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<p>A profusion of circulating candidate biomarkers in heart failure is currently being investigated. Although all will advance our insight into the pathophysiology of heart failure, their potential clinical utility will depend on satisfaction of three key criteria. Assays must be accessible, reliable, and affordable. Secondly, the marker must provide information about cardiac function and prognosis not otherwise available. Finally, measurement of the marker must demonstrably lead to improved management and better clinical outcomes. Despite many promising candidates requiring fuller investigation, currently, only the natriuretic peptides satisfy these requirements.</p>	
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<p>Natriuretic peptides play a central role in cardiovascular, endocrine, and renal homeostasis and can be considered physiologic antagonists to the renin-angiotensin-aldosterone system. ANP and BNP in the circulation are derived primarily from the myocardium, whereas CNP is mainly derived from endothelial cells and the central nervous system. Increased ventricular and atrial diastolic wall stretch augment synthesis and release of BNP and NT-proBNP from cardiomyocytes, and is the principal stimulus controlling BNP production. Circulating BNP and NT-proBNP levels are increased in heart failure in proportion to disease severity, but elevated levels may also be observed in other cardiac and noncardiac disease states, including cardiac arrhythmias, ventricular hypertrophy, myocardial ischemia, pulmonary embolism, acute and chronic cor pulmonale, renal failure, anemia, hyperthyroidism, and sepsis. Fully automated analyses of both BNP and NT-proBNP can be rapidly performed on large hospital-based platforms as well as on small point-of-care devices.</p>	
<b>Natriuretic Peptides in the Diagnosis and Management of Acute Heart Failure</b>	<b>489</b>
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<p>The emergence of BNP or NT-proBNP testing has improved the management of acutely decompensated heart failure patients significantly by aiding in early recognition, prognostication, and treatment. Furthermore, their logical application may not only reduce healthcare costs but also potentially reduce adverse clinical outcomes. This article reviews the understanding of utilizing natriuretic peptide testing to correctly diagnose and manage acute heart failure.</p>	
<b>Natriuretic Peptides in the Diagnosis and Management of Chronic Heart Failure</b>	<b>501</b>
Guido Boerrigter, Lisa C. Costello-Boerrigter, and John C. Burnett, Jr.	
<p>Circulating levels of the BNP system can help in the diagnosis of cardiovascular disease and provide prognostic information not only for patients who have HF but also for the general population and other patient groups. Changes over time also carry prognostic information, and studies are assessing BNP-guided treatment strategies.</p>	

With the identification of circulating molecular forms of BNP, new insights regarding the biology of the BNP system are emerging that may improve the diagnostic and prognostic value of BNP. Likewise, accounting for rs198389 (a common single nucleotide polymorphism that increases BNP levels) may help to further refine the use of components of the BNP system as biomarkers.

### **ST2 and Adrenomedullin in Heart Failure**

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Rahul Kakkar and Richard T. Lee

ST2 is the receptor for interleukin-33, a cytokine with antihypertrophic and antifibrotic effects on the myocardium. Serum levels of the soluble form of ST2 serve as a biomarker for ventricular biomechanical strain and provide prognostic information in patients who have symptomatic heart failure. Adrenomedullin is a vasoactive peptide whose actions run counter to the physiologic derangements of clinical heart failure. It appears that measurements of serum adrenomedullin levels can be used to identify those patients who have advanced heart failure and who are at increased risk for heart failure-related death.

### **Biomarkers of Myocyte Injury in Heart Failure**

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Roberto Latini and Serge Masson

Markers of cardiac myocyte injury have contributed over the years to the diagnosis and to the assessment of size of myocardial infarction. Recent evidence suggests that measurement of the release of cardiac contractile proteins into the bloodstream at lower levels may be useful in the clinical assessment of patients who have acute or chronic heart failure. The advent of a new generation of high-sensitivity immunoassays for cardiac troponins offers challenges for scientists and clinicians and will likely change the understanding and interpretation of cardiac injury.

