Supplementary material

Supplementary Appendix

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Search strategy:

(sGC stimulators) OR (((((guanylate cyclase AND heart failure)) OR riociguat) OR vericiguat) OR (riociguat AND heart failure))

Supplementary Tables

Supplementary Table 1 Baseline characteristics of the included population

Trial	Study Design	Year	Country	Sample Size (T/C)	Mean Age (T/C)	Males (%) (T/C)	Atrial Fibrillation (%) (T/C)	Diabetes Mellitus (%) (T/C)	eGFR (mean) (T/C)	Diuretics (%) (T/C)
Armstrong (VICTORIA trial)	RCT	2020	Ca-da	2526/2524	67.5±12.2/67.2±12.2	76/76	-	-	-	-
Pieske (SOCRATES PRESERVED)	RCT	2017	Germany	93/384	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
Rosenkranz (PAH-CHD)	RCT	2015	Germany	7/23	40±16/37±15	17/17	-	-	-	-
Gheorghiade (SOCRATES REDUCED)	RCT	2015	USA	92/364	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
Bonderman (DILATE-I)	RCT	2014	Austria	69/132	59±40/58±35	88/84	15/11	49/40	68.7±2.4/70±4.7	-
Bonderman (LEPHT)	RCT	2013	Italy	11/25	75±16/70±20	45/36	55/40	45/44	-	-

Trial	ACE Inhibitor (%) (T/C)	ARB (%) (T/C)	Beta-Blocker (%) (T/C)	CCB (%) (T/C)	MRA (%) (T/C)	Sacubitril-Valsartan (%)	NYHA Class	Mean LVEF %	Mean Follow up (weeks)

						(T/C)			
Armstrong (VICTORIA trial)	14/16	14/16	-	-	-	15/16	2–4	29.0±8.3	43
Pieske (SOCRATES PRESERVED)	43.0/39.3	34.4/33.9	81.7/79.2	32.3/36.7	41.9/36.2	-	2–4	56.8±6.25	12
Rosenkranz (PAH-CHD)	-	-	-	-	-	-	2–4	-	12
Gheorghiade (SOCRATES REDUCED)	56.5/62.6	22.8/22.8	90.2/90.1	-	54.3/64.3	-	2–4	29.9±8.5	16
Bonderman (DILATE-I)	67/73	28/29	46/52	-	-	-	2–4	28.2±1.0	16
Bonderman (LEPHT)	27/56	45/32	91/76	55/40	-	-	-	49.5	16

Supplementary Table 2 Inclusion and exclusion criteria of the included studies

Study	Inclusion Criteria	Exclusion Criteria
Armstrong (VICTORIA trial) 2020	Age >18 years; Chronic heart failure; LVEF <45%; elevated pro-BNP within 30 days before randomization; hospitalized 3 months, 3-6 months, or no hospitalization for 3 months before randomization; eGFR of 15-30 ml/1.73 m2 of body surface area; receiving guideline-based medical therapy	Systolic BP <100 mmHg; concurrent/anticipated use of long-acting nitrates, sGC stimulators, PDE-5 inhibitors; use of intravenous inotropes or implanted LVAD
Pieske (SOCRATES PRESERVED) 2017	Worsening chronic heart failure (WCHF) requiring hospitalization (or intravenous [IV] diuretic treatment for HF without hospitalization) with the initiation of study treatment after clinical stabilization	IV inotropes at any time between hospitalization and randomization; Concurrent or anticipated nitrate use; 3. Cardiac comorbidity (HOCM with LOVTO, pericardial or myocardial disease, valvular heart disease; ACS or CABG 60 days before randomization; indication for PCI or CABG; significant cardiac ischemia in stress test; symptomatic carotid stenosis or TIA 30 days before randomization; CHD; Glomerular filtration rate <30 mL/min/1.73 m2; Child-Pugh B or C; Body mass index (BMI) >45; severe pulmonary disease
Rosenkranz (PAH-CHD) 2015	Patients with symptomatic PAH; aged 18–80 years; had a mean pulmonary artery pressure (mPAP) of ≥25 mm Hg, a PVR of >300 dyn·s·cm–5	Patients with pulmonary venous hypertension, indicated by baseline pulmonary capillary wedge pressure >15 mmHg if aged 18–75 years at Visit 1 or >12 mmHg if aged >75 years at Visit 1, were excluded (the 12 mmHg cut-off was not applicable

