Healthy Heart

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Honorary Editor :
Dr. Urmil Shah

From the Desk of Hon. Editor:

We are all well verse with use of Troponin as a bio marker for diagnosis and prognosis of patients suspected of acute coronary syndrome. Similar to Acute Coronary Syndrome (ACS), heart failure continues to be a worldwide growing medical problem, associated with frequent re-admissions, high mortality, and a profound economic impact on health care systems. In the past decade, bio-markers have shifted the way in which heart failure is being managed by the cardiologist. The Natriuretic Peptides (NP) have proved extremely useful in determining whether acute dyspnoea has a cardiac aetiology or not. In addition, recent trials have demonstrated the use of natriuretic peptides in inpatient and outpatient prognosis, as well as in titrating medications in outpatients with chronic heart failure to prevent acute heart failure hospitalizations. Other emerging acute heart failure bio-markers include troponin, ST2. Let us understand natriuretic peptides - BNP / NT-proBNP as a bio-marker for managing patients of heart failures and also its role other cardiac conditions.

New Concept of BNP/NT-proBNP in Management of Heart Failure to Improve Outcomes

What is the role of biomarkers in Heart Failure (HF)?

All the most recent national and international guidelines recommend the Natriuretic Peptides (NPs), and in particular the peptides related to the B-type cardiac peptide hormone (such as BNP and NT-proBNP), as the first line biomarkers for the diagnosis of both acute and chronic Heart Failure (HF). Recent 2017 ACC/AHA/HFSA (Figure 1) guideline recommend the BNP and NT-proBNP measurement for the diagnosis or exclusion of HF in patients with acute dyspnea and de-compensated chronic or HF and also for prognosis of HF with the maximum degree of recommendation - class I. (with level of evidence A). Concentrations of the natriuretic peptides are typically higher in patients with HF (new-onset as well as de-compensated chronic HF) and higher values have reasonably high positive predictive value to diagnose HF whereas lower values confidently exclude the presence of HF. Importantly, higher concentrations of BNP and NT-proBNP are also strongly predictive of adverse outcomes in patients with HF; lower levels correlate with improved outcomes.

For a bio-marker to be useful it must not have only prognostic value but, it should optimally be predictive of therapy response also. The elevated natriuretic peptides value not only identify a patient whose prognosis is bad, but can guide the therapy (Guide-IT) to improved outcome (Figure 2). NPs guided HF therapy is Class IIb indication at present .

2017 ACC/AHA/HFSA HF Guidelines — Figure 1

2017 Heart Failure Clinical Practice Guidelines

Indication	Class	LOE
NPs for diagnosis	I	A
NPs for prognosis	I	A
NPs for predischarge risk assessment	IIa	B-NR
NPs to prevent HF onset	IIa	B-R
NPs to guide HF therapy	IIb	B-NR
Fibrosis/Injury Markers for risk assessment	IIb	B-NR

GUIDE-IT *Outcomes* — Figure 2

Endpoints	NT-proBNP-Guided Strategy vs Usual Care HR (95% CI)	p
Primary endpoint*	0.98 (0.79, 1.22)	.88
CV death	0.94 (0.65, 1.37)	.75
Death by any cause	0.86 (0.62, 1.20)	.37

*First HF hospitalization or CV death.
Felker G, et al. JAMA. 2017;318:713-720

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Could you elaborate on the interaction of biomarkers with HF management ?

