

# sGC Stimulators for Heart Failure: A Meta-Analysis of Randomized Controlled Trials

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## Research Article

**Keywords:** Heart failure, sGC stimulators, Vericiguat, Riociguat

**Posted Date:** December 9th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-116054/v1>

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Original Research

## **sGC Stimulators for Heart Failure: A Meta-Analysis of Randomized Controlled Trials**

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## **Abstract**

### **Background**

Oral sGC stimulators are novel treatments for heart failure (HF). Since individual studies are limited to confirm the efficacy and safety of sGC stimulators in patients with HF, we provide a meta-analysis based on published clinical randomized controlled trials.

### **Methods**

Embase, PubMed, Cochrane and Medline were applied to search for randomized controlled trials (published before March 29, 2020 without language restrictions) by comparing oral sGC stimulators to placebos. Main endpoints were efficacy outcomes, including all-cause mortality, incidence of cardiovascular-events related death or hospitalization, alterations of EQ-5D index, and N-terminal (NT)-pro hormone BNP(NT-proBNP); and safety outcomes included incidence of serious adverse events (SAEs), symptomatic hypotension and syncope.

### **Results**

Six trials were enrolled (N=6255 participants), sGC stimulators yielded a lower incidence of cardiovascular-events related death or hospitalization (OR=0.88, 95% CI=0.79 to 0.98), an improvement in EQ-5D scores (SMD=0.44, 95% CI=0.24 to 0.63), and a lower relative risk of SAEs (OR=0.90, 95% CI=0.81 to 1.00) compared with placebos. Furthermore, NT-proBNP was decreased by riociguat (SMD=-0.79, 95% CI=-1.10 to -0.49), but not by vericiguat (SMD=0.04, 95% CI=-0.18 to 0.25). There was no significant difference in all-cause mortality (OR=0.95, 95% CI=0.83 to 1.09), incidence of symptomatic hypotension (OR=1.15, 95% CI=0.95 to 1.40) and syncope (OR=1.15, 95% CI=0.87 to 1.53) between sGC stimulators and placebos.

## **Conclusion**

Oral sGC stimulators may be beneficial for HF with a good tolerance, further studies are also needed to establish the optimal approach in clinical practice.

## **Keywords**

Heart failure; sGC stimulators; Vericiguat; Riociguat

## **1. Background**

Heart failure (HF) is a progressive, multi-factorial, and heterogeneous syndrome. Currently, medicine strategies in patients with HF are mainly aimed at renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) pathway, and angiotensin converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs),  $\beta$ -receptor blockers and aldosterone antagonists have become the "Golden Triangle" recommended by guidelines. The SOLVD(1)、CIBIS-II(2)、RALES(3) and CHARM-Alternative(4) study showed, even under the intervention of guidelines-recommended drug strategies, the residual risk of cardiovascular death of patients still ranged from 9% to 31%.

Despite signs and symptoms can be improved rapidly with a standard therapy, in the real-world setting, 1 in 6 patients with HFrEF develop worsening HF within 18 months after diagnosed with HF, these patients have a high risk which 2-year mortality was 22.5%, and 56% of these patients were re-hospitalized within 30 days of the worsening HF event(5). Recent 15 years, the morbidity has increased for 44% in China, meanwhile, the overall prognosis of patients with HF is not ideal, the in-hospital mortality was up to 4.1%(6), and the rate of all-cause re-admission within one year is 69%(7).

Despite therapeutic advances, a high unmet medical need still exists in the treatment of HF. In the PARADIGM-HF trial(8), approximately 21.8% of patients who received LCZ696 (a angiotensin–neprilysin Inhibitor (ARNI)) based on the conventional treatment of heart failure, occurred cardiovascular-events related death or hospitalization, in the 27 months of median follow-up duration. In the DAPA-HF trial(9), dapagliflozin (an inhibitor of sodium–glucose cotransporter 2 (SGLT2)) showed great benefit for patients with HFrEF. However, in the dapagliflozin group, about 16.3% of patients occurred worsening heart failure or death from cardiovascular causes, showing great risk of cardiovascular-events related death or hospitalization.

With an increasing burden of HF due to an aging population, there is a tremendous medical need for new effective strategies. Besides relief of short-term symptoms in both HFrEF and HFpEF, novel drugs are required to provide a benefit for mid- and long-term morbidity and mortality, and an improvement in health-related quality of life (HRQoL). Therefore, more experts declare optimize the use of energy of cardiomyocytes may be the target of future research on the therapeutic strategies of HF.

There were several published trials of sGC stimulators for patients with HF, however, since individual studies have limitations to provide a sufficient support to guide the clinical practice, a meta-analysis of randomized controlled trials was established to objectively evaluate effects of this novel medicine the sGC stimulators in patients with HF.

## **2. Methods**

### **2.1 Searching strategies and selection criteria**

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement(10). Selected studies were published before March 29, 2020 by application of Embase, PubMed, CENTRAL (Cochrane Central of Controlled Trials), and Medline. A manual

search was adopted as well. The searching was performed without any language restrictions. The combined text and MeSH terms were used during the searching as followings, “vericiguat” “riociguat” “soluble guanylate cyclase stimulator” and “heart failure”. The complete search term used for PubMed was: (((((((soluble guanylate cyclase stimulator) OR vericiguat) OR BAY 1021189) OR riociguat) OR BAY 63-2521)) AND (“Heart Failure”[Mesh]) OR (((Cardiac Failure) OR Heart Decompensation) OR Myocardial Failure) OR Congestive Heart Failure)))) AND (((randomized controlled trial) OR controlled clinical trial) OR randomized) OR randomly) OR trial). All potentially eligible studies were selected for reviewing irrespective of primary outcomes or languages.

## **2.2 Study selection and data extraction**

Studies were regarded as eligible for enrollment if they were randomized controlled clinical trials performed in adult patients (age over 18 years old) with HF, comparing oral sGC stimulators (riociguat or vericiguat) to placebos, and reporting the number of all-cause death , cardiovascular-events related death or hospitalization, and adverse events, in addition with alterations of NT-proBNP and HRQoL at the end of the interventions. Studies were excluded if not qualified with the aforementioned criteria. Ethical approval was not adopted since this was a systematic review and meta-analysis.

