
**International Journal of Innovative Technologies in Social Science**

e-ISSN: 2544-9435

**Operating Publisher**
**SciFormat Publishing Inc.**
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

| | |
|---|---|
| **ARTICLE TITLE** | NEPRILYSIN INHIBITORS (ARNI) IN THE TREATMENT OF CHRONIC HEART FAILURE — A SYSTEMATIC REVIEW AND CRITICAL APPRAISAL OF THE EVIDENCE |
| **DOI** | https://doi.org/10.31435/ijitss.1(49).2026.4760 |
| **RECEIVED** | 25 November 2025 |
| **ACCEPTED** | 04 February 2026 |
| **PUBLISHED** | 13 February 2026 |
| **LICENSE** | The article is licensed under a **Creative Commons Attribution 4.0 International License.** |

# NEPRILYSIN INHIBITORS (ARNI) IN THE TREATMENT OF CHRONIC HEART FAILURE — A SYSTEMATIC REVIEW AND CRITICAL APPRAISAL OF THE EVIDENCE

***Marcin Schulz*** *(Corresponding Author, Email: mail.schulz.od44@gmail.com)*
*II Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Zabrze, Poland*
*ORCID ID: 0009-0006-4466-5794*

***Karolina Osińska***
*Municipal Hospital in Kędzierzyn-Koźle, Kędzierzyn-Koźle, Poland*
*ORCID ID: 0009-0003-9731-0629*

***Dawid Studziński***
*Municipal Hospital in Zabrze, Zabrze, Poland*
*ORCID ID: 0009-0005-3834-716X*

***Michał Kulczak***
*School of Medicine, Medical University of Silesia, Katowice, Poland*
*ORCID ID: 0009-0006-4968-3318*

***Anna Kołcz***
*School of Medicine, Medical University of Silesia, Katowice, Poland*
*ORCID ID: 0009-0006-1446-2865*

***Agnieszka Morawa***
*Municipal Hospital in Zabrze, Zabrze, Poland*
*ORCID ID: 0009-0001-2325-7998*

**ABSTRACT**

Angiotensin receptor–neprilysin inhibitors (ARNI), with sacubitril/valsartan as the prototypical agent, have fundamentally transformed the pharmacological treatment paradigm of chronic heart failure (HF) [6,11,36,47,48,49,50]. This systematic review synthesizes the available clinical evidence, with a particular focus on the therapeutic efficacy of ARNI across the full continuum of left ventricular ejection fraction [3,4,17,50]. In patients with heart failure with reduced ejection fraction (HFrEF), pivotal randomized trials have consistently demonstrated the superiority of ARNI over conventional angiotensin-converting enzyme inhibitors in lowering cardiovascular mortality and HF-related hospitalizations, while also promoting favorable reverse myocardial remodeling [2,9,10,11,18,26,30,39,41,43,44,49]. In contrast, among individuals with preserved or mildly reduced ejection fraction, the principal clinical benefit is reduction in recurrent HF hospitalizations, with numerically greater treatment effects reported in women [1,3,7,18,23]. In addition, sacubitril/valsartan exhibits clinically relevant renoprotective effects and a favorable safety profile in complex patient populations, including those with diabetes mellitus or advanced chronic kidney disease [4,10,11,18]. Contemporary clinical guidelines position ARNI as a cornerstone of quadruple guideline-directed medical therapy, recommending early initiation during hospitalization and proactive dose up-titration to optimize clinical outcomes [7,8,11,13,21,31,47,48,49,50]. Addressing barriers to implementation—such as treatment-related hypotension and therapeutic inertia—remains essential to reduce the considerable global burden of heart failure [5,7,28,29,34,38].

**KEYWORDS**

HFrEF, HFpEF, Sacubitril/Valsartan, Angiotensin Receptor Neprilysin Inhibitor, Chronic Heart Failure

**CITATION**

Marcin Schulz, Karolina Osińska, Dawid Studziński, Michał Kulczak, Anna Kołcz, Agnieszka Morawa. (2026) Neprilysin Inhibitors (ARNI) in the Treatment of Chronic Heart Failure — a Systematic Review and Critical Appraisal of the Evidence. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.4760

## Methodology

A systematic literature search was undertaken to identify pertinent studies published in 2025. The following electronic databases were comprehensively queried: MEDLINE (via PubMed), Embase, the Cochrane Library, ClinicalTrials.gov, and Scopus. To ensure uniformity in data interpretation and reporting, the search was limited to publications available in the English language.

The search strategy integrated terms related to both the pharmacological intervention and the clinical condition under investigation. Specifically, combinations of the following keywords and Boolean operators were applied: “sacubitril valsartan” OR “ARNI” OR “neprilysin inhibitor” AND “heart failure” OR “chronic heart failure” OR “HFrEF” OR “HFpEF” OR “acute decompensated heart failure”. When supported by individual databases, controlled vocabulary terms, including Medical Subject Headings (MeSH) and Emtree terms, were incorporated to improve the sensitivity and specificity of the search.

An initial screening of titles and abstracts was conducted to identify potentially eligible studies, followed by full-text retrieval for in-depth assessment. Study selection followed a hierarchical framework: randomized controlled trials (RCTs) and meta-analyses were given priority due to their high methodological rigor; subsequently, well-designed observational studies were included; finally, contemporary clinical practice guidelines addressing the role of sacubitril/valsartan and related therapies in heart failure were reviewed to contextualize the evidence and reflect consensus recommendations.

Data extraction focused on key methodological and clinical parameters, including study design, patient characteristics, interventions, outcomes, and principal findings. Any discrepancies in study selection or data interpretation were resolved through reviewer consensus. This structured and systematic approach ensured a rigorous, transparent, and unbiased synthesis of the current evidence regarding sacubitril/valsartan and neprilysin inhibition in the management of heart failure.

## Introduction

The global management of chronic heart failure (HF) continues to pose a major clinical challenge, accounting for a substantial proportion of cardiovascular morbidity and mortality worldwide [1,45,50]. Pharmacological strategies aimed at modulating maladaptive neurohumoral activation constitute a central component of contemporary HF therapy [50]. Within this framework, the natriuretic peptide system reflects a complex hormonal network characterized by an antagonistic balance between the detrimental effects of renin–angiotensin–aldosterone system (RAAS) activation and the compensatory, cardioprotective actions mediated by endogenous natriuretic peptides (NPs) [11,41]. In routine clinical practice, NPs serve as essential biomarkers for the diagnosis of HF, stratification of disease severity, and prognostic assessment [3,39]. The biological activity of these peptides is governed by both their synthesis and degradation, with neprilysin (NEP) playing a pivotal role in their enzymatic clearance [6]. NEP is a zinc-dependent endopeptidase that mediates the breakdown of multiple vasoactive peptides, including atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) [6,36]. Through this mechanism, NEP contributes to the persistence of systemic neurohumoral imbalance, thereby promoting adverse cardiac remodeling and progression of HF [11].

