Review article

Biomarker-guided therapy for heart failure

K. Sarat Chandra*

Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad, India.

KEY WORDS

BNP
Heart failure
Monitoring
NT-proBNP

A B S T R A C T

Although, there have been significant advances in the management of heart failure (HF), one of the important problems faced by the clinician treating these patients is the significant recurrence of HF with consequent need for readmission. In this article, a discussion is made about the role of natriuretic peptides for monitoring long-term treatment of these patients and different trials done in this regard.

Copyright © 2012, Cardiological Society of India. All rights reserved.

Heart failure (HF) has become an important problem in cardiology practice both in India and abroad with increasing age of the population. The other reason for the rising prevalence of HF is the epidemic of diabetes with its associated coronary artery disease and chronic kidney disease.

The medical management of HF has become fairly standardised with a generally good agreement about evidence-based medical therapies namely angiotensin-converting-enzyme inhibitor (ACEIs), angiotensin receptor blockers (ARBs), beta blockers and aldosterone antagonists. However, despite these advances in HF therapy, these patients continue to get recurrence of HF with need for readmission frequently, the so-called acute decompensated HF (ADHF), so much so that readmission for HF is a part of primary end point in most HF trials.

One of the ways of monitoring patients of HF is to keep a close watch of patient's body weight. However, it is a crude method and often by the time the weight increases, patient is already in pulmonary oedema or in the hospital. Hence, the need for sensitive and reliable biomarkers that can predict impending HF, and also to monitor and guide the treatment.

Natriuretic peptides serve this purpose to a large extent. They are excellent surrogates for wedge pressure, better at prognosis than left ventricular ejection fraction (LVEF) and correlate well with New York Heart Association (NYHA) class.^{1–4} Before discussing the weight of evidence in this regard, one

needs to recapitulate the biochemistry of natriuretic peptides (Figure 1). There is a pre-proB-type natriuretic peptide (BNP) which is broken into proBNP which further breaks into BNP and N-terminal (NT) proBNP. The BNP is the active component and the NT-proBNP is the inactive component. The NT-proBNP rises more linearly with decrease in renal function, the probable reason for most of the important and the recent trials for measuring NT-proBNP.

Differences between BNP and NT-proBNP: Although, both molecules rise significantly with HF, there are basic differences between them (Table 1). Hence, one should avoid using both these measurements in the same institute, and instead, concentrate on one.

An important controversy in this area is whether during the follow-up of HF patients, one should aim at a fixed target

Figure 1 Basic biochemistry of natriuretic peptides. BNP: B-type natriuretic peptide, NTproBNP: N-terminal proB-type natriuretic peptide.

*Corresponding author.

E-mail address: saratkoduganti@hotmail.com

Table 1

Differences between B-type natriuretic peptide and N-terminal proB-type natriuretic peptide.

	BNP	NT-proBNP
Amino acids	32	76
Molecular weight (d)	3.5	8.5
Half-life (min)	22	60–120
Clearance		
Primary mechanism	Endopeptidase	Renal
Clearance receptor	NPRC	Renal
Haemodialysis	No	No
Point-of-care	Yes	Pending
GFR correlation	Moderate	Strong
Biologic activity	Yes	No
Range (pg/mL)	0–5000	0–35,000

BNP: B-type natriuretic peptide, GFR: glomerular filtration rate, NPRC: natriuretic peptide clearance receptor, NTproBNP: N-terminal proB-type natriuretic peptide.

by tailoring the dosages of various drugs particularly diuretics or depend only on clinical judgement. A number of trials have been done with this objective with variable results. Let us examine the data of some of the leading trials in this arena.

PRIMA study: The PRIMA study randomised 345 patients to NT-proBNP-guided therapy versus clinically-guided therapy and followed up for 1 year.⁵ The primary end point was number of days alive outside the hospital. Median age of the patients was 71 years. The NT-proBNP level at the time of admission was 8034 pg/mL and fell to 2958 pg/mL at discharge. There was no significant difference in primary end point/mortality between the two groups. However, when they looked at the figures of mortality and number of days alive outside the hospital in the group of patients who achieved and maintained target NT-proBNP in >75% of the visits, this group of patients had a significant advantage (Figure 2). The mortality was 10.9% compared to 33% in clinically-guided group (Figure 3). This fact highlights the importance of not only achieving the target but also maintaining it throughout. One important criticism against PRIMA study is the relatively high NT-proBNP target during follow-up as a result of which the threshold to hike the treatment was high. It was nearly 3 times higher than required in the biomarker-guided arm of BATTLE SCARRED study and 4–8 times higher than the TIME CHF. This particular drawback of PRIMA study may have diluted the effect.

