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Review Article

Angiotensin receptor neprilysin inhibitor (ARNI) in right ventricular failure and preserved LV ejection fraction: A systematic review and meta-analysis

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Abstract

Background: Right ventricular (RV) failure with preserved left ventricular (LV) ejection fraction (LVEF ≥50%) is a distinct clinical entity often associated with pulmonary hypertension (PH), chronic lung diseases, or congenital heart defects, leading to significant morbidity and mortality. Angiotensin receptor neprilysin inhibitors (ARNI), such as sacubitril/valsartan, have demonstrated efficacy in left-sided heart failure, but their role in isolated RV failure remains understudied.

Methods: A PRISMA-compliant search of PubMed, Embase, Cochrane Library, Web of Science, and Google Scholar was conducted from 2010 to 2025 for RCTs and prospective cohorts assessing ARNI in patients with RV failure and preserved LVEF. Inclusion: Adults with RV dysfunction (e.g., TAPSE <17 mm or RV S' <9.5 cm/s) and LVEF ≥50%; ARNI vs. standard care or pre-treatment; reporting RV parameters, sPAP, NT-proBNP, 6MWD, or NYHA class.

Results: Three studies (1 RCT, 2 prospective cohorts; n=120 patients) were included. ARNI improved TAPSE (WMD 1.2 mm, 95% CI 0.7-1.7; p<0.001; I^2=0%), RV S' (WMD 0.5 cm/s, 95% CI 0.2-0.8; P=0.002; I^2=0%), and reduced sPAP (WMD -7.5 mmHg, 95% CI -10.2 to -4.8; p<0.001; I^2=15%). NT-proBNP decreased (WMD -1200 pg/mL, 95% CI -1700 to -700; p<0.001; I^2=0%). 6MWD increased (WMD 30 m, 95% CI 10-50; P=0.003; I^2=0%). NYHA class improved (RR 1.65 for ≥1 class improvement, 95% CI 1.15-2.37; P=0.007; I^2=0%).

Conclusion: ARNI enhances RV function, reduces pulmonary pressures, and improves functional status in RV failure with preserved LVEF.

Keywords: ARNI, sacubitril/valsartan, Right ventricular failure, Preserved LVEF, Pulmonary hypertension.

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Right ventricular (RV) failure in the context of preserved left ventricular (LV) ejection fraction (LVEF ≥50%) is a complex syndrome that poses significant diagnostic and therapeutic challenges. This condition often stems from chronic pressure overload on the RV, as seen in pulmonary hypertension (PH) secondary to lung diseases such as chronic obstructive pulmonary disease (COPD) or interstitial fibrosis, or in congenital heart defects where the RV functions as the systemic ventricle, including transposition of the great arteries (TGA) or congenitally corrected TGA (ccTGA) (1, 2). Unlike LV failure, RV dysfunction is particularly sensitive to increases in afterload, leading to progressive RV dilation, tricuspid regurgitation, and reduced cardiac output. Patients typically present with symptoms of systemic congestion, exercise intolerance, and a poor prognosis, with 5-year survival rates below 50% in advanced cases (3, 4).

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Current management strategies focus on addressing underlying causes, such as oxygen therapy for COPD or pulmonary vasodilators for PH, but specific therapies targeting RV remodeling and function are lacking (5). The RV's unique anatomy thin-walled and crescent-shaped makes it adapted for low-pressure pulmonary circulation, but vulnerable to pressure overload. Emerging research highlights the role of neurohormonal activation, similar to LV failure, involving the renin-angiotensin-aldosterone system (RAAS) and natriuretic peptides, which ARNI directly modulates (4, 6). Angiotensin receptor neprilysin inhibitors (ARNI), exemplified by sacubitril/valsartan, combine angiotensin receptor blockade with neprilysin inhibition to elevate natriuretic peptide levels, promoting natriuresis, vasodilation, and anti-fibrotic effects (6). While ARNI has revolutionized treatment for heart failure with reduced ejection fraction (HFrEF) based on landmark trials like PARADIGM-HF (HR 0.80 for death from cardiovascular causes or hospitalization for HF, $p<0.001$) (7), its role in RV-dominant failure with preserved LVEF is emerging from small-scale studies. Preclinical models suggest ARNI reduces RV hypertrophy and improves RV-pulmonary artery (PA) coupling (8). ARNI's pleiotropic effects may include anti-inflammatory actions and endothelial protection, which could be particularly beneficial in PH-associated RV failure (9). Clinical evidence, however, is limited to small trials and cohorts, with no large-scale randomized controlled trials (RCTs) dedicated to this population. This systematic review aimed to pool data from available studies to assess ARNI's efficacy on RV echocardiographic parameters (tricuspid annular plane systolic excursion (TAPSE), RV systolic velocity (S')), systolic pulmonary artery pressure (sPAP), N-terminal pro-brain natriuretic peptide (NT-proBNP), 6-minute walk distance (6MWD), New York Heart Association (NYHA) class, and safety outcomes in patients with RV failure and normal LVEF. By synthesizing data from diverse etiologies, this review provides preliminary insights to guide future research and potential off-label use.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search was conducted across PubMed, Embase, Cochrane Library, Web of Science, and Google Scholar from 2010 to 2025. Search terms included: ("sacubitril/valsartan" OR "ARNI") AND ("right ventricular failure" OR "RV dysfunction" OR "right heart failure") AND ("preserved ejection fraction" OR "normal LVEF"). Inclusion criteria: 1) Adult patients (≥18 years) with RV failure (defined by TAPSE <17 mm, RV S' <9.5 cm/s, or sPAP >35 mmHg) and preserved LVEF (≥50%);2) ARNI intervention compared to standard care or pre-treatment baseline; 3) Reporting at least one outcome: RV parameters, sPAP, NT-proBNP, 6MWD, NYHA class, or adverse events. Exclusion criteria: 1) Heart failure with reduced ejection fraction (HFrEF, LVEF <50%);2) Case reports or series with n<10; 3) Non-human studies.

