Biochimica et Biophysica Acta 1832 (2013) 2442–2450

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Biomarkers and diagnostics in heart failure ☆

Hanna K. Gaggin, James L. Januzzi Jr. *

Cardiology Division, Massachusetts General Hospital, 55 Fruit Street, Yawkey 5700, Boston, MA, USA

ARTICLE INFO

Article history:
Received 31 August 2012
Received in revised form 29 November 2012
Accepted 22 December 2012
Available online 9 January 2013

Keywords:
Heart failure
Biomarker
Diagnosis
Prognosis
Management

ABSTRACT

Heart failure (HF) biomarkers have dramatically impacted the way HF patients are evaluated and managed. B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are the gold standard biomarkers in determining the diagnosis and prognosis of HF, and studies on natriuretic peptide-guided HF management look promising. An array of additional biomarkers has emerged, each reflecting different pathophysiological processes in the development and progression of HF: myocardial insult, inflammation and remodeling. Novel biomarkers, such as mid-regional pro atrial natriuretic peptide (MR-proANP), mid-regional pro adrenomedullin (MR-proADM), highly sensitive troponins, soluble ST2 (sST2), growth differentiation factor (GDF)-15 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. This article is part of a Special Issue entitled: Heart failure pathogenesis and emerging diagnostic and therapeutic interventions.

1. Introduction

A wide range of cardiovascular disorders that result in the impairment of the heart's ability to fill or to pump out blood may eventually lead to the clinical syndrome of heart failure (HF). In recognition of the multiplicity of causes of the diagnosis, it is not surprising that HF is a common affliction. Currently an estimated 5.8 million people in the United States [1] and 23 million people worldwide [2] are living with HF. As the population ages and treatments for cardiovascular diseases are improving mortality in affected patients, the number of HF patients is expected to grow.

Patients with HF often present with signs and symptoms that are often nonspecific and with a wide differential diagnosis, making diagnosis by clinical presentation alone challenging. Some of the signs and symptoms, such as dyspnea, orthopnea and paroxysmal nocturnal dyspnea, are due to congestion while some are due to lack of adequate cardiac output, including fatigue, weakness and exercise intolerance. This heterogeneity of presentation often results in delays in definitive diagnosis and treatment, and such delays are linked with poor prognosis [3]. Thus, together with HF's well-described risk for death and hospitalization, the growing incidence and prevalence make it a priority.

The evaluation of a patient suspected of HF was traditionally based on clinical assessment with history, physical examination and chest x-ray. However, in isolation, the performance of these methods of diagnosis can be limited in accurately diagnosing HF. As a matter of fact, isolated symptoms and signs correlate poorly with objective methods of cardiac dysfunction [4–6]. One study looked at the relationship between three clinical criteria that combined findings from history, physical examination and chest x-ray for the diagnosis of HF: the Framingham, the Duke and the Boston criteria [7]. All of the clinical criteria were limited in sensitivity (50–73%) and/or specificity (54–78%). Beyond clinical variables, noninvasive imaging studies (such as echocardiography and radionuclide angiography) may be useful to identify or exclude HF. These modalities can determine ventricular ejection fraction and diastolic dysfunction, as well as estimate chamber pressures. Echocardiograms can also provide clues to the underlying etiology of HF and are an essential part of assessment once the diagnosis is secured. However, many patients with abnormal ventricular systolic function on imaging studies are asymptomatic and do not necessarily have the clinical syndrome of HF [8,9]. For example, in one study of community-dwelling urban patients, 48% of patients with left ventricular ejection fraction ≤30% were asymptomatic [8]. Echocardiograms are also costly and time consuming

Abbreviations: ADHERE, Acute Decompensated Heart Failure National Registry; ADM, Adrenomedullin; ANP, Atrial natriuretic peptide; AUC, Area under the curve; BACH, Biomarkers in Acute Heart Failure; BNP, B-type natriuretic peptide; CI, Confidence interval; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; GDF-15, Growth differentiation factor-15; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure; HF, Heart failure; HFpEF, HF with preserved left ventricular ejection fraction; HR, Hazard ratio; hsTn, Highly sensitive troponin; hsTnI, Highly sensitive troponin I; hsTnT, Highly sensitive troponin T; ICON, International Collaborative of NT-proBNP; LVSD, Left ventricular systolic dysfunction; MI, Myocardial infarction; MR-proADM, Mid-regional pro adrenomedullin; MR-proANP, Mid-regional pro atrial natriuretic peptide; NHANES, National Health and Nutrition Examination Survey; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PRIDE, ProBNP Investigation of Dyspnea in the Emergency Department; sST2, Soluble ST2; ST2L, ST2 ligand; Val-HeFT, Valsartan Heart Failure Trial

☆ This article is part of a Special Issue entitled: Heart failure pathogenesis and emerging diagnostic and therapeutic interventions.

* Corresponding author at: 55 Fruit Street, Yawkey 5984, Boston, MA 02114, USA. Tel.: +1 617 726 3443; fax: +1 617 643 1620.

E-mail addresses: hgaggin@partners.org (H.K. Gaggin), jjanuzzi@partners.org (J.L. Januzzi).