Figure 3

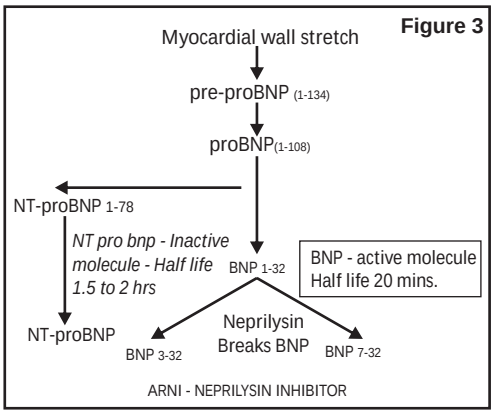
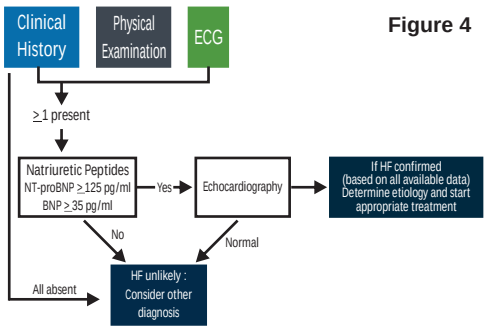


Figure 3 is a schematic presentation of how NPs are produced and released in patients with HF. Increased ventricular wall stretch is the primary inciting event causing a cascade of biomarker release which can be measured to monitor disease severity and ongoing myocardial insult, a quantitative marker of HF. Pro-BNP cleaved in to Active BNP & Inactive NTpro BNP in 1:1 molar ratio Natriuretic peptide levels are best interpreted as a continuous variable. The higher the value, the greater the likelihood that the dyspnoea is due to heart failure. The clinical implications of natriuretic peptide use in AHF revolve around their ability to differentiate cardiac dyspnoea from non-cardiac dyspnoea. NPs levels have been shown to correlate with New York Heart Association (NYHA) functional classes and are inversely related to the calculated EF of the LV. Moreover, BNP levels directly correlate with the measured pulmonary capillary wedge pressures, thus providing an almost accurate estimation of LV systolic dysfunction. Similarly, NTproBNP levels are fast gaining a stronghold in the management and diagnosis of heart failure patients. With a longer half-life when compared to BNP, NT-proBNP survives longer in the plasma and provides similar information regarding heart failure severity and disease progression. Elevated BNP and NT-proBNP reflect a wide array of cardiac pathophysiology such as diastolic function, right ventricular size and function, valvular heart disease, Increase filling pressures, heart rhythm disturbance , and coronary Ischemia. Although natriuretic peptide levels are unable to distinguish systolic from diastolic heart failure, recent ESC guideline (Figure 4) recommend use of bio-marker NPS even before ECHO cardiography and advocate doing ECHO Cardiography to identifies patients of heart failure with preserved systolic function or with reduce systolic function.

Diagnostic Algorithm for a Diagnosis of HF of Non-Acute Onset - ESC Guideline - 2016

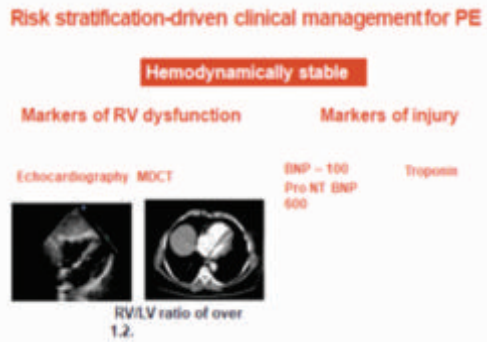
Figure 4



Thus, their use has gained widespread acceptance as standard of care for the management of heart failure patients, also for many other cardiac conditions.

NPs are useful for risk stratification in patient with sub-massive pulmonary embolism (Figure 5), patient with Idiopathic Pulmonary Hypertension and Acute Coronary Syndrome

Figure 5



The reference values of Brain-type Natriuretic Peptide (BNP) and N-Terminal (NT) proBNP are different to exclude or confirm a diagnosis of heart failure. These values also depend on age and gender and are higher in elderly persons and women.

