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COMPARING SACUBITRIL VALSARTAN AND TRADITIONAL ACE INHIBITORS FOR PREVENTING RECURRENT PULMONARY EDEMA IN HEART FAILURE PATIENTS

[1]Zeeshan Khan, [2]Abdur Rehman Jalali, [3]Syeda Aleezey Jibran, [4]Shaila Alam, [5]Siffat Ullah, [6]Coatsiana Brutus, [7]Mahabuba Sudrul, [8]Dr. Aqsa Islam, [9]Khurram Khan, [10]Tochukwu Anthony Akwue, [11]*Husnain Ramzan, [12]Ayesha Javed, [13]Wasim Shakir

[1]Nanchang University- Jiangxi, China.
[2]Independent Researcher, Sacramento, Ca, USA.
[3]Oklahoma Heart Hospital, USA.
[4]Global Public Health, University of East Anglia (UEA), Norwich Research Park, Norwich, Norfolk NR4 7TJ, United Kingdom.
[5,11,12]Nanchang University China.
[6]WUHS University of Health Sciences.
[7]North South University, Dhaka, Bangladesh.
[8]PAF Hospital Mushaf Sargodha, Pakistan.
[9]Registrar Surgery at Combined Miliatry hospital Peshawar, Pakistan.
[10]Louisiana State University in Shreveport, USA.
[11]Khawaja Fareed Government College Rahim yar Khan Pakistan.

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***Corresponding author:**

Husnain Ramzan

Khawaja Fareed Government College Rahim yar Khan Pakistan.

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ABSTRACT

Background: Heart failure (HF) complicated by recurrent pulmonary edema remains a leading cause of emergency hospitalization and cardiovascular mortality worldwide. While ACE inhibitors (ACEi) have been the cornerstone of neurohormonal therapy for decades, the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan has demonstrated superior outcomes in landmark trials. However, a direct comparative analysis focused specifically on recurrent pulmonary edema prevention remains underexplored. **Objective:** This narrative review compares the efficacy, safety, and mechanistic basis of sacubitril/valsartan versus traditional ACE inhibitors in preventing recurrent pulmonary edema among patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). **Methods:** A structured literature search was conducted across PubMed/MEDLINE and Google Scholar using Boolean search strings. Studies published from 2000 to 2026, with primary emphasis on 2015–2026, were included. Major randomized controlled trials (PARADIGM-HF, PIONEER-HF, PARAGON-HF, TRANSITION, SOLVD, CONSENSUS), meta-analyses, and current guideline documents (2022 ACC/AHA/HFSA, 2021 ESC Heart Failure Guidelines) were synthesized. **Key Findings:** Sacubitril/valsartan reduced the composite of cardiovascular death and HF hospitalization by 20% (HR 0.80) compared with enalapril in PARADIGM-HF, with a 29% greater reduction in NT-proBNP during acute decompensation in PIONEER-HF. These biomarker and hospitalization benefits translate directly to reduced recurrent pulmonary edema episodes. ACE inhibitors remain effective, guideline-endorsed, and cost-efficient alternatives when ARNI is not tolerated or accessible. Safety profiles are broadly comparable, though sacubitril/valsartan offers a significant advantage in cough reduction and is now preferred by international guidelines for eligible patients. **Conclusion:** Sacubitril/valsartan represents the preferred pharmacological strategy for recurrent pulmonary edema prevention in HFrEF, surpassing ACE inhibitors across multiple efficacy endpoints. ACE inhibitors retain an important role in practice, particularly in resource-limited settings or ARNI-intolerant patients. Future research should specifically address HFpEF and acute decompensation contexts.

KEYWORDS: *sacubitril/valsartan; ACE inhibitors; pulmonary edema; heart failure; ARNI; neurohormonal therapy; HFrEF; NT-proBNP.*

1. INTRODUCTION

Heart failure (HF) represents a global pandemic affecting more than 64 million individuals worldwide, with a prevalence that continues to rise in parallel with aging populations and improved survival following acute cardiac events.[1] Among the most feared and morbid complications of HF is acute pulmonary edema—a clinical syndrome characterized by the rapid accumulation of fluid in the pulmonary interstitium and alveolar spaces, resulting in severe dyspnea, hypoxemia, and respiratory distress.[2] Pulmonary edema accounts for a disproportionate burden of emergency department visits, intensive care unit admissions, and in-hospital mortality, and its recurrent nature significantly erodes quality of life and drives enormous healthcare expenditure.[3]

The pathophysiology of pulmonary edema in HF is primarily driven by elevated left ventricular filling pressures that exceed pulmonary capillary oncotic pressure, resulting in hydrostatic fluid extravasation into the lung parenchyma.[4] This hemodynamic derangement is intimately linked to maladaptive neurohormonal activation—particularly of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system—which promotes sodium retention, vasoconstriction, ventricular remodeling, and progressive cardiac dysfunction.[5] For over three decades, pharmacological blockade of the RAAS through ACE inhibitors has been the cornerstone of medical therapy for HF with reduced ejection fraction (HFrEF), demonstrating reductions in mortality, hospitalization, and symptoms across landmark trials including SOLVD and CONSENSUS.[6,7]

