evidences also support the usage of sGC stimulators, improved ventricular function, and cardiac index were observed in patients

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with HF.[9,10] Thereinto, 2 mainly types of oral selective sGC simulators, vericiguat and riociguat, are being explored their effects on HF. They can stimulate sGC directly that are independent from NO, and enhance the effect of NO in low-endogenous NO, and low-NO environments to increase cGMP synthesis.[11,12] The elevation of cGMP has been associated with vasodilatation, anti-fibrotic, and anti-inflammatory effects. In previous clinical studies, riociguat was used for the treatment of HF and pulmonary arterial hypertension, vericiguat was mainly applied to HF therapy due to structural and pharmacologic distinction. However, reported results are controversial because of sample heterogeneity or limitation, a comprehensive overview of sGC stimulators is necessary to evaluate their function. Hence that the purpose of this meta-analysis is to evaluate the effects of sGC stimulators on the change of mortality, quality of life, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and serious adverse events (SAEs) in patients with HF.

2. Methods

We collected randomized controlled studies (RCTs) of oral sGC stimulators (vericiguat and riociguat) in patients with HF, and performed a meta-analysis in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[13]

2.1. Data sources

Data were obtained through searching PubMed, Embase, and Cochrane library until February 28, 2018 by 2 trained authors. Research strategy consisted of the following MeSH headings or keywords "soluble guanlate stimulators," "riociguat," "vericiguat," and "heart failure" with publication types restricted to RCT. Searches are based on English language only.

2.2. Study selection

Titles and abstracts were independently assessed, and obviously irrelevant studies were excluded by 2 reviewers. The remaining studies were further evaluated through full-text achievement. Inclusion criteria were: RCTs; adult patients (years >18) with HF; oral sGC stimulators (riociguat or vericiguat); placebo; the primary outcomes contained mortality and quality of life, the secondary outcomes contained SAEs and NT-proBNP. We excluded studies which did not meet the aforementioned criteria from analysis. Ethical approval was not necessary because this was a systematic review and meta-analysis.

2.3. Data extraction and quality assessment

Data were extracted from the included trials by 2 authors independently: basic characteristics of studies (authors, published year, journal, and study design), characteristics of study subjects (average age, sex, comorbidities), intervention and control treatments, New York Heart Association class, left ventricular ejection fraction, follow-up time, severe adverse events, mortality, and clinical outcomes after intervention. To avoid repetitive studies, we would carefully identify when studies had the same first author. If articles derived from the same study, we chose the most complete data to analyze. Disputes between 2 authors were resolved by discussion. Quality assessment of all RCTs contained: allocation concealment, random sequence generation, blinding (defined as single-blind or double-blind, the method of blinding, blinding of participants and outcomes), missing data, the risk of reporting bias, and other biases.[14]

2.4. Statistical analysis

All the data analyses were performed in Review Manager version 5 (The Nordic Cochran Centre, Copenhagen, Denmark) and STATA version 14.0 (Stata Corp, College Station, TX). Chi-squared test and I^2 test were used to examine the heterogeneity of included studies ($P \leq .10$ and $I^2 > 50\%$ indicating significant heterogeneity, respectively). The outcome of SAEs and mortality were calculated by the relative risk (RR) and 95% confidence interval (CI) in a fixed effect model, and the mean change of the quality of life and NT-proBNP from baseline were calculated by the WMD with 95% CI using a random effect model due to high heterogeneity. Potential publication bias was analyzed in Egger test. In addition, sensitivity analyses were performed to assess the stability of results, and a 2-tailed P-value $< .05$ was considered significant.

3. Results

A total of 613 studies were obtained from database search. After excluding duplicates, 5 RCTs fulfilled our inclusion criteria finally, which were published from 2013 to 2017.[15–19] Full text publications and supplemental materials were obtained online. The process of literature search and reasons for exclusion are described in Figure 1. On the whole, the RCTs in our meta-analysis had relatively high quality.

3.1. Characteristics of included trials

A total of 1200 patients from 5 RCTs are summarized in Table 1. The mean age of the patients ranged from 37 to 75 years and mean follow-up duration of 30 days to 16 weeks and compared with placebo. Included participants suffered from HF with preserved ejection fraction (HFpEF, EF > 40%) or reduced ejection fraction (HFrEF, EF < 40%). The dose ranged from 1.25 to 10 mg/d for vericiguat, 0.5 to 2 mg 3 times/d for riociguat. Furthermore, the baseline demographic and medication characteristics are summarized in Table 2. Part of patients had complications, such as atrial fibrillation, diabetes mellitus, and poor renal function. All patients received conventional anti-HF therapies such as diuretics, angiotensin- converting-enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), b-blockers, calcium channel blocker (CCB), and mineralocorticoid receptor antagonist (MRA). The risk of bias of 5 included RCTs was assessed with Cochrane risk of bias tool, most of items indicated low risk (Fig. 2). However, there was insufficient information about some items to permit a definite judgment.