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http://dx.doi.org/10.1016/j.bbadis.2012.12.014

and routine use in HF management is not recommended. Novel noninvasive techniques such as bioelectrical impedance vector analysis estimate body mass and water composition by bioelectrical impedance measurements, resistance and reactance, and may aid in the diagnosis of HF [10], but such measurements are cumbersome and are not specific to the diagnosis of HF, *per se*.

More invasive means such as right heart catheterization may be useful to identify or exclude HF; indeed right heart catheterization is the gold standard in determining cardiac output and chamber pressures such as pulmonary capillary wedge pressure. However, as already articulated, many patients with abnormal cardiac output and chamber pressures do not necessarily have the clinical syndrome of HF, while many patients with HF may have relatively normal measurements in between episodes of symptoms. Lastly, the risks of the nature of invasive monitoring make its role for routine diagnosis and monitoring in HF limited [11].

Accordingly, the role of biomarkers to predict the onset of future HF, to identify its presence when fully developed, to risk stratify affected patients, and possibly to serve as a biological tool to guide therapy for HF has been recently examined.

Indeed, the introduction of objective, noninvasive, biologically meaningful biomarkers to clinical assessment has considerably changed the way HF is diagnosed and monitored. In this article, we will discuss the role of established and novel biomarkers in HF.

2. Progression of HF and the biology of biomarkers

In the evolution of the heart from a) an at-risk but structurally normal organ to b) cardiac insult and injury, to c) ventricular dysfunction, to d) progression into symptomatic HF, it is now known that various remodeling and neurohormonal activation pathways exist whose activity may be leveraged for biological monitoring. Indeed, along the complex path from risk to fully developed HF, there are increasing numbers of injury, remodeling and neurohormonal activation proteins discovered, whose measurements might relay important information about HF (Table 1). Some, such as B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), are well validated and established in their use, while some are still being explored for potential use in the clinical practice.

3. Natriuretic peptides

The natriuretic peptides represent the gold standard for biomarkers in HF, and the understanding about their biology and their clinical use have both grown exponentially since their introduction. Structurally conserved across multiple species, a number of structurally similar natriuretic peptides have been identified: atrial natriuretic peptide (ANP), urodilantin (an isoform of ANP), B-type natriuretic peptide (BNP), C-type natriuretic peptide and Dendroaspis natriuretic peptide [12]. Of these, ANP and BNP are transcribed and primarily produced in the myocytes of the atria and ventricles, respectively [13]; both are produced in response to myocardial stretch due to pressure or volume overload [14], conditions commonly found in HF. The biological functions of ANP and BNP include various compensatory mechanisms such as natriuresis, diuresis, and vasodilation [15,16].

3.1. Diagnosis of HF

BNP production in normal healthy individuals is minimal, with a level of about 10 pg/mL [17]. In conditions of myocardial stretch, the induction of the BNP gene results in the production and secretion of prohormone $proBNP_{1-108}$. This is cleaved into the biologically active BNP_{1-32} (usually referred to as BNP) and biologically inert, but biochemically more stable, $NT\text{-}proBNP_{1-76}$ (usually referred to as NT-proBNP). Both fragments plus the precursor, $proBNP_{1-108,}$ are detected in circulation [18]. The majority of data regarding use of the B-type class has focused on measurement of either BNP or NT-proBNP.

The Breathing Not Properly Study [19] measured BNP levels in 1586 patients presenting to the emergency department with acute dyspnea. Investigators found that patients with clinically diagnosed HF had higher BNP levels compared with those without HF (mean 675 ± 450 vs. 110 ± 225 pg/mL, $p<0.001$). Increasing severity of HF, as measured by New York Heart Association (NYHA) functional class, correlated directly with increasing concentrations of BNP ($p<0.001$). BNP was the best single predictor of a final diagnosis of HF compared with all individual history, physical examination, chest x-ray and laboratory findings. The area under the curve (AUC) for BNP in receiver operating characteristic curve testing was 0.91 (95 percent confidence interval [CI] 0.90 to 0.93; $p<0.001$) for the diagnosis of HF. A cutoff BNP value of 100 pg/mL had a sensitivity of 90% and a specificity of 76%. In addition, BNP was more accurate (83%) than either The National Health and Nutrition Examination Survey (NHANES) criteria (67%) or the Framingham criteria (73%), two established sets of criteria for HF diagnosis. Importantly, the best method of diagnosis of HF was seen when BNP as well as clinical findings were combined (Table 2).

NT-proBNP is cleared via different mechanisms and has a longer half-life than BNP (70 minutes vs. 20 minutes), but it is believed to be rather equivalent for diagnostic evaluation of patients with suspected HF. The use of NT-proBNP in the diagnosis of acutely decompensated HF was first demonstrated in the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study [20], where NT-proBNP had an AUC of 0.94 ($p<.001$) for the diagnosis of HF, again supplementing clinical judgment as BNP did in the Breathing Not Properly study. Subsequently, the International Collaborative of NT-proBNP (ICON) study [21] examined optimal applications of NT-proBNP in 1256 acutely dyspneic patients. Patients with acutely decompensated HF had considerably higher NT-proBNP concentrations, compared with those without HF (4639 vs. 108 pg/mL, $p<0.001$); symptom severity correlated with NT-proBNP concentrations ($p=0.008$). As natriuretic peptide concentrations rise with increasing age, the ICON investigators found the best approach for use of NT-proBNP in HF diagnosis was through use of age-stratified cutoff points; this approach improved the positive predictive value of the assay considerably. Using the age stratified approach

Table 1
Biomarkers of heart failure.

