Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 | Received 14.09.2026 | Accepted 16.09.2026 | Online 20.09.2026

THE SIGNIFICANCE OF NATRIURETIC PEPTIDES AND NEPRILYSIN INHIBITORS IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASES

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Abstract

Background: Natriuretic peptides are central components of the cardiovascular endocrine response to myocardial wall stress. Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) connect pathophysiology, diagnosis, prognosis, and treatment of heart failure (HF). Neprilysin degrades several vasoactive peptides, including natriuretic peptides; therefore, inhibition of neprilysin, combined with angiotensin II type 1 receptor blockade, provides a rational therapeutic strategy. Objective: To review the diagnostic and prognostic value of natriuretic peptides and to assess the role of neprilysin inhibition, particularly sacubitril/valsartan, across the spectrum of HF. Methods: A narrative review was conducted using major randomized trials, international HF guidelines, a joint scientific statement on natriuretic peptides, and regulatory prescribing information. Results: BNP and NT-proBNP are useful for ruling out HF, supporting diagnosis, estimating prognosis, and establishing a baseline for follow-up, although age, atrial fibrillation, renal dysfunction, obesity, and treatment modify interpretation. In HFrEF, sacubitril/valsartan reduced cardiovascular death or HF hospitalization compared with enalapril in PARADIGM-HF. After stabilization from acute decompensated HFrEF, in-hospital initiation produced a greater NT-proBNP reduction than enalapril in PIONEER-HF. Evidence in HFmrEF and HFpEF is more heterogeneous; benefit appears concentrated toward the lower ejection-fraction range and in selected patients. Conclusions: Natriuretic peptides and neprilysin inhibition represent complementary diagnostic and therapeutic applications of the same biological pathway. NT-proBNP is generally preferred for biomarker monitoring during sacubitril/valsartan therapy because BNP is a neprilysin substrate and may rise or change unpredictably after treatment initiation. Clinical decisions must integrate peptide concentrations with symptoms, examination, electrocardiography, imaging, comorbidity, blood pressure, kidney function, and serum potassium.

Keywords: Natriuretic peptides; atrial natriuretic peptide; B-type natriuretic peptide; NT-proBNP; neprilysin; sacubitril/valsartan; heart failure; cardiovascular disease.

Journal of Advances in Drug Research
ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 14.09.2026 Accepted 16.09.2026 Online 20.09.2026

Introduction

Cardiovascular disease remains a major cause of premature death, disability, and hospital admission. Heart failure is a final common clinical pathway for ischemic heart disease, hypertension, cardiomyopathy, valvular disease, and several systemic disorders. Its diagnosis may be difficult because dyspnea, fatigue, ankle swelling, and exercise intolerance are common and nonspecific. Contemporary practice therefore combines clinical probability, electrocardiography, echocardiography, and circulating biomarkers. Natriuretic peptides have a special place in this framework because they reflect the biological response of the myocardium to increased wall stress rather than a single anatomical lesion [5, 7, 15].

The discovery of atrial natriuretic factor established the heart as an endocrine organ [1]. ANP is stored mainly in atrial granules and released rapidly with atrial stretch. BNP is synthesized predominantly in ventricular myocardium under conditions of sustained pressure or volume load. Cleavage of proBNP produces biologically active BNP and the inactive N-terminal fragment NT-proBNP. Both are released into the circulation, but they differ in clearance, half-life, assay behavior, and response to neprilysin inhibition [12, 15].

The same protective system has become a therapeutic target. Neprilysin is a membrane-bound metalloprotease that degrades natriuretic peptides and other vasoactive substrates. Isolated neprilysin inhibition increases compensatory peptides but may also increase angiotensin II, which limits clinical benefit. Sacubitril/valsartan combines a neprilysin prodrug inhibitor with an angiotensin II type 1 receptor blocker and is therefore classified as an angiotensin receptor-neprilysin inhibitor (ARNI). This dual mechanism enhances natriuretic-peptide signaling while suppressing harmful renin-angiotensin-aldosterone system activity [4, 11].

This review evaluates the natriuretic-peptide system from two connected perspectives. First, it examines ANP, BNP, and NT-proBNP as diagnostic and prognostic biomarkers in cardiovascular disease, with emphasis on HF. Second, it summarizes the mechanistic basis, randomized clinical evidence, safety, and practical position of neprilysin inhibition. The purpose is to distinguish what the biomarkers can reliably indicate, what sacubitril/valsartan has been proven to improve, and where uncertainty remains.

