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The Indian Consensus Document on cardiac biomarker

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ABSTRACT

Despite recent advances, the diagnosis and management of heart failure evades the clinicians. The etiology of congestive heart failure (CHF) in the Indian scenario comprises of coronary artery disease, diabetes mellitus and hypertension. With better insights into the pathophysiology of CHF, biomarkers have evolved rapidly and received diagnostic and prognostic value. In CHF biomarkers prove as measures of the extent of pathophysiological derangement; examples include biomarkers of myocyte necrosis, myocardial remodeling, neurohormonal activation, etc. In CHF biomarkers act as indicators for the presence, degree of severity and prognosis of the disease, they may be employed in combination with the present conventional clinical assessments. These make the biomarkers feasible options against the present expensive measurements and may provide clinical benefits.

1. Introduction

A variety of circulating molecules referred to as biomarkers have been introduced in clinical cardiovascular research, including heart failure (HF) research, because of basic science discoveries and technological progress in the last decade. Research papers related to biomarker research in HF have been exponentially circulating over the last decade (Fig. 1). The dissemination of knowledge about biomarkers in HF clinical practice, however, is limited mostly to diagnostic uses of B-type natriuretic peptide (BNP) or its precursor fragment, N-terminal prohormone of brain natriuretic peptide (NT-proBNP). Biomarkers in circulation include a variety of molecules that range from traditional protein-based markers to newer markers and micro RNAs. Protein markers in circulation typically comprise hormones and prohormones with vasoactive properties which include natriuretic peptides

Abbreviations: BNP, B-type natriuretic peptide; HF, heart failure.

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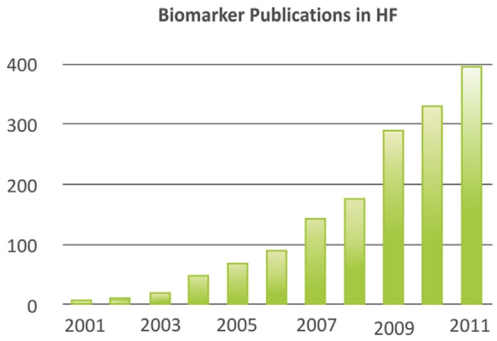


Fig. 1 – "Biomarker" and "Heart failure" articles published from 2001 to 2011.[1]

(NPs), endothelin, mid-regional pro-adrenomedullin, and C-terminal provasopressin (copeptin); structural proteins which include troponins; and various proteins with enzymatic activities which include myeloperoxidase and galectin-3. The current status of biomarker application for diagnosis and management of HF is confusing. A general framework proposed for cardiovascular biomarkers exists and this framework can help to identify the challenges of biomarker adoption for risk prediction, disease management, and treatment selection in HF.[1]

2. Pathogenesis of heart failure

Heart failure is a multi-factorial disease with causes varying in different parts of the world. Minimum 50% of the patients with HF have a reduced ejection fraction (REF) i.e. HF-REF which is the most understood type of HF in terms of the disease pathophysiology and treatment. In approximately two-thirds of cases of systolic HF, coronary artery disease (CAD) is the cause, although hypertension and diabetes are probable contributing factors in many cases. Other factors responsible for HF include a history of viral infections (known or unknown), chemotherapy (e.g., doxorubicin or trastuzumab), alcohol abuse, and 'idiopathic' dilated cardiomyopathy (in some of the cases the cause may be genetic).[2]

The epidemiological profile in HF with preserved ejection fraction (HF-PEF) seems to be different from epidemiological and etiological profile in HF-REF. The patient with HF-PEF is older, and more often female and obese than those with HF-REF. They are less likely to have coronary heart disease and more likely to have hypertension and atrial fibrillation (AF). As compared to patients with HF-REF, the patients with HF-PEF have better prognosis.[2]

When LV systolic function is reduced, the maladaptive changes occur in surviving myocytes and in extracellular matrix after myocardial injury (e.g., myocardial infarction) that lead to pathological 'remodeling' of the ventricle with dilatation and impaired contractility, one measure of which is a reduced EF. In cases of unmanaged systolic dysfunction, there is progressive worsening of these changes over time with an increased enlargement of the left ventricle and declining EF, the patient may be symptomless initially.[2]

This progression occurs due to two mechanisms, of which the first one is occurrence of further events leading to additional myocyte death (e.g., recurrent myocardial infarction). The second mechanism is the systemic responses that are induced by the decline in systolic function, particularly neurohumoral activation. The renin-angiotensin-aldosterone system and sympathetic nervous system are the two key neurohumoral systems activated in HF. These systemic responses cause further myocardial injury; leading to detrimental effects on the blood vessels, kidneys, muscles, lungs, and liver; and form a pathophysiological 'vicious cycle', responsible for various clinical features of the HF syndrome, including myocardial electrical instability.[2]