Myocardial insult	Neurohormonal activation	Remodeling
Myocyte stretch	**Renin angiotensin system**	**Inflammation**
• NT-proBNP, BNP, MR-proANP	• Renin, angiotensin II, aldosterone	• C-reactive protein, tumor necrosis factor α, Fas, interleukins, osteoprotegerin, adiponectin
Myocardial Injury	**Sympathetic nervous system**	**Hypertrophy/Fibrosis**
• Troponin T, troponin I	• Norepinephrine, Chromogranin A	• Matrix metalloproteinases, collagen propeptides, galectin 3, soluble ST2
Oxidative stress	**Arginine vasopressin system**	**Apoptosis**
• Myeloperoxidase, oxidized low-density lipoproteins, MR-proADM	• Arginine vasopressin	• GDF-15

BNP = B-type natriuretic peptide, GDF-15 = growth differentiation factor-15, MR-proADM = mid-regional pro adrenomedullin, MR-proANP = mid-regional pro atrial natriuretic peptide, NT-proBNP = N-terminal pro B-type natriuretic peptide.

Table 2
Multiple logistic regression analysis of predictors of HF (Adapted with permission from [19]).

Predictor	Odds ratio (95% CI)	*p*-Value
BNP > 100 pg/mL	29.60 (17.75–49.37)	<0.001
History of HF	11.08 (6.55–18.77)	<0.001
Cephalization on chest x-ray	10.69 (5.32–21.47)	<0.001
Edema	2.88 (1.81–4.57)	<0.001
History of myocardial infarction	2.72 (1.63–4.54)	<0.001
Rales	2.24 (1.41–3.58)	<0.001
Jugular venous distention	1.87 (1.04–3.36)	0.04
Age (for each year of age)	1.02 (1.00–1.03)	0.04

BNP = B-type natriuretic peptide, HF = heart failure.

(NT-proBNP ≥ 450 pg/mL for age < 50 years, ≥ 900 pg/mL for age 50-75 years or ≥ 1800 pg/mL for age > 75 years.), a sensitivity of 90% and specificity of 84% for acute HF was found. In addition, the ICON investigators found that very low concentrations of NT-proBNP were are particularly handy in excluding HF, with excellent negative predictive value.

Much as in those with acute dyspnea presenting to the emergency department, both BNP and NT-proBNP have been shown to be particularly useful in excluding HF in lesser acute settings such as primary care setting [22].

As noted previously, HF is a heterogeneous group of syndromes that manifest with a common set of symptoms and signs. About half of patients with HF have left ventricular systolic dysfunction (LVSD) and the other half have HF with preserved left ventricular ejection fraction (HFpEF) also known as diastolic HF. In recognition of their biologic trigger for release (common to both types of HF), both BNP and NT-proBNP are accurate for the diagnosis of HF with LVSD or HFpEF with good accuracy [23]. There may be slightly reduced sensitivity with HFpEF, due to generally lower BNP or NT-proBNP values in these patients [24,25], but the overall performance of the assays is acceptable.

The use of BNP and NT-proBNP for the diagnosis of HF has dramatically impacted the standard of care in HF; all major societies including the American College of Cardiology, the American Heart Association, the Heart Failure Society of America and the European Society of Cardiology recommend the use of BNP or NT-proBNP for the diagnosis of HF in their clinical practice guidelines [11,26,27].

3.2. Prognosis

Across the wide stages of HF-from at-risk, apparently well patients to those with end-stage HF, concentrations of BNP and NT-proBNP have been found to be meaningful for predicting outcomes. This prognostic value appears to be additive to other clinical factors, and at least as strong as many of the novel biomarkers discussed below.

The literature on the value of BNP or NT-proBNP to predict adverse outcomes is too large to summarize in one paragraph, but certain aspects are common to the studies examining both peptides in various stages of HF.

In patients with acutely decompensated HF, both BNP and NT-proBNP were found early on to be of considerable significance relative to hard outcomes such as death or recurrent hospitalization. For example, in The Acute Decompensated Heart Failure National Registry (ADHERE) registry [28], among 48629 patients hospitalized with acutely decompensated HF (due to either HF with LVSD or HFpEF), there was a linear relationship between increasing admission BNP and increasing in-hospital mortality, even after adjusting for clinical and laboratory risk factors. Lending further support, Doust and colleagues compiled results from 19 studies that looked at the prognostic power of BNP for death or cardiovascular events [29], and found that each 100 pg/mL increase in BNP was associated with a 35% increase in the relative risk of death (95% CI 22–49%, $p = 0.096$). Similarly, elevated NT-proBNP values on acute HF admission were predictive of both intermediate (death at 76 days) [21] and long-term outcomes (with NT-proBNP values greater than 986 pg/mL predicting death at 1 year) [30]. While these studies focused mainly on the baseline value of either BNP or NT-proBNP for prognosis in acutely decompensated HF, it appears that the final, post-treatment concentration of either peptide may be more prognostic than the baseline value (Fig. 1) [31–33]. This has led to the natural question as to whether in-hospital monitoring of either BNP or NT-proBNP would afford a better ability to identify higher risk patients, with specific targeting of their therapy to reduce risk for short and longer-term adverse outcome [34].

