BIOMARKERS IN HEART FAILURE: THE 2026 UPDATE

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I THE "GOLD STANDARD" PEPTIDES (BNP & NT-PROBNP)

- **NT-proBNP in the ARNI Era:** Preferred over BNP for longitudinal monitoring in patients receiving Sacubitril/Valsartan (**ARNI**) because **NT-proBNP is not a substrate of neprilysin**, whereas BNP degradation is inhibited by sacubitril, causing an expected pharmacological rise in BNP during early treatment.
- **Prognostic Power at Discharge:** Pre-discharge **NT-proBNP** concentration (and a greater than 30 percent reduction from admission) is one of the strongest independent predictors of 30-day heart failure readmission and mortality during the post-discharge vulnerable phase.
- **The Obesity Caveat:** Circulating BNP and NT-proBNP concentrations are **30 to 50 percent lower** in obese patients (**BMI 30 kg/m2 or greater**) due to increased adipose NPR-C clearance receptor expression and suppressed myocardial synthesis; diagnostic rule-out thresholds should be lowered by approximately 50 percent (e.g., BNP less than 50 pg/mL).

II GROWTH DIFFERENTIATION FACTOR-15 (GDF-15)

A Pathophysiology

- **Cellular Origin:** A stress-responsive member of the **Transforming Growth Factor-beta (TGF-beta)** cytokine superfamily expressed across multiple organs.
- **Pathophysiological Signal:** Unlike natriuretic peptides (which reflect biomechanical myocardial wall stretch), **GDF-15** integrates **systemic oxidative stress, inflammation, tissue hypoxia, and cellular senescence**.

B Clinical Status

- **Prognostic Utility: GDF-15** is a powerful independent predictor of **all-cause mortality** and heart failure hospitalization across both **HFrEF** and **HFpEF**.
- **Major Bleeding Risk:** Elevated **GDF-15** strongly predicts major bleeding in patients receiving oral anticoagulation or dual antiplatelet therapy, and is incorporated into the validated **ABC-Bleeding Risk Score** in atrial fibrillation.

III MID-REGIONAL PRO-ADRENOMEDULLIN (MR-PROADM)

A Pathophysiology

- **Endothelial Barrier Marker: Adrenomedullin (ADM)** is a potent vasodilator peptide synthesized by vascular endothelial and smooth muscle cells to stabilize endothelial barrier integrity and prevent interstitial edema; **MR-proADM** is its stable, stoichiometric mid-regional precursor fragment.
- **Pathophysiological Signal:** Reflects **systemic and pulmonary microvascular endothelial dysfunction, capillary leak, and tissue congestion**.

B Clinical Status

- **Short-Term Mortality Prediction:** In the **BACH (Biomarkers in Acute Heart Failure) Trial**, **MR-proADM** was superior to both BNP and NT-proBNP for predicting **short-term (14- to 90-day) all-cause mortality** in patients presenting to the emergency department with acute dyspnea.
- **Residual Congestion Phenotyping:** Elevated **MR-proADM** (alongside biologically active adrenomedullin, **bio-ADM**) identifies persistent systemic tissue congestion and predicts early post-discharge readmission.

IV FIBROSIS AND CONGESTION BIOMARKERS

- **Soluble ST2 (sST2):** Circulating decoy receptor for **Interleukin-33 (IL-33)** that blocks cardioprotective IL-33/ST2L signaling and promotes **myocardial hypertrophy and fibrosis** (**ACC/AHA Class IIb** for additive risk stratification). Because **sST2** has low biological variability and is **largely unaffected by age, BMI, atrial fibrillation, or renal function**, it is well suited for serial prognostic monitoring (threshold less than 35 ng/mL).
- **Galectin-3:** Beta-galactoside-binding lectin secreted by activated macrophages that drives **cardiac fibroblast proliferation and collagen synthesis** (**ACC/AHA Class IIb**); unlike sST2, Galectin-3 concentrations are confounded by reduced eGFR.
- **Carbohydrate Antigen 125 (CA-125 / MUC16):** Glycoprotein synthesized by mesothelial cells of the pleura, pericardium, and peritoneum in response to hydrostatic pressure and inflammatory cytokines; serves as a reliable biomarker of **right-sided heart failure, systemic venous congestion, and serosal effusions (ascites/pleural effusion)**, and guided diuretic therapy in the **CHANCE-HF** trial.