Materials and Methods

This article is a narrative, non-systematic review. It does not report an original patient cohort, a prospective intervention, or a pooled meta-analysis. The evidence base was selected to include foundational work on ANP, contemporary European and North American HF guidelines, the 2023 joint scientific statement of the Heart Failure Association of the European Society of Cardiology, the Heart Failure Society of America, and the Japanese Heart Failure Society, pivotal randomized trials of sacubitril/valsartan, and current regulatory labeling [1, 5, 7-8, 15].

The principal therapeutic trials were PARADIGM-HF for ambulatory HFrEF, PIONEER-HF and TRANSITION for initiation after stabilization during or shortly after an

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ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 14.09.2026 Accepted 16.09.2026 Online 20.09.2026

acute HF admission, PARAGON-HF for HF with preserved ejection fraction, and PARAGLIDE-HF for recently worsened HF with mildly reduced or preserved ejection fraction [9, 11, 13-14, 16-17]. Outcomes were extracted descriptively, including study population, comparator, biomarker response, primary clinical endpoint, tolerability, and limitations. No indirect numerical comparison between trials was performed because populations, run-in procedures, ejection-fraction criteria, endpoints, and follow-up differed.

For diagnostic interpretation, the review focused on the intended use of natriuretic peptides, rule-out thresholds, confounding factors, and the distinction between BNP and NT-proBNP after ARNI initiation. Evidence statements were interpreted in context. A biomarker association was not treated as proof that biomarker-guided intensification improves outcomes, and a post hoc subgroup observation was not presented as equivalent to a prespecified positive primary endpoint. References are listed alphabetically in GOST-style bibliographic form; bracketed numbers correspond to that alphabetical list.

Results

1. Biology of the natriuretic-peptide system

ANP is synthesized as preproANP, processed to proANP, stored in atrial secretory granules, and released when atrial wall tension increases. Corin cleaves proANP into biologically active 28-amino-acid ANP and an N-terminal fragment. BNP is synthesized as preproBNP and then proBNP; cleavage yields active BNP and NT-proBNP. Processing is not always complete, and circulating assays may detect a mixture of mature peptides, precursors, and degradation products. Consequently, a laboratory value is method-dependent and should be interpreted using the local assay and clinical context [12, 15].

ANP and BNP bind natriuretic peptide receptor A, which has intrinsic particulate guanylyl cyclase activity. Receptor activation increases cyclic guanosine monophosphate (cGMP), promotes vasodilation, increases natriuresis and diuresis, reduces renin and aldosterone secretion, moderates sympathetic tone, and opposes myocardial hypertrophy and fibrosis. These actions are compensatory in HF, but their effect may be insufficient because of severe hemodynamic stress, altered processing, receptor desensitization, increased clearance, and enhanced enzymatic degradation [12].

Neprilysin is expressed in multiple tissues, including the kidney and vascular endothelium. It degrades ANP, BNP, bradykinin, adrenomedullin, substance P, and other peptides. NT-proBNP is not a major neprilysin substrate. This biochemical difference becomes clinically important after sacubitril/valsartan is started: BNP may transiently increase or become difficult to interpret because its degradation is inhibited, whereas NT-proBNP more directly reflects changing myocardial wall stress [4, 15].

2. Diagnostic role in suspected heart failure

The strongest routine use of BNP and NT-proBNP is exclusion of HF in patients with compatible symptoms. Low concentrations have high negative predictive value and make HF unlikely, although no biomarker should replace clinical assessment. In the non-acute setting, the 2021 ESC guideline uses BNP below 35 pg/mL or NT-proBNP below 125

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www.jadr.co.in
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pg/mL as rule-out values. In acute presentations, BNP below 100 pg/mL or NT-proBNP below 300 pg/mL makes acute HF unlikely. Values above these thresholds do not independently prove HF; echocardiography and evaluation for alternative causes are required [7].

For acute dyspnea, age-stratified NT-proBNP rule-in values can increase specificity: approximately 450 pg/mL for patients younger than 50 years, 900 pg/mL for those aged 50-75 years, and 1,800 pg/mL for those older than 75 years. These values support rather than replace diagnosis. Very high levels may occur with renal dysfunction, atrial fibrillation, pulmonary hypertension, pulmonary embolism, acute coronary syndromes, sepsis, and advanced age. Conversely, obesity may suppress BNP and NT-proBNP concentrations, so a deceptively low value does not completely exclude HF when clinical probability is high [5, 15].