3.2. Efficacy and safety outcomes

Included RCTs reported the effect of sGC stimulators in patients with HF. There was no difference on mortality between sGC stimulators and placebo groups (1.25, 95% CI = 0.50–3.11, $P = .63$) (Fig. 3), without significant heterogeneity ($I^2 = 0.0\%$, $P = .64$). Health-related quality of life was assessed by using EuroQol Group 5-Dmensional Self-report Questionnaire (EQ-5D) US index scores in 3 studies. Therein, as a subgroup research, 1 study assessed the health status of patients who enrolled in the SOCRATES-PRESERVED trial.[20] According to the pooled results of trials that based on the fixed effect model, the sGC

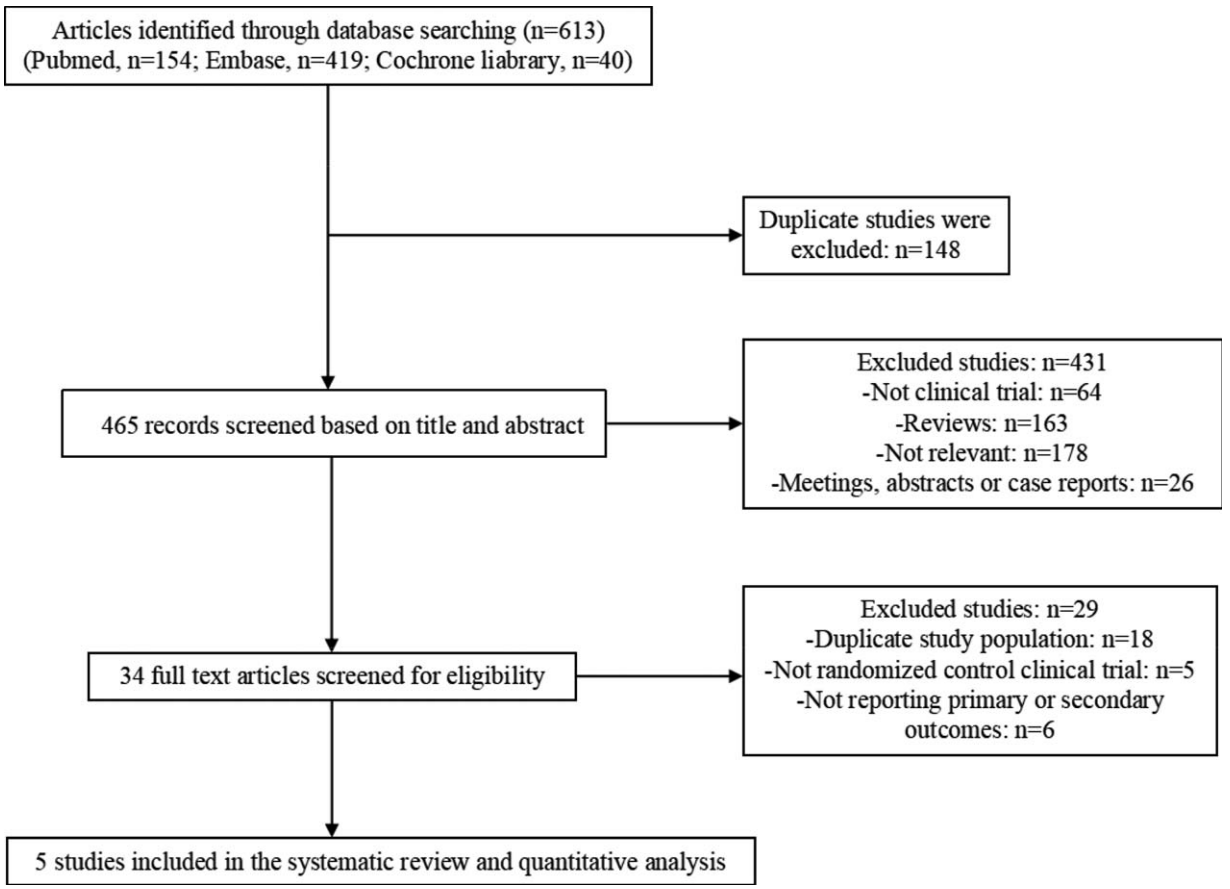

Figure 1. Trial flow chart of search strategy and included criterion.