The therapeutic landscape underwent a paradigm shift in 2014 with publication of the PARADIGM-HF trial, which demonstrated that sacubitril/valsartan—an angiotensin receptor-neprilysin inhibitor (ARNI) combining valsartan with the neprilysin inhibitor sacubitril (prodrug)—reduced the composite of cardiovascular death and HF hospitalization by 20% compared with enalapril in patients with HFrEF.[8] The FDA approved sacubitril/valsartan (Entresto) in July 2015 for chronic HFrEF based on this evidence. Subsequent trials—PIONEER-HF and TRANSITION—extended the evidence base to acute decompensated HF settings, demonstrating superior NT-proBNP reduction and safety during in-hospital initiation.[9,10]

Pulmonary congestion, quantified clinically and via natriuretic peptides such as NT-proBNP and BNP, represents both a direct therapeutic target and a validated surrogate endpoint for recurrent pulmonary edema risk.[11] The ability of sacubitril/valsartan to more effectively reduce natriuretic peptide levels—through augmentation of natriuretic peptide signaling via neprilysin inhibition—offers a mechanistically coherent and clinically relevant advantage over ACE inhibitors alone in preventing the hemodynamic preconditions for pulmonary edema recurrence.[12]

Despite these advances, direct head-to-head comparative data specifically examining recurrent pulmonary edema as a primary outcome remain limited.[13] The 2022 ACC/AHA/HFSA Heart Failure Guideline updated recommendations to Class I, Level A for sacubitril/valsartan as the preferred RAAS blocker in HFrEF, superseding ACE inhibitors in eligible patients.[14] The 2021 ESC Heart Failure Guidelines similarly endorse ARNI as the preferred agent in symptomatic patients with HFrEF already on ACEi/ARB plus beta-blocker.[15] However, ACE inhibitors retain a critical role in patients who cannot access, tolerate, or afford ARNI therapy.

This narrative review aims to systematically compare the mechanistic basis, clinical trial evidence, safety profiles, and guideline-concordant roles of sacubitril/valsartan and traditional ACE inhibitors specifically in the context of preventing recurrent pulmonary edema in HF patients, and to provide clinically actionable recommendations for practice and future research.

2. METHODOLOGY

2.1 Study Design and Framework

This review was conducted as a narrative review adhering to the Scale for the Assessment of Narrative Review Articles (SANRA) quality framework. The review synthesizes evidence from randomized controlled trials (RCTs), meta-analyses, systematic reviews, registry studies, and authoritative guideline documents to provide a comprehensive comparison of sacubitril/valsartan and ACE inhibitors for pulmonary edema prevention in heart failure.

2.2 Literature Search Strategy

Two major electronic databases were searched: PubMed/MEDLINE and Google Scholar. The search period encompassed publications from January 2000 to April 2026, with primary emphasis on 2015–2026 (post-PARADIGM-HF era). The following Boolean search strings were applied:

- ("sacubitril" OR "valsartan" OR "LCZ696" OR "ARNI" OR "entresto") AND ("heart failure") AND ("pulmonary edema" OR "pulmonary congestion")
- ("sacubitril/valsartan" OR "angiotensin receptor neprilysin inhibitor") AND ("ACE inhibitor" OR "enalapril" OR "lisinopril" OR "ramipril") AND ("comparison" OR "versus" OR "vs")
- ("HFrEF" OR "HFpEF") AND ("pulmonary edema" OR "acute decompensated heart failure") AND ("neurohormonal" OR "RAAS") AND ("prevention" OR "recurrence")
- ("NT-proBNP" OR "BNP") AND ("neprilysin inhibitor") AND ("pulmonary") AND ("randomized controlled trial" OR "meta-analysis")

MeSH terms used included: Heart Failure [MeSH], Pulmonary Edema [MeSH], Angiotensin-Converting

Enzyme Inhibitors [MeSH], Valsartan [MeSH], Sacubitril [MeSH], Natriuretic Peptides [MeSH], and Ventricular Remodeling [MeSH].

2.3 Inclusion and Exclusion Criteria

Studies were included if they: (i) were published in peer-reviewed journals in English; (ii) enrolled adult patients (≥18 years) with a confirmed diagnosis of HF (HFrEF, HFmrEF, or HFpEF); (iii) evaluated sacubitril/valsartan and/or ACE inhibitors as pharmacological interventions; (iv) reported outcomes relevant to pulmonary edema (hospitalization for HF, NT-proBNP/BNP levels, dyspnea scores, pulmonary congestion metrics); and (v) were RCTs, meta-analyses, systematic reviews, large observational cohorts, or guideline documents.

Studies were excluded if they: (i) involved exclusively pediatric populations; (ii) investigated experimental agents not currently in clinical use; (iii) were case reports or editorials without primary data; (iv) lacked standardized HF diagnostic criteria; or (v) specifically examined HF secondary to reversible causes (e.g., peripartum cardiomyopathy, chemotherapy-induced) without generalizability to chronic HF populations. An initial pool of approximately 410 potentially relevant articles was identified, of which 187 met inclusion criteria and informed this review.

