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Incorporating Common Biomarkers into the Clinical Management of Heart Failure

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Abstract

Heart failure is a prevalent and costly disease, and its management with polypharmacy is complex. Commonly available biomarkers primarily help to 1) establish or refute the diagnosis of heart failure; 2) help to determine the disease severity; and 3) identify adverse consequences of treatment. Although several of them are commonly ordered (such as electrolytes, renal and liver function), their use is primarily based on broad clinical experience rather than established evidence. The availability of cardiac-specific natriuretic peptide testing has provided an evidence-based breakthrough in our abilities to establish the diagnosis and severity of heart failure, yet the appropriate boundaries to guide management are still in refinement.

Keywords

Biomarker; Markers; Heart failure; NT-proBNP; BNP; Heart failure management; e GFR; Creatinine; Cystatin C; NGAL; Sodium; Hyponatremia; ESR; Natriuretic peptide; Anemia; Albuminuria; Renal insufficiency; Azotemia; Prognosis

A biomarker represents a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [1]. Objective methods of biomarker measurement in medicine have served their role over the years by complementing the clinical scenario in helping understand the appropriateness of their use. With the increasing burden of heart failure and predicted future rise in the morbidity worldwide from it, a central quest has been to optimize the management with the incorporation of biomarkers with the goal to improve morbidity and mortality as well as to reduce overall health care costs.

During the last decade, there has been substantial progress in the use of biomarkers in clinical management of heart failure, and a broad range of clinical biomarkers have been rigorously tested in different mechanistic domains (Fig. 1). In this article we will review the common biomarkers used at all steps in the diagnosis and management of heart failure, with

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a prime focus on those that are widely available to healthcare providers and measured from bio specimens in clinical laboratories.

Biomarkers for Diagnosis in Heart Failure

Acute decompensated heart failure (ADHF) represents one of the most common causes of hospitalizations in the elderly population. This is also where natriuretic peptide testing first established its clinical utility in the diagnosis of heart failure following their pivotal studies over a decade ago [2, 3]. This is reflected in one of the major changes in the recently published ACC/AHA guideline recommendations that has been the incorporation some of the strongest recommendations related to their clinical utility as adjunct to clinical diagnosis of heart failure [4]. A summary of these recommendations is illustrated in Table 1, and studies supporting these recommendations have been extensively reviewed elsewhere [5, 6]. Clearly, natriuretic peptide testing is helpful in aiding to establish the diagnosis of heart failure in patients with ambiguous presentations at the bedside in the absence of confirmatory testing for underlying cardiac insufficiency. However, unlike other conditions where the biomarker levels define the clinical syndrome, natriuretic peptide levels seemed to be best utilized in tracking with clinical status.

Overall, the diagnostic accuracies appear to be similar between the two commercially available types of assays, B-type natriuretic peptide (BNP) and aminoterminal pro-B-type natriuretic peptide (NT-proBNP) as shown in Fig. 2. Both have excellent negative predictive value in the acute setting where a low value effectively excludes a cardiac source of signs and symptoms except for in situations where values are lower than expected (e.g. obesity) [2, 3]. However, there is no direct “conversion” between the two types of natriuretic peptide measurements, and their values are often 5 – 8 times different in absolute values (even up to 20 % variations among BNP assays). Meanwhile, the diagnostic ranges and accuracies in chronic stable heart failure or those with structural heart disease but subclinical presentations may be lower than that established in the acute settings [7]. At the other end of the spectrum, those with less muscle mass (e.g. women, elderly) or those with impaired clearance (e.g. renal insufficiency) may have elevated levels even in the absence of overt heart failure [8–10]. Hence, the interpretation of natriuretic peptide testing values mandates the clinical context, particularly when a change in treatment approach may be warranted (such as initiation of guideline-directed medical therapy [GDMT] with confirmation of the diagnosis of heart failure) [4].

Defining Concomitant Conditions in Heart Failure

An often overlooked but commonly applied use of biomarkers is the determination of concomitant conditions that may confound the heart failure syndrome. This category comes into two types: 1) those that are incorporated as part of longstanding clinical experience; 2) those that are discovered after extensive epidemiology and/or clinical trial data. In the latest guidelines, the initial evaluation of patients newly diagnosed with heart failure includes a complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone [4]. These are largely chosen empirically based on clinical experience in assessing organ function and homeostatic integrity.

