Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Effect of Sacubitril/Valsartan on the Right Ventricular Function and Pulmonary Hypertension in Patients With Heart Failure With Reduced Ejection Fraction: A Systematic Review and Meta-Analysis of Observational Studies

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BACKGROUND: Sacubitril/valsartan (S/V) demonstrated significant effects in improving left ventricular performance and remodeling in patients with heart failure with reduced ejection fraction. However, its effects on the right ventricle remain unclear. This systematic review and meta-analysis aimed to assess the impact of S/V on right ventricular function and pulmonary hypertension.

METHODS AND RESULTS: We searched PubMed, Embase, Cochrane Library, and Web of Science from January 2010 to April 2021 for studies reporting right ventricular and pulmonary pressure indexes following S/V treatment. The quality of included studies was assessed using the Newcastle-Ottawa scale. Variables were pooled using a random-effects model to estimate weighted mean differences with 95% CIs. We identified 10 eligible studies comprising 875 patients with heart failure with reduced ejection fraction (mean age, 62.2 years; 74.0% men), all of which were observational. Significant improvements on right ventricular function and pulmonary hypertension after S/V initiation were observed, including tricuspid annular plane systolic excursion (weighted mean difference, 1.26 mm; 95% CI, 0.33–2.18 mm; P=0.008), tricuspid annular peak systolic velocity (weighted mean difference, 0.85 cm/s; 95% CI, 0.25–1.45 cm/s; P=0.005), and systolic pulmonary arterial pressure (weighted mean difference, 7.21 mm Hg; 95% CI, 5.38–9.03 mm Hg; P<0.001). Besides, S/V had a significant beneficial impact on left heart function, which was consistent with previous studies. The quadratic regression model revealed a certain correlation between tricuspid annular plane systolic excursion and left ventricular ejection fraction after excluding the inappropriate data (P=0.026).

CONCLUSIONS: This meta-analysis verified that S/V could improve right ventricular performance and pulmonary hypertension in heart failure with reduced ejection fraction, which did not seem to be fully dependent on the reverse remodeling of left ventricle.

REGISTRATION: URL: https://www.crd.york.ac.uk/prospero; Unique identifier: CRD42021247970.

Key Words: heart failure ■ meta-analysis ■ pulmonary hypertension ■ right heart function ■ sacubitril/valsartan

Over the past decades, heart failure with reduced ejection fraction (HFrEF) has attracted considerable attention worldwide because of high morbidity and mortality.[1] Sacubitril/valsartan (S/V), a kind of angiotensin receptor neprilysin inhibitor, was recommended by the 2021 European Society of Cardiology Guidelines[2]

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024449

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Sacubitril/valsartan has shown significant effects in improving left ventricular performance and remodeling in patients with heart failure with reduced ejection fraction; however, its effects on the right ventricle remain unclear.
- Our systematic review and meta-analysis demonstrated that sacubitril/valsartan could improve right ventricular function and pulmonary hypertension in patients with heart failure with reduced ejection fraction, which did not seem to be fully dependent on the reverse remodeling of left ventricle.

What Are the Clinical Implications?

- Our meta-analysis suggested a beneficial effect of sacubitril/valsartan on right heart function for patients with heart failure with reduced ejection fraction in clinical practice.
- Multicenter and randomized controlled trials on large cohorts are needed to better elucidate the efficacy and safety of sacubitril/valsartan on the right ventricular system in patients with heart failure with reduced ejection fraction and determine whether the improvement in right ventricular function is exclusively mediated by the improvement in left heart function.

Nonstandard Abbreviations and Acronyms

HFrEF	heart failure with reduced ejection fraction
mPAP	mean pulmonary arterial pressure
PH	pulmonary hypertension
RVD	right ventricular dysfunction
S/V	sacubitril/valsartan
S'	tricuspid annular peak systolic velocity
sPAP	systolic pulmonary arterial pressure
TAPSE	tricuspid annular plane systolic excursion
WMD	weighted mean difference

as a first-line therapy for suitable patients with HFrEF, following the results in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial,[3] which prospectively compared angiotensin receptor neprilysin inhibitor versus angiotensin-converting enzyme inhibitor to determine the impact on overall mortality and morbidity in HFrEF.

Because of the diverse causes and pathogenesis, it is common for patients with HFrEF to have coexisting right ventricular (RV) dysfunction (RVD).[4] Cardiomyopathy and coronary artery disease could involve both ventricles simultaneously.[5] The passive transmission of elevated left-sided filling pressure in patients with HFrEF also contributes to adverse changes in the pulmonary vasculature and right heart.[6] Besides, the prevalence of pulmonary hypertension (PH) was reported to be between 40% and 75% in HFrEF.[6,7]

RVD plays a crucial role and indicates a poor prognosis in the progression of HFrEF.[8] Dini et al[9] have confirmed that RV recovery during follow-up was associated with improved survival in patients with HFrEF. Thus, the therapeutic effect on the right heart should also be concerned when treating HFrEF. To date, the effects of S/V on the left heart function have already been discovered,[10] but its effects on the right heart function remain unclear. Several preclinical trials[11,12] showed that S/V could reduce pulmonary pressures, improve vascular remodeling, and prevent maladaptive RV remodeling as well, in the Sugen5416/hypoxia or pulmonary artery banding rat model. Some observational studies[13,14] reported that these beneficial effects were also seen in patients with HFrEF in clinical practice. Nevertheless, Bayard et al[15] failed to establish any benefits of S/V on RV function. Thus, the effects of S/V on the RV systems remain controversial.

In this context, we conducted a meta-analysis to evaluate the impact of S/V on RV function and PH in patients with HFrEF, as well as on left heart function and biomarkers.

METHODS

Meta-Analysis Protocol

Our study protocol was registered on PROSPERO (International Prospective Register of Systematic Reviews; CRD42021247970). The methods used in practice did not deviate in any way from the prespecified methods in our analysis. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[16] and the Meta-Analysis of Observational Studies in Epidemiology[17] guidelines during all stages of design, implementation, and reporting (Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology Checklist). The methods used in the analysis and materials used to conduct the research are available from the corresponding author on reasonable request.

Study Selection

Inclusion criteria were as follows:

1. Adult patients (aged >18 years) with HFrEF.
2. Patients subjected to "S/V" treatment at the beginning of the trial.

3. Patients with baseline and follow-up data for at least 1 RV function or pulmonary pressure index.
4. Follow-up duration for at least 3 months.
5. Measurement methods were restricted to echocardiography.

Editorials, letters, comments, review articles, case reports, and studies consisting of <10 patients were excluded. Studies in which patients had congenital heart diseases were also excluded. Two independent authors (J.Z. and L.D.) were responsible for performing the study selection process according to titles, abstracts, and full texts, and disagreements were resolved by consultation with a third reviewer (X.G.).

Information Sources and Search Strategy

Two authors (J.Z. and X.Q.) independently performed a systematic search of PubMed, Embase, Cochrane Library, and Web of Science from January 2010 to April 2021. Search terms included "sacubitril-valsartan," "angiotensin receptor-neprilysin inhibitor," "heart failure," and "heart decompensation." The search was restricted to "article." There were no language restrictions. The complete list of search terms used in each database is outlined in Data S1. We also screened the reference lists of included studies for additional eligible studies not retrieved by our search. Moreover, the search was rerun before the final analysis. All citations were exported to Endnote Reference Manager version X9 (Clarivate Analytics).

Data Extraction

Data extraction was performed independently by 2 authors (J.Z. and L.D.). Any disagreements were resolved by consulting a third author (X.G.). The following data were collected: the first author, year of publication, country, study design, treatments of control groups, sample size, patient characteristics (age, sex, mean baseline systolic blood pressure, and heart failure [HF] cause), settings (advanced or chronic HF), methods of measurement, and follow-up duration. Three kinds of indexes were then extracted (RV function and PH, left heart function, and biomarker), comprising baseline and follow-up data.

We extracted indexes representing RV function, including tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular peak systolic velocity (S'), and indexes reflecting pulmonary circulation, including systolic pulmonary arterial pressure (sPAP) and mean pulmonary arterial pressure (mPAP). Meanwhile, indexes of left heart function included left ventricular (LV) ejection fraction (LVEF) and LV end-diastolic volume (LVEDV). As for biomarkers, we selected NT-proBNP (N-terminal pro-B-type natriuretic peptide), which could reflect wall stress.

Risk of Bias

Two independent authors (J.Z. and L.D.) assessed the risk of bias and quality of included studies using the Newcastle-Ottawa scale for observational studies. Disagreements were resolved in consultation with a third author (X.G.). We assessed the following 3 items:

Table 1. Study and Patient Characteristics

First author (y)	Country	Study design	Interventions and controls	Patients, n	Settings	Age, mean±SD, y	Men, %
Nakou (2018)[24]	Greece	Observational study (prospectively)	ARNI ACEI	48	Chronic HFrEF	68±10	60.4
Cacciatore (2020)[22]	Italy	Observational study (prospectively)	ARNI	37	Advanced HF	57.7±7.6	89.2
Bayard (2019)[15]	France	Observational study (prospectively)	ARNI	41	HFrEF	70±10	75.6
Correale (2020)[13]	Italy	Observational study (prospectively)	ARNI	60	HFrEF	66±9	88
Poglajen (2020)[25]	Slovenia	Observational study (prospectively)	ARNI	228	HFrEF	57±11	83
Mazzetti (2020)[23]	Italy	Observational study (prospectively)	ARNI	30	HFrEF	64±10.7	70
Villani (2020)[27]	Italy	Observational study (retrospectively)	ARNI	69	HFrEF	67±12	93
Yenercag (2021)[28]	Turkey	Observational study (retrospectively)	ARNI	150	HFrEF	63.1±12.5	54
Landolfo (2020)[26]	Italy	Observational study (retrospectively)	ARNI	49	HFrEF	76±11	71.4
Masarone (2020)[14]	Italy	Observational study (retrospectively)	ARNI	163	HFrEF	57.9±12.3	68.1