Oral sGC stimulators were compared to any other therapeutic treatments for HF, without restrictions on treatment histories. The evaluated outcomes were as followings: the number of all-cause mortality, cardiovascular events-related death or hospitalization, alterations of EuroQol group 5-dimensional self-report questionnaire (EQ-5D) US index between the baseline and the end of interventions, incidence of serious adverse events at the end of interventions, proportion of participants with symptomatic hypotension or syncope, and changes of NT-proBNP between the baseline and the end of interventions.

### **2.3 Data extraction and assessment**

Titles and abstracts from different studies were reviewed by two independent investigators. Studies qualified for inclusion criteria were retrieved and reviewed for full-text. Trials selected for detailed analysis and data extraction were analyzed by two independent investigators, disagreements were evaluated and resolved by a third investigator.

The following data were extracted from selected studies, basic characteristics of studies (author, published year, sample size, intervention treatment, and mean follow-up duration), features of included patients (average age, gender, body mass index, estimated glomerular filtration rate, NT-proBNP, New York Heart Association (NYHA) classification, left ventricular ejection fraction, comorbidities and background treatment), adverse events, mortality and clinical outcomes after interventions. Two independent reviewers were required to assess the risk for bias according to the PRISMA recommendations, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. The certainty of the evidence was assessed by GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

### **2.4 Statistical analysis**

The efficacy of sGC stimulator for HF was assessed based on four parameters, they are all-cause mortality, incidence of cardiovascular-events related death or hospitalization, changes of EQ-5D US index, and changes of NT-proBNP between the baseline and the end of interventions. The safety of sGC stimulators was estimated for patients with HF based on three indicators, including incidence of serious adverse events, proportions of participants with symptomatic hypotension or syncope at the end of interventions.

NT-proBNP and EQ-5D US index were regarded as continuous variables and reported absolute differences between arithmetic means before and after interventions. Pooled estimates of standardized mean differences of NT-proBNP or log (NT-proBNP) were calculated between intervention groups by using a random-effects model to adequately account for additional uncertainties associated with inter-study variabilities of different sGC stimulators. Meanwhile, pooled estimates of the mean differences in EQ-5D US index were calculated between intervention groups by using a fixed-effects model. For analysis of all-cause mortality, incidence of cardiovascular-event related deaths or hospitalization, proportions of participants with SAEs, symptomatic hypotension and syncope, they were calculated with overall odds ratios (OR) and 95% confidence intervals (CI). For categorical outcomes, pooled estimates were applied by calculating with odds ratios with a fixed-effects model.

A pre-planned sensitivity analysis was performed before the formal meta-analysis of all-cause mortality, incidence of SAEs, and cardiovascular-event related death or hospitalization. This comparison was an important clinical question about the role of sGC stimulators in treatment for HF.

The possibility of publication biases of all-cause mortality, incidence of SAEs, and cardiovascular-events related death or hospitalization were also assessed by means of Egger test, and p value < 0.1 was defined as a significant publication bias. Cochran Q test was performed to assess heterogeneity between studies, p value < 0.1 was defined as a significant heterogeneity. I<sup>2</sup> test was adopted to assess the magnitude of the heterogeneity between studies, values greater than 50% were considered to be moderate-to-high heterogeneity. Stata (version 14.0) was applied for all statistical analysis.

### **3. Results**

### 3.1. Characteristics of included trials

Three hundred and sixty-four studies were identified from databases and manual search after excluding duplicated studies. Finally, six trials published between 2013 to 2020 including 6255 participants were adopted in our analysis(11-16). The detailed process of literature searching and explanations for exclusion were described in figure 1.

Characteristics included in randomized controlled clinical trials, like demographic information and background medications were summarized in figure 2. The mean ages of the patients ranged from 37 to 75 years, and the mean follow-up durations ranged from 30 days to 10.8 months compared with placebos. The baseline characteristics were well matched in sGC stimulators and placebos. The mean body mass index ranged from 22.0 to 31.1 kg/m<sup>2</sup>, the mean eGFR ranged from 52.3 to 68.7 L/min/1.73m<sup>2</sup>, and the mean NT-proBNP ranged from 975 to 4043 pg/ml. All NYHA classifications were equal to or above level II. Included participants were patients with HFpEF (HF with preserved ejection fraction, LVEF is higher than 40%) or HFrEF (HF with reduced ejection fraction, LVEF is lower than 40%). The dose of oral sGC stimulator ranged from 1.25 to 10.0 mg once daily for vericiguat, and 0.5 to 2.0 mg three times daily for riociguat. Some patients presented comorbidities, such as hypertension, atrial fibrillation, diabetes mellitus, coronary artery disease, and decreased renal function. All patients received a background treatment, including diuretics,  $\beta$ -blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), calcium channel blockers (CCBs), and cardiac assistant device. It was noteworthy that around 60% of patients included in the VICTORIA trial received triple anti-HF therapy, and 15% received an angiotensin receptor-neprilysin inhibitors (ARNIs).

The risk of bias within included trials was assessed with Cochrane, most of parameters were indicated to be a low risk (figure 3). However, some parameters could not make a correct assessment since insufficient information was obtained. The results of evidence

quality assessed by GRADE system can be seen in figure 4.

### 3.2 Efficacy outcomes

All-cause mortality was assessed at the end of interventions in the pooled analysis based on all included studies. It was demonstrated that there was no significant difference between sGC stimulators and placebos (OR= 0.95, 95% CI=0.83 to 1.09), and no heterogeneity was observed among different studies ( $I^2=0.0\%$ ,  $p=0.835$ , figure 5). Egger test illustrated that no evident publication bias was observed in this study ( $p=0.176$ ). Further sensitivity analysis indicated that there was a prominent heterogeneity in VICTORIA study (Armstrong 2020) which may affect the stability of all-cause mortality in the pooled analysis (figure 6).

The number of cardiovascular-events related death or hospitalization was assessed in a pooled analysis including 4 studies at the end of the interventions. The results indicated there was a lower incidence of cardiovascular-events related death or hospitalization in patients treated with oral sGC stimulators (overall odds ratio was 0.88, 95% CI=0.79 to 0.98) compared with placebos, and there was no significant heterogeneity between each study ( $I^2=0\%$ ,  $p=0.623$ , figure 5). Moreover, Egger test demonstrated no evident publication bias was found in this study ( $p=0.978$ ). There was a significant decreased incidence of cardiovascular-events related death or hospitalization in sGC stimulator groups rather than placebos in the sensitivity analysis, and no significant heterogeneity was discovered among different studies (figure 6).