Renal Insufficiency—The ability of the kidneys to relieve congestion is perhaps the most important determinant of the clinical course and therapeutic responses in heart failure. However, serum creatinine only reflects a surrogate of renal function and may not be indicative of tubular function or renal hemodynamics. Caution regarding the interpretation of rise in creatinine is warranted as it can be multifactorial. Azotemia is a common contributor and may be easily reversed by holding off diuretic therapy or maintaining

systemic blood pressures. Slight drop in renal function during initiation of drug therapy (particularly ACE inhibitors or mineralocorticoid receptor antagonists) did not translate into worse outcomes. At the other end of the spectrum, the loss in muscle mass with aging may also translate into diminishing glomerular filtration rate despite serum creatinine levels close to the normal range.

Thyroid Disorders—Metabolic abnormalities such as thyroid disorders have long been associated with the heart failure syndrome, and thyroid function testing has long been applied during the initial evaluation as well as the workup for unexplained decompensation or onset of atrial arrhythmia [11]. In the setting of longstanding amiodarone use, drug-induced thyrotoxicity also requires careful longitudinal monitoring. Isolated low triiodothyronine is often associated with poor metabolic states even in the absence of subclinical hypothyroidism, but targeted treatment has yet to demonstrate any benefits [12].

Iron Deficiency and Anemia—Anemia is prevalent in patients with heart failure, and has long been associated with poorer outcomes. However, it is not uncommon to see “transient anemia” that resolves over time [13]. Interestingly, when hemoglobin is targeted, as demonstrated in recent therapeutic studies, a substantial proportion of patients with chronic stable heart failure were found to have iron deficiency (e.g. low iron stores and ferritin, and low transferrin saturation) even in the absence of anemia [14]. Early replacement studies showed promise [15], and definitive studies to justify iron supplementation to improve heart failure morbidity and mortality are ongoing (Table 2).

Hepatic Dysfunction—Elevated liver function studies at presentation are also reflective of hepatic congestion and in the cold and wet patient, reflective of shock liver. Post hoc analysis of liver function tests and outcomes on patients enrolled in the EVEREST trial showed lower albumin and higher bilirubin levels to have a predictive value in mortality and rehospitalization [16]. Low albumin reflective of poor nutritional state has a determined prognostic implication in ADHF, and may also affect pharmacokinetics and drug delivery. Uric acid, another easily obtained marker, is often elevated in heart failure as a marker of oxidative stress, and early studies on oxypurinol benefiting those with elevated uric acids are being validated in an upcoming clinical trial [17, 18].

Biomarkers for Risk Stratification in Heart Failure

Risk stratification is by far the most common approval indication for heart failure biomarkers. In fact, almost all the biomarkers depicted in Fig. 1 have been established based on its prognostic value in heart failure. Notably, the majority of clinical studies evaluating the clinical relevance of biomarkers utilize the “guilt-by-association” approach, where prediction of future development of adverse clinical outcomes may or may not translate into actionable therapeutic maneuvers to alter the natural history. This is perhaps the biggest challenge facing healthcare providers in interpreting clinical evidence that appears robust yet difficult to translate when applying to patient care.

Natriuretic Peptides—The prognostic value of BNP and NT-proBNP are well-established and consistent across the spectrum of heart failure. The challenge, however, is to determine the degree of “modifiable” BNP or NT-proBNP levels where maximizing GDMT (which is a Class 1 indication in the clinical guidelines) continues to be the therapeutic goal [4]. At the same time in several post hoc analyses of treatment trials, there is also a discrepancy between BNP or NT-proBNP levels and the effectiveness of therapies. For example, lower rather than higher levels of NT-proBNP were associated with improved outcomes with rosuvastatin in stable heart failure [19].

Myocardial Necrosis—It has long been recognized that cardiac troponins are elevated in patients with advanced heart failure, and provide incremental prognostic value regardless of assay type [20]. It is particularly relevant in patients admitted for decompensated heart failure, yet the levels do not change dramatically [21]. Although cardiac troponins as markers of myocyte injury are measured routinely as above during the acute hospitalized phase, most of the patients with heart failure may have elevations of cardiac troponin by underlying mechanisms other than epicardial obstruction or stenosis [21]. There has been substantial consideration that subclinical myocardial damage or impaired renal clearance may play a role, either from diastolic load or microvascular ischemia [22•]. Nevertheless, a higher level signifies worse prognosis and a risk of rehospitalization or an adverse event independent of other biomarkers, whereas lower levels are shown to be associated with lower mortality in stable CHF patients [23]. However, once detectable, changes in troponin levels have relatively modest incremental value [24]. To date, few studies have indicated influence on any effects of GDMT on cardiac troponin values.