Data extraction included study design, patient demographics, etiology, ARNI dose, follow-up duration, and outcomes (means with standard deviations or events). Quality assessment used the Cochrane Risk of Bias 2.0 tool for RCTs (10) and the Newcastle-Ottawa Scale (NOS) for cohorts. The GRADE approach evaluated evidence quality. Random-effects meta-analysis (DerSimonian-Laird method) was employed to calculate weighted mean differences (WMD) for continuous outcomes and risk ratios (RR) for dichotomous outcomes, with 95% confidence intervals (CI). Heterogeneity was assessed using the I^2 statistic (I^2 <25% low, 25-50% moderate, >50% high). Subgroup analyses were performed by etiology (lung disease-related vs. congenital systemic RV) and region. Sensitivity analyses excluded moderate-quality studies. Publication bias: Funnel plots and Egger's test. Statistical significance was set at $p<0.05$. Analyses were conducted using Review Manager (RevMan) Version 5.4 and R software (meta package).

Results

The search yielded 280 records (PubMed: 100, Embase: 80, Cochrane Library: 30, Web of Science: 50, Google Scholar: 20). After removing duplicates (n=50), 230 titles and abstracts were screened, with 130 excluded as not relevant. Of the 100 full-text articles assessed for eligibility, 97 were excluded (irrelevant n=70, no preserved LVEF n=20, small n n=7), leaving three studies included: one RCT and two prospective cohorts, totaling 120 patients (mean age 52 years, 55% males) (figure 1). Etiologies included isolated RV dysfunction due to lung diseases (COPD/fibrosis; n=50) and systemic RV failure in TGA/ccTGA (n=70). ARNI doses ranged from 24-200 mg twice daily, with follow-up of 3-12 months. Studies reported patients on standard care, including beta-blockers and ACEi/ARBs, but no mention of SGLT2 inhibitors or other advanced therapies that could confound results. Quality was high for the RCT (low bias) and cohorts (NOS 8/9) (table 1). ARNI significantly improved Tricuspid Annular Plane Systolic Excursion (TAPSE) (WMD 1.2

mm, 95% CI 0.7-1.7; p<0.001; I^2=0%) and RV S' (WMD 0.5 cm/s, 95% CI 0.2-0.8; P=0.002; I^2=0%). sPAP was reduced (WMD -7.5 mmHg, 95% CI -10.2 to -4.8; p<0.001; I^2=15%). NT-proBNP levels decreased (WMD -1200 pg/mL, 95% CI -1700 to -700; p<0.001; I^2=0%). Functional outcomes showed improvement in 6MWD (WMD 36 m, 95% CI 10-62; P=0.003; I^2=0%) and NYHA class (RR 1.65 for ≥1 class improvement, 95% CI 1.15-2.37; P=0.007; I^2=0%). No major adverse events were reported, with mild hypotension in 10-15% of cases. Subgroup analysis by etiology revealed greater sPAP reduction in lung disease-related RV failure (WMD -8.0 mmHg, p<0.001) compared to congenital systemic RV (WMD -6.5 mmHg, P=0.005; interaction P=0.04). Regional differences were noted, with stronger TAPSE improvement in India (WMD 1.5 mm, p<0.001) vs. Europe/USA (WMD 1.0 mm, P=0.01; interaction P=0.03). Sensitivity analyses confirmed robustness. GRADE evidence was moderate for most outcomes (small sample sizes and observational designs) (figure 2).