The basis of much of the effective treatment of HF is interruption of these two key processes. The aforementioned changes are associated with the clinical development of symptoms and worsening of these over time. This results in reduced quality of life, degrading functional capacity, recurring frank decompensation episodes leading to hospitalization and premature death, commonly as a result of arrhythmias or pump failure. These patients have a limited cardiac reserve which also is dependent on atrial contraction, synchronized contraction of atria–ventricles and a normal interaction between the right and left ventricles.[2]

Acute decompensation can result from intercurrent events affecting any of these [e.g., the development of AF or conduction abnormalities, such as left bundle branch block (LBBB)] or imposing an additional hemodynamic load on the failing heart (e.g., anemia). The outcome of HF patients can be improved with effective treatment, with a relative reduction of 30–50% in hospitalization in recent years, and small but significant decrease in mortality.[2]

3. Incidence of heart failure: Indian scenario

Framingham study was a landmark study indicating that the incidence of CHF increases with age and is higher in men than in women. Although data on incidence of HF from India are scarce, a 2013 study from India was conducted to measure the burden of disease. This study was conducted in southern India and it was found that 258 males (82%) and 137 females (73%) had left ventricular HF predominantly, as compared to biventricular HF. In this study, an interesting feature noted was that multi-factorial cause was the commonest etiology for CHF with CAD being the single most common factor contributing to 66% of cases of HF. Out of all cases of CAD in this study, 66% cases of HF were men and 34% were women.[3] Coronary artery disease in the Framingham study, accounted for only 46% of cases of HF in men and 27% of chronic HF cases in women. Following CAD, hypertension was the leading factor accounting for 65.6% of cases in this study, while 45.8% of the population was diabetic. They are, however, not mutually exclusive. In the Indian study, it was also found that myocardial infarction in siblings was a significant risk factor. 69% of the patients in the present study had hypertension; among them 61% were males and 39% were females. There were 310 (62%) males and 190 (38%) females. The highest incidence of HF was observed between 50 and 70 years in both males and females. The researchers from the Indian study

found that major etiology of CHF was a combination of CAD, hypertension and diabetes mellitus, accounting for 23.4% of the cases. The single commonest etiology for HF was CAD.[3]

4. Multiple biomarkers used in heart failure – clinical implications

Heart failure progression is complex and is driven by various biological processes that include inflammation, oxidative stress, neurohormonal activation, vascular remodeling, myocyte injury, and renal impairment. Interest is increasing in the measurement of a diverse biomarker profile, reflective of the underlying biology of HF, in order to risk stratify patients and provide a better understanding of the underlying pathophysiology. A recent study attempted to evaluate the predictive utility of 8 biomarkers, each reflective of varied biological pathways in HF: troponin I (TnI) (myocyte injury), high-sensitivity C-reactive protein (hsCRP) (inflammation), B-type natriuretic peptide (BNP) (neurohormonal activation), uric acid and myeloperoxidase (MPO) (oxidative stress), soluble toll-like receptor-2 (ST2) (myocyte stress), creatinine (renal function) and soluble fms-like tyrosine kinase receptor-1 (sFlt-1) (vascular remodeling), in a multicenter cohort of 1513 ambulatory chronic HF patients.[4]

The researchers hypothesized that a biomarker score summarizing the activity of multiple pathways implicated in HF would improve the ability to classify risk of adverse outcomes for ventricular assist device placement, cardiac transplantation, or death compared with a validated clinical risk prediction algorithm, the Seattle Heart Failure Model (SHFM).[4]

A median follow up was done at 2.5 years and it was found that there were 317 outcomes: 187 patients died; 99 were transplanted; and 31 had a VAD placed. The patients in the highest tertile of the multi-marker score had a 13.7-fold increased risk of adverse outcomes compared with the lowest tertile. The results from this study were in congruence to the Braunwald's hypothesis in 2008 that multiple biomarkers in combination, when classified into categories based on their pathophysiologic effects in HF, would provide a valuable means for risk stratification. A multi-marker score of biomarkers, reflective of diverse biological axes, is a strong predictor of risk and has significantly improved the prediction of outcomes compared with the most commonly used clinical risk score in HF, the SHFM.[4]

The patients who were in the highest multi-marker tertile had around 14-fold unadjusted risk of death, transplant, or VAD placement compared with the lowest tertile. This risk remained nearly 7-fold after adjustment for the SHFM. A substantial ability to discriminate individual patient risk at 1 year was shown by the multi-marker score that was again superior to the SHFM. Multi-marker score in addition to the SHFM appropriately reclassified a large proportion (24.1%) of patients as higher risk.[4]

From these findings, it is evident that multiple biomarkers are useful as a part of an algorithm for assessing prognosis in HF. A score derived from multiple biomarkers, integrating diverse biological pathways in ambulatory chronic HF patients, substantially improves prediction of adverse events beyond current metrics.[4]

