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REVIEW ARTICLE

The role of N-terminal pro-B-type natriuretic peptide in prognostic evaluation of heart failure

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Abstract: Heart failure (HF) is a growing challenge in the Asia Pacific region. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a well-established tool for diagnosis of HF; however, it is relatively underutilized in predicting adverse outcomes in HF. Multiple studies have demonstrated the prognostic role of NT-proBNP in HF. A single value of NT-proBNP >5000 pg/mL predicts a worse outcome in hospitalized patients with HF with reduced ejection fraction (HFrEF). In stable outpatients with HFrEF, NT-proBNP > 1000 pg/mL predicts a poorer prognosis. NT-proBNP provides the same prognostic information in patients with HF with preserved ejection fraction (HFpEF) as in those with HFrEF. An expert panel composed of cardiologists mainly from Asia Pacific region was convened to discuss the utility of NT-proBNP in HF prognostication. This article summarizes available scientific evidence and consensus recommendations from the meeting.

Keywords: Heart failure; Natriuretic peptide; Prognosis

1. INTRODUCTION

Heart failure (HF) is a chronic disabling disease affecting approximately 26 million people globally.[1] The prevalence of HF in Asia Pacific is similar to global estimates ranging from 1.26% to 6.7% in the region.[2] However, substantial gaps remain with regards to information on HF in Asian populations. Emerging evidence indicates that ethnic variations may be present, with analyses of patient registries showing that Asian patients tend to present with initial HF symptoms at a younger age than patients in Western countries.[3–5] HF presents a high economic burden with lengthy and repeated hospitalizations accounting for the majority of healthcare expenditure.[1] As in Western countries, hospitalization for HF appears to be increasing in Asia Pacific region.[6,7] The cost of hospitalization varies substantially within the region, ranging from 813 US dollars in Indonesia to almost 9000 US dollars in South Korea.[8] Identifying HF patients at high risk of morbidity and mortality based on the predicted prognosis may result in significant cost savings, as well as optimization of treatment, prevention of disease progression, and prolongation of survival.[9] Natriuretic peptide (NP), including B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), has been shown to be an effective biomarker not only for diagnosis but also for prognostic evaluation both for patients with HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).[10–16] They also have been used as screening tools for prevention of cardiovascular (CV) events in high-risk patients.[17,18] BNP release is regulated at the level of gene expression, and synthesized in bursts as pre-pro-BNP, which is processed intracellularly to pro-BNP1-108, then cleaved and secreted as a biologically inactive N-terminal fragment N-BNP1-76 (designated NT-proBNP) (plasma half-life ~70 minutes) and the biologically active, 32-amino-acid ring structure BNP77-108 (plasma half-life 22 minutes).[19–22] Both BNP and NT-proBNP are released in a 1:1 ratio in the peripheral circulation. The predominant stimulus for synthesis and release of BNP from the atria and ventricles is thought to be wall stretch. Bioactive BNP77-108 binds to the NP A receptor, stimulating production of the intracellular second messenger cGMP via particulate guanylyl cyclase, and causes beneficial effects in HF (natriuretic, vasodilating, antifibrotic, antihypertrophic, lusitropic, cytoprotective effects).[19–22] Despite these beneficial effects and high circulating levels of BNP fragments in decompensated HF, patients display fluid and salt retention, indicating that HF is a NP-deficient state. Several BNP assays have been developed as previously reviewed[19,23] This article will focus on NT-proBNP as the most widely used assay currently.

Although NP testing has been widely adopted as a tool for diagnosing HF in the emergency room, its use still varies considerably across the region and there is continued controversy regarding whether age- or ethnicity-specific diagnostic cutoffs

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are required. The ADHERE-AP registry, which includes 10 171 HF patients from eight Asia Pacific countries, found that BNP and NT-proBNP levels were assessed in only 7.8% and 8.5% of cases, respectively.[5] In contrast, some national registries have reported greater use of NP for diagnosis, with NP levels assessed in 76.6% of hospitalized HP patients in South Korea, and BNP and NT-proBNP assessed in 22.7% and 32.4% of patients, respectively, in Taiwan.[24,25] Prognostic evaluation of HF patients using NP levels is currently recommended by major international guidelines in Europe and the USA.[26,27] The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) HF guideline recommends to measure BNP or NT-proBNP levels for establishing prognosis or disease severity in chronic HF.[27] However, there is a lack of consensus on how prognostic information from NT-proBNP can be applied to patient management. A consensus meeting of expert panel was held in Singapore on July 12, 2017 with the aim of developing consensus to help clinicians in the region on the use of NT-proBNP as a risk predictor for HF patients in different clinical settings. During the meeting, the panel reviewed the current literature on the prognostic value of NT-proBNP. Based on the scientific evidence and clinical experience of the panel, recommendations were proposed and discussed until agreed upon by all of the panel members. Prognostic cutoffs are recommended acknowledging that prognostic risk is likely to be linear rather than dichotomous. The recommendations and their scientific evidences were provided in this article.

