

# The Role of Biomarkers in the Diagnosis and Management of Heart Failure



**Haitham Shoman and Samer Ellahham\***

*Cleveland Clinic Foundation & Sheikh Khalifa Medical City, Cleveland Clinic, USA*

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\***Corresponding author:** Samer Ellahham, Cleveland Clinic Foundation & Sheikh Khalifa Medical City, Cleveland Clinic, USA, Email: Samerellahham@yahoo.com

## Abstract

Heart failure is a growing challenge both in diagnosis and management globally. Current diagnostic tools have several merits and limitations and the field is in dying need for effective and efficient biomarkers. Emerging biomarkers show promising evidence of revolutionizing the early diagnosis and management of heart failure by cardiologists and non-specialists. Biomarkers are classified according to myocyte changes as such biomarkers in myocyte stress, injury and necrosis, ischemia and fibrosis. In addition, there are biomarkers in heart failure associated with infections, renal dysfunction and neurohormonal biomarkers. This article will briefly discuss key biomarkers with major evidence to galvanize medical field interest in this remarkable field.

**Keywords:** Heart failure; Biomarkers; BNP; NT-proBNP; MR-proANP; MR-proADM; Troponin; GDF-15; Procalcitonin; Gal-3.

**Abbreviations:** ADHF: Acute Decompensated Heart Failure; BNP: Brain Natriuretic Peptide; CHF: Congestive Heart Failure; cTn: Cardiac Troponin; Gal-3: Galectin - 3; GDF-15: Growth Differentiation Factor-15; HF: Heart Failure; LV: Left Ventricle; Ml: Milliliters; MR-proADM: Amino-Terminal Pro-Brain Natriuretic Peptide; MR-proANP: Midregional Pro Atrial Natriuretic Peptide; NT-proBNP: Amino-Terminal Pro-Brain Natriuretic Peptide; NGAL: Neutrophil Gelatinase-Associated Lipocalin; PCT: Procalcitonin; Pg: Picogram

## Introduction

Heart failure (HF) diagnosis and management remains a topic of concern across the world despite the wealth of knowledge on the heart's pathophysiology. Around 8-12% is the risk of mortality from HF and this is still on the rise despite high end technological advancement [1]. Early diagnosis and management remains the gold standard to prevent adverse events and this is why there is a shift toward early diagnostic tools such as the biomarkers. Since current diagnostic tools are in short of sensitivity and specificity, biomarkers have gained significant attention within the last decades owing to their strength in early diagnosis, risk stratification, high sensitivity and specificity and disease progression in patients with HF [2,3]. In order for biomarkers to be used in current practice, they should show severity of ongoing disease and response to treatment to be able to tailor treatment for every individual. This article will offer a brief overview of the role of the biomarkers in the management of heart failure.

## Biomarkers in Heart Failure

### Myocyte stress biomarkers

**B- Natriuretic Peptide (BNP):** BNP is primarily released from the ventricular myocardium mainly due to left ventricular

dysfunction, dilated and hypertrophic ventricles, increased wall tension and increase in intracardiac pressure [4,5]. Pulmonary wedge capillary pressure, pulmonary hypertension and congestive heart failure (CHF) also cause significant changes in BNP levels [4,6].

BNP can act against the physiological abnormalities of heart failure by causing responses as arterial vasodilation, diuresis, natriuresis and reducing the activities of renin-angiotensin-aldosterone system along with the sympathetic nervous system [7]. HF is unlikely in BNP <100pg/ml and is very likely to be present with BNP >400pg/ml while patients with BNP 100-400pg/ml are considered to be within the gray zone [8]. BNP measurement has shown to be very useful in diagnosing and evaluating patients with HF presenting with dyspnea in the emergency department [7,9]. BNP levels are also used in the diagnosis and risk stratification of patients with chronic heart failure and prognosis of patients with HF. In addition, they are used for admission, in-hospital and discharge assessment of patients to evaluate morbidity, mortality and readmission risks [6]. Pre-discharge levels of >600pg/ml indicates intensified treatment prior to discharge [10].

**Amino-terminal pro-brain natriuretic peptide (NT-proBNP):** NT-proBNP is a biomarker for HF and patients suffering from chronic ischemic left ventricular dysfunction [11]. Besides being a biomarker representing the patient's condition and guiding therapy, it is considered cost-effective and can be used to guide HF therapy since it was found that 3-year mortality was reduced in patients under NT-proBNP guided treatment [6,12]. Due to its long half-life, NT-proBNP is considered a more precise index for ventricular stress and a better prognosis and outcomes predictor than BNP [7].

**Midregional pro atrial natriuretic peptide (MR-proANP):** MR-proANP is a stronger biomarker providing diagnostic and prognostic information along with regular natriuretic peptide tests for assessing congestive heart failure (CHF) [13]. Adding MR-proANP BNP and NT-proBNP testing increases the diagnostic accuracy of tests especially with obesity, old age, renal dysfunction and gray zone values, hence it is a robust analyte in HF diagnosis and reducing mortality, morbidity, treatment costs and it is very useful in risk stratification [6]. Due to its higher biological stability, MR-proANP is more superior to BNP and NT-proBNP in death prediction in CHF.