(Contiune)

Table 1. Contiuned

First author (y)	Baseline SBP, mean±SD, mm Hg	Ischemic cause, %	Measurement method	Indexes	Biomarkers	Follow-up, mo
Nakou (2018)[24]	122.7±10.7	69.5	Echocardiography	TAPSE, S', LVEF	NA	6
Cacciatore (2020)[22]	110±11.5	32.4	Echocardiography	TAPSE, sPAP, mPAP, LVEF	NT-proBNP	17.1
Bayard (2019)[15]	NA	58.5	Echocardiography	TAPSE, sPAP, LVEF, LVEDV	NA	3
Correale (2020)[13]	123±20	43	Echocardiography	TAPSE, sPAP, LVEF, LVEDV	NT-proBNP	12
Poglajen (2020)[25]	NA	36	Echocardiography	TAPSE, LVEF	NT-proBNP	12
Mazzetti (2020)[23]	121.11±17	40	Echocardiography	TAPSE, LVEF, LVEDV	NA	6
Villani (2020)[27]	121±18	66.7	Echocardiography	sPAP, LVEF	NT-proBNP	12
Yenercag (2021)[28]	NA	64	Echocardiography	TAPSE, mPAP, LVEF, LVEDV	NT-proBNP	6
Landolfo (2020)[26]	127±14	65.3	Echocardiography	sPAP, LVEF, LVEDV	NA	12
Masarone (2020)[14]	119±14.8	50.9	Echocardiography	TAPSE, S', sPAP, mPAP, LVEF, LVEDV	NA	12

ACEI indicates angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor neprilysin inhibitor; HF, heart failure; HFrEF, HF with reduced ejection fraction; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; S', tricuspid annular peak systolic velocity; SBP, systolic blood pressure; sPAP, systolic pulmonary arterial pressure; and TAPSE, tricuspid annular plane systolic excursion.

selection of cohort (0–4 stars), comparability (0–2 stars), and outcome (0–3 stars), with overall scores of <5 stars, 5 to 7 stars, and >7 stars indicating high, moderate, and low risk of bias, respectively.[18]

Outcome Measures and Statistical Analysis

The main outcomes were changes in RV function and PH (TAPSE, S', sPAP, and mPAP), left heart function (LVEF and LVEDV), and NT-proBNP during the follow-up period. These indexes were all continuous variables, primarily expressed as mean±SD.

Analyses were performed using the Stata 15.1 software package. Continuous variables were pooled using a random-effects model to estimate weighted mean differences (WMDs) with 95% CIs, which were plotted as forest plots. Between-study heterogeneity was quantified using the Cochrane I^2 statistic, with I^2=25% to 50%, 50% to 75%, and >75%, indicating mild, moderate, and severe heterogeneity, respectively.[19] Each study's effect on the overall effect size was assessed by a sensitivity analysis using the leave-one-out approach. Multivariate random-effects meta-regression analysis was performed to explore the sources of heterogeneity between studies. Subgroup analysis was conducted on the basis of HF cause (proportion of patients with ischemic heart disease >50% or ≤50%), mean age (>70 or ≤70 years), country (Italy or others), follow-up durations (>6 or ≤6 months), study design (prospective or retrospective), and sample size (>100 or ≤100). Egger regression tests with a visual inspection of the funnel plot were used to test for publication bias.[20,21] P<0.05 was considered statistically significant.

Another outcome was the relationship between changes in the RV system and the left heart function. First, we used the Shapiro-Wilk test to detect whether the data were normally distributed. If so, Pearson correlation was used. If not, Spearman correlation was used. Analyses were operated using SPSS 26.

RESULTS

Literature Search and Baseline Characteristics

Our literature search identified 3670 publications from January 2010 to April 2021. Following the removal of 1729 duplicates, the titles and abstracts of the remaining 1941 records were screened for eligibility. Of these, we excluded a further 1738 articles. Thus, 10 studies were included in the quantitative and qualitative analyses, with a total of 875 patients, all of which were observational. The literature search process is detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Figure S1).

The baseline characteristics are presented in Table 1. The year of publication was between 2018 and 2020. The mean age of included patients was 62.2 years, and 74.0% of them were men. The included subjects were all patients with HF with ejection fractions of ≤40%. The mean follow-up duration ranged from 3 to 17.1 months. Of the 10 included studies, 6[13,15,22–25] were prospective, and 4[14,26–28] were retrospective. One study[24] had a control group that received angiotensin-converting enzyme inhibitor, whereas the others had no control group. Because it was not meaningful to analyze the only study[24] with a control group separately, we decided to extract the experimental group data from it. Six studies[13,14,22,23,26,27] were from Italy, one[28] was from Turkey, one[15] was from France, one[24] was from Greece, and one[25] was from Slovenia.

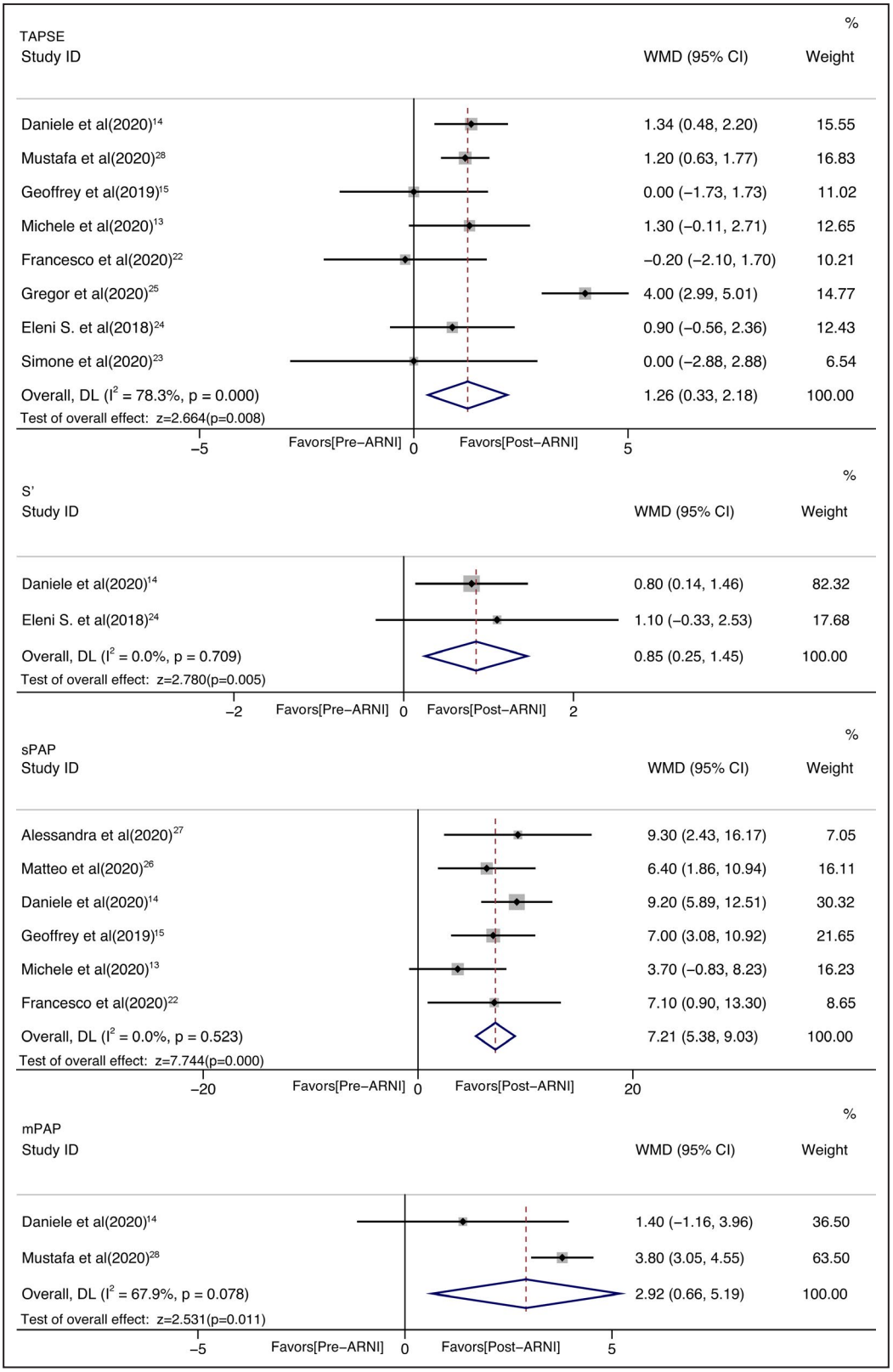

Figure 1. Forest plots showing changes in tricuspid annular plane systolic excursion (TAPSE), tricuspid annular peak systolic velocity (S'), systolic pulmonary arterial pressure (sPAP), and mean pulmonary arterial pressure (mPAP).
ARNI indicates angiotensin receptor neprilysin inhibitor; ID, identifier; WMD, weighted mean difference; and DL, DerSimonian-Laird, a method of the random-effects model.

