

## MECHANISMS

# Biomarkers in Congestive Heart Failure: Clinical Importance

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## ABSTRACT

Congestive heart failure is a serious condition with high prevalence of morbidity and premature mortality. If not properly treated, congestive heart failure (CHF) has the same adverse prognosis as a malignancy. It is important to identify CHF early so that its progression to end-stage heart disease can be avoided. In addition to clinical suspicion, certain biomarkers can be utilized in the diagnosis and management of CHF. Thus, appropriate management of CHF with require clinical diagnosis combined with rational utilization of biomarkers. Recent advances in biochemical technology have confirmed the usefulness of certain biomarkers in the detection diagnosis and treatment of CHF.

**Keywords:** Biomarkers, Clinical diagnosis, Heart failure, Morbidity, Prognosis.

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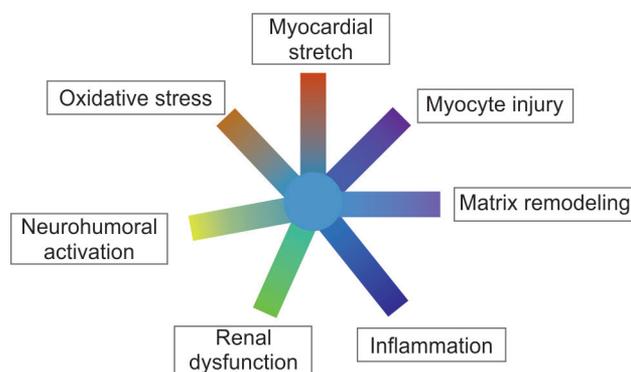
## INTRODUCTION

Although heart failure (HF) remains a fundamentally clinical diagnosis, substantial advances in the understanding of the underlying biology and pathophysiology of this syndrome has led to a greater interest in objective means to quantify its presence, severity, and potential future progression. Among the most intensively studied tools to achieve these goals are circulating biomarkers. A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.<sup>1</sup> Although this definition could encompass a wide array of assessments, conventionally speaking, the term “biomarker” is more often used to refer to substances detectable in blood, urine, or other bodily fluids. As clinical tools, biomarker

measurements have the potential advantages of being readily available, quantitative, reproducible, generally inexpensive, and without requiring specialized expertise for interpretation.

Following the development, commercialization, and clinical successes of the natriuretic peptides as biomarkers of HF, there has been substantially increased interest in HF biomarker science. Biomarkers that are currently available reflect at least seven pathobiological processes operative in HF (Fig. 1),<sup>2</sup> help to identify the specific ones involved in individual patients, and aid in guiding management plans. In conjunction with advances in proteomics and clinical chemistry that have allowed for higher throughput in identifying new potential biomarkers, a dizzying array of candidate markers have been identified that may have potential clinical application in HF (Table 1).<sup>3</sup> This remarkable flurry of activity has led to a metaphorical tsunami in the number of research publications focused on biomarkers in HF.

These biomarkers aid in the diagnosis of HF, provide an estimate of prognosis, and help in the identification of apparently healthy people who are at excessive risk for HF. In the assessment of the clinical value of any individual biomarker, it is important to determine whether it provides independent incremental information when added to previously available information, which can be estimated by determining whether it increases the *c* statistic, as well as by calculating the net reclassification improvement index and the integrated discrimination improvement index. Despite the importance of these rigorous statistical tests, measurements of biomarkers, even those that are not independent predictors of risk on multivariate analysis,



**Fig. 1:** Seven major classes of biomarkers contributing to the biomarker profile in HF<sup>2</sup>

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**Table 1:** Established and emerging biomarkers in HF<sup>3</sup>