In chronic HF, both BNP and NT-proBNP were useful in determining HF prognosis though NT-proBNP appeared to be slightly better at predicting hospitalization [35]. Subsequent analyses from the same cohort [36] showed that serial measurement of BNP and NT-proBNP was better at predicting mortality (median follow-up of 24.5 months) than a single baseline measurement. Interestingly, NT-proBNP threshold value of 1078 pg/mL, as determined by a univariate time-dependent receiver operator characteristic curve, was useful in further determining prognosis by NT-proBNP categories.

Elevated BNP or NT-proBNP levels are also predictors of future HF or other cardiovascular events in asymptomatic patients without

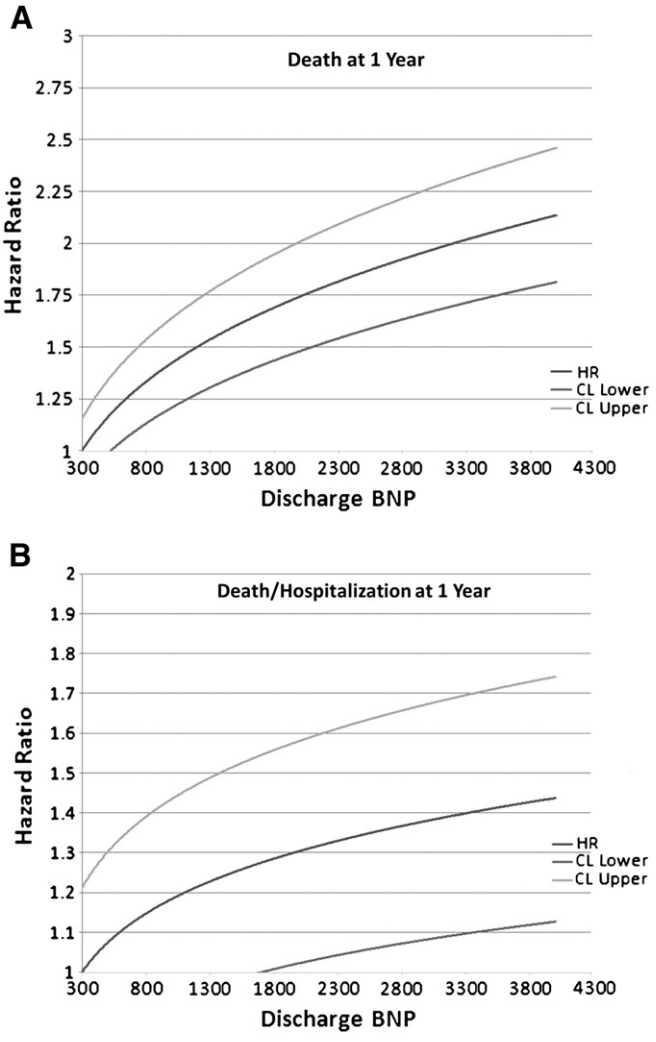

Fig. 1. Adjusted hazard ratio (HR) and 95% confidence interval (CI) for clinical outcomes by discharge B-type natriuretic peptide (BNP) (versus discharge BNP = 300)—results from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) study. Though the focus of initial studies on BNP has been on the predictive ability of baseline BNP values, OPTIMIZE-HF study demonstrates that it was the final achieved BNP concentrations after HF therapy that predicted future outcomes well. Studies exploring BNP-guided HF management are based on this concept of adjusting therapies to achieve a prognostically favorable "final" biomarker concentration. Reproduced with permission from ref. [33].

obvious HF. For example, among 3346 patients from the Framingham Heart Study without established HF [37] each standard deviation increase of log-BNP levels (and similarly for NT-proBNP) was associated with an adjusted increase in the risk of death (27%, $p = 0.009$), first cardiovascular event (28%, $p = 0.03$), new HF (77%, $p < 0.001$), atrial fibrillation (66%, $p < 0.001$), and stroke or transient ischemic attack (53%, $p = 0.002$). Similarly, among patients with established structural heart disease (such as those with chronic stable coronary disease), concentrations of both BNP and NT-proBNP potently predicted onset of future HF as well as death. Natriuretic peptide levels were not significantly related to the risk of coronary heart disease events, however [38,39].

Thus, as previously declared, BNP and NT-proBNP represent the "gold standard" biomarker for prognosis against which other prognostic biomarkers must be compared [40].

3.3. HF management

BNP and NT-proBNP concentrations typically fall with therapies proven to improve mortality in HF such as drug therapy with beta blockers [41], angiotensin converting enzyme inhibitors [42], angiotensin II receptor blockers [43] and aldosterone antagonists [44], as well as following cardiac resynchronization therapy [45]. A decreasing trend in natriuretic peptide levels portends a favorable prognosis and meta-analysis showed substantial improvement in mortality with HF management with a goal to reduce natriuretic peptide concentrations in addition to standard HF management [46]. Large randomized multi-center trials are underway to better explore this personalized, biologically driven approach to care.

3.4. Limitations of natriuretic peptide measurement

There are several important limitations to natriuretic peptides that need to be kept in mind when interpreting their results. Concentrations of both are by no means 100% specific for the clinical diagnosis of "HF," but elevated values for either biomarker usually identifies underlying structural heart disease as well as heightened risk.