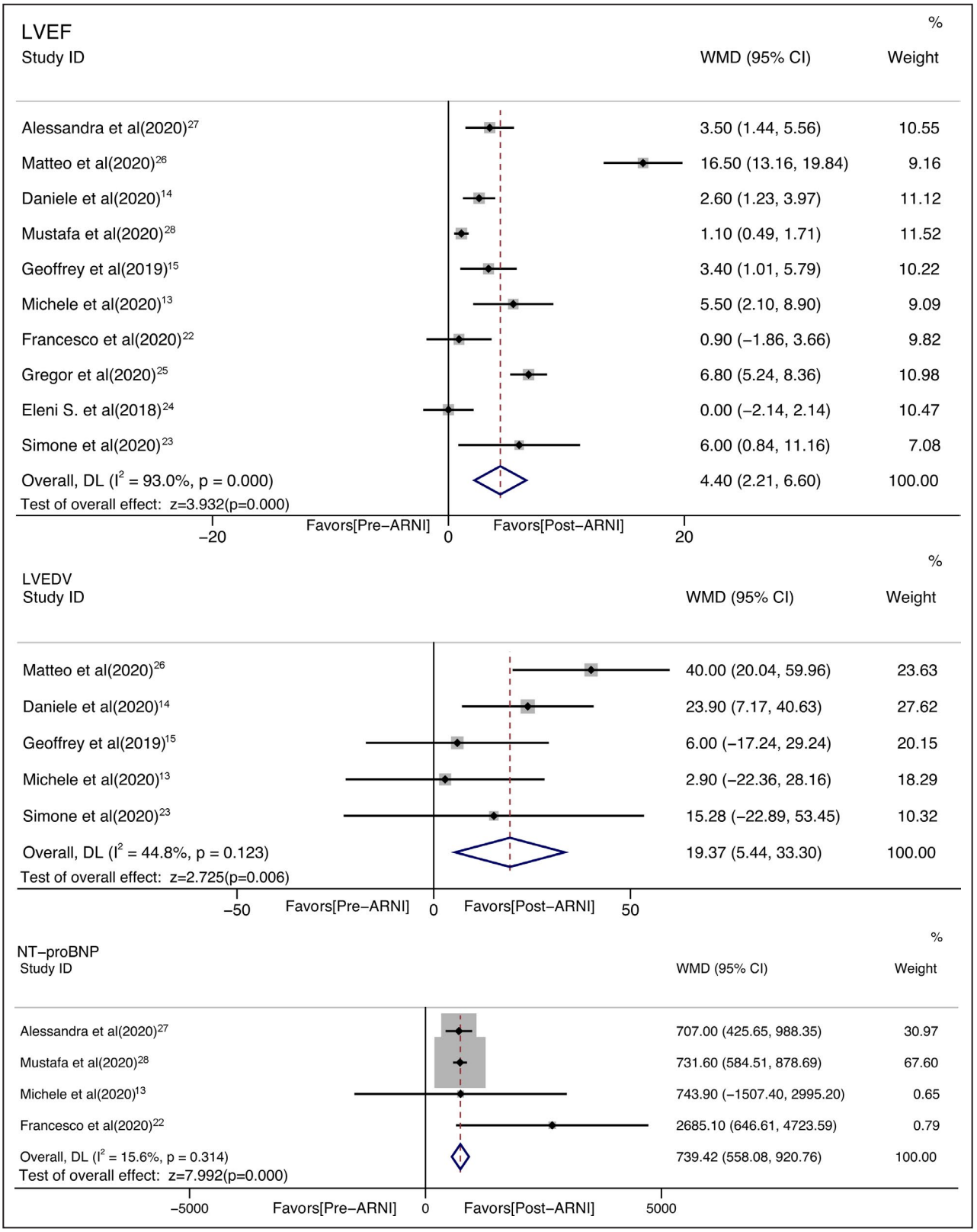

Figure 2. Forest plots showing changes in left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and NT-proBNP (N-terminal pro-B-type natriuretic peptide).
ARNI indicates angiotensin receptor neprilysin inhibitor; ID, identifier; WMD, weighted mean difference; and DL, DerSimonian-Laird, a method of the random-effects model.

Table 2. Results of Random-Effects Meta-Regression Analysis

Covariate	TAPSE		LVEF	
	Coefficient	*P* value	Coefficient	*P* value
Mean age, y	0.203	0.125	1.227	0.004*
HF cause, %	−6.562	0.054	−31.150	0.015*
Sample size	0.022	0.016*	0.051	0.026*

HF indicates heart failure; LVEF, left ventricular ejection fraction; and TAPSE, tricuspid annular plane systolic excursion.
*Statistically significant.

Risk-of-Bias Assessment and Publication Bias

The Newcastle-Ottawa scale scores of the included studies are shown in Table S1, ranging from 6 to 9. Most included studies[13–15,22,23,25–28] had a moderate risk of bias because of the lack of a control group, 4[14,26–28] of which had a higher risk of bias because of the nature of the retrospective studies. The risk of bias was shown to be low in only one study.[24]

With regard to publication bias, we conducted funnel plot analysis for indexes with at least 10 studies[29] and Egger regression for all indexes. The funnel plot of LVEF was basically symmetrical (Figure S2). No significant publication bias was indicated by Egger regression for all indexes ($P>0.05$).

Effects of S/V on RV Function and PH

The pooled data from 8 studies[13–15,22–25,28] (732 patients) showed increases in TAPSE (WMD, 1.26 mm; 95% CI, 0.33 to 2.18 mm; I^2=78.3%; Figure 1 and Table S2). Two studies[14,24] (186 patients) reported data on S', which was improved after the treatment with S/V (WMD, 0.85 cm/s; 95% CI, 0.25–1.45 cm/s; I^2=0.0%; Figure 1 and Table S2). Changes in sPAP (419 patients) and mPAP (350 patients) were available in 6[13–15,22,26,27] and 2[14,28] trials, respectively. We observed significant reductions in sPAP (WMD, 7.21 mm Hg; 95% CI, 5.38–9.03 mm Hg; I^2=0%; Figure 1 and Table S2) and mPAP (WMD, 2.92 mm Hg; 95% CI, 0.66–5.19 mm Hg; I^2=67.9%; Figure 1 and Table S2). All results were statistically significant ($P<0.05$).

Effects of S/V on Left Heart Function and NT-proBNP

The pooled data from 10 studies[13–15,22–28] (850 patients) showed increases in LVEF (WMD, 4.40%; 95% CI, 2.21%–6.60%; I^2=93.0%; Figure 2 and Table S3). Five studies[13–15,23,26] (313 patients) reported data on LVEDV. The mean LVEDV decreased by 19.37 mL (95% CI, 5.44–33.30 mL; I^2=44.8%; Figure 2 and Table S3). NT-proBNP was reported in 4 studies[13,22,27,28] (316

Table 3. Subgroup Analysis of Changes of TAPSE and sPAP Following Treatment With S/V

Subgroup	No. of studies	TAPSE, mm	sPAP, mm Hg
Cause			
Ischemic heart diseases >50%	6	1.13 (0.70 to 1.57), I^2=0%, z=5.10 (P=0.000)	−7.98 (−10.08 to −5.87), I^2=0%, z=−7.43 (P=0.000)
Ischemic heart diseases ≤50%	4	1.44 (−0.75 to 3.63), I^2=86%, z=1.29 (P=0.198)	−4.88 (−8.54 to −1.23), I^2=0%, z=−2.62 (P=0.009)
Age, y			
>70	1	NA	−6.40 (−10.94 to −1.86), z=−2.76 (P=0.006)
≤70	9	1.26 (0.33 to 2.18), I^2=92%, z=2.66 (P=0.008)	−7.36 (−9.36 to −5.35), I^2=1%, z=−7.19 (P=0.000)
Country			
Italy	6	1.07 (0.40 to 1.74), I^2=0%, z=3.15 (P=0.002)	−7.24 (−9.36 to −5.12), I^2=4%, z=−6.69 (P=0.000)
Others	4	1.60 (−0.04 to 3.24), I^2=89%, z=1.91 (P=0.056)	−7.00 (−10.92 to −3.08), z=−3.50 (P=0.000)
Follow-up duration, mo			
>6	6	1.71 (0.02 to 3.40), I^2=87%, z=1.99 (P=0.047)	−7.24 (−9.36 to −5.12), I^2=4%, z=−6.69 (P=0.000)
≤6	4	1.03 (0.53 to 1.53), I^2=0%, z=4.06 (P=0.000)	−7.00 (−10.92 to −3.08), z=−3.50 (P=0.000)
Study design			
Retrospective	4	1.24 (0.77 to 1.72), I^2=0%, z=5.15 (P=0.000)	−8.37 (−10.86 to −5.88), I^2=0%, z=−6.58 (P=0.000)
Prospective	6	1.13 (−0.46 to 2.72), I^2=83%, z=1.40 (P=0.163)	−5.87 (−8.54 to −3.19), I^2=0%, z=−4.30 (P=0.000)
Sample size			
>100	3	2.14 (0.56 to 3.72), I^2=92%, z=2.65 (P=0.008)	−9.20 (−12.51 to −5.89), z=−5.44 (P=0.000)
≤100	7	0.60 (−0.17 to 1.37), I^2=0%, z=1.53 (P=0.125)	−6.34 (−8.52 to −4.15), I^2=0%, z=−5.69 (P=0.000)

Weighted mean differences are pooled estimates with 95% CIs. I^2 values were reported as a measure of heterogeneity. Z scores with associated P values were reported as a test for the overall effect. Ischemic heart disease >50% meant the proportion of patients with heart failure caused by ischemic heart disease was >50% in one study. Ischemic heart disease ≤50% meant the proportion of patients with heart failure caused by ischemic heart disease was ≤50% in one study. NA indicates not applicable; sPAP, systolic pulmonary arterial pressure; S/V, sacubitril/valsartan; and TAPSE, tricuspid annular plane systolic excursion.