<i>Inflammation</i>	<i>Neurohormones</i>
C-reactive protein	Norepinephrine
Tumor necrosis factor- $\alpha$	Renin
TWEAK	Angiotensin II
Interleukin-1, -6, -10, and -18	Aldosterone
Lp-PLA2	Arginine vasopressin/C-terminal pro-arginine vasopressin (copeptin)
Soluble tumor necrosis factor receptors	Endothelin-1
YKL-40	Urocortin
Interleukin-1 receptor antagonist	Chromogranin A and B
Midkine	Adrenomedullin/mid-regional pro-adrenomedullin
Leucine-rich 2-glycoprotein	<i>Myocyte injury and apoptosis</i>
Pentraxin-3	Troponins I and T
CA-125	Myosin light-chain kinase I
S100A8/A9 complex	Heart-type fatty-acid binding protein
Osteoprotegerin	Creatine kinase-MB fraction
Serine protease PR3	sFAS, FAS ligand
Soluble endoglin	Heat shock protein-60
Adiponectin	sTRAIL
<i>Oxidative stress</i>	<i>Myocyte stress</i>
Oxidized low-density lipoproteins	BNP, NT-proBNP, MR-proANP, proBNP1-108
Myeloperoxidase	sST2
Urinary biopyrrins	<i>Cardiovascular stress</i>
Urinary and plasma isoprostanes	Growth differentiation factor-15
Urinary 8-hydroxy-20-deoxyguanosine	<i>Extracardiac involvement</i>
Plasma malondialdehyde	Red blood cell distribution width
<i>Extracellular matrix remodeling</i>	Renal function markers
Matrix metalloproteinases	Renal injury markers
Tissue inhibitor of metalloproteinases	B2-microglobulin
Interleukin-6	Urinary albumin-to-creatinine ratio
Collagen propeptides	Triiodothyronine
N-terminal collagen type III peptide	
Myostatin	
Syndecan-4	
Galectin-3	

CA-125: Cancer antigen 125; Lp-PLA2: Lipoprotein-associated phospholipase; MB: Myocardial band; MR-proANP: Midregional pro-atrial natriuretic peptide; PR3: Proteinase 3 antibodies; sFAS: Soluble FAS; sST2: Somatostatin receptor 2; TWEAK: Tumor necrosis factor-like weak inducer of apoptosis; YKL-40: Chitinase-3-like protein; sTRAIL: TNF-related apoptosis-induced ligand

may nonetheless be of clinical importance because they provide information on the pathogenesis of HF and can help to direct treatment.

### Natriuretic Peptides

Because the signs and symptoms of HF are so non-specific, many patients with suspected HF referred for echocardiography are not found to have an important cardiac abnormality. Where the availability of echocardiography is limited, an alternative approach to diagnosis is to measure the blood concentration of a natriuretic peptide, a family of hormones secreted in increased amounts when the heart is diseased or the load on any chamber is increased.<sup>4</sup> Natriuretic peptide levels also increase with age, but may be reduced in obese patients. A normal natriuretic peptide level in an untreated patient virtually excludes significant cardiac disease, making an

echocardiogram unnecessary.<sup>4,5</sup> Multiple studies have examined the threshold concentration that excludes HF for the two most commonly used natriuretic peptides, B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP).<sup>6-8</sup> The exclusion threshold differs for patients presenting with acute onset or worsening of symptoms (e.g., to a hospital emergency department) and those presenting with a more gradual onset of symptoms.

For patients presenting with acute onset or worsening of symptoms, the optimal exclusion cutoff point is 300 pg/mL for NT-proBNP and 100 pg/mL for BNP. In one other study, midregional atrial (or A-type) natriuretic peptide (MR-proANP), at a cutoff point of 120 pmol/L, was shown to be noninferior to these thresholds for BNP and NT-proBNP in the acute setting.<sup>9</sup> For patients presenting in a nonacute way, the optimum exclusion

cutoff point is 125 pg/mL for NT-proBNP and 35 pg/mL for BNP. The sensitivity and specificity of BNP and NT-proBNP for the diagnosis of HF are lower in nonacute patients.<sup>6-8</sup>

The BNP and NT-proBNP levels improve with treatment of chronic HF,<sup>10</sup> with lowering of levels over time in general, correlating with improved clinical outcomes. Thus, BNP or NT-proBNP “guided” therapy has been studied against standard care without natriuretic peptide measurement to determine whether guided therapy renders superior achievement of guideline-directed medical therapy (GDMT) in patients with HF. However, randomized controlled trials have yielded inconsistent results.