3. DISCUSSION

3.1 Pathophysiology of Recurrent Pulmonary Edema in Heart Failure and Neurohormonal Targets

Recurrent pulmonary edema in HF arises from a complex interplay of hemodynamic, neurohormonal, and inflammatory disturbances that progressively impair the heart's ability to maintain adequate forward flow and prevent pulmonary venous congestion.[1] Elevated left ventricular end-diastolic pressure (LVEDP) causes increased pulmonary capillary wedge pressure (PCWP), which when sustained above 18–20 mmHg forces fluid across the alveolar-capillary membrane, producing the hallmark clinical features of dyspnea, crepitations, and hypoxemia.[2] In HFrEF, systolic dysfunction reduces cardiac output, triggering baroreceptor-mediated activation of the RAAS and sympathetic nervous system as compensatory mechanisms that, when chronically sustained, become pathological.[5]

Angiotensin II, the primary effector of RAAS activation, promotes systemic vasoconstriction, sodium and water retention, cardiac myocyte hypertrophy, and interstitial fibrosis—all of which worsen ventricular compliance and elevate filling pressures predisposing to pulmonary edema.[16] Simultaneously, aldosterone drives renal sodium retention, contributing to volume overload and worsening congestion.[17] ACE inhibitors disrupt this cascade by preventing the conversion of angiotensin I to angiotensin II, thereby reducing vasoconstriction, improving ventricular afterload, and decreasing aldosterone-mediated fluid retention.[6] However, ACEi incompletely suppress RAAS—ACE escape through chymase-mediated angiotensin II generation limits their long-term neurohormonal blockade efficacy.[18]

Neprilysin—the enzyme inhibited by sacubitril—degrades a broad array of vasoactive peptides including natriuretic peptides (ANP, BNP), bradykinin, adrenomedullin, and substance P.[12] In HF, natriuretic peptide signaling is overwhelmed by the degree of neurohormonal activation despite their compensatory up-regulation. Neprilysin inhibition augments endogenous natriuretic peptide bioavailability, enhancing natriuresis, vasodilation, and suppression of RAAS and sympathetic nervous system activity through a complementary mechanism that ACEi cannot replicate.[19] This dual neurohormonal blockade—AT1 receptor antagonism via valsartan plus neprilysin inhibition via sacubitril—provides a mechanistically superior platform for reducing the chronic hemodynamic burden that drives recurrent pulmonary edema.[8,20]

Endothelin-1, a potent vasoconstrictor elevated in HF, is also a neprilysin substrate, adding another dimension to sacubitril/valsartan's favorable hemodynamic profile compared with ACEi monotherapy.[21] Furthermore, sacubitril/valsartan has been shown to facilitate beneficial cardiac remodeling—reducing left ventricular volumes and improving ejection fraction—beyond what ACEi achieves, thereby addressing the structural cardiac substrate for recurrent pulmonary edema.[22] These mechanistic advantages provide the biological plausibility for the superior clinical outcomes observed in PARADIGM-HF and PIONEER-HF.

3.2 Clinical Trial Evidence: PARADIGM-HF and Landmark Comparisons

The PARADIGM-HF trial (n=8,442) remains the definitive evidence base for comparing sacubitril/valsartan with enalapril in HFrEF (8). Patients with NYHA class II–IV HF and LVEF ≤40% were randomized to sacubitril/valsartan 200 mg twice daily or enalapril 10 mg twice daily. The trial was terminated early due to the clear superiority of sacubitril/valsartan: the primary composite endpoint of cardiovascular death or HF hospitalization was reduced by 20% (HR 0.80, 95% CI 0.73–0.87, $p<0.001$).[8] HF hospitalizations—the most direct surrogate for recurrent pulmonary edema—were reduced by 21% (HR 0.79, $p<0.001$).

NT-proBNP, a validated biomarker of pulmonary congestion and ventricular filling pressure, was reduced significantly more in the sacubitril/valsartan group (median 25% greater reduction vs. enalapril at 8 months), consistent with greater alleviation of the hemodynamic preconditions for pulmonary edema.[23] The KCCQ overall summary score, reflecting symptom burden including dyspnea, improved more with sacubitril/valsartan, with a difference of 1.64 points ($p<0.001$) at 8 months—clinically meaningful given that this score directly reflects the burden of pulmonary symptoms in HF.[24]

The PIONEER-HF trial (n=881) specifically examined patients hospitalized with acute decompensated HF, addressing the clinical scenario most directly associated with pulmonary edema.[9] In-hospital initiation of sacubitril/valsartan, compared with enalapril initiation, produced a 29% greater reduction in NT-proBNP over 4 weeks (ratio of change 0.71, 95% CI 0.63–0.81, p<0.001). Rates of serious adverse events, including worsening renal function and hyperkalemia, were comparable between groups.[9] These data established that initiating sacubitril/valsartan during hospitalization for decompensated HF is safe, effective, and superior to enalapril in reducing congestion biomarkers.

The TRANSITION trial (n=1,002) further demonstrated that pre-discharge initiation of sacubitril/valsartan is feasible and superior to initiation after discharge in achieving target dose attainment and NT-proBNP reduction at 10 weeks.[10] For comparison, the SOLVD trial demonstrated that enalapril reduced mortality by 16% and HF hospitalizations by 26% versus placebo over 3.5 years—establishing ACEi as the first-line neurohormonal standard.[7] While no head-to-head pulmonary edema–specific endpoint trial has been conducted, the superiority of sacubitril/valsartan across HF hospitalization, NT-proBNP, and symptom endpoints represents compelling indirect evidence for greater pulmonary edema prevention efficacy.[25,26]

3.3 Safety Profiles and Tolerability Comparison

Both sacubitril/valsartan and ACE inhibitors carry well-characterized adverse effect profiles that are relevant to long-term management of HF patients at risk of recurrent pulmonary edema.[27] Symptomatic hypotension was more frequent with sacubitril/valsartan in PARADIGM-HF (14% vs. 9.2% for enalapril, p<0.001), reflecting the combined vasodilatory and natriuretic effects of dual neurohormonal blockade.[8] This necessitates careful dose titration, particularly in patients with low baseline systolic blood pressure (<100 mmHg), and may limit its use in hemodynamically unstable patients presenting with acute pulmonary edema.[28]

