ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR (ARNI): CURRENT STATUS & EVIDENCE

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I PHARMACOLOGICAL MECHANISM AND THE "WASHOUT" MANDATE

- **The Dual Pathway:** Angiotensin Receptor-Neprilysin Inhibitor (**ARNI: Sacubitril/Valsartan**) simultaneously blocks the Renin-Angiotensin-Aldosterone System (RAAS) and enhances the endogenous natriuretic peptide system.
- **Sacubitril:** A prodrug that inhibits **neprilysin**, preventing the degradation of **Atrial and Brain Natriuretic Peptides (ANP/BNP), bradykinin, and adrenomedullin**, which promotes vasodilation, natriuresis, and anti-fibrotic effects.
- **Valsartan:** An **AT1 receptor blocker** that mitigates the reflex RAAS overactivation caused by baseline heart failure and neprilysin inhibition.
- **The Angioedema Trap:** Both neprilysin and Angiotensin-Converting Enzyme (ACE) degrade bradykinin; combining Sacubitril with an ACE inhibitor causes massive bradykinin accumulation and life-threatening **angioedema**.
- **Mandatory Washout Rule:** A strict **36-hour washout period** is mandatory when switching a patient from an ACE inhibitor to an ARNI. No washout period is required when switching from an ARB to an ARNI.

II LANDMARK CLINICAL TRIAL EVIDENCE

- **PARADIGM-HF (2014) — The Chronic HFrEF Standard:**
  - **Study Design:** Randomized patients with chronic HFrEF (LVEF 40 percent or less, later amended to 35 percent or less) to Sacubitril/Valsartan versus Enalapril.
  - **Key Findings:** Halted early due to overwhelming efficacy; ARNI demonstrated a **20 percent Relative Risk Reduction (RRR)** in the primary composite endpoint of cardiovascular death or heart failure hospitalization, and reduced all-cause mortality by **16 percent**.
  - **PIONEER-HF (2018) and TRANSITION — The Acute Setting:**
  - **Key Findings:** Proved that initiating ARNI in-hospital for acute decompensated heart failure (once hemodynamically stabilized) is safe, does not increase renal failure or angioedema compared to Enalapril, and yields a significantly greater, rapid reduction in **NT-proBNP**.
  - **PROVE-HF (2019) — Reverse Cardiac Remodeling:**
  - **Key Findings:** Demonstrated that the reduction in NT-proBNP with ARNI directly correlates with true **reverse cardiac remodeling** (significant increases in LVEF and reductions in LV end-diastolic and end-systolic volumes) at 6 to 12 months.
  - **PARAGON-HF (2019) — The HFpEF Spectrum:**
  - **Key Findings:** Evaluated ARNI versus Valsartan in HFpEF (LVEF greater than 45 percent) and narrowly missed statistical significance for its primary endpoint ($p = 0.06$).
  - **Subgroup Nuance:** Subgroup analysis demonstrated significant benefit in **women** and in patients with mildly reduced or "below normal" LVEF (**45 to 57 percent**).
  - **PARADISE-MI (2021) — Post-AMI LV Systolic Dysfunction:**
  - **Key Findings:** Tested ARNI versus Ramipril in patients with acute myocardial infarction and transient LV systolic dysfunction without prior heart failure; failed to show a statistically significant reduction in the primary composite endpoint, meaning ARNI is not a routine replacement for ACE inhibitors in uncomplicated post-MI patients.

Clinical Trial	Patient Population	Comparator	Key Primary Outcome & Clinical Impact
PARADIGM-HF (2014)	Chronic HFrEF (LVEF <40%)	Enalapril	**20% RRR** in CV death or HF hospitalization; **16% RRR** in all-cause mortality
PIONEER-HF (2018)	Acute decompensated HFrEF (in-hospital)	Enalapril	Safe in-hospital initiation; rapid and superior reduction in **NT-proBNP**
PROVE-HF (2019)	HFrEF (single-arm remodeling study)	Baseline	NT-proBNP reduction correlated with **LVEF increase** and **LV volume reduction** at 6–12 months
PARAGON-HF (2019)	HFpEF (LVEF >45%)	Valsartan	Missed primary endpoint ($p = 0.06$); significant benefit in **women** and **LVEF 45–57%**
PARADISE-MI (2021)	Acute MI with transient LVSD	Ramipril	No significant difference in primary endpoint; not routine over ACEi in uncomplicated post-MI

III CURRENT GUIDELINE STATUS (ESC 2021/2023 & ACC/AHA 2022)

- **Chronic HFrEF (LVEF less than 40 percent): Class I** recommendation (ACC/AHA 2022: de novo or replacing an ACEi/ARB; ESC 2021: as a replacement for an ACEi, with de novo use an option) to further reduce morbidity and mortality, serving as a foundational pillar of **Quadruple Therapy** (ARNI, Beta-blocker, MRA, SGLT2i).
- **Acute Heart Failure:** In-hospital initiation once hemodynamically stable is supported (ACC/AHA 2022 Class IIa for de novo hospitalized HFrEF), in line with the ESC 2023 Class I recommendation for rapid GDMT optimization before discharge.
- **HFmrEF (LVEF 41 to 49 percent) and HFpEF: Class IIb** consideration; expanded labeling supports use in heart failure with "below normal" LVEF based on pooled PARAGON-HF data.

IV CLINICAL PITFALLS AND BIOMARKER INTERPRETATION

- **The BNP Trap:** Because Sacubitril inhibits neprilysin (the enzyme responsible for degrading active BNP), initiating an ARNI causes an expected, pharmacological **elevation in serum BNP**.
- **Mandatory Monitoring Rule:** Clinicians must **solely use NT-proBNP** (which is not a neprilysin substrate and accurately falls as ventricular wall stress decreases) rather than BNP to monitor volume status and treatment response in patients taking an ARNI.

V PRACTICAL CONSIDERATIONS IN THE INDIAN CLINICAL CONTEXT

- **Generic Availability and Accessibility:** Wide availability of lower-cost generic Sacubitril/Valsartan in India has made it as accessible frontline GDMT in routine Indian practice.
- **The Hypotensive South Asian Phenotype:** Indian patients generally have a lower Body Mass Index (BMI) and lower baseline systolic blood pressure than Western trial cohorts, making the PARADIGM-HF target dose of **200 mg twice daily** frequently unachievable without inducing symptomatic hypotension or presyncope.
- **Pragmatic Micro-Dosing Strategy:** In Indian practice, initiation frequently begins at low doses (**50 mg once or twice daily**), prioritizing the maintenance of the highest tolerated dose, which still provides substantial diuretic-sparing and prognostic benefits over ACE inhibitors.

KEY REFERENCES

- **McDonagh TA, Metra M, Adamo M, et al.:** 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (and 2023 Focused Update), *European Heart Journal*, 2021/2023.
- **Januzzi JL Jr, Prescott MF, Butler J, et al. (PROVE-HF Investigators):** Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction, *JAMA*, 2019.
- **Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt DL, Solomon SD:** *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 12th Ed., Elsevier, 2022.