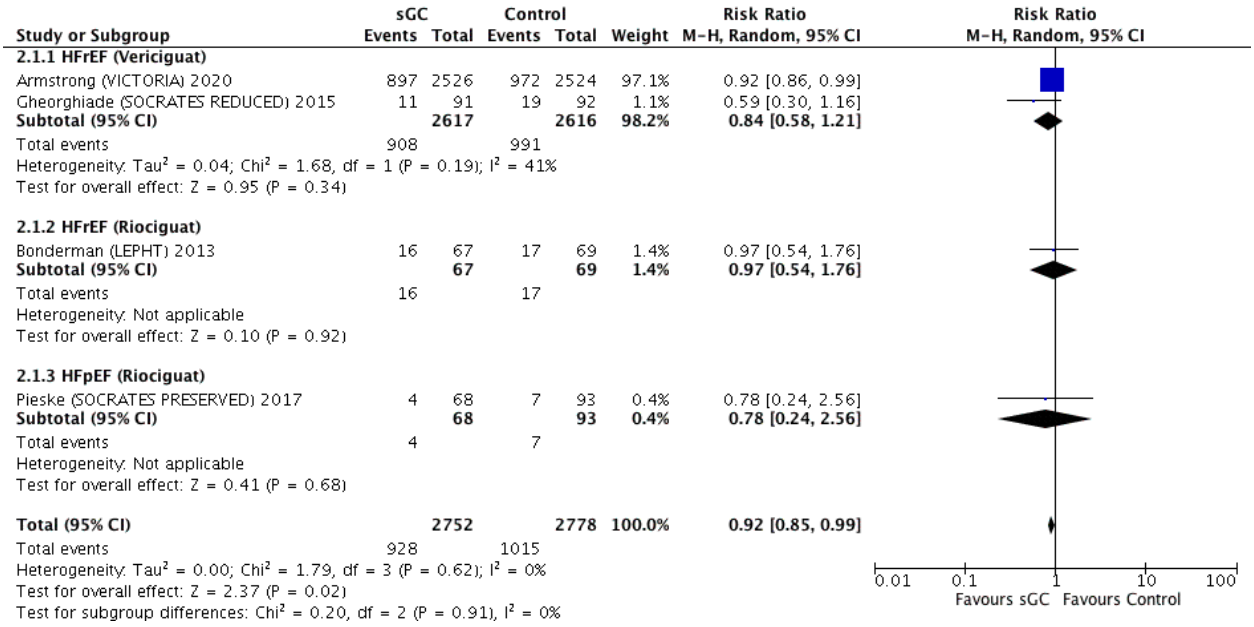
	and a 6MWD of 150–450 m; Patients who had received no prior PAH-specific therapies (treatment-naïve) and those who were receiving ERAs and/or non-intravenous prostanoids at a stable doses for ≥90 days were eligible for inclusion.	to the PAH-CHD population, as all patients were 18–75 years at baseline); Patients receiving PDE-5 inhibitors were excluded.
Gheorghiade (SOCRATES REDUCED) 2015	Worsening chronic heart failure (WCHF) requiring hospitalization (or intravenous [IV] diuretic treatment for HF without hospitalization) with the initiation of study treatment after clinical stabilization	IV inotropes at any time between hospitalization and randomization; Concurrent or anticipated nitrate use; 3. Cardiac comorbidity (HOCM with LOVTO, pericardial or myocardial disease, valvular heart disease; ACS or CABG 60 days before randomization; indication for PCI or CABG; significant cardiac ischemia in stress test; symptomatic carotid stenosis or TIA 30 days before randomization; CHD; Glomerular filtration rate <30 mL/min/1.73 m2; Child-Pugh B or C; Body mass index (BMI) >45; severe pulmonary disease
Bonderman (LEPHTH) 2013	Men and women aged 18–80 years; Heart failure due to ischemic or non-ischemic causes; Left ventricular ejection fraction ≤40%; Mean pulmonary artery pressure ≥25 mmHg at rest (measured by right heart catheterization); Symptomatic despite optimized medical therapy according to published guidelines at a stable	Pulmonary hypertension in groups other than Group 2.1 according to Dana Point classification1; Cardiac decompensation ≤30 days before randomization; Systemic blood pressure <100 mmHg at baseline; Severe renal impairment (glomerular filtration rate <30 mL·min–1); Patients with cardiac ischemia in whom percutaneous coronary intervention or bypass surgery was planned were not considered eligible