The introduction of angiotensin receptor–neprilysin inhibitors (ARNI), exemplified by sacubitril/valsartan, marked a fundamental shift in the pharmacological management of HF [11,50]. ARNI comprises two pharmacologically active components: sacubitril, a selective and potent inhibitor of NEP, and valsartan, a well-established angiotensin II type 1 receptor antagonist (ARB) [6,11]. The therapeutic profile of ARNI is defined by this dual mechanism of action [11]. By inhibiting NEP, sacubitril increases circulating levels of endogenous natriuretic peptides, thereby enhancing their favorable physiological effects, including natriuresis, diuresis, and vasodilation [11]. Importantly, the simultaneous blockade of angiotensin II type 1 receptors by valsartan offsets the potential deleterious increase in angiotensin II activity that may occur with isolated NEP inhibition [11].

This integrated mechanism—combining augmentation of the protective natriuretic peptide system with suppression of RAAS-mediated harm—provides the biological rationale for the robust therapeutic effects observed with ARNI therapy [9,11]. Early pivotal trials demonstrated that, in patients with heart failure with reduced ejection fraction (HFrEF), ARNI significantly lowers rates of morbidity and mortality compared with conventional angiotensin-converting enzyme inhibitor (ACEi) therapy [2,11,26,39]. In addition, ARNI has been shown to facilitate left ventricular (LV) reverse remodeling, leading to measurable improvements in myocardial structure and function [29,33,41]. Beyond its established indications, ARNI is now recognized as one of the four core components of guideline-directed medical therapy (GDMT) [2,23], and its combined use with sodium–glucose cotransporter 2 (SGLT2) inhibitors is increasingly investigated for potential synergistic or additive benefits on both cardiac and renal outcomes [9,43]. Ongoing research continues to broaden the clinical scope of ARNI, extending its evaluation across the full spectrum of ejection fraction, including HFmrEF and HFpEF, as well as in complex patient populations with comorbid conditions such as diabetic cardiomyopathy (DbCM) and chronic kidney disease [3,4,6,7,38].

**Results — Evidence from Randomized Controlled Trials (RCTs)**

*PARADIGM-HF (Heart Failure with Reduced Ejection Fraction, HFrEF)*

The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial firmly established sacubitril/valsartan as a cornerstone therapy for patients with HFrEF [11,16]. In this landmark study, sacubitril/valsartan demonstrated clear superiority over enalapril, resulting in a significant reduction in the composite primary endpoint of heart failure (HF) hospitalization or cardiovascular (CV) death [10,18,26,30]. Therapeutic efficacy was evident across both components of the composite outcome, with reductions observed in the risk of CV mortality as well as first HF hospitalization [18]. Importantly, the relative risk reduction associated with sacubitril/valsartan remained consistent across the full spectrum of baseline N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentrations, indicating preserved efficacy irrespective of initial disease severity [3]. As a result, absolute risk reduction was greatest among patients with the highest NT-proBNP levels, translating into a number needed to treat (NNT) of 16 over 31 months in the highest NT-proBNP quintile, compared with an NNT of 37 in the lowest quintile [3]. Moreover, post hoc analyses confirmed that the magnitude of benefit was comparable in women (HR: 0.76, 95% CI: 0.62–0.94) and men (HR: 0.80, 95% CI: 0.73–0.89), underscoring the consistency of treatment effects across sexes [18].

*PARAGON-HF (Heart Failure with Preserved Ejection Fraction, HFpEF)*

The Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) trial compared sacubitril/valsartan with valsartan in patients with a left ventricular ejection fraction (LVEF) ≥45% [1,3]. The study demonstrated a modest overall benefit, with a 13% reduction in the composite primary endpoint of total HF hospitalizations and CV death [1]. This effect was predominantly driven by a decrease in recurrent HF hospitalizations, while no statistically significant reduction in CV mortality was observed [1].

Subgroup analyses revealed heterogeneity of treatment effects, particularly with respect to sex and measures of adiposity. Sacubitril/valsartan was associated with a greater reduction in the primary composite outcome among women (RR: 0.73, 95% CI: 0.59–0.90) compared with men (RR: 1.03, 95% CI: 0.84–1.25), with a significant interaction by sex (P-interaction = 0.017) [18]. The enhanced benefit observed in women was largely attributable to a more pronounced reduction in total HF hospitalizations [18].

Further evaluation of body composition within PARAGON-HF highlighted important limitations of conventional obesity definitions. A dedicated substudy demonstrated that although 49% of participants met criteria for obesity based on body mass index (BMI ≥30 kg/m²), central adiposity was present in 96% of patients, as assessed by a waist-to-height ratio (WHtR ≥0.5) [1]. WHtR showed a stronger and more linear association with adverse HF outcomes than BMI, suggesting that central adiposity is a nearly universal characteristic of HFpEF rather than a feature of a distinct subgroup [1]. While neprilysin inhibition appeared to confer greater HF-related benefits in individuals with higher BMI (P-interaction ≈0.06), no significant heterogeneity was observed when treatment effects were analyzed across the continuum of WHtR values [1].

*PIONEER-HF / TRANSITION (Initiation during Peri-discharge or Hospitalization)*

The safety and feasibility of early ARNI initiation following acute HF decompensation have been evaluated in dedicated trials involving patients with HFrEF. In the PIONEER-HF trial, initiation of sacubitril/valsartan in hemodynamically stabilized patients hospitalized for acute decompensated HF resulted in greater reductions in NT-proBNP levels and demonstrated a favorable safety profile when compared with enalapril [10,47].

Similarly, the TRANSITION trial assessed the initiation of sacubitril/valsartan either during hospitalization or shortly after discharge [23,45]. The findings confirmed that ARNI therapy could be safely and effectively introduced in stabilized patients, with greater reductions in biomarkers of cardiac stress and higher rates of target dose achievement, particularly among patients with de novo HFrEF [34].

These observations have been extended to patients with worsening HF and an ejection fraction exceeding 40%. The PARAGLIDE-HF trial showed that initiation of sacubitril/valsartan during hospitalization or in the early post-discharge period provided consistent benefits in terms of NT-proBNP reduction and clinical outcomes, while maintaining comparable tolerability and safety—including rates of symptomatic hypotension, hyperkalemia, and worsening renal function—relative to initiation in the outpatient setting [21]. Collectively, these data support the strategic use of hospitalization as an opportunity to commence ARNI therapy [21].