Beyond advancing age and ventricular function as discussed above, other factors influencing the clinical interpretation of BNP or NT-proBNP values are listed in Table 3, and include obesity (which lowers values through a suppression of BNP release), renal failure, atrial arrhythmias, cardiotoxic agents, as well as structural heart disease beyond the clinical diagnosis of HF [47–49].

Specifically with respect to renal function, BNP and NT-proBNP are, in part, passively excreted by the kidneys [50], which are responsible for approximately 25% of the clearance of both peptides. Additionally, as renal failure and HF have overlap in risk factors and epidemiology, it is expected that worse renal function will be accompanied by worse cardiac status. Thus, estimated glomerular filtration rate is inversely related to the concentration of both BNP and NT-proBNP, and both may be significantly elevated in those with renal failure even without obvious clinical HF [51]; adjusted cutoff values have been proposed in renal insufficiency for both.

3.5. Emerging natriuretic peptide assays: mid-regional pro atrial natriuretic peptide (MR-proANP)

ANP production is increased in response to increased atrial wall stretch in HF, but reliable detection of circulating ANP concentrations can be challenging as its half-life is only 2–5 minutes [52]. The 126 amino acid prohormone of ANP, known as proANP, has a longer half-life and makes serum measurement more feasible; a novel assay that detects the mid-regional zone of proANP (MR-proANP) is now available, and has been evaluated as a test for HF.

In the Biomarkers in Acute Heart Failure (BACH) trial [53], MR-proANP was measured in 1641 patients with acute dyspnea. Investigators of the study found that MR-proANP (cutoff point ≥120 pmol/L, sensitivity 97%, specificity 59.9%, accuracy 73.6%) was noninferior to BNP (cutoff point ≥100 pg/mL, sensitivity 95.6%, specificity 61.9%, accuracy 72.7%) in the diagnosis of acute HF and appeared to improve diagnostic accuracy in the BNP grey zone (BNP levels between 100 and 500 pg/mL) and in patients with obesity. In the PRIDE study [54], MR-proANP was found to be an independent predictor of HF diagnosis in a model that included NT-proBNP (odds ratio = 4.34, 95% CI = 2.11–8.92, $p < 0.001$), and correctly reclassified both false negatives and false positives. These results suggest that the combined use of MR-proANP and either BNP or NT-proBNP provides superior diagnostic accuracy than either alone.

Much as with either BNP or NT-proBNP, MR-proANP is prognostic for adverse outcome in patients with acutely decompensated HF. In the PRIDE study [54], elevated MR-proANP was independently prognostic and reclassified mortality risk at 1 year (hazard ratio[HR] = 2.99, $p = 0.001$) and at 4 years (HR = 3.12, $p = 0.001$). Kaplan–Meier curves also showed that MR-proANP was associated with death out to 4 years, by itself or with other biomarkers in a multimarker strategy. In chronic HF, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) investigators [55] measured several biomarkers including MR-proANP and NT-proBNP in 1237 stable patients and followed them for about 4 years. The prognostic accuracy for MR-proANP for mortality was the best with an AUC of 0.74 (95%CI = 0.71–0.77) with an optimal cutoff point of 278 pmol/L, followed by NT-proBNP with an AUC 0.73 and an optimal cutoff of 1181 pg/mL (95% CI = 0.70–0.76). In addition, MR-proANP added independent prognostic information beyond NT-proBNP and clinical risk factors in net reclassification analyses. Changes in MR-proANP over 3 months also appeared to be predictive of future mortality.

3.6. Beyond natriuretic peptides in HF

Although the natriuretic peptides have revolutionized the use of biological measures to evaluate, prognosticate, and possibly manage

Table 3
Factors influencing the clinical interpretation of BNP or NT-proBNP values.

Factors that decrease BNP or NT-proBNP
• Obesity
Factors that increase BNP or NT-proBNP
Heart muscle disease
• Hypertrophic heart muscle diseases
• Infiltrative myocardiopathies, such as amyloidosis
• Acute cardiomyopathies, such as apical ballooning syndrome
• Inflammatory, including myocarditis and chemotherapy
• Coronary artery disease
Valvular heart disease
• Aortic stenosis and regurgitation
• Mitral stenosis and regurgitation
Arrhythmia
• Atrial fibrillation and flutter
Cardiotoxic drugs
• Anthracyclines and related compounds
Renal dysfunction
Anemia
Critical illness
• Bacterial sepsis
• Burns
• Adult respiratory distress syndrome
Stroke
Pulmonary heart disease
• Sleep apnea
• Pulmonary embolism
• Pulmonary hypertension
• Congenital heart disease

BNP = B-type natriuretic peptide, NT-proBNP = N-terminal pro B-type natriuretic peptide.

patients with HF, the biological complexity of HF dictates that measurement of other biomarkers reflecting relevant but independent pathways may be useful.

As reviewed previously [56] and in Table 1, there is a very wide range of possible biological measures to be considered in patients with HF. However, many studies that have identified some of these candidates have been somewhat limited in design or quality. Thus, unless adhering to a strict set of criteria for evaluation (Table 4) [57], it is difficult to know what the many putative "next greatest" biomarkers in HF add beyond the natriuretic peptides. In this regard, we only consider those biomarkers that appear most promising for use in HF; each of the following novel biomarkers was chosen for its pathophysiologic tie to development and progression of HF as well as studies demonstrating the link between the biomarker and clinical diagnosis or outcomes beyond the information already provided by the gold standard HF biomarkers, natriuretic peptides. Given the proven diagnostic value of BNP and NT-proBNP, the focus for each has been for prognostication, rather than diagnosis.