	dose regimen for >30 days before randomization.	
Bonderman (DILATE-I) 2014	signs or symptoms of heart failure; echocardiographic confirmation of preserved left ventricular ejection fraction (LVEF) > 50%; echocardiographic confirmation of preserved ejection fraction with LVEF > 50% and evidence for diastolic dysfunction, by either abnormal relaxation (E/A wave ratio < 1) or diastolic stiffness (E/A wave ratio > 2) in patients with sinus rhythm, or by E wave deceleration time < 150 ms in patients with atrial fibrillation; serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) > 220 ρg/mL; and mean pulmonary artery pressure ≥ 25 mm Hg and pulmonary arterial wedge pressure > 15 mm Hg at rest.	pretreatment within 30 days of randomization with intravenous vasodilators, endothelin receptor antagonists, prostanoids, or phosphodiesterase-5 inhibitors; treatment within 7 days of randomization with nitric oxide donors; pulmonary hypertension of groups other than Dana Point Classification 2.2; systolic blood pressure >180 mm Hg or <95 mm Hg and /or diastolic blood pressure >110 mm Hg; significant coronary, carotid, or peripheral vascular disease. Patients with significant valvular heart disease were excluded.

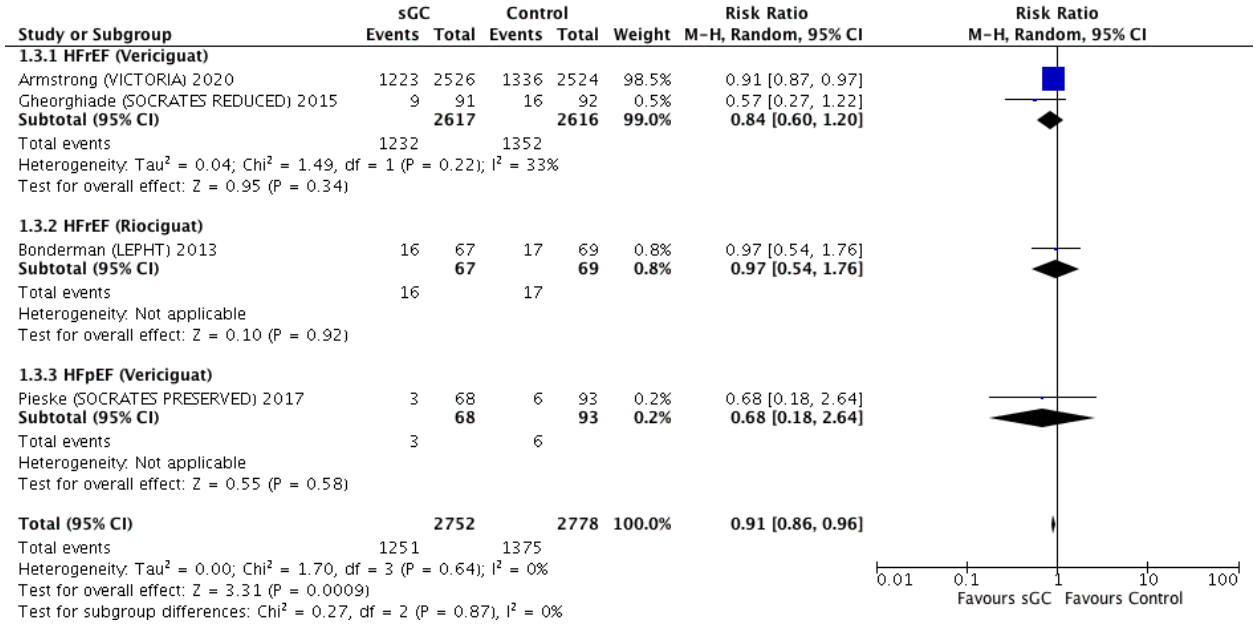
Supplementary Table 3 Definitions of outcomes across included RCTs.