5. Natriuretic peptides in heart failure – relation to clinical outcomes (evidence review)

Over the last decade introduction of BNP started a new paradigm in the use of biomarkers in the evaluation and management of HF. B-type natriuretic peptide and NT-proBNP belong to a family (Fig. 2) of naturally occurring hormones known as NPs. High plasma BNP and NT-proBNP levels, synthesized in the cardiac ventricles, are very specific for elevated filling pressures in the patients with left ventricular dysfunction, and can provide relatively reliable diagnostic and prognostic information.[5]

5.1. *Evidence review*

Plasma BNP and NT-proBNP have been studied mostly as diagnostic tools in HF patients. Two prospective multicenter clinical trials established the role of BNP and NT-proBNP testing in the initial evaluation of the HF patients.[5]

In the multicenter *Breathing Not Properly Study*, using plasma BNP level of 100 pg/mL as "cut off" gave a sensitivity of 90%, specificity of 76% and a diagnostic accuracy of 81% which was superior to clinical assessment alone in a series of 1586 patients presented to the emergency department (ED) with acute dyspnea.[5] Randomized controlled trials comparing a diagnostic strategy involving plasma BNP testing versus clinical assessment alone, plasma BNP testing in the ED improved the diagnosis and treatment of patients with acute dyspnea and hence, reduced the time to discharge and the total expenditure of treatment.[5]

Angurana et al[7] measured BNP in 72 patients of HF with dyspnea. B-type natriuretic peptide helped to distinguish dyspnea of cardiac origin from non-cardiac causes. The mean BNP concentration in patients with CHF ($n = 44$) was found significantly higher than in patients without CHF ($399 + 289.2$ pg/ml versus $84.9 + 42.4$ pg/ml) ($p < 0.001$). Univariate analysis of plasma BNP level at different cut off levels revealed that a value of 175 pg/ml had a sensitivity of 81.8%, specificity of 96.4%, and accuracy of 87.5% for differentiating CHF from lung disease. Congestive heart failure could be predicted better by BNP measurements that added significant, independent explanatory power to other conventionally used clinical variables. The study suggested that rapid measurement of BNP could be a sensitive and specific test for

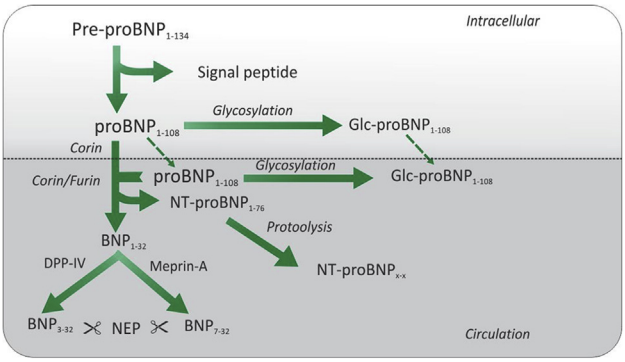


Fig. 2 – The processing cascade of natriuretic peptides.[6]

differentiating the patients with HF from those without, in an urgent care setting. Another study conducted by Krishna et al included monitoring of the BNP levels after coronary stenting in 100 patients suffering from acute coronary syndrome and noted a significant rise in BNP levels post stenting (Table 1).[5]

Recent ACS, angiographic thrombus, raised basal troponin, and presence of LV dysfunction were all associated with high baseline as well as post PCI BNP levels. Elevated BNP levels predicted recent ACS more accurately; in patients with chronic stable angina the BNP levels increased after PCI.[5]

5.2. *BNP guided therapy versus clinically guided therapy*

Randomized controlled trials were reviewed to produce a recommendation on the use of NPs in the monitoring of HF patients. The aim of the comparison was to review the emergence of new studies on the use of NPs in monitoring patients with HF. Three randomized trials compared BNP guided therapy to clinically guided therapy (Table 2).[5]

5.3. *NT-proBNP – relation to clinical outcome*

B-type natriuretic peptide is a member of a family comprising 4 NPs in human that share a common 17-peptide ring structure.[7] Before its activation, BNP is stored as a 108–amino acid polypeptide precursor, proBNP, in secretory granules in both ventricles and, to a lesser extent, in the atria. After proBNP is secreted in response to volume overload and resulting myocardial stretch, it is cleaved to the 76-peptide, biologically inert N-terminal fragment NT-proBNP and the 32-peptide, biologically active hormone BNP. Natriuretic peptide receptors and plasma end peptidases actively clear BNP from the circulation; the plasma half-life is thus short, approximately 20 min. No receptor-mediated clearance of NT-proBNP is known to occur, and NT-proBNP has a correspondingly prolonged half-life of 60–120 min. Thus, plasma NT-proBNP levels tend to be 3–5 times higher than BNP levels. B-type natriuretic peptide and NT-proBNP are generally accepted to be useful for the diagnostic evaluation of the patients with acute dyspnea. Elevated BNP or NT-proBNP levels is associated with increased cardiovascular risk as shown by a recent meta-analysis analyzing data from 40 long term prospective studies involving a total of 10,625 incident cardiovascular outcomes and 87,474 participants.[11]