*Other Randomized Controlled Trials and Meta-analyses*

A comprehensive appraisal of additional randomized trials and meta-analyses further delineates the role of ARNI across diverse clinical scenarios, patient subgroups, and combination therapy strategies, providing a broader contextual framework for its application in contemporary heart failure management.

| Trial/Study Focus | Population/Setting | Key Findings (vs. Control) |
|---|---|---|
| Meta-analysis on AMI/HF | In-hospital initiation in AMI-related HFrEF. | Reduced risk of major adverse CV events (OR 0.45) and HF rehospitalization (OR 0.40). Improved LVEF (MD 3.07%) and reduced LV volumes. Associated with higher rates of hypotension (OR 1.42) [5]. |
| PARADISE-MI | Post-AMI patients (high-risk). | The primary trial did not demonstrate a significant superiority of sacubitril/valsartan over ramipril in reducing CV outcomes [32,47]. |
| ARNI + SGLT2i Combination | HFrEF patients. | After 3 months, the combined therapy led to significant improvements in ventricular and atrial volumetric indices, systolic function (LVEF, LVGLS), and a sustained decrease in NT-proBNP. The addition of SGLT2i to patients already on ARNI resulted in significant improvements [43]. |
| ENVAD-HF | Pilot RCT in stable HeartMate 3 LVAD recipients. | Demonstrated safety and tolerability. Showed a significant improvement in patient-reported outcomes (KCCQ–Overall Summary Score: +10.6, $P$=0.011) and a reduction in the number of blood pressure-lowering medications [10]. |

**Results — Safety and Specific Populations**

*Nephrology (Impact on GFR) and Diabetes*

The therapeutic profile of sacubitril/valsartan (Sac/Val) encompasses clinically meaningful renoprotective effects, with benefits observed across the full spectrum of chronic kidney disease and particularly among patients with concomitant diabetes mellitus (DM). In individuals with heart failure (HF) and type 2 diabetes, Sac/Val has been shown to significantly slow the decline in renal function compared with enalapril [11]. Through neprilysin inhibition, sacubitril contributes to a reduced rate of estimated glomerular filtration rate (eGFR) decline across a wide range of left ventricular ejection fraction (LVEF) categories [4].

Accumulating data indicate that the renoprotective effects of Sac/Val may be dose dependent, especially in patients with proteinuria [11]. Retrospective analyses have demonstrated a significant association between changes in eGFR and the achieved Sac/Val dose, with more pronounced preservation of renal function in patients receiving higher daily doses (200 mg and 400 mg) compared with the lowest dose (50 mg) [11]. Beyond renal effects, Sac/Val appears to exert synergistic anti-remodeling actions in diabetic cardiomyopathy (DbCM), potentially mediated through immunomodulatory pathways and attenuation of inflammatory signaling, thereby influencing disease progression [6]. In patients with diabetes classified as having pre–heart failure with preserved ejection fraction (HFpEF), Sac/Val effectively prevented an increase in the left atrial stiffness index over an 18-month period, an effect not observed with valsartan monotherapy [6].

Importantly, the benefits of angiotensin receptor–neprilysin inhibition extend to patients at the highest risk. Among individuals with heart failure with reduced ejection fraction (HFrEF) receiving kidney

replacement therapy, ARNI use was associated with significantly lower risks of all-cause mortality, cardiovascular (CV) mortality, and HF-related hospitalization compared with conventional renin–angiotensin system (RAS) blockade [4]. These favorable outcomes were closely linked to sustained adherence to ARNI therapy [4]. Moreover, initiation and optimization of ARNI within specialized cardiorenal units did not result in clinically significant deterioration of renal function, as reflected by stable creatinine levels and eGFR over a six-month follow-up period [9].

*Advanced Age and Hypotension*

Advanced age in HF populations is commonly associated with adverse prognostic features, including a higher prevalence of comorbidities and a reduced prognostic nutritional index (PNI), which independently predicts unfavorable outcomes across the HF spectrum [30]. Evidence regarding the efficacy of Sac/Val in elderly patients remains heterogeneous. Observational data indicate that patients receiving contemporary quadruple guideline-directed medical therapy (GDMT), including ARNI, tend to be younger (median age 71 years) than those treated with older two-drug regimens (median age 82 years) [31]. In some real-world cohorts of de novo HFrEF, the association between Sac/Val therapy and reduced hospitalization rates appeared attenuated in patients aged ≥75 years compared with younger individuals [34]. Conversely, other analyses have shown that the prognostic gains associated with achieving optimal medical therapy (OMT) are at least comparable, if not greater, in older patients (>72 years) relative to their younger counterparts [46].

In routine clinical practice, hypotension represents the most frequent dose-limiting adverse effect of ARNI therapy and accounts for treatment discontinuation in approximately 74.4% of cases [38]. In the post–acute myocardial infarction (AMI) setting, patients treated with ARNI experienced a higher incidence of iatrogenic hypotension compared with those receiving standard therapy (odds ratio [OR] 1.42) [5]. To reduce the likelihood of treatment interruption, baseline systolic blood pressure (SBP) ≥110 mmHg at initiation has been identified as an independent predictor of continued Sac/Val therapy [38]. Additionally, in HFrEF populations, initiating Sac/Val as a single agent—without the concurrent introduction of other foundational HF therapies such as beta-blockers, mineralocorticoid receptor antagonists, or SGLT2 inhibitors—was associated with higher rates of treatment persistence [38]. Compared with angiotensin-converting enzyme inhibitors, Sac/Val consistently induces greater reductions in both systolic and diastolic blood pressure [47] and has been shown to significantly improve the cardio-ankle vascular index (CAVI) in patients with hypertension [27].

**Clinical Guidelines and Recommendations — Review of Current Guidelines (AHA/ACC/HFSA 2022 and Updates/Consensus 2024)**

The pharmacological management of chronic heart failure (HF) has evolved substantially over recent years, with angiotensin receptor–neprilysin inhibitors (ARNI) now recognized as a cornerstone of contemporary therapeutic strategies [47,48,49]. Current clinical guidelines, including the 2022 AHA/ACC/HFSA consensus and subsequent updates, strongly recommend ARNI (sacubitril/valsartan) as a key component of guideline-directed medical therapy (GDMT) in eligible patients with heart failure with reduced ejection fraction (HFrEF) [48].

The prevailing standard of care is based on a quadruple-therapy framework, comprising an ARNI or renin–angiotensin system (RAS) inhibitor, a beta-blocker (BB), a mineralocorticoid receptor antagonist (MRA), and a sodium–glucose cotransporter 2 inhibitor (SGLT2i) [7,31,49,50]. A defining feature of updated recommendations is the shift toward earlier and more rapid treatment implementation. Expert consensus increasingly supports abandoning the traditional slow, sequential escalation in favor of prompt, near-simultaneous initiation of all four foundational drug classes [31,49]. This approach is endorsed by the AHA/ACC/HFSA consensus, which advocates rapid dose up-titration (e.g., every 1–2 weeks) [23], as well as by the European Society of Cardiology (ESC), which assigns a Class IB recommendation to rapid GDMT initiation following an episode of acute HF [50].

In patients with heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF), the role of ARNI is more nuanced. Although recent ESC guidelines emphasize SGLT2 inhibitors as first-line therapy in these phenotypes, reflecting robust outcome data [14], pooled analyses indicate that the relative benefits of ARNI are maintained across the entire spectrum of ejection fraction, independent of baseline N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentrations [3,45]. Moreover, clinical trials enrolling patients with EF >40% who were stabilized after a worsening HF event support the continued use and early initiation of ARNI in this high-risk population [7].

The timing of ARNI initiation constitutes another critical aspect of current recommendations. Guidelines highlight the importance of early treatment introduction, particularly during the vulnerable peri-hospitalization period associated with acute HF decompensation [50]. Randomized trials such as PIONEER-HF and TRANSITION have demonstrated that initiating ARNI therapy in hemodynamically stabilized patients is both feasible and safe [4,5,34]. These data underpin the consensus view that hospitalization represents a key opportunity to commence ARNI therapy, thereby enhancing treatment continuity and improving post-discharge outcomes [21].