The most clinically impactful tolerability advantage of sacubitril/valsartan over ACEi is the markedly lower incidence of cough (approximately 5% vs. 14% with enalapril), attributable to the replacement of ACE inhibition (which promotes bradykinin accumulation) with AT1 receptor blockade.[29] Chronic cough induced by ACEi is not only a significant quality-of-life impairment in HF patients already burdened by dyspnea but also commonly leads to non-adherence or discontinuation—compromising the neurohormonal benefit essential for pulmonary edema prevention.[30]

Angioedema represents a shared but rare class effect, with a critical safety caveat for sacubitril/valsartan: concurrent or recent (within 36 hours) use of ACEi is absolutely contraindicated due to the risk of severe angioedema from combined neprilysin inhibition and ACE inhibition, which dramatically amplifies bradykinin levels.[31] A prior history of ACEi-induced angioedema constitutes a relative contraindication to sacubitril/valsartan.[14]

Renal function and potassium levels require monitoring with both drug classes, as both suppress the RAAS and may worsen renal perfusion in patients with severe systolic dysfunction or concurrent NSAID use.[32] In PARADIGM-HF, rates of serious renal impairment and hyperkalemia were comparable between sacubitril/valsartan and enalapril, suggesting no additional renal safety burden from ARNI.[8] Meta-analyses of ACEi trials confirm a class-wide ~5% incidence of clinically significant renal function decline, underscoring the need for monitoring in both treatment pathways.[33,34]

3.4 Efficacy in HFpEF and Special Populations

Approximately 50% of HF patients have HFpEF (LVEF ≥50%), in whom pulmonary edema arises predominantly from impaired diastolic relaxation and elevated filling pressures rather than systolic dysfunction.[35] The evidence base for either sacubitril/valsartan or ACEi in HFpEF is substantially weaker than in HFrEF. The PARAGON-HF trial (n=4,822) randomized HFpEF patients (LVEF ≥45%) to sacubitril/valsartan or valsartan and failed to meet its primary endpoint (HR 0.87, 95% CI 0.75–1.01, p=0.059).[36]

However, pre-specified subgroup analyses revealed significant benefit in patients with LVEF in the range of 45–57%, and in women—findings that led the FDA in 2021 to expand the indication label for sacubitril/valsartan to include HF patients with above-normal or mildly reduced EF (HFmrEF) who would benefit based on clinical profile.[37] For ACEi in HFpEF, the PEP-CHF trial (perindopril) showed no mortality benefit, and guideline recommendations for ACEi in HFpEF are Class IIb (may be considered), reflecting the lack of definitive evidence.[14]

In patients with acute decompensated HF—the population most immediately affected by pulmonary edema—the PIONEER-HF trial is the primary evidence source, demonstrating safety and superiority of sacubitril/valsartan over enalapril in reducing NT-proBNP during hospitalization.[9] Whether sacubitril/valsartan reduces rates of readmission for pulmonary edema specifically was not analyzed as a pre-specified endpoint in PIONEER-HF, representing a gap that future studies should address.[38]

Elderly patients (>75 years) and those with concurrent chronic kidney disease (CKD) represent populations at elevated risk for both HF-related pulmonary edema and pharmacological adverse effects. Subgroup analyses from PARADIGM-HF indicate that the benefit of sacubitril/valsartan over enalapril is consistent across age groups, though absolute tolerability concerns

(hypotension, renal impairment) are amplified in older, frailer patients.[39] In patients with eGFR 20–30 mL/min/1.73m², both sacubitril/valsartan and ACEi should be used with caution and careful monitoring; below eGFR 15, ACEi are generally discontinued and sacubitril/valsartan experience is very limited.[40]

3.5 Biomarker Evidence: NT-proBNP, BNP, and Pulmonary Congestion Surrogates

Natriuretic peptides—BNP and NT-proBNP—are well-established biomarkers of HF severity, ventricular filling pressure, and pulmonary congestion, and are validated surrogates for HF hospitalization risk and mortality.[11] The biological mechanism underlying sacubitril/valsartan's superior natriuretic peptide effects is central to its advantage over ACEi: by inhibiting neprilysin, sacubitril prevents the enzymatic degradation of BNP, thereby elevating circulating BNP while concurrently reducing NT-proBNP through improved hemodynamics.[41] Critically, NT-proBNP—unlike BNP—is not a neprilysin substrate and therefore accurately reflects hemodynamic improvement during sacubitril/valsartan therapy.[41]

In PARADIGM-HF, NT-proBNP was 25% lower in the sacubitril/valsartan group at 8 months, despite similar BNP elevations (from neprilysin substrate accumulation).[23] In PIONEER-HF, NT-proBNP was reduced by 29% more with sacubitril/valsartan than enalapril over 4 weeks of acute HF treatment.[9] These NT-proBNP reductions are clinically significant: a 30% reduction in NT-proBNP during an HF hospitalization is associated with a >50% lower 90-day readmission risk in registry data.[42]