Renal Insufficiency—As stated, the presence of renal insufficiency significantly alters the natural history of heart failure, largely due to the inability to maintain euvolemia and leading to congestive signs and symptoms. Interestingly, transient changes in renal function may or may not be as prognostically salient, but long-term rise in blood urea nitrogen or serum creatinine are strong predictors of adverse clinical events even if they produce transient improvement [25–27]. Newer biomarkers of acute kidney injury have emerged in the heart failure arena, and several studies have demonstrated prognostic value of serum neutrophil gelatinase associated lipocalin (NGAL, commercially available in Europe and in some reference laboratories in the United States) [28–30] and cystatin C [31–33]. These seemed to be not too specific to myocardial dysfunction [34], yet the degree of rise in these biomarkers were lower than that observed in the classic acute kidney injury setting [35••]. Other heart failure biomarkers may also have a substantial dependency of intrinsic renal function than myocardial dysfunction, such as galectin-3 [36–39]. In fact, there was no substantial effect of GDMT on galectin-3 levels [40].

Meanwhile, the acute decompensated state is more often than not complicated by the cardiorenal syndrome. Elevated BUN and creatinine have an established association with worse in-hospital outcomes and long term mortality. This was systematically illustrated by the CART method in the ADHERE registry [41]. BUN and BUN/Cr ratio reflect the neurohormonal activation underlying pathophysiology of heart failure and are independent predictors of short and long term adverse outcomes and mortality when compared to the eGFR, yet not always predictive of therapeutic responses [26]. There appears to be a linear relationship between BUN and outcomes as studied in ASCEND –HF where a lower level of BUN was a marker of early dyspnea relief and improved short term outcomes [42, 43]. On the other hand, worsening or high BUN levels during hospitalization have a poorer prognosis as analyzed in studies including the PROTECT in-hospital risk model [44] and OPTIME-CHF risk model [45].

Hyponatremia—Hyponatremia (often with serum sodium <135 mEq) is more commonly observed in advanced heart failure and is an indicator of dysfunction salt and volume homeostasis [46–48]. While hypervolemic hyponatremia is the most commonly associated form, the added side effect of diuretic therapy in turn leading to it makes it a difficult to treat entity. Targeting hyponatremia has been the therapeutic goal of the drug class of vasopressin receptor antagonists (e.g. tolvaptan, conivaptan), yet their long-term benefits remain to be defined despite adequately correcting hyponatremia [49, 50].

Inflammation—There have been extensive descriptions regarding the association of systemic inflammation with the heart failure syndrome and there are increasing inflammatory markers in clinical development [51–53]. One of the earliest observations regarding the potential use of heart failure biomarkers is the detection of diminished erythrocyte sedimentation rate (ESR) as heart failure worsens but rises upon improvement [54]. Interestingly, this is likely a result of stabilization of hemodynamics and subsequent studies revealed that higher ESR was actually associated with poor outcomes [55, 56]. Intriguingly, those with fulminant myocarditis (including cardiogenic shock) may have more favorable long-term outcomes if surviving the acute episode when compared to those with chronic but persistent myocarditis. Many other inflammatory and oxidative stress (yet clinically available) markers have subsequently demonstrated notable prognostic value in the setting of heart failure - C-reactive protein, myeloperoxidase, soluble ST2, and galectin-3 to name a few [57–63]. However, targeting specific inflammatory pathways (such as anti-tumor necrosis factor alpha antagonists) have yet to demonstrate any improvement long-term outcomes in stable heart failure patients, and may even lead to unwanted adverse effects. Taken together, the contribution of inflammation to heart failure is complex, and in some instances may indeed represent a consequence rather than cause of heart failure progression. That said, appropriate attenuation of inflammatory responses remains a promising and notable therapeutic goal that needs further investigations.

Metabolic Markers—Interestingly, reverse epidemiology holds true for metabolic markers in which a “paradox” is observed. In advanced heart failure, low rather than high levels of cholesterol and apolipoproteins are often associated with poor long-term prognosis [16, 64].