Table 1

Baseline characteristics of the studies included in meta-analysis.

References	Study design	Year	Sample size (n) (C/T)	Interventions (oral sGC stimulators vs. placebo)	NYHA class	LVEF (%) in T group (mean ± SD)	Mean follow-up	Endpoints of meta-analysis
Pieske (SOCRATES-PRESERVED)[13]	RCT	2017	93/384	Vericiguat 1.25, 2.5, 5, or 10 mg vs placebo	2–4	56.8 ± 6.25	12 wk	Mortality, SAE, EQ-5D Index Score, NT-proBNP
Gheorghiade (SOCRATES-REDUCED)[14]	RCT	2015	92/364	Vericiguat 1.25, 2.5, 5, or 10 mg vs placebo	2–4	29.9 ± 8.5	16 wk	Mortality, SAE, NT-proBNP
Bonderman (phase IIb)[17]	RCT	2014	11/25	Riociguat 0.5, 1, or 2 mg vs placebo	NA	NA	6 h, 30 d	Mortality, SAE
Bonderman (DILATE-1)[15]	RCT	2013	69/132	Riociguat 0.5, 1, or 2 mg vs placebo	2–4	28.2 ± 1.0	16 wk	Mortality, SAE, EQ-5D Index Score, NT-proBNP
Rosenkranz (PAH-CHD)[16]	RCT	2015	7/23	Riociguat 1.5 or 2.5 mg vs placebo	2–4	NA	12 wk	Mortality, SAE, EQ-5D Index Score, NT-proBNP

C = control group, DILATE = acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure, EQ-5D = EuroQol Group 5-Dmensional Self-report Questionnaire, LVEF = left ventricular ejection fraction, NA = not available, NYHA = New York Heart Association, PAH-CHD = the patients with persistent/recurrent pulmonary arterial hypertension after correction of congenital heart disease, SAE = serious adverse events, SD = standard deviation, SOCRATES-PRESERVED = soluble guanylate cyclase stimulator in heart failure patients with preserved ejection fraction, SOCRATES-REDUCED = soluble guanylate cyclase stimulator in heart failure patients with reduced ejection fraction, T = treatment group.

Table 2

Characteristics of patients in the included trials.

References	Mean age (y) (T/C)	Males (n%) (T/C)	Atrial fibrillation (n%) (T/C)	DM (n%) (T/C)	eGFR (mean ± SD) (T/C)	Diuretics (n%) (T/C)	ACEI (n%) (T/C)	ARB (n%) (T/C)	β-Blocker (n%) (T/C)	CCB (n%) (T/C)	MRA (n%) (T/C)
Pieske (SOCRATE-PRESERVED)[13]	74 ± 9.1/73 ± 9.8	50.5/51.8	37.6/40.4	50.5/48.2	52.3 ± 20.6/55.6 ± 20.0	91.4/92.2	43.0/39.3	34.4/33.9	81.7/79.2	32.3/36.7	41.9/36.2
Gheorghiade (SOCRATES-REDUCED)[14]	67 ± 13/68 ± 12	79.3/80.5	32.6/34.1	44.6/48.9	57.8 ± 17.4/58.8 ± 20.0	93.5/94.5	56.5/62.6	22.8/22.8	90.2/90.1	NA	54.3/64.3
Bonderman (Phase IIb)[17]	75 ± 16/70 ± 20	45/36	55/40	45/44	NA	NA	27/56	45/32	91/76	55/40	NA
Bonderman (DILATE-1)[15]	59 ± 40/58 ± 35	88/84	15/11	49/40	68.7 ± 2.4/70 ± 4.7	NA	67/73	28/29	46/52	NA	NA
Rosenkranz (PAH-CHD)[16]	40 ± 16/37 ± 15	17/17	NA	NA	NA	NA	NA	NA	NA	NA	NA

ACEI = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker, C = control group, CCB = calcium channel blocker, DM = diabetic mellitus, eGFR = estimated glomerular filtration rate (mL/min/1.73 m^2), MRA = mineralocorticoid receptor antagonist, NA = not available, T = treatment group.

