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Clinical Utility of NT-proBNP in the Diagnosis and Management of Heart Failure: A Comprehensive Review

Abhinav Prithvi Venkata Sesha Kanigicherla[1*], Unnagiri Adinarayana[2], Vasamsetti Kumar Swamy[3], Gorle Sujatha[4], Bura Ramya Sri[4], Setti Gayathri Devi[4]

[1]*University Hospitals Coventry and Warwickshire, United Kingdom*
[2]*Senior Interventional Cardiologist, Surya Global Hospitals, Kakinada, India*
[3]*Cardiac Physician Assistant, Surya Global Hospitals, Kakinada, India*
[4]*PharmD Intern, Department of Pharmacy Practice, Koringa College of Pharmacy, Korangi, India*

Abstract*: Background: Heart failure (HF) is a major global public health problem associated with high morbidity, mortality, and healthcare costs. Early diagnosis and timely management are essential to improve clinical outcomes. N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker released in response to myocardial wall stress, has become an important tool for the diagnosis, prognosis, and therapeutic monitoring of patients with heart failure. Objective: This review aims to summarize the current evidence regarding the clinical utility of NT-proBNP in the diagnosis, risk stratification, prognosis, and management of heart failure, while highlighting factors that influence its interpretation and emerging clinical applications. Methods: A comprehensive literature review was conducted using peer-reviewed articles, clinical guidelines, systematic reviews, and meta-analyses published in major electronic databases, including PubMed, Scopus, and Google Scholar. Relevant studies addressing the diagnostic, prognostic, and therapeutic applications of NT-proBNP in heart failure were reviewed and critically analyzed. Results: NT-proBNP is a highly sensitive biomarker for the diagnosis of both acute and chronic heart failure and provides significant prognostic information regarding disease severity, hospitalization, and mortality. Its measurement aids in differentiating cardiac from non-cardiac causes of dyspnea, assessing treatment response, and identifying patients at increased risk of adverse cardiovascular outcomes. However, NT-proBNP concentrations are influenced by factors such as age, renal dysfunction, obesity, atrial fibrillation, and other comorbidities, which should be considered during clinical interpretation. Conclusion: NT-proBNP plays a pivotal role in the contemporary management of heart failure by facilitating early diagnosis, prognostic assessment, and therapeutic decision-making. When interpreted in conjunction with clinical findings and imaging modalities, it significantly enhances patient care. Continued research into biomarker-guided management strategies and integration with novel diagnostic approaches may further improve outcomes in patients with heart failure.

***Keywords*: NT-proBNP, Heart Failure, Biomarker, Diagnosis, Prognosis, Risk Stratification, Natriuretic Peptides.**

1. Introduction

Heart failure (HF) is a complex clinical syndrome resulting from structural or functional abnormalities of the heart that impair its ability to pump or fill with blood adequately. It represents one of the leading causes of morbidity, mortality, and hospitalization worldwide, affecting more than 64 million people globally. Despite advances in pharmacological and device-based therapies, heart failure continues to impose a significant economic burden on healthcare systems and is associated with poor quality of life and frequent hospital readmissions. Early diagnosis and timely initiation of evidence-based therapy are essential to improve patient outcomes [1], [2].

The diagnosis of heart failure can be challenging because its clinical manifestations, including dyspnea, fatigue, and peripheral edema, are often nonspecific and overlap with those of other cardiopulmonary disorders. Therefore, cardiac biomarkers have become indispensable adjuncts to clinical evaluation, imaging studies, and echocardiography. Among these biomarkers, N-terminal pro-B-type natriuretic peptide (NT-proBNP) has emerged as one of the most reliable indicators for the diagnosis and prognosis of heart failure [3].