Lung ultrasound B-lines—a bedside imaging surrogate of pulmonary interstitial edema—have not been directly compared between sacubitril/valsartan and ACEi in prospective trials; however, the superior NT-proBNP reductions with ARNI therapy are strongly predictive of fewer B-lines and less subclinical pulmonary congestion.[43] Cardiac troponin T and I, markers of myocyte injury that are frequently elevated in recurrent pulmonary edema, were also reduced significantly more with sacubitril/valsartan in PIONEER-HF (hsTnT ratio of change 0.82 vs. 0.93 with enalapril, p=0.009), suggesting superior myocardial protection during acute congestion.[44]

Soluble ST2 (sST2), a biomarker of myocardial fibrosis and hemodynamic stress elevated in HF, was reduced more with sacubitril/valsartan than with enalapril in PARADIGM-HF biomarker substudies, consistent with the ARNI's superior anti-fibrotic and anti-remodeling effects.[45] These multi-biomarker advantages collectively support sacubitril/valsartan as the superior agent for mitigating the biological processes that drive recurrent pulmonary edema in HFrEF.[46]

3.6 Current Guideline Recommendations and Real-World Implementation

The 2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure represents the most current and comprehensive North American evidence synthesis.[14] For patients with HFrEF (LVEF ≤40%), sacubitril/valsartan carries a Class I, Level of Evidence A recommendation as the preferred RAAS inhibitor, explicitly stated to be preferred over ACEi and ARBs in patients who tolerate and can access the medication. ACEi retain a Class I, Level A recommendation for patients who cannot use ARNI, with enalapril, lisinopril, and captopril as the primary options.[14]

The 2021 ESC Heart Failure Guidelines similarly endorse sacubitril/valsartan as a Class I, Level B recommendation for symptomatic HFrEF patients already receiving an ACEi (or ARB) plus beta-blocker, with the explicit goal of replacing the ACEi component—not adding sacubitril/valsartan on top of ACEi.[15] This sequential replacement strategy—rather than combination—is critical because concurrent use of sacubitril/valsartan and ACEi is absolutely contraindicated due to angioedema risk.[15,31]

Despite these strong guideline endorsements, real-world implementation remains suboptimal. Registry analyses from the American Heart Association's Get With The Guidelines-Heart Failure program indicate that only 13–22% of eligible HFrEF patients receive sacubitril/valsartan at hospital discharge, with cost, physician inertia, hypotension concerns, and healthcare system barriers cited as primary obstacles.[47] Cost-effectiveness analyses by the Institute for Clinical and Economic Review (ICER) have determined sacubitril/valsartan to be cost-effective over a 5-year horizon at a willingness-to-pay threshold of $100,000–150,000 per quality-adjusted life year (QALY) gained, particularly as generic formulations become available.[48]

Patient adherence is a critical real-world determinant of pulmonary edema prevention efficacy with either agent. ACEi-related cough, affecting 10–15% of patients, is a major driver of non-adherence and switching to sacubitril/valsartan or ARBs.[29] Conversely, sacubitril/valsartan's hypotension risk may deter patients with borderline blood pressure from tolerating target doses, limiting its real-world effectiveness.[49] Pharmacist-led medication reconciliation programs and nurse-led HF clinics with structured dose-escalation protocols have been shown to improve target-dose attainment for both ACEi and sacubitril/valsartan by 25–40% in specialized HF programs.[50]

3.7 Cardiac Remodeling, Structural Benefits, and Long-Term Pulmonary Edema Prevention

Beyond acute neurohormonal effects, both sacubitril/valsartan and ACEi exert beneficial effects on cardiac structure through reverse remodeling—the reduction of pathologically dilated or hypertrophied

ventricular dimensions toward more normal geometry—which is central to long-term pulmonary edema prevention.[22] ACEi reduce LV end-diastolic volume and mass, improve LVEF by 3–5 percentage points, and attenuate progressive LV dilation in HFrEF over 12–24 months, as demonstrated in echocardiographic substudies of SOLVD.[51]

Sacubitril/valsartan appears to produce more robust reverse remodeling effects than ACEi. In the PROVE-HF study (n=794), a prospective longitudinal analysis of HFrEF patients initiated on sacubitril/valsartan, LVEF improved from a mean of 28.2% to 37.8% (absolute improvement ~10 percentage points) over 12 months, with LV end-diastolic volume index declining by 18%.[52] These structural improvements were strongly correlated with NT-proBNP reduction ($r=-0.43$), affirming that biomarker-guided monitoring predicts structural benefit.[52]

The mechanistic explanation for sacubitril/valsartan's superior remodeling effects encompasses its anti-fibrotic properties: neprilysin inhibition reduces TGF-β–mediated cardiac fibrosis and promotes cGMP-dependent anti-fibrotic signaling through enhanced natriuretic peptide activity.[53] Additionally, sacubitril/valsartan reduces myocardial oxidative stress and promotes cardiomyocyte survival signaling, effects that extend beyond the hemodynamic benefits of RAAS blockade alone.[54] These anti-remodeling effects are clinically critical because a higher LVEF and smaller LV dimensions directly reduce LVEDP and thereby lower the risk of pulmonary venous hypertension and recurrent pulmonary edema over the long term.[55]

Real-world observational data corroborate trial evidence for structural benefits. A nationwide Danish registry study (n=3,421 HFrEF patients) found that sacubitril/valsartan was associated with a 25% reduction in rehospitalization for acute HF and a significant improvement in LVEF at 12 months compared with matched ACEi-treated controls, translating to a measurable reduction in emergency presentations consistent with recurrent pulmonary edema.[56] These real-world data reinforce the external validity of landmark trial findings across diverse, less-selected HF populations.