ANP reflects atrial stretch and can rise early in conditions characterized by increased atrial pressure, including mitral valve disease and atrial fibrillation. Nevertheless, native ANP has a short half-life and is less stable than BNP or NT-proBNP. Mid-regional proANP assays improve analytical stability and may add diagnostic information in selected acute-care settings, but BNP and NT-proBNP remain the dominant biomarkers in international HF algorithms [15].

3. Prognostic and monitoring value

Higher BNP and NT-proBNP concentrations generally identify greater hemodynamic stress and a higher risk of death or HF hospitalization. Serial decline after effective decongestion or disease-modifying therapy is usually associated with a better prognosis. A discharge value can aid risk stratification after acute HF, but the number should not be used in isolation. Congestion on examination, blood pressure, kidney function, sodium, troponin, functional status, and echocardiographic findings add independent information [5, 7, 15].

Randomized studies of natriuretic-peptide-guided treatment have produced mixed results, particularly across age groups and HF phenotypes. Therefore, current guidance supports measurement for diagnosis and prognosis but does not require treatment to be titrated solely to a biomarker target. Guideline-directed medical therapy should be introduced and optimized according to evidence, symptoms, blood pressure, renal function, potassium, and tolerance. A persistently elevated NT-proBNP should prompt reassessment of congestion, adherence, rhythm, ischemia, valvular disease, and comorbidity rather than automatic escalation of one medicine [5, 7-8].

4. Neprilysin inhibition and the rationale for combined blockade

Earlier attempts at isolated neprilysin inhibition produced limited clinical benefit because neprilysin also participates in degradation of vasoconstrictor peptides. Combined ACE and neprilysin inhibition with omapatrilat reduced blood pressure but caused unacceptable angioedema, related to simultaneous accumulation of bradykinin through overlapping pathways. Sacubitril/valsartan avoids ACE inhibition: sacubitril is converted to the active neprilysin inhibitor LBQ657, while valsartan blocks the angiotensin II type 1 receptor. The result is enhancement of endogenous protective peptides together with

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inhibition of angiotensin-mediated vasoconstriction, sodium retention, aldosterone release, hypertrophy, and fibrosis [3-4].

Pharmacodynamic effects include increased urinary cGMP and changes in natriuretic-peptide concentrations. Hemodynamic and structural consequences can include reduced filling pressure, improved arterial and ventricular coupling, natriuresis, and reverse remodeling. These mechanisms are biologically plausible, but clinical value depends on randomized outcome evidence rather than laboratory effects alone.

5. Evidence in heart failure with reduced ejection fraction

PARADIGM-HF enrolled 8,442 patients with symptomatic HFrEF and compared sacubitril/valsartan 200 mg twice daily with enalapril 10 mg twice daily after active run-in phases. The trial was stopped early because of benefit. The primary composite of cardiovascular death or first HF hospitalization occurred in 21.8% with sacubitril/valsartan and 26.5% with enalapril (hazard ratio 0.80). Cardiovascular death, HF hospitalization, and all-cause mortality were also reduced. Symptomatic hypotension was more frequent with sacubitril/valsartan, whereas cough, hyperkalemia, and renal impairment were generally less frequent than with enalapril; angioedema was uncommon in both groups [9].

These findings established ARNI therapy as a disease-modifying treatment in HFrEF. The 2022 AHA/ACC/HFSA guideline recommends ARNI in patients with chronic symptomatic HFrEF to reduce morbidity and mortality and recommends replacement of an ACE inhibitor or angiotensin receptor blocker by ARNI in suitable patients who remain symptomatic. The 2021 ESC guideline positions sacubitril/valsartan as a replacement for an ACE inhibitor in ambulatory HFrEF and recognizes its use as part of foundational therapy [5, 7]. Clinical implementation increasingly favors early initiation of the four foundational HFrEF drug classes: ARNI or another renin-angiotensin-system inhibitor, an evidence-based beta-blocker, a mineralocorticoid receptor antagonist, and a sodium-glucose cotransporter 2 inhibitor.