In general, the following cut off values may be employed for acutely dyspneic patients:

BNP

< 100 pg/mL - HF unlikely

>400 pg/mL - HF likely

100-400 pg/mL - Use clinical judgment

NT-proBNP

< 300 pg/mL - HF unlikely

Age < 50 years, NT-proBNP >450 pg/mL - HF likely

Age 50-75 years, NT-proBNP >900 pg/mL – HF likely

Age >75 years, NT-proBNP >1800 pg/mL – HF likely

Co-morbidities can also influence the interpretation of biomarkers. For example, patients with abnormal renal function and atrial fibrillation typically have higher levels of BNP and NT-proBNP, while obesity decreases the levels of these markers. Because bio-markers can be influenced by co-morbidities, we should be very careful interpreting bio-marker in these associated co-morbid condition a specially atrial fibrillation and altered renal function.

Conditions associated with elevated BNP other than CHF are as follows:

- Acute Renal Failure and Chronic Renal Failure
- Accelerated Hypertension (HTN)
- Pulmonary Diseases such as

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Pulmonary Hypertension, severe Chronic Obstructive Pulmonary Disease (COPD), Pneumonia, Pulmonary Embolism, Adult Respiratory Distress Syndrome (ARDS)

- Cardiac causes -Myocardial Infarction, Atrial Fibrillation, Acute Coronary Syndrome, Cardioversion, Valvular Heart Disease, Myocarditis
- Older age
- Female sex
- Liver cirrhosis
- Hyperthyroidism
- Sepsis
- Chemotherapy

Conditions associated with lower than expected BNP are as follows:

- Obesity
- Flash Pulmonary Edema
- Pericardial Constriction

Do the newly available HF treatments, valsartan / sacubitril and ivabradine, impact biomarker use?

Ivabradine should be considered to reduce the risk of HF hospitalisation and cardiovascular death in symptomatic patients with LVEF $\leq$ 35%, in sinus rhythm and a resting heart rate $\geq$ 70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACEI (or ARB), and an MRA (or ARB). Ivabradine used in this group of patient cause a modest reduction in NT-proBNP levels, which correlates with the degree of heart rate reduction and clinical improvement.

Sacubitril /valsartan (ARNI) is recommended as a replacement for an ACEI to reduce further the risk of HF hospitalisation and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEI, a beta-blocker and a MRAa. Sacubitril / valsartan, an angiotensin receptor-neprilysin inhibitor, has shown superior efficacy to an Angiotensin-Converting Enzyme (ACE) inhibitor in reducing the risks of death and of hospitalization for HF in patients with HFrEF. In the pivotal PARADIGM HF trial, patients treated with sacubitril / valsartan also had a rapid and sustained reduction in NT-proBNP levels compared with patients treated with the ACE inhibitor alone. In addition, a modest increase in BNP level was also seen in patients treated with the drug. The reason for the differential effect on BNP and NT-proBNP levels relates to the mechanism of action of sacubitril (Figure 3). Sacubitril inhibits the breakdown of vasoactive peptides, including Atrial Natriuretic Peptide (ANP), BNP, and C-type natriuretic peptide; in contrast, NT-proBNP is not a substrate for neprilysin. Consequently, endogenous levels of BNP are elevated due to effects of the drug, while NT-proBNP concentrations are unaffected by the direct action of sacubitril. Accordingly, the decrease in NT-proBNP seen with treatment is, in fact, a reflection of the treatment effect of sacubitril / valsartan on the heart. Recently Completed pioneer HF study also showed significant alteration in NPs when Sacubitril /valsartan is used

Where are we in terms of biomarker testing and management of patients with acute HF?

Given the impact of acute HF on the healthcare system, there is a need for biomarker testing to help improve diagnostic accuracy and understand acute prognosis, inpatient HF care, and outcomes of patients with decompensated HF. During the course of inpatient acute HF management, there is often a significant reduction in concentrations of NPs. These reductions are accompanied by better outcomes. Conversely, patients with worse outcomes typically do not have a significant reduction in their biomarker concentrations. This has led to the idea of using biomarkers to gauge a patient's risk at hospital discharge. Both the decrease in natriuretic peptide level from admission level as well as the absolute discharge value are prognostic, with the latter being the more prognostic than the admission level. A relative decrease of less than 30% (Figure 6) in natriuretic peptide level is generally associated with bad short-term prognosis. Careful followup is needed in this group of patients