Alterations of EQ-5D US index scores were evaluated after treatments in 3 different studies. Integrating the data from these studies showed that sGC stimulators led to a greater improvement in EQ-5D scores rather than placebos (SMD=0.44, 95% CI=0.24 to 0.63), there was no significant heterogeneity among different studies ( $I^2=20.8\%$ ,  $p=0.283$ , figure 5).

Changes of NT-proBNP was discovered from the baseline to the end of interventions in four different studies. As the transformation of values could impact on the accuracy of combined data, two sGC stimulators were evaluated separately. The results showed that there was no significant difference in Log (NT-proBNP) in vericiguat groups compared with placebos (SMD= 0.04, 95% CI= -0.18 to 0.25), and no significant heterogeneity was shown among different studies ( $I^2=24.4\%$ ,  $p=0.250$ , figure 5). On the contrary, it was demonstrated that NT-proBNP was significantly decreased in riociguat groups compared with controls (SMD= -0.79, 95% CI= -1.10 to -0.49), and no statistically significant heterogeneity were shown among different studies ( $I^2=0.0\%$ ,  $p=0.366$ , figure 5).

### **3.3 Safety outcomes**

The risks of SAEs were assessed during the treatments in all six studies involved. Combined data from these studies implied that sGC stimulators exhibited a lower incidence of SAEs compared with placebos (OR= 0.90, 95% CI=0.81 to 1.00), and no significant heterogeneity was observed statistically ( $I^2=0.0\%$ ,  $p=0.758$ , figure 7). Moreover, there was no evident publication bias in this analysis ( $p=0.352$ ). However, the sensitivity analysis indicated that the VICTORIA study (Armstrong 2020) had a significant heterogeneity and may affect the stability of the pooled analysis of incidence of SAEs (figure 6).

There were three trials (vericiguat as anti-HF treatment) showing the proportion of participants with symptomatic hypotension or syncope, both of them were adverse events of clinical-interests. Pooled analysis based on these studies illustrated that there was no significant difference in the incidence of symptomatic hypotension in patients treated with oral sGC stimulators compared with controls (OR= 1.15, 95% CI=0.95 to 1.40), and no evident heterogeneity was observed ( $I^2=0.0\%$ ,  $p=0.769$ , figure 7). Furthermore, no significant difference was discovered in the incidence of syncope during sGC interventions compared with controls (OR= 1.15, 95% CI=0.87 to 1.53),

and no heterogeneity was found in these studies either ( $I^2=0.0\%$ ,  $p=0.557$ , figure 7).

## 4. Discussion

Nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway plays an indispensable role in cardiovascular diseases. Reduced sGC activity is associated with microvascular dysfunction in coronary artery, cardiomyocyte stiffness, interstitial fibrosis, and ultimate myocardial dysfunction. It is considered as a driving force behind the progression of myocardial dysfunction in HF(17-20). Novel sGC stimulators can excite sGC directly independent on NO, enhancing effects of NO in a low - endogenous NO environment to increase cGMP synthesis(21, 22). In 2013, riociguat, the first sGC stimulator having made a successful transition from animal experiments to controlled clinical studies in patients, gained a market approval for two life-threatening diseases: pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)(23-26). Preclinical and clinical studies have suggested that another sGC stimulators named vericiguat is an ideal candidate for HF based on its direct vasodilatory properties, as well as improvement of myocardial compliance, diastolic function, and endothelial function. Moreover, it is discovered to facilitate the regulation of vessel tones, ventricular-arterial coupling, and cardiac reserve in HF(27).

Multiple types of sGC stimulators have been discovered currently, such as riociguat (BAY 63-2521), vericiguat (BAY 1021189), praliciguat (IW-1973), and so forth. Riociguat is approved to be an effective therapeutic treatment for PAH and CTEPH in many preclinical and clinical studies, and has obtained a market approval in 2013(23-26). However, application of riociguat in other cardiovascular indications, such as HF, is limited by its short half-life(28). Vericiguat is more suitable for patients with HF, because of an ideal stability, a good tolerance, and no needs to monitor renal function and electrolytes. The VICTORIA trial, having published its primary and secondary outcomes in March 28, 2020(13), including death from cardiovascular causes or first

hospitalization for heart failure, death from any cause, and incidence of clinical interested symptomatic hypotension and syncope, while exploratory outcomes including changes in quality of life health-related summary measurements and the relationships among treatment effect, baseline biomarkers, and genetic variation, have not yet been published. Another phase IIb trial named VITALITY-HFpEF trial is still undergoing to determine the efficacy and safety of vericiguat on quality of life and exercise tolerance in patients with HFpEF(29). Praliciguat is another type of novel oral sGC stimulator, which might be a potential therapeutic drug for HFpEF. Another phase II trial named CAPACITY-HFpEF trial, which is designed to evaluate the efficacy and safety of praliciguat in patients with HFpEF, is on its way as well(30). Further attention needs to be paid to the results generated from these trials.

Our findings demonstrated that sGC stimulators presented a decreased incidence of cardiovascular-events related death or hospitalization, and an improvement in HRQoL in patients with HF compared with placebos. Besides, sGC stimulators riociguat exhibited a greater reduction of NT-proBNP during the treatment but not in vericiguat. In addition, sGC stimulators manifested a good tolerance and a lower risk of SAEs compared with placebos. However, sGC stimulators presented no effects on all-cause mortality and the risks of clinical-interested adverse events. These findings illustrated that sGC stimulators can be a potential therapeutic strategy to make an improvement of HF.

The improvement of HRQoL in patients was assessed by the incidence of cardiovascular-events related death or hospitalization, and the changes of EQ-5D US index scores. Our analysis indicated that vericiguat exhibited a greater decrease of cardiovascular-events related death or hospitalization, both riociguat and vericiguat showed an improvement of EQ-5D US index scores. Therefore, sGC stimulators can be effective for improving overall health status of patients with HF. However, all different doses of riociguat and vericiguat were merged together to do the analysis, which may

impact on the changes of EQ-5D scores to some extent. In SOCRATES-PRESERVED trial, a high dose of vericiguat (10 mg) played a significant role in improving quality of life, while dose-dependent effects were not observed with riociguat(11). This suggested that a high dose of vericiguat may be required to achieve a desired efficacy, surely, more dose-finding trials are needed to verify the most suitable dose of sGC stimulators in patients with heart failure.