The scope of ARNI use is also expanding within specialized patient populations as new evidence emerges. The 2023 HFSA expert consensus advises that pharmacological management in patients supported with a left ventricular assist device (LVAD) should remain aligned with established GDMT principles for HFrEF. With respect to chronic kidney disease (CKD), although major randomized trials largely excluded patients with advanced renal impairment (eGFR <30 mL/min/1.73 m²) [4,18], real-world observational studies offer encouraging insights. In cohorts of HFrEF patients undergoing kidney replacement therapy (KRT), ARNI treatment was associated with lower all-cause and cardiovascular mortality compared with conventional RAS blockade, underscoring the clinical relevance of strict adherence to ARNI therapy in this particularly vulnerable population [4].

## Discussion

*Interpretation*

Robust evidence derived from randomized controlled trials (RCTs), most notably PARADIGM-HF and PARAGON-HF, firmly positions neprilysin inhibition with angiotensin receptor–neprilysin inhibitors (ARNI), particularly sacubitril/valsartan (S/V), as a central element of contemporary chronic heart failure (CHF) management across the full range of left ventricular ejection fraction (LVEF) [3,17,50]. In heart failure with reduced ejection fraction (HFrEF), S/V has consistently demonstrated superiority over enalapril, yielding significant reductions in all-cause mortality, cardiovascular (CV) death, and heart failure hospitalizations (HFH) [18,39,44,49]. These clinical benefits are closely linked to marked left ventricular reverse remodeling (LVRR) and consequent improvements in cardiac structure and function [33,41,43]. Importantly, the relative risk reduction achieved with S/V remains stable irrespective of baseline N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, translating into the greatest absolute benefit among patients with the highest NT-proBNP concentrations, who represent the highest-risk subgroup [3].

In heart failure with preserved (HFpEF) and mildly reduced ejection fraction (HFmrEF), S/V predominantly confers benefit through a reduction in recurrent HF hospitalizations, while the impact on mortality is less pronounced than that observed in HFrEF [3,7,23]. A key insight emerging from analyses of the PARAGON-HF cohort challenges the conventional reliance on body mass index (BMI) to define obesity-related HFpEF phenotypes [1]. The waist-to-height ratio (WHtR) proved to be a stronger prognostic indicator, nearly ubiquitous in the HFpEF population and linearly associated with adverse outcomes, supporting the concept that central adiposity is a fundamental characteristic of HFpEF rather than a discrete BMI-defined subgroup [1]. Furthermore, subgroup analyses from both PARADIGM-HF and PARAGON-HF suggest that the therapeutic effects of S/V are broadly consistent between sexes, although women with HFpEF exhibited numerically greater reductions in total HF hospitalizations [18].

Beyond traditional endpoints, emerging data indicate additional benefits of S/V in complex cardiovascular contexts, including improvements in quality of life and right ventricular performance in patients with systemic right ventricular (sRV) failure [15,37]. Moreover, S/V has been associated with antiarrhythmic properties, reflected by lower rates of ventricular tachycardia (VT) and ventricular fibrillation (VF), and a reduced need for implantable cardioverter-defibrillator (ICD) interventions in patients with HFrEF [13,50].

*Clinical Implications*

The accumulated evidence strongly advocates for early and broad implementation of ARNI therapy to maximize clinical benefit and alleviate the substantial socioeconomic burden associated with CHF [8]. Real-world data demonstrate a clear dose–response relationship, whereby attainment of higher S/V doses (e.g., target dose 200 mg twice daily) is associated with significantly fewer all-cause hospitalizations and lower overall healthcare costs, highlighting the imperative to overcome barriers to dose titration [8]. Clinicians should therefore prioritize dose optimization rather than defaulting to minimal dosing, a practice that remains common despite strong guideline recommendations [8]. This approach is particularly critical given that the therapeutic effectiveness of S/V is closely tied to adherence, with meaningful benefits largely confined to patients achieving high medication adherence (proportion of days covered ≥80%) [2,4].

The well-documented renoprotective effects of S/V—including its dose-dependent attenuation of eGFR decline and favorable outcomes even in advanced chronic kidney disease (CKD) and in patients receiving kidney replacement therapy—suggest that concerns regarding renal function should not lead to premature discontinuation, provided that potassium levels are carefully monitored [4,11,13]. In addition, the absence of an observed association between S/V use and increased dementia risk, despite theoretical concerns related to neprilysin inhibition, offers reassurance regarding long-term neurocognitive safety [25]. Evidence supporting early initiation, particularly among patients with de novo HFrEF, further justifies prompt commencement of S/V during the vulnerable post-hospitalization period following worsening HF (WHF), a strategy that may enhance adherence and clinical outcomes in this high-risk phase [7,34].

*Knowledge Gaps*

Despite compelling trial and real-world data, important gaps remain in the optimal deployment of ARNI therapy. Globally, utilization rates remain suboptimal, frequently limited by clinical inertia, tolerability issues—most notably hypotension—and fragmented models of care [8,38]. A large proportion of patients initiating S/V remain on the lowest available dose, underscoring the persistent disconnect between evidence-based dosing strategies and routine clinical practice [8].

Although the short- to mid-term safety profile of S/V is well established, particularly with respect to hypotension and hyperkalemia [7,18], long-term data evaluating hard renal endpoints—such as progression to sustained renal replacement therapy—remain scarce, with most studies relying on surrogate measures such as eGFR decline [11,39]. In addition, the optimal sequencing of the modern four foundational therapies (ARNI, beta-blockers, mineralocorticoid receptor antagonists [MRA], and SGLT2 inhibitors) remains uncertain, as definitive RCTs comparing rapid simultaneous initiation with conventional stepwise titration are lacking, especially outside acute decompensation settings [23]. Finally, although current evidence does not suggest adverse neurocognitive effects, extended follow-up remains essential given the theoretical mechanisms involved and the prolonged latency of neurodegenerative disorders [12,25].

*Future Directions*

Future investigations should focus on translating established efficacy into optimized, real-world treatment strategies. A key priority is the conduct of large, prospective RCTs comparing immediate and rapid initiation of quadruple therapy—including S/V—with traditional gradual sequencing in stable CHF populations, as exemplified by emerging trial designs such as the planned NovCon Sequencing Study [23].

In HFpEF, further work is required to refine patient selection and risk stratification, potentially by prioritizing markers such as WHtR over BMI in trial enrollment to better identify individuals most likely to derive cardiovascular benefit from S/V [1]. Long-term randomized and observational studies addressing definitive renal outcomes, including progression to end-stage kidney disease (ESKD) and the requirement for kidney replacement therapy (KRT), are also needed to clarify the durability of ARNI-mediated nephroprotection, particularly in patients with pre-existing CKD [1,4,11,13].

To address persistent adherence and titration challenges, future research should evaluate system-level interventions—such as pharmacist-led HF programs or telemonitoring-based support—to reduce clinical inertia and facilitate achievement and maintenance of target S/V doses [8]. Finally, comprehensive real-world analyses linking specific S/V dosing strategies to long-term cost-effectiveness outcomes, including quality-adjusted life years and total healthcare expenditures, are essential to inform health policy and reimbursement frameworks, ensuring that clinical benefits are translated into sustainable healthcare value [8].