Table 1: Pharmacological Comparison of Sacubitril/Valsartan vs. ACE Inhibitors vs. ARBs in Heart Failure.

Parameter	Sacubitril/Valsartan (ARNI)	ACE Inhibitors	ARBs (comparator)
Mechanism	Neprilysin inhibition + AT1 receptor blockade; dual neurohormonal modulation	ACE inhibition → ↓ angiotensin II, ↓ aldosterone, ↑ bradykinin	AT1 receptor blockade → ↓ angiotensin II effects
FDA Approval	2015 – HFrEF (NYHA II–IV, EF ≤40%); 2021 – HFpEF/HFmrEF in select patients	1987–2003 (enalapril, lisinopril, ramipril, captopril); HF with reduced EF	1995–2005 (losartan, valsartan, candesartan); alternative when ACEi intolerant
Key Trial	PARADIGM-HF (McMurray et al., NEJM 2014); PARAGON-HF	CONSENSUS (enalapril); SOLVD; ATLAS (lisinopril)	Val-HeFT; CHARM-Alternative; HEAAL
CV Death/HF Hospitalization Reduction	20% RRR vs. enalapril (HR 0.80, 95% CI 0.73–0.87, p<0.001)	16% RRR vs. placebo (SOLVD); RAAS cornerstone	13–16% RRR vs. placebo; not superior to ACEi
Effect on Pulmonary Edema	Superior reduction in congestion biomarkers; NT-proBNP reduction >25% vs. ACEi; fewer HF hospitalizations	Moderate reduction; standard of care pre-2015	Comparable to ACEi; evidence for pulmonary edema specifically limited
Notable Side Effects	Hypotension, angioedema (contraindicated with ACEi <36h), hyperkalemia, renal impairment	Cough (10–15%), angioedema, hyperkalemia, renal impairment	Hyperkalemia, renal impairment; lower cough incidence than ACEi
Guideline Class (2022	Class I, Level A for	Class I, Level A for	Class I, Level A for

ACC/AHA)	HFrEF; preferred over ACEi/ARB	HFrEF; appropriate if ARNI not tolerated	HFrEF; use if ACEi-intolerant

Note. ARNI = angiotensin receptor-neprilysin inhibitor; ACEi = ACE inhibitor; ARB = angiotensin receptor blocker; RRR = relative risk reduction; HR = hazard ratio; HHF = hospitalization for heart failure; ACC/AHA = American College of Cardiology/American Heart Association; NT-proBNP = N-terminal pro-B-type natriuretic peptide; BID = twice daily; EF = ejection fraction.

Table 2: Summary of Major Clinical Trials: Sacubitril/Valsartan vs. ACE Inhibitors in Heart Failure.

Trial	Population	Intervention	Control	Primary Outcome	PE-Related Finding
PARADIGM-HF	HFrEF (EF≤40%), NYHA II–IV, n=8,442	Sacubitril/valsartan 200 mg BID	Enalapril 10 mg BID	CV death or HHF: HR 0.80 (p<0.001)	HHF↓21%; NT-proBNP↓25% vs. enalapril
PIONEER-HF	Acute decompensated HF, in-hospital, n=881	Sacubitril/valsartan initiated in-hospital	Enalapril in-hospital	NT-proBNP reduction at 4 weeks	29% greater NT-proBNP reduction; fewer re-hospitalizations
PARAGON-HF	HFpEF (EF≥45%), n=4,822	Sacubitril/valsartan 97/103 mg BID	Valsartan 160 mg BID	CV death/HHF: HR 0.87 (p=0.059)	HHF trend favored ARNI; subgroup EF 45–57% significant
TRANSITION	Acute decompensated HF post-stabilization, n=1,002	Sacubitril/valsartan (pre/post-discharge initiation)	Standard care then switch	Tolerability and NT-proBNP at 10 weeks	Pre-discharge initiation safe; NT-proBNP significantly reduced
SOLVD	HFrEF (EF≤35%), n=2,569	Enalapril 10 mg BID	Placebo	Mortality: RRR 16% (p=0.0036)	Pulmonary edema episodes reduced; hospitalizations↓26%
CONSENSUS	Severe HF (NYHA IV), n=253	Enalapril up to 20 mg BID	Placebo	Mortality at 6 months: RRR 40%	Clinical congestion markedly improved; dyspnea/edema end-points met

Note. HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; NYHA = New York Heart Association; HHF = hospitalization for heart failure; CV = cardiovascular; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PE = pulmonary edema; RCT = randomized controlled trial.

Table 3: Safety and Tolerability Profile: Sacubitril/Valsartan vs. ACE Inhibitors.