Outcome	Definition
Hospitalization	When a patient is admitted to the emergency room for at least 24 hours or is admitted to the hospital for at least 24 hours or the next calendar day if dates were not available
All-cause mortality	Death due to any cause (cardiovascular and non-cardiovascular)
Cardiovascular mortality	Any death due to cardiovascular cause, including sudden cardiac death, acute Myocardial Infarction, heart failure, stroke, and death due to other cardiovascular causes
Hypotension	Systolic blood pressure (SBP) <80 and diastolic bp less than 60 mmHg
Syncope	Transient loss of consciousness due to hypotension followed by spontaneous recovery.
Anemia	Decrease in RBC mass measures as Hb concentration <13 mg/dl for males and <12 mg/dl for females

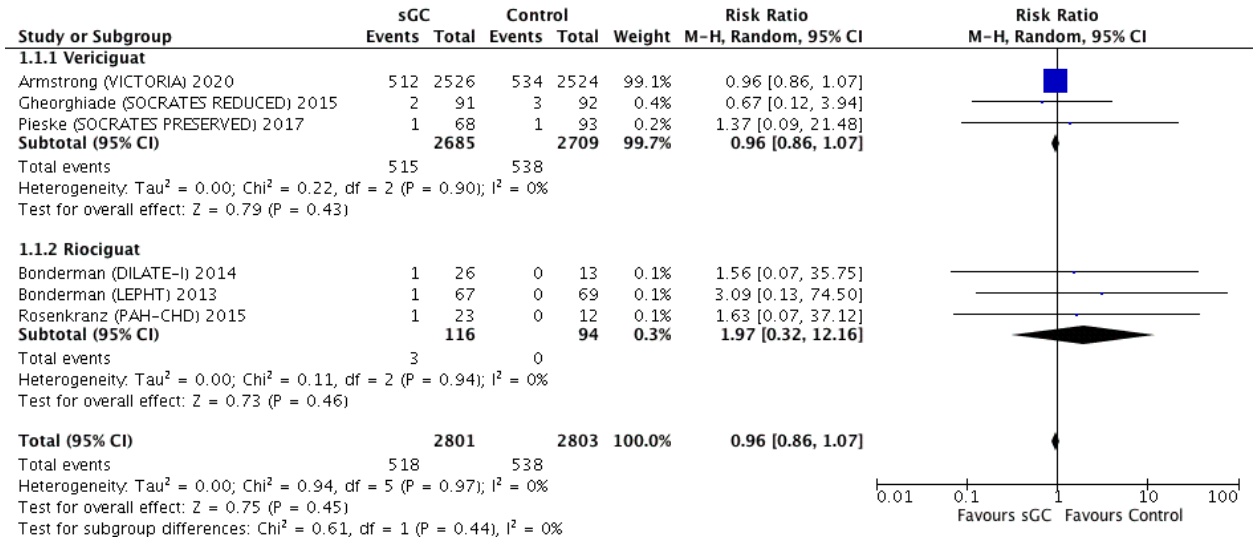
Supplementary Figures:



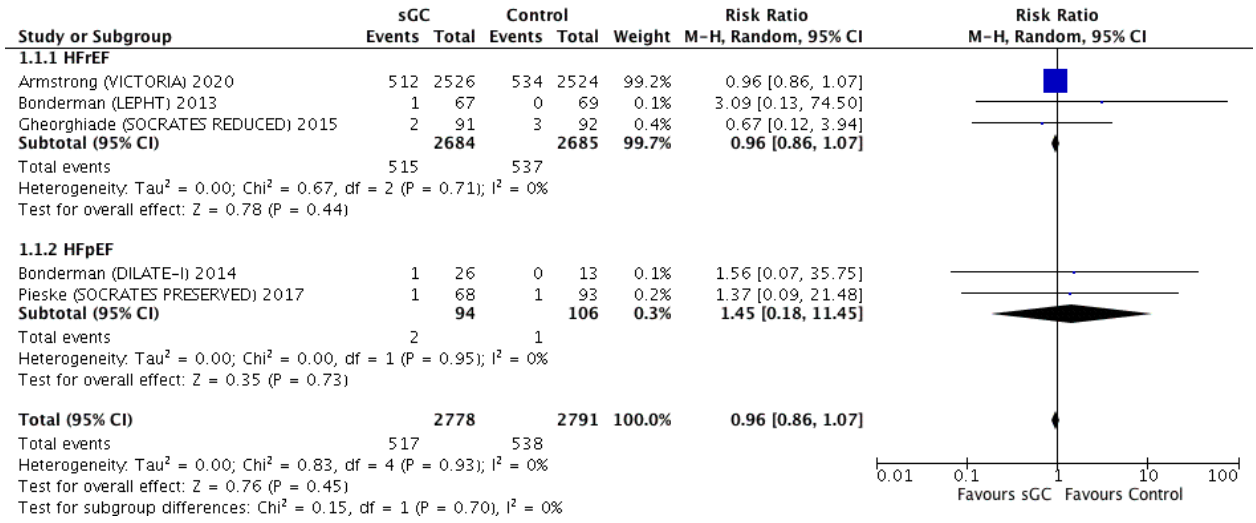
Supplementary Figure 1 Forest Plot for the primary composite endpoint stratified by type of sGC stimulator and HF; showing an individual and pooled RR for RCTs comparing vericiguat and riociguat in both HFrEF and HFpEF to control.



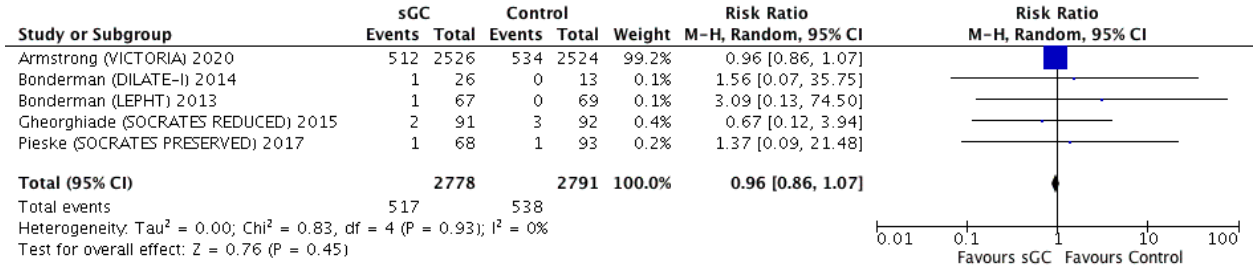
Supplementary Figure 2 Forest Plot for hospitalization endpoint stratified by type of sGC stimulator and HF; showing an individual and pooled RR for RCTs comparing vericiguat and riociguat in both HFrEF and HFpEF to control.



