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Which biomarkers do clinicians need for diagnosis and management of heart failure with reduced ejection fraction?

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ABSTRACT

While there have been significant recent advances in the medical management of chronic HF (including the use of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone blockers), the ability to characterize, monitor, and predict a patient's response to HF therapy is poor.
Risk stratification is important in patients with chronic heart failure and enables informed decisions about treatment and end-of-life care. Clinical parameters, such as advanced age, higher NYHA functional class, reduced left ventricular ejection fraction, lower body mass index, renal dysfunction, and anemia have all been associated with poor outcomes in HF. More recently, heart failure biomarkers have considerably changed the way we take care of our HF patients. BNP and NT-proBNP are endorsed by current guidelines and are now the gold standard biomarkers to confirm the diagnosis and to evaluate the prognosis of heart failure. Studies on natriuretic peptide-guided HF therapy look promising. Novel biomarkers, such soluble ST2, growth differentiation factor-15, highly sensitive troponins and Galectin-3, show potential in assessing prognosis beyond the established natriuretic peptides, but their role in the clinical care of the patient is still partially defined and more studies are needed.

1. Introduction

Heart failure (HF) is a life-threatening disease and a major public health issue [1]. At present, an estimated 26 million people worldwide are living with HF. Moreover, heart failure patients are frequently hospitalized, causing a financial burden on every healthcare system. Although the prognosis of HF has improved over the past 50 years due to a wide range of pharmacological and device therapies, it remains among the most serious diagnoses, with high mortality rate: only 50% of all patients would survive up to 4 years. The main terminology used to describe HF is historical and is based on measurement of LV ejection fraction (EF). Up to half of HF cases occur in the setting of reduced EF (HFrEF) and the other half in the setting of preserved EF (HFpEF). Marked gaps and variations in the quality of care for HF exist. There are thus substantial opportunities to improve care and outcomes for heart failure [2].

In the ESC guidelines [3], HFrEF is defined as a clinical syndrome characterized in most patients by typical symptoms (e.g., dyspnea and fatigue at rest and/or with exertion and ankle swelling) and signs (elevated jugular pressure and pulmonary crackles) caused by underlying structural and/or functional heart disease and characterized by a reduced EF (<40%). However, these symptoms and signs are neither specific nor sensitive for diagnosing HF. Diagnosis of HFrEF thus remains challenging, even for experienced clinicians. Indeed, many of the symptoms are non-discriminating and many of the signs resulting from sodium and water retention resolve quickly with diuretic therapy and may be absent in patients receiving such treatment. Therefore, symptoms and signs are of limited diagnostic value [3]. As many as 50% of the patients referred to cardiologists from primary care physicians have been originally misdiagnosed with conditions other than heart failure. Finally, once the diagnosis of HFrEF is made, assessing the stability and the prognosis of the patient and whether he receives optimal therapy remains difficult. Therefore, the use of cardiac biomarkers in the diagnosis and management of heart failure may help to facilitate better clinical judgment. It is in this setting that interest in biomarkers is increasing over the last decade. This review will focus on biomarkers useful for the diagnosis and management of patients with HFrEF

2. What makes a biomarker useful?

For a biomarker to be useful for a clinician (Fig. 1), the following conditions are necessary [4–6]. The biomarker should be as follows:

- Broadly available
- Available at a reasonable cost on short notice
- Accurate and precise
- Giving consistent results

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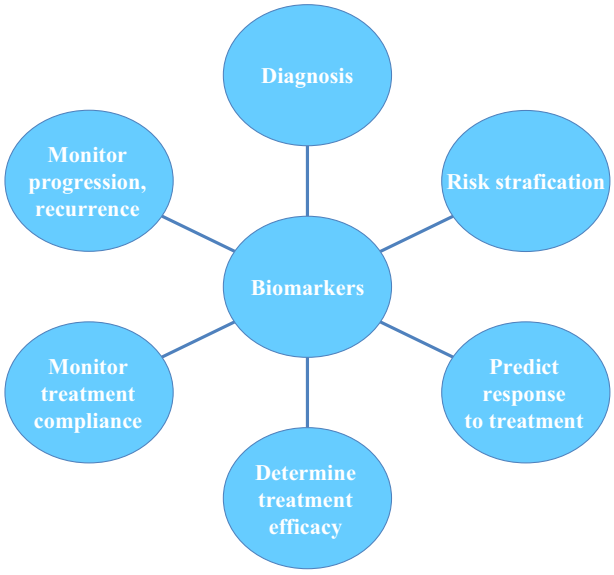

Fig. 1. What biomarkers are good for?

- Adding new information to the clinical workup
- Responsive to interventions
  - Non-pharmacologic
  - Pharmacologic
- Reimbursed

The National Academy of Clinical Biochemistry has comparable goals in a consensus document: an ideal biomarker in HF enables clinicians (i) to identify possible underlying (and potentially reversible) causes of HF; (ii) to confirm the presence or absence of the HF syndrome; and (iii) to estimate the severity of HF and risk of disease progression.