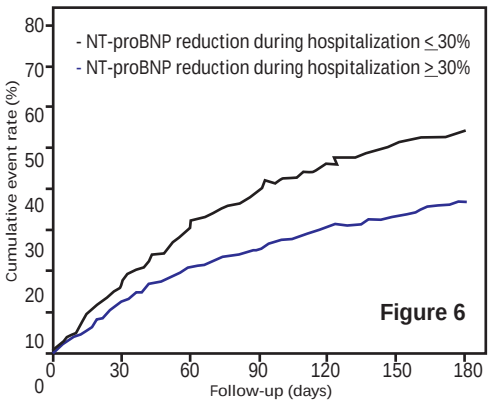


Figure 6

With careful disease management, many patients experience stabilization of HF in the outpatient setting. What are the clinical considerations in evaluating - managing optimally these stable patients at follow-up ?

Stability in HF is an ephemeral concept. Patients who are asymptomatic or mildly symptomatic and who have not been recently hospitalized might be considered stable, but remain at risk for

adverse events. In the recently completed PARADIGM-HF trial, at 1 year nearly 8 to 10% of patients have cardiovascular death or HF hospitalization despite optimal medical treatment in this kind of relatively stable patient.

A key clinical consideration in stable patients is recognizing that these patients have some degree of unattended residual risk that may not be revealed by their professed symptom burden or quality of life - NP Level may additionally help in identifying this high risk group patients. The time when patients are stable is the time to consider optimization of their long-term HF regimen in order to provide them with the best possible long-term outcomes. Optimization generally refers to initiation and titration of established GDMTs (such as an ACE Inhibitor, Aldosterone Receptor Blocker (ARB), beta blocker, or aldosterone antagonist), but also requires integration of novel therapies, such as sacubitril / valsartan and ivabradine (Figure 7). There is also the need to reconsider and intensify device-based therapies, including defibrillators and cardiac resynchronization devices, which have been shown to provide benefit even in these more stable populations.

Aren't NT-proBNP and BNP levels How can you help patients recognize worsening HF in advance of readmission?

There are a number of things that are important in helping patients take control of their disease. Weight-based monitoring for assessing recurrence of congestion, despite having limitations, remains an important indicator of worsening HF, in the absence of invasive hemodynamic measures or device-based assessments. Patients should be encouraged to self-monitor their weight on a daily basis and inform their clinicians if there is rapid weight gain, which may be a sign of fluid changes, or rapid weight loss, even in the absence of worsening symptoms. Volume overload and congestion are much easier to manage when they are modest than when they are advanced.

It is also important to encourage patients to report sentinel symptoms, including chest discomfort, worsening palpitations, new exertional symptoms, progressive dyspnea, worsening lower extremity edema, and or abdominal girth. All of these signs/symptoms along with frequent checking of biomarker NPs are critical, because if patients wait too long, they end up presenting at the emergency department, where they are likely to be admitted & carries very high risk.