Supplementary Figure 3 Forest Plot for the all-cause mortality stratified by type of sGC stimulators; showing an individual and pooled RR for RCTs comparing vericiguat and riociguat to control.

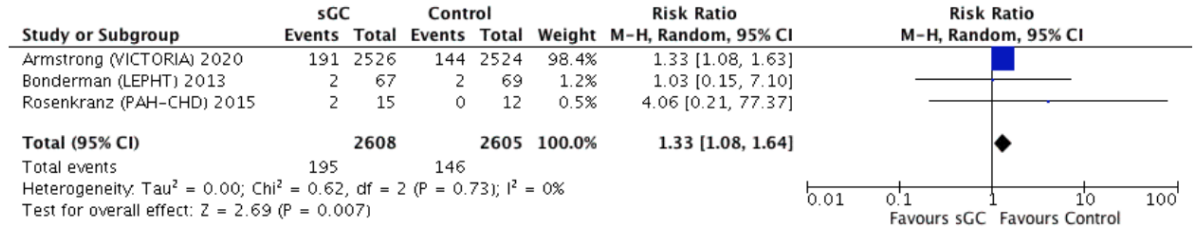


Supplementary Figure 4: Forest Plot for the all-cause mortality stratified by type of heart failure (HFrEF and HFpEF); showing an individual and pooled RR for RCTs comparing sGC stimulators to control.

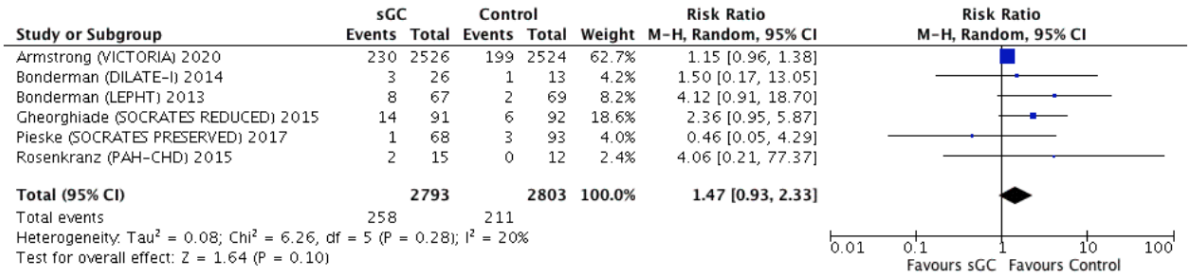


Supplementary Figure 5 Sensitivity analysis (exclusion of PAH-CHD study) of all-cause mortality showing an individual and pooled RR for RCTs comparing sGC stimulators to control.

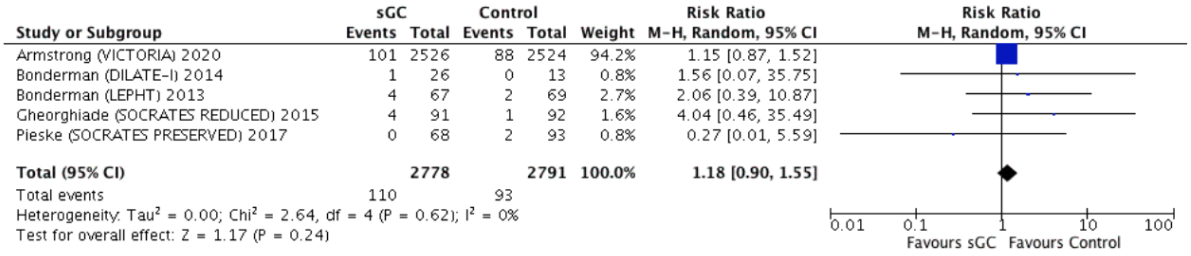
A. Anemia



B. Hypotension



C. Syncope/Stroke



Supplementary Figure 6 Forest Plot for a. anemia, b. hypotension and c. syncope showing an individual and pooled RR for RCTs comparing sGC stimulators to control.