**Midregional pro adrenomedullin (MR-proADM):** MR-proADM outperforms BNP and NT-proBNP in predicting mortality within 90 days [14]. It is also a robust tool in risk stratification of patients with acute and chronic HF and is associated with higher risks of both morbidity and mortality [15,16]. Despite some studies suggesting the robustness of MR-proADM, more work is still needed to define its complete role in the clinical setting and HF management.

### Myocyte injury/necrosis biomarkers

**Cardiac Troponins (cTn):** cTnT is found to be occurring in left ventricular (LV) hypertrophy and systolic dysfunction while cTnI is associated with impaired hemodynamics, LV dysfunction, elevated BNP and higher mortality [6,17,18]. More studies are needed to look at the long term predictability of cTn [6].

### Myocyte ischemia biomarkers

**Growth Differentiation Factor-15 (GDF-15):** GDF-15 is found to be increased in patients who died after acute myocardial infarction especially in myocardial areas with irreversible damages [19]. It was also found to be associated with reduced endothelium-dependent vasodilation in resistance vessels, plaque burden, LV mass and hypertrophy, coronary artery disease and HF [20]. GDF-15 acts as a protective agent in hypertrophy and injury of the cardiac muscle [19]. It has been shown to be a strong predictor for all cause, cardiovascular and non-cardiovascular mortality outweighing NT-proBNP or C-reactive protein in HF patients [21].

### Renal dysfunction biomarker

**Neutrophil Gelatinase-Associated Lipocalin (NGAL):** In HF, the heart and kidney are both affected and NGAL is an

exceptional biomarker to be used in patients with kidney injuries since it is found in urine [22-24]. NGAL is helpful for clinicians to tailor HF therapy based on the patients' renal function more effectively and avoid the use of nephrotoxic drugs [6]. In patients with acute decompensated HF (ADHF) and high NGAL levels, there is increased morbidity and mortality. In addition, those with increased levels of NGAL and BNP carry the worst prognosis [25].

### HF with infection biomarker

**Procalcitonin (PCT):** PCT is a biomarker found in the circulation as a result of bacterial endotoxins and infections such as underlying pneumonia [26]. It was found to be useful in allowing clinicians to initiate the appropriate antibiotic therapy and hence reduce the risk of morbidity and mortality [27]. PCT helps in differentiating between cardiac and non-cardiac dyspnea. It helps in increasing the diagnostic accuracy of underlying infections where PCT levels >0.25ng/ml require antibiotics and levels <0.5ng/ml did not [6]. To further increase diagnostic accuracy, PCT can be added to BNP in patients with HF and suspecting underlying pneumonia. More randomized controlled trials would be needed to lay out its exact role in therapy guidance.

### Neurohormonal biomarker

**Copeptin:** In patients with HF following an acute myocardial infarction, copeptin was found to be a strong biomarker of morbidity related cardiovascular events and mortality [28]. A study showed that adding copeptin to MR-proADM produced best results in predicting 14-day mortality [15]. There is emerging evidence that copeptin has a great prognostic potential to HF, but more clinical trials are needed to further define its role in HF management.

### Myocyte fibrosis biomarker

**ST2:** ST2, a novel biomarker, is independent from natriuretic peptides giving it a unique predictive value for HF. Its prognostic strength could be increased when associated with other natriuretic peptides [29]. It is useful in risk stratification and its levels are higher in patients who died within a year of diagnosis [6]. Levels of >0.20ng/ml show higher risk of mortality in patients with or without HF [30]. ST2 is relatively a new biomarker and future studies are necessary to assist in its role in guiding HF management.

**Galectin-3 (Gal-3):** Raised Gal-3 levels are seen in cardiac hypertrophy, fibrosis, remodeling, ventricular dysfunction and ADHF and are the strongest predictors of 60-day mortality compared to some natriuretic peptides [31,32]. In order to increase diagnostic and prognostic accuracy, adding Gal-3 to NT-proBNP yield better results [32]. A study suggests that ventricular remodeling shows higher Gal-3 linked to LV end diastolic volume changes [33]. Unlike natriuretic peptides that are increased in HF severity, Gal-3 reflects interstitial fibrosis

and pathophysiological changes independent of HF severity [34]. Thus it can be seen prior to clinically evident HF making it useful in prediction and prevention of the disease. Studies show that Gal-3 could also be helpful in the guidance of HF management.

This is a short review article to give an overview of the available and emerging biomarkers. It is meant to be a highlight rather than an in-depth review.

### Conclusion

Heart failure is a growing epidemic worldwide. There are several challenges still existing in diagnosis and management. The emerging field of biomarker research is promising and deserves utmost attention. This mini-review is conducted to give a highlight about this promising field. The authors have no doubt that while it is a long journey, the field of biomarkers has added and will provide a groundbreaking methodology in early diagnosis and optimal management of heart failure. Outcome based research through randomized controlled clinical trials will certainly position biomarkers in heart failure in most relevant clinical practice guidelines.

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