2. ACUTE HOSPITALIZED HF PATIENTS

The 2017 ACC/AHA HF guideline gives a strong recommendation for the measurement of NP levels to establish prognosis or disease severity in patients with chronic HF.[27] This recommendation is supported by multiple clinical studies demonstrating the value of NT-proBNP for assessing the risk of death or CV events in these patients. Pascual-Figal et al[28] conducted a single-center, prospective study of patients admitted to the emergency department with shortness of breath. Among the patients who were diagnosed with HF, NT-proBNP levels were found to be significantly higher in the 9% of patients who died during hospitalization. The optimal cut-off value of NT-proBNP for predicting death was 5500 pg/mL with an accuracy 77%, sensitivity 100%, positive predictive value (PPV) 29%, and negative predictive value (NPV) 100%.[28] In a pooled analysis of 1256 patients with acute HF from three clinical trials, Januzzi et al[10] found the optimal cut-off point for predicting 76-day mortality was 5180 pg/mL (sensitivity, 68%; specificity, 72%; PPV, 19%; NPV, 96%). In 2014, Salah et al reported the results of a pooled analysis of seven prospective cohorts of patients hospitalized for clinically validated, acute decompensated HF (n = 1301), who were discharged alive and their NT-proBNP levels were measured at admission and discharge. The study found the higher the NT-proBNP value at discharge, the worse the prognosis. For patients with NT-proBNP levels between 5001 and 15 000 pg/mL at discharge, 24% had died at 180 days after discharge; more than double that of patients whose discharge levels were between 1500 and 5000 pg/mL.[29]

Regarding timing of assessment of NT-proBNP levels for prognosis during hospitalization, the 2017 ACC/AHA guideline gave a strong recommendation to measure NP levels at admission. There is also a recommendation to repeat the evaluation predischarge, as the relative change in NP levels after hospital treatment can also predict the risk of mortality or rehospitalization for HF.[27,29–31] Salah et al demonstrated that a reduction in NT-proBNP levels of ≥30% between admission and discharge resulted in a 180-day all-cause mortality rate more than half that of those with a reduction of <30%.[29] These results were further echoed in a systematic review, which included nine studies in HFrEF patients examining thresholds for percentage change in NT-proBNP, the majority of which used a threshold of 30% or less between admission and discharge. All of these studies found that patients who achieved the threshold percentage change in NT-proBNP before discharge had a reduced risk of the composite outcomes of mortality and readmission.[31] Based on the above evidences, the following recommendations were proposed:

1. A single value of NT-proBNP >5000 pg/mL for hospitalized patients with HFrEF predicts a greater risk of mortality and poor outcomes. The higher the NT-proBNP concentration, the poorer the prognosis.
2. NT-proBNP measurements may be considered for hospitalized patients with HFrEF upon admission and predischarge, with the baseline NT-proBNP levels measured as soon as possible (at least in the first 24 hours of hospitalization for acute HF patients).
3. A reduction of NT-proBNP levels ≥30% between admission and discharge predicts a better clinical outcome.
4. The level of NT-proBNP and the reduction of NT-proBNP should not be used as the only criterion to determine admission and discharge of patients. NT-proBNP provides additional information to support clinical decision-making at admission, triage, and discharge.