Table 4. Subgroup Analysis of Changes of LVEF and NT-proBNP Following Treatment With S/V

Subgroup	No. of studies	LVEF, %	NT-proBNP, ng/dL
Cause			
Ischemic heart diseases >50%	6	4.19 (1.43 to 6.96), I^2=94%, z=2.97 (P=0.003)	−726.32 (−856.67 to −595.97), I^2=0%, z=−10.92 (P=0.000)
Ischemic heart diseases ≤50%	4	4.76 (1.68 to 7.84), I^2=78%, z=3.03 (P=0.002)	−1775.71 (−3674.27 to 122.84), I^2=36%, z=−1.83 (P=0.067)
Age, y			
>70	1	16.50 (13.16 to 19.84), z=9.68 (P=0.000)	NA
≤70	9	3.10 (1.47 to 4.74), I^2=86%, z=3.73 (P=0.000)	−739.42 (−920.76 to −558.08), I^2=73%, z=−7.99 (P=0.000)
Country			
Italy	6	5.70 (1.92 to 9.48), I^2=92%, z=2.95 (P=0.003)	−1107.46 (−2198.07 to −16.85) I^2=44%, z=−1.99 (P=0.047)
Others	4	2.83 (−0.22 to 5.87), I^2=94%, z=1.82 (P=0.069)	−731.60 (−878.69 to −584.51), z=−9.75 (P=0.000)
Follow-up duration, mo			
>6	6	5.83 (2.49 to 9.16), I^2=93.1%, z=3.43 (P=0.001)	−1107.46 (−2198.07 to −16.85), I^2=44%, z=−1.99 (P=0.047)
≤6	4	1.77 (0.10 to 3.45), I^2=62.0%, z=2.07 (P=0.038)	−731.60 (−878.69 to −584.51), z=−9.75 (P=0.000)
Study design			
Retrospective	4	5.54 (1.64 to 9.45), I^2=96%, z=2.78 (P=0.005)	−726.32 (−856.67 to −595.97), I^2=0%, z=−10.92 (P=0.000)
Prospective	6	3.64 (0.98 to 6.30), I^2=85%, z=2.68 (P=0.007)	−1775.71 (−3674.27 to 122.84), I^2=36%, z=−1.83 (P=0.067)
Sample size			
>100	3	3.44 (0.27 to 6.61), I^2=96%, z=2.13 (P=0.033)	−731.60 (−878.69 to −584.51), z=−9.75 (P=0.000)
≤100	7	4.99 (1.32 to 8.66), I^2=92%, z=2.67 (P=0.008)	−1107.46 (−2198.07 to −16.85), I^2=44%, z=−1.99 (P=0.047)

Weighted mean differences are pooled estimates with 95% CIs. I^2 values were reported as a measure of heterogeneity. Z scores with associated P values were reported as a test for the overall effect. Ischemic heart disease >50% meant the proportion of patients with heart failure caused by ischemic heart disease was >50% in one study. Ischemic heart disease ≤50% meant the proportion of patients with heart failure caused by ischemic heart disease was ≤50% in one study. LVEF indicates left ventricular ejection fraction; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and S/V, sacubitril/valsartan.

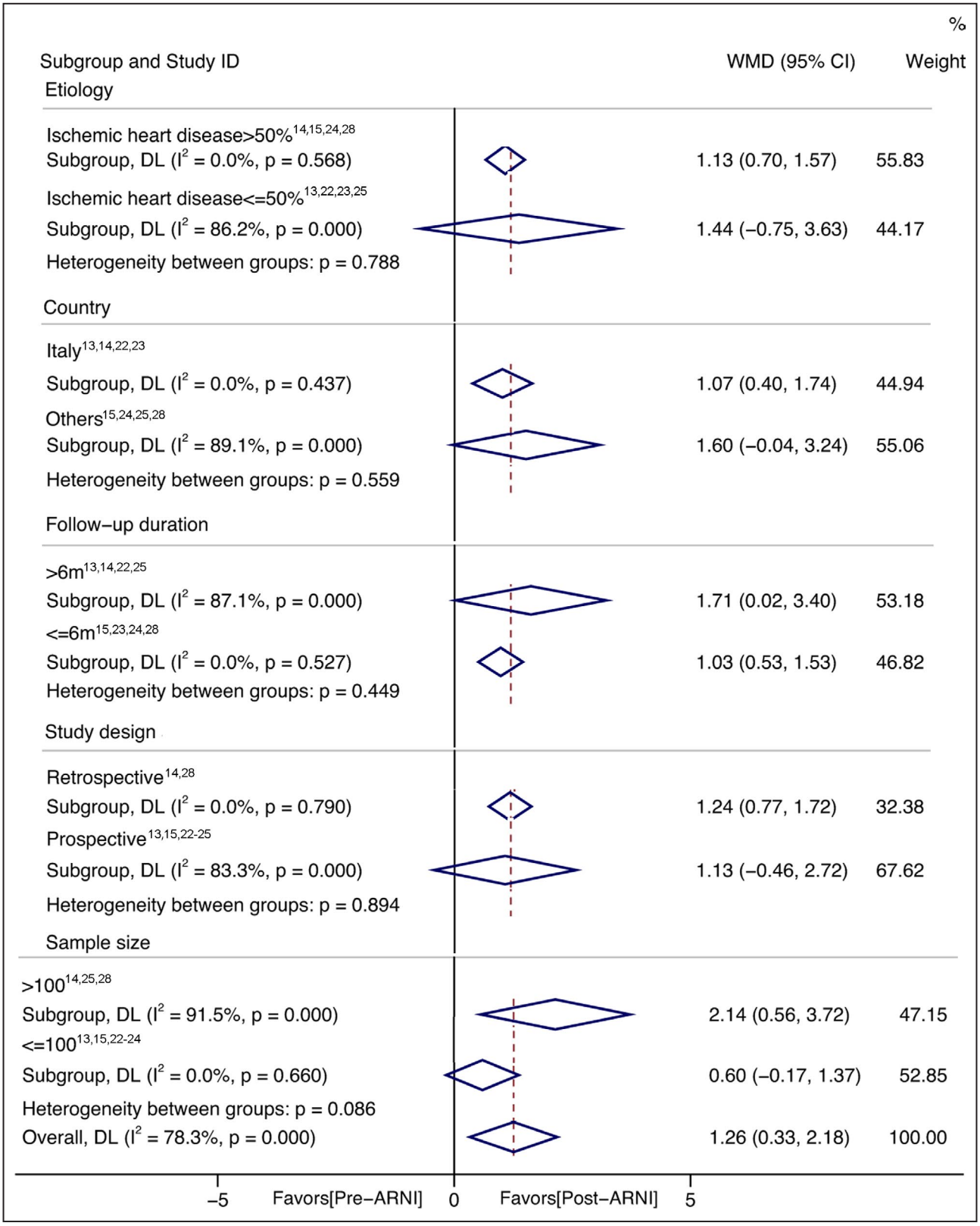

Figure 3. Forest plots for subgroup analysis of tricuspid annular plane systolic excursion, according to heart failure cause, country, follow-up duration, study design, and sample size.
ARNI indicates angiotensin receptor neprilysin inhibitor; ID, identifier; WMD, weighted mean difference; and DL, DerSimonian-Laird, a method of the random-effects model.

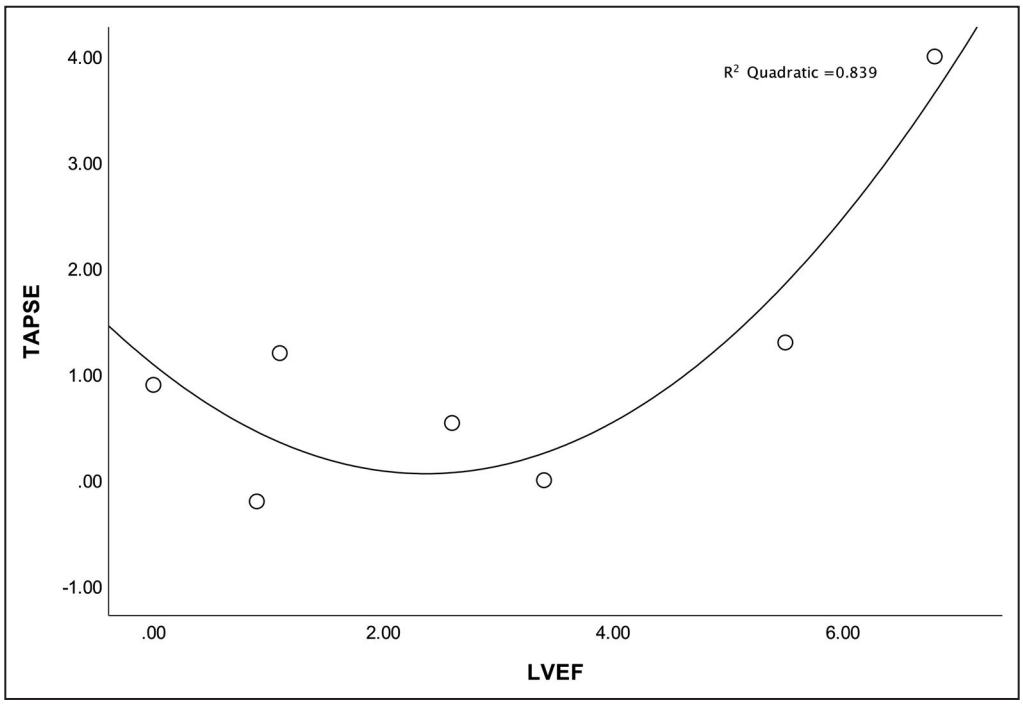

Figure 4. Fitting curve using quadratic curve model to explore the relationship between tricuspid annular plane systolic excursion (TAPSE) and left ventricular ejection fraction (LVEF) changes.

patients), which was significantly decreased following S/V (WMD, 739.42 ng/dL; 95% CI, 558.08–920.76 ng/dL; I^2=15.6%; Figure 2 and Table S3).

Sensitivity Analysis

Results of sensitivity analysis using the leave-one-out approach were consistent with those of the initial analysis. Therefore, we thought our results had good robustness and extrapolation.

Meta-Regression and Subgroup Analysis

Multivariate meta-regression analysis revealed that the sample size might contribute to the heterogeneity observed in TAPSE (P<0.05; Table 2). In addition, mean age, HF cause, and sample size were also found to be possible sources of heterogeneity in LVEF (P<0.05; Table 2). Meta-regression was not performed for others because of the low number of studies reporting those indexes.

The results of subgroup analysis are presented in Tables 3 and 4. The proportion of patients with ischemic heart disease >50%, retrospective design, and sample size >100 showed statistically significant improvements in TAPSE, and the increases were also seen in both short- and long-term follow-up (Figures S3 through S5). Moreover, the I^2 statistic of TAPSE was reduced to 0% when the analysis was conducted in accordance with HF cause, country, follow-up duration, and study design (Figure 3). In terms of sPAP, the results of subgroup analysis conducted on the basis of 6 baseline characteristics were all statistically significant. Improvements in LVEF were also meaningful in most subgroups. NT-proBNP seemed to decline significantly in studies with patients with ischemic heart disease >50%.