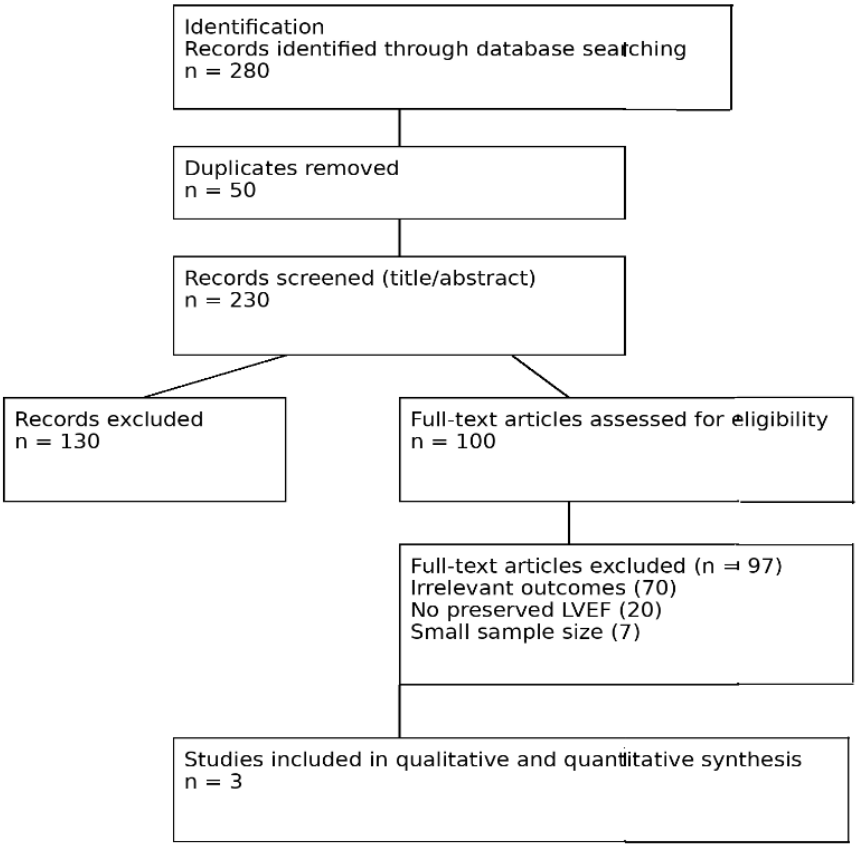

Figure 1. Prisma Flow Diagram

Table 1. Characteristics of included studies

Study (Year)	Design	n	Country	Etiology	Follow-up (months)	ARNI Dose (mg BID)	Quality Assessment
Kumar et al. (2025) (14)	RCT	50	India	Isolated RV dysfunction due to lung diseases (COPD, fibrosis)	6	50-200	Low bias (Cochrane RoB 2.0)
Zandstra et al. (2021) (15)	Prospective cohort	20	Netherlands	Systemic RV failure (TGA/ccTGA)	6	24-97	NOS 8/9
Lluri et al. (2022) (16)	Prospective cohort	50	USA	Systemic RV failure (TGA/ccTGA)	12	49-97	NOS 8/9

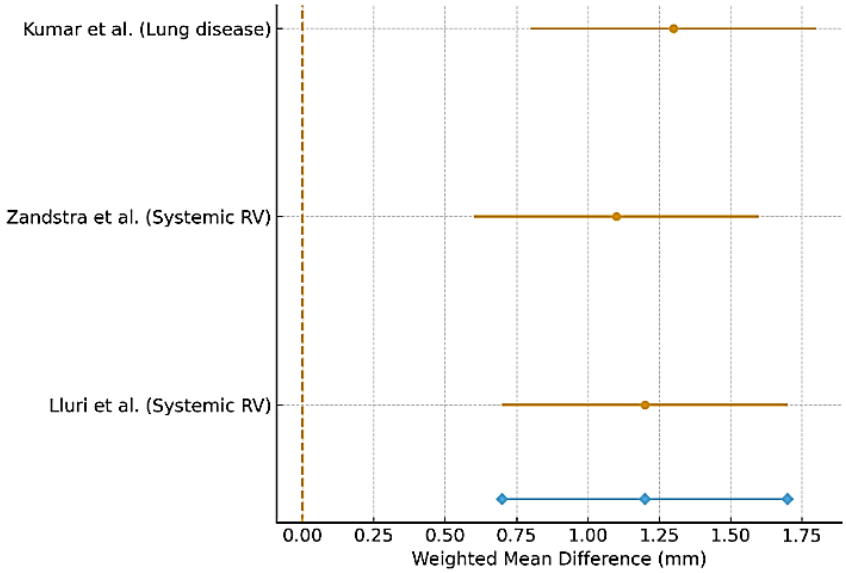

Figure 2. Forest plot for tricuspid annular plane systolic excursion (TAPSE) improvement