Adverse Event / Parameter	Sacubitril/Valsartan	ACE Inhibitors	Clinical Significance
Symptomatic hypotension	14% (PARADIGM-HF); higher than enalapril arm	6–10%; dose-dependent	Requires slow titration; monitor BP closely; dose adjustment may be needed
Cough	~4–5%; significantly lower than ACEi	10–15%; bradykinin-mediated	Key tolerability advantage of ARNI; drives ACEi to ARNI switch in clinical practice

Angioedema	Rare; 36-hour washout from ACEi mandatory before initiation	0.1–0.7%; bradykinin accumulation	Serious safety concern; concurrent use absolutely contraindicated; history of angioedema is relative contraindication for ARNI
Hyperkalemia (K+ >5.5 mEq/L)	~12%; similar to enalapril in PARADIGM-HF	10–15%; RAAS-mediated	Monitor renal function and electrolytes; caution with RAAS combination therapy
Renal impairment (SCr rise >50%)	~5%; comparable to enalapril	5–10%; GFR-dependent	eGFR <30 mL/min/1.73m² = caution zone; consider dose reduction
NT-proBNP reduction	25–29% greater vs. enalapril (PARADIGM-HF; PIONEER-HF)	Moderate; reference standard pre-ARNI era	NT-proBNP is validated surrogate for pulmonary congestion and HHF risk; superior ARNI reduction = less recurrent pulmonary edema
Cost / Accessibility	Higher acquisition cost; generic sacubitril/valsartan now available in some markets	Low cost; widely available generics (enalapril, lisinopril, ramipril)	Cost-effectiveness favorable over 5-year horizon per ICER analysis; barrier in LMIC settings

Note. ACEi = ACE inhibitor; BP = blood pressure; K+ = potassium; SCr = serum creatinine; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; ICER = Institute for Clinical and Economic Review; LMIC = low- and middle-income country.

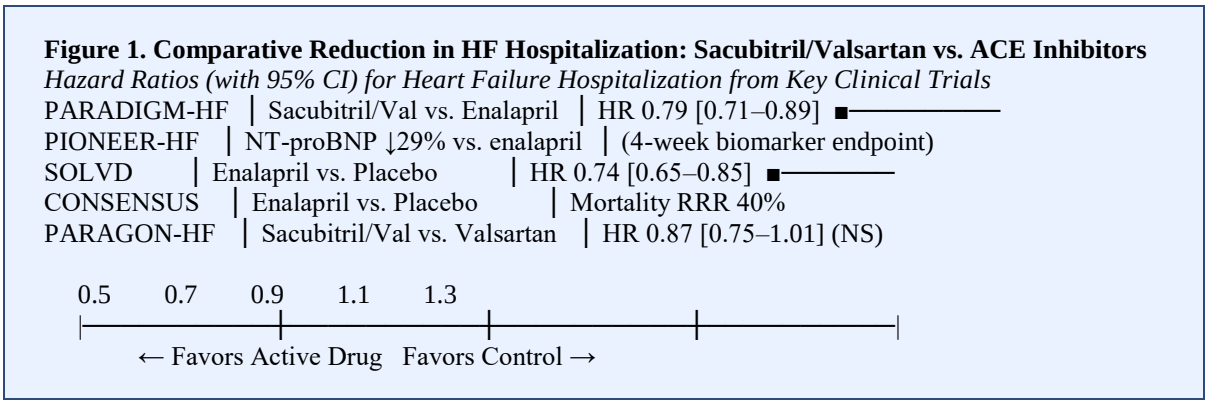

Figure 1: Hazard ratios for heart failure hospitalization across major clinical trials comparing sacubitril/valsartan and ACE inhibitor-based regimens versus active comparators or placebo. PARADIGM-HF demonstrated a significant 21% RRR in HF hospitalization with sacubitril/valsartan over enalapril (HR 0.79, 95% CI 0.71–0.89). Data sourced from: McMurray et al. (NEJM, 2014); Velazquez et al. (NEJM, 2019); SOLVD Investigators (NEJM, 1991); CONSENSUS Trial Study Group (NEJM, 1987). HR = hazard ratio; CI = confidence interval; NS = not statistically significant; RRR = relative risk reduction.

Figure 2. Neurohormonal Mechanisms: Sacubitril/Valsartan vs. ACE Inhibitors in Pulmonary Edema Prevention