Correlation Analysis

To test whether the improvements in the RV system correlated with those in the left heart function, we did a correlation analysis. After performing the Shapiro-Wilk test, we adopted Pearson correlations for 2 pairs of indexes (TAPSE and LVEDV; sPAP and LVEDV), and the potential relationships between others were calculated using Spearman correlations.

There was no significant correlation of improvements between RV system and left heart indexes (TAPSE and LVEF, r=0.359, P=0.382; TAPSE and LVEDV, r=0.310, P=0.690; sPAP and LVEF, r=0.543, P=0.266; sPAP and LVEDV, r=0.427, P=0.573) (Figure S6). Nevertheless, a distinct correlation between sPAP and LVEDV (r=1.000) emerged after removing one significantly deviated data point in the scatterplot.[26] Although the scatterplot of TAPSE and LVEF also showed one deviated data point,[23] the preliminary analysis after the data point was discarded did not show a significant correlation.

Subsequently, a certain correlation appeared to be found in the quadratic regression model for TAPSE and LVEF (P=0.026). The regression equation was y=1.09−0.87x+0.18x^2 (Figure 4).

DISCUSSION

As far as we know, this present study comprising 875 patients is the first meta-analysis to evaluate the effects of S/V on RV function and PH in patients with HFrEF, which included all appropriate studies to date. The pooled results showed that S/V significantly improved TAPSE and S', and reduced sPAP and mPAP as well. The former 2 indexes reflect the functional state of the right ventricle, whereas the latter directly reflect the state of the pulmonary circulation. We also observed remarkable improvements in LVEF and reductions in LVEDV, reflecting the benefits of S/V on left heart function, which were in line with the conclusion reported in a previous meta-analysis.[10]

The mechanisms by which S/V improves RV function and PH have not been fully elucidated. However, the pathogenesis of RVD with the pharmacological mechanism of S/V could offer several possible explanations. The pathogenesis of RVD in HFrEF could be artificially divided into 3 categories: pressure overload, ischemic heart disease, and cardiomyopathy. In a pressure-overload RV, to accommodate the increased afterload, adaptive cardiomyocyte hypertrophy initially occurs,[30] with subsequent oxygen supply-demand imbalance and RV ischemia,[31] gradually leading to RV fibrosis,[32] RV dilation, and clinical decompensation eventually.[33] Neurohormonal activation (upregulation of angiotensin II, adrenergic overstimulation, and increased expression of natriuretic peptides), oxidative stress, and cell death play pivotal roles throughout the whole RVD progression.[31] Besides, with regard to arrhythmogenic right ventricular cardiomyopathy being a model of RV cardiomyopathy, it was reported that the upregulated expression of transforming growth factor-β1 acting downstream of angiotensin II could induce the fibrotic gene expression in vivo, leading to RV fibrosis.[34–36] Sacubitril/valsartan, as the name implies, has dual effects: inhibition of neprilysin and inactivation of the renin-angiotensin-aldosterone system. Through inactivation of many neurohormones, such as angiotensin II, aldosterone, and endothelin-1, modulation of gene expression, such as transforming growth factor-β1, and promotion of reendothelization, S/V leads to natriuresis, vasodilation, and antiapoptotic, antifibrotic, anti-inflammatory, and antithrombotic reactions, as well as decreased cardiac hypertrophy, and ultimately improves cardiac decompensation.[37–39] In short, S/V might improve RV function by inducing RV function recovery and decreasing its afterload by multiple mechanisms, which has been demonstrated in a preclinical study.[11]

We conducted subgroup analysis to find the sources of heterogeneity among studies and described the differences of pooled results between the subgroups. HF cause, country, follow-up duration, and study design contributed to the heterogeneity observed in TAPSE. Interestingly, we observed significant improvements in TAPSE in patients with ischemic heart disease, and significant decreases of sPAP and NT-proBNP were also found in this population. Together with the significant improvement of S' observed in the ischemic population, our findings suggest that S/V might have better therapeutic effects on the right heart in HFrEF caused by ischemic heart disease than those with nonischemic causes. Notably, this finding might be explained by the hypothesis that the neprilysin level may be higher in such a population, providing more targets for S/V and thus leading to better improvements. More studies are needed to clarify the underlying mechanisms in the future. However, Balmforth et al[40] concluded that the benefits of S/V on the primary composite outcome and cardiovascular mortality over enalapril were similar across causative categories in the analysis of PARADIGM-HF. It could be explained that the clinical outcomes are influenced by multiple factors, including but not limited to right heart dysfunction. Analysis stratified by follow-up duration showed striking effects of S/V on all 4 indexes in both short- and long-term follow-up. This suggested that S/V had a rapid therapeutic effect within 6 months. In a prospective pilot study of 13 patients with HFrEF, Khan et al[41] also observed a short-term reduction in pulmonary arterial pressure at 1-week follow-up after S/V initiation. The PIONEER-HF (Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure) trial[42] showed that the greater reduction in the NT-proBNP concentration was evident as early as week 1. Consequently, it is of great benefit for eligible patients to initiate therapy as early as possible. Notably, because of the small sample size, these results should be interpreted with caution.

The correlation analysis showed a possible relationship between improvements of the RV system and LV reverse remodeling. We found that the improvements in sPAP may depend on that in LVEDV, confirming what Correale et al[13] previously discovered, that sPAP changes were proportional to LV end-systolic volume changes. It could be explained in such a way that the improved left ventricle reduced the backward transmission of left-sided filling pressure to the pulmonary circulation, resulting in lower pulmonary arterial pressure. Interestingly, the nonlinear correlation for the quadratic model indicated better improvement in TAPSE was in accordance with that in LVEF within a certain scope. Only when LVEF improves to a certain extent will TAPSE improves. Besides, the scatterplot of TAPSE and LVEDV also showed a delayed improvement trend rather than a linear correlation. This nonlinear relationship makes us speculate that the

beneficial effects of S/V on RV function might be related to the reverse remodeling of the LV and a direct effect on the right heart. As we mentioned above, the results need to be interpreted cautiously because of the small sample size. Hence, further studies are necessary to confirm the role of S/V in the treatment of isolated RV dysfunction independent of LV remodeling.

Limitations

Certainly, the present meta-analysis has several limitations. First, the main limitation was that the included studies were all observational, which did not have the power to infer cause and effect. Although only one included study had a control group, nearly all patients were treated with stable angiotensin-converting enzyme inhibitor or angiotensin receptor blocker doses for a certain period before S/V initiation, and after switching to S/V, we have observed incremental improvements. Second, inherent to many meta-analyses, the sample sizes of most included studies were small. Third, because of the restricted numbers of studies about the effect of S/V on the right heart system, the published year and region of studies included in our analysis were relatively concentrated. Hence, because of several limitations, the results of this meta-analysis should be interpreted cautiously.

CONCLUSIONS

This meta-analysis suggested a new therapeutic role for S/V, and verified that S/V could improve RV function and PH in HFrEF, which did not seem to be fully dependent on the reverse remodeling of LV. Moreover, these effects may be particularly pronounced in patients with ischemic heart disease. S/V had a significant therapeutic effect on both LV and RV function within 6 months, increasing over time. It is of extreme importance for eligible patients to initiate S/V therapy as early as possible. Multicenter and randomized controlled trials on large cohorts are needed to better elucidate the efficacy and safety of S/V on the RV system in patients with HFrEF and determine whether the improvement in RV function is exclusively mediated by improvement in left heart function.

ARTICLE INFORMATION

Received October 25, 2021; accepted March 3, 2022.

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Sources of Funding

This work was supported by the National Natural Science Foundation of China (82170397).

Disclosures

None.

Supplemental Material

Data S1
Tables S1–S3
Figures S1–S6
PRISMA 2020 Checklist, MOOSE Checklist

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Supplemental Material

Data S1

Search Strategy

We performed a systematic search of PubMed, Embase, Cochrane Library and Web of Science from 01/2010 to 04/2021. The search was restricted to 'Article'. There was no language restriction.

PubMed search strategy:

((((((((((Ventricular Dysfunction, Right) OR Right Ventricular Dysfunction) OR Dysfunction, Right Ventricular) OR Dysfunctions, Right Ventricular) OR Right Ventricular Dysfunctions) OR Ventricular Dysfunctions, Right) OR right ventricular failure)) 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 Myocardial Failure) OR Congestive Heart Failure) OR Heart Failure, Congestive) OR Heart Failure, Left-Sided) OR Heart Failure, Left Sided) OR Left-Sided Heart Failure) OR Left Sided Heart Failure)))) AND ((((((((((sacubitril-valsartan) OR sacubitril valsartan sodium hydrate) OR sacubitril valsartan drug combination) OR sacubitril) OR entresto) OR LCZ 696) OR LCZ696) OR LCZ-696) OR Sacubitril/valsartan) OR Angiotensin Receptor-Neprilysin Inhibitor) OR Sacubitril/Valsartan)

Filters: from 2010 – 2021

Total 1332

Embase search strategy:

('heart right ventricle function'/exp OR 'heart right ventricle function':ab,ti OR 'right ventricular dysfunction':ab,ti OR 'dysfunction, right ventricular':ab,ti OR 'dysfunctions, right ventricular':ab,ti OR 'right ventricular dysfunctions':ab,ti OR 'ventricular dysfunctions, right':ab,ti OR 'right ventricular failure':ab,ti OR 'heart failure'/exp OR 'cardiac failure':ab,ti OR 'heart decompensation':ab,ti OR 'decompensation, heart':ab,ti OR 'heart failure, right-sided':ab,ti OR 'heart failure, right sided':ab,ti OR 'right-sided heart failure':ab,ti OR 'right sided heart failure':ab,ti OR 'myocardial failure':ab,ti OR 'congestive heart failure':ab,ti OR 'heart failure, congestive':ab,ti OR 'heart failure, left-sided':ab,ti OR 'heart failure, left sided':ab,ti OR 'left-sided heart failure':ab,ti OR 'left sided heart failure':ab,ti) AND ('sacubitril plus valsartan'/exp OR 'sacubitril-valsartan':ab,ti OR 'sacubitril valsartan sodium hydrate':ab,ti OR 'sacubitril valsartan drug combination':ab,ti OR 'sacubitril':ab,ti OR 'entresto':ab,ti OR 'lcz 696':ab,ti OR 'lcz696':ab,ti OR 'lcz-696':ab,ti OR 'angiotensin receptor-neprilysin inhibitor':ab,ti OR 'sacubitril/valsartan':ab,ti) AND [2010-2021]/py AND [article]/lim

Total 834

The Cochrane Library search strategy:

#1 MeSH descriptor: [Heart Failure] explode all trees

#2 (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 (myocardial failure) OR (congestive heart failure) OR (heart failure, congestive)

OR (heart failure, left-sided) OR (heart failure, left sided) OR (left-sided heart failure) OR (left sided heart failure)

#3 #1 OR #2

#4 MeSH descriptor: [Ventricular Dysfunction, Right] explode all trees

#5 (heart right ventricle function) OR (right ventricular dysfunction) OR (dysfunction, right ventricular) OR (dysfunctions, right ventricular) OR (right ventricular failure)

#6 #4 OR #5

#7 #3 OR #6

#8 (sacubitril plus valsartan) OR (sacubitril-valsartan) OR (sacubitril valsartan sodium hydrate) OR (sacubitril valsartan drug combination) OR (sacubitril) OR (entresto) OR (lcz 696) OR (lcz696) OR (lcz-696) OR (angiotensin receptor-neprilysin inhibitor)

#9 #7 AND #8

2010.01-2021.04；Trial

Total 245

Web of Science search strategy:

#1 (TS = (sacubitril-valsartan OR sacubitril valsartan sodium hydrate OR sacubitril valsartan drug combination OR sacubitril OR entresto OR LCZ 696 OR LCZ696 OR LCZ-696 OR Sacubitril/valsartan OR Angiotensin Receptor-Neprilysin Inhibitor OR Sacubitril/Valsartan))

#2 (TS=(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 Myocardial Failure or Congestive Heart Failure or Heart Failure, Congestive or Heart Failure, Left-Sided or Heart Failure, Left Sided or Left-Sided Heart Failure or Left Sided Heart Failure or Ventricular Dysfunction, Right or Right Ventricular Dysfunction or Dysfunction, Right Ventricular or Dysfunctions, Right Ventricular or Right Ventricular Dysfunctions or Ventricular Dysfunctions, Right or right ventricular failure))

#3 Restrictive conditions: Time period: 2010-2021; Article types: ARTICLE

#4 #1 and #2 AND #3

Total 1259

Table S1. Quality assessment of included studies according to the Newcastle-Ottawa Scale (NOS).

First Author (Year)	Selection	Comparability	Outcome	Score/Maximum
Eleni S. (2018)[24]	★★★★	★★	★★★	9/9
Francesco (2020)[22]	★★★	★	★★★	7/9
Geoffrey (2019)[15]	★★★	★	★★★	7/9
Michele (2020)[13]	★★★	★	★★★	7/9
Gregor (2020)[25]	★★★	★	★★★	7/9
Simone (2020)[23]	★★★	★	★★★	7/9
Alessandra (2020)[27]	★★	★	★★★	6/9
Mustafa (2020)[28]	★★	★	★★★	6/9
Matteo (2020)[26]	★★	★	★★★	6/9
Daniele (2020)[14]	★★	★	★★★	6/9

A maximum of 4 stars for selection, 2 for comparability and 3 for the outcome.

Table S2. Changes of RV system indices following the treatment of S/V.

First Author (Year)	TAPSE (mm)		S' (cm/sec)		sPAP (mmHg)		mPAP (mmHg)	
	Pre-S/V	Post-S/V	Pre-S/V	Post-S/V	Pre-S/V	Post-S/V	Pre-S/V	Post-S/V
Eleni S. (2018)[24]	14.8 ±2.8	15.7 ±2.2	10.2 ± 2.8	11.3 ± 2.1	NA	NA	NA	NA
Francesco (2020)[22]	16.5 ± 4.6	16.3 ± 3.7	NA	NA	45.3 ± 12.3	40.6 ± 11.1	32.9 ± 9.9	29.7 ± 9.5
Geoffrey (2019)[15]	18±4	18±4	NA	NA	39 ± 10	32±8	NA	NA
Michele (2020)[13]	16.5 ± 4.0	17.8 ± 3.9	NA	NA	34.7 ± 12.5	31.0 ± 12.8	NA	NA
Gregor (2020)[25]	17 ± 5	21 ± 6	NA	NA	NA	NA	NA	NA
Simone (2020)[23]	17 ± 4	17 ± 7	NA	NA	NA	NA	NA	NA
Alessandra (2020)[27]	NA	NA	NA	NA	48.6 ±22.8	39.3±18.1	NA	NA
Mustafa (2020)[28]	18.5 ± 2.6	19.7 ± 2.4	NA	NA	NA	NA	33.9 ± 3.7	30.1 ± 2.9
Matteo (2020)[26]	NA	NA	NA	NA	38.8 ± 10.7	32.4 ± 12.2	NA	NA
Daniele (2020)[14]	18.76 ± 3.7	19.3 ± 3.2	10.4 ± 3.2	11.2 ± 2.9	38.3 ± 15.7	29.1 ± 14.8	24.1 + 12.6	22.7 ± 10.9

TAPSE, tricuspid annular plane systolic excursion; S', tricuspid annular peak systolic velocity; sPAP, systolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; S/V, sacubitril/valsartan; NA, not applicable.

Table S3. Changes of left heart indices and NT-proBNP following the treatment of S/V.

First Author (Year)	LVEF (%)		LVEDV (mL)		NT-proBNP (ng/dL)	
	Pre-S/V	Post-S/V	Pre-S/V	Post-S/V	Pre-S/V	Post-S/V
Eleni S. (2018)[24]	30.23 ±3.7	30.23 ± 3.7	NA	NA	NA	NA
Francesco (2020)[22]	23.5 ± 5.8	24.4 ± 6.3	NA	NA	4943.0 ± 5326.8	2257.9 ± 3413.1
Geoffrey (2019)[15]	32.6±5	36 ± 6	172±49	166 ± 58	NA	NA
Michele (2020)[13]	34.0 ± 9.2	39.5 ± 9.8	177.3 ± 71.1	174.4 ± 70.1	3049.1 ± 5775.1	2305.2 ± 6768.4
Gregor (2020)[25]	29.7% ± 8	36.5% ± 9	NA	NA	NA	NA
Simone (2020)[23]	28 ± 8	34 ± 12	178.36 ± 64.15	163.08 ± 85.22	NA	NA
Alessandra (2020)[27]	29.5±5.2	33±7	NA	NA	1819 ±798	1112 ±886
Mustafa (2020)[28]	30.6 ± 2.9	31.7 ± 2.5	NA	NA	1627.3 ± 826.3	895.7 ± 402.5
Matteo (2020)[26]	33.8 ± 6.8	50.3±9.8	169.7 ± 51.4	129.7 ± 49.4	NA	NA
Daniele (2020)[14]	28.9 ± 6.4	31.5 ± 6.2	237.2 ± 87.6	213.3 ± 64.8	NA	NA

LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; NT-proBNP, N terminal pro B type natriuretic peptide; S/V, sacubitril/valsartan; NA, not applicable.

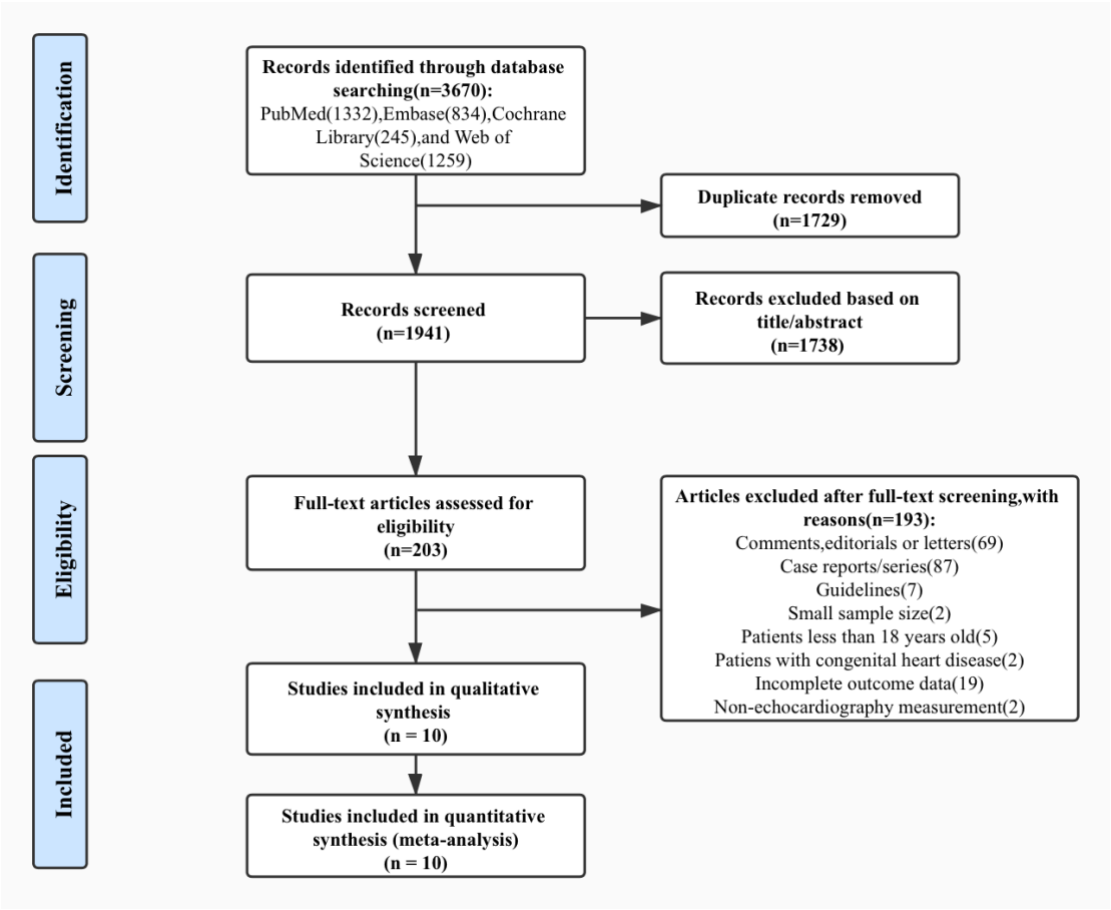

Figure S1. Preferred Reporting Items of Systematic Review and Meta-Analysis (PRISMA) flowchart of study selection.