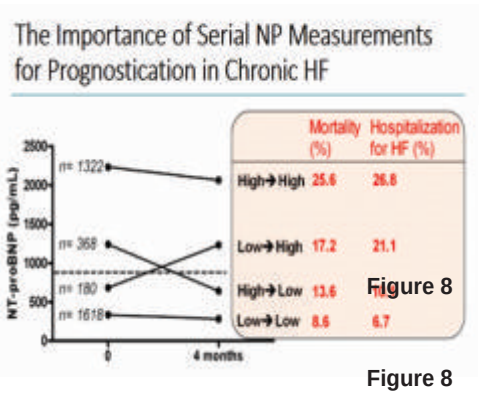
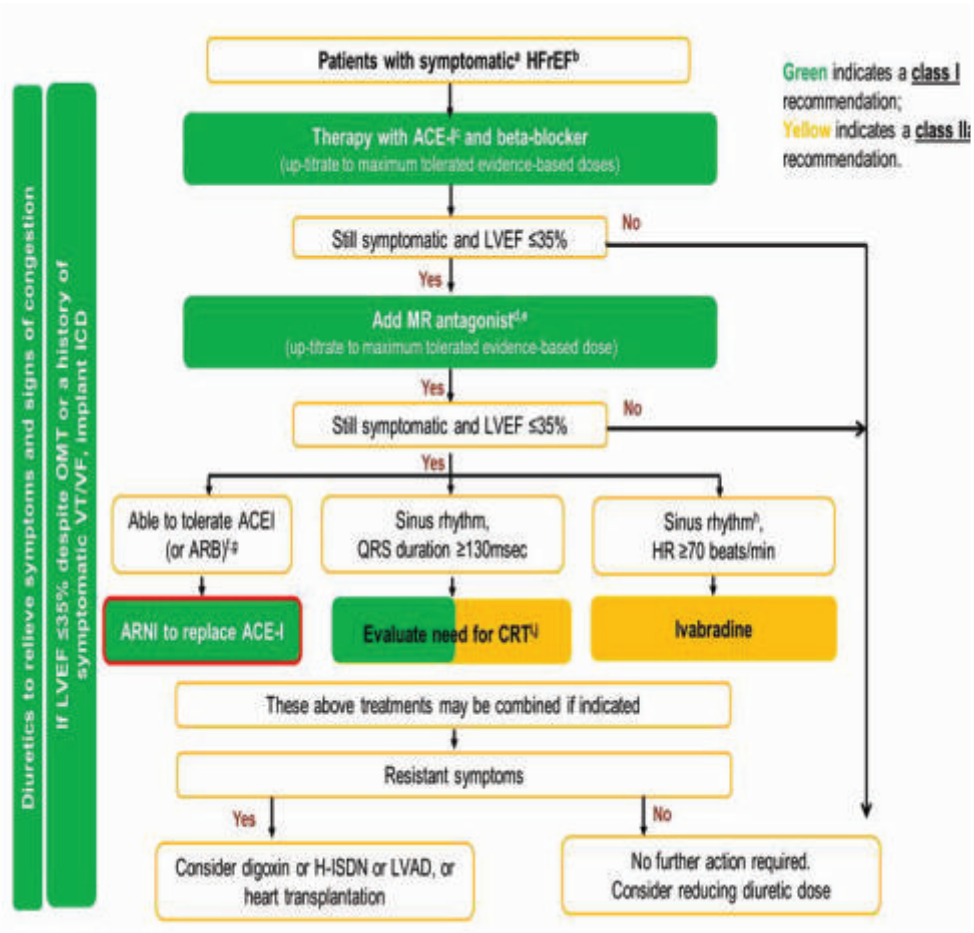