NT-proBNP is an inactive cleavage product released into the circulation during the synthesis of B-type natriuretic peptide (BNP) by ventricular cardiomyocytes in response to increased myocardial wall stress, pressure overload, or volume expansion. Compared with BNP, NT-proBNP has a longer plasma half-life and greater analytical stability, making it a preferred biomarker in routine clinical practice. Elevated NT-proBNP concentrations correlate closely with the severity of ventricular dysfunction and provide valuable information for diagnosis, risk stratification, prognosis, and monitoring of therapeutic response in patients with both acute and chronic heart failure [4], [5].

2. Physiology of NT-proBNP

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a biologically inactive peptide released predominantly by ventricular cardiomyocytes in response to increased myocardial

*Corresponding author: kumarvasamsetti751@gmail.com

wall stress caused by pressure overload, volume expansion, or ventricular dysfunction. It is produced during the synthesis of B-type natriuretic peptide (BNP), a key hormone involved in maintaining cardiovascular homeostasis. The secretion of NT-proBNP reflects the degree of myocardial stress and has become an important biomarker for the diagnosis and management of heart failure [7].

The NPPB gene, located on chromosome 1, encodes the precursor protein pre-proBNP, which consists of 134 amino acids. After the removal of a 26-amino-acid signal peptide, proBNP (108 amino acids) is formed within ventricular myocytes. ProBNP is subsequently cleaved by the enzymes corin and furin into two equimolar fragments: the biologically active hormone BNP (32 amino acids) and the biologically inactive NT-proBNP (76 amino acids). Both fragments are released simultaneously into the bloodstream in response to myocardial stretch [8].

BNP exerts its physiological effects by binding to natriuretic peptide receptor-A (NPR-A), activating guanylyl cyclase and increasing intracellular cyclic guanosine monophosphate (cGMP) production. This signaling pathway promotes vasodilation, natriuresis, diuresis, suppression of the renin–angiotensin–aldosterone system (RAAS), inhibition of sympathetic nervous system activity, and reduction of cardiac fibrosis and ventricular remodeling. Although NT-proBNP is biologically inactive and does not directly contribute to these physiological effects, its plasma concentration accurately reflects BNP secretion and myocardial stress [9].

Compared with BNP, NT-proBNP has a longer plasma half-life (approximately 60–120 minutes versus 20 minutes for BNP) and demonstrates greater biochemical stability, making it a more reliable biomarker for laboratory measurement. NT-proBNP is primarily cleared through renal excretion, whereas BNP is eliminated through receptor-mediated internalization and enzymatic degradation by neprilysin. Consequently, NT-proBNP concentrations are often elevated in patients with renal dysfunction, requiring careful interpretation in clinical practice [4].

Several physiological and pathological factors influence circulating NT-proBNP levels. Plasma concentrations generally increase with advancing age and are higher in women than in men. Elevated levels are also observed in conditions such as chronic kidney disease, atrial fibrillation, pulmonary hypertension, acute coronary syndrome, and sepsis, even in the absence of overt heart failure. Conversely, obesity is associated with relatively lower NT-proBNP concentrations due to enhanced peptide clearance and reduced secretion. These factors should be considered when interpreting NT-proBNP values to avoid diagnostic errors [6].

Overall, NT-proBNP serves as a sensitive indicator of myocardial wall stress and ventricular dysfunction. Its physiological relationship with BNP and its favorable analytical characteristics have established NT-proBNP as one of the most widely used biomarkers for diagnosing heart failure, assessing disease severity, guiding therapy, and predicting clinical outcomes [2].

3. Factors Affecting NT-proBNP Levels

Interpretation of N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations requires consideration of several physiological and pathological factors that may influence circulating levels independently of heart failure. Although NT-proBNP is a highly sensitive biomarker of myocardial wall stress, its specificity may be reduced in the presence of comorbid conditions. Understanding these factors is essential for accurate diagnosis, risk stratification, and therapeutic decision-making.