5.4. *Interpretation and differential diagnosis of elevated natriuretic peptide levels*

Elevated concentrations of BNP or NT-proBNP are powerfully associated with the presence of HF; however, neither is 100% diagnostic for HF. The BNP as well as NT-proBNP levels may increase in different other disease states, and individual patient factors may influence results. Among the spectrum of HF syndromes, HF-PEF and systolic dysfunction may raise BNP or NT-proBNP levels; HF-PEF fraction may express lower levels of both peptides in comparison to HF due to systolic dysfunction. In addition, other relevant cardiac diagnoses, including right ventricular failure (due to primary cardiac pathology, or secondary to pulmonary embolism or pulmonary hypertension), valvular heart disease, and arrhythmias such as atrial fibrillation may cause elevation of BNP or NT-proBNP.[12]

Apart from cardiovascular variables, NP concentrations are influenced by renal dysfunction and advancing age that may generate higher values without overt HF; obesity on the other hand may result in unexpectedly lower NP concentrations, even in those with HF. To troubleshoot complex situations such as renal disease, adjustment in cut off points may help (Table 3).[12]

Another important situation is the patient with a gray zone BNP or NT-proBNP value. Approximately, 20% of the patients with acute dyspnea have BNP or NT-proBNP levels that are above the cut off point to exclude HF but too low to definitively identify it. Knowledge of the differential diagnosis of non-HF elevation of NP, as well as interpretation of the BNP (Fig. 3) or NT-proBNP (Fig. 4) value in the context of a clinical assessment is essential; gray zone values are not without prognostic meaning, however, and should be approached with caution.[13]

In the patients with significant renal failure (estimated glomerular filtration rate, 60 mL/min/1.73 m^2) and body mass index 35 kg/m^2 different decision limits must be used (see text).

Different decision limits must be used (see text).

Table 1 – B-type natriuretic peptide levels in post PCI patients.[5]

Pre PCI	Post PCI
Patients with baseline BNP levels>100 pg/ml	45% of patients with BNP >100 pg/ml
Patients with baseline BNP levels<100 pg/ml	20% of patients with BNP >100 pg/ml

6. BNP levels in renal impairment, obesity and gray zones

6.1. *Renal impairment*

There is a high coincidence rate of CHF and chronic kidney disease (CKD), also known as 'cardio–renal interaction'. Higher NP concentrations have been reported in HF patients who are also suffering from CKD. The values of NT-proBNP and glomerular filtration rate (GFR) have been noted to be inversely and independently related. In the patients with impaired renal function (GFR <60 ml/min/1.73 m^2), a higher NT-proBNP cut off point of 1200 pg/ml may effectively maximize sensitivity and specificity of HF diagnosis. So, in the case of CHF and CKD coincidence, classic NP guided algorithms may still be appropriate, though cut points need to be readjusted for renal function. A similar interaction has also been noted between BNP and GFR.[14]

6.2. *Obesity*

Natriuretic peptide values are remarkably lower in obese HF patients than in non-obese patients. But, the implications of these lowered concentrations are not yet well understood (Table 4).[15]

Table 2 – Trials comparing BNP guided therapy with clinically guided therapy.[5]

Study	Population	Intervention	Comparison	Implication
Beck-da-Silva, 2005[8]	■ (LVEF) of 40% or less ■ Symptomatic HF (New York Heart Association class II–IV) for at least 3 months or previous hospital admission due to HF ■ Age (mean): 65 years. ■ < 50% males	- β-blocker dosage up-titrated according to plasma BNP levels plus standard care	- β-blocker dosage up-titrated according standard care	A trend toward better quality of life was seen in the BNP group as compared to the clinically guided group
Jourdain, 2007 STARS-BNP[9]	■ Symptomatic (New York Heart Association functional class II–III) systolic HF defined by left ventricular ejection fraction (LVEF) <45% ■ Age (mean): 65 years ■ <50% females	- Medical therapy was increasingly used with the aim of lowering plasma BNP levels (target <100 pg/ml) - Each class of therapy modified according to the judgment of the investigator	- Medical therapy was adjusted on the basis of the physical examination and usual para clinical and biological parameters	BNP guided strategy reduced the risk of CHF-related death or hospital stay for CHF
Pfisterer, 2009 TIME-CHF[10]	■ Dyspnea (New York Heart Association class ≥II with current therapy), a history of hospitalization for HF within the last year ■ Age (mean): 76 years ■ <50% females ■ Age subgroups: <75 years; ≥75 years)	- BNP guided plus symptom guided medical therapy - Medical therapy to reduce BNP levels to 2 times or less than the upper limit of normal (<400 pg/ml in patients <75 years and <800 pg/ml in patients ≥75 years) and symptoms to NYHA class of II or less	- Symptom guided medical therapy - Medical therapy to reduce symptoms to NYHA class of II or less	HF therapy guided by N-terminal BNP did not improve overall clinical outcomes or quality of life compared with symptom guided treatment HF therapy guided by N-terminal BNP improved outcomes in patients aged 60–75 years but not in those aged 75 years or older