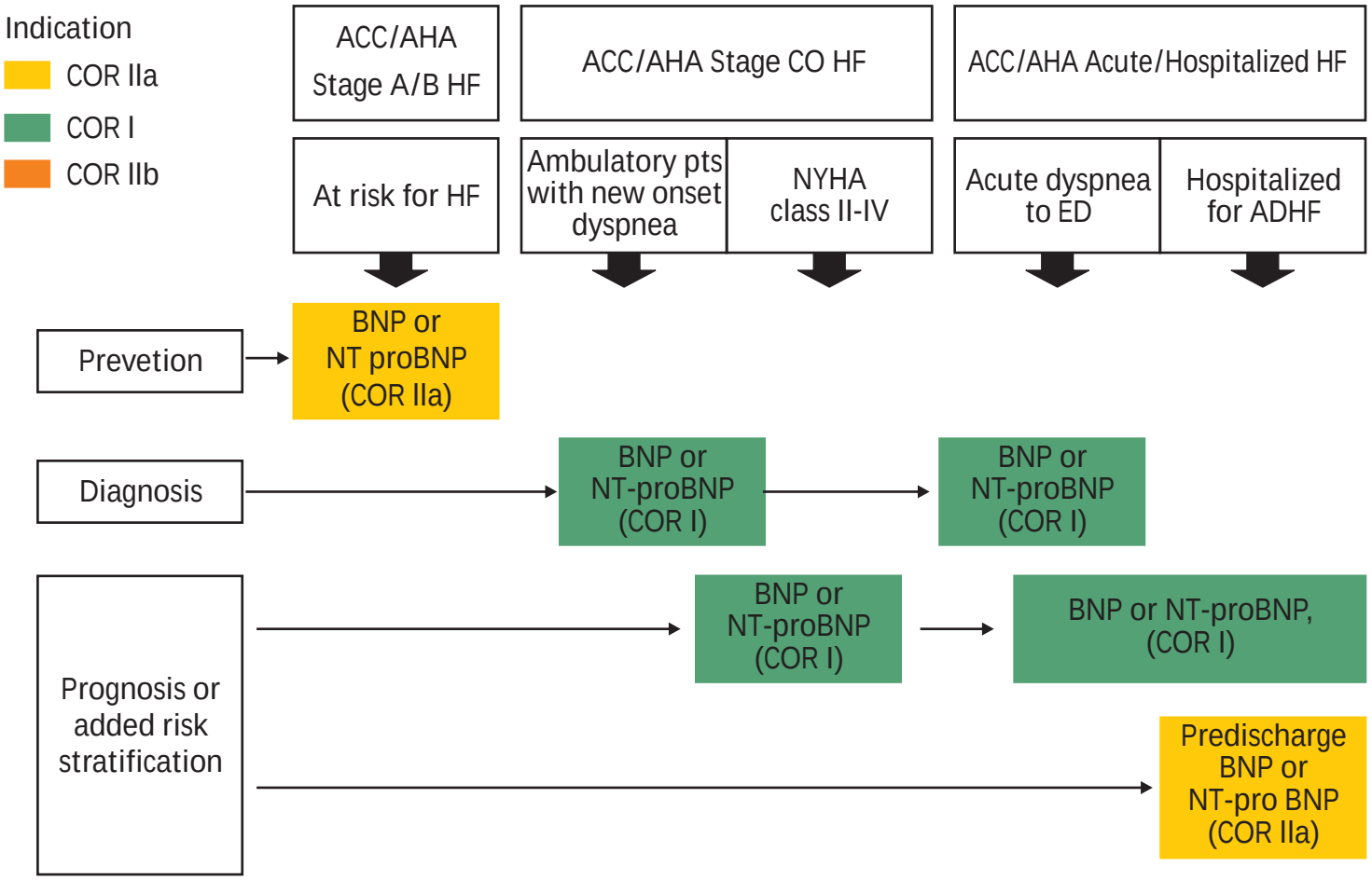
Figure 8

Figure 7



Biomarker Indications for Use
2017 ACC/AHA/HFSA Recommendations

Figure 9



Latest 2017 recommendation suggest that BNP / NP-proBNP is Class I indication for patient presenting with acute dyspnea in ER and Ambulatory patient with new onset of dyspnea as diagnostic workup and also for relatively stable looking patient having NYHA Class II - IV and hospitalized patient with Acute Heart Failure for prognosis and improving long term outcome for patient having heart failure with wider availability of measuring NPs, bio-marker - BNP/NTpro BNP must be used in our day to day practice to improve diagnosis of patient suspected of HF, to know the prognosis of our patients and optimize treatment in high risk patients to improve long term out come in this deadly disease.

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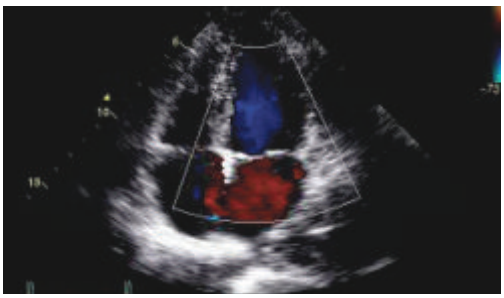

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