Establishing the Vulnerability of Heart Failure

Multiple biomarkers have been evaluated to assess the utility in predicting the incidence of heart failure. Of these only NT-proBNP and urinary albumin-to-creatinine ratio showed consistent incremental value in heart failure risk, while several other clinically available inflammatory and renal biomarkers showed promise [65, 66]. A recent randomized control trial STOP-HF used BNP levels as a screening test to establish collaborative care showed reduced incidence of LV dysfunction and heart failure [67]. Albuminuria has shown to have a significant association with heart failure incidence in some studies, with the ARIC study shedding particular light on the independent association even in the absence of hypertension, diabetes mellitus, or chronic kidney disease [68–70]. Screening and treatment for albuminuria, although well established as a biomarker for hypertensive and diabetic renal disease, remains a topic of study to determine if a cost effective way of screening the at-risk general population could be sought in the light of preventing heart failure and kidney disease. If it does get established, whether normotensive non-diabetic albuminuric patients can be effectively treated with renin-angiotensin aldosterone receptor blockade would also be an important question to be looked into. Glycated hemoglobin, a marker of glycemic control, may provide predictive value in the development of and hospitalization for heart failure [71, 72].

Biomarkers for Therapeutic Guidance in Heart Failure

By far the most common biomarkers utilized in monitoring and therapeutic guidance in heart failure are electrolytes and renal markers to monitor adverse consequences of GMDT. Potassium abnormalities and renal insufficiency remain the two most common parameters for serial monitoring. Clinical guidelines for specific medications (such as mineralocorticoid receptor antagonists) mandate judicious monitoring and careful titration following drug initiation [4]. Optimization of electrolyte levels during diuretic therapy helps prevent the

occurrence of arrhythmias and tailor intensity of diuresis. Interval measurements of these standard chemistry tests have also been endorsed on routine follow up visits particularly in those receiving diuretic therapy to maintain euvolemia, even though prospective validation of such approaches is not available [4].

The logical extension of natriuretic peptide testing beyond establishing diagnosis and prognosis is the potential ability of natriuretic peptide testing in guiding therapy either at the time of discharge or in an ambulatory care setting. Instead of tracking clinical status, a set threshold for therapeutic target has been sought, in the same manner as many chronic diseases such as diabetes mellitus, hypertension, or hyperlipidemia. There have now been several of such trials conducted in a prospective, randomized manner (among which one actually is a blinded study which is a quite extraordinary prospective strategy-testing study). Overall, the safety of natriuretic peptide testing to guide medical therapy is well established as none of the trials showed higher adverse events as critics may have warned early about overzealous decongestive therapy. However, the overall results remained mixed. The most definitive study to date, BATTLE-SCARRED, showed overall improvement in outcomes with an NT-proBNP guided approach equivalent to guideline-based therapy, although the trend appeared to be more robust in those under 75 years of age [73]. The PROTECT study helped understand that NT-ProBNP guided management in the outpatient setting with a decrease in levels over time was associated with an improvement of overall outcomes in terms QOL, rehospitalization, echocardiographic improvement of LV dimensions, not only in the younger patients, but also in those over 75 years of age [74]. In contrast, the TIME-CHF and some other studies yielded negative results [75], thus calling for further investigations. It is important to point out that while several biomarkers have demonstrated important prognostic values in the ADHF setting, few actually are broadly use to guide management. The only reliable study that may point to triage potential is that predischarge BNP levels may predict those that may have higher risk of readmissions, and thus follow-up and aggressiveness of care can be better tailored accordingly [76].

Biomarkers for Establishing Mechanism in Clinical Practice

The conundrum of incorporating biomarkers into clinical practice has been the lack of data to support informed decisions based on biomarker levels to triage therapeutic interventions. Existing biomarkers in heart failure have yet to provide sufficient confidence to distinguish “responders” versus “non-responders.” Furthermore, the benefits of guideline-directed medical therapy in heart failure have been established by rigorously-conducted large multi-center randomized clinical trials that demonstrated favorable impact on morbidity and mortality. The role of specific biomarkers to define a disease mechanism (so-called stratified medicine or precision medicine) is evolving, and has been successfully deployed in other medical fields, and even within specific areas in cardiology (e.g. antiplatelet therapy in acute coronary syndromes with positive cardiac troponin). Recently, a unique example of discovering a pathophysiologic mechanism of peripartum cardiomyopathy has emerged, whereby a truncated prolactin molecule produced during late term and post-delivery may lead to progressive microvascular dysfunction and may be amenable to targeting prolactin production by bromocriptine [77, 78]. Hence, the ability to measure such protein fragments may pave a way to a more targeted therapeutic approach.