1) Age

NT-proBNP concentrations increase progressively with age, even in healthy individuals. This age-related elevation is attributed to reduced myocardial compliance, subclinical cardiac remodeling, and decreased renal clearance. Consequently, higher diagnostic cut-off values are recommended for older adults to improve diagnostic accuracy in heart failure [4].

2) Sex

Women generally have higher NT-proBNP concentrations than men of the same age. Hormonal influences, particularly estrogen, and differences in body composition are thought to contribute to these variations. Therefore, sex-specific differences should be considered when interpreting NT-proBNP results [7].

3) Renal Dysfunction

Renal impairment is one of the most significant non-cardiac determinants of elevated NT-proBNP levels. Because NT-proBNP is primarily eliminated by the kidneys, reduced glomerular filtration rate (GFR) leads to decreased clearance and increased plasma concentrations. In patients with chronic kidney disease (CKD), elevated NT-proBNP values should be interpreted cautiously and correlated with clinical findings and echocardiographic assessment [6].

4) Obesity

Obesity is associated with lower circulating NT-proBNP levels compared with individuals of normal body weight. Increased expression of natriuretic peptide clearance receptors in adipose tissue and reduced cardiac secretion are believed to contribute to this phenomenon. As a result, heart failure may be underdiagnosed in obese patients if standard diagnostic thresholds are applied [10].

5) Atrial Fibrillation

Patients with atrial fibrillation (AF) frequently exhibit elevated NT-proBNP concentrations due to increased atrial and ventricular wall stress, irrespective of heart failure status. Therefore, higher NT-proBNP values should be interpreted carefully in patients with AF to avoid overestimation of heart failure severity [3].

6) Acute Coronary Syndrome

Myocardial ischemia and infarction stimulate NT-proBNP release secondary to increased ventricular wall tension and myocardial injury. Elevated NT-proBNP levels in patients with acute coronary syndrome (ACS) are associated with increased risk of heart failure, recurrent cardiovascular events, and mortality [11].

7) Pulmonary Diseases

Pulmonary hypertension, pulmonary embolism, and chronic obstructive pulmonary disease (COPD) may increase NT-proBNP concentrations due to right ventricular pressure overload. These elevations may occur even in the absence of left ventricular dysfunction, necessitating careful clinical evaluation [12].

8) Sepsis and Critical Illness

Patients with sepsis or systemic inflammatory response syndrome often demonstrate elevated NT-proBNP levels due to myocardial depression, inflammatory cytokine release, and renal dysfunction. In these settings, elevated NT-proBNP does not necessarily indicate heart failure and should be interpreted alongside clinical and imaging findings [13].

9) Anemia

Anemia can increase cardiac output and myocardial workload, leading to ventricular wall stress and elevated NT-proBNP concentrations. Correction of anemia may reduce NT-proBNP levels in some patients [14].

10) Medications

Several cardiovascular medications influence NT-proBNP levels. Effective treatment with angiotensin receptor-neprilysin inhibitors (ARNIs), ACE inhibitors, β-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 (SGLT2) inhibitors often reduces NT-proBNP concentrations as cardiac function improves. Unlike BNP, NT-proBNP is not degraded by neprilysin and therefore remains a preferred biomarker for monitoring patients receiving sacubitril/valsartan therapy [2].

4. NT-proBNP in Heart Failure Diagnosis

Heart failure (HF) is a clinical syndrome characterized by symptoms and signs resulting from structural or functional impairment of ventricular filling or ejection of blood. Because the presenting symptoms, such as dyspnea, fatigue, and peripheral edema, are nonspecific, diagnosis based solely on clinical assessment may be challenging. Measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP) has become an essential component of the diagnostic evaluation of patients with suspected heart [2].

NT-proBNP is released from ventricular cardiomyocytes in response to increased myocardial wall stress caused by pressure overload or volume expansion. Elevated circulating concentrations reflect ventricular dysfunction and correlate with the severity of heart failure. In patients presenting with acute dyspnea, NT-proBNP effectively differentiates heart failure from non-cardiac causes, facilitating rapid diagnosis and appropriate treatment [15].