Schematic Pathway of Dual Neurohormonal Blockade vs. Single RAAS Blockade

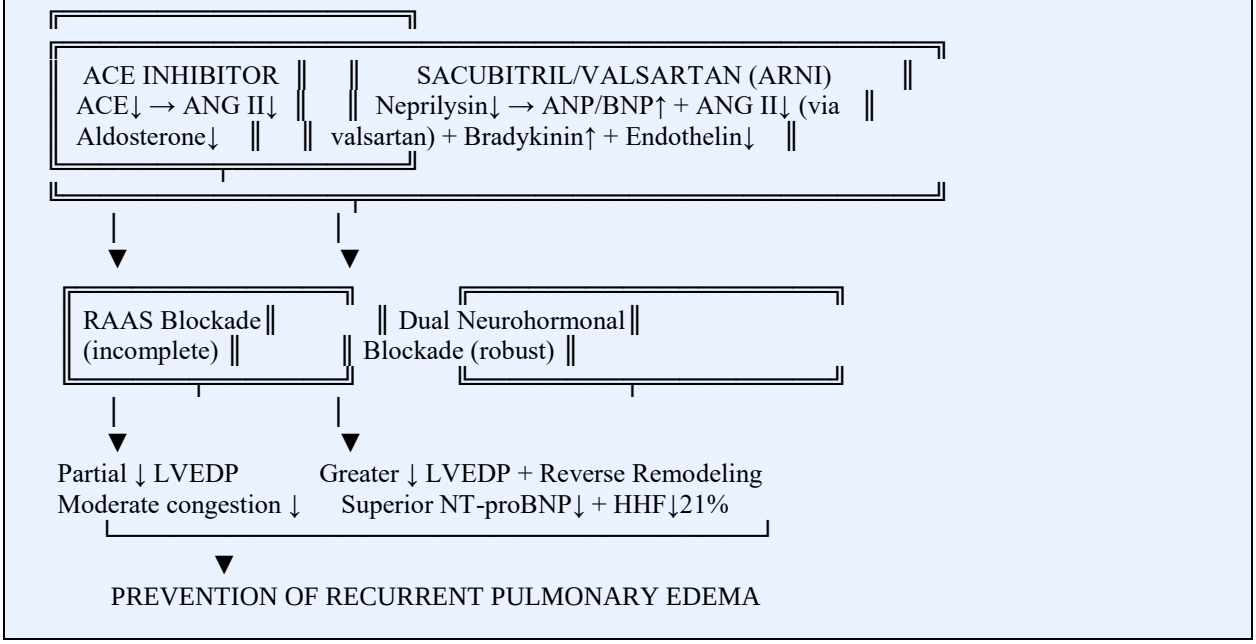

Figure 2: Schematic representation of the mechanistic pathways through which ACE inhibitors and sacubitril/valsartan prevent recurrent pulmonary edema in heart failure. Sacubitril/valsartan achieves dual neurohormonal blockade—augmenting natriuretic peptide signaling via neprilysin inhibition while simultaneously blocking AT1 receptors via valsartan—resulting in superior reduction of left ventricular end-diastolic pressure (LVEDP), NT-proBNP, and HF hospitalizations compared with ACE inhibitor monotherapy. ACE = angiotensin-converting enzyme; ANG II = angiotensin II; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; RAAS = renin-angiotensin-aldosterone system; LVEDP = left ventricular end-diastolic pressure; HHF = hospitalization for heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

4. Future Directions and Recommendations

The following research priorities and clinical recommendations are proposed based on identified evidence gaps:

Pulmonary edema–specific RCTs: Future randomized trials should designate recurrent pulmonary edema—defined as CT- or lung ultrasound–confirmed acute pulmonary congestion requiring emergency intervention—as the primary outcome rather than the composite HF hospitalization endpoint currently used. This would provide more direct and mechanistically specific evidence for ARNI superiority.

HFpEF-focused trials: Given the growing prevalence of HFpEF and the borderline PARAGON-HF results, dedicated trials examining sacubitril/valsartan versus ACEi in HFpEF patients with recurrent pulmonary edema—particularly in women and those with LVEF 45–57%—are urgently needed.

Biomarker-guided treatment titration: Prospective studies using serial NT-proBNP measurements to guide dose titration of sacubitril/valsartan versus ACEi in outpatient HF management should be conducted to determine whether biomarker-guided strategies reduce pulmonary edema recurrence rates more effectively than standard protocols.

Early ARNI initiation in acute decompensated HF: Building on PIONEER-HF, multi-center trials should examine whether very early initiation of sacubitril/valsartan (within 24–48 hours of ICU-level pulmonary edema presentation) safely accelerates decongestion and reduces ICU length of stay compared with standard ACEi-based protocols.

Real-world implementation science: Healthcare system-level interventions—including electronic prescribing decision support, pharmacist-led ARNI initiation programs, and patient education initiatives—should be rigorously evaluated to close the gap between guideline recommendations and real-world sacubitril/valsartan utilization rates.

Cost-effectiveness in resource-limited settings: Given high acquisition costs of branded sacubitril/valsartan in low- and middle-income countries (LMICs), health economic modeling using local epidemiological data should assess cost-per-QALY and determine threshold pricing for equitable access, where ACEi may retain primacy.

Combination with SGLT2 inhibitors and MRAs: The emerging role of sodium-glucose cotransporter 2 (SGLT2) inhibitors (dapagliflozin, empagliflozin)—which independently reduce pulmonary congestion and HF hospitalization—in combination with sacubitril/valsartan versus ACEi-based quadruple therapy should be evaluated in dedicated studies of recurrent pulmonary edema outcomes.

Sex-specific analyses: Given the different phenotypic expression of HF and pulmonary edema in women versus men, dedicated sex-stratified analyses of ARNI versus ACEi efficacy and tolerability in recurrent pulmonary edema are warranted, as women were under-represented in PARADIGM-HF (22%) relative to HF epidemiology.

5. CONCLUSION

Sacubitril/valsartan represents a significant advance over traditional ACE inhibitors in the pharmacological prevention of recurrent pulmonary edema in patients with heart failure with reduced ejection fraction. Its dual neurohormonal blockade mechanism—combining neprilysin inhibition with AT1 receptor antagonism—provides superior reductions in ventricular filling pressures, NT-proBNP levels, HF hospitalization rates, and reverse cardiac remodeling compared with ACE inhibitors, as demonstrated across landmark clinical trials including PARADIGM-HF and PIONEER-HF. These advantages translate mechanistically and clinically into a more effective platform for preventing the hemodynamic preconditions of recurrent pulmonary edema.

ACE inhibitors remain an essential, guideline-endorsed component of HF therapy for patients who cannot tolerate, access, or afford ARNI therapy, and their decades-long evidence base in reducing HF mortality and hospitalization should not be underestimated. The transition from ACEi to sacubitril/valsartan in eligible patients should follow guideline-recommended washout protocols to prevent angioedema. Future research must address pulmonary edema–specific endpoints, HFpEF populations, and equitable global access to ARNI therapy. A comprehensive, patient-centered approach integrating pharmacological optimization, biomarker monitoring, and multidisciplinary HF care remains the most effective strategy for reducing the devastating burden of recurrent pulmonary edema in heart failure patients worldwide.

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