4. Mid-regional pro adrenomedullin (MR-proADM)

Adrenomedullin (ADM) [58] was initially found in pheochromocytoma cells in the adrenal medulla and has potent vasodilatory effects. Since then, ADM has been found in various organs including the heart, where it appears to increased myocardial contractility through a cyclic AMP-independent mechanism [58]. In addition, it appears to increase nitric oxide synthesis in conditions where cytokine production is increased [59]. Circulating levels of ADM are elevated in HF and correlate with decreasing left ventricular ejection fraction, increasing pulmonary artery pressures and the presence of diastolic dysfunction and restrictive filling patterns [60,61]. Infusion of ADM in HF patients results in significant vasodilation, increase in cardiac index and reduction of pulmonary capillary wedge pressure [62]. Thus, ADM release appears to be a compensatory mechanism in HF.

While ADM itself is difficult to measure, a commercial assay measuring the mid-regional portion of the stable prohormone of ADM, MR-proADM, has been developed and used to explore its role in HF. In the BACH study [53], MR-proADM was powerfully prognostic for death at 90 days, adding prognostic value beyond natriuretic peptides. Subsequent data from the PRIDE study [54] solidified a potential prognostic role for MR-proADM; among 560 patients MR-proADM had the best AUC for mortality at 1 year. After 1 year, MR-proANP and NT-proBNP had higher AUCs.

In chronic HF, MR-proADM appears to be similarly prognostic. The Australia-New Zealand Heart Failure Study [63] was a randomized trial of carvedilol in 297 patients with ischemic left ventricular dysfunction. Investigators measured MR-proADM before and after treatment and found that above median levels of MR-proADM predicted increased risk of mortality (risk ratio of 3.92, 95% CI = 1.76–8.7) and of HF hospitalization (risk ratio of 2.4, 95% CI = 1.3–4.5) independent of traditional clinical and echocardiographic factors. Treatment with carvedilol reduced the risk of death or HF hospitalization in patients with above-median levels of NT-proBNP, MR-proADM or both.

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.

Table 4
Criteria for evaluation of new biomarker [57].

Criteria
1. Thorough methods must be used, and the marker should be evaluated across a wide range of patients using rigorous and contemporary statistical methods
2. Results should be easily obtained within a short period of time and provide acceptable level of accuracy-defined biological variation and low analytical imprecision
3. Results should reflect important pathophysiological process in HF presence and progression
4. Results should provide clinical useful information beyond status quo

HF = heart failure.

4.1. Cardiac troponins

Cardiac troponins have traditionally been used for the diagnostic evaluation for acute myocardial infarction (MI), but there are several other disorders where cardiac troponins are elevated. One such disorder is HF [64]. The mechanisms of troponin release in HF are numerous and include MI type 1, MI type 2 (in the presence or absence of coronary artery disease respectively), as well as other non-coronary causes, including cytotoxicity, apoptosis, and inflammation. Regardless of underlying etiologies of troponin elevation in patients with HF, concentrations of the biomarker are strongly prognostic. With the emergence of highly sensitive troponin (hsTn) assays, where myocardial necrosis is now detected in a great majority of patients with HF syndromes, the ability of the biomarker to provide prognostic value is even more refined.

In patients with acutely decompensated HF, Xue et al. [65] demonstrated that concentrations of highly sensitive troponin I (hsTnI) were frequently elevated, and typically more so in those patients destined for a complication. Further, in serial measurements, hsTnI typically rose (or remained elevated) in subjects with impending complications. In another analysis of patients with acutely decompensated HF, Pascual-Figal and colleagues [66] combined results from testing for highly sensitive troponin T (hsTnT) with NT-proBNP and soluble ST2 (a biomarker discussed below), showing enhanced prognostic value with the addition of each biomarker (Fig. 2). In a subsequent analysis from this cohort, the investigators compared hsTnT with conventional TnT, showing that the highly sensitive assay was particularly of prognostic value in those patients with undetectable conventional TnT results [67].

Among those with chronic HF, similar hsTn results have been reported. For example, in the Valsartan Heart Failure Trial (Val-HeFT) [68] of 4053 chronic stable HF patients without overt evidence of myocardial ischemia or infarction, detectable TnT (~10%, measured with a conventional assay) was associated with an increased risk of death (HR 2.08, 95% CI 1.72–2.52) and first hospitalization for HF (HR 1.55, 95% CI 1.25–1.93) at 2 years in Cox proportional hazards models adjusted for clinical risk factors. Using the hsTnT method, 92% were found to have detectable myocardial necrosis, which predicted a linear increase in mortality in multivariable models (HR of 1.05, 95% CI = 1.04–1.07, $p<0.0001$). Addition of hsTnT to models adjusting for clinical risk factors as well as BNP improved prognostic discrimination significantly. In a larger study [69] combining patients from the Val-HeFT study and the GISSI-HF study, an increasing hsTnT concentration strongly predicted increased risk of mortality, but modestly improved test performance beyond the information already given by the baseline values. Of note, there was no significant change in hsTnT values between baseline and follow up values.