Table 3 – Suggested cut off points for BNP and NT-proBNP use in several situations.[12]

	Cutoff value pg/mL	Sensitivity %	Specificity %	PPV %	NPV %
To exclude ADHF					
BNP	30–50	97	62	71	96
NT-proBNP	300	99	68	62	99
To identify ADHF					
Single cut off point strategy					
BNP	100	90	76	79	89
NT-proBNP	900	90	85	76	94
Multiple cut point strategy					
BNR, gray zone approach	100 to exclude; 100–400: gray zone 400 to rule in	90 [a]	73 [a]	75 [a]	90 [a]
	450 for age 50 years	63	91	86	74
NT-proBNP, age-stratified approach	900 for age 50–75 years 1800 for age 75 years	90	84	88	66
Special situations: renal dysfunction (GFR 60 mL min 1.73 m^2)					
BNP	200	88	63	83	72
NT-proBNP	• 1200, all ages Or • Age-stratified approach, above	89	72	74	94
Obesity					
BNP	170 for BMI 25 kg/m^2	90	77	78	90
	110 for 8MI 25–35 kg/m^2	90	77	77	90
	54 for BMI 35 kg/m^2	91	70	70	91
NT-proBNP	900, no adjustment for BMI	87	76	79	90
	Age-stratified cut points, no adjustment for BMI	86	90	85	95

PPV indicates positive predictive value; NPV, negative predictive value; ADHF, acutely decompensated heart failure; BNP, brain natriuretic peptide; NT-proBNP amino-terminal pro-B-type natriuretic peptide; GFR, glomerular filtration rate; and BMI, body mass index.
[a] Indicates not applicable.

6.3. *Gray zone*

Identification of a single cut off point to empirically rule in or rule out every dyspneic patient with HF is a challenge. The clinically prevalent algorithms are non-specific and customarily inappropriate as 'black or white' diagnoses can't be made based on them. So, to adequately screen patients, two cut off points are necessary: one to effectively rule out HF in mildly dyspneic patients and eliminate unneeded hospitalizations, and another to rule in diagnosis and administer prompt, appropriate treatment. The 'gray zone' between these two cut off points in which NP concentrations cannot be utilized as summarily to guide management decisions is the problem area.[4] A gray zone NP value should not be considered entirely uninformative, though it is often not as revealing in HF diagnosis. Rather, an intermediate NP value indicates the need for further clinical examination, and may still aid in patient prognosis (Table 5).[14]

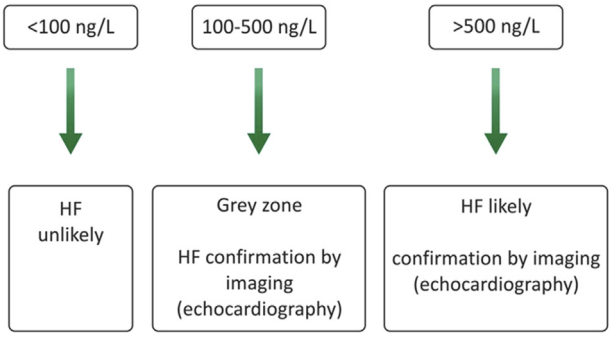
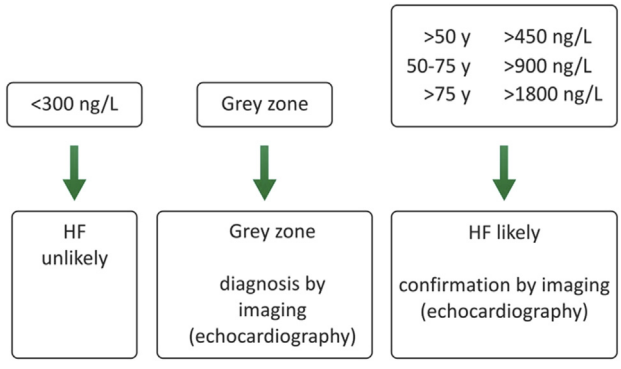


Fig. 3 – Brain natriuretic peptide interpretation in the patients with acute dyspnea without severe renal failure.[13]

7. Role of BNP testing in emergency department

Natriuretic protein assays should be used as tools and not as absolute thresholds for making decisions. A variety of



The use of age-adjusted NT-proBNP cut off values in the acute setting compensates only for minor renal dysfunction. In case of significant renal failure (estimated glomerular filtration rate, 60 mL/min/1.73 m^2)

Fig. 4 – N-terminal proBNP interpretation in the patients with acute dyspnea without severe renal failure.[13]

Table 4 – Interpretation of NP levels in special situations.[15]

Causes of elevated NP levels other than CHF
- LV dysfunction
- Previous heart failure
- Advanced age
- Renal dysfunction
- Acute coronary syndrome
- Pulmonary disease (e,g., acute respiratory distress syndrome, lung disease with right heart failure)
- Pulmonary embolism
- High output states (e.g., sepsis, cirrhosis, hyperthyroidism)
- Atrial fibrillation