6. Initiation after acute decompensated heart failure

PIONEER-HF randomized 881 patients hospitalized with acute decompensated HFrEF after hemodynamic stabilization. Sacubitril/valsartan produced a greater time-averaged proportional reduction in NT-proBNP than enalapril over eight weeks. Rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between groups, although the trial was not powered primarily for clinical outcomes [16]. The study supports initiation before discharge in appropriately stabilized patients rather than delaying all disease-modifying therapy until a later outpatient visit.

TRANSITION compared pre-discharge with early post-discharge initiation in 1,002 stabilized patients. Approximately half of patients in each strategy achieved the target dose by ten weeks, supporting feasibility while also showing that gradual titration and close follow-up are commonly needed [17]. Before initiation, clinicians should confirm adequate blood pressure, clinical stability, acceptable potassium and kidney function, and absence of contraindications. Patients receiving an ACE inhibitor require a 36-hour washout before the first ARNI dose to reduce angioedema risk [4, 17].

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Volume 17, Issue 04 Received 14.09.2026 Accepted 16.09.2026 Online 20.09.2026

7. Evidence in HFmrEF and HFpEF

PARAGON-HF enrolled patients with symptomatic HF and left ventricular ejection fraction of 45% or higher. Sacubitril/valsartan did not produce a statistically significant reduction in the primary composite of total HF hospitalizations and cardiovascular death compared with valsartan, although the rate ratio favored treatment. Prespecified and subsequent analyses suggested greater benefit in patients with ejection fraction below the median and in women, but these observations require cautious interpretation [13].

PARAGLIDE-HF studied patients with ejection fraction above 40% after a recent worsening HF event and found a greater reduction in NT-proBNP with sacubitril/valsartan than with valsartan. A pooled participant-level analysis with PARAGON-HF supported reduction in worsening HF events, particularly when ejection fraction was below normal [11]. These data do not justify treating all HFpEF as a single uniform phenotype. Current US guidance allows consideration of ARNI in selected HFpEF and HFmrEF patients, particularly toward the lower end of the ejection-fraction spectrum, while the strongest contemporary outcome recommendation across HFmrEF and HFpEF is for SGLT2 inhibition [5, 8].

8. Biomarker interpretation during ARNI therapy

Neprilysin inhibition changes the metabolism of BNP but not NT-proBNP in the same way. BNP can rise early after sacubitril/valsartan even when ventricular wall stress is improving. NT-proBNP usually falls when the treatment response is favorable and is preferred when a clinician needs to reassess peptide concentration after ARNI initiation. A rising BNP should therefore not automatically be interpreted as clinical deterioration without considering the date of treatment initiation, symptoms, examination, weight, renal function, and imaging [2, 15].

The distinction also prevents a therapeutic paradox. Sacubitril/valsartan may amplify biologically active natriuretic-peptide signaling while lowering NT-proBNP because reduced myocardial stress decreases proBNP release. Thus, higher functional peptide activity and a lower inactive marker can occur simultaneously. Documentation should identify the exact assay; “natriuretic peptide increased” is too vague for meaningful follow-up.

9. Safety, contraindications, and practical dosing

The usual target dose of sacubitril/valsartan is 97/103 mg twice daily. A lower starting dose, commonly 24/26 mg twice daily, is appropriate for patients not taking an ACE inhibitor or ARB, those previously receiving low doses, and selected patients with renal or hepatic impairment; 49/51 mg twice daily is another standard starting dose. Dose is generally doubled every two to four weeks as tolerated [4]. These are general principles, and local labeling should guide the exact regimen.

Blood pressure, serum potassium, and kidney function should be assessed before and after initiation and during titration. Symptomatic hypotension, hyperkalemia, and worsening renal function require evaluation of volume status, diuretic dose, interacting medicines, and severity before therapy is modified. Sacubitril/valsartan must not be

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Volume 17, Issue 04 Received 14.09.2026 Accepted 16.09.2026 Online 20.09.2026

administered concomitantly with an ACE inhibitor or within 36 hours of the last ACE-inhibitor dose. It is contraindicated in patients with a history of angioedema related to ACE-inhibitor or ARB therapy and should not be used during pregnancy. Concomitant aliskiren in patients with diabetes is contraindicated in US labeling [4].