In at-risk subjects, such as older, community dwelling patients, detection of hsTnT appears to predict future development of HF (hsTnT >12.94 pg/mL had an incidence rate per 100 person-years of 6.4 [95% CI = 5.8–7.2]; adjusted HR 2.48 [95% CI = 2.04–3.00]) and cardiovascular death (incidence rate per 100 person-years of 4.8 [95% CI = 4.3–5.4]; adjusted HR 2.91 [95% CI = 2.37–3.58]) [70]. In this population, hsTnT change >50% predicted incidence of HF and cardiovascular death beyond baseline measures.

At present, while measurement of troponin is recommended to exclude MI in patients presenting with acutely decompensated HF [71], because of unclear therapeutic ramifications of the risk predicted by

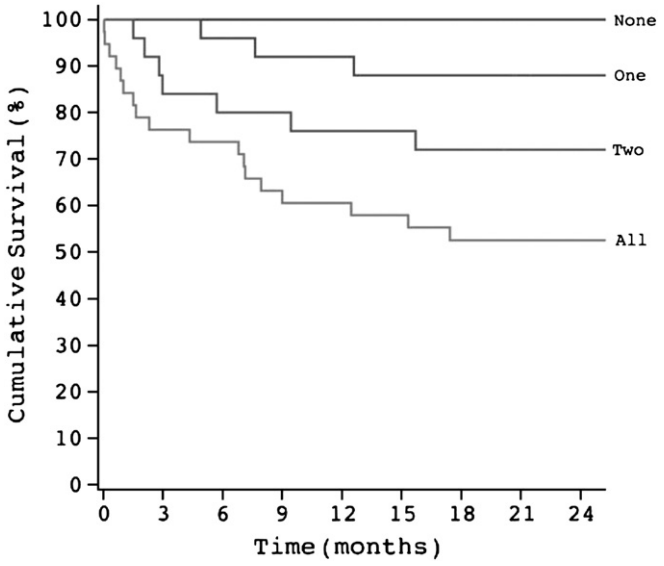

Fig. 2. Kaplan–Meier survival curves according to the presence of none, one, two or all three biomarkers—a multi-marker panel including soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide (NT-proBNP), predicted worsening clinical outcomes better than any single biomarker. Reproduced with permission from [66]. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure.

its elevation, the role of troponin testing for risk stratification in non-acute settings remains only partially defined.

5. Soluble ST2 (sST2)

ST2 is a unique biomarker with pluripotent effects *in vivo*. ST2 is believed to have immunomodulatory function as a cell-surface marker of T helper type 2 lymphocytes and was initially described in the context of cell proliferation, inflammatory states and autoimmune diseases [72]. Importantly, however, the ST2 system is also strongly induced in mechanical strain of cardiac fibroblasts or cardiomyocytes [73] and appears to be intimately involved in cardiac remodeling and fibrosis in HF. Through binding of its ligand (interleukin-33, which has anti-fibrosis and anti-remodeling effects) to either ST2 ligand (ST2L) or a soluble "decoy receptor" version (sST2), the ST2 system represents an inducible pathway participant in mitigation of biomechanical stress. Clinically, concentrations of sST2 are predicted by a phenotype of cardiac decompensation and remodeling [74]. Compared to other biomarkers, such as natriuretic peptides, advantages of sST2 include that its concentration is not affected by age, renal function or body mass index [75].

Prognostically speaking, sST2 represents a valid contender to be added to the natriuretic peptides. Among 593 patients presenting with acute dyspnea [76,77], there was a concentration-dependent relationship between sST2 and many clinical markers of HF severity including left ventricular ejection fraction and NYHA functional classification. An elevated sST2 was prognostic in both acutely decompensated HF patients (HR = 9.3, $p = 0.003$) and in all dyspnea patients (HR = 5.6, $p < 0.001$) in multivariable analyses and surpassed NT-proBNP for predicting death; the AUC for predicting 1-year mortality was 0.80 ($p < 0.001$). In recognition of the independent importance of NT-proBNP for prognosis, it is noteworthy that the combination of a natriuretic peptide and sST2 was a stronger predictor of death than either alone. Another study of patients with acutely decompensated HF [78] found that a percent change in sST2 during treatment for acute HF was also predictive of 90-day mortality (AUC 0.783, $p < 0.001$).

On the outpatient side, in an analysis of more than 1100 patients with chronic HF [79], patients with the highest decile of sST2 concentration had a HR of 3.2 (95% CI = 2.2–4.7, $p < 0.0001$) compared those with the lowest decile of sST2. While the prognostic power of sST2 was similar to that of NT-proBNP in this study, again, having both biomarkers was the best strategy in determining prognosis. When sST2 and NT-proBNP were added to an established clinical risk model, the Seattle heart failure model, 15% of subjects were reclassified ($p = 0.017$).

With the development of a highly sensitive assay for its measurement [75], the potential utility of sST2 continues to grow, with emerging data solidifying the potential role of sST2 across a broader demographic of patients. For example, among a normal population of subjects in the community [80], concentrations of the biomarker predicted future HF, even when adjusted for other novel and established biomarkers and clinical variables.