NP levels lower than expected
- Obesity
- Flash pulmonary edema
- Heart failure etiology upstream from LV (e.g., acute mitral regurgitation, mitral stenosis)
- Cardiac tamponade
- Pericardial constriction

CHF, congestive heart failure; LV, left ventricle; NP, natriuretic peptide.

conditions other than CHF can lead to increased levels: acute coronary syndrome, pre existing structural heart disease, right ventricular strain, critical illness, or end-stage renal failure.[16]

B-type natriuretic peptide independently predicts high left ventricular end-diastolic pressure and capillary pulmonary artery pressure. These pressures correlate well to the NYHA (New York Heart Association) classification of severity of HF, and inversely correlate to left ventricular ejection fraction. It has been shown by some studies that BNP and NT-proBNP can reliably predict the presence or absence of left ventricular dysfunction on echocardiography in symptomatic and asymptomatic HF patients presenting to ED.[17]

Last decade has seen that BNP has the potential clinical usefulness for differential diagnosis of dyspnea and for risk stratification of the patients with CHF. The European Society of Cardiology Task Force has recommended that the algorithm for HF diagnosis should include an NP assay as the first step along with electrocardiography (ECG) and chest X-ray.[17]

The key symptom of CHF and of many other respiratory diseases, with high associated morbidity and mortality, is acute dyspnea. It is unfortunate to observe that emergency physicians' accuracy in diagnosing CHF is about 60%. In the EPIDASA study, conducted on patients older than 65 years with acute dyspnea, the in-hospital mortality was 16%, with a higher mortality (21%) in the patients with CHF. The treatment in ED was inappropriate in 32% patients, and led to a higher mortality, highlighting the importance of accurate diagnosis and early accurate treatment in the ED. The initial general practitioner diagnosis of HF was confirmed in only 34% of the cases in a prospective study in UK. The clinical indecision at the ED leads to inappropriate hospitalization and use of potentially dangerous therapy. The ED physician is uncertain of the diagnosis (intermediate probability) in one-third of patients.[18]

Many studies have evaluated and validated both NP in the diagnosis of CHF in acute dyspnea. Maisel et al[19] performed the largest studies for BNP and Januzzi et al[20] for NT-proBNP. Following few observations are worth noting from these studies:

- A BNP concentration >100 pg/mL is a strong independent predictor of CHF
- Accuracy of BNP (83%) was more than either the NHANES criteria (67%) or the Framingham criteria (73%), two commonly used sets of criteria for diagnosing CHF
- The diagnostic accuracy of BNP at a cut off of 100 pg/ml was 83.4%
- The negative predictive value of this threshold was particularly high (98%)

The patients who presented in the ED with dyspnea were included in the PRIDE (ProBNP Investigation of Dyspnea in the Emergency Department) study. N-terminal proBNP was found to be highly sensitive and specific for the diagnosis of acute CHF, with an optimal cut off of 900 pg/ml. The strongest independent predictor of a final diagnosis of acute CHF was increased NT-proBNP. Clinical judgment alone for diagnosing acute CHF was inferior to NT-proBNP testing alone.