3. Heart failure biomarkers

Biomarkers in HFrEF could be classified into different categories, each reflecting different pathophysiological processes involved in the development and progression of HF [7]. HFrEF is indeed a syndrome mainly initiated by cardiac volume or pressure overload (myocardial stretch), but several other mechanisms are involved: e.g., myocyte injury, inflammation, and extracellular matrix remodeling (Table 1).

Biomarkers have dramatically changed the way HFrEF patients are evaluated and managed. Over the last decade, natriuretic peptides, particularly B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP), have emerged as powerful markers of diagnosis, prognosis, and management of HF patients [8]. Being relatively specific for cardiac dysfunction, BNP and NT-proBNP will be the main focus of this document.

Table 1
Biomarkers in HFrEF, divided into categories (not exhaustive).

Myocardial stretch/stress
Natriuretic peptides (ANP, BNP, CNP, NT-proANP, NT-proBNP, and mid-regional pro-ANP)
Soluble ST2 receptor (sST2)
Growth differentiation factor 15 (GDF-15)
Myocyte injury
Troponin I and T
Extracellular matrix remodeling
Galectin-3

ANP—atrial natriuretic peptide, BNP—brain natriuretic peptide, CNP—C-type natriuretic peptide, NT-proANP, NT-proBNP, and mid-regional pro-ANP.

Additional biomarkers have emerged, each reflecting the different pathophysiological processes involved in the development and progression of HFrEF [7]. Novel biomarkers, such as soluble ST2 (sST2), growth differentiation factor (GDF)-15, highly sensitive troponins, and Galectin-3, show potential in determining prognosis beyond the established natriuretic peptides, but their role in the clinical care of the patient is still partially defined and more studies are needed. Since several biological pathways are activated during left ventricular remodeling and HFrEF evolution, the future might be an integrated approach utilizing multiple biomarkers to better predict mortality, stratify our patients, and reduce re-hospitalizations, thus lowering health-care costs. These biomarkers will be briefly introduced in this review and will be detailed elsewhere in this issue.

3.1. Myocardial stretch

3.1.1. Natriuretic peptides

Three major natriuretic peptides (atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP)) counter the effects of volume overload or adrenergic activation of the cardiovascular system. ANP is synthesized primarily in the atria, stored in granules, and, under minor triggers such as exercise, released into the circulation. BNP has minimal storage in granules and is synthesized in response to volume expansion and pressure overload and secreted in bursts primarily by the ventricles. CNP is a product of endothelial cells and may be protective in post-myocardial infarction remodeling. Upon release into the circulation, ANP and BNP bind to various tissues and induce vasodilation, natriuresis, and diuresis [9–12].

3.1.1.1. BNP and NT-proBNP. Following translation of the BNP gene, an initial gene product is produced, pre-proBNP$_{1-134}$. This peptide undergoes rapid removal of a 26 amino acid signal peptide, which results in the formation of a 108 amino acid pro-hormone, proBNP$_{1-108}$ [13]. Subsequently, proBNP$_{1-108}$ is cleaved by proteolytic enzymes to release two portions: a 76 amino acid amino-terminal portion, NT-proBNP$_{1-76}$, an inactive fragment, and the biologically active 32-amino-acid molecule BNP$_{1-32}$, which possesses a characteristic 17-amino acid disulfide bound ring essential for biological activity (Table 2, Fig. 2). Clearance of natriuretic peptides is mediated through natriuretic peptide receptors-C, degradation by neutral endopeptidase, and by direct renal clearance.

3.1.1.1.1. Clinical applications: natriuretic peptides for HF diagnosis. Many patients presenting with acute dyspnea have multiple comorbidities that may complicate their diagnosis and management. Diagnostic uncertainty in the setting of acute dyspnea is associated with longer hospitalizations, increased health care costs, and higher likelihood for repeated HF hospitalization or death [14].

The utility of blood BNP or NT-proBNP testing in the initial evaluation of patients with acute heart failure has been well established by several studies. Used in conjunction with other clinical information, rapid measurement of BNP has been shown to be useful in establishing or excluding the diagnosis of congestive HF in patients with acute dyspnea [15]. In a series of 1586 patients presenting to the emergency department with acute dyspnea from the multicenter *Breathing-Not-Properly Study*, using a BNP level of 100 pg/mL as a diagnostic "cutoff" gave a sensitivity of 90%, specificity of 73% and a diagnostic

Table 2
Important patient-specific factors that may influence natriuretic peptide value.

	BNP	NT-proBNP
Age	Increase	Increase
Female sex	Increase	Increase
Anemia	Increase	Increase
Renal dysfunction	Increase	Increase
Obesity	Reduce	Reduce