3. PATIENTS WITH CHRONIC HFREF

In HFrEF patients with worsening HF symptoms but not requiring emergency hospital admission, the relative change of NT-proBNP levels over time can more effectively predict prognosis than clinical evaluation only in outpatient clinics. This was shown in a study of 71 outpatients with recently destabilized HF, wherein changes of NT-proBNP levels at week 2, week 3, week 4, and 6 months from baseline were predictive of CV death and/or HF hospitalization during follow-up, while changes in clinical disease severity scores were not predictive of subsequent events.[32]

NT-proBNP assessment is also a useful prognostic tool in the outpatient setting for stable HF patients.[33,34] The Valsartan Heart Failure Trial (Val-HeFT) included patients with stable HFrEF (n = 5100) to be treated with valsartan or placebo and the NT-proBNP levels were measured at study entry and at 4 months.[33] Patients were classified into four groups according to their NT-proBNP levels changes at the two time points (ie, high to high, high to low, low to high, and low to low), with a threshold of NT-proBNP <1078 pg/mL used for the low category and ≥1078 pg/mL for the high category. The study found that HFrEF patients with NT-proBNP values <1078 pg/mL after treatment (high to low and low to low) had a better prognosis than those with higher values.[33] Patients in the high-to-low group had comparable all-cause mortality outcomes to patients in the low-to-low group (7.2% and 8.9%, respectively), while patients who maintained high levels of NT-proBNP at month 4 (high to high) had similar increased mortality to those who had worsening NT-proBNP levels (low to high) at month 4 (25.7% and 21.1%, respectively).[33] The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study showed similar results to that of the Val-HeFT study. The PARADIGM-HF study included stable HFrEF patients and treated with either angiotensin-receptor-neprilysin inhibitors (ARNI) or angiotensin-converting enzyme inhibitors (ACEI).[34] Patients with NT-proBNP levels ≤1000 pg/mL after 1 month of treatment had 59% lower risk of CV death or HF hospitalization at 3 years follow-up compared with those with NT-proBNP levels >1000 pg/mL at the same timepoint.[34] Concentrations of both BNP and NT-proBNP often decline in

response to HF treatment.[33,35–38] In the PARADIGM-HF study, both BNP and NT-proBNP levels decreased after treatment with ACEI. However, only NT-proBNP levels were significantly reduced after treatment with ARNI and no significant reduction in BNP levels.[34] This difference is attributed to the neprilysin inhibitor component of ARNI, which prevents degradation of BNP by neprilysin; while it has no effect on NT-proBNP.[39] This indicates that NT-proBNP is a more suitable biomarker than BNP for evaluating prognosis and monitoring treatment in HF patients treated with ARNI. Based on the above evidences, the following recommendations were proposed:

1. A baseline value of NT-proBNP is useful for HFrEF patient in outpatient settings.
2. A NT-proBNP value >1000 pg/mL indicates an increased risk of death or hospitalization; the higher the NT-proBNP level, the greater risk of worse outcomes.
3. NT-proBNP levels may be measured again after treatment. If NT-proBNP level remains ≥ 1000 pg/mL, this indicates greater risk of poor outcomes.
4. In patients with NT-proBNP level remains ≥1000 pg/mL after treatment, the medications for HF should be optimized or patients should be referred to HF specialists to intensify the treatment.
5. In HF patients treated with ARNI, NT-proBNP is the preferred NP biomarker for prognostic testing.

4. PATIENTS WITH HFPEF

A prospective multicenter longitudinal study in New Zealand and Singapore was conducted to compare the differences in epidemiology and outcomes between patients with HFrEF and HFpEF.[40] The study found that risk of all-cause mortality was lower in the HFpEF group than in the HFrEF group; however, when the risk was adjusted for NT-proBNP, the difference in mortality was no longer apparent.[40] In other words, increased levels of NT-proBNP portended the same increased risk of mortality in patients with both HFpEF and HFrEF. While clinicians may anticipate better outcomes overall in their HFpEF patients compared with HFrEF patients, a high or rising NT-proBNP level should indicate a greater risk of worse outcomes and prompt investigation for the cause of this, such as hemodynamic status, renal impairment, atrial fibrillation, or ongoing ischemia. These findings are applicable in both Asian and Western settings. Additionally, a prospective patient registry study in South Korea found that while patients with HFpEF (n = 528) had significantly lower NT-proBNP levels than those with HFrEF (n = 1142), the relationship between increasing NT-proBNP levels and prognosis did not differ between the two populations.[41] These results suggest that NT-proBNP is a valuable prognostic tool in HFpEF patients, and that increasing NT-proBNP values can be indicative of worse prognosis in these patients. Based on the above evidences, the following recommendations were proposed:

1. NT-proBNP provides the same important prognostic information in HFpEF as in HFrEF.
2. NT-proBNP levels are lower in HFpEF patients than in HFrEF. However, the increased NT-proBNP levels in HFpEF should also be taken as a marker of increased risk of adverse outcomes.