The European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) recommend NT-proBNP testing as a first-line biomarker in patients with suspected heart failure. For non-acute settings, an NT-proBNP concentration below 125 pg/mL effectively excludes heart failure, whereas in acute presentations, a value below 300 pg/mL has a high negative predictive value for ruling out acute heart failure. Age-adjusted diagnostic thresholds (>450 pg/mL for patients <50 years, >900 pg/mL for those aged 50–75 years, and >1800 pg/mL for patients >75 years) improve diagnostic accuracy in emergency settings [3].

NT-proBNP is valuable in diagnosing both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Although levels are generally lower in HFpEF than in HFrEF, elevated NT-proBNP concentrations remain strongly associated with increased cardiac filling pressures and ventricular dysfunction. However, interpretation should account for factors such as age, renal dysfunction, obesity, and atrial fibrillation, which may independently influence NT-proBNP concentrations [6].

5. Prognostic Value of NT-proBNP

Beyond its diagnostic utility, NT-proBNP is a powerful prognostic biomarker in patients with acute and chronic heart failure. Numerous studies have demonstrated that elevated NT-proBNP concentrations are independently associated with increased risks of mortality, recurrent hospitalization, disease progression, and adverse cardiovascular events. Higher baseline levels indicate greater myocardial stress and more advanced ventricular dysfunction [5].

Serial measurement of NT-proBNP provides valuable information regarding treatment response and disease progression. A significant reduction in NT-proBNP levels following initiation of guideline-directed medical therapy is associated with improved survival and reduced rates of hospitalization. Conversely, persistently elevated or increasing NT-proBNP concentrations despite treatment suggest ongoing myocardial injury, inadequate therapeutic response, and a poorer clinical prognosis [16].

NT-proBNP also plays an important role in risk stratification. Patients with markedly elevated concentrations are more likely to require intensive monitoring, advanced heart failure therapies, or referral to specialized heart failure centers. In addition, NT-proBNP predicts adverse outcomes following acute coronary syndrome, valvular heart disease, atrial fibrillation, and chronic kidney disease, making it a versatile biomarker across a broad spectrum of cardiovascular disorders [11].

Several clinical trials have evaluated NT-proBNP-guided therapy, demonstrating that adjusting treatment based on serial NT-proBNP measurements may reduce cardiovascular events and improve outcomes in selected patient populations, particularly younger patients with HFrEF. However, current international guidelines recommend that biomarker-guided therapy should complement, rather than replace, comprehensive clinical assessment [3], [17].

6. NT-proBNP-Guided Therapy

NT-proBNP-guided therapy is a treatment strategy in which serial measurements of NT-proBNP are used alongside clinical assessment to optimize the management of patients with heart failure (HF). Since NT-proBNP concentrations reflect myocardial wall stress and ventricular dysfunction, reductions

in NT-proBNP during treatment are generally associated with improved cardiac function and better clinical outcomes. Rather than relying solely on symptoms, clinicians may use serial NT-proBNP measurements to assess treatment response and guide medication titration [2].

Several clinical trials have investigated the effectiveness of NT-proBNP-guided therapy. The STARS-BNP trial demonstrated that adjusting heart failure therapy to achieve lower BNP concentrations reduced cardiovascular events compared with standard care. Similarly, the BATTLESCARRED trial reported improved long-term survival among younger patients managed using natriuretic peptide-guided treatment [18], [19].

The GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment) trial evaluated whether targeting NT-proBNP concentrations below 1,000 pg/mL improved outcomes in patients with heart failure and reduced ejection fraction (HFrEF). Although the trial was terminated early because of futility and did not demonstrate a significant reduction in the primary endpoint compared with usual care, patients who achieved lower NT-proBNP levels experienced fewer cardiovascular events and improved clinical outcomes. These findings suggest that NT-proBNP is a valuable marker of treatment response even if routine biomarker-guided therapy is not universally recommended [17].