NT-proBNP is a remarkable biomarker for HF, patients with HF often present a higher level of NT-proBNP. Besides, a higher level of NT-proBNP indicates a deterioration and a poor prognosis of HF(31-35). Our findings suggested that vericiguat cannot significantly reduce the level of NT-proBNP. However, the data from SOCRATES-REDUCED trial demonstrated a greater reduction of NT-proBNP in the group treated with 10mg vericiguat(12). This finding suggested that a desired efficacy of vericiguat might be achieved with a dose of 10mg. Compared with vericiguat, riociguat showed a significant reduction of NT-proBNP in the pooled analysis. These findings suggest that, when it comes to evaluate the effects of sGC stimulators on the level of NT-proBNP, different types of HF must be taken into consideration. Besides, insufficient durations of interventions and different mechanisms involved in these two sGC stimulators should also be considered.

The common major of SAEs in sGC stimulators are syncope, hypotension, ventricular tachycardia, and pulmonary hemorrhage. Symptomatic hypotension and syncope are two of the most clinically-focused adverse events in sGC stimulators. The pooled analysis indicated that HF patients showed a lower risk of SAEs, suggesting sGC stimulators were well tolerated and did not deteriorate the prognosis of HF patients, while sGC stimulators had no effects on the risks of clinically-interested adverse events.

In the sensitivity analysis of all-cause mortality, the VICTORIA trial presented a prominent heterogeneity. The follow-up durations must be considered since it only took

about 10.8 months to reach the expected number of events in VICTORIA trial(13), implying the collecting time might be insufficient. If the collecting time were extended, it would be much more convinced about the benefits of sGC stimulators. However, inaccurate data on all-cause mortality can also be obtained from other trials due to the design bias of the studies. Therefore, more studies with optimized design are needed to further clarify the effects of these two drugs on all-cause mortality. In the sensitivity analysis of incidence of SAEs showed the VICTORIA trial produces heterogeneity. The VICTORIA trial is a large-scale phase III trial of vericiguat in patients with HFrEF with a longer follow-up duration than other included trials in this study. Thus, exploration of underlying mechanisms requires application of trials with a larger sample size, a longer follow-up, and some additional prognostic endpoints.

## **5. Limitations**

Our study has some limitations. Firstly, although most of included trials were famous studies and published in high-impact journals, potential bias may still exist, such as pharmaceutical industry funding, lacking detection bias, and open-label design in the later stage(14, 15). Secondly, the subtypes of HF were not distinguished in our study, patients enrolled in some trials were with HF associated with congenital heart diseases or pulmonary artery hypertension. Additionally, limited data were gathered since some ongoing trials have not published final outcomes(13, 29, 30, 36). Thirdly, the efficacy of these two sGC stimulators were not analyzed respectively due to limited data, leading to a vague effect about the dose-dependent response in these two drugs. Fourthly, the application of riociguat can be limited in HF owing to its short half-life. Therefore, the exact mechanisms of riociguat in HF are still unclear, and further experiments are needed to excavate its potential mechanisms in HF. Fifthly, designs of different trials may bring inherent limitations, such as different follow-ups, various durations of interventions, and multiple dosages of medications, which might impact the accuracy of results. Sixthly, indicators to evaluate the efficacy of anti-HF medications were incomplete in most trials, such as circulatory blood pressure, cardiac index, and left

ventricular ejection fraction, resulting that the efficacy of sGC stimulators cannot be comprehensively evaluated in our analysis. In the future, more subsequent studies with optimized designs are required to further determine the efficacy and safety of these sGC stimulators.

## 6. Conclusion

Our findings clearly proved that oral sGC stimulators may be beneficial with a good tolerance for patients with HF, however, further studies are needed to establish the optimal approach to the application of sGC stimulators in clinical practice.

## Declaration

**Ethics approval and consent to participate:** Not applicable.

**Consent for publication:** Not applicable.

**Availability of data and materials:** All data generated or analysed during this study are included in this manuscript, the datasets used and analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** All authors disclosed no relevant relationships.

**Funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Authors' contributions:** Shi and Yu wrote the main manuscript text. Shi, Yu and Wang reviewed these different studies, extracted data and analyzed the extracted data independently. Shi prepared figure. Zhou reviewed the manuscript.

