

## The Evolving Utility and Applications of NT-proBNP in the Diagnosis and Management of Heart Failure

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### ABSTRACT

Heart failure (HF) remains a significant healthcare challenge, with increasing morbidity and economic burden. N-Terminal pro B-type Natriuretic Peptide (NT-proBNP) is a well-established cardiac biomarker widely used in HF for diagnosis, risk stratification and therapeutic guidance. This mini-review summarizes the current and emerging roles of NT-proBNP in HF management, with a focus on its diagnostic, prognostic and therapeutic utility. NT-proBNP is a valuable diagnostic tool, especially in emergency settings, for distinguishing HF from other causes of dyspnea and it has been incorporated into clinical guidelines for both acute and primary care settings. Additionally, NT-proBNP serves as a robust prognostic marker, correlating with disease severity, mortality and hospitalization rates. NT-proBNP-guided therapy has shown promise in optimizing treatment, although its benefit in certain patient populations remains debated. Furthermore, NT-proBNP is associated with longer hospital stays and can inform discharge planning and reduce healthcare costs. Our recent study explored the use of NT-proBNP to triage the need for inpatient echocardiography, finding that it may safely reduce length of stay without harm, warranting further investigation. As novel therapies for HF emerge, including SGLT2 inhibitors and neprilysin inhibitors, NT-proBNP's role in monitoring treatment response and guiding therapy adjustments remains a key area for ongoing research. Overall, NT-proBNP continues to be a cornerstone in HF diagnosis and management, with potential for broader applications in improving patient outcomes and reducing healthcare costs.

**Keywords:** Heart failure; Biomarker; NT-proBNP; Echocardiography

### INTRODUCTION

Heart Failure (HF) continues to pose significant challenges to healthcare systems as the associated morbidity and economic costs are prodigious and are expected to increase further over the coming decades. Management of HF at both the patient level and at the system level must continue to iterate and innovate so as to ameliorate the burden on healthcare systems in the coming years.

N-terminal pro B-type Natriuretic Peptide (NT-proBNP) is a frequently employed cardiac biomarker in HF with proven utility in the areas of diagnosis, risk stratification and therapeutic guidance. This mini-review summarizes the current roles for NT-proBNP in contemporary HF diagnosis and management and outlines the findings of our recent study which proposes a novel

application for NT-proBNP in the rapidly-changing HF management landscape [1]. The N-terminal fragment of pro B-type Natriuretic Peptide (NT-proBNP) is a HF biomarker that is released in response to myocardial stretch and stress, making it a valuable biomarker for HF diagnosis and management [2,3]. The following paragraphs outline the contemporary diagnostic, prognostic and other applications of NT-proBNP.

### LITERATURE REVIEW

#### Diagnostic utility of NT-proBNP

The use of NT-proBNP in the emergency department to assist in diagnosis of HF has been the best-studies application for the biomarker, where it has proven to be useful in differentiating

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causes of dyspnoea. Januzzi and colleagues at Massachusetts general hospital conducted a series of studies including PRIDE and ICON-RELOADED that established various applications for NT-proBNP in the emergency department [4,5]. Their work was central to the formulation of current guideline-endorsed cut-offs for NT-proBNP and demonstrated that NT-proBNP was useful for clinicians in ruling acute HF in or out in patients presenting with dyspnoea for investigation. A very low NT-proBNP of <300 pg/mL was shown to strongly exclude the presence of acute HF while a significantly elevated NT-proBNP makes a diagnosis of HF likely. Their work, as well as that of several other groups, has shown that the addition of NT-proBNP measurement to standard care in this patient population leads to more accurate diagnosis and HF as well as fewer inappropriate hospitalizations and improved patient outcomes.

Other studies have demonstrated a similar diagnostic utility for NT-proBNP in the primary care setting as well, where measurement of serum NT-proBNP in patients presenting to primary care practitioners with dyspnoea enhanced diagnostic accuracy [6].

The measurement of NT-proBNP is strongly endorsed by both the American and European cardiac societies for evaluating patients with acute dyspnoea and possible heart failure to guide diagnosis and initial management.

## DISCUSSION

### Prognostic utility NT-proBNP

NT-proBNP levels correlate with the severity of heart failure and have been shown to independently predict adverse outcomes, including mortality and hospitalization. Long term studies have demonstrated that higher NT-proBNP levels are associated with increased mortality rates, making it a robust prognostic marker in this setting. Regular monitoring of NT-proBNP in heart failure patients provides valuable information about disease progression and guides clinical decision making. In hospitalized patients with acute HF, NT-proBNP level correlate with risk of readmission and mortality [7,8].