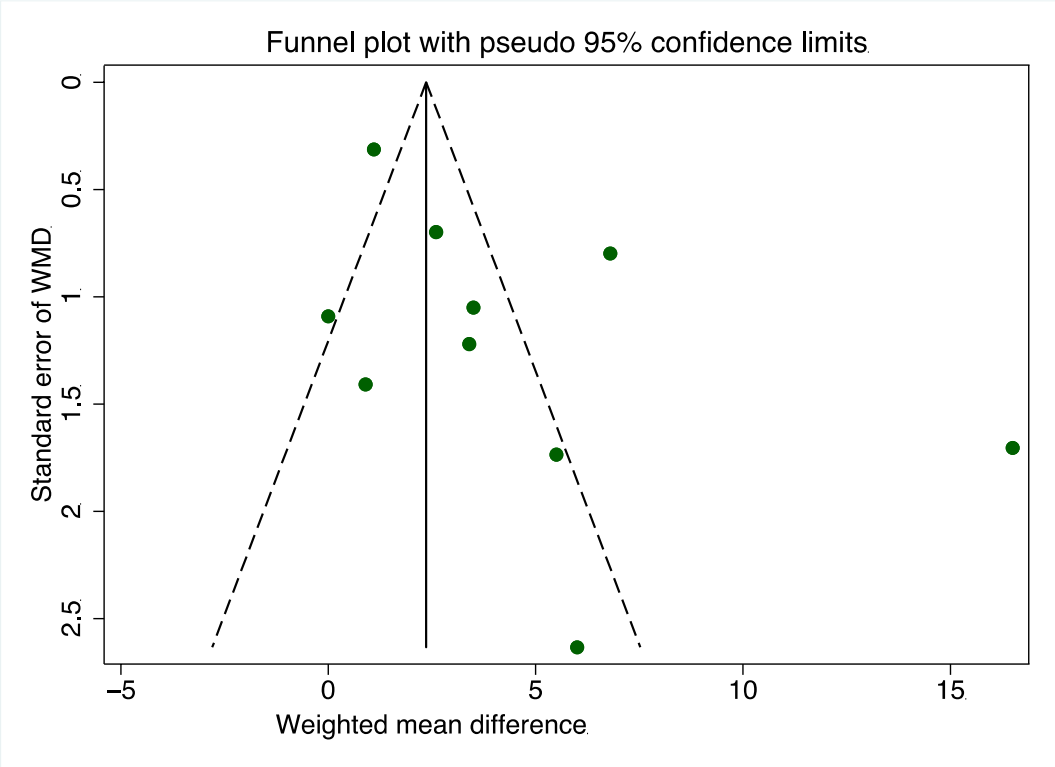

Figure S2. Funnel plots estimating publication bias for LVEF.

LVEF, left ventricular ejection fraction; WMD, weighted mean differences.

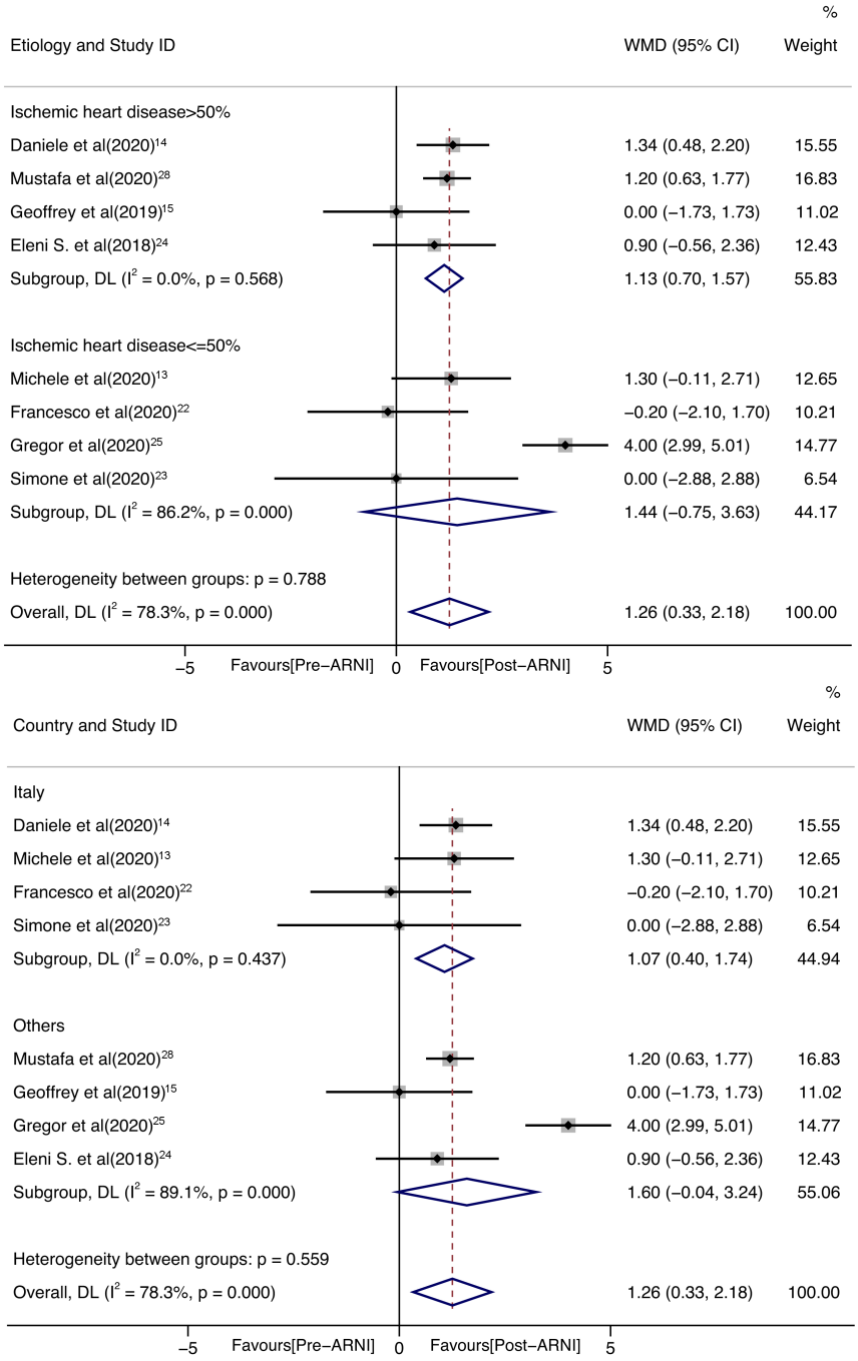

Figure S3. Subgroup analysis of effects of S/V on TAPSE according to HF etiology and country.

S/V, sacubitril/valsartan; TAPSE, tricuspid annular plane systolic excursion; WMD, weighted mean differences; CI, confidence interval; ARNI, angiotensin receptor neprilysin inhibitor; HF, heart failure.