The positive and negative natriuretic peptide-guided therapy trials differ primarily in their study populations, with successful trials enrolling younger patients and only those with heart failure with reduced ejection fraction. In addition, a lower natriuretic peptide goal and/or a substantial reduction in natriuretic peptides during treatment are consistently present in the positive “guided” therapy trials.<sup>11</sup> Although most trials examining the strategy of biomarker “guided” HF management were small and underpowered, two comprehensive meta-analyses concluded that BNP-guided therapy reduces all-cause mortality in patients with chronic HF compared with usual clinical care,<sup>12,13</sup> especially in patients <75 years of age. This survival benefit may be attributed to increased achievement of GDMT. In some cases, BNP or NT-proBNP levels may not be easily modifiable. If the BNP or NT-proBNP value does not fall after aggressive HF care, risk for death or hospitalization for HF is significant. On the contrary, some patients with advanced HF have normal BNP or NT-proBNP levels or have falsely low BNP levels because of obesity and heart failure with preserved ejection fraction (HFpEF). All of these patients should still receive appropriate GDMT.

### **Biomarkers of Myocardial Injury: Cardiac Troponin T or I**

Abnormal concentrations of circulating cardiac troponin are found in patients with HF, often without obvious myocardial ischemia and frequently in those without underlying coronary artery disease. This suggests ongoing myocyte injury or necrosis in these patients. In chronic HF, elaboration of cardiac troponins is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates. Similarly, in patients with acute decompensated HF, elevated cardiac troponin levels are associated with worse clinical outcomes and mortality; decrease in troponin levels over time with treatment is associated with a better prognosis

than persistent elevation in patients with chronic or acute HF. Given the tight association with acute coronary syndrome (ACS) and troponin elevation as well as the link between myocardial infarction and the development of acute HF, the measurement of troponin I or T should be routine in patients presenting with acutely decompensated HF syndromes. With the introduction of high-sensitivity cardiac troponin (hs-cTn) methods optimized for use at the troponin 99th percentile (corresponding to the upper reference limit of a healthy, normal population), it is expected that elevated hs-cTn will be more frequently detected in HF.

### **Extracellular Matrix Markers**

The extracellular matrix (ECM) of the heart is increasingly recognized to be important in the pathophysiology of HF progression; deleterious remodeling of the ECM is an important process that takes place through the degradation of collagen and other matrix proteins by collagenases, matrix metalloproteinases (MMPs), and mediated by tissue inhibitors of metalloproteinases. Extracellular matrix is important in ventricular remodeling. Serum peptides derived from collagen metabolism reflect both the synthesis and degradation of collagen and thus, constitute a “window” on the ECM. The ratio of pro-collagen type I aminoterminal propeptide (PINP), a marker of collagen synthesis, to collagen type I cross-linked carboxyterminal telopeptide, a marker of collagen breakdown, is a useful serum marker of collagen accumulation. A multimarker panel consisting of increased levels of MMP-2, tissue inhibitor of MMP-4, and collagen III N-terminal propeptide (PIIINP), accompanied by decreased levels of MMP-8, has been reported to be characteristic of HFpEF.<sup>14</sup> Elevated ECM turnover has also been reported in patients with acute decompensated heart failure (ADHF).<sup>15</sup>

### **Aldosterone**

Aldosterone is a stimulant of collagen synthesis that enhances cardiac fibrosis in HF and in ventricular hypertrophy secondary to pressure overload. The administration of the aldosterone receptor antagonist spironolactone in patients with chronic HF in Randomized Aldactone Evaluation Study (RALES) reduced elevated levels of markers of collagen synthesis (PINP and PIIINP) and was associated with clinical benefit.<sup>16</sup> In patients with acute MI complicated by HF, levels of PINP and PIIINP rose.<sup>16</sup> The administration of eplerenone, a specific aldosterone antagonist, was reported to have reduced elevated levels of PINP and PIIINP, findings associated with reductions in mortality and hospitalization for HF.<sup>17</sup>

## Markers of Inflammation

The elevation of C-reactive protein (CRP), an inflammatory biomarker, in HF has been confirmed and expanded on as assay methods have improved.<sup>18</sup> The concentrations of a number of proinflammatory cytokines, such as tumor necrosis factor- $\alpha$  and interleukin (IL)-6, have also been reported to have been elevated in HF. In elderly subjects without HF, abnormal elevations in three inflammatory markers (CRP, tumor necrosis factor- $\alpha$ , and IL-6) were reported to have been associated with a significant, 4-fold increase in the development of HF.<sup>19</sup> The presence and levels of these biomarkers were correlated with the severity of HF; they appeared to have been independent predictors of outcome and to have provided important clues to the pathogenesis of HF. They could, in the future, become useful in testing novel anti-inflammatory therapies in such patients.