## Conclusions

The integrated body of evidence confirms that sacubitril/valsartan (ARNI) constitutes a transformative pillar in the management of chronic heart failure, conferring clinically meaningful benefits across the entire spectrum of ejection fraction [1,3]. In patients with heart failure with reduced ejection fraction (HFrEF), its efficacy in lowering cardiovascular mortality and reducing hospitalization rates is strongly supported by both pivotal randomized trials and real-world longitudinal analyses [2,18,49]. The therapeutic impact of ARNI extends beyond conventional neurohumoral inhibition, as reflected by significant improvements in left ventricular reverse remodeling, ventricular–arterial coupling, and overall myocardial efficiency [19,41]. Moreover, the scope of ARNI use has broadened to encompass complex clinical populations, including stable recipients of mechanical circulatory support with HeartMate 3 left ventricular assist devices (LVAD), in whom therapy has demonstrated an acceptable safety profile and improvements in patient-reported quality of life [10]. In pediatric cohorts, ARNI therapy has been associated with marked reductions in NT-proBNP levels, a biomarker validated for prognostic risk stratification in children with systolic ventricular dysfunction [26].

From a practical standpoint, optimal heart failure management should emphasize early and effective initiation of ARNI therapy to maximize clinical outcomes. Evidence from the PARAGLIDE-HF trial supports in-hospital initiation of sacubitril/valsartan following hemodynamic stabilization after a worsening heart failure event, demonstrating both safety and efficacy even in patients without prior exposure to renin–angiotensin system inhibitors [7,21]. Clinicians should proactively pursue dose escalation toward target dosing (97/103 mg twice daily), as higher doses are associated with enhanced renoprotective effects—particularly in individuals with concomitant proteinuria—and with substantial reductions in overall healthcare expenditures [8,11]. To address the principal dose-limiting adverse effect of hypotension, initiation is ideally undertaken in patients with systolic blood pressure ≥110 mmHg, while maintaining high treatment adherence (proportion of days covered ≥80%) remains critical to preserving survival benefits in real-world practice [2,38]. In this context, the adoption of multidisciplinary care models, including integrated cardiorenal units and nurse-led heart failure clinics, is strongly encouraged to overcome implementation barriers and facilitate successful titration of foundational quadruple therapy without inducing clinically significant renal impairment [9,42,44].

Ongoing safety surveillance remains an essential component of long-term ARNI therapy; however, current data offer substantial reassurance regarding neurocognitive safety. Large retrospective cohort studies have demonstrated no increased incidence of dementia compared with conventional renin–angiotensin system blockade, and circulating biomarkers of neurodegeneration do not indicate acute neuronal injury following ARNI initiation [12,25]. Additionally, incorporation of advanced right ventricular functional assessment—such as free wall right ventricular longitudinal strain (fwRVLS)—into routine clinical evaluation may provide independent prognostic information for risk stratification among patients receiving ARNI therapy [28,29]. In summary, sacubitril/valsartan represents a major advancement in cardiovascular pharmacotherapy, and its systematic implementation through early initiation and rapid optimization strategies is essential to meaningfully reduce the global burden of heart failure.

## REFERENCES


1. Peikert, A., Vaduganathan, M., Claggett, B. L., Kulac, I. J., Litwin, S., Zile, M., Desai, A. S., Jhund, P. S., Butt, J. H., Lam, C. S. P., Martinez, F., Van Veldhuisen, D. J., Zannad, F., Rouleau, J., Lefkowitz, M., McMurray, J. J. V., Solomon, S. D., & Packer, M. (2025). Near-universal prevalence of central adiposity in heart failure with preserved ejection fraction: the PARAGON-HF trial. *European heart journal*, *46*(25), 2372–2390. https://doi.org/10.1093/eurheartj/ehaf057
2. Cho, D. H., Choi, J., Youn, J. C., Kim, M. N., Lee, C. J., Son, J. W., & Yoo, B. S. (2025). Angiotensin receptor-neprilysin inhibitor adherence and outcomes in heart failure with reduced ejection fraction. *ESC heart failure*, *12*(1), 603–612. https://doi.org/10.1002/ehf2.15117
3. Kondo, T., Jhund, P. S., Anand, I. S., Claggett, B. L., Desai, A. S., Docherty, K. F., Lam, C. S. P., Lefkowitz, M. P., Maggioni, A. P., Martinez, F. A., Redfield, M. M., Rouleau, J. L., Van Veldhuisen, D. J., Zannad, F., Zile, M. R., Packer, M., Solomon, S. D., & McMurray, J. J. V. (2025). Effects of Sacubitril/Valsartan According to Natriuretic Peptide Levels in Patients Enrolled in PARADIGM-HF and PARAGON-HF. *JACC. Heart failure*, *13*(6), 927–939. https://doi.org/10.1016/j.jchf.2024.12.010
4. Jung, M. H., Cho, D. H., Choi, J., Kim, M. N., Lee, C. J., Son, J. W., Kim, Y., Youn, J. C., & Yoo, B. S. (2025). Angiotensin receptor-neprilysin inhibitors in concurrent heart failure with reduced ejection fraction and kidney failure. *ESC heart failure*, *12*(5), 3405–3415. https://doi.org/10.1002/ehf2.15359
5. Di Pietro, G., Improta, R., Severino, P., D'Amato, A., Birtolo, L. I., De Filippo, O., Lattanzio, A., De Cristofaro, R., Galardo, G., D'Ascenzo, F., Badagliacca, R., Sardella, G., Volterrani, M., Fedele, F., Vizza, C. D., & Mancone, M. (2025). The in-hospital administration of sacubitril/valsartan in acute myocardial infarction: A meta-analysis. *ESC heart failure*, *12*(2), 998–1012. https://doi.org/10.1002/ehf2.15082
6. Karuna, N., Kerrigan, L., Edgar, K., Ledwidge, M., McDonald, K., Grieve, D. J., & Watson, C. J. (2025). Sacubitril/Valsartan attenuates progression of diabetic cardiomyopathy through immunomodulation properties: an opportunity to prevent progressive disease. *Cardiovascular diabetology*, *24*(1), 206. https://doi.org/10.1186/s12933-025-02741-5
7. Nouhravesh, N., Gunn, A. H., Cyr, D., Hernandez, A. F., Morrow, D. A., Velazquez, E. J., Ward, J. H., Sarwat, S., Sharma, K., Williamson, K. M., Starling, R. C., Lepage, S., Zieroth, S., Solomon, S. D., & Mentz, R. J. (2025). Sacubitril/valsartan versus valsartan initiation in patients naïve to renin-angiotensin system inhibitors: Insights from PARAGLIDE-HF. *European journal of heart failure*, *27*(8), 1418–1425. https://doi.org/10.1002/ejhf.3579
8. Rung, J. M., Barrett, T. S., LeJeune, K., Richards, S. B., Raina, A., & Sinoway, L. (2025). Dosing patterns and dose effects of sacubitril/valsartan: A claims-based retrospective cohort study. *PloS one*, *20*(3), e0320216. https://doi.org/10.1371/journal.pone.0320216