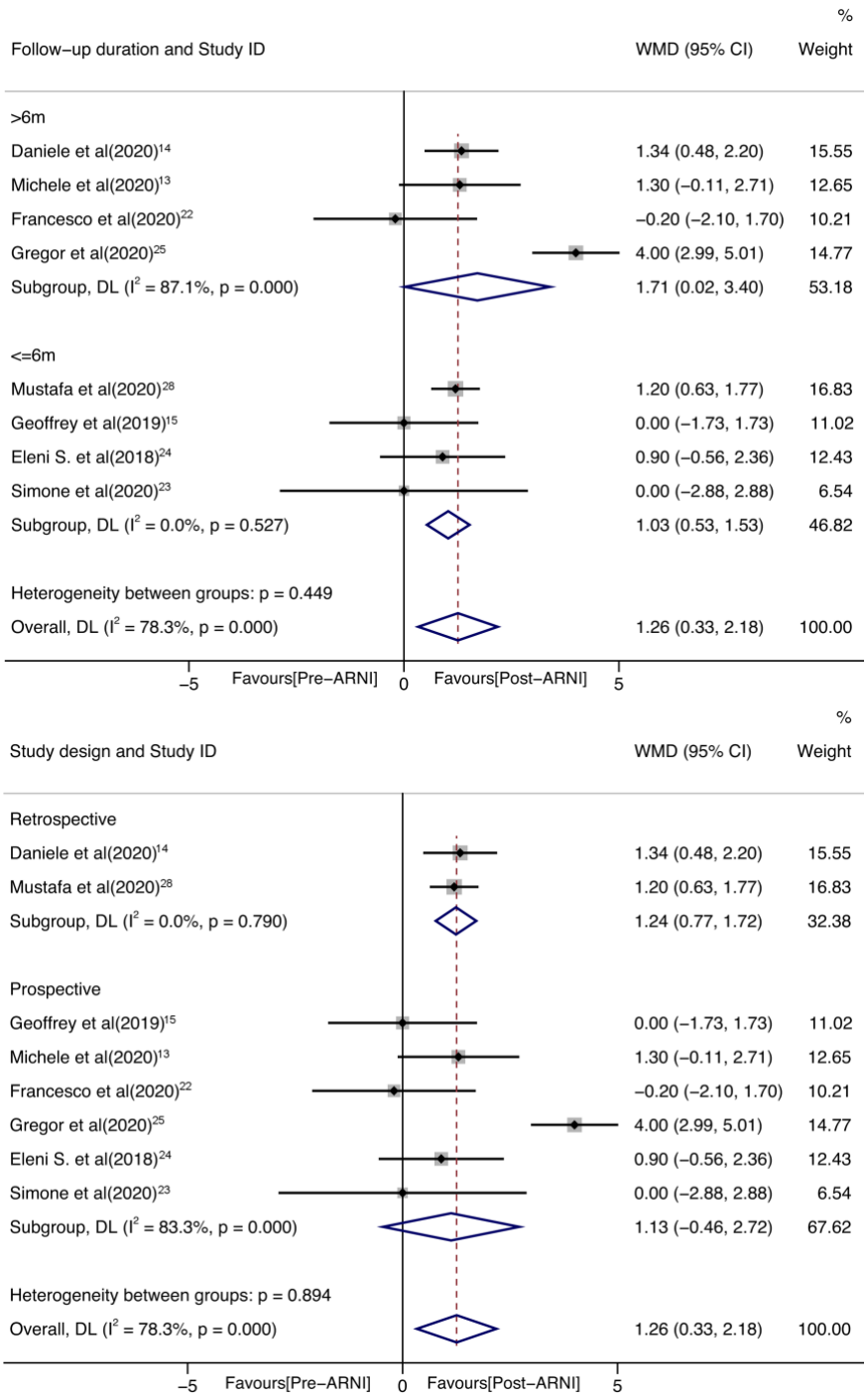

Figure S4. Subgroup analysis of effects of S/V on TAPSE according to follow-up duration and study design.

S/V, sacubitril/valsartan; TAPSE, tricuspid annular plane systolic excursion; WMD, weighted mean differences; CI, confidence interval; ARNI, angiotensin receptor neprilysin inhibitor; HF, heart failure.

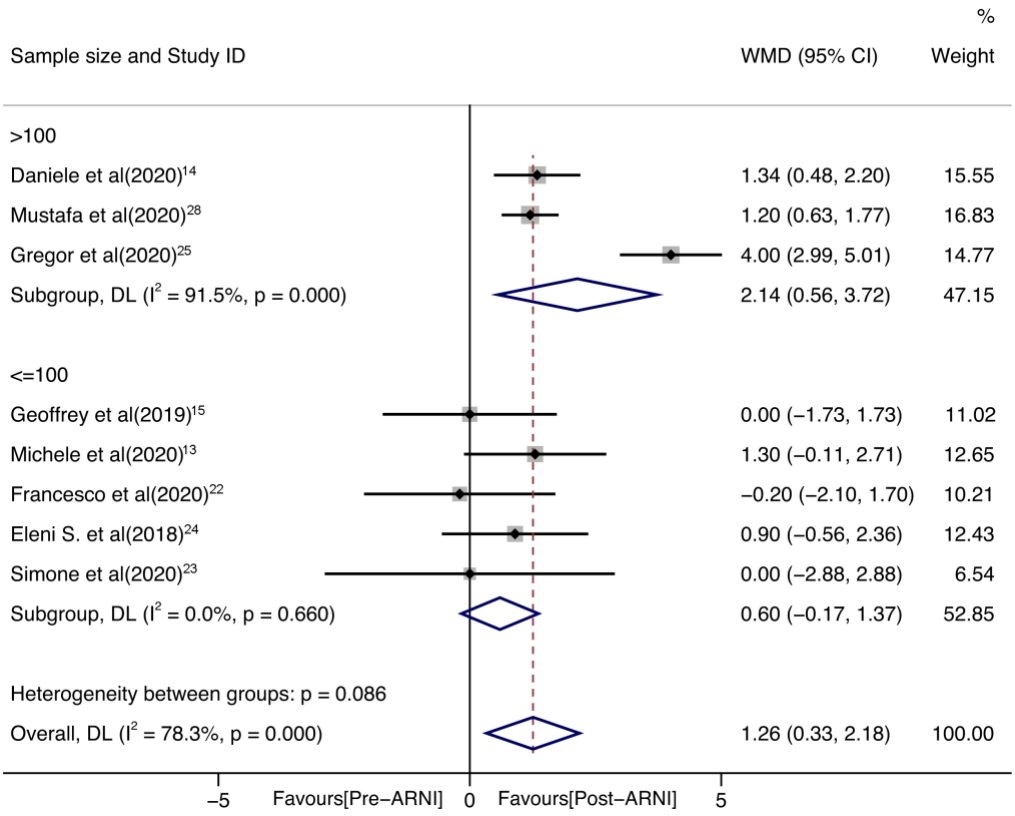

Figure S5. Subgroup analysis of effects of S/V on TAPSE according to sample size.

S/V, sacubitril/valsartan; TAPSE, tricuspid annular plane systolic excursion; WMD, weighted mean differences; CI, confidence interval; ARNI, angiotensin receptor neprilysin inhibitor; HF, heart failure.

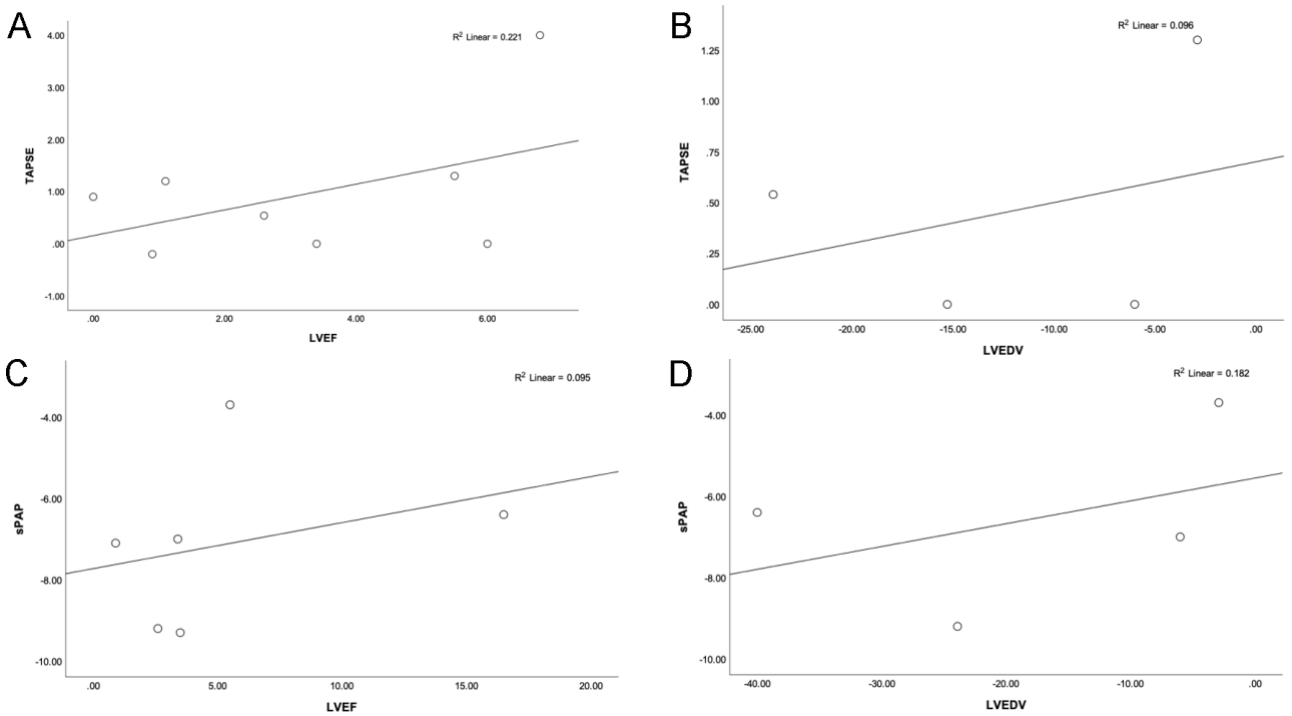

Figure S6. Correlation analysis of RV system and left heart function. (A) TAPSE and LVEF; (B) TAPSE and LVEDV; (C) sPAP and LVEF; (D) sPAP and LVEDV.

TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary arterial pressure; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; RV, right ventricular.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4,5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Data S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8, 9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8
RESULTS			

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 10, Table S1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 10, Figure 1,2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 10, Figure 1,2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 12
	23b	Discuss any limitations of the evidence included in the review.	Page 16
	23c	Discuss any limitations of the review processes used.	Page 16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 17
Competing interests	26	Declare any competing interests of review authors.	Page 17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplemental material

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

MOOSE checklist.

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4,5
2	Hypothesis statement	5
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	N/A
8	Search strategy, including time period included in the synthesis and keywords	6, Data S1
9	Effort to include all available studies, including contact with authors	N/A
10	Databases and registries searched	6
11	Search software used, name and version, including special features used (eg, explosion)	7
12	Use of hand searching (eg, reference lists of obtained articles)	6
13	List of citations located and those excluded, including justification	6, Figure S1
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	N/A
16	Description of any contact with authors	N/A
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6, 7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	7
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	N/A
21	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	7
22	Assessment of heterogeneity	8

23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8
24	Provision of appropriate tables and graphics	2 supplemental checklists, Data S1
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure1, Figure2
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	11, Table 3
28	Indication of statistical uncertainty of findings	11,12, Table 3, Figure 3
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10, Table S1, Figure S2
30	Justification for exclusion (eg, exclusion of non–English-language citations)	N/A
31	Assessment of quality of included studies	10
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	13-15
33	Generalisation of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16
34	Guidelines for future research	16
35	Disclosure of funding source	17

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta- analysis of Observational Studies in Epidemiology. A Proposal for Reporting. JAMA. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.