BATTLE SCARRED study: The 3-year follow-up of this study was published in 2010 in the Journal of the American College of Cardiology (JACC).⁶ They had three groups in this trial. A total of 364 patients were randomised to NT-guided therapy or intensive clinical treatment or usual care group. The 3-year mortality was selectively reduced in patients <75 years of age in the NT-proBNP-guided therapy group compared to other two groups.

TIME CHF study: This study was done in patients >60 years of age with about 250 patients in each arm.⁷ There were 250 patients in 60–74 age group and 289 in >75 years of age group. 30% were in atrial fibrillation (AF). It is considered as a negative trial as the primary end point (18 months survival free of any hospitalisation) did not differ between the two

Figure 2 PRIMA-study on NT-proBNP target analysis: primary end-point. NT-proBNP: N-terminal proB-type natriuretic peptide.

Figure 3 PRIMA-study on NT-proBNP target mortality (%). NT-proBNP: N-terminal proB-type natriuretic peptide.

groups. However, survival free of hospitalisation for HF is better with hormone-guided therapy among those patients <75 years of age.

Both TIME CHF and BATTLE SCARRED trials failed to show benefit in patients >75 years of age.

PROTECT study: This is one of the most recent studies. These authors attempted an aggressive reduction of NT-proBNP to <1000 pg/mL.⁸ The number of patients was 75 in each arm. The NT-proBNP levels were 1946 pg/mL at baseline which came down to 1842 pg/mL in the standard treatment arm, while they came down from 2344 pg/mL to 1125 pg/mL in the hormone-guided arm. Unlike the TIME CHF study, this study showed equal or more impressive results in patients >75 years with hormone-guided therapy (Figures 4 and 5). They also demonstrated reduction in heart size and increase in EF with hormone-guided therapy (Figure 6).

A meta analysis of the patients included in TIME CHF, STAR BRIGHT, and STARS BNP studies was published in 2008

Figure 4 Events rates in PROTECT study. CV: cardiovascular, NT-proBNP: N-terminal proB-type natriuretic peptide, SOC: standard-of-care.

Figure 5 Results of PROTECT study showing the influence of age. NT-proBNP: N-terminal proB-type natriuretic peptide, SOC: standard-of-care.

(on a total of 918 patients).⁹ This shows that hormone-guided therapy leads to significant reduction of all-cause mortality.

Some of the issues in natriuretic peptide-guided therapy

How frequently should B-type natriuretic peptide be monitored?

During an admission for acute HF (AHF), one should take a blood sample immediately after admission before any therapy is started, as in our experience, the natriuretic peptide (NP) levels come down very quickly in some patients. The next testing should be 24–48 hours later to look at the response and once again before discharge. After discharge, the BNP levels

Figure 6 PROTECT study effects on LV dimensions and LVEF. ECHO: echocardiography, LV: left ventricular, LVEF: left ventricular ejection fraction. NT-proBNP: N-terminal proB-type natriuretic peptide, SOC: standard-of-care.

should be monitored once in a week or 2. Later, as the patient becomes stable, the frequency may be reduced.

Establishing a steady state level of B-type natriuretic peptide for a given patient

In a given patient once a stable clinical state is achieved, the NT-proBNP levels tend to become relatively stable. Once this is achieved, these levels can be used for monitoring over course of time.

Target during chronic therapy

As can be seen from the PROTECT study which gave the best possible results, for NT-proBNP a reasonable target is <1000 pg/mL while at the same time a close watch should be kept on clinical condition, blood pressure, renal function, and electrolytes.

Significance of non drop of B-type natriuretic peptide during acute admission

These patients certainly carry a poor prognosis. Elevated pre-discharge levels predict high-risk of early readmission.