## Adrenomedullin

Adrenomedullin is a vasodilator peptide derived in part from the heart, but also synthesized in vascular smooth muscle and endothelial cells. Because of its short half-life and instability, an assay for the MR sequence of its precursor [mid-regional pro-adrenomedullin (MR-proADM)] has been developed and reported to be an independent predictor of mortality in ADHF and of adverse outcomes in chronic HF.<sup>20</sup> While this marker has excellent sensitivity in detecting HF, its specificity has been questioned because of reported elevations in sepsis, glomerulonephritis, and chronic renal failure—perhaps not surprising given its synthesis in multiple tissues. While promising for predicting short-term prognosis, more data are needed before MR-proADM is to be considered ready for prime-time clinical use. For example, considerable depth of understanding regarding the clinical response to an elevated MR-proADM is required before testing would be justified.

## Copeptin

The concentration of circulating arginine vasopressin is elevated in patients with severe HF, but as is the case with ANP and adrenomedullin, its direct measurement is fraught with difficulties. Instead, copeptin, the C-terminal segment of pre-provasopressin, has been reported to be an excellent surrogate highly predictive of adverse outcomes in patients with ADHF.<sup>21</sup>

## Neutrophil Gelatinase-associated Lipocalin

Neutrophil gelatinase-associated lipocalin, a polypeptide marker of renal injury,<sup>22</sup> is elevated in patients with ADHF and renal failure, i.e., with the cardiorenal syndrome. Its elevation at the time of hospital discharge is a

strong indicator of renal tubular damage and of adverse prognosis.

## Kidney Injury Molecule-1

Kidney injury molecule-1 is a glycoprotein expressed in the proximal tubule in renal injury and both its presence in patients with HF and its correlation with NT-proBNP suggest that renal involvement occurs in many patients with severe HF.<sup>23</sup>

## Quiescin Q6

The field of proteomics is likely to provide distinct “fingerprints” of circulating proteins in a variety of disorders, including HF.<sup>24</sup> Just as genome-wide association studies represent an unbiased (i.e., not hypothesis-driven) search for genetic variants, liquid chromatography combined with mass spectroscopy has been used to carry out a search for plasma proteins in the proteome of patients with ADHF.<sup>25</sup> This approach revealed that quiescin Q6 (QSOX1), a protein involved in the formation of disulfide bridges, was (along with BNP) associated with ADHF. After the discovery and isolation of QSOX1, its association with ADHF was validated in a second group of patients. Then, QSOX1 was reported to have been induced in the hearts of rats with HF following thoracic aortic constriction, lending credence to the specificity of this marker.<sup>25</sup> The challenge now is to determine its biological significance and whether it provides information that could be useful to clinicians.

## High-sensitivity ST2

Soluble ST2 reflects activity of an IL-33-dependent cardioprotective signaling axis and is a diagnostic and prognostic marker in acute HF and ST2 is a potent indicator of prognosis in chronic HF and offers a moderate improvement in risk stratification when used in combination with conventional markers.

The ST2 is an IL-1 receptor family member expressed in cardiomyocytes, fibroblasts, and vascular endothelial cells. The ST2 is part of a cardioprotective signaling system composed of paracrine interactions between IL-33 produced by cardiac fibroblasts and transmembrane ST2 receptors on cardiac myocytes. The ST2 exists in both transmembrane and soluble forms, and soluble ST2 is a candidate biomarker in cardiovascular disease. In response to inflammation and cardiac stress, IL-33/ST2 signaling becomes activated, and the soluble form of ST2 is released into the circulation. The soluble form of ST2 acts as a decoy receptor, sequestering and inhibiting IL-33, potentially explaining why higher circulating levels reflect increased cardiac risk.<sup>26</sup> Compared with other biomarkers, such as natriuretic peptides, advantages of somatostatin receptor 2 (sST2) include that its concentra-

tion is not affected by age, renal function, or body mass index. Prognostically speaking, sST2 represents a valid contender to be added to the natriuretic peptides. With preliminary data suggesting benefit of therapies that mitigate ventricular remodeling among patients with elevated sST2 concentrations, the potential of its use to “guide” therapy for prevention of HF complications appears promising.