With preliminary data suggesting benefit of therapies that mitigate ventricular remodeling among patients with elevated sST2 concentrations [81], the potential of its use to "guide" therapy for prevention of HF complications appears promising.

6. Growth differentiation factor (GDF)-15

GDF-15 is a member of the transforming growth factor-β cytokine superfamily, and participates in mitigation of myocardial stress and remodeling; expression of GDF-15 is strongly induced in cardiomyocytes in response to metabolic stress such as cardiac ischemia (nitric oxide-dependent) or pressure overload state (angiotensin 2-dependent) [82–85]. Accordingly, GDF-15 is elevated in acute MI and HF [86–88]. GDF-15 appears to be involved in the regulation of cell differentiation and tissue repair with possible anti-apoptotic and anti-hypertrophic effects and closely linked with tissue remodeling [82,83].

Kempf and colleagues [86] measured circulating levels of GDF-15 in 455 chronic HF patients. About 75% of the study participants had GDF-15 levels above the upper limit of normal, and increasing GDF-15 concentration was associated with increasing symptom severity of HF. When GDF-15 was divided into quartiles, higher values were associated with increased risk of death during a follow up of 2 years (10.0%, 9.4%, 33.4% and 56.2% respectively, $p < 0.001$). Even after adjusting for various traditional risk factors that included NT-proBNP, GDF-15 remained an independent predictor of mortality (adjusted HR for 1 unit in the natural log scale 2.26, 95% CI 1.52–3.37, $p < 0.001$). Further data from 1734 patients from the Val-HeFT study [89] lent support to the use of GDF-15 in this context. The biomarker was measured at baseline and after 12 months of treatment with the angiotensin receptor blocker valsartan or placebo. Similar to the study by Kempf and colleagues, the large majority of the patients (85%) had abnormal concentrations (>1200 ng/L). These high levels were associated with features of advanced HF and other biomarkers of neurohormonal activation, inflammation, myocyte injury and renal dysfunction. In a multiple-variable Cox regression model that included clinical risk factors, BNP, high-sensitivity C-reactive protein and hsTnT, GDF-15 was an independent predictor of death (HR 1.007, 95% CI 1.001–1.014). After randomization, over the ensuing 12 months, GDF-15 levels increased (median increase 145 ng/L in the placebo group and 173 ng/L in the valsartan group, $p = 0.94$ for comparison between the groups) and such an increase was associated with increased risk of death and first morbid event even after adjusting for other risk factors. Despite the link between GDF-15 and the angiotensin II receptor [90], no interaction between risk and treatment with valsartan was observed [89]. Thus, much as with many novel markers, the promise of therapy guidance using GDF-15 is not yet realized.

7. Galectin-3

Galectin-3 [91] is a macrophage product member of the lectin family and is found on a wide variety of cells and tissues surfaces. Its function appears to be related to the inflammatory cascade following cardiac injury, as well as pathways regulating cardiac contractility. It has a number of biological roles, including and especially the formation of fibrosis; in a pioneering study from the lab of Pinto [92], the galectin-3 gene was significantly expressed in rat HF models, and with pericardial instillation of galectin-3, considerable deposition of collagen was observed. Further, other studies have shown that galectin-3 genetic knockout mouse models are resistant to left ventricular pressure and volume overload, with a slower progression to LV dysfunction or HF.

Clinically, galectin-3 was first measured in subjects from the PRIDE study [93]. Patients with HF had higher levels of galectin-3 compared with those without HF (median 9.2 ng/mL vs. 6.9 ng/mL, $p<0.001$), but for the diagnosis of HF, NT-proBNP outperformed galectin-3. On the other hand, galectin-3's ability to predict 60-day mortality was superior to NT-proBNP even after adjusting for traditional risk factors. However, similar to previously discussed biomarkers of prognosis, adding galectin-3 to NT-proBNP and other risk factors provided the best strategy for predicting prognosis in HF.

In patients with chronic, ambulatory HF, concentrations of galectin-3 were found to be prognostic [94–96]; interestingly, consistent with the possibility that biomarkers of fibrosis such as galectin-3 are particularly important in HFpEF (where diastolic non-compliance is the primary mechanism of HF), de Boer and colleagues [97] reported that galectin-3 was especially predictive of death in those subjects with HF but without LVSD.

While therapy interactions with standard HF medications are not yet found for galectin-3, among a large cohort of participants with HF due to LVSD in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study [96], Gullestad and colleagues showed that lower galectin-3 concentrations predicted response to therapy with cholesterol lowering, suggesting that the biomarker may be used to triage patients to different therapy strategies; those with lower galectin-3, and hence likely to survive their HF long enough for ischemic heart disease to become relevant, would most benefit from statin therapy.

8. Conclusion

Traditional methods of assessment and management of HF are limited by subjective interpretation, time consumption, cost or invasive nature. Biomarkers theoretically offer convenient, objective, safe and biologically relevant insight that complements clinical findings of the HF patient. Whether for determining diagnosis, prognosis, or deciding on therapy choice, the field of HF biomarkers is rich with biomarkers reflective of different mechanism of HF development and progression. With different biomarkers reflecting HF presence, the various pathways involved in its progression, as well as identifying unique therapy options for HF management, a multi-biomarker approach to the HF patient is not far ahead, allowing the unique opportunity for specifically tailoring care to the individual.

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