**Acknowledgements:** Not applicable.

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# Figures

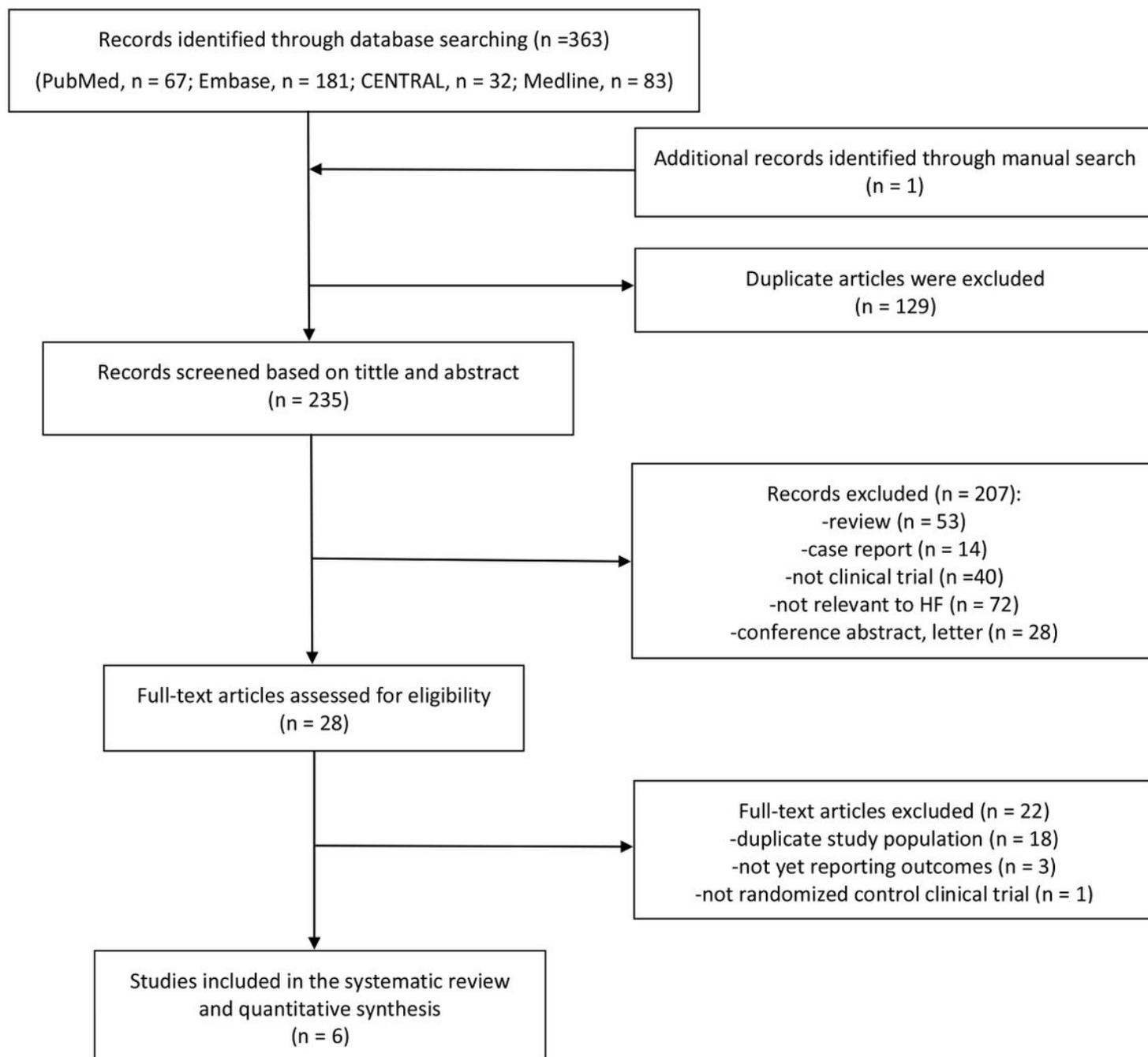


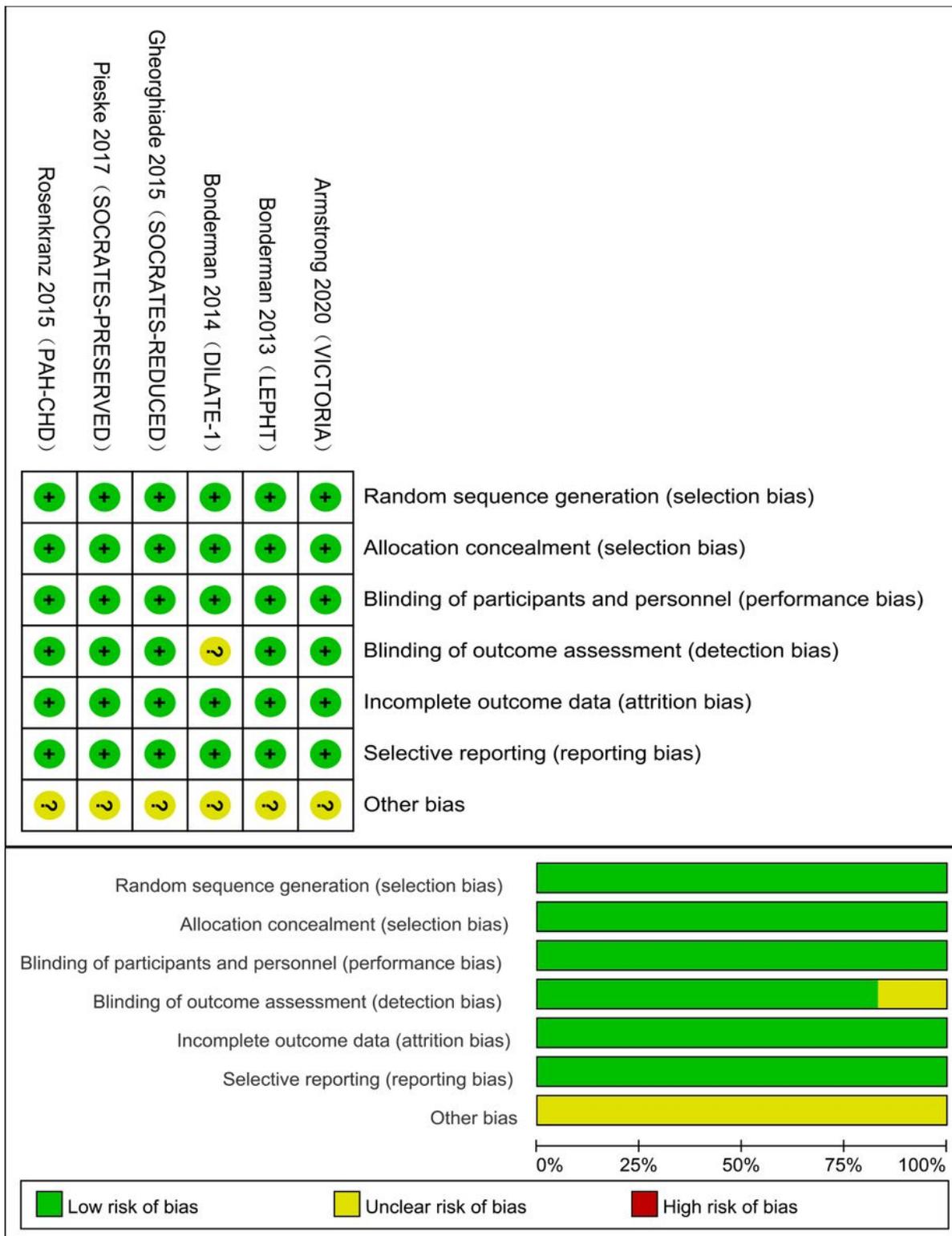
Figure 1

The detailed process of literature searching and explanations for exclusion were described in figure 1.