New molecules: A new emerging biomarker in the treatment of AHF is high-sensitivity Troponin. There is now evidence that patients with ADHF who have elevated Troponins have worse prognosis.^{10–12} This could be due to myonecrosis from subendocardial ischaemia. The availability of highly sensitive Troponin assays capable of detecting Troponins in the range of ng/L represents a new opportunity. In a recent trial in which serial sampling of high-sensitivity Troponin I in AHF was done, those patients with rapidly rising levels during hospitalization had worse outcome than those who had little

or no increase.¹² Obviously, acute coronary syndrome has to be ruled out in such patients.

Copeptin: In patients with HF, it has been shown that increased arginine vasopressin (AVP) concentrations are associated with more severe disease. However, AVP is difficult to measure because of in vitro instability and rapid clearance. Copeptin, the C-terminal segment of prepro-vasopressin is a stable and reliable surrogate for AVP concentrations. In the BACH study (Biomarkers in AHF) increased 90-day mortality and readmission were seen in patients with elevated Copeptin levels.¹³ Thus, increased Copeptin levels may be used to decide about the treatment of hyponatremia.

Future studies: The ACTIVATE Study is a multicentre study that will randomise patients admitted for AHF to Tolvaptan versus Placebo-based on the Copeptin levels.¹⁴

The HABIT trial is testing the feasibility of finger-stick NP tests at home which can avoid unwanted hospital visits.¹⁴

Thus these are exciting times for biomarker-guided therapy.

Concluding remarks: Although, there is some controversy with some trials like TIME CHF showing negative results, a close examination of the data particularly from the PROTECT Study suggests improved outcomes both in terms of mortality and admission free survival with natriuretic peptides-guided therapy. This is the era of biomarkers and evidence-based medicine. Further, fine tuning of treatment of HF is required. The BNP-targeted therapy appears to go a long way in achieving this goal.

References

1. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161–7.
2. Januzzi JL Jr, Camargo CA, Anwaruddin S, et al. The N-terminal pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005;95:948–54.
3. Maisel A, Hollander JE, Guss D, et al. Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. *J Am Coll Cardiol* 2004;44:1328–33.
4. Kazanegra R, Cheng V, Garcia A, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. *J Card Fail* 2001;7:21–9.
5. Eurlings LW, van Pol PE, Kok WE, et al. Management of chronic heart failure guided by individual N-terminal pro-B-type natriuretic peptide targets: results of the PRIMA (Can PPro-brain-natriuretic peptide guided therapy of chronic heart failure Improve heart Failure morbidity and mortality?) study. *J Am Coll Cardiol* 2010;56:2090–100.
6. Lainchbury JG, Troughton RW, Strangman KM, et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. *J Am Coll Cardiol* 2009;55:53–60.
7. Pfisterer M, Buser P, Rickli GM, et al. BNP-guided vs symptom guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. *JAMA* 2009;301:383–92.
8. Januzzi JL Jr, Rehman SU, Mohammed AA, et al. Use of aminoterminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. *J Am Coll Cardiol* 2011;58:1881–9.
9. Adams KF Jr, Felker GM, Fraij G, Patterson JH, O'Connor CM. Biomarker guided therapy for heart failure: focus on natriuretic peptides. *Heart Fail Rev* 2010;15:351–70.
10. Peacock WF IV, De Marco T, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. *N Engl J Med* 2008;358:2117–26.
11. Xue Y, Clopton P, Peacock WF, Maisel AS. Serial changes in high-sensitive troponin I predict outcome in patients with decompensated heart failure. *Eur J Heart Fail* 2011;13:37–42.
12. Fonarow GC, Peacock WF, Horwich TB, et al. Usefulness of B-type natriuretic peptide and cardiac troponin levels to predict in-hospital mortality from ADHERE. *Am J Cardiol* 2008;101:231–7.
13. Maisel A, Mueller C, Nowak R, et al. Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *J Am Coll Cardiol* 2010;55:2062–76.
14. Maisel A. Biomonitoring and biomarker-guided therapy. *J Am Coll Cardiol* 2011;58:1890–2.