Current international guidelines recognize NT-proBNP as an important biomarker for diagnosis and prognosis, while emphasizing that treatment decisions should be based primarily on comprehensive clinical evaluation together with guideline-directed medical therapy (GDMT). Serial NT-proBNP measurements may be particularly useful in selected high-risk patients to monitor disease progression, evaluate therapeutic response, and identify those requiring closer follow-up or advanced heart failure therapies [2], [3].

7. NT-proBNP in Special Populations

A. Heart Failure with Preserved Ejection Fraction (HFpEF)

NT-proBNP is an important diagnostic and prognostic biomarker in HFpEF. Although circulating levels are generally lower than those observed in HFrEF due to less ventricular dilation, elevated NT-proBNP remains strongly associated with increased filling pressures, symptom severity, hospitalization, and mortality. Current ESC guidelines recommend NT-proBNP as part of the diagnostic evaluation for suspected HFpEF [3].

B. Chronic Kidney Disease (CKD)

Patients with chronic kidney disease often exhibit elevated NT-proBNP concentrations because of reduced renal clearance and concurrent cardiovascular abnormalities. Despite higher baseline values, NT-proBNP retains significant diagnostic and prognostic value in CKD when interpreted in conjunction with renal function and echocardiographic findings. Higher diagnostic thresholds are often required in this population [6].

C. Elderly Patients

Advancing age is associated with progressive increases in NT-proBNP concentrations due to age-related myocardial changes, reduced renal function, and increased cardiovascular comorbidity. Therefore, age-specific cut-off values improve diagnostic accuracy and reduce false-positive diagnoses of heart failure in older adults [2].

D. Obesity

Obese individuals generally have lower circulating NT-proBNP concentrations than non-obese individuals. Increased expression of natriuretic peptide clearance receptors in adipose tissue and decreased peptide secretion contribute to reduced biomarker levels. Consequently, standard diagnostic cut-off values may underestimate heart failure in obese patients [10].

E. Atrial Fibrillation

NT-proBNP concentrations are frequently elevated in patients with atrial fibrillation due to increased atrial and ventricular wall stress, even in the absence of heart failure. Elevated values should therefore be interpreted cautiously, and diagnosis should incorporate imaging findings and clinical assessment [3].

F. Acute Coronary Syndrome (ACS)

Following myocardial infarction, NT-proBNP concentrations increase rapidly as a consequence of myocardial injury and ventricular dysfunction. Elevated levels predict the development of heart failure, recurrent ischemic events, and cardiovascular mortality, making NT-proBNP an important prognostic biomarker after ACS [11].

G. Diabetes Mellitus

Patients with diabetes mellitus are at increased risk of developing heart failure. Elevated NT-proBNP levels may identify subclinical cardiac dysfunction before overt symptoms develop and can assist in cardiovascular risk stratification. Recent evidence also demonstrates significant reductions in NT-proBNP concentrations following treatment with sodium-glucose cotransporter-2 (SGLT2) inhibitors, reflecting improved cardiac function [20].

H. Pregnancy

NT-proBNP concentrations remain relatively stable during uncomplicated pregnancy but may increase in pregnancy-related cardiovascular disorders such as peripartum cardiomyopathy and preeclampsia. Measurement of NT-proBNP can assist in distinguishing physiological symptoms of pregnancy from pathological cardiac dysfunction [11].

8. Limitations of NT-proBNP

Despite its well-established clinical utility, NT-proBNP has several limitations that should be considered during interpretation.

1) Lack of Disease Specificity

Elevated NT-proBNP levels are not exclusive to heart failure. Conditions such as chronic kidney disease, atrial fibrillation, pulmonary hypertension, sepsis, acute coronary syndrome, and advanced age can significantly increase circulating concentrations, potentially reducing diagnostic specificity [2].