Neprilysin has multiple substrates, creating theoretical concerns beyond natriuretic peptides. Clinical surveillance has not established a major cognitive safety signal in the studied HF populations, but long-term pharmacovigilance remains appropriate. Severe hepatic impairment is an evidence gap, and dosing or avoidance must follow current product information. Clinical benefit should not be generalized to patients with cardiogenic shock, persistent symptomatic hypotension, or unstable organ function who were not represented in the pivotal stable-treatment populations.

10. Broader cardiovascular diagnostic relevance

Natriuretic peptides are elevated in many conditions other than left-sided HF. Atrial fibrillation raises concentrations through atrial stretch, rapid rate, and structural remodeling. Pulmonary hypertension and right ventricular strain can markedly increase BNP and NT-proBNP. Acute coronary syndromes may increase peptide release and provide prognostic information, while valvular lesions generate chamber-specific pressure and volume stress. These associations are clinically useful but reduce diagnostic specificity. The biomarker should answer a defined question, most commonly whether HF contributes to symptoms and what level of risk is present [5, 15].

ANP remains pathophysiologically important even though routine laboratories more often measure BNP or NT-proBNP. It responds rapidly to atrial stretch and participates in sodium balance, vascular tone, and suppression of the renin-angiotensin-aldosterone system. In atrial fibrillation, chronic atrial remodeling may eventually impair storage and release despite earlier elevation. In valvular heart disease, concentrations can track hemodynamic burden, but intervention decisions remain based on symptoms, ventricular response, pulmonary pressure, valve anatomy, and guideline criteria rather than ANP alone.

Discussion

The natriuretic-peptide pathway provides an unusually coherent bridge from mechanism to bedside practice. Myocardial stress activates a protective endocrine response; BNP and NT-proBNP allow part of that response to be measured; neprilysin inhibition prolongs the activity of several compensatory peptides. Nevertheless, each application has different evidentiary limits. A diagnostic threshold is not a therapeutic target, and a treatment mechanism is not a substitute for randomized clinical outcomes.

For diagnosis, BNP and NT-proBNP are best used as rule-out tests within a structured pathway. A low value in a patient with low or intermediate clinical probability can prevent unnecessary echocardiography and redirect investigation. An elevated value should trigger cardiac imaging and etiological assessment rather than immediate assignment of an HF diagnosis. This is particularly important in older adults, atrial fibrillation, chronic kidney disease, and pulmonary disease, where elevations may be multifactorial. In obesity, lower-than-expected concentrations should be interpreted cautiously [7, 15].

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ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 14.09.2026 Accepted 16.09.2026 Online 20.09.2026

For prognosis, repeated NT-proBNP measurement can reveal biological trajectory, but management should remain multidimensional. A fall in NT-proBNP after decongestion or ARNI initiation is reassuring; failure to fall may identify residual risk. However, therapy should not be withheld because the marker is already low, nor intensified blindly because it remains high. The four foundational HFrEF therapies improve outcomes through complementary mechanisms, and their implementation should not depend on reaching a peptide target [5, 8].

The most persuasive therapeutic evidence for neprilysin inhibition concerns HFrEF. PARADIGM-HF demonstrated superiority over a proven ACE inhibitor, not merely over placebo, for major clinical outcomes [9]. Its run-in design means participants had to tolerate target doses before randomization, which can make tolerability appear better than in unselected practice. Real-world initiation should therefore be individualized, particularly in patients with low systolic pressure, advanced kidney disease, frailty, or high diuretic requirement.

Hospitalization for worsening HF is an opportunity to initiate or optimize therapy once the patient is stable. PIONEER-HF and TRANSITION show that sacubitril/valsartan can be introduced during this vulnerable phase with appropriate monitoring [16-17]. The key word is stabilized: absence of escalating intravenous therapy, adequate blood pressure, and acceptable renal and potassium status are necessary. Early follow-up is important because dose, diuretic requirement, renal function, and congestion can change rapidly after discharge.

The evidence gradient across ejection fraction should be communicated honestly. In HFrEF, the clinical-outcome benefit is established. In HFpEF, PARAGON-HF narrowly missed its primary endpoint, and later analyses suggest that benefit may extend into mildly reduced or lower-preserved ejection fraction [11, 13]. Sex-related heterogeneity is scientifically interesting but should not be converted into an absolute rule for an individual. HFpEF management requires attention to congestion, hypertension, atrial fibrillation, obesity, diabetes, kidney disease, ischemia, and valvular pathology. SGLT2 inhibitors have the strongest broad outcome evidence in this phenotype under the 2023 ESC focused update [8].