### **Growth-Differentiation Factor-15 in Heart Failure**

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Tibor Kempf and Kai C. Wollert

The stress-responsive transforming growth factor- $\beta$ -related cytokine, growth-differentiation factor-15 (GDF-15), is emerging as a new biomarker in patients with cardiovascular disease. The circulating levels of GDF-15 are elevated and independently related to an adverse prognosis in acute coronary syndrome and left- or right-sided heart failure. GDF-15 adds significant prognostic information to established clinical and biochemical risk markers in these conditions. Elevated levels of GDF-15 may identify patients who have non-ST-elevation acute coronary syndrome who derive the greatest benefit from an invasive treatment strategy. As with other heart failure biomarkers, including BNP, it is currently not known what specific therapies could be used to reduce the risk associated with elevated levels of GDF-15 in heart failure. Further elucidation of the pathobiology and upstream inducers of this new biomarker may lead to new therapeutic concepts that address the risk associated with elevated GDF-15 levels. A commercial assay for GDF-15 should be available in the near future.

### **Inflammatory Biomarkers in Heart Failure Revisited: Much More than Innocent Bystanders**

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Stephan von Haehling, Joerg C. Schefold, Mitja Lainscak, Wolfram Doehner, and Stefan D. Anker

Chronic heart failure is viewed as a state of chronic inflammation. Many inflammatory markers have been shown to be up-regulated in patients who have this condition, but the markers' roles in clinical decision making have not yet been fully

elucidated. A panel of biomarkers is likely to have a strong impact on patient management. Inflammatory biomarkers are interesting candidates that could answer specific clinical questions on their own or complement a multi-marker approach. This article provides a broad overview of several inflammatory biomarkers, including the pro-inflammatory cytokines tumor necrosis factor- $\alpha$ , interleukin (IL)-6, IL-1, IL-18, and the soluble receptors TNFR-1, TNFR-2, IL-6R, and gp130. In addition to these acute phase reactants, several adhesion molecules, and lipopolysaccharide-signaling pathways are discussed.

### **Biomarkers of Oxidative Stress in Heart Failure**

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Barry H. Trachtenberg and Joshua M. Hare

Oxidative stress is the relative excess of reactive oxygen species (ROS) versus endogenous defense mechanisms. Abundant evidence has demonstrated the role of ROS, along with reactive nitrogen species (RNS), in the pathophysiology of cardiovascular disease, including heart failure. Many biomarkers of oxidative stress have been studied as surrogates of oxidative damage. Recently, markers of impaired nitric oxide signaling have also been identified. Many biomarkers have been associated with prognosis and mortality, and some may even be modified by therapy. However, the clinical utility is limited by less than optimal standardization techniques and the lack of sufficient large-sized, multimarker prospective trials.

### **Newer Biomarkers in Heart Failure**

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Sachin Gupta, Mark H. Drazner, and James A. de Lemos

The pathophysiology of heart failure is complex, and the list of biomarkers representing distinct pathophysiologic pathways is growing rapidly. This article focuses on some promising newer biomarkers that have contributed to a better understanding of pathophysiologic mechanisms involved in heart failure but for which less data are currently available: osteoprotegerin, galectin-3, cystatin C, chromogranin A, and the adipokines adiponectin, leptin, and resistin. Despite the intriguing early information from these newer markers, none is ready for routine clinical use. Much additional study is needed to determine how these biomarkers will fit into diagnostic and treatment algorithms for patients who have heart failure.

### **Biomarkers of Extracellular Matrix Turnover**

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Faiez Zannad and Bertram Pitt

The extracellular cardiac matrix (ECCM) plays an important role in the support of myocytes and fibroblasts. ECCM turnover is influenced by ischemia, stretch, inflammation, and neurohormonal mediators. Myocardial fibrosis is the consequence of several pathologic processes mediated by mechanical, neurohormonal, and cytokine factors. It is a major determinant of diastolic dysfunction and pumping capacity and may result in tissue heterogeneity, dys-synchrony, and arrhythmias. The measurement of various serum peptides arising from the metabolism of collagen types 1 and 3, of degradation fragments, and of specific metalloproteinases may provide noninvasive assessment of fibrosis. ECCM biomarkers are clinically useful tools, particularly given the potential for cardioprotective and cardioreparative pharmacologic strategies.