9. León-Román, J., Azancot, M. A., Marouco, C., Patricio-Liebana, M., Zamora, J. I., Ramos Terrades, N., Toapanta, N., Núñez-Delgado, S., Mendez Fernandez, A. B., & Soler, M. J. (2025). A New Era in the Management of Cardiorenal Syndrome: The Importance of Cardiorenal Units. *Cardiorenal medicine*, *15*(1), 174–183. https://doi.org/10.1159/000543294
10. Cikes, M., Brugts, J. J., Claggett, B., Jorde, U. P., Milicic, D., Planinc, I., Ruschitzka, F., Uriel, N., Kulac, I., Jakus, N., Loncaric, F., Puskaric, F., Sipus, D., Gasparovic, H., Rubis, P., van Laake, L. W., Rudez, I., Hegarova, M., Sestan, G., Wisniowska-Smialek, S., … Solomon, S. D. (2025). Angiotensin-Neprilysin Inhibition and Left Ventricular Assist Device Therapy: Primary Results of the ENVAD-HF Trial. *JACC. Heart failure*, *13*(11), 102657. https://doi.org/10.1016/j.jchf.2025.102657
11. Kato, T., Nakano, Y., Yasukawa, N., Oonishi, M., & Hamada, Y. (2025). Dose-dependent renoprotective effects of sacubitril/valsartan in heart failure: a retrospective study. *Renal failure*, *47*(1), 2538830. https://doi.org/10.1080/0886022X.2025.2538830
12. Prausmüller, S., Wurm, R., Ponleitner, M., Stögmann, E., Hülsmann, M., & Pavo, N. (2025). Effect of Initiation With Sacubitril/valsartan on Blood Neurodegeneration Markers in HFrEF. *Journal of cardiac failure*, *31*(6), 967–971. https://doi.org/10.1016/j.cardfail.2025.01.021
13. Arzhangzadeh, A., Nikoo, M. H., Haghjoo, M., Rasekh, F., Shojaei, S., Mousavi, A., Nozhat, S., Narimani-Javid, R., Bazroodi, H., Neisi, S., Mojibpour, M., Abedini, M., Eslamzadeh, S., Drissi, H. B., & Shafiei, S. (2025). The Effect of Sacubitril/Valsartan on Supraventricular and Ventricular Arrhythmias in Patients With Heart Failure. *Annals of noninvasive electrocardiology: the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc*, *30*(3), e70081. https://doi.org/10.1111/anec.70081
14. Ingimarsdóttir, I. J., Vishram-Nielsen, J. K. K., Einarsson, H., Goldfeder, S., Mewton, N., Barasa, A., Basic, C., Oerlemans, M. I. F. J., Niederseer, D., Shchendrygina, A., Gustafsson, F., Ruschitzka, F., Kida, K., Mohty, D., Rakotonoel, R. R., Tun, H. N., Hrafnkelsdóttir, T. J., & Saldarriaga, C. (2025). Diagnostic and therapeutic practice for HFpEF across continents and regions: An international survey. *ESC heart failure*, *12*(1), 487–496. https://doi.org/10.1002/ehf2.15084
15. Mathur, R., Baroopal, A., Chaudhary, C. R., Hakim, A., & Verma, M. (2025). Efficacy of Angiotensin Receptor Neprilysin Inhibitor (ARNI) in right ventricular systolic dysfunction and preserved LV ejection fraction: A randomized clinical trial. *Indian heart journal*, *77*(1), 42–44. https://doi.org/10.1016/j.ihj.2025.01.002
16. Zhao, Y. M., Luo, J. T., Pang, K. F., Feng, Y., Tan, J. P., Liu, M., & Lin, Z. H. (2025). Clinical efficacy of sacubitril/valsartan combined with cardiac rehabilitation in patients with heart failure after acute myocardial infarction: a single-center randomized trial. *BMC cardiovascular disorders*, *25*(1), 246. https://doi.org/10.1186/s12872-025-04682-z
17. Albertini, M., Waldmann, V., David, P., Barat, A., Legendre, A., Chaussade, A. S., Iserin, L., & Ladouceur, M. (2025). Safety and Efficacy of Dapagliflozin in Patients With Systemic Right Ventricular Dysfunction: DAPA-SRV Trial.
18. *Journal of the American Heart Association*, *14*(11), e040302. https://doi.org/10.1161/JAHA.124.040302
19. Chimura, M., Butt, J. H., Matsumoto, S., McMurray, E. G. M., Henderson, A. D., Talebi, A., Desai, A. S., Lefkowitz, M. P., Rizkala, A. R., Rouleau, J. L., Solomon, S. D., Swedberg, K., Zile, M. R., Packer, M., Jhund, P. S., & McMurray, J. J. V. (2025). Comprehensive Analysis of the Effects of Sacubitril/Valsartan According to Sex Among Patients With Heart Failure and Reduced Ejection Fraction in PARADIGM-HF. *Journal of the American Heart Association*, *14*(9), e038249. https://doi.org/10.1161/JAHA.124.038249
20. Mizutani, H., Fujimoto, N., Nakamori, S., Kokawa, T., Ishiyama, M., Omori, T., Moriwaki, K., Sato, Y., Goto, I., Sugiura, E., Ishida, M., Kurita, T., Koji, T., Okamoto, R., Murashima, S., Tanigawa, T., Sakuma, H., & Dohi, K. (2025). Effects of Sacubitril/Valsartan on Myocardial Tissue in Heart Failure With Left Ventricular Ejection Fraction Below 50. *Circulation journal: official journal of the Japanese Circulation Society*, *89*(7), 901–911. https://doi.org/10.1253/circj.CJ-24-0934
21. Sadasivan, C., Gagnon, L. R., Hazra, D., Wang, K., Youngson, E., Thomas, J., Chan, A. Y. M., Paterson, D. I., McAlister, F. A., Dzwiniel, T., Tymchak, W., Christian, S., & Oudit, G. Y. (2025). Early genetic screening and cardiac intervention in patients with cardiomyopathies in a multidisciplinary clinic. *ESC heart failure*, *12*(3), 1942–1955. https://doi.org/10.1002/ehf2.15202
22. Sadasivan, C., Gagnon, L. R., Hazra, D., Wang, K., Youngson, E., Thomas, J., Chan, A. Y. M., Paterson, D. I., McAlister, F. A., Dzwiniel, T., Tymchak, W., Christian, S., & Oudit, G. Y. (2025). Early genetic screening and cardiac intervention in patients with cardiomyopathies in a multidisciplinary clinic. *ESC heart failure*, *12*(3), 1942–1955. https://doi.org/10.1002/ehf2.15202
23. Anker, S. D., Friede, T., Butler, J., Talha, K. M., Placzek, M., Diek, M., Nosko, A., Stas, A., Kluge, S., Jarczak, D., Deheer, G., Rybczynski, M., Bayes-Genis, A., Edelmann, F., Filippatos, G., Hasenfuß, G., Haverkamp, W., Lainscak, M., Landmesser, U., Macdougall, I. C., … Karakas, M. (2025). Ferric carboxymaltose assessment of morbidity and mortality in patients with iron deficiency and chronic heart failure (FAIR-HF2-DZHK05) trial: Baseline characteristics and comparison to other relevant clinical trials. *European journal of heart failure*, *27*(8), 1436–1443. https://doi.org/10.1002/ejhf.3658