2) Influence of Obesity

Obesity is associated with lower NT-proBNP concentrations due to enhanced peptide clearance and reduced secretion, increasing the possibility [10].

3) Renal Dysfunction

Because NT-proBNP is primarily eliminated by the kidneys, impaired renal function results in elevated baseline concentrations independent of heart failure severity, necessitating higher diagnostic thresholds in patients with chronic kidney disease [7].

4) Biological and Analytical Variability

NT-proBNP levels vary according to age, sex, ethnicity, body mass index, and laboratory assay methods. These variations should be considered when interpreting serial measurements [21].

5) Limited Role as a Standalone Test

Although NT-proBNP is highly sensitive, it should not be used in isolation. Clinical history, physical examination, electrocardiography, imaging studies, and echocardiography remain essential for confirming the diagnosis of heart failure [2].

9. Future Perspectives

Rapid advances in cardiovascular medicine continue to expand the clinical applications of NT-proBNP.

1) Personalized Medicine

Serial NT-proBNP measurements may facilitate individualized treatment strategies by identifying patients who respond favorably to guideline-directed medical therapy and those requiring treatment intensification [3].

2) Multimarker Approaches

Combining NT-proBNP with biomarkers such as high-sensitivity cardiac troponin, soluble ST2, Galectin-3, and growth differentiation factor-15 (GDF-15) may improve diagnostic accuracy and long-term prognostic assessment compared with single biomarker strategies [6].

3) Artificial Intelligence and Machine Learning

Artificial intelligence (AI) algorithms integrating NT-proBNP with clinical, imaging, and laboratory data have shown promise for early heart failure detection, prediction of hospitalization, and individualized risk assessment. Further prospective studies are required before widespread implementation [22].

4) Point-of-Care Testing

Portable point-of-care NT-proBNP assays may enable rapid diagnosis in emergency departments, outpatient clinics, and resource-limited settings, facilitating earlier initiation of treatment and reducing healthcare costs [4].

5) Emerging Therapeutic Monitoring

Future research is expected to clarify the role of NT-proBNP in monitoring responses to newer heart failure therapies, including sodium-glucose cotransporter-2 (SGLT2) inhibitors, vericiguat, omecamtiv mecarbil, and novel anti-inflammatory agents. Ongoing clinical trials continue to evaluate NT-proBNP as a surrogate endpoint for therapeutic efficacy [3].

10. Conclusion

N-terminal pro-B-type natriuretic peptide (NT-proBNP) has emerged as one of the most valuable and extensively validated biomarkers in the diagnosis and management of heart failure. Its high sensitivity, excellent negative predictive value, and strong prognostic significance make it an indispensable tool for identifying heart failure, differentiating cardiac from non-cardiac causes of dyspnea, assessing disease severity, and predicting hospitalization and mortality. Serial measurement of NT-proBNP also provides important information regarding therapeutic response and long-term clinical outcomes.

Although NT-proBNP concentrations may be influenced by factors such as age, renal dysfunction, obesity, atrial fibrillation, and other comorbid conditions, careful interpretation in conjunction with clinical evaluation and imaging studies substantially enhances diagnostic accuracy. Current international guidelines recommend the use of NT-proBNP as an integral component of the evaluation and management of patients with suspected or established heart failure.

Recent advances in biomarker-guided therapy, multimarker strategies, point-of-care testing, and artificial intelligence-based risk prediction are expected to further expand the clinical applications of NT-proBNP. Future research should focus on standardizing population-specific diagnostic thresholds, improving interpretation in special populations, and integrating NT-proBNP with novel biomarkers and precision medicine approaches to optimize patient outcomes.

In conclusion, NT-proBNP remains the cornerstone biomarker for contemporary heart failure care. Its incorporation into routine clinical practice enables earlier diagnosis, more accurate risk stratification, individualized therapeutic monitoring, and improved clinical decision-making, ultimately contributing to better patient outcomes and reduced healthcare burden.

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