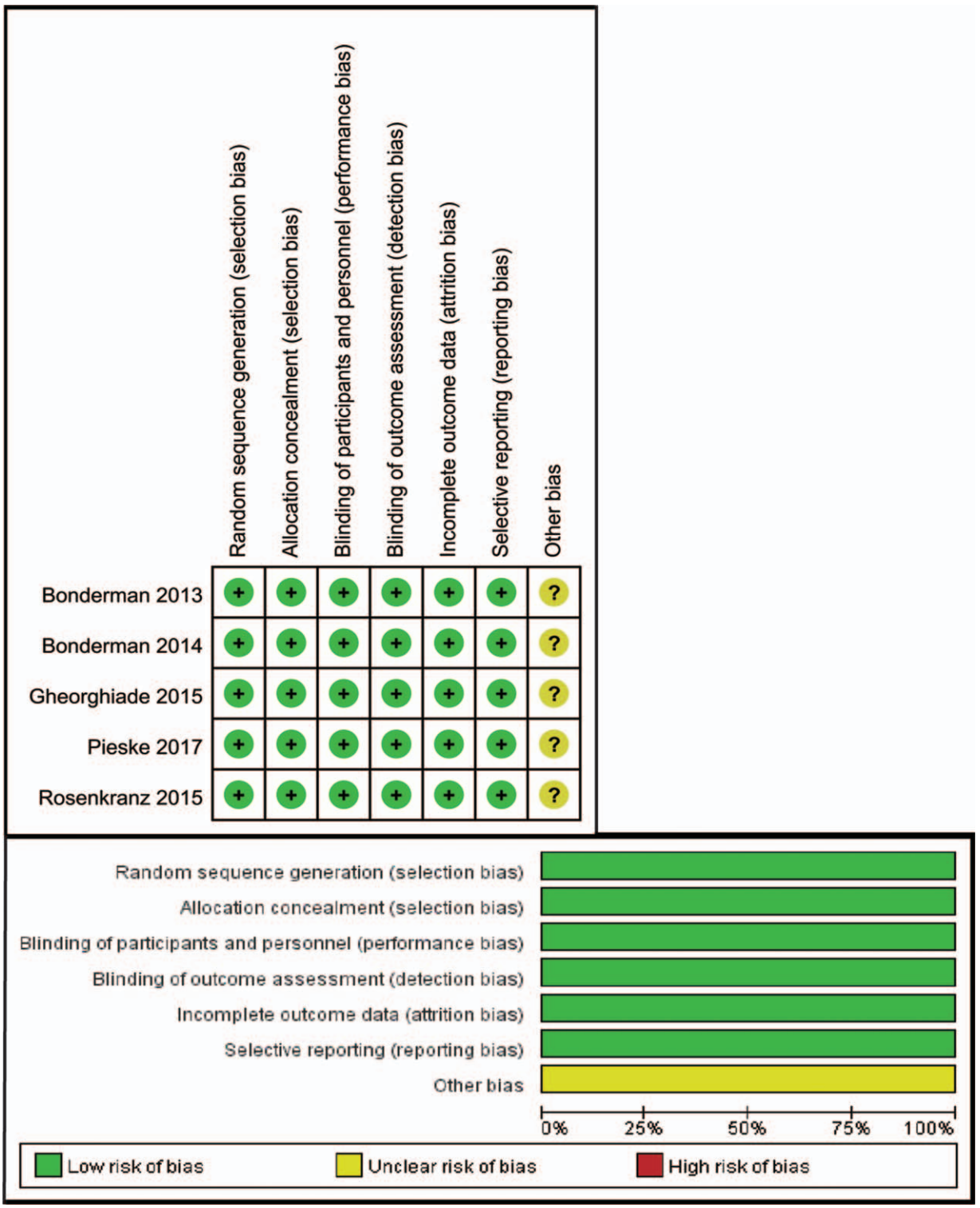

Figure 2. Quality assessment of included randomized controlled trials.

stimulators significantly improved the quality of life in patients with HF (0.04, 95% CI = 0.02–0.05, $P < .001$) (Fig. 4). There was not significant heterogeneity in the 3 studies ($I^2 = 11\%$, $P = .33$).

Four studies investigated the effect of sGC stimulators on the change of NT-proBNP from baseline. Considered the values transformation was really complexed and could affect accuracy, so we analyzed this value in 2 studies separately. Log (NT-proBNP) was used in vericiguat group, which supported that vericiguat did not statistically reduce the values of log (NT-proBNP) as compared with placebo (0.04, 95% CI = −0.18 to 0.25, $P = .74$) (Fig. 5), without significant heterogeneity ($I^2 = 24.1\%$, $P = .25$). However, the totally reverse results were