While biological defects remain the primary targets of therapeutic intervention, caution should be exercised if the characteristic of the biomarkers of interest is not well defined. The concept of “worsening renal function” is an excellent example to illustrate this point. For decades, a rise in serum creatinine in the setting of acute decompensated heart failure is often attributed to poor outcomes, leading to the belief that preventing renal dysfunction by reducing the incidence of this creatinine rise will be therapeutically beneficial [79, 80].

During the last decade, therapeutic strategies targeting this have not fulfilled the promise. Recent exploration of this concept has led to the revelation that such changes may also depend on the ability of the kidneys to diuresis, and that adequate decongestion despite rise in serum creatinine may not lead to adverse outcomes [27, 81].

Conclusion

Despite robust studies on biomarkers, heart failure has always and still continues to be a clinical diagnosis, although the subjective nature of the patients' self-reported symptoms often complicates the scenario. While a simple blood test cannot replace a clinician's judgment, it can certainly, in the appropriate circumstances, aid in cost effective care. As with any new test or procedure, the newer biomarkers will have to be proved as easily available, cost effective and beneficial in terms of mortality, morbidity and health related quality of life. Prognostically, they certainly seem interdependent with an additive value. We have to realize that forecasting the course of heart failure involves a fine balance between therapeutic interventions and patient tolerability. Although biomarkers show much promise as therapeutic targets, the picture needs to be considered as a whole to determine the feasibility in an era of cost effective medicine. The ideal focus would be if we have to our disposal reliable and effective markers at the stage of prevention so we can curb the very occurrence of this progressive syndrome.

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Fig. 1. Clinically available biomarkers for Heart Failure. Reprinted from *JACC: Heart Failure*, Braunwald E, "Heart Failure," 2013; 1(1): 1-20, with permission from Elsevier

Fig. 2. Relative diagnostic accuracies of natriuretic peptide testing [3, 82, 83]

Table 1
Clinical guideline recommendations for biomarker testing in heart failure

Biomarker, Application	Setting	COR	LOE
Natriuretic peptides			
Diagnosis or exclusion of HF	Ambulatory, Acute	I	A
Prognosis of HF	Ambulatory, Acute	I	A
Achieve GDMT	Ambulatory	IIa	B
Guidance of acutely decompensated HF therapy	Acute	IIb	C
Biomarkers of myocardial injury			
Additive risk stratification	Acute, Ambulatory	I	A
Biomarkers of myocardial fibrosis			
Additive risk stratification	Ambulatory	IIb	B
	Acute	IIb	A

Abbreviations: HF = heart failure; GDMT = guideline-directed medical therapy; COR = class of recommendation; LOE = level of evidence

Data from *Journal of the American College of Cardiology*, Yancy CW, et al., "2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines," (DOI:10.1016/j.jacc.2013.05.019) ©2013, with permission from Elsevier

Table 2
Commonly available biomarkers in heart failure

Biomarker	Diagnosis of HF	Risk stratification	HF therapy guidance
Electrolyte disturbances			
Sodium	-	+++	+
Potassium	-	++	++ (electrolytes)
End-organ function			
Creatinine/eGFR	-	+++	+
BUN	-	+++	+
Cystatin C	-	+++	+
Bilirubin	-	+++	+/-
Albumin	-	+++	+/-
Comorbid conditions			
Hemoglobin	-	+++	++ (anemia)
RDW	-	+++	+
TSH	-	+	++ (thyroid disease)
Hemoglobin A1c	-	+	++ (diabetes mellitus)
C-Reactive Protein	-	++	+/-
Cardiac-specific			
BNP/NT-proBNP	+++	+++	++
Cardiac troponin	++	+++	+

eGFR = estimated glomerular filtration rate; BUN = blood urea nitrogen; RDW = red cell distribution width; TSH = thyroid stimulating hormone; BNP = B-type natriuretic peptide; NT-proBNP = aminoterminal pro-BNP