Study	Sample size (T/C) n	Interventions (T/C)	Mean follow-up	Mean age (T/C) y	Number of men (T/C) n%	NYHA class	MBI(T/C) kg/m <sup>2</sup>	eGFR (T/C) L/min/1.73m <sup>2</sup>	LVEF (T/C) %	NT-proBNP (T/C) pg/ml				
<b>Vericiguat</b>														
Armstrong 2020 [13] (VICTORIA)	2526/2524	Vericiguat 10mg VS Placebo	10.8 months	67.5±12.2/67.2±12.2	76.0/76.1	II-IV	27.7±5.8/27.9±6.1	61.3±27.0/61.7±27.3	29.0±8.3/28.8±8.3	2803±2019/2821±1912				
Pieske 2017 [11] (SOCRATES-PRESERVED)	384/93	Vericiguat 1.25, 2.5, 5 or 10mg VS Placebo	12 weeks	73.3±9.8/74.0±9.0	52.9/50.5	II-IV	30.2±5.9/30.1±6.5	55.5±20.1/52.3±20.6	56.8±4.1/57.0±4.5	1276±1199/975±1175				
Gheorghiadze 2015 [12] (SOCRATES-REDUCED)	364/92	Vericiguat 1.25, 2.5, 5 or 10mg VS Placebo	16 weeks	68±12/67±13	80.5/79.3	II-IV	28±5/27±5	58.6±20.0/57.8±17.4	29.9±8.4/28.6±8.5	2960±3027/4043±2393				
<b>Riociguat</b>														
Rosenkranz 2015 [14] (PAH-CHD)	12/23	Riociguat 1.25, 2.5mg VS Placebo	12 weeks	37±15/40±16	17.4/16.7	≥II	22±3/24±3	NA	NA	NA				
Bonderman 2014 [16] (DILATE-1)	25/11	Riociguat 0.5, 1, 2mg VS Placebo	6 hours, 30 days	69.3±22.4/75.1±16.0	36/45	NA	31.1±8.2/30.2±7.0	NA	NA	1483±1592/2019±1383				
Bonderman 2013 [15] (LEPHT)	132/69	Riociguat 0.5, 1, 2mg VS Placebo	16 weeks	57.7±35/58.9±40	84/88	II-IV	28.8±0.7/28.7±0.7	68.6±2.9/68.7±2.4	28.2±0.8/27.1±0.6	NA				
Study	DM (T/C) n%	Hypertension (T/C) n%	Atrial fibrillation (T/C) n%	Atrial flutter (T/C) n%	CAD (T/C) n%	CKD (T/C) n%	COPD (T/C) n%	Diuretics (T/C) n%	β-Blocker (T/C) n%	ACEI (T/C) n%	ARB (T/C) n%	MRA (T/C) n%	CCB (T/C) n%	Cardiac assistant device (T/C) n%
<b>Vericiguat</b>														
Armstrong 2020 [13] (VICTORIA)	48.6/45.3	79.3/79.0	43.5/46.4	7.1/8.4	59.8/56.8	NA	17.1/17.3	NA	93.2/93.0	73.3/73.6	NA	69.3/71.4	NA	42.3/42.5
Pieske 2017 [11] (SOCRATES-PRESERVED)	48.2/50.5	90.4/91.4	40.4/37.6	NA	NA	39.8/46.2	NA	92.2/91.4	79.2/81.7	39.3/43.0	33.9/34.4	36.2/41.9	36.7/32.3	NA
Gheorghiadze 2015 [12] (SOCRATES-REDUCED)	48.9/44.6	78.8/76.1	34.1/32.6	NA	52.5/55.4	40.7/41.3	NA	94.5/93.5	90.1/90.2	62.6/56.5	22.8/22.8	64.3/54.3	NA	27.7/28.2
<b>Riociguat</b>														
Rosenkranz 2015 [14] (PAH-CHD)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bonderman 2014 [16] (DILATE-1)	44/45	NA	72/64	NA	20/9	NA	12/36	68.0/64.0	76/91	56/27	32/45	36/64	40/55	NA
Bonderman 2013 [15] (LEPHT)	40.2/49.3	NA	12.5/14.5	1.4/0.8	42.4/49.3	NA	NA	92.4/95.7	51.5/46.4	72.7/66.7	28.8/27.5	75.8/76.8	NA	57.6/63.8

**Figure 2**

Characteristics included in randomized controlled clinical trials, like demographic information and background medications were summarized in figure 2. The mean ages of the patients ranged from 37 to 75 years, and the mean follow-up durations ranged from 30 days to 10.8 months compared with placebos. The baseline characteristics were well matched in sGC stimulators and placebos. The mean body mass index ranged from 22.0 to 31.1 kg/m<sup>2</sup>, the mean eGFR ranged from 52.3 to 68.7 L/min/1.73m<sup>2</sup>, and the mean NT-proBNP ranged from 975 to 4043 pg/ml. All NYHA classifications were equal to or above level II. Included participants were patients with HFpEF (HF with preserved ejection fraction, LVEF is higher than 40%) or HFrEF (HF with reduced ejection fraction, LVEF is lower than 40%).



**Figure 3**

The risk of bias within included trials was assessed with Cochrane, most of parameters were indicated to be a low risk (figure 3).

## SGC Stimulators Compared to Placebos for Heart Failure

**Patient or population:** Heart Failure

**Setting:**

**Intervention:** sGC Stimulators

**Comparison:** Placebos

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebos	Risk difference with sGC stimulators
Cardiovascular-Events Related Death or Hospitalization	6182 (4 RCTs)	⊕⊕⊕⊕ HIGH	<b>OR 0.88</b> (0.79 to 0.98)	363 per 1,000	<b>29 fewer per 1,000</b> (53 fewer to 5 fewer)
Alterations of NT-proBNP or log (NT-proBNP)	888 (4 RCTs)	⊕⊕⊗⊗ LOW <sup>ab</sup>	-	-	<b>SMD 0.29 lower</b> (0.76 lower to 0.18 higher)
Alterations of EQ-5D US Index	558 (3 RCTs)	⊕⊕⊕⊗ MODERATE <sup>a</sup>	-	The mean the Change of EQ-5D US Index was <b>0</b>	<b>MD 0.03 higher</b> (0.02 higher to 0.05 higher)
All-cause Death	6256 (6 RCTs)	⊕⊕⊗⊗ LOW <sup>ab</sup>	<b>OR 0.95</b> (0.83 to 1.09)	193 per 1,000	<b>8 fewer per 1,000</b> (27 fewer to 14 more)
Serious Adverse Events	6256 (6 RCTs)	⊕⊕⊕⊗ MODERATE <sup>a</sup>	<b>OR 0.90</b> (0.81 to 1.00)	338 per 1,000	<b>23 fewer per 1,000</b> (45 fewer to 0 fewer)