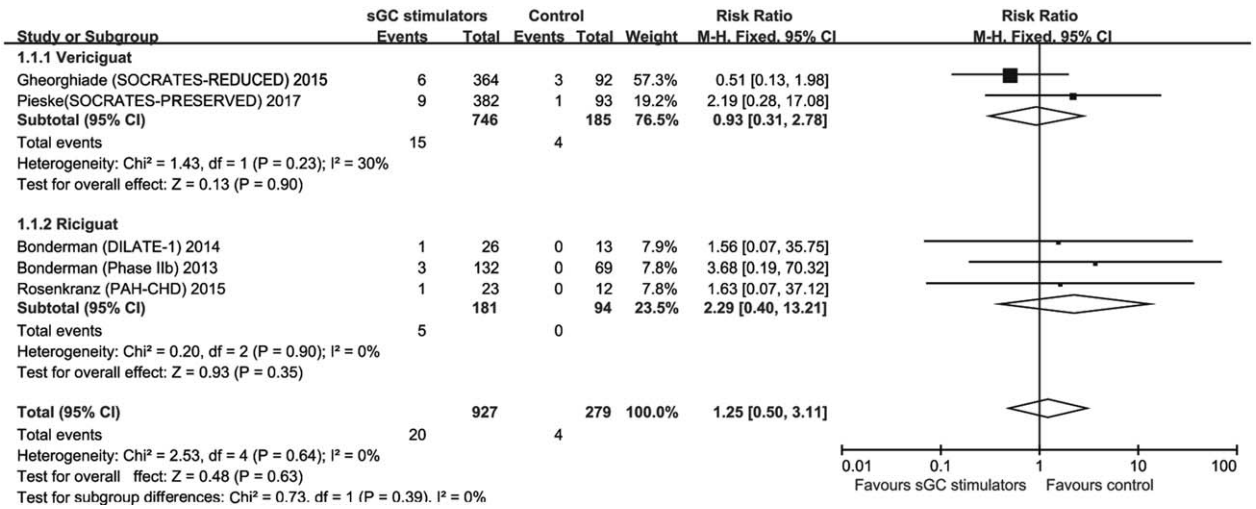

Figure 3. Meta-analysis of the effect of soluble guanylate cyclase stimulators on the mortality in patients with heart failure. CI = confidence interval, SOCRATES-PRESERVED = soluble guanylate cyclase stimulator in heart failure patients with preserved ejection fraction, SOCRATES-REDUCED = soluble guanylate cyclase stimulator in heart failure patients with reduced ejection fraction.

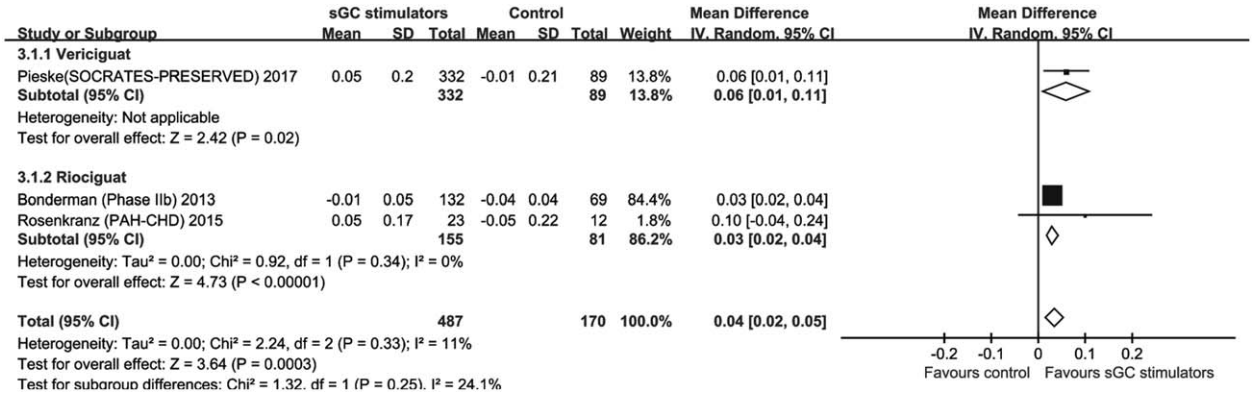

Figure 4. Meta-analysis of the effect of soluble guanylate cyclase stimulators on the change of EuroQol Group 5-Dmensional Self-report Questionnaire US index in patients with heart failure. CI = confidence interval, SOCRATES-PRESERVED = soluble guanylate cyclase stimulator in heart failure patients with preserved ejection fraction, SOCRATES-REDUCED = soluble guanylate cyclase stimulator in heart failure patients with reduced ejection fraction.