5. NP-GUIDED HF THERAPY

The use of NPs to guide treatment decision in stable HFrEF patients has been investigated recently. In a meta-analysis including 11 small randomized trials involving 2000 patients, Troughton et al[42] evaluated the effect of NP-guided HF therapy using either BNP or NT-proBNP and compared with usual care. The results showed that, in patients aged <75 years, all-cause mortality was significantly lower in the NP-guided treatment group than in the usual care group; this difference was not seen in patients aged ≥75 years.[42] Additionally, the risk of hospitalization due to HF or CV disease was also significantly lower in the NP-guided treatment group than in the usual care group, regardless of age.[42] The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) study was a randomized controlled trial with larger cohort to evaluate whether the results from previous smaller studies could be confirmed.[43] Patients with HFrEF (n = 894) with NT-proBNP values >2000 pg/mL or BNP >400 pg/mL in the previous 30 days were randomized to either biomarker-guided therapy (ie, where HF therapy was titrated with the goal of achieving NT-proBNP <1000 pg/mL) or to usual care in accordance with current HF guidelines. The trial was terminated early due to a lack of significant difference between the groups for the primary outcome of time-to-first HF hospitalization or CV mortality. However, the achieved drug doses for HF in GUIDE-IT were not different between the two groups and there were also similar proportions of patients in each treatment group who achieved the target NT-proBNP level of <1000 pg/mL at 12 months.[43] In a previous single-center study in which HF patients received either biomarker-guided therapy or usual care, patients in the biomarker-guided group demonstrated a 44% decrease in NT-proBNP over the study period, compared with just 5% in the usual care group, with significantly fewer CV events in the biomarker-guided group.[44] One reason for the variation between these study results is that there may be differences in the control group in terms of how usual care is defined. In the GUIDE-IT study, patients in the usual care group attended more study-related clinic visits and had more HF therapy adjustments than would typically occur in standard clinical practice.[43] The results of GUIDE-IT do not appear to impact the prognostic value of assessing NT-proBNP in stable HF patients. More importantly, these data demonstrated that, in clinical practice, NT-proBNP values can be used as a tool to help overcome physician inertia and enhance up-titration of HF medications in stable HF patients, especially for those who are treated in the outpatient setting. A more recent meta-analysis including the GUIDE-IT showed no significant difference between the NP-guided group vs guideline-directed group in all-cause mortality and HF hospitalization. Subgroup analysis suggested that NP-guided treatment was associated with decreased all-cause hospitalizations in younger patients (<72 years).[45]

6. ASIAN DATA

The cut-off point values recommended in this article are mainly based on the data from Europe and North America. Few studies have been conducted to evaluate whether NT-proBNP levels vary significantly between Western and Asian populations. One study conducted in healthy individuals from the USA and Vietnam found that American participants had a marginally higher median concentration of NT-proBNP than the Vietnamese participants (28 vs 16 ng/L, respectively; $p < 0.001$).[46] However, the authors observed that the NT-proBNP values for both groups were substantially below the values required for diagnostic or prognostic thresholds for HF, therefore, concluding that the difference in values was not clinically significant.[46] A recent study involving patients from Singapore and New Zealand demonstrated that NT-proBNP was more accurate for Asian than Western population in diagnosis of acute decompensated HF due to the lower average age of HF presentation in Asian countries.[47] Another study also showed that NT-proBNP was equally prognostic for HF patients in both Asian and Caucasian

populations.[48] However, further studies are necessary to confirm the utility of these recommendations, particularly with regards to the use of NT-proBNP to guide treatment in stable HF patients. Although there are no diagnostically or prognostically important differences in NT-proBNP levels between Asian and Western HF populations reported in the literature, further studies specifically for Asian patients would be beneficial for confirming the validity of the cut-off values recommended in this article.

In conclusion, NPs, specifically NT-proBNP, have demonstrated prognostic value for patients with either HFrEF or HFpEF and who are either hospitalized or are outpatients. Moreover, evidence from clinical trials has enabled the elucidation of NT-proBNP cut-off levels to help determine which patients are at increased risk of poor outcomes in different clinical settings.

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