24. Karamchand, S., Chipamaunga, T., Naidoo, P., Naidoo, K., Rambiritch, V., Ho, K., Chilton, R., McMahon, K., Leisegang, R., Weich, H., & Hassan, K. (2025). Novel Versus Conventional Sequencing of β-Blockers, Sodium/Glucose Cotransportor 2 Inhibitors, Angiotensin Receptor-Neprilysin Inhibitors, and Mineralocorticoid Receptor Antagonists in Stable Patients With Heart Failure With Reduced Ejection Fraction (NovCon Sequencing Study): Protocol for a Randomized Controlled Trial. *JMIR research protocols*, *14*, e44027. https://doi.org/10.2196/44027
25. Chen, Q. F., Lu, Y., Katsouras, C. S., Peng, Y., Sun, J., Li, M., Liu, C., Yao, H., Lian, L., Feng, X., Lin, W. H., & Zhou, X. D. (2025). Characteristics, outcomes and the necessity of continued guideline-directed medical therapy in patients with heart failure with improved ejection fraction. *Annals of medicine*, *57*(1), 2442535 https://doi.org/10.1080/07853890.2024.2442535
26. Jung, K., Kim, J. H., Bea, S., Ko, H. Y., You, S. C., Choi, E. K., Lee, S., Lim, M., Kim, G. J., Kang, D. Y., & Shin, J. Y. (2025). Association between sacubitril/valsartan and risk of dementia in patients with heart failure: a nationwide cohort study. *European heart journal. Cardiovascular pharmacotherapy*, *11*(5), 412–421. https://doi.org/10.1093/ehjcvp/pvaf024
27. Shaddy, R., Gong, J., Garito, T., Solar-Yohay, S., Zhang, S., Prescott, M. F., Bonnet, D., Kantor, P. F., Burch, M., Mao, C., Cilliers, A., Canter, C., Law, Y., Grutter, G., Wang, J. K., Jeewa, A., Rossano, J., & PANORAMA-HF investigators (2025). Association between NT-proBNP changes and clinical outcomes in paediatric patients with heart failure: Insights from PANORAMA-HF and PARADIGM-HF. *ESC heart failure*, *12*(4), 3042–3052. https://doi.org/10.1002/ehf2.15326
28. Shimizu, K., Tabata, T., Iwakawa, M., Ikeda, Y., Ikeda, T., Nonaka, S., Sato, S., Nakagami, T., Mikamo, H., & Kinoshita, T. (2025). Potential Effects of Sacubitril/Valsartan on the Cardio-ankle Vascular Index in Hypertensive Patients. *Internal medicine (Tokyo, Japan)*, *64*(10), 1470–1475. https://doi.org/10.2169/internalmedicine.4041-24
29. Lu, H., Inciardi, R. M., Abanda, M., Shah, A. M., Cikes, M., Claggett, B. L., Prasad, N., Lam, C. S. P., Redfield, M., McMurray, J. J. V., Pfeffer, M. A., Solomon, S. D., Hegde, S. M., & Skali, H. (2025). Multiparametric Assessment of Right Ventricular Dysfunction in Heart Failure: An Analysis From PARAGON-HF. *Journal of the American Heart Association*, *14*(1), e037380. https://doi.org/10.1161/JAHA.124.037380
30. Pastore, M. C., Mandoli, G. E., Giannoni, A., Ginetti, F. R., Correale, M., Brunetti, N. D., Guaricci, A. I., Piscitelli, L., Degiovanni, A., Patti, G., Malagoli, A., Moderato, L., Carluccio, E., Marino, P. N., Emdin, M., & Cameli, M. (2025). Right ventricular strain predicts outcome in patients receiving sacubitril/valsartan: A sub-analysis of DISCOVER-ARNI. *ESC heart failure*, *12*(4), 2878–2886. https://doi.org/10.1002/ehf2.15297
31. Solano, S., Yang, M., Tolomeo, P., Kondo, T., Shen, L., Jhund, P. S., Anand, I. S., Desai, A. S., Lam, C. S. P., Maggioni, A. P., Martinez, F. A., Rouleau, J. L., Vaduganathan, M., van Veldhuisen, D. J., Zannad, F., Zile, M. R., Packer, M., Solomon, S. D., & McMurray, J. J. V. (2025). Clinical Characteristics and Outcomes of Patients With Heart Failure With Preserved Ejection Fraction and With Reduced Ejection Fraction According to the Prognostic Nutritional Index: Findings From PARADIGM-HF and PARAGON-HF. *Journal of the American Heart Association*, *14*(1), e037782. https://doi.org/10.1161/JAHA.124.037782
32. Möckel, M., Pudasaini, S., Feldmann, K., Baberg, H. T., Levenson, B., Malzahn, J., Mansky, T., Michels, G., Günster, C., & Jeschke, E. (2025). Prescription of guideline-directed medical therapy in heart failure: impact on mortality and readmission. *ESC heart failure*, *12*(4), 2791–2802. https://doi.org/10.1002/ehf2.15280
33. Amir, O., Elbaz-Greener, G., Carasso, S., Claggett, B., Barbarash, O., Zaman, A., Christersson, C., Kiatchoosakun, S., Anonuevo, J., Opolski, G., Vaghaiwalla, M. F., van der Meer, P., Zhou, Y., Mann, D. L., Kober, L., Steg, G., Jering, K., Kulac, I., De Pasquale, C. G., McMurray, J. J. V., … PARADISE-MI Investigators and Committees (2025). Association between body mass index and clinical outcomes in patients with acute myocardial infarction and reduced systolic function: Analysis of PARADISE-MI trial data. *European journal of heart failure*, *27*(3), 558–565. https://doi.org/10.1002/ejhf.3542
34. Takahashi, T., Kusunose, K., Imai, T., Furukawa, Y., Okada, T., Kadokami, T., Kanzaki, Y., Matsuda, H., Mizukoshi, K., Kida, K., Matsue, Y., Sata, M., Tanaka, A., & Node, K. (2025). Impact of early in-hospital initiation of sacubitril/valsartan on left ventricular reverse remodelling in acute heart failure. *European heart journal. Cardiovascular pharmacotherapy*, *11*(7), 565–573. https://doi.org/10.1093/ehjcvp/pvaf061
35. Bhatt, A. S., Vaduganathan, M., Jena, B. P., Suminska, S., Eid, C., Schwende, H., & Senni, M. (2025). Real-world comparative effectiveness of sacubitril/valsartan versus RAS inhibition alone in patients with de novo heart failure. *ESC heart failure*, *12*(3), 1682–1692. https://doi.org/10.1002/ehf2.15183
36. Chedid El Helou, M., Nandar, P. P., Tereshchenko, L. G., Jacob, M., Bhat, P., Vest, A. R., Bhattacharya, S., Hsich, E., Collier, P., Tang, W. H. W., Soltesz, E., Tong, M. Z., Starling, R. C., & Martyn, T. (2025). Factors associated with the use of guideline-directed medical therapy in patients with left ventricular assist device. *European journal of heart failure*, *27*(4), 650–655. https://doi.org/10.1002/ejhf.3591
37. Nishikimi, T., Nakagawa, Y., Miyamoto, S., Kanamori, T., Inazumi, H., Yanagisawa, H., Moriuchi, K., Kinoshita, H., Tamamura, Y., Takahama, H., Minamino, N., & Ono, K. (2025). Responses of B-type natriuretic peptide (BNP), mature BNP and proBNP to sacubitril/valsartan differs between responders and non-responders. *Open heart*, *12*(1), e002990. https://doi.org/10.1136/openhrt-2024-002990