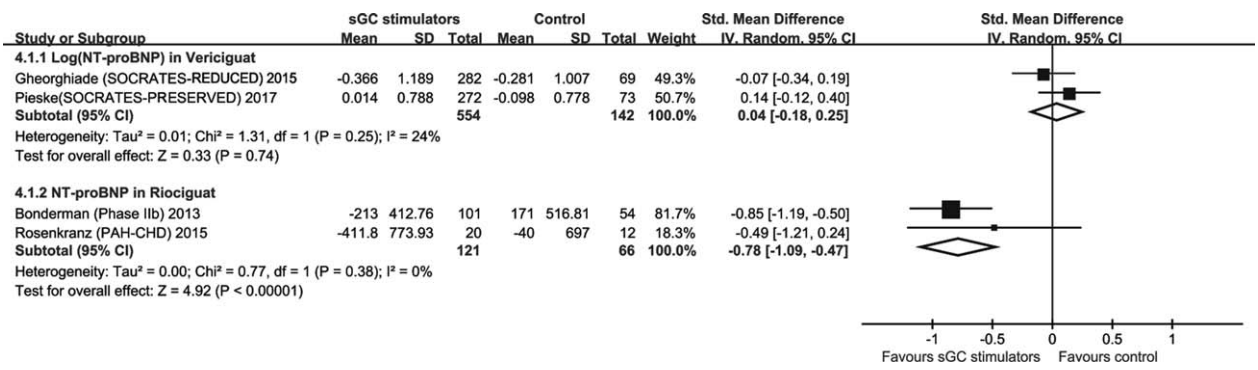

Figure 5. Meta-analysis of the effect of soluble guanylate cyclase stimulators on the change of log (NT-proBNP) and NT-proBNP in patients with heart failure. CI = confidence interval, SOCRATES-PRESERVED = soluble guanylate cyclase stimulator in heart failure patients with preserved ejection fraction, SOCRATES-REDUCED = soluble guanylate cyclase stimulator in heart failure patients with reduced ejection fraction.

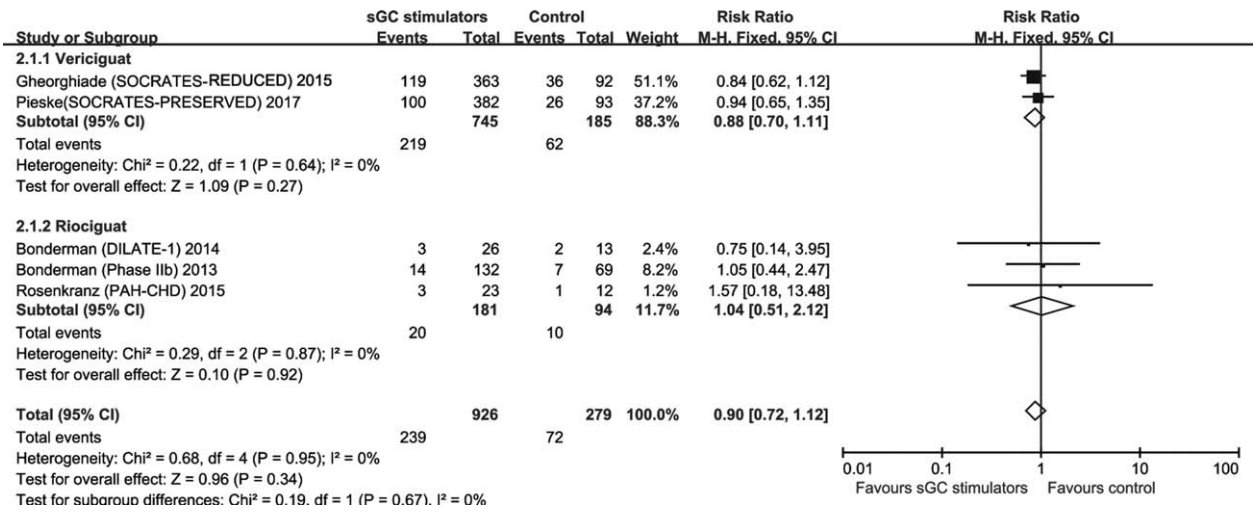

Figure 6. Meta-analysis of the effect of soluble guanylate cyclase stimulators on the serious adverse events (SAEs) in patients with heart failure. CI = confidence interval, SOCRATES-PRESERVED = soluble guanylate cyclase stimulator in heart failure patients with preserved ejection fraction, SOCRATES-REDUCED = soluble guanylate cyclase stimulator in heart failure patients with reduced ejection fraction.

achieved in the riociguat therapy with drastically reduced values of NT-proBNP (−0.78; 95% CI=−1.01 to −0.47; $P<.01$) (Fig. 5). No heterogeneity was found ($I^2=0.0\%$, $P=.38$).