### Galectin-3 (Gal-3)

Galectin-3 (Gal-3) is a beta-galactoside-binding lectin that appears to be a mediator of cardiac fibrosis. Higher concentrations of Gal-3 are markers of cardiac fibrosis. Gal-3 is an indicator not only of myocardial fibrosis, but also other fibrotic conditions, including liver cirrhosis and pulmonary fibrosis, all of which could increase the risk for overall mortality. Beyond the association with all-cause mortality, a recent case-control study demonstrated an association of Gal-3 with HF risk after ACSs.<sup>27</sup> It is associated with increased risk for incident HF and mortality. Gal-3 has been related to mortality in patients with acute and chronic HF. The potential clinical role of Gal-3 may be pathobiological rather than prognostic in nature. Future studies evaluating the role of Gal-3 in cardiac remodeling may provide further insights into the role of Gal-3 in the pathophysiology of HF. In patients with chronic, ambulatory HF, concentrations of galectin-3 are found to be prognostic; interestingly, consistent with the possibility that biomarkers of fibrosis, such as galectin-3 are particularly important in HFpEF (where diastolic noncompliance is the primary mechanism of HF).

### Multimarker Approaches

There has recently been an interest in multimarker strategies to examine panels of biomarkers that assess different pathophysiologic pathways. An early study in patients with HF with reduced ejection fraction reported that a combination of proBNP, high-sensitivity CRP (hsCRP), and myeloperoxidase (a marker of oxidative stress) provided greater predictive accuracy than did any of these markers individually.<sup>28</sup> Subsequently, multimarker approaches to predict the risk for mortality in patients with ADHF,<sup>29</sup> the development of HF,<sup>30</sup> and cardiovascular disease-related death in community-based cohorts<sup>31</sup> have been described.

In a recent study of ambulatory patients with chronic HF, Ky et al<sup>32</sup> tested the hypothesis that a group of seven biomarkers, each reflecting a different pathophysiologic pathway, could be combined into a multimarker score that would predict the risk for an adverse outcome, defined as death, cardiac transplantation, or placement of a ventricular-assist device. Each of these seven biomarkers and their

pathways were reported to have been independently associated with such an outcome. These biomarkers were BNP (neurohormonal activation), soluble fms-like tyrosine kinase receptor (vascular remodeling), hsCRP (inflammation), ST2 (myocyte stretch), cTnI (myocyte injury), uric acid (oxidative stress), and creatinine (renal function). The combined multimarker integer score provided an excellent assessment of risk, with the hazard ratios of the intermediate- and higher-risk tertiles (adjusted for clinical risk) significantly elevated, to 3.5 and 6.8 respectively, compared with that of the lowest-risk tertile.

### Guidelines

The American College of Cardiology Foundation/American Heart Association (AHA) HF guidelines<sup>33</sup> have given BNP and NT-proBNP a Class I recommendation for both diagnosis and prognosis of HF (level of evidence: A). The use of these natriuretic peptides for guiding HF management received a Class IIa recommendation for chronic HF (level of evidence: B) and IIb for acute HF (level of evidence: C). The TnT or TnI received Class I recommendation (level of evidence: A) for prognosis and in detection of acute myocardial infarction as the precipitant of acute HF, while biomarkers of myocardial fibrosis, soluble ST2, and galectin-3 received Class IIb recommendations (level of evidence: B for chronic and A for acute HF).

European Society of Cardiology recommends natriuretic peptides as IIa (C).<sup>34</sup>

### CONCLUSION

The applications of biomarkers in HF, particularly the NPs, have revolutionized HF management. The next stage in biomarker evolution is taking the insight of underlying physiologic mechanisms that biomarkers provide and applying this knowledge to better understand complex disease mechanisms. Biomarkers can be used to identify pathologic processes in patients with HF and, thereby, to help direct specific therapy. This enhanced understanding can then be integrated into disease management, which will lead to better therapies and ultimately to improved patient outcomes.

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