The interaction between ARNI therapy and laboratory testing deserves special emphasis. Because BNP is degraded by neprilysin, its concentration may be altered directly by treatment. NT-proBNP is not degraded by neprilysin and is therefore the clearer choice for monitoring myocardial stress after sacubitril/valsartan begins [2, 15]. This does not make BNP useless; it means that the trend must be interpreted with knowledge of therapy and assay timing. Switching assays during follow-up can create apparent biological change that is actually analytical.

Safety is inseparable from benefit. The 36-hour ACE-inhibitor washout is mandatory, not optional. Previous ACE inhibitor- or ARB-related angioedema, pregnancy, severe hypotension, and relevant labeling restrictions must be recognized. Blood pressure, potassium, and renal function need active surveillance. When hypotension develops, assessment of congestion and nonessential blood-pressure-lowering drugs may allow preservation of disease-modifying therapy. In hyperkalemia or renal deterioration,

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ISSN: 2230-7761
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Volume 17, Issue 04 Received 14.09.2026 Accepted 16.09.2026 Online 20.09.2026

reversible contributors should be sought before abandoning a treatment with proven benefit [4-5].

This review has limitations. It is narrative rather than systematic, and it emphasizes major guidelines and pivotal trials rather than every observational study. Diagnostic assays are not interchangeable, and local laboratory methods can affect decision limits. Clinical trials enrolled selected populations and do not resolve every question in advanced renal disease, severe hepatic impairment, cardiogenic shock, pregnancy, or very frail older adults. Subgroup findings in HFpEF remain less certain than the primary HFrEF evidence. Finally, recommendations evolve as new trials and regulatory updates appear; clinicians should verify current local guidance at the point of care.

Future research should refine phenotype-specific selection for ARNI therapy beyond ejection fraction alone, establish better reference approaches for natriuretic peptides in obesity, atrial fibrillation, and kidney disease, and clarify whether multi-marker or imaging-integrated strategies improve outcomes. Studies should also distinguish biologically active peptide forms from immunoreactive fragments. Such work may make the natriuretic-peptide system more precise both as a diagnostic signal and as a therapeutic pathway.

Summary table: Key clinical trials

Trial	Population	Comparison	Key result
PARADIGM-HF	8,442 patients, symptomatic HFrEF	Sacubitril/valsartan 200 mg BID vs enalapril 10 mg BID	CV death/HF hospitalization: 21.8% vs 26.5% (HR 0.80); stopped early for benefit
PIONEER-HF	881 patients, stabilized after acute decompensation	Sacubitril/valsartan vs enalapril	Greater NT-proBNP reduction at 8 weeks; not powered for clinical outcomes
TRANSITION	1,002 stabilized patients	Pre-discharge vs early post-discharge initiation	About half of patients in each strategy reached the target dose by 10 weeks
PARAGON-HF	HF, EF ≥45%	Sacubitril/valsartan vs valsartan	Primary endpoint not statistically significant; possible benefit in lower EF and women
PARAGLIDE-HF	EF >40%, recently worsened HF	Sacubitril/valsartan vs valsartan	Greater NT-proBNP reduction; pooled analysis with PARAGON-HF

Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 Received 14.09.2026 Accepted 16.09.2026 Online 20.09.2026

Trial	Population	Comparison	Key result
			suggested reduced worsening-HF events

Conclusion

Natriuretic peptides are core biomarkers in contemporary cardiovascular medicine. BNP and NT-proBNP are most valuable for excluding HF, supporting diagnosis, and estimating prognosis when interpreted together with clinical assessment and cardiac imaging. ANP remains fundamental to the physiology of atrial stretch and cardiovascular homeostasis, although its short half-life limits routine use compared with BNP and NT-proBNP.

Neprilysin inhibition translates this endogenous protective pathway into disease-modifying treatment. Sacubitril/valsartan has robust outcome evidence in symptomatic HFrEF, can be initiated after stabilization from acute decompensation, and may benefit selected patients with HFmrEF or lower-range HFpEF. NT-proBNP is generally preferred to BNP for follow-up during ARNI therapy. Safe treatment requires correct ACE-inhibitor washout, blood-pressure assessment, and monitoring of renal function and potassium. The most accurate clinical approach treats the peptide value, the cardiac phenotype, and the patient's overall condition as complementary information rather than interchangeable substitutes.

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