Drug-related SAEs were reported after sGC stimulators therapy in all the studies, which mainly contained ventricular tachycardia, syncope, hypotension, and pulmonary hemorrhage. The pooled data did not show a difference in SAEs between sGC stimulators and placebo group (0.90, 95% CI=0.72– 1.12, $P=.34$) (Fig. 6), and no significant heterogeneity ($I^2=0.0\%$, $P=.953$). Based on the fixed effect model, 2 studies dealt with patients using vericiguate showed RR of 0.88 (95% CI=0.70–1.11, $P=.27$) without evidence of heterogeneity ($I^2=0.0\%$, $P=.64$). While other 3 studies analyzed the effects of riociguat that suggested a RR of 1.04 (95% CI=0.51–2.12, $P=.92$) without obvious heterogeneity ($I^2=0.0\%$, $P=.87$).

3.3. Publication bias and sensitivity analysis

Funnel plots and Egger test were implemented to evaluate the potential publication bias of mortality and SAE (Fig. 7A and B). We did not observe publication bias in the assessment ($P=.250$ and $P=.171$). Meanwhile, the publication bias for the change of EQ-5D US index score and NT-proBNP were not tested because of the insufficient studies. Sensitivity analyses were also used to test the stability of our estimates (Fig. 8A and B), there were no significant modification after excluding each study one by one.

4. Discussion

We achieved some important findings in this meta-analysis. First, sGC stimulators had no beneficial or detrimental effects on mortality. Second, sGC stimulators would improve quality of life in the patients with HF. Third, 2 kinds of sGC stimulators have different effects on the level of plasma NT-proBNP. There was remarkably reduction of NT-proBNP in the treatment of riociguat but not in vericiguat group. Fourth, sGC stimulators appeared well tolerant without an excess in drug-related SAEs as compared with placebo.

Cytosolic sGC-derived cGMP production regulates vascular rhythm and myocardium contractility in vascular smooth muscle

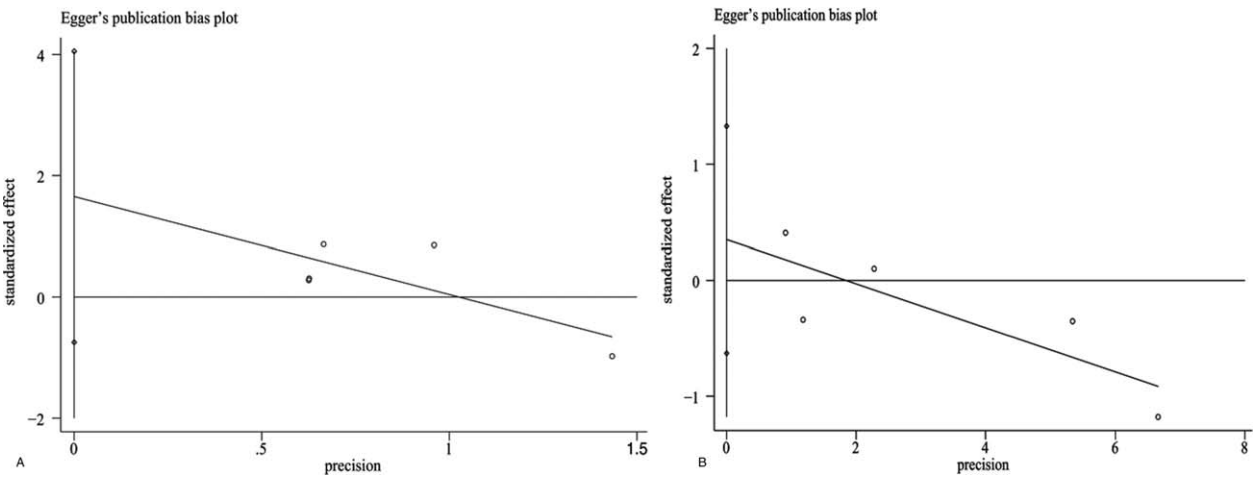

Figure 7. The funnel plot for publication bias about the mortality (A) and serious adverse events (B).