### Using NT-proBNP to monitor response to treatment

NT-proBNP-guided therapy has emerged as a promising approach in chronic HF management where tailoring treatment based on NT-proBNP levels helps optimize medication dosages and adjust therapy, leading to better symptom control and reduced hospitalizations. By this approach, a change in symptoms corresponding to a significant increase in NT-proBNP from baseline would indicate an exacerbation of stable chronic HF as a cause of the symptoms. There remains some ambiguity as to which patient groups would benefit most from routine NT-proBNP monitoring, as not all trials have shown a benefit from biomarker-guided HF management [9-11].

### NT-proBNP and hospital length of stay

A significantly elevated NT-proBNP on hospital admission has been shown to correlate with longer hospital Length of Stay (LOS) in various patient populations, providing an early indication of probable patient outcomes and requirements and affording health systems an opportunity to plan patient journeys [12,13]. Similarly, NT-proBNP measurement in some clinical scenarios has a direct impact on time to patient discharge [14].

In our recent study we sought to identify whether patients with a clinician determined low pre-test probability for heart failure were able to be safely discharged. We evaluated all patients with known or suspected HF-including de-novo presentations that may be consistent with HF, but without any known history of cardiac pathology and triaged their priority for Trans-Thoracic Echocardiography (TTE) using serum NT-proBNP. Patients with a very low NT-proBNP (<300) and no alternate indication for inpatient TTE, such as a new murmur or suspected valve pathology, suspected pulmonary embolus or suspected myocardial infarction and who were otherwise ready for discharge from hospital were referred for an outpatient TTE. We found that this approach led to a significant reduction in hospital LOS without any associated harm signals. While this study was small in scale and did have several limitations, the main finding, that NT-proBNP appears to be a safe and effective tool for triaging the requirement for inpatient echocardiography in patients with a low clinical likelihood for HF, is consistent with earlier NT-proBNP studies and warrants further exploration in future studies.

### Using NT-proBNP to reduce health system costs

The clinical utilities of NT-proBNP measurement as detailed above are cost-saving for healthcare systems. Improvements in the accuracy and rapidity of HF diagnoses would be expected to have beneficial flow-on financial effects, where rapid initiation and up titration of appropriate therapies and avoidance of inappropriate therapies and hospitalization would lead to lower healthcare cost expenditure. Several studies in this area have borne out this assumption and the application of NT-proBNP was associated with significant cost-savings [15,16]. Siebert et al, in their economic modelling of NT-proBNP-supported clinical assessment, that NT-proBNP use decreased average inpatient management costs by 10%, with cost savings of US\$2,337 per patient ED visit.

### NT-proBNP in the evolving HF therapies

The HF landscape continues to evolve rapidly as emerging medication classes, particularly neprilysin inhibitors, Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors and soluble guanylate cyclase stimulators continue to change the HF treatment paradigm. The mechanisms of some newer medication classes are known to modify serum cardiac biomarker levels, potentially clouding interpretation of patients taking these medications [17]. Similarly, changing treatment strategies such as rapid up titration in dedicated HF clinics have been shown to reduce patient outcomes such as all-cause mortality and re-hospitalization for heart failure but the utility

of serial NT-proBNP measurements with this treatment strategy was not clearly demonstrated [18].

How and when NT-proBNP can be most effectively and efficiently applied in the diagnosis and management of HF in the context of rapid changing HF therapy is an evolving question and should continue to be assessed.

## CONCLUSION

HF will continue to be a major issue for patients and healthcare systems in the coming years as the scale of the problem continues to expand. The evidence supporting the use of NT-proBNP in HF has evolved over the last two decades and there are now numerous applications for it in clinical practices that are supported by robust evidence. As new medication classes such and treatment strategies play an expanding role in HF management, the application of existing diagnostic tools such as cardiac biomarkers to new clinical settings and towards novel clinical end points will be important in driving improved patient outcomes and reducing associated costs. Our recent work has suggested that NT-proBNP can be used to triage requirement for inpatient echocardiography, with resultant reductions in hospital LOS identifying additional applications for existing diagnostic tools should be an area of future research.

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