Biomarker	Primary Biological Pathway	Confounded by CKD / eGFR?	Confounded by Obesity?	Key Clinical / Trial Role
NT-proBNP	Myocardial wall stretch	**Yes** (markedly elevated in CKD)	**Yes** (lowered by 30–50%)	**Class I** diagnosis & prognosis; safe in **ARNI** (**PARADIGM-HF, STRONG-HF**)
sST2	Biomechanical strain, inflammation, & fibrosis (IL-33 decoy)	**No** (independent of eGFR)	**No**	Serial acute/chronic HF prognostication (cut-off **<35 ng/mL**)
Galectin-3	Macrophage activation & collagen fibrosis	**Yes** (elevated in CKD)	No	Identifies fibrotic remodeling phenotype
MR-proADM	Endothelial barrier stress & capillary leak	Moderately	No	Superior to NPs for **30- to 90-day mortality** in acute HF (**BACH Trial**)
CA-125	Serosal mesothelial stretch & venous congestion	**No**	No	Quantifies **right heart failure / serosal congestion** (**CHANCE-HF**)

V LANDMARK TRIALS AND EVIDENCE

- **PARADIGM-HF (2014) and PIONEER-HF (2019):** Demonstrated that **Sacubitril/Valsartan** transiently increases BNP while significantly lowering **NT-proBNP**, establishing NT-proBNP as the preferred natriuretic peptide for monitoring patients on ARNI therapy.
- **BACH Trial (2010) and GREAT Network:** Proved that **MR-proADM** outperforms BNP and NT-proBNP for 90-day mortality prediction in acute heart failure.
- **BIOSTAT-CHF Study (2017):** Demonstrated that multi-marker profiling incorporating **NT-proBNP, GDF-15, sST2, FGF-23, and CA-125** improves risk prediction for mortality and rehospitalization in suboptimally treated heart failure patients.
- **STRONG-HF Trial (2022):** Validated serial **NT-proBNP** monitoring as a safety gatekeeper during rapid up-titration of GDMT to full doses within **2 weeks of discharge** (with close follow-up over 6 weeks) after an acute heart failure admission (withholding beta-blocker up-titration if NT-proBNP rose by more than 10 percent above pre-discharge levels and increasing diuretics).

VI CLINICAL LIMITATIONS AND DIAGNOSTIC PITFALLS

- **Renal Dysfunction (CKD):** Both **NT-proBNP** and **GDF-15** are cleared partially by renal filtration and accumulate as eGFR declines (below 60 mL/min/1.73 m2), requiring higher diagnostic cut-offs.
- **Age-Adjusted Acute HF Rule-In Cut-offs (ICON Study / ESC Guidelines):** To account for age-related increases in **NT-proBNP**, acute heart failure rule-in thresholds are age-stratified (**greater than 450 pg/mL for age under 50 years; greater than 900 pg/mL for age 50 to 75 years; and greater than 1,800 pg/mL for age over 75 years**), while **less than 300 pg/mL** rules out acute HF across all ages.

VII PRACTICAL CONSIDERATIONS IN THE INDIAN CLINICAL CONTEXT

- **Assay Availability and Cost:** While **NT-proBNP** and **hs-cTn** are widely available across Indian cities, novel biomarkers such as **sST2, GDF-15, and MR-proADM** remain largely restricted to tertiary referral centers; in resource-limited settings, **CA-125** is an inexpensive, widely available assay that independent studies support for tracking right-sided congestion.
- **Comorbid CKD and Anemia Confounding:** Because Indian heart failure patients present at a younger age with a high prevalence of **diabetic kidney disease and nutritional anemia** (both of which elevate baseline NT-proBNP independent of filling pressures), integrating **sST2** or **CA-125** with clinical and VExUS ultrasound assessment prevents inappropriate over-diuresis.

KEY REFERENCES

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