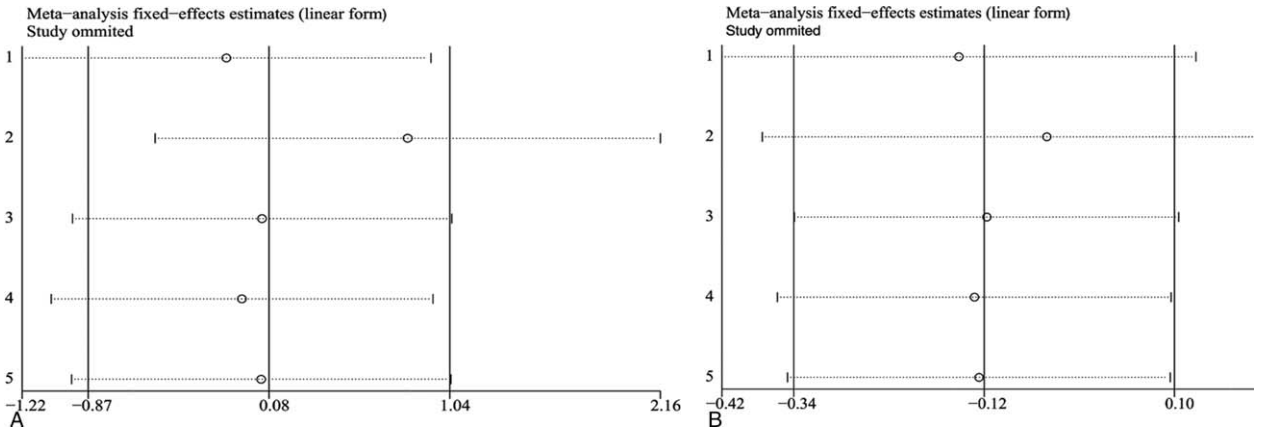

Figure 8. The sensitivity analyses for the mortality (A) and serious adverse event (B).

cells and cardiac myocytes.[21–23] The NO-sGC-cGMP signaling pathway represents a therapeutic target in HF.[24] In our meta-analysis, both sGC stimulators had no significant impact on the mortality in HF patients, which were well tolerated and did not worsen the prognosis of HF. Meanwhile, higher EQ-5D US index scores were achieved after using of vericigaut and riociguat, which reflected the improved health of patients with HF.[25,26] Moreover, SOCRATES-PRESERVED trial reported higher doses of vericigaut (5 and 10 mg) mainly played the import role in increasing scores. But dose-dependent effects are not observed in the treatment of riociguat. Because we merged all different doses of vericiguat and riociguat to analyze, which avoided the effects of different doses on some degree. On the whole, sGC stimulators should be favorable for improving overall health status of patients.

It has been demonstrated that the mean level of plasma NT-proBNP is a major biomarker, which will be higher in patients with HF.[27,28] Moreover, higher level of NT-proBNP is a critical marker of deteriorative HF that may be associated with poor prognosis.[29,30] The pooled data of veriguat treatment showed no significant different in NT-proBNP reduction compared with placebo in SOCRATES-PRESERVED study.[20] However, a reduction has been observed with high dose of vericiguat in SOCRATES-REDUCED.[16] Although gathered data suggested that vericiguat did not have significant effect on the change of NT-proBNP level, the influence about different types of patients with HF should be considered. Dose-response relationship and insufficient treatment duration could be considered. Furthermore, the fact that NT-proBNP decreased dramatically in the treatment of riociguat at the similar treatment duration. We analyzed NT-porBNP in 2 sGC stimulators therapy separately to avoid complicated value transformation, the difference between vericiguat and riociguat may be explained by different protocol and the characteristics of patients at baseline. Additionally, more studies are needed to explore the potential mechanism of 2 kinds of sGC stimulators in patients with HF.

It is important to recognize that several drug-related SAEs were reported in the included studies, no significant statistical differences between sGC stimulators group and placebo group. However, the number of SAEs in the treatment of vericiguat seemed to be more than riociguat group and placebo group. This is a meaningful finding that should be explored in larger sample size, and longer follow-up as well as additional prognostic endpoints would be implemented to understand the exact mechanisms.

This study has many strengths. All included studies are high-quality, randomized, and controlled trials, which by design prevent the influence of both known and unknown confounding factors. The results detect the difference and disclose the positive function of sGC stimulators, providing reliable references for subsequent researchers. However, some limitations of this meta-analysis should not be neglected. The dose–response relationship within 2 subtypes of sGC stimulators were not analyzed due to insufficient sample size and short treatment duration, which may cause bias to some degree. Meanwhile, the subtypes of patients with HF were also not distinguished completely, limited data cannot be gathered because of unpublished ongoing studies.[31,32] Outcome data were incomplete for most trials, such as blood pressure, cardiac index, and ejection fraction. Additionally, the lack of effective method to implement value transformation may lead to overestimation or underestimation of the effect size. Finally, inherent limitations due to the pooling data from different control groups, follow-up time, and dosage of medicines, which might influence accuracy of the results. Consequently, more relative data and long-term benefits should be observed in the future.

5. Conclusion

In conclusion, these findings from our study suggest that oral sGC stimulators vericiguat and riociguat elicit benefits on health-related quality of life in patients with HF, with good tolerance and safety. But they may not bring long-term benefits. As novel anti-HF medicines, sGC stimulators can be add-on therapies for the management of patients with HF.

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Writing – review & editing: Jing Huang.

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