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

### GRADE Working Group grades of evidence

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

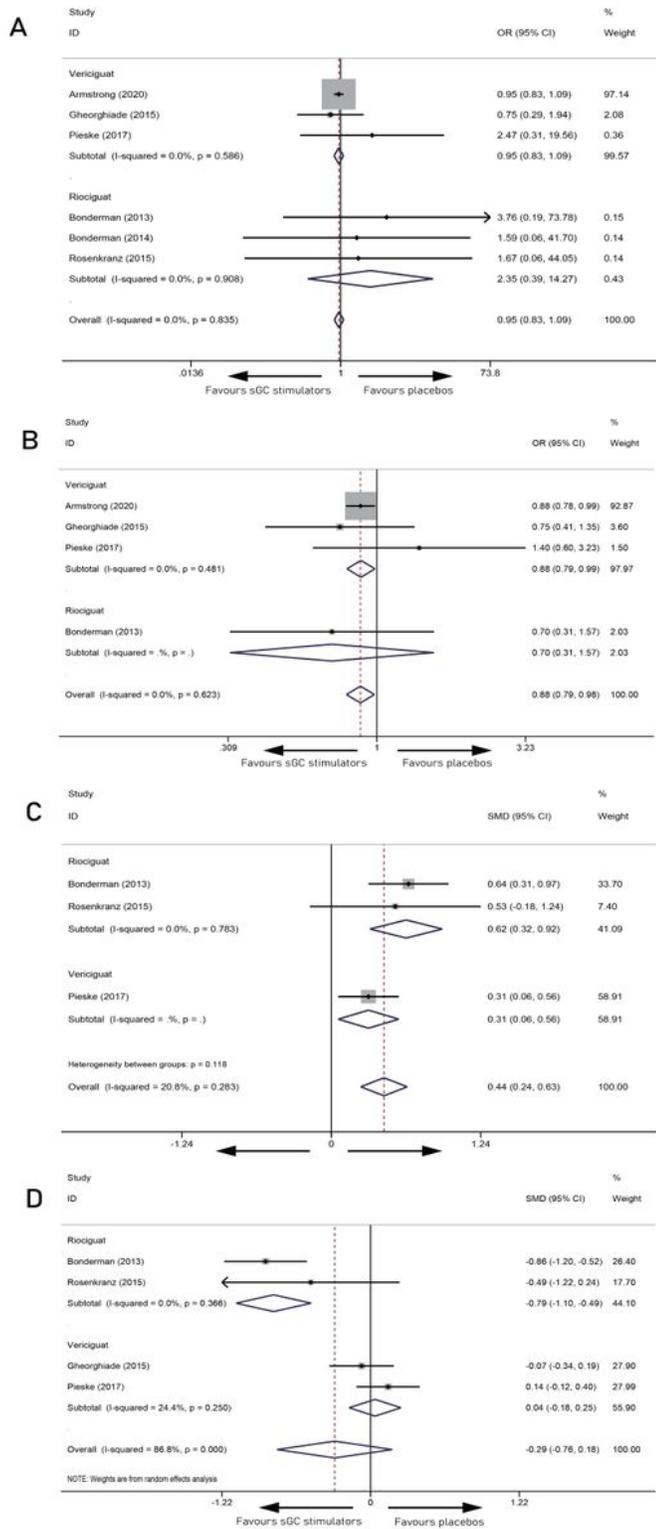
### Explanations

a. includes patients with heart failure associated with congenital heart diseases or pulmonary arterial hypertension