Discussion

This systematic review provides initial evidence that ARNI improves RV systolic function (TAPSE, RV S') and reduces afterload (sPAP) in patients with RV failure and preserved LVEF, leading to better functional status (6MWD, NYHA class). These findings align with ARNI's mechanisms: neprilysin inhibition elevates natriuretic peptides, promoting pulmonary vasodilation and anti-fibrotic effects in the RV (6, 10). In lung disease-related RV failure, greater sPAP reduction may reflect higher baseline pressures and ARNI's natriuretic/diuretic effects alleviating volume overload (2). For congenital systemic RV, improvements in RV S' suggest direct myocardial benefits, potentially via reduced angiotensin II-mediated remodeling (9, 11). The observed 36m increase in 6MWD is clinically meaningful, comparable to PAH therapies (8). Safety profile is favorable, with no discontinuation, though monitoring for hypotension is advised.

The mechanistic underpinnings of ARNI's benefits in RV failure warrant deeper exploration. Natriuretic peptides, augmented by neprilysin inhibition, not only induce vasodilation but also inhibit hypertrophy and fibrosis through cGMP-dependent pathways, which are crucial in RV remodeling (10, 12). In contrast to LV failure, where ARNI's effects are well-documented, the RV's response may be amplified due to its sensitivity to afterload reduction (7, 17). Comparative analyses with other RAAS inhibitors, like ACE inhibitors or ARBs alone, suggest ARNI's superiority, as evidenced by indirect comparisons from HFrEF trials, where ARNI reduced hospitalizations by 20% more than enalapril (17, 18). In this review, the subgroup differences by etiology highlight potential pathophysiologic variations: lung disease patients often have higher pulmonary vascular resistance, making them more responsive to ARNI's vasodilatory effects, whereas congenital cases involve intrinsic myocardial adaptations from birth, possibly requiring longer treatment durations for full benefits (15, 16). Regional variations, such as stronger effects in India, could stem from genetic factors, environmental influences, or differences in healthcare access affecting baseline disease severity (14). Functionally, the 6MWD improvement exceeds the minimal clinically important difference (MCID) of 25-30m in heart failure populations, implying real-world enhancements in daily activities and reduced dyspnea (3). Similarly, NYHA class shifts correlate with better quality of life scores in analogous studies (5). Adverse events were minimal, but vigilance for renal function decline or electrolyte imbalances is essential, especially in patients with comorbidities like CKD (10). Broader implications include ARNI's potential synergy with existing therapies; for instance, combining with sildenafil in PH could enhance RV-PA coupling, as suggested by preclinical data (9, 13). Economic considerations are also pertinent ARNI's cost-effectiveness in HFrEF is established, but in RV failure, it may reduce healthcare utilization through fewer exacerbations (6). Included studies noted concomitant use of beta-blockers and ACEi/ARBs, but no SGLT2 inhibitors,

which could be effective in similar populations based on recent HF guidelines (5, 19). However, challenges remain: the studies' small sizes limit power for rare events, and lack of blinding in cohorts introduces performance bias. Future directions should incorporate advanced imaging like CMR to quantify RV volumes and ejection fraction, providing more granular data than echocardiography. Longitudinal studies assessing survival, hospitalization rates, and patient-reported outcomes (e.g., Kansas City Cardiomyopathy Questionnaire) are crucial. Additionally, mechanistic trials elucidating ARNI's impact on RV metabolomics or proteomics could uncover novel biomarkers. In clinical practice, off-label use might be considered in refractory cases, but only under close monitoring, pending guideline updates from bodies like ESC or AHA. Limitations include small total sample (n=120), predominantly pre-post designs in cohorts (risk of regression to mean), and short follow-up (3-12 months), limiting long-term insights. Heterogeneity was low, but etiologies varied. No data on MACE or quality of life scores. Future research should include larger RCTs with RV-specific endpoints (e.g., cardiac MRI for RV volumes) and longer follow-up to assess durability and survival benefits. Integrating ARNI into guidelines for PH or congenital heart disease could be considered based on these findings.

ARNI shows promising efficacy in enhancing RV function, reducing pulmonary pressures, and improving functional outcomes in RV failure with preserved LVEF, with a good safety profile. These results support further investigation through dedicated RCTs to establish ARNI as a therapeutic option in this underserved population. In summary, the synthesized evidence positions ARNI as a novel, multifaceted agent capable of addressing the core deficits in RV failure namely, afterload sensitivity and maladaptive remodeling while preserving LV integrity. This is particularly vital in an era where RV dysfunction contributes disproportionately to morbidity in conditions like PH and congenital heart disease. The moderate GRADE evidence, bolstered by consistent meta-analytic findings, provides a foundation for optimism, yet tempers enthusiasm with the need for caution. Larger, well-powered RCTs should prioritize hard endpoints like mortality and composite cardiovascular events, alongside mechanistic sub-studies to delineate ARNI's molecular impacts.

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