38. Neijenhuis, R. M. L., Nederend, M., van Groningen, A. E., Jongbloed, M. R. M., Vliegen, H. W., Jukema, J. W., Kiès, P., & Egorova, A. D. (2025). Sacubitril/valsartan is associated with improvements in quality of life in adult congenital heart disease patients with systemic right ventricular failure. *Open heart*, *12*(1), e003009. https://doi.org/10.1136/openhrt-2024-003009
39. Iwasaki, E., Kohyama, N., Inamoto, M., Nagao, M., Sunaga, T., Suzuki, H., Ebato, M., & Kogo, M. (2025). Factors Associated With Sacubitril/Valsartan Continuation and the Methods of Combining Heart Failure Medications in Patients With Heart Failure. *The Annals of pharmacotherapy*, *59*(4), 301–310. https://doi.org/10.1177/10600280241277354
40. Hu, Y., Ma, F., Hu, M., Shi, B., Pan, D., & Ren, J. (2025). Development and validation of a machine learning model to predict the risk of readmission within one year in HFpEF patients: Short title: Prediction of HFpEF readmission. *International journal of medical informatics*, *194*, 105703. https://doi.org/10.1016/j.ijmedinf.2024.105703
41. Armentaro, G., Cassano, V., Magurno, M., Pastura, C. A., Divino, M., Severini, G., Martire, D., Miceli, S., Maio, R., Mazza, E., Montalcini, T., Pujia, A., & Sciacqua, A. (2025). Gliflozines as add-on to Arni in echocardiographic, sarcopenic and oxidative stress parameters in elderly patients with chronic heart failure. *Aging clinical and experimental research*, *37*(1), 158. https://doi.org/10.1007/s40520-025-03049-w
42. Dini, F. L., Cioffi, G., Carluccio, E., Ghio, S., Pugliese, N. R., Correale, M., Dattilo, G., Palazzuoli, A., & Working Group on Heart Failure of the Italian Society of Cardiology (2025). Insights into the Benefits of Reverse Remodeling from an Echocardiographic Pressure/Volume Loop Model in Patients With Heart Failure Treated With Sacubitril/Valsartan. *The American journal of cardiology*, *254*, 21–29. https://doi.org/10.1016/j.amjcard.2025.06.012
43. Laborante, R., Delvinioti, A., Tudor, A. M., Lenkowicz, J., Iacomini, C., Iaconelli, A., Paglianiti, D. A., Galli, M., Rodolico, D., Patarnello, S., Restivo, A., Ciliberti, G., Rizzo, G., Bianchini, E., Busti, M., Sensini, L., Valentini, V., Scambia, G., Gasbarrini, A., Crea, F., … D'Amario, D. (2025). Temporal trends in guideline-recommended medical therapy after an acute heart failure decompensation event: an observational analysis from Generator Heart Failure DataMart. *BMJ open*, *15*(2), e088998. https://doi.org/10.1136/bmjopen-2024-088998
44. Fumarulo, I., Pasquini, A., La Vecchia, G., Pellizzeri, B., Sten, A., Garramone, B., Vaccarella, M., Ravenna, S. E., Lombardo, A., Burzotta, F., Pitocco, D., & Aspromonte, N. (2025). Evaluation of the Effects of the Sodium-Glucose Cotransporter 2 Inhibitors and Sacubitril/Valsartan Combined Therapy in Patients with HFrEF: An Echocardiographic Study. *International journal of molecular sciences*, *26*(12), 5651. https://doi.org/10.3390/ijms26125651
45. Shahim, A., Linde, C., Savarese, G., Dahlström, U., Lund, L. H., & Hage, C. (2025). Implementation of guideline-recommended therapies in heart failure with reduced ejection fraction according to heart failure duration: An analysis of 55 581 patients from the Swedish Heart Failure (SwedeHF) Registry. *European journal of heart failure*, *27*(3), 421–431. https://doi.org/10.1002/ejhf.3565
46. Zhu, T., & Song, Y. (2025). Efficacy of Sacubitril/Valsartan Combined With Metoprolol on Cardiac Function, Cardiac Remodeling, and Endothelial Function in Patients With Coronary Heart Disease and Heart Failure. *British journal of hospital medicine (London, England: 2005)*, *86*(4), 1–16. https://doi.org/10.12968/hmed.2025.0120
47. Sharfo, A., Lahn Sørensen, A., Eik Nielsen, E., Raymond, I. E., Boas Soja, A. M., & Hecht Olsen, M. (2025). OPTIHEART: determinants and prognostic importance of optimal medical treatment in patients with heart failure with reduced ejection fraction discharged from a heart failure clinic from 2018 to 2020. *Blood pressure*, *34*(1), 2481229. https://doi.org/10.1080/08037051.2025.2481229
48. Wang, G., Zhang, R., Li, X., Zuo, S., Zhang, B., Zhao, Y., Sun, S., Zhang, J., & Liu, X. (2025). Efficacy of sacubitril/valsartan on improving clinical symptoms in patients with acute myocardial infarction complicated with heart failure: a retrospective study. *PeerJ*, *13*, e18873. https://doi.org/10.7717/peerj.18873
49. Ye, S., Guo, N., Li, J., Zhao, J., Zong, D., & Wang, L. (2025). Early sacubitril/valsartan therapy reduces ventricular remodeling and cardiac events in patients with acute anterior myocardial infarction. *European journal of pharmacology*, *1007*, 178188. https://doi.org/10.1016/j.ejphar.2025.178188
50. Berge, K., Schirmer, H., Øvrebotten, T., Nahoui, H., Gullestad, L., Ingul, C. B., Hole, T., Mo, R., Larsby, K., Norekvål, T. M., Omland, T., Ørn, S., & Myhre, P. L. (2025). Improvements in medical therapy and prognosis for patients with HFrEF following the 2021 ESC HF guidelines. *ESC heart failure*, *12*(5), 3343–3352. https://doi.org/10.1002/ehf2.15337
51. Appenzeller, F., Harm, T., Sigle, M., Aidery, P., Kreisselmeier, K. P., Baas, L., Goldschmied, A., Gawaz, M. P., & Müller, K. A. L. (2025). Left ventricular function improvement during angiotensin receptor-neprilysin inhibitor treatment in a cohort of HFrEF/HFmrEF patients. *ESC heart failure*, *12*(2), 1151–1165. https://doi.org/10.1002/ehf2.15100