b. the 95% Confidence Interval includes 1

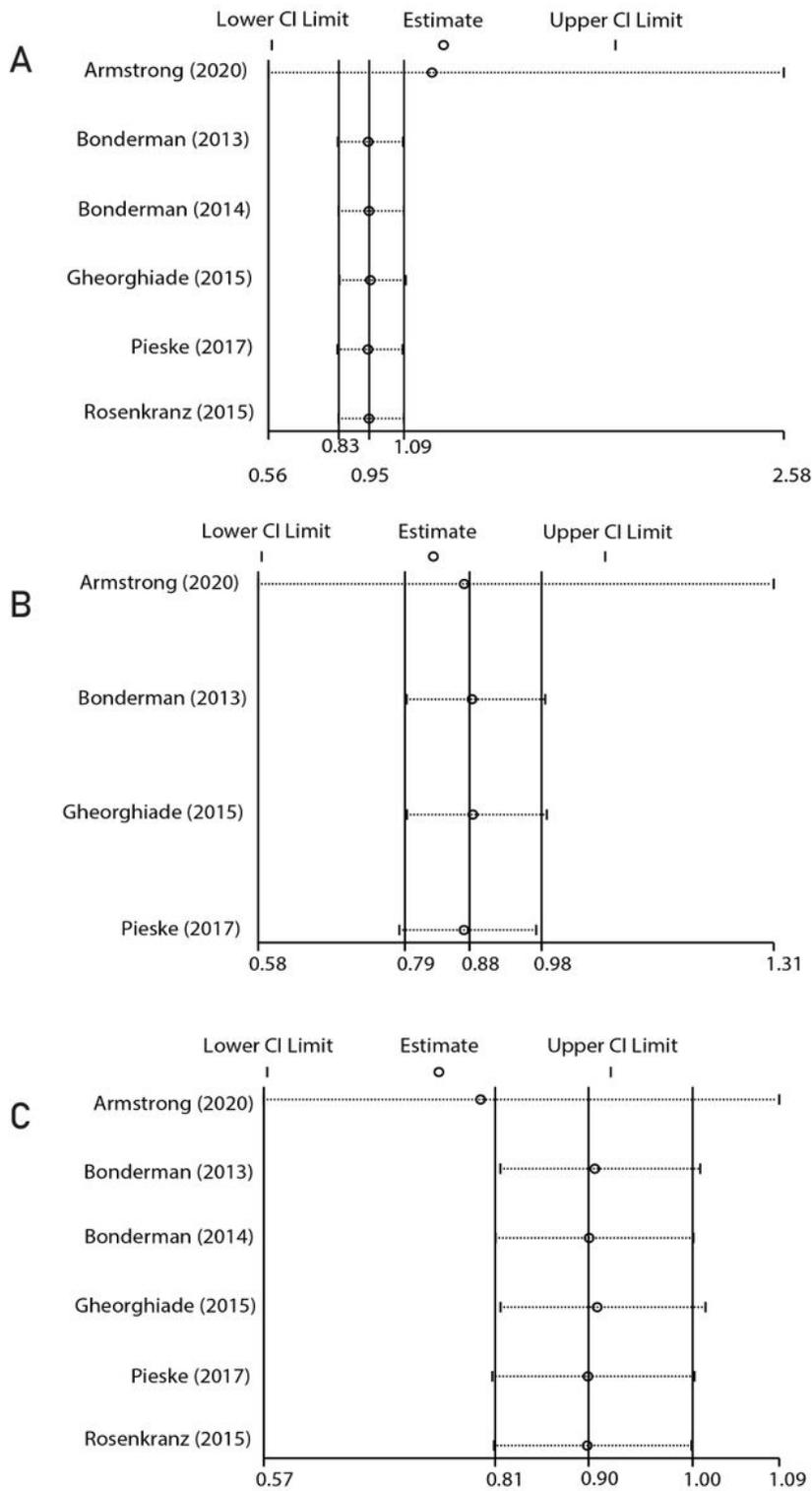
## Figure 4

some parameters could not make a correct assessment since insufficient information was obtained. The results of evidence quality assessed by GRADE system can be seen in figure 4.



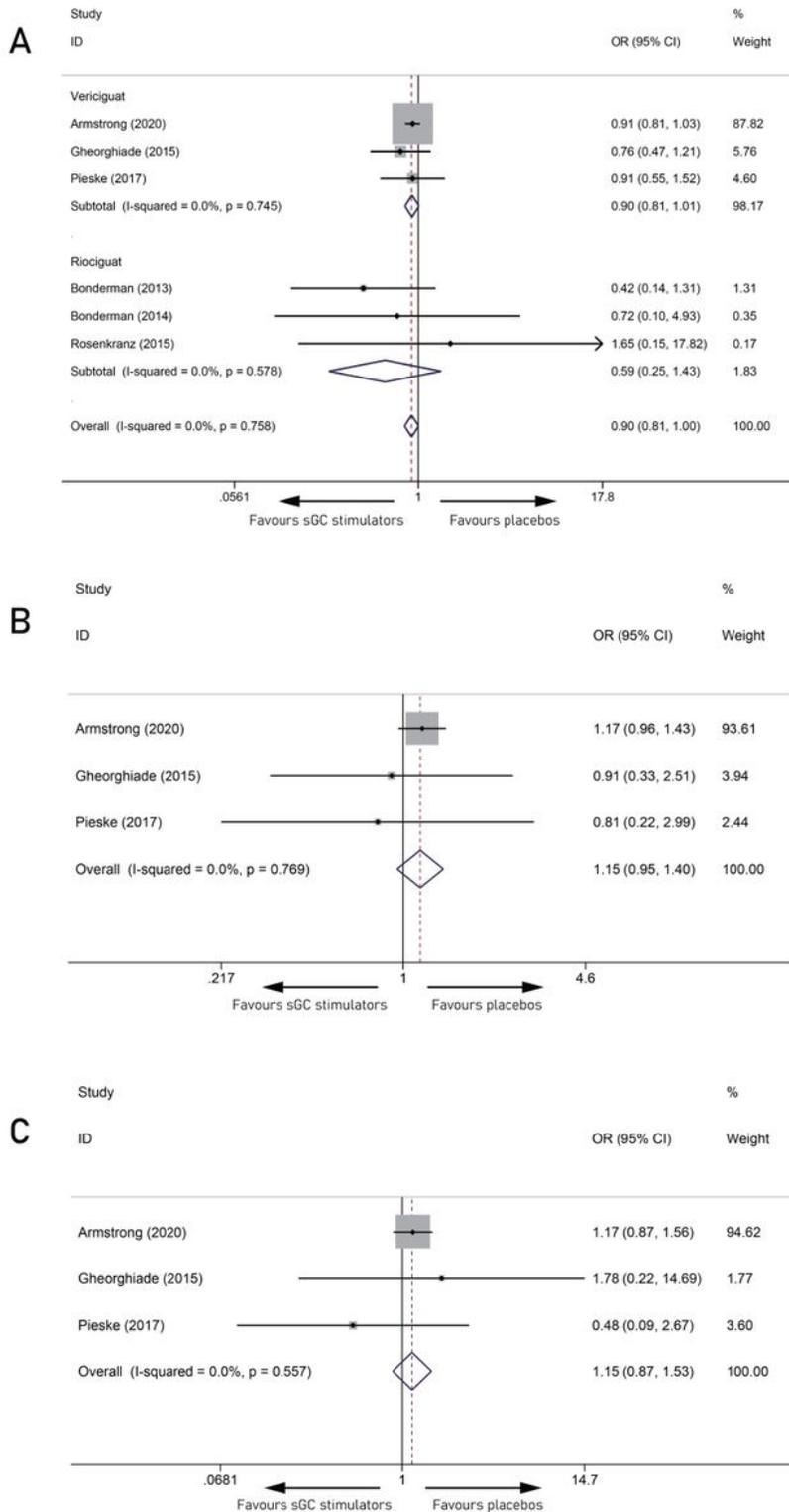
**Figure 5**

All-cause mortality was assessed at the end of interventions in the pooled analysis based on all included studies. It was demonstrated that there was no significant difference between sGC stimulators and placebos (OR= 0.95, 95% CI=0.83 to 1.09), and no heterogeneity was observed among different studies ( $I^2=0.0\%$ ,  $p=0.835$ , figure 5).



**Figure 6**

Egger test illustrated that no evident publication bias was observed in this study ( $p=0.176$ ). Further sensitivity analysis indicated that there was a prominent heterogeneity in VICTORIA study (Armstrong 2020) which may affect the stability of all-cause mortality in the pooled analysis (figure 6).



**Figure 7**

The risks of SAEs were assessed during the treatments in all six studies involved. Combined data from these studies implied that sGC stimulators exhibited a lower incidence of SAEs compared with placebos (OR= 0.90, 95% CI=0.81 to 1.00), and no significant heterogeneity was observed statistically (I<sup>2</sup>=0.0%, p=0.758, figure 7).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryRawdata.pdf](#)