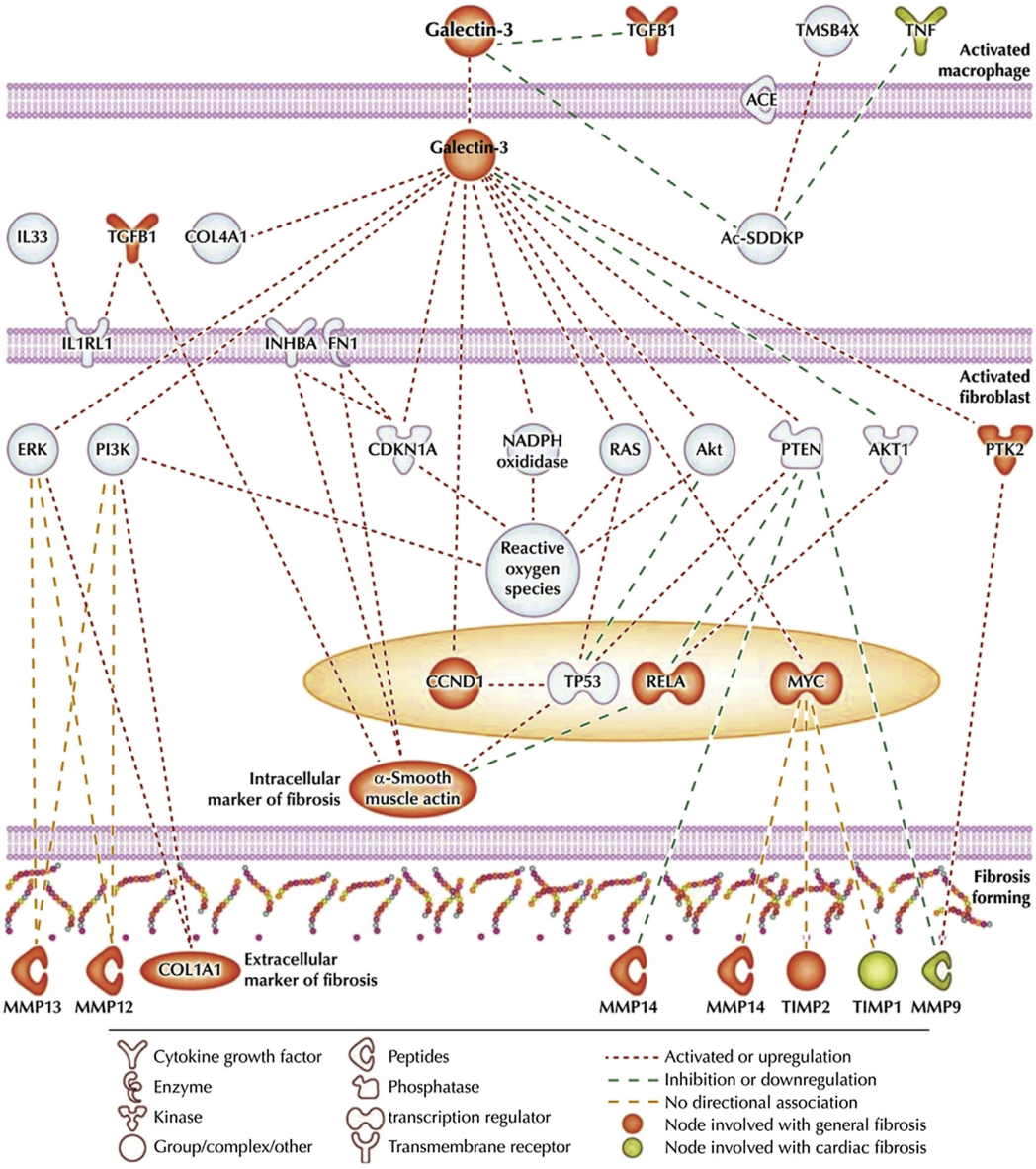
8. Neurobiomarkers in heart failure: galectin-3

Galectins are part of a family of lectins which bind β-galactosides. These galectins are expressed in vertebrates as well as in invertebrates and even in lower organisms, such as sponge

Table 5 – Diagnostic value of BNP (TriageBNP®): Study summaries.[21]

	Logeart[22]	Dao[23]	Lainchbury[24]	Maisel[19]	Ray[25]
Number of patients	166	250	205	1586	308
Mean age	67	ND	70	64	80
Acute CHF (%)	70	39	34	47	46
Male (%)	67	94	49	56	50
Threshold value (pg/ml)	300	100	208	100	250
Sensitivity (%)	88 [NA]	94 [89–97]	94 [NA]	90 [88–92]	78 [71–84]
Specificity (%)	87 [NA]	94 [89–97]	70 [NA]	76 [73–79]	90 [84–93]

MA: not available.
Grossly, the higher is the mean age of the population evaluated, the higher is the threshold value of BNP and NT-proBNP; 95% CI for sensitivity and specificity were given when available [CI].



The network represents molecular relationships among different gene products. Node shapes indicate the functional class of the gene product, whereas node colors indicate a role in general fibrosis (orange) or cardiac fibrosis (green). Edge colors indicate upregulation or activation (red), downregulation or inhibition (green), or involvement without clear directionality (yellow).

ACE, angiotensin-converting enzyme; AcSDKP, N-acetyl-Ser-Asp-Lys-Pro; AKT1, RAC-α serine/threonine-protein kinase; CCND1,cyclin D1; CDKN1A,cyclin-dependent kinase inhibitor 1A; COL1A1, collagen, type I, α-1; COL4A1, collagen, type IV, α-1; ERK, extracellular signal-regulated kinase; FN1,fibronectin 1; IL1RL1, interleukin 1 receptor-like 1; IL33, interleukin 33; INHBA, inhibin βA; MMP, matrix metalloproteinase; MYC, v-mycmyelocytomatosis viral oncogene homolog (avian); NADPH, nicotinamide adenine dinucleotide phosphate; PI3K,phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; PTK2, protein tyrosine kinase 2; TGFB1, transforming growth factor β-1; TIMP, tissue inhibitor of metalloproteinase; TMSB4X,thymosin β-4; TNF, tumor necrosis factor; TP53,tumor protein p53; RELA, V-relreticuloendotheliosis viral oncogene homolog A;NFKBIZ, nuclear factor of κ light polypeptide gene enhancer in B-cells 3.

Fig. 5 – Galectin-3 pathway.[27]

and fungus, which suggest an important role in biology. Presently, 15 members of the galectin family have been observed in vertebrates. In a seminal paper by Sharma et al[26] it was observed that galectin-3 is increased in decompensated HF. The authors of the paper opined that galectin-3 may be a factor that should be considered as a novel target for intervention in HF due to the observation that galectin-3 was upregulated well before the transition to overt HF.[24]

Galectin-3 has many effects in various organs. It has been shown that activated macrophages secrete galectin-3 in the failing or stressed heart. Increased expression levels of galectin-3 are associated with the tendency to develop decompensated HF, and in clinical cohorts, increased plasma galectin-3 levels are linked with worse prognosis. Consequently, galectin-3 may be proclaimed as a novel biomarker, but it may also be in the pathophysiologic circle of HF ("culprit biomarker"), and therefore it may also be a target for intervention. The suggested pathways of galectin-3 are displayed in Fig. 5.[26]

But, uncertainties are present in proclaiming galectin-3 as a novel biomarker. Regulation of galectin-3 is unknown at a transcriptional and translational level in the heart. It has been demonstrated in mechanistic studies that cardiac fibroblasts and macrophages are the main sources for galectin-3, and that the TGF-β/Smad pathway is involved. Regulation is also governed by inflammatory signals. But, it is confusing as to which signals govern the production and secretion of galectin-3. Also, proof-of-principle experiments (e.g., in galectin-3 deficient mice or in pharmacologic studies), to show that galectin-3 is unequivocally contributing to the onset and progression of cardiac remodelling are lacking. Again, data on therapeutic aspects involving galectin-3 expression and signaling are lacking.[26]

Available clinical data suggest that plasma and/or serum galectin-3 is increased in acute and chronic HF. Galectin-3 could be of value to predict prognosis in HF patients. Galectin-3 in clinical diagnosis and/or decision making is less convincing as we do not have enough data available to support the use of the same for this purpose.[27]

Studies have indicated that standard treatment of HF is related to lowering of galectin-3 expression and levels; it can be argued that galectin-3 could be a potential target for therapy. In few small trials, galectin-specific agents have been tested but these agents have not been evaluated in experimental or clinical HF. Results of studies testing targeted therapy against galectins should stress for their value in this devastating disease.[27]

9. Multi-marker strategy for complex patients

Heart failure is a major public health issue. In order to provide an accurate individualization of HF risk and care, the approach should include a profile of laboratory data, in addition to clinical and imaging data. It is clinically important to identify the most vulnerable patients, especially considering that many therapeutic interventions are available today. Although many novel biomarkers have been proposed and tested this goal has not been yet reached. The complexity of the biochemical network involved in the pathophysiology of HF suggests the ineffectiveness of a single marker to reflect all the features of this disease syndrome. Combining more markers would help in better characterization of HF patients and thus create newer options for treatment and identification of patients that need a close follow up.

The multi-marker approach, considering various biochemical pathways simultaneously, bases its robustness on a suitable choice of indices known to be individually associated with HF. Biomarker combination choice is essential to the performance of the multi-marker strategy.[28]

A major issue in choosing the biomarker profile is the proportional increase in financial burden. Hence, for cost effective evaluation, a biomarker combination has to be used. Heavily influence results would appear from statistical analysis and analytical performance of the different elements of the combination.[28]

10. Conclusion

Use of NT-proBNP or BNP for management of HF is warranted in view of the increasing prevalence of this serious condition and the need to consider a broadening spectrum of dysfunction for treatment. In addition, the complexity of treatment is increasing with a number of agents demonstrated as effective through randomized controlled trials. B-type natriuretic peptide and NT-proBNP have comparable clinical utility, and both help in excluding acute HF. Their use prior to discharge in hospitalized patients aids risk stratification. In addition, Galectin-3 may be a factor that should be considered as a novel target for intervention in HF due to the observation that galectin-3 was upregulated well before the transition to overt HF. There will be variable clinical expertise available to diagnose and manage the increasing cohort of HF patients with the passage of time, and an objective indicator to assist optimal prescription of medications is necessary. At present, plasma measurements of BNP or NT-proBNP, along with selective use of Galectin-3, constitutes the best candidate for this function.

11. Recommendations for physicians

B-type natriuretic peptide and NT-proBNP are not routinely used for bedside diagnosis of CHF. This testing is very much useful in the ED, particularly in patients presenting with dyspnea when one is uncertain regarding diagnosis of HF. Sometimes, there could be concurrence of CHF with respiratory failure or asthma like illness. In this scenario, serial measurements of cardiac biomarkers can help to diagnose as well as plan optimal therapeutic strategies in cases with CHF. The measurement of cardiac biomarkers also helps to predict the prognosis and optimal timing for discharging a patient.

B-type natriuretic peptide, in conjunction with Galectin-3, may be used to identify those patients at higher risk of readmission or death thus allowing the physician to better match the level of care to an individual patient's needs. These biomarkers are helpful to physicians, emergency physicians, and cardiologists in day-to-day practice.

Conflicts of interest

All authors have none to declare.

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